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*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration inhalation MRL. Available data for hydrogen cyanide indicate serious adverse effects occurring at the lowest reported adverse effect levels in both humans and animals.

Rationale for Not Deriving an MRL: Available human data are limited to case reports of exposure to hydrogen cyanide, most of which do not have exposure data. Studies with exposure data indicate brief exposures to 200–452 ppm are associated with serious neurological effects (coma with slight loss of peripheral vision after recovery, brain damage), metabolic effects (lactic acidosis indicative of impaired respiration), and death (Bonsall 1984; Singh et al. 1989). These studies are not considered suitable for MRL derivation.

Reliable NOAELs and LOAELs identified for hydrogen cyanide in acute-duration inhalation studies in animals are shown in Table A-1. The only effect noted below the lowest reported LC_{50} value of 143 ppm (Ballantyne 1983a) was depressed respiration; the calculated DC_{50} (estimated concentration associated with a 50% decrease in the respiratory rate) in mice was 63 ppm (Matijak-Schaper and Alarie 1982). This effect was considered a serious LOAEL; therefore, it is not considered suitable as the basis for the acute-duration inhalation MRL. A study of auditory function and histology in rats by Fechter et al. (2002) reported a no-observed-adverse-effect level (NOAEL) of 50 ppm hydrogen cyanide for a 3.5-hour exposure (some deficits were observed when hydrogen cyanide exposure was concurrent with noise exposure). However, the study by Fechter et al. (2002) is not suitable for derivation of an MRL because the ear was the only organ evaluated in this study; therefore, the identified NOAEL may not be protective of more sensitive effects of hydrogen cyanide exposure.

In addition to the reliable studies reported in Table A-1, a study in monkeys reported neurological impairments, cardiological effects, and respiratory distress following exposure to ≥100 ppm for 30 minutes (Purser et al. 1984). However, due to critical study design deficiencies (one monkey/group; no control group), NOAEL and LOAEL values were not established. Therefore, this study is not suitable for MRL derivation.

Table A-1. NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Hydrogen Cyanide

		Effect level (ppm hydrogen cyanide)			
Species	Duration	NOAEL	SLOAEL	Effect	Reference
Rat	3.5 hours	50			Fechter et al. 2002
Mouse	30 minutes		63	Calculated DC_{50} (estimated 50% decrease in respiratory rate)	Matijak-Schaper and Alarie 1982

Table A-1. NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Hydrogen Cyanide

Species	Duration	Effect level (ppm hydrogen cyanide) NOAEL	SLOAEL	Effect	Reference
Mouse	40 minutes		327	33% lethality; clinical signs of toxicity in survivors (gasping, labored breathing, lethargy, loss of righting reflex, convulsions, tremors)	Ma et al. 2021
Mouse	3 minutes		400	90% lethality	Hume et al. 1995

DC_{50} = concentration associated with 50% depression in respiratory rate; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data to support derivation of an intermediate-duration inhalation MRL. The database for hydrogen cyanide is limited to one occupational study in humans (Blanc et al. 1985), a single-exposure level study in rats with a very limited scope (O'Flaherty and Thomas 1982), and a series of a poorly-reported studies in dogs (Valade 1952).

Rationale for Not Deriving an MRL: The intermediate-duration inhalation database for hydrogen cyanide is very limited. The only identified human study, a human occupational study by Blanc et al. (1985), is not considered adequate for MRL derivation. This study evaluated former workers from a silver reclaiming factory reporting an average employment of an intermediate-duration (11 months). Based on worker-recall 7–30 months post-employment, subjective symptoms experienced during employment included decreased weight, loss of appetite, respiratory irritation, chest pain, nausea or vomiting, skin rash (which persisted in some post-employment), eye irritation, headache, dizziness, and fatigue; skin rash and headache persisted in some post-employment. When evaluated 7–30 months after exposure ceased, serum thyroid-stimulating hormone (TSH) levels were elevated compared to laboratory reference values. Major limitations of this study include exposure levels measured only at one point in time after the factory shut down (15 ppm) and either reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment or assessment of endpoints only 7–30 months after exposure ceased.

Only one intermediate-duration animal study evaluating hydrogen cyanide was considered adequate to make a NOAEL/LOAEL determination. This study in rats evaluated potential cardiovascular effects of brief, intermittent exposure to hydrogen cyanide (12.5 minutes/day at 4-day intervals) over a 20-day period (O'Flaherty and Thomas 1982). The study reported evidence of potential cardiovascular damage (increased serum creatine phosphokinase [CPK] activity 2-hours post exposure) at the only exposure concentration of 200 ppm. However, CPK levels did not show any time-dependence (findings were not dependent upon the number of previous exposures), suggesting that observations may reflect acute exposures rather than cumulative exposure over the 20-day experimental duration. Changes in CPK activity were not associated with any histopathological changes in the heart at the end of the exposure period. Due to the limited scope of this study, it is not considered adequate for the derivation of an intermediate-duration MRL for cyanide in the absence of support from additional studies.

Other intermediate-duration inhalation data for hydrogen cyanide are restricted to a series of a poorly-reported studies in dogs intermittently exposed to 50 ppm for 28–96 days (Valade 1952). Effects noted by the study authors included lethality, serious neurological effects (tremors, ataxia, brain atrophy), gastrointestinal effects, and dyspnea. However, due to poor reporting of study design and results and lack of a control group, interpretation of the study results (e.g., number of affected animals at different timepoints) was not possible. Most notably, it is unclear if reported deaths were attributable to exposure, as some appeared to occur long after the exposure period ceased. Thus, due to poor data reporting, this study was considered inadequate for NOAEL/LOAEL determination or the derivation of an intermediate-duration MRL for cyanide.

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data to support derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived for cyanide because of the lack of suitable data in humans; no animal data were identified. The human chronic-duration inhalation database for cyanide is limited to occupational studies in workers in electroplating and metal processing jobs (Banerjee et al. 1997; Chandra et al. 1988; El Ghawabi et al. 1975; Janagam et al. 2008; Knoblauch et al. 2020; Kumar et al. 1992). Collectively, these studies have reported associations between some adverse effects and occupational exposure to cyanide, primarily neurological, respiratory, and thyroid effects with limited evidence for hematological and hepatic effects. However, the available occupational studies were not considered adequate for deriving a chronic-duration inhalation MRL for one or more of the following reasons:

- Limited or lack of information on exposure levels
- Small size of cohort
- Probable concurrent dermal exposure with liquid cyanide
- Concurrent exposure to other compounds (e.g., gasoline, hydrochloric acid, copper cyanide)

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration oral MRL. Human studies are limited to case reports. Most acute-duration oral studies in animals administered cyanide via oral bolus administration, which is considered less relevant to human exposure (due to saturation of detoxification pathways). Only one acute-duration drinking water study in animals was identified (de Sousa et al. 2007); however, this study was not considered suitable for MRL derivation due to study limitations precluding reliable NOAEL/LOAEL determinations.

Rationale for Not Deriving an MRL: Endpoints identified as potential sensitive effects of cyanide following oral exposure based on human and animal studies (thyroid, neurological, male reproductive effects) were considered as candidate critical effects for the acute-duration oral MRL for cyanide.

No adequate acute-duration human data were available; human studies are limited to case reports following intentional (homicide/suicide) or accidental exposure. For animal data, studies that employed bolus (e.g., gavage) dosing are omitted from MRL consideration because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures from dietary sources or drinking water for the general population. The only acute-duration oral toxicity data for cyanide following drinking water exposure in animals are provided by a series of studies by de Sousa et al. (2007). In these studies, rat dams were exposed to 0.2–6.4 mg CN^-/kg/day as potassium thiocyanate or 0.4–12 mg CN^-/kg/day as potassium cyanide on GDs 6–20. Relevant to the candidate critical endpoints discussed above, brains and thyroid glands were evaluated for histopathological changes in dams and their offspring on GD 20 (dams only) or PND 22. As discussed in Section 2.13, thyroid effects noted in this study (increased resorption vacuoles) are of uncertain biological relevance, and are therefore not suitable as the basis for an MRL. Neurological findings following exposure to potassium thiocyanate included brain gliosis in dams on GD 20 or PND 22 at ≥0.6 mg CN^-/kg/day, CNS congestion and neuronophagia in dams on GD 20 or PND 22 at 6.4 mg CN^-/kg/day, and brain gliosis, neuronophagia, and CNS congestion in PND 22 offspring at 6.4 mg CN^-/kg/day. Neurological findings following exposure to potassium cyanide at 12 mg CN^-/kg/day included hemorrhagic areas, gliosis, necrosis, neuronophagia, and CNS congestion in dams at GD 20 and PND 22 and gliosis, neuronophagia, and CNS congestion in PND 22 pups. However, neurological findings from this study were not considered suitable for MRL derivation for the following reasons:

- Study limitations of de Sousa et al. (2007): Incidence data were not reported. Rather, lesion intensity was reported only when all animals in a dose group showed the same alteration. This method of reporting allowed identification of adverse effects; however, it did not allow for reliable NOAEL/LOAEL identification. Additionally, only a small number of animals (four per group) underwent histological evaluation.

- Acute-duration oral database limitations: Only a single acute-duration drinking water study was identified.

- Oral database inconsistencies: Findings of brain lesions were not confirmed in longer-duration studies. No histopathological brain lesions were observed in adult rats or mice following exposure to sodium cyanide in drinking water for 13 weeks at doses up to 12.5 or 28.8 mg CN^-/kg/day, respectively (NTP 1993).

