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.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL as available studies are limited and suggested serious effects at the lowest exposure levels.

Rationale for Not Deriving an MRL: Available studies of human inhalation exposure to copper and compounds were not sufficient to identify effect levels. Human studies on acute-duration inhalation exposure that met inclusion criteria include one experimental study of five men exposed to copper-only welding fume (Markert et al. 2016), occupational studies reporting metal fume fever in workers exposed to copper dust or fumes (Armstrong et al. 1983; Gleason 1968), and human case reports of accidental inhalation exposure (Donoso et al. 2007; Gibson et al. 2011). The only endpoint evaluated in the controlled exposure study (Markert et al. 2016) was serum C-reactive protein, which is an inadequate basis for determining a LOAEL or NOAEL. Neither the occupational studies nor case reports provided adequate exposure concentration information, precluding their use for MRL derivation.

Two acute-duration inhalation studies in animals exposed to copper compounds were located (Drummond et al. 1986; Poland et al. 2022). Poland et al. (2022) conducted 2-week studies of rats exposed to copper sulfate pentahydrate or dicopper oxide. In that study, LOAELs of 0.71 and 1.78 mg Cu/m^3, respectively, were identified for respiratory effects (alveolar histiocytosis, bronchioloalveolar hyperplasia, and/or increased lung weight) (Poland et al. 2022). NOAELs in this study were 0.18 and 0.71 mg Cu/m^3, respectively.

The second study (Drummond et al. 1986) involved acute-duration inhalation exposure to copper sulfate, and included evaluations of lethality, respiratory, and immunological effects in mice and limited respiratory effects in hamsters. However, the exposure concentrations reported in the study are uncertain; therefore, effect levels could not be determined. Drummond et al. (1986) reported exposure concentrations both in terms of sulfate (reporting values of 0.09, 0.1, 0.43, 0.93, and 2.53 mg SO_4/m^3) and in terms of "calculated mg metal/m^3" (reporting values of 0.12, 0.13, 0.56, 1.21, and 3.3 mg metal/m^3, respectively). The reported copper concentrations are inconsistent with the concentrations reported in terms of sulfate. For example, the copper concentration (from copper sulfate) corresponding to 2.53 mg SO_4/m^3 would be 1.67 mg Cu/m^3 (calculated as mg SO_4/m^3 x [molecular weight of copper/molecular weight of sulfate]). Copper concentrations based on the reported sulfate concentrations would be 0.06, 0.07, 0.28, 0.62, and 1.67 mg Cu/m^3, respectively. This discrepancy was limited to the copper concentrations, as the aluminum concentrations reported as "mg metal/m^3" for exposures to aluminum sulfate compounds in the study were consistent with the corresponding sulfate concentrations. It is uncertain whether the study authors incorrectly reported the sulfate concentrations or the copper concentrations for the copper sulfate exposures.

In the mouse studies (Drummond et al. 1986), increased mortality was seen at the lowest exposures, at reported sulfate concentrations of 0.09–0.1 mg SO_4/m^3. Copper concentrations corresponding to these sulfate concentrations would be 0.06–0.07 mg Cu/m^3, much lower than the NOAELs identified in the 2-week rat studies (Poland et al. 2022). Alternatively, if the "calculated mg metal/m^3" concentrations are correct, mortalities would be at concentrations of 0.12–0.13 mg Cu/m^3; these concentrations are slightly lower than the NOAEL of 0.18 mg Cu/m^3 for rats exposed to copper sulfate pentahydrate in the study by

Poland et al. (2022). No other studies of mice exposed to copper compounds by inhalation were located. In addition, no rat studies examining immunotoxicity endpoints such as those evaluated by Drummond et al. (1986) were located. In the absence of studies that refute the mortality findings at low exposure concentrations reported by Drummond et al. (1986), the available data are not considered adequate for MRL derivation, because NOAELs in the rat studies were at exposure concentrations higher than those inducing mortality in mice.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL as available studies evaluated limited endpoints and were not sufficient to establish the critical effect of intermediate-duration inhalation exposure.

Rationale for Not Deriving an MRL: One human study of intermediate-duration inhalation exposure met inclusion criteria: a case-control study of general population exposure to copper in particulate matter (Rammah et al. 2019). In this study, no association was observed between risk of stillbirth and modeled copper concentration in $PM_{2.5}$ during pregnancy (Rammah et al. 2019). These data do not provide an adequate basis for MRL derivation. Animal toxicity studies include two studies in rabbits that only identified NOAELs for respiratory and immune effects (Johansson et al. 1983, 1984) and a comprehensive study of rats exposed to dicopper oxide by inhalation for 4 weeks that identified a NOAEL and LOAEL of 0.18 and 0.35 mg Cu/m^3, respectively, for respiratory effects including alveolar histiocytosis, bronchioloalveolar hyperplasia, and/or increased lung weights (Poland et al. 2022). The available studies examined a limited number of potential endpoints, and there is uncertainty regarding whether the respiratory tract is the most sensitive target tissue. Therefore, an intermediate-duration inhalation MRL could not be derived.

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL as available data do not clearly identify a critical effect.

Rationale for Not Deriving an MRL: Human studies of chronic-duration inhalation exposure to copper that met inclusion criteria include occupational exposure studies (Askergren and Mellgren 1975; Finelli et al. 1981; Fouad and Ramadan 2022; Mourad and El-Sherif 2022; Saadiani et al. 2013; Suciu et al. 1981) and cohort studies of general population exposure to copper in airborne particular matter (Boogaard et al. 2013; Gehring et al. 2015; Ostro et al. 2015; Peralta et al. 2021; Yu et al. 2021b). The occupational exposure studies are limited because the workers were simultaneously exposed to several other heavy metals, and it was not possible to discern effects of copper alone.

Boogaard et al. (2013) evaluated the change in spirometry parameters before and after implementation of traffic reduction measures in the Netherlands, and observed improvement in FVC with a decrease of 27.2 ng Cu/m^3 in mean copper concentration in ambient air. Two cohort studies examined the association between modeled concentrations of copper in ambient particulate matter and cardiovascular outcomes (Ostro et al. 2015; Peralta et al. 2021). In a cohort of 101,884 current and former female teachers and administrators, Ostro et al. (2015) observed an association between increased mortality from ischemic heart disease and increased copper concentration in particulate matter. In a cohort study of 563 older men in Massachusetts (Peralta et al. 2021), copper concentrations in $PM_{2.5}$ were associated with decreased (improved) heart-rate-corrected QT interval. These data are insufficient to identify a critical effect of chronic-duration inhalation exposure to copper.

No chronic-duration inhalation animal studies were located.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.02 mg/kg/day
Critical Effect: Gastrointestinal effects
Reference: Pizarro et al. 1999
Point of Departure: $BMDL_{10}$ of 0.055 mg/kg/day
Uncertainty Factor: 3
LSE Graph Key: 6
Species: Human

MRL Summary: An acute-duration oral MRL of 0.02 mg Cu/kg/day was derived for copper based on gastrointestinal effects of abdominal pain, vomiting, and nausea in female adults ingesting copper sulfate in drinking water for 2 weeks (Pizarro et al. 1999). The MRL is based on a benchmark dose lower confidence limit associated with 10% extra risk ($BMDL_{10}$) of 0.055 mg/kg/day, which was divided by a total uncertainty factor of 3 for human variability; a partial uncertainty factor was applied because the direct effects of copper on the gastrointestinal tract are unlikely to be substantially impacted by toxicokinetic differences among individuals.

The acute-duration oral MRL of 0.02 mg Cu/kg/day reflects the intake of administered copper in addition to dietary background. It is intended to protect against gastrointestinal effects in people who receive adequate copper intake from diet and/or supplements. People who have copper deficiency may be given therapeutic doses at or above the MRL.

It should be noted that the acute-duration oral MRL may or may not be adequately protective for people with Wilson's disease, as the degree of protection will depend on their dietary and water intake levels as well as the degree to which their disease is medically controlled.

Selection of the Critical Effect: Numerous experimental studies and case reports support the identification of the gastrointestinal tract as a sensitive endpoint of toxicity in humans acutely exposed to copper in drinking water or in contaminated beverages (Araya et al. 2001, 2003a, 2003c; Chuttani et al. 1965; Gotteland et al. 2001; Knobeloch et al. 1994; Olivares et al. 2001; Pizarro et al. 1999, 2001; Spitalny et al. 1984).

Controlled exposure studies provide the most reliable information on gastrointestinal effects in humans, including dose-response information. Table A-1 shows NOAEL and LOAEL values for acute-duration controlled oral exposure studies in humans. It should be noted that the NOAEL and LOAEL doses reflect supplemented copper and do not include contributions from dietary intake or tap water. As the table shows, the controlled exposure studies demonstrate LOAELs between 0.012 and 0.1 mg Cu/kg/day for nausea, vomiting, abdominal pain, and/or delayed gastric emptying.

Table A-1. Summary of Gastrointestinal NOAEL and LOAEL Values in Humans after Acute-Duration Oral Exposure to Copper

Number and sex of subjects	Exposure conditions	NOAEL in mg Cu/kg/day	LOAEL in mg Cu/kg/day	Effect	Reference
30 male and 31 female healthy adults (mean ages 28.7 and 32 years, respectively)	Once as 200 mL bolus after overnight fast	0.006 (2 mg Cu/L)	0.012 (4 mg Cu/L)	Nausea in 5/53 subjects	Olivares et al. 2001
179 adult men and women (median age ~40 years)	Once as 200 mL bolus after overnight fast	0.012 (4 mg Cu/L)	0.018 (6 mg Cu/L)	Increased frequency of nausea in 17/179 subjects	Araya et al. 2001
269 healthy adult women (median ages 27–37 years across groups)	Once as 200 mL bolus after overnight fast	0.012 (4 mg Cu/L)	0.018 (6 mg Cu/L)	Nausea in 50/269 subjects	Araya et al. 2003c
15 male and 16 female healthy adults (mean age 32 years)	Once as 200 mL bolus after overnight fast	ND	0.03 (10 mg Cu/L)	Nausea (6/31 subjects) and vomiting (2/31 subjects)	Gotteland et al. 2001
15 male and 16 female healthy adults (mean ages 37 and 33 years, respectively)	Once as 300 mL bolus after overnight fast	ND	0.046 (10 mg Cu/L)	Nausea in 9/30 subjects; delayed gastric emptying	Araya et al. 2003a
60 healthy adult women (mean age 32–36 years across groups)	2 weeks, daily in water (plain, as tea, or with powdered juice mix)	0.03 (1 mg Cu/L)	0.07 (3 mg Cu/L)	Abdominal pain, nausea, and/or vomiting	Pizarro et al. 1999
45 healthy adult women (mean age 25.6 years)	1 week daily in water (plain, as tea, or with powdered juice mix)	ND	0.1 (5 mg Cu/L)	Nausea, vomiting, and/or abdominal pain	Pizarro et al. 2001

LOAEL = lowest-observed adverse-effect level; NOAEL = no-observed-adverse-effect level; ND = not determined

Animal studies have identified gastrointestinal, hepatic, renal, and reproductive system effects at much higher doses (≥2 mg Cu/kg/day) following acute-duration oral exposure to copper. Since the dietary requirement for copper is much higher in rodents (0.5–1 mg Cu/kg/day) than in humans (0.013 mg Cu/kg/day for a 70-kg human), it is not surprising that rodents tolerate higher doses. Given that there are several well-conducted controlled experiments in humans that identify effect levels lower than any of the animal studies, and laboratory animals' dietary requirement exceeds the dietary requirement in humans by more than 30-fold, only human studies were considered for MRL derivation. The human studies consistently demonstrate gastrointestinal symptoms of nausea and vomiting as the critical effect of acute-duration oral exposure to copper.

