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 substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Carbon disulfide
CAS Numbers: 75-15-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: 0.2 ppm (0.6 mg/m^3)
Critical Effect: Increased total lipid levels in hepatic microsomal fraction
Reference: Freundt et al. 1974b
Point of Departure: LOAEL of 20 ppm ($LOAEL_{HEC}$ of 16 ppm)
Uncertainty Factor: 90
LSE Graph Key: 2
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of 0.2 ppm was derived for carbon disulfide based on altered lipid homeostasis (increased total lipid levels in hepatic microsomal fractions) in rats exposed to concentrations ≥20 ppm for 8 hours; a no-observed-adverse-effect level (NOAEL) was not identified (Freundt et al. 1974b). The provisional MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 20 ppm, which was converted to a $LOAEL_{HEC}$ of 16 ppm and divided by a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: Endpoints identified as known (neurological), presumed (cardiovascular), or suspected (altered lipid homeostasis, male reproductive, developmental) human health effects following inhalation exposure based on systematic review (Appendix C) were considered as candidate critical effects for the acute-duration inhalation MRL. No reliable acute-duration human data are available. In animals, effects associated with altered lipid homeostasis were the only adverse effects noted below the lowest concentration associated with increased mortality following acute-duration inhalation exposure to carbon disulfide (Table A-1). Due to the large dose spacing in the developmental study by Lehotzky et al. (1985), the true NOAEL and LOAEL for observed effects lie within the wide interval between the lowest tested concentration of 3.2 ppm and next lowest concentration of 225 ppm, identified as a serious LOAEL for developmental effects (Table A-1). However, data reporting was inadequate for benchmark dose (BMD) modeling to estimate benchmark concentration (BMC) and 95% lower confidence limit on the benchmark concentration (BMCL) levels for developmental effects. Therefore, the effect associated with the lowest identified LOAEL of 20 ppm (altered lipid homeostasis) identified in the study by Freundt et al. (1974b) was selected as the critical effect for the acute-duration inhalation MRL. Additional support for this critical endpoint is provided by intermediate- and chronic-duration inhalation studies in rats, which report altered lipid homeostasis at all evaluated concentrations tested in rats (Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980); see *Other Additional Studies or Pertinent Information that Lend Support to this MRL* below.

Table A-1. Selected LOAEL Values in Animals for Acute-Duration Inhalation Exposure to Carbon Disulfide

Species	Duration	Effect level (ppm) NOAEL	LOAEL	Effect	Reference
Rat	8 hours	ND	20	***Altered lipid homeostasis:*** 15% increase in total lipids in the hepatic microsomal fraction	Freundt et al. 1974b
Mouse	60 minutes	ND	220	***Death:*** LC_{50}	Gibson and Roberts 1972
Rat	8 days GDs 7–15 6 hours/day	3.2	225 (SLOAEL)	***Developmental:*** 35% perinatal mortality; delayed eye opening; altered motor activity; impaired motor coordination; altered operant conditioning	Lehotzky et al. 1985
Mouse	30 minutes	119.5	577.6	***Neurological:*** Impaired operant training	Liang et al. 1983
Rabbit	12 days GDs 6–18 6 hours/day	304.1	597.9 (SLOAEL)	***Developmental:*** Increased postimplantation loss and early resorptions; 9% decrease in fetal body weight	Denny and Gerhart 1991
Rat	6 hours	300	600	***Altered lipid homeostasis:*** Decreased *ex vivo* hepatic cholesterol synthesis	Simmons et al. 1988
Rat	14 days 10 hours/day	ND	600 (SLOAEL)	***Neurological:*** Narcotic-like stupor; ataxia; hind-limb splay	Wilmarth et al. 1993
Rat	8 days GDs 7–15 6 hours/day	225	642 (SLOAEL)	***Neurological:*** Tremor and muscle weakness in dams that died	Lehotzky et al. 1985
Rat	1 hour	ND	642	***Neurological:*** Decrease in brain noradrenaline; increase in brain dopamine	Magos et al. 1974
Rat	2 weeks 6 hours/day 5 days/week	500	800	***Neurological:*** Slight gait impairment and ataxia in males; increased foot splay in females	Moser et al. 1998
Rat	18 hours	ND	803 (SLOAEL)	***Cardiovascular:*** Decreased cardiac rate ***Neurological:*** Severe narcosis; straightening of hindlimbs	Tarkowski and Sobczak 1971

Selected study for derivation of acute-duration inhalation MRL.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: Freundt et al. (1974b) was selected as the principal study because it identifies the lowest LOAEL for the critical effect (altered lipid homeostasis). Based on systematic review (Appendix C), this study was considered a first tier, medium confidence study for the evaluation of altered lipid homeostasis.

Summary of the Principal Study:

Freundt KJ, Schauenburg KJ, Eichhorn P. 1974b. Effect of acute exposure to carbon disulfide vapour upon some components of the hepatic-microsomal enzyme system in rats. Arch Toxicol 32:233-240.

Groups of adult female Wistar rats (5–15/group) were exposed to reagent-grade carbon disulfide via whole-body inhalation at concentrations of 20, 100, or 400 ppm for 8 hours. Additional groups of rats served as air-only controls (n=23) or were exposed to 400 ppm and then examined 36 hours later (recovery group; n=10). After the exposure period (or recovery period), rats were sacrificed. Livers were weighed and processed for determination of total lipid levels in the microsomal fraction. Liver weights were not reported; however, measured liver weights were used for reporting of lipid levels in mg/g of liver wet weight. Specific phospholipid levels (phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, sphingomyeline, lysophosphatidylcholine) and neutral lipid levels (cholesterol, triglycerides, diglycerides, free fatty acids) were determined in six animals/group in the main group and nine animals in the recovery group. Microsomal protein levels and activities in the microsomal fraction were determined in 7–13 rats/group from the main group only.

The total lipid content in the microsomal fraction of the liver was significantly increased by 15, 32, and 72% at 20, 100, and 400 ppm, respectively. Observed changes were attributable to elevated changes in neutral lipids (increased triglycerides at ≥20 ppm, cholesterol and free fatty acids at ≥100 ppm, and diglycerides at 400 ppm), as well as phospholipids (increased sphingomyeline at ≥20 ppm, phosphatidylcholine at ≥100 ppm, and lysophosphatidycholine at 400 ppm). After 36 hours, total lipid levels in rats exposed to 400 ppm were returning to normal, but were still significantly elevated by 25%, including residual increases in triglycerides, cholesterol, and sphingomyeline. The microsomal total protein content was increased by 16% at 400 ppm at the end of exposure.

Selection of the Point of Departure for the MRL: The LOAEL of 20 ppm for elevated total lipid levels in the microsomal fraction of hepatic tissue was selected as the point of departure (POD) for the acute-duration inhalation MRL.

In order to identify the POD, benchmark dose (BMD) modeling was attempted for total lipid levels in female rats reported by Freundt et al. (1974b). The data modeled for hepatic microsomal lipid levels are shown in Table A-2. 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. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data for total lipid levels in hepatic microsomes; all models were deemed questionable by BMDS using constant or non-constant variance. Therefore, the LOAEL of 20 ppm was selected as the POD for the provisional acute-duration inhalation MRL. This LOAEL is considered a minimal LOAEL because findings are slight in magnitude (15%), representing the start of the dose-response curve, with effects of greater magnitude at higher concentrations (e.g., 72% increase at 400 ppm) in this study and following longer-duration exposure (Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980). Findings from the 400-ppm dose group also suggest that acute-duration effects may be partially reversible (total lipid levels were elevated by only 25% by 36 hours post-exposure).

Table A-2. Selected Lipid Levels in the Hepatic Microsomal Fraction in Male Rats Following Inhalation Exposure to Carbon Disulfide for 8 Hours

	Concentration (ppm)			
	0	20	100	400
Total lipids (mg/g wet weight)	6.0±1.4[a] (23)	6.9±0.7[b] (6)	7.9±0.9[c] (5)	10.3±3.1[c] (15)

[a]Mean±SD (number of animals). SD values calculated from reported SE values (SD = SE * √N).
[b]p<0.05.
[c]p<0.01.

N = number of animals; SE = standard error of the mean; SD = standard deviation

Source: Freundt et al. 1974b

Adjustment for Intermittent Exposure: Because effects observed at the LOAEL were mild and transient following a single 8-hour exposure, an adjustment to 24-hour exposure may overestimate toxic effects. Therefore, no adjustment was made for continuous exposure.

Human Equivalent Concentration: The LOAEL of 20 ppm was converted to a $LOAEL_{HEC}$ based on dosimetric adjustments for systemic effects using the ratio of animal:human blood gas partition coefficients (EPA 1994). For carbon disulfide, the rat partition coefficient is 2.8 ppm (WHO 1979) and human blood:air partition coefficient is 3.61 (Kramer et al. 2016).

$$LOAEL_{HEC} = LOAEL \times \frac{rat\ partion\ coefficient}{human\ partition\ coefficent} = 20\ ppm \times \frac{2.8}{3.61} = 16\ ppm$$

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

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

Subsequently, the provisional MRL for acute-duration exposure to carbon disulfide via inhalation is:

$$Provisional\ MRL = \frac{LOAEL_{HEC}}{(UF)} = \frac{16\ ppm}{90} = 0.18\ ppm \approx 0.2\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that altered lipid homeostasis is a suspected target of carbon disulfide toxicity in humans following inhalation exposure based on inadequate evidence in humans and a moderate level of evidence in laboratory animals (Appendix C).

Several cohort studies of viscose rayon workers reported associations between cumulative carbon disulfide exposure and elevated total serum cholesterol levels (Jhun et al. 2007; Kotseva and De Bacquer 2000; NIOSH 1984a; Stanosz et al. 1994b; Vanhoorne et al. 1992a). Some of these studies also reported elevated serum LDL and/or decreased serum HDL levels in exposed workers (NIOSH 1984a; Stanosz et al. 1994b; Vanhoorne et al. 1992b). Historical exposure levels in these cohorts ranged from 0.58 to 36 ppm. A prospective cohort also observed increased serum triglycerides over a 5-year exposure to concentrations up to 21 ppm (Chrostek-Maj and Czeczotko 1995a). However, several other occupational studies with historical exposure levels ranging from 0.42 to 60 ppm did not exhibit any associations with any adverse serum lipid level effects (see Section 2.9 for citations). In general, findings from these occupational studies are challenging to interpret due to limited details on exposure for many studies (e.g., broad historical ranges), lack of control for concurrent chemical exposures in statistical analyses, and lack of control for any confounding factors in approximately 80% of all available studies, such as known risk factors for elevated serum lipids (e.g., smoking, alcohol intake, BMI, etc.).

Most available data from animals more clearly show that altered lipid homeostasis can occur following inhalation exposure; however, data are only available from a few studies and findings from acute-duration studies show some inconsistencies. Acute-duration inhalation studies other than Freundt et al. (1974b) were shorter in duration (6 hours versus 8 hours), in a different rat strain (Wistar versus F-344), in males versus females, and showed inter-study inconsistencies from the same laboratory (Simmons et al. 1988, 1989). Simmons et al. (1988) reported decreased *ex vivo* hepatic cholesterol synthesis following a single 6-hour exposure to 600 ppm, while Simmons et al. (1989) did not observe the same effect after 6-hour exposures for 1–3 days. The study authors attributed the discrepancy to decreased animal number (and therefore statistical power) in the latter study. Based on these issues, ATSDR considers the support from the intermediate- and chronic-duration animal studies to outweigh the conflicting evidence from the Simmons et al. (1988, 1989) studies with regard to animal evidence of altered lipid homeostasis. Altered lipid homeostasis has been observed at all evaluated intermediate- and chronic-duration concentrations tested in rats (Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980). In the intermediate-duration studies, serum cholesterol, phospholipid, and triglyceride levels generally increased in a concentration- and duration-dependent manner following exposure to concentrations ≥74 ppm for 2– 8 months; however, a plateauing of effects appeared to occur between 321 and 546 ppm. This may be due to overt toxicity occurring at 546 pm, including >20% decreases in body weight and hindlimb paralysis (Wrońska-Nofer 1973). Liver lipid synthesis increased by 38–82% in a concentration-related manner after 8 months. Chronic-duration data are limited to a 44–58% increase in total and esterified serum cholesterol levels in female rats exposed to 321 ppm for 12–15 months; this study only evaluated a single exposure level (Wrońska-Nofer et al. 1980). Recovery groups were not employed in the intermediate- and chronic-duration studies, so reversibility of these effects following repeated exposure are unknown.

While findings pertaining to lipid homeostasis appear to be mild, and at least partially reversible, they are considered adverse and relevant to human exposure due to the numerous adverse health effects in humans associated with high cholesterol (e.g., cardiovascular disease). This is particularly relevant for carbon disulfide since alterations in lipid homeostasis and metabolism are a proposed mechanism of atherosclerosis seen in some viscose rayon workers (Huang et al. 2004; Wrońska-Nofer et al. 2002). In support, the chronic-duration lipid homeostasis study discussed above also observed increase esterified cholesterol levels in the aortic walls of exposed rats (Wrońska-Nofer et al. 1980).

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Carbon disulfide
CAS Numbers: 75-15-0
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.

Rationale for Not Deriving an MRL: Endpoints identified as known (neurological), presumed (cardiovascular), or suspected (altered lipid homeostasis, male reproductive, developmental) human health effects following inhalation exposure based on systematic review (Appendix C) were considered as candidate critical effects for the intermediate-duration inhalation MRL. There are no human studies evaluating potential health effects following intermediate-duration exposure to carbon disulfide. The most sensitive effects in animals following intermediate-duration inhalation exposure are male reproductive effects (Table A-3).

Table A-3. Selected LOAEL Values in Animals for Intermediate-Duration Inhalation Exposure to Carbon Disulfide

		Effect level (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	10 weeks 5 days/week 2 hours/day	ND	16	***Male reproduction:*** Increased incidence of teratospermias, 3.2% decrease in sperm motility, and 9% decrease in sperm beat cross frequency; 28% decrease in serum LH	Huang et al. 2012
Rat	21 days 8 hours/day GDs 1–21	ND	32 (SLOAEL)	***Developmental:*** Club foot in F1 and F2 fetuses and microcephaly in F2 fetuses	Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983
Rat	13 weeks 6 hours/day 5 days/week	ND	50	***Neurological:*** Slight gait impairments	Moser et al. 1998
Rat	8 months 6 days/week 5 hours/day	ND	74	***Altered lipid homeostasis:*** Increased serum lipids; increased liver cholesterol synthesis	Wrońska-Nofer 1973
Rat	8 months 6 days/week 5 hours/day	ND	177	***Altered lipid homeostasis:*** Increased serum lipids; increased liver cholesterol synthesis	Wrońska-Nofer 1972

Table A-3. Selected LOAEL Values in Animals for Intermediate-Duration Inhalation Exposure to Carbon Disulfide

		Effect level (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	14 weeks 6 hours/day	ND	225	***Cardiovascular:*** Increased blood pressure; decreased cardiac output; increased vascular resistance	Morvai et al. 2005

GD = gestation day; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

In order to identify the most sensitive POD, BMD modeling was attempted for male reproductive effects reported by Huang et al. (2012). BMD modeling was attempted for serum luteinizing hormone and sperm effects (increased teratospermia, decreased sperm beat cross frequency, decreased progressive sperm motility) using a BMR of 1 standard deviation. Model fits were obtained for sperm beat cross frequency and sperm motility only, resulting in BMCL values of 5.7 and 2.7 ppm, respectively. Of the candidate PODs (Table A-4), the lowest BMCL of 2.7 ppm based on decreased progressive sperm motility was selected as the POD.

Table A-4. Candidate PODs for Intermediate-Duration Inhalation MRL based on Male Reproductive Effects in Rats Exposed to Carbon Disulfide (Huang et al. 2012)

	Effect level (ppm)			
Effect	NOAEL	LOAEL	BMCL	BMC
Decreased serum luteinizing hormone	ND	16	NA	NA
Increased teratospermia incidence	ND	16	NA	NA
Decreased sperm beat cross frequency	ND	16	5.8	15
Decreased progressive sperm motility	ND	16	2.7	11

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

The BMCL of 2.7 ppm was adjusted for continuous exposure (2 hours/24 hours; 5 days/7 days) to a $BMCL_{ADJ}$ of 0.16 ppm and converted into a $BMCL_{HEC}$ of 0.12 ppm using the ratio of rat:human blood gas partition coefficients of 0.78 (see acute-duration inhalation MRL for details). Using the $BMCL_{HEC}$ of 0.12 ppm as the final POD and a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) would result in a provisional intermediate-duration inhalation MRL of 0.004 ppm. However, this value is not proposed for the intermediate-duration inhalation MRL for the following reasons:

- There is some uncertainty regarding the biological significance of small deviations in sperm parameters in rodents. The standard BMR of 1 standard deviation may be overly conservative, as human data indicate that there is a range of acceptable deviation for these parameters (WHO 2021).

