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 effect reported in viscose rayon workers exposed to carbon disulfide. Available occupational studies provide evidence of increase 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 has 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.

- **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

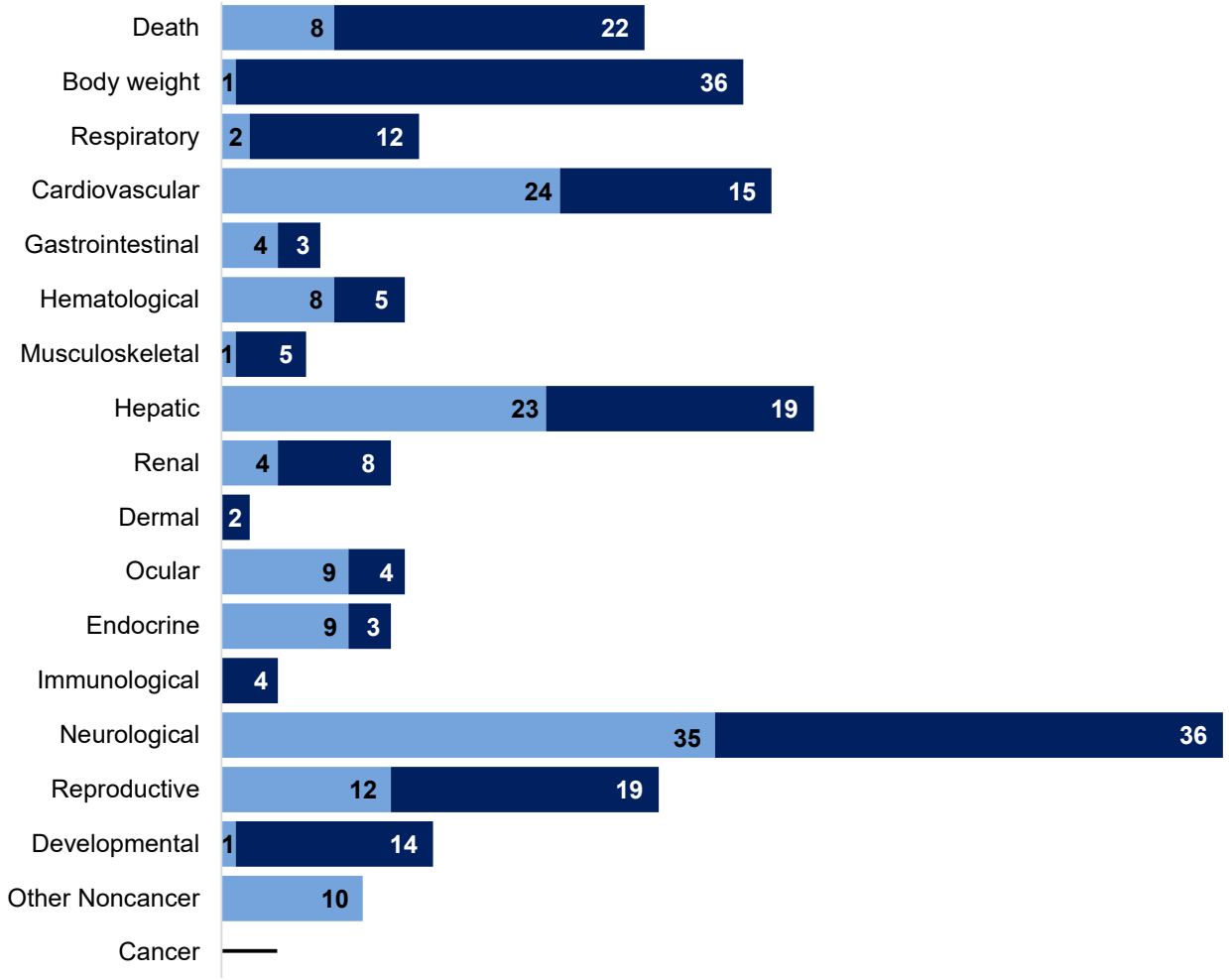
following inhalation exposure. Animal data regarding histopathological damage to the testes are also mixed.

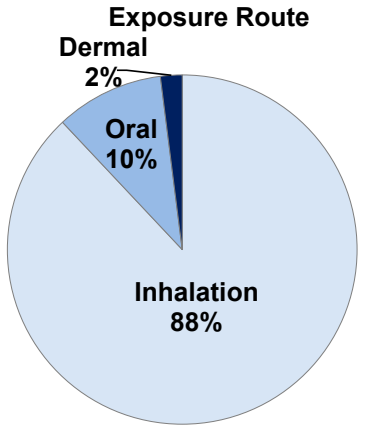
- **Developmental Endpoints:** Developmental effects are a suspected health effect associated with carbon disulfide exposure based on inadequate evidence in humans and a moderate level of evidence in laboratory animals. A single study in humans did not observe an association between occupational exposure 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.