Selection of the Principal Study: The study by Pizarro et al. (1999) was selected for derivation of the acute-duration oral MRL. While Pizarro et al. (1999) did not identify the lowest LOAEL, subjects in the studies by Araya et al. (2001, 2003a, 2003c), Gotteland et al. (2001), and Olivares et al. (2001) were exposed via bolus dosing after an overnight fast, while subjects in the study by Pizarro et al. (1999) consumed the copper-containing water over the course of the day. Bolus dosing may exacerbate gastrointestinal effects that are attributable to direct contact, as the amount of copper in contact with the stomach lining is much higher. In contrast, intermittent consumption of copper-containing water over the day more closely approximates environmental exposure conditions. Furthermore, the subjects in the study by Pizarro et al. (1999) were exposed for 2 weeks, while subjects in the studies by Araya et al. (2001, 2003a, 2003c) and Gotteland et al. (2001) were exposed on a single day. Finally, of the available controlled exposure studies, only Pizarro et al. (1999) provided information on both dietary copper intake and copper concentrations in household tap water. Thus, Pizarro et al. (1999) was selected as the principal study.

Summary of the Principal Study:

Pizarro F, Olivares M, Uauy, R, et al. 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect 107:117-121.

A group of 60 healthy women in Chile were divided into four exposure sequence groups, with mean ages within each group of 32.9–36.3 years. The mean body weight of the participants was 64 kg. Each group consumed water containing 0, 1, 3, or 5 mg/L ionic copper as copper sulfate pentahydrate (0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day, respectively) for a 2-week period followed by a 1-week rest, followed by the next dose of copper in the sequence. Each group of women was assigned to a different order of copper concentrations to consume over an 11-week period. For example, the first group was assigned to consume the control group drinking water for 2 weeks followed by a 1-week rest period, then drank the water containing 1 mg Cu/L for 2 weeks followed by a 1-week rest. This process continued in the same group with the water containing 3 and 5 mg Cu/L. Ultimately, each dose was tested in all 60 women; therefore, there were 60 women in each dose group, and each woman served as her own control. Each week, the women received a bottle containing copper sulfate solution and were asked to mix the contents of the bottle with 3 L of their drinking water. The subjects recorded daily water consumption and reported any symptoms during each 2-week exposure period. If a participant presented diarrhea, abdominal pain, or vomiting, they were told not to ingest copper-containing water for the next 2 days and consumption began once symptoms disappeared. Blood samples were collected 1 week before the study, at the end of the first 2-week exposure period, and at the end of the study; the blood was analyzed for levels of serum copper, AST, ALT, and GGT activities, and hemoglobin. The average dietary intake of copper in study participants, based on a 24-hour dietary recall, was 1.7 mg Cu/day (0.0266 mg Cu/kg/day using the study-reported average body weight of 64 kg). The study authors measured the copper content of the subjects' tap water, and found it to be <0.1 mg/L.

Daily doses of supplemental copper (not including dietary or tap water contributions) were calculated using reported daily intake of copper from the copper sulfate solution (0.04, 1.74, 4.68, and 7.94 mg) and the average of the mean reported body weights across the four groups (64 kg). Daily doses were 0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day for exposure concentrations of 0, 1, 3, and 5 mg Cu/L, respectively. No significant alterations in levels of serum copper, ceruloplasmin, hemoglobin, or liver enzymes were observed. Twenty-one subjects reported gastrointestinal symptoms, predominantly nausea, at some point during the study period. Nine of those subjects reported 12 episodes of diarrhea with or without abdominal pain, and the study authors reported no association between copper concentration in water and diarrhea. Eight of these episodes of diarrhea occurred during the 2 weeks of the study, independent of copper concentration. Twelve subjects reported abdominal pain, nausea, and/or vomiting;

the incidences were 3/60, 1/60, 10/60, and 9/60 in the 0, 0.0272, 0.0731, and 0.124 mg Cu/kg/day groups, respectively (see Table A-2). There was a significant difference between the incidences at concentrations of ≤1 mg Cu/L (0.0272 mg Cu/kg/day) versus ≥3 mg/L (0.0731 mg Cu/kg/day). No other differences between groups were found.

Table A-2. Incidence of Gastrointestinal Symptoms in Women Exposed to Copper in Drinking Water for 2-Week Periods

	Drinking water doses in mg Cu/kg/day			
Symptoms	0.0006 (control)	0.0272	0.0731	0.124
Abdominal pain only	2/60	1/60	3/60	2/60
Vomiting only	0/60	0/60	1/60	2/60
Nausea only	1/60	0/60	6/60	5/60
Total symptoms	3/60	1/60	10/60	9/60

Source: Pizarro et al. 1999

Selection of the Point of Departure for the MRL: The $BMDL_{10}$ of 0.055 mg/kg/day for gastrointestinal symptoms of abdominal pain, nausea, and vomiting in females was selected as the basis for the acute-duration oral MRL.

Incidence data for total gastrointestinal symptoms (abdominal pain, vomiting, and nausea, see Table A-2) were fit to all dichotomous models in EPA's Benchmark Dose Software (BMDS; version 3.3.2) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-values ($p \geq 0.1$), visual inspection of the dose-response curve, benchmark dose lower confidence limit (BMDL) <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. The dichotomous Hill model was recommended but was not selected, as the number of dose groups in the data should generally be at least one more than the number of parameters in a model. In this case, the dichotomous Hill model uses four parameters and the incidence data have four dose groups. The Multistage Degree 1 was the only viable alternative and the BMDL from this model was selected as the point of departure (POD). Table A-3 presents the benchmark dose (BMD) and BMDL values considered for MRL derivation, and Figure A-1 presents the curve from the chosen model.

Table A-3. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Women Following Exposure to Copper in Drinking Water Daily for 2 Weeks (Pizarro et al. 1999)

					Scaled residuals[c]	
Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose below BMD	Dose above BMD
Dichotomous Hill	0.051	0.032	0.29	145.93	-0.72	0.18
Gamma[d]			0.04	149.56	1.43	-0.63
Log-Logistic[e]			0.04	149.54	1.4	-0.62
Log-Probit[e]			0.09	147.62	1.60	-0.94
Multistage Degree 3[f]			0.03	149.87	1.39	-0.50
Multistage Degree 2[f]			0.03	149.87	1.39	0.50

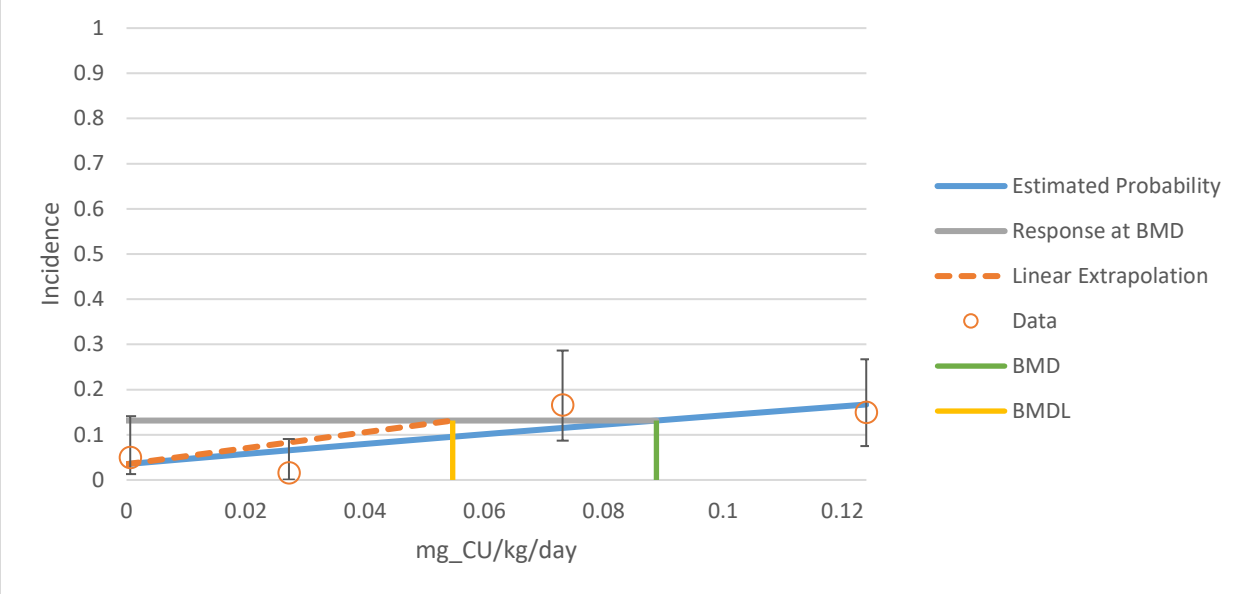
Table A-3. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Women Following Exposure to Copper in Drinking Water Daily for 2 Weeks (Pizarro et al. 1999)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Multistage Degree 1[f,g]	**0.089**	**0.055**	**0.11**	**147.92**	**1.25**	-0.35
Weibull[d]			0.04	149.62	1.42	-0.60
Logistic			0.08	148.26	1.65	-0.58
Log-Probit			0.04	149.16	1.35	-0.67
Probit			0.09	148.1	1.58	-0.59
Quantal Linear	0.089	0.055	0.11	147.92	1.25	-0.35

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. Only the Multistage Degree 1, Quantal Linear, and Dichotomous Hill models provided adequate fit to the data. The dichotomous Hill model had the same number of parameters as the number of dose levels in the data; therefore, it was not selected. The Multistage Degree 1 and Quantal Linear models converged on the same form and this model was selected (Multistage Degree 1).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Figure A-1. Fit of Frequentist Multistage Degree 1 Model to Data on Copper for Gastrointestinal Illness in Female Adults, Daily for 2 Weeks (Pizarro et al. 1999)



Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{10}$ is divided by a total uncertainty factor of 3:

- 3 for human variability. A partial uncertainty factor for human variability was applied because the direct effects of copper on the gastrointestinal tract are unlikely to be substantially impacted by toxicokinetic differences among individuals. However, an uncertainty factor for human variability remains necessary because the principal study (Pizarro et al. 1999) was of healthy adult women, and there are some health conditions that may influence sensitivity to these effects. For example, health conditions that reduce the pH of gastric secretions (e.g., acute *H. pylori* infection, some neuroendocrine tumors or gastrinomas, rebound acid hypersecretion after stopping proton pump inhibitor therapy) may result in higher concentrations of free copper ions in contact with the gastrointestinal tract than those seen in healthy individuals at the same dose. In addition, health conditions that result in damage to the integrity of the gastrointestinal tract (ulcers, acid reflux) may also increase a person's sensitivity to oral copper exposure. The prevalence of these conditions is relatively high in the United States, so including an uncertainty factor of 3 for human variability is necessary to ensure that the MRL is adequately protective for these susceptible subpopulations.

$$MRL = \frac{BMDL_{10}}{UF} = \frac{0.055\ mg/kg/day}{3}$$

$$= 0.01833\ mg/kg/day\ (rounded\ to\ 0.02\ mg\ Cu/kg/day)$$

It should be noted that the acute-duration oral MRL may or may not be adequately protective for people with Wilson's disease, as the degree of protection will depend on their dietary and water intake levels as well as the degree to which their disease is medically controlled.

The acute-duration oral MRL of 0.02 mg Cu/kg/day reflects the intake of administered copper in addition to dietary background. The doses used in BMD modeling were doses of copper from copper sulfate solution provided to the participants in the study by Pizarro et al. (1999), whose average dietary copper intake was estimated[5] to be ~1.7 mg Cu/day or ~0.027 mg Cu/kg/day. This intake level is similar to estimates of dietary or dietary plus supplement copper intake in the United States (1.0–2.6 mg Cu/day; see Section 5.6, General Population Exposure).

Other Additional Studies or Pertinent Information that Lend Support to this MRL: In addition to the acute-duration controlled human exposure studies, there is an intermediate-duration controlled human exposure study that provides support for the critical effect (Araya et al. 2003b). The concentration-dependence of gastrointestinal symptoms was demonstrated in a study by Araya et al. (2003c), in which volunteers were exposed to the same copper dose in different volumes of water. The study authors observed a higher symptom frequency with higher copper concentrations (lower water volumes) when the intake (dose) was held constant. For example, a dose of 0.8 mg Cu administered in 100 mL of water induced nausea in 13% of subjects, while the same dose in 150 or 200 mL of water induced nausea in 9 and 7% of subjects, respectively (Araya et al. 2003c).