- The candidate intermediate-duration inhalation MRL based on sperm effects in rats would be lower than the proposed chronic-duration inhalation MRL based on neurological effects in humans. The confidence in the chronic-duration MRL is much higher due to both the endpoint and the study population.

Based on this information, it is proposed that the derivation of a provisional chronic-duration MRL of 0.1 ppm based on human data from seven occupational studies on a well-established target of carbon disulfide toxicity (peripheral neuropathy) is preferable over a provisional intermediate-duration MRL of 0.004 ppm based on rodent data based on an endpoint (male reproductive toxicity) with some uncertainties.

The next lowest candidate POD is based on developmental effects reported in a series of studies by Tabacova and colleagues (Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983). However, these studies are not considered of sufficient quality to serve as the basis for the MRL. Based on systematic review (Appendix C), these studies are considered third tier studies due to multiple methodological and reporting deficiencies. However, these studies do indicate potential for serious developmental effects at 32 ppm, precluding consideration of any candidate PODs >32 ppm as the potential basis for the intermediate-duration inhalation MRL.

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Carbon disulfide
CAS Numbers:	75-15-0
Date:	October 2024
Profile Status:	Draft for Public Comment
Route:	Inhalation
Duration:	Chronic
Provisional MRL:	0.1 ppm (0.3 mg/m^3)
Critical Effect:	Impaired peripheral nerve conduction
Reference:	Cirla and Graziano 1981; Godderis et al. 2006; Hirata et al. 1996; Johnson et al. 1983; Kim et al. 2000; Reinhardt et al. 1997a; Yoshioka et al. 2017
Point of Departure:	95% lower confidence limit of the weighted median NOAEL/LOAEL boundary of 4.02 ppm (POD_{ADJ} of 0.957 ppm)
Uncertainty Factor:	10
LSE Graph Key:	56
Species:	Human

MRL Summary: A provisional chronic-duration inhalation MRL of 0.1 ppm was derived for carbon disulfide based on impaired peripheral nerve conduction velocity in humans reported in several occupational exposure studies. The MRL is based on the duration-adjusted 95% lower confidence limit of the weighted median of 0.957 ppm calculated from the observed NOAEL/LOAEL boundary identified from seven occupational cohort studies (Cirla and Graziano 1981; Godderis et al. 2006; Hirata et al. 1996; Johnson et al. 1983; Kim et al. 2000; Reinhardt et al. 1997a; Yoshioka et al. 2017) and a total uncertainty factor of 10 for human variability.

Selection of the Critical Effect: Endpoints identified as known (neurological), presumed (cardiovascular), or suspected (altered lipid homeostasis, male reproductive, developmental) human health effects following inhalation exposure based on systematic review (Appendix C) were considered as candidate critical effects for the chronic-duration inhalation MRL.

Most of the available information on the chronic-duration toxicity of carbon disulfide vapor comes from numerous epidemiological studies of workers, predominately from the viscose rayon industry. While the entire body of evidence was considered, only occupational studies rated as tier 1 or tier 2 studies in risk of bias assessment with reliable exposure estimates allowing for NOAEL/LOAEL determinations were considered during the selection of a critical effect (Appendix C). Studies that were determined to have definite or probable high risk of bias for the key systematic review question "Is there confidence in the exposure characterization?" were excluded from consideration due to low confidence in the exposure estimates.

Reliable LOAELs were identified for neurological effects, cardiovascular effects, altered lipid homeostasis, and ophthalmological effects (Table A-5). The NOAEL and LOAEL ranges for these effects show considerable overlap; however, the lowest LOAEL was identified for neurological effects. Additionally, strength of evidence based on the number of studies and quality of the studies and overall database is strongest for neurological effects (see Appendix C). Specifically, all LOAELs shown in Table A-5 are based on impaired peripheral nerve conduction velocity. Therefore, impaired nerve conduction velocity was selected as the critical effect for derivation of the provisional chronic-duration inhalation MRL for carbon disulfide.

Table A-5. Summary of NOAELs and LOAELs for Sensitive Effects Reported in Epidemiological Studies of Carbon Disulfide

	Range (ppm)	Median (ppm)	References
Neurological (impaired nerve conduction velocity)			
NOAELs	4.02–5.64	4.85	Cirla and Graziano 1981; Johnson et al. 1983; Reinhardt et al. 1997a; Yoshioka et al. 2017
LOAELs	2.9–9.35	7.60	Godderis et al. 2006; Hirata et al. 1996; Johnson et al. 1983; Kim et al. 2000; Ruijten et al. 1990, 1993; Yoshioka et al. 2017
Cardiovascular (elevated blood pressure)			
NOAELs	6.44–14	7.5	Schramm et al. 2016; Tolonen et al. 1976; Vertin 1978
LOAELs	3.36–8.26	5.00	Kim et al. 2000; NIOSH 1984a; Takebayashi et al. 2004
Altered lipid homeostasis (elevated total serum cholesterol and/or LDL levels)			
NOAELs	5.6–14	6.44	Cai and Bao 1981; Schramm et al. 2016; Vertin 1978
LOAELs	3.36–8.26	5.81	Kim et al. 2000; NIOSH 1984a
Ophthalmological (retinal microaneurysms)			
NOAELs	5.6	5.6	Cai and Bao 1981
LOAELs	3.36–8.26	5.81	Kim et al. 2000; NIOSH 1984a
Developmental (congenital malformations)			
NOAELs	5.2	5.2	Zhou et al. 1988
LOAELs			
Male reproductive (fertility, sexual desire, sperm parameters, serum testosterone levels)			
NOAELs	5–8.26	8.1	NIOSH 1983, 1984a; Takebayashi et al. 2004
LOAELs			

LDL = low-density lipoprotein; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Summary of the Principal Study: Rather than selecting an individual study as the principal study, a group of seven studies that provide information on the NOAEL/LOAEL boundary were selected as the principal studies (see the *Selection of the Point of Departure for the MRL* section below for information on criteria for selecting these studies). Citations for the principal studies are listed below; summaries of these studies are included in Table A-6.

Cirla AM, Graziano C. 1981. Health impairment in viscose-rayon workers with carbon disulfide risk below 30 mg/m3: An exposed-controls study. G Ital Med Lav 3:69-73.

Godderis L, Braeckman L, Vanhoorne M, et al. 2006. Neurobehavioral and clinical effects in workers exposed to CS(2). Int J Hyg Environ Health 209(2):139-150. https://doi.org/10.1016/j.ijheh.2005.09.005.

Hirata M, Ogawa Y, Goto S. 1996. A cross-sectional study on nerve conduction velocities among workers exposed to carbon disulphide. Med Lav 87(1):29-34.

Johnson BL, Boyd J, Burg JR, et al. 1983. Effects on the peripheral nervous system of worker's exposure to carbon disulfide. Neurotoxicology 4(1):53-65.

Kim JS, Lim HS, Cheong HK, et al. 2000. Validity and cost-effectiveness of diagnostic procedures in CS2 poisoning. Ind Health 38(4):385-395. https://doi.org/10.2486/indhealth.38.385.

Reinhardt F, Drexler H, Bickel A, et al. 1997a. Electrophysiological investigation of central, peripheral and autonomic nerve function in workers with long-term low-level exposure to carbon disulphide in the viscose industry. Int Arch Occup Environ Health 70(4):249-256. https://doi.org/10.1007/s004200050215.

Yoshioka N, Takebayashi T, Nishiwaki Y, et al. 2017. Changes of median nerve conduction velocity in rayon manufacturing workers: A 6-year cohort study. J Occup Health 59(2):187-193. https://doi.org/10.1539/joh.16-0255-OA.

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Reference: Cirla and Graziano 1981

Study type and population: Retrospective cohort of 50 male viscose rayon workers (26–55 years old) and 50 matched male referents from Italy. Duration of exposure of workers was 3–12 years.

Measured air concentration: Mean values during a 12-year period (stationary air sampling)
Range: 10–25 mg/m^3 (3.2–8.0 ppm)

Analysis: Matching was based on sex, age (±3 years), physical feature (normal, slim, fat), work shift (daily, rotating), smoking history (never, light, heavy, very heavy, past only), alcohol history (never, light, heavy, very heavy, past only), socioeconomic status (all blue-collar), contractual skill, basic instruction (never above 8 years of school), district of birth and residence, and presumably the diet (one time a day at the canteen of the factory and generally eating uses of the rural tradition). Statistical analysis was based on paired Student's t-test comparisons.

Results:

Mean ± SD of peroneal nerve maximal motor conduction velocity (m/second), NS
- Exposed: 50.1±5.1
- Referent: 51.1±5.3

Mean ± SD of peroneal nerve slow fiber motor conduction velocity (m/second), NS
- Exposed: 42.1±5.7
- Referent: 43.9±6.5

Interpretation: Motor nerve conduction velocity in the peroneal nerve was not significantly different between exposed and referent groups; therefore, the midpoint of the range of means (5.6 ppm) is considered a NOAEL for altered nerve conduction velocity.

Reference: Godderis et al. 2006

Study type and population: Retrospective cohort of 85 viscose rayon workers, including 60 workers with "low" exposure (<31 mg/m^3 [10 ppm]) and 25 workers with "high" (>31 mg/m^3 [10 ppm]) exposure, and 66 unexposed referents from Belgium. Average duration of exposure of workers was 10.5 years. The mean ages of the exposed workers and referents were 37.2 and 41.2 years, respectively.

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Measured air concentration: Annual geometric mean ± SD since 1983 (personal air monitoring)
All exposed: 15.3±3.0 mg/m^3 (4.91 ppm)
Low exposure: 8.9±1.1 mg/m^3 (2.9 ppm)
High exposure: 59.2±5.2 mg/m^3 (19.0 ppm)

Cumulative exposure index: Geometric mean ± SD
Low: 59.5±17.1 mg/m^3*years (19.1 ppm-years)
High: 746.6±116.1 mg/m^3*years (239.8 ppm-years)

Analysis: Subjects were excluded for history of ethyl abuses, cerebral contusion, cerebro-vascular accident, epilepsy, diabetes, or depression. Data were analyzed using ANOVA for comparison of means between exposure groups and referents with multiple logistic regression analysis, using race, shift work, BMI, smoking, educational level, age, alcohol use, personality score (NSC-60), and motivation as covariates. For some outcome variables, lognormal transformation was needed in order to compare exposure groups, including sural sensory nerve conduction and peroneal motor nerve conduction velocity.

Results:

Geometric mean ± SE of log(peroneal nerve motor conduction velocity) (m/second)

- All fibers, NS
  - All exposed: 47.71±1.01
  - High exposed: 47.48±1.02
  - Low exposed: 47.81±1.01
  - Referent: 48.39±1.01
- Fastest fibers, NS
  - All exposed: 49.00±1.01
  - High exposed: 47.84±1.02
  - Low exposed: 49.48±1.02
  - Referent: 49.66±1.02
- Slowest fibers, NS
  - All exposed: 38.53±1.03
  - High exposed: 36.72±1.06
  - Low exposed: 39.28±1.04
  - Referent: 38.47±1.04

Geometric mean ± SE of log(sural nerve sensory conduction velocity) (m/second), p<0.001

- All exposed: 36.81±1.09
- High exposed: 27.6±1.24
- Low exposed: 41.39±1.09
- Referent: 55.58±1.02

Multiple logistic regression analysis, β (SE):

- High exposed: -0.18 (0.07), p≤0.01
- Low exposed: -0.13 (0.05), p≤0.01

Interpretation: Significant association between carbon disulfide exposure and sural nerve sensory nerve conduction velocity, after adjustment for confounders, in both low- and high-exposure group; therefore, the geometric mean exposure of the low exposure group (2.9 ppm) is a LOAEL for impaired nerve conduction velocity.

Reference: Hirata et al. 1996

Study type and population: Retrospective cohort of 46 viscose rayon workers (mean age of 43.9 years), including 24 current workers and 22 former workers, and 26 age-matched unexposed referents from Japan. Average duration of exposure of workers was 11.4 years. For the former workers, the average duration since cessation of exposure was 6.28±7.50 years.

Measured air concentration: Personal sampling (conducted 5 years prior to study), 8-hour TWA level:
Arithmetic mean: 4.76 ppm
Range: 2.3–17 ppm

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Analysis: Subjects were excluded for history of neurological disease or injury or if they consumed more than 80 mL alcohol daily. Data were analyzed using Student's t test and ANOVA with multiple comparison by Scheffe's method.

Results:

Mean ± SD of ulnar nerve conduction velocities (m/second)

- Motor conduction velocity, NS
  - All exposed: 54.0±3.74
  - Current: 53.8±3.56
  - Former: 54.3±3.90
  - Referent: 54.9±3.57
- Slow fiber motor conduction velocity, NS
  - All exposed: 50.5±4.20
  - Current: 49.6±4.47
  - Former: 51.3±3.84
  - Referent: 51.9±4.45
- Mixed nerve conduction velocity, NS
  - All exposed: 58.5±3.80
  - Current: 57.8±3.64
  - Former: 59.3±3.81
  - Referent: 59.1±3.58

Mean ± SD of peroneal nerve motor conduction velocity (m/second)

- All exposed: 43.2±2.61, p<0.05
- Current: 42.6±2.81, p<0.05
- Former: 43.4±2.11
- Referent: 44.9±2.70

Mean ± SD of sural nerve sensory conduction velocity (m/second)

- All exposed: 49.9±5.04, p<0.05
- Current: 49.1±4.82, p<0.05
- Former: 50.0±5.06
- Referent: 53.4±4.96

Interpretation: Significant association between carbon disulfide exposure and sural nerve sensory nerve conduction velocity and peroneal nerve motor conduction velocity in exposed workers. Therefore, the mean exposure of 4.76 ppm is a LOAEL for impaired nerve conduction velocity. Multiple comparison analysis indicates that findings are no longer significant in former workers, suggesting reversibility of effects in this population.

Reference: Johnson et al. 1983

Study type and population: Retrospective cohort of 145 male viscose rayon workers (mean age of 38.5 years) and 212 male referents (mean age 33.9 years) from the United States (Tennessee). Average duration of exposure of workers was 12.1 years.

Measured air concentration: Current mean (median) 8-hour TWAs (personal sampling)
Referent: 0.2 ppm
Exposed: 7.3 ppm
Low (n=44): 1.2 (1.0) ppm
Moderate (n=61): 5.1 (4.1) ppm
High (n=40): 12.6 (7.6) ppm

Cumulative exposure index:
Low (n=44): 500–1,000 ppm-months
Moderate (n=61): 1,000–1,500 ppm-month
High (n=40): ≥1,500 ppm-months

Analysis: The numbers of men from minority groups and women were too small for valid comparisons; therefore, subjects were restricted to white male workers. Current and cumulative exposure data were analyzed using multivariate ANOVA, including age as a confounder. A two-way ANOVA was used to evaluate dose-effect relationships for nerve conduction velocities.

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Results:

Mean ± SD of nerve conduction velocities, adjusted to temperature and terminal distance (m/second)

- Ulnar nerve motor conduction velocity, NS
  - All exposed: 55.9±6.3
  - High: 55.0±6.6
  - Moderate: 56.8±6.0
  - Low: 55.5±6.4
  - Referent: 56.9±6.7
- Sural nerve sensory conduction velocity
  - All exposed: 40.4±4.0, p<0.01
  - High: 40.5±3.0
  - Moderate: 39.8±3.7
  - Low: 41.2±5.2
  - Referent: 41.8±3.4

Mean ± SD of nerve conduction velocities, adjusted to temperature and terminal distance (m/second)

- Peroneal nerve motor conduction velocity
  - All exposed: 43.2±4.9, p<0.05
  - High: 41.8±4.5, p<0.05
  - Moderate: 43.4±4.8
  - Low: 43.7±5.1
  - Referent: 45.3±4.4

Cumulative exposure assessment:
F-value (df): 122.8 (2,115)
PR>F: 0.05

Interpretation: Significant associations were observed between cumulative carbon disulfide exposure and peroneal nerve motor nerve conduction velocity. Group analysis indicated that conduction velocity was only significantly decreased in the highest exposure group. Therefore, the median exposures of 4.1 and 7.6 ppm are considered NOAEL and LOAEL values, respectively, for impaired nerve conduction velocity. A significant decrease in sural nerve sensory conduction velocity was observed in all workers (combined) compared to referents; however, exposure group data did not reveal a concentration-dependent effect.

