Toxicological Profile for Carbon Disulfide

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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August 1996	Final toxicological profile released

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The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Carbon disulfide is a clear, colorless, or faintly yellow colored volatile liquid. It is released to the environment from both natural and anthropogenic sources. The ocean, marshes, and coastal areas appear to be important natural sources of carbon disulfide. Average reported background levels of carbon disulfide in the oceans range from about 16 to 18 picomoles/L (0.0012–0.0014 µg/L). Estimates from the 1980s suggested that natural sources of carbon disulfide were greater than anthropogenic releases; however, later modeling results suggest that the major source of carbon disulfide derives from industrial emissions (58%), while the oceans contribute about 34% and the remainder arises from terrestrial sources. The most important anthropogenic source of carbon disulfide emissions occurs from industrial releases. The production of viscose rayon fibers is the most prominent industrial source of carbon disulfide emissions; related industries include cellophane and cellulosic sponge manufacturing. However, no rayon production facilities are currently operating in the United States. Carbon disulfide is also used in the production of certain pesticides (dithiocarbamates) and may be released during environmental degradation of these compounds, such as metam salts, dazomet, or thiram. In the past, a large use of carbon disulfide was to produce carbon tetrachloride; however, the use of carbon tetrachloride has decreased dramatically in recent years, so the demand for carbon disulfide for this particular use is no longer as important as it was several decades ago.

When released to the environment, carbon disulfide partitions primarily to the atmosphere where it is degraded by reaction with photochemically produced hydroxyl radicals in the troposphere to produce carbonyl sulfide. If released to water, carbon disulfide can hydrolyze slowly under alkaline conditions; however, volatilization to the atmosphere will be the overwhelming environmental fate process. The potential for carbon disulfide to bioconcentrate in aquatic organisms is low. Carbon disulfide released to soils from an accidental spill or other release should also rapidly volatilize to the atmosphere. If small amounts remain on soil surfaces, the compound could potentially leach into groundwater since it does not adsorb strongly to soil.

The general population is primarily exposed to carbon disulfide from inhalation of ambient air. Data for 2024 showed a median concentration of carbon disulfide across various monitoring stations in the United States of 0.318 µg/m^3 (0.102 ppb), with a maximum value of 17.4 µg/m^3 (5.6 ppb). Much higher levels are often detected under occupational exposure settings such as facilities that manufacture viscose rayon

fibers where levels >10 ppm have been observed; however, industrial hygiene standards and controls have resulted in most facilities maintaining exposure levels <10 ppm. While inhalation is the predominant route of exposure in occupational settings, dermal exposure may also occur. Carbon disulfide was once used as a fumigant in agriculture, so detectable levels were observed on grains, legumes, and other fruit and vegetable products. However, this use has been discontinued since the 1980s in the United States; exposure from consumption of food products is therefore not a current exposure pathway. The likelihood of exposure to carbon disulfide via drinking water is low due to the volatility of the chemical.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of carbon disulfide comes predominantly from acute- and intermediate-duration inhalation studies in animals and chronic-duration occupational studies in humans. Most occupational studies are from the viscose rayon industry. While it is acknowledged that other exposures occur in this industry, carbon disulfide is considered the predominant chemical exposure. Some acute- and intermediate-duration oral studies in animals are available, with only a few animal studies evaluating dermal exposure.

As illustrated in Figure 1-1, sensitive effects following inhalation exposure to carbon disulfide are neurological, cardiovascular, ophthalmological (ocular), altered lipid homeostasis (hepatic), male reproductive, and developmental effects. Figure 1-2 illustrates that sensitive effects following oral exposure to carbon disulfide include developmental and neurological effects. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Neurological effects are a known health effect for humans following inhalation exposure and a presumed health effect for humans following oral exposure.
- Cardiovascular effects are a presumed health effect for humans following inhalation exposure.
- Ophthalmological effects are a presumed health effect for humans following inhalation exposure.
- Altered lipid homeostasis is a suspected health effect for humans following inhalation exposure.
- Male reproductive effects are a suspected health effect for humans following inhalation exposure.
- Developmental effects are a suspected health effect for humans following inhalation or oral exposure.

Figure 1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to Carbon Disulfide

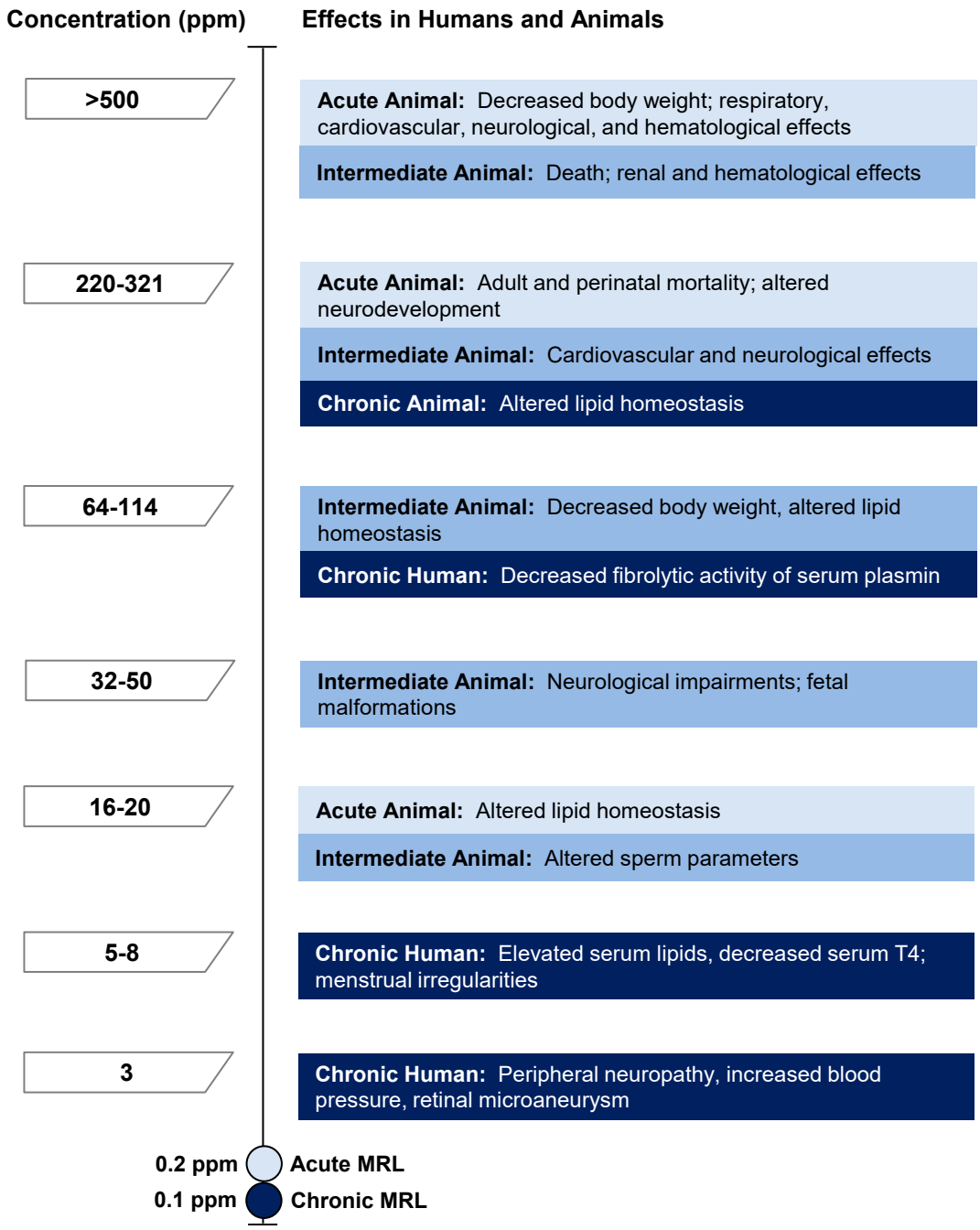
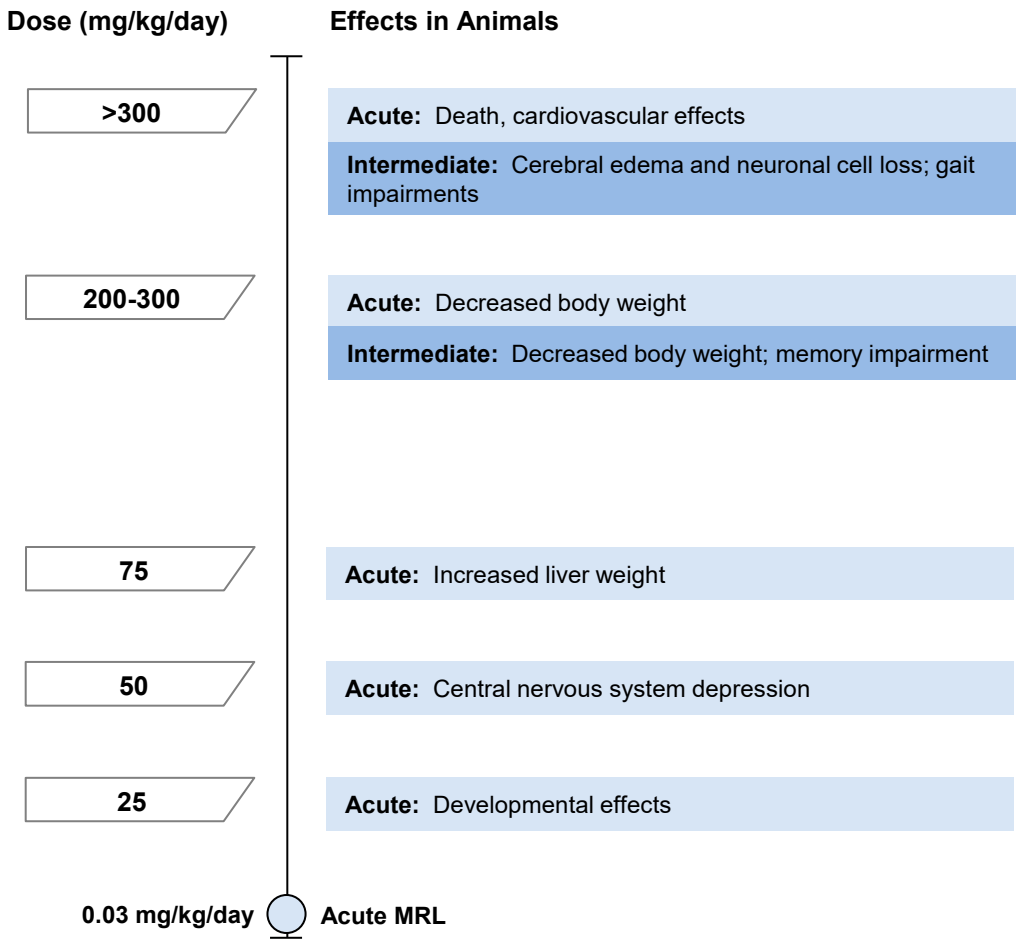


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Carbon Disulfide



Neurological Effects. Neurological effects are a commonly evaluated and reported endpoint in occupational cohorts exposed to carbon disulfide, particularly peripheral neuropathy. At low concentrations (<10 ppm), the most frequently reported, objective, and quantifiable endpoint is impaired 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). Peripheral neuropathy may be reversible at low concentrations but is reportedly persistent at higher concentrations (Seppalainen and Tolonen 1974; Yoshioka et al. 2017). Overt polyneuritis or polyneuropathy are common findings among isolated occupational cases with very high exposure levels (≥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). Acute psychosis has also been reported in workers exposed to very high levels, ranging as high as 300–800 ppm; however, reported cases are pre-1940, prior to modern industrial hygiene practices (DOL 1940; Gordy and Trumper 1938, 1940; Paluch 1948; Vigliani 1950). Numerous inhalation studies in animals indicate that the peripheral nervous system, spinal cord, and optic nerve are sensitive targets, although tested exposure concentrations are often much higher than levels experienced by the average modern worker (Section 2.15). There is some evidence of hearing loss and impaired vestibular function associated with inhalation exposure to carbon disulfide in conjunction with noise exposure in both humans and animals (Carreres Pons et al. 2017; Chalansonnet et al. 2018, 2020; Chang et al. 2003; Venet et al. 2017). Oral data are limited, but reported overt clinical signs in animals at high doses include 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). Findings were associated with impaired caudal nerve conduction (Liu et al. 2024). One study in rats reported impairments in learning and memory, cerebral edema, and neuronal loss in the cortex and hippocampus (Wang et al. 2017).

Cardiovascular Effects. Increased prevalence of, and risk of death from, cardiovascular disease (e.g., coronary heart disease, stroke, myocardial infarction, hypertension) has been reported in several occupational cohorts of viscose rayon factories or other workers exposed to carbon disulfide, particularly in past decades, with occupational exposure levels of ≥10 ppm (Section 2.5). The prevalence of coronary or ischemic heart disease and elevated blood pressure has also been increased in some cohorts exposed to lower concentrations (Kotseva et al. 2001; Takebayashi et al. 2004). A meta-analysis by Tan et al. (2002) of 11 occupational studies published between 1970 and 1996 determined a positive association between occupational exposure and prevalence of cardiovascular disease. Though limited in number, available

inhalation studies in animals report altered cardiac function following inhalation exposure to carbon disulfide (Morvai et al. 2005; Tarkowski and Sobczak 1971).

Ophthalmological Effects (Ocular). 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). However, a large longitudinal cohort study from Finland did not observe this effect, despite much higher historical exposure levels. No ophthalmological changes were observed in an intermediate-duration inhalation study in rats and mice (Phillips 1983a, 1983b, 1983c). While ocular irritation was noted in animals exposed to higher concentrations during cage-side evaluations (Holson 1992), this finding was attributed to direct ocular contact with carbon disulfide vapor (classified as dermal exposure). In order to restrict systematic review to studies evaluating the systemic effects of inhalation exposure, only studies including ophthalmological examinations were considered (e.g., slit lamp bio-microscopy, fundoscopy, etc.). It is noted that tests of visual acuity are discussed and evaluated as neurological, not ophthalmological, effects.

Altered Lipid Homeostasis (Hepatic). There is some evidence that normal lipid homeostasis in humans is perturbed following occupational exposure to carbon disulfide, with elevated serum cholesterol and/or lipid levels in some studies (Jhun et al. 2007; Kotseva and De Bacquer 2000; Stanosz et al. 1994b; Vanhoorne et al. 1992a). However, a number of studies did not observe associations under similar exposure conditions (see Section 2.9 for citations). In animals, a limited number of studies have reported elevated liver lipid synthesis, elevated liver lipid/cholesterol content, and elevated serum lipid and/or cholesterol levels following acute-, intermediate-, and chronic-duration inhalation exposure (Freundt et al. 1974b; Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980). There is minimal evidence of additional hepatic effects following carbon disulfide exposure to concentrations least 5-fold higher than levels associated with alterations in lipid homeostasis, including transient impairments in liver function (Gibson and Roberts 1972) and altered serum enzymes (Phillips 1983a). There is no evidence for histopathological changes in the liver of rodents following inhalation exposure (Magos and Butler 1972; Morvai et al. 2005; Phillips 1983a, 1983b, 1983c; Sills et al. 1998b). Therefore, systematic review was restricted to hepatic endpoints related to altered lipid homeostasis.

Male Reproductive Effects. A few studies provide evidence of potential associations between self-reported impairments in male sexual function and occupational exposure to carbon disulfide (Cirla et al. 1978; 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). Animal studies reported altered mating behaviors in male rats following inhalation exposure to carbon disulfide at concentrations much higher than levels experienced by the average worker (Tepe and Zenick 1984; Zenick et al. 1984). There is inconsistent evidence for damage to sperm and/or for alterations to male reproductive hormones in available human and animal studies (Section 2.16).

Developmental Effects. 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). In animals, developmental effects (increased postimplantation loss/fetal resorptions, decreased fetal body weight, decreased neonatal viability, fetal malformations) have been observed in both rats and rabbits following inhalation exposure during gestation (Denny and Gerhart 1991; Holson 1992; Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983; Saillenfait et al. 1989). Postnatal exposure was associated with increased perinatal mortality, delayed reflex ontology, and impaired neurodevelopment (Lehotzky et al. 1985). Similar developmental effects occurred in rats and rabbits in oral gestational exposure studies; in oral studies, rabbits were distinctly more sensitive compared to rats (NCTR 1984a, 1984b). However, another oral study in rats did not observe adverse developmental effects under similar conditions (Tsai et al. 2000).

Cancer. Studies of occupational cohorts with exposure to carbon disulfide have not observed excess deaths attributable to neoplasms (Liss and Finkelstein 1996; Lyle 1981; MacMahon and Monson 1988; Nurminen and Hernberg 1985; Swaen et al. 1994). Studies from rubber workers suggest potential associations between solvent exposure, including carbon disulfide, and lymphocytic leukemia and/or lymphosarcoma; however, data are inadequate to attribute findings to any specific solvent (Checkoway et al. 1984; Wilcosky et al. 1984). There are no studies in animals evaluating carcinogenic potential for carbon disulfide. The Integrated Risk Information System (IRIS 2002), International Agency for Research on Cancer (IARC 2023), and National Toxicology Program (NTP 2021) have not evaluated the potential for carbon disulfide to cause carcinogenicity in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of acute- and chronic-duration inhalation MRLs for carbon disulfide. As illustrated in Figure 1-3, the most sensitive endpoints in animals appear to hepatic effects (specifically altered lipid homeostasis) as well as the male reproductive, developmental, and neurological effects. In humans, neurological, cardiovascular, and ocular (ophthalmological) effects

appear to be the most sensitive targets of carbon disulfide toxicity following occupational exposure. While workers may be exposed via multiple routes, inhalation is assumed to be the predominant route of exposure. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

The oral database was considered adequate for derivation of an acute-duration oral MRL for carbon disulfide. As illustrated in Figure 1-4, the developing organism and neurological system appear to be the most sensitive targets of carbon disulfide toxicity following oral exposure. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Carbon Disulfide – Inhalation

Available data indicate that the neurological, cardiovascular, ocular (ophthalmological), hepatic (altered lipid homeostasis), and male reproductive systems and the developing organism appear to be the most sensitive targets of carbon disulfide inhalation exposure.
Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively.

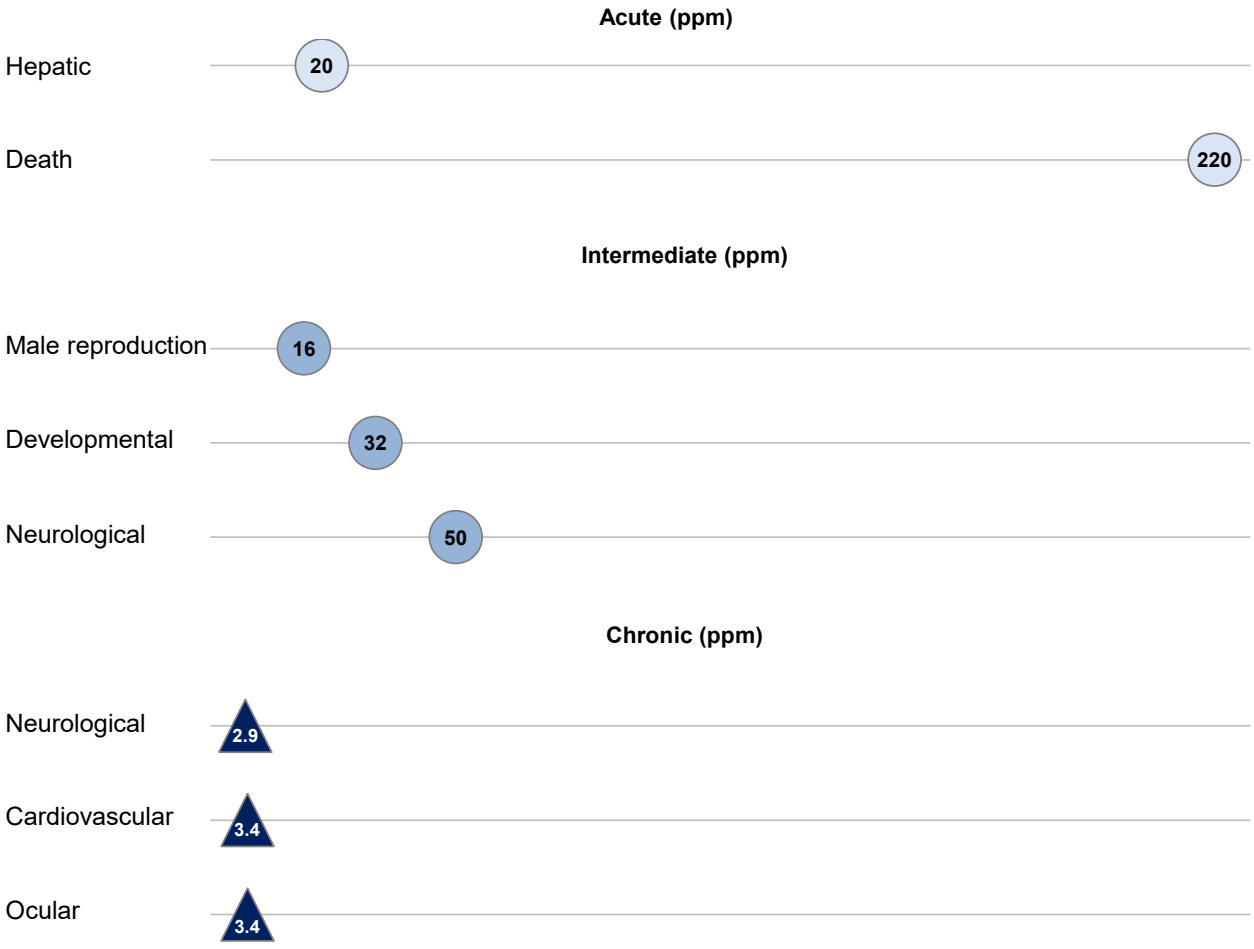


Figure 1-4. Summary of Sensitive Targets of Carbon Disulfide – Oral

Available data indicate that the developing organism and neurological system are the most sensitive targets of carbon disulfide oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No oral data were available for humans.

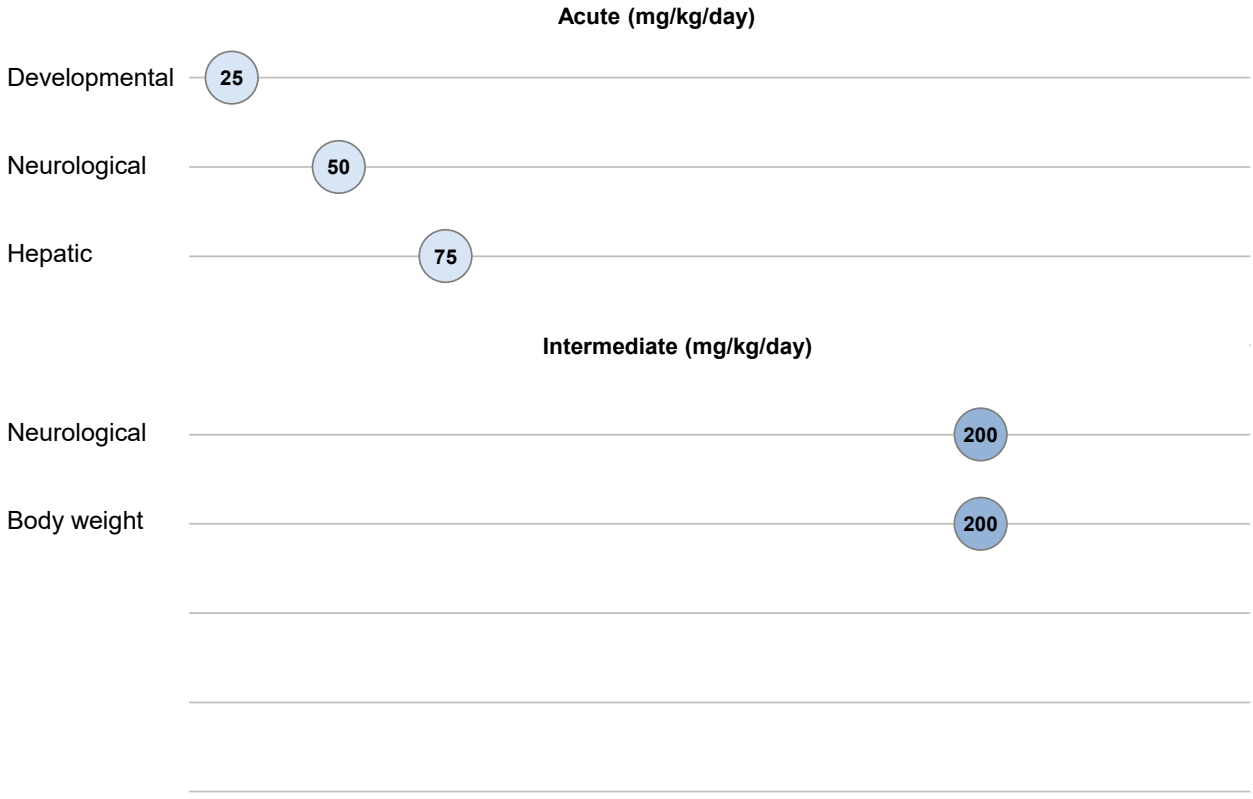


Table 1-1. Minimal Risk Levels (MRLs) for Carbon Disulfide[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**Acute**	**0.2 ppm** (0.6 mg/m^3)	Increased total lipid levels in hepatic microsomal fraction	$LOAEL_{HEC}$	16 ppm	UF: 90	Freundt et al. 1974b
	Intermediate	None	–	–	–	–	–
	Chronic	**0.1 ppm** (0.3 mg/m^3)	Impaired peripheral nerve conduction	Weighted $median_{ADJ}$[b]	0.957 ppm	UF: 10	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
Oral	**Acute**	**0.03 mg/kg/day**	Increased resorptions per litter	LOAEL	25 mg/kg/day	UF: 1,000	NCTR 1984b
	Intermediate	None	–	–	–	–	–
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]The 95% lower confidence interval of the weighted median was calculated from the observed NOAEL/LOAEL boundary identified from seven occupational cohort studies. Additional details and rationale are provided in Appendix A.

ADJ = adjusted for continuous/daily exposure; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of carbon disulfide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to carbon disulfide, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to carbon disulfide was also conducted; the results of this review are presented in Appendix C.

Human occupational studies with reliable exposure estimates and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal data are presented in Table 2-3. Results of epidemiological studies meeting inclusion criteria are provided in tables in relevant sections of Chapter 2; see Appendix B for details regarding prioritization of human data.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies.

Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “Serious” effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of carbon disulfide have been evaluated in 91 human and 78 animal studies meeting inclusion criteria for this profile. Review of literature evaluating the toxicity of compounds that are metabolized by the body into carbon disulfide, such as disulfiram (Antabuse) and certain pesticides (thiocarbamates), is outside the scope of this profile. Additional information on inclusion criteria for the profile can be found in Appendix B.

As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in humans and animals. For the purposes of Figure 2-1, all human studies with occupational exposure to carbon disulfide were classified as inhalation, despite potential for concurrent dermal exposures. Lastly, a few human studies included in the profile evaluated urinary levels of the metabolite 2-thiothiazolidine-4-carboxylic acid (TTCA; also known as 2-thio-1,3-thiazolidine-4-carboxylic acid) as a biomarker of exposure but lacked information pertaining to possible exposure sources; therefore, these studies are not included in Figure 2-1 due to unknown route(s) of exposure.

Nearly all available human data are from occupational cohort studies, primarily in the viscose rayon industry. Human studies were predominantly focused on cardiovascular, hepatic (serum lipid levels), and

neurological effects. While carbon disulfide is the predominant chemical exposure at viscose rayon factories, it is acknowledged that co-exposure to other chemicals frequency occurs at low levels (NIOSH 1977). The most common is hydrogen sulfide, with other potential exposures including tin oxide, zinc oxide and sulfate, sodium hydroxide, sulfuric acid, and lead, but these exposures are considered minimal compared to carbon disulfide (Hernberg et al. 1970; Johnson et al. 1983). Since none of the identified studies attempted to control for concurrent chemical exposures in statistical analyses and many studies provided only limited details on exposure (e.g., broad historical ranges), findings from occupational studies discussed throughout health effects sections of Chapter 2 should be interpreted with caution. More details on the quality and confidence in available epidemiological studies evaluating potential associations between carbon disulfide exposure and key health effects in occupational exposure studies can be found in Appendix C.

For animals, most of the data are from acute- and intermediate-duration inhalation studies, including several studies examining a comprehensive set of health effects. The most examined endpoints in these studies were body weight, neurological effects, and mortality. Chronic-duration inhalation data are limited to a single study evaluating limited endpoints (body weight, cardiovascular, and hepatic endpoints). The animal oral database is limited to acute- and intermediate-duration studies focusing primarily on body weight, cardiovascular, hepatic, neurological, and developmental effects. The dermal animal database is limited to two acute-duration studies and one intermediate-duration study. Cancer effects were not evaluated in animals via any route.

As outlined in Chapter 1, neurological, cardiovascular, ophthalmological, altered lipid homeostasis, male reproductive, and developmental effects appear to be the most sensitive targets of toxicity following inhalation exposure to carbon disulfide. The oral database is limited, but available data indicate that the most sensitive targets appear to be the developing organism and the neurological system. A systematic review was conducted on the available human and animal studies for these endpoints. The information in these studies indicate the following on the potential targets of carbon disulfide toxicity:

- **Neurological Endpoints:** Neurological effects are a known health effect associated with carbon disulfide exposure via the inhalation route based on a high level of evidence in humans and laboratory animals and a presumed health effect associated with carbon disulfide exposure via the oral route based on a high level of evidence in laboratory animals. Neurological effects, specifically peripheral neuropathy, are the most sensitive and consistent adverse effects reported in viscose rayon workers exposed to carbon disulfide. Available occupational studies provide evidence of increased severity of peripheral effects with both increased concentration and duration of exposure. Central nervous system effects, including symptoms resembling Parkinsonism and neuropsychological effects (including psychosis), were also observed in highly

exposed workers. Inhalation studies in animals support that the peripheral nervous system is a target of carbon disulfide toxicity, with damage to the central nervous system at higher concentrations. No human data are available for the oral route but limited oral data in animals reported clinical signs consistent with peripheral nervous system and/or central nervous system damage consistent with findings from inhalation studies.

- **Cardiovascular Endpoints (inhalation only):** Cardiovascular effects are a presumed health effect associated with carbon disulfide exposure via the inhalation route based on a moderate level of evidence in humans and a high level of evidence in laboratory animals. Several occupational studies reported increased prevalence of cardiovascular disease in workers exposed to carbon disulfide. Increased mortality due to cardiovascular disease has been reported in occupations with high exposure, such as spinners in viscose rayon factories, especially for workers exposed prior to implementation of current industrial hygiene standards. In humans, it is unclear if there is an association between occupational exposure and elevated blood pressure or altered electrocardiogram (ECG) findings. Animal evidence for altered cardiac function (e.g., altered ECG, elevated blood pressure, decreased cardiac output) following inhalation exposure studies support that the cardiovascular system is a target of toxicity. While the cardiovascular system is not a sensitive target of oral exposure, atherosclerotic lesions develop when animals are given carbon disulfide in conjunction with a high-fat diet.

- **Ophthalmological Endpoints (ocular; inhalation only):** Ophthalmological effects are a presumed health effect associated with carbon disulfide exposure via the inhalation route based on a moderate level of evidence in humans. Increased prevalence and severity of retinal microaneurysms have been reported in several cohorts of viscose rayon workers; the few observed exceptions may be due to potential differences in genetic susceptibility of different ethnic groups. In one study, no ophthalmological changes were observed in rats or mice exposed to carbon disulfide via inhalation for 90 days; no other animal studies evaluated this endpoint. Eye irritation was noted in animals exposed to higher concentrations, but this was attributed to direct ocular contact with carbon disulfide vapor (classified as dermal exposure). In order to focus on systemic effects of inhalation exposure, eye irritation was not included in the systematic review. It is also noted that tests of visual acuity are discussed and evaluated with neurological effects.

- **Altered Lipid Homeostasis (hepatic; inhalation only):** Altered lipid homeostasis is a suspected health effect associated with carbon disulfide exposure via the inhalation route based on inadequate evidence in humans and a moderate level of evidence in laboratory animals. Elevated blood cholesterol levels have been reported in several occupational cohort studies of workers exposed to carbon disulfide; however, several others did not observe associations at similar exposure levels. In laboratory animals, elevated liver lipid synthesis, liver lipid/cholesterol content, and serum lipid and/or cholesterol levels have been observed in a limited number of studies in rats following acute-, intermediate-, and chronic-duration inhalation exposure. Systematic review was restricted to hepatic endpoints associated with lipid homeostasis and metabolism, as there is minimal evidence of additional hepatic effects following carbon disulfide exposure. When observed, effects (including transient impairments in liver function and altered serum enzymes) occurred at concentrations at least 5-fold higher than those associated with altered lipid homeostasis.

- **Male Reproductive Endpoints (inhalation only):** Male reproductive effects are a suspected health effect associated with carbon disulfide exposure via the inhalation route based on inadequate evidence in humans and a moderate level of evidence in laboratory animals. In

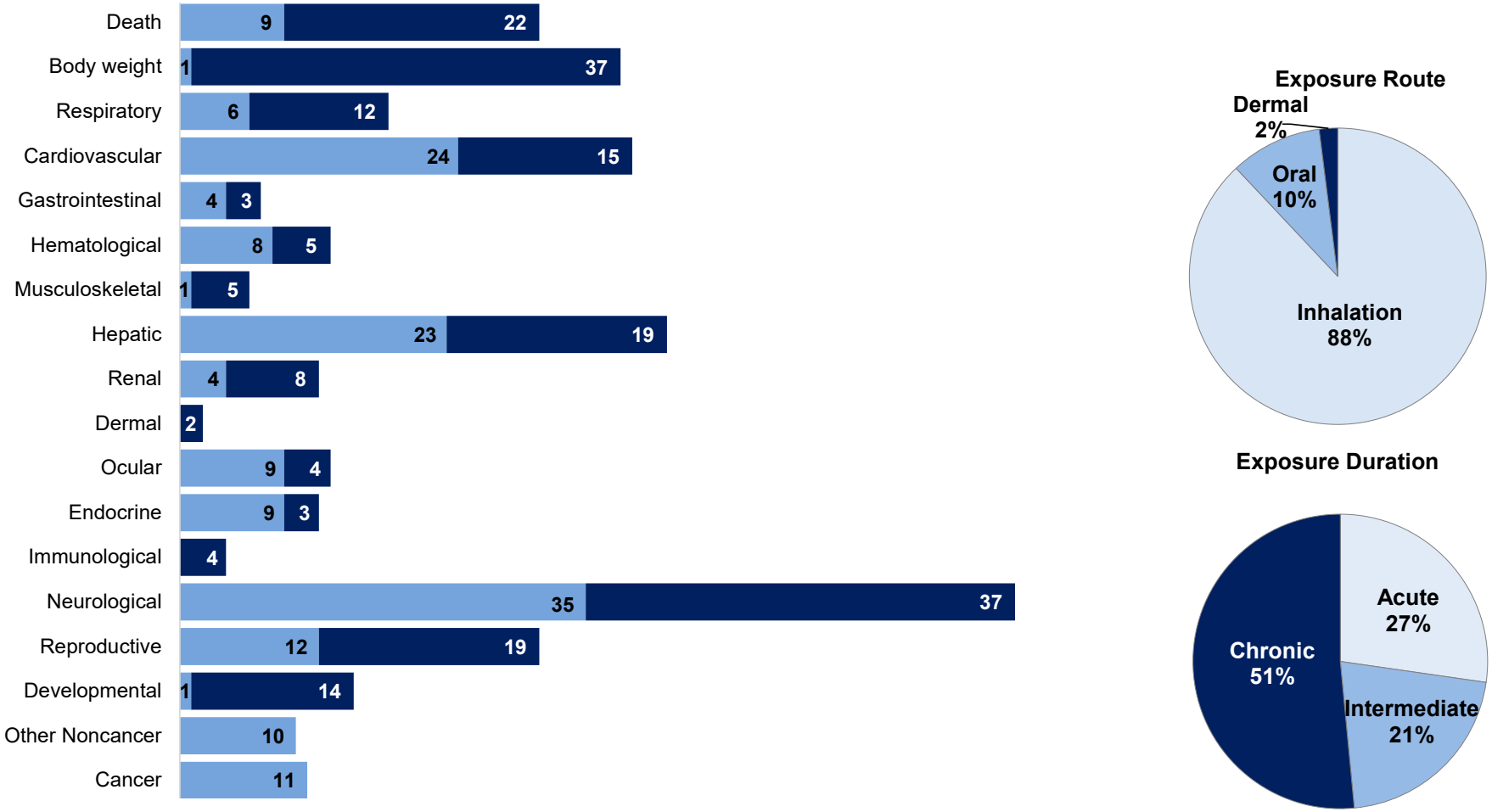
occupationally exposed males, there is no evidence of impaired fertility, but some male workers reported reduced libido and/or impotence. Consistent with this, animal studies reported altered mating behaviors in male rats following inhalation exposure to carbon disulfide. Both human and animal data are mixed concerning potential effects of carbon disulfide on sperm parameters following inhalation exposure. Animal data regarding histopathological damage to the testes are also mixed.

- **Developmental Endpoints:** Developmental effects are a suspected health effect associated with carbon disulfide exposure based on inadequate evidence in humans and a moderate level of evidence in laboratory animals. A single study in humans did not observe an association between occupational exposure during pregnancy and congenital malformations. In animals, developmental effects were observed in both rats and rabbits following inhalation or oral exposure to carbon disulfide, including increased resorptions, delayed growth and development, and increased visceral and skeletal malformations.

Figure 2-1. Overview of the Number of Studies Examining Carbon Disulfide Health Effects*

Most studies examined the potential neurological, cardiovascular, or hepatic effects of carbon disulfide

The number of studies evaluating health effects in humans and animals are approximately equal (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 169 studies (including those finding no effect) meeting inclusion criteria (see Appendix B) have examined toxicity; most studies examined multiple endpoints. All human occupational studies were classified as inhalation studies, although there is potential for concurrent dermal exposure.

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Carreres Pons et al. 2017									
1	Rat (Long-Evans) 16 F	5 days 6 hours/day 15 minutes/hour (WB)	0, 250	BW, HP, NX	Bd wt Neuro	250 250			
Freundt et al. 1974b									
2	Rat (Wistar) 5–23 F	8 hours (WB)	0, 20, 100, 400	BI	Hepatic		20[b]		Increase in total lipids in hepatic microsomal fraction
Gibson and Roberts 1972									
3	Rat (Sprague-Dawley) 4 M	60 minutes (WB)	0, 110	BC, OF	Hepatic		110		Transient impairment in liver function (increased BSP retention); decreased hepatic bile and blood flow
Hardin et al. 1981; NIOSH 1980									
4	Rat (Sprague-Dawley) 18–42 F	13 days GDs 6–18 7 hours/day (WB)	0, 19.3, 39.3	BW, DX	Bd wt Develop	39.3 39.3			
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997									
5	Rat (Fischer-344) 8–9 M, 8–9 F	2 weeks 6 hours/day 5 days/week (WB)	0, 50, 500, 800	BW, HP, NX	Bd wt Resp Cardio Hepatic Renal Neuro Repro	800 800 800 800 800 500 800	800		Slight gait impairment and ataxia in males, increased foot splay in females
Hiddemen et al. 1966									
6	Rat ChR-CD 6 M	4 hours (WB)	3,000, 3,500	LE, CS, BW, GN	Death			3,500	100% mortality

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Lehotzky et al. 1985									
7	Rat (CFY) 3–4 F	8 days GDs 7–15 6 hours/day (WB)	0, 3.2, 225, 642	LE, CS, BW, DX	Death			642	33% maternal mortality
					Neuro	225		642	Tremor and muscle weakness in dams that died
					Develop	3.2		225	35% perinatal mortality; delayed eye opening; altered motor activity, impaired motor coordination, altered operant conditioning
Magos 1970									
8	Rat Porton-Wistar 12 M	2–10 days 4 hours/day (WB)	0, 642	BI	Neuro		642		Decrease in brain noradrenaline levels days 2–10; transient decrease in brain dopamine levels on day 2 only
Magos and Butler 1972									
9	Rat Porton-Wistar 8–16 M	4 hours (WB)	0, 642	HP	Hepatic	642			
Magos et al. 1974									
10	Rat (Wistar) 12 M	1 hour (H)	0, 642	BI	Neuro		642		Decrease in brain noradrenaline, increase in brain dopamine
Nash et al. 1981									
11	Rat Crl-CD 4 M	10 minutes (H)	1,660, 8,760, 35,100, 81,100	CS, BW, OF	Resp	81,000			
NIOSH 1980									
12	Rat (Sprague-Dawley) 12 M	5 days 7 hours/day (WB)	0, 20, 40	RX	Repro	40			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Simmons et al. 1988									
13	Rat (Fischer-344) 8–12 M	6 hours (WB)	0, 30, 75, 150, 300, 600	BI, OW, HP	Hepatic	300	600		Decreased *ex vivo* hepatic cholesterol synthesis
Simmons et al. 1989									
14	Rat (Fischer-344) 4 M	1–3 days 6 hours (WB)	0, 600	BI, OW, HP	Hepatic	600			
Tarkowski and Sobczak 1971									
15	Rat (Wistar) 7 M	18 hours (WB)	0, 803	CS, BI, OF	Resp			803	Decreased respiratory rate
					Cardio			803	Decreased cardiac rate
					Neuro			803	Severe narcosis, straightening of hindlimbs
Wilmarth et al. 1993									
16	Rat (Sprague-Dawley) 6 M	14 days 10 hours/day (WB)	0, 600, 800	CS, BW, BC	Bd wt		600	800	LOAEL: 14% body weight loss SLOAEL: 32% body weight loss
					Neuro			600	Narcotic-like stupor; ataxia, hindlimb splay
Zenick et al. 1984									
17	Rat (Long-Evans) 12–14 M	5 days 6 hours/day (WB)	0, 607	BW, RX	Bd wt	607			
					Repro	607			
Gibson and Roberts 1972									
18	Mouse (Swiss-Webster) 4 M	60 minutes (WB)	0, 54, 110, 230, 550	LE	Death			220	LC_{50}

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gibson and Roberts 1972									
19	Mouse (Swiss-Webster) 4 M	60 minutes (WB)	0, 110, 230	OF	Hepatic		110		Transient impairment in liver function (increased BSP retention)
Gibson and Roberts 1972									
20	Mouse (Swiss-Webster) 4 M	5 days 60 minutes/day (WB)	0, 110	BC	Hepatic	110			
Lewis et al. 1999									
21	Mouse C57BL/6 60–61 F	5 days 6 hours/day (WB)	0, 50, 500, 800	LE, CS, BW, GN, HP	Bd wt	800			
					Cardio	800			
Cardiac effects evaluated in 10/group									
Liang et al. 1983									
22	Mouse (CD-1) 3–5 M	30 minutes (WB)	0, 119.5, 577.6, 2,162.6, 3,670.2	CS	Neuro	119.5	577.6		Impaired operant training
NIOSH 1980									
23	Mouse (CD-1) 12 M	5 days 7 hours/day (WB)	0, 20, 40	RX	Repro	40			
Denny and Gerhart 1991									
24	Rabbit (New Zealand White) 24 F	12 days GDs 6–18 6 hours/day (WB)	0, 60.9, 100.0, 304.1, 597.9, 1,168.6	LE, CS, FI, BW, HE, DX	Death			1,168.6	12.5% maternal death
					Bd wt	597.9		1,168.6	20% decrease in maternal body weight
					Resp	597.9		1,168.6	Labored respiration
					Hemato	597.9	1,168.6		Increased segmented neutrophils and decreased lymphocytes
					Neuro	597.9		1,168.6	Ataxia

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Develop	304.1		597.9	Increased postimplantation loss and early resorptions; 9% decrease in fetal body weight
Denny and Gerhart 1991									
25	Rabbit (New Zealand) 6 F	12 days GDs 6–18 6 hours/day (WB)	100, 300, 1,000, 3,000	LE, CS, FI, BW, DX	Death			3,000	100% mortality
					Resp			3,000	Labored breathing
					Develop	300		1,000	Increased postimplantation loss and early resorptions; >20% decrease in fetal body weight; increased external fetal malformations (compared to historical controls)
Qingfen et al. 1999									
26	Rabbit (New Zealand) 10 M, 10 F	1–2 weeks 6 days/week 3 hours/day (WB)	0, 321	NX	Neuro	321			
INTERMEDIATE EXPOSURE									
Eskin et al. 1988									
27	Monkey (Macaque) 1–5 F	5–13 weeks 5 days/week 6 hours/day (WB)	0, 256	OF, OP, HP	Neuro			256	Significant and permanent loss of visual acuity; damage to optic nerve; retinal ganglion cell degeneration
Merigan et al. 1988									
28	Monkey (Macaque) 1–5 F	5–13 weeks 5 days/week 6 hours/day (WB)	0, 256	BC, CS, OF, OP	Neuro			256	Severely reduced visual acuity and contrast sensitivity; damage to optic nerve; retinal ganglion cell degeneration

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Chalansonnet et al. 2018									
29	Rat (Long-Evans) 16–65 F	4 weeks 5 days/week 6 hours/day (WB)	0, 250	CS, BW, HP, NX	Bd wt	250			
					Neuro		250		Altered post-rotary nystagmus (decreased saccade number)
Clerici and Fechter 1991									
30	Rat (Long-Evans) 4 M	5 or 12 weeks 5 days/week 6 hours/day (WB)	0, 500	CS, BW, NX	Neuro		500		Decrease in auditory startle reflex amplitude
Frantik 1970									
31	Rat (albino) 18–42 M	10 months 5 days/week 7 hours/day (NS)	0, 48, 385, 770	LE, CS, NX	Neuro	48	385	770	LOAEL: Impaired motor strength, motor incoordination SLOAEL: Hindlimb paralysis, atrophy, tremor
Graham and Popp 1992a; Phillips 1983a									
32	Rat (Fischer-344) 15 M, 15 F	90 days 5 days/week 6 hours/day (WB)	0, 49.3, 297.1, 798.4	LE, CS, BW, FI, HE, BC, UR, OP, GN, OW, HP, NX	Bd wt	297.1	798.4 F	798.4 M	LOAEL: 17% decreased body weight SLOAEL: 20% decreased body weight
					Resp	798.4			
					Cardio	798.4			
					Gastro	798.4			
					Hemato	297.1	798.4		Increased segmented neutrophils and decreased lymphocytes in both sexes; mild decreases in RBC and platelet counts in males
					Musc/skel	798.4			
					Hepatic	798.4 F			
						297.1 M	798.4 M		Elevated serum ALT and AST
					Renal	798.4			
					Ocular	798.4			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	798.4			
					Immuno	798.4			
					Neuro	297.1		798.4	Ataxia, axonal degeneration and swelling in peripheral nerves, axonal swelling in spinal cord
					Repro	798.4			
Graham and Popp 1992b; Phillips 1983b									
33	Rat (Sprague-Dawley) 15 M, 15 F	90 days 5 days/week 6 hours/day (WB)	0, 49.3, 297.1, 798.4	LE, CS, BW, FI, HE, BC, UR, OP, GN, OW, HP, NX	Bd wt	297.1	798.4 F	798.4 M	LOAEL: 16% decrease in body weight SLOAEL: 27% decrease in body weight
					Resp	798.4			
					Cardio	798.4			
					Gastro	798.4			
					Hemato	798.4			
					Musc/skel	798.4			
					Hepatic	798.4			
					Renal	798.4			
					Ocular	798.4			
					Endocr	798.4			
					Immuno	798.4			
					Neuro	297.1		798.4	Ataxia, foot drag, axonal degeneration and swelling in peripheral nerves, axonal swelling in spinal cord
					Repro	798.4			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997									
34	Rat (Fischer-344) 16–18 M, 16–18 F	13 weeks 6 hours/day 5 days/week (WB)	0, 50, 500, 800	BW, HP, NX	Bd wt	800 F 50 M	500 M	800 M	LOAEL: 14% decrease in terminal body weight SLOAEL: 21% decrease in terminal body weight
					Resp	800			
					Cardio	800			
					Hepatic	800			
					Renal	800			
					Neuro	50 F	50 M	500	LOAEL: Slight gait impairments SLOAEL: Moderate-to-severe diffuse axonal swelling in sensory regions of lumbar spinal cord; diffuse axonal swelling in cervical spinal cord, decreased nerve CV, moderate gait impairments, decreased grip strength, ataxia
					Repro	800			
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997									
35	Rat (Fischer-344) 8–9 M, 8–9 F	8 weeks 6 hours/day 5 days/week (WB)	0, 50, 500, 800	BW, HP, NX	Bd wt	800 F 500 M	800 M		15% decrease in terminal body weight
					Resp	800			
					Cardio	800			
					Hepatic	800			
					Renal	800			
					Neuro	50		500	Gait abnormalities in both sexes; minimal-to-mild multifocal axonal swelling of sensory regions of the cervical and lumbar spinal cord and hindlimb foot splay in males; ataxia in females
					Repro	800			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997									
36	Rat (Fischer-344) 8–9 M, 8–9 F	4 weeks 6 hours/day 5 days/week (WB)	0, 50, 500, 800	BW, HP, NX	Bd wt	800 F 500 M	800 M		10% decrease in terminal body weight
					Resp	800			
					Cardio	800			
					Hepatic	800			
					Renal	800			
					Neuro	50	500		Gait abnormalities in females, decreased hindlimb grip strength in males
					Repro	800			
Hirata et al. 1992									
37	Rat (Wistar) 12 F	15 weeks 5 days/week 6 hours/day (WB)	0, 200, 800	LE, BW, CS, NX	Bd wt	200	800		10% decrease in body weight
					Neuro	200	800		Delayed auditory brain stem responses
Holson 1992									
38	Rat (Sprague-Dawley) 15–24 F	34–49 days (2 weeks premating through GD 19) 6 hours/day (WB)	0, 126, 250, 502	LE, CS, BW, FI, GN, RX, DX	Bd wt	250	502		10% decrease in maternal body weight on GD 20
					Resp	250	502		Clinical signs of nasal irritation
					Repro	250	502		Dystocia in 2/12 dams; 4% decrease in livebirth index
					Develop	250		502	100% postnatal death in 3/12 litters between PND 0 and 4
Huang et al. 2012									
39	Rat (Sprague-Dawley) 6 M	10 weeks 5 days/week 2 hours/day (WB)	0, 16, 80, 401	BC, RX	Repro		16		Abnormal sperm morphology and decreased motility; decreased serum LH

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morvai et al. 2005									
40	Rat (Sprague-Dawley) 10 M	14 weeks 6 hours/day (WB)	0, 225	BW, FI, WI, OW, HP, OF	Bd wt			225	23% decrease in body weight
					Resp	225			
					Cardio		225		Increased blood pressure; decreased cardiac output and blood flow to the lung and kidney; increased vascular resistance in the lung, kidney, and brain
					Musc/skel	225			
					Hepatic	225			
					Renal	225			
					Neuro	225			
NIOSH 1980									
41	Rat (Sprague-Dawley) 30–60 F	7–8 weeks 3 weeks pre-mating through GD 18 5–7 days/week 7 hours/day (WB)	0, 19.3, 39.3	BW, RX, DX	Bd wt	39.3			
					Repro	39.3			
					Develop	39.3			
Rebert and Becker 1986									
42	Rat (Long-Evans) 10 F	11 weeks 7 hours/day (WB)	0, 400, 800	LE, CS, BW, NX	Bd wt	400	800		15% decrease in body weight
					Neuro	400	800		Increased latency of signal conduction in peripheral nerves and brainstem (sensory and auditory-evoked potentials)
Saillenfait et al. 1989									
43	Rat (Sprague-Dawley) 20–23 F	15 days GDs 6–20 6 hours/day (WB)	0, 104.5, 197.5, 396.9, 817.2	LE, BW, RX, DX	Bd wt	197.5	396.9	817.2	LOAEL: 19% decrease in maternal body weight gain SLOAEL: 48% decrease in maternal body weight gain

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Develop	197.5	396.9	817.2	LOAEL: 6–7% decrease in fetal body weight SLOAEL: Increased litter incidence of club foot; 14–20% decrease in fetal body weight
Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983									
44	Rat (albino) 30–32 F	21 days 8 hours/day GDs 1–21 (F0 and F1 dams) (WB)	0, 0.01, 3.2, 32, 64	BW, BI, DX	Bd wt	32		64	Decrease in F0 (27%) and F1 (74%) maternal body weight gain
					Develop			32	Club foot in F1 and F2 fetuses and microcephaly in F2 fetuses
Tepe and Zenick 1984									
45	Rat (Long-Evans) 7–11 M	10 weeks 5 days/week 5 hours/day (WB)	0, 600	BW, BC, OW, HP, RX	Bd wt	600			
					Repro		600		Decreased epididymal sperm count, decreased ejaculated sperm count, altered mating behavior (shorter time to mount and ejaculate)
Tepe and Zenick 1984									
46	Rat (Long-Evans) 15–29 M	10 weeks 5 days/week 5 hours/day (WB)	0, 350, 600	BW, BC, OW, HP	Bd wt	600			
					Repro	350	600		Reduced plasma testosterone
Wrońska-Nofer 1972									
47	Rat (Wistar) 6–8 F	8 months 6 days/week 5 hours/day	0, 177	BW, BI, BC	Hepatic		177		Increased serum cholesterol, phospholipids, triglycerides; increased liver cholesterol synthesis

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Wrońska-Nofer 1973									
48	Rat (Wistar) 7–8 NS	8 months 6 days/week 5 hours/day (WB)	0, 74, 161, 321, 546	BW, BC, BI	Bd wt	321		546	26% decrease in body weight
					Hepatic		74		Increased serum lipids; increased liver cholesterol synthesis
					Neuro	321		546	Paralysis of hindlimbs and muscle weakness
Zenick et al. 1984									
49	Rat (Long-Evans) 12–14 M	10 weeks 5 days/week 6 hours/day (WB)	0, 607	BW, BC, HP, RX	Bd wt		607		10% decrease in body weight gain
					Repro		607		Altered mating behavior (reduced ejaculation and mount latency; decreased ejaculate sperm counts)
Lewis et al. 1999									
50	Mouse C57BL/6 9–10 F	Up to 20 weeks 5 days/week 6 hours/day (WB)	0, 50, 500, 800	LE, CS, BW, GN, HP	Bd wt	800			
					Cardio	50	500		Fatty deposits in aortic leaflet
Phillips 1983c									
51	Mouse (B6C3F1) 10 M, 12 F	90 days 5 days/week 6 hours/day (WB)	0, 49.3, 297.1, 798.4	LE, CS, FI, BW, HE, BC, UR, OP, GN, OW, HP, NX	Death			798.4	20% mortality in males; 17% mortality in females
					Bd wt	297.1	798.4		10% decrease in body weight
					Resp	798.4			
					Cardio	798.4			
					Gastro	798.4			
					Hemato	297.1	798.4		Decreased RBC count, total hemoglobin, and hematocrit
					Musc/skel	798.4			
					Hepatic	798.4			
					Renal	297.1		798.4	Nephropathy and renal tubular degeneration
					Ocular	798.4			
					Endocr	798.4			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	798.4			
					Neuro	297.1		798.4	Degeneration of peripheral nerves
					Repro	798.4			
Hardin et al. 1981; NIOSH 1980									
52	Rabbit (New Zealand) 18–32 F	15 days GDs 7–21 7 hours/day (WB)	0, 19.3, 39.3	BW, DX	Bd wt	39.3			
					Develop	39.3			
NIOSH 1980									
53	Rabbit (New Zealand) 30–60 F	7–8 weeks 3 weeks pre-mating through GD 21 5–7 days/week 7 hours/day (WB)	0, 19.3, 39.3	BW, RX, DX	Bd wt	39.3			
					Repro	39.3			
					Develop	39.3			
Qingfen et al. 1999									
54	Rabbit (New Zealand) 10 M, 10 F	3 weeks 6 days/week 3 hours/day (WB)	0, 321	NX	Neuro		321		Impaired retinal function
CHRONIC EXPOSURE									
Cai and Bao 1981									
55	Human 197–185 F	>1 year, (occupational)	0, 15	RX	Repro		15		Menstrual disturbances, pregnancy toxemia
Cirla and Graziano 1981									
56	Human 50 M	3–12 years (occupational)	0, 5.6	CS, BC, HE, OP, OF, NX	Cardio	5.6			
					Hemato	5.6			
					Hepatic	5.6			
					Ocular	5.6			
					Neuro	5.6			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
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									
57	Human 72–1,552 per study	>1 year (occupational)	2.9-5.64	NX	Neuro	4.02[c]			Impaired peripheral nerve conduction velocity; 95% lower confidence limit of the weighted median NOAEL/LOAEL boundary from seven occupational cohort studies
Godderis et al. 2006									
58	Human 25–66 NS	10.5 years (occupational)	0, 2.9, 19.0	NX	Neuro		2.9		Decreased sural nerve SCV and SNAP; polyneuropathy and impaired motor coordination
Hirata et al. 1996									
59	Human 22–26 NS	11.4 years (occupational)	0, 4.76	NZ	Neuro		4.76		Decreased peroneal nerve MCV and sural nerve SCV
Johnson et al. 1983; NIOSH 1984a									
60	Human 145–212 M	12.1 years (occupational)	0.2, 1.0, 4.1, 7.6	CS, NX	Neuro	4.1	7.6		Decreased peroneal nerve MCV and sural nerve SVC
Kim et al. 2000									
61	Human 203–887 M, 112–350 F	1–≥15 years (occupational)	0, 3.36	CS, BC, HE, OF, OP, NX	Cardio		3.36		Hypertension
					Hemato	3.36			
					Ocular		3.36		Retinal microaneurysms
					Neuro		3.36		Abnormal nerve CV; abnormal findings on neuropsychological testing (MMPI); impaired hearing; subjective neurological symptoms
					Other noncancer	3.36			
Luo et al. 2011									
62	Human 78–81 M, 11–30 F	20.7 years (occupational)	0, 5.51, 14.2	BC	Hepatic	14.2			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NIOSH 1983									
63	Human 204–236 M	13.7 years (occupational)	0, 8.1	RX	Repro	8.1			
NIOSH 1984a									
64	Human 146–233 M	12.6 years (occupational)	0.2, 8.26	BC, OF, OP	Cardio		8.26		Increased systolic blood pressure
					Hepatic		8.26		Increased total cholesterol, total lipids, and LDL
					Ocular		8.26		Retinal microaneurysms and hemorrhages
					Endocr	8.26			
					Repro	8.26			
					Other noncancer	8.26			
Nishiwaki et al. 2004									
65	Human 125–324 M	19.6 years (occupational)	0, 4.87 ppm	NX	Neuro	4.87			
Reinhardt et al. 1997a									
66	Human 191–222 NS	6 years (occupational)	0, 4.02	OF, NX	Cardio	4.02			
					Neuro	4.02			
Ruijten et al. 1990									
67	Human 37, 45 M	20 years (occupational)	0, 8.25	NX	Neuro		8.25		Decreased peroneal nerve CVSF
Ruijten et al. 1993									
68	Human 31, 44 M	26.1 years (occupational)	0, 8.16	NX	Neuro		8.16		Decreased peroneal nerve MCV and median and ulnar nerve SCVs

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Schramm et al. 2016									
69	Human 137–290 NS	16.8 years (occupational)	0, 6.44	BC, OF	Cardio	6.44			
					Hepatic	6.44			
					Other noncancer	6.44			
Takebayashi et al. 2004									
70	Human 359–391 M	16.9 years (occupational)	0, 5	CS, BC, HE, OF	Cardio		5		Elevated systolic blood pressure
					Hemato	5			
					Hepatic	5			
					Endocr		5		Decreased serum T4
					Repro	5			
					Other noncancer	5			
Tolonen et al. 1976									
71	Human 391–417 M	Duration not specified (occupational)	0, 7.5	CS, OF	Cardio	7.5			
Vertin 1978									
72	Human 100 NS	Duration not specified (occupational)	0, 14	BC, OF	Cardio	14			
					Hepatic	14			
Visconti et al. 1967									
73	Human 18–57 NS	2-8 years (occupational)	0, 114	HE	Hemato		114		Decreased fibrolytic activity of serum plasmin
Yoshioka et al. 2017									
74	Human 337–347 M	22.1 years (occupational)	0, 2.84, 5.64, 9.35	NX	Neuro	5.64	9.35		Decreased median nerve SCV
Zhou et al. 1988									
75	Human 265 F	15 years (occupational)	0, 5.2	RX	Repro		5.2		Menstrual irregularities
					Develop	5.2			

Table 2-1. Levels of Significant Exposure to Carbon Disulfide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Wrońska-Nofer et al. 1980									
76	Rat (Wistar) 7–8 F	12-15 months 6 days/week 5 hours/day (WB)	0, 321	BW, BC, BI, HP	Bd wt	321			
					Cardio	321			
					Hepatic		321		Elevated total and esterified serum cholesterol

Shaded rows indicate the MRL principal studies.