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Cyanide and compounds
CAS Numbers:	Various
Date:	October 2024
Profile Status:	Draft for Public Comment
Route:	Oral
Duration:	Intermediate
Provisional MRL:	0.04 mg/kg/day
Critical Effect:	Thyroid effects (elevated thyroid weight, decreased serum T4)
Reference:	Tyner and Greeley 2023
Point of Departure:	3.96 mg CN^-/kg/day
Uncertainty Factor:	100
LSE Graph Key:	34
Species:	Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.04 mg CN^-/kg/day was derived for cyanide based on elevated absolute and relative thyroid weight and decreased serum T4 levels in rats exposed to sodium cyanide in drinking water at a LOAEL of 11.50 mg CN^-/kg/day for 13 weeks; a NOAEL of 3.96 mg CN^-/kg/day (Tyner and Greeley 2023). The MRL is based on the NOAEL of 3.96 mg CN^-/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Endpoints identified as potential sensitive effects of cyanide toxicity (thyroid, neurological, male reproductive effects) based on human and animal studies were considered as candidate critical effects for the intermediate-duration oral MRL for cyanide. No adequate intermediate-duration human data were available. For animal data, studies that employed bolus (e.g., gavage) dosing are omitted from MRL consideration because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures from dietary sources or drinking water for the general population. In addition, oral studies in dogs are omitted from consideration. As discussed in Section 3.1.6, dogs are not considered suitable animal models from which to extrapolate the toxicity of cyanide to humans because dogs have a relatively low amount of the detoxifying enzymes (Drawbaugh and Marrs 1987; Himwich and Saunders 1948; NIH/NINDS 2016a, 2016b; Rockwood et al. 2003), making them unusually susceptible to cyanide toxicity compared to humans or other mammals. Additionally, interpretation of findings from intermediate-duration studies identified in dogs (Kamalu 1991, 1993; Kamalu and Agharanya 1991) were further confounded due to concurrent disease in study animals.

Table A-2 shows available NOAELs and LOAELs in rodents for candidate critical effects identified in intermediate-duration animal drinking water and dietary studies. The lowest LOAELs were identified in rats exposed to 300 ppm sodium cyanide in drinking water 13 weeks in studies by NTP (1993) and Tyner and Greeley (2023). Since calculated intakes in these studies were comparable (12.5 and 11.50 mg CN^-/kg/day, respectively), both endpoints were further examined as potential critical effects.

Table A-2. NOAEL and LOAEL Values for Candidate Critical Effects in Animals Following Intermediate-Duration Oral Exposure to Cyanide Compounds via Drinking Water or Diet

Species	Duration (subroute)	Effect level (mg CN^-/kg/day) NOAEL	LOAEL	Effect	Compound	Reference
Thyroid effects						
Fischer-344 rat	13 weeks (W)	12.5[a]			NaCN	NTP 1993
Fischer-344 rat	13 weeks (W)	3.96	11.50	Increased absolute (35%) and relative (40%) thyroid weights; decreased serum T4 (14%)	NaCN	Tyner and Greeley 2023
B6C3F1 mouse	13 weeks (W)	28.8[a]			NaCN	NTP 1993
Rat (NS)	11.5 months (F)	ND	47	Decreased plasma T4 at 4 months (55%) and 11 months (26%); decreased T4 secretion rate at 4 months (63%)	KSCN	Philbrick et al. 1979
Rat (NS)	11.5 months (F)	ND	53	Decreased plasma T4 at 4 months (52%); decreased T4 secretion rate at 4 months (68%) and 11 months (27%)	KCN	Philbrick et al. 1979
Neurological effects						
Fischer-344 rat	13 weeks (W)	12.5			NaCN	NTP 1993
B6C3F1 mouse	13 weeks (W)	28.8			NaCN	NTP 1993
Rat (NS)	11.5 months (F)	ND	47	Modest myelin degeneration in spinal cord	KSCN	Philbrick et al. 1979
Rat (NS)	11.5 months (F)	ND	53	Modest myelin degeneration in spinal cord	KCN	Philbrick et al. 1979
Male reproductive effects						
Fischer-344 rat	13 weeks (W)	4.5	12.5	Decreased absolute left epididymal (7%), cauda epididymal (13%), and testes weights (8%); decreased number of spermatid heads per testis (14%) and total spermatid count (14%)	NaCN	NTP 1993
Fischer-344 rat	13 weeks (W)	11.50			NaCN	Tyner and Greeley 2023

Table A-2. NOAEL and LOAEL Values for Candidate Critical Effects in Animals Following Intermediate-Duration Oral Exposure to Cyanide Compounds via Drinking Water or Diet

Species	Duration (subroute)	Effect level (mg CN^-/kg/day) NOAEL	LOAEL	Effect	Compound	Reference
B6C3F1 mouse	13 weeks (W)	8.6	24.3	Decreased weight of left epididymis (10%) and cauda epididymis (18%)	NaCN	NTP 1993

[a]Thyroid NOAEL based on lack of histopathological changes; thyroid weight and serum thyroid hormone levels were not assessed by NTP (1993).

Selected study for the intermediate-duration inhalation MRL derivation.

CN^- = cyanide; (F) = feed; KCN = potassium cyanide; KSCN = potassium thiocyanide; LOAEL = lowest-observed-adverse-effect level; NaCN = sodium cyanide; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; T4 = thyroxine; (W) = drinking water

In the NTP (1993) study, the adverse effect identified at 12.5 mg CN^-/kg/day was male reproductive effects in rats. Reported effects include decreased absolute weight of the left (but not right) testes, along with decreased absolute weight of the left epididymis and cauda epididymis; decreased number of spermatid heads per testis (but not spermatid heads per gram testis); and decreased total spermatid count. However, these findings were not reproduced in the repeat study by Tyner and Greeley (2023) at calculated intakes up to 11.50 mg CN^-/kg/day. Tyner and Greeley (2023) proposed that male reproductive effects noted in the NTP (1993) study may have been attributable to decreased water consumption in the highest dose group rather than due to direct toxic effects. To control for this, Tyner and Greeley (2023) included a water-restricted control group to match measured water consumption at the highest dose level. While a nonsignificant trend toward lower sperm motility was observed in rats exposed to 11.50 mg CN^-/kg/day compared to standard controls, this trend was not apparent when compared to the water-restricted control. Similarly, findings of decreased sperm concentration were non-dose-related and not significant compared to the water-restricted control. No adverse changes in male reproductive organ weights were observed compared to either the water-restricted or the *ad libitum* control groups. However, it is noted that decreased water intake at the highest concentration (300 ppm) was greater in the study by NTP (1993; 18%) than the study by Tyner and Greeley (2023; 11%). Therefore, it is still unclear if the greater decrease in water intake observed in the NTP study confounded the observed male reproductive findings. Based on concerns raised by the Tyner and Greeley (2023) study, there are too many uncertainties surrounding the findings from the NTP (1993) study to use these findings to support selection of male reproductive effects as the critical effect.

In the Tyner and Greeley (2023) study, the adverse effect identified in rats at 11.50 mg CN^-/kg/day was increased absolute and relative thyroid weights and reduced serum T4. These findings are statistically significant compared to both standard and water-restricted controls. While no changes in thyroid histology were observed at doses up to 12.5 mg CN^-/kg/day in the NTP (1993) study, thyroid weights and serum thyroid hormone levels were not assessed. Since thyroid effects have been reported in dietary studies in rats at higher doses (Philbrick et al. 1979), as well as human populations with high dietary cassava intake (Cliff et al. 1986; Delange and Ermans 1971), adverse effects on the thyroid are selected as the critical effects for intermediate-duration oral exposure to cyanide.

Systematic review conclusions support selection of thyroid effects over male reproductive effects as the critical effect, as there is stronger evidence for thyroid effects compared to male reproductive effects following oral exposure (see Appendix C). Thyroid effects following oral exposure are presumed health effects based on low evidence in humans, moderate evidence in animals, and supporting mechanistic data, while male reproductive effects are suspected health effects based on no human data and moderate evidence in animals. Furthermore, the NOAEL of 3.96 mg CN^-/kg/day associated with the lowest LOAEL for thyroid effects is comparable to the NOAEL of 4.5 mg CN^-/kg/day associated with the lowest LOAEL for male reproductive effects. Thus, selection of thyroid effects as the critical effect should be protective of potential male reproductive effects.

Selection of the Principal Study: Tyner and Greeley (2023) was selected as the principal study because it provided the lowest candidate point of departure (POD) (3.96 ppm) for the critical effect (thyroid effects).

Summary of the Principal Study:

Tyner MC, Greeley MA. (2023). A new 90-day drinking water study of sodium cyanide in rats to further evaluate National Toxicology Program findings and inform risk assessment. Birth Defects Res 115(7):722-752. https://doi.org/10.1002/bdr2.2163.

Groups of 20 male Fischer-344 rats were administered sodium cyanide at doses of 0, 3, 10, 30, 100, or 300 ppm in drinking water for 13 weeks. The study authors calculated daily intake levels of 0, 0.23, 0.81, 2.41, 7.46, or 21.66 mg NaCN/kg/day, respectively. Doses in cyanide were calculated to be 0, 0.12, 0.43, 1.28, 3.96, and 11.50 mg CN^-/kg/day, respectively. Additional details on dose conversions can be found in Table A-3.

Table A-3. Dose Conversions for Tyner and Greely (2023)

Dose (ppm)	Dose (mg NaCN/kg/day)[a]	Dose (mg CN^-/kg/day)[b]
3	0.23	0.12
10	0.81	0.43
30	2.41	1.28
100	7.46	3.96
300	21.66	11.50

[a]Reported by the study authors. Due to ambiguity in dose reporting (reported as doses in terms of the anion in text but as administered compound in Table 1 of the study report), the study authors were contacted for clarification. It was confirmed via personal communication (Tyner 2024) that the reported doses were in terms of the administered compound (NaCN).
[b]Calculated based on the ratio of molecular weights for sodium cyanide (49.01 g/mol) and cyanide (26.02 g/mol). Conversions were calculated as follows: dose in mg NaCN × (26.02/49.01) = dose in CN^-.

CN = cyanide; NaCN = sodium cyanide

An additional control group was included, and water consumption was restricted based on levels consumed at the high-dose group. Animals were observed twice daily for clinical signs. Body weights and food consumption were monitored weekly and water consumption was recorded twice weekly. Ophthalmological examinations occurred prior to dosing and after the dosing and recovery periods. Urinalysis and blood collection for hematology and clinical chemistry were done after dosing and recovery periods. Blood was also collected for thyroid hormone analysis (TSH, T3, and T4) on days 28, 56, 90, 118, and 160. Prior to sacrifice, animals were fasted and placed in metabolic cages. Ten animals

were sacrificed following the final dose and 10 animals were sacrificed following a 10-week untreated recovery period. Following sacrifice, a necropsy was performed including all external surfaces of the brain and thoracic, abdominal, and pelvic cavities and organs. Weights of organs were recorded (adrenal glands, epididymides [total and cauda], heart, kidneys, liver, pituitary, prostate with seminal vesicles and coagulating glands, spleen, testes, thymus, and thyroid with parathyroids [weighed after fixation]). Tissues were fixed for histopathology (testes, epididymides, prostate gland, seminal vesicles, eyes with optic nerve, brain, pituitary, parathyroid, thyroid, any macroscopic lesion). Sperm parameters were measured and graded in a semi-quantitative manner (according to Stump et al. 2008 and 2014).