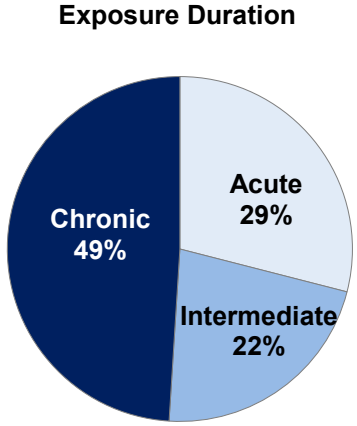
Figure 2-1. Overview of the Number of Studies Examining Carbon Disulfide Health Effects*

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

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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			

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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 Cardio	800 800			
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			

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
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
					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			

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
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
Clerici and Fechter 1991									
29	Rat (Long-Evans) 4 M	5 or 12 weeks 5 days/week 6 hours/day (WB)	0, 500	BW, CS, NX	Neuro		500		Decrease in auditory startle reflex amplitude
Frantik 1970									
30	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									
31	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			

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
					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			
					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									
32	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			

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, foot drag, axonal degeneration and swelling in peripheral nerves, axonal swelling in spinal cord
					Repro	798.4			
Herr et al. 1998; Moser et al. 1998; Sills et al. 1998a, 1998b; Valentine et al. 1997									
33	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			

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) 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			
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	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			

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
Hirata et al. 1992									
36	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									
37	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									
38	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
Morvai et al. 2005									
39	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			

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
					Renal	225			
					Neuro	225			
NIOSH 1980									
40	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									
41	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									
42	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
					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

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
Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983									
43	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									
44	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									
45	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									
46	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
Wrońska-Nofer 1973									
47	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

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
Zenick et al. 1984									
48	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									
49	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									
50	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			
					Immuno	798.4			
					Neuro	297.1		798.4	Degeneration of peripheral nerves
					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
Hardin et al. 1981; NIOSH 1980									
51	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									
52	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									
53	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									
54	Human 197–185 F	>1 year, (occupational)	0, 15	RX	Repro		15		Menstrual disturbances, pregnancy toxemia
Cirla and Graziano 1981									
55	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									
56	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									
57	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									
58	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									
59	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									
60	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			

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
Luo et al. 2011									
61	Human 78–81 M, 11–30 F	20.7 years (occupational)	0, 5.51, 14.2	BC	Hepatic	14.2			
NIOSH 1983									
62	Human 204–236 M	13.7 years (occupational)	0, 8.1	RX	Repro	8.1			
NIOSH 1984a									
63	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									
64	Human 125–324 M	19.6 years (occupational)	0, 4.87 ppm	NX	Neuro	4.87			
Reinhardt et al. 1997a									
65	Human 191–222 NS	6 years (occupational)	0, 4.02	OF, NX	Cardio	4.02			
					Neuro	4.02			
Ruijten et al. 1990									
66	Human 37, 45 M	20 years (occupational)	0, 8.25	NX	Neuro		8.25		Decreased peroneal nerve CVSF

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
Ruijten et al. 1993									
67	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
Schramm et al. 2016									
68	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									
69	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									
70	Human 391–417 M	Duration not specified (occupational)	0, 7.5	CS, OF	Cardio	7.5			
Vertin 1978									
71	Human 100 NS	Duration not specified (occupational)	0, 14	BC, OF	Cardio	14			
					Hepatic	14			
Visconti et al. 1967									
72	Human 18–57 NS	2-8 years (occupational)	0, 114	HE	Hemato		114		Decreased fibrolytic activity of serum plasmin

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
Yoshioka et al. 2017									
73	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									
74	Human 265 F	15 years (occupational)	0, 5.2	RX	Repro		5.2		Menstrual irregularities
					Develop	5.2			
Wrońska-Nofer et al. 1980									
75	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 a provisional 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 provisional 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 provisional 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)