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration MRL of 0.2 ppm. The LOAEL of 20 ppm was converted into a $LOAEL_{HEC}$ of 16 ppm and then divided by a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation of animal to humans with dosimetric adjustment, 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive a chronic-duration MRL of 0.1 ppm; the median of 4.02 ppm for the NOAEL/LOAEL boundary from seven occupational exposure studies was adjusted from occupational to continuous exposure to a $median_{ADJ}$ value of 0.957 ppm and then divided by a total uncertainty factor of 10 (for human variability); see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemistry; BSP = sulfobromophthalein sodium; Cardio = cardiovascular; CS = clinical signs; CV = conduction velocity; CVSF = conduction velocity of slower motor fibers; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (H) = head-only; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = concentration producing 50% death; LDL = low-density lipoprotein; LE = lethality; LH =luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCV = motor nerve conduction velocity; MMPI = Minnesota Multiphasic Personality Inventory; MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; RBC = red blood cells; Repro = reproductive; Resp = respiratory; RX = reproductive function; SCV = sensory nerve conduction velocity; SLOAEL = serious LOAEL; SNAP = sensory nerve action potential; T4 = thyroxine; UR = urinalysis; (WB) = whole body; WI = water intake

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Acute (≤14 days)

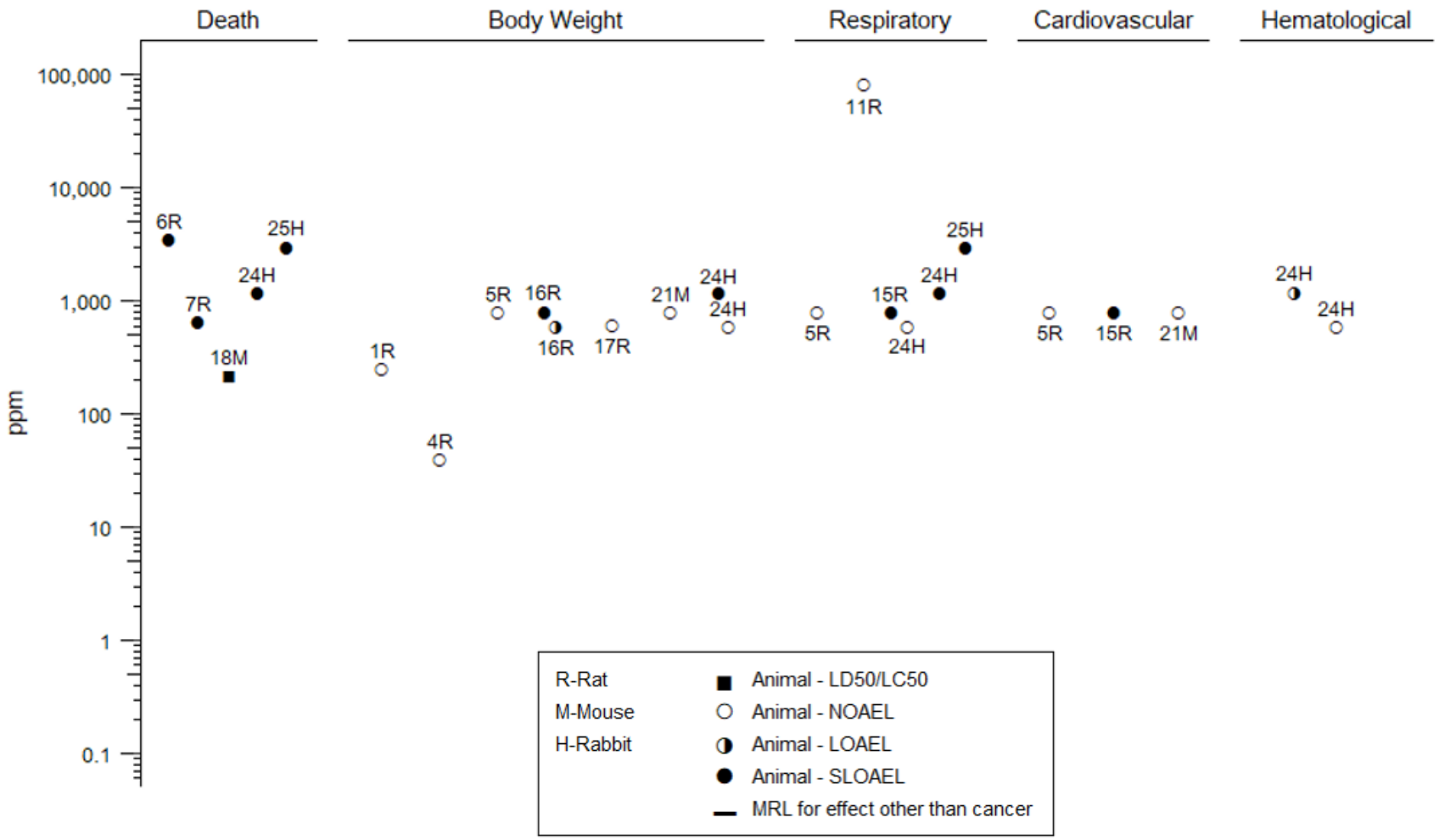


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Acute (≤14 days)

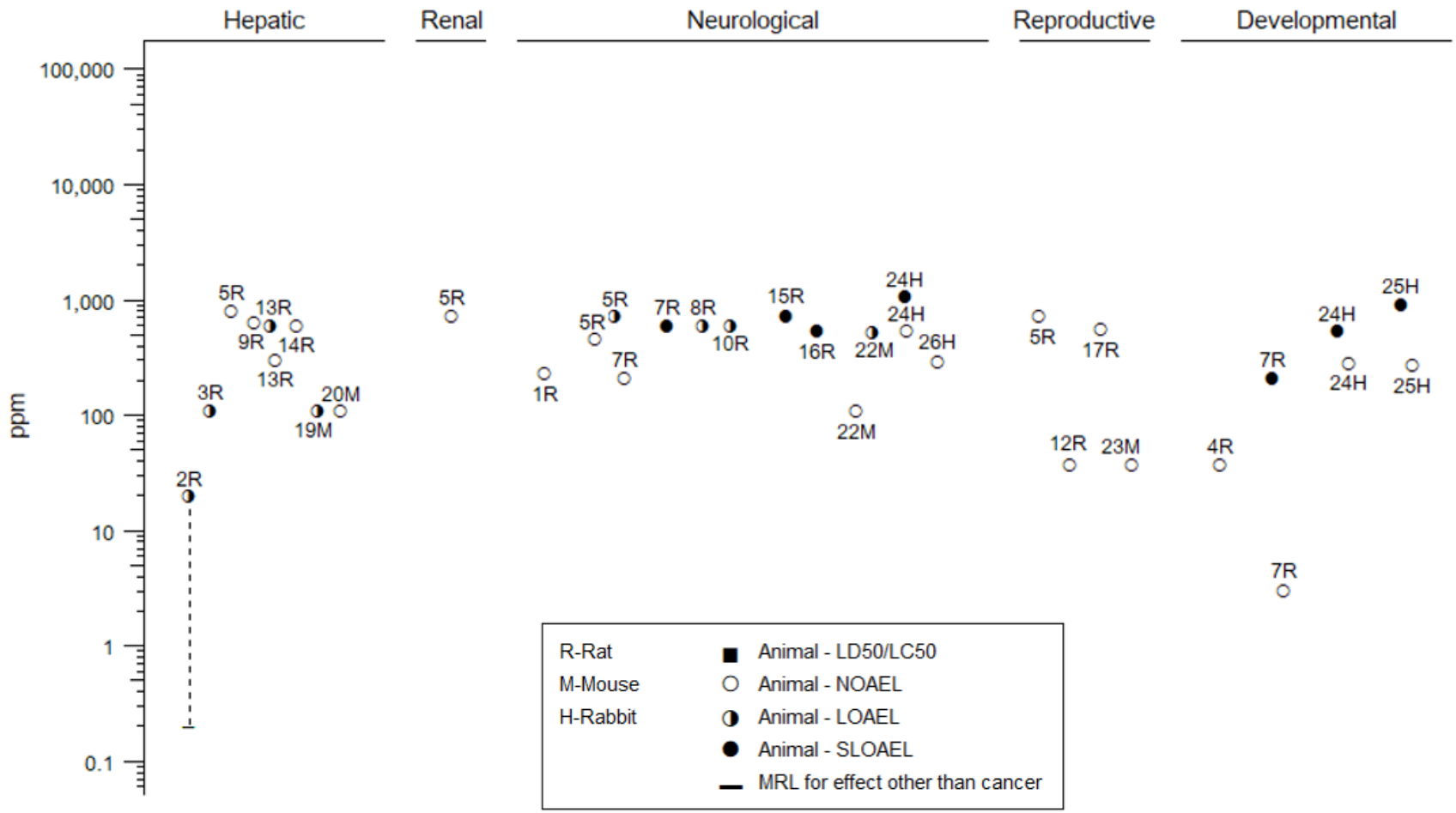


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

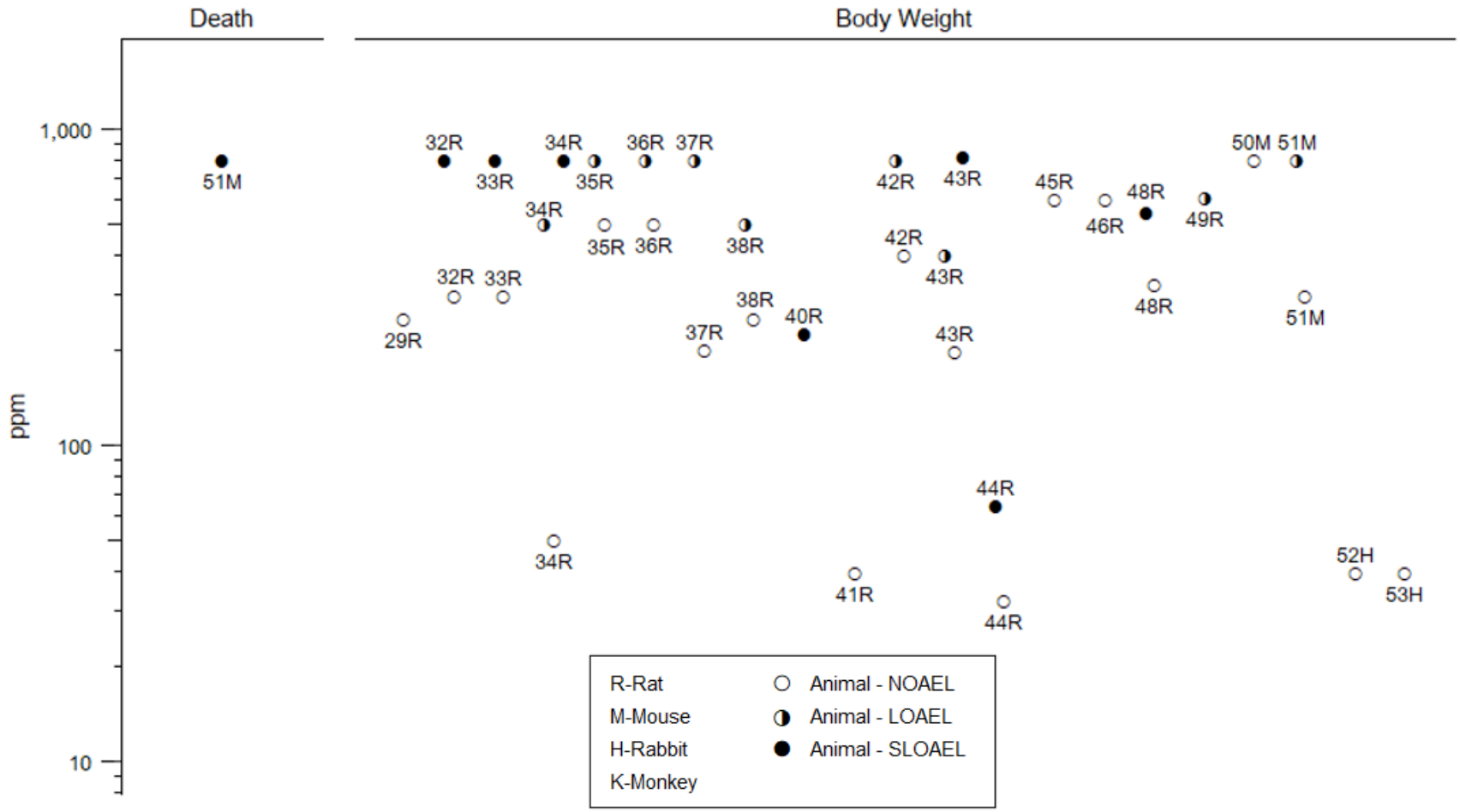


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

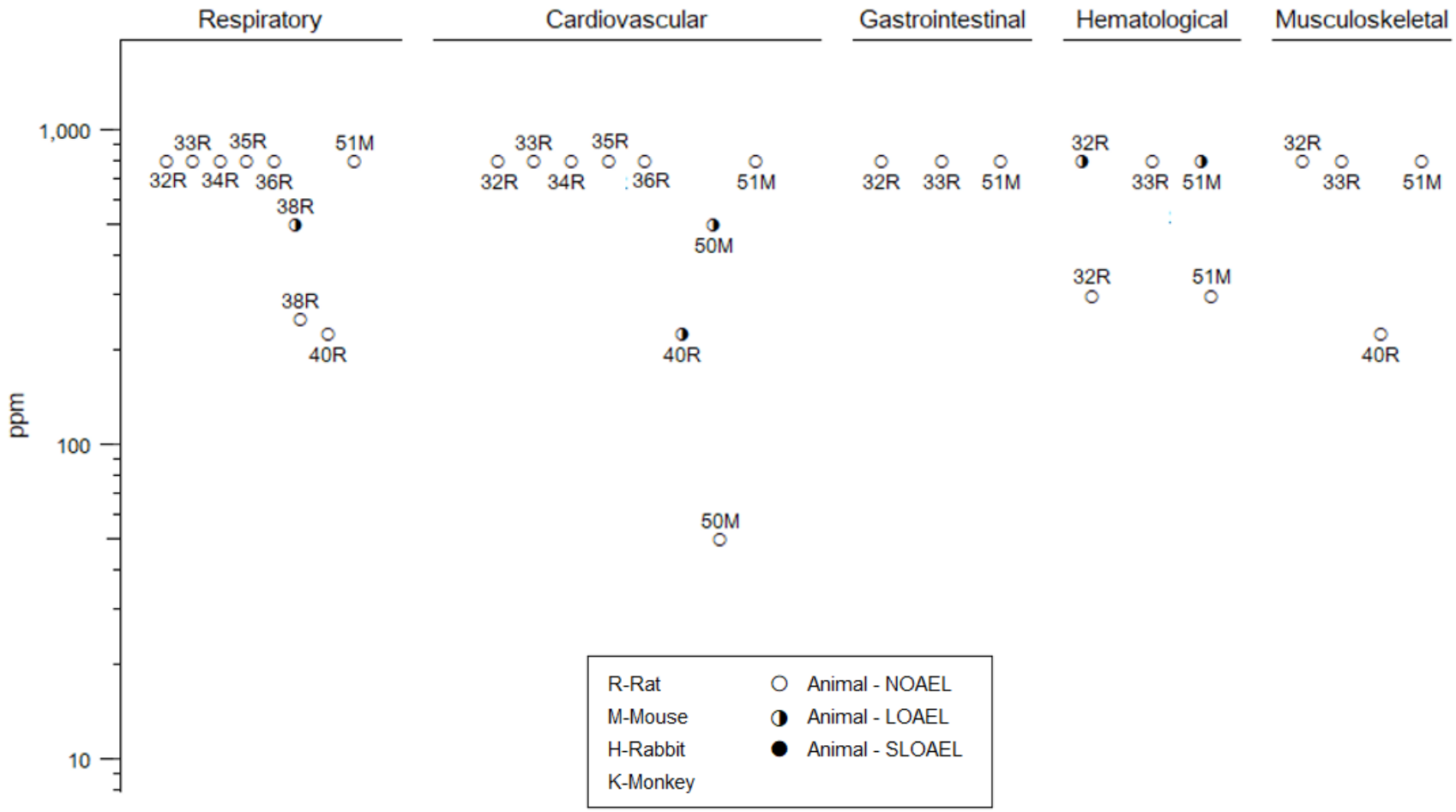


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

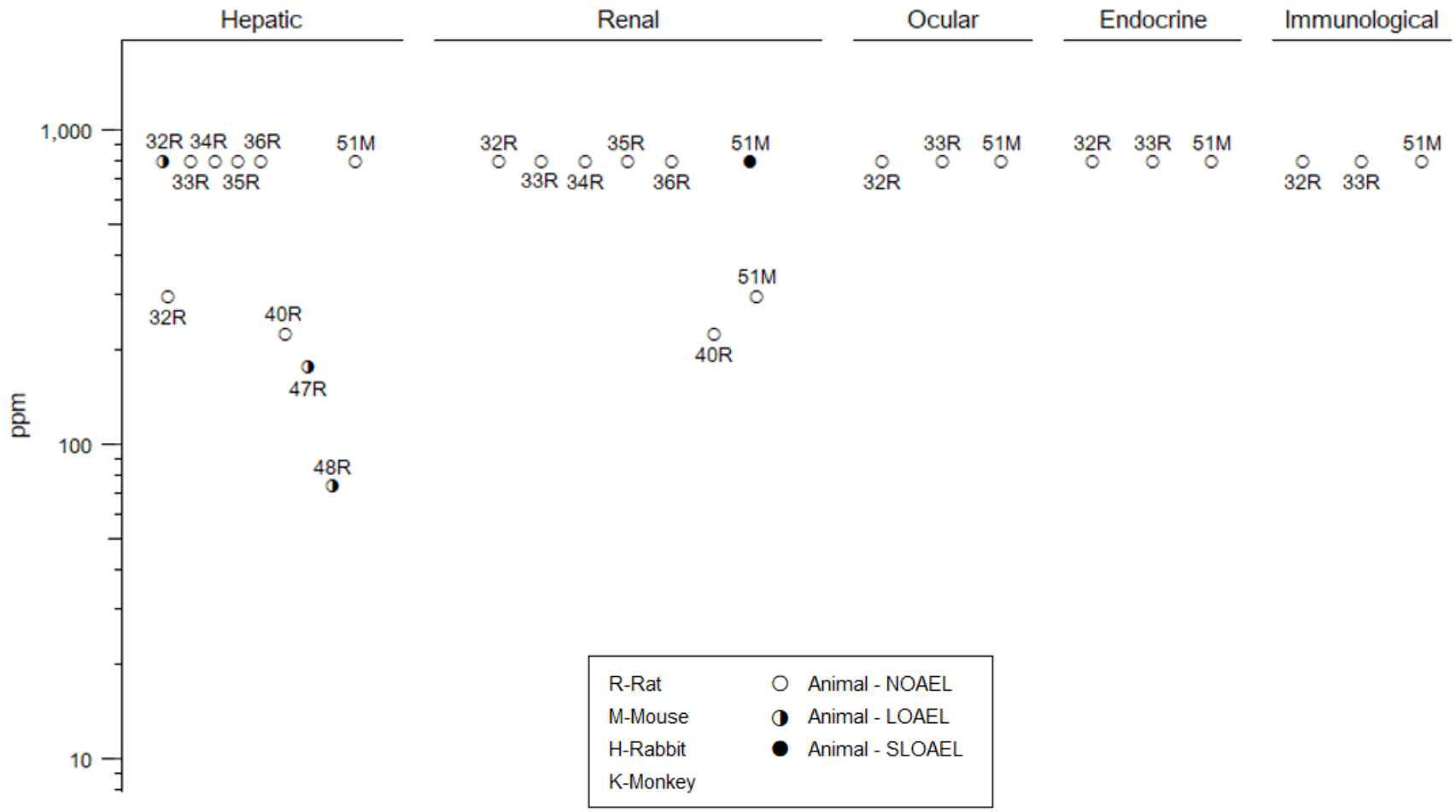


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

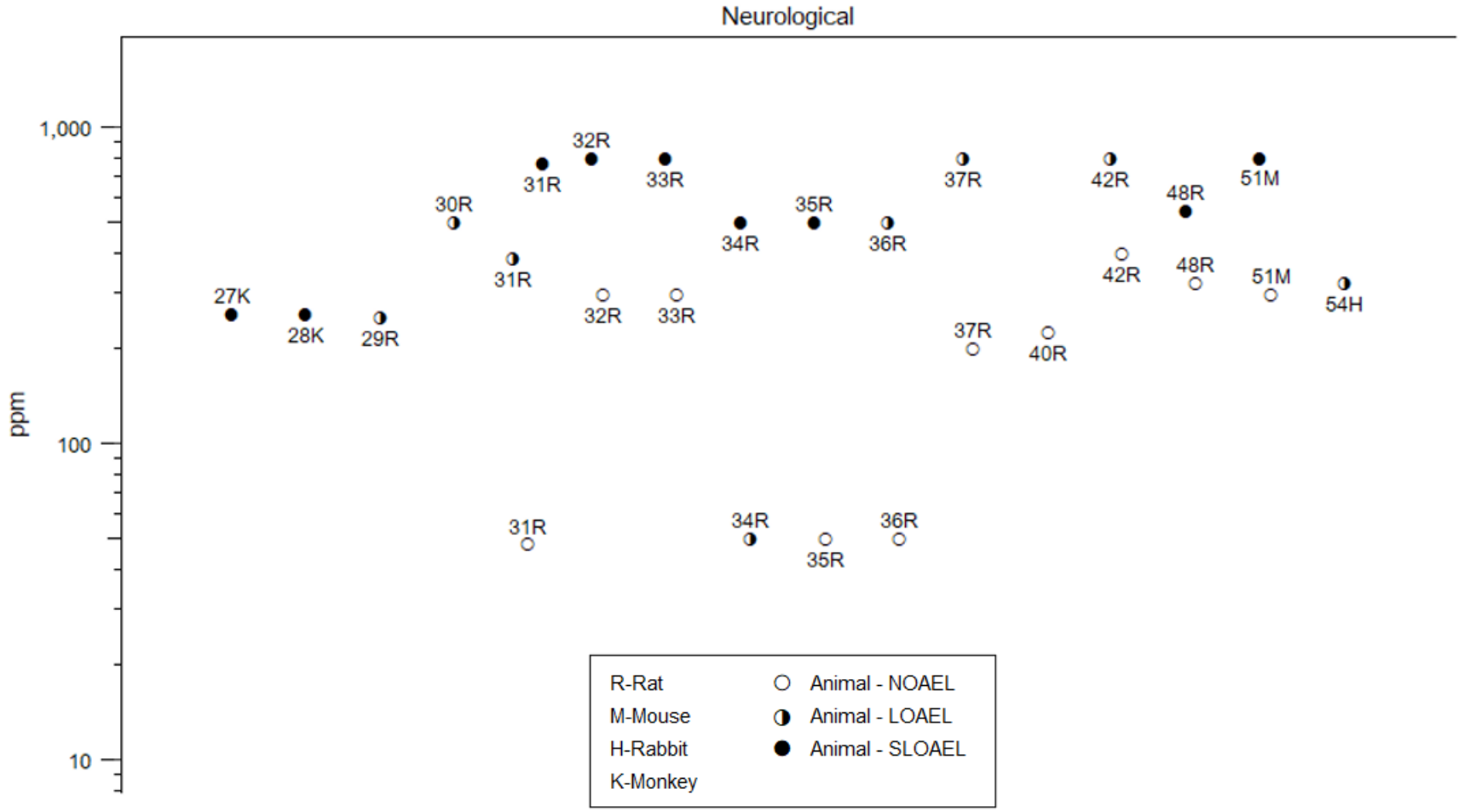


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

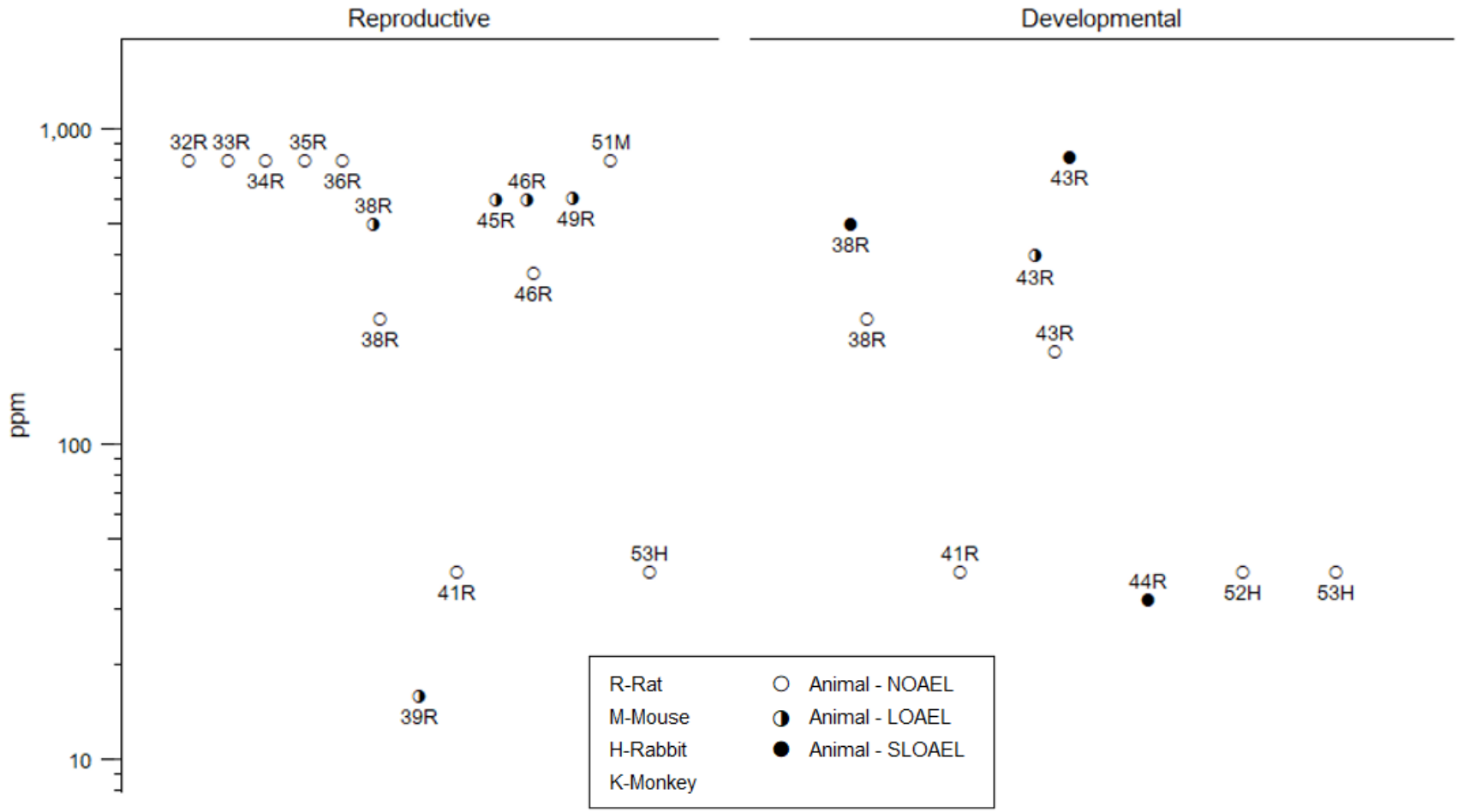


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Chronic (≥365 days)

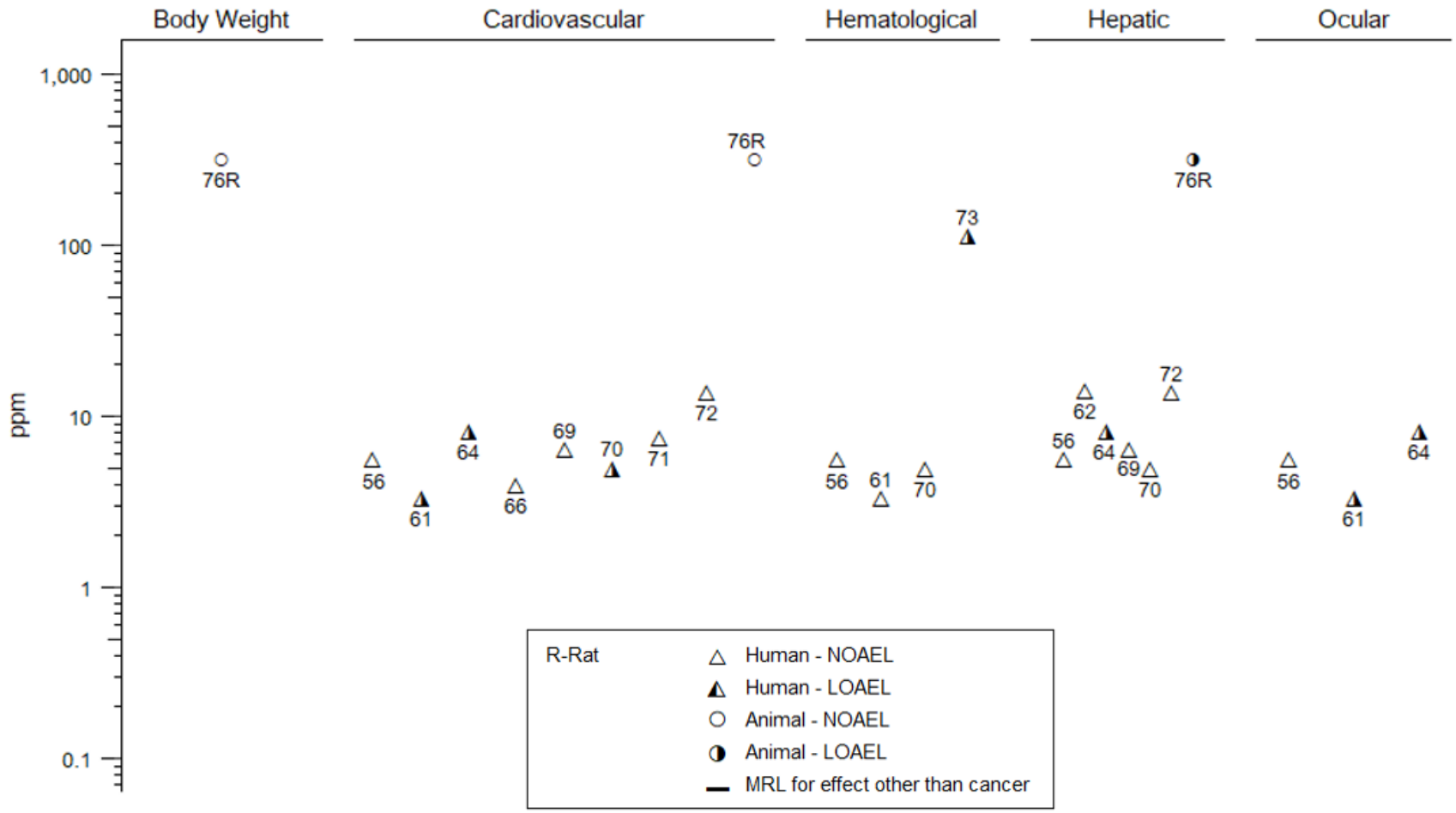


Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Chronic (≥365 days)

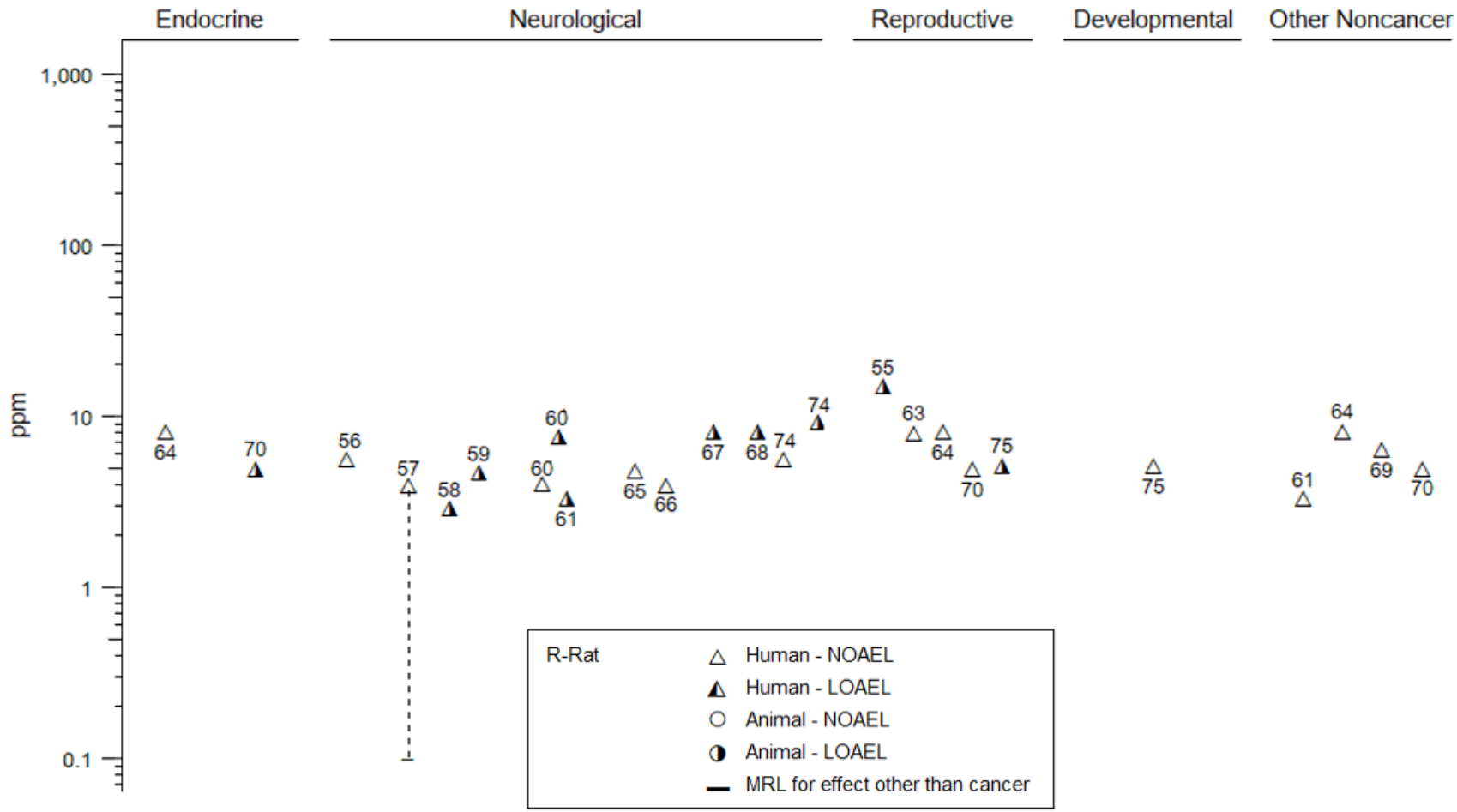


Table 2-2. Levels of Significant Exposure to Carbon Disulfide – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Hoffmann and Klapperstück 1990									
1	Rat (Wistar) 6–12 M	Once (GO)	0, 126, 253, 373, 506, 632	LE, CS, OF	Cardio	253	373		ECG alterations (prolonged QT interval)
Kanada et al. 1994									
2	Rat (Sprague-Dawley) 4–5 M	Once (G)	0, 300	BI	Neuro		300		Decreased norepinephrine in the midbrain, hypothalamus, and medulla oblongata; increased dopamine in the medulla oblongata
NCTR 1984a									
3	Rat (Sprague-Dawley) 22–27 F	10 days GDs 6–15 (GO)	0, 100, 200, 400, 600	LE, CS, BW, OW, DX	Bd wt	200		400	46% decrease in maternal body weight gain (corrected for uterine weight)
					Neuro	200		400	Hindlimb paralysis in dams
					Develop	100	200	400	LOAEL: 6% decrease in fetal weight SLOAEL: 16% decrease in fetal body weight
NCTR 1984a									
4	Rat (Sprague-Dawley) 6 F	10 days (GO)	0, 10, 50, 100, 200, 400	LE, CS, BW, OW	Bd wt	100		200	>20% decrease in body weight gain
					Neuro	10	50	400	LOAEL: Lethargy SLOAEL: Hindlimb paralysis, ataxia, tremor
Tsai et al. 2000									
5	Rat (Sprague-Dawley) 5–6 F	10 days GDs 6–15 (GO)	0, 300, 600, 1,200	LE, BW, RX, DX	Bd wt	600	1,200		10% decrease in maternal body weight gain
					Develop	1,200			
Gibson and Roberts 1972									
6	Mouse (Swiss-Webster) 4 M	Once (GO)	0, 1,890	OF	Hepatic		1,890		Transient impairment in liver function (increased BSP retention)

Table 2-2. Levels of Significant Exposure to Carbon Disulfide – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gibson and Roberts 1972									
7	Mouse (Swiss-Webster) NS M	Once (GO)	NS	LE	Death			3,020	LD_{50}
Keil et al. 1996									
8	Mouse (B6C3F1) 5 F	5 days (G)	0, 138, 551, 1,102	LE, BW, HE, OW, HP, IX	Death			1,102	40% mortality
					Bd wt	551	1,102		>10% decrease in body weight
					Hemato	1,102			
					Immuno	1,102			
NCTR 1984b									
9	Rabbit (New Zealand White) 26–30 F	14 days GDs 6–19 (GO)	0, 25, 75, 150	LE, CS, BW, OW, DX	Bd wt	150			
					Hepatic	25	75		Increased absolute and relative liver weight
					Develop		25[b]	150	LOAEL: 32% resorptions/litter (12% in control) SLOAEL: 19% fetuses with malformations, 31% decrease in live fetuses/litter, 61% resorptions/litter
NCTR 1984b									
10	Rabbit (New Zealand) 5–8 F	14 days GDs 6–19 (GO)	0, 50, 100, 200, 400, 600	LE, CS, BW, OW, DX	Death			400	87.5% maternal mortality
					Bd wt	200			
					Neuro	100		200	Convulsions
					Develop	100		200	4/5 litters with complete resorption

Table 2-2. Levels of Significant Exposure to Carbon Disulfide – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Gao et al. 2014; Wang et al. 2016									
11	Rat (Wistar) 20 M	6 weeks 6 days/week (GO)	0, 200, 400, 600	CS, BW, NX	Bd wt		200	400	LOAEL: 10% decrease in body weight SLOAEL: 22% decrease in body weight
					Neuro	200		400	Tremors, moderate-to-severe gait impairments
Liu et al. 2023									
12	Rat (Wistar) NS M	8 weeks 7 days/week (G)	0, 300, 600	CS, BW, BI, NX	Bd wt			300	20% decrease in body weight
					Neuro		300	600	LOAEL: Mild gait impairments, motor incoordination SLOAEL: Severe gait impairments, resting tremor
Liu et al. 2024									
13	Rat (Wistar) 9 M	8 weeks 7 days/week (G)	0, 300, 600	NX	Neuro		300	600	LOAEL: Mild gait impairments, motor incoordination, impaired caudal nerve conduction velocity SLOAEL: Severe gait impairments
Song et al. 2009									
14	Rat (Wistar) 20 M	12 weeks 5 days/week (GO)	0, 300, 500	CS, NX	Neuro		300	500	LOAEL: Mild gait impairments (incoordination, hindlimb splay, tip-toe walking) SLOAEL: Ataxia, severe gait impairments, inability to support weight

Table 2-2. Levels of Significant Exposure to Carbon Disulfide – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Wang et al. 2017									
15	Rat (Wistar) 14 M	20 days (GO)	0, 200, 400, 600	BW, BI, HP, NX	Bd wt	200	400	600	LOAEL: 13% decrease in body weight SLOAEL: 22% decrease in body weight
					Neuro		200	400	LOAEL: Impaired memory SLOAEL: Cerebral edema; neuronal loss in cortex and hippocampus; learning impairment

Shaded rows indicate the MRL principal studies.

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration MRL of 0.03 mg/kg/day. The LOAEL of 25 mg/kg/day was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation of animal to humans, 10 for human variability); see Appendix A for more detailed information regarding the MRL.

Bd wt or BW = body weight; BI = biochemistry; BSP = sulfobromophthalein sodium; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; ECG = electrocardiogram; F = female(s); GD = gestation day; (G) = gavage; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immunotoxicity; LD50 = dose producing 50% death, LE = lethality LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; RX = reproductive function; SLOAEL = serious LOAEL

Figure 2-3. Levels of Significant Exposure to Carbon Disulfide – Oral
Acute (≤14 days)

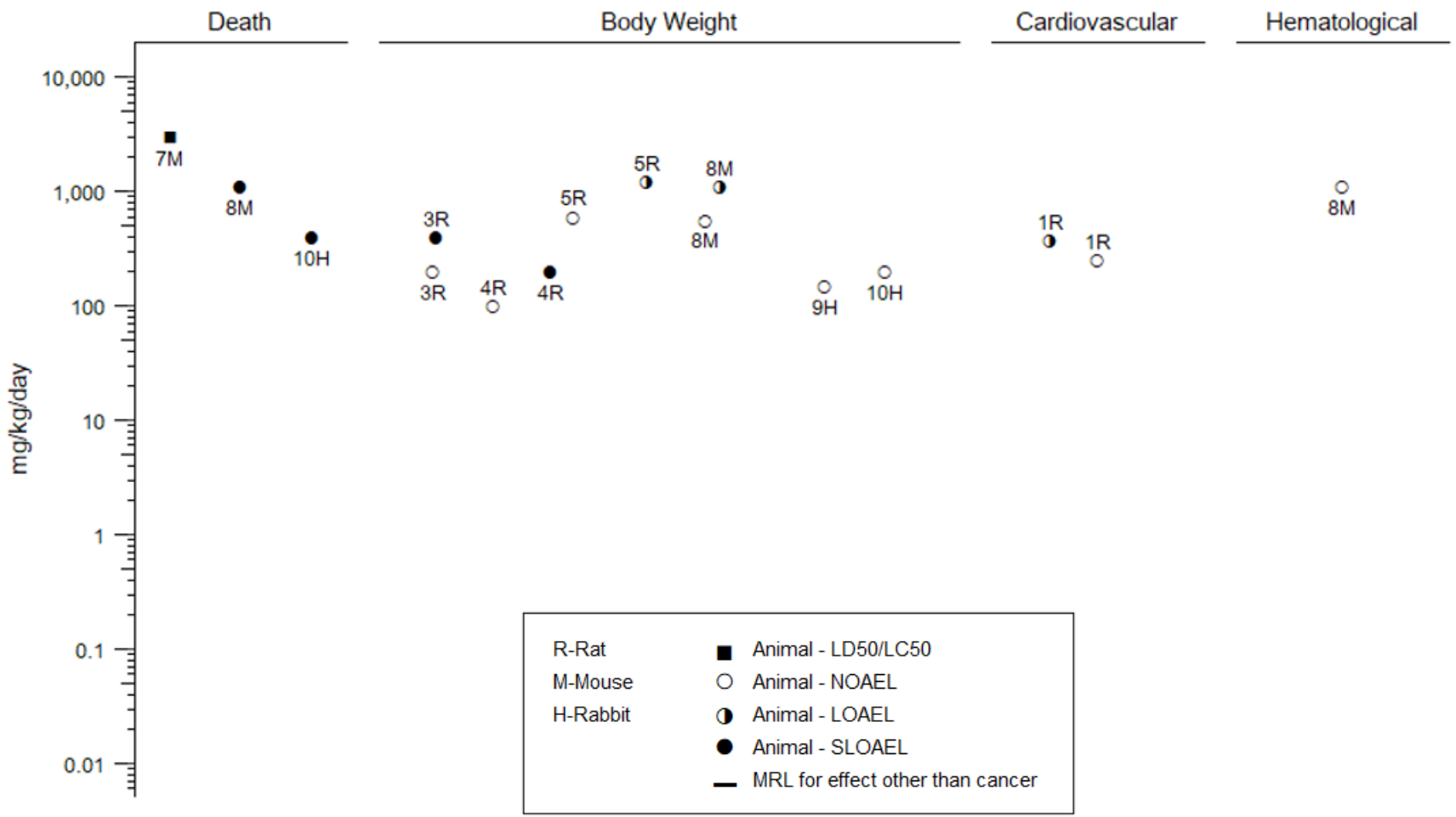


Figure 2-3. Levels of Significant Exposure to Carbon Disulfide – Oral
Acute (≤14 days)

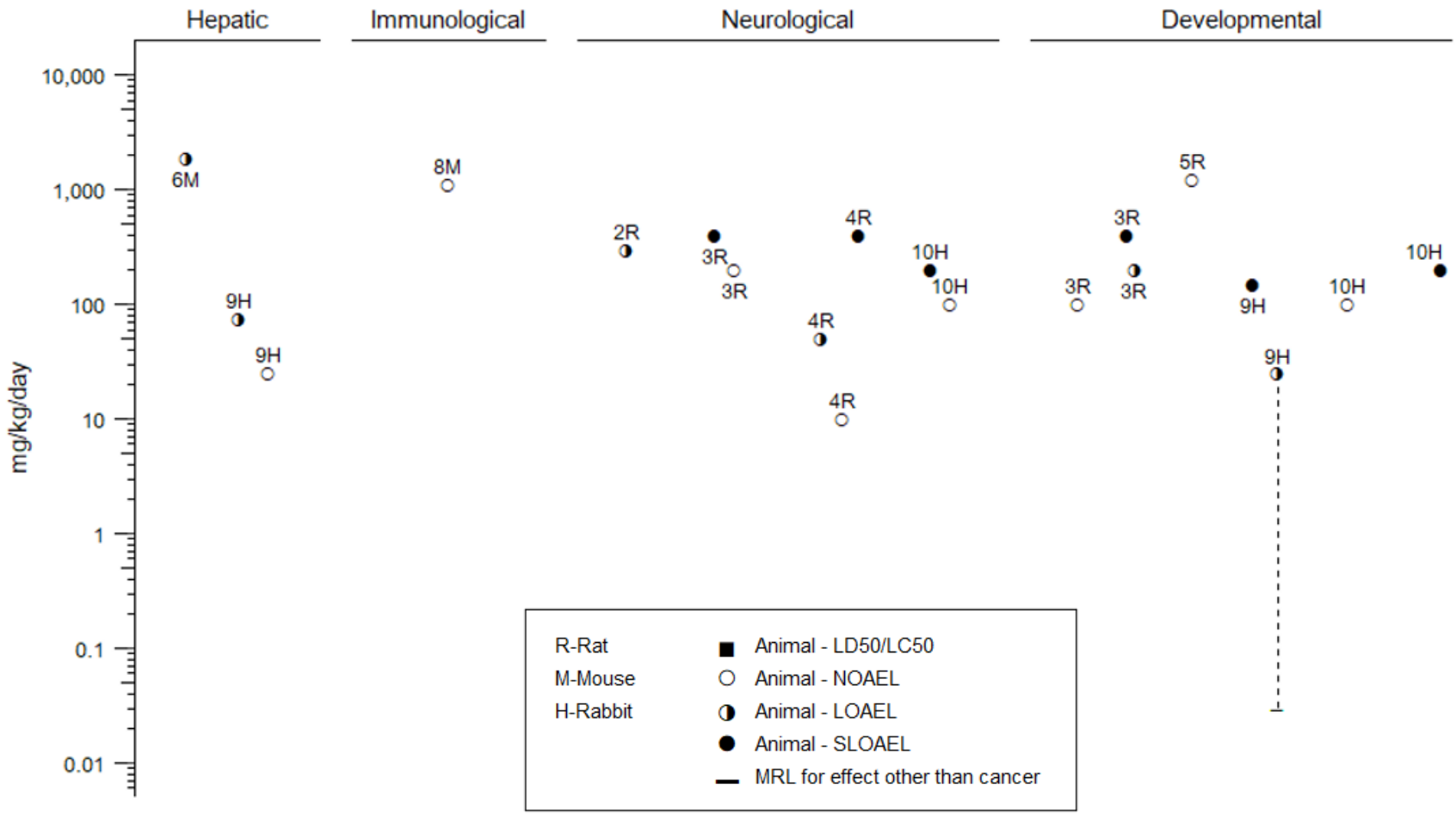


Figure 2-3. Levels of Significant Exposure to Carbon Disulfide – Oral
Intermediate (15–364 days)

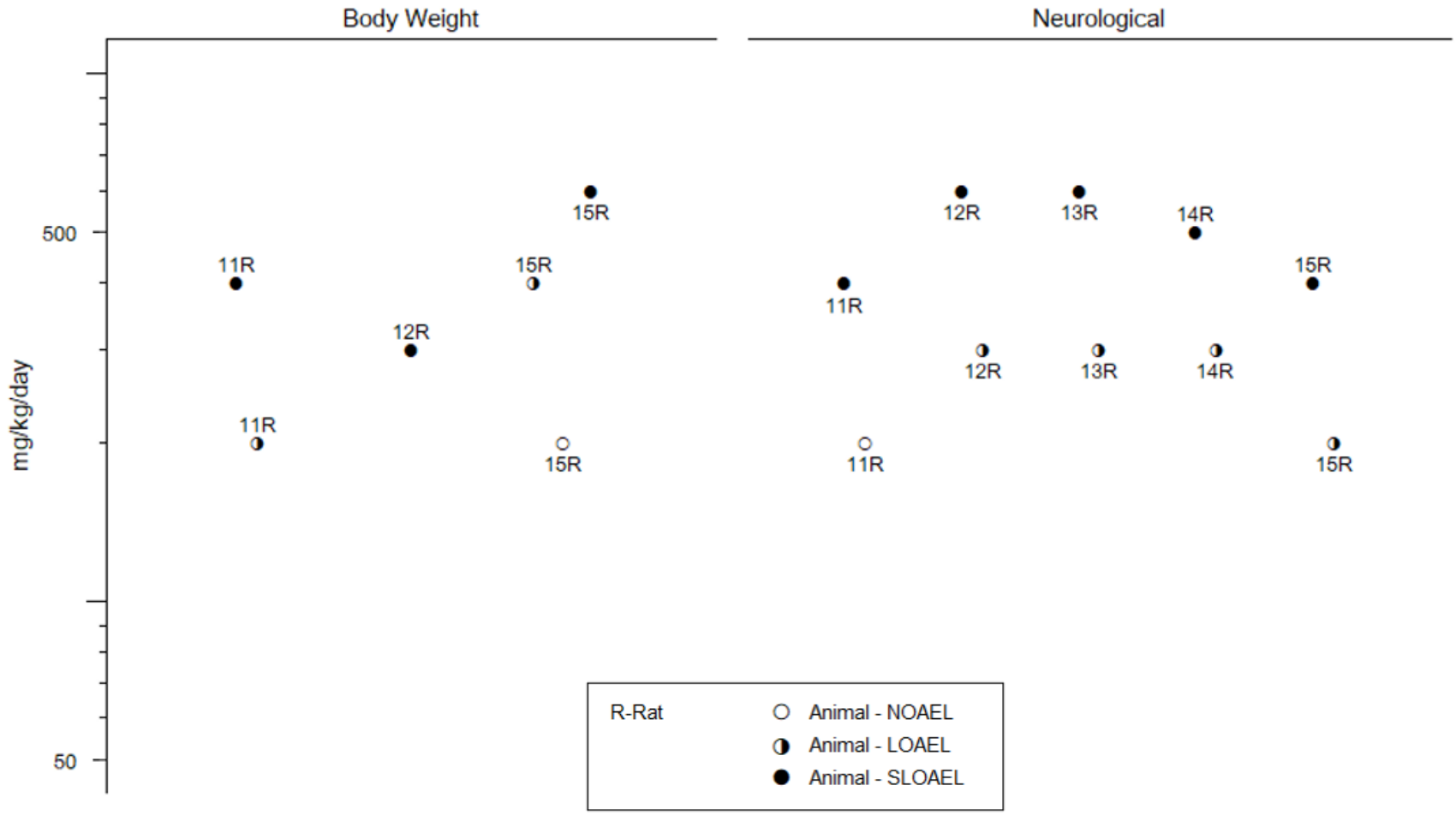


Table 2-3. Levels of Significant Exposure to Carbon Disulfide – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Chou et al. 2005								
Mouse BALB/c-nu 3 F	10 minutes	0, 10, 15, 20%	HP, OF	Dermal		20		Skin necrosis
Hueper 1936								
Rabbit (NS) 5 NS	4 days	100%	CS	Dermal		100		Skin blistering, ulceration, inflammation
INTERMEDIATE EXPOSURE								
Holson 1992								
Rat (Sprague-Dawley) 15–24 F	34–49 days (2 weeks premating through GD 19) 6 hours/day	0, 126, 250, 502 ppm in air	CS	Ocular	250	502		Eye irritation

CS = clinical signs; F = female; GD = gestational day; HP = histopathology; NS = not specified; OF = organ function

2.2 DEATH

There are limited data pertaining to death following acute-duration exposure to high levels of carbon disulfide. Mortalities were reported in a community in India following an accidental release of large amounts of carbon disulfide, hydrogen sulfide, and sulfuric acid from a viscose rayon plant (Kamat 1994). Exposure concentrations were not stated. Three case reports cited in Gosselin et al. (1984) indicated that ingestion of half an ounce of an unspecified concentration of carbon disulfide resulted in death.

Several epidemiology studies evaluated potential associations between occupational exposure to carbon disulfide and increased risk of mortality from one or more causes (Table 2-4). The most common cause of mortality associated with increased risk of death in exposed viscose rayon workers is cardiovascular disease. This is most clearly shown in a longitudinal study of a Finnish cohort with a 15-year follow-up reported in a series of studies (Hernberg and Tolonen 1981; Hernberg et al. 1973, 1976; Nurminen and Hernberg 1985; Nurminen et al. 1982; Tolonen et al. 1979). In this cohort, exposure levels were very high prior to 1950, 10–60 ppm during the 1950s, 4–18 ppm at the start of the follow-up period, and <10 ppm after 1972. When all analyses from this cohort are viewed together, the increased risk of death due to coronary heart disease observed at the 5- and 10-year follow-ups are attributable to higher exposures prior to 1972. Analysis for the period after reduced exposure levels did not observe increased risk of death due to coronary heart disease. Other available mortality studies reporting increased risk of cardiovascular-related death in workers exposed to carbon disulfide do not break down analyses to evaluate potential impact of recent reductions in exposure, but generally acknowledge that early higher exposures likely contribute to observed effects (Balcarova and Halik 1991; Liss and Finkelstein 1996; Swaen et al. 1994; Sweetnam et al. 1987; Tiller et al. 1968) or show evidence of increased risk at higher exposure levels using dichotomized datasets (MacMahon and Monson 1988). Historical exposure concentrations in these studies range from 2.6 to 48 ppm. An exception was Lyle (1981), which did not observe excess death from ischemic heart disease or circulatory disease in workers who were employed in a viscose rayon factory in the United Kingdom at least 1 year between 1957 and 1968 when median carbon disulfide levels ranged from 6 to 35 ppm.