No dose-related mortality occurred. One death in the water-restricted control group showed no effects on necropsy. No clinical signs or effects on body weights or food consumption were observed. Water consumption was decreased in the 100 and 300 ppm groups by 11% compared to the *ad libitum* control but by the end of recovery, water consumption was comparable across all groups. No effects were noted in ophthalmology, hematology, serum chemistry, or urinalysis. Serum T4 was significantly decreased at 300 ppm after 90 days compared to both *ad libitum* control (14%) and water-restricted control (13%); these effects were no longer evident after a 28-day recovery period. Other thyroid hormones did not differ from control at the end of the exposure period; however, serum TSH was significantly decreased at 300 ppm at the end of the 28-day recovery period (compared to water-restricted controls only). The biological significance of this finding is unclear, particularly because serum TSH was significantly higher in water-restricted controls compared to *ad libitum* controls and because similar findings were not observed during the exposure period. Dose-related increases in absolute and relative thyroid (with parathyroid) weights were observed at ≥30 ppm, with elevations reaching statistical significance compared to both *ad libitum* and water-restricted controls at 300 ppm (35–40%). Organ weights were comparable to controls following the recovery period. There were no other treatment-related effects in measured organ weights. There were no treatment-related histological findings in the thyroid, liver, or male reproductive organs; findings in other organs (including the brain) were not specifically discussed. No statistically significant, exposure-related changes were observed in sperm concentration, production, or motility were observed.

Selection of the Point of Departure for the MRL: The NOAEL of 3.96 mg CN^-/kg/day for increased absolute and relative thyroid weight and decreased serum T4 in rats reported by Tyner and Greeley (2023) was selected as the POD for the intermediate-duration oral MRL.

In order to identify the most sensitive POD, benchmark dose (BMD) modeling was attempted for all thyroid endpoints reported by Tyner and Greeley (2023) when data were amenable to modeling. The data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS; version 3.3) using a benchmark response (BMR) of 1 standard deviation (SD). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% lower confidence limit on the BMD (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen.

The datasets used for BMD modeling are presented in Table A-4 (absolute thyroid weight, serum T4 levels); relative thyroid weight data were reported without variance data and were therefore not amenable for modeling. For absolute thyroid weight and serum T4 levels, inclusion of two control groups by Tyner and Greeley (2023) presented a challenge for modeling, as the *ad libitum* control was the appropriate control for the first three doses while the water-restricted control was the appropriate control for the two highest doses. To evaluate both options, models were run using two datasets for each endpoint, one with

all exposure groups and the *ad libitum* control and one with all exposure groups and the water-restricted control.

Table A-4. Thyroid Endpoints in Male Rats Following Drinking Water Exposure to Sodium Cyanide for 13 Weeks

	Dose (CN^-/kg/day)						
Endpoint[a]	0 (ad lib)	0 (restrict)	0.12	0.43	1.28	3.96	11.50
Absolute thyroid weights (g)	0.0104± 0.0015 (10)	0.0105± 0.0012 (9)	0.0096± 0.0018 (10)	0.0106± 0.0019 (10)	0.0122± 0.0024 (10)	0.0122± 0.0032 (10)	0.0140± 0.0029[b] (10)
Serum T4 (pg/mL)	51,120± 4,313.8 (10)	50,530± 7,154.8 (9)	45,870± 8,903.4 (10)	47,450± 4,468.7 (10)	47,300± 8,065.2 (10)	48,340± 3,022.2 (10)	44,200± 3919.5[b] (10)

[a]Mean±SD (number of animals).
[b]p<0.05.

ad lib = *ad libitum*; restrict = water-restricted; SD = standard deviation

Source: Tyner and Greeley (2023)

No adequate model fits were achieved for serum T4 data using either constant or nonconstant variance with either control group. While model fits were achieved using constant variance for absolute thyroid weight using either the *ad libitum* or water-restricted control data, the model control response SD values were >1.5-fold different than the actual response SD, lending considerable uncertainty to the standard BMR (1 SD). The large SDs of the data result in model estimates having large SDs. Consequently, this leads to increased uncertainty in BMD estimates. The BMDL is described as the lower confidence interval of the BMD. With large SDs in BMD estimates, in some extreme cases, the BMDL estimates could be much lower than the NOAEL, which is questionable. Using nonconstant variance, a limited number of models provided statistical fits to the data for the *ad libitum* control (Exponential 5 model) and the water-restricted control (Exponential 5, Hill). While modeled SD values did not differ as widely as seen with the constant variance model, the BMDL estimates (0.74 mg CN^-/kg/day for *ad libitum* control; 0.79 CN^-/kg/day for water-restricted control) were markedly lower than the empirical NOAEL of 3.96 CN^-/kg/day (as well as the dose below the NOAEL, 1.28 CN^-/kg/day). Therefore, the nonconstant model results were also considered questionable for this dataset. BMD model outputs for *ad libitum* and water-restricted controls are shown in Tables A-5 and A-6, respectively.

Table A-5. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: *Ad Libitum* Control (Tyner and Greeley 2023)

	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)			Scaled residuals	
Model			Test 4 p-value[b]	AIC	Dose near BMD	Control dose group
Constant variance						
Exponential 3[c,d]			–	–	–	–
Exponential 5[c]	3.07	1.89	0.37	-550.65	-0.82	0.36
Hill[c]			0.01	-541.96	0.00	-0.78
Polynomial Degree 2[c]	7.36	5.21	0.27	-550.56	0.48	-0.25

Table A-5. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: *Ad Libitum* Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Polynomial Degree 3[c]	7.36	5.21	0.27	-550.56	0.48	-0.25
Power[c]	7.36	5.21	0.27	-550.56	0.48	-0.25
Linear	7.36	5.19	0.27	-550.56	0.48	-0.25
Nonconstant variance						
Exponential 3[c,d]			0.06	-550.87	0.56	-0.27
Exponential 5[c]	1.02	0.75	0.43	-554.35	0.15	0.74
Hill[c]			0.06	-550.70	0.18	-0.06
Polynomial Degree 2[c]			0.08	-551.61	0.40	-0.17
Polynomial Degree 3[c]			0.08	-551.61	0.40	-0.17
Power[c]			0.08	-551.61	0.40	-0.17
Linear			0.08	-551.61	0.40	-0.17

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Restricted model.
[d]BMD computation failed.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Table A-6. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: Water-Restricted Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Constant variance						
Exponential 3[c,d]			–	–	–	–
Exponential 5[c]	1.37	1.00	0.14	-539.15	-0.03	0.58
Hill[c]	6.77	4.64	0.19	-540.37	0.31	-0.07
Polynomial Degree 2[c]	7.40	5.22	0.27	-541.93	0.46	-0.14
Polynomial Degree 3[c]	7.39	5.22	0.27	-541.93	0.46	-0.14
Power[c]	7.39	5.22	0.27	-541.93	0.46	-0.14
Linear	7.39	5.21	0.27	-541.93	0.46	-0.14

Table A-6. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: Water-Restricted Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Nonconstant variance						
Exponential 3[c,d]			0.05	-542.50	0.54	-0.15
Exponential 5[c]	0.96	0.71	0.47	-546.56	0.14	0.92
Hill[c]	0.94	0.79	0.56	-546.89	0.28	0.96
Polynomial Degree 2[c]			0.07	-543.25	0.38	-0.05
Polynomial Degree 3[c]			0.07	-543.25	0.38	-0.05
Power[c]			0.07	-543.25	0.38	-0.05
Linear			0.07	-543.25	0.38	-0.05

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Restricted model.
[d]BMD computation failed.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Alternative datasets were also attempted where the water-restricted control data were modeled with only the two highest doses (groups in which animals demonstrated decreased water intake). For these datasets, no models adequately fit the serum T4 data or absolute thyroid weights assuming constant or nonconstant variance, confirming the difficulty of the control group variability.

Due to model uncertainties discussed above and challenges regarding which control group was the most appropriate to use for BMD modeling, the NOAEL of 3.96 mg CN^-/kg/day was selected as the POD.

Calculations: None. Available PBPK models (Stamyr et al. 2015; Tran et al. 2020a, 2020b) are specific to human external-to-internal dose extrapolation. These models are not suitable for oral dose extrapolation between species.

Uncertainty Factors: The following uncertainty factors were applied to the NOAEL to derive the MRL:

- Uncertainty factor of 10 for extrapolation from animals to humans
- Uncertainty factor of 10 for human variability

Subsequently, the provisional oral MRL for intermediate-duration exposure to cyanide is:

$$Provisional\ MRL = \frac{NOAEL}{(UF)} = \frac{3.96\ mg\ CN^-/kg/day}{10 \times 10}$$

$$= 0.00396\ mg\ CN^-/kg/day \approx 0.04\ mg\ CN^-/kg/day$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that thyroid effects are a presumed health effect following exposure to cyanide based on a low level of evidence in humans, a moderate level of evidence in animals, and supporting mechanistic data (see Appendix C).

Thyroid effects following cyanide exposure can result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland (VanderLaan and Bissell 1946). Thiocyanate competes with iodine to bind the sodium-iodine symporter and has a higher binding affinity than the endogenous ligand (De Groef et al. 2006; EPA 2010; Tonacchera et al. 2004). Reduced serum thyroid hormone levels, increasingly elevated levels of TSH, and goiter are typical sequelae of chronic-duration cyanide exposure observed in tropical populations reliant on cassava as the main staple of the diet (Cliff et al. 1986; Delange and Ermans 1971; Ermans et al. 1980). While inhalation data are limited and do not provide reliable dose-response data, occupational studies provide additional support for the potential association between cyanide exposure and thyroid effects. Enlargement of the thyroid gland, altered iodine uptake, decreased thyroid hormone levels, and/or increased TSH were observed in workers occupationally exposed to cyanide at electroplating or silver-reclaiming factories (Banerjee et al. 1997; Blanc et al. 1985; El Ghawabi et al. 1975).