Reference: Kim et al. 2000

Study type and population: Subcohort of 262 viscose rayon workers and 49 unexposed referents from a larger retrospective cohort in Korea (1,237 workers, 315 referents). Mean ages of the large cohort were 32.5–38.6 years. Duration of exposure of workers was 1–≥15 years.

Measured air concentration: Historical range of mean 8-hour TWA levels ("direct measurements" in different workplaces)
1986-1992: 0.43–6.28 ppm

Cumulative exposure index:
Referents (n=49): 0 ppm-years
Low (n=67): 0.1–49.9 ppm-years
Moderate (n=74): 50.0–149.9 ppm-years
High (n=72): ≥150 ppm-years

Analysis: Data were analyzed by comparing the proportion of subjects with abnormal findings across four exposure categories, adjusting for age. Dose-response relationship was evaluated by test of linearity by Cochran-Mantel-Haenszel chi-square test.

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Results:

Prevalence of abnormal sensory or motor nerve conduction (median, ulnar, peroneal, and/or tibial nerve):

- All exposed: 28.7
- High: 36.1
- Moderate: 34.5
- Low: 30.1
- Referent: 7.3

p-trend <0.001

Prevalence ratio (95% CI):

- Exposed/non-exposed: 4.14 (1.59–10.79)

Interpretation: The prevalence of abnormal sensory and/or motor nerved conduction velocity was significantly increased in exposed workers, compared to control. Cumulative exposure analysis showed an association with concentration-duration. Based on available exposure data, the midpoint of the range of exposure means (3.36 ppm) is a LOAEL for impaired nerve conduction velocity.

Reference: Reinhardt et al. 1997a

Study type and population: Retrospective cohort of 222 viscose rayon workers (mean age 35 years) and 191 unexposed referents (mean age 33 years) from Germany. Median duration of exposure of workers was 6 years.

Measured air concentration: Median (range) current air concentrations
4.02 (0.2–30) ppm

Note: The study authors calculated cumulative exposure indices for analyses; however, cumulative exposure indices were not reported.

Analysis: Subjects were excluded for alcohol-related neuropathy, diabetes mellitus, and previous work with exposure to potentially neurotoxic solvents. Data were analyzed using cumulative exposure indices and multiple linear regression analysis, using age, weight, height, HbA1c, cigarette consumption (in pack-years), and alcohol consumption as covariates.

Results:

Median (range) of peroneal nerve motor conduction velocity (m/second)

- Exposed: 48.00 (35.50–58.80)
- Referent: 49.80 (34.30–58.60)

Multiple linear regression analysis, β

- Exposed versus referent: -0.78, p<0.05
- Cumulative exposure: -0.05, NS

Mean (SD) of sural nerve sensory conduction velocity (m/second)

- Exposed: 48.70 (39.70–58.90)
- Referent: 49.10 (41.00–58.30)

Multiple linear regression analysis, β

- Exposed versus referent: +0.39, NS
- Cumulative exposure: -0.75, NS

Interpretation: Cumulative exposure was not significantly associated with motor or sensory nerve conduction velocity, after adjustment for confounders. Therefore, the median exposure value of 4.02 is considered a NOAEL for impaired nerve conduction velocity.

Table A-6. Summary of the Principal Studies Examining Peripheral Nerve Conduction Velocity in Workers Exposed to Carbon Disulfide

Reference: Yoshioka et al. 2017

Study type and population: Longitudinal cohort of 347 male viscose rayon workers (mean age 36.1 years) and 337 unexposed male referents (mean age 36.2 years) from Japan. Average duration of exposure of workers was 22.1 years at baseline (1992–1993). Workers were re-examined at 6-year follow-up (1998–1999). In the exposure group, 121 workers ceased employment and/or exposure during the 6-year follow-up period (ex-exposed).

Measured air concentration: During 6-year follow-up period (breathing zone measurements)

1st Tertile: 0.8–4.6 ppm (mean 2.84 ppm)
2nd Tertile: 4.7–6.6 ppm (mean 5.64 ppm)
3rd Tertile: 6.6–16.0 ppm (mean 9.35 ppm)

Mean (exposed): 5.96
Mean (ex-exposed) 3.93

Analysis: Subjects were excluded for medical history of cerebrovascular or cardiovascular disease. Data were analyzed using ANOVA with the Tukey-Kramer method. Multiple linear regression was conducted, adjusting for age, BMI, education status (high school or above versus junior high school or below), smoking status (former or current smoker versus never smoked), and alcohol consumption (occasional or habitual drinker versus non-drinker).

Results:

Mean ± SD of reduction in median nerve motor conduction velocity over 6-year follow-up (m/second), NS

- Currently exposed: -1.60±3.70
- Ex-exposed: -1.61±3.37
- 1st tertile: -1.62±3.56
- 2nd tertile : -1.36±3.92
- 3rd tertile: -1.81±3.64
- Referent: -1.52±3.49

Multiple linear regression analysis, β

- 1st tertile versus referent: -0.074, NS
- 2nd tertile versus referent: 0.259, NS
- 3rd tertile versus referent: -0.187, NS

Mean ± SD of reduction in median nerve sensory conduction velocity over 6-year follow-up (m/second)

- Currently exposed: -4.47±3.94, p<0.05
- Ex-exposed: -3.26±3.79
- 1st tertile: -4.23±3.76
- 2nd tertile: -4.27±3.65
- 3rd tertile: -4.89±4.39, p<0.05
- Referent: -3.38±3.97

Multiple linear regression analysis, β

- 1st tertile versus referent: -0.153, NS
- 2nd tertile versus referent: -0.350, NS
- 3rd tertile versus referent: -1.021, p<0.05

Interpretation: Exposure to carbon disulfide in the highest tertile was associated with a significant reduction in median nerve sensory conduction velocity over the 6-year follow-up period, after adjusting for confounders. Therefore, the mean exposures of 5.64 and 9.34 ppm are considered NOAEL and LOAEL values, respectively, for impaired nerve conduction velocity.

ANOVA = analysis of variance; BMI = body mass index; CI = confidence interval; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; NS = not significant; SD = standard deviation; SE = standard error; TWA = time-weighted average

Selection of the Point of Departure for the MRL: The 95% lower confidence limit of the weighted median of 4.02 ppm based on the NOAEL/LOAEL boundary for impaired peripheral nerve conduction in the seven principal studies was selected as the POD for the chronic-duration inhalation MRL.

In order to determine the POD, occupational studies providing adequate exposure assessments to estimated NOAEL and/or LOAEL determinations for impaired peripheral nerve conduction velocity in workers exposed to carbon disulfide were considered as principal studies for the derivation of the chronic-duration inhalation MRL (Table A-7).

Table A-7. NOAEL and LOAEL Values for Occupational Cohort Studies Evaluating Altered Peripheral Nerve Conduction in Viscose Rayon Workers

	Measured air concentration (ppm)		
Study	NOAEL	LOAEL	Measurement metric[a]
Cirla and Graziano 1981	5.6		Midpoint; range of means over 12 years (3.2–8.0 ppm)
Godderis et al. 2006		2.9	Annual geometric mean
Hirata et al. 1996		4.76	Mean 8-hour TWA (measured 5 years prior)
Johnson et al. 1983	4.1	7.6	Current median 8-hour TWA
Kim et al. 2000		3.36	Midpoint; range of means (1986-1992; 0.43–6.28 ppm)
Reinhardt et al. 1997a	4.02		Current median
Ruijten et al. 1990		8.25[b]	Mean TWA exposure over duration of employment
Ruijten et al. 1993		8.16[c]	Mean TWA exposure over duration of employment
Yoshioka et al. 2017	5.64	9.35	Mean air concentrations during 6-year study
Median	4.85	7.60	

[a]Central estimate of exposure, as reported by the study author (best available).
[b]Calculated from reported mean cumulative exposure of 165 ppm-years divided by the mean exposure of 20 years; value is consistent with the reported range of means (1–17 ppm).
[c]Calculated from reported mean cumulative exposure of 213 ppm-years divided by mean exposure of 26.1 years.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; TWA = time-weighted average

Typically, the POD would be the highest NOAEL below the lowest LOAEL or the lowest free-standing LOAEL. The problem with this approach being applied to the occupational worker nerve conduction studies is that there is substantial overlap in reported NOAELs and LOAELs. The overlap between the lower end of the LOAEL range and the NOAEL range does not support selection of any single NOAEL or LOAEL as a POD. As an alternative approach, the following was assumed:

1. A NOAEL/LOAEL boundary exists and is located somewhere within the range of overlapping NOAELs and LOAELs.
2. Each NOAEL and LOAEL in this range represents an independent estimate of the NOAEL/LOAEL boundary.
3. The best estimate of the NOAEL/LOAEL boundary is the weighted median of the set of overlapping NOAELs and LOAELs (weighted for study size, which assumes greater confidence in estimates from larger studies).
4. The lower 95% confidence limit on the median was selected as the POD to account for uncertainty in the estimated weighted median.

This approach avoids having to make a highly uncertain selection of a single study as the basis for the POD. Instead, this approach utilizes information from multiple studies to identify an exposure that is most likely to be the NOAEL/LOAEL boundary, a threshold exposure level at which neurological effects may (or may not) occur. The POD is then set at the lower 95% confidence limit of the NOAEL/LOAEL boundary to account for uncertainty in the estimate.

Overlapping NOAELs and LOAELs include all LOAELs that are less than or equal to the highest NOAEL for the outcome (5.64 ppm; Yoshioka et al. 2017), plus all NOAELs that are greater than or equal to the lowest LOAEL (2.9 ppm; Godderis et al. 2006). That is, all the values from Table A-7 that fall within the NOAEL/LOAEL boundary range of 2.9–5.64 ppm were included in the calculation of the POD. Based on these criteria, all studies had at least one value included in the MRL calculation (Table A-8), with the exception of Ruitjen et al. (1990, 1993), which only identified LOAEL values >5.64 ppm. Therefore, the studies by Ruitjen et al. (1990, 1993) were excluded from the POD calculation. NOAEL/LOAEL values were used instead of BMC/BMCL values for each study for the following reasons:

- Quantitative data were not available or not amenable to modeling (e.g., reported for only a single exposure group): Cirla and Graziano 1981; Hirata et al. 1996; Kim et al. 2000; Reinhardt et al. 1997a.

- Available quantitative data are amenable to modeling; however, the only values reported are raw values unadjusted for key confounders (e.g., age, height, BMI): Godderis et al. (2006); Johnson et al. (1983); and Yoshioka et al. (2017). For these cohorts, NOAEL/LOAEL determinations based on multivariable regressions accounting for confounders are considered more reliable estimates of the true adverse effect levels.

- As reviewed by Price et al. (1996), several groups have obtained raw data from NIOSH for the Johnson et al. (1983) study and conducted BMD modeling, including modeling with adjustment for confounders; however, only BMC values (not BMCL) values were calculated. Calculated BMC values (11.8–20.0 ppm) are outside the NOAEL/LOAEL boundary range identified for the derivation of the provisional chronic-duration inhalation MRL and are therefore not useful for this analysis.

Table A-8. NOAEL and LOAEL Values for Studies Defining the NOAEL/LOAEL Boundary for Altered Peripheral Nerve Conduction

Study	Study type	Subject number	POD	Measured air concentration[a] (ppm)
Cirla and Graziano 1981	Retrospective cohort	100	NOAEL	5.6
Godderis et al. 2006	Retrospective cohort	151	LOAEL	2.9
Hirata et al. 1996	Retrospective cohort	72	LOAEL	4.76
Johnson et al. 1983	Retrospective cohort	357	NOAEL	4.1
Kim et al. 2000	Retrospective cohort	311	LOAEL	3.36
Reinhardt et al. 1997a	Retrospective cohort	413	NOAEL	4.02
Yoshioka et al. 2017	Longitudinal cohort	684	NOAEL	5.64
			Median NOAEL/LOAEL boundary (95% CI[b])	**4.10 (3.36, 5.60)**
			Weighted[c] median NOAEL/LOAEL boundary (95% CI[b])	**4.76 (4.02, 5.64)**

[a]POD values are based on the best available central estimate of exposure, as reported by the study author (see Table A-7 for details).
[b]The 95% CI for the median was calculated using a nonparametric bootstrap (the 97.5th percentile of 10,000 calculations of the weighted median where the probability of selection of any study to include in each median was N_study/N_all studies)
[c]Median weighted based upon the number of subjects in the study. The lower CI (4.02 ppm) is the selected POD for the chronic-duration inhalation MRL.

CI = confidence interval; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; POD = point of departure

Adjustment for Intermittent Exposure: The POD of 4.02 ppm (based on the 95% confidence interval on the weighted median) was adjusted for a continuous exposure scenario, assuming a standard work week of 8 hours/day, 40 hours/week.

$$POD_{ADJ} = POD_{\square} \times \frac{\text{hours/day}}{24\ hours} \times \frac{\text{days/week}}{7\ days} = 4.02\ ppm \times \frac{8\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.957\ ppm$$

Uncertainty Factor: The following uncertainty factors were then applied to the POD_{ADJ} to derive the MRL.

- 10 for human variability

Subsequently, the provisional inhalation MRL for chronic-duration exposure to carbon disulfide is:

$$Provisional\ MRL = \frac{POD_{ADJ}}{(UF)} = \frac{0.957\ ppm}{10} = 0.0957\ ppm \approx 0.1\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Based upon systematic review, the nervous system is a known target of carbon disulfide toxicity in humans following inhalation exposure based on a high level of evidence in humans and a high level of evidence in laboratory animals (Appendix C).

In humans, there is strong evidence for exposure-related damage to the peripheral nervous system. Findings from occupational cohorts clearly show associations that are both concentration- and duration-dependent. Altered nerve conduction velocity, which is the most sensitive neurological endpoint associated with carbon disulfide exposure, has been reported in several cohorts of viscose rayon workers (Hirata et al. 1996; Kim et al. 2000; Johnson et al. 1983; Ruijten et al. 1990, 1993; Seppalainen and Tolonen 1974; Vanhoorne et al. 1995; Yoshioka et al. 2017). Some of these studies also reported increased self-reported symptoms of polyneuropathy at exposure concentrations ranging from 0.43 to 36 ppm, such as pain, insensitive spots, paresthesia, numbness, and difficulty walking (Kim et al. 2000; Vanhoorne et al. 1994). Overt polyneuritis or polyneuropathy are common findings among highly exposed workers (≥100 ppm), including impaired nerve conduction, subjective complaints, decreased pain sensitivity, tremors, and abnormal movements resembling early Parkinsonism (Chapman et al. 1991; Chu et al. 1995; Lancranjan et al. 1972; Peters et al. 1988; Vasilescu 1976).

In animals, evidence of peripheral nerve damage includes impaired peripheral nerve conduction velocity and behavioral/clinical evidence of peripheral nerve damage (e.g., foot drag, hindlimb paralysis) (Frantik 1970; Graham and Popp 1992a; Herr et al. 1998; Phillips 1983a, 1983b, 1983c; Rebert and Becker 1986; Wrońska-Nofer 1973). Some of the clinical signs may be associated with damage to both the peripheral nerves as well as observed damage to nerve tracts in the spinal cord (Graham and Popp 1992a; Phillips 1983a, 1983b; Valentine et al. 1997).

The proposed mechanism of action (MOA) for peripheral neuropathy following carbon disulfide is biologically plausible in humans. The proposed MOA is based on the formation of crosslinked neurofilaments resulting in axonal damage via the following steps: (1) formation of dithiocarbamate protein adducts; (2) adducts decompose or oxidize to form an electrophile; (3) electrophile reactions with protein nucleophiles, resulting in protein crosslinking; (4) progressive cross-linking of stable neurofilament during axonal anterograde transport; (5) crosslinked masses block transport at nodes of Ranvier (impeding peripheral nerve signals); and (6) axonal swelling and degeneration (Graham et al. 1995; Harry et al. 1998; Health Canada 1999; Llorens 2013; Newhook et al. 2001). These protein adducts have been demonstrated in rats following inhalation exposure to carbon disulfide (Valentine et al. 1993, 1997).