Histological changes in the gastrointestinal tract have been observed in experimental animal studies of intermediate duration, providing additional evidence for the gastrointestinal symptoms exhibited by

[5]For the four groups of subjects (receiving copper dosing in different sequences), Pizarro et al. (1999) reported average copper intakes of 1.4, 1.7, 1.8, and 1.9 mg Cu/day from food based on 24-hour diet recall. The average intake across groups was 1.725 mg Cu/day; this value was divided by the reported average body weight of 64 kg to estimate the dietary intake of 0.027 mg Cu/kg/day.

humans. In a combined repeat-dose and reproductive/developmental toxicity screening study of rats, significant increases in the incidence of squamous cell hyperplasia in the stomach were seen after 30–38 days of gavage exposure to doses ≥3 mg Cu/kg/day in females and ≥13 mg Cu/kg/day in males (Chung et al. 2009). NTP (1993) also observed increased incidences of squamous mucosa hyperplasia of forestomach in male and female rats at doses of 44–46 mg Cu/kg/day for 15 days and 33–34 mg Cu/kg/day for 13 weeks.

In animals exposed orally to copper for acute and intermediate durations, other effects (body weight, hepatic, renal, reproductive, and neurological) occurred at much higher doses (≥2 mg Cu/kg/day) (e.g., Al-Musawi et al. 2022; Guo et al. 2021; Husain et al. 2023; Kumar et al. 2019; Temiz et al. 2021).

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.02 mg/kg/day (adopted acute-duration MRL)
Critical Effect: See acute-duration oral MRL
Reference: Pizarro et al. 1999 (see acute-duration oral MRL)
Point of Departure: See acute-duration oral MRL
Uncertainty Factor: See acute-duration oral MRL
LSE Graph Key: 6
Species: Human

MRL Summary: The acute-duration oral MRL of 0.02 mg Cu/kg/day was adopted as the intermediate-duration oral MRL. The intermediate-duration database was assessed for suitability for MRL derivation, but the study with the lowest LOAEL (Araya et al. 2003b, 2004) yielded a higher BMDL (0.11 mg Cu/kg/day) for gastrointestinal symptoms in humans than the BMDL (0.055 mg Cu/kg/day for the same effect in humans; Pizarro et al. 1999) used as the POD for the acute-duration oral MRL. Additionally, the critical effect of gastrointestinal symptoms may result in part from a direct contact effect dependent on the concentration of copper present at a given time in the stomach rather than duration of exposure. Therefore, the acute-duration MRL is expected to be protective for intermediate-duration exposure scenarios.

Selection of the Critical Effect: See worksheet for acute-duration oral MRL.

Selection of the Principal Study: See worksheet for acute-duration oral MRL.

Summary of the Principal Study: See worksheet for acute-duration oral MRL.

Selection of the Point of Departure for the MRL: See worksheet for acute-duration oral MRL.

Calculations: See worksheet for acute-duration oral MRL.

Uncertainty Factor: See worksheet for acute-duration oral MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Gastrointestinal effects were recorded in a controlled experiment in humans exposed to copper in drinking water for 2 months (Araya et al. 2003b, 2004). In Araya et al. (2003b, 2004), significant increases in the proportion of subjects reporting at least one gastrointestinal symptom (nausea, vomiting, diarrhea, or abdominal pain) were seen at doses of 0.11 and 0.17 mg Cu/kg/day (corresponding to water concentrations of 4 and 6 mg Cu/L, respectively). A study in infants reported no increase in the reporting of gastrointestinal symptoms following daily exposure to doses up to 0.319 mg Cu/kg/day for 9 months (Olivares et al. 1998).

Histological changes in the gastrointestinal tract have been observed in experimental animal studies, providing additional evidence for the gastrointestinal symptoms exhibited by humans. In a combined repeat-dose and reproductive/developmental toxicity screening study of rats, significant increases in the incidence of squamous cell hyperplasia in the stomach were seen after 30–38 days of gavage exposure to

doses ≥3 mg Cu/kg/day in females and ≥13 mg Cu/kg/day in males (Chung et al. 2009). NTP (1993) also observed increased incidences of squamous mucosa hyperplasia of forestomach in male and female rats at doses of 44–46 mg Cu/kg/day for 15 days and 33–34 mg Cu/kg/day for 13 weeks.

As shown in Table A-4, animal studies of intermediate-duration oral exposure to copper have also identified hepatic, body weight, neurological, and reproductive system effects at doses ≥2.3 mg Cu/kg/day (Guo et al. 2021; Kline et al. 1971; Liu et al. 2020a, 2020b, 2021a, 2021b; Temiz et al. 2021).

Table A-4. Summary of Lowest LOAEL Values for Health Effects Following Intermediate-Duration Oral Exposure to Copper

Species (sex)	Frequency/ duration	NOAEL (mg Cu/kg/day)	LOAEL (mg Cu/kg/day)	Effect	Reference
Gastrointestinal effects					
Human; 1,365 adult men and women (mean ages 37–38 years)	2 months daily in water used for consumption, beverages, and soups	0.055 (2 mg Cu/L)	0.11 (4 mg Cu/L)	Increased incidence of gastrointestinal symptoms	Araya et al. 2003b, 2004
Human; 7 men and women (mean age 42 years)	12 weeks, daily by capsule	0.15	ND	No difference in gastrointestinal symptoms incidence	Pratt et al. 1985
Human; 80 exposed and 48 unexposed male and female infants	9 months (from 3 to 12 months of age) in water used for consumption and formula	0.319 (2 mg/L)	ND	No gastrointestinal symptoms observed	Olivares et al. 1998
Rat (F)	38 days Daily (gavage)	0.83	3	Increased incidence of squamous cell hyperplasia in the stomach	Chung et al. 2009
Body weight effects					
Pig (NS)	88 days (feed)	1.7	2.3	17% reduction in body weight gain	Kline et al. 1971
Mouse (M and F)	42 days daily (gavage)	ND	4	Terminal body weight decreased 15%	Liu et al. 2020a, 2020b, 2021a, 2021b
Neurological effects					
Rat (M)	16 weeks daily (gavage)	ND	2.6	Decreased locomotor activity and neuromuscular coordination, decreased passive avoidance response, less exploration time	Kumar et al. 2019

Table A-4. Summary of Lowest LOAEL Values for Health Effects Following Intermediate-Duration Oral Exposure to Copper

Species (sex)	Frequency/ duration	NOAEL (mg Cu/kg/day)	LOAEL (mg Cu/kg/day)	Effect	Reference
Hepatic effects					
Human; 11 men and 11 women (mean ages 33.5 and 29 years, respectively)	6 weeks, daily in food		ND	No effect on serum enzyme levels	O'Connor et al. 2003
Human; 7 men and women (mean age 42 years)	12 weeks, daily by capsule	0.15	ND	No effect on serum enzyme levels	Pratt et al. 1985
1,365 adult men and women (mean ages 37–38 years)	2 months daily in water used for consumption, beverages, and soups	0.17	ND	No effect on serum enzyme levels	Araya et al. 2003b, 2004
80 exposed and 48 unexposed male and female infants	9 months (from 3 to 12 months of age) in water used for consumption and formula	0.319	ND	No effect on serum bilirubin or AST, ALT, or GGT activities	Olivares et al. 1998
Rat (M)	28 days 2 times/week (gavage)	ND	3.9	Increased serum AST, ALT, and LDH centrilobular and vacuolar degeneration, dilatation of sinusoid, focal necrosis, and inflammatory cell infiltration in all or most animals	Temiz et al. 2021
Reproductive effects					
Mouse (M)	42 days daily (gavage)	ND	3.9	Increased sperm malformations and decreased sperm motility and concentration	Guo et al. 2021

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female(s); GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

The study by Araya et al. (2003b, 2004) identified the lowest NOAEL and corresponding LOAEL for adverse health outcomes (gastrointestinal symptoms) and was considered for possible use in deriving the intermediate-duration oral MRL. Araya et al. (2004) provided more detail on the copper dosing and gastrointestinal symptoms, so information from this publication was used. For groups given measured concentrations of 0.05, 2.02, 3.71, or 5.77 mg Cu/L in drinking water, corresponding daily copper intakes provided by Araya et al. (2004) were 0.08, 3.6, 6.9, and 11 mg/day, respectively. To calculate the dose, a

reference body weight of 65 kg for all adults (the midpoint between the default body weights for adult men [70 kg] and women [60 kg]) was used, resulting in doses of 0.001, 0.056, 0.11, and 0.17 mg Cu/kg/day. Incidences of at least one gastrointestinal symptom were 40/343, 50/327, 65/355, and 67/340 for the control through high dose groups, respectively (Araya et al. 2004).

BMD modeling was applied to the incidence data for gastrointestinal symptoms reported by Araya et al. (2004). The data were fit to all available dichotomous models in EPA's BMDS (version 3.3.2) using the extra risk option. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-values ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among the recommended, viable models providing adequate fit to the data, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was selected as the POD. The results of the BMD modeling for incidence of gastrointestinal symptoms in adults are presented in Table A-5.

Table A-5. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Adults Following Exposure to Copper in Drinking Water Daily for 2 Months (Araya et al. 2004)

Model	BMD_{10}[a] (mg Cu/kg/day)	$BMDL_{10}$[a] (mg Cu/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	0.26	0.059	NA	1,210.26	-0.000012	NR
Gamma[d]	0.18	0.12	0.84	1,206.62	-0.35	NR
Log-Logistic[e,f]	**0.18**	**0.11**	**0.86**	**1,206.56**	**-0.33**	**NR**
Log-Probit[e]	0.18	0.14	0.29	1,208.75	-0.57	NR
Multistage Degree 3[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Multistage Degree 2[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Multistage Degree 1[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Weibull[d]	0.18	0.12	0.84	1,206.62	-0.35	NR
Logistic	0.18	0.13	0.71	1,206.95	-0.40	NR
Log-Probit	0.19	0	0.81	1,208.32	-0.10	NR

Table A-5. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Adults Following Exposure to Copper in Drinking Water Daily for 2 Months (Araya et al. 2004)

Model	BMD_{10}[a] (mg Cu/kg/day)	$BMDL_{10}$[a] (mg Cu/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Probit	0.18	0.13	0.73	1,206.90	-0.39	NR
Quantal Linear	0.18	0.12	0.84	1206.62	-0.35	NR

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also, the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models provided adequate fit to the data (chi-square goodness-of-fit p-values ≥0.1). BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Log-Logistic).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NR = BMD is higher than the highest dose tested; residual not available.

The selected model was the Log-Logistic model, which resulted in a BMDL of 0.11 mg Cu/kg/day. This BMDL is higher than the BMDL of 0.055 mg Cu/kg/day for same endpoint in the acute-duration human study by Pizarro et al. (1999) that was used as the POD for the acute-duration oral MRL. Therefore, ATSDR adopted the acute-duration oral MRL of 0.02 mg Cu/kg/day for intermediate-duration exposure. As noted previously, the critical effect of gastrointestinal symptoms may result from a direct contact effect that depends more on the concentration of copper present at a given time in the gastrointestinal system than on exposure duration. The concentration-dependence of gastrointestinal symptoms was demonstrated in a study by Araya et al. (2003c), in which volunteers were exposed to the same copper dose in different volumes of water. The study authors observed a higher symptom frequency with higher copper concentrations (lower water volumes) when the intake (dose) was held constant. For example, a dose of 0.8 mg copper administered in 100 mL of water induced nausea in 13% of subjects, while the same dose in 150 or 200 mL of water induced nausea in 9 and 7% of subjects, respectively (Araya et al. 2003c). Therefore, the acute-duration MRL is expected to be protective for intermediate-duration exposure scenarios.

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of chronic-duration oral MRL because available studies do not clearly identify the critical effects.

Rationale for Not Deriving an MRL: Human studies that met inclusion criteria did not provide sufficient dose-response information to examine the chronic-duration oral toxicity of copper. Two large prospective cohort studies used estimates of dietary copper intake based on food frequency questionnaires to examine associations with dementia (Wei et al. 2022, United States) and hypertension (He et al. 2022, China). Wei et al. (2022) estimated intake of copper from diet and supplements at enrollment in the cohort (1987–1989) and again a few years later (1993–1995) based on responses to a validated food frequency questionnaire administered by an interviewer. Subjects were followed for 20 years; an increase in dietary copper intake of 1 mg Cu/day was associated with increased risk of incident dementia. He et al. (2022) estimated dietary intake at baseline using three consecutive 24-hour recall surveys administered by a nutritionist, coupled with household food inventories on the same days; the participants were followed for a median duration of 6.1 years. Estimated copper intake ≥1.57 mg/day was associated with an increase in risk of incident hypertension (He et al. 2022). Both studies are limited because they do not account for either changes in diet over time or copper intake from water or local sources.