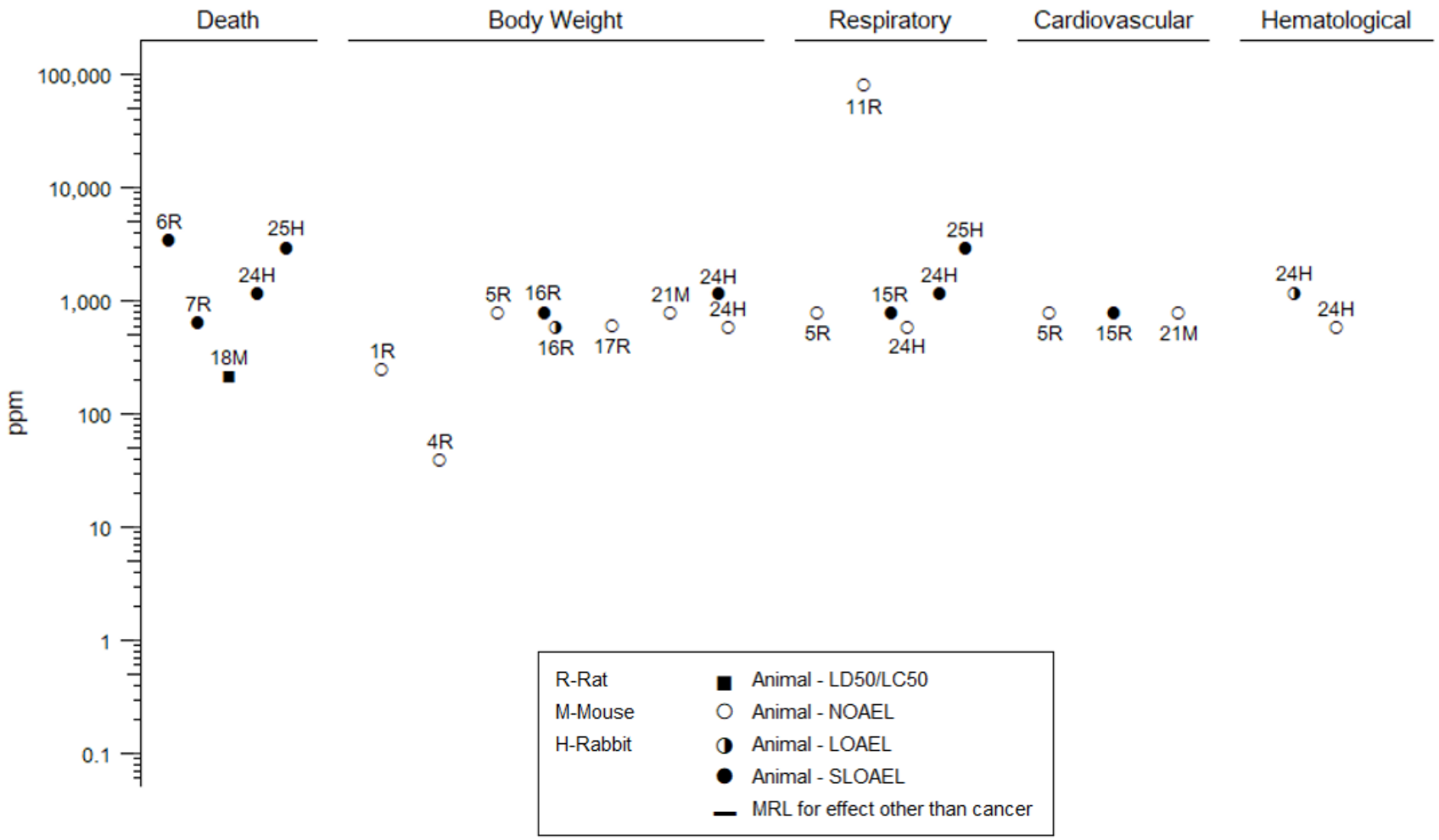

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Acute (≤14 days)