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Carbon disulfide
CAS Numbers: 75-15-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
Provisional MRL: 0.03 mg/kg/day
Critical Effect: Increased resorptions/litter
Reference: NCTR 1984b
Point of Departure: LOAEL of 25 mg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 9
Species: Rabbit

MRL Summary: A provisional acute-duration oral MRL of 0.03 mg/kg/day was derived for carbon disulfide based on developmental effects (increased resorptions per litter) in rabbits exposed to concentrations ≥25 mg/kg/day from GDs 6–19; a NOAEL was not identified (NCTR 1984b). The provisional MRL is based on a LOAEL of 25 mg/kg/day, which was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Endpoints identified as presumed (neurological) or suspected (developmental) human health effects following oral exposure based on systematic review (Appendix C) were considered as candidate critical effects for the provisional acute-duration oral MRL. No reliable acute-duration human data are available. In animals, the most sensitive effects following acute-duration oral exposure are developmental effects (Table A-9). Therefore, developmental effects were selected as the critical effect for the acute-duration oral MRL.

Table A-9. Selected LOAEL Values in Animals for Acute-Duration Oral Exposure to Carbon Disulfide

		Effect level (mg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rabbit	14 days GDs 6–19	ND	25	***Developmental:*** 32% resorptions per litter (compared to 12% in controls)	NCTR 1984b
Rat	10 days	10	50	***Neurological:*** Lethargy	NCTR 1984a
Rabbit	14 days GDs 6–19	75	150 (SLOAEL)	***Developmental:*** 19% fetuses with malformations; 31% decrease in live fetuses/litter; 61% resorptions/litter	NCTR 1984b
Rabbit	14 days GDs 6–19	100	200 (SLOAEL)	***Neurological:*** Convulsions ***Developmental:*** 4/5 litters with complete resorption	NCTR 1984b
Rat	10 days GDs 6–15	100	200	***Developmental:*** 6% decrease in fetal weight	NCTR 1984a

Table A-9. Selected LOAEL Values in Animals for Acute-Duration Oral Exposure to Carbon Disulfide

Species	Duration	Effect level (mg/kg/day) NOAEL	LOAEL	Effect	Reference
Rat	Once	ND	300	***Neurological:*** Decreased norepinephrine and increased dopamine in the brain	Kanada et al. 1994
Rat	10 days GDs 6–15	200	400 (SLOAEL)	***Neurological:*** Hindlimb paralysis in dams	NCTR 1984a

Selected study for derivation of acute-duration oral MRL.

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

Selection of the Principal Study: NCTR (1984b) was selected as the principal study because it identifies the lowest LOAEL for the critical effect (developmental toxicity).

Summary of the Principal Study:

NCTR. 1984b. Teratologic evaluation of carbon disulfide (CAS No. 75-15-0) administered to New Zealand white rabbits on gestational days 6 through 19. Research Triangle Park, NC: National Center for Toxicological Research. PB84192350. NCTR222802031.

Carbon disulfide was administered to artificially-inseminated New Zealand White rabbits (26–30/group) at doses of 0, 25, 75, or 150 mg/kg/day via gavage in corn oil on GDs 6–19. Does were sacrificed on GD 30. Females were weighed and observed for clinical signs of toxicity. At sacrifice, the gravid uterus was weighed, and the number of implantations sites, live, dead, and resorbed fetuses were recorded. All live fetuses were weighed and examined for gross external, visceral, and skeletal malformations. Each dose was tested in two separate replicates, and statistics were conducted for dose, replicate, and dose x replicate.

No exposure-related mortality was observed. Occasional clinical signs were observed shortly after dosing, predominately at 150 mg/kg/day. The most frequent was reduction or lack of daily fecal output in up to 7/26 animals and alopecia in up to 4/26 animals; other findings were limited to a few animals across all dose groups. Maternal weight gain during gestation was decreased at ≥75 mg/kg/day; however, no exposure-related differences were noted once body weights were controlled for gravid uterine weight (which was decreased at ≥75 mg/kg/day due to increased resorptions). Maternal absolute and relative liver weights were elevated at ≥75 mg/kg/day. At sacrifice on day 30, there were no differences in corpora lutea, implantation sites, or preimplantation loss per doe. However, the number of resorptions/litter was increased by 2.9-, 4.2-, and 5.4-fold at 25, 75, and 150 mg/kg/day, respectively. Consistent with this finding, the percent resorptions per litters was also significantly increased at all exposure doses (mean values of 12.30, 32.47, 41.60, and 61.16% resorptions at 0, 25, 75, and 150 mg/kg/day, respectively). The number of live fetuses/litter was significantly decreased at 150 mg/kg/day only, compared to control. There was a trend toward decreased average live fetal body weight across dose groups; however, no pairwise effects were noted. Regarding malformations among fetuses, there was a significant increase in percent fetuses malformed per litter at 150 mg/kg/day (19.21%) compared to control (5.72%); however, there was no characteristic malformation associated

with carbon disulfide exposure. Males were affected to a greater extent than females. The teratogenic effect of carbon disulfide appears to be more severe in males at the 150 mg/kg/day dose than in females (when separated by dose, $p<0.036$ for males and 0.481 for females), whereas the percent live fetuses and average fetal body weight is not sex-dependent.

Selection of the Point of Departure for the MRL: The LOAEL of 25 mg/kg/day for increased resorptions/litter was selected as the POD for the acute-duration oral MRL.

In order to identify the POD, BMD modeling was attempted for both resorptions per litter and percent resorptions per litter reported by NCTR (1984b). The litter resorption data modeled are shown in Table A-10. Data were fit to all available continuous models in EPA's BMDS (version 3.3) using a BMR of 5% relative deviation since data are for a developmental endpoint. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL (95% lower confidence limit on the BMD) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data for either dataset. All models for resorptions per litter or percent resorptions per litter were deemed questionable or unusable by BMDS using constant or non-constant variance. Therefore, the LOAEL of 25 mg/kg/day was selected as the POD for the acute-duration oral MRL.

Table A-10. Resorption Data for Pregnant Rabbits Following Gavage Exposure to Carbon Disulfide on GDs 6–19

	Dose (mg/kg/day)			
	0	25	75	150
Percent resorptions per litter[a]	12.30±21.15 (27)	32.47±38.37[b] (23)	41.60±40.96[c] (28)	61.16±37.25[c] (25)
Resorptions per litter[a]	0.85±1.30 (27)	2.45±3.17[d] (23)	3.54±3.97[e] (28)	4.56±3.35[e] (25)

[a]Mean±SD (number of animals). SD values calculated from reported SEM values (SD = SEM * √N).
[b]$p<0.05$, as reported by the study authors.
[c]$p<0.01$, as reported by the study authors.
[d]$p<0.05$, as calculated by Student's t-test for this review (Graph-Pad).
[e]$p<0.01$, as calculated by Student's t-test for this review (Graph-Pad).

GD = gestation day; N = number of animals; SEM = standard error of the mean; SD = standard deviation

Source: NCTR 1984b

Adjustment for Intermittent Exposure: None

Uncertainty Factor: The following uncertainty factors were applied to the LOAEL to derive the MRL:

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

Subsequently, the provisional MRL for acute-duration exposure to carbon disulfide via oral exposure is:

$$Provisional\ MRL = \frac{LOAEL}{(UF)} = \frac{25\ mg/kg/day}{1{,}000} = 0.025\ mg/kg/day\ \approx 0.03\ mg/kg/day$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Based upon systematic review, the developmental system is a suspected target of carbon disulfide toxicity in humans based on inadequate data in humans and a moderate level of evidence in laboratory animals (Appendix C).

Data pertaining to developmental toxicity in humans are limited to a single occupational-exposure study, which did not observe an association between occupational exposure during pregnancy and congenital malformations (Zhou et al. 1988).

In animals, developmental effects have been observed in two species (rats and rabbits) following oral exposure to carbon disulfide during gestation (NCTR 1984a, 1984b). Of the two species, rabbits appear to be more susceptible. In the dose-range-finding study for the principal study, complete resorption was observed in four of five litters following maternal exposure to 200 mg/kg/day on GDs 6–19, with high maternal mortality at ≥400 mg/kg/day (NCTR 1984b). In rats, developmental effects were observed at ≥200 mg/kg/day, including mild decreases in fetal weight; maternal toxicity was observed at 400 mg/kg/day (NCTR 1984a). However, another gestational exposure study did not observe exposure-related effects on fetal weight at concentrations up to 1,200 mg/kg/day, despite maternal toxicity (decreased body weight) at 1,200 mg/kg/day (Tsai et al. 2000).

Inhalation exposure studies also reported developmental effects in both rats and rabbits following gestational exposure to carbon disulfide, including increased postimplantation loss, decreased fetal body weight, decreased neonatal viability, and fetal malformations (Denny and Gerhart 1991; Holson 1992; Saillenfait et al. 1989; Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983). Postnatal exposure was associated with increased perinatal mortality, delayed reflex ontology, and impaired neurodevelopment (Lehotzky et al. 1985).

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Carbon disulfide
CAS Numbers: 75-15-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: The intermediate-duration oral database is limited. No human studies were identified. The lowest identified LOAELs in the four available animal studies (Table A-11) are markedly higher (≥200 mg/kg/day) than the lowest identified acute-duration LOAEL (25 mg/kg/day), precluding derivation of an intermediate-duration oral MRL.

Table A-11. Selected LOAEL Values in Animals for Intermediate-Duration Oral Exposure to Carbon Disulfide

		Effect level (mg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	20 days	ND	200	***Neurological*:** Impaired memory	Wang et al. 2017
Rat	6 weeks	ND	200	***Body weight:*** 10% decrease in body weight	Gao et al. 2014; Wang et al. 2016
Rat	8 weeks	ND	300	***Neurological:*** Mild gait impairments, motor incoordination, impaired nerve conduction	Liu et al. 2023, 2024
Rat	12 weeks	ND	300	***Neurological:*** Mild gait impairments	Song et al. 2009
Rat	6 weeks	200	400 (SLOAEL)	***Neurological:*** Tremors; moderate-to-severe gait impairments	Gao et al. 2014; Wang et al. 2016

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

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Carbon disulfide
CAS Numbers: 75-15-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No human or animal studies evaluating potential effects of chronic-duration oral exposure to carbon disulfide were identified, precluding derivation of chronic-duration oral MRL.

Agency Contacts (Chemical Managers): Custodio Muianga

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CARBON DISULFIDE

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 carbon disulfide.

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 carbon disulfide. 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 carbon disulfide 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 carbon disulfide 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

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

Immunological effects
Neurological effects
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 Carbon Disulfide released in 1996. All literature cited in the previous (1996) toxicological profile were considered for inclusion in the updated profile; thus, the literature search was restricted to studies published between January 1994 and June 2022. The following main databases were searched in June 2022:

- 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 carbon disulfide. 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 carbon disulfide were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2022	(75-15-0[rn] AND (1994:3000[dp] OR 1994:3000[mhda] OR 1994:3000[edat] OR 1994:3000[crdat])) OR ((("Carbon bisulfide"[tw] OR "Carbon bisulphide"[tw] OR "Carbon disulfide"[tw] OR "carbon disulphide"[tw] OR "Carbondisulfide"[tw] OR "Methanedithione"[tw] OR "Carbon sulfide (CS2) "[tw] OR "Dithiocarbonic anhydride"[tw] OR "Dithiocarbonic, anhydrous"[tw] OR "Sulphocarbonic anhydride"[tw] OR "Sulphuret of carbon"[tw] OR "Weeviltox"[tw]) AND (1994:3000[dp] OR 1994:3000[edat] OR 1994:3000[crdat])) NOT medline[sb])
NTRL	
06/2022	"Carbon bisulfide" OR "Carbon bisulphide" OR "Carbon disulfide" OR "carbon disulphide" OR "Carbondisulfide" OR "Methanedithione" "Carbon sulfide" "Dithiocarbonic anhydride" OR "Dithiocarbonic, anhydrous" OR "Sulphocarbonic anhydride" OR "Sulphuret of carbon" OR "Weeviltox"
Toxcenter	
06/2022	FILE 'TOXCENTER' ENTERED AT 08:28:36 ON 15 JUN 2022 CHARGED TO COST=EH038.15.02.LB.04 L1 15306 SEA FILE=TOXCENTER 75-15-0 L2 15206 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 11992 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 6648 SEA FILE=TOXCENTER L3 AND PY>=1994 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)

Table B-2. Database Query Strings

Database search date	Query string
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (NONHUMAN MAMMALS)/ORGN L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 3495 SEA FILE=TOXCENTER L4 AND L37 L39 361 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 299 SEA FILE=TOXCENTER L38 AND BIOSIS/FS L41 2786 SEA FILE=TOXCENTER L38 AND CAPLUS/FS L42 49 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 3078 DUP REM L39 L40 L42 L41 (417 DUPLICATES REMOVED) L*** DEL 361 S L38 AND MEDLINE/FS L*** DEL 361 S L38 AND MEDLINE/FS L44 361 SEA FILE=TOXCENTER L43 L*** DEL 299 S L38 AND BIOSIS/FS L*** DEL 299 S L38 AND BIOSIS/FS L45 140 SEA FILE=TOXCENTER L43 L*** DEL 2786 S L38 AND CAPLUS/FS L*** DEL 2786 S L38 AND CAPLUS/FS L46 2536 SEA FILE=TOXCENTER L43 L*** DEL 49 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 49 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 41 SEA FILE=TOXCENTER L43 L48 2717 SEA FILE=TOXCENTER (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2022	Compound searched: 75-15-0
NTP	
06/2022	"75-15-0" "Carbon bisulfide" "Carbon disulfide" "Carbondisulfide" "Carbon bisulphide" "carbon disulphide" "Methanedithione" "Carbon sulfide" "Dithiocarbonic anhydride" "Dithiocarbonic, anhydrous" "Sulphocarbonic anhydride" "Sulphuret of carbon" "Weeviltox"
Regulations.gov	
06/2022	"Carbon bisulfide"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Carbon bisulphide" "Carbon disulfide" "carbon disulphide" "Carbondisulfide" "Methanedithione" "Carbon sulfide(CS2)" "Dithiocarbonic anhydride" "Dithiocarbonic, anhydrous" "Sulphocarbonic anhydride" "Sulphuret of carbon" "Weeviltox"
NIH RePORTER	
05/2023	Fiscal Year: Active Projects; Text Search: "Carbon bisulfide" OR "Carbon bisulphide" OR "Carbon disulfide" OR "carbon disulphide" OR "Carbondisulfide" OR "Methanedithione" OR "Carbon sulfide" OR "Dithiocarbonic anhydride" OR "Dithiocarbonic, anhydrous" OR "Sulphocarbonic anhydride" OR "Sulphuret of carbon" OR "Weeviltox" (advanced); Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 3,621
- Number of records identified from other strategies: 204
- Total number of records to undergo literature screening: 3,825

B.1.2 Literature Screening

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

- 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: 3,825
- Number of studies considered relevant and moved to the next step: 419

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: 419

- Number of studies cited in the previous draft of the toxicological profile: 307
- Total number of studies cited in the profile: 426

Prioritization of Human Data. The epidemiological database for carbon disulfide is extensive, but is largely focused on a small number of endpoints: cardiovascular, lipid homeostasis, ophthalmological, neurological, and male reproductive endpoints. For endpoints with few epidemiological studies, all relevant human data and study designs were considered. For the data-rich endpoints, the inclusion criteria defined in Table B-1 were refined to facilitate the selection of chronic-duration human studies of greater utility in assessing the hazards of carbon disulfide, and only studies meeting the refined criteria were included in the Toxicological Profile. The refined criteria are shown below, and Table B-4 summarizes how the criteria were applied to the available epidemiological data by health outcome.

