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.

This section only discusses the MRLs for cobalt. ATSDR has derived MRLs for external exposure to ionizing radiation, which are applicable to external exposures to cobalt radiation, so additional data for the derivation of MRLs for radioactive cobalt are not needed. The MRLs for ionizing radiation are discussed in the Toxicological Profile for Ionizing Radiation (ATSDR 1999).

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 0.0003 mg Co/m^3 ($3x10^{-4}$ mg Co/m^3)
Critical Effect: Increased neutrophils in bronchoalveolar lavage fluid
Reference: Viegas et al. 2022a, 2022b
Point of Departure: NOAEL of 0.2 mg Co/m^3 ($NOAEL_{HEC}$ of 0.01 mg Co/m^3)
Uncertainty Factor: 30
LSE Graph Key: 9
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.0003 mg Co/m^3 ppm was derived for cobalt based on an increased percent neutrophils in BALF in rats exposed to concentrations of 2.2 mg Co/m^3 as cobalt sulfate heptahydrate for 4 hours (Viegas et al. 2022a, 2022b). The MRL is based on a NOAEL of 0.2 mg Co/m^3, which was converted to a human equivalent concentration NOAEL ($NOAEL_{HEC}$) of 0.01 mg Co/m^3 and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Endpoints evaluated in the available acute-duration inhalation studies were limited to acute lethality and respiratory endpoints. Available NOAELs and LOAELs for respiratory effects are shown in Table A-1. The lowest concentration associated with lethality was 32 mg Co/m^3 (Viegas et al. 2022a). Although the acute-duration inhalation database is limited, systematic review (Appendix C) determined that respiratory effects are a known target of cobalt toxicity in humans following inhalation exposure. Therefore, respiratory toxicity was selected as the critical effect for the acute-duration inhalation MRL.

Table A-1. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Acute-Duration Inhalation Exposure to Cobalt and Compounds

Species (strain)/ number	Duration/ frequency	NOAEL (mg Co/m^3)	LOAEL (mg Co/m^3)	Effect	Compound	Reference
Human 15 M	6 hours	ND	0.038	Subjective complaints of respiratory irritation; unspecified decrease in FVC	Hard metal dust	Kusaka et al. 1986a
Rat (SD) 5 F	4 hours	0.2	2.2	Increased BALF neutrophils, decreased BALF cell viability	Cobalt sulfate heptahydrate[a]	Viegas et al. 2022a, 2022b
Rat (Albino) 1–33 M	30 minutes	7	26	Gross lung lesions, pulmonary edema	Cobalt hydrocarbonyl[b]	Palmes et al. 1959

Table A-1. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Acute-Duration Inhalation Exposure to Cobalt and Compounds

Species (strain)/ number	Duration/ frequency	NOAEL (mg Co/m^3)	LOAEL (mg Co/m^3)	Effect	Compound	Reference
Rat (Wistar) 5 M, 5 F	14 days 6 hours/day	9.86	33.87	Increased BALF levels of LDH and polymorphonuclear neutrophils	Cobalt tetraoxide	Burzlaff et al. 2022a

[a]Test substance was likely converted to cobalt sulfate hexahydrate in the inhalation chamber due to relative humidity <70% (Redhammer et al. 2007; Viegas 2024).
[b]Exposure to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen.

Selected study for the acute-duration inhalation MRL derivation.

BALF = bronchoalveolar lavage fluid; F = females; FVC = forced vital capacity; LDH = lactate dehydrogenase; M = males; ND = not determined; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: One human study and three animal studies were identified that evaluated respiratory effects following acute-duration inhalation exposure to cobalt and cobalt compounds. In the human study, a group of 15 young men were exposed to hard metal dust containing mean cobalt concentrations of 0.038 mg Co/m^3 (range 0.004–0.076 mg Co/m^3 (Kusaka et al. 1986a). While all subjects reported respiratory irritation, including coughing, expectoration, or a sore throat, and the study authors reported a significant decrease in FVC after the 6-hour exposure, quantitative data were not provided. Additionally, the study authors did indicate that "no dose-effect relation" could be discerned; however, this claim is unsubstantiated by the available data, and it is unclear how this would be ascertained based on the exposure paradigm. While previous case studies by Harding (1950) and Davison et al. (1983) indicated that cobalt is a potentially toxic substance in hard metal exposure, hard metal is composed of a combination of cobalt, tungsten, and/or tungsten carbide. Due to these study limitations, this study is not considered adequate to serve as the basis for an MRL.

Three studies in rats reported respiratory effects characterized by inflammatory changes in the lungs following acute-duration inhalation exposure to cobalt compounds (Burzlaff et al. 2022a; Palmes et al. 1959; Viegas et al. 2022a, 2022b). Of these, the most sensitive is the study exposing rats to cobalt sulfate heptahydrate, which reported elevated neutrophils in BALF at ≥2.2 mg Co/m^3 (Viegas et al. 2022a, 2022b). The study by Burzlaff et al. (2022a) also reported BALF alterations following exposure to cobalt tetraoxide at a higher concentration. The differences in adverse effect level between Viegas et al. (2022a) and Burzlaff et al. (2022a) is attributable to differences in bioaccessibility of cobalt in the administered compound. A series of studies by this group of researchers suggests two groupings of compounds based on high acute toxicity (cobalt metal power, cobalt dihydroxide, cobalt monoxide, and cobalt sulfate heptahydrate) and low acute toxicity (cobalt tetraoxide, cobalt sulfide) (Danzeisen et al. 2022a, 2022b; Derr et al. 2022; van den Brule et al. 2022; Verougstraete et al. 2022; Viegas et al. 2022a). Toxicity findings in these studies are correlated with bioaccessibility of cobalt in the various compounds.

Regarding the LOAEL endpoint of elevated neutrophils in BALF identified in the study by Viegas et al. (2022a, 2022b), neutrophil-mediated inflammation is considered a key event in particle-induced lung inflammation and toxicity (Lam et al. 2023). In support, Viegas et al. (2022a, 2022b) reported that inflammatory changes at the LOAEL (2.2 mg Co/m^3) progressed to histopathological changes at the next

tested concentration (6.7 mg Co/m^3). Furthermore, data from several other inhalation studies with particulates support that increased neutrophils in BALF correlated well with histological changes in the alveoli in 90-day studies in rats (Weber et al. 2023). Weber et al. (2023) proposed that progressive inflammatory changes were associated with macrophage destruction, which decreased particle clearance from the lungs.

Based on these findings, the study by Viegas et al. (2022a, 2022b), which identified an early key event for respiratory toxicity following exposure to a cobalt compound belonging to the "high acute toxicity" group (cobalt sulfate heptahydrate), appears to be an appropriate, health-protective study on which to base the acute-duration inhalation MRL. While the administered NOAEL is higher than the LOAEL identified by Kusaka et al. (1986a), the $NOAEL_{HEC}$ of 0.03 mg Co/m^3 is below the human LOAEL (see ***Human Equivalent Concentration*** section for calculations below).

Summary of the Principal Study:

Viegas V, Burzlaff A, Brock TO, et al. 2022a. A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 3: Inflammatory response following acute inhalation exposure correlates with lower tier data. Regul Toxicol Pharmacol 130:105127. http://doi.org/10.1016/j.yrtph.2022.105127.

Viegas V, Burzlaff A, Brock TO, et al. 2022b. Supplementary data: A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 3: Inflammatory response following acute inhalation exposure correlates with lower tier data. Regul Toxicol Pharmacol 130. http://doi.org/10.1016/j.yrtph.2022.105127.

Groups of female Crl:CD (SD) rats were exposed to cobalt sulfate heptahydrate at 0, 0.1, 0.3, 1, 10, or 30 mg/m^3 via whole-body inhalation for 4 hours and sacrificed at the following timepoints (five per timepoint): 4, 8, and 16 hours postexposure and 1, 7, 16, and 32 days postexposure. While the initial test compound was cobalt sulfate heptahydrate, this compound is unstable at room temperature at humidity levels <70%; at lower humidity levels, the compound is converted into cobalt sulfate hexahydrate (Redhammer et al. 2007). Based on personal communication with study authors (Viegas 2024), it is likely that the analytically verified concentrations were cobalt sulfate hexahydrate based on the temperature (20–23°C) and humidity (25–31% at lower concentrations, 46–51% at the highest concentration) of the inhalation chambers. Using the ratio of molecular weights for cobalt (58.933 g/mol) and cobalt sulfate hexahydrate (263.11 g/mol), cobalt concentrations were calculated to be 0, 0.02, 0.07, 0.2, 2.2, and 6.7 mg Co/m^3.

BALF was collected for biochemical analysis. Histopathology was conducted on the lungs and upper respiratory system at 1 and 16 days postexposure only. Histopathology data were not reported as incidence data. Rather, the data were reported based on severity score (1–4) for four histopathological markers for inflammation (perivascular inflammatory edema, alveolar pulmonary edema, pneumonia) and upper respiratory tract reactivity (hyperplasia, metaplasia), adjusted by the number of animals affected as well as the spread of the effect (focal, multifocal, locally extensive, no modifier), and then normalized to 1,000 mg/m^3 exposure (to be comparable across various concentrations utilized for eight cobalt compounds tested in this study). The normalized score was reported on a scale of 0–100.

The mass median aerodynamic diameter (MMAD) was 1.87 µM. No deaths occurred. The percentages of neutrophils in BALF were significantly increased by approximately 3.3- and 4.5-fold at 2.2 and 6.7 mg Co/m^3, respectively, at 1-day postexposure. Increases were also observed at 6.7 mg Co/m^3 at 8 hours postexposure and at 2.1 mg Co/m^3 at 16 hours postexposure. Values returned to control levels at 7 days and beyond (data presented graphically). The study authors also noted decreased BALF cell viability at ≥2.2 mg Co/m^3 at 4–16 hours postexposure. Particle-laden macrophages were occasionally noted at

6.7 mg Co/m^3. No histopathological changes were observed the day after exposure; however, by 16 days postexposure, squamous cell metaplasia of the epiglottis in the larynx was observed in almost all rats tested at 6.7 mg Co/m^3. The normalized severity score was approximately 20 based on this upper respiratory tract reactivity. The study authors stated that the 1 mg/m^3 (0.2 mg Co/m^3) level is a NOAEL for inhalation toxicity for this compound based on study results.

Selection of the Point of Departure for the MRL: The NOAEL of 0.2 mg Co/m^3 for elevated neutrophils in BALF was selected as the point of departure (POD) for the acute-duration inhalation MRL.

Effects observed at the LOAEL include increased percentage of neutrophils in BALF and decreased BALF cell viability. Data were reported graphically for BALF neutrophils in the supplemental files (Viegas et al. 2022b); quantitative data were obtained via personal communication with study authors (Viegas 2024). Data for 1-day postexposure were selected for benchmark dose (BMD) modeling because it showed the best dose-response data (Table A-2). Data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS) (version 3.3.2) using a benchmark response (BMR) of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, benchmark concentration lower confidence limit (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data. Therefore, the NOAEL of 0.2 mg Co/m^3 was selected as the POD for the acute-duration inhalation MRL.

Table A-2. Neutrophils in Bronchoalveolar Lavage Fluid in Female Rats 1 Day After a 4-Hour Inhalation Exposure to Cobalt Sulfate Heptahydrate

	Concentration in mg Co/m^3					
	0	0.02	0.07	0.2	2.2	6.7
Neutrophils (%)	4.6±3.31[a] (5)	1±0.61 (5)	8.1±4.74 (5)	3.9±2.3 (5)	15.1±2.48[b] (5)	20.8±11.56[b] (5)

[a]Mean±standard deviation (number of animals).
[b]p<0.01.

Source: Viegas 2024; Viegas et al. 2022b

Adjustment for Intermittent Exposure: The NOAEL of 0.2 mg Co/m^3 was adjusted from intermittent exposure to continuous exposure using the following equation:

$$NOAEL_{ADJ} = 0.2\ mg\ Co/m^3 \times \frac{4\ hours}{24\ hours} = 0.03\ mg\ Co/m^3$$

Human Equivalent Concentration: While an inhalation PBPK model for cobalt is available (Unice et al. 2020a), this model was inadequate for interspecies extrapolation because model assumptions are based on human data for insoluble cobalt dust. There are no rat PBPK models to allow for interspecies extrapolation, and there are no models based on kinetics for soluble cobalt compounds. Therefore, a HEC was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

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

where VR = ventilation rate, DF = deposition fraction, k = 1-clearance rate, RH = particle retention half-time, SA = alveolar surface area, n = exposure days, R = rat, and H = human.

For this equation, deposition fractions for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD 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-3. 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. The TWA values were then used in the calculation of the deposition fraction (to represent TWA deposition over a 24-hour period).

Table A-3. MPPD Model (Version 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Deposition/clearance	Deposition only	Deposition only
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]	1.95 g/cm^3	1.95 g/cm^3
Aspect ratio	1	1
Diameter, MMAD[a]	1.87 µm	1.87 µm
GSD[a]	2.49	2.49
Inhalability adjustment	On	On
Exposure conditions		
Aerosol concentration ($NOAEL_{ADJ}$)	0.03 mg Co/m^3	0.03 mg Co/m^3
Breathing frequency	102 breaths/minute (default)	14.7 breaths/minute (calculated TWA)[b]
Tidal volume	2.1 mL (default)	875 mL (calculated TWA)[c]
Breathing scenario	Nose only	Nasal/oronasal-mouth breather[d]

Table A-3. MPPD Model (Version 3.04) Inputs and Results for Rat and Human Models

Parameters	Rats	Humans
Deposition/clearance	Deposition only	Deposition only
Results		
Alveolar region deposition fraction (Total pulmonary deposition fraction)	0.0363	0.1462

[a]Viegas et al. (2022b).
[b]Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).
[c]Tidal volumes are 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).
[d]Breathing scenario is assumed nasal with sleep and at rest and oronasal-mouth with light activity.

ADJ = adjusted; GSD = geometric standard deviation; NOAEL = no-observed-adverse-effect level; 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 $NOAEL_{HEC}$. Table A-4 lists the values used within the equation and the source of these values. The exposure days (n) are 1 day to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure. Since clearance data are not available for cobalt sulfate heptahydrate, clearance data for nickel sulfate were used to approximate clearance in humans and rats (Oller et al. 2014).

$$NOAEL_{HEC} = 0.03\ mg/m^3 \times \frac{0.22\frac{m^3}{day}}{20\frac{m^3}{day}} \times \frac{0.0363}{0.1462} \times \frac{\frac{1-(1-0.289\ day^{-1})^1}{1-(1-0.289\ day^{-1})}}{\frac{1-(1-0.277\ day^{-1})^1}{1-(1-0.277\ day^{-1})}} \times \frac{1}{1.04} \times \frac{54\ m^2}{0.34\ m^2}$$

$$NOAEL_{HEC} = 0.01\ mg\ Co/m^3$$

Table A-4. Values Used to Calculate the $NOAEL_{HEC}$ for Cobalt

Variable	Rats value (R)	Human value (H)	Source
Ventilation rate (VR)	0.22 m^3/day	20 m^3/day	EPA (1994)
Deposition fraction (DF)	0.0363	0.1462	Calculated using MPPD software
Clearance rate	0.289 day^{-1}	0.277 day^{-1}	Calculated from retention half-times in Oller et al. (2014)[a]
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
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA (1994)
Exposure days (n)	1 day	1 day	Viegas et al. (2022a)

[a]Total clearance rate= ln2/retention half-time; example: 0.693/2.4 days = 0.289 day^{-1}.

HEC = human equivalent concentration; ln = natural logarithm; MPPD = Multiple-Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

Uncertainty Factor: The following uncertainty factors were applied to the $NOAEL_{HEC}$ to derive the MRL:

- Uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- Uncertainty factor of 10 for human variability

Subsequently, the MRL for acute-duration exposure to cobalt via inhalation is:

$$MRL = \frac{NOAEL_{HEC}}{(UF)} = \frac{0.01\ mg\ Co/m^3}{3\ \times 10}$$

$$MRL = 0.0003\ mg\ Co/m^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that the respiratory tract is a known target of cobalt toxicity in humans following inhalation exposure based on a high level of evidence in humans and laboratory animals (Appendix C).