Table 2-4. Results of Epidemiological Studies Evaluating Mortality in Viscose Rayon Workers

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Balcarova and Halik 1991 Longitudinal cohort; 251 workers from two viscose rayon factories (mean age and employment duration not reported) and 124 unexposed referents (Czechoslovakia)	Measured air concentrations, range of means: 1966–1975: Spinners: <16–48 ppm Other areas: <16 ppm After 1975: All areas: <9.6 ppm	Mortalities between 1975 and 1985	
		All cases	↑ (spinners versus referents) ↔ (other areas versus referents)
		Cardiovascular diseases	↑ (spinners versus referents) ↔ (other areas versus referents)
		Myocardial infarction	↑ (spinners versus referents) ↔ (other areas versus referents)
Hernberg and Tolonen 1981; Hernberg et al. 1973, 1976; Nurminen and Hernberg 1985; Nurminen et al. 1982; Tolonen et al. 1979 Longitudinal cohort; 343 workers (ages 25–64 years; median employment 11 years) employed in viscose rayon factory for at least 5 years between 1942 and 1967 (employed up to 25 years by 1967) and 343 matched referents from paper mill; subjects were followed for up to 15 years (Finland)	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1971: 4–30 ppm 1972–1982: <10 ppm Geometric mean air concentration of carbon disulfide only in different departments: 1967: 4–18 ppm	CHD deaths 1967–1972 1967–1975 1967–1977 1967–1980 1967–1982 1972–1977 1977–1980	 ↑ (workers versus referents) ↔ (workers versus referents) ↑ (workers versus referents) ↑ (workers versus referents) ↔ (workers versus referents ↔ (workers versus referents) ↔ (workers versus referents)
		Other cardio- and cerebro-vascular deaths 1967–1977 1967–1980 1967–1982	 ↔ (workers versus referents) ↔ (workers versus referents) ↔ (workers versus referents)
		All causes 1967–1982	↔ (workers versus referents)
		Neoplasms 1967–1982	↔ (workers versus referents)
Liss and Finkelstein 1996 Retrospective mortality cohort; 251 former male workers from a viscose rayon factory (average age at death of 71.3 years); compared to general population of Ontario (Mortality Data Base at Statistics Canada) (Canada)	Measured air concentrations (1985–1991), range: 3–45.8 ppm *Brief (10-minute) exposures up to 254.4 ppm were measured during cutting activities.* Some workers classified as "high-exposure," not further defined.	Proportional mortality:	
		Cancer	↔
		Circulatory disease	↔
		IHD	↔
		Mortality from cerebro-vascular disease (stroke)	↑ (high exposure, ≥65 years versus general population, ≥65 years) ↑ (high exposure versus low exposure)
		Respiratory disease	↑ (workers versus general population)
		Digestive disease	↔

Table 2-4. Results of Epidemiological Studies Evaluating Mortality in Viscose Rayon Workers

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Lyle 1981 Retrospective cohort; 351 male workers from a viscose rayon factory (employed at least 1 year between 1957 and 1968; 115 men with occasional exposure for a mean of 5.75 years and 224 with regular exposure for a mean of 8.55 years); compared to general population (United Kingdom)	Measured air concentrations (1957–1974), range of medians: 6–35 ppm	Deaths through 1978	
		All causes	↔
		IHD	↔
		Circulatory diseases	↔
		Neoplasia	↔
		Chronic bronchitis	↔
MacMahon and Monson 1988 Retrospective cohort; 10,418 men employed in the viscose rayon industry between 1957 and 1979 (including 4,448 “most” exposed, 2,230 “least” exposed, and 3,311 unexposed); compared to the National Death Index (United States)	Exposure categories based on job; no quantitative exposure estimates.	Deaths through mid-1983, compared to general population	
		All causes	↔
		All cancer Digestive Respiratory Genitourinary Lymphatic/ hematopoietic	↓ (least exposed) ↔ ↔ ↓ (most exposed) ↔
		All circulatory disease	↑ (no exposure) ↔ (least exposed) ↑ (most exposed)
		Arteriosclerotic heart disease	↔ (least exposed) ↑ (most exposed)
		Cerebro-vascular disease	↔
		Respiratory	↓ (least exposed)
		Digestive	↓ (most exposed)
		Genitourinary	↔
		Suicide	↑ (most exposed)

Table 2-4. Results of Epidemiological Studies Evaluating Mortality in Viscose Rayon Workers

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Swaen et al. 1994 Prospective cohort; 1,434 male workers from a viscose textile plant (employed at least 6 months between 1947 and 1980) and 1,888 male referents (Netherlands)	Current TWA exposure levels: 7.1 ppm Range of means, ambient air: 1949–1969: 2.6–26 ppm 1970–1983: 2.9–48 ppm 1984–1990: 2.9–34 ppm Range of means, personal sampling: 1979: 4.8–7.4 ppm 1984–1990: 4.8–18 ppm	Mortalities through 1988 (versus referent)	
		Total	↓
		Infection disease	↔
		Neoplasm	↔
		Circulatory	↑
		Respiratory	↔
		Digestive	↔
Sweetnam et al. 1987; Tiller et al. 1968 Retrospective cohort; 1,980 males (ages 45–64 years) who worked for ≥1 year at a viscose rayon factory between 1950 and 1964; compared to national rates for England and Wales (England)	Reported air concentrations: Spinning: >20 ppm Other areas: mostly <20 ppm (17% of measurements >20 ppm)	Death from CHD 1933–1962	↑ (viscose spinners) ↔ (viscose makers, all) ↑ (viscose operatives, >10 years exposure) ↔ (non-process workers, all) ↑ (non-process workers, >10 years exposure)
		Death from IHD 1950–1982	↑ (viscose spinners) ↔ (viscose makers) ↑ (non-process fitter) ↔ (other non-process workers)
		Death from other circulatory disease 1950–1982	↑ (viscose spinners) ↔ (viscose makers) ↔ (non-process workers)

↑ = association; ↓ = inverse association; ↔ = no association; CHD = coronary heart disease; IHD = ischemic heart disease; TWA = time-weighted average

The only other mortalities associated with carbon disulfide exposure in viscose rayon workers reported in single cohorts include increased risk of death from respiratory disease in a Canadian cohort (Liss and Finkelstein 1996) and increased risk of suicide in an American cohort (MacMahon and Monson 1988). Other cohorts have not observed increased risk from respiratory diseases; in fact, some have observed decreased risk, likely due to the healthy worker effect (Lyle 1981; MacMahon and Monson 1988; Swaen et al. 1994). No other studies specifically evaluated risk of suicide in workers occupationally exposed to carbon disulfide.

In rats, the 4-hour inhalation lethality curve is steep, with 0% mortality at 3,000 ppm and 100% mortality at 3,500 ppm (Hiddemen et al. 1966). In male Swiss-Webster mice, a 60-minute median lethal concentration (LC_{50}) of 220 ppm was reported (Gibson and Roberts 1972). Another acute-duration study reported no exposure-related deaths in female C57BL/6 mice at concentrations up to 800 ppm (Lewis et al. 1999). In other acute-duration inhalation studies, increased mortality was only reported in pregnant animals and/or their offspring. In rats, 33% mortality was observed among dams during gestation at 642 ppm, with 35% perinatal mortality among pups at 225 ppm (Lehotzky et al. 1985). In rabbits, 12.5 and 100% maternal mortality was observed during gestational exposure to 1,168.6 and 3,000 ppm, respectively (Denny and Gerhart 1991).

In longer-duration inhalation studies, the only exposure-related mortalities reported were the death of 4 of 22 B6C3F1 mice (2/10 males, 2/12 females) following intermittent inhalation exposure to 798.4 ppm for 90 days (Phillips 1983c). Lewis et al. (1999) observed no exposure-related deaths in C57Bl/6 mice exposed to concentrations up to 800 ppm for 20 weeks when mice were fed standard diets; however, 37% of mice fed atherosclerotic (high-fat) diets died during the first week of exposure to 800 ppm. In rats, no exposure-related deaths were observed following intermittent exposure to concentrations up to approximately 800 ppm for 11–15 weeks (Hirata et al. 1992; Phillips 1983a, 1983b; Rebert and Becker 1986; Valentine et al. 1997). In contrast to acute-duration studies, pregnant rats do not appear uniquely susceptible with longer-duration exposure, with no exposure-related mortalities reported after intermittent exposure to concentrations up to 817.2 ppm for 15 days during gestation (Saillenfait et al. 1989) or 502 ppm for 2 weeks premating through GD 19 (Holson 1992).

An oral median lethal dose (LD_{50}) of 3,020 mg/kg was reported in male Swiss-Webster mice following gavage exposure (Gibson and Roberts 1972). Another study reported the death of two of five female B6C3F1 mice following a single gavage exposure to 1,102 mg/kg (Keil et al. 1996). In other acute-duration studies, no exposure-related deaths were reported in healthy rats following exposure to carbon disulfide at doses up to 632 mg/kg once (Hoffmann and Klapperstück 1990) or 600 mg/kg/day for 10 days (NCTR 1984a; Tsai et al. 2000). However, when placed under cardiac stress (coronary occlusion), rats exposed once to 632 mg/kg or to 253 mg/kg/day for 4 weeks were more susceptible to cardiac-related death, showing a 28–30% decrease in survival compared to stressed controls (Hoffmann 1987; Hoffmann and Klapperstück 1990). See Section 2.5 (Cardiovascular) for more details.

2.3 BODY WEIGHT

Data pertaining to body weight in humans and exposure to carbon disulfide are limited. In one retrospective cohort of 119 viscose rayon workers, carbon disulfide was associated with anorexia and weight loss (over the entire course of employment) compared to 79 unexposed referents (Vanhoorne et al. 1992b). Measured occupational exposure levels ranged from 1.3 to 36 ppm. Conversely, there is limited evidence that carbon disulfide may alter metabolism, resulting in metabolic syndrome and potentially obesity; this is discussed in Section 2.18 (Other Noncancer).

In acute-duration inhalation studies in rodents, most studies showed no body weight effects at concentrations up to 800 ppm (Carreres Pons et al. 2017; Lewis et al. 1999; Moser et al. 1998; Zenick et al. 1984). However, Wilmarth et al. (1993) reported body weight loss in rats exposed to ≥600 ppm for 10 hours/day for 14 days. Body weight decreases were also observed in mice fed an atherogenic (high-fat) diet during exposure to 800 ppm for 5 days, compared to similarly fed control mice (Lewis et al. 1999).

In longer-duration inhalation studies in rats, the lowest concentration associated with decreased body weights was 225 ppm, which caused a 23% decrease in body weight gain in male rats following intermittent exposure for 14 weeks (Morvai et al. 2005). However, this study may be an outlier, as several studies reported a lack of body weight effects in male or nonpregnant female rats following intermediate-duration exposure to concentrations ranging from 297.1 to 401 ppm (Guo et al. 2014; Phillips 1983a, 1983b; Rebert and Becker 1986; Wrońska-Nofer 1973). At higher concentrations, almost all intermediate-duration inhalation studies reported body weight or body weight gain decreases >10% following intermittent exposure to ≥500 ppm (Hirata et al. 1992; Moser et al. 1998; Phillips 1983a, 1983b; Rebert and Becker 1986; Valentine et al. 1997; Zenick et al. 1984). Exceptions included a lack of body weight effects at concentrations up to 600 ppm in 10-week studies in male rats (Tepe and Zenick 1984) or up to 800 ppm in a 13-week study in female rats (Valentine et al. 1997). Male rats generally appear to be more susceptible to body weight effects, with some studies showing effects in males but not females (Moser et al. 1998; Valentine et al. 1997) and others showing serious body weight decreases in males (>20%) at exposures associated with less serious effects (10–19%) in females (Phillips 1983a, 1983b). In the only chronic-duration inhalation study identified, no effects on body weight were observed in female rats exposed to 321 ppm for 12–15 months (Wrońska-Nofer et al. 1980).

Data for body weight effects following intermediate-duration inhalation exposure are limited and inconsistent in mice. A 10% decrease in body weight was reported in male and female B6C3F1 mice intermittently exposed to 798.4 ppm for 90 days (Phillips 1983c), but no body weight effects were observed in C57BL/6 mice at concentrations up to 800 ppm for up to 20 weeks (Lewis et al. 1999; NIOSH 1980). However, as observed in the acute-duration study by the same study authors, body weight decreases were observed in mice fed an atherogenic (high-fat) diet during exposure to 800 ppm for ≥4 weeks, compared to similarly fed control mice (Lewis et al. 1999).

Pregnant animals may have increased susceptibility to body weight effects following inhalation exposure to carbon disulfide. The lowest LOAEL identified for body weight effects in pregnant rats was 64 ppm for a 27% decrease in maternal body weight gain in F0 dams and a 74% decrease in maternal body weight gain in F1 dams; each generation was exposed on gestational days (GDs) 1–21 only (Tabacova et al. 1983). In other gestational exposure studies in rats, maternal body weight gain was unchanged at concentrations ≤250 ppm, decreased 10–19% at 396.9–502 ppm, and decreased 48% at 817.2 ppm (Holson 1992; NIOSH 1980; Saillenfait et al. 1989). In pregnant rabbits, a 20% decrease in maternal body weight was observed after acute-duration exposure to 1,168.6 ppm on GDs 6–18; no effects were noted at ≤597.9 ppm (Denny and Gerhart 1991). Exposure during gestation or premating through gestation did not alter body weights of pregnant rabbits at concentrations up to 39.3 ppm (NIOSH 1980).

Data pertaining to body weight effects in animals following oral exposure to carbon disulfide are limited and inconsistent. A series of 10-day gavage studies reported >20% decreases in body weight gain in nonpregnant rats at ≥200 mg/kg/day but not in pregnant rats until 400 mg/kg/day; no body weight effects were noted in pregnant rabbits at doses up to 200 mg/kg/day (NCTR 1984a). Another 10-day gavage study in pregnant Sprague-Dawley rats reported a 10% decrease in maternal body weight at 1,200 mg/kg/day; no changes were observed at ≤600 mg/kg/day (Tsai et al. 2000). A 5-day gavage study in mice reported a 10% decrease in body weight at 1,102 mg/kg/day; no changes were observed at ≤551 mg/kg/day (Keil et al. 1996). In intermediate-duration oral studies in rats, no body weight effects were observed at gavage doses up to 253 mg/kg/day for 4 weeks (Hoffmann and Klapperstück 1990); however, body weight decreases of 10 and >20% were observed at 200 and ≥400 mg/kg/day, respectively, in a 6-week study (Gao et al. 2014; Wang et al. 2016), and body weight decreases ≥20% were observed at ≥300 mg/kg/day in an 8-week study (Liu et al. 2023).

2.4 RESPIRATORY

Data pertaining to respiratory effects in humans following exposure to carbon disulfide are very limited. Following an accident involving a railroad car, 27 individuals were exposed via inhalation to an unspecified concentration of carbon disulfide. Subtle and transient changes in pulmonary function manifested as reduced vital capacity and decreased partial pressure of arterial oxygen (Spyker et al. 1982). Dyspnea was reported in 77 of the 123 persons following an accidental release of large amounts of carbon disulfide, hydrogen sulfide, and sulfuric acid from a viscose rayon plant in India (Kamat 1994). Exposure concentrations were not stated. In a population-based, longitudinal study in the Wuhan-Zhuhai cohort from China, Song et al. (2023) reported an association between biomarkers of carbon disulfide exposure (urinary levels of TTCA) and impaired lung function, specifically a declining peak expiratory flow (PEF). Cross-sectional analysis of the cohort revealed that individuals with higher levels of urinary TTCA showed a reduction in the ratio between the forced expiratory volume and the forced vital capacity (FEV_1/FVC) and a reduced PEF, compared to individuals with lower levels of urinary TTCA (Song et al. 2023). The association between respiratory function and urinary TTCA levels was examined in children (median age 7.1 years) from Korea in a cross-sectional study (Park et al. 2024). Unlike Song et al. (2023), this study did not find an association between urinary level TCCA and FEV_1, FEV_1/FVC, or respiratory resistance. The average age of participants in Song et al. (2023) study was 54.88 years; this may be one factor for the discrepancy in results. A population-based study in New York, New Jersey, and Connecticut did not observe an association between ambient carbon disulfide levels during a child's birth year (by zip code) and childhood asthma outcomes in 151 children with mild to severe asthma (Li et al. 2021a). Children were a mean age of 12 years old, and the median ambient air level (based on U.S. EPA National Air Toxic Assessment database and zip code) was 0.00182 ppb. A case-control study consisting of 252 asthmatic children and 69 healthy controls from China also found no association between carbon disulfide exposure (assessed by urinary levels of TTCA) and asthma in children (Kuang et al. 2021).

Adverse respiratory effects reported in laboratory animals following inhalation exposure are limited to clinical signs associated with central nervous system depression. Decreased respiratory rates associated with severe narcosis were observed in male rats exposed to 803 ppm via inhalation for 18 hours (Tarkowski and Sobczak 1971). Similarly, labored respiration was noted in rabbit does prior to death following inhalation exposure to ≥1,168.6 ppm for up to 12 days during gestation (Denny and Gerhart 1991). No changes in respiratory rates were observed in male rats during or immediately following a brief 10-minute inhalation exposure to carbon disulfide at concentrations up to 81,000 ppm (Nash et al.

1981). Clinical signs of nasal irritation (red material around the nose for up to an hour post-exposure) were reported in rats intermittently exposed to 502 ppm for up to 49 days (Holson 1992).

No exposure-related changes in nasal cavity or lung histology were observed in rats intermittently exposed to concentrations up to 800 ppm for 2–13 weeks (Sills et al. 1998b). No exposure-related changes in lung weight or histology were observed following intermittent inhalation exposure to carbon disulfide in rats at concentrations up to 225 ppm for 14 weeks (Morvai et al. 2005) or in rats or mice at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c).

2.5 CARDIOVASCULAR

The cardiovascular system is a sensitive target of carbon disulfide toxicity in both humans and animals following inhalation exposure. Based upon systematic review (Appendix C), the cardiovascular system is a presumed target of carbon disulfide toxicity in humans via inhalation exposure based on a moderate level of evidence in humans and a high level of evidence in laboratory animals. Limited data from animal studies report cardiovascular effects in animals following oral exposure.

Numerous occupational cohort studies, primarily in the viscose rayon industry, evaluated potential associations between exposure to carbon disulfide and adverse cardiovascular effects. In general, findings from these studies should be interpreted with caution due to the lack of statistical control for any confounding factors in approximately 70% of all available studies. For example, most studies lacked adjustment for confounders such as known risk factors for cardiovascular disease (e.g., smoking, alcohol intake, body mass index [BMI], etc.) or use of medications to control risk factors (e.g., blood pressure medication, cholesterol lowering medication). Shift work (in any industry) has also been shown to have negative effects on cardiovascular health. Given that most individuals in the viscose rayon industry work under shift conditions, this may be an important (but omitted) confounding factor when evaluating cardiovascular disease in these workers (Gelbke et al. 2009). More details on the quality and confidence in available epidemiological studies evaluating cardiovascular effects can be found in Appendix C. As discussed in Appendix B, due to the availability of numerous cohort studies evaluating the potential association between cardiovascular effects and exposure to carbon disulfide, cross-sectional, case series, and case report studies of cardiovascular endpoints are not discussed below and did not meet inclusion criteria for the systematic review.

As discussed in Section 2.2, increased risk of death from cardiovascular disease has been reported in workers exposed to carbon disulfide in the viscose rayon industry, particularly in decades prior to 1980 with much higher occupational exposure levels (Table 2-4). Historical exposure concentrations in these studies range from 2.6 to 60 ppm.

In addition to mortality from cardiovascular disease, the risk or prevalence of cardiovascular disease has been evaluated in several occupational studies of workers exposed to carbon disulfide (Table 2-5). In the Finnish cohort discussed in Section 2.2 (regarding cardiovascular mortalities), there was no difference in the history of myocardial infarctions at the start of the study in 1967/1968; however, at the 5-year follow-up, workers with historical exposure concentrations >10 ppm had an increased risk of myocardial infarction (fatal and nonfatal combined), compared to matched referents without exposure (Hernberg et al. 1970; Tolonen et al. 1975). Workers also had increased prevalence of angina. Myocardial infarction and angina were not discussed in longer-term follow-ups of this cohort. An increased risk of myocardial infarction was also reported in Czechoslovakian viscose rayon workers exposed to historical concentrations >16 ppm (n=72), but not <16 ppm (n=179), compared to 124 unexposed referents (Balcarova and Halik 1991). Kotseva et al. (2001) reported increased prevalence of coronary heart disease in 91 male viscose rayon workers from Bulgaria with estimated high cumulative exposure index to carbon disulfide (based on job history and exposure duration), but not moderate exposure index, compared to 81 referents. Exposure levels ranged from 0.42 to 10.4 ppm. Most Japanese rayon cohorts did not find increased prevalence of heart disease at carbon disulfide levels of 5–30 ppm (Sugimoto et al. 1978), angina at carbon disulfide levels of 3–12 ppm (Tolonen et al. 1976), or markers of atherosclerosis (carotid or aortic stiffness) at carbon disulfide levels of 5 ppm (Takebayashi et al. 2004). However, workers in one Japanese cohort categorized as having “high” exposure (8.7 ppm) had increased risk of ischemic heart disease, compared to referents (Takebayashi et al. 2004). Additional cohorts did not observe increased prevalence of cardiovascular disease in workers exposed to concentrations ranging from 0.58 to 36 ppm (NIOSH 1984a; Vanhoorne et al. 1992a; Vertin 1978).

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Balcarova and Halik 1991 Longitudinal cohort; 251 workers from two viscose rayon factories (mean age and employment duration not reported) and 124 unexposed referents (Czechoslovakia)	Measured air concentrations, range of means: 1966–1975: Spinners: <16–48 ppm Other areas: <16 ppm After 1975: All areas: <9.6 ppm	Myocardial infarctions 1975–1985	↑ (spinners versus referents) ↑ (spinners versus other areas)
Bortkiewicz et al. 1997 Retrospective cohort; 152 male workers (ages 24–66 years; employed 5–38 years) from a chemical fiber plant and 93 age-matched male referents (Poland)	Mean daily exposure concentration, (range): 5.81 (0.56–35.04) ppm Estimated cumulative lifetime exposure, mean (range): 16,600 (487.1–149,787) ppm	Heart rate variability	↑ (workers versus referents) ↑ (CEI)
Bortkiewicz et al. 2001 Retrospective cohort; 177 male workers (ages 24–66 years; employed 5–38 years) from a chemical fiber plant and 93 male referents (ages 23–65 years) (Poland)	Mean daily exposure concentration, (range): 5.81 (0.56–35.04) ppm Estimated cumulative lifetime exposure, mean (range): 18,293 (487.1–149,823) ppm	Heart rate	↔ (workers versus referents) ↑ (CEI) ↔ (exposure duration)
		SBP	↔ (workers versus referents) ↔ (CEI) ↔ (exposure duration)
		DBP	↔ (workers versus referents) ↔ (CEI) ↑ (exposure duration)
		Abnormal ECG At rest 24-hour period	 ↔ (workers versus referents) ↑ (workers versus referents)
Chang et al. 2007 Retrospective cohort; 251 male workers (mean age 46 years; mean employment 18.8 years) from the viscose rayon industry and 226 referent male administrative clerks (mean age 42 years) (Taiwan)	Measured air concentrations, overall mean (range of means across different work areas): 14.5 (1.6–20.1) ppm CEI (ppm-years) Q1: <58 Q2: 58–220 Q3: 221–342 Q4: 343–468 Q5: ≥469	Hypertension[a]	↑ (workers versus referents) ↑ (CEI) ↑ (employment duration)
		SBP, DBP	↑ (workers versus referents)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Chrostek-Maj and Czeczotko 1995a Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	SBP, DBP	↔ (workers versus referents) ↔ (baseline versus follow-up)
		Abnormal ECG	↔ (workers versus referents) ↔ (baseline versus follow-up)
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Hypertension[a]	↔ (workers versus referents)
		SBP, DBP	↔ (workers versus referents)
		Abnormal ECG	↔ (workers versus referents)
Franco et al. 1982 Retrospective cohort; 70 workers (mean age 40.2 years) from a viscose rayon factory and 70 referents matched for age, height, and weight with similar distribution of alcohol and cigarette consumption habits (Italy)	Measured air concentrations, center of the aisle (area separating machines); range of means: 1963–1972: 3.2–8.0 ppm 1974–1979: ≤1.6 ppm Measured air concentrations, workstations; mean: 1963–1970: not measured 1971: 27 ppm 1972: 8.0 ppm 1979: 7.6 ppm	SBP, DBP	↔ (workers versus referents)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Hernberg et al. 1970; Tolonen et al. 1975, 1976 Longitudinal cohort; 343 workers (ages 25–64 years; median employment 11 years) employed in viscose rayon factory for at least 5 years between 1942 and 1967 (employed up to 25 years by 1967) and 343 matched referents from paper mill; subjects were followed for up to 15 years (Finland)	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1971: 4–30 ppm 1972–1977: <10 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Myocardial infarctions 1967/1968 1967–1972	 ↔ (workers versus referents) ↑ (workers versus referents)
		Angina 1967/1968 1972	 ↑ (workers versus referents) ↑ (workers versus referents)
		SBP, DBP 1967/1968 1972	 ↑ (workers versus referents) ↑ (workers versus referents)
		Abnormal ECG 1967/1968	 ↔ (workers versus referents)
Jhun et al. 2007 Retrospective cohort; 198 retired viscose rayon factory workers (182 men, 16 women; mean age 58 years) with history of carbon disulfide poisoning[b] (median employment of 13.0 years and median retirement of 13.8 years) and 198 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.8 (0.1–6.6) ppm *Historical air monitoring data were unavailable.*	SBP, DBP	↓ (workers versus referents)
		Abnormal ECG	↑ (workers versus referents)
		ECG component Heart rate PQ interval QRS amp/axis QT interval QTc RV5+SV1	 ↔ (workers versus referents) ↓ (workers versus referents) ↔ (workers versus referents) ↔ (workers versus referents) ↔ (workers versus referents) ↔ (workers versus referents)
Jhun et al. 2009 Retrospective cohort; 170 retired viscose rayon factory workers (153 men, 17 women; median age 58 years) with history of carbon disulfide poisoning[c] and 170 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.6 (0.12–6.58) ppm *Historical air monitoring data were unavailable.*	High blood pressure[a]	↔ (workers versus referents)
		SBP	↔ (workers versus referents)
		DBP	↓ (workers versus referents)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Kamal et al. 1991 Retrospective cohort; 253 workers (mean age 39.37 years; mean employment 15.4 years) from a viscose rayon factory and 99 unexposed referents (mean age 41.2 years) (Egypt)	Exposure levels from factory records: 20–45 ppm	Abnormal ECG	↑ (workers versus referents) ↔ (exposure duration)
		ECG component P duration/amp P-R segment P-R interval QRS duration QT interval R-R interval	 ↓ (workers versus referents) ↓ (workers versus referents) ↔ (workers versus referents) ↑ (workers versus referents) ↓ (workers versus referents) ↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Hypertension[a]	↑ (CEI)
		Abnormal ECG	↔ (CEI)
Kotseva and De Bacquer 2000 Retrospective cohort; 252 viscose rayon factory workers (111 men, 141 women; mean age 43 years; employed ≥1 year) and 252 age- and sex-matched referents (Bulgaria)	Measured current air concentrations, range: 3.2–21 ppm CEI (mg/m^3 x years): Moderate: <300 High: ≥300	Hypertension[a]	↔ (workers versus referents)
		CHD	↑ (high cumulative versus referents)
Kotseva et al. 2001 Retrospective cohort; 91 male workers (median age 39.5 years) from a viscose rayon factory and 81 male referents (median age 41.1 years) (Belgium)	Measured current air concentrations, range: 0.42–10.4 ppm CEI based on historical and current air concentration data (mg/m^3 x years): Moderate: <150 High: ≥150	Ischemic ECG	↑ (high exposure versus referents)
		CHD	↑ (high exposure versus referents)
		SBP, DBP	↔ (workers versus referents)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Myocardial infarction	↔ (workers versus referents) ↔ (CEI)
		Angina	↔ (workers versus referents) ↔ (CEI)
		SBP	↑ (workers versus referents) ↑ (CEI)
		DBP	↔ (workers versus referents) ↔ (workers versus referents)
		Abnormal ECG	↔ (workers versus referents) ↔ (CEI)
Reinhardt et al. 1997a Retrospective cohort; 222 exposed workers (median age 35 years; median employment 6 years) from viscose rayon industry and 191 unexposed referents (mean age 33 years) (Germany)	Measured current air concentrations, median (range): 4.02 (0.2–30) ppm *CEI not reported.*	Heart rate variability	↔ (workers versus controls) ↔ (CEI)
Schramm et al. 2016 Retrospective cohort; 290 workers (mean age 43.5 years; mean employment of 16.8 years) from the rayon industry and 137 unexposed referents (mean age 44.7 years) (Germany)	Measured air concentrations, range of means 1992–2009 (Göen et al. 2014): 2.48–10.4 ppm CEI: 256.3 ppm-years	Hypertension	↔ (workers versus referents)
		SBP	↔ (workers versus referents)
		DBP	↓ (workers versus referents)
Sugimoto et al. 1978 Retrospective cohort; 420 rayon filament workers (mean age 41.3 years; mean employment 17.0 years) and 390 unexposed referents (mean age 42.1 years) (Japan)	Historical TWA exposure levels, ranges: Before 1955: 15–30 ppm After 1955: 5–15 ppm Worker "Index of Exposure Dosages" calculated based on TWA levels and work history: Mean: 162.5	Hypertension	↔ (workers versus referents)
		Atherosclerosis	↔ (workers versus referents)
		Heart disease (CHD, valvular diseases, ECG abnormalities)	↔ (workers versus referents) ↔ (index of exposure)
		SBP, DBP	↔ (workers versus referents) ↔ (index of exposure)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Takebayashi et al. 2004 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 391 males from 11 viscose rayon factories including 251 current employees (mean age 34.7 years, mean employment 10.9 years prior to study and 6 years during study) and 140 former employees (mean age 35.9 years, mean employment 10.9 years prior to study and 2 years during study), and 359 male referents (mean age 34.6 years) (Japan)	Geometric mean air concentrations, measured twice yearly 1993–1998: Current: 5.0 ppm Former: 2.9 ppm Exposure categories for 1992-1998, measured internal exposure in mg urinary TTCA/g Cr (estimated external exposure levels in ppm): Low: 0.6 (2.4) Mid-low: 1.3 (4.6) Mid-high: 2.1 (6.4) High: 3.6 (8.7)	SBP	↑ (current versus referents) ↔ (former versus referents)
		DBP	↔ (workers versus referents)
		Carotid or aortic stiffness	↔ (workers versus referents)
		IHD	↑ (high exposure versus referents)
Tolonen et al. 1976 Retrospective cohort; 417 male workers (ages 35–54 years) from viscose rayon industry and 391 unexposed referents from a cuprammonium rayon plant (Japan)	Measured air concentrations(1966–1972), TWA means: 3–12 ppm	Angina	↔ (workers versus referents)
		Abnormal ECG	↔ (workers versus referents)
		SBP, DBP	↔ (workers versus referents)
Vanhoorne et al. 1992a Retrospective cohort; 115 male workers (median age 34 years; employed at least 1 year) from a viscose rayon factory and 76 unexposed referents (median age 33.5 years) (Belgium)	Measured current air concentrations, range: 1–36 ppm CEI based on current air concentration data; the study authors indicated that working conditions had not changed since 1932 (mg/m^3 x years): Low: 1–300 High: >300	Angina	↔ (workers versus referents)
		Myocardial infarction	↔ (workers versus referents)
		Abnormal ECG	↔ (workers versus referents)
		IHD	↔ (workers versus referents)
		SBP, DBP	↑ (workers versus referents) ↑ (CEI)

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Cardiovascular Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Vertin 1978 Longitudinal cohort; 100 shift workers from a viscose rayon factory, 100 unexposed shift workers, and 100 unexposed non-shift workers; all workers were >40 years old and were examined at baseline and 3 years later (The Netherlands)	Historical measured air concentrations (1967–1975), range of means in spinning scenarios: Cake: 9–15 ppm Spool: 14–19 ppm Continuous: 15–19 ppm	Risk of CHD (based on 39 variables)	↔ (workers versus referents)
		SBP, DBP	↔ (workers versus referents)
		Abnormal ECG	↔ (workers versus referents)

[a]High blood pressure/hypertension defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg.
[b]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) "significant" workplace carbon disulfide exposure for ≥2 years; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, cerebral hemorrhage, central nervous system dysfunction, psychological disorder, hypertension, coronary artery disease, peripheral neuropathy, retinal aneurysm, optic neuritis, other retinal change, sensorineural hearing loss, renal function abnormality, liver function abnormality, or genital organ dysfunction.
[c]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) workplace carbon disulfide exposure; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, central nervous system dysfunction, cerebral hemorrhage, peripheral polyneuropathy, retinal micro-aneurysm, retinopathy other than micro-aneurysm, optic neuritis, sensory neural hearing loss, psychosis, or coronary artery disease.

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; CHD = coronary heart disease; Cr = creatinine; DBP = diastolic blood pressure; ECG = electrocardiogram; IHD = ischemic heart disease; LOD = level of detection; Q = quartile or quintile; SBP = systolic blood pressure; TTCA = 2-thiothiazolidine-4-carboxylic acid (carbon disulfide metabolite); TWA = time-weighted average

Results of occupational cohort studies provide conflicting evidence regarding associations between carbon disulfide exposure and elevated blood pressure (Table 2-5). For studies reporting a positive association between either clinical hypertension (systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg) or elevated systolic/diastolic blood pressure measurements, the reported exposure metrics (means, range of means, or geometric means) ranged from 0.43 to 33.5 ppm (Chang et al. 2007; Hernberg et al. 1970; Kim et al. 2000; NIOSH 1984a; Takebayashi et al. 2004; Tolonen et al. 1975, 1976). Vanhoorne et al. (1992a) also reported an association between occupational exposure and elevated systolic and diastolic blood pressure, but only provided the overall range of exposure (1–36 ppm). In contrast, no differences in blood pressure values or the risk or prevalence of hypertension between exposed workers and unexposed referents were observed in 11 additional studies of similar occupational

cohorts with exposure metrics (0.42–30 ppm) that show substantial overlap with studies reporting associations (Table 2-5).

Results of occupational cohort studies also provide conflicting evidence regarding associations between carbon disulfide exposure and abnormalities in electrocardiograms (ECGs) and measures of heart rate variability (Table 2-5). Studies reporting a positive association between either ECG abnormalities or heart rate variability had exposure metrics ranging from 3.8 to 45 ppm (Bortkiewicz et al. 1997, 2001; Jhun et al. 2007; Kamal et al. 1991; Kotseva et al. 2001). As observed for blood pressure, nine additional studies in similar occupational cohorts with overlapping exposure metrics (1–36 ppm) did not observe any differences in ECG and/or heart rate variability between exposed workers and unexposed referents (Table 2-5).

Tan et al. (2002) conducted a meta-analysis of 11 cohort studies published between 1970 and 1996 that evaluated the potential association between carbon disulfide exposure and the prevalence of cardiovascular disease. Studies included in the meta-analysis are shown in Table 2-6. The pooled analysis determined a positive association between occupational exposure, with a relative risk of 1.56 (95% confidence interval of 1.12–2.1).

Table 2-6. Cohort Studies Evaluating Associations Between Occupational Exposure to Carbon Disulfide and Heart Disease Included in the Meta-Analysis Conducted by Tan et al. (2002)

Study	Country	Exposure level (ppm)[a]	Result[b]
Hernberg et al. 1970	Finland	10–30	↑
Vertin 1978	The Netherlands	≤20	↔
Lyle 1981	United Kingdom	6–35	↔
Hernberg and Tolonen 1981	Finland	≤10	↑
Wilcosky and Tyroler 1983	United States	≤10	↔
Nurminen and Hernberg 1985	Finland	≤10	↔
Sweetnam et al. 1987	United Kingdom	≤10	↔
MacMahon and Monson 1988	United States	≤10	↑
Swaen et al. 1994	The Netherlands	≤7	↑

Table 2-6. Cohort Studies Evaluating Associations Between Occupational Exposure to Carbon Disulfide and Heart Disease Included in the Meta-Analysis Conducted by Tan et al. (2002)

Study	Country	Exposure level (ppm)[a]	Result[b]
Liss and Finkelstein 1996	Canada	Not reported	↔
Pepłońska et al. 1996	Poland	Not reported	↑

[a]As reported in Table 1 of Tan et al. (2002). The exposure levels reported for MacMahon and Monson (1988) and Wilcosky and Tyroler (1983) could not be confirmed in the original reports; therefore, these studies did not meet inclusion criteria for Table 2-5 (see Appendix B). Pepłońska et al. (1996) also did not meet inclusion criteria due to lack of exposure data. Conversely, exposure levels were identified in the primary report by Liss and Finkelstein (1996); therefore, this study is included in Table 2-5 above.
[b]Based on relative risk ratios calculated by Tan et al. (2002) for the meta-analysis.

↑ = association; ↔ = no association

Several of the occupational cohort studies discussed above, as well as others, have suggested associations between exposure to carbon disulfide and other health endpoints that are known risk factors for cardiovascular disease, such as hypercholesterolemia and metabolic syndrome; these endpoints are discussed in Sections 2.9 (Hepatic) and 2.19 (Other Noncancer), respectively.

Some animal studies have reported cardiovascular lesions in rodents following inhalation exposure to carbon disulfide, particularly in animals fed high-fat, atherogenic diets. Rats administered carbon disulfide at ≥16 ppm for up to 6 months exhibited myocardial edema, microhemorrhages, distention of the lumen, attenuation of myocardial vessels, and irregular thickening of the aorta wall (Antov et al. 1985). However, dose-response data from this study is difficult to interpret due to reporting inadequacies (lack of quantitative data; lack of explicit reporting of findings [or lack thereof] in control animals); therefore, this study was not included in the LSE table. In mice, atherosclerotic lesions (fatty deposit formation in aortic valve tissues) were increased in mice following intermittent inhalation exposure to ≥500 ppm for 4–20 weeks; no effect was seen at 1 week at concentrations up to 800 ppm (Lewis et al. 1999). In both studies, when rats and mice were fed atherogenic diets, effects were seen at lower concentrations (≥3.2 and ≥50 ppm, respectively). Similarly, while no atherosclerotic changes were observed in the aorta of rats intermittently exposed to 321 ppm via inhalation for up to 15 months, similarly exposed rats fed an atherogenic diet had increased cholesterol content in the aortic wall and lipid infiltrates of the coronary arteries and aortic valves (Wrońska-Nofer et al. 1980). Rats or mice fed standard diets did not show exposure-related changes in cardiovascular histology following intermittent inhalation exposure to carbon disulfide at concentrations up to 800 ppm up to 13 weeks (Phillips 1983a, 1983b, 1983c; Sills et al. 1998b); these studies did not evaluate atherogenic diets.

A limited number of inhalation studies in rats have reported altered cardiac function following exposure to carbon disulfide. Decreased cardiac rate associated with severe narcosis were observed in male rats exposed to 803 ppm via inhalation for 18 hours (Tarkowski and Sobczak 1971). In an intermediate-duration inhalation study, increased blood pressure, decreased cardiac output and blood flow to the lung and kidney, and increased vascular resistance in the lung, kidney, and brain were reported in rats following intermittent exposure to 225 ppm for 14 weeks. These changes were not associated with any histopathological changes in the heart or vascular systems of the examined organs.

Altered cardiac function has also been reported in a limited number of oral studies in rats following gavage exposure to carbon disulfide. However, some of the observed effects may be secondary to central nervous system depression rather than direct effects on the cardiovascular system. A single gavage exposure ≥506 mg/kg resulted in a significant reduction in blood pressure in conscious, unrestrained rats when measured 5–10 hours post-exposure; no changes in heart rate were observed in the 24-hour monitoring period (Hoffmann and Klapperstück 1990). However, a single dose of 632 mg/kg appeared to increase sensitivity to anesthesia, with significantly reduced heart rates compared to control when given an hour prior to anesthetization (Hoffmann 1987; Hoffmann and Klapperstück 1990). Significant alterations measured on an ECG while under anesthesia include prolonged QT and PR intervals at ≥373 and ≥506 mg/kg, respectively (Hoffmann and Klapperstück 1990). A single carbon disulfide exposure did not increase the occurrence or rate of arrhythmias when rats were placed under pathophysiological stress (coronary occlusion by surgical ligation or aconitine-induced arrhythmia), compared to controls (Hoffmann 1987; Hoffmann and Klapperstück 1990). Despite this, rats exposed once to carbon disulfide an hour prior to the surgical ligation procedure had a 30% lower survival rate under cardiac stress (Hoffmann 1987). When a similar study was conducted after exposure to 126 or 253 mg/kg/day for 4 weeks, the following effects were observed: no changes in conscious rats; widening of QRS complex on the ECG and reduced left ventricular systolic blood pressure in anesthetized rats at 253 mg/kg/day; and decreased time to arrythmia and a 28% decrease in survival rate under cardiac stress via aconitine-induced arrhythmia (Hoffmann and Klapperstück 1990). Due to induction of cardiac stress (rather than evaluation under baseline physiological conditions), NOAEL/LOAEL determinations for cardiac effects reported by Hoffmann (1987) and Hoffmann and Klapperstück (1990) are not included in Table 2-2.

Mechanisms of Cardiotoxicity. Proposed mechanisms of cardiotoxicity include altered lipid homeostasis and metabolism (see Section 2.9), impaired fibrinolytic activities (see Section 2.7), and subclinical

hypothyroidism (see Section 2.13) (Huang 2004; Tolonen et al. 1975). It has also been proposed that carbon disulfide releases normal inhibition of elastase, resulting in the increased elasticity of vascular walls, which in turn increases the susceptibility for aneurysms (Huang 2004). Wrońska-Nofer et al. (2002) suggested a role for increased oxidative stress, specifically lipoprotein oxidation, in the development of atherosclerosis and increased coronary heart disease risk. Luo et al. (2011) also proposed that markers of oxidative stress observed in workers exposed to carbon disulfide, including elevated blood malondialdehyde and superoxide dismutase levels and decreased total blood antioxidant levels, may contribute to development of atherosclerosis. Furthermore, some have suggested that lipid peroxidation mediated by free radicals is an early effect of low-density lipoprotein (LDL) cholesterol oxidation (caused by many oxidants). Thus, long-term inhalation exposure to carbon disulfide could result in oxidative modifications of LDL cholesterol, playing a role in the pathogenesis of atherosclerosis. Cardiotoxicity may also occur due to direct cytotoxic effects on cardiac cells secondary to a decrease in the available energy sources; cardiac cells cultured with carbon disulfide showed depleted cell energy stores (Tan et al. 2003).

Subclinical hypothyroidism has been linked with cardiovascular risk factors, such as elevated blood pressure, lipid levels, atherosclerosis, and heart failure (Suh and Kim 2015). In fact, a study of 9,020 U.S. adults showed that individuals with subclinical hypothyroidism are at a greater risk of death associated with cardiovascular disease, compared to the general population (Inoue et al. 2020). Alterations in thyroid hormone levels can impact the cardiovascular system via numerous mechanisms, including altered regulation, absorption, and metabolism of lipid synthesis; direct action on myocytes, altering cardiac phenotype and contractility; and alterations in cardiovascular hemodynamics (Biondi and Klein 2004; Suh and Kim 2015). However, a systematic review by Printemps et al. (2022), did not find strong evidence for an endocrine-dependent mode of action (MOA) for cardiotoxicity associated with exposure to carbon disulfide. One potential endocrine-dependent MOA reviewed included hypothyroidism as an early key event, resulting in subsequent key events of inflammation, oxidized LDL, and generation of reactive oxygen species, ending in development of atherosclerosis. Excessive oxidative damage in general, not directly downstream of hypothyroidism, was also postulated as a potential non-endocrine-dependent MOA underlying altered cholesterol homeostasis, resulting in development of atherosclerosis. Based on the available data, namely evidence of direct interactions between carbon disulfide and LDL cholesterol, there is stronger support for the non-endocrine-dependent MOA.

Bobnis et al. (1976) evaluated the possibility that atherosclerotic lesions associated with carbon disulfide may be autoimmune in nature. However, data indicated that the β-lipoprotein isolated from carbon

disulfide exposed workers is antigenically identical to lipoproteins isolated from healthy nonexposed controls. The study authors concluded that these findings suggested no immunologic component involved in the increase of atherosclerotic lesions found in carbon disulfide-exposed workers.

2.6 GASTROINTESTINAL

Nausea and vomiting were reported in approximately 50% of 123 persons following an accidental release of large amounts of carbon disulfide, hydrogen sulfide, and sulfuric acid from a viscose rayon plant in India; exposure concentrations were not reported (Kamat 1994). In a review of 100 occupational carbon disulfide poisonings observed in two viscose rayon plants in the early 1940s, "gastric disturbances" were observed in 28% of cases (Vigliani 1954). Estimated average exposure levels in these case reports were 0.45–1 mg/L (145–321 ppm).

Other human data are limited to two occupational cohort studies of viscose rayon workers (Table 2-7). Both studies are limited by concomitant exposure to other chemicals, the subjective nature of reported symptoms, lack of quantification of precise exposure concentrations, and pairwise statistical comparisons (exposed versus unexposed) that did not adjust for confounding factors. In the first study, workers exposed to 1–36 ppm for an average of 4.2 years were asked to recall the prevalence of gastrointestinal symptoms over the duration of their employment (Vanhoorne et al. 1992b). In this cohort, the cumulative exposure index was associated with increased subjective recall of all gastrointestinal complaints (e.g., anorexia, nausea, vomiting, and flatulence), compared to unexposed referents. However, a similar study did not observe an increase in subjective complaints of nausea or loss of appetite in workers exposed to 0.2–30 ppm for an average of 6 years, compared to unexposed referents (Reinhardt et al. 1997b).

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Gastrointestinal Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Reinhardt et al. 1997b Cross-sectional; 222 male workers (ages 23–59 years; employed <1–6 years) from the viscose rayon industry and 191 unexposed referents (ages 21–58 years) (Germany)	Measured air concentration, median (range): 4.02 (0.2–30) ppm	Subjective report of digestive symptoms (nausea or loss of appetite)	↔ (workers versus referents)

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Gastrointestinal Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Vanhoorne et al. 1992b Retrospective cohort; 191 male workers (median age 32 years; employed a mean of 4.2 years) from the viscose rayon industry and 79 unexposed referents (median age 34.3 years) (Belgium)	Measured current air concentration, range: 1–36 ppm CEI (ppm-years): Median: 57.8 Mean: 124.1	Subjective complaint (any time during employment): Any complaint Anorexia, nausea vomiting, flatulence Diarrhea, blood or mucus in stools, constipation, abdominal pain	 ↑ (workers versus referents) ↑ (workers versus referents) ↔ (workers versus referents)

↑ = association; ↔ = no association; CEI = cumulative exposure index (number of years worked × exposure levels)

It is noted that reported gastrointestinal findings in human studies may be secondary to neurological effects rather than direct effects on the gastrointestinal system (see Section 2.15, Neurological for more details).

Studies evaluating potential gastrointestinal effects in animals following exposure to carbon disulfide are limited to a single series of 90-day inhalation studies in rats and mice (Phillips 1983a, 1983b, 1983c). In these studies, no exposure-related changes in gastrointestinal histology were observed in either species following intermittent exposure to carbon disulfide at concentrations up to 798.4 ppm.

2.7 HEMATOLOGICAL

Data pertaining to hematological effects in humans following exposure to carbon disulfide are limited to three occupational studies (Table 2-8). Available studies have several limitations, some of which include potential concomitant exposure to other chemicals (e.g., hydrogen sulfide), lack of quantification of precise exposure concentrations, and/or lack of adequate statistical adjustment for relevant confounding factors.

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Hematological Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Chrostek-Maj and Czeczotko 1995a Prospective cohort; 114 males (ages 20–45 years; employed 5 years) from a plant producing carbon disulfide (Poland)	Measured air concentrations, range: <LOD–21 ppm	RBC count	↔ (current versus pre-employment)
		WBC count	↔ (current versus pre-employment)
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Platelets	↔ (workers versus referents)
		Partial thromboplastin time	↔ (workers versus referents)
		Prothrombin time	↔ (workers versus referents)
		Thrombin-antithrombin complex III	↔ (workers versus referents)
		Fibrinogen	↔ (workers versus referents)
		Plasminogen	↔ (workers versus referents)
Drexler et al. 1995 Cross-sectional; 247 male workers (ages 21–56 years; employed 4–220 months) from the viscose rayon industry and 222 matched male referents (Germany)	Measured air concentrations, median (range): 4 (<0.2–65.7) ppm	Fibrolytic activity	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Hemoglobin levels	↔ (workers versus referents) ↔ (CEI)
		WBC count	↔ (workers versus referents) ↔ (CEI)

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Hematological Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Omae et al. 1998 Cross-sectional; Cross-sectional; Japanese Rayon Workers' Health Study Group; 432 males from 11 viscose rayon factories (mean age 35.46 years, mean employment 13.43 years), and 402 male referents (mean age 35.77 years) (Japan)	Measured current air concentrations, geometric mean (range): 3.36 (<LOD–39.70) ppm	Thrombin	↔ (workers versus referents)
		Tissue plasminogen activator	↔ (workers versus referents)
		Plasminogen activator inhibitor	↔ (workers versus referents)
Sidorowicz et al. 1980 Retrospective cohort; 35 workers exposed to carbon disulfide (25–55 years of age; employed 5–20 years) and 18 unexposed referents (25–53 years of age) (Poland)	Historical air concentrations, range: 6.4–13 ppm	RBC count	↔ (workers versus referents)
		Hematocrit	↔ (workers versus referents)
		Hemoglobin	↔ (workers versus referents)
Takebayashi et al. 2004 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 391 males from 11 viscose rayon factories including 251 current employees (mean age 34.7 years, mean employment 10.9 years prior to study and 6 years during study) and 140 former employees (mean age 35.9 years, mean employment 10.9 years prior to study and 2 years during study), and 359 male referents (mean age 34.6 years) (Japan)	Geometric mean air concentrations, measured twice yearly 1993–1998: Current: 5.0 ppm Former: 2.9 ppm	Fibrinogen	↔ (workers versus referents)
		Tissue plasminogen activator	↔ (workers versus referents)
		Plasminogen activator inhibitor	↔ (workers versus referents)
		Thrombin-antithrombin complex III	↔ (workers versus referents)
Visconti et al. 1967 Retrospective cohort; 57 workers from a viscose factory (ages 22–45 years; employed 2–8 years) and 18 unexposed referents (ages 21–45 years) (Yugoslavia)	Measured air concentrations, range of means across 15 workplaces: 59–169 ppm	Fibrolytic activity Plasmin	↓ (workers versus referents) ↓ (duration of exposure)
		Plasminogen	↓ (workers versus referents) ↔ (duration of exposure)

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; LOD = level of detection; Q = quartile; RBC = red blood cell; TWA = time-weighted average; WBC = white blood cell

In the few available studies, there is no evidence of adverse effects on red or white blood cell parameters following occupational exposure to carbon disulfide. In a prospective occupational study of workers who produced carbon disulfide, red blood cell and white blood cell counts did not differ from preemployment values after exposure to concentrations up to 21 ppm for 5 years (Chrostek-Maj and Czeczotko 1995a). Blood cell parameters also did not differ from unexposed controls at baseline or at the 5-year follow-up examination. In retrospective cohorts, no changes were seen in red or white blood cell parameters in workers exposed to concentrations ranging from 0.43 to 6.28 ppm for 1–≥15 years (Kim et al. 2000) or in red blood cell parameters in workers exposed concentrations ranging from 6.4 to 13 ppm for 5–20 years (Sidorowicz et al. 1980). Additionally, Kim et al. (2000) reported no associations between hematological parameters and calculated cumulative exposure indices (duration of employment × exposure level).

One study suggested that occupational exposure to high concentrations of carbon disulfide may alter blood coagulation. Fibrolytic activity (both serum plasmin and plasminogen) was decreased in workers exposed to 59–169 ppm for 2–8 years (Visconti et al. 1967). When evaluated with respect to duration of employment, serum plasmin activity (but not plasminogen) decreased with increasing exposure duration. Occupational studies evaluating lower exposure levels (<10 ppm) did not observe alterations in blood coagulation parameters in exposed workers, compared to referents (Cirla and Graziano 1981; Drexler et al. 1995; Omae et al. 1998; Takebayashi et al. 2004).

In animals, there is also limited information on potential hematological effects following exposure to carbon disulfide. In Fischer-344 rats, several hematological changes were noted after intermittent exposure to 798.4 ppm for 90 days, including increased segmented neutrophils and decreased lymphocytes in both sexes and mild decreases in red blood cell and platelet counts in males (Phillips 1983a). However, these effects were not observed in similarly exposed Sprague-Dawley rats (Phillips 1983b). In B6C3F1 mice, intermittent exposure to 798.4 ppm for 90 days resulted in a decrease in red blood cell count, total hemoglobin, and hematocrit (Phillips 1983c). In pregnant rabbits, an increase in segmented neutrophils and a decrease in lymphocytes were observed following exposure to 1,168.3 ppm for 6 hours/day on GDs 6–18 (Denny and Gerhart 199).

2.8 MUSCULOSKELETAL

The prevalence of dental fracture (along with gingivitis) increased with an increase in the calculated cumulative exposure index (number of years worked × exposure levels) for carbon disulfide in a cohort of 1,237 viscose rayon workers exposed to concentrations ranging from 0.43 to 6.28 ppm for 1–≥15 years

and 315 unexposed referents (Kim et al. 2000). Limitations of this study include concomitant exposure to other chemicals and lack of adequate statistical adjustment for relevant confounding factors. No additional studies were located regarding musculoskeletal effects in humans after exposure to carbon disulfide.

Data pertaining to potential musculoskeletal effects in animals following exposure to carbon disulfide are very limited. No exposure-related changes in musculoskeletal histology were observed following intermittent inhalation exposure to carbon disulfide in rats at concentrations up to 225 ppm for 14 weeks (Morvai et al. 2005) or in rats or mice at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c). Muscular rigidity associated with tremors and gait impairments was reported in rats following "high-dose" exposure via gavage for 6 weeks; tremors were observed at ≥400 mg/kg/day but the dose response and incidence data were not provided for muscular rigidity observations (Gao et al. 2014). These findings are considered secondary to carbon disulfide induced neuropathy (Gao et al. 2014; Wang et al. 2016); see Section 2.15, Neurological, for more details.

2.9 HEPATIC

The hepatic system, specifically altered lipid homeostasis and metabolism, is a sensitive target of carbon disulfide toxicity in humans and animals following inhalation exposure to carbon disulfide. Based upon systematic review (Appendix C), 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. Human and animal data on hepatic endpoints other than lipid homeostasis are very limited, but do not provide clear evidence for additional hepatotoxicity following exposure to carbon disulfide.

Altered Lipid Homeostasis. Numerous occupational cohort studies, primarily in the viscose rayon industry, evaluate potential associations between exposure to carbon disulfide and potential changes in serum lipid levels (Table 2-9). In general, findings from these studies should be interpreted with caution due to the 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.) or use of cholesterol-lowering medications. More details on the quality and confidence in available epidemiological studies evaluating hepatic effects can be found in Appendix C. As discussed in Appendix B, due to the availability of numerous cohort studies evaluating the potential association between serum lipid levels and exposure to carbon disulfide, cross-sectional, case series, and case report

studies of these endpoints are not discussed below and did not meet inclusion criteria for the systematic review.