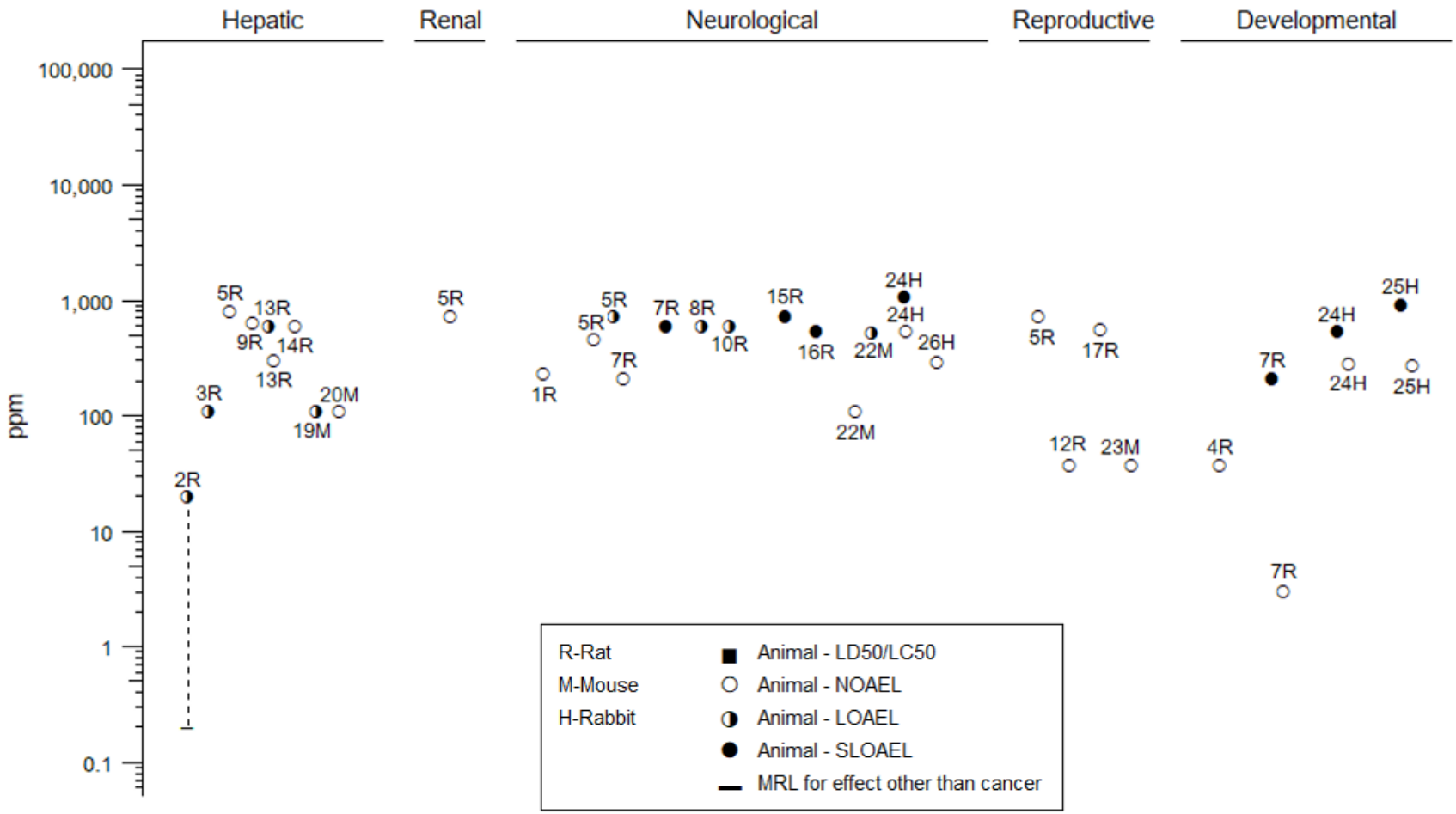

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

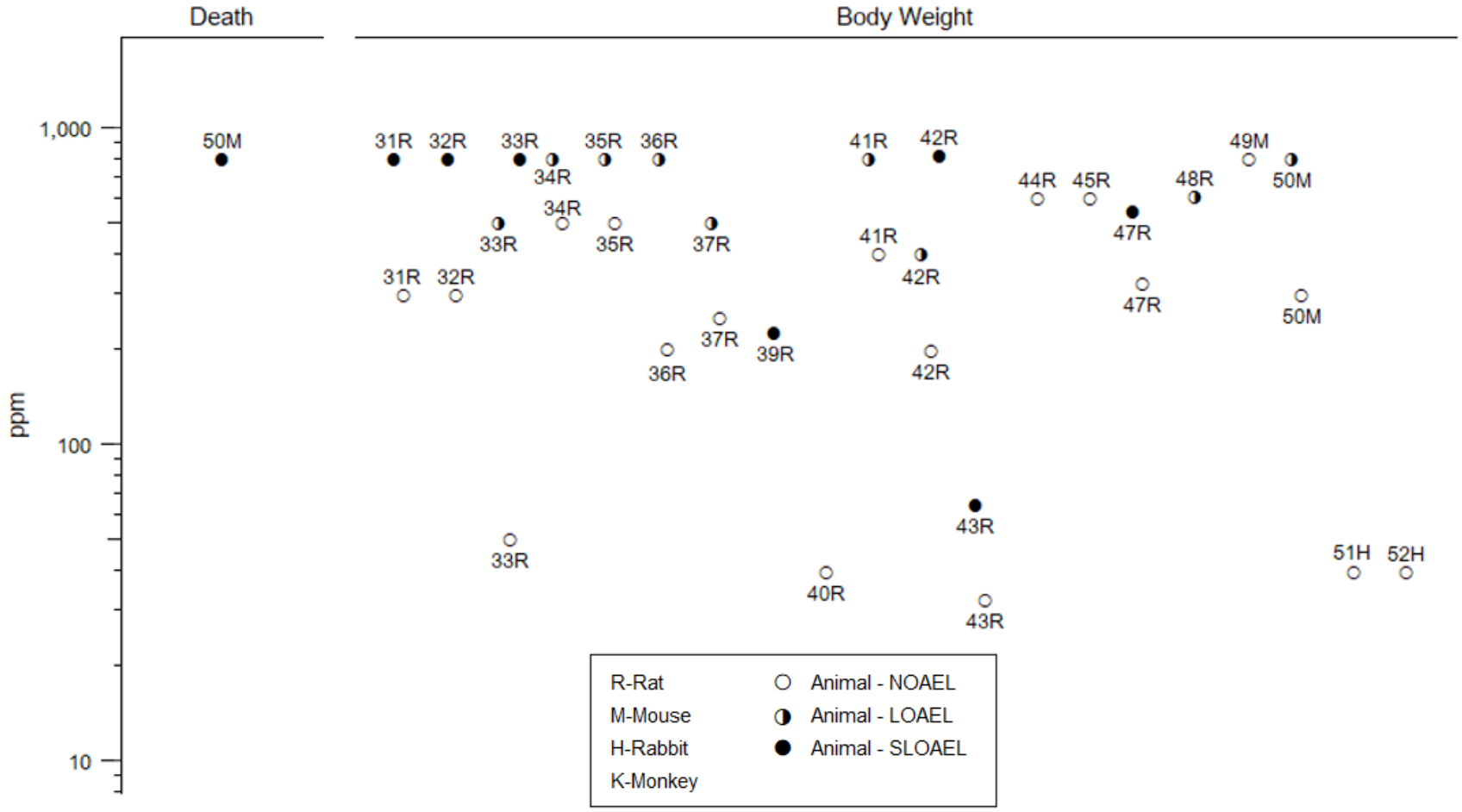

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