- Only studies in which exposure was measured prior to outcome determination (cohort studies) were included. Study designs that lacked this clear temporality data (e.g., cross-sectional studies) were excluded, as they cannot draw conclusions regarding causality (Mann 2003). This approach is supported by conclusions reported in published review of EPA quality considerations for epidemiological studies in risk assessment, which indicate that cross-sectional studies are lower quality than cohort studies and should only be considered as supplemental material for regulatory use (LaKind et al. 2023). However, cumulative exposure index analyses conducted in cross-sectional studies were included, as these study designs estimated exposure levels prior to outcome determination. Therefore, several occupational studies that are referred to as "cross-sectional" by study authors (e.g., Johnson et al. 1983) meet inclusion criteria due to inclusion of historical exposure data and/or estimates of cumulative exposure based on current exposure metrics. For the purposes of the profile, the cumulative exposure analyses from these occupational studies are classified as cohort analyses.

- Case series, case reports, and other studies lacking control/referent groups were excluded.

- Only studies for which exposure was assessed via external monitoring or validated biomarker (TTCA in urine). Studies that just evaluated "exposed" compared to "unexposed" without measures of exposure were not included since these studies would not provide any relevant dose-response data.

- Studies that only evaluated endpoints that were mechanistic in nature (e.g., oxidative stress) were not included in the systematic review. Where relevant, these studies were discussed in the mechanisms of toxicity sections in Chapter 2.

- Studies evaluating toxicity of compounds that metabolize into carbon disulfide, such as disulfiram (Antabuse) and certain pesticides (thiocarbamates), were not included; they are considered outside the scope of this profile due to exposure to compounds other than the profile chemical.

Table B-4. Application of Selection Criteria to Epidemiological Data by Health Outcome

Outcome	Selection process
Death	All studies included
Body weight	All studies included
Respiratory	All studies included

Table B-4. Application of Selection Criteria to Epidemiological Data by Health Outcome

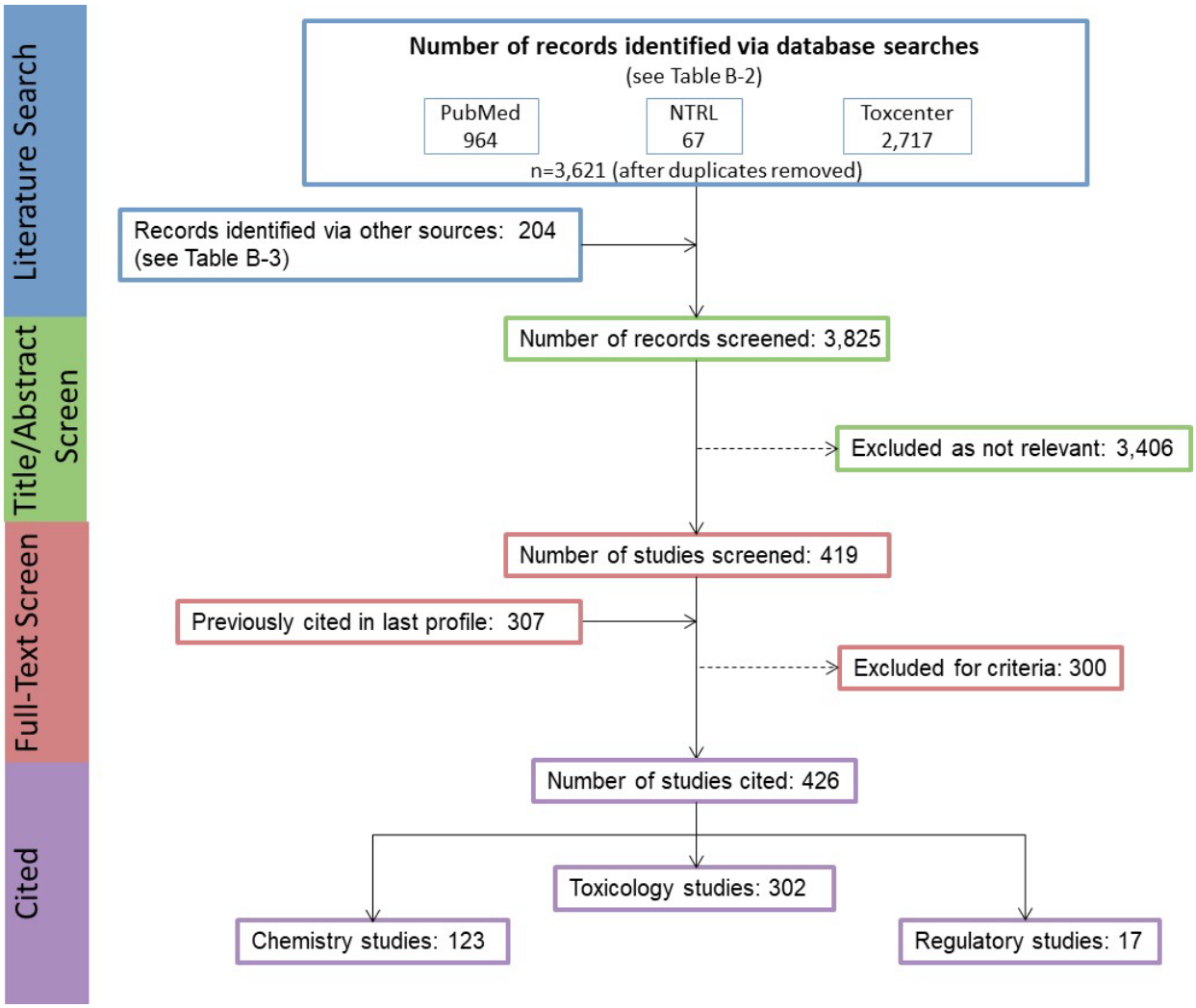
Outcome	Selection process
Cardiovascular	Criteria applied
Gastrointestinal	All studies included
Hematological	All studies included
Musculoskeletal	No studies identified
Hepatic	Lipid homeostasis and metabolism: Criteria applied Other endpoints: All studies included
Renal	All studies included
Dermal	All studies included
Ocular	Criteria applied
Endocrine	All studies included
Immunological	No studies identified
Neurological	Criteria applied
Reproductive	Male reproductive: Criteria applied Female reproductive: All studies included
Developmental	No studies identified
Other noncancer	Criteria applied (diabetes/metabolic syndrome)
Cancer	All studies included

Prioritization of Animal Data. The neurological endpoint is extremely well studied in rodents following intermediate-duration inhalation exposure. To facilitate the selection of animal studies of greater utility in assessing the neurological dose-response effects of carbon disulfide, single exposure level studies evaluating neurological effects in rodents following intermediate-duration inhalation exposure were excluded unless they were evaluating a specialized endpoint (e.g., visual or auditory function).

As noted for human studies, animal studies evaluating disulfiram and thiocarbamates were not included (outside scope of profile).

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

Figure B-1. June 2022 Literature Search Results and Screen for Carbon Disulfide



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

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 carbon disulfide, 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 carbon disulfide:

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

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

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

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 carbon disulfide. 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 1996 Toxicological Profile for Carbon Disulfide; thus, the literature search was restricted to studies published between January 1994 and June 2022. See Appendix B for the databases searched and the search strategy.

A total of 3,825 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 carbon disulfide.

Title and Abstract Screen. In the Title and Abstract Screen step, 3,825 records were reviewed; 63 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 159 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 159 documents (169 studies), 122 documents (120 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 Carbon Disulfide 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 carbon disulfide identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include numerous occupational exposure studies and a limited number of general population exposure studies. These studies suggest that the cardiovascular, ophthalmological, hepatic (altered lipid homeostasis), and neurological systems may be targets of carbon disulfide exposure following long term inhalation exposure. Animal studies evaluated a comprehensive set of endpoints following inhalation exposure, a limited set of endpoints following oral exposure, and dermal studies were limited to two acute-duration and one intermediate-duration studies evaluating dermal and ocular effects only. Cardiovascular, altered lipid homeostasis, neurological, male reproductive, and developmental effects

were considered sensitive outcomes following inhalation exposure in animals, and neurological and developmental effects were considered sensitive outcomes following oral exposure in animals (i.e., effects were observed at low concentrations or doses). Based on effects noted in human and animal studies, epidemiological and experimental studies examining cardiovascular effects, ophthalmology, altered lipid synthesis, neurological effects, male reproductive endpoints, and developmental effects following inhalation exposure and neurological and developmental effects following oral exposure were carried through to Steps 4–8 of the systematic review. There were 120 studies (published in 122 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Carbon Disulfide Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Prospective/Longitudinal		2	6		2		4	1		1	1		5	1		2	
cohort		1	4				1	0		1	1		3	1		0	
Retrospective cohort	1		18	2	4	1	16	2		8	4		23	11	1	6	
	1		12	1	1	0	7	2		6	2		21	7	0	2	
Population																1	
																1	
Cross-sectional					2		2	1			4		2	1		1	
					0		0	0			3		2	0		1	
Case series		2		2									2				
		2		2									2				
Experimental							1						1				
							0						1				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

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 Carbon Disulfide 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	7 2	5 3	3 1		1 1		7 4	1 0					11 10	4 0	4 3		
Intermediate-duration	20 14	7 0	9 3	3 0	3 2	4 0	9 3	7 1		3 0	3 0	3 0	16 15	15 7	6 3		
Chronic-duration	1 0		1 0				1 1										
Oral studies																	
Acute-duration	6 4		2 2		1 1		3 3					1 1	4 4		4 3		
Intermediate-duration	3 3		1 1			1 1							5 5				
Chronic-duration																	
Dermal studies																	
Acute-duration									2 2								
Intermediate-duration										1 1							
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of carbon disulfide 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 Carbon Disulfide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular effects							
Retrospective cohort studies							
Bortkiewicz et al. 1997	++	+	+	–	+	++	Second
Bortkiewicz et al. 2001	++	+	+	–	+	++	Second
Chang et al. 2007	+	+	+	–	+	++	Second
Franco et al. 1982	++	–	++	–	+	++	Second
Jhun et al. 2007	+	–	++	–	+	++	Second
Jhun et al. 2009	+	–	++	–	+	++	Second
Kamal et al. 1991	+	– –	++	– –	+	++	Second
Kim et al. 2000	+	–	++	+	–	++	Second
Kotseva and DeBacquer 2000	++	+	++	–	+	++	Second
Kotseva et al. 2001	+	+	++	–	+	++	Second
Liss and Finkelstein 1996	–	– –	–	– –	–	+	Third
NIOSH 1984a	+	+	+	++	+	++	First
Reinhardt et al. 1997a	+	–	+	–	–	+	Second
Schramm et al. 2016	+	+	++	+	+	++	First
Sugimoto et al. 1978	+	–	+	– –	+	+	Second

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

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Sweetnam et al. 1987; Tiller et al. 1968	–	– –	–	– –	–	+	Third
Tolonen et al. 1976	+	–	+	+	+	+	Second
Vanhoorne et al. 1992a	–	+	+	–	+	++	Second
Prospective/Longitudinal cohort studies							
Barlcarova and Halik 1991	–	– –	+	–	–	–	Third
Chrostek-Maj and Czeczotko 1995a	+	– –	– –	– –	–	–	Third
Finnish Longitudinal cohort studies (Hernberg and Tolonen 1981; Hernberg et al. 1970, 1973, 1976; Nurminen and Hernberg 1985; Nurminen et al. 1982; Tolonen et al. 1975, 1979)	++	–	++	–	+	++	Second
Swaen et al. 1994	+	– –	+	–	–	++	Second
Takebayashi et al. 2004	+	+	+	++	+	++	First
Vertin 1978	–	– –	++	+	+	–	Second
Outcome: Altered lipid homeostasis (inhalation only)							
Retrospective cohort studies							
Chang et al. 2007	+	–	+	–	++	++	Second
Cirla and Graziano 1981	++	–	++	+	++	++	Second
Franco et al. 1982	++	–	++	–	++	++	Second

Table C-8. Summary of Risk of Bias Assessment for Carbon Disulfide—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?	
Hernberg et al. 1971	++	–	++	–	++	++	Second
Jhun et al. 2007	+	–	++	–	++	++	Second
Jhun et al. 2009	+	–	++	–	++	++	Second
Kim et al. 2000	+	–	++	+	–	++	Second
Kotseva and DeBacquer 2000	++	+	++	–	++	++	Second
Kotseva et al. 2001	+	+	++	–	++	++	Second
Luo et al. 2011	–	–	++	–	++	++	Second
NIOSH 1984a	+	+	+	++	+	++	First
Schramm et al. 2016	+	–	++	+	++	++	Second
Sidorowicz et al. 1980	–	– –	++	– –	++	+	Third
Stanosz et al. 1994b	+	– –	++	–	++	++	Second
Sugimoto et al. 1978	+	–	+	– –	++	+	Second
Vanhoorne et al. 1992a	–	+	+	–	++	+	Second
Prospective/longitudinal cohort studies							
Chrostek-Maj and Czeczotko 1995a	+	– –	– –	– –	++	–	Third
Takebayashi et al. 2004	+	–	+	++	++	++	Second
Raitta et al. 1974	+	–	+	– –	++	++	Second

Table C-8. Summary of Risk of Bias Assessment for Carbon Disulfide—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?	
Vertin 1978	–	– –	++	+	+	–	Second
Outcome: Ophthalmological effects (inhalation only)							
Retrospective cohort studies							
Cirla and Graziano 1981	++	–	++	+	++	++	Second
Kim et al. 2000	+	–	++	+	–	++	Second
NIOSH 1984a	+	+	+	++	–	++	Second
Sugimoto et al. 1976	–	–	+	– –	+	++	Second
Sugimoto et al. 1977	+	–	+	– –	+	++	Second
Sugimoto et al. 1978	+	–	+	– –	++	+	Second
Vanhoorne et al. 1996	+	+	+	–	++	++	Second
Longitudinal cohort studies							
Raitta et al. 1974	+	–	+	– –	++	++	Second
Raitta and Tolonen 1975	+	–	+	– –	+	++	Second
Outcome: Neurological effects							
Retrospective cohort studies							
Chang et al. 2003	–	+	++	–	++	++	Second
Cirla and Graziano 1981	++	–	++	+	+	++	Second

Table C-8. Summary of Risk of Bias Assessment for Carbon Disulfide—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?	
Godderis et al. 2006	+	+	++	+	+	++	First
Foa et al. 1976	+	–	+	–	+	++	Second
Hirata et al. 1996	+	–	+	+	++	++	Second
Johnson et al. 1983; NIOSH 1984a	+	–	++	+	++	++	Second
Kim et al. 2000	+	–	++	+	+	++	Second
Raitta et al. 1981	+	+	+	– –	+	++	Second
Reinhardt et al. 1997a	+	–	+	+	++	+	Second
Reinhardt et al. 1997b	+	–	+	+	++	+	Second
Ruijten et al. 1990	+	–	+	+	++	+	Second
Ruijten et al. 1993	+	–	+	+	++	+	Second
Seppalainen and Tolonen 1974	+	– –	–	– –	++	+	Second
Vanhoorne et al. 1995	+	+	–	–	++	++	Second
Vanhoorne et al. 1996	+	+	+	–	++	++	Second
Prospective/longitudinal cohort studies							
Cassitto et al. 1993	–	–	–	–	–	–	Third
Chrostek-Maj and Czeczotko 1995b	+	– –	– –	– –	–	+	Third
Nishiwaki et al. 2004	+	+	+	++	++	++	First

Table C-8. Summary of Risk of Bias Assessment for Carbon Disulfide—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?	
Raitta et al. 1974	+	–	+	– –	++	++	Second
Yoshioka et al. 2017	+	+	+	++	++	++	First
Outcome: Male reproductive effects							
Retrospective cohort studies							
Cirla et al. 1978	+	–	–	–	–	+	Third
Guo et al. 2016	+	–	+	++	++	++	Second
NIOSH 1983	+	+	+	+	–	+	Second
NIOSH 1984a	+	+	+	++	–	++	Second
Takebayashi et al. 2003	+	+	+	+	–	++	Second
Vanhoorne et al. 1993	+	–	+	–	+	++	Second
Vanhoorne et al. 1994 (Study 1)	+	–	+	–	–	+	Second
Vanhoorne et al. 1994 (Study 2)	+	–	+	–	–	+	Second
Wägar et al. 1981	+	–	+	–	+	++	Second
Wägar et al. 1983	+	–	+	–	+	++	Second