Findings in occupational cohorts of workers exposed to cobalt include reports of adverse respiratory symptoms (e.g., cough, phlegm, wheezing), impaired lung function, and asthma (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a, 1986b; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993; Walters et al. 2012). In laboratory animals, acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Palmes et al. 1959; Viegas et al. 2022a). Dose- and duration-dependent damage throughout the respiratory tract is consistently observed in rodents following intermediate- or chronic-duration inhalation exposure (Burzlaff et al. 2022a; NTP 1991, 1998, 2014). Specifically, the critical effect of elevated neutrophils in BALF has also been observed in Wistar rats exposed to cobalt sulfate heptahydrate at concentrations ≥0.46 mg Co/m^3 for 28 days (Burzlaff et al. 2022a, 2022b). Respiratory effects have also been noted in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1987; Kerfoot 1974).

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: The available intermediate-duration inhalation data are not considered adequate for derivation of an intermediate-duration inhalation MRL for cobalt. No human exposure studies for this duration were identified. While numerous laboratory animal studies are available, an MRL based on the available studies would result in an intermediate-duration inhalation MRL value lower than the chronic-duration inhalation MRL value based on human data. Due to the higher confidence in an MRL based on human data, no intermediate-duration inhalation MRL is proposed for cobalt.

Rationale for Not Deriving an MRL: No studies evaluating cobalt toxicity in humans following intermediate-duration inhalation exposure were identified. However, animal toxicity studies evaluating a comprehensive set of endpoints were available (Burzlaff et al. 2022a; NTP 1991, 2014). These studies consistently identify the respiratory system as the most sensitive target of toxicity for various cobalt compounds in both rats and mice. Additional studies confirm that the respiratory tract is a target of toxicity in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1992; Kerfoot 1974).

The NOAELs and LOAELs for respiratory effects from intermediate-duration inhalation studies are presented in Table A-5. The lowest LOAEL identified for intermediate-duration inhalation exposure (0.114 mg Co/m^3; NTP 1991) was identified as a potential POD for the intermediate-duration inhalation MRL. BMD modeling was attempted for all respiratory lesions in female rats and male and female mice reported at 0.114 mg Co/m^3 by NTP (1991); male rat squamous metaplasia data were not amenable to modeling (incidence was 100% at all administered concentrations). Incidence data for these lesions are presented in Table A-6. The data amenable to modeling were fit to all available dichotomous models in EPA's BMDS (version 3.3.2) using the extra risk option with a BMR of 10%. Adequate model fit was judged as described in the acute-duration section above. Model fits were obtained for squamous metaplasia in female rats only, resulting in benchmark concentration (BMC) and BMCL values of 0.029 and 0.021 mg Co/m^3, respectively. That BMCL value of 0.021 mg Co/m^3 provided the lowest candidate POD (Table A-7).

Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds

Species (strain)/ number	Duration/ frequency	NOAEL (mg Co/m^3)	LOAEL (mg Co/m^3)	Effect	Compound	Reference
Rat (F344/N) Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours + 12 minutes[a]/day	ND	0.114	Squamous metaplasia of the larynx in both sexes in rats and mice; histiocytic infiltrates in the lungs in male mice	Cobalt sulfate heptahydrate[b]	NTP 1991
Pig 5 NS	3 months 5 days/week 6 hour/day	ND	0.115	Decreased lung compliance	Cobalt metal	Kerfoot 1974
Rabbit (NS) 8 M	17 weeks 5 days/week 6 hours/day	ND	0.4	Moderate lung inflammation and accumulation of macrophages	Cobalt metal	Johansson et al. 1987
Rat (Wistar) 10 M, 10 F	28 days 6 hours/day	ND	0.43	Slight focal squamous metaplasia and inflammatory changes; increased BALF LDH levels and neutrophils in males	Cobalt sulfate heptahydrate[c]	Burzlaff et al. 2022a, 2022b
Rabbit (NS) 8 M	4 months 5 days/week 6 hours/day	0.5	ND		Cobalt chloride	Johansson et al. 1991
Rabbit (NS) 8 M	4 months 5 days/week 6 hours/day	ND	0.6	Inflammatory lesions in the lung; increased cellularity of BALF	Cobalt chloride	Johansson et al. 1992
Rat (F344/N) 10 M, 10 F	14 weeks 5 days/week 6 hours + 12 minutes[a]/day	ND	0.625	Chronic active inflammation in lung, pulmonary alveolar proteinosis; increased relative lung weight	Cobalt metal	NTP 2014
Mouse (B6C3F1) 10 M, 9–10 F	14 weeks 5 days/week 6 hours + 12 minutes[a]/day	ND	0.625	Squamous metaplasia of the larynx; cytoplasmic vacuolization of bronchiole epithelium and alveolar histiocytic cellular infiltration	Cobalt metal	NTP 2014

Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds

Species (strain)/ number	Duration/ frequency	NOAEL (mg Co/m^3)	LOAEL (mg Co/m^3)	Effect	Compound	Reference
Mouse (B6C3F1) 5 M, 5 F	16 days 5 days/week 6 hours + 12 minutes[a]/day	0.19	1.8 (SLOAEL)	Inflammation and necrosis of respiratory epithelium (larynx, trachea, bronchioles, nasal turbinates); degeneration of olfactory epithelium	Cobalt sulfate heptahydrate[b]	NTP 1991
Rat (F344/N) 5 M, 5 F	16 days 5 days/week 6 hours + 12 minutes[a]/day	ND	2.5	Minimal cytoplasmic vacuolization of bronchiolar epithelium; minimal-to-mild atrophy and necrosis of olfactory epithelium	Cobalt metal	NTP 2014
Mouse (B6C3F1) 5 M, 5 F	17 days 5 days/week 6 hours + 12 minutes[a]/day	ND	2.5	Minimal-to-mild nasal lesions; minimal cytoplasmic vacuolization of bronchiolar epithelium with histiocytic infiltrates in males	Cobalt metal	NTP 2014
Rat (Wistar) 10 M, 10 F	28 days 6 hours/day	3.76	15.05	Alveolar lipoproteinosis, increased LDH and polymorphonuclear neutrophils in BALF	Cobalt tetraoxide	Burzlaff et al. 2022a

Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds

Species (strain)/ number	Duration/ frequency	NOAEL (mg Co/m^3)	LOAEL (mg Co/m^3)	Effect	Compound	Reference
Rat (F344/N) 5 M, 5 F	16 days 5 days/week 6 hours + 12 minutes[a]/day	1.8	19 (SLOAEL)	Respiratory tract lesions (inflammation, necrosis, hyperplasia, metaplasia, acanthosis, fibrosis, histiocytic infiltration)	Cobalt sulfate heptahydrate[b]	NTP 1991

[a]Exposure was for 6 hours plus T_{90} time (12 minutes); T_{90} time = the time to reach 90% of the target chamber concentration.
[b]Exposure chamber analysis showed that aerosolization of the test substance (cobalt sulfate heptahydrate) resulted in exposure to cobalt sulfate hexahydrate (Behl et al. 2015).
[c]Cobalt sulfate heptahydrate is unstable at room temperature and humidity levels <70% (Redhammer et al. 2007), converting into cobalt sulfate hexahydrate. It is likely that the analytically determined concentrations were in terms of cobalt sulfate hexahydrate, consistent with Behl et al. (2015). While temperature and humidity were not reported for this study, humidity was <70% in the inhalation chamber in other studies by this laboratory (Viegas 2024).

BALF = bronchoalveolar lavage fluid; F = females; FVC = forced vital capacity; LDH = lactate dehydrogenase; M = males; ND = not determined; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Table A-6. Sensitive Respiratory Lesions Rats and Mice Following Intermittent Exposure to Cobalt Sulfate Heptahydrate for 13 Weeks

	Concentration (mg Co/m^3)					
	0	0.114	0.346	1.11	3.78	11.4
Squamous metaplasia of the larynx						
Male rats	0/10[a]	9/9[b]	10/10[b]	10/10[b]	10/10[b]	10/10[b]
Female rats	1/10	7/8[b]	10/10[b]	10/10[b]	10/10[b]	10/10[b]
Male mice	0/10	7/10[b]	10/10[b]	5/9[c]	9/10[b]	10/10[b]
Female mice	0/10	8/10[b]	8/10[b]	8/9[b]	9/10[b]	9/9[b]
Histiocytic infiltrates in the lungs						
Male mice	0/10	10/10[b]	9/10[b]	10/10[b]	10/10[b]	10/10[b]

[a]Affected animals/total animals.
[b]$p<0.01$.
[c]$p<0.05$.

Source: NTP 1991

Table A-7. Candidate PODs for Intermediate-Duration Inhalation MRL based on Respiratory Effects in Rodents Exposed to Cobalt Sulfate Heptahydrate for 13 Weeks

	Effect level (mg Co/m^3)			
Effect (species, sex)	NOAEL	LOAEL	BMCL	BMC
Squamous metaplasia of the larynx (rat, male)	ND	0.114	ND	ND
Squamous metaplasia of the larynx (rat, female)	ND	0.114	0.021	0.029
Squamous metaplasia of the larynx (mouse, male)	ND	0.114	NA	NA
Squamous metaplasia of the larynx (mouse, female)	ND	0.114	NA	NA
Histiocytic infiltrates in the lungs (mouse, male)	ND	0.114	NA	NA

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the benchmark concentration; LOAEL = lowest-observed-adverse-effect level; NA = not applicable (modeling attempted; no adequate models); ND = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure

Source: NTP 1991

The BMCL of 0.021 mg Co/m^3 was adjusted for continuous exposure (6.2 hours/24 hours; 5 days/7 days) to a $BMCL_{ADJ}$ of 0.0039 mg Co/m^3 and converted into a $BMCL_{HEC}$ of 0.0023 mg Co/m^3 using the methodology and equations shown in the acute-duration MRL section above and the values shown in Table A-8. Using the $BMCL_{HEC}$ of 0.0023 mg Co/m^3 as the final POD and a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) would result in an intermediate-duration inhalation MRL of 0.00008 mg Co/m^3 ($8x10^{-5}$ mg Co/m^3). However, this value is not proposed for the intermediate-duration inhalation MRL because the value would be lower than the chronic-duration inhalation MRL based on respiratory effects in humans. The confidence in the chronic-duration MRL is much higher due to study population (human), which precludes the need for interspecies extrapolation and associated uncertainties.

Table A-8. Values Used to Calculate the $BMCL_{HEC}$ for Cobalt

Variable	Rats value (R)	Human value (H)	Source
Ventilation rate (VR)	0.17 m^3/day	20 m^3/day	EPA (1994)[a]
Deposition fraction (DF)	0.0653	0.1370	Calculated using MPPD software
Clearance rate	0.289 day^{-1}	0.277 day^{-1}	Calculated from retention half-times in Oller et al. (2014)[b]
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
Alveolar surface area (SA)	0.34 m^2	54 m^2	EPA (1994)
Exposure days (n)	91 days	91 days	NTP (1991)

[a]The average of the starting and final body weights from the dose groups above and below the BMCL (0.144 kg) from NTP (1991) was used to calculate the VR (instead of the default body weight of 0.124 kg provided in EPA 1994).
[b]Total clearance rate= ln2/retention half-time; example: 0.693/2.4 days = 0.289 day^{-1}.

HEC = human equivalent concentration; ln = natural logarithm; MPPD = Multiple-Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL: 0.0001 mg Co/m^3 ($1x10^{-4}$ mg Co/m^3)
Critical Effect: Respiratory reduced spirometry parameter values
Reference: Nemery et al. 1992
Point of Departure: NOAEL of 0.0053 mg/m^3 ($NOAEL_{ADJ}$ of 0.0013 mg/m^3)
Uncertainty Factor: 10
LSE Graph Key: 28
Species: Human

MRL Summary: A chronic-duration inhalation MRL of 0.0001 mg Co/m^3 was derived for cobalt based on reduced spirometry parameter values in workers exposed chronically to cobalt in air (Nemery et al. 1992). The MRL is based on a NOAEL of 0.0053 mg Co/m^3, which was adjusted for intermittent exposure to a continuous exposure concentration of 0.0013 mg Co/m^3 and divided by a total uncertainty factor of 10 for human variability.

Selection of the Critical Effect: Several occupational studies examining chronic-duration inhalation exposure to cobalt support respiratory toxicity as the critical effect (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993). Chronic-duration inhalation studies in animals support that the respiratory system is the most sensitive target of cobalt toxicity in rodents (NTP 1998, 2014; Wehner et al. 1977). The lowest LOAEL for respiratory effects is 0.0151 mg Co/m^3 for reduced spirometry parameters, coughing, wheezing, and upper airway irritation; this finding is associated with a NOAEL of 0.0053 mg Co/m^3 (Nemery et al. 1992). Case studies show that the sensitization of lymphocytes by cobalt potentially plays a crucial role in some of the respiratory effects (e.g., wheezing, asthma) that are observed in the exposed workers (Krakowiak et al. 2005; Shirakawa et al. 1988, 1989). Limitations of Kusaka et al. (1986a) and Swennen et al. (1993) is the workers' co-exposure to tungsten, carbide, and cobalt. A study by Gennart and Lauwerys (1990) measured the cobalt air concentrations from two rooms where the workers were moving between freely and no stay times were provided. The absence of this information did not allow estimation of the average exposure for the workers; therefore, a reliable exposure estimate cannot be determined and this study cannot be used to derive an MRL. Sauni et al. (2010) conducted a case study of occupational asthma in cobalt plant workers in Finland from 1967 to 2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m^3. Until 1987, cobalt was being produced from pyrite ore concentrate, which resulted in occupational co-exposures to sulphur dioxide (SO_2) and ammonia (NH_3). These gases are both known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using byproducts of metallurgic industry as raw material, which eliminated the co-exposure to the irritant gases, and the incidence of asthma reduced to only one case. Therefore, it is likely that the health effects observed in this study were due to the co-exposure to sulphur dioxide and ammonia and not cobalt alone. Due to this reason, Sauni et al. (2010) cannot be used to derive an MRL.

Rats, mice, and hamsters showed lethality, respiratory effects, and cancer effects after chronic-duration inhalation exposure to cobalt at concentrations higher than those in the human studies (NTP 1998, 2014; Wehner et al. 1977). Wehner et al. (1977) used a high concentration of 7.9 mg Co/m^3 for a lifetime exposure in hamsters, resulting in lung inflammation and emphysema. In the NTP (1998) study, mice

showed respiratory effects at the lowest exposure concentration in the chronic-duration inhalation database (0.06 mg Co/m^3) in addition to cancer effects, which included hyperplasia of the squamous epithelium in the larynx. Although rats did not show serious respiratory health effects, the lowest concentration caused cancer effects in rats (alveolar/bronchiolar neoplasms along with metaplasia of the nose and epiglottis) (NTP 1998). In the NTP (2014) study, the concentration of 1.25 mg Co/m^3 produced serious respiratory and cancer effects in both rats and mice; cancer effects included increased incidence of mononuclear cell leukemia in rats and increased rate of alveolar/bronchiolar carcinoma in mice. The NOAELs and LOAELs for chronic-duration inhalation exposure studies are presented below in Table A-9.