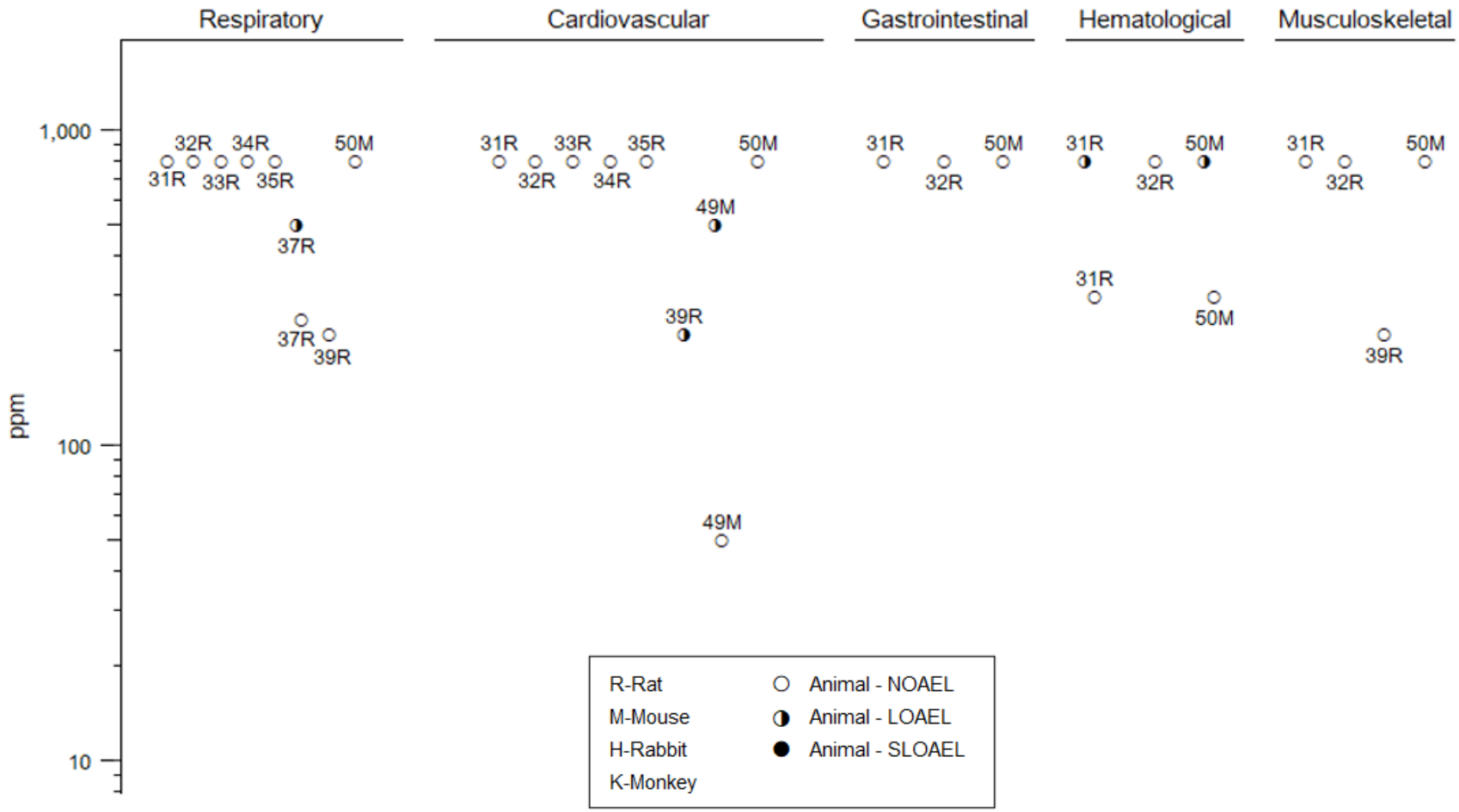

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

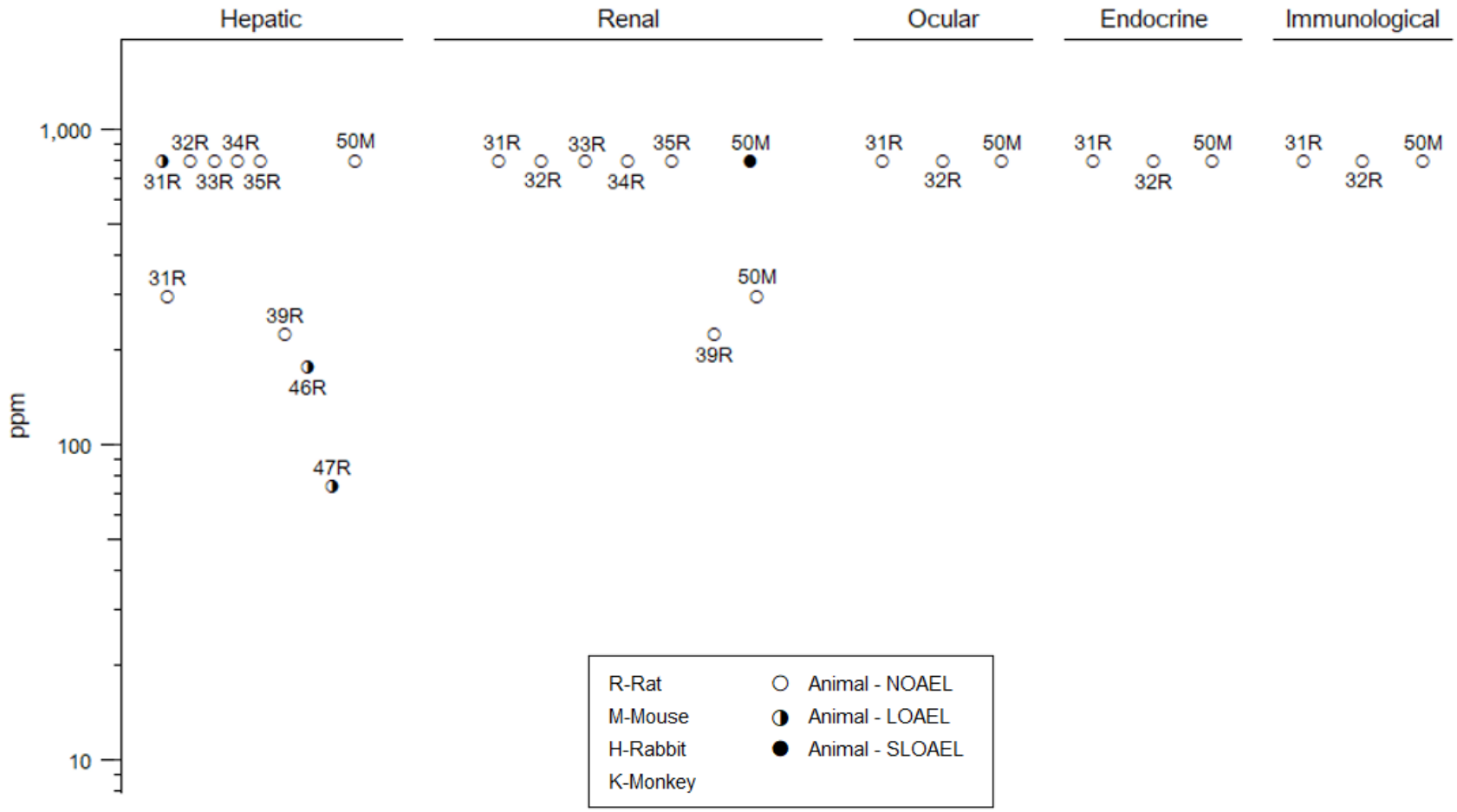