Agency Contact (Chemical Manager): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data to support derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived for cyanide because of the lack of suitable data in humans and animals.

Available human data are limited to populations that have high intake of cassava root; however, studies of these populations are not appropriate for MRL derivations because findings are confounded by co-exposure to other compounds (e.g., scopoletin) as well as concurrent nutritional deficiencies (Makene and Wilson 1972; Obidoa and Obasi 1991; Osuntokun 1972; Osuntokun et al. 1969). Additionally, external exposure estimates are not available, and biomarker exposure was often available only at (or after) diagnosis with thyroid or neurological abnormalities.

Two inadequate chronic-duration oral studies in animal studies were identified. One study found no significant cyanide-dependent effects in rats exposed to hydrogen cyanide in the diet for 2 years at doses as high as 7.8 mg CN^-/kg/day for males or 10.4 mg CN^-/kg/day for females (Howard and Hanzal 1955). However, the reliability of this study is low because evaporation of the cyanide from the feed resulted in unstable cyanide levels throughout the experiment and uncertainties as to the dose-response for cyanide. The other is a foreign-language study in dogs that only used one dog per dose and lacked a concurrent control (Hertting et al. 1960).

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CYANIDE

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 cyanide.

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

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

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the Toxicological Profile for Cyanide released in 2006. All literature cited in the previous (2006) toxicological profile was considered for inclusion in the updated profile; thus, the literature search was restricted to studies published between January 2004 and August 2023. The following main databases were searched in July and August 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 cyanide. 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 cyanide 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	
08/2023	(("Hydrogen Cyanide"[mh:noexp] AND ("Hydrogen Cyanide/toxicity"[mh] OR "Hydrogen Cyanide/adverse effects"[mh] OR "Hydrogen Cyanide/poisoning"[mh] OR "Hydrogen Cyanide/pharmacokinetics"[mh] OR "Hydrogen Cyanide/blood"[mh] OR "Hydrogen Cyanide/cerebrospinal fluid"[mh] OR "Hydrogen Cyanide/urine"[mh] OR "Hydrogen Cyanide/antagonists and inhibitors"[mh] OR ("Hydrogen Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Hydrogen Cyanide/pharmacology"[majr] OR ("Hydrogen Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Hydrogen Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Hydrogen Cyanide"[mh] AND (("Neoplasms"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"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 ("Cyanides"[mh:noexp] AND ("Cyanides/toxicity"[mh] OR "Cyanides/adverse effects"[mh] OR "Cyanides/poisoning"[mh] OR "Cyanides/pharmacokinetics"[mh] OR "Cyanides/blood"[mh] OR "Cyanides/cerebrospinal fluid"[mh] OR "Cyanides/urine"[mh] OR "Cyanides/antagonists and inhibitors"[mh] OR ("Cyanides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Cyanides/pharmacology"[majr] OR ("Cyanides"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Cyanides"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR ("Cyanides"[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 ("Sodium Cyanide/toxicity"[mh] OR "Sodium Cyanide/adverse effects"[mh] OR "Sodium Cyanide/poisoning"[mh] OR "Sodium Cyanide/pharmacokinetics"[mh] OR "Sodium Cyanide/blood"[mh] OR "Sodium Cyanide/cerebrospinal fluid"[mh] OR "Sodium Cyanide/urine"[mh] OR "Sodium Cyanide/antagonists and inhibitors"[mh] OR ("Sodium Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Sodium Cyanide/pharmacology"[majr] OR ("Sodium Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	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 ("Sodium Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Sodium Cyanide"[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 ("Potassium Cyanide/toxicity"[mh] OR "Potassium Cyanide/adverse effects"[mh] OR "Potassium Cyanide/poisoning"[mh] OR "Potassium Cyanide/pharmacokinetics"[mh] OR "Potassium Cyanide/blood"[mh] OR "Potassium Cyanide/cerebrospinal fluid"[mh] OR "Potassium Cyanide/urine"[mh] OR "Potassium Cyanide/antagonists and inhibitors"[mh] OR ("Potassium Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Potassium Cyanide/pharmacology"[majr] OR ("Potassium Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Potassium Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Potassium Cyanide"[mh] AND (("Neoplasms"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"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 ("cyanogen"[nm] AND ("Nitriles/toxicity"[mh] OR "Nitriles/adverse effects"[mh] OR "Nitriles/poisoning"[mh] OR "Nitriles/pharmacokinetics"[mh] OR "Nitriles/blood"[mh] OR "Nitriles/cerebrospinal fluid"[mh] OR "Nitriles/urine"[mh] OR "Nitriles/antagonists and inhibitors"[mh] OR ("Nitriles/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Nitriles/pharmacology"[majr] OR ("Nitriles"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Nitriles"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR ("Nitriles"[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 ((1762-95-4[rn] OR 333-20-0[rn] OR 540-72-7[rn]) AND ("Thiocyanates/toxicity"[mh] OR "Thiocyanates/adverse effects"[mh] OR "Thiocyanates/poisoning"[mh] OR "Thiocyanates/pharmacokinetics"[mh] OR "Thiocyanates/blood"[mh] OR "Thiocyanates/cerebrospinal fluid"[mh] OR "Thiocyanates/urine"[mh] OR "Thiocyanates/antagonists and inhibitors"[mh] OR ("Thiocyanates/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Thiocyanates/pharmacology"[majr] OR ("Thiocyanates"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	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 ("Thiocyanates"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Thiocyanates"[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 ("Calcid"[tw] OR "Calcium cyanide"[tw] OR "Calcium dicyanide"[tw] OR "Calcyan"[tw] OR "Calcyanide"[tw] OR "Cyanide of calcium"[tw] OR "Cyanogas"[tw] OR "Degesch Calcium Cyanide A-Dust"[tw] OR "Copper cyanide"[tw] OR "Copper monocyanide"[tw] OR "Copper(+1) cyanide"[tw] OR "Copper(1+) cyanide"[tw] OR "Copper(I) cyanide"[tw] OR "Cupricin"[tw] OR "Cuprous cyanide"[tw])) AND 2004:3000[dp] (((("Cyanide"[tw] OR "Aero Liquid HCN"[tw] OR "Agent AC"[tw] OR "Ammonium isothiocyanate"[tw] OR "Ammonium rhodanate"[tw] OR "Ammonium rhodanide"[tw] OR "Ammonium sulfocyanate"[tw] OR "Ammonium sulfocyanide"[tw] OR "Ammonium thiocyanate"[tw] OR "Calcium dicyanide"[tw] OR "Calcyan"[tw] OR "Calcyanide"[tw] OR "Carbon hydride nitride"[tw] OR "Carbononitridic chloride"[tw] OR "CHLORCYAN"[tw] OR "Chlorocyan"[tw] OR "Chlorocyanide"[tw] OR "Chlorocyanogen"[tw] OR "Chloronitrile"[tw] OR "Copper monocyanide"[tw] OR "Cupricin"[tw] OR "Cyanasalt H"[tw] OR "Cyanasalt S"[tw] OR "Cyanic chloride"[tw] OR "Cyanides"[tw] OR "Cyanobrik"[tw] OR "Cyanochloride"[tw] OR "Cyanogas"[tw] OR "Cyanogen"[tw] OR "Cymag"[tw] OR "Cynanide"[tw] OR "Dicyan"[tw] OR "Dicyanogen"[tw] OR "EDN Fumigas"[tw] OR "Ethanedinitrile"[tw] OR "Evercyn"[tw] OR "Feratox"[tw] OR "Formic anammonide"[tw] OR "Formonitrile"[tw] OR "Hydrocyanic acid"[tw] OR "M-44 capsules"[tw] OR "Nitriloacetonitrile"[tw] OR "Oxalic acid dinitrile"[tw] OR "Oxalonitrile"[tw] OR "Potassium argentocyanide"[tw] OR "Potassium bis(cyano-C)argentate"[tw] OR "Potassium cyanoargentate"[tw] OR "Potassium dicyanoargentate"[tw] OR "Potassium isothiocyanate"[tw] OR "Potassium rhodanate"[tw] OR "Potassium sulfocyanate"[tw] OR "Potassium thiocyanate"[tw] OR "Potassium thiocyanide"[tw] OR "Prussic acid"[tw] OR "Prussite"[tw] OR "Rhodanid"[tw] OR "Rhodanine, ammonium salt"[tw] OR "Sodium isothiocyanate"[tw] OR "Sodium rhodanate"[tw] OR "Sodium rhodanide"[tw] OR "Sodium sulfocyanate"[tw] OR "Sodium sulfocyanide"[tw] OR "Sodium thiocyanate"[tw] OR "Sodium thiocyanide"[tw] OR "Thiocyanate sodium"[tw] OR "Thiocyanic acid, ammonium salt"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Thiocyanic acid, potassium salt"[tw] OR "Thiocyanic acid, sodium salt"[tw] OR "Weedazol tl"[tw] OR "Zaclondiscoids"[tw] OR "Zyklon B"[tw]) NOT medline[sb]) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR renal OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR dermal OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal*

Table B-2. Database Query Strings

Database search date	Query string
	OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)) AND 2004:3000[dp]
NTRL	
07/2023	Limited to 2004-present, Terms in the title or keyword "Cyanide" OR "Aero Liquid HCN" OR "Agent AC" OR "Ammonium isothiocyanate" OR "Ammonium rhodanate" OR "Ammonium rhodanide" OR "Ammonium sulfocyanate" OR "Ammonium sulfocyanide" OR "Ammonium thiocyanate" OR "Calcium dicyanide" OR "Calcyan" OR "Calcyanide" OR "Carbon hydride nitride" OR "Carbononitridic chloride" OR "CHLORCYAN" OR "Chlorocyan" OR "Chlorocyanide" OR "Chlorocyanogen" OR "Chloronitrile" OR "Copper monocyanide" OR "Cupricin" OR "Cyanasalt H" OR "Cyanasalt S" OR "Cyanic chloride" OR "Cyanides" OR "Cyanobrik" OR "Cyanochloride" OR "Cyanogas" OR "Cyanogen" OR "Cymag" OR "Cynanide" OR "Dicyan" OR "Dicyanogen" OR "EDN Fumigas" OR "Ethanedinitrile" OR "Evercyn" OR "Feratox" OR "Formic anammonide" OR "Formonitrile" OR "Hydrocyanic acid" OR "M-44 capsules" OR