Table A-9. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt

Species (sex)	Frequency/ duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Compound	Reference
Human (M, F)	Current employees; duration of employment not reported (occupational)	0.0053 (0.0013)	0.0151 (0.0027)	Decreased FEV_1 (5%) and FVC (5%); increased cough (11/91), wheezing (4/91), and upper airway irritation (40/91) in workers	Cobalt metal	Nemery et al. 1992
Human (M, F)	21 years (occupational)	0.0175 (0.004)	ND		Cobalt metal	Deng et al. 1991
Human (M,F)	8 years (occupational)	ND	0.125 (0.03)	Dyspnea and wheezing	Hard metal	Swennen et al. 1993
Human (M, F)	3 years (occupational)	ND	0.126 (0.03)	2.7% decrease in FEV_1 in exposed workers	Hard metal	Kusaka et al. 1986b
Rat (M, F)	105 weeks 5 days/week 6 hours/day	ND	0.12 (0.02) (SLOAEL)	Hyperplasia and metaplasia of upper and lower respiratory tract tissues; pulmonary fibrosis; inflammatory changes in lungs	Cobalt sulfate heptahydrate[a]	NTP 1998
Mice (M, F)	105 weeks 5 days/week 6 hours/day	ND	0.11 (0.02) (SLOAEL)	Squamous metaplasia of the larynx	Cobalt sulfate heptahydrate[a]	NTP 1998
Rats (M, F)	105 weeks 5 days/week 6 hours/day	ND	1.25 (0.223) (SLOAEL)	Hyperplasic and metaplastic pulmonary and nasal lesions	Cobalt metal	NTP 2014
Mice (M, F)	105 weeks 5 days/week 6 hours/day	ND	1.25 (0.223) (SLOAEL)	Hyperplasic and metaplastic pulmonary and nasal lesions	Cobalt metal	NTP 2014

Table A-9. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt

Species (sex)	Frequency/ duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Compound	Reference
Hamster	Lifetime 5 days/week 7 hours/day	ND	7.9 (1.4) (SLOAEL)	Lung Inflammation and emphysema	Cobalt oxide	Wehner et al. 1977

[a]Exposure chamber analysis showed that aerosolization of the test substance (cobalt sulfate heptahydrate) resulted in exposure to cobalt sulfate hexahydrate (Behl et al. 2015).

Selected study for the chronic-duration inhalation MRL derivation.

ADJ = adjusted; F = females; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: The Nemery et al. (1992) study tested the lowest concentrations among all human and animal studies and demonstrated a dose-response relationship between reduced spirometry parameter values and cobalt exposure. Therefore, the Nemery et al. (1992) study was selected as the critical study because it identified the lowest NOAEL for chronic-duration inhalation exposure and a corresponding LOAEL.

While this study has limitations (discussed below in the ***Summary of the Principal Study***), available data based on findings from the group analysis showing impaired lung function and increased subjective complaints of respiratory symptoms in the high-exposure group support identification of the low-exposure group mean (0.0053 mg Co/m^3) as a NOAEL for respiratory effects. While causality cannot be determined in studies with cross-sectional design, findings from the systematic review presented in Appendix C (*Respiratory effects are a known health effect for humans following inhalation exposure to cobalt*) support that observed exposure-related effects are likely attributable to occupational exposure to cobalt.

Summary of the Principal Study:

Nemery B, Casier P, Roosels D, et al. 1992. Survey of cobalt exposure and respiratory health in diamond polishers. Am Rev Respir Dis 145:610-616. http://doi.org/10.1164/ajrccm/145.3.610.

In a cross-sectional study, 194 diamond polishers from 10 different workshops were examined with 6–28 people from each workshop participating. In 8 out of 10 workshops, the polishing disks used were primarily cobalt-containing disks, while two workshops almost exclusively used cast iron polishing disks. Participation in the workshops varied from 56 to 100%, and low participation from some workshops reflects the fact that only workers who used cobalt disks were initially asked to be in the study, rather than a high refusal rate (only eight refusals were documented). A year later, three additional workshops with workers engaged in diamond sawing, cleaving, or jewelry drawing were studied as an unexposed control group (n=59 workers). All study subjects were administered questionnaires to report medical history and lifestyle factors, provided urine samples, and underwent clinical examination and lung function tests. Area and personal air samples were collected and analyzed for cobalt and iron. Other potential co-exposure substances (e.g., diamond dust and carbide) were not assessed. Sampling for area air determinations started 2 hours after work began and continued until 1 hour before the end of the workday.

Personal air samples were collected from the breathing zone of a few workers per workshop for four successive 1-hour periods. Air samples were not collected for one workshop; however, data from an identical workshop were used as a proxy since urinary cobalt levels between workers from both workshops were similar.

Nemery et al. (1992) showed a correlation (R=0.92) between the results of work area cobalt levels and personal cobalt air sampling, with area air sampling reporting lower concentrations than personal air samples in all workshops except one. The correlation between cobalt exposure, measured as urinary levels of cobalt, and air samples was significant (R=0.85–0.88) when one workshop with poor hygienic conditions was excluded. The study authors noted that the available methods used for air sampling may have underestimated the exposure levels. The polishing workshops were divided into two cobalt exposure groups: low (n=102) and high (n=91). Mean personal air sampling cobalt exposure concentrations were 0.0004, 0.0053, and 0.0151 mg/m^3 in the control, low-exposure, and high-exposure groups, respectively. Other metals, such as copper and chromium, were detected, and some workers had previous occupational exposure to asbestos (use of asbestos containing glues), which was judged insufficient by the study authors to produce a functional impairment. The study authors noted that cobalt appears to be the only relevant exposure; however, details on the exposure duration were not provided.

Characteristics of the three groups were similar, with the exception that men in the referent group were slightly younger and taller than men in the exposed groups. The average respective ages in the control, low-, and high-exposure groups were 28.2, 32.1, and 32.8 years for men and 21.1, 25.9, and 25.4 years for women. The average respective heights in the control, low-, and high-exposure groups were 177.6, 175.9, and 174.2 cm for men and 163.6, 164.1, and 164.2 cm for women. For smoking status, 47, 41, and 37% of subjects had never smoked, 32, 41, and 50% were smokers, and 20, 18, and 13% were ex-smokers in the control, low-, and high-exposure groups, respectively.

Workers in the high-exposure groups were more likely to report eye, nose, and throat irritation and cough, compared to other groups. Cough was more frequently reported by female polishers than male polishers. No exposure-related difference was observed for other respiratory symptoms including dyspnea and wheezing. Reduced lung function in the high-exposure group was demonstrated by significantly lowered FVC and FEV_1, even after consideration of smoking status. Additionally, maximal mid-expiratory flow and mean PEF rates were significantly lower in the high-exposure group compared to controls and the low-exposure group. The work-related upper airway effects were seen in 30% of controls, 26% of low dose individuals, and 43% of high dose individuals. Work-related cough was not observed in the control subjects but was observed in 4% of the low-dose exposure group and in 12% of the high-dose exposure group. There was no correlation between cobalt exposure and respiratory effects on an individual level within this group; correlations occurred only on a group level: low, high, and control. However, the higher rate of smokers in exposed workers, compared to control, confounds interpretation of the incidence of work-related cough; no group analyses with adjustment for smoking status were performed. Two-way analysis of variance showed that exposure-related effects on spirometric parameters in the high-dose exposure groups were present in men and women. Women appeared to be more affected than men, but the difference was not significant. Spirometric parameters did not differ significantly between the controls and the low-exposure dose group. Smoking did exert a strong effect on lung function, but lung function remained inversely correlated with exposure to cobalt, independent of smoking. The spirometric parameters for men and women and the combined unweighted values for FVC and FEV_1 are presented in Table A-10.

Table A-10. FVC and FEV_1 Values in Humans Exposed to Inhaled Cobalt in an Occupational Setting[a]

Dose (mg Co/m^3)		0.0004 (control)		0.0053 (low exposure)		0.0151 (high exposure)	
Number (total/men/women)		59/46/13		102/93/9		92/73/19	
Parameter		Mean	SD	Mean	SD	Mean	SD
FVC (mL)	Men	5,648	936	5,445	754	5,184	799
	Women	4,033	688	4,018	627	3,733	592
	Total (weighted)	5,292	1,110.6	5,319	845.2	4,884	960.85
FEV_1 (mL)	Men	4,644	803	4,451	679	4,191	712
	Women	3,416	634	3,468	384	3,123	599
	Total (weighted)	4,373	920.31	4,364	714.24	3,970	813.04

[a]Means and standard deviations for men and women are raw data from Table 4 in Nemery et al. (1992). Total (weighted) combines data for men and women to calculate the weighted means and standard deviations of the data.

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SD = standard deviation

Source: Nemery et al. (1992)

In addition to limitations described above (e.g., lack of control for other potential exposures, use of proxy exposure data), there are additional study limitations to consider. As with all cross-sectional studies, causality between cobalt exposure and observed outcomes cannot be definitively determined. Also, the statistical analysis for spirometry data did not adjust for known characteristics that can affect lung function in addition to smoking status, such as age and height. Lastly, the exposure duration for workers was not reported.

Selection of the Point of Departure for the MRL: The NOAEL of 0.0053 mg/m^3 for reduced respiratory function in male and female workers was selected as the basis for the chronic-duration inhalation MRL. The weighted data for spirometric parameters in both males and females (presented in Table A-10) were amenable to BMD modeling. The weighted data for FVC and FEV_1 were each modeled separately, and each dataset was fit to all available continuous models in EPA's BMDS (version 3.3.2). Adequate model fit was judged as described in the acute-duration section above. A BMR of 1 standard deviation from the control mean was selected in the absence of a biologically based BMR.

Results of the BMD modeling for FVC and FEV_1 are presented in Tables A-11 and A-12, respectively. Using the criteria listed above, only the Linear model provides an adequate fit to the FVC and the FEV_1 data. However, for both endpoints, both the BMC and BMCL values were higher than the maximum concentration in the dataset, lending considerable uncertainty to the model. These results are due, in part, to the large variance in the control groups, which directly impacts the outcome of the default BMR of 1 standard deviation. Based on BMC and BMCL values outside the range of concentrations in the dataset, the extrapolated BMCL values were not considered suitable as the basis for the POD for the MRL. In the absence of a suitable BMD model, the NOAEL of 0.0053 mg/m^3 for reduced respiratory function in male and female workers was selected as the POD for the chronic-duration inhalation MRL.

Table A-11. Model Predictions (Constant Variance) for FVC in Workers Exposed to Cobalt Chronically via Inhalation (Nemery et al. 1992)

Model	BMD_{1SD}[a] (mg/m^3)	$BMDL_{1SD}$[a] (mg/m^3)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 3[d]			NA	4,194.69	-9.07×10^{-7}	NA
Exponential 5[d]			NA	4,194.69	-1.99×10^{-7}	NA
Hill[d]			NA	4,194.69	-1.04×10^{-6}	NA
Polynomial Degree 2[d]			0.01	4,192.95	1.74	NA
Power[d]			NA	4,194.69	4.16×10^{-8}	NA
Linear	0.0294	0.0193	0.21	4,194.24	-0.3210	NA

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); FVC = forced vital capacity; NA = not applicable, goodness-of-fit test could not be performed

Table A-12. Model Predictions (Constant Variance) for FEV_1 in Workers Exposed to Cobalt Chronically via Inhalation (Nemery et al. 1992)

Model	BMD_{1SD}[a] (mg/m^3)	$BMDL_{1SD}$[a] (mg/m^3)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 3[d]			NA	4,106.64	-6.99×10^{-7}	NA
Exponential 5[c,d]			NA	4,108.64	-4.67×10^{-7}	NA
Hill[d]			NA	4,108.64	5.73×10^{-7}	NA
Polynomial Degree 2[d]			<0.0001	4,120.19	-0.157	2.541
Power[d]			NA	4,106.64	-6.60×10^{-7}	NA
Linear	0.0258	0.0177	0.25	4,105.97	-0.294	NA

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); FEV_1 = forced expiratory volume in 1 second; NA = not applicable, goodness-of-fit test could not be performed

Adjustment for Intermittent Exposure: Assuming workers in Nemery et al. (1992) were exposed only at work, the NOAEL was adjusted to account for a continuous work-day exposure (0.0053 mg/m^3, Table A-9). A typical workweek of 8 hours/day, 5 days/week was assumed:

$$NOAEL_{ADJ} = 0.0053\ mg/m^3\ \times \frac{8\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0013\ mg/m^3$$

Uncertainty Factor: The $NOAEL_{ADJ}$ is divided by a total uncertainty factor of 10:

- 10 for human variability

Subsequently, the MRL for chronic-duration exposure to cobalt via inhalation is:

$$MRL = \frac{NOAEL}{UFs} = \frac{0.0013\ mg\ Co/m^3}{10}$$

$$MRL = 0.00013\ mg\ Co/m^3\ \ (rounded\ to\ 0.0001\ mg\ Co/m^3)$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that the respiratory tract is a known target of cobalt toxicity in humans following inhalation exposure based on a high level of evidence in humans and laboratory animals (Appendix C).

Findings in occupational cohorts of workers exposed to cobalt include reports of adverse respiratory symptoms (e.g., cough, phlegm, wheezing), impaired lung function, and asthma (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a, 1986b; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993; Walters et al. 2012). In laboratory animals, acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Viegas et al. 2022a; Palmes et al. 1959). Dose- and duration-dependent damage throughout the respiratory tract is consistently observed in rodents following intermediate- or chronic-duration inhalation exposure (Burzlaff et al. 2022a; NTP 1991, 1998, 2014). Respiratory effects have also been noted in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1987; Kerfoot 1974).

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Cobalt and compounds
CAS Numbers:	7440-48-8
Date:	October 2024
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL:	0.03 mg Co/kg/day
Critical Effect:	Transient polycythemia (clinically elevated red blood cell levels)
Reference:	Davis and Fields 1958
Point of Departure:	Minimal LOAEL of 1 mg Co/kg/day
Uncertainty Factor:	30
LSE Graph Key:	1
Species:	Human

MRL Summary: An acute-duration oral MRL of 0.03 mg Co/kg/day was derived for cobalt based on a hematological endpoint of transient production of polycythemia (clinically elevated red blood cell levels) in humans orally exposed to cobalt chloride for 7–14 days (Davis and Fields 1958). The MRL is based on a minimal LOAEL of 1 mg Co/kg/day, which was divided by a total uncertainty factor of 30 (10 for human variability and 3 for use of a minimal LOAEL).

Selection of the Critical Effect: The most sensitive effects in humans following acute-duration oral exposure to cobalt are gastrointestinal upset, impaired thyroid function, and hematological effects. However, based on systematic review (Appendix C), gastrointestinal effects are not classifiable as to their toxicity to humans following oral exposure to cobalt; therefore, they were not considered as a potential critical effect. The NOAELs and LOAELs for hematological and thyroid effects in humans and animals are shown in Table A-13. The lowest LOAELs for hematological and thyroid effects ranged from 0.54 to 1 mg Co/kg/day in humans (Davis and Fields 1958; Paley et al. 1958; Roche and Layrisse 1956). However, the study by Paley et al. (1958) was determined to be a third-tier study based on risk of bias evaluation (Appendix C). Due to high risk of bias associated with this study, it was not considered further for MRL development. Therefore, remaining candidate MRLs for thyroid and hematological effects had equivalent LOAELs of 1 mg Co/kg/day based on LOAELs. Based on systematic review of the entire oral database (Appendix C), evidence is stronger for hematological effects (presumed health effect based on a moderate level of evidence in humans and high level of evidence in animals) than thyroid effects (suspected health effect based on a low level of evidence in humans and a moderate level of evidence in animals). Since effects occur at the same exposure level, the health effect with a stronger weight-of-evidence (hematological effects) was selected as the critical effect.