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

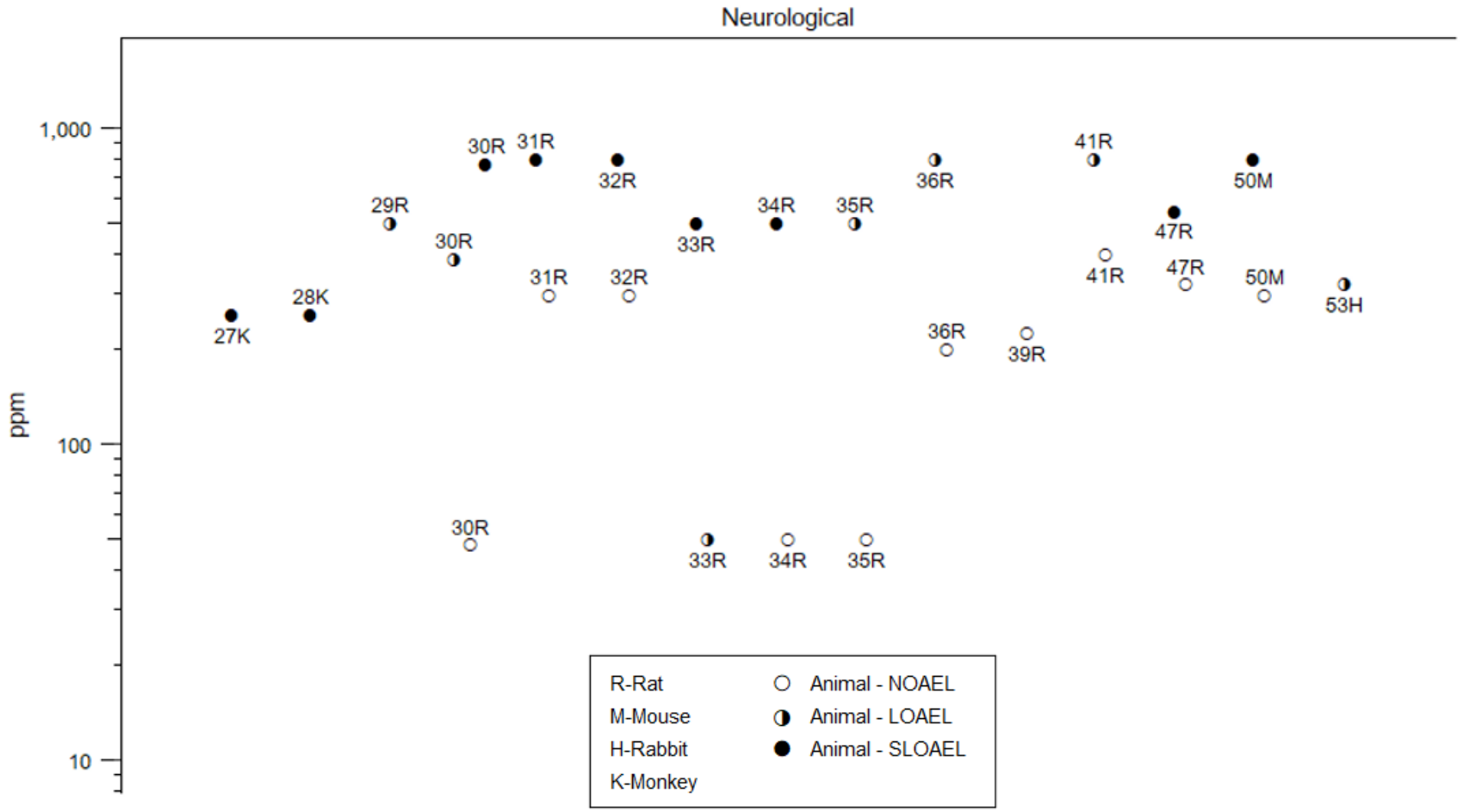

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Intermediate (15–364 days)