Table B-2. Database Query Strings

Database search date	Query string
	"Nitriloacetonitrile" OR "Oxalic acid dinitrile" OR "Oxalonitrile" OR "Potassium argentocyanide" OR "Potassium bis(cyano-C)argentate" OR "Potassium cyanoargentate" OR "Potassium dicyanoargentate" OR "Potassium isothiocyanate" OR "Potassium rhodanate" OR "Potassium sulfocyanate" OR "Potassium thiocyanate" OR "Potassium thiocyanide" OR "Prussic acid" OR "Prussite" OR "Rhodanid" OR "Rhodanine, ammonium salt" OR "Sodium isothiocyanate" OR "Sodium rhodanate" OR "Sodium rhodanide" OR "Sodium sulfocyanate" OR "Sodium sulfocyanide" OR "Sodium thiocyanate" OR "Sodium thiocyanide" OR "Thiocyanate sodium" OR "Thiocyanic acid, ammonium salt" OR "Thiocyanic acid, potassium salt" OR "Thiocyanic acid, sodium salt" OR "Weedazol tl" OR "Zaclondiscoids" OR "Zyklon B"
Toxcenter	
08/2023	FILE 'TOXCENTER' ENTERED AT 17:32:05 ON 15 AUG 2023 L1 1317 SEA FILE=TOXCENTER ((540-72-7 OR 333-20-0) AND PY>2003) NOT PATENT/DT L2 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L3 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT) L4 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L5 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L6 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L7 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L8 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L9 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L10 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L11 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L12 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L13 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L14 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L15 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L16 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L17 QUE (ENDOCRIN? AND DISRUPT?) L18 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L19 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L20 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L21 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR

Table B-2. Database Query Strings

Database search date	Query string
	NEOPLAS?)
	L22 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L23 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L24 QUE (NEPHROTOX? OR HEPATOTOX?)
	L25 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L26 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L27 QUE L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26

	L35 QUE L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L17 OR L18 OR L19 OR L20 OR L23 OR L24 OR L25 OR L26
	L36 309 SEA FILE=TOXCENTER L1 AND L35
	L37 1 SEA FILE=TOXCENTER L1 AND (NEONAT? OR NEWBORN? OR DEVELOPMENTAL ?)
	L38 79 SEA FILE=TOXCENTER (L1 AND (DEVELOPMENT OR L21 OR L22)) NOT (SYNTHESIS/TI OR DESIGN/TI OR DRUG? OR TREATMENT? OR THERAP? OR ANTI-TUMOR? OR ANTI-TUMOUR? OR ANTI-CANCER OR ANTICANCER OR ANTI-NEOPLASTIC OR ANTINEOPLASTIC OR ANTI-CARCINOGEN? OR ANTICARCINOGEN?)
	L39 366 SEA FILE=TOXCENTER L36 OR L37 OR L38
	L41 16 SEA FILE=TOXCENTER L39 AND BIOSIS/FS
	D SCAN L41
	L111 11591 SEA FILE=TOXCENTER ((74-90-8 OR 143-33-9 OR 151-50-8 OR 592-01-8 OR 544-92-3 OR 506-61-6 OR 460-19-5 OR 506-77-4 OR 1762-95-4 OR 57-12-5) AND PY>2003) NOT PATENT/DT
	L112 5165 SEA FILE=TOXCENTER L111 AND L27
	L113 95 SEA FILE=TOXCENTER L111 AND (NEONAT? OR NEWBORN? OR DEVELOPMENT AL?)
	L114 810 SEA FILE=TOXCENTER (L111 AND (DEVELOPMENT OR L21 OR L22)) NOT (SYNTHESIS/TI OR DESIGN/TI OR DRUG? OR TREATMENT? OR THERAP? OR ANTI-TUMOR? OR ANTI-TUMOUR? OR ANTI-CANCER OR ANTICANCER OR ANTI-NEOPLASTIC OR ANTINEOPLASTIC OR ANTI-CARCINOGEN? OR ANTICARCINOGEN?)
	L115 5165 SEA FILE=TOXCENTER L112 OR L113 OR L114
	L116 670 SEA FILE=TOXCENTER L115 AND MEDLINE/FS
	L117 4495 SEA FILE=TOXCENTER L115 NOT MEDLINE/FS
	L118 1035 SEA FILE=TOXCENTER L115 AND BIOSIS/FS
	L119 4618 DUP REM L116 L117 (547 DUPLICATES REMOVED)
	L*** DEL 670 S L115 AND MEDLINE/FS
	L*** DEL 670 S L115 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L120 670 SEA FILE=TOXCENTER L119 L*** DEL 4495 S L115 NOT MEDLINE/FS L*** DEL 4495 S L115 NOT MEDLINE/FS L121 3948 SEA FILE=TOXCENTER L119 L122 3948 SEA FILE=TOXCENTER (L120 OR L121) NOT MEDLINE/FS L124 3393 SEA FILE=TOXCENTER L122 AND (L35 OR L113 OR L114) D SCAN

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
07/2023	Compounds searched: 74-90-8, 143-33-9, 151-50-8, 592-01-8, 544-92-3, 506-61-6, 460-19-5, 506-77-4, 1762-95-4, 57-12-5, 333-20-0, 540-72-7
NTP	
07/2023	"Cyanide" "Cyanides" "Ammonium thiocyanate" "Cyanogen" 74-90-8 143-33-9 151-50-8 592-01-8 544-92-3 506-61-6 460-19-5 506-77-4 1762-95-4 57-12-5 333-20-0 "Ammonium rhodanate" "Chlorocyan" "Chloronitrile" "Cyanochloride" "Cyanogas" "Cynanide" "Dicyan" "Ethanedinitrile" "Formonitrile" "Hydrocyanic acid" "Potassium dicyanoargentate" "Potassium thiocyanate" "Prussic acid" "Rhodanid" "Sodium thiocyanate" "Zyklon B"
Regulations.gov	
07/2023	Limited to 2004-present; dockets/notices "74-90-8"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"143-33-9" "151-50-8" "592-01-8" "544-92-3" "506-61-6" "460-19-5" "506-77-4" "1762-95-4" "57-12-5" "333-20-0" "Cyanide" "Cyanides" "Ammonium rhodanate" "Ammonium thiocyanate" "Chlorocyan" "Chloronitrile" "Cyanochloride" "Cyanogas" "Cyanogen" "Cynanide" "Dicyan" "Ethanedinitrile" "Formonitrile" "Hydrocyanic acid" "Potassium dicyanoargentate" "Prussic acid" "Rhodanid" "Zyklon B" "Potassium thiocyanate" "Sodium thiocyanate"
NPIRS	
08/2023	Compounds searched: 74-90-8, 143-33-9, 151-50-8, 592-01-8, 544-92-3, 506-61-6, 460-19-5, 506-77-4, 1762-95-4, 57-12-5, 333-20-0, 540-72-7
NIH RePORTER	
01/2024	Search Criteria-- Fiscal Year: Active Projects; Text Search: "Cyanide" OR "Aero Liquid HCN" OR "Agent AC" OR "Ammonium isothiocyanate" OR "Ammonium rhodanate" OR "Ammonium rhodanide" OR "Ammonium sulfocyanate" OR "Ammonium sulfocyanide" OR "Ammonium thiocyanate" OR "Calcid" OR "Calcium dicyanide" OR "Calcyan" OR "Calcyanide" OR "Carbon hydride nitride" OR "Carbononitridic chloride" OR "CHLORCYAN" OR "Chlorocyan" OR "Chlorocyanide" OR "Chlorocyanogen" OR "Chloronitrile" OR "Copper monocyanide" OR "Cupricin" OR "Cyanasalt H" OR "Cyanasalt S" OR "Cyanic chloride" OR "Cyanides" OR "Cyanobrik" OR "Cyanochloride" OR "Cyanogas" OR "Cyanogen" OR "Cymag" OR "Cynanide" OR "Dicyan" OR "Dicyanogen" OR "EDN Fumigas" OR "Ethanedinitrile" OR "Evercyn" OR "Feratox" OR "Formic anammonide" OR "Formonitrile" OR "Hydrocyanic acid" OR "M-44 capsules" OR "Nitriloacetonitrile" OR "Oxalic acid dinitrile" OR "Oxalonitrile" OR "Potassium argentocyanide" OR "Potassium bis(cyano-C)argentate" OR "Potassium cyanoargentate" OR "Potassium dicyanoargentate" OR "Potassium isothiocyanate" OR "Potassium rhodanate" OR "Potassium sulfocyanate" OR "Potassium thiocyanate" OR "Potassium thiocyanide" OR "Prussic acid" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Prussite" OR "Rhodanid" OR "Rhodanine, ammonium salt" OR "Sodium isothiocyanate" OR "Sodium rhodanate" OR "Sodium rhodanide" OR "Sodium sulfocyanate" OR "Sodium sulfocyanide" OR "Sodium thiocyanate" OR "Sodium thiocyanide" OR "Thiocyanate sodium" OR "Thiocyanic acid, ammonium salt" OR "Thiocyanic acid, potassium salt" OR "Thiocyanic acid, sodium salt" OR "Weedazol tl" OR "Zaclondiscoids" OR "Zyklon B" (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): 5,213
- Number of records identified from other strategies: 134
- Total number of records to undergo literature screening: 5,347

B.1.2 Literature Screening

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

- 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.