Table A-13. Select NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to Cobalt and Compounds

Species	Duration	NOAEL (mg Co/kg/day)	LOAEL (mg Co/kg/day)	Effect	Compound	Reference
Hematological effects						
Human 8–16 M	7–14 days	0.03	ND		Cobalt (II)	Hoffmeister et al. 2018
Human 5 M	7–14 days	ND	1	Polycythemia (14% increase in erythrocyte levels, compared to pre-exposure values)	Cobalt chloride	Davis and Fields 1958
Rat 6 M	7 days	ND	12.5	Increased hematocrit and hemoglobin levels	Cobalt chloride hexahydrate	Shrivastava et al. 2008
Rat 8 M	7 days	ND	12.5	Increased red blood cell count, hematocrit, and hemoglobin; increased percent granulocytes and monocytes	Cobalt chloride hexahydrate	Shrivastava et al. 2010
Rat 8 M	8 days	12.4	24.8	Increased hematocrit, hemoglobin, and reticulocytes	Cobalt chloride hexahydrate	Paternian and Domingo 1988
Rat 20 M	Once	ND	161	Increased hematocrit	Cobalt chloride hexahydrate	Domingo and Llobet 1984
Thyroid effects						
Human 3 M	10–14-days	ND	0.54	Impaired thyroid uptake of radioactive iodine-131	Cobalt chloride	Paley et al. 1958
Human 12 NS	14 days	ND	1	Impaired thyroid uptake of radioactive iodine-131	Cobalt chloride	Roche and Layrisse 1956

Selected study for the acute-duration oral MRL derivation.

M = males; ND = not determined; NS = not specified

Selection of the Principal Study: Davis and Fields (1958) was selected as the principal study because it identifies the lowest LOAEL for the critical effect (hematological effects).

Summary of the Principal Study:

Davis JE, Fields JP. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495. http://doi.org/10.3181/00379727-99-24395.

Five apparently healthy men, ages 20–47 years, were administered a daily dose split equally across mealtimes of cobalt chloride, as a 2% solution diluted in either water or milk daily. The subjects were regularly dosed for 14 days with equally divided doses at mealtimes. It is noted that one of these subjects (subject 4) continued treatment past 14 days; these data are not included in this acute-duration analysis. In this study, each subject served as their own control, and blood samples were collected from each

subject 7–14 days prior to the onset of oral administration. Each of the five subjects received 150 mg cobalt chloride per day for up to 14 days. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell count, hemoglobin percentage, leukocyte count, reticulocyte percentage, and thrombocyte count. A crucial limitation of this study was that there was only one dose used in this study, which all five participants received.

Exposure to cobalt resulted in the development of polycythemia (as reported by the study authors) in all five subjects. The erythrocyte data from the study were only presented graphically. In order to understand the magnitude of the effect, the graph (Figure 1 in the publication) was digitized using an open-source software, Curve Snap, to better inform the oral acute-duration MRL derivation. Digitized data are presented in Tables A-14 (baseline data) and A-15 (data during treatment period). At baseline, the red blood cell numbers averaged over subjects over 4 days prior to exposure were 5.6 million cells/mm^3. At the end of exposure for 7–14 days, the average red blood cell number had increased to 6.4 million cells/mm^3, an increase in 14%. For all five subjects, measured values at the end of the exposure were above the clinically normal red blood cell levels for adult male men of 4.7–6.1 million cells/mm^3 (NLM 2022a). Erythrocyte counts returned to baseline levels (within medical norms) for all individuals 4–9 days after cessation of cobalt administration.

Table A-14. Data Extracted from Figure 1 in Davis and Fields (1958): Erythrocyte Levels Before Administered Cobalt Exposure (Red Blood Cells in Millions/mm^3)

Person #	Symbol	Pretreatment day 1	Pretreatment day 2	Pretreatment day 3	Pretreatment day 4	Average
1	●	6.0	6.1	5.8	6.2	6.0
3	•	5.7	5.6	5.5	5.6	5.6
4	□	5.6	5.6	5.5	5.5	5.6
5	o	5.5	5.5	5.6	5.7	5.6
6	Δ	5.6	5.3	5.5	5.4	5.5
					Average pretreatment erythrocytes levels (in millions/mm^3):	**5.6**

Table A-15. Data Extracted from Figure 1 in Davis and Fields (1958): Erythrocyte Levels During Acute-Duration Cobalt Exposure for 7–14 days (Red Blood Cells in Millions/mm^3)

		Days of acute cobalt exposure															
Person #	Symbol	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Average Days 7–14
1	●	6.0			6.2		6.4		6.5	6.6	7.2	**6.7**					6.8
3	•	5.6	5.8	5.9	6.1	6.4	6.5	6.5	**6.3**								6.3
4	□	5.6	5.6	5.7		5.7	6.0	6.0	6.2		6.4	6.5	6.5	6.4	6.3		6.4
5	o	5.5	5.7	5.9		5.8	6.0		6.1		6.3	6.5		6.4	**6.4**		6.3
6	Δ	5.4	5.5	5.5		5.6	5.9	6.0		6.2		6.2		6.2	6.4	**6.4**	6.3
Average erythrocytes after exposure for 7–14 days (in millions/mm^3): 6.4																	
Average erythrocytes on the final day of exposure (in millions/mm^3): 6.4																	
Percent increase in erythrocyte levels after acute-duration exposure for 7–14 days, compared to pretreatment levels: 14%																	

No conclusions can be made regarding other hematological findings from this study due to inadequate data reporting. All subjects in this study (including the four exposed for ≤14 days, the one exposed >14 days at 1 mg Co/kg/day, a sixth subject exposed for >14 days to a different exposure paradigm) showed increased reticulocyte counts ranging from 1.9 to 2.7% (normal range 0.5–2.5%; NLM 2022b), with all but one showing an increase of at least 2-fold. Based on data-reporting, it cannot be determined which subjects had values above the normal range of 0.5–2.5% (NLM 2022b), or which individual showed a mild change <2-fold. Similarly, increases in hemoglobin percentages were reported to a "lesser extent" in subjects, compared to observed increases in red blood cell levels. Increases in all subjects were reportedly 6–11%, compared to pre-exposure values; hemoglobin values per subject were not reported. No exposure-related changes in total leukocyte or thrombocyte counts were observed, compared to pre-exposure values.

Selection of the Point of Departure for the MRL: Davis and Fields (1958) identified a LOAEL of 1 mg Co/kg/day for polycythemia indicated by increased levels of erythrocytes in human males exposed daily for up to 14 days. Data from the study identified a minimal LOAEL of 1 mg Co/kg/day for this effect, which was used as the POD to derive an MRL. The study reported a daily high dose intake of 150 mg cobalt chloride/day, which was converted to a daily dose of cobalt using a reference body weight of 70 kg for adult humans:

$$150\ mg\ CoCl_2/day = 150 \times \frac{58.9 \frac{g}{mol}\ Co}{128.8 \frac{g}{mol}\ CoCl_2} = 68.1\ mg\ Co/day$$

Based on assuming a 70-kg body weight of the subjects in the study:

$$\frac{68\ mg\ Co/day}{70\ kg\ (body\ weight\ of\ an\ adult\ human\ male)} = \sim 1\ mg\ Co/kg/day$$

The available data in Davis and Fields (1958) are not amenable to BMD modeling as the study only tested one exposure dose.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The minimal LOAEL is divided by a total uncertainty factor of 30:

- 10 for human variability
- 3 for use of a minimal LOAEL; the finding was considered a minimal LOAEL based on transient nature of effect (hematological levels returned to baseline for all individuals 4–9 days after cessation of cobalt administration) as well as mild nature of the effect (average erythrocyte levels were just above the clinically normal range of 4.7–6.1 million cells/mm^3 for adult male men)

Subsequently, the MRL for acute-duration exposure to cobalt via oral exposure is:

$$MRL = \frac{LOAEL}{UFs} = \frac{1\ mg\ Co/kg/day}{10 \times 3}$$

$$MRL = 0.03\ mg\ Co/kg/day$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that the hematological system is a presumed target of cobalt toxicity in humans following oral exposure based on a moderate level of evidence in humans and a high level of evidence laboratory animals (Appendix C).

Available animal studies corroborate the effects seen in the limited human database. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).

Based on limited available human data, the acute-duration oral MRL of 0.03 mg Co/kg/day should be protective of other side effects reported in controlled trials and/or case reports of cobalt supplementation (e.g., gastrointestinal distress, thyroid effects), reported at doses ≥0.54 mg Co/kg/day (Paley et al. 1958; Roche and Layrisse 1956).

Agency Contact (Chemical Managers): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.02 mg Co/kg/day
Critical Effect: Elevated red blood cells
Reference: Danzeisen et al. 2020a
Point of Departure: $BMDL_{1SD}$ of 1.95 mg Co/kg/day
Uncertainty Factor: 100
LSE Graph Key: 53
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.02 mg Co/kg/day was derived for cobalt based on elevated red blood cell counts in male rats exposed to cobalt chloride hexahydrate at concentrations ≥2.48 mg Co/kg/day for 90 days (Danzeisen et al. 2020a). The MRL is based on a $BMDL_{1SD}$ of 1.9 mg Co/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Endpoints identified as presumed (hematological) or suspected (thyroid) human health effects following oral exposure based on systematic review (Appendix C) were considered as candidate critical effects for the intermediate-duration inhalation MRL. The NOAELs and LOAELs identified for these endpoints in humans and animals are presented in Table A-16. Review of the available data indicate that hematological effects are the most sensitive effects; therefore, they are selected as the critical effect for derivation of the intermediate-duration oral MRL.

Table A-16. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Cobalt and Compounds

Species	Duration	NOAEL (mg Co/kg/day)	LOAEL (mg Co/kg/day)	Effect	Compound	Reference
Hematological effects						
Human 5 M, 5 F	31 days	0.013	ND		Cobalt chloride	Finley et al. 2013
Human 5 M, 5 F	91 days	0.013	ND		Cobalt chloride	Tvermoes et al. 2014
Human 8–16 M	21 days	0.03	ND		Cobalt (II)	Hoffmeister et al. 2018
Rat 10 M, 10 F	90 days	0.74	2.48	Increased red blood cell count, hemoglobin, and hematocrit in males	Cobalt chloride hexahydrate	Danzeisen et al. 2020a
Rat 4–6 M	8 weeks	0.62	2.5	Increased red blood cell count and hemoglobin	Cobalt chloride hexahydrate	Stanley et al. 1947

Table A-16. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Cobalt and Compounds

Species	Duration	NOAEL (mg Co/kg/day)	LOAEL (mg Co/kg/day)	Effect	Compound	Reference
Rat 6–30 M	150 days 5 days/week	ND	10	Increased red blood cell count, hemoglobin, and hematocrit	Cobalt chloride	Murdock 1959
Rat 8–15 M	30 days	8.99	13.8	Decreased hemoglobin	Cobalt chloride	Chetty et al. 1979
Rat 20 M	13 weeks	ND	16.5	Increased hematocrit and hemoglobin	Cobalt chloride	Domingo et al. 1984
Rat 3–8 M	4 months	ND	18	Increased red blood cell count and hemoglobin levels	Cobalt chloride	Holly 1955
Rat 3 M	98 days	ND	20	Increased red blood cell count, hemoglobin level, and packed cell volume	Cobalt chloride hexahydrate	Corrier et al. 1985
Rat 10 M, 10 F	90 days	73.4	220	Increased red blood cell count, hemoglobin, and hematocrit in males	Cobalt tetroxide	Danzeisen et al. 2020a
Thyroid effects						
Human 5 M, 5 F	31 days	0.013	ND		Cobalt chloride	Finley et al. 2013
Human 5 M, 5 F	91 days	0.013	ND		Cobalt chloride	Tvermoes et al. 2014
Human 20–55 F	13 weeks	0.57	ND		Cobalt chloride	Holly 1955
Rat 10 M, 10 F	90 days	7.44	ND		Cobalt chloride hexahydrate	Danzeisen et al. 2020a
Rat 3–8 M	4 months	18	ND		Cobalt chloride	Holly 1955
Mouse 6 F	45 days	ND	45 (SLOAEL)	Degeneration and necrotic changes in thyroid epithelial cells; lymphocytic infiltration	Cobalt chloride	Shrivastava et al. 1996
Rat 10 M, 10 F	90 days	734			Cobalt tetroxide	Danzeisen et al. 2020a

Selected study for the intermediate-duration oral MRL derivation.

F = females; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: The Danzeisen et al. (2020a) in rats was selected as the principal study because it identifies the lowest LOAEL for the critical effect (hematological effects).

Available human studies do not identify adverse hematological effects following intermediate-duration oral exposure to cobalt supplements at doses up to 0.03 mg Co/kg/day (Finley et al. 2013; Hoffmeister et al. 2018; Tvermoes et al. 2014). The principal study for the acute-duration MRL (Davis and Fields 1958) also evaluated hematological effects in two subjects following intermediate-duration exposure. As described in the acute-duration MRL worksheet, graphically-presented data were digitized using an open-source software, Curve Snap, to estimate changes in red blood cell counts. One subject was exposed to 1.0 mg Co/kg/day for a total of 15 days, showing an approximate 18% increase in red blood cell count at the end of exposure, compared to pre-exposure levels. The second subject was exposed to 0.8 mg Co/kg/day for 15 days, at which point, no alterations in red blood cell counts were observed compared to pre-exposure values. The dose for the subject was increased to 1 mg Co/kg/day for an additional 7 days, at which point, red blood cell levels were increased by approximately 5%. These data suggest that the no adverse effect level may be around 0.8 mg Co/kg/day for intermediate-duration oral studies; however, with only a single subject per dose group, this study is of insufficient study design to make that determination. However, the comparability of that value (0.8 mg Co/kg/day) to the NOAEL value of 0.74 mg Co/kg/day from the rat study by Danzeisen et al. (2020a) lends support to the selection of the rat study as the principal study for derivation of the intermediate-duration oral MRL.

Summary of the Principal Study:

Danzeisen R, Williams DL, Viegas V, et al. 2020a. Bioelution, bioavailability, and toxicity of cobalt compounds correlate. Toxicol Sci 174(2): 311-325. http://doi.org/10.1093/toxsci/kfz249.

In an OECD 408 guideline repeat-dose toxicity study, groups of male and female Crl:CD(SD) rats (10/sex/group) were exposed to 0, 3, 10, or 30 mg cobalt chloride hexahydrate/kg/day (0, 0.74, 2.48, and 7.44 mg Co/kg/day, as per the study authors) for 90 days via gavage in 0.5% hydroxypropyl methylcellulose. Animals were sacrificed immediately after exposure. Additional animals (5/sex/group) served as the recovery group; were similarly exposed to 0 or 30 mg cobalt chloride hexahydrate/kg/day, and were sacrificed 28 days after the end of exposure. Parameters monitored included clinical observations, body weight, food and water consumption, neurological and observational screening, functional tests, hematology and clinical biochemistry, ophthalmology, and reproductive endpoints (serum hormone levels, estrous cyclicity). At sacrifice, gross necropsy was conducted and selected organs were weighed and examined for a complete histopathological examination conducted as per OECD 408 guidelines.

All rats survived. No exposure-related clinical signs or alterations in neurobehavioral screening or functional testing were observed. No changes in food or water consumption were seen. Body weight effects were noted throughout exposure at the highest dose ranging from 5 to 14% decrease from day 8 onward; at necropsy, final body weights were reduced by 11% in males and 9% in females. Body weights remained reduced by 17% in males and 14% in females at the end of the recovery period, compared to controls. Adverse hematological effects were noted in male rats at ≥2.48 mg Co/kg/day and female rats at 7.44 mg Co/kg/day. In males, findings at 2.48 and 7.44 mg Co/kg/day included elevations in red blood cell counts (9.2 and 18.9%, respectively), hemoglobin levels (10.7 and 25.6%, respectively), and hematocrit (10.3 and 24.2%, respectively). In females, red blood cell counts, hemoglobin levels, and hematocrit were elevated by 9.8, 13.4, and 13.7%, respectively, at 7.44 mg Co/kg/day. Red blood cell parameters were comparable to control in both sexes at the end of the 28-day recovery period. No changes in urinalysis or ophthalmology were observed. No changes in hormone levels or estrous cyclicity were observed. At sacrifice, no gross pathological changes were noted and no exposure-related changes in organ weight were observed. The only organs specifically mentioned as having “no effect” were testes and prostate. Dose-depended increases in erythroid hyperplasia were observed in the bone marrow at 2.48 mg Co/kg/day (4/10 males, 7/10 females) and 7.44 mg Co/kg/day (7/10 males, 7/10 females), compared to control and 0.74 mg Co/kg/day (0/10 incidence for both sexes). This lesion was not

observed at the end of the recovery period. The study authors specifically noted that there were no macroscopic or histopathological findings in the heart or thyroid at any dose. No other measured endpoints were explicitly discussed. In the methods section, the study authors stated: "Due to the wealth of parameters measured in these studies, only those endpoints that were affected by the treatment are reported." Based on this statement, it is assumed that all parameters set forth in the OECD 408 guidelines that are not discussed in the results section represented no adverse effect levels.