Three animal studies of chronic-duration oral exposure were located, but included only limited toxicological evaluations. One study in mice exposed for 850 days evaluated only survival and body weight and no other health outcomes (Massie and Aiello 1984). In the remaining two experiments, young or adult monkeys were exposed to copper in milk (young) or feed (both) for 3 years (Araya et al. 2012). These studies evaluated body weight, limited hematology and serum chemistry endpoints, and liver histopathology, and identified NOAELs of 5.5 and 7.5 mg Cu/kg/day (Araya et al. 2012). Neither the human studies nor the animal studies provide sufficient information to determine the critical effects of chronic-duration oral exposure to copper.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR COPPER

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 copper.

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

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Copper released for public comment in 2022; thus, the literature search was restricted to studies published between January 2020 and October 2023. The following main databases were searched in October 2023:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for copper. 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 copper were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2023	((((("Copper/toxicity"[mh] OR "Copper/adverse effects"[mh] OR "Copper/poisoning"[mh] OR "Copper/pharmacokinetics"[mh]) OR ("Copper/blood"[mh] OR "Copper/cerebrospinal fluid"[mh] OR "Copper/urine"[mh]) OR ("Copper/antagonists and inhibitors"[mh]) OR ("Copper/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper sulfate/toxicity"[mh] OR "Copper sulfate/adverse effects"[mh] OR "Copper sulfate/poisoning"[mh] OR "Copper sulfate/pharmacokinetics"[mh]) OR ("Copper sulfate/blood"[mh] OR "Copper sulfate/cerebrospinal fluid"[mh] OR "Copper sulfate/urine"[mh]) OR ("Copper sulfate/antagonists and inhibitors"[mh]) OR ("Copper sulfate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper/pharmacology"[majr] OR "Copper sulfate/pharmacology"[majr]) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[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 (("Copper"[mh] OR "Copper sulfate"[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 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 (142-71-2[rn] OR 10380-28-6[rn]) OR (("Copper"[mh] OR "Copper Sulfate"[mh]) AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) AND (2022/08/07:3000[mhda]))) OR (("Copper D-gluconate"[tiab] OR "Copper di-D-gluconate"[tiab] OR "Copper gluconate"[tiab] OR "Copper(2+) D-gluconate, (1:2)"[tiab] OR "Copper(2+) di(D-gluconate)"[tiab] OR "Copper(II)gluconate"[tiab] OR "Cupric gluconate"[tiab] OR "D-Gluconic acid, copper complex"[tiab] OR "D-Gluconic acid, copper salt"[tiab] OR "D-Gluconic acid, copper(2+) salt"[tiab] OR "Gluconic acid, copper salt, D-"[tiab] OR "Gluconic acid, copper(2+) salt"[tiab] OR "Helshas Cu"[tiab] OR "Labicuper"[tiab]) AND (2022/08/07:3000[edat] OR 2022/08/07:3000[crdat]))
	((((("Copper"[tw] OR "1721 Gold"[tw] OR "3EC-M3S-HTE"[tw] OR "3EC-M3VLP18"[tw] OR "ANAC 110"[tw] OR "ATS Adocopper IW"[tw] OR "BAC 13B-NK120"[tw] OR "Bronze powder"[tw] OR "C 100 (metal)"[tw] OR "C.I. 77400"[tw] OR "C.I. Pigment Metal 2"[tw] OR "Caswell No. 227"[tw] OR "CDA 101"[tw] OR "CDA 102"[tw] OR "CDA 110"[tw] OR "CDA 122"[tw] OR "CDX (metal)"[tw] OR "CE 1110"[tw] OR "CE 7 (metal)"[tw] OR "CF-T 8GD-SV"[tw] OR "CF-T 9A-HP-STD"[tw] OR "CF-T 9B-THE"[tw] OR "CF-T 9FZ-SV"[tw] OR "CFW 100-156"[tw] OR "CI 77400"[tw] OR "CI Pigment metal 2"[tw] OR "CU M3"[tw] OR "Cu-At-W 250"[tw] OR "Cubrotec 5000"[tw] OR "Cuivre metal"[tw] OR "Cutox 6010"[tw] OR "Cutox 6030"[tw] OR "DD Paste TH 9910"[tw] OR "Double Thin F-NP"[tw] OR "DT GLMP"[tw] OR "E 115 (metal)"[tw] OR "Gold bronze"[tw] OR "GT (metal)"[tw] OR "NDP-III"[tw] OR "NT-TAX-M"[tw] OR "NT-TAX-O"[tw] OR "OFHC Cu"[tw] OR "Paragard T 380a"[tw] OR "Paragard t380a"[tw] OR "Pigment metal 2"[tw] OR "Silcoat FCC-SP 99"[tw] OR "Tatum-T"[tw] OR "Unicoat 2845"[tw] OR "USLP-SE"[tw] OR "All Clear Root Destroyer"[tw] OR "Aqua Maid Permanent Algaecide"[tw] OR "Aquatronics Snail-A-Cide Dri-Pac Snail Powder"[tw] OR "Blue stone"[tw] OR "Blue vitriol"[tw] OR "Bonide Root Destroyer"[tw] OR "Cuivrol"[tw] OR "CuSO4"[tw] OR "Delcup"[tw] OR "EarthTec"[tw] OR "Hylinec"[tw] OR "Incracide 10A"[tw] OR "Incracide E 51"[tw] OR "MAC 570"[tw] OR "Monocopper sulfate"[tw] OR "Roman vitriol"[tw] OR "Trinagle"[tw] OR "CuCl2"[tw] OR "Eriocholcite"[tw] OR "cupric"[tw] OR "cuprous"[tw] OR ("cu"[tiab] NOT ("chronic urticaria"[tiab] OR "cognitively unimpaired"[tiab] OR "callous unemotional"[tiab] OR "cocaine users"[tiab]))) NOT medline[sb]) AND (2022/08/07:3000[edat] OR 2022/08/07:3000[crdat]))) AND (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 tract" OR "respiratory organ" OR "respiratory system" OR "respiratory volume" OR "respiratory function" OR "respiratory effect" OR "respiratory organ" OR "respiratory toxicity" 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 system" OR "cardiovascular function" OR "cardiovascular effect" OR "cardiovascular organ" OR "cardiovascular toxicity" 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

Table B-2. Database Query Strings

Database search date	Query string
	"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 system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" 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 system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "dermal exposure" OR "dermal contact" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin acanthosis" OR "skin exposure" OR "skin contact" OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR "endocrine system" OR "endocrine function" OR "endocrine effect" OR "endocrine gland" OR "endocrine toxicity" 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" OR "mechanism of absorption" OR "mechanism of distribution" OR "mechanism of excretion" OR "mechanism of metabolism" OR "mechanism of toxic effect" OR "adverse effect" OR "adverse effects" OR poisoning OR morbidity OR inflammation OR antagonist

Table B-2. Database Query Strings

Database search date	Query string
	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 "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES 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 wistar OR wood-mouse OR zebra-fish OR zebrafish) ((("Copper/toxicity"[mh] OR "Copper/adverse effects"[mh] OR "Copper/poisoning"[mh] OR "Copper/pharmacokinetics"[mh]) OR ("Copper/blood"[mh] OR "Copper/cerebrospinal fluid"[mh] OR "Copper/urine"[mh]) OR ("Copper/antagonists and inhibitors"[mh]) OR ("Copper/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper sulfate/toxicity"[mh] OR "Copper sulfate/adverse effects"[mh] OR "Copper sulfate/poisoning"[mh] OR "Copper sulfate/pharmacokinetics"[mh]) OR ("Copper sulfate/blood"[mh] OR "Copper sulfate/cerebrospinal fluid"[mh] OR "Copper sulfate/urine"[mh]) OR ("Copper sulfate/antagonists and inhibitors"[mh]) OR ("Copper sulfate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper/pharmacology"[majr] OR "Copper sulfate/pharmacology"[majr]) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[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 (("Copper"[mh] OR "Copper sulfate"[mh]) AND

Table B-2. Database Query Strings

Database search date	Query string
	(("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR ((10125-13-0[rn] OR 10257-54-2[rn] OR 1184-64-1[rn] OR 12019-06-6[rn] OR 12125-21-2[rn] OR 1317-38-0[rn] OR 1317-39-1[rn] OR 1344-67-8[rn] OR 1344-69-0[rn] OR 1344-70-3[rn] OR 17599-81-4[rn] OR 20427-59-2[rn] OR 527-09-3[rn] OR 7440-50-8[rn] OR 7447-39-4[rn] OR 7492-68-4[rn] OR 7758-89-6[rn] OR 7758-98-7[rn] OR 7758-99-8[rn] OR 82010-82-0[rn]) NOT ("Copper"[mh] OR "Copper Sulfate"[mh])) OR (142-71-2[rn] OR 10380-28-6[rn]) OR ("Copper D-gluconate"[tiab] OR "Copper di-D-gluconate"[tiab] OR "Copper gluconate"[tiab] OR "Copper(2+) D-gluconate, (1:2)"[tiab] OR "Copper(2+) di(D-gluconate)"[tiab] OR "Copper(II)gluconate"[tiab] OR "Cupric gluconate"[tiab] OR "D-Gluconic acid, copper complex"[tiab] OR "D-Gluconic acid, copper salt"[tiab] OR "D-Gluconic acid, copper(2+) salt"[tiab] OR "Gluconic acid, copper salt, D-"[tiab] OR "Gluconic acid, copper(2+) salt"[tiab] OR "Helshas Cu"[tiab] OR "Labicuper"[tiab])) AND (2020/01/01:3000[mhda] OR 2020/01/01:3000[edat] OR 2020/01/01:3000[crdat] OR 2020/01/01:3000[dp])) ((((("Copper"[tw] OR "1721 Gold"[tw] OR "3EC-M3S-HTE"[tw] OR "3EC-M3VLP18"[tw] OR "ANAC 110"[tw] OR "ATS Adocopper IW"[tw] OR "BAC 13B-NK120"[tw] OR "Bronze powder"[tw] OR "C 100 (metal)"[tw] OR "C.I. 77400"[tw] OR "C.I. Pigment Metal 2"[tw] OR "Caswell No. 227"[tw] OR "CDA 101"[tw] OR "CDA 102"[tw] OR "CDA 110"[tw] OR "CDA 122"[tw] OR "CDX (metal)"[tw] OR "CE 1110"[tw] OR "CE 7 (metal)"[tw] OR "CF-T 8GD-SV"[tw] OR "CF-T 9A-HP-STD"[tw] OR "CF-T 9B-THE"[tw] OR "CF-T 9FZ-SV"[tw] OR "CFW 100-156"[tw] OR "CI 77400"[tw] OR "CI Pigment metal 2"[tw] OR "CU M3"[tw] OR "Cu-At-W 250"[tw] OR "Cubrotec 5000"[tw] OR "Cuivre metal"[tw] OR "Cutox 6010"[tw] OR "Cutox 6030"[tw] OR "DD Paste TH 9910"[tw] OR "Double Thin F-NP"[tw] OR "DT GLMP"[tw] OR "E 115 (metal)"[tw] OR "Gold bronze"[tw] OR "GT (metal)"[tw] OR "NDP-III"[tw] OR "NT-TAX-M"[tw] OR "NT-TAX-O"[tw] OR "OFHC Cu"[tw] OR "Paragard T 380a"[tw] OR "Paragard t380a"[tw] OR "Pigment metal 2"[tw] OR "Silcoat FCC-SP 99"[tw] OR "Tatum-T"[tw] OR "Unicoat 2845"[tw] OR "USLP-SE"[tw] OR "All Clear Root Destroyer"[tw] OR "Aqua Maid Permanent Algaecide"[tw] OR "Aquatronics Snail-A-Cide Dri-Pac Snail Powder"[tw] OR "Blue stone"[tw] OR "Blue vitriol"[tw] OR "Bonide Root Destroyer"[tw] OR "Cuivrol"[tw] OR "CuSO4"[tw] OR "Delcup"[tw] OR "EarthTec"[tw] OR "Hylinec"[tw] OR "Incracide 10A"[tw] OR "Incracide E 51"[tw] OR "MAC 570"[tw] OR "Monocopper sulfate"[tw] OR "Roman vitriol"[tw] OR "Trinagle"[tw] OR "CuCl2"[tw] OR "Eriocholcite"[tw] OR "cupric"[tw] OR "cuprous"[tw] OR ("cu"[tiab] NOT ("chronic urticaria"[tiab] OR "cognitively unimpaired"[tiab] OR "callous unemotional"[tiab] OR "cocaine users"[tiab]))) NOT medline[sb]) AND (2020/01/01:3000[edat] OR 2020/01/01:3000[crdat] OR 2020/01/01:3000[dp]))) AND (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 tract" OR "respiratory organ" OR "respiratory system" OR "respiratory volume" OR "respiratory function" OR "respiratory effect" OR "respiratory organ" OR "respiratory toxicity" 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