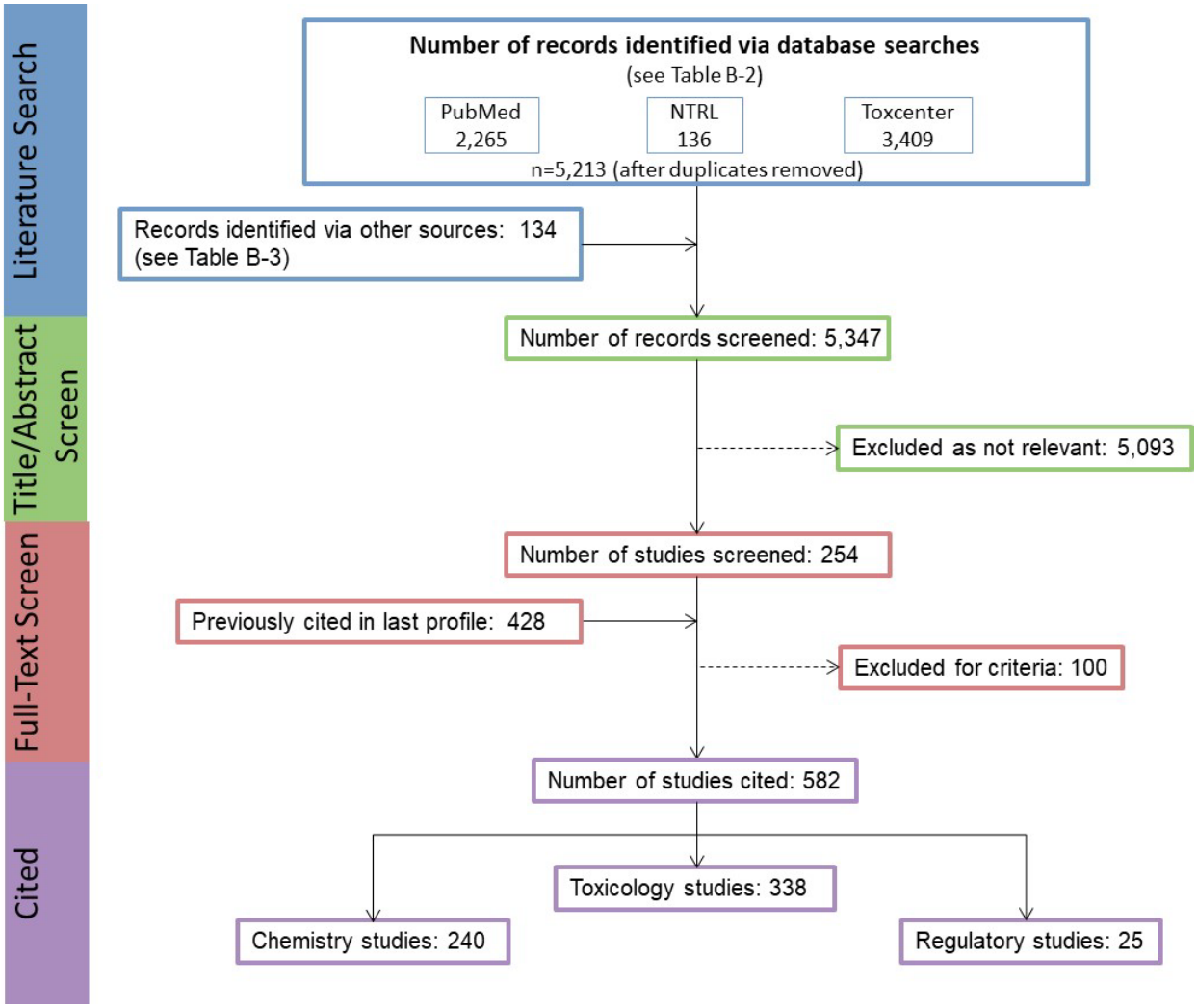
- Number of titles and abstracts screened: 5,347
- Number of studies considered relevant and moved to the next step: 254

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: 254
- Number of studies cited in the pre-public draft of the toxicological profile: 428
- Total number of studies cited in the profile: 582

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

Figure B-1. August 2023 Literature Search Results and Screen for Cyanide



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

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 cyanide, 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 cyanide:

- 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 cyanide. The inclusion criteria used to identify relevant studies examining the health effects of cyanide are presented in Table C-1.

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

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

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

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

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

Prioritization of Human Data. The database of case-reports and case-series reviews of cyanide-related deaths and poisonings is extensive. Due to the well-established acute lethality of cyanide via all routes, as well as the mechanism of acute toxicity, comprehensive review and inclusion of these studies was not performed for this profile. Case reports were included when the provided key information on dose-response or hazard identification, and recent reviews were relied upon when available.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of cyanide. 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 2006 Toxicological Profile for Cyanide; thus, the literature search was restricted to studies published between January 2004 and August 2023. See Appendix B for the databases searched and the search strategy.

A total of 5,347 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 5,347 records were reviewed; 21 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 115 health effect documents (documents identified in the update literature search and

documents cited in older versions of the profile) was performed. From those 115 documents (143 studies), 29 documents (37 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

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

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for cyanide identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include numerous case studies and case-series reports; as indicated in Section C-1, only a limited number of case studies and case-series reports were included in the profile. Case studies and case-series reports included in the report were not included in the formal systematic review due to inherent high risk of bias and low confidence based on study design. However, where appropriate, consistent findings from

numerous case studies were considered during the adjustment of the confidence rating (with regards to consistency and/or severity of observed effects). Available epidemiological studies include a limited number of occupational exposure studies and population-based studies of communities with high dietary cassava intake. When evaluated together, these studies suggest that the thyroid and neurological system may be susceptible to cyanide toxicity at sublethal exposure levels. Animal studies evaluated a comprehensive set of endpoints following oral exposure, with only limited information at sublethal exposure levels via inhalation and dermal routes. Based on oral studies, animal data suggest that the thyroid, neurological system, and male reproductive systems may be susceptible to cyanide toxicity. Therefore, thyroid, neurological, and male reproductive effects were considered sensitive outcomes following oral exposure and underwent systematic review. Due to paucity of data, particularly a lack of dose-response information, systematic review was not conducted via the inhalation route. There were 37 studies (published in 29 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review. Hertting et al. (1960) was not carried through systematic review, despite evaluating the male reproductive system in dogs following oral exposure, because it is a foreign language study with an English abstract; therefore, systematic review questions could not be answered. However, due to use of a single animal per exposure group and lack of a concurrent control, it is not considered a reliable study (therefore, it was not translated into English for systematic review).

APPENDIX C

Table C-3. Overview of the Health Outcomes for Cyanide 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	1 1	1 1	1 1	1 1					1 1	1 1	1 1		2 2				
Case control																	
Cross-sectional		3 3	2 2	1 1	2 2		2 2	1 0	1 0	4 4	1 1	1 1	4 4			1 0	
Case series		3 3	2 2					1 1	1 1				7 7				
Controlled exposure		1 1								1 1							
Oral studies																	
Cohort																	
Case control																	
Population											2 2		4 4				
Case series		7 7	2 2	4 4	1 0	2 2		1 1		1 1			21 21			3 3	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series		3 3	2 2				1 1						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 Cyanide Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration		5 5	2 2						1 0	1 1			10 9				
Intermediate-duration	1 1	3 1	2 0	1 1	2 0	2 0	2 0	2 0					2 2				
Chronic-duration																	
Oral studies																	
Acute-duration	4 0	4 2	5 2				9 4	6 3			4 2		13 11	8 4	5 3	4 2	
Intermediate-duration	18 10	5 3	7 1	4 1	6 3		15 9	9 6	4 2	3 2	11 7	2 0	9 7	10 9	4 3	3 2	
Chronic-duration		1 0	1 0	1 1			1 0	2 1					2 1				
Dermal studies																	
Acute-duration		6 6		1 1					1 1	3 3			8 8				
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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

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

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

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

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

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

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

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of cyanide health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

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

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Thyroid effects							
Population							
Delange and Ermans 1971	+	–	+	– –	+	+	Second
Cliff et al. 1986	+	–	+	–	+	+	Second
Outcome: Neurological effects							
Population							
Money 1958	– –	– –	+	– –	+	+	Second
Osuntokun 1968	+	–	+	–	++	+	Second
Osuntokun 1972	+	–	+	–	++	+	Second
Osuntokun et al. 1969	++	–	+	–	++	+	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 Cyanide—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?	Other bias: Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	Risk of bias tier
Outcome: Thyroid effects										
Oral acute exposure										
de Sousa et al. 2007	+	+	+	+	–	+	–	–	++	Second
Hawk et al. 2016	–	+	+	+	+	++	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Avais et al. 2018	++	+	++	+	++	–	–	–	++	Second
Kamalu 1991, 1993; Kamalu and Agharanya 1991	+	+	–	+	++	–	–	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	–	++	++	Second
NTP 1993 (mice)	++	+	++	+	++	+	–	++	++	Second
Philbrick et al. 1979	–	–	++	–	++	–	–	++	+	Third
Soto-Blanco et al. 2002	++	+	++	+	++	+	++	++	++	First
Sousa et al. 2002	+	+	+	+	++	++	+	++	++	First
Tyner 2024; Tyner and Greeley 2023	++	+	++	+	++	++	++	++	++	First

Table C-9. Summary of Risk of Bias Assessment for Cyanide—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?	Other bias — Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	Risk of bias tier
Outcome: Neurological effects										
Oral acute exposure										
de Sousa et al. 2007	+	+	+	+	–	+	–	–	++	Second
Hawk et al. 2016	–	–	+	–	+	++	+	+	++	First
Ishaku et al. 2018	++	+	++	++	++	+	–	++	++	Second
Ogundele et al. 2014b	+	+	++	+	++	+	+	++	++	First
Rice et al. 2018 (dose-finding)	++	–	+	–	+	+	–	+	++	Second
Rice et al. 2018 (operant training)	++	+	+	+	+	+	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Gerhart 1986	–	–	–	–	++	+	–	++	++	Third
Gerhart 1987	–	–	–	–	++	+	–	++	++	Third
Ishaku et al. 2018	++	+	++	++	++	+	–	++	++	Second
Kamalu 1991, 1993	+	–	–	–	+	–	– –	+	++	Third
Mathangi et al. 2011	+	+	++	+	++	+	+	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	+	++	++	First
NTP 1993 (mice)	++	+	++	+	++	+	+	++	++	First
Philbrick et al. 1979	–	–	++	–	++	–	–	++	+	Second