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Chang et al. 2007 Retrospective cohort; 251 male workers (mean age 46 years; mean employment 18.8 years) from the viscose rayon industry and 226 referent administrative clerks (mean age 42 years) (Taiwan)	Measured air concentrations, overall mean (range of means): 14.5 (1.6–20.1) ppm	Hypercholesterolemia[a]	↔ (workers versus referents)
		LDL-C	↔ (workers versus referents)
		HDL-C	↔ (workers versus referents)
		Clinically elevated triglycerides[b]	↔ (workers versus referents)
Chrostek-Maj and Czeczotko 1995a Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	Total cholesterol	↔ (workers versus referents) ↑ (baseline versus follow-up)
		VLDL-C	↔ (workers versus referents) ↔ (baseline versus follow-up)
		Triglycerides	↑ (workers versus referents) ↑ (baseline versus follow-up)
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Total cholesterol	↔ (workers versus referents)
		HDL-C	↔ (workers versus referents)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Franco et al. 1982 Retrospective cohort; 70 workers (mean age 40.2 years) from a viscose rayon factory and 70 referents matched for age, height, and weight with similar distribution of alcohol and cigarette consumption habits (Italy)	Measured air concentrations, center of the aisle (area separating machines); range of means: 1963–1972: 3.2–8.0 ppm 1974–1979: ≤1.6 ppm Measured air concentrations, workstations; mean (range) 1963–1970: not measured 1971: 27 ppm 1972: 8.0 ppm 1979: 7.6 ppm	Total cholesterol	↔ (workers versus referents)
		HDL-C	↔ (workers versus referents)
		Triglycerides	↔ (workers versus referents)
Hernberg et al. 1971 Longitudinal cohort; 343 men (ages 25–64 years; employed for a median of 11 years) from a viscose rayon factory and 343 matched unexposed referents (ages 25–64 years) (Finland)	Historical air concentrations: Prior to 1950: 20–30 ppm After 1950s: <20 ppm Geometric mean air concentration in different departments: 1967: 4–18 ppm	Total cholesterol	↔ (workers versus referents)
		Triglycerides	↔ (workers versus referents)
		Free fatty acids	↔ (workers versus referents)
		Total serum lipids	↔ (workers versus referents)
Jhun et al. 2007 Retrospective cohort; 198 retired viscose rayon factory workers (182 men, 16 women; mean age 58 years) with history of carbon disulfide poisoning[c] (median employment of 13.0 years and median retirement of 13.8 years) and 198 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.8 (0.1–6.6) ppm *Historical air monitoring data were unavailable.*	Total cholesterol	↑ (workers versus referents)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Jhun et al. 2009 Retrospective cohort; 170 retired viscose rayon factory workers (153 men, 17 women; median age 58 years) with history of carbon disulfide poisoning[d] and 170 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.6 (0.12–6.58) ppm *Historical air monitoring data were unavailable.*	Reduced HDL-C[e]	↔ (workers versus referents)
		Elevated triglycerides[f]	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Total cholesterol	↔ (workers versus referents) ↔ (CEI)
Kotseva and De Bacquer 2000 Retrospective cohort; 252 viscose rayon factory workers (111 men, 141 women; mean age 43 years; employed ≥1 year) and 252 age- and sex-matched referents (Bulgaria)	Measured current air concentrations, range: 3.2–21 ppm CEI (mg/m^3 x years): Moderate: <300 High: ≥300	High cholesterol[g]	↑ (workers versus referents) ↑ (CEI)
Kotseva et al. 2001 Retrospective cohort; 91 male workers (median age 39.5 years) from a viscose rayon factory and 81 male referents (median age 41.1 years) (Belgium)	Measured current air concentrations, range: 0.42–10.4 ppm CEI based on historical and current air concentration data (mg/m^3 x years): Moderate: <150 High: ≥150	Total cholesterol	↔ (workers versus referents)
		LDL-C	↔ (workers versus referents)
		HDL-C	↔ (workers versus referents)
		Triglycerides	↔ (workers versus referents)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Luo et al. 2011 Retrospective cohort; 89 workers (78 males, 11 females; mean age 46.5 years) from a viscose rayon factory and 111 referents (81 males, 30 females; mean age 45 years) (China)	Historical exposure levels (1999), mean Low: 5.51 ppm High: 14.2 ppm CEI (ppm-years): Low: 0-60 High: >60	Total cholesterol	↔ (workers versus referents)
		Triglycerides	↔ (workers versus referents)
		High cholesterol[a]	↔ (workers versus referents)
		Elevated triglycerides[f]	↔ (workers versus referents)
		Dislipoproteinemia[h]	↔ (workers versus referents)
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Total cholesterol	↑ (CEI)
		LDL-C	↑ (CEI)
		HDL-C	↔ (CEI)
		Triglycerides	↓ (CEI)
		Total lipids	↑ (CEI)
Raitta et al. 1974 Longitudinal cohort; 100 male workers (mean age 48 years; exposed a mean of 15 years) And 97 male referents (mean age 47 years) (Finland) *Subset of workers from larger Finnish cohort (Hernberg et al. 1970)*	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1972: 4–30 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Total cholesterol Baseline (1967) Follow-up (1972)	 ↔ (workers versus referents) ↔ (workers versus referents)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Schramm et al. 2016 Retrospective cohort; 290 workers (mean age 43.5 years; mean employment of 16.8 years) from the rayon industry and 137 unexposed referents (mean age 44.7 years) (Germany)	Measured air concentrations, range of means 1992–2009 (Göen et al. 2014): 2.48–10.4 ppm CEI: 256.3 ppm-years	LDL-C	↔ (workers versus controls) ↔ (CEI)
		HDL-C	↔ (workers versus controls) ↔ (CEI)
		Triglycerides	↔ (workers versus referents) ↔ (CEI)
Stanosz et al. 1994b Retrospective cohort; 237 female workers (mean age 42.9 years, exposed for 1–>20 years) from a viscose rayon factory and 70 unexposed female referents from a textile factory (mean age 42.1 years) (Poland)	Historical air concentrations, range: 5–7 ppm	Total cholesterol	↑ (workers versus referents; ages 40–49 or 50–55) ↔ (workers versus referents; ages 25–39 or duration of employment)
		LDL-C	↑ (workers versus referents; ages 40–49 or 50–55 or >11 years employed) ↔ (workers versus referents; ages 25–39 or employed 1–10 years)
		HDL-C	↓ (workers versus referents; ages 40–49 or 50–55 or >11 years employed) ↔ (workers versus referents; ages 25–39 or employed 1–10 years)
		Triglycerides	↔ (workers versus referents)
		Free fatty acids	↔ (workers versus referents)
Sugimoto et al. 1978 Retrospective cohort; 420 rayon filament workers (mean age 41.3 years; mean employment 17.0 years) and 390 unexposed referents (mean age 42.1 years) (Japan)	Historical TWA exposure levels, ranges: Before 1955: 15–30 ppm After 1955: 5–15 ppm Worker “Index of Exposure Dosages” calculated based on TWA levels and work history: Mean: 162.5	Total cholesterol	↔ (workers versus referents)
		Triglycerides	↔ (workers versus referents)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Takebayashi et al. 2004 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 391 males from 11 viscose rayon factories including 251 current employees (mean age 34.7 years, mean employment 10.9 years prior to study and 6 years during study) and 140 former employees (mean age 35.9 years, mean employment 10.9 years prior to study and 2 years during study), and 359 male referents (mean age 34.6 years) (Japan)	Geometric mean air concentrations, measured twice yearly 1993–1998: Current: 5.0 ppm Former: 2.9 ppm	Total cholesterol	↔ (current versus referents) ↔ (former versus referents)
		LDL-C	↔ (current versus referents) ↔ (former versus referents)
		HDL-C	↑ (current versus referents) ↔ (former versus referents)
		Triglycerides	↔ (current versus referents) ↔ (former versus referents)
Vanhoorne et al. 1992a Retrospective cohort; 115 male workers (median age 34 years; employed at least 1 year) from a viscose rayon factory and 76 unexposed referents (median age 33.5 years) (Belgium)	Measured current air concentrations, range: 1–36 ppm CEI based on current air concentration data; the study authors indicated that working conditions had not changed since 1932 (mg/m^3 x years): Low: 1–300 High: >300	Total cholesterol	↔ (workers versus referents) ↑ (CEI)
		LDL-C	↔ (workers versus referents) ↑ (CEI)
		HDL-C	↔ (workers versus referents) ↓ (CEI)
		Triglycerides	↔ (workers versus referents) ↔ (CEI)

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Blood Lipid Levels

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Vertin 1978 Longitudinal cohort; 100 shift workers from a viscose rayon factory, 100 unexposed shift workers, and 100 unexposed non-shift workers; all workers were >40 years old and were examined at baseline and 3 years later (The Netherlands)	Historical measured air concentrations (1967–1975), range of means in spinning scenarios: Cake: 9–15 ppm Spool: 14–19 ppm Continuous: 15–19 ppm	Total cholesterol	↔ (workers versus referents)

[a]Hypercholesterolemia defined by Chang et al. (2007) and Luo et al. (2011) as total cholesterol ≥240 mg/dL (6.21 mmol/L).
[b]Clinically elevated triglyceride levels defined by Chang et al. (2007) as levels ≥200 mg/dL (2.26 mmol/L).
[c]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) "significant" workplace carbon disulfide exposure for ≥2 years; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, cerebral hemorrhage, central nervous system dysfunction, psychological disorder, hypertension, coronary artery disease, peripheral neuropathy, retinal aneurysm, optic neuritis, other retinal change, sensorineural hearing loss, renal function abnormality, liver function abnormality, or genital organ dysfunction.
[d]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) workplace carbon disulfide exposure; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, central nervous system dysfunction, cerebral hemorrhage, peripheral polyneuropathy, retinal micro-aneurysm, retinopathy other than micro-aneurysm, optic neuritis, sensory neural hearing loss, psychosis, or coronary artery disease.
[e]Reduced HDL-C defined by Jhun et al. (2009) as levels <40 mg/dL (1.03 mmol/L) for men or <50 mg/dL (1.3 mmol/L) for women.
[f]Elevated triglycerides defined by Jhun et al. (2009) and Luo et al. (2011) as levels ≥150 mg/dL (1.7 mmol/ L).
[g]High cholesterol defined by Kotseva and De Bacquer (2000) as >5.17 mmol/L (200 mg/dL).
[h]Dyslipoproteinemia defined by Luo et al. (2011) as total cholesterol ≥240 mg/dL or triglyceride levels ≥150 mg/dL.

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LOD = level of detection; Q = quartile; VLDL = very low-density lipoprotein; TWA = time-weighted average

Only three cohort studies evaluated potential associations between occupational exposure to carbon disulfide and clinically defined hypercholesterolemia (Table 2-9). The risk of high cholesterol (defined as serum levels ≥5.17 mmol/L [200 mg/dL]) was increased in Bulgarian viscose rayon workers exposed to carbon disulfide concentrations ranging from 3.2 to 21 ppm for at least 1 year, compared to unexposed referents (Kotseva and De Bacquer 2000). The risk was also associated with the calculated cumulative exposure index in this cohort. In contrast, Chang et al. (2007) and Luo et al. (2011) did not observe increased prevalence of hypercholesterolemia in Taiwanese or Chinese viscose rayon workers, respectively. Taiwanese workers were exposed to concentrations ranging from 1.6 to 20.1 ppm for an average of 18.8 years and Chinese workers were exposed to concentrations ranging from 1.72 to

24.9 ppm for an average of 20.7 years. However, both Chang et al. (2007) and Luo et al. (2011) defined clinically elevated cholesterol as ≥240 mg/dL. Since the mean serum cholesterol level in workers and referents in the Taiwanese and Chinese cohorts were comparable and were all <200 mg/dL, it does not appear that using the lower "cut-off" for clinically high cholesterol would alter the conclusions of Chang et al. (2007) or Luo et al. (2011). Findings from other studies evaluating potential associations between total serum cholesterol levels (without consideration of clinical adversity of findings) and occupational exposure to carbon disulfide are also mixed. Elevated total serum cholesterol levels were reported in workers from four cohorts exposed to carbon disulfide levels ranging from 0.58 to 36 ppm (Jhun et al. 2007; NIOSH 1984a; Stanosz et al. 1994b; Vanhoorne et al. 1992a). However, several additional studies (>10) in similar occupational cohorts with similar or higher exposure metrics did not observe any differences in total cholesterol levels between exposed workers and unexposed referents (Table 2-9).

In addition to total cholesterol levels, a few cohort studies specifically evaluated levels of low-density lipoprotein cholesterol (LPL-C), high-density lipoprotein cholesterol (HPL-C), and triglyceride levels. Specifically, studies were looking for potential associations with elevated LPL-C and triglyceride and/or decreased HPL-C levels, which are all risk factors for cardiovascular disease and metabolic syndrome. As observed for total cholesterol, findings are inconsistent across studies, with no clear exposure-response pattern. Three cohorts reported elevated LDL-C at concentrations ranging from 0.58 to 36 ppm (NIOSH 1984a; Stanosz et al. 1994b; Vanhoorne et al. 1992b), only two of which also observed decreased HDL-C levels (Stanosz et al. 1994b; Vanhoorne et al. 1992b). However, no evidence of elevated LDL-C and/or decreased HDL-C were observed in other cohorts exposed to concentrations ranging from 0.42 to 30 ppm (Table 2-9). A single prospective cohort study reported elevated serum triglycerides in workers exposed to carbon disulfide concentrations up to 21 ppm for 5 years compared to both pre-employment values and unexposed referent values (Chrostek-Maj and Czeczotko 1995a). None of the other 13 cohort studies identified observed an association between occupational exposure to carbon disulfide and elevated serum triglyceride levels at concentrations ranging from 0.42 to 36 ppm (Table 2-9).

In a German-language study briefly described in a secondary source (Freundt and Lieberwirth 1974b, as cited in NRC 2009), no changes in serum cholesterol were observed in four volunteers following exposure to 20 ppm for 8 hours/day for up to 4 days, compared to pre-exposure serum levels. This study is not included in the LSE table or the systematic review (Appendix C) since study results cannot be independently evaluated.

As discussed for human studies and in Section 2.5 (Cardiovascular), carbon disulfide appears to alter lipid homeostasis in animals. Acute-duration inhalation exposures to 20–400 ppm for 8 hours resulted in an increase in total lipids in the hepatic microsomal fraction of female Wistar rats, including an increase in phosphatidylcholine, phosphatidylinositol, phosphatidylserine, sphingomyelin, lysophosphatidylcholine, cholesterol, triglycerides, and free fatty acids (Freundt et al. 1974b). The alterations occurred quickly and were partially reversible after 36 hours. Exposure was also associated with a reversible inhibition in oxidative drug metabolism by rat liver microsomes, which was attributed to dysfunction of the oxidative chain due to altered lipid patterns in the microsomal membranes. Following exposure for only 6 hours, no changes in total liver lipid levels were observed in male F-344 rats at concentrations up to 600 ppm (Simmons et al. 1988). Similarly, total hepatic cholesterol levels were unchanged following exposure to 600 ppm for 6 hours/day for up to 3 days (Simmons et al. 1989). Liver slices from rats exposed to 600 ppm showed reduced liver cholesterol synthesis *ex vivo* in the study by Simmons et al. (1988) but not in the Simmons et al. (1989) study; the study authors attributed this difference to variability in the data and the larger sample size of the 1988 study (8–12/group) compared to the 1989 study (4/group).

In contrast to the acute-duration study by Simmons et al. (1988), which utilized *ex vivo* methodology, intermediate-duration studies reported increased liver cholesterol synthesis in rats using *in vivo* measurement methods following intermittent exposure to concentrations ≥74 ppm (lowest concentration tested) for 8 months (Wrońska-Nofer 1972, 1973). This finding was associated with increased circulating serum lipids. In a chronic-duration study, both total and esterified serum cholesterol were elevated in rats intermittently exposed to 321 ppm for up to 15 months (only concentration tested); co-exposure to an atherogenic diet exacerbated findings (Wrońska-Nofer et al. 1980).

Several studies support the findings by Freundt et al. (1974b) suggesting that elevated lipid content in the hepatic microsomal fraction following carbon disulfide exposure results in transient suppression of hepatic microsomal enzymes. However, the adversity of transient suppression of enzymatic activity in the absence of additional evidence of hepatotoxicity is unclear. In mice, intermittent inhalation exposure to 482 ppm for up to 23 days resulted in a marked reduction in cytochrome P-450 and cytochrome c-reductase content after 2–3 days (Järvisalo et al. 1977). However, the level returned to normal by the 23rd day of treatment. Additionally, male mice orally exposed to 3–300 mg/kg/day for 1–14 days showed rapid, reversible, dose-related suppression of hepatic microsomal enzymes (Masuda and Yasoshima 1988; Masuda et al. 1986). The following enzyme activities were decreased: hydroxylation of aniline, *O*-dealkylation of *p*-nitroanisole, 7-ethoxycoumarin and 7-ethoxyresorufin, *N*-demethylation of *N,N*-dimethylaniline, NADPH-cytochrome P-450 reductase activity, and P-450-associated peroxidase

activity. Transient reductions in hepatic microsomal enzymes have also been observed in rats following a single oral exposure to 1,263 mg/kg (Bond and DeMatteis 1969).

Mechanisms of Altered Lipid Homeostasis. In a systematic review of mechanisms of cardiotoxicity, Printemps et al. (2022) proposed that excessive oxidative damage alters cholesterol homeostasis. Data reviewed shows evidence of direct interactions between carbon disulfide and LDL cholesterol. It has also been proposed that altered LDL homeostasis is secondary to carbon disulfide-induced hypothyroidism, which would result in inflammation and oxidized LDL. However, Printemps et al. (2022) concluded that there is stronger support for the non-endocrine-dependent MOA.

Other Hepatic Endpoints. Additional hepatic data in humans are limited (Table 2-10). One retrospective study reported increasing prevalence of serum levels of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) above normal clinical ranges in viscose rayon workers with increasing estimated cumulative exposure to carbon disulfide (Kim et al. 2000). However, when prevalences were compared between exposed workers and controls, only serum ALP showed a clear increase between the two groups (Kim et al. 2000). The historical range of carbon disulfide exposure levels for workers employed at least 1 year was 0.43–6.28 ppm. Cumulative carbon disulfide exposure was associated with increased liver size in viscose rayon workers from a Belgian cohort exposed to concentrations ranging from 1 to 36 ppm for an average of 4.2 years (Vanhoorne et al. 1992b). However, no associations were observed between exposure in this cohort and elevated activities of serum AST, ALT, or ALP. Cumulative exposure was associated with elevated serum γ-glutamyl transferase (GGT) levels; however, the number of individuals with serum GGT levels above the upper reference value in humans did not differ between exposed and reference groups. Similarly, in a prospective cohort, no differences in serum bilirubin, AST, ALT, or ALP were observed in workers exposed to carbon disulfide concentrations up to 21 ppm for 5 years, compared to either pre-employment values or unexposed referent values (Chrostek-Maj and Czeczotko 1995a). In cross-sectional studies, hepatic serum enzyme levels were not associated with current exposure levels in viscose rayon workers (Drexler et al. 1995; Kuo et al. 1997; NIOSH 1984a; Takebayashi et al. 1998).

In a German-language study briefly described in a secondary source (Freundt and Lieberwirth 1974b, as cited in NRC 2009), no changes in serum hepatic enzymes or bilirubin levels were observed in four volunteers following exposure to 20 ppm for 8 hours/day for up to 4 days, compared to pre-exposure serum levels. This study is not included in the LSE table or the systematic review (Appendix C) since study results cannot be independently evaluated.

Table 2-10. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Hepatic Endpoints

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Chrostek-Maj and Czeczotko 1995a Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	AST	↔ (workers versus referents) ↔ (baseline versus follow-up)
		ALP	↔ (workers versus referents) ↔ (baseline versus follow-up)
		ALT	↔ (workers versus referents) ↔ (baseline versus follow-up)
		Bilirubin	↔ (workers versus referents) ↔ (baseline versus follow-up)
Drexler et al. 1995 Cross-sectional analysis; 247 male workers (ages 21–56 years; employed 4–220 months) from the viscose rayon industry and 222 matched male referents (Germany)	Measured current air concentrations, median (range): 4 (<0.2–65.7) ppm	AST	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 15 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Prevalence of clinical values outside the normal range:	
		AST	↔ (workers versus referents) ↑ (CEI)
		ALT	↔ (workers versus referents) ↑ (CEI)
		ALP	↑ (workers versus referents) ↑ (CEI)
		Bilirubin	↔ (workers versus referents) ↑ (CEI)
Kuo et al. 1997 Cross-sectional; 118 workers (113 males, 5 females; mean age 49.8 years; mean employment 23.7 years) from a viscose rayon factory and 44 referents (mean age 51.3 years) (Taiwan)	Measured current area sampling concentrations, range of means: 0.10–54.60 ppm Measured current personal sampling concentrations, range of means: 0.7–27.99 ppm	AST	↔ (workers versus referents)
		ALT	↔ (workers versus referents)

Table 2-10. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Hepatic Endpoints

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
NIOSH 1984a Cross-sectional; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 unexposed referents (mean age 33.9 years) (United States, Tennessee)	Current exposure level, range of means (by job): 0.58–12.64 ppm	AST	↔ (workers versus referents)
		ALT	↔ (workers versus referents)
		GGT	↔ (workers versus referents)
Takebayashi et al. 1998 Cross-sectional; cohort of 432 male exposed workers from viscose rayon factory and 402 referent workers (Japan)	Mean measured air concentrations (Omae et al. 1998): 4.48 ppm	AST	↔ (workers versus referents)
		ALT	↔ (workers versus referents)
		ALP	↔ (workers versus referents)
		GGT	↔ (workers versus referents)
		LDH	↔ (workers versus referents)
Vanhoorne et al. 1992b Retrospective cohort; 119 male workers (median age 32 years; mean employment 4.2 years) from a viscose rayon factory and 79 male referents (median age 34.3 years) (Belgium)	Personal monitoring levels, range from 17 job areas (1981–1986): 1–36 ppm CEI: Median: 57.8 ppm-years	Liver size	↑ (cumulative index)
		AST	↓ (cumulative index)
		ALT	↔
		ALP	↔
		GGT	↑ (cumulative index)
		GGT above upper reference value	↔ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; ALP = alkaline phosphatase; ALT= alanine aminotransferase; AST = aspartate aminotransferase; CEI = cumulative exposure index; GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; LOD = level of detection; Q = quartile; TWA = time-weighted average

Consistent with human data, animal data evaluating other hepatic endpoints are also limited. One older study evaluated liver function in small groups of rats or mice (n=4) following exposure to carbon disulfide (Gibson and Roberts 1972). Single 60-minute exposures to inhalation concentrations of 110 ppm in both rats and mice resulted in transient impairments in liver function, as measured by increased sulfobromophthalein sodium (BSP) retention for up to 4 hours post-exposure. BSP clearance was normal in both species by 12 hours post-exposure; however, in rats, decreased hepatic bile and blood flow was observed at this timepoint. At 230 ppm, BSP retention persisted at 12 hours post-exposure in mice; this concentration was not evaluated in rats. The same transient BSP retention was observed in mice following a single gavage administration of 1,890 mg/kg (Gibson and Roberts 1972).

In the study by Gibson and Roberts (1972) no evidence of exposure-related changes in serum ALT or ALP were observed in mice exposed to 110 ppm for 60 minutes for 1 or 5 days; serum biochemistry was not evaluated in other species. Serum ALT and AST were elevated 2–3-fold in male F-344 rats following exposure to 798.4 ppm for 90 days; similar findings in female rats were observed but were <2-fold and of unclear biological significance (Phillips 1983a). No changes in serum ALT or AST were observed in similarly exposed Sprague-Dawley rats or B6C3F1 mice at concentrations up to 798.4 ppm for 90 days (Phillips 1983b, 1983c).

In inhalation studies, no exposure-related changes in liver weight and/or histology were observed in rats exposed to 642 ppm for 4 hours (Magos and Butler 1972), rats exposed to ≤600 ppm for 6 hours/day for 1–3 days (Simmons et al. 1988, 1989), rats exposed to 225 ppm for 14 weeks (Morvai et al. 2005), or rats or mice exposed to concentrations ≤800 ppm for up to 13 weeks (Phillips 1983a, 1983b, 1983c; Sills et al. 1998b). In a gavage study in rabbits, maternal absolute and relative liver weights were elevated following exposure to ≥75 mg/kg/day on GDs 6–9 (NCTR 1984b). No changes in maternal liver weights were observed at 25 mg/kg/day. No oral studies evaluating liver histology following exposure to carbon disulfide were identified.

Several studies have also shown that exposure to carbon disulfide can cause rapid, transient reductions in various mixed-function oxidase (MFO) microsomal enzymes in the rodent liver following inhalation exposure (Järvisalo et al. 1977) or oral exposure (Bond and DeMatteis 1969; El-Masry et al. 1976; Freundt et al. 1974b; Masuda and Yasoshima 1988; Masuda et al. 1986). While this effect is not directly adverse, it could influence toxicity of future exposures (see Section 3.4).

2.10 RENAL

Data pertaining to renal effects in humans following exposure to carbon disulfide are limited. A series of occupational case reports indicate that chronic-duration exposure to carbon disulfide may cause toxic nephropathy (Yan et al. 2019). In these nine cases, subjects were occupationally exposed for an average of 13.2 years to carbon disulfide and showed abnormal urinalysis findings (proteinuria, hematuria); four subjects had chronic renal failure and five had increased serum creatinine and blood urea nitrogen (BUN). Renal biopsy showed renal arteriosclerosis and various renal lesions, including moderate to severe nodular mesangial hyperplasia, renal tubular atrophy, rental tubular interstitial fibrosis, and moderate chronic inflammatory cell infiltration. Additional occupational studies examine limited endpoints and

provide minimal, if any, evidence of renal toxicity in workers exposed to carbon disulfide (Table 2-11). Additionally, these studies have several limitations, some of which include potential concomitant exposure to other chemicals, lack of quantification of precise exposure concentrations, and/or lack of adequate statistical adjustment for relevant confounding factors.

Table 2-11. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Renal Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Chrostek-Maj and Czeczotko 1995a Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	Serum creatinine	↔ (workers versus referents) ↔ (baseline versus follow-up)
		Urinalysis parameters (unspecified)	↔ (workers versus referents) ↔ (baseline versus follow-up)
Hernberg et al. 1971 Retrospective cohort; 343 men (ages 25–64 years; employed for a median of 11 years) from a viscose rayon factory and 343 matched unexposed referents (ages 25–64 years) (Finland)	Historical air concentrations: Prior to 1950: 20–30 ppm After 1950s: <20 ppm Geometric mean air concentration in different departments: 1967: 4–18 ppm	Plasma creatinine	↑ (workers versus referents) ↔ (duration of exposure)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Prevalence of clinical values outside the normal range:	
		Serum creatinine	↔ (workers versus referents) ↔ (CEI)
		Serum BUN	↔ (workers versus referents) ↔ (CEI)
		Urine protein	↑ (workers versus referents) ↑ (CEI)

Table 2-11. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Renal Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Kuo et al. 1997 Cross-sectional; 118 workers (113 males, 5 females; mean age 49.8 years; mean employment 23.7 years) from a viscose rayon factory and 44 referents (mean age 51.3 years) (Taiwan)	Measured current area sampling concentrations, range of means: 0.10–54.60 ppm Measured current personal sampling concentrations, range of means: 0.7–27.99 ppm	Serum creatinine	↔ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; BUN = blood urea nitrogen; CEI = cumulative exposure index; LOD = level of detection; Q = quartile; TWA = time-weighted average

In a prospective cohort study, serum creatinine and urinalysis parameters did not differ in 114 workers employed for 5 years at a plant producing carbon disulfide, compared to pre-employment values or 62 unexposed referents (Chrostek-Maj and Czeczotko 1995a). Mean measured air levels during that period ranged from below the level of detection to 21 ppm. In a retrospective study of 343 viscose rayon workers exposed to carbon disulfide at a geometric mean exposure level of 4–18 ppm for a median of 11 years, plasma creatinine levels were slightly elevated compared to matched controls (Hernberg et al. 1971). Duration of employment was not associated with plasma creatinine levels. In a larger retrospective cohort of viscose rayon workers, no differences were observed in the prevalence of serum creatinine or BUN values outside the normal clinical range between 1,237 workers and 315 unexposed referents; however, the prevalence of elevated urine protein levels was increased in workers compared to referents (Kim et al. 2000). Increased prevalence of elevated urine protein levels was also associated with the calculated cumulative exposure index (number of years worked × exposure levels). In a cross-sectional study, serum creatinine was not elevated in 118 viscose rayon workers exposed to 0.1–54.6 ppm, compared to 44 unexposed referents (Kuo et al. 1997).

Data pertaining to potential renal effects in animals following exposure to carbon disulfide are limited. No exposure-related changes in kidney weight and/or histology were observed following intermittent inhalation exposure to carbon disulfide in rats at concentrations up to 225 ppm for 14 weeks (Morvai et al. 2005) or up to 800 ppm for up to 13 weeks (Phillips 1983a, 1983b; Sills et al. 1998b). In mice, nephropathy and renal tubular degeneration were observed following intermittent inhalation exposure to 798.4 ppm for 90 days (Phillips 1983c).

2.11 DERMAL

Severe blisters that progressed to hemorrhagic blisters covered by a thin membrane observed in viscose rayon workers have been attributed to dermal exposure to carbon disulfide. These blisters appeared on the fingers in spite of wearing rubber gloves (Hueper 1936). Blisters, ulceration, and inflammation were observed on rabbit ears following exposure to carbon disulfide for up to 4 days under conditions similar to those experienced by workers, both with and without protective rubber covering (Hueper 1936). In mice, a 10-minute dermal exposure to 20% solution of carbon disulfide resulted in skin necrosis (Chou et al. 2005).

2.12 OCULAR

The ocular system, specifically the vascular system in the retina, is a sensitive target of carbon disulfide toxicity in humans following inhalation exposure to carbon disulfide. Similar vascular effects were not observed in exposed animals, although ocular irritation occurred at high concentrations. Based upon systematic review (Appendix C), ophthalmological effects associated with systemic exposure to carbon disulfide are a presumed target of carbon disulfide toxicity in humans following inhalation exposure based on moderate evidence in humans. It is noted that eye irritation effects attributable to direct ocular contact with carbon disulfide vapor were excluded from systematic review, as these are classified as dermal exposure (Table 2-3). Additionally, effects related to visual function are discussed and evaluated in Section 2.15 (Neurological).

Numerous occupational cohort studies, primarily in the viscose rayon industry, evaluate potential associations between exposure to carbon disulfide and ophthalmological changes in the eye (Table 2-12). In general, findings from these studies should be interpreted with caution due to the lack of control for any confounding factors in approximately 80% of all available studies, such as known risk factors for vascular disease, which could contribute to the predominant finding of retinal microaneurysm (e.g., smoking, alcohol intake). More details on the quality and confidence in available epidemiological studies evaluating ophthalmological effects can be found in Appendix C. As discussed in Appendix B, due to the availability of numerous cohort studies evaluating the potential association between ophthalmological changes and exposure to carbon disulfide, cross-sectional, case series, and case report studies of these endpoints are not discussed below and did not meet inclusion criteria for the systematic review.

Increased prevalence of retinal microaneurysm were observed in several retrospective cohorts of viscose rayon workers (Table 2-12), including workers from a Korean cohort exposed to mean concentrations of 0.43–6.28 ppm for 1–≥15 years (Kim et al. 2000), an American cohort exposed to 0.58–33.5 ppm for a mean of 12.6 years (calculated cumulative exposure of 1,249.9 ppm-months) (NIOSH 1984a), a Belgian cohort exposed to ≥10 ppm (Vanhoorne et al. 1996), and Japanese cohorts exposed to 3–12 or >20 ppm (Sugimoto et al. 1976, 1977). Studies that stratified by exposure (Sugimoto et al. 1976; Vanhoorne et al. 1996) showed that both the prevalence and/or severity of microaneurysms increased with increased exposure, and Sugimoto et al. (1976) also showed that severity was associated with duration of exposure. The study in the American cohort also reported increased prevalence of retinal hemorrhages (NIOSH 1984a).

Table 2-12. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Ophthalmological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Abnormal ophthalmic exam	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Retinal microaneurysm	↑ (workers versus referents) ↑ (CEI)

Table 2-12. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Ophthalmological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Retinal microaneurysms	↑ (workers versus referents) ↑ (CEI)
		Retinal hemorrhages	↑ (workers versus referents) ↑ (CEI)
Raitta and Tolonen 1975 Longitudinal cohort; 38 male workers (mean age 51 years; exposed a mean of 20 years, including 20 currently exposed and 18 formerly exposed) and 40 male unexposed referents (mean age 49 years) (Finland) *Subset of workers from Raitta et al. (1974)*	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1972: 4–30 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Interocular pressure	
		Abnormal oculo-sphygmography results (altered hemodynamics)	↑ (workers versus referents) ↑ (current versus referents) ↔ (former versus referents)
Sugimoto et al. 1976 Retrospective cohort, 289 viscose rayon workers (mean age 42.1 years; mean employment duration 10.8 years) and 49 unexposed referents (mean age 43.3 years) (Japan)	Exposure level groups (based on job category): High: 20 ppm Low: <20 ppm	Retinal microaneurysm	↑ (workers versus referents) ↑ (high versus low) ↑ (exposure duration)

Table 2-12. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Ophthalmological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Sugimoto et al. 1977 Retrospective cohort, 419 viscose rayon workers (mean age 41.1 years; mean employment duration 17.0 years) and 391 unexposed referents (mean age 42.1 years) (Japan)	Measured air concentrations, TWA means 1966–1972: 3–12 ppm *Exposure details from Tolonen et al. (1976)*	Retinal microaneurysm	↑ (workers versus referents)
Sugimoto et al. 1977 Retrospective cohort, 188 viscose rayon workers (mean age 45.2 years; mean employment duration 8.8 years) and 76 unexposed referents (mean age 40.9 years) (Finland) *Subset of workers from larger Finnish cohort (Hernberg et al. 1970)*	Historical air concentrations of carbon disulfide and hydrogen sulfide (Tolonen et al. 1976): 1950s: 20–60 ppm 1960s: 10–30 ppm 1970s: 5–10 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Retinal microaneurysm	↔ (workers versus referents)
Sugimoto et al. 1978 Retrospective cohort; 420 rayon filament workers (mean age 41.3 years; mean employment 17.0 years) and 390 unexposed referents (mean age 42.1 years) (Japan)	Historical TWA exposure levels, ranges: Before 1955: 15–30 ppm After 1955: 5–15 ppm Worker “Index of Exposure Dosages” calculated based on TWA levels and work history: Mean: 162.5	Retinal microaneurysm	↑ (workers versus referents)

Table 2-12. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Ophthalmological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Vanhoorne et al. 1996 Retrospective cohort; 123 workers (median age 33.5 years) from a viscose rayon factory and 67 unexposed referents (median age 35.2 years) (Belgium)	Historical range of air concentrations: 1–36.0 ppm Exposure categories (below and above TLV [at the time]): Low: <10 ppm High: ≥10 ppm CEI: 71.9 ppm-years	Retinal microaneurysm	↑ (high versus referents) ↔ (low versus referents) ↑ (CEI)
		Retinal bleeding	↔ workers versus referents)
		Intraocular pressure	↑ (high versus referents) ↔ (low versus referents) ↔ (CEI)

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; Q = quartile; TLV = threshold limit value; TWA = time-weighted average

No ophthalmological changes were observed in a small cohort of Italian viscose rayon workers exposed to mean concentrations ranging from 3.2 to 8.0 ppm (Cirla and Graziano 1981). More notably, occupational exposure was not associated with retinal microaneurysm prevalence in various subcohorts from a longitudinal study of Finnish viscose rayon workers (Raitta et al. 1974; Sugimoto et al. 1977). Workers had been exposed to wide range of carbon disulfide exposure levels (5–60 ppm) for an average of 15–17 years of, with peaks >100 ppm. Despite a lack of clear changes in ophthalmological examinations, oculosphygmography revealed altered hemodynamics in a small group (n=20) of currently exposed workers from this group, compared to referents, suggesting mild effects on ocular capillaries (Raitta and Tolonen 1975). Effects were not attributable to alterations in blood pressure or interocular pressure, as these did not differ from the referent group. In a small group (n=18) of formerly exposed workers from this cohort (mean duration of 4 years since cessation of employment), no differences in ocular hemodynamics were observed.

No exposure-related changes to the eye were observed via ophthalmological examination (slit lamp bio-microscopy) or histological examination (light microscopy) in rats or mice following intermittent inhalation exposure to carbon disulfide at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c). However, clinical signs of eye irritation were reported in female rats exposed to 502 ppm in air for 6 hours/day up to 49 days; these findings were attributed to direct contact with carbon disulfide vapor (Holson 1992).

Mechanisms of Ophthalmological Effects. It has been proposed that carbon disulfide releases normal inhibition of elastase, resulting in increased elasticity of vascular walls, which in turn increases the susceptibility for aneurysms (Huang et al. 2004). Qingfen et al. (1999) proposed that lipid peroxidation may contribute to retinal damage associated with carbon disulfide exposure.

2.13 ENDOCRINE

A limited number of human studies have evaluated potential associations between endocrine endpoints and carbon disulfide exposure, primarily thyroid hormone levels. Available studies include two well-conducted occupational cohort studies (NIOSH 1984a; Takebayashi et al. 1998, 2003) and a few additional occupational studies in viscose rayon or unspecified artificial fiber workers with several limitations (Table 2-13). These limitations, including limited details on exposure measurement timing and methodology, potential concomitant exposure to other chemicals, small group sizes, and/or lack of adequate statistical adjustment for relevant confounding factors, preclude meaningful interpretation of results. Potential associations between carbon disulfide exposure and diabetes are discussed with metabolic syndrome in Section 2.18 (Other Noncancer).

Table 2-13. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Endocrine Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Cirla et al. 1978 Retrospective cohort; 254 workers from a viscose rayon factory and 54 unexposed referents; exposed 2–31 years (Italy)	Exposure level based on exposure categories (ppm): Very light/light: <19 Moderate: 19–39* Heavy: 39–77* Heavy in past: 58–77** Heavy, then suspended: 39–77, then transferred to “clean” department *Last 3 years <19 ppm **Last 12 years <19 ppm	Clinical hypothyroidism (possible mild or confirmed)	↑ (very light/light versus referent) ↑ (heavy versus referent) ↔ (heavy in past versus referent)
		Serum T4	↓ (very light/light versus referent) ↓ (heavy versus referent) ↓ (heavy in past versus referent)
		Serum Free-T4	↔ (workers versus referents)
		Serum T3	↔ (workers versus referents)

Table 2-13. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Endocrine Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
El-Sobkey et al. 1979 Cross-sectional; 30 workers from a viscose rayon factory and 13 unexposed referents; 17 workers exposed <20 years and 13 workers exposed >20 years (Egypt)	Measured air concentrations, range: 0.0083–0.02 ppm	Serum T4	↓ (workers versus referents) ↓ (<20 years versus referents) ↓ (>20 years versus referents)
Lancranjan et al. 1972 Cross-sectional; 109 workers from two artificial fiber factories and 40 unexposed referents; Factory 1: 89 workers aged 18–48 years, employed 7 months–3.3 years Factory 2: 20 workers aged 35–51 years, employed 12–31 years (Hungary)	Reported air concentrations, range: Factory 1: 72–96 ppm Factory 2: 19–29 ppm	Thyroid function (uptake of radioiodine)	↔ (workers versus referents)
		Serum thyroid hormone levels (unspecified)	↔ (workers versus referents)
NIOSH 1984a Retrospective cohort with a cross-sectional analysis; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Exposure levels, range of means (by job), 1957–1979: Historical: 0.58–33.5 ppm Current: 0.58–12.64 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Serum T4	↔ (current versus referents) ↔ (CEI)
		Serum T3	↓ (current versus referents) ↔ (CEI)
		Serum TSH	↔ (current versus referents) ↔ (CEI)

Table 2-13. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Endocrine Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Stanosz et al. 1994a Cross-sectional; 90 females (mean age 39.7 years; employed 0.5–>20 years) from the viscose rayon industry and 50 unexposed female referents (mean age 40.1 years) (Poland)	Measured air concentrations, range: 5.01–7.01 ppm	Diurnal urinary excretion of adrenaline	↓ (workers versus referents)
Takebayashi et al. 1998 Cross-sectional; Japanese Rayon Workers' Health Study Group; 432 males from 11 viscose rayon factories, including 309 spinning and refining workers (mean age 34.9 years, mean employment 13.8 years) and 123 other exposed workers (mean age 36.9 years, mean employment 12.6 years), and 402 male referents (mean age not reported) (Japan)	Mean measured air concentrations (Omae et al. 1998): 4.48 ppm	Insulin level (non-fasting)	↓ (workers versus referents)
		Serum TSH, T3, T4, TBG	↔ (workers versus referents)
		Serum ACTH	↔ (workers versus referents)
Takebayashi et al. 2003 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 392 males from 11 viscose rayon factories, including 259 current employees (mean age 35.6 years, mean employment 19.3 years) and 133 former employees (mean age 36.8 years, mean employment 15.6 years, retired an average of 4 years), and 352 male referents (mean age 35.9 years) (Japan)	Geometric mean of the mean air concentrations, measured twice yearly 1993–1998: 5.02 ppm	Fasting insulin level	↔ (current versus referents) ↔ (former versus referents)
		Serum T4	↓ (current versus referents) ↔ (former versus referents)
		Serum T3	↔ (current versus referents) ↔ (former versus referents)
		Serum TSH	↔ (current versus referents) ↔ (former versus referents)
		Serum TBG	↔ (current versus referents) ↔ (former versus referents)
		Serum ACTH	↔ (current versus referents) ↔ (former versus referents)

Table 2-13. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Endocrine Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Vanhoorne et al. 1993 Retrospective cohort; 117 males (median age 32.0 years; employed >1 year) from viscose rayon industry and 66 male referents (median age 34.8 years) (Belgium)	Measured current air concentration, range: 1–36 ppm CEI (ppm-years): Median: 27.8 Mean: 122.9	Serum T4	↔ (workers versus referents) ↔ (CEI)
Wägar et al. 1981 Retrospective cohort; 15 males from viscose rayon plant (mean age 50.2 years; employed 10–36 years) and 16 matched referents (Finland)	Historical air concentrations, ranges: 1940s: "very high" 1950s: 20–40 ppm 1960s: 10–30 ppm 1970s: <10 ppm	Serum cortisol, T3, T4, TSH, TBG	↔ (workers versus referents)
		TRH simulation test	↔ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; ACTH = adrenocorticotropic hormone; T3 = triiodothyronine; T4 = thyroxine; TBG = thyroxine binding globulin; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone

Takebayashi et al. (1998, 2003) reported various endocrine endpoints at baseline and a 6-year follow-up examination in the Japanese Rayon Worker's Heath Study Group cohort. In this cohort, markers of endocrine function were measured in male viscose rayon workers (432 at baseline in 1992–1993, 392 at the 6-year follow-up in 1998–1999) and unexposed referents (402 at baseline, 352 at follow-up) from 11 factories in Japan. Mean carbon disulfide levels were 4.48 ppm at baseline and 5.02 ppm during the 6-year follow-up period. At baseline, no changes in serum thyroid hormone levels were observed in workers, compared to referents. At follow-up, current workers (exposed on average for 19.3 years) showed reduced serum thyroxine (T4) levels compared to referents; this association held after adjustment for confounders. Serum T4 levels were comparable to referents in formerly exposed workers, who were exposed on average for 15.6 years, but unexposed on average for the past 4 years. No changes in serum triiodothyronine (T3), thyroid stimulating hormone (TSH), or thyroxine binding globulin (TBG) were observed at follow-up. Takebayashi et al. (1998, 2003) also evaluated markers of pancreatic function. While non-fasting serum insulin levels were decreased in workers at baseline, compared to referents, no associations were observed at follow-up in fasting insulin levels (no changes in non-fasting or fasting serum glucose were observed at baseline or follow-up, respectively; see Section 2.18). Additionally, no

changes in adrenocorticotrophic hormone were observed at either baseline or follow-up. This was a well-conducted study with a longitudinal design with a high follow-up rate, adequate subject number, both external and internal measures of exposure, and adequate statistical analyses that accounted for key confounders.

NIOSH (1984a) conducted both a retrospective and cross-sectional analysis of thyroid hormone levels in a cohort study of 146 exposed workers and 233 referents. In this study, current exposure levels, which ranged from a mean level of 0.58 to 12.64 ppm, were inversely associated with serum T3 levels; no associations were observed with serum T4 or TSH levels. When cumulative exposure analyses were conducted, accounting for key confounders, no associations were observed between carbon disulfide exposure and serum thyroid hormone levels. The calculated mean cumulative exposure level was 1,249.9 ppm-months; the mean duration of employment was 12.6 years.

Findings pertaining to thyroid effects in the remaining occupational studies with major limitations are mixed. Serum T4 levels were decreased in 30 workers exposed to 0.0083–0.02 ppm, compared to 13 unexposed referents (El-Sobkey et al. 1979). Cirla et al. (1978) reported decreased serum T4 levels in 87 workers exposed to <19 ppm and 127 workers exposed to 39–77 ppm, compared to 54 unexposed referents; no data were provided for the 23 workers exposed to 19–36 ppm. Of the exposed workers, a small percentage (5–8%) showed decreases consistent with possible mild hypothyroidism, and only one worker exposed to 39–77 ppm had "true" hypothyroidism. No associations were observed between exposure and serum free-T4 or T3 levels. In other studies, no changes in serum thyroid hormone levels or tests of thyroid function were observed in 15 workers exposed to 10–40 ppm, compared to 16 matched referents (Wägar et al. 1981); 109 exposed to 19–96 ppm, compared to 40 unexposed referents (Lancranjan et al. 1972); or 117 workers exposed to 1–36 ppm, compared to 66 matched referents (Vanhoorne et al. 1993).

Additional findings from these occupational studies are limited to decreased diurnal urinary excretion of adrenaline in 90 female workers exposed to 5.01–7.01 ppm, compared to 50 unexposed referents (Stanosz et al. 1994a) and no difference in serum cortisol levels between 15 workers exposed to 10–39 ppm, compared to 16 matched referents (Wägar et al. 1981).

Data pertaining to potential endocrine effects in animals following exposure to carbon disulfide are very limited. No exposure-related histopathological changes were observed in endocrine organs (e.g., thyroid,

adrenal gland, pituitary gland, pancreas) in rats or mice following intermittent inhalation exposure to carbon disulfide at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c).

Mechanisms of Altered Thyroid Homeostasis. While evidence for thyroid effects following exposure to carbon disulfide is mixed, a review by Printemps et al. (2022) proposed a mechanism in which the metabolite thiourea inhibits thyroid peroxidase, which is a key enzyme required for thyroid hormone synthesis. This proposed MOA is based on i*n vivo* rat data and *in vitro Escherichia coli* data. However, it is unknown if exposure to carbon disulfide would result in metabolic production of thiourea in sufficient quantities to result in thyroid peroxidase inhibition.

Taken together, there is limited data from a well-conducted longitudinal study in humans suggesting that occupational exposure to carbon disulfide may be associated with perturbations in thyroid hormone homeostasis, and mechanistic data provide a plausible mechanism of action. However, most available data in humans provide conflicting findings from occupational studies with major limitations, and no available animal data evaluate thyroid hormone levels.

2.14 IMMUNOLOGICAL

No studies evaluating immunological endpoints in humans following exposure to carbon disulfide were identified.

Data pertaining to potential immune effects in animals following exposure to carbon disulfide are very limited. In inhalation studies, no exposure-related histopathological changes were observed in immune organs (e.g., thymus, spleen, bone marrow) in rats or mice following intermittent exposure to carbon disulfide at concentrations up to 798.4 ppm for 90 days (Phillips 1983a, 1983b, 1983c). In the only oral study evaluating immune system endpoints, no exposure-related changes were observed in thymus or spleen weight, thymus cellularity, or natural killer cell activity in female mice following a 5-day exposure to carbon disulfide at gavage doses up to 1,102 mg/kg/day (Keil et al. 1996).

2.15 NEUROLOGICAL

The neurological system is a sensitive target of carbon disulfide toxicity in both humans and animals following inhalation exposure. Limited data from oral studies in animals are consistent with the inhalation database. Based upon systematic review (Appendix C), the neurological system is a known

target of carbon disulfide toxicity in humans following inhalation exposure based on a high level of evidence in humans and laboratory animals. For oral exposure, the neurological system is a presumed target of carbon disulfide toxicity in humans based on no data in humans and a high level of evidence in laboratory animals.

In humans, acute-duration exposure to high concentrations of carbon disulfide can result in muscle weakness, fainting, and loss of consciousness. These effects were observed in 36–39% of 123 persons exposed to carbon disulfide following an accidental release of carbon disulfide, hydrogen sulfide, and sulfuric acid from a viscose rayon factory in India (Kamat 1994). Giddiness and headache were reported in 77–78% of exposed individuals, with additional effects including blurred vision, weakness, tremor, unsteadiness, and irritability in 8–29% of individuals. Exposure concentrations were not stated. In a study designed to evaluate toxicokinetics in human volunteers, "occasional slight headache" was reported in an unknown percentage of subjects exposed to 17–51 ppm for 1–4 hours (Teisinger and Soucek 1949). Additional information on acute neurological effects comes from outbreaks following two industrial accidents at a Polish viscose rayon factory in which 600 workers were exposed to very high levels of carbon disulfide (326–451 ppm) and hydrogen sulfide (83–246 ppm) in 1943 (Paluch 1948). Adverse effects reported included symptoms consistent with encephalopathy (severe headache, paresthesia, exhaustion, neurosis, depression) in 30% of workers, marked polyneuritis in 52% of workers, and mild cases of psychosis (agitation, hallucinations, hyperirritability, depression, somnolence) in 18% of workers.

Similar to the Polish industrial accidents, acute attacks of psychosis have been reported in several cases of highly exposed workers to carbon disulfide in viscose rayon manufacturing, particularly in the churn and spinning departments prior to 1940 (DOL 1940; Gordy and Trumper 1938, 1940). Occurrence was frequent enough to be described as "viscose insanity" in the United States, with symptoms including dramatic changes in personality, violent and destructive behaviors, excitement, confusion, incoherence, and hallucinations. Symptoms may last for days after "poisoning" and may reoccur with continued exposure. Some cases presented as a slower onset with less severe psychosis symptoms with continued exposure rather than a sudden acute attack following acute high exposure, and developed additional psychological symptoms including depression, anxiety, and insomnia. Exposure levels were not reported for these case studies, but cases were documented prior to 1940 when exposure levels in viscose rayon factories were often >10 ppm (Foa et al. 1976; NIOSH 1984a; Raitta et al. 1974, 1981; Seppalainen and Tolonen 1974). However, in a review of 100 cases of "carbon disulfide intoxication" in Italian yarn and staple fiber factory workers between 1940 and 1942, Vigliani (1950) reported that cases associated with

acute-duration exposure (<4 hours) were rare, and only observed at carbon disulfide levels of 160–800 ppm. Exposure to 160–800 or 110–160 ppm was associated with "chronic intoxication" within a few months or 1 year, respectively. Chronic-duration exposure to concentrations of 60–110 ppm resulted in only sporadic cases of "mild intoxication," and carbon disulfide intoxication was never observed at concentrations <50 ppm (Vigliani 1950). Of the 100 cases of intoxication, only 6 showed psychosis; however, Vigliani (1950) did not indicate which exposure levels and durations were associated with cases of psychosis.

While the toxicokinetic study and occupational case reports discussed above provide evidence of neurological effects following acute-duration exposure to carbon disulfide, none were included in the LSE table or Appendix C (Systematic Review) due to lack of exposure information, lack of incidence data, and/or co-exposure to high levels of other compounds.

Most information available on neurotoxic effects of chronic-duration exposure to carbon disulfide in humans comes from occupational epidemiology studies. These studies, primarily in the viscose rayon industry, evaluate potential associations between exposure to carbon disulfide and potential neurological effects. The most well-studied endpoint in humans is peripheral neuropathy; additional evaluations include subjective complaints, neuropsychiatric and neuropsychological evaluations, color vision, audiometry, and brain imaging studies. In general, findings from these studies should be interpreted carefully due to the lack of control for one or more key confounding factors in approximately 85% of all available studies, such as known risk factors for neurological impairments (e.g., alcohol intake, diabetes, etc.) or factors shown to impact neurological measures (e.g., BMI for nerve conduction velocity) (Buschbacher 1998; Cinar et al. 2013). More details on the quality and confidence in available epidemiological studies evaluating neurological effects can be found in Appendix C. As discussed in Appendix B, due to the availability of numerous cohort studies evaluating the potential association between neurological effects and chronic-duration exposure to carbon disulfide, cross-sectional, case series, and case report studies of these endpoints did not meet inclusion criteria for the systematic review. However, a few case series and industrial hygiene reports from highly exposed workers are discussed below to demonstrate potential progression of adverse neurological effects with increasing exposure concentrations.

Peripheral Neuropathy: As shown in Table 2-14, a consistent finding following chronic-duration occupational exposure to carbon disulfide is impaired peripheral nerve conduction in motor and/or sensory nerve fibers. These studies collectively show that, compared to unexposed referent groups,

workers are unlikely to have impaired nerve conduction at concentrations below approximately 3 ppm, may have impairments between 4 and 8 ppm, and consistently show impairments at >8 ppm (Table 2-14). 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. 1995). However, others did not observe increased subjective symptoms in workers at similar exposure levels (Johnson et al. 1983). Vanhoorne et al. (1995), which only reported exposure as a range from 1 to 36 ppm, also reported impaired electromyograph (EMG) findings in the legs. However, no abnormalities in reflexes or position, vibration, tactile, or pain sensation were noted upon clinical examination.

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Peripheral Neuropathy

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Peroneal nerve MCV	↔ (workers versus referents)
		Peripheral neuropathy (diagnosed by EMG or clinical diagnosis)	↔ (workers versus referents)
		Subjective complaints (weakness, pain or numbness in extremities)	↔ (workers versus referents)
Godderis et al. 2006 Retrospective cohort, 85 workers, including 60 low exposed and 25 high exposed (mean age 37.2 years, mean employment 10.5 years) from a viscose rayon factory and 66 unexposed referents (mean age 41.2 years) (Belgium)	Measured air concentrations, yearly geometric mean: All: 4.91 ppm Low (<10 ppm): 2.9 ppm High (>10 ppm): 19.0 ppm CEI, geometric mean: Low: 19.1 ppm-years High: 239.8 ppm-years	Peroneal nerve MCV	↔ (workers versus referents)
		Sural nerve SCV	↓ (low or high versus referents)
		Sural nerve SNAP	↓ (low or high versus referents)
		Diagnosis of polyneuropathy	↓ (low or high versus referents)
		Abnormal sensation in one or more sensory functions (temperature, vibration, touch, pinprick, position)	↓ (low or high versus referents)

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Peripheral Neuropathy

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
		Motor coordination (finger tapping)	↓ (low or high versus referents)
		Position tremor	↑ (low exposure group versus referents)
		Subjective sensory motor complaints	↑ (high exposure group versus referents)
Hirata et al. 1996 Retrospective cohort; 46 workers (mean age 43.9 years, exposed for a mean of 11.4 years) from a viscose rayon fiber factory, including 24 current workers and 22 former workers (mean of 6.28 years post-employment), and 26 age-matched referents (Japan)	Measured historical concentrations, mean 8-hour TWA: 4.76 ppm *Exposure indices for subjects in this study were not calculated (previous sampling performed on different subject group 5 years prior to study).*	Ulnar nerve MCV	↔ (workers versus referents)
		Peroneal nerve MCV	↓ (current versus referents) ↔ (previous versus referents)
		Sural nerve SCV	↓ (current versus referents) ↔ (previous versus referents)
Johnson et al. 1983; NIOSH 1984a Retrospective cohort; 145 male workers (mean age 38.5 years; mean employment of 12.1 years) from a viscose rayon plant and 212 referents from an artificial fiber plant (mean age 33.9 years) (United States, Tennessee)	Current measured air concentrations, 8-hour TWA mean (median) in ppm: Workers: 7.3 Low: 1.2 (1.0) Mid: 5.1 (4.1) High: 12.6 (7.6) Referent group: 0.2 CEI (ppm-months) Low: 500–1,000 Mid: 1,000–1,500 High: ≥1,500	Ulnar nerve MCV	↔ (workers versus referents) ↔ (high versus referents) ↔ (CEI)
		Peroneal nerve MCV	↓ (workers versus referents) ↔ (low/mid versus referents) ↓ (high versus referents) ↓ (CEI)
		Sural nerve SCV	↓ (workers versus referents) ↔ (high versus referents) ↔ (CEI)
		Subjective complaints of peripheral neuropathy (weakness, hand trembling, difficulty walking, numbness in extremities, leg pain)	↔ (workers versus referents)

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Peripheral Neuropathy

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Abnormal NCV	↑ (workers versus referents) ↑ (CEI)
		Subjective neurological symptoms (paresthesia, numbness, walking disturbance)	↑ (workers versus referents) ↑ (CEI)
Reinhardt et al. 1997a Retrospective cohort; 222 exposed workers (median age 35 years; median employment 6 years) from viscose rayon industry and 191 unexposed referents (mean age 33 years) (Germany)	Measured current air concentrations, median (range): 4.02 (0.2–30) ppm *CEI levels were not reported.*	Motor nerve function (MCV; MAP)	↔ (workers versus referents)
		Sensory nerve function (SMS EP, thermal thresholds)	↔ (workers versus referents)
		Clinical neurological examination	↔ (workers versus referents)
Ruijten et al. 1990 Retrospective cohort; 45 workers (mean age 49 years; mean employment 20 years) from a viscose rayon plant and 37 unexposed referents (mean age 48 years) (The Netherlands)	Measured air concentrations, mean personal air measurements over past 3 years: Supervisors: 1 ppm Spinning: 6 ppm Bleaching: 12 ppm Historical air concentrations[a], mean: Zone 1: 8 ppm Zone 2: 17 ppm CEI: 165 ppm-years	Peroneal nerve MCV CVSF	 ↔ (workers versus referents) ↔ (CEI) ↓ (workers versus referents) ↓ (CEI)
		Sural nerve SCV	↔ (workers versus referents) ↔ (CEI)
Ruijten et al. 1993 Retrospective cohort; 44 workers (mean age 51.9 years; mean employment 26.1 years) from a viscose rayon plant and 31 unexposed referents (mean age 51.9 years) (The Netherlands)	CEI: 213 ppm-years *Follow-up of Ruijten et al. (1990)*	Peroneal nerve MCV	↓ (CEI)
		Sural nerve SCV	↔ (CEI)
		Median nerve MCV SCV	 ↔ (CEI) ↓ (CEI)
		Ulnar nerve MCV SCV	 ↔ (CEI) ↓ (CEI)

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Peripheral Neuropathy

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Seppalainen and Tolonen 1974 Retrospective cohort; 118 male workers (mean age 50 years; median employment 15 years) from a viscose rayon plant and 100 male referents (mean age 48 years); examined in 1967 and 1972 (Finland)	Historical air concentrations, range 1960s: 10–30 ppm Pre-1960: 20–40 ppm *Exposure concentrations reported by Seppalainen et al. (1972)*	Motor nerve function (MCV of median, ulnar, deep peroneal, and posterior tibial nerve)	↓ (workers versus referents)
		Motor nerve function (CVSF of ulnar and deep peroneal nerves)	↓ (workers versus referents)
		Sensory nerve function (SCV of the median and ulnar nerves)	↔ (workers versus referents)
Vanhoorne et al. 1995 Retrospective cohort; 111 workers (mean age 34.6 years) at viscose rayon factory and 74 non-exposed referents (mean age 33.7 years) (Belgium)	Historical range of measured 8-hour TWA air concentrations (17 jobs): 1–36.0 ppm CEI (ppm-years): Q1: 0 Q2: 0.3–96.3 Q3: 96.6–193 Q4: >193	Self-reported polyneuropathy in legs (pain, tingling, insensitive spots, fatigue, cold feet, cold spots in legs or feet)	↑ (CEI)
		Abnormal clinical examination of legs (reflexes; position, vibration, tactile, pain sensation)	↔ (workers versus referents)
		Abnormal electro-myographic findings in extensor digitorum brevis (slow recruitment pattern)	↑ (CEI)
		Fibular nerve MCV	↓ (CEI)

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Peripheral Neuropathy

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Yoshioka et al. 2017 Longitudinal cohort; 347 exposed male workers (mean age 36.1 years, mean work duration of 22.1 years) from viscose rayon factory (including 121 workers who ceased employment/exposure during the 6-year follow-up period) and 337 referent males (mean age 36.2 years); 6-year follow-up (baseline: 1992–1993 and follow-up: 1998–1999) (Japan)	Measured air concentrations during study period, mean (range) in ppm: T1: 2.84 (0.8–4.6) T2: 5.64 (4.7–6.6) T3: 9.35 (6.6–16.0) Mean (exposed): 5.96 Mean (ex-exposed) 3.93	Median nerve MCV	↔ (exposed versus referents) ↔ (ex-exposed versus referents)
		Median nerve SCV	↓ (T3 versus referents)

[a]Historical air concentrations were provided for the "old" bleaching department; no further details were provided (Ruijten et al. 1990).