Table B-2. Database Query Strings

Database search date	Query string
	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 system" OR "cardiovascular function" OR "cardiovascular effect" OR "cardiovascular organ" OR "cardiovascular toxicity" 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 system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" 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 system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "dermal exposure" OR "dermal contact" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin acanthosis" OR "skin exposure" OR "skin contact" OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR "endocrine system" OR "endocrine function" OR "endocrine effect" OR "endocrine gland" OR "endocrine toxicity" 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

Table B-2. Database Query Strings

Database search date	Query string
	"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" OR "mechanism of absorption" OR "mechanism of distribution" OR "mechanism of excretion" OR "mechanism of metabolism" OR "mechanism of toxic effect" OR "adverse effect" OR "adverse effects" 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 "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES 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 wistar OR wood-mouse OR zebra-fish OR zebrafish)
NTRL	
10/2023	Date Published 2019 to 2023, Title or Keyword field copper OR cupric OR cuprous
Toxcenter	
10/2023	FILE 'TOXCENTER' ENTERED AT 10:39:30 ON 04 OCT 2023 L1 325170 SEA 7440-50-8 L2 22300 SEA 10125-13-0 OR 10257-54-2 OR 10380-28-6 OR 1184-64-1 OR 12019-06-6 OR 12125-21-2 OR 13005-35-1 OR 1317-38-0 OR 1317-39-1 OR 1344-67-8 OR 1344-69-0 L3 39282 SEA 1344-70-3 OR 142-71-2 OR 17599-81-4 OR 20427-59-2 OR 4180-12-5 OR 527-09-3 OR 7447-39-4 OR 7492-68-4 OR 7758-89-6 OR 7758-98-7 OR 7758-99-8 OR 82010-82-0 L4 366811 SEA L1 OR L2 OR L3 L5 304934 SEA L4 NOT PATENT/DT L6 17407 SEA L5 AND ED>=20220804 L7 17376 SEA L6 AND PY>2018

Table B-2. Database Query Strings

Database search date	Query string
	ACT TOXQUERY/Q

	L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L23 QUE (ENDOCRIN? AND DISRUPT?)
	L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L30 QUE (NEPHROTOX? OR HEPATOTOX?)
	L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L33 QUE 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

Table B-2. Database Query Strings

Database search date	Query string
	OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 L34 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?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (NONHUMAN MAMMALS)/ORGN L38 QUE L36 OR L37 --------- L50 7690 SEA L7 AND L38 L51 871 SEA L50 AND MEDLINE/FS L52 1312 SEA L50 AND BIOSIS/FS L53 2026 DUP REM L51 L52 (157 DUPLICATES REMOVED) L*** DEL 871 S L50 AND MEDLINE/FS L*** DEL 871 S L50 AND MEDLINE/FS L54 867 SEA L53 L*** DEL 1312 S L50 AND BIOSIS/FS L*** DEL 1312 S L50 AND BIOSIS/FS L55 1159 SEA L53 L56 1159 SEA (L54 OR L55) AND BIOSIS/FS D SCAN L56 Limited to py 2019-present and entry date 7/2019-present FILE 'TOXCENTER' ENTERED AT 09:41:02 ON 04 AUG 2022 CHARGED TO COST=EH038.08.02.LB.04 DIS SAVED ACT COPPER/A --------- L1 (306093)SEA FILE=TOXCENTER 7440-50-8 L2 (19689)SEA FILE=TOXCENTER 10125-13-0 OR 10257-54-2 OR 10380-28-6 OR 1184-64-1 OR 12019-06-6 OR 12125-21-2 OR 13005-35-1 OR 1317-38-0 OR 1317-39-1 OR 1344-67-8 OR 1344-69-0 L3 (35864)SEA FILE=TOXCENTER 1344-70-3 OR 142-71-2 OR 17599-81-4 OR 20427-59-2 OR 4180-12-5 OR 527-09-3 OR 7447-39-4 OR 7492-68-4 OR 7758-89-6 OR 7758-98-7 OR 7758-99-8 OR 82010-82-0 L4 (343873)SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 (50997)SEA FILE=TOXCENTER L4 AND ED>=20190701 L6 (42493)SEA FILE=TOXCENTER L5 NOT PATENT/DT L7 (42493)SEA FILE=TOXCENTER L6 NOT TSCATS/FS L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)

Table B-2. Database Query Strings

Database search date	Query string
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L23 QUE (ENDOCRIN? AND DISRUPT?) L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L30 QUE (NEPHROTOX? OR HEPATOTOX?) L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L33 QUE 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 OR L30 OR L31 OR L32 L34 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?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE L33 OR L34 OR L35 L37 QUE (NONHUMAN MAMMALS)/ORGN L38 QUE L36 OR L37 L39 (18027)SEA FILE=TOXCENTER L7 AND L38 L40 (17269)SEA FILE=TOXCENTER L39 AND PY>2018 L41 (2479)SEA FILE=TOXCENTER L40 AND MEDLINE/FS L42 (3474)SEA FILE=TOXCENTER L40 AND BIOSIS/FS L43 (11296)SEA FILE=TOXCENTER L40 AND CAPLUS/FS L44 (20)SEA FILE=TOXCENTER L40 NOT (L41 OR L42 OR L43) L45 (15088)DUP REM L41 L42 L44 L43 (2181 DUPLICATES REMOVED) L46 (2478)SEA FILE=TOXCENTER L45 L47 (3082)SEA FILE=TOXCENTER L45 L48 (9510)SEA FILE=TOXCENTER L45 L49 (18)SEA FILE=TOXCENTER L45 L50 12610 SEA FILE=TOXCENTER (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS --------- L51 3082 SEA FILE=TOXCENTER L50 AND BIOSIS/FS

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2023	Compounds searched: 7440-50-8; 7758-98-7; 7758-99-8; 10257-54-2; 17599-81-4; 7447-39-4; 1344-67-8; 7758-89-6; 10125-13-0; 1317-39-1; 1317-38-0; 1344-70-3; 12019-06-6; 82010-82-0; 527-09-3; 13005-35-1; 4180-12-5; 142-71-2; 1344-69-0; 12125-21-2; 20427-59-2; 1184-64-1; 7492-68-4; 10380-28-6
NTP	
10/2023	Limited 2010-present "copper" "cupric" "cuprous"
Regulations.gov	
10/2023	Limited to 2019–present copper cupric cuprous
NPIRS	
1/2024	SEARCH CRITERIA Active Ingredient: Copper as elemental (CAS #: 7440-50-8) (PC Code: 22501), Copper carbonate hydroxide (CAS #: 1184-64-1) (PC Code: 22901), Copper hydroxide (CAS #: 20427-59-2) (PC Code: 23401), Copper sulfate pentahydrate (CAS #: 7758-99-8) (PC Code: 24401), Copper sulfate monohydrate (CAS #: 10257-54-2) (PC Code: 24402), Copper sulfate (anhydrous) (CAS #: 7758-98-7) (PC Code: 24408), Copper oxide, black (CAS #: 1317-38-0) (PC Code: 42401), Copper 8-hydroxyquinoline (CAS #: 10380-28-6) (PC Code: 24002), Copper oxide (Cu2O) (CAS #: 1317-39-1) (PC Code: 25601), Cuprous and cupric oxide, mixed (CAS #: 82010-82-0) (PC Code: 42403)

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Submission Date Start: 2014-01-01
NIH RePORTER	
10/2023	Search Criteria Fiscal Year: Active Projects Text Search: "copper" OR "cupric" OR "cuprous" (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): 15,262
- Number of records identified from other strategies: 183
- Total number of records to undergo literature screening: 15,445

B.1.2 Literature Screening

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

- 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.

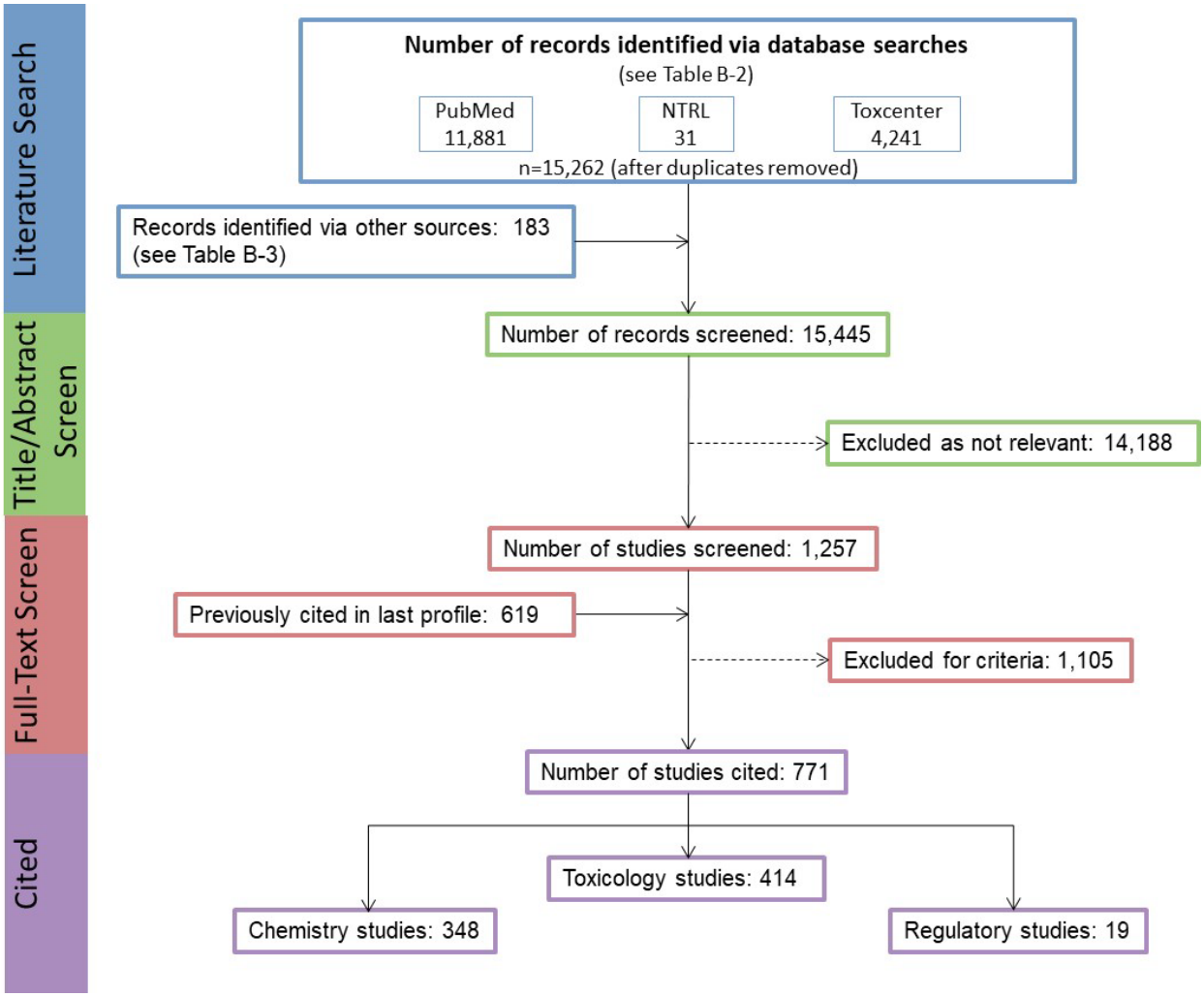
- Number of titles and abstracts screened: 15,445
- Number of studies considered relevant and moved to the next step: 1,257

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: 1,257
- Number of studies cited in the pre-public draft of the toxicological profile: 619
- Total number of studies cited in the profile: 771

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

Figure B-1. October 2023 Literature Search Results and Screen for Copper



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

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 copper, 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 copper:

- 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 copper. The inclusion criteria used to identify relevant studies examining the health effects of copper 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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of copper. 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 Copper released for public comment in 2022. See Appendix B for the databases searched and the search strategy.