Table C-9. Summary of Risk of Bias Assessment for Cyanide—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	Other 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?	Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	
Soto-Blanco et al. 2002	++	+	++	+	++	+	+	++	++	First
Oral chronic exposure										
Howard and Hanzal 1955	–	–	–	–	–	– –	–	–	++	Third
Outcome: Male reproductive effects										
Oral acute exposure										
Hawk et al. 2016	–	+	+	+	+	++	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Gerhart 1986	–	+	–	+	++	+	–	++	++	Second
Gerhart 1987	–	+	–	+	++	+	–	++	++	Second
Kamalu 1991, 1993	+	+	–	+	+	–	– –	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	–	++	++	Second
NTP 1993 (mice)	++	+	++	+	++	+	–	++	++	Second
Oyewopo et al. 2021a	+	+	++	+	++	+	–	++	++	Second
Oyewopo et al. 2021b	++	+	++	+	++	–	–	++	+	Second
Shivanoor and David 2015	+	+	+	+	+	–	+	+	–	First
Tyner 2024; Tyner and Greeley 2023	++	+	++	+	++	++	++	++	++	First
Oral chronic exposure										

Table C-9. Summary of Risk of Bias Assessment for Cyanide—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	Other 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?	Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	
Howard and Hanzal 1955	–	–	–	–	–	– –	–	–	++	Third

++ = 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 cyanide 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 cyanide and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

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

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

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

Table C-12. Key Features of Study Design for Experimental Animal Studies

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

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

Table C-13. Presence of Key Features of Study Design for Cyanide—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Thyroid effects					
Case series					
Delange and Ermans 1971	No	Yes	Yes	Yes	Moderate
Cliff et al. 1986	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Cyanide—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Neurological effects					
Population					
Money 1958	No	Yes	Yes	No	Low
Osuntokun 1968	No	Yes	Yes	Yes	Moderate
Osuntokun 1972	No	Yes	Yes	Yes	Moderate
Osuntokun et al. 1969	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Thyroid effects					
Oral acute exposure					
de Sousa et al. 2007	Yes	No	No	No	Very Low
Hawk et al. 2016	Yes	Yes	No	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Very Low
Oral intermediate exposure					
Avais et al. 2018	Yes	No	No	Yes	Low
Kamalu 1991, 1993; Kamalu and Agharanya 1991	Yes	Yes	No	Yes	Moderate
NTP 1993 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1993 (mice)	Yes	Yes	No	Yes	Moderate
Philbrick et al. 1979	Yes	Yes	No	Yes	Moderate
Soto-Blanco et al. 2002	Yes	No	Yes	Yes	Moderate
Sousa et al. 2002	Yes	No	Yes	Yes	Moderate
Tyner and Greeley 2023	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological effects					
Oral acute exposure					
de Sousa et al. 2007	Yes	No	No	No	Very Low
Hawk et al. 2016	Yes	Yes	Yes	Yes	High
Ishaku et al. 2018	Yes	Yes	Yes	Yes	Moderate
Ogundele et al. 2014a	Yes	No	Yes	Yes	Moderate
Rice et al. 2018	No	No	Yes	Yes	Low
Rice et al. 2018	No	Yes	Yes	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Low
Oral intermediate exposure					
Gerhart 1986	Yes	Yes	No	Yes	Moderate
Gerhart 1987	Yes	Yes	No	Yes	Moderate
Ishaku et al. 2018	Yes	Yes	Yes	Yes	Moderate
Kamalu 1993	Yes	Yes	No	Yes	Moderate
Mathangi et al. 2011	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1993 (mice)	Yes	Yes	No	Yes	Moderate
Philbrick et al. 1979	Yes	Yes	No	No	Low
Soto-Blanco et al. 2002	Yes	No	No	Yes	Low
Oral chronic exposure					
Howard and Hanzal 1955	Yes	No	No	No	Very Low
Outcome: Male reproductive effects					
Oral acute exposure					
Hawk et al. 2016	Yes	Yes	No	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Low
Oral intermediate exposure					
Gerhart 1986	Yes	Yes	Yes	Yes	High
Gerhart 1987	Yes	Yes	Yes	Yes	High
Kamalu 1991, 1993	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mice)	Yes	Yes	Yes	Yes	High
Oyewopo et al. 2021a	Yes	Yes	No	Yes	Low

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oyewopo et al. 2021b	Yes	Yes	Yes	Yes	Moderate
Shivanoor and David 2015	Yes	Yes	Yes	Yes	High
Tyner and Greeley 2023	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Howard and Hanzal 1955	Yes	No	Yes	No	Low

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

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

	Initial study confidence	Initial confidence rating
Outcome: Thyroid effects		
Oral acute exposure		
Animal studies		
de Sousa et al. 2007	Very Low	Moderate
Hawk et al. 2016	Moderate	
Sabourin et al. 2016	Very Low	
Oral intermediate exposure		
Animal studies		
Avais et al. 2018	Low	High
Kamalu 1991, 1993; Kamalu and Agharanya 1991	Moderate	
NTP 1993 (rat)	Moderate	
NTP 1993 (mice)	Moderate	
Philbrick et al. 1979	Moderate	
Soto-Blanco et al. 2002	Moderate	
Sousa et al. 2002	Moderate	
Tyner and Greeley 2023	High	

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

	Initial study confidence	Initial confidence rating
Oral chronic exposure		
Human studies		
Delange and Ermans 1971	Moderate	Moderate
Cliff et al. 1986	Moderate	
Outcome: Neurological effects		
Oral acute exposure		
Animal studies		
de Sousa et al. 2007	Very Low	High
Hawk et al. 2016	High	
Ishaku et al. 2018	Moderate	
Ogundele et al. 2014a	Moderate	
Rice et al. 2018	Low	
Rice et al. 2018	Moderate	
Sabourin et al. 2016	Low	
Oral intermediate exposure		
Animal studies		
Gerhart 1986	Moderate	High
Gerhart 1987	Moderate	
Ishaku et al. 2018	Moderate	
Kamalu 1993	Moderate	
Mathangi et al. 2011	High	
NTP 1993 (rat)	Moderate	
NTP 1993 (mice)	Moderate	
Philbrick et al. 1979	Low	
Soto-Blanco et al. 2002	Low	
Oral chronic exposure		
Human studies		
Money 1958	Low	Moderate
Osuntokun 1968	Moderate	
Osuntokun 1972	Moderate	
Osuntokun et al. 1969	Moderate	
Animal studies		
Howard and Hanzal 1955	Low	Low
Outcome: Male reproductive effects		
Oral acute exposure		
Animal studies		
Hawk et al. 2016	Moderate	Moderate
Sabourin et al. 2016	Low	

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

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Gerhart 1986	High	High
Gerhart 1987	High	
Kamalu 1991, 1993	High	
NTP 1993 (rat)	High	
NTP 1993 (mice)	High	
Oyewopo et al. 2021a	Low	
Oyewopo et al. 2021b	Moderate	
Shivanoor and David 2015	High	
Tyner 2024; Tyner and Greeley 2023	High	
Oral chronic exposure		
Animal studies		
Howard and Hanzal 1955	Low	Low

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for thyroid, neurological, and male reproductive effects following oral exposure are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with cyanide exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Thyroid effects			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	-1 risk of bias	Moderate
Outcome: Neurological effects			
Human studies	Moderate	-1 risk of bias +1 large magnitude of effect +1 consistency in body of evidence	High
Animal studies	High	-1 risk of bias +1 large magnitude of effect	High

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Male reproductive			
Animal studies	High	-1 risk of bias -1 unexplained inconsistency (drinking water studies) +1 consistency in body of evidence (gavage studies)	Moderate

Table C-17. Confidence in the Body of Evidence for Cyanide

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Thyroid effects (oral exposure)	Low	Moderate
Neurological effects (oral exposure)	High	High
Male reproductive effects (oral exposure)	No data	Low

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans

- Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

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

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

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

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

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

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

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

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

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

In the seventh step of the systematic review of the health effects data for cyanide, 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 cyanide is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Cyanide

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Thyroid (oral)	Low	Effect	Low
Neurological (oral)	High	Effect	High
Animal studies			
Thyroid (oral)	Moderate	Effect	Moderate
Neurological (oral)	High	Effect	High
Male reproductive (oral)	Moderate	Effect	Moderate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

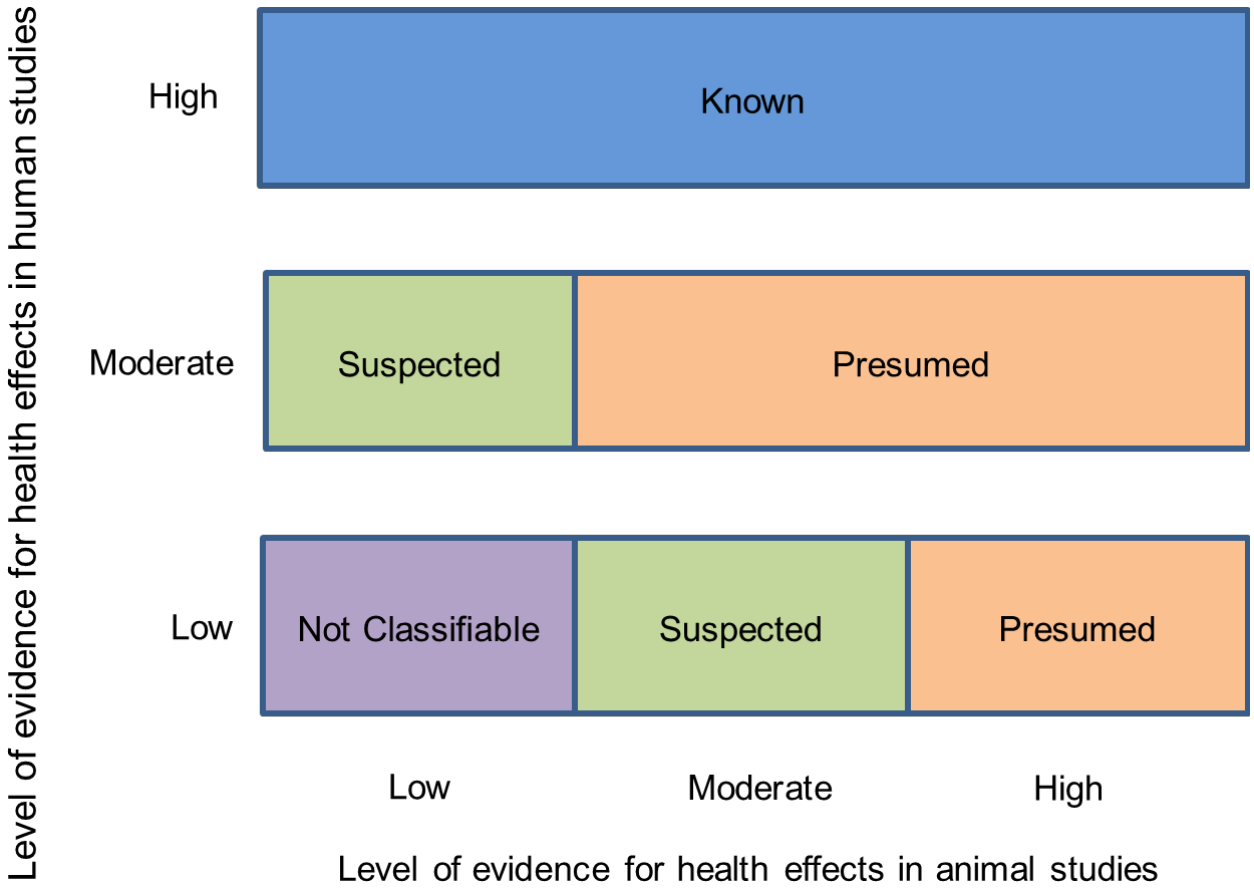
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