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; CVSF = conduction velocity of slower motor fibers; EMG = electromyography; MAP = muscle action potentials; MCV = motor conduction velocity; NCV = nerve conduction velocity; Q = quartile; SCV = sensory conduction velocity; SMS EP = somatosensory evoked potential; SNAP = sensory nerve action potential; T = tertile; TWA = time-weighted average

The most informative studies regarding peripheral neuropathy stratify workers into different exposure groups for statistical analysis, providing dose-response information (Godderis et al. 2006; Johnson et al. 1983; Yoshioka et al. 2017). In a retrospective study, Johnson et al. (1983) showed that an increase in the calculated cumulative exposure index (ppm-months) was associated with a decrease in the peroneal nerve motor nerve conduction velocity in viscose rayon workers exposed for an average of 12.1 years; additional details from this study are also available in an unpublished report by NIOSH (1984a). When stratified by current air concentration levels, only workers in the high exposure group (median of 7.6 ppm) showed nerve conduction values below the referent group. Workers in the low (median of 1.0 ppm) and middle (median of 4.1 ppm) exposure groups were comparable to the referent group. Similarly, in a longitudinal study in viscose rayon workers, Yoshioka et al. (2017) observed exposure-related decrements in median nerve sensory conduction velocity in workers from the highest exposure tertile (mean 9.35 ppm) over a 6-year period, compared to referents. Differences observed in workers from the middle tertile (mean 5.64 ppm) were no longer apparent once adjusted for key confounders, and workers from the lowest tertile (mean 2.84 ppm) were comparable to referent values with and without

adjustments. Workers had been exposed, on average, for 22.1 years in this cohort. While Godderis et al. (2006) observed peripheral nerve impairments in both low-exposure (<10 ppm) and high-exposure (>10 ppm) groups of workers, findings showed clear exposure-related associations for impaired sensory nerve conduction velocity, polyneuropathy, impaired sensation, and prevalence of subjective sensory motor complaints.

In the study by Johnson et al. (1983), the small decreases in conduction velocities were within normal clinical ranges and were not associated with subjective symptoms of neuropathy, suggesting a mild presymptomatic nerve impairment. Consistent with this conclusion, a lack of impaired nerve conduction in previously exposed workers in the longitudinal study (workers who did not continue employment throughout the entire 6-year follow-up period) suggests that findings are reversible (Yoshioka et al. 2017). However, studies evaluating higher exposure levels in workers exposed prior to 1960 (20–40 ppm) reported that removal from the exposure environment for up to 4 years did not lead to improvement of the nerve conduction velocity (Seppalainen and Tolonen 1974). However, it was noted that when individuals were removed from carbon disulfide exposure for 10–15 years, there was an equal division of people with either normal or decreased conduction velocities. While lower exposures may be associated with subclinical and reversible effects, several case series or industrial hygiene reports of "carbon disulfide poisoning" (unspecified concentrations) or exposures ≥100 ppm indicate overt polyneuritis or polyneuropathy as common findings among highly exposed workers, 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).

Cognitive and Psychomotor Abilities. Several occupational studies also evaluated the cognitive state of workers exposed to carbon disulfide (Table 2-15). However, endpoints evaluated, tests used for evaluation, and findings across studies are variable. Occupational studies evaluated cognitive skills included tests of intelligence, attention and memory, and visuomotor abilities. In a prospective cohort, Chrostek-Maj and Czeczotko (1995b) performed neuropsychological exams before and 5 years after the start of employment at a carbon disulfide manufacturing facility; exposure levels were purportedly 0 (assumed undetectable) to 21 ppm during the 5-year period. In the exposed group, the prevalence of abnormal findings on neuropsychological tests of visuomotor skills (Bender) and memory and attention were increased at the end of the 5-year period compared to pre-exposure values and referent values. In a retrospective study of two Italian viscose rayon cohorts, one with "high" exposure (58–64 ppm) and one with "low" exposure (19–39 ppm), performance was impaired on one test of the Wechsler Intelligence

Scale (Picture Completion) in the "high" cohort, compared to the "low" cohort, but not the other test (Block Design); the general level of intellectual functioning was comparable between groups by design as determined by the Raven Progressive Matrices (Foa et al. 1976). The "high" cohort also showed impaired memory and attention on the Pauli Test, impaired memory on the Rey test, and impaired visuomotor skills in the Visual Motor Speed Test, compared to the "low" cohort. The study authors noted that performance on the Pauli and Rey Tests by the "low" cohort was also lower than the expected performance of a "reference population;" since no referent group was included, it is assumed that this is referring to the performance by the general population. Italian viscose rayon workers exposed to lower concentrations also showed reduced performance on measures of intelligence, memory, attention, and visuomotor abilities in one study reporting exposures of 0.6–2.67 ppm (Cassitto et al. 1993) but not another with exposures of 3.2–8.0 ppm (Cirla and Graziano 1981). Kim et al. (2000) reported increased subjective complaints of memory defects in workers with exposure concentrations ranging from 0.43 to 6.28 ppm. In other cohorts, no exposure-related associations were observed between occupational exposure and altered performance on psychomotor, memory, or attention tasks, or subjective complaints of memory issues (Godderis et al. 2006; NIOSH 1984a; Reinhardt et al. 1997b).

Table 2-15. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Neuropsychological or Cognitive Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Cassitto et al. 1993 Longitudinal study; workers from a viscose rayon factory (Italy) 1974–1975: 97 workers (mean age of 39.29 years; mean employment of 14.52 years) and 27 unexposed referents (Italy) 1989–1990: 212 workers, only 6 of which were in original cohort (mean age of 40.28 years; mean employment of 12.88 years)	Measured air concentrations, means: 1962–1971: 19 ppm 1972–1980 Preparation: 0.6 ppm Spinning: 2 ppm Washing: 1 ppm 1988 Preparation: 0.74 ppm Spinning: 2.67 ppm Washing: 1.39 ppm	Perceptive abilities and reasoning (Picture completion, block design, Raven PM38)	↓ (1974–1975 workers versus referents) ↔ (1974–1975 workers versus 1989–1990 workers)
		Personality dimensions (Eysenck MPI, Cattel Anxiety Scale)	↔ (1974–1975 workers versus referents) ↔ (1974–1975 workers versus 1989–1990 workers)
		Memory, attention, and visuomotor abilities (Pauli, Symbol Digit, Rey)	↓ (1974–1975 workers versus referents) ↔ (1974–1975 workers versus 1989–1990 workers)

Table 2-15. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Neuropsychological or Cognitive Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Chrostek-Maj and Czeczotko 1995b Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	Prevalence of abnormal psychiatric findings (pseudoneurotic symptoms and syndromes)	↑ (workers versus referents) ↑ (baseline versus follow-up)
		Prevalence of Abnormal psychological findings (Bender, Graham Kendall, Benton tests)	↑ (workers versus referents) ↑ (baseline versus follow-up)
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Neuropsychological tests (intelligence, memory)	↔ (workers versus referents)
Foa et al. 1976 Retrospective cohort; 34 workers (mean age 49.41 years; mean employment 18.35 years) from a viscose rayon factory with high exposure levels (Factory A) and 34 matched referents (mean age 47.82 years; mean employment 19.29 years) from a viscose rayon factory with low recent exposure levels (Factory B) (Italy)	Measured historical concentrations, TWA (year): Factory A: 1943–1963: 96 ppm 1963–1971: 64 ppm After 1971: 58 ppm Factory B: 1943–1963: 96 ppm 1963–1971: 19–39 ppm After 1971: 19 ppm	Measures of intelligence Picture completion Block Design Raven	 ↓ (Factory A versus B) ↔ (Factory A versus B) ↔ (Factory A versus B)
		Personality indicators Eysenck MPI Neuroticism Extraversion Cattel Anxiety Scale	 ↔ (Factory A versus B) ↓ (Factory A versus B) ↑ (Factory A versus B)
		Memory, attention, and visuomotor abilities (Pauli, visual motor speed, Rey PMR1)	↓ (Factory A versus B) ↓ (Factory A and B versus reference performance values)

Table 2-15. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Neuropsychological or Cognitive Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Godderis et al. 2006 Retrospective cohort, 85 workers, including 60 low exposed and 25 high exposed (mean age 37.2 years, mean employment 10.5 years) from a viscose rayon factory and 66 unexposed referents (mean age 41.2 years) (Belgium)	Measured air concentrations, yearly geometric mean: All: 4.91 ppm Low (<10 ppm): 2.9 ppm High(>10 ppm): 19.0 ppm CEI, geometric mean: Low: 19.1 ppm-years High: 239.8 ppm-years	Visuomotor and memory tests (simple reaction time, symbol digit substitution, digit span)	↔ (workers versus referents)
		Subjective complaints (memory, mood, personality changes)	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Abnormal findings on MMPI (neuro-psychological screen)	↑ (workers versus referents) ↑ (CEI)
		Subjective neurological symptoms (memory defects, easy excitation, personality changes)	↑ (workers versus referents) ↑ (CEI)
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Psychological (POMS, MMPI)	↔ (workers versus referents)
		Sensory-perceptual (Neisser test; visual search)	↓ (low versus referent) ↔ (moderate versus referent) ↓ (high versus referent)
		Psychomotor (Reaction time, coordination)	↔ (workers versus referents)
		Memory (digit span)	↔ (workers versus referents)

Table 2-15. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Neuropsychological or Cognitive Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Reinhardt et al. 1997b Retrospective cohort; 222 exposed workers (median age 35 years; median employment 6 years) from viscose rayon industry and 191 unexposed referents (mean age 33 years) (Germany)	Measured current air concentrations, median (range): 4.02 (0.2–30) ppm *CEI levels were not reported.*	Neuropsychological tests (Benton visual retention, d2 test)	↔ (workers versus referents)
		Subjective neurological complaints (e.g., memory problems)	↔ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure index; LOD = level of detection; MMPI = Minnesota Multiphasic Personality Inventory; MPI = Maudsley Personality Index; POMS = Profile of Mood States; Q = quartile; TWA = time-weighted average

Neuropsychological Effects. A few studies reported mental health changes in some workers exposed to carbon disulfide; however, findings are difficult to interpret due to study design and/or reporting limitations (Table 2-15). In the prospective cohort by Chrostek-Maj and Czeczotko (1995b) described above (exposure up to 21 ppm for 5 years), the prevalence of "pseudoneurotic" symptoms (not further defined) increased in the exposed group compared to both pre-exposure and referent prevalence. Similarly, in the retrospective study of "high" and "low" exposure Italian cohorts, increased depressive behaviors (decreased extraversion) and increased anxiety scores were identified in the "high" cohort, compared to the "low" cohort (Foa et al. 1976). It was not discussed how scores in the "low" cohort compared to expected scores from the general population on these administered tests (Eysenck Maudsley Personality Index [MPI] and Cattel Anxiety Scale). Italian viscose rayon workers exposed to lower levels (0.6–2.67 ppm) did not differ from unexposed referents on the Eysenck MPI or Cattel Anxiety Scale (Cassitto et al. 1993). In a Korean cohort, Kim et al. (2000) reported an association between cumulative exposure to carbon disulfide in a cohort of viscose rayon workers exposed to historical mean concentrations of 0.43–6.28 ppm and an increase in the number of "any abnormal category" on the Minnesota Multiphasic Personality Inventory (MMPI) neuropsychological test. No further details on observed abnormalities in the MMPI test were provided; however, subjective reports of personality changes and easy excitation were increased in exposed workers, compared to referents. In an American cohort, no mental health changes were associated with occupational exposure to carbon disulfide, as assessed by the MMPI or Profile of Mood States evaluations (NIOSH 1984a).

Neuroimaging and Neurophysiology. Since some case series and industrial hygiene studies reported encephalopathy in workers with carbon disulfide "poisoning" (Aaserud et al. 1988, 1992); some cohorts have conducted brain imaging or function tests in workers exposed to carbon disulfide (Table 2-16). In the prospective cohort by Chrostek-Maj and Czeczotko (1995b) described above (exposure up to 21 ppm for 5 years), the prevalence of abnormal electroencephalogram (EEG) findings (slow or plate waves) was increased in exposed workers at the 5-year follow-up, compared to baseline. However, no changes were observed between exposed and referent workers. Computed tomography (CT) scans of the 20 "worst" psychiatric patients from the exposed workers also revealed evidence of brain atrophy in 12/20 examined brains, most frequently in the frontal lobe. No control brains were examined (Chrostek-Maj and Czeczotko 1995b). Abnormal EEG findings (slow-wave abnormalities) were also reported in a cohort of Finnish viscose rayon workers exposed to concentrations ranging from 10 to 40 ppm for a median duration of 15 years (Seppalainen and Tolonen 1974). No magnetic resonance imaging (MRI) abnormalities have been detected in viscose rayon workers exposed to concentrations ranging from 0.43 to 6.28 ppm for 1–≥15 years (Kim et al. 2000) or to a geometric mean concentration of 4.87 ppm for a mean duration of 19.6 years (Nishiwaki et al. 2004). However, when a subset of workers and referents suspected of neuropathy (n=298) were evaluated from the Kim et al. (2000) cohort, an increase in prevalence of abnormal MRI findings was associated with the calculated cumulative exposure index (number of years worked × exposure levels).

In a case series review of former viscose rayon workers diagnosed with carbon disulfide "poisoning," MRIs showed an increased number of cerebral lacunae in cases with histories of higher exposure (1,069.74 ppm-months) compared to cases with histories of lower exposure (198.48 ppm-months) (Cho et al. 2002). Abnormal MRI findings noted in both groups included periventricular hyperintensities, primarily in frontal and occipital lobes, and white-matter hyperintensities in frontal and parietal lobes. No differences were observed in total, verbal, or performance IQs between high and low exposure groups.

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Neurological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Chang et al. 2003 Retrospective cohort; 131 male workers from a viscose rayon plant with exposure to noise levels of 80–91 dB (mean age 48.3 years); mean employment 20.8 years), 105 unexposed males exposed to similar noise levels (83–90 dB; mean age 42.2 years; mean employment 12.1 years), and 110 male referents (72–82 dB; mean age 42.0 years; mean employment 11.3 years) (Taiwan)	Measured air concentrations, categories: Low (n=46) <14.6 ppm High (n=85) ≥14.6 ppm CEI (ppm-years): Q1: <37 Q2: 37–214 Q3: 215–453 Q4: 454–483 Q5: >483	Hearing loss (>25 dB at 0.5, 1, and 2 kHz)	↑ (High exposure versus referent) ↔ (Noise-only versus referents) ↑ (Q2–Q5 versus referent)
Chrostek-Maj and Czeczotko 1995b Prospective cohort; 114 males (ages 19–46 years) employed for 5 years at a plant producing carbon disulfide and 62 unexposed controls (ages 20–45 years) (Poland)	Measured air concentrations, range: <LOD–21 ppm	Prevalence of Abnormal EEG (slow or plate wave)	↔ (workers versus referents) ↑ (baseline versus follow-up)
Cirla and Graziano 1981 Retrospective cohort, 50 male workers (ages 26–55 years; employed 3–12 years) from a viscose rayon industry and matched male referents (Italy)	Measured air concentration during 12-year period, range of mean values: 3.2–8.0 ppm	Subjective complaints (headache, sleep disturbances)	↔ (workers versus referents)
Godderis et al. 2006 Retrospective cohort, 85 workers, including 60 low exposed and 25 high exposed (mean age 37.2 years, mean employment 10.5 years) from a viscose rayon factory and 66 unexposed referents (mean age 41.2 years) (Belgium)	Measured air concentrations, yearly geometric mean: All: 4.91 ppm Low (<10 ppm): 2.9 ppm High(>10 ppm): 19.0 ppm CEI, geometric mean: Low: 19.1 ppm-years High: 239.8 ppm-years	Subjective complaints of disequilibrium	↑ (workers versus referents)
		Subjective complaints (sleeping issues, fatigue)	↔ (workers versus referents)

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Neurological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm CEI (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Prevalence of: Color vision disorder	↔ (workers versus referents) ↔ (CEI)
		Abnormal audiometry	↑ (workers versus referents) ↑ (CEI)
		Abnormal MRI	↔ (workers versus referents) ↑ (CEI)
		Subjective neurological symptoms (insomnia, diplopia, dysarthrosis)	↑ (workers versus referents) ↑ (CEI)
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Visual acuity	↔ (workers versus referents)
		Depth perception	↔ (workers versus referents)
		Color vision	↔ (workers versus referents)
Nishiwaki et al. 2004 Longitudinal cohort; 217 currently exposed male workers (mean age 35.4 years, mean work duration of 19.6 years at follow-up) and 125 ex-exposed male workers (mean age 36.8 years; median time since cessation of 4.1 years) from viscose rayon factory and 324 referent males (mean age 35.8 years); baseline evaluation conducted in 1992–1993, follow-up evaluation in 1998–1999 (Japan)	Measured air concentrations during study period, ppm: Q1: 2.47 Q2: 4.54 Q3: 6.20 Q4: 8.10 Geometric mean: 4.87	MRI abnormalities (hyperintense spots in cerebrum, cerebellum, or brain stem)	↔ (exposed versus referents) ↔ (ex-exposed versus referents)
		Cerebral atrophy	↔ (exposed versus referents) ↔ (ex-exposed versus referents)

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Neurological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Raitta et al. 1974 Longitudinal cohort; 100 male workers (mean age 48 years; exposed a mean of 15 years) And 97 male referents (mean age 47 years) (Finland) *Subset of workers from larger Finnish cohort (Hernberg et al. 1970)*	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1972: 4–30 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Visual acuity at 5-year follow-up	↔ (workers versus referents)
Raitta et al. 1981 Retrospective cohort; 62 male workers (mean age 43 years; exposed a mean of 16 years) And 40 male referents (mean age 43.5 years) (Finland) *Subset of workers from larger Finnish cohort (Hernberg et al. 1970)*	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm after 1960: 4–30 ppm Geometric mean air concentration of carbon disulfide only in different departments (Hernberg et al. 1971): 1967: 4–18 ppm	Color discrimination	↓ (workers versus referents)
Ruijten et al. 1990 Retrospective cohort; 45 workers (mean age 49 years; mean employment 20 years) from a viscose rayon plant and 37 unexposed referents (mean age 48 years) (The Netherlands)	Measured air concentrations, mean personal air measurements over past 3 years: Supervisors: 1 ppm Spinning: 6 ppm Bleaching: 12 ppm Historical air concentrations[a], mean: Zone 1: 8 ppm Zone 2: 17 ppm CEI: 165 ppm-years	Color discrimination	↔ (workers versus referents) ↔ (CEI)

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Other Neurological Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Seppalainen and Tolonen 1974 Retrospective cohort; 118 male workers (mean age 50 years; median employment 15 years) from a viscose rayon plant and 100 male referents (mean age 48 years); examined in 1967 and 1972 (Finland)	Historical air concentrations, range 1960s: 10–30 ppm Pre-1960: 20–40 ppm *Exposure concentrations reported by Seppalainen et al. (1972)*	Abnormal EEG (slow-wave abnormalities)	↑ (workers versus referents)
Vanhoorne et al. 1996 Retrospective cohort; 123 workers (median age 33.5 years) from a viscose rayon factory and 67 unexposed referents (median age 35.2 years) (Belgium)	Historical range of air concentrations: 1–36.0 ppm Exposure categories (below and above TLV [at the time]): Low: <10 ppm High: ≥10 ppm CEI: 71.9 ppm-years	Visual acuity	↓ (workers versus referents) ↔ (CEI)
		Color discrimination	↑ (high versus referents) ↔ (low versus referents) ↑ (CEI)
		Abnormal ERG	↑ (workers versus referents) ↑ (CEI)
		Abnormal EOG	↑ (workers versus referents)

[a]Historical air concentrations were provided for the "old" bleaching department; no further details were provided (Ruijten et al. 1990).

↑ = association; ↓ = inverse association; ↔ = no association; CEI = cumulative exposure; EEG = electroencephalogram; EOG = electrooculogram; ERG = electroretinogram; LOD = level of detection; MRI = magnetic resonance imaging; Q = quartile or quintile; T = tertile; TLV = threshold limit value; TWA = time-weighted average

Neurosensory. Auditory and visual function have only been evaluated in a limited number of cohort studies (Table 2-16). An increase in the incidence of hearing loss, defined as hearing thresholds ≥40 dB at 1 and 4 kHz, was associated with increased cumulative exposure in a large Japanese cohort of viscose rayon workers with 12.5% incidence in the highest quartile of cumulative exposure ≥150 ppm-years, compared to 1.4% in referents (Kim et al. 2000). The prevalence of hearing loss was nearly 3-fold higher in workers exposed to concentrations up to 6.28 ppm for at least 1 year, compared to referents. Increased risk of hearing loss was also associated with cumulative exposure to carbon disulfide in a Taiwanese viscose rayon plant (Chang et al. 2003). In this study, hearing loss was defined as >25 dB at 0.5, 1, and 2 kHz. Chang et al. (2003) also included both an unexposed, low noise exposure referent group as well as a noise-only referent group since noise levels were elevated in the carbon disulfide factory. The

prevalence of hearing loss in the carbon disulfide workers was 67.9% compared with 34 and 26% in the noise-only and control groups, respectively. The data suggest that co-exposure to both carbon disulfide and noise leads to greater hearing impairment than noise-only exposure at 85 dB. Due to the risk of hearing loss associated with occupational exposure to carbon disulfide, the Occupational Safety and Health Administration (OSHA) has designated carbon disulfide as an ototoxic chemical (OSHA 2018).

Impaired color discrimination has been reported in workers with a history of exposure to carbon disulfide concentrations ≥10 ppm; this impairment has not been observed at lower exposure concentrations (Kim et al. 2000; Raitta and Tolonen 1975; Ruijten et al. 1990; Vanhoorne et al. 1996). One study reported alterations in electrical activity in the eye (electroretinogram [ERG], electrooculogram) in association with observed effects (Vanhoorne et al. 1996). However, no clear associations have been observed between long-term occupational exposure to carbon disulfide and visual acuity (NIOSH 1984a; Raitta et al. 1974; Vanhoorne et al. 1996).

Subjective Complaints. Other neurological effects reported in viscose rayon workers include subjective complaints of insomnia, diplopia, and dysarthrosis (Kim et al. 2000). However, no associations between subjective complaints of sleep disturbances or headaches and carbon disulfide exposure were observed in viscose rayon workers exposed to concentrations up to 8.0 ppm for up to 12 years (Cirla and Graziano 1981).

Animal inhalation studies evaluating neurotoxicity of carbon disulfide, most often conducted in rats, provide support that this compound is neurotoxic. In general, exposure levels used in animal studies are considerably higher than the exposures seen in occupational settings.

In inhalation studies, overt signs of neurotoxicity consistent with central nervous system depression were observed in rats at acute-duration concentrations ≥600 ppm, including muscular weakness, hindlimb splay or paralysis, tremor, ataxia, or narcosis (Lehotzky et al. 1985; Moser et al. 1998; Tarkowski and Sobczak 1971; Wilmarth et al. 1993). Exposure to similar concentrations (≥546 ppm) for intermediate durations was associated with hindlimb paralysis, foot drag, ataxia, atrophy, and tremor in rats (Frantik 1970; Phillips 1983a, 1983b; Wrońska-Nofer 1973). Ataxia was reported in rabbits exposed to ≥1,168.6 ppm for 12 days (Denny and Gerhart 1991).

Neurobehavioral tests also showed impairments in rodents following inhalation exposure to carbon disulfide. Concentration-related impairments in operant training were observed in mice following a 30-minute exposure to carbon disulfide at ≥577.6 ppm (Liang et al. 1983). In longer-duration studies, slight gait impairments were noted in a functional observation battery (FOB) in male rats exposed to 50 ppm for 13 weeks (Moser et al. 1998). Gait impairments increased in a time-concentration-related manner, progressing from slight to marked impairments in both sexes with exposure duration of 4, 8, or 13 weeks at 500 and 800 ppm. Additional findings in the FOB observed primarily in the high exposure group included decreased grip strength, increased foot splay, ataxia, tremor, and abnormal pupil response (Moser et al. 1998). Impaired motor strength and coordination were observed in rats intermittently exposed to ≥385 ppm for 10 months (Frantik 1970). In another study, a decreased startle reflex was observed in rats intermittently exposed to 500 ppm for 5 or 12 weeks (Clerici and Fechter 1991). This was attributed to impaired neuromuscular integrity, as no changes in hearing function or acoustic tone thresholds were noted. The behavior recovered to 70% of a normal response following a 4-week recovery period.

Consistent with human studies, altered nerve conduction has been reported in rats. Decreased nerve conduction velocity was observed in rats following intermittent exposure to ≥500 ppm for 13 weeks (Herr et al. 1998). This was accompanied by increased caudal tail nerve action potential amplitudes at 800 ppm. No changes in caudal nerve neurophysiology were observed at concentrations <800 ppm after exposure for 2, 4, or 8 weeks (Herr et al. 1998). Daily exposure (7 hours/day) for 11 weeks to 800 ppm resulted in increased latencies of the ventral caudal nerve action potential, the somatosensory evoked potential, and the brainstem auditory-evoked potential (BAEP) in rats; no changes were observed at 400 ppm (Rebert and Becker 1986). Specifically, the component of the BAEP that was delayed was component 5, which indicates central tract dysfunction. No clear exposure-related changes were observed for visual (flash) evoked potentials (Rebert and Becker 1986). Delayed BAEPs were also observed in rats exposed to 800 ppm, but not 200 ppm, for 15 weeks (Hirata et al. 1992). Consistent with findings by Rebert and Becker (1986), the latencies were delayed between components 3 and 5 (the olivary nucleus and the inferior colliculus), indicating central tract dysfunction. Rats recovered 2–6 weeks after carbon disulfide exposure ceased.

Five female monkeys intermittently exposed to 256 ppm for 5–13 weeks suffered permanent visual impairment with degeneration of retinal ganglion cells (Eskin et al. 1988; Merigan et al. 1988). None of the monkeys developed retinal microaneurysms or hemorrhages, which are signs of ocular toxicity following occupational exposure in humans (Section 2.12), indicating that optic nerve damage can occur

at exposure levels below those that cause retinal vascular effects. Impaired retinal function, as assessed via ERG, was observed in rabbits intermittently exposed to 321 ppm for 3 weeks (decreased b-wave amplitudes), compared to controls (Qingfen et al. 1999). No changes in retinal function were observed with shorter exposure durations (up to 2 weeks). In rats, no exposure-related ERG changes were observed at concentrations up to 800 ppm for 11 weeks (Rebert and Becker 1986).

No exposure-related changes in hearing or cochlear histology were observed in rats intermittently exposed to 250 ppm for 5 days (Carreres Pons et al. 2017). However, combined exposure of carbon disulfide along with noise can alter effects seen in rats exposed to noise alone, with some scenarios potentiating hearing loss and others attenuating cochlear damage. For example, co-exposure of carbon disulfide at 250 ppm and "impulse" noise in rats for 5 days potentiates the cochlear damage caused by impulse noise alone, defined as 84 dB delivered as 7-millisecond pulses separated by 15-second rest, repeated over 6 hours (Carreres Pons et al. 2017). However, the same exposure concentration was protective of cochlear damage caused by continuous noise of 89 dB delivered continuously over 6 hours/day for 5 days (Carreres Pons et al. 2017). In other studies, greater auditory deficiency was seen in rats co-exposed to carbon disulfide concentrations ≥250 ppm and 106 dB when noise exposure was steady over 6 hours/day, 5 days/week for 4 weeks, compared to noise exposure alone (Chalansonnet et al. 2020; Venet et al. 2017). However, hearing loss was attenuated when carbon disulfide plus noise (at the same exposure levels) were delivered intermittently (15 minutes/hour or 2 x 15 minutes/hour for 6 hours) 5 days/week for 4 weeks (Chalansonnet et al. 2020). The mechanisms responsible for these apparently contradictory findings are unclear but may involve neurochemical disturbances or altered metabolism of nerve cells. Functional impairment of the vestibular system was seen in rats exposed to 250 ppm for 6 hours/day, 5 days/week for 4 weeks in the absence of any histological changes to the peripheral vestibular system (Chalansonnet et al. 2018). This impairment became more severe when rats were co-exposed to 250 ppm and noise of 106 dB for 4 weeks (6 hours/day, 5 days/week) compared to 250 ppm alone or noise alone (Chalansonnet et al. 2018).

Morphological changes in the tibial and/or sural nerve have been consistently observed in rats and mice exposed to approximately 800 ppm for ≥8 weeks (Graham and Popp 1992a, 1992b; Phillips 1983a, 1983b, 1983c; Sills et al. 1998b). The most common finding is axonal swelling, but degeneration and regeneration have also been observed in some animals. Damage to the tibial nerve was not observed in rats following exposure to concentrations up to 800 ppm for 2 or 4 weeks (Sills et al. 1998b). No morphological changes were observed in the caudal tail nerve of rats following exposure to 800 ppm for

13 weeks except a higher proportion of unmyelinated axon fibers in the ventral nerve sheath (Herr et al. 1998).

Exposure- and duration-related axonal swelling in the sensory nerve tracts of the spinal cord have been reported in rats following inhalation exposure to concentrations ≥500 ppm for ≥8 weeks (Graham and Popp 1992a, 1992b; Phillips 1983a, 1983b; Sills et al. 1998b; Valentine et al. 1997). Axonal swelling has been reported in the fasciculus gracilis nerve tracts of the cervical spinal cord and the lateral funiculus and ventro-medial nerve tracts. Axonal swelling first appears as minimal-to-mild multifocal lesions after 8 weeks of exposure at 500 ppm, progressing to more diffuse and severe swelling with increased exposure concentration (800 ppm) or duration (13 weeks). Axonal swelling in the spinal cord was not observed at concentrations up to approximately 800 ppm for 2 or 4 weeks in rats (Sills et al. 1998b; Valentine et al. 1997) or 90 days in mice (Phillips 1983c). No histopathological changes were observed in the brain of rats or mice exposed to concentrations up to approximately 800 ppm for up to 13 weeks (Phillips 1983a, 1983b, 1983c; Sills et al. 1998b) or rats exposed to 225 ppm for 14 weeks (Morvai et al. 2005).

Limited data suggest alterations in brain catecholamines following acute-duration inhalation exposure to carbon disulfide. Rats exposed to 642 ppm for 1 hour or for 4 hours/day for 2 days showed increased dopamine and decreased noradrenaline in the brain (Magos 1970; Magos et al. 1974). However, dopamine levels returned to baseline in rats similarly exposed for 5 or 10 days, while noradrenaline levels continued to decrease (Magos 1970).

Only a limited number of studies evaluated potential neurological effects in animals following oral exposure to carbon disulfide; however, available results are consistent with effects observed in inhalation studies. Clinical signs of toxicity in rats following acute- or intermediate-duration exposure progress from mild effects (incoordination, lethargy, tip-toe walking, hindlimb splay, mild ataxia) at 200–300 mg/kg/day to severe effects (paralysis, tremor, severe gait impairments, and ataxia) at ≥400 mg/kg/day (Gao et al. 2014; Liu et al. 2023, 2024; NCTR 1984a; Song et al. 2009; Wang et al. 2016). Gavage exposure for 8 weeks was also associated with impaired caudal nerve conduction at ≥300 mg/kg/day and dopaminergic cell necrosis and death in the substantia nigra at 600 mg/kg/day (Liu et al. 2023, 2024). One acute-duration study in rats reported lethargy when exposed to 50 mg/kg/day for 10 days (NCTR 1984a); however, no intermediate-duration studies evaluating doses <200 mg/kg/day were identified. Convulsions were reported in pregnant rabbits exposed to ≥200 mg/kg/day for 14 days (NCTR 1984b).

One oral study evaluated cognitive effects (learning and memory) and brain histology in male rats following exposure to ≥200 mg/kg/day for 20 days (Wang et al. 2017). In the Morris water maze, initial learning was impaired at ≥400 mg/kg/day, while memory was impaired at all tested doses (≥200 mg/kg/day). Evaluation of the water content of the brain revealed cerebral edema at ≥400 mg/kg/day, with morphological evidence of neuronal destruction in the cortex and hippocampus. Quantification of neurons revealed significant neuronal loss in the hippocampus at ≥400 mg/kg/day; findings were associated with increased markers of apoptosis.

Decreased noradrenaline in the midbrain, hypothalamus, and medulla oblongata were observed in rats 2 hours after they received a single dose of 300 mg/kg via gavage (Kanada et al. 1994). No changes in acetylcholine levels were observed in the hippocampus.

A duration-related decrease in the *ex vivo* response of the anococcygeal muscle to noradrenaline was observed in muscle tissue obtained from rats exposed to carbon disulfide at 12.5 mg/kg/day for 1, 2, or 4 weeks via gavage (Gandhi and Venkatakrishna-Bhatt 1993). Interpretation of *ex vivo* results in terms of *in vivo* toxicity is difficult; however, findings may indicate a block of calcium influx, a delay of the calcium efflux, an inhibition of the uptake of calcium, a decreased sensitivity to calcium by the muscle, or a combination of these mechanisms. Due to challenges associated with interpreting findings from *ex vivo* studies, this study was not included in the LSE table.

Mechanisms of Neurotoxicity. Several secondary sources have reviewed potential mechanisms of carbon disulfide-induced peripheral neuropathy (Graham et al. 1995; Harry et al. 1998; EC/HC 2000; Llorens 2013; Newhook et al. 2001). The proposed mechanism for peripheral nerve and spinal cord degenerative changes associated with carbon disulfide is the formation of crosslinked neurofilaments 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 crosslinking of stable neurofilaments during axonal anterograde transport; (5) crosslinked masses block transport at nodes of Ranvier (impeding peripheral nerve signals); and (6) axonal swelling and degeneration. Other proposed mechanisms of carbon disulfide neurotoxicity include metal ion chelation and induction of vitamin B6 deficiency.

Parkinson's-like changes associated to carbon disulfide exposure could arise from dysregulation of the dopaminergic pathway in the central nervous system. Liu et al. (2023) provided several lines of evidence that gavage exposure to 600 mg/kg/day for 8 weeks results in direct damage to dopaminergic neuronal

synapses in rats. Exposed rats showed synaptic injury in dopaminergic neurons in the substantia nigra pars compacta, based upon decreased co-staining of synaptophysin (a synaptic marker) and tyrosine hydroxylase (a dopamine rate-limiting enzyme). These findings were associated with necrosis and cell death in dopaminergic neurons. Specifically, necroptosis of neurons is triggered by aggregation and phosphorylation of α-synuclein, which interacts with necrosome complexes to trigger cell death. Additionally, carbon disulfide exposure may lead to the translocation of α-synuclein into the mitochondria resulting in mitochondrial dysfunction, increased oxidative stress, and neuronal damage (Liu et al. 2024). Monkey studies suggest that damage and lymphoid infiltration in the globus pallidus, which lies downstream of the dopaminergic system, could also underlie Parkinson's-like changes (Huang 2004; Huang et al. 2004). However, limited available human data indicate a normal presynaptic dopaminergic pathway, distinguishing carbon disulfide poisoning from Parkinson's disease (Huang 2004; Huang et al. 2004).

Additional studies have reported dysregulation of the dopaminergic pathway in the central nervous system. Increased dopamine levels have been reported in the medulla oblongata in rats exposed once to 300 mg/kg via gavage (Kanada et al. 1994) and in the brain in rats exposed to 642 ppm for 1 hour (Magos et al. 1974) or for 4 hours/day for 2 days (Magos 1970). In the brain, these changes were associated with concomitant decreases in noradrenaline levels. Magos (1970) proposed that changes were due to inhibition of dopamine-β-hydroxylase by carbon disulfide, which would prevent the conversion of dopamine into noradrenaline. However, continued exposure for 5 or 10 days (4 hours/day) resulted in a return of brain dopamine levels to baseline with continued decreases in noradrenaline levels, suggesting alternate (or additional) mechanisms. While brain levels of dopamine returned to baseline after the initial exposure period, adrenal gland stores of dopamine continued to increase over the 5–10-day exposure period (Magos 1970). Caroldi et al. (1984) reported increased dopamine levels in the adrenal gland associated with a decreased rate of dopamine turnover following a 4-hour exposure to ≥321 ppm. These changes were attributed to inhibition of dopamine-β-hydroxylase by the study authors.

Less has been postulated about mechanisms involved with other central nervous system effects of carbon disulfide, such as cognitive or neuropsychiatric effects. These effects may be due to decreased nitric oxide synthase activity, which impairs neurotransmitter release and synaptic plasticity (Guo et al. 2008).

In a systematic review, Printemps et al. (2022) evaluated the strength of the evidence supporting different proposed endocrine-disrupting and non-endocrine-disruption MOAs for neurotoxicity associated with exposure to carbon disulfide. Specifically, thyroid hormone disruption was a proposed MOA for

cognitive effects associated with carbon disulfide exposure in some studies. An adverse outcome pathway (AOP), which links inhibition of thyroid peroxidase activity to adverse neurodevelopment outcomes (AOP42), was specifically suggested; however, at the time of the systematic review, no molecular initiating events from this pathway had been investigated for carbon disulfide. Printemps et al. (2022) also reviewed several of the MOAs listed above, including formation of crosslinked neurofilaments due to dithiocarbamate protein adducts, alterations in the dopamine system, and decreased nitric oxide synthase activity. An additional proposed MOA is excessive oxidative damage in neural tissue. Based on the available data, Printemps et al. (2022) concluded that there is likely more than one relevant MOA underlying sensorimotor and cognitive impairments. While all proposed MOAs are biologically plausible, available evidence does not indicate that carbon disulfide targets the neuroendocrine system specifically. Therefore, based on systematic review, there is stronger support for "systemic" neurological toxicity, over an endocrine-dependent MOA.

2.16 REPRODUCTIVE

The male reproductive system is a sensitive target of carbon disulfide toxicity in both humans and animals following inhalation exposure. Data evaluating the potential effects of carbon disulfide exposure on the function of the female reproductive system are limited. No studies evaluating potential reproductive effects in humans or animals following oral exposure to carbon disulfide were identified. Based upon systematic review (Appendix C), the male system is a suspected target of carbon disulfide toxicity in humans following inhalation exposure based on inadequate evidence in humans and moderate evidence in laboratory animals.

Male Reproductive Toxicity. Several occupational cohort studies, primarily in the viscose rayon industry, evaluated potential associations between exposure to carbon disulfide and potential changes in male reproductive endpoints (Table 2-17). In general, findings from these studies should be interpreted with caution due to the lack of control for key confounding factors in almost all available studies, such as known risk factors for altered male reproductive performance or fertility (e.g., smoking, alcohol intake, parity of partner, time since last ejaculate, etc.), or use of medication to treat fertility or erectile dysfunction. More details on the quality and confidence in available epidemiological studies evaluating male reproductive effects can be found in Appendix C. As discussed in Appendix B, due to the availability of several cohort studies evaluating the potential association between male reproductive effects and exposure to carbon disulfide, cross-sectional, case series, and case report studies of these endpoints are not discussed below and did not meet inclusion criteria for the systematic review.

Table 2-17. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Male Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
Cirla et al. 1978 Retrospective cohort; 254 workers from a viscose rayon factory and 54 unexposed referents; exposed 2–31 years (Italy)	Exposure level based on exposure categories (ppm): Very light/light: <19 Moderate: 19–39* Heavy: 39–77* Heavy in past: 58–77** Heavy, then suspended: 39–77, then transferred to "clean" department *Last 3 years <19 ppm **Last 12 years <19 ppm	Serum hormone levels	
		FSH	↔ (very light/light versus referent) ↓ (heavy versus referent) ↔ (heavy in past versus referent)
		FSH levels below clinical norms	↑ (very light/light versus referent) ↑ (heavy versus referent) ↔ (heavy in past versus referent)
		LH	↔ (very light/light versus referent) ↓ (heavy versus referent) ↔ (heavy in past versus referent)
		LH levels below clinical norms	↔ (workers versus referents)
		Testosterone	↔ (workers versus referents)
		Prolactin	↔ (workers versus referents)
		Sexual behavior (self-reported)	
		Intercourse frequency	↓ (very light/light versus referent) ↓ (heavy versus referent) ↓ (heavy in past versus referent)
		Impotency	↑ (very light/light versus referent) ↑ (heavy versus referent) ↑ (heavy in past versus referent)
Guo et al. 2016 Retrospective cohort; 76 male workers (mean age 32.28 years; mean employment of 10.05 years) and 94 matched male referents (mean age 33.34 years) (China)	Measured TWA air concentrations 2010–2014, mean ± SD: 3.12 ± 0.89 ppm	Serum hormone levels	
		FSH	↑ (workers versus referents)
		LH	↑ (workers versus referents)
		Testosterone	↓ (workers versus referents)
		SHBG	↓ (workers versus referents)
		Semen analysis parameters	
		Volume	↔ (workers versus referents)

Table 2-17. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Male Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
		Liquefaction time	↑ (workers versus referents)
		Sperm analysis parameters	
		Viability	↓ (workers versus referents)
		Density	↔ (workers versus referents)
		Total count	↔ (workers versus referents)
		Motility	↓ (workers versus referents)
		Total abnormalities	↑ (workers versus referents)
		Sperm head	↑ (workers versus referents)
		Sperm neck	↔ (workers versus referents)
		Sperm tail	↑ (workers versus referents)
		Abnormal chromatin structure	↑ (workers versus referents)
NIOSH 1983 Retrospective cohort; 236 men from a viscose rayon factory (mean age 38.5 years, mean employment 13.7 years) and 204 male referents (mean age 34.8 years) and their wives (United States, Tennessee)	Historical air monitoring data (annual air exposure metrics): Mean: 8.1 ppm T1: 0 ppm T2: 0.2–5 ppm T3: >5 ppm	Fetal loss	↓ (workers versus referents) ↑ (duration of employment)
		Standardized fertility ratio	↔ (workers versus referents)
		Time between live births	↔ (workers versus referents)
NIOSH 1984a Retrospective cohort; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Historical exposure levels 1957–1979, range of means (by job): 0.58–33.5 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Ejaculate volume	↔ (workers versus referents) ↔ (CEI)
		Sperm count	↔ (workers versus referents) ↔ (CEI)
		Percent abnormal sperm	↔ (workers versus referents) ↔ (CEI)
		Self-reported reduced libido or impotence	↔ (workers versus referents)

Table 2-17. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Male Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
Takebayashi et al. 2003 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 392 males from 11 viscose rayon factories, including 259 current employees (mean age 35.6 years, mean employment 19.3 years) and 133 former employees (mean age 36.8 years, mean employment 15.6 years, retired an average of 4 years), and 352 male referents (mean age 35.9 years) (Japan)	Geometric mean of the mean air concentrations, measured twice yearly 1993–1998: 5.02 ppm	Hypothalamo-hypophysial axis (FSH, LH, ACTH)	↔ (workers versus referents)
		Testosterone	↔ (workers versus referents)
		Reduced sexual desire	↔ (workers versus referents)
Vanhoorne et al. 1993 Retrospective cohort; 117 males (median age 32.0 years; employed >1 year) from viscose rayon industry and 66 male referents (median age 34.8 years) (Belgium)	Measured current air concentration, range: 1–36 ppm CEI (ppm-years): Median: 57.8 Mean: 122.9	LH, FSH, prolactin, testosterone	↔ (workers versus referents) ↔ (CEI)
Vanhoorne et al. 1994 Retrospective cohort; 116 men (employed a median of 4.5 years) from a viscose rayon plant and 79 referents (Belgium)	Measured current air concentrations, ranges: Low: 0.3–9.6 ppm High: >9.6 ppm CEI (ppm-years), ranges: Low: 0.3–96 ppm-years High: >96 ppm-years	Prevalence of self-reported sexual complaints (decreased libido, impotence)	↑ (high exposed versus referents) ↑ (CEI)
		Reproductive history (number of children, intervals between consecutive children)	↔ (workers versus referents) ↔ (CEI)
Vanhoorne et al. 1994 Retrospective cohort; 43 men (median age 33.3 years) from a viscose rayon plant and 35 referents (median age 33.2 years) (Belgium)	Measured current air concentrations, ranges: Low: 0.3–9.6 ppm High: >9.6 ppm CEI (ppm-years): Median: 71.9	Sperm parameters (motility, concentration, morphology, viability)	↔ (workers versus referents) ↔ (CEI)

Table 2-17. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Male Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
Wägar et al. 1981 Retrospective cohort; 15 males from viscose rayon plant (mean age 50.2 years; employed 10–36 years) and 16 matched referents (Finland)	Historical air concentrations, ranges: 1940s: "very high" 1950s: 20–40 ppm 1960s: 10–30 ppm 1970s: <10 ppm	Serum FSH	↑ (workers versus referents)
		Serum LH	↑ (workers versus referents)
		Serum testosterone	↔ (workers versus referents)
		Serum prolactin	↔ (workers versus referents)
		Self-reported sexual impotence	↑ (workers versus referents)
Wägar et al. 1983 Retrospective cohort; 69 males from viscose rayon plant (mean age 40.5 years; employed 1–36 years) and 22 referents (mean age 38.7 years) (Finland)	Historical air concentrations, medians: Viscose filament: 1960s: 6–12 ppm 1970s: <10 ppm Rayon staple 1960s: 6–25 ppm 1970s: 3–13 ppm	Serum FSH	↑ (workers versus referents)
		Serum LH	↔ (workers versus referents)
		Serum testosterone	↔ (workers versus referents)
		SHBG	↔ (workers versus referents)
		Serum estradiol	↔ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; ACTH = adrenocorticotropic hormone; CEI = cumulative exposure index; Cr = creatinine; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SD = standard deviation; SHBG = sexual hormone binding globulin; T = tertile; TTCA = 2-thiothiazolidine-4-carboxylic acid (carbon disulfide metabolite); TWA = time-weighted average

There is limited evidence that long-term exposure to high concentrations may impair sexual function in men; however, there is no evidence of impaired fertility from the few studies available (Table 2-17). Self-reported decreases in sexual libido and/or performance were reported in some male workers exposed to carbon disulfide at concentrations of approximately 10 ppm for mean durations of ≥4.5 years, compared to unexposed referents (Vanhoorne et al. 1994; Wägar et al. 1981). However, the Vanhoorne et al. (1994) study did not observe an association between cumulative occupational exposure and measures of reproductive history (number of children, intervals between consecutive children) that would suggest reduced male fertility in exposed workers. Cirla et al. (1978) also reported decreased self-reported frequency of sexual intercourse and increased frequency of impotence in married male workers "lightly" exposed for 2–28 years (<19 ppm) or more heavily exposed for 4–30 years (39–79 ppm); findings for men moderately exposed (19–39 ppm) were not reported. At lower concentrations (5.02 ppm), no changes in sexual desire were reported in a cohort of male workers employed for a mean of 19.3 years (Takebayashi et al. 2003). In overlapping study cohorts from a Tennessee viscose rayon factory (NIOSH

1983, 1984a), no differences in sexual desire, sexual performance, or fertility were observed in workers (and their unexposed wives), compared to referents. Historical mean carbon disulfide levels ranged from 0.58 to 33.5 ppm, with a mean annual exposure level of 8.1 ppm. Unexpectedly, a decrease in the risk of fetal loss was observed in unexposed wives of exposed male workers, compared to referents, while duration of employment was associated with a slight increase in the risk of fetal loss (NIOSH 1983).

There is inconsistent evidence for sperm damage in males occupationally exposed to carbon disulfide (Table 2-17). Increased semen liquefaction time, decreased sperm viability, decreased sperm motility, and increased total sperm abnormalities (including head, tail, and abnormal chromatin structure) were found in workers exposed to mean air concentrations of 3.12 ppm, compared to referents (Guo et al. 2016). However, despite differing from control values, sperm motility and percent abnormalities fell within normal World Health Organization (WHO) criteria ranges; normal ranges for liquefaction time and viability were not reported. No differences in semen or sperm parameters were observed in other occupational cohorts with higher reported exposure levels ranging from 0.58 to 33.5 ppm (NIOSH 1984a; Vanhoorne et al. 1994).

Similar to sperm data, findings pertaining to reproductive hormone levels in males occupationally exposed to carbon disulfide are inconsistent (Table 2-17). Elevated serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) and decreased serum testosterone were found in workers exposed to mean air concentrations of 3.12 ppm, compared to referents (Guo et al. 2016). Sexual hormone binding globulin (SHBG) levels were also decreased in workers, but they were within the normal biological range. Serum FSH and LH were also elevated in workers exposed to 10–40 ppm for 10–36 years, compared to referents; no changes in serum testosterone or prolactin were observed (Wägar et al. 1981). Serum FSH was also elevated in workers exposed to 3–25 ppm for 1–36 years, compared to referents; no changes were observed in serum testosterone, estradiol, LH, or SHBG (Wägar et al. 1983). In contrast, serum FSH and LH were decreased in workers exposed to 39–79 ppm for an average of 15 years; no association was observed in workers exposed to <39 ppm (Cirla et al. 1978). No associations were observed for serum testosterone or prolactin. No exposure-related changes in serum LH, FSH, testosterone, or prolactin were observed in workers exposed to concentrations ranging from 1 to 36 ppm for at least 1 year; mean cumulative exposure was 122.9 ppm-years (Vanhoorne et al. 1993).

Following acute-duration exposure, no exposure-related changes in mating behaviors or sperm parameters were observed in rats intermittently exposed to 607 ppm for 5 days (Zenick et al. 1984). Similarly, no exposure-related sperm head abnormalities were observed in rats or mice following intermittent exposure

to concentrations up to 40 ppm for 5 days (NIOSH 1980). However, a series of 10-week studies in Long-Evans rats showed alterations in mating behavior (Tepe and Zenick 1984; Zenick et al. 1984). Exposure to concentrations ≥600 ppm resulted in reduced ejaculation and mounting and a decrease in the ejaculated sperm counts. In one study, findings were associated with a reduction in epididymal sperm counts (Tepe and Zenick 1984); this was not confirmed in the two additional studies using the same rat strain and similar exposure protocols (Tepe and Zenick 1984; Zenick et al. 1984). Similarly, while neither study evaluating copulatory behavior observed a reduction in serum testosterone, another group of similarly exposed rats showed a 49% decrease in plasma testosterone following exposure to 600 ppm for 10 weeks (Tepe and Zenick 1984). Neither study observed histopathological changes in the testes.

Another series of studies evaluated potential adverse effects on the male reproductive effects in Sprague-Dawley rats exposed to concentrations ranging from 16 to 401 ppm (Guo et al. 2014, 2015; Huang et al. 2012). Slight, but exposure-related, increases in abnormal sperm morphology were observed, with teratospermias observed in 3.33 to 7.17% of sperm in exposed animals, compared to 1.50% in controls (Huang et al. 2012). Similarly, the percentage of sperm with progressive motility was slightly decreased in exposed animals (24.83–22.00%) compared with controls (28.00%). Changes in serum hormone levels included an approximate 35% decrease in LH at ≥16 ppm, 18% increase in FSH by 18% at 401 ppm, and 10% decrease in testosterone at 401 ppm (Huang et al. 2012). Guo et al. (2014, 2015) also reported exposure-related histopathological changes in the testes at ≥16 ppm; however, quantitative data were not provided, precluding ability to establish accurate NOAEL and LOAEL determinations. Qualitatively reported findings included mild degeneration of seminiferous tubules and impaired spermatogenesis at ≥16 ppm and severe degeneration and collapse of seminiferous tubules, vacuolation of Sertoli cells, and loss of mature spermatids at 401 ppm. These studies proposed that mitochondrial apoptosis brought about by a dramatic decrease in mitochondrial transmembrane potential underly observed testicular effects.

In other studies, no exposure-related lesions were observed in the testes or epididymides of F-344 or Sprague-Dawley rats or B6C3F1 exposed to concentrations up to approximately 800 ppm for up to 13 weeks (Phillips 1983a, 1983b, 1983c; Sills et al. 1998b).

Female Reproductive Toxicity. Human data pertaining to toxicity to the female reproductive system are limited (Table 2-18). In a community study of spontaneous abortion, occupation, and air pollution in Finland, no relationship was observed between carbon disulfide exposure at work or via ambient outdoor air and miscarriage rates (Hemminki and Niemi 1982). However, no occupational exposure estimates

were available in this study, and ambient air levels were very low (~3 ppb). Rates of spontaneous abortion, stillbirth, premature or overdue delivery, or pregnancy toxemia were not increased in female workers who were pregnant while working at one of five viscose rayon plants in China, with mean exposure levels ranging from 0.55 to 9.8 ppm (Zhou et al. 1988). However, women from the Chinese viscose rayon plants had a higher rate of self-reported menstrual disorders, namely irregularity and unusual bleeding, than matched unexposed referents (Zhou et al. 1988). Increased rates of menstrual disturbances, including changes in durations and menstrual aches (defined as the need for a pain killer or "absence from duty"), and toxemia of pregnancy were also reported in another cohort of Chinese viscose rayon workers exposed to mean concentrations ranging from 12 to 18 ppm (Cai and Bao 1981). Cases of premature birth were not elevated in this cohort, compared to referents, either.

Table 2-18. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Female Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
Cai and Bao 1981 Retrospective cohort; 183 female workers from viscose rayon plant (including 100 pregnant women; >1 year exposure) and 197 unexposed referents (included 104 pregnant women) (China)	Measure concentrations, mean: Summer: 18 ppm Winter: 12 ppm	Menstrual disturbances (changes in duration, aches)	↑ (workers versus referents)
		Pregnancy toxemia	↑ (workers versus referents)
		Premature birth	↔ (workers versus referents)
Hemminki and Niemi 1982 Community-based cohort; 1,792 cases of spontaneous abortion; ambient exposure determined based on regional mean exposure data and subjects' residential addresses (Finland)	Occupational exposure: Yes/No based on employment in viscose rayon factory Ambient exposure categories for analysis: Less polluted: <3 ppb More polluted: >3 ppb	Spontaneous abortion	↔ (work exposure) ↔ (ambient air exposure)

Table 2-18. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Female Reproductive Effects

Reference, study type, and population	Exposure concentration (ppm)/TTCA mg/g Cr	Outcome evaluated	Result
Zhou et al. 1988 Retrospective cohort; 265 female workers (>15 years old, exposed >1 year) from five viscose rayon plants and 291 unexposed referents (>15 years old) (China)	Measure concentrations, range of means (1970–1985): 0.55–9.8 ppm	Spontaneous abortion	↔
		Stillbirth	↔
		Premature or overdue delivery	↔
		Pregnancy toxemia	↔
		Self-reported menstrual disorders (irregularity, unusual bleeding)	↑ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; Cr = creatinine; TTCA = 2-thiothiazolidine-4-carboxylic acid (carbon disulfide metabolite)

A small (4%) decrease in the livebirth index was observed in female rats exposed to 502 ppm for 2 weeks prior to mating through GD 19 (Holson 1992). Dystocia was also observed in 2/12 dams at this exposure level. No adverse reproductive effects were observed in rats similarly exposed to concentrations up to 250 ppm (Holson 1992). No adverse reproductive effects were noted in rat dams or rabbit does exposed to concentrations up to 39.3 ppm for 3 weeks prior to mating through GD 18 or 21, respectively (NIOSH 1980).

No exposure-related lesions were observed in the female reproductive organs of F-344 or Sprague-Dawley rats or B6C3F1 mice exposed to concentrations up to approximately 800 ppm for up to 13 weeks (Phillips 1983a, 1983b, 1983c; Sills et al. 1998b).

2.17 DEVELOPMENTAL

Human data pertaining to potential developmental effects following carbon disulfide exposure are very limited. Available data indicate that the developing organism is a sensitive target of carbon disulfide in animals following inhalation and oral exposure. Based upon systematic review (Appendix C), 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.

In the Chinese female reproductive cohort discussed in Section 2.16 and shown in Table 2-18, rates of congenital malformations were not increased in female workers who were pregnant while working at one

of five viscose rayon plants, with mean exposure levels ranging from 0.55 to 9.8 ppm (Zhou et al. 1988). No additional studies evaluating potential developmental effects in humans following exposure to carbon disulfide were identified.

In traditional developmental study designs in rats and rabbits, no adverse developmental effects were observed following maternal inhalation exposure to concentrations up to 250 ppm or 304.1 ppm during gestation in rats or rabbits, respectively (Denny and Gerhart 1991; Hardin et al. 1981; Holson 1992; NIOSH 1980; Saillenfait et al. 1989). At higher gestational exposure concentrations in rats, male and female fetal body weights were decreased by 6–7% at 396.9 ppm and 14–20% at 817.2 ppm, and the litter incidence of club foot was elevated at 817.2 ppm (Saillenfait et al. 1989). When dams were exposed to 502 ppm for 2 weeks premating through GD 19, 100% postnatal death was observed in 3/12 litters between postnatal days (PNDs) 0 and 4 (Holson 1992). In rabbits, a dose-range finding study utilizing small groups (six per dose) observed increased post-implantation loss, early resorptions, a 23% decrease in fetal body weight, and increased external fetal malformations compared to historical controls (Denny and Gerhart 1991). These findings were confirmed in the main teratology study, which showed increased post-implantation loss, early resorptions, and a 9–33% decrease in fetal body weight at concentrations ≥597.9 ppm and increased malformations at 1,169.6 ppm (Denny and Gerhart 1991). At 1,168.6 ppm, visceral and skeletal malformations were observed in 4/7 and 3/7 of litters, respectively, compared to 2/22 and 1/22 control litters, respectively. However, no single visceral or skeletal malformation was increased compared to control. In both rat studies, developmental findings were only observed at concentrations observed with maternal toxicity (decreased body weight); however, in the rabbit study, maternal body weight effects were not noted until 1,168.6 ppm in the main teratology study.

In a gestational exposure study in rats designed to evaluate postnatal development, perinatal mortality of 35 and 50% was observed following maternal exposure to 225 and 642 ppm, respectively (Lehotzky et al. 1985). The study authors did not define the perinatal period in which deaths were observed; however, neurobehavioral testes were evaluated in pups through PND 90. Increased maternal mortality was also observed at 642 ppm, but not at 225 ppm. Additional effects noted at ≥225 ppm in surviving pups included hyperirritability, delayed eye opening, delayed ontogeny of reflexes, and altered performance on neurobehavioral tests between PNDs 23 and 90 (impaired motor coordination, altered motor activity, increased sensitivity to amphetamine-induced hyperactivity, and altered operant conditioning).