The study authors determined a systemic NOAEL of 0.74 mg Co/kg/day and LOAEL of 2.48 mg Co/kg/day based on hematological effects. The study authors determined a reproductive NOAEL of >7.44 mg Co/kg/day based on the complete absence of findings on any reproductive parameter.

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 1.95 mg Co/kg/day for elevated red blood cell counts in male rats was selected as the POD for the intermediate-duration oral MRL.

In order to identify the POD, BMD modeling was attempted for red blood cell parameters in male rats reported by Danzeisen et al. (2020a), with standard deviation data obtained via personal communication with the study author (Viegas 2023). The red blood cell parameters modeled are shown in Table A-17. Data were fit to all available continuous models in EPA's BMDS (version 3.3.2) using a BMR of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data for hemoglobin levels. Model outputs for red blood cell data are shown in Table A-18. Model fit for elevated red blood cells in male rats is shown in Figure A-1 (Linear model).

Table A-17. Red Blood Cell Parameters in Male Rats Exposed to Cobalt Chloride Hexahydrate for 90 Days via Gavage

	Concentration in mg/kg/day (mg Co/kg/day)			
	0	3 (0.74)	10 (2.48)	30 (7.44)
Red blood cells (x10e6/µL)	9.455±0.461[a] (10)	9.325±0.580 (10)	10.325±0.756[b] (10)	11.245±0.746[c] (10)
Hemoglobin (mmol/L)	10.35±0.34 (10)	10.50±0.46 (10)	11.46±0.89[b] (10)	13.00±0.61[c] (10)

[a]Mean±SD (number of animals).
[b]p<0.01.
[c]<0.001.

Sources: Danzeisen et al. 2020a; Viegas 2023

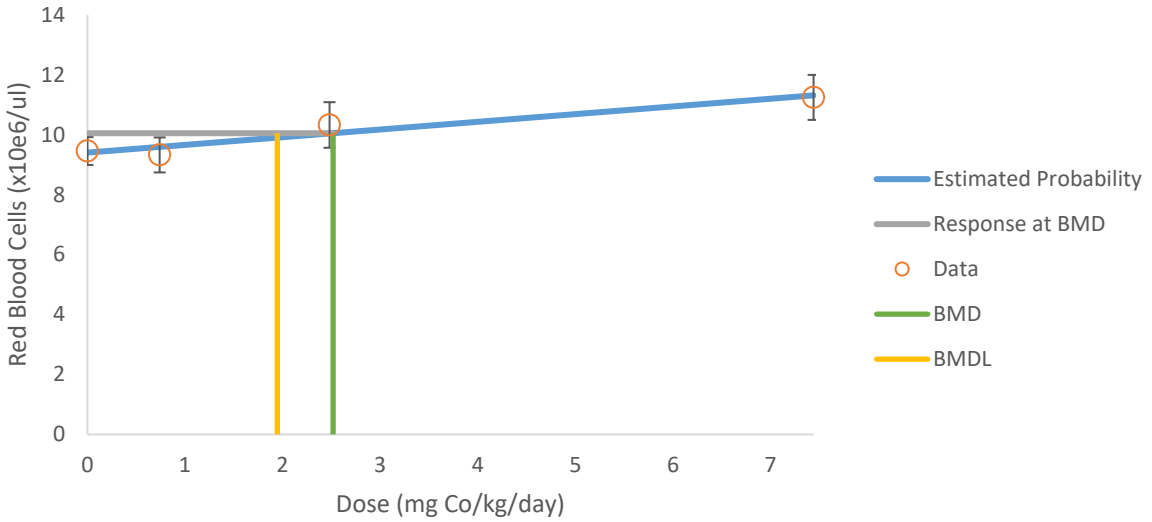
Table A-18. Model Predictions (Constant Variance) for Red Blood Cell Count in Male Rats Exposed to Cobalt Chloride Hexahydrate for 90 Days Via Gavage (Danzeisen et al. 2020a; Viegas 2023)

Model	BMD_{1SD}[a] (mg Co/kg/day)	$BMDL_{1SD}$[a] (mg Co/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 3[d]	2.71	2.13	0.11	84.92	1.51	-0.33
Exponential 5[d]			NA	84.75	-0.33	$2.56x10^{-8}$
Hill[d]	2.38	1.24	0.64	82.75	-0.33	$1.85x10^{-7}$
Polynomial Degree 2[d]	2.52	1.95	0.13	84.57	1.39	-0.32
Polynomial Degree 3[d]	2.52	1.95	0.13	84.57	1.39	-0.34
Power[d]	2.52	1.95	0.13	84.57	1.39	-0.33
Linear[e]	**2.52**	**1.95**	**0.13**	**84.57**	**1.39**	**-0.33**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Selected model. All models except Exponential 5 provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). While the model with the lowest AIC is the Hill model, this model is overparameritized for the dataset (n=4 dose groups); therefore, the model with the next lowest AIC was selected (Linear; the polynomial 2-degree and power models converged on the linear model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-1. Fit of Linear Model to Red Blood Cell Count in Male Rats Following Oral Exposure to Cobalt Chloride Hexahydrate for 90 Days (Danzeisen et al. 2020a; Viegas 2023)



Adjustment for Intermittent Exposure: Not applicable.

Human Equivalent Concentration: While PBPK models are available for cobalt oral dosimetry (ICRP 1995; Legget 2008; Unice et al. 2014a), these models are inadequate for interspecies extrapolation because they are specific to humans.

Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Subsequently, the MRL for intermediate-duration exposure to cobalt via oral exposure is:

$$MRL = \frac{BMDL_{1SD}}{UFs} = \frac{1.95\ mg/kg/day}{10 \times 10}$$

$$MRL = 0.0195\ mg\ Co/kg/day\ \ (Rounded\ to\ 0.02\ mg\ Co/kg/day)$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that the hematological system is a presumed target of cobalt toxicity in humans following oral exposure based on a moderate level of evidence in humans and a high level of evidence laboratory animals (Appendix C).

Polycythemia has been reported in healthy human volunteers orally exposed to cobalt chloride at a dose of 1 mg Co/kg/day for 7–15 days (Davis and Fields 1958). However, no changes in hematological parameters were observed in humans exposed to low-dose cobalt supplements at mean doses of 0.03 mg Co/kg/day for 7–21 days (Hoffmeister et al. 2018) or 0.013 mg Co/kg/day for up to 91 days (Finley et al. 2013; Tvermoes et al. 2014). These findings in humans are consistent with the oral intermediate-duration MRL of 0.02 mg Co/kg/day based on hematological findings in rats in the 90-day study by Danzeisen et al. (2020a).

Available animal studies corroborated the effects seen in the limited human database. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).

Based on limited available human data, the intermediate-duration oral MRL of 0.02 mg Co/kg/day should be protective of gastrointestinal intolerance reported in some patients following intermediate-duration oral exposure to cobalt supplements at doses at or above doses 0.36 mg Co/kg/day (Duckham and Lee 1976; Holly 1955).

Agency Contact (Chemical Managers): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
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 no studies were identified that examined chronic-duration oral exposure to cobalt in either humans or animals.

Rationale for Not Deriving an MRL: No adequately conducted chronic-duration oral studies in humans or laboratory animals were identified that adhered to ATSDR guidelines and investigated health effects resulting from chronic-duration oral exposure to cobalt or its compounds.

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR COBALT

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 cobalt.

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 cobalt. 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 cobalt 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 cobalt are presented in Table B-1.

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

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
In vitro (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

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

Reproductive effects
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

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Cobalt released for public comment in 2023. All literature cited in the previous (2023) toxicological profile were considered for inclusion in the updated profile; thus, the literature search was restricted to studies published between September 2020 and June 2023. The following main databases were searched in June 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 cobalt. 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 cobalt 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	
06/2023	(((Cobalt[mh] OR 7440-48-4[rn] OR 10026-22-9[rn] OR 10124-43-3[rn] OR 10141-05-6[rn] OR 10210-68-1[rn] OR 1307-96-6[rn] OR 1308-04-9[rn] OR 1308-06-1[rn] OR 1317-42-6[rn] OR 21041-93-0[rn] OR 27016-73-5[rn] OR 513-79-1[rn] OR 61789-51-3[rn] OR 71-48-7[rn] OR 7646-79-9[rn] OR 917-69-1[rn] OR "cobalt tetraoxide"[nm] OR "cobalt(II) acetate"[nm] OR 10026-17-2[rn] OR 10026-18-3[rn] OR 13817-37-3[rn] OR 33485-99-3[rn]) AND (("Cobalt/toxicity"[mh] OR "Cobalt/adverse effects"[mh] OR "Cobalt/poisoning"[mh] OR "Cobalt/pharmacokinetics"[mh]) OR ("Cobalt"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Cobalt"[mh] AND toxicokinetics[mh:noexp]) OR ("Cobalt/blood"[mh] OR "Cobalt/cerebrospinal fluid"[mh] OR "Cobalt/urine"[mh]) OR ("Cobalt"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Cobalt"[mh] AND ("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 ("Cobalt/antagonists and inhibitors"[mh]) OR ("Cobalt/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Cobalt/pharmacology"[majr]) OR ("Cobalt"[mh] AND (("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

Table B-2. Database Query Strings

Database search date	Query string
	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 21158-51-0[rn]) AND (2020/09/01:3000[mhda] OR 2020/09/01:3000[crdt] OR 2020/09/01:3000[edat] OR 2020:3000[dp]) (((Cobalt[mh] AND 2022/04/01:3000[mhda]) OR (("(Sulfido)cobalt"[tw] OR "Acetic acid, cobalt(2+) salt"[tw] OR "Acetic acid, cobalt(3+) salt"[tw] OR "Aquacat"[tw] OR "Arsanylidynecobalt"[tw] OR "C.I. Pigment Black 13"[tw] OR "Carbonic acid, cobalt(2+) salt"[tw] OR "CI Pigment Black 13"[tw] OR "Co mesoporphyrin"[tw] OR "Cobalt (2+) sulfate"[tw] OR "cobalt (II) acetate"[tw] OR "cobalt (II) carbonate"[tw] OR "cobalt (II) chloride"[tw] OR "cobalt (II) hydroxide"[tw] OR "cobalt (II) meso-porphyrin"[tw] OR "cobalt (II) napthenate"[tw] OR "cobalt (II) naphthenate"[tw] OR "cobalt (II) nitrate"[tw] OR "cobalt (II) oxide"[tw] OR "cobalt (II) sulfate"[tw] OR "cobalt (II,III) oxide"[tw] OR "cobalt (III) acetate"[tw] OR "cobalt (III) oxide"[tw] OR "Cobalt 59"[tw] OR "Cobalt acetate"[tw] OR "Cobalt arsenide"[tw] OR "Cobalt bis(nitrate)"[tw] OR "Cobalt Black"[tw] OR "Cobalt Brown"[tw] OR "Cobalt carbonate"[tw] OR "cobalt carbonyl"[tw] OR "Cobalt chloride"[tw] OR "Cobalt di(acetate)"[tw] OR "Cobalt diacetate"[tw] OR "Cobalt dichloride"[tw] OR "Cobalt dihydride"[tw] OR "Cobalt dihydroxide"[tw] OR "Cobalt dinitrate"[tw] OR "Cobalt dinitrate hexahydrate"[tw] OR "Cobalt fume"[tw] OR "Cobalt hydroxide"[tw] OR "Cobalt I, (dihydrogen 7,12-diethyl-3,8,13,17-tetramethyl-2,18-porphinedipropionato(2-))-"[tw] OR "Cobalt mesoporphyrin"[tw] OR "Cobalt mesoporphyrin IX"[tw] OR "Cobalt Metal"[tw] OR "Cobalt metal powder"[tw] OR "Cobalt metal, dust and fume"[tw] OR "Cobalt monoarsenide"[tw] OR "Cobalt monocarbonate"[tw] OR "Cobalt monooxide"[tw] OR "Cobalt monosulfate"[tw] OR "Cobalt monosulfide"[tw] OR "Cobalt monoxide"[tw] OR "Cobalt muriate"[tw] OR "Cobalt naphthenate"[tw] OR "Cobalt naphthenates"[tw] OR "Cobalt nitrate"[tw] OR "Cobalt octacarbonyl"[tw] OR "Cobalt oxide"[tw] OR "Cobalt peroxide"[tw] OR "Cobalt sesqioxide"[tw] OR "Cobalt sesquioxide"[tw] OR "Cobalt spar"[tw] OR "Cobalt sulfate"[tw] OR "Cobalt sulfide"[tw] OR "Cobalt sulphate"[tw] OR "cobalt sulphide"[tw] OR "Cobalt tetracarbonyl dimer"[tw] OR "Cobalt tetraoxide"[tw] OR "Cobalt triacetate"[tw] OR "Cobalt trioxide"[tw] OR "Cobalt(2+) acetate"[tw] OR "Cobalt(2+) carbonate"[tw] OR "Cobalt(2+) diacetate"[tw] OR "Cobalt(2+) dichloride"[tw] OR "Cobalt(2+) dihydroxide"[tw] OR "Cobalt(2+) dinitrate"[tw] OR "Cobalt(2+) hydroxide"[tw] OR "Cobalt(2+) nitrate"[tw] OR "Cobalt(2+) oxide"[tw] OR "Cobalt(2+) sulfate"[tw] OR "Cobalt(2+) sulfide"[tw] OR "Cobalt(3+) acetate"[tw] OR "Cobalt(3+) oxide"[tw] OR "Cobalt(3+) triacetate"[tw] OR "Cobalt(II) acetate"[tw] OR "Cobalt(II) carbonate"[tw] OR "Cobalt(II) chloride"[tw] OR "Cobalt(II) hydroxide"[tw] OR "Cobalt(II) mesoporphyrin"[tw] OR "Cobalt(II) naphthenate"[tw] OR "Cobalt(II) nitrate"[tw] OR "Cobalt(II) oxide"[tw] OR "Cobalt(II) sulfate"[tw] OR "Cobalt(II) sulfide"[tw] OR "Cobalt(II) sulphate"[tw] OR "Cobalt(II,III) oxide"[tw] OR "Cobalt(III) acetate"[tw] OR "Cobalt(III) oxide"[tw] OR "Cobalt, (sulfido)-"[tw] OR "Cobalt, [dihydrogen 7,12-diethyl-3,8,13,17-tetramethyl-2,18-porphinedipropionato(2-)]-"[tw] OR "Cobalt, [dihydrogen mesoporphyrin IX-ato(2-)]-"[tw] OR "Cobalt, arsinidyne-"[tw] OR "Cobalt, di-mu-carbonylhexacarbonyldi-"[tw] OR "Cobalt, elemental"[tw] OR "Cobalt-59"[tw] OR "Cobaltate(2-), [7,12-diethyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-κN21,κN22,κN23,κN24]-, hydrogen (1:2), (SP-4-2)-"[tw] OR "Cobalti protoporphyrin"[tw] OR "Cobaltic acetate"[tw] OR "Cobaltic oxide"[tw] OR "Cobaltic-cobaltous oxide"[tw] OR "Cobalto-cobaltic oxide"[tw] OR "Cobalto-cobaltic tetroxide"[tw] OR "Cobaltosic oxide"[tw] OR "Cobaltous acetate"[tw] OR "Cobaltous