A total of 15,445 records relevant to all sections of the toxicological profile were identified in the literature search (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 copper.

Title and Abstract Screen. In the Title and Abstract Screen step, 15,445 records were reviewed; 56 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 174 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 174 documents (181 studies), 57 documents (61 studies) were included in the qualitative review.

There are extensive databases of human and animal data pertaining to copper, but the quality of the data varies widely. Studies were selected for inclusion in the toxicological profile if they provided adequate information for hazard identification and/or dose-response assessment. Basic study quality criteria were

developed for epidemiological data and for animal studies using oral administration. These criteria were applied to the studies included after full-text screening, and only studies meeting these criteria were considered in the toxicological profile. There were few animal studies of inhalation exposure to copper, so all studies identified were included.

A priori Study Quality Screen for Human Studies. Several hundred human studies were identified in the literature searches. Copper is an essential mineral that occurs naturally in food and water, and humans are exposed to a range of baseline copper doses from these sources. Therefore, the most reliable hazard identification and dose-response information from human studies comes from studies of controlled exposure and/or studies of clearly elevated exposures (e.g., occupational settings where copper is the primary exposure). For this toxicological profile, all human controlled exposure studies examining health outcomes (not mechanistic endpoints) were included. Case reports and case series, while not epidemiological studies, were included in the assessment if there was clear evidence of excess exposure to copper.

For the updated profile, studies of occupational settings were included if:

- Copper was the primary exposure (by exposure concentration or industrial activity, such as copper smelting) or one of few constituents of the exposure mix were included, and exposure measures (air concentrations or biomarkers) demonstrated a differential copper exposure between groups. Examples of studies excluded by this criterion include studies of manganese workers (Ge et al. 2020, 2021, 2022), rare earth miners (Liu et al. 2021c), automotive technicians (Akinwande et al. 2021), and refinery workers (Ajeel et al. 2021).
- The referent group had lower or no exposure to copper or other heavy metals. For example, two studies (Haase et al. 2021, 2022) were excluded because the referent group used in these studies was exposed to lead dust and dust of precious metals.

After applying the criteria, four occupational studies were selected for inclusion.

Studies of populations without quantified exposure to exogenous copper were excluded. Many studies examined associations between various health outcomes and copper concentrations in urine, serum/blood, hair, nails, or other physiological fluids or tissues in the general population. These studies did not distinguish between conditions of copper deficiency, adequacy, and excess, and as such, do not inform hazard identification. In addition, perturbation of copper homeostasis may result from various health conditions, leading to the potential for reverse causation or confounding in these studies.

For the updated profile, human epidemiological studies of the general population (non-occupational settings) were included if they met the following criteria:

- Copper concentration in food, water, or air was measured or estimated for individual subjects in the study (e.g., ecological study designs were not included).
- Exposure was not measured after outcome.
- The statistical analysis of the association considered at least one potential covariate. Studies limited to bivariate analyses (i.e., Pearson or Spearman correlation coefficients), or analyses limited to comparison between copper concentrations/biomarkers in cases and controls were not included.

Applying the criteria above resulted in the selection of 11 studies of general population exposure.

A priori Study Quality Screen for Animal Studies using Oral Administration. Among animal toxicity studies using oral administration identified in the literature searches, the quality of the studies varied widely. For example, some studies did not report the form of copper administered, some reported the

dose or concentration inconsistently, and some did not clearly distinguish between mg/kg body weight and mg/kg diet. Many studies administered copper in diet or drinking water without reporting intake levels. Water intake (but not dietary intake) was shown to decrease with increasing copper concentration (NTP 1993), so reference intake rates may overestimate the dose of copper from drinking water studies.

Of the animal studies using oral administration, studies were included in the profile if:

- The form of copper (compound) administered was clearly reported.
- The concentration(s) or dose(s) were consistently reported as either the compound (e.g., mg $CuSO_4$/kg) or as copper (mg Cu/kg).
- When reported as mg/kg, the study clearly reported the value as mg/kg body weight or mg/kg diet.
- The dose of copper or copper compound administered was reported or could be reliably estimated. Studies that used drinking water administration but did not provide water intake information were not included.
- Additionally, a number of studies examined animals with genetic defects similar to Wilson's disease (e.g., Long-Evans Cinnamon rats and Bedlington terrier dogs) were not included.

Applying these criteria resulted in the selection of 82 animal oral toxicity studies for inclusion in the toxicological profile.

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)

Table C-2. Data Extracted From Individual Studies

No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Documents for copper and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels of Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for copper identified in human and animal studies are presented in Table C-3 and C-4, respectively. The available human toxicity studies primarily evaluated the gastrointestinal endpoint including in controlled-exposure studies. Observational and controlled-exposure cohort studies and population level studies have examined a wide range of endpoints in humans. Animal studies examined all endpoints following oral exposure to copper. A very limited number of animal studies examined toxicity following inhalation exposure. Gastrointestinal and hepatic effects were considered sensitive outcomes of oral copper exposure, as effects were observed at low doses in humans and animals and are commonly reported in case reports of human exposures. Respiratory effects were considered a sensitive outcome of inhalation copper exposure because they were seen at low exposure levels in animals and reported in some occupational studies of inhalation exposure. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. Case reports and case series, as well as community and occupational health investigations that did not include referent groups, were not included in the formal systematic review due to inherent high risk of bias and low confidence based on study design. However, consistent findings from these studies were considered during the adjustment of the confidence rating (with regards to consistency and/or severity of observed effects). There were 61 studies (published in 57 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 Copper Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other noncancer	Cancer
Inhalation Studies																	
Cohort		3 1	2 1									1 1					1 1
Case Control												1 1			1 0		
Population		5 4	2 2	1 1	1 1		1 1		1 1	1 1	1 1		1 1	1 1		2 2	
Case Series		8 8		1 1	1 1		1 1	1 1					1 1				
Oral Studies																	
Cohort			1 1	1 0									1 1				
Case Control	2 0		1 0	9 8	2 0		7 0					1 1	1 1				
Population			3 0	1 0	2 2		1 0						2 1			1 0	
Case Series		9 9	10 10	15 15	20 20	2 2	19 19	19 19	6 6		3 3	2 2	4 4				
Dermal Studies																	
Cohort																	
Case Control																	
Population																	
Case Series					1 1		1 1		2 2			4 4					

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 Copper Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other noncancer	Cancer
Inhalation Studies																	
Acute-duration		4 3										2 2					
Intermediate-duration	1 0	3 1			1 0		1 0	1 0				1 0	1 0				
Chronic-duration																	
Oral Studies																	
Acute-duration	1 1		1 1	2 2			4 4	4 3						6 4	1 0		
Intermediate-duration	31 17	8 1	10 3	7 5	10 8	2 1	27 19	16 12			6 0	6 3	17 11	22 16	5 3	1 1	
Chronic-duration	2 0				1 1		1 0										
Dermal Studies																	
Acute-duration																	
Intermediate-duration																	
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

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?

For the copper profile, the OHAT guidance on the question "Is there confidence in the exposure characterization?" was interpreted to only detract modestly from the rating in consideration of reporting of copper purity in studies. Studies were rated as probably low risk of bias (+) on this question if purity was not reported but the study does report that the test article was obtained from a commercial supplier of research chemicals, and if there is nothing in the study suggesting a risk of the test article decomposition during dosing or storage.

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 copper health effects studies (observational epidemiology, 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 Copper—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: Gastrointestinal effects							
Cohort studies							
Buchanan et al. 1999	+	+	–	–	–	++	Second
Pettersson et al. 2003	++	+	+	+	+	++	First
Case-control studies							
Buchanan et al. 1999	+	+	++	+	+	++	First
Outcome: Hepatic effects (no studies)							
Outcome: Respiratory effects							
Cohort studies							
Boogaard et al. 2013	++	+	–	–	++	++	Second
Gehring et al. 2015	++	+	+	–	+	++	First
Yu et al. 2021b	++	+	+	–	+	++	First

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

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Cross-sectional studies							
Fouad and Ramadan 2022	+	–	+	–	+	++	Second
Saadiani et al. 2023	+	–	+	–	+	++	Second
Mourad and El-Sherif 2022	+	–	+	–	–	++	Second

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

Table C-9. Summary of Risk of Bias Assessment for Copper–Human-Controlled Exposure 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 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: Gastrointestinal effects (oral only)								
Oral acute exposure								
Araya et al. 2001	++	++	++	+	+	+	++	First
Araya et al. 2003a	++	++	++	++	+	+	++	First
Araya et al. 2003c	++	++	++	+	+	+	++	First
Gotteland et al. 2001	++	++	++	++	–	+	++	First
Olivares et al. 2001	+	+	+	+	–	+	++	First
Pizarro et al. 1999	++	++	++	++	+	+	++	First
Pizarro et al. 2001	++	++	++	++	–	+	++	First
Oral intermediate exposure								
Araya et al. 2003b, 2004	++	++	++	++	–	+	++	First
Olivares et al. 1998	–	–	+	+	–	–	++	Second
Pratt et al. 1985	+	++	++	+	–	–	–	Second
Outcome: Hepatic effects (oral only)								
Oral acute exposure								
Pizarro et al. 1999	++	++	++	++	+	+	++	First
Pizarro et al. 2001	++	++	++	+	–	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Copper–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
Oral intermediate exposure								
Araya et al. 2003b, 2004	++	++	++	++	–	+	++	First
O'Connor et al. 2003	++	++	++	++	–	+	++	First
Olivares et al. 1998	–	–	+	+	–	–	++	Second
Pratt et al. 1985	+	++	++	+	–	–	–	Second
Rojas-Sobarzo et al. 2013	++	++	++	+	++	+	++	First
Outcome: Respiratory effects (no studies)								

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

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Gastrointestinal effects (oral only)									
Oral acute exposure									
Husain et al. 2021 (rat)	–	+	+	+	+	–	+	+	First
Yamamoto et al. 2004 (shrew)	–	+	+	+	–	–	++	++	First
Oral intermediate exposure									
Chung et al. 2009 (rat)	+	+	+	+	+	–	+	+	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 13 weeks, feed)	+	+	++	+	++	++	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–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: Hepatic effects									
Inhalation acute exposure									
Poland et al. 2022 (rat, sulfate)	++	+	+	+	++	++	++	++	First
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Oral acute exposure									
Alhusaini et al. 2018a (rat)	+	+	–	–	++	+	+	++	First
Alhusaini et al. 2018b (rat)	–	+	–	–	++	+	+	++	First
Haywood 1980 (rat)	–	+	+	+	+	–	+	+	First
Haywood and Comerford 1980 (rat)	–	+	+	+	++	–	+	+	First
Oral intermediate exposure									
Abe et al. 2008 (rat)	+	+	++	–	+	+	+	++	First
Adele et al. 2023 (rat)	–	+	–	+	++	–	+	+	First
Chung et al. 2009 (rat)	+	+	+	+	+	+	+	+	First