In a series of studies utilizing a non-traditional two-generation exposure design in rats, developmental endpoints were evaluated in F1 and F2 offspring following F0 and F1 maternal exposure to 0.01, 3.2, 32,

or 64 ppm on GDs 1–21 only (Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983). Unlike traditional two-generation studies, F1 animals were not exposed postnatally during development, and some dams were sacrificed prior to delivery while others were allowed to deliver. Despite the several limitations in this series of reports (discussed below), there is clear evidence of teratogenicity observed at ≥32 ppm, including increased fetal incidence of club foot in F1 and F2 pups and microcephaly in F2 pups. The study authors also noted increased incidence of hydrocephaly in F2 fetuses at ≥0.01 ppm and transient neurobehavioral alterations in F2 pups (impaired coordination and gait deficits) at 3.2 ppm. 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. The U.S. EPA Environmental Protection Agency (EPA) also raised questions regarding the ability to accurately measure and administer the lowest exposure level (IRIS 2002). These limitations preclude meaningful interpretation of findings at 0.01 or 3.2 ppm; therefore, these exposure levels cannot be identified as either NOAEL or LOAEL values. Thus, the LOAEL value for this study is set at 32 ppm, based on clear evidence of increased external malformations, and no NOAEL determination was included in the LSE table or figure.

Oral developmental data are limited to studies in rats and rabbits evaluating post-implantation gestational exposure in rats and rabbits. In rats, no evidence of changes in fetal survival or malformations or variations were observed at maternal doses up to 1,200 mg/kg/day on GDs 6–15 (NCTR 1984a; Tsai et al. 2000). One study reported a 6–16% decrease in fetal weight at ≥200 mg/kg/day following exposure from GD 6 to 15; maternal toxicity (decreased body weight, hindlimb paralysis) was observed at ≥400 mg/kg/day (NCTR 1984a). However, the other 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).

Rabbits may be more sensitive to developmental effects than rats following oral exposure to carbon disulfide. In a preliminary dose-range finding gestational exposure 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 higher concentrations (NCTR 1984b). In the main teratology study, increased resorptions/litter were observed at all tested concentrations (≥25 mg/kg/day) (NCTR 1984b). The total number of malformations was increased at 150 mg/kg/day, compared to control; however, there was no single, characteristic malformation associated with carbon disulfide exposure. There was a dose-related trend toward decreased fetal body weight, but none of the dose groups differed from control.

2.18 OTHER NONCANCER

There are limited human data on potential associations between carbon disulfide exposure and increased risk or prevalence of diabetes and/or metabolic syndrome, or risk factors associated with these metabolic disorders (Table 2-19). However, findings are too limited and inconsistent to draw any conclusions.

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Metrics of Diabetes and/or Metabolic Syndrome

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Hernberg et al. 1971; Raitta et al. 1974 Longitudinal cohort; 343 workers (ages 25–64 years; median employment 11 years) employed in viscose rayon factory for at least 5 years between 1942 and 1967 and 343 matched referents from paper mill; follow-up in small subcohort of 100 exposed and 97 referents (Finland)	Measured air concentrations of carbon disulfide and hydrogen sulfide: 1940s: 20–131 ppm 1950s: 10–60 ppm 1960–1972: 4–30 ppm Geometric mean air concentration in different departments: 1967: 4–18 ppm	Glucose tolerance Baseline (1967) Follow-up (1972)	 ↔ (workers versus referents) ↔ (workers versus referents)
Jhun et al. 2007 Retrospective cohort; 198 retired viscose rayon factory workers (182 men, 16 women; mean age 58 years) with history of carbon disulfide poisoning[a] (median employment of 13.0 years and median retirement of 13.8 years) and 198 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.8 (0.1–6.6) ppm *Historical air monitoring data are unavailable.*	Blood glucose	↑ (workers versus referents)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Metrics of Diabetes and/or Metabolic Syndrome

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Jhun et al. 2009 Retrospective cohort; 170 retired viscose rayon factory workers (153 men, 17 women; median age 58 years) with history of carbon disulfide poisoning[b] and 170 age- and sex-matched referents (Korea)	Recent air monitoring data, median (range): 3.6 (0.12–6.58) ppm *Historical air monitoring data unavailable*	Metabolic syndrome (overall risk)	↑ (workers versus referents)
		Individual component risk: Abdominal obesity	↑ (workers versus referents)
		Reduced HDL-C	↔ (workers versus referents)
		Elevated blood pressure	↔ (workers versus referents)
		Elevated fasting glucose	↑ (workers versus referents)
		Elevated triglycerides	↔ (workers versus referents)
Kim et al. 2000 Retrospective cohort; 1,237 workers (887 men, 350 women; mean age 35.3 years; employed 1–≥15 years) from a viscose rayon factory and 315 unexposed referents (203 men, 112 women; mean age 32.5–38.6 years) (Korea)	Historical range of mean 8-hour TWA (1986–1992): 0.43–6.28 ppm Cumulative exposure index (ppm-years): Q1: 0 Q2: 0.1–49.9 Q3: 50.0–149.9 Q4: ≥150	Glucose tolerance	↔ (workers versus referents) ↔ (CEI)
NIOSH 1984a Retrospective cohort with a cross-sectional analysis; 146 male workers (mean age 38.2 years; mean employment 12.6 years) from a rayon staple factory and 233 referents (mean age 33.9 years, mean employment 8.7 years) (United States, Tennessee)	Exposure levels, range of means (by job), 1957–1979: Historical: 0.58–33.5 ppm Current: 0.58–12.64 ppm CEI (ppm-months): Mean: 1,249.9 Low: 500–1,000 Moderate 1,000–1,500 High: >1,500 Background (referent) exposure: Mean current: 0.2 ppm CEI: 20.8 ppm-months	Fasting blood glucose	↑ (current versus referents) ↔ (CEI)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Metrics of Diabetes and/or Metabolic Syndrome

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Schramm et al. 2016 Retrospective cohort; 290 workers (mean age 43.5 years; mean employment of 16.8 years) from the rayon industry and 137 unexposed referents (mean age 44.7 years) (Germany)	Measured air concentrations, range of means 1992–2009 (Göen et al. 2014): 2.48–10.4 ppm CEI: 256.3 ppm-years	BMI	↔ (workers versus controls) ↔ (CEI)
		Waist circumference	↔ (workers versus controls)
		Diabetes	↔ (workers versus controls) ↔ (CEI)
Sugimoto et al. 1978 Retrospective cohort; 420 rayon filament workers (mean age 41.3 years; mean employment 17.0 years) and 390 unexposed referents (mean age 42.1 years) (Japan)	Historical TWA exposure levels, ranges: Before 1955: 15–30 ppm After 1955: 5–15 ppm Worker "Index of Exposure Dosages" calculated based on TWA levels and work history: Mean: 162.5	Prevalence of diabetes	↔ (workers versus referents)
		Obesity index	↔ (index of exposure)
		Skinfold thickness	↔ (index of exposure)
Takebayashi et al. 2003 Longitudinal cohort; Japanese Rayon Workers' Health Study Group; 392 male viscose rayon workers (259 current employees and 133 former employees) and 352 referent workers; mean employment 19.3 years for current workers and 15.6 years for former workers, with average of 4 years since employment ceased (Japan)	Geometric mean of the mean air concentrations, measured twice yearly 1993–1998: 5.02 ppm	Fasting blood glucose level	↔ (current versus referents) ↔ (former versus referents)
		Fasting A1C level	↔ (current versus referents) ↔ (former versus referents)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Carbon Disulfide and Metrics of Diabetes and/or Metabolic Syndrome

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Takebayashi et al. 1998 Cross-sectional; Japanese Rayon Workers' Health Study Group; 432 male viscose rayon workers (309 spinning and refining workers, 123 other workers) and 402 unexposed referents from 11 factories; mean employment of 12.6–13.8 years (Japan)	Mean measured air concentrations (Omae et al. 1998): 4.48 ppm	Blood glucose level (non-fasting)	↔ (workers versus referents)
		A1C level (non-fasting)	↑ (workers versus referents)
Xu et al. 2021 Population-based cross-sectional study; 3,338 from Wuhan or Zhuhai City (ages 18–80 years old) (China)	Urinary TTCA levels (μg/mmol): Q1: <0.279 Q2: 0.279–0.746 Q3: 0.746–2.412 Q4: ≥2.412	Fasting plasma glucose levels	↔ (Q2 versus Q1) ↔ (Q3 versus Q1) ↔ (Q4 versus Q1) ↑ (continuous)
		Risk of diabetes	↔ (Q2 versus Q1) ↑ (Q3 versus Q1) ↔ (Q4 versus Q1) ↑ (continuous)

[a]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) "significant" workplace carbon disulfide exposure for ≥2 years; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, cerebral hemorrhage, central nervous system dysfunction, psychological disorder, hypertension, coronary artery disease, peripheral neuropathy, retinal aneurysm, optic neuritis, other retinal change, sensorineural hearing loss, renal function abnormality, liver function abnormality, or genital organ dysfunction.
[b]Criteria to qualify as a worker with history of carbon disulfide poisoning were: (1) workplace carbon disulfide exposure; (2) regular health checkups; and (3) diagnosis of one or more of the following disorders: cerebral infarction, central nervous system dysfunction, cerebral hemorrhage, peripheral polyneuropathy, retinal micro-aneurysm, retinopathy other than micro-aneurysm, optic neuritis, sensory neural hearing loss, psychosis, or coronary artery disease.

↑ = association; ↓ = inverse association; ↔ = no association; A1C = hemoglobin A1C; CEI = cumulative exposure index; HDL-C = high-density lipoprotein cholesterol; Q = quartile; TTCA = 2-thiothiazolidine-4-carboxylic acid (carbon disulfide metabolite); TWA = time-weighted average

A few occupational studies found elevated blood glucose levels in workers exposed to carbon disulfide at concentrations of ≥3 ppm, compared to referents (Jhun et al. 2007, 2009; NIOSH 1984a), while no associations were observed in other occupational studies of similar or higher exposure levels (Takebayashi et al. 1998, 2003). Occupational studies that tested workers for glucose tolerance did not observe impairments associated with exposure, either with a history of low exposure levels (0.43–6.28 ppm; Kim et al. 2000) or much higher exposure levels (10–60 ppm; Hernberg et al. 1971; Raitta et al. 1974). Consistent with these findings, the prevalence of diabetes was not associated with occupational exposure to carbon disulfide in the rayon industry in Germany (Schramm et al. 2016) or Japan (Sugimoto

et al. 1978). In a population-based, cross-sectional study in China, the risk of diabetes was increased with increasing urinary levels of TTCA (a metabolite of carbon disulfide) when TTCA was treated as a continuous variable (Xu et al. 2021). However, when the population was split into quartiles based on urinary TTCA levels, this association was only observed in the third quartile, suggesting a lack of exposure-response. Similarly, fasting plasma glucose levels were correlated with serum TTCA levels, but quartile analysis did not reveal a clear exposure response.

The overall risk of metabolic syndrome, defined as abdominal obesity, reduced serum HDL-C levels, elevated serum triglycerides, elevated blood pressure, and elevated fasting blood glucose levels, was increased in retired viscose rayon factory workers with a history of "carbon disulfide poisoning," compared to age- and sex-matched referents (Jhun et al. 2009). Individual components of metabolic syndrome that were associated with exposure included abdominal obesity and fasting blood glucose. "Carbon disulfide poisoning" was not further defined, and only recent air monitoring data were available for this cohort (0.12–6.58 ppm). No other studies identified specifically evaluated metabolic syndrome. However, no associations were observed between occupational exposure and BMI or waist circumference in workers exposed to 2.48–10.4 ppm (Schramm et al. 2016) or obesity or skinfold thickness in workers exposed to 5–30 ppm (Sugimoto et al. 1978).

Mechanisms of Altered Glucose Homeostasis. Rich et al. (2016) proposed that carbon disulfide dysregulates normal glucose metabolism via disruption of the tryptophan metabolism pathway. Several studies have shown that carbon disulfide alters the balance between different forms of vitamin B_6; this imbalance disrupts the kynurenine pathway through which tryptophan is metabolized.

2.19 CANCER

Data pertaining to cancer in humans following exposure to carbon disulfide are limited. As discussed in Section 2.2 (Death), occupational studies have not observed excess deaths attributable to neoplasms in cohorts of workers exposed to carbon disulfide (Liss and Finkelstein 1996; Lyle 1981; MacMahon and Monson 1988; Nurminen and Hernberg 1985; Swaen et al. 1994).

Checkoway et al. (1984) reported a nested case-control study of 11 cases of lymphocytic leukemia and 1,350 controls in rubber workers to evaluate potential associations with solvent exposure. These cases were identified from the 15 cases that were first presented by Arp et al. (1983), excluding 4 cases that had benzene exposure, and solvent-specific analyses were conducted. Categories of exposure were based on

process descriptions for the person's job classification and not on ambient air measurements. Of the 11 cases, 7 had carbon disulfide exposure based on job history. Analysis showed an association between exposure to carbon disulfide and increased risk of lymphocytic leukemia. This association was noted for other solvents used in the rubber industry (e.g., carbon tetrachloride, ethyl acetate, hexane). Another study on this cohort of rubber workers evaluated potential associations between solvent exposures in the rubber industry and mortalities due to stomach cancer, respiratory system cancers, prostate cancer, lymphosarcoma, or lymphatic leukemia (Wilcosky et al. 1984). The risk of mortality from lymphatic leukemia (n=6) and, to a lesser extent, lymphosarcoma (n=7) was increased in workers with a history of exposure to carbon disulfide. Similar findings were observed for carbon tetrachloride in this cohort. The study authors noted that the small number of cases and multiple solvent exposures in this cohort preclude firm conclusions regarding associations between any specific solvent and risk of lymphocytic leukemia and/or lymphosarcoma.

The association between maternal exposure to carbon disulfide during pregnancy and childhood cancers was examined in a case-control study consisting of 15,744 cancer cases in children 0–19 years of age and 283,141 controls (Chen et al. 2024). Maternal exposure to carbon disulfide was classified as "ever/never" exposed based on residential proximity to industrial releases using EPA's Toxics Release Inventory (TRI) site data. Analysis showed children of ever-exposed mothers had an increased risk of ependymoma.

No association between ambient air levels of carbon disulfide and incidence of colorectal cancer in Arkansas was observed in an ecological study (Su et al. 2022). Ambient emissions of carbon disulfide were not associated with lung cancer in an ecological study using several U.S. data sources from 2000 to 2017 (Kamis et al. 2021).

No studies were located regarding cancer in animals after exposure to carbon disulfide.

IRIS (2002), IARC (2023), and NTP (2021) have not evaluated the potential for carbon disulfide to cause carcinogenicity in humans.

2.20 GENOTOXICITY

Available evidence indicates that carbon disulfide is not mutagenic. However, there is limited evidence that carbon disulfide, or a reactive metabolite, may be clastogenic and/or deoxyribonucleic acid (DNA)

damaging to at least some cell types. The results of *in vitro* and *in vivo* genotoxicity studies with carbon disulfide are summarized in Tables 2-20 and 2-21, respectively.

Table 2-20. Genotoxicity of Carbon Disulfide *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium TA98, TA100*; Escherichia coli* WP2 uvrA	Reverse mutation	–	–	Donner et al. 1981
S. typhimurium TA1535, TA1537, TA98, TA100	Reverse mutation	–	–	Haworth et al. 1983
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Reverse mutation	–	–	Hedenstedt et al. 1979
S. typhimurium TA1535, TA1537, TA98, TA100	Reverse mutation	–	–	May 1992
Mammalian cells				
Primary human lymphocytes	Chromosome aberrations	+	–	Garry et al. 1990
Primary human sperm	Chromosome aberrations	Not tested	+	Le and Fu 1996
Primary human lymphocytes	Sister chromatid exchange	+	–	Garry et al. 1990
Human embryonic lung WI-38 cells	Unscheduled DNA synthesis	–	–	NIOSH 1980

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

Table 2-21. Genotoxicity of Carbon Disulfide *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Human (inhalation)	HPRT mutations (circulating lymphocytes)	–	Pappuswamy et al. 2018
Rat (inhalation)	Dominant lethal mutations	–	NIOSH 1980
Mouse (inhalation)	Reverse mutation (host-mediated TA98 implanted in peritoneal cavity)	–	NIOSH 1980
Human (inhalation)	Chromosome aberrations (circulating lymphocytes)	+	Pappuswamy et al. 2018
Rat (inhalation)	Chromosome aberrations (bone marrow)	–	NIOSH 1980

Table 2-21. Genotoxicity of Carbon Disulfide *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Human (inhalation)	Sister chromatid exchanges (circulating lymphocytes)	+	Pappuswamy et al. 2018
Mouse (inhalation)	Micronuclei (bone marrow)	–	Dance 1992
Human (inhalation)	DNA damage (buccal cells)	+	Pappuswamy et al. 2023
Human (inhalation)	Unscheduled DNA synthesis (circulating lymphocytes)	–	Pappuswamy et al. 2018
Human (inhalation)	Oxidative DNA damage (urinary 8-OH-dG)	+	Song et al. 2023
Human (inhalation)	Oxidative DNA damage (urinary 8-OH-dG)	+	Xu et al. 2021
Mouse (intraperitoneal)	Oxidative DNA damage (8-OH-dG in uterine tissue)	+	Yang et al. 2014
Mouse (intraperitoneal)	DNA damage (endometrial cells)	+	Zhang et al. 2013
Nonmammalian eukaryotic organisms			
Drosophila melanogaster	Sex-linked recessive lethal mutations	–	Donner et al. 1981
D. melanogaster	Sex-linked recessive lethal mutations	–	NIOSH 1980

+ = positive result; – = negative result; 8-OH-dG = 8-hydroxy-2-deoxyguanosine; DNA = deoxyribonucleic acid

Several studies indicate that carbon disulfide is not mutagenic in bacterial systems with or without metabolic activation (Donner et al. 1981; Hedenstedt et al. 1979; May 1992; NIOSH 1980). In a host-mediated assay, mutations were not induced in *Salmonella typhimurium* implanted into the peritoneal cavity of mice prior to inhalation exposure to carbon disulfide (NIOSH 1980). Additionally, carbon disulfide did not induce dominant lethal mutations in rats (NIOSH 1980) or sex-linked recessive mutations in *Drosophila melanogaster* (Donner et al. 1981; NIOSH 1980). Mutations at the HPRT locus were not elevated in workers occupationally exposed to low levels of carbon disulfide (0.46 ppm) in the viscose rayon industry (Pappuswamy et al. 2018).

There is some evidence that carbon disulfide and/or a reactive metabolite is clastogenic. *In vitro*, carbon disulfide induced chromosome aberrations and sister chromatid exchanges in primary human lymphocytes with metabolic activation, but not without metabolic activation, suggesting that transformation to a reactive metabolite is required for clastogenicity (Garry et al. 1990). However, chromosome aberrations were induced in cultured human sperm in the absence of metabolic activation; tests were not conducted in the presence of metabolic activation in this study (Le and Fu 1996). Both chromosomal aberrations and sister chromatid exchanges were elevated in circulating lymphocytes of

workers occupationally exposed to low levels of carbon disulfide (0.46 ppm) in the viscose rayon industry (Pappuswamy et al. 2018). In *in vivo* studies in animals, neither chromosome aberrations nor micronuclei were induced in rat or mouse bone marrow, respectively, following acute-duration inhalation exposure to concentrations up to 40 ppm in rats (NIOSH 1980) or 4,671 mg/m^3 (1,500 ppm) in mice (Dance 1992).

Unscheduled DNA synthesis was not observed in human embryonic lung cells with or without metabolic activation (NIOSH 1980). Similarly, unscheduled DNA synthesis was not observed in circulating lymphocytes from workers occupationally exposed to low levels of carbon disulfide (0.46 ppm) in the viscose rayon industry (Pappuswamy et al. 2018). However, the percent DNA damage detected in the Comet assay was increased in buccal cells of rubber workers from India exposed to unreported levels of carbon disulfide when subjects were dichotomized by smoking status (Pappuswamy et al. 2023). Additionally, population-based, cross-sectional studies from the Wuhan-Zhuhai cohort from China reported positive associations between biomarkers of carbon disulfide exposure (urinary levels of TTCA) and biomarkers of oxidative DNA damage (urinary 8-hydroxy-2-deoxyguanosine [8-OHdG] levels) (Song et al. 2023; Xu et al. 2021). In mice, a single intraperitoneal injection of carbon disulfide induced direct DNA damage in endometrial cells and 8-OHdG in uterine tissue (Yang et al. 2014; Zhang et al. 2013).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Absorption:
  - Available data from human and animal studies indicate that carbon disulfide is extensively and rapidly absorbed via inhalation, oral, and dermal routes.
  - Inhalation studies indicate that a minimum of 80% of the inhaled dose in humans is absorbed. Similar results were observed in laboratory animals, with absorption of approximately 70–80% of the administered dose.
  - No information on the oral absorption of carbon disulfide in humans was identified. In rats, at least 63% of an intragastric dose was absorbed, based on measurements of carbon disulfide in exhaled air.
  - Dermal absorption of carbon disulfide occurs in animals and humans; however, accurate quantitative estimates have not been reported.

- Distribution:
  - Absorbed carbon disulfide is distributed throughout the body. Because of its lipophilic nature, its distribution is greatest in organs, such as the brain and liver.
  - Carbon disulfide is also distributed to the developing fetus and into breast milk.

- Metabolism:
  - Carbon disulfide is metabolized by cytochrome P-450 to an unstable oxygen intermediate that either spontaneously degrades to atomic sulfur and carbonyl sulfide or hydrolyzes to form atomic sulfur and monothiocarbonate. Carbonyl sulfide is converted to monothiocarbonate, which degrades to generate carbonyl sulfide or forms carbon dioxide and hydrogen sulfide.
  - Conjugation of carbon disulfide or carbonyl sulfide with endogenous glutathione results in formation of TTCA and 2-oxythiazolidine-4-carboxylic acid, respectively.
  - Species differences exist in the metabolism of carbon disulfide. Oxidation of sulfur to inorganic sulfate occurs in animals but is not a significant metabolic pathway in humans. However, this observation is based on limited data.

- Excretion:
  - Renal excretion is the primary route of excretion of carbon disulfide metabolites.
  - Unmetabolized carbon disulfide is exhaled in air, with small amounts (<1%) excreted in the urine.

- Toxicokinetics models:
  - No pharmacokinetic models for carbon disulfide were identified.

3.1.1 Absorption

Inhalation Exposure. Studies conducted on human subjects reported rapid and extensive absorption of inhaled carbon disulfide. Rapid absorption was demonstrated in a study conducted on volunteers exposed

to 17–51 ppm for 1–4 hours (Teisinger and Soucek 1949). The amounts of carbon disulfide retained in the body and excreted by the lungs and kidneys were determined by measuring the carbon disulfide in inspired and expired air, blood, and urine during and after completion of the experiment until it disappeared from the urine and blood. About 80% of the inhaled carbon disulfide was retained during the first 15 minutes of exposure, which decreased to about 40% after 45 minutes and remained at that level for the rest of the exposure period. Systemic absorption of at least 80% of the total inhaled dose indicates high bioavailability via the inhalation route. The degree of retention did not depend on the exposure concentration. Only 5% of the retained carbon disulfide at the end of the exposure period was subsequently eliminated in the exhaled air. About 0.06% of the retained carbon disulfide was excreted unchanged in the urine and was detectable 24 hours after exposure. In another retention study involving exposure to vapor for an unspecified period (Soucek 1957), about 10–30% of the retained carbon disulfide was exhaled and <1% was excreted in urine as carbon disulfide. The concentration of inhaled carbon disulfide was not reported. About 70–90% of absorbed carbon disulfide was metabolized.

Studies in animals indicate that carbon disulfide is rapidly absorbed following inhalation exposure. Absorption of carbon disulfide was studied by evaluating pulmonary and urinary excretion of carbon disulfide during and after exposure. Studies in rats show rapid uptake of inhaled carbon disulfide during a 180-minute exposure, with a blood half-time of 6–9 minutes (Moorman et al. 1998). Blood levels reached a plateau after approximately 90 minutes, with blood concentration proportional to exposure level at concentrations of 50–800 ppm. However, peak blood levels were lower in females than males (Moorman et al. 1998). Studies in rabbits indicate that an equilibrium concentration of carbon disulfide is reached after inhalation exposure to 20–150 ppm for 1.5–2.0 hours (Toyama and Kusano 1953). About 70–80% of the inhaled carbon disulfide was absorbed. After termination of exposure, 15–30% of the absorbed carbon disulfide was excreted through the lungs and <0.1% was excreted by the kidneys. In dogs exposed to 25–60 ppm carbon disulfide, equilibrium concentrations in blood were attained after 0.5–2.0 hours (McKee et al. 1943). Desaturation of blood carbon disulfide was almost complete within the first 30–60 minutes after exposure. Approximately 8–13% of the retained carbon disulfide was exhaled, <0.5% was excreted in the urine, and none was excreted in the feces. Excretion in the urine occurred within 2 hours of exposure. Freundt et al. (1975) observed that an equilibrium concentration of carbon disulfide in blood was attained after exposure of rats to 400 ppm carbon disulfide for 1 hour. Equilibrium was reached in liver and blood 1–8 hours after exposure. Elimination of free carbon disulfide from these tissues was rapid, with an estimated half-life in the blood of 35 minutes and in the liver of approximately 1 hour.

The data presented above indicate that carbon disulfide is absorbed by humans and animals following inhalation exposure and reaches equilibrium rapidly (0.5–8 hours) across a wide range of doses and exposure durations.

Oral Exposure. No studies were located regarding absorption of carbon disulfide following oral exposure of humans. In rats, intragastric administration of 10 mg/kg ^{14}C-carbon disulfide resulted in exhalation of 63% of the dose within 4 hours as unchanged carbon disulfide (DeMatteis and Seawright 1973). It is evident from these results that a large fraction of orally administered carbon disulfide is absorbed by rats.

Dermal Exposure. Dermal exposure of humans to aqueous solutions of carbon disulfide resulted in significant absorption through the skin. A series of experiments were performed to investigate the rate of absorption of carbon disulfide by immersion of the hand in aqueous solutions of increasing concentrations (0.33–1.67 g/L) for 1 hour (Dutkiewicz and Baranowska 1967). Absorption was calculated indirectly by determining carbon disulfide elimination by the lung or directly by measuring carbon disulfide concentration in the solutions before and after immersion of the hand. Rates of absorption of carbon disulfide, determined from analysis of the solutions, ranged from 0.232 to 0.789 mg/cm^2/hour and were about 10 times higher than rates calculated from lung excretion of carbon disulfide. In the former case, 25% of the absorbed dose was exhaled in the desaturation period; in the latter, only 3% was eliminated in the expired air. These findings suggest that carbon disulfide excretion varies with the route of absorption. This study provided only brief details of the experimental procedure, and therefore, factors other than absorption through the skin (e.g., evaporation) may have accounted for the reduced carbon disulfide concentration noted at the end of the experimental period. Nevertheless, these results suggest that rapid absorption of carbon disulfide can occur in humans through skin. Occupational exposure of persons with pathological skin conditions has also been noted to increase the dermal absorption of carbon disulfide (Drexler et al. 1995). *In vitro*, the short-term dermal absorption rates for carbon disulfide through cadaver skin, when applied in isopropyl myristate, were 33.8 µg/cm^2/hour for 10 minutes and 4.38 µg/cm^2/hour for 60 minutes, based on the amount of carbon disulfide on the receptor fluid and in the skin (Fasano and McDougal 2008). A skin permeability coefficient of 0.0033 cm/hour was calculated.

The limited information available on skin absorption in animals indicates that carbon disulfide is appreciably absorbed. Exposure of rabbit skin to high concentrations of the vapor (≥800 ppm) for 1 hour resulted in detectable amounts of carbon disulfide in the breath (Cohen et al. 1958). A linear relationship was noted between the dermal exposure concentration and the amount of carbon disulfide exhaled. No

detectable carbon disulfide was found in the breath of rabbits exposed to 150 ppm vapor by skin contact for 6 hours (Cohen et al. 1958).

3.1.2 Distribution

Absorbed carbon disulfide is taken up by the blood (McKee et al. 1943) and is distributed throughout the body (Brieger 1967). Milk from nursing mothers occupationally exposed to carbon disulfide was found to contain an average of 12.3 µg carbon disulfide/100 mL (Cai and Bao 1981). Exposure concentrations of carbon disulfide ranged from 9.3 to 21.1 ppm for a 6.5-hour period. Exposure to 7.4–40 ppm for a shorter duration (2–4 hours) resulted in a lower average milk concentration of 6.8 µg/100 mL.

The distribution of carbon disulfide following inhalation exposure has been studied in rabbits and rats (Toyama and Kusano 1953). In rabbits, blood equilibrium concentrations of carbon disulfide were reached after exposure to 20–150 ppm for 1.5–2.0 hours. In rats exposed to 60–350 ppm carbon disulfide, distribution was primarily to the brain, kidney, and liver. Blood equilibrium concentrations for various carbon disulfide exposures in rats were not reported. Although carbon disulfide was rapidly eliminated from rat tissues during the first 6–8 hours after exposure, low concentrations of carbon disulfide were still detected in the tissues 20 hours after exposure. A separate study reported that equilibrium concentrations of carbon disulfide in blood were attained in dogs after 0.5–2.0 hours of exposure to 25–60 ppm carbon disulfide (McKee et al. 1943). Desaturation was largely complete within the first 30–60 minutes after inhalation exposure. Anesthetized male Sprague-Dawley rats exposed to 640 ppm carbon disulfide had an exponential increase in carbon disulfide in the blood which reached an apparently steady state after 90 minutes of exposure. In all tissues except fat, the carbon disulfide concentration approached steady state within 4–5 hours of exposure. Loss of free carbon disulfide was rapid from all tissues except the liver and kidneys, which retained 25 and 29%, respectively, at 8 hours postexposure (McKenna and DiStefano 1977).

Inhalation exposure of pregnant mice to carbon disulfide during gestation resulted in rapid absorption and distribution of carbon disulfide and its metabolites in embryonic and fetal tissues within 1 hour (Danielsson et al. 1984). Pregnant mice were exposed via inhalation to 25 microcuries (µCi) ^{35}S- or ^{14}C-carbon disulfide for 10 minutes on GD 9, 14, or 17. The levels of ^{35}S-labelled metabolites in the embryonic neuroepithelium were higher in the fetal brain than in the maternal brain during early gestation (GD 9). The concentrations in the fetal brain, eyes, and skeleton exceeded that of other fetal organs during mid-gestation (GD 14). In late gestation (GD 17), the levels in the fetal and maternal brain were

relatively low, but high uptake of radioactivity was seen in the placenta, fetal blood, liver, and eyes. During early gestation, the distribution of ^{14}C-labelled metabolites was similar to that of ^{35}S-labelled metabolites with an immediate higher uptake in the embryo (including neuroepithelium) than in the maternal serum. On GDs 14 and 17, radioactivity was present in the ventricle of the fetal brain. High levels were detected in the fetal liver and blood at late gestation (GD 17). In contrast to ^{35}S-labelled metabolites, ^{14}C-labelled metabolites were retained longer (up to 24 hours) in the fetal brain and liver. High concentrations of ^{14}C-labelled metabolites were also seen in the fetal urinary tract. Thus, the distribution pattern varied with the age of the conceptus and also with the radiolabel of carbon disulfide. These results indicate that carbon disulfide and its metabolites pass through the placenta at all stages of gestation and localize selectively in various tissues of the body.

The distribution of free carbon disulfide and bound carbon disulfide liberated by acid hydrolysis was investigated in the tissues of white rats after a large, single subcutaneous dose (approximately 361 mg/kg) of carbon disulfide (Bartonicek 1957, 1959). Results of these studies indicate that following absorption, free carbon disulfide is rapidly removed from the blood and tissues. Negligible blood levels were present 11 hours after the dose was administered (Bartonicek 1957, 1959). Initially, free carbon disulfide accumulated in the blood, adrenals, and brain, but levels in the organs rapidly decreased, and only very small amounts were present after 10–16 hours.

A similar rapid reduction of free carbon disulfide levels in the blood was noted when radiolabelled ^{35}S-carbon disulfide was administered parenterally to guinea pigs (Strittmatter et al. 1950). About 20–50% of intracardially injected ^{35}S-carbon disulfide was retained; the amount of material retained depended on the concentration of dose administered. The largest amount of radiolabel appeared in the liver (0.42–0.56 µg) and the least amount in the brain (0.03–0.05 µg) at 1.5 hours following injection. Only 10% of the labelled compound remained in the tissues after 48 hours. Urinary and fecal excretion was not reported. In guinea pigs exposed to carbon disulfide vapors (13.6–25.7 ppm), the liver contained the most ^{35}S-label, followed by the blood, then the brain. Forty-eight hours later, 30–50% of ^{35}S-label remained in the tissues such as blood, liver, brain, kidney, and skin. The urinalyses revealed that urinary ^{35}S-label was about 30% of the retained sulfur, with about 85 or 90% of it appearing in the first 24-hour output, the larger part of the metabolized material in the urine being excreted as inorganic sulfate. The feces contained about 5–15% metabolized ^{35}S-label, the amount of which increased with the increasing dose of carbon disulfide.

Only metabolites of carbon disulfide were found 3 hours after a dose of ^{14}C- or ^{35}S-labeled carbon disulfide was intraperitoneally administered (Snyderwine and Hunter 1987). Distribution varied with the age of the rat and the radiolabel injected. Following intraperitoneal administration of ^{14}C-carbon disulfide, 4–9% of the dose was metabolized to carbon dioxide depending on age. Significantly more carbon disulfide was metabolized to carbon dioxide by 30- and 40-day-old rats than by 1–20-day-old rats. The biotransformation products of carbon disulfide that were covalently bound remained in tissues from rats of all ages. Twenty-four hours after dosing with ^{35}S-labeled carbon disulfide, up to 13 times more labeled metabolites were covalently bound in organs from 1-day-old rats than in similar organs from 40-day-old rats.

The data presented above indicate that the absorbed carbon disulfide is rapidly distributed via blood to other tissues irrespective of the route of exposure.

3.1.3 Metabolism

Limited information is available on the biotransformation of carbon disulfide in humans, and the metabolic products of carbon disulfide are not completely known. Beauchamp et al. (1983) provided an overview of carbon disulfide metabolism based on *in vivo* animal studies, *in vitro* assays, and postulated pathways of metabolism. *In vivo* animal studies and in *in vitro* assays demonstrate that carbon disulfide is metabolized by cytochrome P-450 to an unstable oxygen intermediate. *In vitro* assays indicate that the unstable intermediate may either spontaneously degrade to atomic sulfur and carbonyl sulfide or hydrolyze to form atomic sulfur and monothiocarbonate. The atomic sulfur generated in these reactions may either covalently bind to macromolecules or be oxidized to products such as sulfate. It was postulated that carbonyl sulfide may be converted to monothiocarbonate by carbonic anhydrase and that monothiocarbonate may further spontaneously degrade, regenerating carbonyl sulfide or forming carbon dioxide and sulfide bisulfide ion (HS^-). The HS^- formed may subsequently be oxidized to sulfate or other nonvolatile metabolites.

Dithiocarbamates are the products of the reaction of carbon disulfide with amino acids (Brieger 1967). *In vitro* studies demonstrated that carbon disulfide readily combines with the amino acids in human blood, the half-life of this reaction being approximately 6.5 hours (Soucek 1957). Thiocarbamide has been found in the urine of exposed workers (Pergal et al. 1972b). After inhalation exposure of male subjects, up to 90% of the retained carbon disulfide was metabolized while the remainder was eliminated unchanged by various routes (McKee et al. 1943). High levels of thiocarbamide and trace amounts of

2-thio-5-thiazolidinone were identified by chromatographic analysis of the urine of workers exposed to carbon disulfide by inhalation (Pergal et al. 1972a, 1972b). Van Doorn et al. (1981a, 1981b) reported conjugation of carbon disulfide or carbonyl sulfide with endogenous glutathione to yield TTCA and 2-oxythiazolidine-4-carboxylic acid, respectively. High concentrations (approximately 320 mM) of TTCA were detected in the urine of women exposed to approximately 32 ppm (100 mg/m^3) carbon disulfide through inhalation.

The formation of trithiocarbonates has been demonstrated *in vitro* under physiological conditions due to reaction of carbon disulfide with various thiols (Souza et al. 2017). Trithiocarbonates either underwent slow cyclization to TTCA or decayed to carbon disulfide. The rate of formation of trithiocarbonates was pH-dependent, while decay was pH-independent.

In contrast to the results obtained in animals, oxidation to inorganic sulfate does not appear to contribute significantly to the metabolism of carbon disulfide in humans. A marked increase in inorganic sulfate excretion in the urine was noted in a case study of a young worker with signs of carbon disulfide poisoning because of exposure to high levels of the vapor; no increase was noted in the amount of inorganic sulfate excreted in the urine (Djerassi and Lumbroso 1968). However, exact dose, mode of exposure, and duration were not presented in the study.

Carbon disulfide is oxidized by the liver MFO system to carbonyl sulfide, which then undergoes further desulfurization, releasing elemental sulfur. This reaction has been shown to occur *in vitro* (Dalvi et al. 1974; DeMatteis 1974). *In vivo* studies in rats using ^{14}C-labelled carbon disulfide demonstrated that significant amounts (80%) of $^{14}CO_2$, are exhaled after exposure to carbon disulfide. Following intraperitoneal administration of approximately 100 mg carbon disulfide/kg, about 5% of the total dose was excreted in the breath as carbon dioxide. This amount was increased to 13% in animals pretreated with phenobarbital to induce liver microsomal enzymes (DeMatteis and Seawright 1973). Snyderwine and Hunter (1987) found that 4–9% of an intraperitoneally administered dose of ^{14}C-carbon disulfide was excreted as $^{14}CO_2$ in expired air, with 30- and 40-day-old rats excreting more (9 versus 4%) $^{14}CO_2$, than 1–20-day-old rats. Increased expiration of $^{14}CO_2$ in older rats was attributed to increased hepatic MFO activity at 30–40 days, compared to 1–20 days, resulting in increased metabolism of carbon disulfide to carbon dioxide.

The metabolic formation of carbonyl sulfide from carbon disulfide was confirmed in an *in vivo* study (Dalvi and Neal 1978). After intraperitoneal injection of ^{14}C-carbon disulfide in nonpretreated rats,

carbonyl sulfide was excreted by the lung in greater quantities than carbon dioxide. Pretreatment with phenobarbital, however, resulted in a greater amount of excretion of carbon dioxide than carbonyl sulfide. In both experiments, excretion of ^{14}C-carbonyl sulfide and carbon dioxide accounted for 14–43% of the total administered radioactivity, with about twice as much carbon dioxide. These results indicate that phenobarbital treatment caused induction of cytochrome P-450 which catalyzed the conversion of carbon disulfide to carbonyl sulfide faster in pretreated rats than in rats not pretreated with phenobarbital. The role of the cytochrome P-450 monooxygenase system in catalyzing carbonyl sulfide formation was also confirmed by *in vitro* studies (Dalvi et al. 1974, 1975). The rate of carbonyl sulfide formation was NADPH-dependent and increased with microsomes obtained from phenobarbital-treated rats.

In a study designed to examine the effect of P-450 induction on the metabolism of carbon disulfide to TTCA, rats were treated with nothing, ethanol, phenobarbital, 3-methylcholanthrene, or both phenobarbital and ethanol before being exposed to carbon disulfide at 50 ppm for 6 hours (Kivistö et al. 1995). After 7 days, the pretreatment regimens were repeated in the same rats, and the rats were again exposed to carbon disulfide at 500 ppm for 6 hours. None of the inducers had any effect on urinary excretion of TTCA. About 7.6 and 2.3% of the dose was excreted as TTCA at 50 and 500 ppm, respectively, suggesting saturation. However, the investigators speculated that saturation may not have occurred because the physical activity level of the rats was reduced at 500 ppm, suggesting that carbon disulfide uptake at 500 ppm may also have been reduced because of the lowered respiratory rate. They also noted that the saturation observed in rats is not likely to occur in humans at the prevailing occupational exposure concentrations. Saturation of TTCA production was observed in an oral study in rats (Kivistö et al. 1995). In rats treated with a single gavage dose of 1, 10, 30, or 100 mg/kg, 4.6, 2.4, 1.7, and 0.8%, respectively, of the dose was excreted in the urine as TTCA. A 13-week study in rats also indicates saturation of carbon disulfide metabolism at high inhalation exposure levels, with plateauing of blood carbon disulfide and urinary TTCA levels at concentrations ≥500 ppm (Moorman et al. 1998).

The effect of P-450 induction or glutathione depletion on carbon disulfide metabolism to TTCA in rats following oral exposure has also been studied (Kivistö et al. 1995). The rats were pretreated with nothing, acetone, phenobarbital, 3-methylcholanthrene, or three inhibitors of glutathione production, namely phorone, diethylmaleate, or buthionine sulfoximine, before being given a single gavage dose of carbon disulfide at 26–34 mg/kg. Phenobarbital decreased the output of TTCA by 21% during the first 12 hours of the urine collection. None of the other P-450 inducers had any effects on TTCA excretion, and the investigators suggested that the effect of phenobarbital may have been a result of cytochrome P-450 aggregation. Buthionine sulfoximine, an inhibitor of glutathione production, reduced the total

output of TTCA by 37%. Phorone and diethylmaleate pretreatment, which transiently reduce glutathione, decreased TTCA excretion.

3.1.4 Excretion

Following inhalation exposure, the primary route of excretion of unmetabolized carbon disulfide in humans is exhalation. In one study, it was estimated that 6–10% of the carbon disulfide that was taken up was excreted by the lungs (McKee et al. 1943). In a study conducted on humans, carbon disulfide levels in the exhaled breath decreased rapidly on cessation of exposure (Soucek 1957). The excretion by the lung accounted for 10–30% of the absorbed carbon disulfide. Less than 1% was excreted unchanged in the urine. The remaining 70–90% of the dose was metabolized. The details regarding carbon disulfide exposure levels were not available. A correlation was established between carbon disulfide exposure of rayon workers and urinary excretion of a metabolite or metabolites that catalyzed the reaction of iodine with sodium azide (Djuric 1967). This test indicated exposures to carbon disulfide above 16 ppm but failed to identify specific urinary metabolites. The failure to detect carbon disulfide exposure <16 ppm may be because of interference with the reaction by dietary sulfur containing compounds.

An occupational study in 10 rayon factory workers in China showed that the carbon disulfide metabolite, TTCA, undergoes first-order elimination kinetics, based on urinary excretion studies (Chang et al. 2002). First-order elimination kinetics for TTCA was also observed in rats (Cox et al. 1996). Mean urinary elimination half-times following inhalation exposure in rats for TTCA and total thioesters were 5.2 and 8.5 hours, respectively (Cox et al. 1996).

In dogs exposed to 25–60 ppm carbon disulfide for 0.5–2.0 hours, approximately 8–13% of the carbon disulfide that was taken up was exhaled; <0.5% was excreted in the urine (McKee et al. 1943). Experimental details and control information are limited in this study. Inhalation exposure of rabbits to 20–150 ppm carbon disulfide for 1.5–2 hours resulted in excretion of 15–30% of the absorbed carbon disulfide via the lung and <0.1% by the kidney after termination of exposure (Toyama and Kusano 1953). In rats exposed to 500–800 ppm for 180 minutes, absorbed carbon disulfide was rapidly eliminated from the blood with elimination half-times of 41–77 minutes; elimination was biphasic (Moorman et al. 1998).

In guinea pigs, carbon disulfide metabolites are excreted as inorganic sulfur compounds in the urine (Strittmatter et al. 1950). Inhalation exposure to 25.7 ppm ^{35}S-carbon disulfide for 40 hours resulted in excretion of the 61% absorbed dose within 48 hours, mainly in the urine (33% of absorbed dose) with

smaller amounts in expired air (15%) and feces (13%). The remaining 39% of the labelled compound was found in the carcass, skin, liver, and brain. The metabolized material was excreted in the urine predominantly in the form of inorganic sulfur compounds; some organosulfur derivatives were also present. Most of the unmetabolized carbon disulfide was excreted in the expired air.

The studies discussed above indicate that the lungs are the primary route of excretion of unmetabolized carbon disulfide in humans and animals exposed by inhalation, whereas the kidneys are the primary route of excretion of carbon disulfide metabolites.

No studies were located regarding excretion of carbon disulfide in humans after oral exposure. Rats administered 10 mg ^{14}C-carbon disulfide/kg by gavage excreted 63.2% of the dose as unchanged carbon disulfide in the breath (DeMatteis and Seawright 1973).

Following dermal exposure of humans to aqueous solutions of carbon disulfide of increasing concentrations (0.33–1.67 g/L) for 1 hour, only 3% of the absorbed carbon disulfide was eliminated by the lungs (Dutkiewicz and Baranowska 1967). For details and study limitations, see Section 3.1.1.

Exposure of rabbit skin to high concentrations of carbon disulfide vapor (800 ppm and above) for 1 hour resulted in detectable amounts of carbon disulfide in the breath of the animals (Cohen et al. 1958). A linear relationship was noted between the exposure concentration and the amount of carbon disulfide in the exhaled breath.

Appreciable amounts of absorbed carbon disulfide are excreted unchanged in breath regardless of the route of exposure. Small amounts of carbon disulfide are excreted in the sweat and saliva of exposed individuals. In mice injected intraperitoneally with 30.2–41.9 µg of ^{35}S-carbon disulfide, about 13–23% of the radiolabel was excreted via the lung (Strittmatter et al. 1950). Rats receiving 10 mg ^{14}C-carbon disulfide/kg by intraperitoneal injection excreted about 70% of the dosed material as unchanged carbon disulfide in the breath (DeMatteis and Seawright 1973). Rats receiving 19 mg/kg ^{14}C-carbon disulfide intraperitoneally excreted 58–83% free carbon disulfide in expired air in the 3 hours following dosing (Snyderwine and Hunter 1987). Younger rats expired significantly more free carbon disulfide than older rats. In another study (Dalvi and Neal 1978), intraperitoneal administration of ^{14}C-carbon disulfide to rats resulted in excretion of carbonyl sulfide by the lungs in greater quantities than carbon dioxide. Pretreatment of rats with phenobarbital, however, resulted in a greater amount of excretion of carbon

dioxide than carbon disulfide. In both experiments, excretion of ^{14}C-carbonyl sulfide and carbon dioxide accounted for 14–43% of the total administered radioactivity, with about twice as much carbon dioxide.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

No PBPK models for carbon disulfide were identified.

3.1.6 Animal-to-Human Extrapolations

Toxicokinetics studies show that absorption, distribution, and excretion of carbon disulfide are similar in humans and animals, although limited quantitative data are available particularly in humans and non-primates. However, metabolism of carbon disulfide differs slightly between humans and animals, adding some uncertainty in extrapolations from animals to humans. In animals, oxidation of sulfur to inorganic sulfate occurs (Beauchamp et al. 1983); whereas limited data indicate that it is not a significant metabolic pathway in humans (Djerassi and Lumbroso 1968). Available data on this apparent difference are inadequate to quantify the impact of extrapolation between species. Additionally, this reported difference would only be relevant for animal-to-human extrapolations for endpoints potentially mediated through this specific metabolic pathway.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to carbon disulfide are discussed in Section 5.7, Populations with Potentially High Exposures.

There have been no human studies to determine the health effects of exposure to carbon disulfide in children, or whether children are more or less susceptible to the potential health effects of carbon disulfide at a given exposure level and duration of exposure. There is no information on whether the effects reported in adults following occupational exposures would be similarly observed in children.

Since there are limited data on the toxicity of carbon disulfide in children, it is assumed that the toxicity of carbon disulfide in children is similar to the toxicity observed in adults. Available developmental toxicity data from animal studies indicate that developmental toxicity in rats was generally observed at high inhalation and oral exposure levels associated with maternal toxicity (Holson 1992; NCTR 1984a; Saillenfait et al. 1989). However, a series of inhalation studies in rats reported effects below maternally toxic concentrations (Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983). Additionally, in rabbits, developmental effects were noted at exposure levels lower than those associated with maternal toxicity, particularly in oral studies (Denny and Gerhart 1991; NCTR 1984b). Therefore, it is unclear based on unavailable data if the developing fetus or infant will be more (or less) susceptible to carbon disulfide toxicity compared to an adult.

There are studies that have investigated particular metabolic traits that may result in hyper-susceptibility to carbon disulfide (Djuric et al. 1973; Stokinger and Scheel 1973). The study conducted by Djuric et al. (1973) reported on 72 workers who had been divided into three groups: 18 exposed to carbon disulfide at levels below the industrial air limit of 20 ppm (60 mg/m^3) (control group), 21 who had been exposed to levels >20 ppm but had shown no signs or symptoms of carbon disulfide intoxication (resistant group), and 33 who had polyneuritis or other signs of overexposure and had been removed from exposure (susceptible group). All individuals were administered an oral dose of 0.5 g of disulfiram (Antabuse), a compound that produces carbon disulfide when metabolized. It was assumed that carbon disulfide and disulfiram are metabolized by the same or similar enzyme system, and determination of diethyl dithiocarbamates (DDC) in urine after disulfiram administration was used to evaluate the rate at which sulfur compounds are metabolized. The excretion of DDC was significantly lowest in the susceptible group (49.70 μg/mg creatinine) when compared to both the control (160.05 μg/mg creatinine) and resistant (90.04 μg/mg creatinine) groups. These results led to the suggestion that the reduced ability of the symptomatic workers to metabolize this compound would lead to hyper susceptibility to carbon disulfide and would thus be associated with the clinical signs observed in that group. No supporting data have been located, however.

The study authors (Djuric et al. 1973) suggested that carbon disulfide exposure causes a decrease in excretion of DDC, especially in once-poisoned workers; thus, carbon disulfide exposure produced a disturbance in the metabolism of sulfur compounds. They also suggested that in the susceptible worker group, this decreased metabolic conversion appeared to persist even 5–10 years after exposure, and carbon disulfide exposure may therefore have led to an irreversible metabolic disturbance. The study authors did not speculate on the mechanism of actual metabolic inhibition, nor did they propose any genetic hypothesis.

Because it appears that one common mechanism of the cerebral, cardiovascular, and hepatic effects may be an acceleration of the arteriosclerotic process, individuals at risk for arteriosclerosis or those with early arteriosclerosis would probably be at increased risk for health effects following exposure to carbon disulfide (NIOSH 1978). The mechanism for carbon disulfide acceleration of atherosclerotic plaque formation involves direct injury to the vessel endothelium and changes in lipid homeostasis and metabolism. Studies in animals indicate that ingestion of high-fat diets increases susceptibility to atherosclerotic changes associated with carbon disulfide exposure (Antov et al. 1985; Lewis et al. 1999; Wrońska-Nofer et al. 1980).

Three other groups are recognized as being unusually susceptible to carbon disulfide: individuals with alcohol use disorder (including those treated with Antabuse), those with neuropsychic disorders, and those with vitamin B_6 deficiency (Djuric et al. 1973; Lefaux 1968; Peters et al. 1982). Individuals experiencing ethanol intoxication may also have increased susceptibility to acute-duration carbon disulfide exposures. Carbon disulfide reduces the levels of vitamin B_6, which in turn upsets carbohydrate metabolism, particularly the cerebral carbohydrates (Lefaux 1968).

There is limited evidence that genetic differences based on ethnicity may infer differential susceptibility based on occupational data for retinal microaneurysms (Sugimoto et al. 1977). While almost all available cohort studies reported retinal microaneurysms in workers exposed to >10 ppm (NIOSH 1984a; Sugimoto et al. 1976, 1977, 1978; Vanhoorne et al. 1996), a cohort in Finnish workers exposed to concentrations ranging from 5–60 ppm did not observe this association (Raitta and Tolonen 1975; Sugimoto et al. 1977).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to carbon disulfide are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by carbon disulfide are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The most sensitive biomarker for carbon disulfide that correlates best with exposure is urinary levels of the metabolite, TTCA. TTCA is formed when carbon disulfide reacts with glutathione in the body. Based on occupational exposure scenarios, TTCA has been shown to be associated with carbon disulfide exposure and uptake (Beauchamp et al. 1983; Campbell et al. 1985; Drexler et al. 1994). The American Conference of Governmental Industrial Hygienists (ACGIH) established a biological exposure index (BEI) for carbon disulfide based on urinary TTCA levels (ACGIH 1994); the BEI is a guidance value for evaluating biological monitoring data. TTCA correlates well with personal air sampling concentrations of carbon disulfide ranging from 0.2 to 30 ppm (Drexler et al. 1994; Göen et al. 2014; Meuling et al. 1990). Several studies reported increased excretion of TTCA in the urine of rayon factory workers or workers in facilities that utilize carbon disulfide (Kivistö 2000; Meuling et al. 1990; Tan et al. 2000; Thienpont et al. 1990; van Poucke et al. 1990). Cox et al. (1998) compared urinary TTCA from workers in a Virginia viscose rayon plant with those in a Tennessee rubber product facility and found that those with higher exposures to carbon disulfide had correspondingly higher urinary levels of TTCA.

One limitation of urinary TTCA levels is that this compound has been detected at low concentrations (range, 0.005–0.15 mg/g creatinine) in persons not exposed to carbon disulfide (Kivistö 2000; Lee et al. 1995). The source of this TTCA is thought to be from dietary intake, especially the consumption of brassica vegetables (e.g., cabbage, Brussels sprouts) (Kivistö 2000; Simon et al. 1994). Therefore, in persons who eat large amounts of these vegetables, measurements of urinary TTCA may overestimate carbon disulfide exposure. Baseline sampling is therefore necessary to correct for nonworkplace exposure sources.

Due to the limitations in the methodology for measuring carbon disulfide directly in blood, exhaled breath, and urine of exposed individuals, direct measurement of this compound is not the most sensitive test for determining the extent of exposure (Beauchamp et al. 1983; Campbell et al. 1985; Djuric 1967; McKee et al. 1943; WHO 1979). Additionally, these biomarkers often did not correlate well with

external exposures, especially at low concentrations. Measuring urinary carbon disulfide thiometabolites (iodine-azide test) or total concentration of urinary thio compounds (including mercapturic acids and other sulfur-containing carbon disulfide metabolites) may be potential biomarkers; however, these compounds are not specific for carbon disulfide exposure and the sensitivity of the detection methods is poor (Beauchamp et al. 1983; Tan et al. 2000; Van Doorn et al. 1981a).

3.3.2 Biomarkers of Effect

The battery of biomarkers discussed here may be used as indicators of probable carbon disulfide exposure. However, the physiological effects of carbon disulfide poisoning are numerous and range from mild to severe. Their utilization as biomarkers of effect is confounded by their occurrence in response to other epidemiological, nutritional, and environmental factors. Their significance as biomarkers is further reduced by the fact that these effects occur with great variance in the cohort-exposed population.

The following are proposed as likely biomarkers of effect for carbon disulfide; however, more information about their possible correlation with actual carbon disulfide exposure and their reliability and consistency is necessary before they can be utilized to indicate level or duration of exposure or predict potential health effects.

Changes in lipid homeostasis and metabolism are the most obvious biomarkers of carbon disulfide's vasculopathic effects. Hypercholesterolemia (Toyama and Sakurai 1967) and high β-lipoproteins in the blood (Prerovska and Drdkova 1967) have been observed by investigators following long-term occupational carbon disulfide exposure. Elevated blood lipid concentrations following long-term carbon disulfide exposure in humans may be an appropriate indicator of ensuing arteriosclerosis, clinical vasculopathy, and increased risk of cardiovascular disease (El-Sobkey et al. 1979). However, the accuracy and reliability of this parameter as a potential biomarker of exposure for carbon disulfide is questionable since many things can cause changes in lipid homeostasis. Additionally, the usefulness of this biomarker of effect may be dependent on concentration. In the studies discussed above, exposure concentrations were estimated to be 40–50 ppm with occasional peaks of ≥300 ppm (Toyama and Sakurai 1967) and 200 ppm (Prerovska and Drdkova 1967). In an industrial setting where concentrations of carbon disulfide were <5 ppm, no association was seen between urinary TTCA levels in workers and total serum cholesterol or its subfractions (Domergue et al. 2016).

More specific blood lipid parameters, however, may prove to be useful in the future. Changes have been observed in lipid homeostasis when a cytochemical enzymological examination of leukocytes and platelets was carried out for >600 exposed workers (Micu et al. 1985). Researchers found high levels of lymphocytic lipids and low levels of granulocytic lipids. Another investigator found elevated serum cholesterol and fatty acids and low cholesterol ester levels in an 11-week study of dogs. However, only the experimental animal group fed a high-fat diet showed altered lipid homeostasis. The exposed groups on normal and high-carbohydrate diets had normal serum lipid content (Lewey et al. 1941).

Several neurological parameters may be useful as more specific biomarkers of polyneuropathy from carbon disulfide exposure. CT scans, magnetic resonance imaging, and pneumoencephalography (PEG) may indicate early cerebral/cerebellar atrophy in humans (Beauchamp et al. 1983; Peters et al. 1988). EMGs have detected signs of neurogenic lesions in humans, and changes in brain EEG patterns in animals have accompanied carbon disulfide-induced central nervous system toxicity. Moreover, neurophysiological methods may be utilized to detect decreasing nerve conduction velocity, which is a biomarker of peripheral nervous system effects (WHO 1981).

In studying the effects of carbon disulfide exposure on enzyme systems of carbohydrate metabolism, McKee et al. (1943) observed that the succinic-oxidase system was inhibited. They noted a 10% decrease in the activity of this system. Carbohydrate metabolism is crucial in proper neural function; thus, succinic-oxidase activity may serve as an appropriate biomarker of nervous system effects (McKee et al. 1943).

The concentration of crosslinked red blood cell spectrin has been suggested as a marker of nerve protein crosslinking damage (Valentine et al. 1993, 1997). The proposed sequence of events is formation of dithiocarbamate protein adducts that subsequently decompose to form isothiocyanate adducts. These latter adducts can then cause the actual crosslinking of both spectrin and nerve protein. Crosslinking leads to slower nerve conduction velocities. As new red blood cells must be made to replace the damaged spectrin, the crosslinking of this protein may serve as a longer-term biomarker of carbon disulfide exposure.

In conclusion, the following summarizes possible correlative biological markers of early carbon disulfide poisoning: (1) abnormal lipid homeostasis/metabolism as indicated by hypercholesterolemia; (2) electromyographical indications of neural lesions; (3) decreased nerve conduction velocity; (4) lower succinic-oxidase enzyme activity; and (5) erythrocyte spectrin. While these biological markers are not

specific for carbon disulfide, one or more of these markers in combination may prove to be a useful biomarker for carbon disulfide effects.