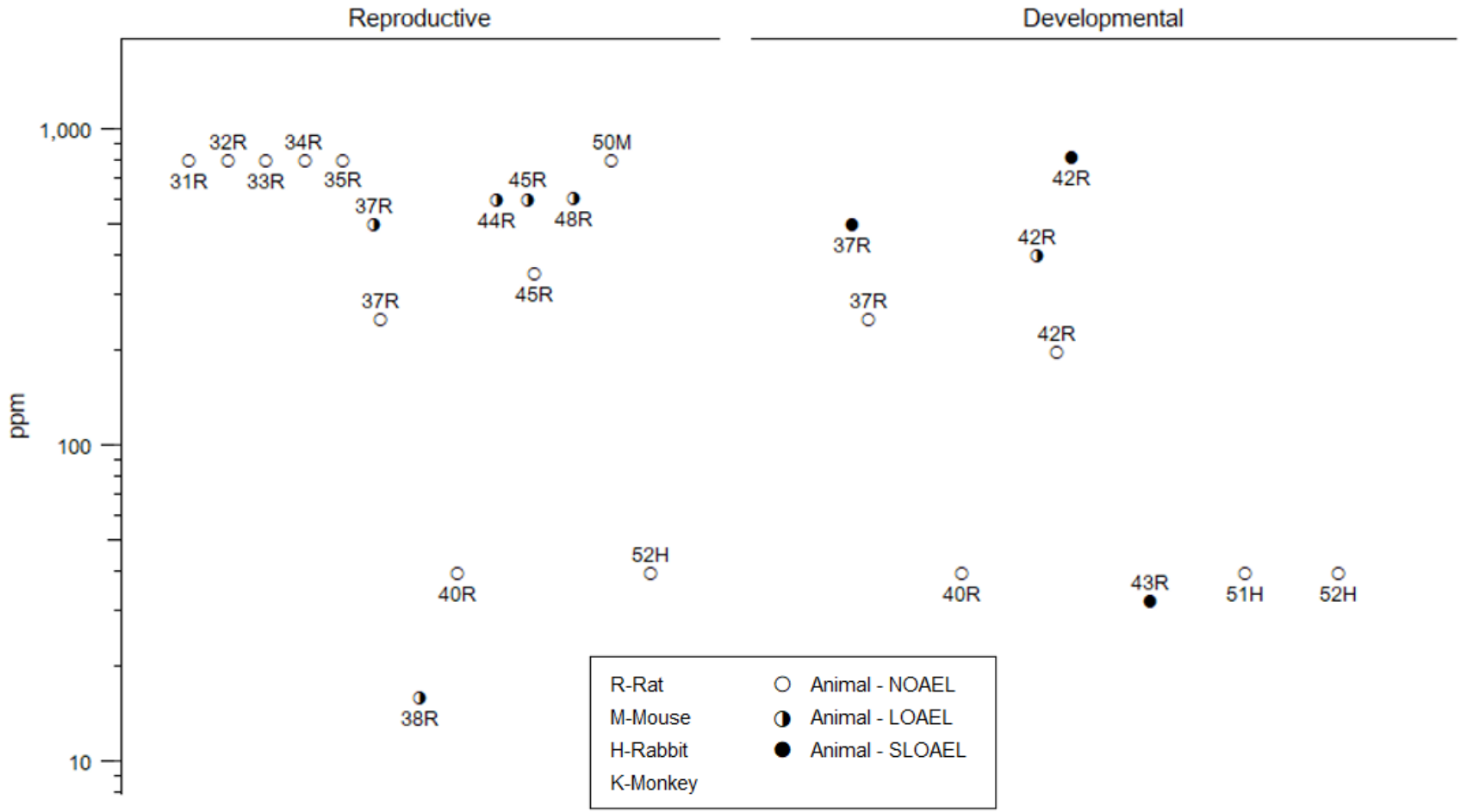

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Chronic (≥365 days)