Table C-8. Summary of Risk of Bias Assessment for Carbon Disulfide—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: Developmental effects							
Retrospective cohort studies							
Zhou et al. 1988	+	–	+	+	–	–	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 Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Cardiovascular effects (inhalation only)									
Inhalation acute-duration exposure									
Lewis et al. 1999	++	+	+	+	+	+	+	++	First
Tarkowski and Sobczak 1971	–	+	+	–	–	–	–	+	Third
Inhalation intermediate-duration exposure									
Antov et al. 1985	–	+	+	+	+	–	–	++	Second
Lewis et al. 1999	+	+	+	+	+	–	+	++	First
Morvai et al. 2005	–	+	+	+	++	+	++	+	First
Phillips 1983a	++	+	+	+	+	++	++	++	First
Phillips 1983b	++	+	+	+	+	++	++	++	First
Phillips 1983c	++	+	+	+	+	++	++	++	First
Wrońska-Nofer et al. 1980	–	+	+	+	+	–	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Ophthalmological effects (inhalation only)									
Inhalation intermediate-duration exposure									
Phillips 1983a	++	+	+	+	+	++	++	++	First
Phillips 1983b	++	+	+	+	+	++	++	++	First
Phillips 1983c	++	+	+	+	+	++	++	++	First
Outcome: Altered lipid homeostasis (inhalation only)									
Inhalation acute-duration exposure									
Freundt et al. 1974b	–	–	++	+	–	+	+	++	First
Simmons et al. 1988	–	–	++	+	+	+	+	++	First
Simmons et al. 1989	–	–	++	+	+	+	+	++	First
Inhalation intermediate-duration exposure									
Wrońska-Nofer 1973	–	–	++	+	+	–	+	++	First
Wrońska-Nofer 1972	–	–	++	+	+	–	+	++	First
Inhalation chronic-duration exposure									
Wrońska-Nofer et al. 1980	–	–	+	+	+	–	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Neurological effects									
Inhalation acute-duration exposure									
Carreres Pons et al. 2017	–	–	++	+	++	–	+	++	First
Denny and Gerhart 1991 (main study)	++	– –	+	+	++	++	–	++	Second
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997 (2 weeks)	++	–	++	+	+	+	++	+	First
Lehotzky et al. 1985	–	–	+	–	++	–	–	++	Third
Liang et al. 1983	–	–	+	–	–	+	–	+	Third
Magos 1970	–	–	+	+	++	+	++	++	First
Magos et al. 1974	–	–	+	+	+	–	++	++	First
Qingfen et al. 1999	+	–	+	+	++	–	+	++	First
Tarkowski and Sobczak 1971	–	–	+	+	++	–	++	++	First
Wilmarth et al. 1993	–	–	+	+	++	+	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate-duration exposure									
Clerici and Fechter 1991	–	–	+	+	++	–	+	++	First
Eskin et al. 1988	–	–	+	+	++	–	–	++	Second
Frantik 1970	–	–	+	–	+	–	–	–	Third
Graham and Popp 1992a; Phillips 1983a	++	–	++	+	++	++	++	++	First
Graham and Popp 1992b; Phillips 1983b	++	–	++	+	++	++	++	++	First
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997 (4 weeks)	++	–	++	+	+	+	++	+	First
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997 (8 weeks)	++	–	++	+	+	+	++	+	First
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997 (13 week)	++	–	++	+	+	+	++	+	First
Hirata et al. 1992	–	–	++	+	++	–	++	++	First
Merigan et al. 1988	–	–	+	+	++	–	–	++	Second
Morvai et al. 2005	–	–	++	+	++	+	++	++	First
Phillips 1983c	++	–	++	+	++	++	++	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Qingfen et al. 1999	+	–	+	+	++	–	+	++	First
Rebert and Becker 1986	–	–	+	+	+	++	++	++	First
Wrońska-Nofer 1973	–	–	–	+	+	–	–	++	First
Oral acute-duration exposure									
Kanada et al. 1994	–	–	+	+	–	–	+	++	Second
NCTR 1984a (preliminary)	++	++	++	++	++	++	+	++	First
NCTR 1984a (teratology)	++	++	++	++	++	++	+	++	First
NCTR 1984b (preliminary)	++	++	++	++	++	++	+	++	First
NCTR 1984b (teratology)	++	++	++	++	++	++	+	++	First
Oral intermediate-duration exposure									
Gao et al. 2014; Wang et al. 2016	+	–	++	–	++	+	–	++	Second
Liu et al. 2023	–	–	+	–	+	–	+	++	Second
Liu et al. 2024	–	–	+	–	+	–	+	++	Second
Song et al. 2009	+	–	++	–	–	+	–	++	Third
Wang et al. 2017	+	–	++	–	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Male reproductive effects (inhalation only)									
Inhalation acute-duration exposure									
NIOSH 1980 (mouse)	+	– –	+	+	+	+	–	++	Second
NIOSH 1980 (rat)	+	– –	+	+	+	+	–	++	Second
Sills et al. 1998b (2 weeks)	++	–	++	+	+	+	++	+	First
Zenick et al. 1984	–	+	+	+	–	+	+	++	First
Inhalation intermediate-duration exposure									
Guo et al. 2014	+	+	+	+	++	+	+	++	First
Guo et al. 2015	+	+	+	+	+	+	+	++	First
Huang et al. 2012	+	+	+	++	+	–	++	++	First
Phillips 1983a	++	+	+	+	+	++	++	++	First
Phillips 1983b	++	+	+	+	+	++	++	++	First
Phillips 1983c	++	+	+	+	+	++	++	++	First
Sills et al. 1998b (4 weeks)	++	–	++	+	+	+	++	+	First
Sills et al. 1998b (8 weeks)	++	–	++	+	+	+	++	+	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Sills et al. 1998b (13 weeks)	++	–	++	+	+	+	++	+	First
Tepe and Zenick 1984 (Study 1)	–	–	+	–	+	–	–	++	Second
Tepe and Zenick 1984 (Study 2)	–	+	+	+	+	–	+	++	First
Zenick et al. 1984	–	+	+	+	–	+	+	++	First
Outcome: Developmental effects									
Inhalation acute-duration exposure									
Denny and Gerhart 1991 (dose-range finding)	++	+	++	+	++	+	–	++	Second
Denny and Gerhart 1991 (main study)	++	+	++	+	++	+	+	++	First
Hardin et al. 1981; NIOSH 1980 (rat, gestation)	+	–	++	+	++	–	+	++	First
Lehotzky et al. 1985	–	–	+	–	–	–	–	–	Third
Inhalation intermediate-duration exposure									
Hardin et al. 1981; NIOSH 1980 (rabbit, gestation)	+	–	++	+	++	–	+	++	First
Holson 1992	++	–	++	+	++	+	+	++	First
NIOSH 1980 (rat, premate)	+	–	++	+	++	–	+	++	First
NIOSH 1980 (rabbit, premate)	+	–	++	+	++	–	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Carbon Disulfide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Saillenfait et al. 1989	+	–	++	+	++	+	+	++	First
Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983	–	–	+	–	–	–	–	++	Third
Oral acute-duration exposure									
NCTR 1984a (teratology)	++	++	++	++	++	++	++	++	First
NCTR 1984b (preliminary)	++	++	++	++	++	++	++	++	First
NCTR 1984b (teratology)	++	++	++	++	++	++	++	++	First
Tsai et al. 2000	–	–	+	+	++	–	+	++	First

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

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to carbon disulfide 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 carbon disulfide 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 cardiovascular, altered lipid homeostasis, ophthalmological, neurological, male reproductive, and developmental 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 Carbon Disulfide—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Cardiovascular effects					
Retrospective cohort studies					
Bortkiewicz et al. 1997	No	Yes	Yes	Yes	Moderate
Bortkiewicz et al. 2001	No	Yes	Yes	Yes	Moderate
Chang et al. 2007	No	Yes	Yes	Yes	Moderate
Franco et al. 1982	No	Yes	Yes	Yes	Moderate
Jhun et al. 2007	No	Yes	Yes	Yes	Moderate
Jhun et al. 2009	No	Yes	Yes	Yes	Moderate
Kamal et al. 1991	No	Yes	Yes	Yes	Moderate
Kim et al. 2000	No	Yes	Yes	Yes	Moderate
Kotseva and DeBacquer 2000	No	Yes	Yes	Yes	Moderate
Kotseva et al. 2001	No	Yes	Yes	Yes	Moderate
Liss and Finkelstein 1996	No	Yes	No	Yes	Low
NIOSH 1984a	No	Yes	Yes	Yes	Moderate
Reinhardt et al. 1997a	No	Yes	Yes	Yes	Moderate
Schramm et al. 2016	No	Yes	Yes	Yes	Moderate
Sugimoto et al. 1978	No	Yes	Yes	Yes	Moderate
Sweetnam et al. 1987; Tiller et al. 1968	No	Yes	No	Yes	Low
Tolonen et al. 1976	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1992a	No	Yes	Yes	Yes	Moderate
Prospective/longitudinal cohort studies					
Barlcarova and Halik 1991	No	Yes	Yes	Yes	Moderate
Chrostek-Maj and Czeczotko 1995a	No	Yes	Yes	Yes	Moderate
Finnish Longitudinal cohort studies (Hernberg and Tolonen 1981; Hernberg et al. 1970, 1973, 1976; Nurminen and Hernberg 1985; Nurminen et al. 1982; Tolonen et al. 1975, 1979)	No	Yes	Yes	Yes	Moderate
Swaen et al. 1994	No	Yes	Yes	Yes	Moderate
Takebayashi et al. 2004	No	Yes	Yes	Yes	Moderate
Vertin 1978	No	Yes	Yes	No	Low

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

Reference	Key features				
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Altered lipid homeostasis (inhalation only)					
Retrospective cohort studies					
Chang et al. 2007	No	Yes	Yes	Yes	Moderate
Cirla and Graziano 1981	No	Yes	Yes	Yes	Moderate
Franco et al. 1982	No	Yes	Yes	Yes	Moderate
Hernberg et al. 1971	No	Yes	Yes	Yes	Moderate
Jhun et al. 2007	No	Yes	Yes	Yes	Moderate
Jhun et al. 2009	No	Yes	Yes	Yes	Moderate
Kim et al. 2000	No	Yes	Yes	Yes	Moderate
Kotseva and DeBacquer 2000	No	Yes	Yes	Yes	Moderate
Kotseva et al. 2001	No	Yes	Yes	Yes	Moderate
Luo et al. 2011	No	Yes	Yes	Yes	Moderate
NIOSH 1984a	No	Yes	Yes	Yes	Moderate
Schramm et al. 2016	No	Yes	Yes	Yes	Moderate
Sidorowicz et al. 1980	No	Yes	Yes	No	Low
Stanosz et al. 1994b	No	Yes	Yes	Yes	Moderate
Sugimoto et al. 1978	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1992a	No	Yes	Yes	Yes	Moderate
Prospective/longitudinal cohort studies					
Chrostek-Maj and Czeczotko 1995a	No	Yes	Yes	Yes	Moderate
Takebayashi et al. 2004	No	Yes	Yes	Yes	Moderate
Raitta et al. 1974	No	Yes	Yes	Yes	Moderate
Vertin 1978	No	Yes	Yes	No	Low
Outcome: Ophthalmological effects (inhalation only)					
Retrospective cohort studies					
Cirla and Graziano 1981	No	Yes	Yes	Yes	Moderate
Kim et al. 2000	No	Yes	Yes	Yes	Moderate
NIOSH 1984a	No	Yes	Yes	Yes	Moderate
Sugimoto et al. 1976	No	Yes	Yes	Yes	Moderate
Sugimoto et al. 1977	No	Yes	Yes	Yes	Moderate
Sugimoto et al. 1978	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1996	No	Yes	Yes	Yes	Moderate

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

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Raitta et al. 1974	No	Yes	Yes	Yes	Moderate
Raitta and Tolonen 1975	No	Yes	Yes	Yes	Moderate
Outcome: Neurological effects					
Retrospective cohort studies					
Chang et al. 2003	No	Yes	Yes	No	Low
Cirla and Graziano 1981	No	Yes	Yes	Yes	Moderate
Godderis et al. 2006	No	Yes	Yes	Yes	Moderate
Foa et al. 1976	No	Yes	Yes	Yes	Moderate
Hirata et al. 1996	No	Yes	Yes	Yes	Moderate
Johnson et al. 1983; NIOSH 1984a	No	Yes	Yes	Yes	Moderate
Kim et al. 2000	No	Yes	Yes	Yes	Moderate
Raitta et al. 1981	No	Yes	Yes	Yes	Moderate
Reinhardt et al. 1997a	No	Yes	Yes	Yes	Moderate
Reinhardt et al. 1997b	No	Yes	Yes	Yes	Moderate
Ruijten et al. 1990	No	Yes	Yes	Yes	Moderate
Ruijten et al. 1993	No	Yes	Yes	Yes	Moderate
Seppalainen and Tolonen 1974	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1995	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1996	No	Yes	Yes	Yes	Moderate
Prospective/longitudinal cohort studies					
Cassitto et al. 1993	No	Yes	Yes	Yes	Moderate
Chrostek-Maj and Czeczotko 1995b	No	Yes	Yes	Yes	Moderate
Nishiwaki et al. 2004	No	Yes	Yes	Yes	Moderate
Raitta et al. 1974	No	Yes	Yes	Yes	Moderate
Yoshioka et al. 2017	No	Yes	Yes	Yes	Moderate
Outcome: Male reproductive effects					
Retrospective cohort studies					
Cirla et al. 1978	No	Yes	Yes	Yes	Moderate
Guo et al. 2016	No	Yes	Yes	Yes	Moderate
NIOSH 1983	No	Yes	Yes	Yes	Moderate
NIOSH 1984a	No	Yes	Yes	Yes	Moderate
Takebayashi et al. 2003	No	Yes	Yes	Yes	Moderate

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

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Vanhoorne et al. 1993	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1994 (Study 1)	No	Yes	Yes	Yes	Moderate
Vanhoorne et al. 1994 (Study 2)	No	Yes	Yes	Yes	Moderate
Wägar et al. 1981	No	Yes	Yes	Yes	Moderate
Wägar et al. 1983	No	Yes	Yes	Yes	Moderate
Outcome: Developmental effects					
Retrospective cohort studies					
Zhou et al. 1988	No	Yes	Yes	Yes	Moderate

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

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Cardiovascular effects (inhalation only)					
Inhalation acute-duration exposure					
Lewis et al. 1999	Yes	Yes	Yes	Yes	High
Tarkowski and Sobczak 1971	Yes	Yes	Yes	No	Low
Inhalation intermediate-duration exposure					
Antov et al. 1985	Yes	Yes	Yes	No	Moderate
Lewis et al. 1999	Yes	Yes	Yes	Yes	High
Morvai et al. 2005	Yes	Yes	Yes	Yes	High
Phillips 1983a	Yes	Yes	Yes	Yes	High

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

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Phillips 1983b	Yes	Yes	Yes	Yes	High
Phillips 1983c	Yes	Yes	Yes	Yes	High
Wrońska-Nofer et al. 1980	Yes	Yes	Yes	Yes	High
Outcome: Ophthalmological effects (inhalation only)					
Inhalation intermediate-duration exposure					
Phillips 1983a	Yes	Yes	Yes	Yes	High
Phillips 1983b	Yes	Yes	Yes	Yes	High
Phillips 1983c	Yes	Yes	Yes	Yes	High
Outcome: Altered lipid homeostasis (inhalation only)					
Inhalation acute-duration exposure					
Freundt et al. 1974b	Yes	Yes	No	Yes	Moderate
Simmons et al. 1988	Yes	Yes	Yes	Yes	High
Simmons et al. 1989	Yes	No	Yes	Yes	Moderate
Inhalation intermediate-duration exposure					
Wrońska-Nofer 1973	Yes	Yes	Yes	Yes	High
Wrońska-Nofer 1972	Yes	Yes	Yes	Yes	High
Inhalation chronic-duration exposure					
Wrońska-Nofer et al. 1980	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Carreres Pons et al. 2017	Yes	Yes	Yes	Yes	High
Denny and Gerhart 1991 (main study)	Yes	Yes	Yes	Yes	High
Herr et al. 1998; Moser et al. 1998 (2 week)	Yes	Yes	Yes	Yes	High
Lehotzky et al. 1985	Yes	No	Yes	No	Moderate
Liang et al. 1983	No	No	Yes	No	Low
Magos 1970	Yes	Yes	Yes	Yes	High
Magos et al. 1974	Yes	Yes	Yes	Yes	High
Qingfen et al. 1999	Yes	Yes	Yes	Yes	High
Tarkowski and Sobczak 1971	Yes	Yes	Yes	No	Moderate