3.4 INTERACTIONS WITH OTHER CHEMICALS

There is limited information on compounds that interact with carbon disulfide to alter its toxicity. Agents that induce hepatic microsomal enzymes (e.g., phenobarbital, various alcohols, chlordane) can increase toxicity of carbon disulfide exposure in rodents (Dalvi et al. 2008; El-Masry et al. 1976; Freundt et al. 1974a; Magos and Butler 1972; Magos et al. 1973; Snyderwine et al. 1988). Co-exposure to ethanol and carbon disulfide, in particular, appears to result in greater-than-additive neurotoxicity and hepatotoxicity in rats (Opacka et al. 1984; Wrońska-Nofer et al. 1986). Also, concurrent exposure of carbon disulfide and ethanol had adverse effects on the cardiovascular system (decreased heart rate and increased QRS duration) in rats (Morvai et al. 2005).

Exposure to combinations of air toxics in ambient air, including carbon disulfide, may increase severity of childhood asthma outcomes. In a population-based study in New York, New Jersey, and Connecticut, a machine-learning based study of various combinations of air toxic exposure levels during a child's birth year (by zip code) and childhood asthma outcomes in 151 children with mild to severe asthma revealed an increased risk of emergency room visits due to asthma with combined exposure to acetaldehyde, carbon disulfide, and polychlorinated biphenyls (Li et al. 2021a). Risk of emergency room visit was not associated with acetaldehyde or carbon disulfide alone; it was associated with exposure to polychlorinated biphenyls alone, but the association was stronger with combined exposure.

Many studies have shown suppression of hepatic microsomal enzymes in laboratory animals following inhalation exposure to carbon disulfide (Bond and DeMatteis 1969; El-Masry et al. 1976; Freundt et al. 1974b; Järvisalo et al. 1977; Masuda and Yasoshima 1988; Masuda et al. 1986). Due to this, carbon disulfide could potentiate toxicity of compounds that require cytochrome P-450 microsomal metabolism for detoxification or decrease toxicity for compounds that require microsomal metabolism in the liver to exert a toxic effect. For example, data from human studies support inhibition of ethanol and amidopyrine metabolism following exposure to carbon disulfide (Freundt et al. 1976; Mack et al. 1974). Carbon disulfide-induced inhibition of ethanol metabolism in humans occurred when carbon disulfide exposure was combined with moderate intake of alcohol, resulting in an increase in blood acetaldehyde levels. Similarly, oxidative N-demethylation of amidopyrine was inhibited in humans co-exposed to carbon disulfide (Mack et al. 1974).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of carbon disulfide is presented in Table 4-1. Carbon disulfide (also frequently referred to as carbon bisulfide) is an inorganic, linear, small molecule with a single carbon atom double-bonded with two sulfur atoms on opposite sides.

Table 4-1. Chemical Identity of Carbon Disulfide

Characteristic	Information	Reference
Chemical name	Carbon disulfide	NLM 2023
Synonym(s) and registered trade name(s)	Carbon bisulphide; carbon disulphide; carbon sulfide; carbon sulphide; dithiocarbonic anhydride; sulphocarbonic anhydride; Weeviltox®; Caswell No. 162®	NLM 2023
Chemical formula	CS_2	NLM 2023
SMILES	C(=S)=S	NLM 2023
Chemical structure	S=C=S	NLM 2023
CAS Registry Number	75-15-0	NLM 2023

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of carbon disulfide is presented in Table 4-2. Pure carbon disulfide is a clear colorless liquid with a pleasant odor, while the commercial version may contain small traces of other sulfur-containing substances such as hydrogen sulfide, which may give it a yellow color and unpleasant odor. It is a highly volatile, flammable, and mobile liquid that is miscible in several solvents.

Table 4-2. Physical and Chemical Properties of Carbon Disulfide

Property	Information	Reference
Molecular weight	76.15 g/mol	NLM 2023
Color	Clear, colorless, or faintly yellow	Sax and Lewis 1987
Physical state	Highly refractive, mobile liquid	Windholz 1983
Melting point	-110.8°C -111.7°C	Weast 1989 NLM 2023
Boiling point	46.5°C (at 760 torr)	Windholz 1983

Table 4-2. Physical and Chemical Properties of Carbon Disulfide

Density		
at 15°C	1.27055 g/mL	Windholz 1983
at 20°C	1.2632 g/mL	Windholz 1983
at 30°C	1.24817 g/mL	Windholz 1983
Odor	Purest distillates have sweet, pleasing, and ethereal odor; commercial and reagent grades have foul sulfuric "rotten egg" smell	ATSDR 1999; Flick 1985; Windholz 1983
Odor threshold:		
Water	0.0026 mg/L (faint odor)	Verschueren 1983
Air	0.31–0.65 mg/m^3 (0.1–0.2 ppm)	ACGIH 1986
	Low=0.0243 mg/m^3 (0.008 ppm)	Ruth 1986
	High=23.1 mg/m^3 (7.39 ppm)	Ruth 1986
	0.31 mg/m^3 (0.1 ppm) (response in 50% of subjects)	MCA 1968
	0.65 mg/m^3 (0.21 ppm) (response in 100% of subjects)	MCA 1968
	0.05 mg/m^3 (0.016 ppm) (perception in humans)	Verschueren 1983
	0.04 mg/m^3 (0.01 ppm) (nonperception with adverse reflex response in humans)	Verschueren 1983
Taste threshold	No data	
Solubility:		
Water		
at 20°C	2,940 mg/L	Windholz 1983
at 22°C	2,300 mg/L	Verschueren 1983
Organic solvents	Miscible with anhydrous methanol, ethanol, ether, benzene, chloroform, carbon tetrachloride, and oils	Windholz 1983
Partition coefficients:		
Log K_{ow}	1.84–2.16 (calculated)	Verschueren 1983
Log K_{oc}	1.68	NLM 2023
Vapor pressure		
at 0°C	127.0 mmHg	Flick 1985
at 10°C	200 mmHg	Verschueren 1983
at 20°C	260 mmHg	Verschueren 1983
at 20°C	297.5 mmHg	Timmerman 1978
at 25°C	353.6 mmHg	Worthing 1987
at 30°C	430 mmHg	Verschueren 1983
Henry's law constant at 25°C	1.33x10^{-2} atm m^3/mol	EPA 1981a
Autoignition temperature	100°C	Windholz 1983; Sax and Lewis 1987
	125–135°C	Worthing 1987
Flashpoint	-30°C (closed cup)	NFPA 1986; Sax and Lewis 1987; Windholz 1983
Flammability limits in air	1–50% (v/v) (explosive range)	Flick 1985; Windholz 1983
	1.3–50%	NFPA 1986; OSHA 2022
Conversion factors	0.32 ppm=1 mg/m^3	Beauchamp et al. 1983

Table 4-2. Physical and Chemical Properties of Carbon Disulfide

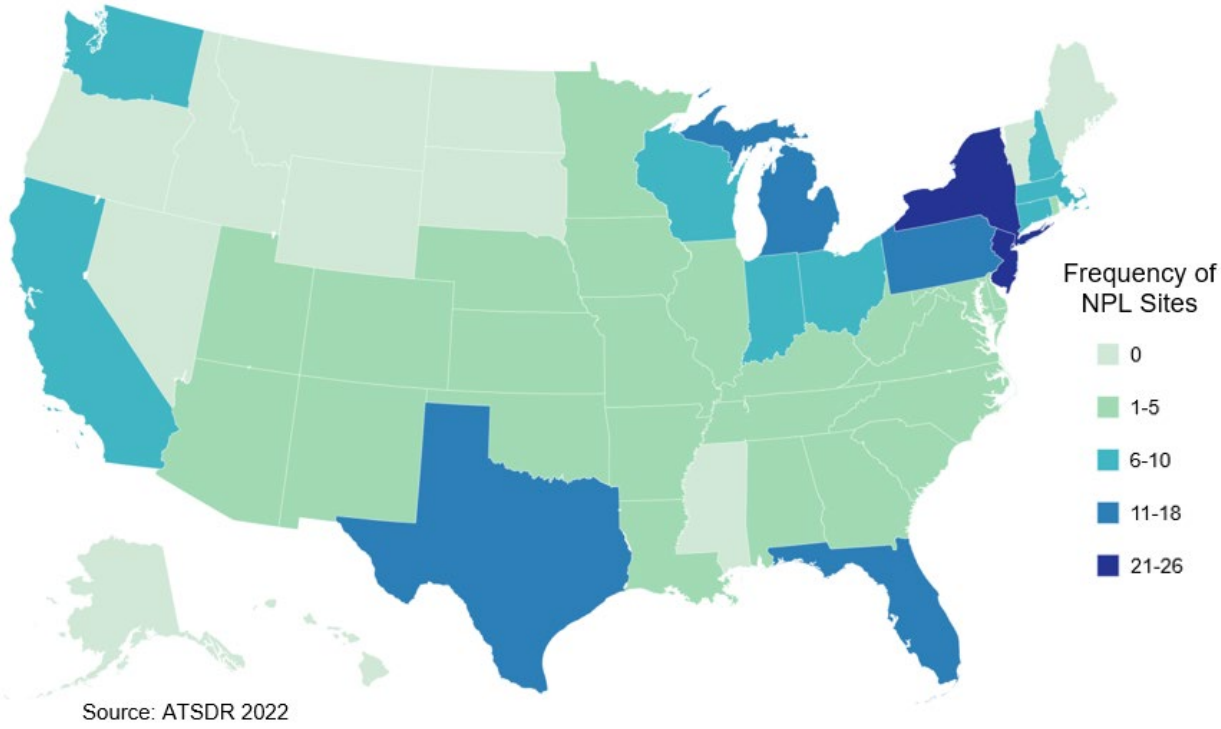
Explosive limits	Lower=1% Upper=50%	NLM 2023

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Carbon disulfide has been identified in at least 246 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which carbon disulfide has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 243 are located within the United States, 1 is located in the Virgin Islands, and 2 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Carbon Disulfide Contamination



- The main route of carbon disulfide exposure for the general population would be through inhalation of ambient air; however, atmospheric concentrations of carbon disulfide are usually low.

- Inhalation exposure under occupational settings is the most prominent route of human exposure. Workers involved in the manufacture of carbon disulfide, and production of products using this compound such as regenerated cellulose materials, are exposed to much higher levels than the general population. Dermal exposure is also possible in workplace settings.

- Carbon disulfide is released to the environment in emissions from manufacturing and use facilities and is also emitted through natural processes such as composting, and volcanic and geothermal activity. Oceans, marshes, and coastal areas are important biogenic sources of carbon disulfide.

- Carbon disulfide is expected to partition mainly to the air. In air, carbon disulfide will react with photochemically generated hydroxyl radicals and has an estimated half-life of 5.5 days.

- Carbon disulfide released to water can hydrolyze slowly; however, the overwhelming portion will volatilize to air. The potential for carbon disulfide to bioconcentrate in aquatic organisms is low. Similarly, carbon disulfide released to soil will quickly volatilize to the atmosphere, but a small portion may leach into groundwater since it is mobile in soil surfaces.

Carbon disulfide has both natural and anthropogenic sources (WHO 2002). Although there is a great deal of uncertainty in the estimates, globally, at least 40%, and perhaps as much as 80%, of releases are due to natural sources (EC/HC 2000; WHO 2002). The primary anthropological disposition of carbon disulfide in the environment is related to its use as an industrial solvent and chemical intermediate. Releases from industrial processes are almost exclusively to the atmosphere. Releases of the compound to surface waters and soils are expected to partition rapidly to the atmosphere through volatilization. Hydrolysis and biodegradation do not appear to be important processes in determining the environmental fate of carbon disulfide. It has been detected at generally low levels in ambient air, surface water, groundwater, and human milk. Concentrations in environmental media are greatest near source areas (e.g., industrial point sources, oceans and marshes, volcanoes).

Inhalation of carbon disulfide in workplace air is generally the main route of human exposure to the compound, with skin exposure also important when the solvent is handled manually.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Carbon disulfide was first manufactured commercially around 1880 (Timmerman 1978). Carbon disulfide is commercially manufactured by the reaction of sulfur with charcoal or methane (Lay et al. 2012). Ethane, propane, and propene have also been used, but to a much lower extent as compared to methane. Since the methane process was first introduced in the early 1950s, it has surpassed the older charcoal process in the production of carbon disulfide, which is no longer used in the United States, Europe, or Japan (Lay et al. 2012). In areas where natural gas or methane is not readily available or when the plant size is small, the charcoal process may still be used in the production of carbon

disulfide. Carbon disulfide is normally available both in technical and reagent grades with >99% purity (Lay et al. 2012).

Historical trends in carbon disulfide production closely paralleled those of the viscose rayon industry, one of its largest users (Timmerman 1978; WHO 1981). Production increased by nearly 50% between 1941 and 1969, from 242,000 to 362,000 metric tons. This increase was partly due to a sudden rise in demand for carbon tetrachloride, an intermediate in the production of fluorocarbon propellants and refrigerants; carbon disulfide is used in the production of carbon tetrachloride. The 1969 production level remained relatively stable until about 1974 when it declined sharply to the 1975 level of 217,000 metric tons (Timmerman 1978). There are no active rayon manufacturers in the United States (EPA 2011). Carbon disulfide may still be used in the United States for the manufacturing of other regenerated cellulose products such as cellulosic films, cellulosic sponges, and food casings. National aggregate production volumes reported in more recent years, 2016–2019, for carbon disulfide were between 250 million and <500 million pounds annually (~113,000–<227,000 metric tons) for 10 reporting companies (3M [two locations]; Arkema Delaware Inc. [two locations]; Chemtrade Holdco US Inc.; Equilon Enterprises LLC; Nouryon Chemicals LLC; Nouryon Functional Chemicals LLC; Tessenderlo Kerley, Inc; Viscofan USA); more precise information is not available based on confidential business information (CBI) (EPA 2022c).

Table 5-1 summarizes information on companies that reported the production, import, or use of carbon disulfide for the Toxics Release Inventory (TRI) in 2023 (TRI23 2025). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Carbon Disulfide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	5	100	49,999,999	1, 3, 4, 5, 6, 12, 13
AR	2	10,000	999,999	1, 2, 3, 5, 9, 10, 12
CA	12	0	999,999	1, 3, 5, 6, 12, 13, 14
CT	1	10,000	99,999	6
DE	1	1,000,000	9,999,999	1, 3, 6
FL	1	0	99	1, 13
GA	1	100,000	999,999	6
ID	1	1,000,000	9,999,999	2, 3, 6
IL	8	0	9,999,999	1, 3, 5, 6, 12, 13, 14
IN	3	0	9,999	1, 5, 7, 12, 13, 14
KS	5	0 (or N/A)	999,999 (or N/A)	1, 5, 10, 14

Table 5-1. Facilities that Produce, Process, or Use Carbon Disulfide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
KY	3	100 (or N/A)	999,999 (or N/A)	1, 5, 6, 14
LA	17	0	9,999,999	1, 3, 5, 6, 12, 13, 14
MI	1	1,000	9,999	1, 5
MN	2	0	9,999	1, 2, 3, 5, 6, 9, 10, 13
MO	2	100,000	999,999	6, 12
MS	1	100	999	1, 5, 6
MT	1	0	99	1, 6, 13, 14
ND	3	0	999,999	1, 5, 13
NJ	1	0	99	12
NM	1	0	99	1, 5
NY	2	1,000	999,999	1, 3, 5, 6, 12
OH	10	0 (or N/A)	99,999 (or N/A)	1, 5, 6, 12, 14
OK	6	0 (or N/A)	999,999 (or N/A)	1, 5, 7, 8, 14
PA	3	10,000	999,999	1, 5, 10, 13
TN	4	1,000 (or N/A)	999,999 (or N/A)	1, 5, 6, 10
TX	34	0 (or N/A)	9,999,999 (or N/A)	1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14
UT	3	0	9,999	1, 3, 5, 6, 7, 14
WA	4	0	9,999,999	1, 2, 3, 5, 6, 13, 14
WY	1	1,000	9,999	1, 5, 6

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state. Facilities may report N/A (not applicable) instead of a numeric value "if the waste stream that contains or contained the EPCRA Section 313 chemical is not directed to the relevant environmental medium, or if leaks, spills, and fugitive emissions cannot occur" (EPA 2022d).
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Note: Facilities that report N/A for amounts on site do not report activities/uses.

EPCRA = Emergency Planning and Community Right-to-Know Act

Source: TRI23 2025 (Data are from 2023)

5.2.2 Import/Export

Viscofan USA Inc. and Chemtrade Holdco US Inc. reported that approximately 3 and 1 million pounds of carbon disulfide were imported in 2018, and 2019, respectively (EPA 2022c). Five other manufacturers declared this information as CBI and three manufacturers declared no imports. Between 2019 and 2024,

the top importers of carbon disulfide to the United States were Canada (approximately 1–2 million pounds), Indonesia (approximately 0–500 thousand pounds), and Germany (approximately 0–55 thousand pounds) (USITC 2024). Nine of the domestic chemical companies reporting to the CDR declared zero exports or that information as CBI in 2019. Nouryon Functional Chemicals LLC reported exports of 41 million pounds of carbon disulfide for 2019 (EPA 2022c). Between 2019 and 2024, the highest exports of carbon disulfide from the United States were to Columbia (approximately 36–54 million pounds), Mexico (approximately 1–10 million pounds), and Peru (approximately 0–6 million pounds) (USITC 2024).

5.2.3 Use

Carbon disulfide has been an important industrial chemical since the 1800s because of its many useful properties, including its ability to solubilize fats, rubbers, phosphorus, sulfur, and other elements (Sine 1989; Timmerman 1978; Windholz 1983). Because of its ability to dissolve phosphorus, it was once widely used to produce matches but was later replaced by another chemical. Carbon disulfide's fat solvent properties also made it indispensable in preparing fats, lacquers, and camphor; refining petroleum jelly and paraffin; and extracting oil from bones, palm stones, olives, and rags. It was also used in processing India rubber sap from tropical trees. In all these extraction processes, however, carbon disulfide has been replaced by other solvents (Davidson and Feinleib 1972).

Its fat, rubber, and metal solvent properties have made carbon disulfide highly suitable for a variety of other continuing industrial applications including the following: vulcanization and manufacture of rubber and rubber accessories; production of resins, xanthates, thiocyanates, plywood adhesives, and flotation agents; solvent and spinning-solution applications primarily in the manufacture of rayon; polymerization inhibition of vinyl chloride; conversion and processing of hydrocarbons; petroleum-well cleaning; brightening of precious metals in electroplating; thin film deposition of nickel; as an agent to increase corrosion and wear-resistance in metals; rust removal from metals; and removal and recovery of metals and other elements from wastewater and other media (Davidson and Feinleib 1972; EPA 1978; Sine 1989; WHO 1981; Windholz 1983). It has also been used in industry as a means to promote sulfation in the synthesis of rare earth sulfides used in semiconductors, as a regenerator for transition metal sulfide catalysts, as a development restrainer in photography and lithography, and as a solvent to remove printing on recycled plastics (Timmerman 1978).

Carbon disulfide's most important industrial use has been in the manufacture of regenerated cellulose rayon by the viscose process (viscose rayon) (Davidson and Feinleib 1972; EPA 1978; NIOSH 1977; Timmerman 1978; WHO 1981). Historically in the United States, the approximate end uses of carbon disulfide were rayon production (44%); agriculture and other chemicals (35%); rubber chemicals (18%); and cellophane and other regenerated cellulosics such as sponges (3%) (Smith and Timmerman 2003). Currently, there are no operating manufacturers of rayon in the United States, although other regenerated cellulose products are still produced (EPA 2011). More recent end use data were not available. Carbon disulfide is also used in the production in dithiocarbamate pesticides (Campanale et al. 2023; Lay et al. 2012).

Another historic industrial use for carbon disulfide has been as a feedstock for carbon tetrachloride production (NIOSH 1977; Timmerman 1978). While only 10% of U.S. carbon disulfide production was used to produce carbon tetrachloride in 1960, this increased to 32% in 1974, largely because of a rapid increase in the demand for carbon tetrachloride for the production of fluorocarbon propellants and refrigerants (Timmerman 1978). Environmental and toxicity concerns related to the manufacture and use of carbon tetrachloride have led to a decrease in demand for carbon disulfide for this purpose. In 1991, the last remaining carbon tetrachloride plant in the United States that employed the carbon disulfide synthetic route was closed permanently (Smith and Timmerman 2003).

In agriculture, carbon disulfide was previously used as a fumigant to control insects in stored grain, normally mixed with carbon tetrachloride to reduce the fire hazard (Sine 1989; Worthing 1987). It was also previously used to remove botfly larva infestations from the stomachs of horses and ectoparasites from swine (Rossoff 1974). However, use of carbon disulfide as a grain fumigant was voluntarily cancelled after 1985 (EPA 1985). Carbon disulfide is not currently registered for use as a pesticide in the United States (EPA 2023a).

An intensive specialty use is to desorb charcoal sampling tubes in National Institute for Occupational Safety and Health (NIOSH) methods for airborne organics (NIOSH 1984b). Carbon disulfide is used extensively in research laboratory chemical synthetics methods (Dunn and Rudorf 1989).

5.2.4 Disposal

Carbon disulfide is a very flammable liquid that burns to produce carbon dioxide and sulfur dioxide. Therefore, it is a good candidate for controlled incineration, provided that a sulfur dioxide scrubber is

used. Some methods proposed by the EPA (1981b) include liquid injection incineration at a temperature range of 650–1,600°C, rotary kiln incineration at a temperature range of 820–1,600°C, and fluidized bed incineration at a temperature range of 450–980°C. Adsorption to activated coal with hydrogen sulfide in the absence of free oxygen yields a process that can regenerate large percentages of sulfur for reuse (UNEP 1985). It is not recommended that landfills be used as a disposal method because of the high flammability of this compound (UNEP 1985). No information was found on quantities and locations of disposal. The EPA Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) guideline for reportable quantities is 100 pounds (EPA 2022a).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022d). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022d).

5.3.1 Air

Estimated releases of 7,205,362 pounds (~3,268 metric tons) of carbon disulfide to the atmosphere from 137 domestic manufacturing and processing facilities in 2023, accounted for about 97% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2025). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Carbon Disulfide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	5	55,126	22	0[l]	1	0	55,148	1	55,149
AR	2	1,345,784	393	0	0	0	1,346,177	0	1,346,177

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Carbon Disulfide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
CA	11	12,663	917	0	3,011	110	12,665	4,036	16,701
CT	1	718	0	0	0	0	718	0	718
DE	1	1,386	0	0	0	0	1,386	0	1,386
FL	1	330	0	0	0	0	330	0	330
GA	1	1,084	0	0	0	0	1,084	0	1,084
ID	1	970	0	0	0	0	970	0	970
IL	8	2,461,661	114,027	0	4	0	2,461,672	114,020	2,575,692
IN	3	3,996	0	0	1	0	3,996	1	3,997
KS	4	717,846	18,754	0	0	0	736,600	0	736,600
KY	3	1,037	0	0	0	0	1,037	0	1,037
LA	17	318,244	88	0	6	0	318,332	6	318,338
MI	1	62	3	0	0	7	62	10	72
MN	2	935	0	0	0	0	935	0	935
MO	2	367	191	0	0	0	367	191	558
MS	1	1,970	50	0	56	0	2,020	56	2,076
MT	1	1,230	0	0	0	0	1,230	0	1,230
ND	2	3,369	6	6	0	0	3,381	0	3,381
NJ	1	10	0	0	0	5	10	5	15
NM	1	2,500	0	1	0	0	2,501	0	2,501
NY	2	293,009	591	0	445	0	293,011	1,033	294,045
OH	10	24,769	3	0	0	0	24,769	3	24,772
OK	6	11,629	255	3,500	0	0	11,884	3,500	15,385
PA	3	75,454	0	0	0	0	75,454	0	75,454
TN	4	1,760,076	99,000	0	0	0	1,760,076	99,000	1,859,076
TX	35	102,415	6	980	2	0	103,402	2	103,404
UT	3	730	15	0	12	0	730	27	757
WA	4	5,680	14	0	0	0	5,694	0	5,694

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Carbon Disulfide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	1	311	0	0	0	0	311	0	311
Total	137	7,205,362	234,335	4,488	3,539	122	7,225,954	221,892	7,447,846

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.
[l]Due to reporting guidelines, a zero may represent that the facility or facilities in each state's row reported "0," and "NA," or left the cell blank in their Form R submission.

RF = reporting facilities; UI = underground injection

Source: TRI23 2025 (Data are from 2023)

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Carbon disulfide emissions estimated from the 2020 inventory are summarized in Table 5-3 (EPA 2020).

Table 5-3. Carbon Disulfide Emissions to the Air Based on 2020 National Emissions Inventory

Emission sector	Pounds emitted
Industrial processes; chemical manufacturing	4,034,570
Industrial processes; NEC	3,887,846

Table 5-3. Carbon Disulfide Emissions to the Air Based on 2020 National Emissions Inventory

Emission sector	Pounds emitted
Agriculture; livestock waste	277,299
Industrial processes; pulp and paper	152,282
Industrial processes; petroleum refineries	120,376
Waste disposal	60,573
Industrial processes; storage and transfer	57,204
Fuel combustion; industrial boilers, ICEs; natural gas	35,000
Industrial processes; non-ferrous metals	30,530
Fuel combustion; industrial boilers, ICEs; other	20,737
Industrial processes; cement manufacture	18,937
Fuel combustion; electric generation; coal	13,958
Solvent; industrial surface coating and solvent use	9,718
Fuel combustion; industrial boilers, ICEs; biomass	4,532
Fuel combustion; industrial boilers, ICEs; coal	3,449
Industrial processes - ferrous metals	1,510
Fuel combustion; electric generation; natural gas	570
Fuel combustion; commercial/institutional; biomass	383
Fuel combustion; electric generation - other	348
Fuel combustion; commercial/institutional; other	89
Fuel combustion; electric generation; biomass	80
Industrial processes; oil and gas production	79
Fuel combustion; industrial boilers, ICEs; oil	33
Solvent - degreasing	31
Fuel combustion; comm/institutional; coal	13
Bulk gasoline terminals	11
Fuel combustion; commercial/institutional; natural gas	4
Industrial processes - mining	1
Gas stations	1

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2020

The largest single source of anthropogenic release of carbon disulfide has been in the viscose rayon industry. Zumkehr et al. (2017) reported emissions of carbon disulfide from rayon production as 23±12 Gg S per year (gigagrams sulfur per year). However, additional anthropogenic sources of carbon disulfide release have been reported. Small amounts of carbon disulfide have also been detected in a landfill simulator (Vogt and Walsh 1985) and in the odoriferous emissions from a sewage treatment plant (Ruby et al. 1987). Carbon disulfide emissions were measured in the combustion of 15 barbeque charcoal

products from five countries (6 in Korea, 4 in China, 3 in Indonesia, 1 in Malaysia, and 1 in the United States) at rates of 0.22–125 μg/m^3 (mean of 12 μg/m^3); the highest level was measured in Korean products while the lowest level was measured in the product from the United States (Mahmudur Rahman and Kim 2012).

Additional sources of anthropogenic releases of carbon disulfide may include environmental breakdown of dithiocarbamate pesticides in the environment (Campanale et al. 2023). For example, usage of metab potassium, dazomet, and thiram in the United States in 2018 were approximately 50 million tons, <1 million tons, and <0.2 million tons, respectively (USGS 2018a, 2018b, 2018c). However, no estimates of the amount of carbon disulfide released into the atmosphere from these pesticide usages were available.

Carbon disulfide was one of seven sulfur-gas emission rates assessed from problem drywall installed in U.S. homes (LBNL 2011). Historically, carbon disulfide was used in the processing of rubber, but changing technology made the old practices outmoded. Nevertheless, carbon disulfide was measured as 6.88, 3.37, 29.72, and 1.69% of the volatile emissions in mixing, shaping, vulcanization, and storage, respectively, in the production of rubber products (Huang et al. 2022). Automotive tire wear has been suggested as a potential source of atmospheric carbon disulfide. The emission of carbon disulfide from pyrolysis of scrap tires decreased with increasing temperature (650–1,050°C) and decreased with an increase in oxygen supply (Fullana et al. 2000).

Emissions of carbon disulfide in aerobic and anaerobic/aerobic composting were measured as 0.4 and <0.1 g/ton of compost, respectively (Smet et al. 1999). Degradation occurring in a wastewater treatment plant (WWTP) also contributes to carbon disulfide emissions; an emission factor of 17±5 μg/ton wastewater was determined from a full-scale sequencing batch reactor WWTP (Li et al. 2021b).

There are several known natural sources of carbon disulfide, including wetlands (Hines et al. 1993), oceans (Chin and Davis 1993), plant roots (Piluk et al. 1998), and microbial activity in soils (Banwart and Bremner 1975; Kanda et al. 1995). The emission rate estimated for microbial degradation of algae in a eutrophic lake was 0.35 mg/m^2·day (Wang et al. 2023). Estimates from the 1980s suggested that natural sources of carbon disulfide were 4–5 times greater than anthropogenic releases; however, later modeling results suggest that the major source of carbon disulfide derives from industrial emissions (58%), while the oceans contribute about 34%, and the remainder comes from terrestrial sources (EC/HC 2000). Lennartz et al. (2021) produced monthly resolved modelled oceanic emissions of carbonyl sulfide and carbon disulfide over the period of 2000–2019, reported in terms of their sulfur content. Maximum

monthly mean concentrations of carbon disulfide were shown to vary the most in the summer months in the northern temperate regions (23–66°N) from 4.3 Gg S per month (gigagrams sulfur per month) in June 2011 and 6.0 Gg S per month in June 2018 but show less variability in the winter months (e.g., between 0.8 and 1.2 Gg S per month in December). An average flux of 0.068±0.068 μmol/m^2·day was estimated in sampled areas in the Western Pacific Ocean (Xu et al. 2023).

During analytical measurements of sulfur compounds at five wetland areas in Florida, carbon disulfide was often not detected, while large amounts of dimethylsulfide were found (Cooper et al. 1987). However, low levels of carbon disulfide were consistently detected in samples collected from the same area using a slightly modified procedure (Hines et al. 1993). Based on their measurements and assumptions in the study of sulfur emissions from a North Carolina salt marsh, Aneja et al. (1980) estimated that carbon disulfide produced by marshes (0.022 g sulfur/m^2 per year) contributes <0.07% of biogenic sulfur and <8% to the stratospheric aerosol layer. DeMello et al. (1987) speculated that carbon disulfide generation from coastal areas in Florida was related to the concentration of organic matter in the sediment. Staubes et al. (1987) found that humic soils were stronger sources for biogenic sulfur than soils with lower organic content; however, a low humic content coupled with high moisture favors the production of carbon disulfide over dimethylsulfide.

5.3.2 Water

Estimated releases of 234,335 pounds (~106 metric tons) of carbon disulfide to surface water from 137 domestic manufacturing and processing facilities in 2023, accounted for about 3.2% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2025). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI23 2025). These releases are summarized in Table 5-2.

Carbon disulfide is widely found in coastal and ocean waters and extensive study has been done to determine levels over the different types of water bodies. In ocean surface water, carbon disulfide may be produced through photochemical reactions with dissolved organic matter during daylight conditions and through abiotic reactions involving sulfur radicals and microbial processes during nighttime conditions (Xu et al. 2024a, 2024b). Photochemical production rates in surface seawater of the Bay of Bengal and the East Indian Ocean were 2.77±0.231 ng/L·day ($3.64x10^{-2}$±$3.03x10^{-3}$ nmol/L·day) and 1.32±0.526 ng/L·day ($1.74x10^{-2}$±$6.91x10^{-3}$ nmol/L·day), respectively (Xu et al. 2024a). In the West North Pacific Ocean, the production rate was 1.91±0.0.349 ng/L·day ($2.51x10^{-2}$±$4.58x10^{-3}$ nmol/L·day) (Xu et al.

2024b). Estimated rates of dark/biological production of carbon disulfide in surface water were 0.190±0.0193 ng/L·day ($2.50x10^{-3}$±$2.53x10^{-4}$ nmol/L·day) in the Bay of Bengal, 0.065±0.0258 ng/L·day ($8.52x10^{-4}$±$3.39x10^{-4}$ nmol/L·day) in the East Indian Ocean, and 0.102±0.0.0792 ng/L·day ($1.34x10^{-3}$±$1.04x10^{-3}$ nmol/L·day) in the West North Pacific Ocean (Xu et al. 2024a, Xu et al. 2024b). Carbon disulfide has also been detected in the vent fluids and sediment surface waters of undersea hydrothermal sites (Marchand et al. 1994).

Lennartz et al. (2021) estimated the globally integrated annual emissions of carbonyl sulfide and carbon disulfide from the world's oceans from 2000 to 2019, reported in terms of their sulfur content. The results for carbon disulfide are shown in Table 5-4.

Table 5-4. Global Annual Emissions of Carbon Disulfide from Oceans

Year	Emissions (Gg S)[a]
2000	160.8
2001	160.0
2002	161.2
2003	160.3
2004	172.0
2005	169.1
2006	175.3
2007	173.4
2008	175.0
2009	179.7
2010	189.2
2011	179.5
2012	181.2
2013	181.3
2014	170.1
2015	175.0
2016	181.5
2017	189.7
2018	187.8
2019	177.3
Mean (standard deviation)	174.97 (9.3)

[a]Carbon disulfide emissions were reported in terms of their sulfur content (Gg S). 1 Gg (Gigagram) =1,000 metric tons.

Source: Lennartz et al. 2021

5.3.3 Soil

Estimated releases of 3,539 pounds (~1.6 metric tons) of carbon disulfide to soil from 137 domestic manufacturing and processing facilities in 2023, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2025). An additional 4,488 pounds (~2.0 metric tons), constituting <1% of the total environmental emissions, were released via underground injection (TRI23 2025). These releases are summarized in Table 5-2.

Emissions of carbon disulfide from soil and plant material occurs naturally due to the metabolism of organic substances from soil bacteria and plants during the growing season (EC/HC 2000). Increases in soil moisture, temperature, organic content, and light increase the rate of carbon disulfide production from soil. The Canadian government estimated that 35,000 metric tons of carbon disulfide are released to the Canadian environment from its production in soil (EC/HC 2000). Fain et al. (1987) reported 0.9 mg/L carbon disulfide (dry weight basis) in a typical refinery oily waste applied to a land treatment unit.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Releases of carbon disulfide to the environment as a result of industrial activity are expected to be primarily to the atmosphere. Any carbon disulfide released to surface waters in effluent streams is expected to partition rapidly to the atmosphere as a result of the high ratio of vapor pressure to the solubility (Henry's law constant=1.33×10^{-2} atm m^3/mol) of the compound. Hydrolysis is not a significant removal mechanism since the evaporation half-life from a saturated solution is estimated to be 11 minutes (EPA 1978).

Water. Although no information was found evaluating the partitioning of carbon disulfide from water onto sediments, it is not expected to be removed significantly from the aquatic phase through adsorption. The low K_{oc} value, determined from a log K_{ow} of 1.94 and a regression-derived equation, is 48 (EPA 2012). This indicates high soil mobility, but carbon disulfide will probably be less mobile in soils of high organic content.

Sediment and Soil. Although Roy and Griffin (1985) did not conduct adsorption studies, they classified carbon disulfide as a mobile solvent exhibiting a low tendency to be retained by soils. Carbon disulfide released to soils in spills should rapidly volatilize to the atmosphere, but a portion of the compound remaining on soil surfaces could be available for transport into groundwater since it does not have much affinity for soil particles. Farwell et al. (1979) indicated that carbon disulfide volatilizes from a variety of soils, although rates were not provided.

Other Media. The bioconcentration of carbon disulfide was measured in carp (*Cyprinus carpio*); at starting concentrations of 50 and 5 μg/L, the respective bioconcentration factors (BCFs) were <6.1 and <60 (J-CHECK 2025a). Estimated BCF and bioaccumulation factors were 8.9 and 6.6, respectively (EPA 2012). These values indicate that carbon disulfide is not expected to bioaccumulate in aquatic organisms.

5.4.2 Transformation and Degradation

Air. Carbon disulfide reacts with hydroxyl radicals in the troposphere to produce carbonyl sulfide. The lifetime of carbon disulfide in the troposphere, assuming a reaction rate constant of 4.3×10^{-13} cm^3/molecule-second, is 73 days (Cox and Sheppard 1980). The half-life for this same reaction is estimated to be 5.5 days, calculated from an experimental rate constant of 2.9×10^{-12} cm^3/molecule-second (Arnts et al. 1989).

The photo-oxidation products of carbon disulfide in the laboratory were identified as carbon monoxide, carbonyl sulfide, sulfur dioxide, and a polymer that adhered to the sides of the reaction vessel (Heicklen et al. 1971). Although carbon disulfide absorbs light at wavelengths of 280–350 nm, dissociation does not occur under environmental conditions because of low molar absorptivity (Atkinson et al. 1978; Wood and Heicklen 1971) and direct photolysis of carbon disulfide in the atmosphere does not appear to be significant. EPA (1978) stated that the information available indicated that carbon disulfide is relatively persistent in the atmosphere. For the atmospheric oxidation of carbon disulfide to sulfur dioxide, carbonyl sulfide, and carbon monoxide, the half-life was estimated to be about 12 days.

According to Wine et al. (1981), electronically excited carbon disulfide is rapidly produced in the troposphere from absorption of solar photons. This excited carbon disulfide reacts with oxygen on a time scale of 1–2 weeks to yield carbony1 sulfide, the predominant sulfur-containing compound in the troposphere.

The lifetime of carbon disulfide in the atmosphere has been estimated to be 12 days, too short a time to reach the stratosphere. Removal was suggested to occur by a hydroxyl radical reaction or an oxygen atom reaction, but not by dissociation (Khalil and Rasmussen 1984).

Based on the estimates of a lifetime in the troposphere for carbon disulfide on the order of weeks and the troposphere to stratosphere turnover time on the order of years, very little tropospheric carbon disulfide is expected to be transported to the stratosphere (EPA 1986).

Water. Carbon disulfide is stable to hydrolysis in the pH region of environmental concern (pH 4–10). At pH 13, carbon disulfide has a hydrolysis half-life at of about 1 hour at 25°C; by extrapolation, at pH 9, carbon disulfide has a half-life of 1.1 years (EPA 1978). In oxygenated seawater, carbon disulfide was found to be stable for >10 days (Lovelock 1974). The volatilization half-life from a saturated water solution has been estimated to be 11 minutes (EPA 1978). Based on data from the East Indian Ocean and the Bay of Bengal, removal timeframes of 3–7 days were determined for carbon disulfide in surface water; variation in removal was related to seawater temperature and dissolved oxygen concentrations (Xu et al. 2024a). The compound apparently does not undergo biodegradation at rates that are competitive with its volatilization from surface waters. In a biodegradation study with 30 mg/L sludge and 100 mg/L carbon disulfide, only 2% of degradation measured by gas chromatography analysis was observed after 28 days (J-CHECK 2025b).

Sediment and Soil. No data were found in the available literature on the biodegradation of carbon disulfide in soil. However, since the chemical is rapidly volatilized (high Henry's law constant) and probably highly mobile in soil (low K_{oc}), it is unlikely that it remains in the soil long enough to be significantly biodegraded.

Microbial degradation of large amounts of carbon disulfide in soil would not be expected to be significant since this compound is a soil disinfectant and toxic to bacteria. Hydrolysis of carbon disulfide on wet soil surfaces is also unlikely (EPA 1986). Oxidation of carbon disulfide by a *Thiobacillus* species isolated from soil has been observed (Plas et al. 1993).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to carbon disulfide depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens.

Concentrations of carbon disulfide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on carbon disulfide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-5 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6.

Table 5-5. Lowest Limit of Detection Based on Standards

Media	Detection limit[a,b]	Reference
Air	0.01–0.5 ppbv (0.03-1.6 µg/m^3)	EPA 2024a
Drinking water	0.026 µg/L	NEMI 2023
Surface water and groundwater	0.026 µg/L	NEMI 2023
Soil	87 µg/kg	WQP 2025
Sediment	0.96 µg/kg	WQP (2025)
Urine[c]	11.2 µg/L	CDC (2022)

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Unit conversion: ppb = µg/L (aqueous); = µg/kg (sediment and soil); ppbv = 24.45 concentration µg/m^3/76.14 g/mol (air).
[c]Metabolite: 2-thiothiazolidine-4-carboxylic acid (TTCA).

Table 5-6. Summary of Environmental Levels of Carbon Disulfide[a]

Media	Low	High	For more information
Outdoor air	0.002 ppbv (0.007 µg/m^3)	22 ppbv (68.5 µg/m^3)	Section 5.5.1
Indoor air, nonoccupational	0.005 ppbv (0.015 µg/m^3)	1.06 ppbv (3.29 µg/m^3)	Section 5.5.1
Surface water (µg/L	0.0125	0.99	Section 5.5.2
Groundwater (µg/L)	0.062	60	Section 5.5.2
Soil (µg/kg)	–	–	Section 5.5.3
Sediment (µg/kg)	1.6	32.9	Section 5.5.3

[a]Unit conversion: ppb = µg/L (aqueous); = µg/kg (sediment and soil); ppbv = 24.45 concentration µg/m^3/76.14 g/mol (air). Summary values represent most recent ambient data available. Ranges do not reflect values below the limit of detection.

Detections of carbon disulfide in air, water, and soil at NPL sites are summarized in Table 5-7.

Table 5-7. Carbon Disulfide Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (µg/L)	19	29.3	65.7	37	26
Soil (µg/kg)	21.5	30.8	23.6	30	23
Air (ppbv)	2.81	4.92	10.4	17	12

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Data for 2019–2024 obtained from EPA's Air Quality System (AQS) database are presented in Table 5-8 (EPA 2024a). Median air concentrations reported in the AQS between 2019 and 2024 were 0.1–0.3 µg/m^3 (0.03–0.09 ppbv), and maximum values were 12.1–68.5 µg/m^3 (3.9–22 ppbv). Logue et al. (2010, 2011) studied air pollutant concentrations at four sites in Pennsylvania from 2006 to 2008 and found carbon disulfide arithmetic mean concentrations of 0.07–0.14 µg/m^3 (0.02–0.045 ppbv); 81% of the samples did not contain carbon disulfide. Carbon disulfide contributed 4.2% of volatile organic compounds (VOCs) measured in the atmosphere at one of five urban sites in Texas (Conley et al. 2005). Analysis of outdoor air at 74 residential homes in Ottawa Canada during 2002–2003 found carbon disulfide in 22% of all samples at a concentration range of 0.015–0.38 µg/m^3 (0.0048–0.12 ppbv) and an arithmetic mean of 0.04 µg/m^3 (0.01 ppbv) (Zhu et al. 2005). The estimated global background level of carbon disulfide has been reported as 1.2 µg/m^3 (0.38 ppbv) (Rosenbaum et al. 1999). Fresh and aged smoke from western U.S. wildfires contained low levels of carbon disulfide (<0.01 µg/m^3) (O'Dell et al. 2020). A summary of the available outdoor air monitoring data is presented in Table 5-9.

Table 5-8. Percentile Distribution of Annual Mean Carbon Disulfide Concentrations (µg/m^3) Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of U.S. locations	10th	50th	75th	95th	Maximum
2019	77	0.039	0.189	0.868	1.65	35.2
2020	67	0.046	0.123	0.236	0.874	68.5
2021	71	0.007	0.052	0.203	0.691	50.4
2022	70	0	0.089	0.281	0.984	12.1
2023	54	0	0.130	0.328	1.29	38.3
2024[c]	46	0.206	0.318	0.405	0.696	17.4

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to µg/m^3.
[b]24-hour sampling period.
[c]As of November 19, 2024.

Source: EPA 2024a

Table 5-9. Outdoor Air Monitoring Data for Carbon Disulfide

Location	Geographic type	Date(s)	Range (µg/m^3)	Mean (µg/m^3)	Notes	Reference
Four sites near Pittsburgh, Pennsylvania	Urban, industrial	2006–2008	–	0.07–0.14 (arithmetic mean)	n=56; 19% detection frequency	Logue et al. 2010, 2011
Ottawa, Canada	Residential	2002–2003	0.015–0.38	0.04 (arithmetic mean)	n=74; 22% detection frequency	Zhu et al. 2005
Western United States	Wildfire smoke plume	July–August 2018	–	ND (median, <1 to >3-day-old smoke)	n=902; 73% detection frequency (fresh smoke, <1 day old), 27% detection frequency (aged smoke, >3 days old)	O'Dell et al. 2020
East Palestine, Ohio	Hazardous waste train derailment site	March–November 2023	2.10–2.20	2.30	n=2,146; 0.1% detection frequency	EPA 2024b

ND = not detected

In a study of indoor air in suburban and rural homes in New Jersey between December 2003 and April 2006, carbon disulfide was detected in 3 of 100 samples at a 95th percentile of <1.6 µg/m^3 and maximum of 4.4 µg/m^3 (1.4 ppbv) (Weisel et al. 2008). Analysis of indoor air at 75 residential homes in Ottawa

Canada during 2002–2003 detected carbon disulfide in 67% of all samples at a concentration range of 0.015–3.29 μg/m^3 (0.0048–1.05 ppbv) and an arithmetic mean of 0.34 μg/m^3 (0.11 ppbv) (Zhu et al. 2005). Carbon disulfide has been detected in the air inside passenger cars and buses (Besis et al. 2023). A summary of the available indoor air monitoring data is presented in Table 5-10.

Table 5-10. Indoor Air Monitoring Data for Carbon Disulfide

Location	Geographic type	Date(s)	Range (μg/m^3)	Mean (μg/m^3)	Notes	Reference
13 counties across New Jersey	Suburban and rural residences	December 2003–April 2006	<1.6–4.4	–	n=100; 3% detection frequency	Weisel et al. 2008
Ottawa, Canada	Residential	2002–2003	0.015–3.29	0.34 (arithmetic mean)	n=75; 67% detection frequency	Zhu et al. 2005

ND = not detected

Air levels of carbon disulfide in occupational exposure settings are much higher than ambient exposure levels. Historical occupational exposure levels in viscose rayon factories were typically >10 ppm (Wägar et al. 1981), with brief exposures as high as 254.4 ppm reported for specific jobs (Liss and Finkelstein 1996). However, improvements in working conditions, processes, and other technical improvements have reduced occupational air levels. For example, occupational exposure to carbon disulfide in a viscose rayon factory was reduced by nearly 50% between 1992 and 2009, with median (95th percentile) exposure levels of 4.15 (12.5) ppm in 1992 and 2.48 (6.74) ppm in 2009 (Göen et al. 2014). Additional exposure level details for different departments in this factory can be found in Section 5.7.

In a similar study, Bulat et al. (2002) measured carbon disulfide air concentrations before and after technical improvements in a viscose rayon factory. Exposure was reduced up to 95% for employees with the highest initial exposure levels (see Table 5-11).

Table 5-11. Personal Air Exposure Measurements by Job Type Before and After Technical Improvements[a]

Job title	Viscose preparator	Spinner	First spinner
Before improvement, inside mask[b]	14.7 (9.2–20.2) mg/m^3 4.72 (2.9–6.49) ppm	NR	NR
Before improvement, outside mask[c]	90.2 (62.8–139.5) mg/m^3 28.0 (20.2–44.8) ppm	111.5 (93.8–132.6) mg/m^3 35.8 (30.1–42.58) ppm	100.9 (75.3–185.3) mg/m^3 32.4 (24.2–59.5) ppm

Table 5-11. Personal Air Exposure Measurements by Job Type Before and After Technical Improvements[a]

Job title	Viscose preparator	Spinner	First spinner
After improvement, inside mask	10.1 (6.0–17.0) mg/m^3 3.24 (1.93–5.46) ppm	5.4 (3.95–7.37) mg/m^3 1.7 (1.28–2.37) ppm	6.3 (3.3–11.9) mg/m^3 2.0 (1.1–3.82) ppm
After improvement, outside mask	20.8 (1.3–34.44) mg/m^3 6.68 (0.42–11.06) ppm	8.11 (5.71–11.53) mg/m^3 2.6 (1.83–3.7) ppm	40.27[d] mg/m^3 12.93 ppm

[a]Geometric means and 95% confidence intervals. Unit conversion: ppm = 24.45 concentration mg/m^3/76.14 g/mol.
[b]Air measurements were sampled from inside the respirator via flexible tubing fitted through the facemask and affixed to workers face with adhesive tape.
[c]Air measurements were sampled outside the mask via tubes fixed on either the shoulder or collar of the worker.
[d]Only one measurement available.

NR = not reported

Source: Bulat et al. 2002

Limited data regarding the presence of carbon disulfide at hazardous waste sites were located. On February 3, 2023, a freight train carrying hazardous materials derailed in East Palestine, Ohio. Some of the cars caught fire, while others spilled their loads into an adjacent stream. In air samples collected at the train derailment site between March and November 2023, carbon disulfide was reported at 0.706, 0.867, and 0.674 ppb (2.20, 2.70, and 2.10 µg/m^3) in three samples collected at various points of the year (EPA 2024b). Carbon disulfide was below the reporting limits (ranging from 0.514 to 1.64 ppb [1.60–5.10 µg/m^3]) in the remaining samples.

5.5.2 Water

Carbon disulfide has been detected at <1–160 µg/L in surface water, groundwater, and oceans. Reported concentrations are typically higher in groundwater due to the volatility of carbon disulfide. Summaries of the available surface and groundwater monitoring data are reported in Tables 5-12 and 5-13. Municipal drinking water monitoring data were not located.

Table 5-12. Carbon Disulfide Concentrations in Surface Water

Location	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Global oceans	–	8.4x10^{-5}–0.029	0.0012	n=1,813	Lennartz et al. 2020
Global oceans	–	–	0.0014	–	Lennartz et al. 2021

Table 5-12. Carbon Disulfide Concentrations in Surface Water

Location	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
34 urban/ agricultural impacted streams and 4 undeveloped sites across 24 states and Puerto Rico	November 2012–June 2014	0.0125–0.2378	0.0553	Detected in 14 streams	Bradley et al. 2017
Linsley Pond, Connecticut	July 29–30, 2004	~<0.15 – ~0.53		n=11; values estimated from figure	Hu et al. 2007
United States	2019	0.51–0.99	0.82	n=59; 5.1% quantification frequency; two below reporting limit	WQP 2025
	2020	0.1–0.3	0.07	n=68; 14% quantification frequency; seven below limit of quantification; two below reporting limit	
	2021	0.1–0.46	0.08	n = 29; 45% quantification frequency; 15 below reporting limit	
	2022	–	–	n = 16; 0% quantification frequency; four below limit of quantification; three below reporting limit	
	2023	0.01–0.02	0.015	n = 29; 14% quantification frequency; three below reporting limit	
	2024	0.01–0.03	0.018	n = 32; 16% quantification frequency	
Rhine River, the Netherlands	1992–1997	NR–0.9	–		Miermans et al. 2000
Meuse River, the Netherlands	1992–1997	NR–4.5	–		
Northern Delta Area of the Rhine-Meuse-Scheldt Rivers, the Netherlands	1992–1997	NR–0.1	–		

Table 5-12. Carbon Disulfide Concentrations in Surface Water

Location	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Westerscheldt Estuary, the Netherlands	1992–1997	NR–0.1	–		
Hazardous waste train derailment site, East Palestine, Ohio	February 2023	<1–<100	–	n=14; not detected above reporting limits	EPA 2024c

NR = not reported

Table 5-13. Carbon Disulfide Concentrations in Groundwater

Location	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Wells across the United States	2013–2019	0.062–4.236	–	n=1,537 wells; 1.6% quantification frequency; estimated at 0.05–5.844 µg/L in 185 wells	Bexfield et al. 2022
United States	2019	0.1–11.5	1.33	52% quantification frequency; 100 below reporting limit	WQP 2025
	2020	0.1–68	1.96	46% quantification frequency; 39 below reporting limit	
	2021	0.1–68.8	1.65	63% quantification frequency; 51 below reporting limit	
	2022	0.1–61	1.72	69% quantification frequency; 104 below reporting limit	
	2023	0.978–160	2.65	67% quantification frequency; 115 below reporting limit	
	2024	0.01–4.5	0.484	51% quantification frequency; 49 below reporting limit	
Palermo Wellfield Superfund Site	2019	0.29–1	0.592	n=27; 19% quantification frequency	WQP 2025
	2020	–	–	n=4; 0% quantification frequency	

Table 5-13. Carbon Disulfide Concentrations in Groundwater

Location	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Hazardous waste train derailment site, East Palestine, Ohio	June-July 2024	<1–NA	–	n=2; not detected above reporting limits	EPA 2024c

NR = not reported

Reported average concentrations of carbon disulfide levels in ocean water collected from various locations were 15.7 picomoles/L (0.0012 µg/L) (Lennartz et al. 2020) and 18 picomoles/L (0.0014 µg/L) (Lennartz et al. 2020, 2021). Using data from the National Water-Quality Assessment project (NAWQA) and the U.S. Geological Survey (USGS), Bexfield et al. (2022) conducted a national study of VOC concentrations in 1537 wells sampled in 23 principal aquifer surveys over the span of 2013–2019. Carbon disulfide was found at less than the detection limit (0.05–0.8613 µg/L) in 1,324 wells, at estimated levels of 0.05–5.844 µg/L in 185 wells, and at measured concentrations of 0.062–4.236 µg/L in 25 wells (Bexfield et al. 2022). Thirty-eight U.S. streams were monitored from 2012 to 2014 for 719 compounds; carbon disulfide was found in 14 streams at ~0.055 µg/L (~55 ng/L) (Bradley et al. 2017). Carbon disulfide was found at a maximum concentration of <0.53 µg/L in a stratified lake in Connecticut; the highest levels were at the deepest level (Hu et al. 2007). Carbon disulfide was detected in about 40% of the 95 monitoring wells in the Glassboro study area of New Jersey; it was not detected in 30 public supply wells (Stackelberg et al. 2001).

The EPA maintains a Water Quality Portal (WQP) database that aggregates air monitoring data from the National Water Information System (NWIS) and STORage and RETrieval (STORET) system. Based on limited sampling, carbon disulfide is not typically detected in water, and concentrations are <1 µg/L. In groundwater, average concentrations are <5 µg/L, but maximums up to 160 µg/L were reported.

Miermans et al. (2000) studied Dutch surface water of the Rhine River, Meuse River, Northern Delta Area of the Rhine-Meuse-Scheldt Rivers, and Westersceldt Estuary; carbon disulfide was found at 0.9, 4.5, 0.1, and 0.1 µg/L, respectively.

Limited water monitoring data for hazardous waste sites were located. An average of 0.591 µg/L carbon disulfide (range 0.29–1 µg/L, 19% detected in 27 samples) was reported in groundwater at the Palermo Wellfield Superfund Site in 2019; carbon disulfide was not detected in four groundwater samples

collected in 2020 (WQP 2025). Carbon disulfide was below the reporting limit (ranging from 1 to 100 µg/L) in surface water samples collected at the East Palestine, Ohio train derailment site collected in February 2023, and below the reporting limit (1 µg/L) in two groundwater samples collected in the summer of 2024 (EPA 2024c).

5.5.3 Sediment and Soil

Limited soil and sediment monitoring data for carbon disulfide were located, which are summarized in Table 5-14. Carbon disulfide is not expected to be commonly detected in surface soil and sediments due to its volatility. Concentrations in submerged sediments ranged from 4.6 to 32.9 µg/kg (WQP 2025).

Table 5-14. Carbon Disulfide Concentrations in Soil and Sediment

Location	Date(s)	Range (µg/kg)	Mean concentration (µg/kg)	Notes	Reference
Sediment					
United States	2019	–	–	n=37; 0% quantification frequency	WQP 2025
	2020	4.6–32.9	16.7	n=235; 1.7% quantification frequency	
	2021	5.4–23	11.8	n=124; 12% quantification frequency; 13 below the limit of quantitation	
Palermo Wellfield Superfund Site	2021	1.6–14	6.37	n=5; 60% quantification frequency	WQP 2025
Soil					
United States	2023	–	–	n=10; 0% quantification frequency	WQP 2025

5.5.4 Other Media

Carbon disulfide's previous use as a fumigant resulted in residues on grains, legumes, and other fruit and vegetable products (Daft 1987; Heikes 1987; Lovegren et al. 1979). Current studies of carbon disulfide concentrations in food products were not located. Carbon disulfide concentrations of 1,500 ppm in the root of Oriental ginseng (*Panax ginseng*), 0.2 ppm in the stem of kohlrabi (*Brassica oleracea*), and unspecified levels the fruit of shiitake (*Lentinus edodes*) have been reported (USDA 2025). Carbon disulfide was found in *Charybdis feriatus* crabs at 217.2, 203.9, and 29.8 µg/kg in the leg, body, and carapace, respectively (Chung 1999).

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to low levels of carbon disulfide in ambient air. Reported median levels in outdoor ambient air range from 0.052 to 0.318 μg/m^3 (EPA 2024a). Limited food monitoring data were available and no municipal drinking water data were located. Carbon disulfide exposure from consumption of food products is not considered a current exposure pathway due to its discontinued use as a fumigant in agriculture. While carbon disulfide has been detected in surface and groundwater, likelihood of ingestion of carbon disulfide via drinking water is low due to the volatility of the chemical. For the general population, absorption through the skin is a much less important route of exposure than inhalation, and oral exposure is negligible.

Vapor intrusion may be a potential source of carbon disulfide exposure, although indoor and ambient sources may also contribute to indoor air levels. The EPA (2016) includes carbon disulfide in its Vapor Intrusion Screening Levels (VISL) Calculator, indicating that it is sufficiently volatile and sufficiently toxic to be considered a concern for vapor intrusion from soil and groundwater. Accordingly, ATSDR recommends that health assessors should evaluate potential health implications of vapor intrusion for carbon disulfide during site risk assessments.

Carbon disulfide may volatilize from water; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily time weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. Using median outdoor air levels (0.318 μg/m^3) (EPA 2024a) as discussed in Section 5.5.1 and groundwater levels in the absence of municipal water data (2.149 μg/L, mean of reported range) (Bexfield et al. 2022) as discussed in Section 5.5.2, Reasonable Maximum Exposure (RME) levels for carbon disulfide were calculated for different exposure groups (Table 5-15).