Table C-10. Summary of Risk Bias Assessment for Copper–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?	
Dab et al. 2023 (mouse)	–	+	+	+	++	+	+	+	First
Epstein et al. 1982 (rat)	+	+	++	–	++	–	++	++	First
Fuentealba et al. 2000 (rat)	–	+	–	+	+	–	+	–	Second
Haywood 1980 (rat)	–	+	+	+	+	–	+	+	First
Haywood and Comerford 1980 (rat)	–	+	+	+	++	–	+	+	First
Haywood and Loughran 1985 (rat)	–	+	+	+	+	– –	+	+	First
Kumar et al. 2015, 2016a, 2016b (rat)	+	+	++	+	+	+	++	++	First
Kumar and Sharma 1987 (rat)	+	+	–	+	– –	–	+	++	First
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	+	+	+	+	+	–	+	–	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–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 1993 (rat, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat,13 weeks, feed)	+	+	++	+	++	++	++	++	First
Patwa and Flora 2020 (rat)	–	+	–	+	++	+	+	+	First
Rana and Kumar 1980 (rat)	– –	+	–	–	–	–	+	++	Second
Sakhaee et al. 2012 (rat)	+	+	++	–	+	–	+	++	First
Sakhaee et al. 2014 (mouse)	+	+	++	+	+	–	+	++	First
Seven et al. 2018 (rat)	+	+	–	–	+	+	+	++	First
Sugawara et al. 1995 (rat)	+	+	+	+	++	– –	+	+	First
Suttle and Mills 1966 (pig, Experiment 1)	++	+	++	+	++	–	++	++	First
Suttle and Mills 1966 (pig, Experiment 2)	++	+	++	+	++	–	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–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
Temiz et al. 2021 (rat)	+	+	–	+	++	–	+	+	First
Wu et al. 2020 (mouse)	–	+	++	–	++	+	+	++	First
Yu et al. 2021a (rat)	+	+	–	+	+	– –	+	+	First
Zhang et al. 2020 (pig)	+	+	+	+	+	–	+	+	First
Oral chronic exposure									
Araya et al. 2012 (monkey)	+	+	+	–	++	–	+	++	First
Outcome: Respiratory effects									
Inhalation acute exposure									
Poland et al. 2022 (rat, sulfate)	++	+	+	+	++	++	++	++	First
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Johansson et al. 1983 (rabbit)	+	+	+	+	+	–	+	+	First
Johansson et al. 1984 (rabbit)	+	+	+	+	+	–	+	+	First

Table C-10. Summary of Risk Bias Assessment for Copper–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
Oral intermediate exposure									
Chung et al. 2009 (rat)	+	+	+	+	+	+	+	+	First
Draper et al. 2023 (rat)	++	+	++	+	++	++	++	+	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	+	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 15 days, water)	+	+	++	+	+	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat,13 weeks, feed)	+	+	++	+	++	++	++	++	First

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

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to copper 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 copper 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 gastrointestinal and neurological health 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.

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.

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

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	Initial study confidence
Outcome: Gastrointestinal effects					
Cohort studies					
Buchanan et al. 1999	No	Yes	Yes	Yes	Moderate
Pettersson et al. 2003	No	Yes	Yes	Yes	Moderate
Case-control studies					
Buchanan et al. 1999	No	Yes	Yes	Yes	Moderate
Outcome: Hepatic effects (no studies)					
Outcome: Respiratory effects					
Cohort studies					
Boogaard et al. 2013	No	Yes	Yes	Yes	Moderate
Gehring et al. 2015	No	Yes	Yes	Yes	Moderate
Yu et al. 2021b	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Fouad and Ramadan 2022	No	Yes	Yes	Yes	Moderate
Saadiani et al. 2023	No	Yes	Yes	Yes	Moderate
Mourad and El-Sherif 2022	No	Yes	Yes	Yes	Moderate

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

Reference	Key feature: Concurrent Control Group	Sufficient number of subjects per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Gastrointestinal effects					
Oral acute exposure					
Araya et al. 2001	Yes	Yes	Yes	Yes	High
Araya et al. 2003a	Yes	Yes	Yes	Yes	High
Araya et al. 2003c	Yes	Yes	Yes	Yes	High
Gotteland et al. 2001	Yes	Yes	Yes	Yes	High

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

Reference	Key feature: Concurrent Control Group	Key feature: Sufficient number of subjects per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Olivares et al. 2001	Yes	Yes	Yes	Yes	High
Pizarro et al. 1999	Yes	Yes	Yes	Yes	High
Pizarro et al. 2001	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Araya et al. 2003b, 2004	Yes	Yes	Yes	Yes	High
Olivares et al. 1998	Yes	Yes	Yes	Yes	High
Pratt et al. 1985	Yes	No	No	No	Very Low
Outcome: Hepatic effects					
Oral acute exposure					
Pizarro et al. 1999	Yes	Yes	No	Yes	Moderate
Pizarro et al. 2001	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Araya et al. 2003b, 2004	Yes	Yes	No	Yes	Moderate
O'Connor et al. 2003	Yes	Yes	No	Yes	Moderate
Olivares et al. 1998	Yes	Yes	No	Yes	Moderate
Pratt et al. 1985	Yes	No	No	No	Very Low
Rojas-Sobarzo et al. 2013	Yes	Yes	No	Yes	Moderate
Outcome: Respiratory effects (no studies)					

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Gastrointestinal effects					
Oral acute exposure					
Husain et al. 2021 (rat)	Yes	No	Yes	No	Low
Yamamoto et al. 2004 (shrew)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Chung et al. 2009 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat,13 weeks, feed)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Poland et al. 2022 (rat, sulfate)	Yes	No	No	No	Very Low
Poland et al. 2022 (rat, oxide)	Yes	No	No	No	Very Low
Inhalation intermediate exposure					
Poland et al. 2022 (rat, oxide)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Alhusaini et al. 2018a (rat)	Yes	No	Yes	Yes	Moderate
Alhusaini et al. 2018b (rat)	Yes	No	Yes	Yes	Moderate
Haywood 1980 (rat)	Yes	No	Yes	No	Low
Haywood and Comerford 1980 (rat)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Abe et al. 2008 (rat)	Yes	No	Yes	Yes	Moderate
Adele et al. 2023 (rat)	Yes	No	No	Yes	Low
Chung et al. 2009 (rat)	Yes	Yes	Yes	No	Moderate
Dab et al. 2023 (mouse)	Yes	No	No	Yes	Low

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Epstein et al. 1982 (rat)	Yes	No	Yes	Yes	Moderate
Fuentealba et al. 2000 (rat)	Yes	No	Yes	No	Low
Haywood 1980 (rat)	Yes	No	Yes	No	Low
Haywood and Comerford 1980 (rat)	Yes	No	No	Yes	Low
Haywood and Loughran 1985 (rat)	Yes	Yes	Yes	No	Moderate
Kumar et al. 2015, 2016a, 2016b (rat)	Yes	Yes	Yes	Yes	High
Kumar and Sharma 1987 (rat)	Yes	Yes	No	No	Low
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	Yes	No	Yes	No	Low
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat,13 weeks, feed)	Yes	Yes	Yes	Yes	High
Patwa and Flora 2020 (rat)	Yes	No	Yes	Yes	Moderate
Rana and Kumar 1980 (rat)	Yes	Yes	Yes	Yes	High
Sakhaee et al. 2012 (rat)	Yes	Yes	Yes	Yes	High
Sakhaee et al. 2014 (mouse)	Yes	Yes	No	Yes	Moderate
Seven et al. 2018 (rat)	Yes	No	Yes	Yes	Moderate
Sugawara et al. 1995 (rat)	Yes	No	No	Yes	Low
Suttle and Mills 1966 (pig, Experiment 1)	Yes	No	No	Yes	Low
Suttle and Mills 1966 (pig, Experiment 2)	Yes	No	No	Yes	Low
Temiz et al. 2021 (rat)	Yes	No	Yes	Yes	Moderate
Wu et al. 2020 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Yu et al. 2021a (rat)	Yes	Yes	Yes	Yes	High
Zhang et al. 2020 (pig)	Yes	No	Yes	Yes	Moderate
Oral chronic exposure					
Araya et al. 2012 (monkey)	Yes	No	Yes	Yes	Moderate
Outcome: Respiratory effects					
Inhalation acute exposure					
Poland et al. 2022 (rat, sulfate)	Yes	No	Yes	Yes	Moderate
Poland et al. 2022 (rat, oxide)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Poland et al. 2022 (rat, oxide)	Yes	Yes	Yes	Yes	High
Johansson et al. 1983 (rabbit)	Yes	No	Yes	No	Low
Johansson et al. 1984 (rabbit)	Yes	No	Yes	No	Low
Oral intermediate exposure					
Chung et al. 2009 (rat)	Yes	Yes	Yes	Yes	High
Draper et al. 2023 (rat)	Yes	No	Yes	No	Low
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 13 weeks, feed)	Yes	Yes	Yes	Yes	High

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

	Initial study confidence	Initial confidence rating
Outcome: Gastrointestinal effects		
Oral acute exposure		
Animal Studies		
Husain et al. 2021	Low	Moderate
Yamamoto et al. 2004 (shrew)	Moderate	
Human studies		
Araya et al. 2001	High	High
Araya et al. 2003a	High	
Araya et al. 2003c	High	
Gotteland et al. 2001	High	
Olivares et al. 2001	High	
Pizarro et al. 1999	High	
Pizarro et al. 2001	High	
Oral intermediate exposure		
Animal studies		
Chung et al. 2009	High	High
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 day, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat,13 weeks, feed)	High	
Human studies		
Araya et al. 2003b, 2004	High	High
Olivares et al. 1998	High	
Pratt et al. 1985	Very Low	
Buchanan et al. 1999	Moderate	
Pettersson et al. 2003	Moderate	
Buchanan et al. 1999	Moderate	
Outcome: Hepatic Effects		
Inhalation acute exposure		
Animal studies		
Poland et al. 2022 (rat, sulfate)	Very Low	Very Low
Poland et al. 2022 (rat, oxide)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Poland et al. 2022 (rat, oxide)	Moderate	Moderate
Oral acute exposure		
Animal studies		
Alhusaini et al. 2018a (rat)	Moderate	Moderate

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

	Initial study confidence	Initial confidence rating
Alhusaini et al. 2018b (rat)	Moderate	
Haywood 1980 (rat)	Low	
Haywood and Comerford 1980 (rat)	Low	
Human studies		
Pizarro et al. 1999	Moderate	Moderate
Pizarro et al. 2001	Moderate	
Oral intermediate exposure		
Animal studies		
Abe et al. 2008 (rat)	Moderate	High
Adele et al. 2023 (rat)	Low	
Chung et al. 2009 (rat)	Moderate	
Dab et al. 2023 (mouse)	Low	
Epstein et al. 1982 (rat)	Moderate	
Fuentealba et al. 2000 (rat)	Low	
Haywood 1980 (rat)	Low	
Haywood and Comerford 1980 (rat)	Low	
Haywood and Loughran 1985 (rat)	Moderate	
Kumar et al. 2015, 2016a, 2016b (rat)	High	
Kumar and Sharma 1987 (rat)	Low	
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	Low	
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 days, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat,13 weeks, feed)	High	
Patwa and Flora 2020 (rat)	Moderate	
Rana and Kumar 1980 (rat)	High	
Sakhaee et al. 2012 (rat)	High	
Sakhaee et al. 2014 (mouse)	Moderate	
Seven et al. 2018 (rat)	Moderate	
Sugawara et al. 1995 (rat)	Low	
Suttle and Mills 1966 (pig, Experiment 1)	Low	
Suttle and Mills 1966 (pig, Experiment 2)	Low	
Temiz et al. 2021 (rat)	Moderate	
Wu et al. 2020 (mouse)	High	
Yu et al. 2021a (rat)	High	
Zhang et al. 2020 (pig)	Moderate	

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

	Initial study confidence	Initial confidence rating
Human studies		
Araya et al. 2003b, 2004	Moderate	Moderate
O'Connor et al. 2003	Moderate	
Olivares et al. 1998	Moderate	
Pratt et al. 1985	Very Low	
Rojas-Sobarzo et al. 2013	Moderate	
Oral chronic exposure		
Animal studies		
Araya et al. 2012 (monkey)	Moderate	Moderate
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Poland et al. 2022 (rat, sulfate)	Moderate	Moderate
Poland et al. 2022 (rat, oxide)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Poland et al. 2022 (rat, oxide)	High	High
Johansson et al. 1983 (rabbit)	Low	
Johansson et al. 1984 (rabbit)	Low	
Inhalation intermediate exposure		
Human studies		
Boogaard et al. 2013	Moderate	Moderate
Gehring et al. 2015	Moderate	
Yu et al. 2021b	Moderate	
Fouad and Ramadan 2022	Moderate	
Saadiani et al. 2023	Moderate	
Mourad and El-Sherif 2022	Moderate	
Oral intermediate exposure		
Animal studies		
Chung et al. 2009 (rat)	High	High
Draper et al. 2023 (rat)	Low	
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 days, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat, 13 weeks, feed)	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for gastrointestinal and hepatic effects 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 copper 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: Gastrointestinal effects			
Human studies	High	+1 Consistency in the body of evidence	High
Animal studies	High	+1 Consistency in the body of evidence	High
Outcome: Hepatic effects			
Human studies	Moderate	-1 Indirectness: length of time between exposure and outcome assessment	Low
Animal studies	High	+1 Consistency in the body of evidence	High
Outcome: Respiratory effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High	None	High

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

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Gastrointestinal effects	High	High
Hepatic effects	Low	High
Respiratory effects	Low	High

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9, and C-10). 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 copper, 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 copper is presented in Table C-20.