Table B-2. Database Query Strings

Database search date	Query string
	carbonate"[tw] OR "Cobaltous chloride"[tw] OR "Cobaltous diacetate"[tw] OR "Cobaltous dichloride"[tw] OR "Cobaltous hydroxide"[tw] OR "Cobaltous naphthenate"[tw] OR "Cobaltous nitrate"[tw] OR "Cobaltous oxide"[tw] OR "Cobaltous sulfate"[tw] OR "Cobaltous sulfide"[tw] OR "Di-mu-carbonylhexacarbonyldicobalt"[tw] OR "Dichlorocobalt"[tw] OR "Dicobalt carbonyl"[tw] OR "Dicobalt octacarbonyl"[tw] OR "Dicobalt oxide"[tw] OR "dicobalt trioxide"[tw] OR "Monocobalt oxide"[tw] OR "Naftolite"[tw] OR "Naphthenic acid, cobalt salt"[tw] OR "Naphthenic acids, cobalt salt"[tw] OR "Naphthenic acids, cobalt salts"[tw] OR "Nitric acid, cobalt(2+) salt"[tw] OR "Octacarbonyldicobalt"[tw] OR "Sphaerocobaltite"[tw] OR "Sulfuric acid, cobalt(2+) salt"[tw] OR "Super cobalt"[tw] OR "Sycoporite"[tw] OR "Tricobalt tetraoxide"[tw] OR "Tricobalt tetroxide"[tw] OR "Zaffre"[tw] OR "cobalt hydride"[tw] OR "cobalt(II) hydride"[tw] OR "cobalt(2+) hydride"[tw] OR "cobalt dihydride"[tw] OR "cobaltous hydride"[tw] OR "cobalt nitride"[tw] OR "glucosaminic acid cobalt"[tw] OR "cobalt fluoride"[tw] OR "cobalt difluoride"[tw] OR "cobalt trifluoride"[tw] OR "cobalt(2+) difluoride"[tw] OR "cobalt(3+) trifluoride"[tw] OR "cobalt(II) fluoride"[tw] OR "cobalt(III) fluoride"[tw] OR "cobaltic fluoride"[tw] OR "cobaltous fluoride"[tw]) NOT medline[sb])) 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 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

Table B-2. Database Query Strings

Database search date	Query string
	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 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

Table B-2. Database Query Strings

Database search date	Query string
	wistar OR wood-mouse OR zebra-fish OR zebrafish)) AND (2020/09/01:3000[mhda] OR 2020/09/01:3000[crdt] OR 2020/09/01:3000[edat] OR 2020:3000[dp])
NTRL	
06/2023	Date limit 2020-2023 Search Titles OR Keywords; "cobalt" OR "cobaltic" OR "cobalto" OR "cobaltosic" OR "cobaltous" OR "dicobalt" OR "monocobalt" OR "tricobalt" OR "dichlorocobalt"
Toxcenter	
06/2023	FILE 'TOXCENTER' ENTERED AT 13:13:40 ON 02 JUN 2023 L1 102164 SEA FILE=TOXCENTER 7440-48-4 OR 10026-17-2 OR 10026-18-3 OR 10026-22-9 OR 10124-43-3 OR 10141-05-6 OR 10210-68-1 OR 1307-96-6 OR 1308-04-9 OR 1308-06-1 OR 1317-42-6 OR 13817-37-3 OR 21041-93-0 OR 21158-51-0 OR 27016-73-5 OR 513-79-1 OR 61789-51-3 OR 71-48-7 OR 7646-79-9 OR 917-69-1 L2 102098 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 83010 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 15967 SEA FILE=TOXCENTER L3 AND PY>2019 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE 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 OR L29 L31 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?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (NONHUMAN MAMMALS)/ORGN L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 7202 SEA FILE=TOXCENTER L4 AND L37 L39 545 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 1156 SEA FILE=TOXCENTER L38 AND BIOSIS/FS L41 1628 DUP REM L39 L40 (73 DUPLICATES REMOVED) L*** DEL 545 S L38 AND MEDLINE/FS L*** DEL 545 S L38 AND MEDLINE/FS L42 545 SEA FILE=TOXCENTER L41 L*** DEL 1156 S L38 AND BIOSIS/FS L*** DEL 1156 S L38 AND BIOSIS/FS L43 1083 SEA FILE=TOXCENTER L41 L44 1083 SEA FILE=TOXCENTER (L42 OR L43) AND BIOSIS/FS D SCAN L44

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2023	7440-48-4; 10026-22-9; 10124-43-3; 10141-05-6; 10210-68-1; 1307-96-6; 1308-04-9; 1308-06-1; 1317-42-6; 21041-93-0; 21158-51-0; 27016-73-5; 513-79-1; 61789-51-3; 71-48-7; 7646-79-9; 917-69-1; 33485-99-3; 10026-17-2; 10026-18-3; 13817-37-3
NTP	
06/2023	Date limit: 2020-2023 or not dated; Content types Reports & Publications; Systematic Reviews; ROC Profiles, Reviews, or Candidates "7440-48-4" "cobalt" "10124-43-3" "7646-79-9" "cobaltous" "dicobalt" "tricobalt" "dichlorocobalt" "10026-22-9" "10141-05-6" "0210-68-1" "1307-96-6" "1308-04-9" "1308-06-1" "1317-42-6" "21041-93-0" "21158-51-0" "27016-73-5" "513-79-1" "61789-51-3" "71-48-7" "917-69-1" "33485-99-3" "10026-17-2" "10026-18-3" "13817-37-3"
Regulations.gov	
06/2023	Dockets, no date limit Document, limited to notices, limited to EPA or FDA), and limited to posted date 2020-01-01 to 2023-05-31 cobalt "cobaltous" "dicobalt" "tricobalt" "dichlorocobalt" "7440-48-4" "10026-22-9" "10124-43-3" "10141-05-6" "10210-68-1" "1307-96-6" "1308-04-9" "1308-06-1" "1317-42-6" "21041-93-0" "21158-51-0" "27016-73-5" "513-79-1" "61789-51-3" "71-48-7" "7646-79-9" "917-69-1" "33485-99-3" "10026-17-2" "10026-18-3" "13817-37-3"
NPIRS	
06/2023	Active Ingredient: Cobalt naphthenate (CAS #: 61789-51-3) (PC Code: 25101), Naphthenic acids, cobalt salts (CAS #: 61789-51-3) (PC Code: 25101)

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
11/2023	Search Criteria Fiscal Year: Active Projects Text Search: "cobalt" OR "cobaltic" OR "cobalto" OR "cobaltosic" OR "cobaltous" OR "dicobalt" OR "monocobalt" OR "tricobalt" OR "dichlorocobalt" (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): 2,098
- Number of records identified from other strategies: 223
- Total number of records to undergo literature screening: 2,321

B.1.2 Literature Screening

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

- 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.

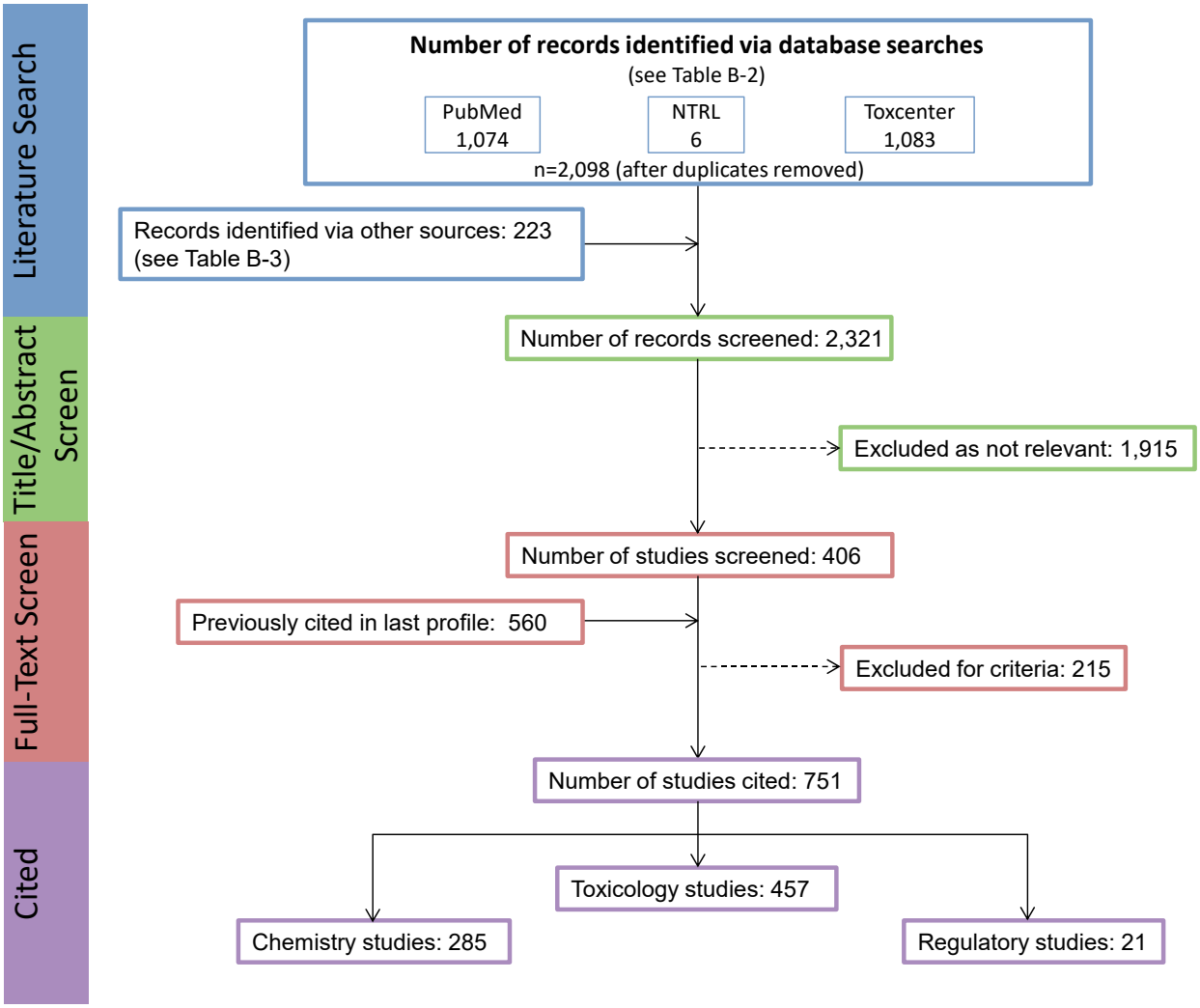
- Number of titles and abstracts screened: 2,321
- Number of studies considered relevant and moved to the next step: 406

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: 406
- Number of studies cited in the pre-public draft of the toxicological profile: 560
- Total number of studies cited in the profile: 751

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

Figure B-1. June 2023 Literature Search Results and Screen for Cobalt



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

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 cobalt, 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 cobalt:

- 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 cobalt. The inclusion criteria used to identify relevant studies examining the health effects of cobalt 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. Numerous general population studies evaluated potential associations cobalt levels in the blood or urine and adverse health outcomes without assessment of potential sources of exposure. Since cobalt is a trace essential element (part of the vitamin B12 complex), these studies are of limited usefulness because cobalt levels are often detected at background levels. Therefore, epidemiology studies included in this profile were restricted to those with known exposure above background levels (e.g., occupational exposure). Additionally, individuals with durable medical implants containing cobalt, such as total joint replacement, may be exposed to cobalt from these devices. Since this profile is focused on environmental exposures via inhalation, oral, and dermal exposure routes, studies focused on the kinetics and/or toxicity associated with medical implants were not included.

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 cobalt. 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 Cobalt released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 2,321 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 cobalt.

Title and Abstract Screen. In the Title and Abstract Screen step, 2,321 records were reviewed; 26 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 147 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 147 documents (194 studies), 64 documents (86 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 Document for Cobalt and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.20 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 cobalt identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include numerous occupational exposure studies and a limited number of and controlled exposure and case reports of healthy subjects and patients taking cobalt supplements. Occupational studies identify the respiratory tract as the primary target of cobalt toxicity following inhalation exposure. Controlled exposure and case report studies indicate that hematological, gastrointestinal, and endocrine (thyroid) effects are the most sensitive targets of oral toxicity. Based on effects noted in human and animal studies, studies examining respiratory endpoints following inhalation exposure and hematological, gastrointestinal, or thyroid endpoints following oral exposure were carried through to Steps 4–8 of the systematic review. There were 86 studies (published in 64 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 Cobalt 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		8 5	3 1		2 1			1 1	1 1		2 0	4 0				1 0	14 4
Case control		1 1															
Population		7 5			2 1						2 1	1 0				1 0	
Case series		5 4										2 2					
Meta-analysis																	2 0
Oral studies																	
Cohort																	
Case control			1 0	4 4	9 4		3 0	2 0			7 4	2 0	1 0		1 0		
Population																	
Case series											4 4						
Dermal studies																	
Cohort																	
Case control																	
Population									1 1								
Case series									3 3								
Meta-analysis												1 1					

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 Cobalt 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	1	6															
	0	6															
Intermediate-duration	12	15	8	7	8	7	10	10	6	2	7	10	9	8		4	
	9	14	1	0	6	0	5	3	0	0	1	4	4	8		1	
Chronic-duration	5	5	4	4		4	4	4	4	2	4	4	4	4			4
	4	5	0	0		0	1	0	0	0	0	0	0	2			4
Oral studies																	
Acute-duration	4	1	7	3	4		6	7		1		4	8	2	2	3	
	3	0	6	2	4		4	6		0		3	7	1	0	3	
Intermediate-duration	20	4	9	4	14	3	11	7	2	2	5	8	10	19	7	7	
	7	0	4	0	9	0	3	2	0	0	1	3	4	13	6	6	
Chronic-duration																	
Dermal studies																	
Acute-duration												6					
												6					
Intermediate-duration	1								1	2							
	0								1	2							
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 cobalt health effects studies (observational epidemiology, controlled-exposure human studies, and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Cobalt—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: respiratory effects (inhalation only)							
Cohort studies							
Al-Abcha et al. 2021	+	–	–	+	–	+	Second
Andersson et al. 2020	+	–	+	+	+	+	Second
Linna et al. 2003	+	+	+	+	+	+	First
Gennart and Lauwerys 1990	+	–	–	–	+	–	Second
Kusaka et al. 1986a	+	–	+	+	+	+	Second
Kusaka et al. 1986b	+	–	+	+	+	+	Second
Rehfisch et al. 2012	+	–	+	–	–	+	Second
Verougstraete et al. 2004	+	–	+	+	+	+	Second
Case-control							
Roto 1980	–	–	+	+	+	+	Second
Case-series							
Al-Abcha et al. 2021	– –	–	+	–	+	+	Second
Demedts et al. 1984	– –	–	+	– –	++	++	Second
Sauni et al. 2010	– –	–	+	–	+	+	Second
Walters et al. 2014	– –	+	+	–	+	+	Second

Table C-8. Summary of Risk of Bias Assessment for Cobalt—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Cross-sectional							
Walters et al. 2012	+	–	+	–	+	+	Second
Hamzah et al. 2014	+	–	+	+	+	+	Second
Meyer-Bisch et al. 1989	+	–	+	+	+	+	Second
Roto 1980	+	–	+	+	+	+	Second
Swennen et al. 1993	+	+	+	+	+	+	First
Nemery et al. 1992	+	–	+	+	+	+	Second
Deng et al. 1991	–	–	+	–	+	+	Second
Outcome: thyroid effects (oral only)							
Case series							
Chamberlain 1961	–	–	–	+	+	–	Third
Little and Sunico 1958	–	–	–	–	+	–	Third
Washburn and Kaplan 1964	–	–	–	+	–	–	Third