Table 5-15. Reasonable Maximum Exposure of Carbon Disulfide for Daily Inhalation Dose and Administered Dermal Dose for the Target Person

Exposure group	Inhalation (µg/m^3)	Dermal (µg/kg/day)
Birth–<1 year	2.3	0.0095
1–<2 years	2.3	0.0088
2–<6 years	2.3	0.0075
6–<11 years	2.3	0.0061
11–<16 years	2.3	0.0050
16–<21 years	2.3	0.0046
Adult	2.3	0.0045
Pregnant and breastfeeding women	2.3	0.0045

Source: ATSDR 2025

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to carbon disulfide is expected to be highest among certain occupational groups (e.g., workers involved in the production of recovered cellulose products). While historical occupational exposure levels were high (>10 ppmv in workplace air), current exposure levels are lower. Occupational monitoring data obtained since the year 2000 report central estimates (medians or means) ranging from 1.86 to 5.96 ppmv in 2009 (Göen et al. 2014; Guo et al. 2016; Jhun et al. 2007, 2009; Yoshioka et al. 2017). While lower than historical values, this exposure is still approximately 2–3 orders of magnitude above ambient exposure levels (see Section 5.6). Occupations with potential for exposure to carbon disulfide include chemical manufacturing workers using carbon disulfide in producing thiocarbamates or other end products, cellophane manufacturing, viscose sponge production, and laboratory specialty workers (e.g., researchers using carbon disulfide). Viscose rayon production is no longer an occupational exposure setting of relevance for the United States (EPA 2011).

Nursing infants of women occupationally exposed to carbon disulfide may also be at increased risk of exposure, as carbon disulfide is excreted in breast milk, and can be detected for up to a month or more following exposure (Cai and Bao 1981; Pellizzari et al. 1982).

Persons living in certain source-dominated areas may be at risk for higher than background exposures to carbon disulfide. These may include persons living near industries and facilities that manufacture and use carbon disulfide (e.g., viscose rayon plants, sponge manufacturers). For example, measured carbon disulfide levels outside 10 residences within 1 mile of the Nylonge sponge manufacturing facility in

Elyria, Ohio over a 20-day period in September to October of 1998 ranged from <1.1 to 290 ppb (ATSDR 1999). Participants were instructed to collect samples when they perceived odors to be "significant;" some of the descriptors used for the odor included rotten eggs, sulfur, burning, sewer gas, and pungent. Of particular concern would be a worker with occupational exposure to carbon disulfide who also lives close enough to the plant to be exposed to elevated levels at home as well. Elevated biomarkers of exposure (e.g., urinary concentrations of carbon disulfide or its metabolites) have been reported in children who live close (15 km) to a factory emitting carbon disulfide into the atmosphere, compared to children living 400 km away (Helasova 1969).

In addition, members of the general population living in the vicinity of industrial point emission sources are exposed to higher than background levels of carbon disulfide. The compound has been detected in both ambient air and water in low concentrations, with somewhat higher concentrations in localized areas around industrial and disposal sites. For example, ambient air levels of carbon disulfide from October 2020 to September 2021 ranged from 1.6 to 7.4 ppbv in various community locations in Kalamazoo, Michigan near Graphic Packaging International, LLC, and the Kalamazoo Water Reclamation Plant (MDHHS 2023). The exposure levels in the upper range for these communities are more than twice the upper range exposure levels reported in ambient air across the United States in 2022 (Section 5.6). In 2008, predicted vapor intrusion for buildings near the former Industrial Chemical Supply Company (ICSC) hazardous water properties in Tampa, Florida from wells contaminated with carbon disulfide ranged from 0.16 to 0.3 ppbv; well concentrations were not reported (ATSDR 2008). No information was found regarding the number of people potentially exposed in the vicinity of hazardous waste sites. However, since carbon disulfide has been found near hazardous waste sites, people living near them may be exposed to higher than background levels.

Göen et al. (2014) studied workplace air levels of carbon disulfide and creatinine concentrations of the carbon disulfide metabolite, TTCA, in urine of factory workers of a viscose rayon manufacturing facility located in Germany. Cross-sectional studies were conducted in 1992 and 2009 and supplemented with company internal data. The results comparing personal air monitoring of carbon disulfide exposure and urinary TTCA levels from 1992 versus 2009 in different departments (job function and location) of the facility are shown in Tables 5-16 and 5-17, respectively. Personal carbon disulfide air monitoring data were significantly correlated with urinary TTCA levels in 2009; correlation analysis was not conducted for 1992 data. The study authors concluded that exposures to carbon disulfide have decreased over this time period as engineering controls and other safety measures have reduced air levels in these settings; however, the study authors noted that the data do not show a linear trend over the temporal period.

Table 5-16. Carbon Disulfide Personal Air Monitoring (ppm) in a Rayon Factory in 1992 and 2009

Department	Number of measurements	Median	95th percentile	Range
1992				
Spinning of textile rayon	109	2.95	7.23	0.52–19.3
Spinning of technical rayon	95	5.54	15.4	0.87–18.3
Washing of textile rayon spools	37	8.86	28.1	1.11–65.7
Post-treatment	95	3.83	7.07	<0.20–16.9
Rayon ageing and filter cleaning	16	1.70	–	<0.20–5.11
All exposed workers	352	4.15	15.4	<0.20–65.7
2009				
Spinning of textile rayon	52	3.36	6.46	0.480–13.2
Spinning of technical rayon	63	2.97	11.5	0.195–20.9
Washing of textile rayon spools	23	2.01	3.86	<0.20–5.65
Post-treatment	56	1.86	6.15	0.460–11.4
Rayon ageing and filter cleaning	12	2.60	3.62	1.36–3.92
All exposed workers	209	2.48	6.71	<0.20–20.9

Source Göen et al. (2014)

Table 5-17. 2-Thiothiazolidine-4-carboxylic Acid (mg/g Creatinine) Concentration in Urine of Workers in a Rayon Factory in 1992 and 2009

Department	Number of measurements	Median	95th percentile	Range
1992				
Spinning of textile rayon	112	1.31	3.29	0.03–6.37
Spinning of technical rayon	97	2.76	7.43	0.04–11.0
Washing of textile rayon spools	40	3.72	7.96	0.40–11.6
Post-treatment	96	1.49	4.26	0.05–6.72
Rayon ageing and filter cleaning	17	0.65	2.23	0.23–2.23
All exposed workers	362	1.63	5.57	0.03–11.6
2009				
Spinning of textile rayon	53	0.97	2.12	0.08–4.68
Spinning of technical rayon	65	1.02	2.78	0.09–5.27
Washing of textile rayon spools	22	0.46	1.81	0.06–2.20
Post-treatment	54	0.58	2.47	0.04–3.50
Rayon ageing and filter cleaning	12	0.80	1.54	0.48–5.27
All exposed workers	209	0.86	0.86	0.04–5.27

Source Göen et al. (2014)

In a similar study, Vermeulen et al. (2005) reported urine TTCA levels in rubber workers from nine factories (three rubber tire, five general rubber goods, and one retreading company) based on departments using biomonitoring data collected from January to July 1997; results are presented in Table 5-18.

Table 5-18. Weekday Urinary Levels of 2-Thiothiazolidine-4-carboxylic Acid in Rubber Workers by Department

Department	Number of subjects	Number of measurements	Arithmetic mean in µmol/mol creatinine (mg/g creatinine)[a]	Geometric mean in µmol/mol creatinine (mg/g creatinine)[a]
Mixing	10	30	15 (0.022)	7 (0.01)
Pre-treating	14	41	16 (0.023)	8 (0.01)
Molding	27	76	34 (0.049)	11 (0.016)[b]
Curing	24	67	27 (0.039)	16 (0.023)[b]
Finishing	9	25	42 (0.061)	13 (0.019)
Shipping	3	8	15 (0.022)	14 (0.020)
Engineer service	14	38	17 (0.025)	7 (0.01)

[a]To facilitate comparison across studies, urinary levels reported in µmol/mol creatinine were converted to mg/g creatinine based on the molecular weights of 2-thiothiazolidine-4-carboxylic acid (163.2 g/mol = 0.1632 mg/µmol; NLM 2024a) and creatinine (113.12 g/mol; NLM 2024b). 1 µmol 2-thiothiazolidine-4-carboxylic acid/1 mol creatinine = 0.1632 mg 2-thiothiazolidine-4-carboxylic acid/113.12 g creatinine = 0.001443 mg 2-thiothiazolidine-4-carboxylic acid/g creatinine. Example calculation: 15 µmol/mol creatinine x 0.001443 = 0.022 mg/g creatinine.
[b]Mean weekday urinary biomarker levels of subjects in a department significantly higher than Sunday urinary biomarker levels (paired *t*-test); $p < 0.05$.

Source: Vermeulen et al. 2005

Levels of the carbon disulfide metabolite, TTCA, were measured in the urine of individuals after completing their shift in a rayon factory (Chang et al. 2002). Levels of TTCA were excreted about 34% within the first 2 hours after exposure; the mean half-life for excretion was 8.7 hours, with total elimination by 22–24 hours.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of carbon disulfide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of carbon disulfide.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

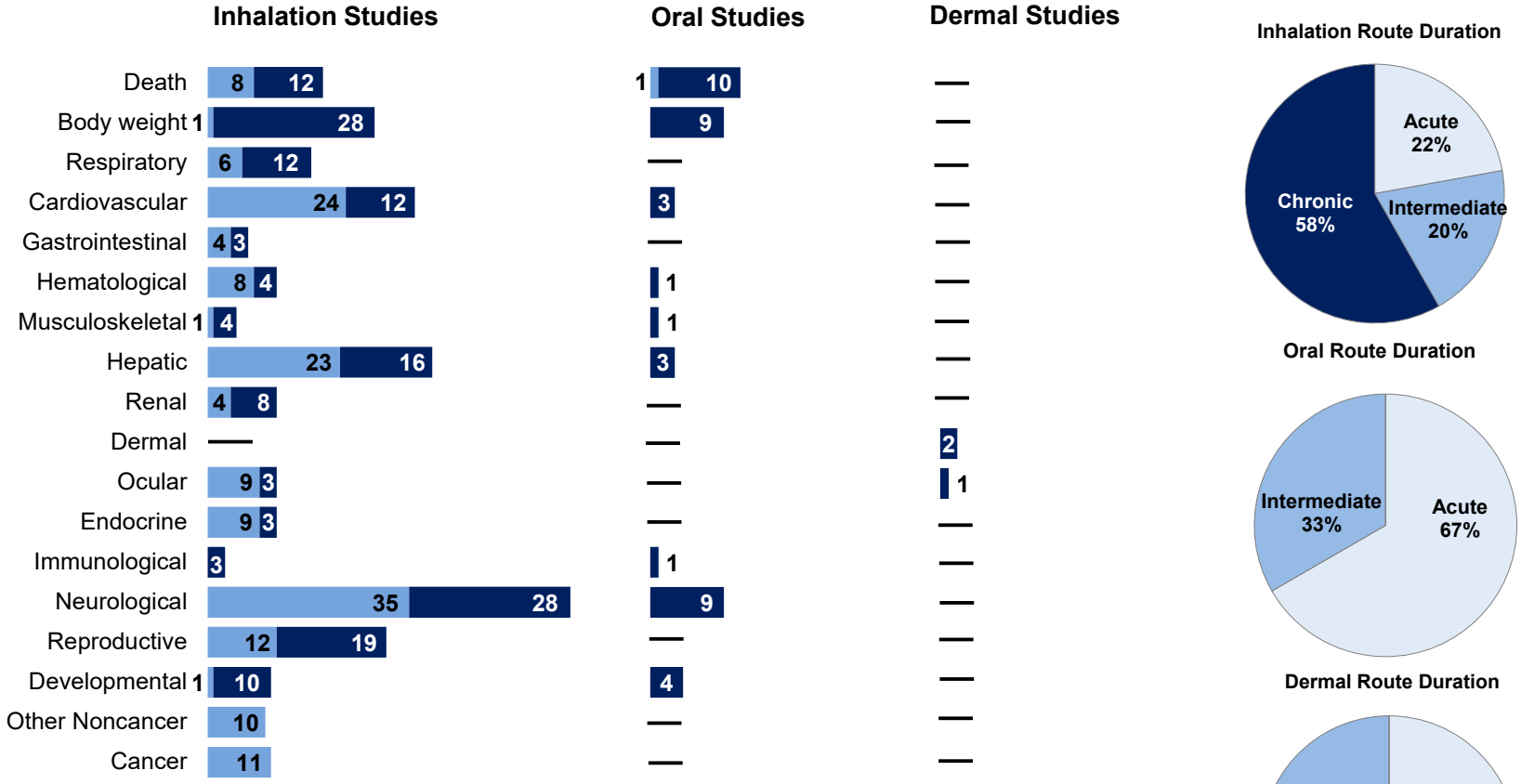
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to carbon disulfide that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of carbon disulfide. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As shown in Figure 6-1, information on the health effects in humans are available predominantly for inhalation exposure (from both human and animal studies), with a limited animal oral database, and a few dermal studies in animals. For the purposes of Figure 6-1, all occupational human studies were classified as inhalation, despite the potential for concurrent dermal exposure. Additionally, human studies that evaluated urinary levels of TTCA as a biomarker of exposure but did not have any information pertaining to possible exposure sources are not included in Figure 6-1 due to unknown route(s) of exposure.

Figure 6-1. Summary of Existing Health Effects Studies on Carbon Disulfide by Route and Endpoint*

Potential neurological, cardiovascular, and hepatic effects were the most studied endpoints

The majority of the studies examined inhalation exposure in animals and humans and are approximately equal



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; most studies examined multiple endpoints. All human occupational studies were classified as inhalation studies, although there is potential for concurrent dermal exposure.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL. However, the MRL is based on the only study identifying an effect below the lowest LC_{50} value. Additional studies evaluating key health effects (identified in the systematic review) at low concentrations may better inform the dose-response curve at sublethal concentrations and decrease uncertainty in the acute-duration inhalation MRL. The oral database is adequate to derive an acute-duration oral MRL.

Additional low-dose studies designed to identify a NOAEL for the critical effect (developmental effects) could decrease uncertainty in the acute-duration oral MRL; however, the oral route is not the predominant route of concern for human exposure so additional studies may not be necessary.

Intermediate-Duration MRLs. While animal data were available to support derivation of an intermediate-duration inhalation MRL, an intermediate-duration inhalation MRL was not derived due to higher confidence in chronic-duration human studies. Occupational studies in humans evaluating key health effects (identified in the systematic review) after exposure for intermediate-duration exposures may be useful, especially if they are well-designed and control for confounders (e.g., co-exposures, sex, age, height, BMI, disease-specific risk factors). The oral database is inadequate to derive an intermediate-duration oral MRL. Since inhalation is the most likely route of exposure to carbon disulfide, additional studies on the effects of carbon disulfide following intermediate-duration oral exposure may not be necessary.

Chronic-Duration MRLs. The inhalation database is adequate to derive a chronic-duration inhalation MRL. Additional well-conducted, longitudinal occupational studies that are well-controlled for confounders (e.g., co-exposures, sex, age, height, BMI, disease-specific risk factors) may further refine the NOAEL/LOAEL boundary used for the basis of the MRL. The oral database is inadequate to derive a chronic-duration oral MRL; no chronic-duration oral studies were identified. Since inhalation is the most

likely route of exposure to carbon disulfide, additional studies on the effects of carbon disulfide following chronic-duration oral exposure may not be necessary.

Health Effects. Identification of data needs for health effects is limited to targets included in the systematic review and endpoints with major data gaps.

Cardiovascular. Numerous occupational studies indicated that the cardiovascular system is a target of carbon disulfide toxicity via inhalation exposure, and a limited number of animal studies support these findings (Section 2.5). Additional well-conducted, longitudinal occupational studies could help establish if current occupational hygiene standards are protective, especially if they are well-controlled for key confounders including known risk factors for cardiovascular disease (e.g., smoking, alcohol intake, BMI, etc.) or use of medications to control risk factors (e.g., blood pressure medication, cholesterol lowering medication). Specifically, additional studies on cerebrovascular effects may be useful, as there are limited data on this endpoint. More information regarding the mechanism(s) of cardiovascular effects would also be helpful.

Altered lipid homeostasis. Data pertaining to altered lipid homeostasis in humans from occupational studies are mixed (Section 2.9). In a German-language study available only from a secondary source, serum cholesterol levels were not altered in four volunteers following exposure to 20 ppm for 8 hours/day for up to 4 days, compared to pre-exposure levels (Freundt and Lieberwirth 1974b, as cited in NRC 2009). The number of animal studies are limited but indicate that inhalation exposure can increase lipid content in hepatic microsomes, lipid synthesis in the liver, and circulating levels of serum lipids and cholesterol (Freundt et al. 1974b; Wrońska-Nofer 1972, 1973; Wrońska-Nofer et al. 1980). Additional well-conducted, longitudinal occupational studies could help establish if carbon disulfide shows a true association with altered serum cholesterol levels in workers. Importantly, studies should be well-controlled for key confounders including known risk factors for elevated serum lipids (e.g., smoking, alcohol intake, BMI, etc.) or use of cholesterol-lowering medications. Additional low-concentration studies in animals evaluating a comprehensive set of endpoints pertaining to lipid metabolism and homeostasis could also help better establish a dose-response. Specifically, studies evaluating the time-course of effects of carbon-disulfide exposure on lipid synthesis in both sexes in various rat strains would help reduce and/or explain inconsistencies in the limited database. More information regarding the mechanism(s) of altered lipid homeostasis would also be helpful.

Ophthalmological effects. Numerous occupational studies indicated that the vascular system of the retina is a target of carbon disulfide toxicity via inhalation exposure (Section 2.12). Additional well-conducted, longitudinal occupational studies could help establish if current occupational hygiene standards are protective, especially if they are well-controlled for key confounders including known risk factors for vascular disease (e.g., smoking, alcohol intake). More information regarding the mechanism(s) of retinal effects would also be helpful.

Immunotoxicity. There are no data that suggest that the immune system is a target for carbon disulfide exposure for any route or in any species. However, there are no available studies evaluating immune function. A screening study to investigate routine immune parameters to evaluate functional parameters (e.g., macrophage activity, T-cell activity, mitogen response, cell-mediated immune response) and immunopathology may be useful to determine if there is an immune system effect that has been overlooked.

Neurotoxicity. Numerous occupational and animal studies indicated that the neurological system is a target of carbon disulfide toxicity via inhalation exposure, and a limited number of oral studies in animal are consistent with these findings (Section 2.15). While the peripheral nervous system appears to be the most sensitive target of toxicity in humans, the central nervous system (including the visual and auditory systems) is also a target. Additional well-conducted, longitudinal occupational studies could help establish if current occupational hygiene standards are protective, especially if they are well-controlled for key confounders including known risk factors for neurological impairments (e.g., alcohol intake, diabetes, etc.) or factors shown to impact neurological measures (e.g., BMI for nerve conduction velocity).

Reproductive. There are limited and inconsistent human data that indicate that chronic-duration inhalation exposure to carbon disulfide can affect the reproductive system in both males and females. In males, sperm morphology, hormone levels, and libido have been altered by occupational exposure to carbon disulfide in some studies (Guo et al. 2016; Vanhoorne et al. 1994; Wägar et al. 1981); however, there is no evidence of impaired fertility (NIOSH 1983; Vanhoorne et al. 1994). Additional well-conducted, longitudinal occupational studies could help re-evaluate inconsistencies in male reproductive findings, especially if they are well-controlled for key confounders including known risk factors for altered male reproductive performance or fertility (e.g., smoking, alcohol intake, parity of partner, time since last ejaculate, etc.) or use of medication to treat fertility or erectile dysfunction. In females, self-reported menstrual

irregularities have been associated with occupational exposure to carbon disulfide (Cai and Bao 1981; Zhou et al. 1988), although more serious effects, such as increased miscarriage, stillbirth, premature birth, or pregnancy toxemia, have not been consistently noted (Cai and Bao 1981; Hemminki and Niemi 1982; Zhou et al. 1988). Data in animals support potential adverse effects in males only, with altered mating behavior and some evidence of testicular and sperm damage following inhalation exposure (Guo et al. 2014, 2015; Huang et al. 2012; Tepe and Zenick 1984; Zenick et al. 1984). Additional reproductive studies on other species, such as mice, rabbits, dogs, and monkeys, may be useful to determine the dose-effect relationship between exposure and reproductive end points.

Developmental. Human data are inadequate to evaluate potential developmental effects of carbon disulfide exposure. Data from two species (rats, rabbits) via two routes (inhalation, oral) indicate that the developing fetus may be a sensitive target of toxicity (Section 2.17). In addition, neurobehavioral effects have been reported in the offspring of exposed animal mothers (Lehotzky et al. 1985; Tabacova et al. 1983). Additional low-dose data following pre- and/or peri-natal exposure, especially pertaining to neurodevelopmental effects, may be useful to determine dose-response data for a potentially susceptible population.

Epidemiology and Human Dosimetry Studies. There are many epidemiological studies that address the effects of inhalation exposure to carbon disulfide. These are predominantly occupational studies from the viscose rayon industry. Clearly, occupational workers, as well as communities around hazardous waste sites or point-emission sources, are at risk for exposure to levels of carbon disulfide that have been associated with adverse health effects. The biggest drawback in the existing studies is the lack of the ability to establish a clear dose relationship between exposure and effect. More precise measurements of exposure, control of exposure to other chemicals, control for other key confounders specific to the examined health outcome, and long-term follow-up of occupational cohorts may lead to a better understanding of the dose-effect of carbon disulfide. Monitoring of populations around hazardous waste sites where carbon disulfide is known to be present may also be useful.

Biomarkers of Exposure and Effect. Methods for detecting carbon disulfide or its metabolites in exhaled breath, blood, urine, and tissues are available. The most sensitive biomarker for carbon disulfide that correlates best with external exposure is urinary levels of the metabolite, TTCA (Beauchamp et al. 1983; Campbell et al. 1985; Drexler et al. 1994). However, certain vegetables (e.g., cabbage, Brussels sprouts) can increase levels of TTCA, resulting in detection of TTCA in unexposed individuals with high

dietary intakes (Simon et al. 1994; Kivistö 2000). Therefore, in persons who eat large amounts of these vegetables, measurements of urinary TTCA may overestimate carbon disulfide exposure. Studies designed to better quantify community baseline levels could help correct for nonworkplace exposure sources.

No biomarkers were identified that are specific to or particularly useful in characterizing the effects induced by exposure to carbon disulfide. The most well-characterized target organs of carbon disulfide toxicity in humans are the nervous system (particularly the peripheral nervous system), heart, and eye; however, damage to these organs may result from exposure to other chemicals. Additional investigations to identify subtle biochemical changes to serve as biomarkers of effects from carbon disulfide exposure would be useful in detecting early, subtle signs of carbon disulfide-induced damage.

Absorption, Distribution, Metabolism, and Excretion. There are human and animal data that address the absorption, distribution, metabolism, and excretion of carbon disulfide following inhalation exposure (Chapter 3). Data indicate rapid and extensive absorption of inhaled carbon disulfide, distribution throughout the body, and primary excretion by exhalation. Carbon disulfide is metabolized by cytochrome P-450 to an unstable oxygen intermediate that in turn can either degrade to sulfur and carbonyl sulfide or hydrolyze to sulfur and monothiocarbonate. Biotransformation of carbon disulfide in humans exposed by the inhalation route causes metabolites to be excreted in the urine, and carbonyl sulfide and carbon dioxide in the breath. The data that exist for humans are largely supported by animal studies (rabbits and dogs) for this route. However, there are very few animal and human data regarding the pharmacokinetics of carbon disulfide following oral or dermal exposure, making assessment of relative rates very difficult (Cohen et al. 1958; DeMatteis and Seawright 1973; Dutkiewicz and Baranowska 1967). The limited data indicate that a range fraction of orally administered carbon disulfide is absorbed by rats. Carbon disulfide is appreciably absorbed via the dermal route in rabbits. Animal data suggest that there are two major pathways. Steady-state phenomena do play a role in the retention and excretion of carbon disulfide, with less exposed individuals retaining more of the chemical than chronically exposed individuals (Beauchamp et al. 1983). Additional information regarding the pharmacokinetics of carbon disulfide following oral and dermal exposure would be useful.

Comparative Toxicokinetics. Both human and animal data indicate that the target organs for carbon disulfide are similar across species (Cohen et al. 1958; DeMatteis and Seawright 1973; Dutkiewicz and Baranowska 1967; Freundt et al. 1975; McKee et al. 1943; Soucek 1957; Teisinger and Soucek 1949; Toyama and Kusano 1953). There are no studies that directly compare the toxicokinetics across species.

Most of the animal studies on toxicity endpoints have used high doses. The studies in rats, mice, and rabbits have generally been consistent in their conclusions regarding the pharmacokinetics of carbon disulfide. Data from species other than rodents would also be useful for determining the species most comparable to humans, so that animal toxicity data can be better evaluated. No striking differences between the results of rodent studies and those from human studies were noted except that sulfate excretion is far more important in animals than in humans, except in the latter for exposure to high doses of carbon disulfide (Strittmatter et al. 1950). Additional information on the comparative pharmacokinetics following exposure from the oral and dermal routes would be useful, as most of the data currently available are from inhalation studies. The volatility of carbon disulfide may well affect kinetic parameters measured in dermal exposures, and metabolic parameters following oral exposures could differ from those following inhalation exposure. Once these data are available, development of PBPK models would be useful to extrapolate exposure levels between species and/or routes.

Children's Susceptibility. It is unknown if developing fetuses, infants, or children are uniquely susceptible to carbon disulfide toxicity. As discussed above (under Developmental Toxicity), human data are inadequate. In animals, it has been shown that carbon disulfide passes through the placenta to the fetus (Danielsson et al. 1984), and several studies reported developmental effects at exposure levels below those associated with maternal toxicity (Denny and Gerhart 1991; Lehotzky et al. 1985; NCTR 1984a, 1984b). Additional studies at low, non-maternally toxic doses, are needed to fully evaluate children's susceptibility.

Physical and Chemical Properties. The physical and chemical properties of carbon disulfide are sufficiently well defined to allow an assessment of its environmental fate (EPA 2022b; Flick 1985; MCA 1968; NFPA 1986; NIOSH 1984b; OSHA 2022; Sax and Lewis 1987; Timmerman 1978; Verschueren 1983; Weast 1989; Windholz 1983; Worthing 1987). Therefore, no data needs have been identified at this time.

Production, Import/Export, Use, Release, and Disposal. The TRI lists data on the releases of carbon disulfide to air, water, and soil from U.S. industrial sources (TRI23 2025). Data are available on emissions from natural sources such as oceans (Lennartz et al. 2021). U.S. production volumes and import/export data are available from the Chemical Data Reporting (CDR) and the United States International Trade Commission (USITC) (EPA 2022c; USITC 2024). Disposal methods include liquid injection incineration, rotary kiln incineration, and fluidized bed incineration (EPA 1981b; UNEP 1985); however, data on the efficiency of these methods are lacking. This information would be useful in

identifying the media of concern for human exposure and populations at risk of adverse health effects from exposure to carbon disulfide.

Environmental Fate. Releases of carbon disulfide to the environment as a result of industrial activity are expected to be primarily to the atmosphere. Carbon disulfide volatilizes from a variety of soils (Farwell et al. 1979). Carbon disulfide reacts with hydroxyl radicals in the troposphere to produce carbonyl sulfide (Cox and Sheppard 1980). Further oxidation would produce sulfur dioxide, a major contributor to the greenhouse effect (Cox and Sheppard 1980). The lifetime of carbon disulfide in the troposphere is ~73 days (Cox and Sheppard 1980). Carbon disulfide is stable to hydrolysis in the pH region of environmental concern (pH 4–10), with a hydrolysis half-life at pH 13 of about 1 year (EPA 1976). No data are available concerning the biodegradation of carbon disulfide in soil. Concerted efforts should be made to measure the spatial and temporal variations in the atmospheric levels of carbon disulfide in the vicinity of specific point or nonpoint sources. Although volatilization is the primary fate of carbon disulfide released to the environment (Farwell et al. 1979; Roy and Griffin 1985), data on the partitioning of carbon disulfide from water onto sediments and on the hydrolysis rate of carbon disulfide in surface and groundwater could be useful in determining the persistence of low levels of the compound in the environment. Additional information on the transport and transformation of carbon disulfide in soils, particularly on biotransformation, would also be useful.

Bioavailability from Environmental Media. Carbon disulfide is absorbed following inhalation of contaminated ambient air (Soucek 1957; Teisinger and Soucek 1949) and from dermal contact with contaminated soils or water (ATSDR 2025; Helasova 1969). Data are lacking on the bioavailability of carbon disulfide following ingestion of contaminated soils and groundwater or foods grown with contaminated water. This information would be useful in determining the importance of these routes of exposure.

Food Chain Bioaccumulation. BCF values of <6 and <60 were measured in fish (J-CHECK 2025a) and a value of 8.9 was estimated from a regression-based method. Based on these data, carbon disulfide does not significantly bioaccumulate in aquatic organisms. No information was available on the bioaccumulation of carbon disulfide in organisms at other trophic levels in aquatic environments. Monitoring for the accumulation of carbon disulfide in organisms from several trophic levels would be useful in estimating the levels of carbon disulfide to which humans are exposed through dietary intake.

Exposure Levels in Environmental Media. Studies of background levels of carbon disulfide in air have been conducted (Conley et al. 2005; Cooper and Saltzman 1993; EPA 2024a; Logue et al. 2010, 2011; Rosenbaum et al. 1999; Zhu et al. 2005), but site-specific concentration data for ambient air, drinking water, and biota, particularly at hazardous waste sites, are lacking. These data would be helpful in estimating the exposure of the general population as well as those living near hazardous waste sites. The sites with highest concentrations of carbon disulfide need to be determined. In addition, estimates of human intake from various media would be helpful in assessing human exposure for carbon disulfide for populations living near hazardous waste sites.

Reliable and current monitoring data for the levels of carbon disulfide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of carbon disulfide in the environment can be used in combination with the known body burden of carbon disulfide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Carbon disulfide can be detected in exhaled breath, blood, urine, and breastmilk, and metabolites can be detected in urine, exhaled air, and blood (ACGIH 1986; Cai and Bao 1981; Chang et al. 2002; Göen et al. 2014; Helasova 1969; Pellizzari et al. 1982; Teisinger and Soucek 1949; Vermeulen et al. 2005; WHO 1979). However, because of the rapid metabolism and elimination of carbon disulfide, these fluid and breath levels do not correlate well with environmental levels, except for the urinary marker, TTCA. In addition, the interaction of carbon disulfide with other potential confounders may affect the reliability of urinary metabolites as biomarkers of exposure. Biomarkers may therefore be of limited utility in the quantitative assessment of human exposure to carbon disulfide at hazardous waste sites; however, biomarkers may be useful in qualitatively establishing that possible exposure has occurred.

Additional information on biological monitoring is necessary for assessing the need to conduct health studies on general populations and on those populations living near hazardous waste sites.

Exposures of Children. Exposure pathways and biomarkers of exposure for children will be similar to those for adults. Biological monitoring studies for children of workers employed in industries that produce, transport, or store this product, or for children who reside in close proximity to facilities that produce carbon disulfide would be useful.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2025) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding carbon disulfide in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for carbon disulfide.

Table 7-1. Regulations and Guidelines Applicable to Carbon Disulfide

Agency	Description	Information	Reference
	Air		
EPA	RfC	0.7 mg/m^3 (0.2 ppm)	IRIS 2002
WHO	Air quality guidelines	100 µg/m^3 (0.03 ppm)[a] averaged over 24 hours	WHO 2000
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2023b
	RfD	0.1 mg/kg/day	IRIS 2002
WHO	Drinking water quality guidelines	Not listed	WHO 2022
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2025
	Cancer		
HHS	Carcinogenicity classification	Not evaluated	NTP 2021
EPA	Carcinogenicity classification	Not evaluated	IRIS 2002
IARC	Carcinogenicity classification	Not evaluated	IARC 2025
	Occupational		
OSHA	PEL (8-hour TWA) for general industry	20 ppm (60 mg/m^3)[b]	OSHA 2023a
	Ceiling limit	30 ppm	
	Maximum peak for an 8-hour shift	100 ppm for 30 minutes	
	PEL (8-hour TWA) for construction and shipyards	20 ppm (60 mg/m^3)[c]	OSHA 2023b, 2023c
NIOSH	REL (up to 10-hour TWA)	1 ppm (3 mg/m^3)[d]	NIOSH 2019
	STEL (15-minute TWA)	10 ppm (30 mg/m^3)	
	IDLH	500 ppm	

Table 7-1. Regulations and Guidelines Applicable to Carbon Disulfide

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[e]		
	10-minute	17 ppm	
	30-minute	17 ppm	
	60-minute	13 ppm	
	4-hour	8.4 ppm	
	8-hour	6.7 ppm	
	AEGL 2[e]		
	10-minute	200 ppm	
	30-minute	200 ppm	
	60-minute	160 ppm	
	4-hour	100 ppm	
	8-hour	50 ppm	
	AEGL 3[e]		
	10-minute	600 ppm	
	30-minute	600 ppm	
	60-minute	480 ppm	
	4-hour	300 ppm	
	8-hour	150 ppm	
DOE	PACs-air		DOE 2025a
	PAC-1[f]	13 ppm	
	PAC-2[f]	160 ppm	
	PAC-3[f]	480 ppm	

[a]A guideline value of 20 µg/m^3 (0.006 ppm), averaged over 30 minutes, based on sensory effects, is recommended when carbon disulfide is used as an index substance for viscose emissions (WHO 2000).
[b]Reflects the exposure limit that was in effect prior to the issuance of newer limits (carbon disulfide PEL of 4 ppm and STEL of 12 ppm) on January 19, 1989, which were then vacated by the Eleventh Circuit Court of Appeals on July 7, 1992 (NIOSH 2018).
[c]Skin designation.
[d]Skin notation.
[e]Definitions of AEGL terminology are available from EPA (2018c).
[f]Definitions of PAC terminology are available from DOE (2025b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

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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: July 2025
Profile Status: Final
Route: Inhalation
Duration: Acute
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: An 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 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, sphingomyelin, 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 sphingomyelin at ≥20 ppm, phosphatidylcholine at ≥100 ppm, and lysophosphatidylcholine 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 sphingomyelin. 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 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 MRL for acute-duration exposure to carbon disulfide via inhalation is:

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

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: July 2025
Profile Status: Final
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 an 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, derivation of a 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 selected over derivation of an 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:	July 2025
Profile Status:	Final
Route:	Inhalation
Duration:	Chronic
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:	57
Species:	Human

MRL Summary: A 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 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" (>40 g/week for >2 years), 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 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 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 nerve 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 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.

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

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

- 10 for human variability

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

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

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 neurofilaments during axonal anterograde transport; (5) crosslinked masses block transport at nodes of Ranvier (impeding peripheral nerve signals); and (6) axonal swelling and degeneration (EC/HC 2000; Graham et al. 1995; Harry et al. 1998; 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: July 2025
Profile Status: Final
Route: Oral
Duration: Acute
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: An 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 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 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 $p<0.481$ for females), whereas the percent live fetuses and average fetal body weight were not related to sex.

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 MRL for acute-duration exposure to carbon disulfide via oral exposure is:

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

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 post-implantation 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: July 2025
Profile Status: Final
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: July 2025
Profile Status: Final
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 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)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects

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

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 literature search was conducted 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. The initial literature search, which was performed in June 2022, was restricted to studies added to databases since January 1994. An updated literature search was performed after the Toxicological Profile for Carbon Disulfide Draft for Public Comment was released in October 2024 to identify any additional studies added to databases between January 2021 and January 2025.

The following main databases were searched in June 2022 and/or January 2025:

- 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	
01/2025	(75-15-0[rn] OR "Carbon Disulfide"[mh] 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 (2021:3000[dp] OR 2022/06/01:3000[mhda] OR 2022/06/01:3000[edat] OR 2022/06/01:3000[crdat])
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	
01/2025	Limited to 2021 to present "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"
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"

Table B-2. Database Query Strings

Database search date	Query string
Toxcenter	
01/2025	FILE 'TOXCENTER' ENTERED AT 17:52:17 ON 14 JAN 2025 CHARGED TO COST=ET027.02.03.LB.02 L1 16816 SEA 75-15-0 L2 13162 SEA L1 NOT PATENT/DT L3 943 SEA L2 AND ED>=20220601 L4 1470 SEA L2 AND PY>2020 L5 1478 SEA L3 OR L4 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L21 QUE (ENDOCRIN? AND DISRUPT?) L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)

Table B-2. Database Query Strings

Database search date	Query string
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L28 QUE (NEPHROTOX? OR HEPATOTOX?) L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L31 QUE 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 OR L30 L32 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?) L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L34 QUE L31 OR L32 OR L33 L35 QUE (NONHUMAN MAMMALS)/ORGN L36 QUE L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 838 SEA L5 AND L38 L40 15 SEA L39 AND MEDLINE/FS L41 814 DUP REM L39 (24 DUPLICATES REMOVED) L*** DEL 838 S L5 AND L38 L*** DEL 838 S L5 AND L38 L42 814 SEA L41 L43 789 SEA L42 AND EN/LA L44 814 SEA L42 NOT LA/FA L45 25 SEA L42 NOT L43 D CLUSTER D SEL D SET L*** DEL 838 S L5 AND L38 L*** DEL 838 S L5 AND L38 L46 814 SEA L41 L47 789 SEA L46/ENGLISH D SCAN L45 D SCAN L43
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

Table B-2. Database Query Strings

Database search date	Query string
	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, 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

Table B-2. Database Query Strings

Database search date	Query string
	L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 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	
01/2025; 06/2022	Compounds searched: 75-15-0

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NTP	
01/2025	Limited 2020 to present "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"
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	
01/2025; 06/2022	"Carbon bisulfide" "Carbon bisulphide" "Carbon disulfide" "carbon disulphide" "Carbondisulfide" "Methanedithione" "Carbon sulfide(CS2)" "Dithiocarbonic anhydride" "Dithiocarbonic, anhydrous" "Sulphocarbonic anhydride" "Sulphuret of carbon" "Weeviltox"
NIH RePORTER	
02/2025	Search Criteria: 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
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	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2022 pre-public comment search 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

The 2025 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and Toxcenter (after duplicate removal): 1,001
- Number of records identified from other strategies: 24
- Total number of records to undergo literature screening: 1,025

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on carbon disulfide during the pre- and post-public comment drafts:

- Title and abstract screen
- Full text screen

Pre-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered (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

Pre-Public Comment 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 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

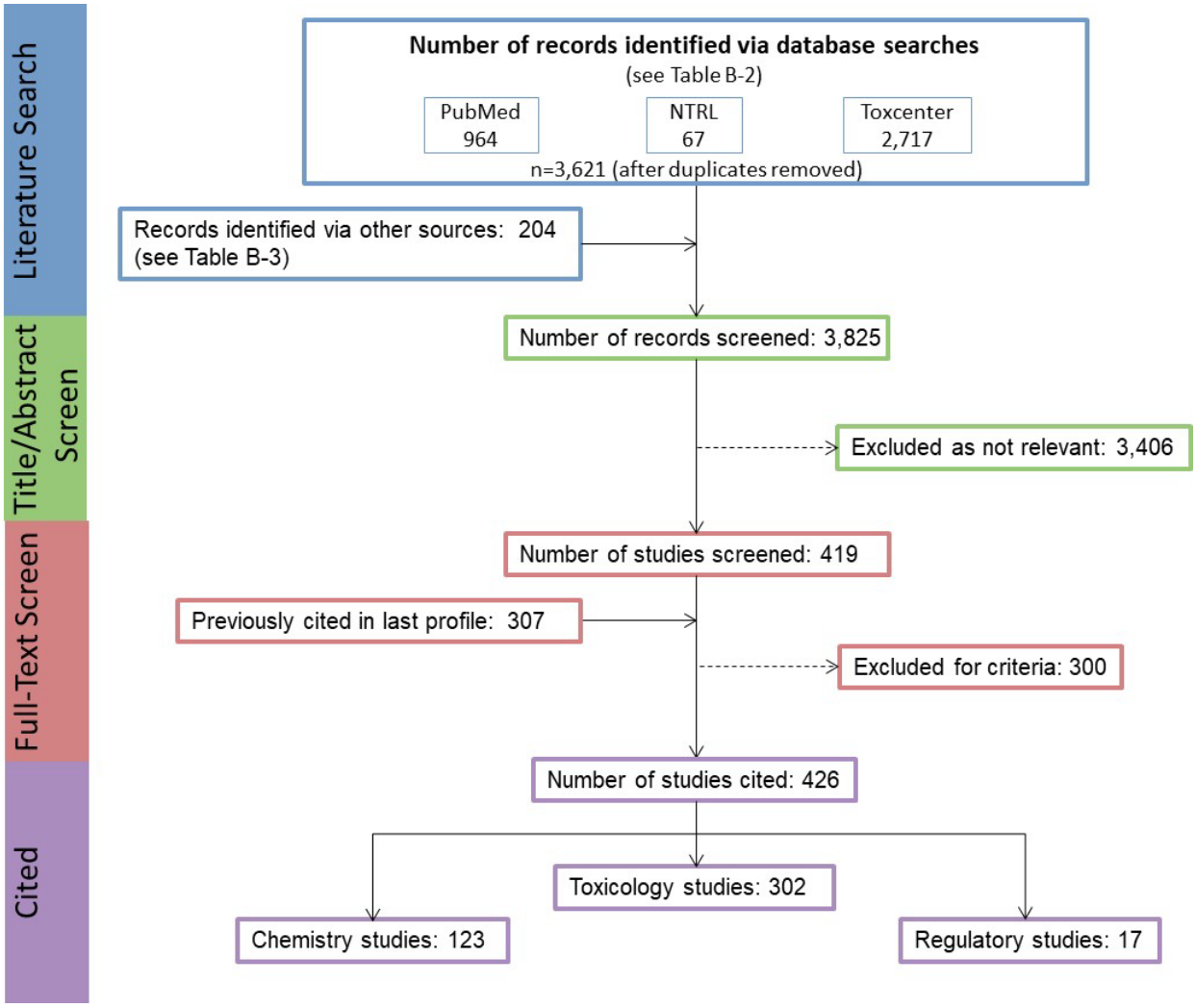
Outcome	Selection process
Death	All studies included
Body weight	All studies included
Respiratory	All studies included
Cardiovascular	Criteria applied
Gastrointestinal	All studies included
Hematological	All studies included
Musculoskeletal	No studies identified
Hepatic	Lipid homeostasis and metabolism: 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 pre-public literature search and screening is presented in Figure B-1.

Figure B-1. June 2022 Pre-Public Comment Literature Search Results and Screen for Carbon Disulfide*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

Post-Public Comment 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.

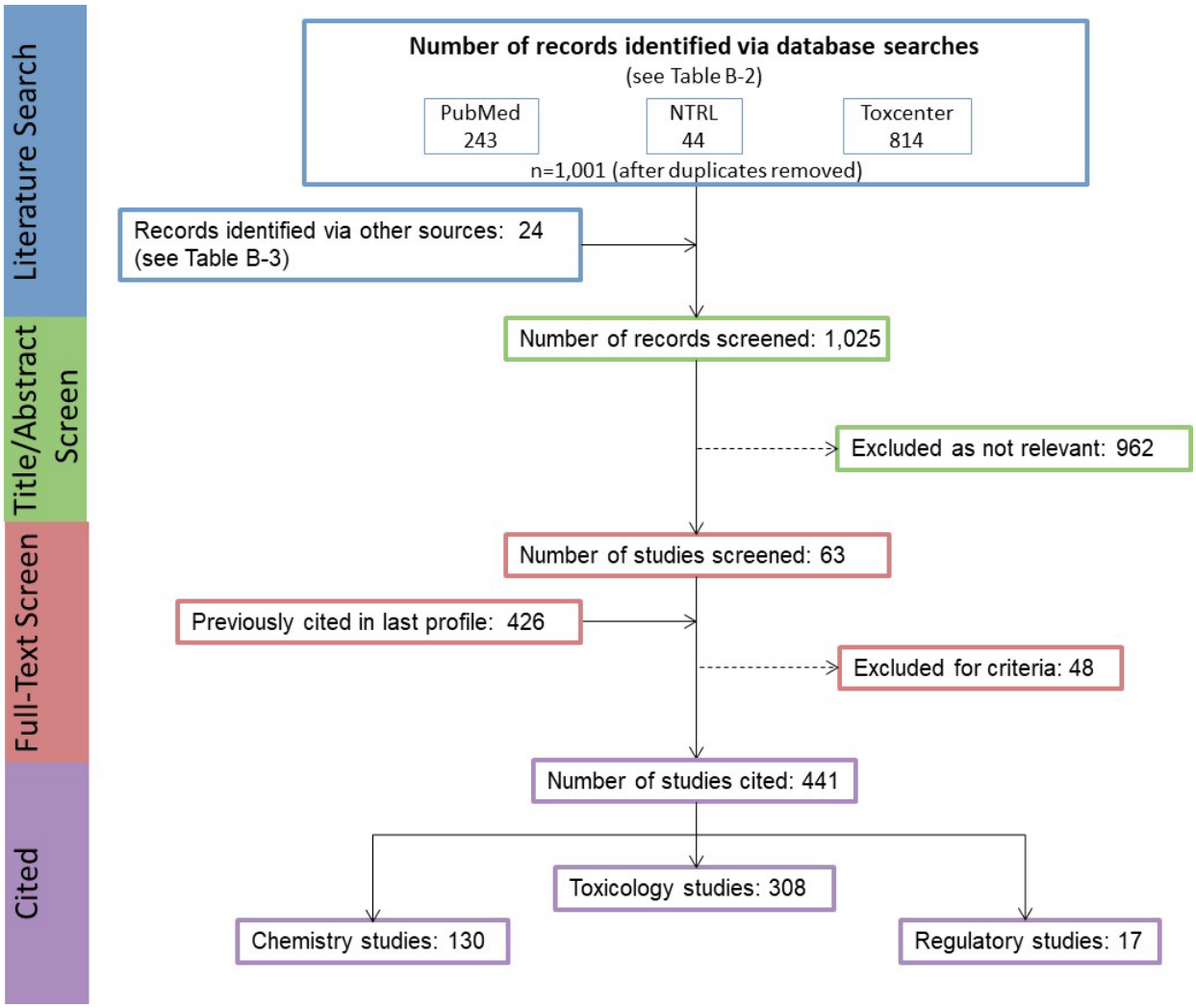
- Number of titles and abstracts screened: 1,025
- Number of studies considered relevant and moved to the next step: 63

Post-Public Comment 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: 63
- Number of studies cited in the pre-public draft of the toxicological profile: 426
- Total number of studies cited in the profile: 441

A summary of the results of the post-public comment literature search and screening is presented in Figure B-2.

Figure B-2. January 2025 Post-Public Comment Literature Search Results and Screen for Carbon Disulfide*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

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 literature searches were intended to update the Toxicological Profile for Carbon Disulfide. See Appendix B for the databases searched and the search strategy.

A total of 3,825 and 1,025 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

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, 169 documents (inclusive of all literature searches) 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 171 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 171 documents (180 studies), 124 documents (121 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 evaluated using the systematic review process. There were 121 studies (published in 124 documents) examining these potential outcomes were 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 cohort		3 2	6 4		2		4 1	1 0		1 1	1 1		5 3	1 1		2 0	2 0
Retrospective cohort	1 1		18 12	2 1	4 1	1 0	16 7	2 2		8 6	4 2		23 21	11 7	1 0	6 2	4 0
Case control		1 0															3 3
Population																1 1	
Cross-sectional		1 0			2 0		2 0	1 0			4 3		2 2	1 0		1 1	
Case series		2 2		2 2									2 2				
Experimental							1 0						1 1				
Ecological																	2 0
Oral studies																	
All study types																	
Dermal studies																	
All study types																	

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	21 14	7 0	9 3	3 0	3 2	4 0	9 3	7 1		3 0	3 0	3 0	17 16	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 De Bacquer 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
Sweetnam et al. 1987; Tiller et al. 1968	–	– –	–	– –	–	+	Third

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
Tolonen et al. 1976	+	–	+	+	+	+	Second
Vanhoorne et al. 1992a	–	+	+	–	+	++	Second
Prospective/Longitudinal cohort studies							
Balcarova 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
Hernberg et al. 1971	++	–	++	–	++	++	Second
Jhun et al. 2007	+	–	++	–	++	++	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
Jhun et al. 2009	+	–	++	–	++	++	Second
Kim et al. 2000	+	–	++	+	–	++	Second
Kotseva and De Bacquer 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
Vertin 1978	–	– –	++	+	+	–	Second
Outcome: Ophthalmological effects (inhalation only)							
Retrospective cohort studies							

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
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
Godderis et al. 2006	+	+	++	+	+	++	First
Foa et al. 1976	+	–	+	–	+	++	Second
Hirata et al. 1996	+	–	+	+	++	++	Second
Johnson et al. 1983; NIOSH 1984a	+	–	++	+	++	++	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
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
Raitta et al. 1974	+	–	+	– –	++	++	Second
Yoshioka et al. 2017	+	+	+	++	++	++	First
Outcome: Male reproductive effects							
Retrospective cohort studies							
Cirla et al. 1978	+	–	–	–	–	+	Third

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
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
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								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?	
Inhalation intermediate-duration exposure									
Chalansonnet et al. 2018	–	–	+	+	+	–	+	++	First
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

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?	
Phillips 1983c	++	–	++	+	++	++	++	++	First
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

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
Wang et al. 2017	+	–	++	–	++	++	+	++	First
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

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

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition / exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Sills et al. 1998b (8 weeks)	++	–	++	+	+	+	++	+	First
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

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?	
NIOSH 1980 (rabbit, premate)	+	–	++	+	++	–	+	++	First
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 De Bacquer 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					
Balcarova 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				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
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 De Bacquer 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: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
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: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
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: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Wilmarth et al. 1993	Yes	Yes	Yes	No	Moderate
Inhalation intermediate-duration exposure					
Chalansonnet et al. 2018	Yes	Yes	Yes	Yes	High
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

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
Song et al. 2009	Yes	Yes	Yes	Yes	High
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

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 (rat)	Yes	Yes	Yes	Yes	High
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		
Balcarova 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 De Bacquer 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		
Wrońska-Nofer 1973	High	High

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

	Initial study confidence	Initial confidence rating
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 De Bacquer 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	
Sugimoto et al. 1978	Moderate	

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

	Initial study confidence	Initial confidence rating
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	
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	High
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		
Chalansonnet et al. 2018	High	
Clerici and Fechter 1991	Moderate	
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	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	
Cirla and Graziano 1981	Moderate	Moderate
Godderis et al. 2006	Moderate	
Foa et al. 1976	Moderate	

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

	Initial study confidence	Initial confidence rating
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	
Inhalation intermediate-duration exposure		
Animal studies		

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

	Initial study confidence	Initial confidence rating
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
Holson 1992	High	
NIOSH 1980 (rat)	High	

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

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

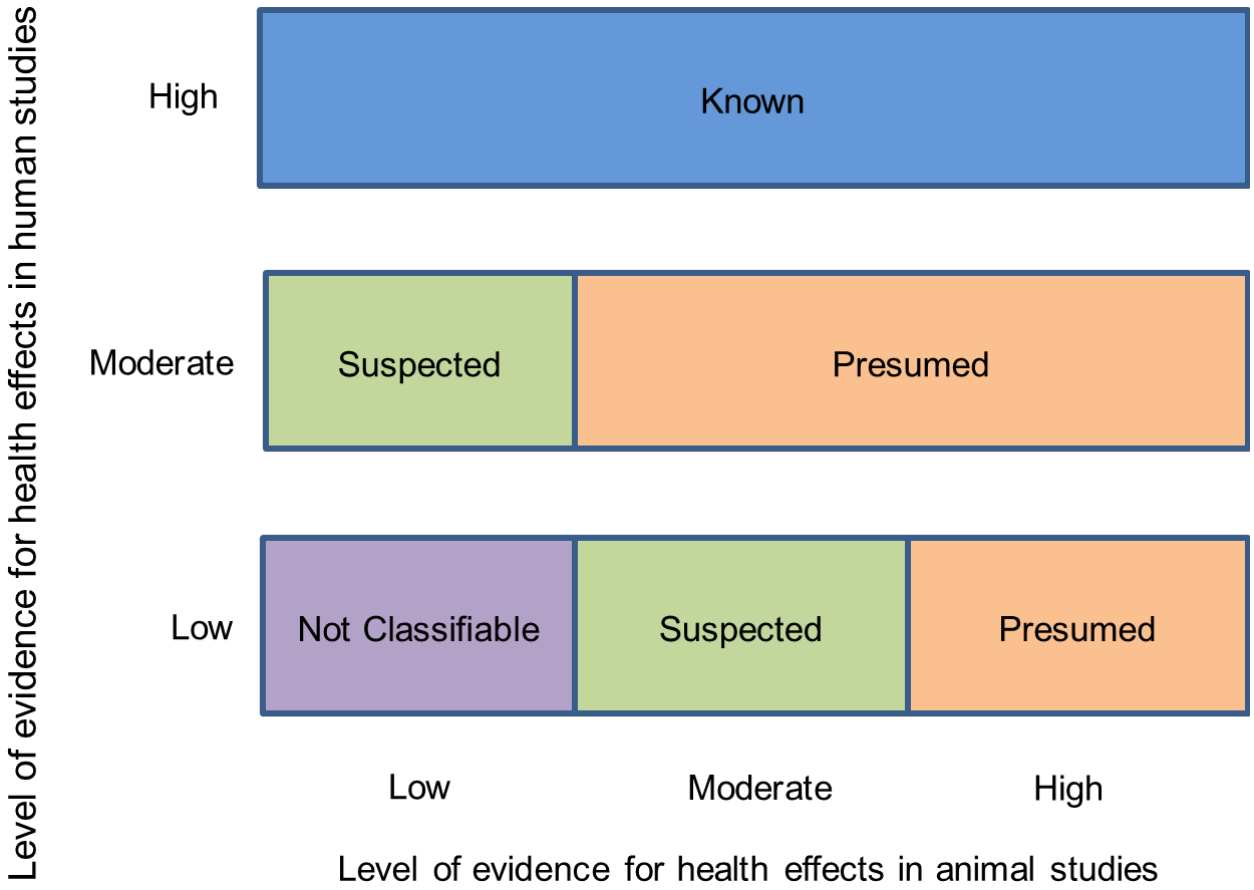
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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									

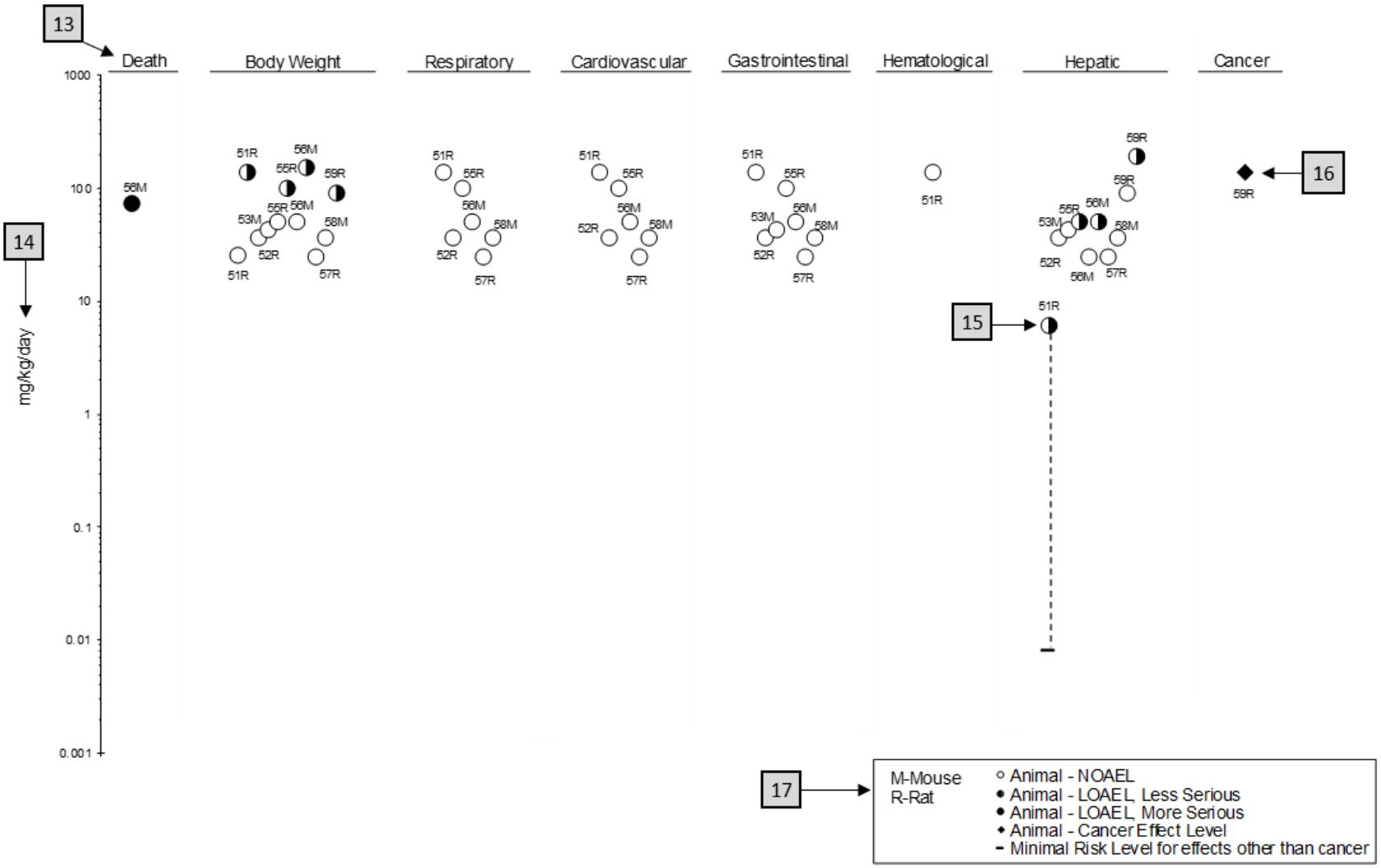
[a]The number corresponds to entries in Figure 2-x.

(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).

APPENDIX D

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.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://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
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