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

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Wilmarth et al. 1993	Yes	Yes	Yes	No	Moderate
Inhalation intermediate-duration exposure					
Clerici and Fechter 1991	Yes	No	Yes	Yes	Moderate
Eskin et al. 1988	Yes	No	Yes	No	Low
Frantik 1970	Yes	Yes	No	No	Low
Graham and Popp 1992a; Phillips 1983a	Yes	Yes	Yes	Yes	High
Graham and Popp 1992b; Phillips 1983b	Yes	Yes	Yes	Yes	High
Herr et al. 1998; Moser et al. 1998 (4 weeks)	Yes	Yes	Yes	Yes	High
Herr et al. 1998; Moser et al. 1998 (8 weeks)	Yes	Yes	Yes	Yes	High
Herr et al. 1998; Moser et al. 1998 (13 weeks)	Yes	Yes	Yes	Yes	High
Hirata et al. 1992	Yes	Yes	Yes	Yes	High
Merigan et al. 1988	Yes	No	Yes	No	Low
Morvai et al. 2005	Yes	Yes	No	No	Low
Phillips 1983c	Yes	Yes	Yes	Yes	High
Qingfen et al. 1999	Yes	Yes	Yes	Yes	High
Rebert and Becker 1986	Yes	No	Yes	Yes	Moderate
Wrońska-Nofer 1973	Yes	Yes	No	No	Low
Oral acute-duration exposure					
Kanada et al. 1994	No	Yes	Yes	Yes	Moderate
NCTR 1984a (preliminary)	Yes	Yes	Yes	No	Moderate
NCTR 1984a (teratology)	Yes	Yes	Yes	Yes	High
NCTR 1984b (preliminary)	Yes	Yes	Yes	Yes	High
NCTR 1984b (teratology)	Yes	Yes	Yes	Yes	High
Oral intermediate-duration exposure					
Gao et al. 2014; Wang et al. 2016	Yes	Yes	Yes	Yes	High
Liu et al. 2023	Yes	No	Yes	No	Low
Liu et al. 2024	Yes	Yes	Yes	Yes	High
Song et al. 2009	Yes	Yes	Yes	Yes	High

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

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Wang et al. 2017	Yes	Yes	Yes	Yes	High
Outcome: Male reproductive effects (inhalation only)					
Inhalation acute-duration exposure					
NIOSH 1980 (mouse)	Yes	Yes	No	Yes	Moderate
NIOSH 1980 (rat)	Yes	Yes	No	Yes	Moderate
Sills et al. 1998b (2 weeks)	Yes	Yes	No	No	Low
Zenick et al. 1984	Yes	Yes	Yes	Yes	High
Inhalation intermediate-duration exposure					
Guo et al. 2014	Yes	Yes	Yes	No	Moderate
Guo et al. 2015	Yes	Yes	Yes	No	Moderate
Huang et al. 2012	Yes	Yes	Yes	Yes	High
Phillips 1983a	Yes	Yes	No	Yes	Moderate
Phillips 1983b	Yes	Yes	No	Yes	Moderate
Phillips 1983c	Yes	Yes	No	Yes	Moderate
Sills et al. 1998b (4 weeks)	Yes	Yes	No	No	Low
Sills et al. 1998b (8 weeks)	Yes	Yes	No	No	Low
Sills et al. 1998b (13 weeks)	Yes	Yes	No	No	Low
Tepe and Zenick 1984 (Study 1)	Yes	Yes	Yes	Yes	High
Tepe and Zenick 1984 (Study 2)	Yes	Yes	Yes	Yes	High
Zenick et al. 1984	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation acute-duration exposure					
Denny and Gerhart 1991 (range-finding)	No	No	Yes	Yes	Low
Denny and Gerhart 1991 (main study)	Yes	Yes	Yes	Yes	High
NIOSH 1980 (rat)	Yes	Yes	Yes	Yes	High
Lehotzky et al. 1985	Yes	No	No	Yes	Low
Inhalation intermediate-duration exposure					
NIOSH 1980 (rabbit)	Yes	Yes	Yes	Yes	High
Holson 1992	Yes	Yes	Yes	Yes	High
NIOSH 1980 (rat)	Yes	Yes	Yes	Yes	High

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

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
NIOSH 1980 (rabbit)	Yes	Yes	Yes	Yes	High
Saillenfait et al. 1989	Yes	Yes	Yes	Yes	High
Tabacova et al. 1983	Yes	Yes	Yes	Yes	High
Oral acute-duration exposure					
NCTR 1984a	Yes	Yes	Yes	Yes	High
NCTR 1984b (preliminary)	Yes	Yes	No	Yes	Moderate
NCTR 1984b (teratology)	Yes	Yes	Yes	Yes	High
Tsai et al. 2000	Yes	Yes	Yes	Yes	High

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

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

	Initial study confidence	Initial confidence rating
Outcome: Cardiovascular effects (inhalation only)		
Inhalation acute-duration exposure		
Animal studies		
Lewis et al. 1999	High	High
Tarkowski and Sobczak 1971	Low	
Inhalation acute-duration exposure		
Animal studies		
Antov et al. 1985	Moderate	High
Lewis et al. 1999	High	
Morvai et al. 2005	High	
Phillips 1983a	High	

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

	Initial study confidence	Initial confidence rating
Phillips 1983b	High	
Phillips 1983c	High	
Inhalation chronic-duration exposure		
Human studies		
Barlcarova and Halik 1991	Moderate	Moderate
Bortkiewicz et al. 1997	Moderate	
Bortkiewicz et al. 2001	Moderate	
Chang et al. 2007	Moderate	
Chrostek-Maj and Czeczotko 1995a	Moderate	
Finnish Longitudinal cohort studies (Hernberg and Tolonen 1981; Hernberg et al. 1970, 1973, 1976; Nurminen and Hernberg 1985; Nurminen et al. 1982; Tolonen et al. 1975, 1979)	Moderate	
Franco et al. 1982	Moderate	
Jhun et al. 2007	Moderate	
Jhun et al. 2009	Moderate	
Kamal et al. 1991	Moderate	
NIOSH 1984a	Moderate	
Kim et al. 2000	Moderate	
Kotseva and DeBacquer 2000	Moderate	
Kotseva et al. 2001	Moderate	
Liss and Finkelstein 1996	Low	
Reinhardt et al. 1997a	Moderate	
Schramm et al. 2016	Moderate	
Sugimoto et al. 1978	Moderate	
Swaen et al. 1994	Moderate	
Takebayashi et al. 2004	Moderate	
Sweetnam et al. 1987; Tiller et al. 1968	Low	
Tolonen et al. 1976	Moderate	
Vanhoorne et al. 1992a	Moderate	
Vertin 1978	Low	
Outcome: Altered lipid homeostasis (inhalation only)		
Inhalation acute-duration exposure		
Animal studies		
Freundt et al. 1974b	Moderate	High
Simmons et al. 1988	High	
Simmons et al. 1989	Moderate	
Inhalation intermediate-duration exposure		
Animal studies		

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

	Initial study confidence	Initial confidence rating
Wrońska-Nofer 1973	High	High
Wrońska-Nofer 1972	High	
Inhalation chronic-duration exposure		
Human studies		
Chang et al. 2007	Moderate	Moderate
Chrostek-Maj and Czeczotko 1995a	Moderate	
Cirla and Graziano 1981	Moderate	
Franco et al. 1982	Moderate	
Hernberg et al. 1971	Moderate	
Jhun et al. 2007	Moderate	
Jhun et al. 2009	Moderate	
Kim et al. 2000	Moderate	
Kotseva and DeBacquer 2000	Moderate	
Kotseva et al. 2001	Moderate	
Luo et al. 2011	Moderate	
NIOSH 1984a	Moderate	
Raitta et al. 1974	Moderate	
Schramm et al. 2016	Moderate	
Sidorowicz et al. 1980	Low	
Stanosz et al. 1994b	Moderate	
Sugimoto et al. 1978	Moderate	
Takebayashi et al. 2004	Moderate	
Vanhoorne et al. 1992a	Moderate	
Vertin 1978	Low	
Animal studies		
Wrońska-Nofer et al. 1980	High	High
Outcome: Ophthalmological effects (inhalation only)		
Inhalation intermediate-duration exposure		
Animal studies		
Phillips 1983a	High	High
Phillips 1983b	High	
Phillips 1983c	High	
Inhalation chronic-duration exposure		
Human studies		
Cirla and Graziano 1981	Moderate	Moderate
Kim et al. 2000	Moderate	
NIOSH 1984a	Moderate	
Sugimoto et al. 1976	Moderate	
Sugimoto et al. 1977	Moderate	

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

	Initial study confidence	Initial confidence rating
Sugimoto et al. 1978	Moderate	
Vanhoorne et al. 1996	Moderate	
Raitta et al. 1974	Moderate	
Raitta and Tolonen 1975	Moderate	
Outcome: Neurological effects		
Inhalation acute-duration exposure		
Animal studies		
Carreres Pons et al. 2017	High	High
Denny and Gerhart 1991 (main study)	High	
Herr et al. 1998; Moser et al. 1998 (2 weeks)	High	
Lehotzky et al. 1985	Moderate	
Liang et al. 1983	Low	
Magos 1970	High	
Magos et al. 1974	High	
Qingfen et al. 1999	High	
Tarkowski and Sobczak 1971	Moderate	
Wilmarth et al. 1993	Moderate	
Inhalation intermediate-duration exposure		
Animal studies		
Clerici and Fechter 1991	Moderate	High
Eskin et al. 1988	Low	
Frantik 1970	Low	
Graham and Popp 1992a; Phillips 1983a	High	
Graham and Popp 1992b; Phillips 1983b	High	
Herr et al. 1998; Moser et al. 1998 (4 weeks)	High	
Herr et al. 1998; Moser et al. 1998 (8 weeks)	High	
Herr et al. 1998; Moser et al. 1998 (13 weeks)	High	
Hirata et al. 1992	High	
Merigan et al. 1988	Low	
Morvai et al. 2005	Low	
Phillips 1983c	High	
Qingfen et al. 1999	High	
Rebert and Becker 1986	Moderate	
Wrońska-Nofer 1973	Low	
Inhalation chronic-duration exposure		
Human studies		
Chang et al. 2003	Low	Moderate
Cirla and Graziano 1981	Moderate	
Godderis et al. 2006	Moderate	

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

	Initial study confidence	Initial confidence rating
Foa et al. 1976	Moderate	
Hirata et al. 1996	Moderate	
Johnson et al. 1983	Moderate	
Kim et al. 2000	Moderate	
Raitta and Tolonen 1975	Moderate	
Reinhardt et al. 1997a	Moderate	
Reinhardt et al. 1997b	Moderate	
Ruijten et al. 1990	Moderate	
Ruijten et al. 1990	Moderate	
Seppalainen and Tolonen 1974	Moderate	
Vanhoorne et al. 1995	Moderate	
Vanhoorne et al. 1996	Moderate	
Cassitto et al. 1993	Moderate	
Chrostek-Maj and Czeczotko 1995b	Moderate	
Nishiwaki et al. 2004	Moderate	
Raitta et al. 1974	Moderate	
Yoshioka et al. 2017	Moderate	
Oral acute-duration exposure		
Animal studies		
Kanada et al. 1994	Moderate	High
NCTR 1984a (preliminary)	Moderate	
NCTR 1984a (teratology)	High	
NCTR 1984b (preliminary)	High	
NCTR 1984b (teratology)	High	
Oral intermediate-duration exposure		
Animal studies		
Gao et al. 2014; Wang et al. 2016	High	High
Liu et al. 2023	Low	
Liu et al. 2024	High	
Song et al. 2009	High	
Wang et al. 2017	High	
Outcome: Male reproductive effects (inhalation only)		
Inhalation acute-duration exposure		
Animal studies		
NIOSH 1980 (rat)	Moderate	High
NIOSH 1980 (rat)	Moderate	
Sills et al. 1998b (2 weeks)	Low	
Zenick et al. 1984	High	

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

	Initial study confidence	Initial confidence rating
Inhalation intermediate-duration exposure		
Animal studies		
Guo et al. 2014	Moderate	High
Guo et al. 2015	Moderate	
Huang et al. 2012	High	
Phillips 1983a	Moderate	
Phillips 1983b	Moderate	
Phillips 1983c	Moderate	
Sills et al. 1998b (4 weeks)	Low	
Sills et al. 1998b (8 weeks)	Low	
Sills et al. 1998b (13 weeks)	Low	
Tepe and Zenick 1984 (Study 1)	High	
Tepe and Zenick 1984 (Study 2)	High	
Zenick et al. 1984	High	
Inhalation chronic-duration exposure		
Human studies		
Cirla et al. 1978	Moderate	Moderate
Guo et al. 2016	Moderate	
NIOSH 1983	Moderate	
NIOSH 1984a	Moderate	
Takebayashi et al. 2003	Moderate	
Vanhoorne et al. 1993	Moderate	
Vanhoorne et al. 1994 (Study 1)	Moderate	
Vanhoorne et al. 1994 (Study 2)	Moderate	
Wägar et al. 1981	Moderate	
Wägar et al. 1983	Moderate	
Outcome: Developmental effects (inhalation only)		
Inhalation chronic-duration exposure		
Human studies		
Zhou et al. 1988	Moderate	Moderate
Inhalation acute-duration exposure		
Animal studies		
Denny and Gerhart 1991 (dose range-finding)	Low	High
Denny and Gerhart 1991 (main study)	High	
NIOSH 1980 (rat)	High	
Lehotzky et al. 1985	Low	
Inhalation intermediate-duration exposure		
Animal studies		
NIOSH 1980 (rabbit)	High	High

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

	Initial study confidence	Initial confidence rating
Holson 1992	High	
NIOSH 1980 (rat)	High	
NIOSH 1980 (rabbit)	High	
Saillenfait et al. 1989	High	
Tabacova et al. 1983	High	
Oral acute-duration exposure		
NCTR 1984a	High	High
NCTR 1984b (preliminary)	Moderate	
NCTR 1984b (teratology)	High	
Tsai et al. 2000	High	

C.6.2 Adjustment of the Confidence Rating

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

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

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Cardiovascular effects (inhalation only)			
Human studies	Moderate	-1 Risk of bias +1 Large magnitude of effect	Moderate
Animal studies	High		High
Outcome: Altered lipid homeostasis (inhalation only)			
Human studies	Moderate	-1 Risk of bias -1 Unexplained inconsistency	Very low
Animal studies	High	-1 Unexplained inconsistency	Moderate
Outcome: Ophthalmological effects (inhalation only)			
Human studies	Moderate	-1 Risk of bias +1 Consistency in the body of evidence	Moderate
Animal studies	High	-1 Unexplained inconsistency (limited data)	Moderate
Outcome: Neurological effects			
Human studies, inhalation only	Moderate	-1 Risk of bias +1 Consistency in the body of evidence +1 Dose response	High
Animal studies	High	+1 Consistency in the body of evidence +1 Large magnitude of effect	High
Outcome: Male reproductive effects (inhalation only)			
Human studies	Moderate	-1 Risk of bias -1 Unexplained inconsistency	Very low
Animal studies	High	-1 Unexplained inconsistency	Moderate
Outcome: Developmental effects (inhalation only)			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High	-1 Unexplained inconsistency	Moderate

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

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Cardiovascular effects (inhalation only)	Moderate	High
Altered lipid homeostasis (inhalation only)	Very low	Moderate
Neurological effects	High	High
Male reproductive effects (inhalation only)	Very low	Moderate
Developmental effects	Low	Moderate

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 carbon disulfide, 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 carbon disulfide is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Carbon Disulfide

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies (inhalation only)			
Cardiovascular	Moderate	Health effect	Moderate
Altered lipid homeostasis	Very low	Health effect	Inadequate
Ophthalmological effects	Moderate	Health effect	Moderate
Neurological effects	High	Health effect	High
Male reproductive	Very low	Health effect	Inadequate
Developmental	Low	No health effect	Inadequate
Animal studies			
Cardiovascular (inhalation only)	High	Health effect	High
Altered lipid homeostasis (inhalation only)	Moderate	Health effect	Moderate
Ophthalmological effects (inhalation only)	Moderate	No health effect	Inadequate
Neurological effects	High	Health effect	High
Male reproductive (inhalation only)	Moderate	Health effect	Moderate
Developmental	Moderate	Health effect	Moderate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