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

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human Studies			
Gastrointestinal effects	High	Health effect	High
Hepatic effects	Low	No health effect	Inadequate
Respiratory effects	Low	Health effect	Low
Animal Studies			
Gastrointestinal effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Respiratory effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

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

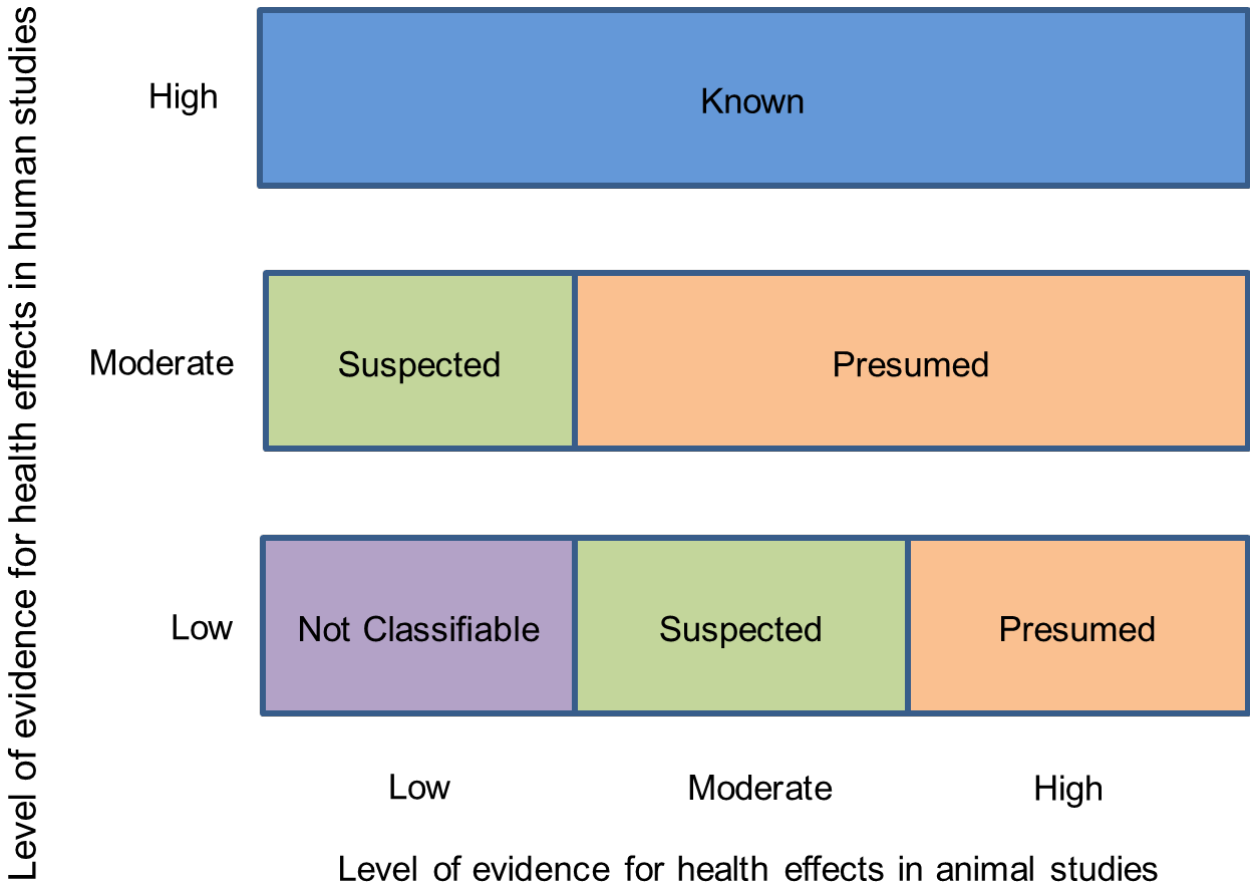
The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the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

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**

- Low level of evidence in human studies **AND** moderate level of evidence in animal studies

- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



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

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

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

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. 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 copper are listed below and summarized in Table C-21.

Known Health Effects

- High level of evidence for gastrointestinal effects in humans exposed orally in controlled-exposure studies of acute-duration exposure to copper sulfate in drinking water (Araya et al. 2001, 2003a; Pizarro et al. 1999, 2001) and intermediate-duration exposure to copper sulfate in drinking water or other juice (Araya et al. 2003b, 2003c, 2004; Olivares et al. 2001). Supporting information comes from case reports/series (Banerjee et al. 2023; Bupta et al. 2023; Du and Mou 2019; Franchitto et al. 2008; Galust et al. 2023; Gamakaranage et al. 2011; Griswold et al. 2017; Hassan et al. 2010; Higny et al. 2014; Lubica et al. 2017; Malik and Mansur 2011; Shankar et al. 2023; Tsao et al. 2020) and community health investigations (Knobeloch et al. 1994, 1998).
- High level of evidence for gastrointestinal effects in mice, rats, and shrews from acute-duration exposure to copper chloride or copper sulfate (Husain et al. 2021; Yamamoto et al. 2004); and intermediate-duration exposure to copper monochloride or copper sulfate pentahydrate (Chung et al. 2009; NTP 1993).

Presumed Health Effects

Respiratory

- Low level of evidence for respiratory effects in humans exposed via inhalation based on epidemiological studies (Boogaard et al. 2013; Fouad and Ramadan 2022; Gehring et al. 2015; Mourad and El-Sherif 2022; Saadiani et al. 2023; Yu et al. 2021b). Supporting information comes from occupational health investigations (Askergren and Mellgren 1975; Plamenac et al. 1985; Suciu et al. 1981) and case reports of inhalation exposure (Donoso et al. 2007; Pimentel and Marques 1969; Pimentel and Menezes 1975; Stark 1981; Villar 1974; Villar and Nogueira 1980).
- High level of evidence for respiratory effects in rats exposed by inhalation for acute durations to copper sulfate pentahydrate or dicopper oxide (Poland et al. 2022) and for an intermediate duration to dicopper oxide (Poland et al. 2022). Respiratory effects were also seen in rats exposed orally to copper sulfate pentahydrate for an intermediate duration (Draper et al. 2023).

Hepatic

- Low level of evidence for hepatic effects in human studies; no changes in hepatic enzyme levels were observed after acute-duration (Pizarro et al. 1999, 2001) or intermediate-duration oral exposure to copper sulfate (Araya et al. 2003b, 2004; O'Connor et al. 2003; Olivares et al. 1998; Rojas-Sobarzo et al. 2013) or copper gluconate (Pratt et al. 1985). Information from occupational health investigations (Suciu et al. 1981), case reports (Du and Mou 2019; Griswold et al. 2017; Gunay et al. 2006; Hassan et al. 2010; Malik and Mansur 2011; Mortazavi and Jafari-Javid 2009; Shankar et al. 2023; Sinkovic et al. 2008; Yadla et al. 2015; Yang et al. 2004), and human mutations that result in copper accumulation suggest that hepatic effects are possible.
- High level evidence of effects in rats and mice exposed to copper compounds via oral administration for acute (Alhusaini et al. 2018a, 2018b; Haywood 1980; Haywood and Comerford 1980) and intermediate durations (Dab et al. 2023; Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980; Haywood and Comerford 1980; Haywood and Loughran 1985; Kumar et al. 2015, 2016a, 2016b; Kumar and Sharma 1987; Liu et al. 2020a, 2020b, 2021a, 2021b; NTP 1993; Patwa and Flora 2020; Rana and Kumar 1980; Sakhaee et al. 2012, 2014; Seven et al. 2018; Sugawara et al. 1995; Temiz et al. 2021; Wu et al. 2020; Yu et al. 2021a) and in pigs after intermediate-duration oral exposure (Suttle and Mills 1966).

Table C-21. Hazard Identification Conclusions for Copper

Outcome	Hazard identification
Gastrointestinal effects	Known
Hepatic effects	Presumed
Respiratory effects	Presumed

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

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

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

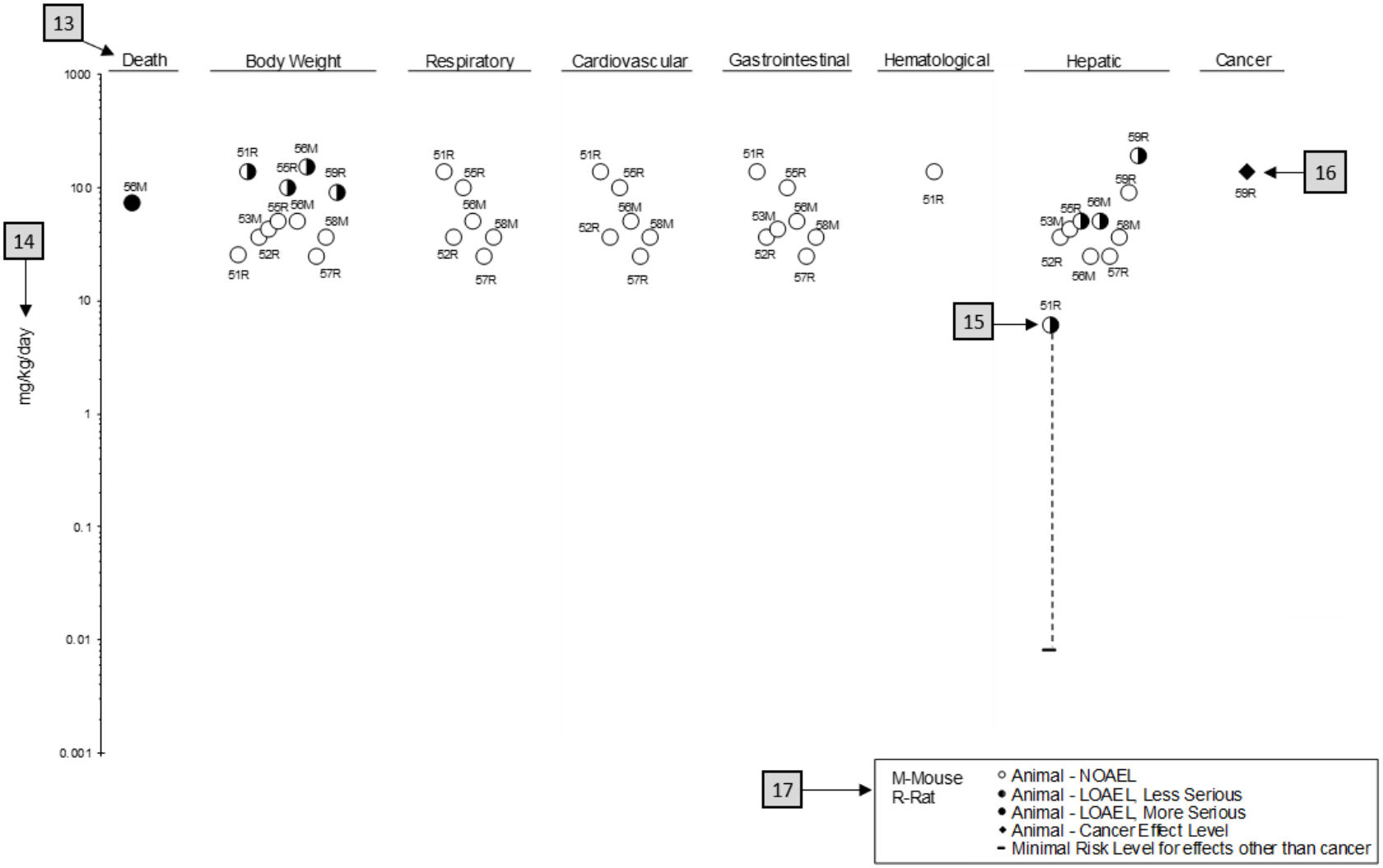
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

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

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

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or 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