++ = 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 of Bias Assessment for Cobalt—Human-Controlled Exposure 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 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 effects (inhalation)								
Inhalation acute-duration exposure								
Kusaka et al. 1986a	–	–	–	+	–	+	+	Second
Outcome: gastrointestinal effects (oral only)								
Oral acute-duration exposure								
Paley et al. 1958	–	–	–	+	+	–	–	Third
Oral intermediate-duration exposure								
Duckham and Lee 1976	–	–	–	–	+	–	–	Third
Holly 1955	–	–	–	+	–	–	–	Third
Paley et al. 1958	–	–	–	+	+	–	–	Third
Outcome: hematological effects (oral only)								
Oral acute-duration exposure								
Davis and Fields 1958	–	+	+	+	+	–	+	Second
Hoffmeister et al. 2018	–	++	++	++	++	+	++	First
Oral intermediate-duration exposure								
Davis and Fields 1958	–	+	+	+	+	–	+	Second
Duckham and Lee 1976	–	+	+	+	–	–	+	Second
Finley et al. 2013	–	+	+	+	+	–	+	Second

Table C-9. Summary of Risk of Bias Assessment for Cobalt—Human-Controlled Exposure 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 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
Hoffmeister et al. 2018	–	++	++	++	++	+	++	First
Holly 1955	–	+	+	+	–	–	+	Second
Taylor et al. 1977	–	+	+	+	–	–	–	Second
Tvermoes et al. 2014	–	+	+	+	+	–	+	Second
Outcome: thyroid effects (oral only)								
Oral acute-duration exposure								
Roche and Layrisse 1956	–	+	+	+	+	–	+	Second
Paley et al. 1958	–	+	+	–	+	–	–	Third
Oral intermediate-duration exposure								
Duckham and Lee 1976	–	+	+	–	+	–	–	Second
Finley et al. 2013	–	+	+	+	+	–	+	Second
Gross et al. 1955	–	–	–	+	+	+	–	Second
Holly 1955	–	+	+	+	–	–	–	Second
Kriss et al. 1955	–	–	–	+	+	+	–	Second

Table C-9. Summary of Risk of Bias Assessment for Cobalt—Human-Controlled Exposure 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 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
Paley et al. 1958	–	+	+	–	+	–	–	Third
Tvermoes et al. 2014	–	+	+	+	+	–	+	Second

++ = 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-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: respiratory effects (inhalation only)									
Inhalation acute-duration exposure									
Burzlaff et al. 2022a (rat)	++	+	++	+	++	++	+	++	First
Palmes et al. 1959 (rat)	–	+	+	–	+	–	–	+	Second
Viegas et al. 2022a, 2022b (rat)	+	+	+	+	+	–	–	+	Second
Inhalation intermediate-duration exposure									
Kerfoot 1974 (mini pig)	–	+	++	–	++	–	+	+	First
Johansson et al. 1987 (rabbit)	–	+	++	–	++	–	+	+	First
Johansson et al. 1991 (rabbit)	–	+	++	–	++	–	+	+	First
Johansson et al. 1992 (rabbit)	–	+	++	–	++	–	+	+	First
Burzlaff et al. 2022a, 2022b (rat)	++	+	++	+	++	++	+	++	First

Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	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?	
NTP 2014 (rat, mouse)	+	+	++	+	++	++	+	++	First
Bucher et al. 1990; NTP 1991 (rat, mouse)	+	+	++	+	++	++	+	++	First
Palmes et al. 1959 (rat, guinea pig)	–	+	+	–	+	–	–	+	Second
Inhalation chronic-duration exposure									
Behl et al. 2015; NTP 2014 (rat, mouse)	+	+	++	+	+	++	+	++	First
Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse)	+	+	++	+	++	++	+	++	First
Wehner et al. 1977 (hamster)	+	+	++	–	++	–	+	++	First

Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	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?	
Outcome: gastrointestinal effects (oral only)									
Oral acute-duration exposure									
Akinrinde et al. 2016c (rat)	–	+	–	+	–	–	+	–	Second
Richardson et al. 2018 (rat)	–	+	+	+	+	–	–	+	Second
Salami et al. 2023 (rat)	–	+	+	+	–	–	+	+	Second
Oral intermediate-duration exposure									
Danzeisen et al. 2020a (rat)	+	+	++	+	+	++	++	–	First
Domingo et al. 1984	–	+	–	+	–	–	+	–	Second
Holly 1955	–	+	–	+	–	–	+	–	Second

Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: hematological effects (oral only)									
Oral acute-duration exposure									
Shrivastava et al. 2008 (rat)	+	+	++	+	+	+	+	++	First
Shrivastava et al. 2010 (rat)	+	+	++	+	+	+	+	++	First
Domingo and Llobet 1984 (rat)	–	+	++	+	+	+	+	+	First
Paternain and Domingo 1988 (rat)	–	+	+	+	–	+	+	+	First
Oral intermediate-duration exposure									
Chetty et al. 1979 (rat)	–	+	+	+	+	–	+	++	First
Corrier et al. 1985 (rat)	+	+	+	+	–	–	+	++	First
Domingo et al. 1984 (rat)	–	+	++	+	–	–	–	++	Second
Danzeisen et al. 2020a (rat)	+	+	++	+	+	++	+	++	First

Table C-10. Summary of Risk of Bias Assessment for Cobalt—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
Holly 1955 (rat)	–	+	–	+	–	–	+	–	Second
Krasovskii and Fridlyand 1971 (rat)	–	+	–	+	–	–	–	–	Third
Murdock 1959 (rat)	–	+	–	+	–	–	+	+	Second
Pedigo et al. 1988 (mouse)	–	+	+	+	+	–	+	+	First
Stanley et al. 1947 (rat)	–	+	–	+	+	–	+	+	First
Outcome: thyroid effects (oral only)									
Oral intermediate-duration exposure									
Danzeisen et al. 2020a (rat)	+	+	++	+	+	++	+	–	First
Holly 1955	–	+	–	+	–	–	+	–	Second
Shrivastava et al. 1996	–	+	+	+	–	–	+	–	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 cobalt 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 cobalt 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-11, C-12, and C-13, 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-11. 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-12. 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-13. 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 studies examining respiratory effects from inhalation studies and hematological, gastrointestinal, and thyroid effects observed in the observational epidemiology, controlled-exposure human studies, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for Cobalt—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory effects (inhalation only)					
Cohort studies					
Al-Abcha et al. 2021	No	Yes	Yes	Yes	Moderate
Andersson et al. 2020	No	Yes	Yes	Yes	Moderate
Linna et al. 2003	No	Yes	Yes	Yes	Moderate
Gennart and Lauwerys 1990	No	Yes	No	Yes	Low
Kusaka et al. 1986a	No	Yes	Yes	Yes	Moderate
Kusaka et al. 1986b	No	Yes	Yes	Yes	Moderate
Rehfisch et al. 2012	No	Yes	Yes	Yes	Moderate
Verougstraete et al. 2004	No	Yes	Yes	Yes	Moderate
Case-control					
Roto 1980	No	No	Yes	Yes	Low
Case series					
Al-Abcha et al. 2021	No	Yes	Yes	No	Low
Demedts et al. 1984	No	Yes	Yes	No	Low
Sauni et al. 2010	No	Yes	Yes	No	Low
Walters et al. 2014	No	Yes	Yes	No	Low
Cross-sectional studies					
Walters et al. 2012	No	No	Yes	Yes	Low
Hamzah et al. 2014	No	No	Yes	Yes	Low
Meyer-Bisch et al. 1989	No	No	Yes	Yes	Low
Roto 1980	No	No	Yes	Yes	Low
Swennen et al. 1993	No	No	Yes	Yes	Low
Nemery et al. 1992	No	No	Yes	Yes	Low
Deng et al. 1991	No	No	Yes	Yes	Low
Outcome: Thyroid effects (oral only)					
Case series					
Chamberlain 1961	No	Yes	Yes	No	Low
Little and Sunico 1958	No	Yes	Yes	No	Low
Washburn and Kaplan 1964	No	Yes	Yes	No	Low

Table C-15. Presence of Key Features of Study Design for Cobalt—Human-Controlled Exposure Studies

Reference	Key features				
	Concurrent control group	Sufficient number of subjects	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute-duration exposure					
Kusaka et al. 1986a	Yes	No	Yes	Yes	Moderate
Outcome: Gastrointestinal effects (oral only)					
Oral acute-duration exposure					
Paley et al. 1958	Yes	No	No	No	Very Low
Oral intermediate-duration exposure					
Duckham and Lee 1976	Yes	No	No	No	Very Low
Holly 1955	Yes	No	No	No	Very Low
Paley et al. 1958	Yes	No	No	No	Very Low
Outcome: Hematological effects (oral only)					
Oral acute-duration exposure					
Davis and Fields 1958	Yes	No	Yes	Yes	Moderate
Hoffmeister et al. 2018	Yes	No	Yes	Yes	Moderate
Oral intermediate-duration exposure					
Davis and Fields 1958	Yes	No	Yes	No	Low
Duckham and Lee 1976	Yes	No	Yes	Yes	Moderate
Finley et al. 2013	Yes	No	Yes	Yes	Moderate
Hoffmeister et al. 2018	Yes	No	Yes	Yes	Moderate
Holly 1955	Yes	No	Yes	Yes	Moderate
Taylor et al. 1977	Yes	No	No	Yes	Low
Tvermoes et al. 2014	Yes	No	Yes	Yes	Moderate
Outcome: Thyroid effects (oral only)					
Oral acute-duration exposure					
Roche and Layrisse 1956	Yes	No	Yes	Yes	Moderate
Paley et al. 1958	Yes	No	Yes	Yes	Moderate
Oral intermediate-duration exposure					
Duckham and Lee 1976	Yes	No	Yes	No	Low
Finley et al. 2013	Yes	No	Yes	Yes	Moderate
Gross et al. 1955	Yes	No	Yes	No	Low
Holly 1955	Yes	No	No	No	Very Low
Kriss et al. 1955	Yes	No	Yes	No	Low
Paley et al. 1958	Yes	No	Yes	No	Low
Tvermoes et al. 2014	Yes	No	Yes	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Cobalt—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute-duration exposure					
Burzlaff et al. 2022a (rat)	Yes	Yes	Yes	No	Moderate
Palmes et al. 1959 (rat)	Yes	Yes	No	No	Low
Viegas et al. 2022a, 2022b (rat)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate-duration exposure					
Kerfoot 1974 (mini pig)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1987 (rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1991 (rabbit)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1992 (rabbit)	Yes	No	Yes	Yes	Moderate
Burzlaff et al. 2022a, 2022b (rat)	Yes	Yes	Yes	No	Moderate
NTP 2014 (rat, mouse)	Yes	Yes	Yes	Yes	High
Bucher et al. 1990; NTP 1991 (rat, mouse)	Yes	Yes	Yes	Yes	High
Palmes et al. 1959 (rat, guinea pig)	Yes	Yes	Yes	No	Moderate
Inhalation chronic-duration exposure					
Behl et al. 2015; NTP 2014 (rat, mouse)	Yes	Yes	Yes	Yes	High
Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse)	Yes	Yes	Yes	Yes	High
Wehner et al. 1977 (hamster)	Yes	Yes	Yes	Yes	High
Outcome: Gastrointestinal effects (oral only)					
Oral acute-duration exposure					
Akinrinde et al. 2016c	No	Yes	Yes	No	Low
Richardson et al. 2018 (rat)	Yes	Yes	No	Yes	Moderate
Salami et al. 2023	Yes	Yes	Yes	Yes	High
Oral intermediate-duration exposure					
Danzeisen et al. 2020a	Yes	Yes	Yes	No	Moderate
Domingo et al. 1984	Yes	No	Yes	No	Low
Holly 1955	No	Yes	Yes	No	Low

Table C-16. Presence of Key Features of Study Design for Cobalt—Experimental Animal Studies

Reference	Key feature				
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Hematological effects (oral only)					
Oral acute-duration exposure					
Shrivastava et al. 2008 (rat)	Yes	Yes	Yes	Yes	High
Shrivastava et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Domingo and Llobet 1984 (rat)	Yes	Yes	Yes	Yes	High
Paternain and Domingo 1988 (rat)	Yes	Yes	Yes	Yes	High
Oral intermediate-duration exposure					
Chetty et al. 1979 (rat)	Yes	Yes	Yes	Yes	High
Corrier et al. 1985 (rat)	Yes	No	Yes	Yes	Moderate
Domingo et al. 1984 (rat)	Yes	No	Yes	Yes	Moderate
Danzeisen et al. 2020a (rat)	Yes	Yes	Yes	Yes	High
Holly 1955 (rat)	Yes	No	Yes	No	Low
Krasovskii and Fridlyand 1971 (rat)	Yes	No	Yes	No	Low
Murdock 1959 (rat)	Yes	No	Yes	No	Low
Pedigo et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Stanley et al. 1947 (rat)	Yes	No	Yes	No	Low
Outcome: Thyroid effects (oral only)					
Oral intermediate-duration exposure					
Danzeisen et al. 2020a	Yes	Yes	Yes	No	Moderate
Holly 1955	No	Yes	Yes	No	Low
Shrivastava et al. 1996	Yes	Yes	Yes	No	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-17. 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-17.

Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects (inhalation only)		
Inhalation acute-duration exposure		
Animal studies		
Burzlaff et al. 2022a (rat)	Moderate	Moderate
Palmes et al. 1959 (rat)	Low	
Viegas et al. 2022a, 2022b (rat)	Moderate	
Human studies		
Kusaka et al. 1986a	Moderate	Moderate
Inhalation intermediate-duration exposure		
Animal studies		
Kerfoot 1974 (mini pig)	Moderate	High
Johansson et al. 1987 (rabbit)	Moderate	
Johansson et al. 1991 (rabbit)	Moderate	
Johansson et al. 1992 (rabbit)	Moderate	
Burzlaff et al. 2022a, 2022b (rat)	Moderate	
NTP 2014 (rat, mouse)	High	
Bucher et al. 1990; NTP 1991 (rat, mouse)	High	
Palmes et al. 1959 (rat, guinea pig)	Moderate	
Inhalation chronic-duration exposure		
Animal studies		
Behl et al. 2015; NTP 2014 (rat, mouse)	High	High
Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse)	High	
Wehner et al. 1977 (hamster)	High	
Human studies		
Al-Abcha et al. 2021 (cohort)	Moderate	Moderate
Al-Abcha et al. 2021 (case-series)	Low	
Andersson et al. 2020	Moderate	
Linna et al. 2003	Moderate	
Deng et al. 1991	Low	
Gennart and Lauwerys 1990	Low	
Kusaka et al. 1986a	Moderate	
Kusaka et al. 1986b	Moderate	
Rehfisch et al. 2012	Moderate	
Verougstraete et al. 2004	Moderate	
Roto 1980 (case-control)	Low	
Demedts et al. 1984	Low	
Sauni et al. 2010	Low	
Walters et al. 2012	Low	
Walters et al. 2014	Low	

Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies

	Initial study confidence	Initial confidence rating
Hamzah et al. 2014	Low	
Meyer-Bisch et al. 1989	Low	
Roto 1980 (cross-sectional)	Low	
Swennen et al. 1993	Low	
Nemery et al. 1992	Low	
Outcome: Gastrointestinal effects (oral only)		
Oral acute-duration exposure		
Animal studies		
Akinrinde et al. 2016c	Low	High
Richardson et al. 2018 (rat)	Moderate	
Salami et al. 2023	High	
Human studies		
Paley et al. 1958	Very Low	Very Low
Oral intermediate-duration exposure		
Animal studies		
Danzeisen et al. 2020a	Moderate	Moderate
Domingo et al. 1984	Low	
Holly 1955	Low	
Human studies		
Duckham and Lee 1976	Very Low	
Holly 1955	Very Low	
Paley et al. 1958	Very Low	Very Low
Outcome: Hematological effects (oral only)		
Oral acute-duration exposure		
Animal studies		
Shrivastava et al. 2008 (rat)	High	High
Shrivastava et al. 2010 (rat)	High	
Domingo and Llobet 1984 (rat)	High	
Paternain and Domingo 1988 (rat)	High	
Human studies		
Davis and Fields 1958	Moderate	
Hoffmeister et al. 2018	Moderate	Moderate
Oral intermediate-duration exposure		
Animal studies		
Chetty et al. 1979 (rat)	High	
Corrier et al. 1985 (rat)	Moderate	
Domingo et al. 1984 (rat)	High	
Danzeisen et al. 2020a (rat)	Moderate	
Holly 1955 (rat)	Low	
Krasovskii and Fridlyand 1971 (rat)	Low	

Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies

	Initial study confidence	Initial confidence rating
Murdock 1959 (rat)	Low	
Pedigo et al. 1988 (mouse)	High	
Stanley et al. 1947 (rat)	Low	
Human studies		
Davis and Fields 1958	Moderate	Moderate
Duckham and Lee 1976	Low	
Finley et al. 2013	Moderate	
Hoffmeister et al. 2018	Moderate	
Holly 1955	Low	
Taylor et al. 1977	Low	
Tvermoes et al. 2014	Moderate	
Outcome: Thyroid effects (oral only)		
Oral acute-duration exposure		
Human studies		
Roche and Layrisse 1956	Moderate	Moderate
Paley et al. 1958	Moderate	
Oral intermediate-duration exposure		
Animal studies		
Danzeisen et al. 2020a	Moderate	Moderate
Holly 1955	Low	
Shrivastava et al. 1996	Moderate	
Human studies		
Chamberlain 1961	Low	Moderate
Duckham and Lee 1976	Low	
Finley et al. 2013	Moderate	
Gross et al. 1955	Low	
Holly 1955	Very Low	
Kriss et al. 1955	Low	
Little and Sunico 1958	Low	
Paley et al. 1958	Low	
Tvermoes et al. 2014	Moderate	
Washburn and Kaplan 1964	Low	

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 respiratory effects following inhalation exposure and hematological, gastrointestinal, and thyroid effects following oral exposure are presented in Table C-18. 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 cobalt exposure is presented in Table C-19.