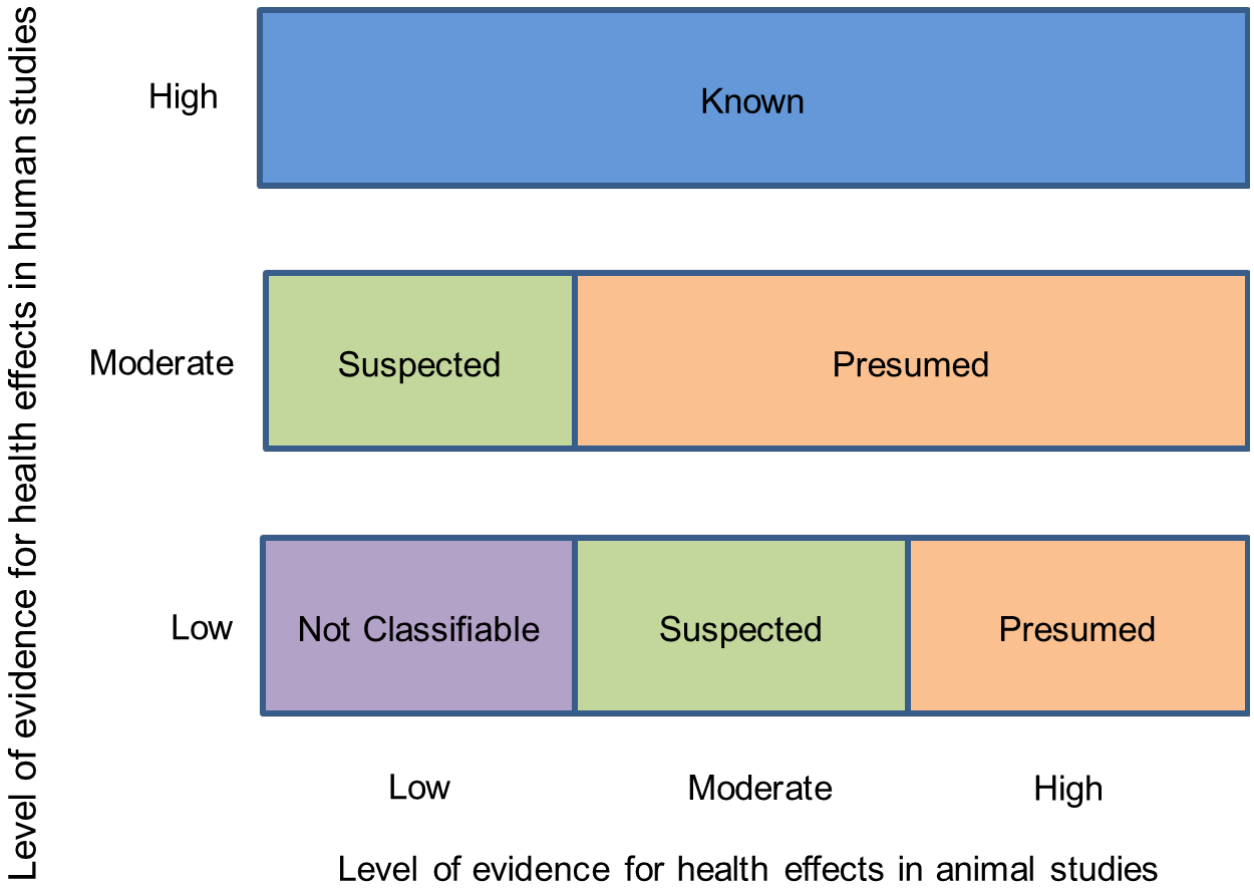
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

Known Health Effects

- Neurological effects (inhalation)

- Neurological effects are a commonly evaluated and reported endpoint in occupational cohorts exposed to carbon disulfide, particularly peripheral neuropathy.
  - At low concentrations (<10 ppm) findings include alterations in nerve conduction velocity (Hirata et al. 1996; Kim et al. 2000; Johnson et al. 1983; Ruijten et al. 1990, 1993; Seppalainen and Tolonen 1974; Vanhoorne et al. 1995; Yoshioka et al. 2017). Some of these studies also reported increased self-reported symptoms of polyneuropathy at exposure concentrations ranging from 0.43 to 36 ppm, such as pain, insensitive spots, paresthesia, numbness, and difficulty walking (Kim et al. 2000; Vanhoorne et al. 1994).
  - Studies indicate that neuropathy may be reversible at low concentrations (<10 ppm) but may be persistent at concentrations >20 ppm (Seppalainen and Tolonen 1974; Yoshioka et al. 2017).
  - Overt polyneuritis or polyneuropathy are common findings among highly exposed workers (≥100 ppm), including impaired nerve conduction, subjective complaints, decreased pain sensitivity, tremors, and abnormal movements resembling early Parkinsonism (Chapman et al. 1991; Chu et al. 1995; Lancranjan et al. 1972; Peters et al. 1988; Vasilescu 1976).
- The nervous system is a sensitive endpoint of carbon disulfide toxicity in animals following inhalation exposure. The most common neurological findings include impaired peripheral nerve conduction velocity and behavioral/clinical evidence peripheral nerve damage (e.g., foot drag, hindlimb paralysis) (Frantik 1970; Graham and Popp 1992a; Herr et al. 1998; Phillips 1983a, 1983b, 1983c; Rebert and Becker 1986; Wrońska-Nofer 1973) and damage to the sensory nerve tracts in the spinal cord (Graham and Popp 1992a; Phillips 1983a, 1983b; Valentine et al. 1997).

Presumed Health Effects

- Cardiovascular effects (inhalation)
  - A meta-analysis by Tan et al. (2002) of 11 studies published between 1970 and 1996 determined a positive association between occupational exposure and prevalence of cardiovascular disease.
  - Increased risk of death from cardiovascular disease has been reported in several occupational cohorts of carbon disulfide exposure, particularly in past decades with higher occupational exposure levels (>10 ppm) (Section 2.5).
  - Increased prevalence of cardiovascular disease has also been reported in some workers exposed to carbon disulfide, including myocardial infarction, ischemic or coronary heart disease, and/or angina (Balcarova and Halik 1991; Hernberg et al. 1970; Kotseva et al. 2001; Takebayashi et al. 2004; Tolonen et al. 1975). However, others did not observe associations at similar exposure levels (Sugimoto et al. 1978; Tolonen et al. 1976; Vanhoorne et al. 1992a; Vertin 1978).
  - Evidence for associations between occupational carbon disulfide exposure and elevated blood pressure and abnormal ECGs are inconsistent (Section 2.5)
  - A limited number of inhalation studies in rats have reported altered cardiac function following exposure to carbon disulfide, including decreased cardiac rate (Tarkowski and Sobczak 1971) and increased blood pressure and decreased cardiac output (Morvai et al. 2005).
  - While the cardiovascular system is not a sensitive target of oral exposure to carbon disulfide, atherosclerotic lesions occurred in animals exposed to carbon disulfide when also exposed to a high-fat diet (Antov et al. 1985; Lewis et al. 1999).
- Ophthalmological effects (inhalation)
  - Increased prevalence of retinal microaneurysms has been reported in several cohorts of viscose rayon workers from multiple countries, including the United States, Belgium Korea, and Japan (Kim et al. 2000; NIOSH 1984a; Sugimoto et al. 1976, 1977; Vanhoorne et al.

1996). In some cohorts, prevalence and severity was associated with both increased exposure concentration and duration.
    - There may be differences in susceptibility because retinal microaneurysms were not increased in a Finnish cohort with exposure concentrations comparable to, or higher than, effected cohorts from other countries, although mild changes in retinal hemodynamics were observed (Raitta et al. 1974; Sugimoto et al. 1977).
    - Ophthalmological data from animals are limited to a series of 90-day inhalation studies in rats and mice, which did not observe any adverse effects at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c).
- Neurological effects (oral)
    - No oral data in humans are available.
    - Oral data in animals are limited but available data report cognitive impairments and overt clinical signs at doses ≥200 mg/kg/day, including incoordination and gait impairments, lethargy, ataxia, tremor, paralysis, and convulsions (Gao et al. 2014; Liu et al. 2023, 2024; NCTR 1984a, 1984b; Song et al. 2009; Wang et al. 2016, 2017). Impaired caudal nerve conduction was reported at ≥300 mg/kg/day (Liu et al. 2024) and brain edema and cortical and hippocampal neuronal loss were reported at ≥400 mg/kg/day (Wang et al. 2017).

Suspected Health Effects

- Altered lipid homeostasis (inhalation)
    - Elevated serum cholesterol has been associated with increased cumulative carbon disulfide exposure in some cohorts of viscose rayon workers (Jhun et al. 2007; Kotseva and De Bacquer 2000; Stanosz et al. 1994b; Vanhoorne et al. 1992a), but not several others at similar exposure levels (Section 2.9).
    - In animals, elevated liver lipid synthesis, liver lipid/cholesterol content, and serum lipid and/or cholesterol levels have been observed in following acute-, intermediate-, and chronic-duration inhalation exposure (Freundt et al. 1974b; Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980). However, data are available only from a few studies, and evaluations at low concentrations following repeated exposures are lacking. Confidence in the evidence was downgraded due to conflicting findings from acute-duration inhalation studies by Simmons et al. (1988, 1989), in which Simmons et al. (1988) reported *decreased* hepatic cholesterol synthesis and Simmons et al. (1989) reported no change in cholesterol synthesis at the same concentration. The study authors attributed the inconsistency to lack of statistical power in the later study; however, findings are still in conflict with elevated synthesis observed by Wrońska-Nofer (1972). This may be due to different methodology. Simmons et al. (1988) measured synthesis *ex vivo*, while Wrońska-Nofer (1972) measured synthesis *in vivo*. Additionally, Simmons et al. (1988) evaluated male F-344 rats after a 6-hour exposure and Wrońska-Nofer (1972) evaluated female Wistar rats after exposure for 8 months.
- Male reproductive effects (inhalation)
    - A few studies provide evidence of potential associations between self-reported impairments in male sexual function and occupational exposure to carbon disulfide (Vanhoorne et al. 1994; Wägar et al. 1981). However, there is no evidence of impaired fertility in male workers exposed to carbon disulfide (NIOSH 1983; Vanhoorne et al. 1994).
    - Evidence for associations between occupational carbon disulfide exposure and sperm damage or altered male reproductive hormone levels are inconsistent (Section 2.16).
    - Animal studies reported altered mating behaviors in male rats following inhalation exposure to carbon disulfide (Tepe and Zenick 1984; Zenick et al. 1984).
    - Similar to human data, findings in animals pertaining to altered sperm parameters, serum hormone levels, and histopathological changes the testes are inconsistent between studies (Section 2.16).

- Developmental effects (inhalation, oral)
  - Data in humans are limited to a single study that did not observe an association between occupational exposure during pregnancy and congenital malformations (Zhou et al. 1988).
  - Developmental effects (increased postimplantation loss, decreased fetal body weight, decreased neonatal viability) have been reported in both rats and rabbits following inhalation exposure during gestation to exposures >500 ppm, with visceral and skeletal malformations at >800 ppm (Denny and Gerhart 1991; Holson 1992; Saillenfait et al. 1989). Postnatal exposures ≥225 ppm were associated with delayed reflex ontology and impaired neurodevelopment (Lehotzky et al. 1985).
  - In contrast to traditional teratology studies described above, a series of studies utilizing a non-traditional two-generation exposure design reported malformations in F1 and F2 rats at ≥32 ppm (Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983). However, there are numerous limitations and discrepancies within and between these reports, including transiency of effects and low exposure levels, lack of examination of all endpoints at higher exposure levels, different control groups for lower and higher exposure groups, and lack of clear exposure-response.
  - Developmental effects have been observed both rats and rabbits in oral gestational exposure studies at ≥200 and 25 mg/kg/day, respectively (NCTR 1984a, 1984b). Another oral study in rats did not observe adverse developmental effects at concentrations up to 1,200 mg/kg/day (Tsai et al. 2000).

Table C-19. Hazard Identification Conclusions for Carbon Disulfide

Outcome	Hazard identification
Cardiovascular (inhalation)	Presumed
Altered lipid homeostasis (inhalation)	Suspected
Ophthalmological effects (inhalation)	Presumed
Neurological effects (inhalation)	Known
Neurological effects (oral)	Presumed
Male reproductive effects (inhalation)	Suspected
Developmental (inhalation, 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)

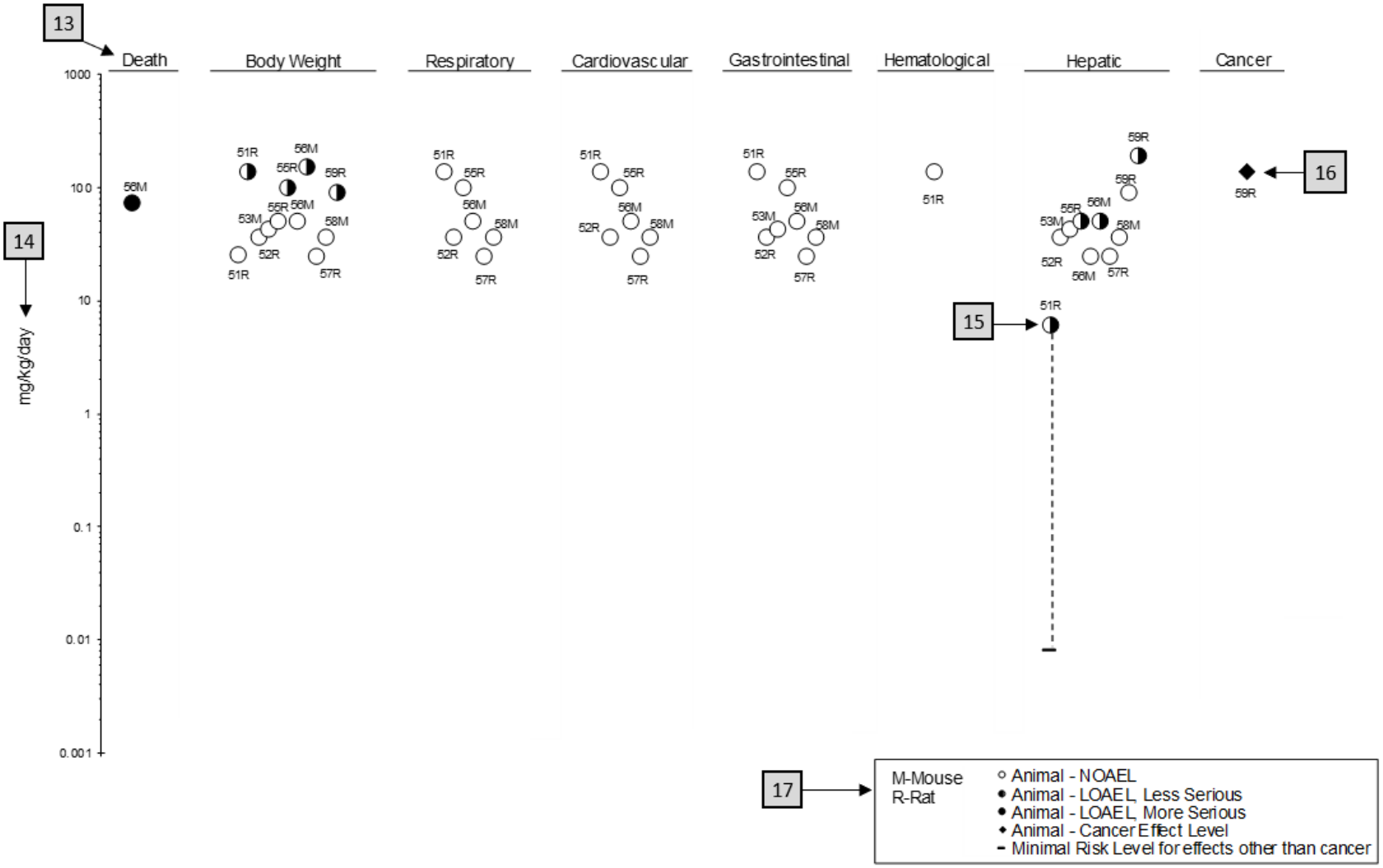
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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