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

Known Health Effects

- Neurological effects (oral exposure)
  - There is evidence of regional outbreaks of neurological disease in African communities reliant on a diet rich in cassava as a carbohydrate source (Howlett et al. 1990; Ministry of Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). While other compounds in cassava may

contribute to observed effects, findings are strengthened by strong evidence of neurological effects from case reports and case-series reports that the CNS is a primary target following high-level cyanide exposure (see Section 2.15 for references). Even single exposures to high doses have resulted in permanent neurological dysfunction (Carella et al. 1988; Chin and Calderon 2000; Feldman and Feldman 1990; Grandas et al. 1989; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995; Uitti et al. 1985; Zaknun et al. 2005).

- Damage to the tissues of the CNS have been observed in animal studies following acute- and intermediate-duration exposure to cyanide compounds (de Sousa et al. 2007; Philbrick et al. 1979; Soto-Blanco et al. 2002). Data at nonlethal doses in animals are limited, with few studies evaluating sensitive neurobehavioral outcomes, particularly repeat-dose exposure via relevant exposure routes (drinking water or dietary exposures), increasing risk of bias. However, bolus administration studies are consistent with human poisoning cases, showing neurobehavioral changes at low doses (Hawk et al. 2016; Ishaku et al. 2018; Mathangi et al. 2011; Ogundele et al. 2014b) and overt and severe clinical signs of neurotoxicity prior to death at lethal doses (Gerhart 1987; Rice et al. 2018; Sabourin et al. 2016).
- Numerous plausible mechanisms of neurotoxicity have been proposed for cyanide; however, CNS effects are likely due to inhibition of cytochrome c oxidase activity and subsequent rapid biochemical changes in the brain such as changes in ion flux, neurotransmitter releases, and potentially oxidative stress (Chance and Erecinska 1971; Gibson and Greenwood 1963; Johnson and Isom 1985; Kanthasamy et al. 1991a, 1994; Persson et al. 1985; Pettersen and Cohen 1993; Smith 1996)

Presumed Health Effects

- Thyroid effects (oral exposure)
  - There is limited evidence of endemic goiter and altered thyroid function in African communities reliant on a diet rich in cassava as a carbohydrate source (Cliff et al. 1986; Delange and Ermans 1971).
  - Adverse thyroid effects (altered serum hormones, enlarged thyroid) have been reported in rats and rabbits following intermediate-duration oral exposure to cyanide compounds (Avais et al. 2018; Philbrick et al. 1979; Tyner and Greeley 2023). At lower doses, evidence of induction of potential homeostatic mechanisms for thyroid function (dose-related increases in the number of resorption vacuoles in the thyroid gland) in the absence of clear evidence of altered thyroid function have also been reported (de Sousa et al. 2007; Sousa et al. 2002)
  - The proposed mechanism of action for thyroid toxicity is competitive inhibition of the sodium-iodine symporter by the metabolite thiocyanate, which has a higher binding affinity than the physiological ligand, iodine (De Groef et al. 2006; EPA 2010; Tonacchera et al. 2004).
  - Considering the well-established competitive inhibition of the sodium-iodine symporter by thiocyanate, the hazard conclusion of suspected health effect based on low evidence in humans and moderate evidence in animals was upgraded to presumed health effect, incorporating evidence from all three data streams (human, animal, mechanistic).

Suspected Health Effects

- Male reproductive effects (oral exposure)
  - There are no data regarding potential male reproductive effects in humans following oral exposure to cyanide.
  - Data from drinking water studies in animals are inconsistent. Male reproductive effects were reported in rats (decreased weight of the testes, epididymis, cauda epididymis, and sperm effects) and mice (decreased cauda epididymis) in a 13-week study conducted by NTP (1993); however, these findings were not reproducible in a study in rats conducted by Tyner and Greeley (2023) designed to replicate the NTP (1993) study. Tyner and Greeley (2023)

attributed findings in the NTP (1993) study to decreased water intake at the highest dose. Tyner and Greeley (2023) also observed decreased water intake, to a lesser extent; no adverse male reproductive effect were observed compared to either water-restricted or ad libitum controls. Nonsignificant trends observed in sperm effects compared to *ad libitum* controls were no longer observed compared to water-restricted controls.

- Intermediate-duration gavage studies consistently reported mild, adverse effects on the male reproductive system (Gerhart 1986, 1987; Oyewopo et al. 2021a, 2021b; Shivanoor and David 2015). No adverse effects were noted in acute-duration bolus studies (Hawk et al. 2016; Sabourin et al. 2016).
- No animal studies evaluating male reproductive function (i.e., fertility) were identified, but the NTP (1993) study concluded that observed effects were unlikely to adversely impact fertility in rodents.
- No cyanide-specific mechanistic studies pertaining specifically to male reproductive toxicity were identified. EPA (2010) proposed that cyanide-associated hypothyroidism could potentially underlie male reproductive effects observed in some studies. However, a review by Williams and DeSesso (2023) challenged this proposal, pointing out that the perchlorate anion has a much higher affinity for the sodium iodide symporter compared to thiocyanide, but shows no evidence of adverse effects on the male reproductive system.

Table C-19. Hazard Identification Conclusions for Cyanide

Outcome	Hazard identification
Thyroid effects (oral)	Presumed
Neurological effects (oral)	Known
Male reproductive effects (oral)	Suspected

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

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

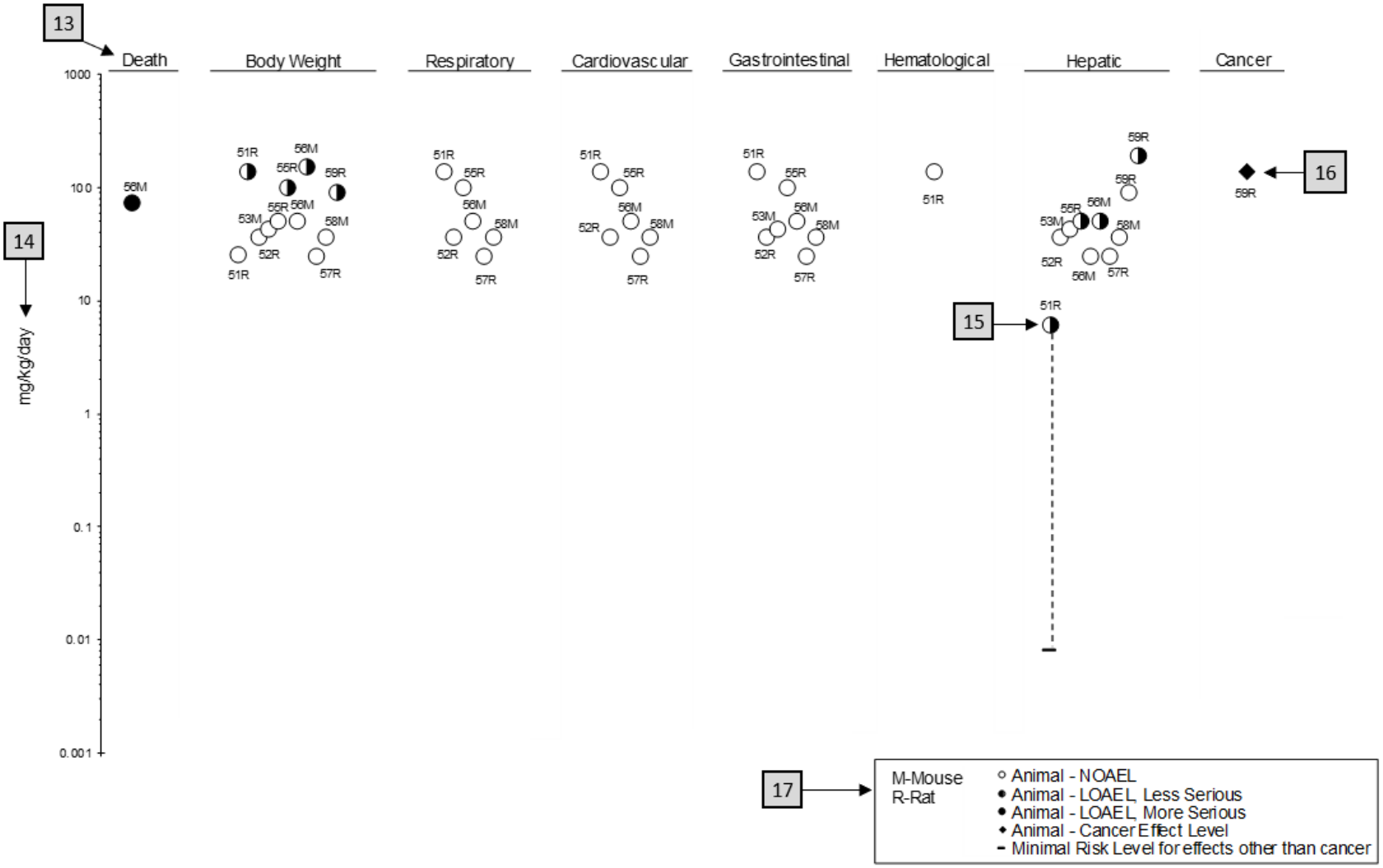
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

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

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

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

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result