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects (inhalation only)			
Human studies	Moderate	+1 Consistency in body of evidence	High
Animal studies	High	+1 Consistency in body of evidence	High
Outcome: Gastrointestinal effects (oral only)			
Human studies	Very low	-2 Risk of bias	Very low
Animal studies	High	-1 Risk of bias -1 Unexplained inconsistency	Low
Outcome: Hematological effects (oral only)			
Human studies	Moderate	-1 Risk of bias +1 Consistency in body of evidence	Moderate
Animal studies	High	-1 Risk of bias +1 Consistency in body of evidence	High
Outcome: Thyroid effects (oral only)			
Human studies	Moderate	-1 Risk of bias -1 Imprecision +1 Consistency in body of evidence	Low
Animal studies	Moderate		Moderate

Table C-19. Confidence in the Body of Evidence for Cobalt

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects (inhalation only)	High	High
Gastrointestinal effects (oral only)	Very low	Low
Hematological effects (oral only)	Moderate	High
Thyroid effects (oral only)	Low	Moderate

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-5, C-6, and C-7). 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 cobalt, 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 cobalt is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Cobalt

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation)	High	Health effect	High
Gastrointestinal effects (oral)	Very low	Health effect	Inadequate
Hematological effects (oral)	Moderate	Health effect	Moderate
Thyroid effects (oral)	Low	Health effect	Low
Animal studies			
Respiratory effects (inhalation)	Moderate	Health effect	Moderate
Gastrointestinal effects (oral)	Low	Health effect	Low
Hematological effects (oral)	High	Health effect	High
Thyroid effects (oral)	Moderate	Health effect	Moderate

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

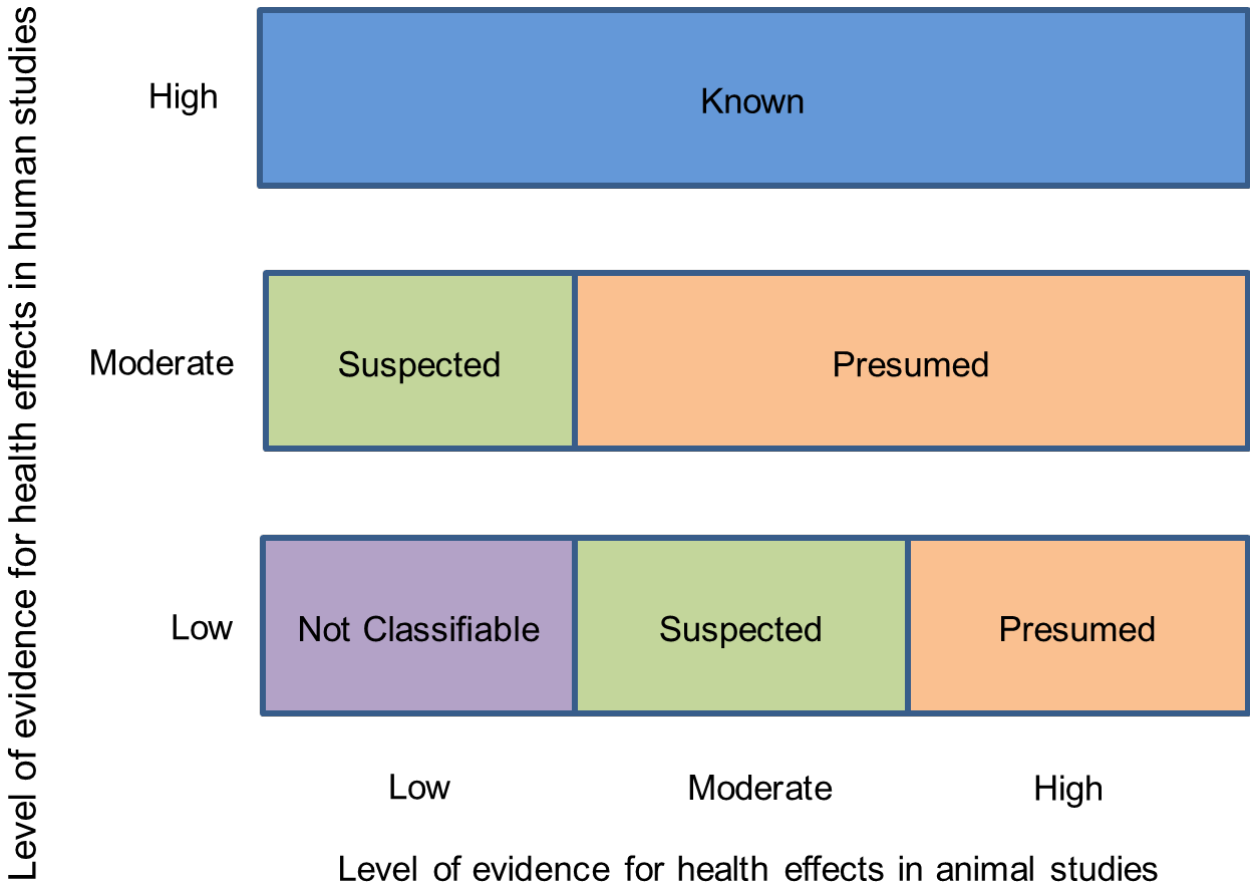
The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the 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 cobalt are listed below and summarized in Table C-21.

Known Health Effects

- Respiratory effects following inhalation exposure
  - High level of evidence in epidemiological studies of humans occupationally exposed to cobalt by inhalation.
    - Exposed workers showed altered spirometry and increased evidence of pulmonary irritation and dyspnea (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a; Linna et al. 2003; Meyer-Bisch et al. 1989; Nemery et al. 1992; Swennen et al. 1993; Verougstraete et al. 2004).
    - Some occupational studies reported increased risk of asthma in cobalt-exposed workers (Kusaka et al. 1986b; Linna et al. 2003; Roto 1980; Walters et al. 2012).
    - There is also limited evidence of impaired lung function after acute-duration inhalation exposure in humans (Kusaka et al. 1986a).
  - High level of evidence in studies of rodents exposed to cobalt and its compounds by inhalation.
    - Acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Palmes et al. 1959; Viegas et al. 2022a).
    - Widespread respiratory damage was consistently observed in rats and mice following intermittent intermediate- or chronic-duration inhalation exposure, with severity of lesions increasing in a dose- and duration-dependent manner (Burzlaff et al. 2022a; NTP 1991, 1998, 2014).
    - In other species, intermediate-duration inhalation exposure resulted in inflammatory changes in rabbit lungs (Johansson et al. 1987) and decreased respiratory compliance, a metric of mechanical ventilation, in pigs (Kerfoot 1974).
  - Based on high evidence from human and animal studies, respiratory effects following inhalation exposure to cobalt and cobalt compounds are classified as known health effects.

Presumed Health Effects

- Hematological effects following oral exposure
  - Moderate level of evidence in human studies that showed polycythemia after acute- and intermediate-duration oral exposure to cobalt in healthy individuals (Davis and Fields 1958). Cobalt supplementation has also been shown to elevate red blood cell count when given to anemic patients (Duckham and Lee 1976; Taylor et al. 1977).
  - High level of evidence in animal studies after oral exposure to cobalt and its compounds. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).
  - Mechanistic data indicate that cobalt can mimic hypoxic conditions via interference with HIF-1α, which would stimulate erythropoiesis (Hoffmeister et al. 2018; Yuan et al. 2003).
  - Based on moderate level of evidence from human studies and high level of evidence from animal studies, with support from a plausible mechanism of action, an increase in erythrocytes is classified as a presumed health effect following oral exposure.

Suspected Health Effects

- Thyroid effects following oral exposure
  - Low level evidence in human studies.
    - There is limited evidence from case reports of goiter or impaired thyroid function in some patients taking cobalt as a treatment for anemia associated with sickle-cell anemia, pregnancy, or chronic renal disease (Chamberlain 1961; Duckham and Lee 1976; Gross et al. 1955; Kriss et al. 1955; Little and Sunico 1958; Washburn and Kaplan 1964).
    - Transient impairments in thyroid function were observed following acute- or intermediate-duration oral exposure to cobalt in some controlled human studies (Paley et al. 1958; Roche and Layrisse 1956). Other studies at similar or lower doses showed no effects (Finley et al. 2013; Holly 1955; Tvermoes et al. 2014).
  - Data from animal studies are limited but provide a moderate level of evidence based on severity of histopathological changes in the thyroid of mice following intermediate-duration exposure to high cobalt doses (Shrivastava et al. 1996).
  - A proposed mechanism for thyroid effects is decreased iodine uptake resulting from cobalt blocking the organic binding of iodine (Paley et al. 1958).
  - Based on low level of evidence from human studies and moderate level of evidence from animal studies, with support from a plausible mechanism of action, impaired thyroid function is classified as a suspected health effect following oral exposure.

Not Classifiable Effects

- Gastrointestinal effects following oral exposure
  - Data in humans pertaining to gastrointestinal effects are considered inadequate. While reported at low administered doses, evidence is restricted to subjective reports of gastrointestinal intolerance in humans following oral exposure to cobalt as a potential treatment for anemia or hyperthyroidism (Duckham and Lee 1976; Holly 1955; Paley et al. 1958).
  - A low level of evidence in animals is provided by a studies reporting alterations to the structure of the walls of the small intestine and delays in gastric emptying time in rats following acute-duration exposure to cobalt (Akinrinde et al. 2016c; Salami et al. 2023). However, intermediate-duration studies did not report any damage to the gastrointestinal tract in rats following oral exposure to cobalt (Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955).
  - Based on inadequate data in humans and a low level of evidence from animals, gastrointestinal effects are not classifiable as toxic effects following oral exposure to cobalt.

Table C-21. Hazard Identification Conclusions for Cobalt

Outcome	Hazard identification
Respiratory effects (inhalation exposure)	Known
Gastrointestinal effects (oral exposure)	Not classifiable
Hematological effects (oral exposure)	Presumed
Thyroid effects (oral exposure)	Suspected

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									

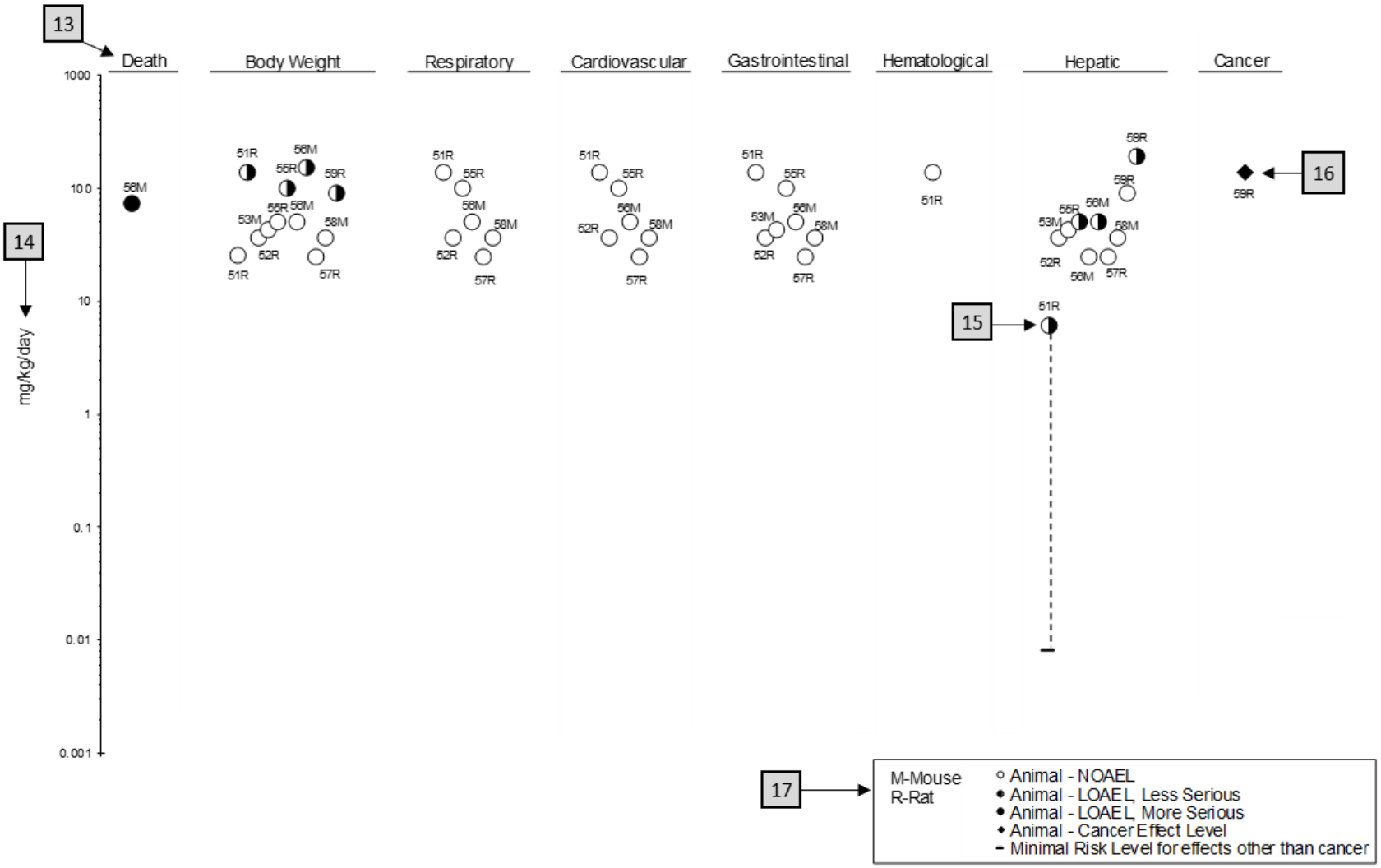
[a]The number corresponds to entries in Figure 2-x.

(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 3.2Children 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