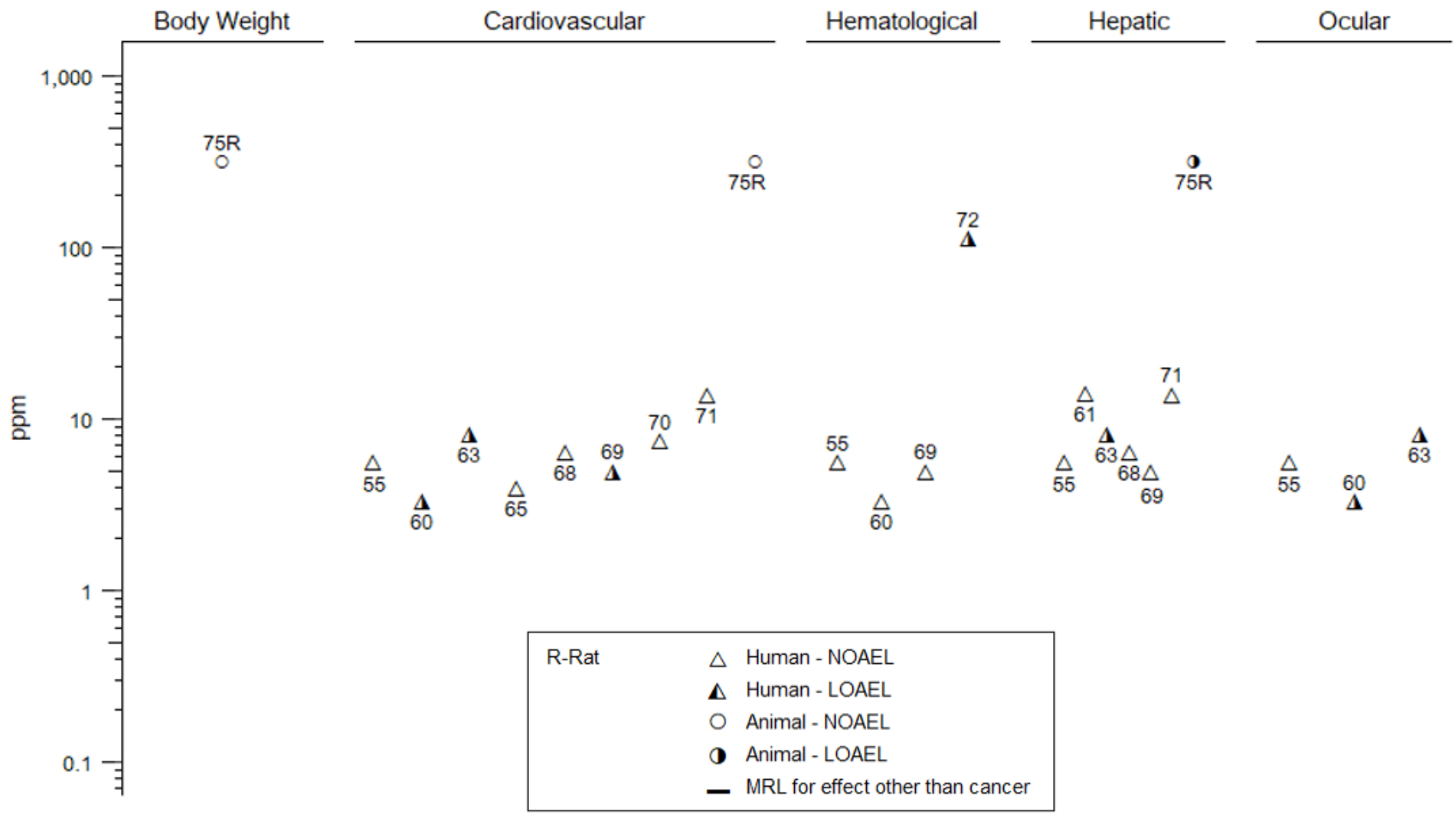

Figure 2-2. Levels of Significant Exposure to Carbon Disulfide – Inhalation
Chronic (≥365 days)

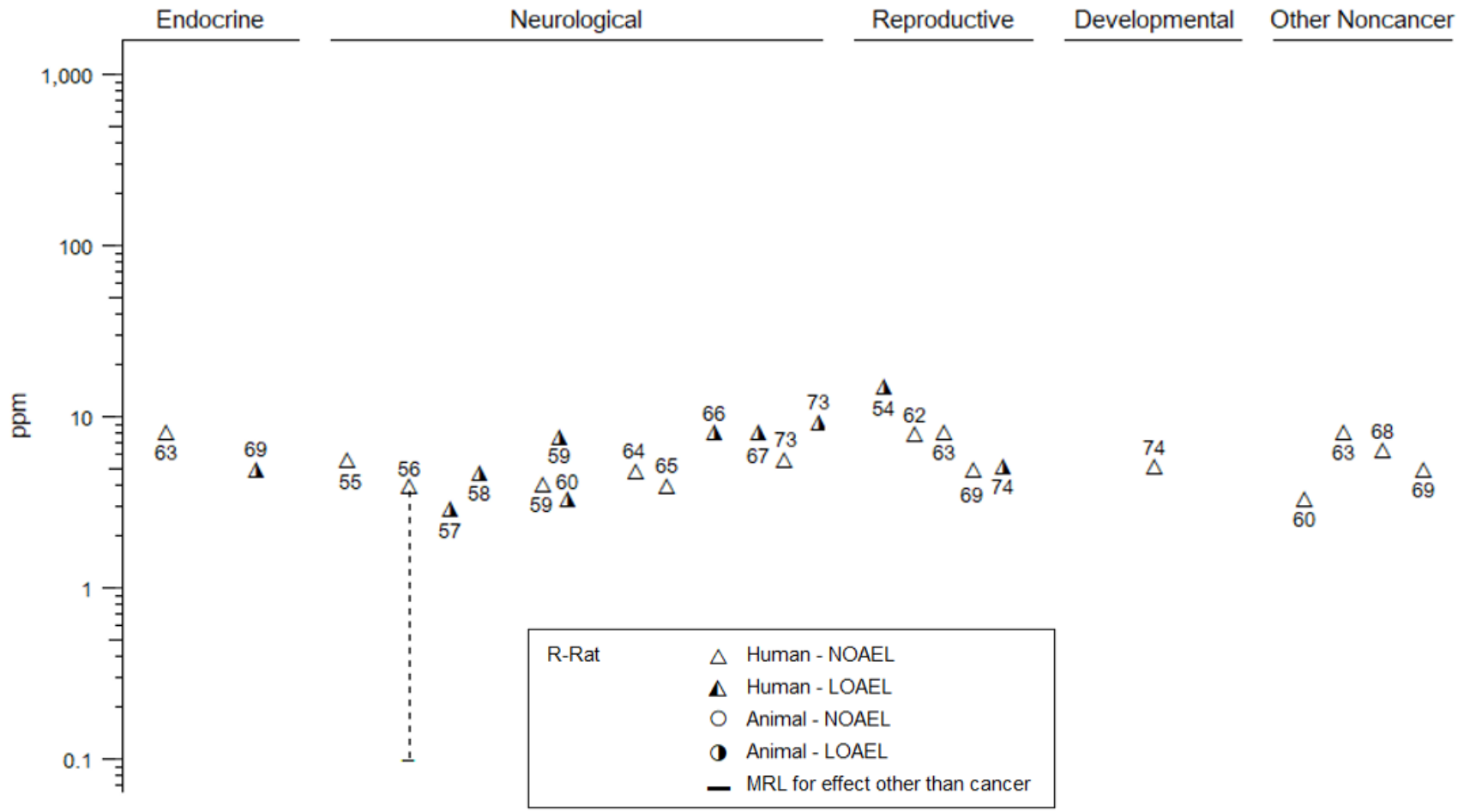

Table 2-2. Levels of Significant Exposure to Carbon Disulfide – Oral (mg/kg/day)

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			

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									
6	Mouse (Swiss-Webster) 4 M	Once (GO)	0, 1,890	OF	Hepatic		1,890		Transient impairment in liver function (increased BSP retention)
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

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
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
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

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
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
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 a provisional 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 provisional 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)

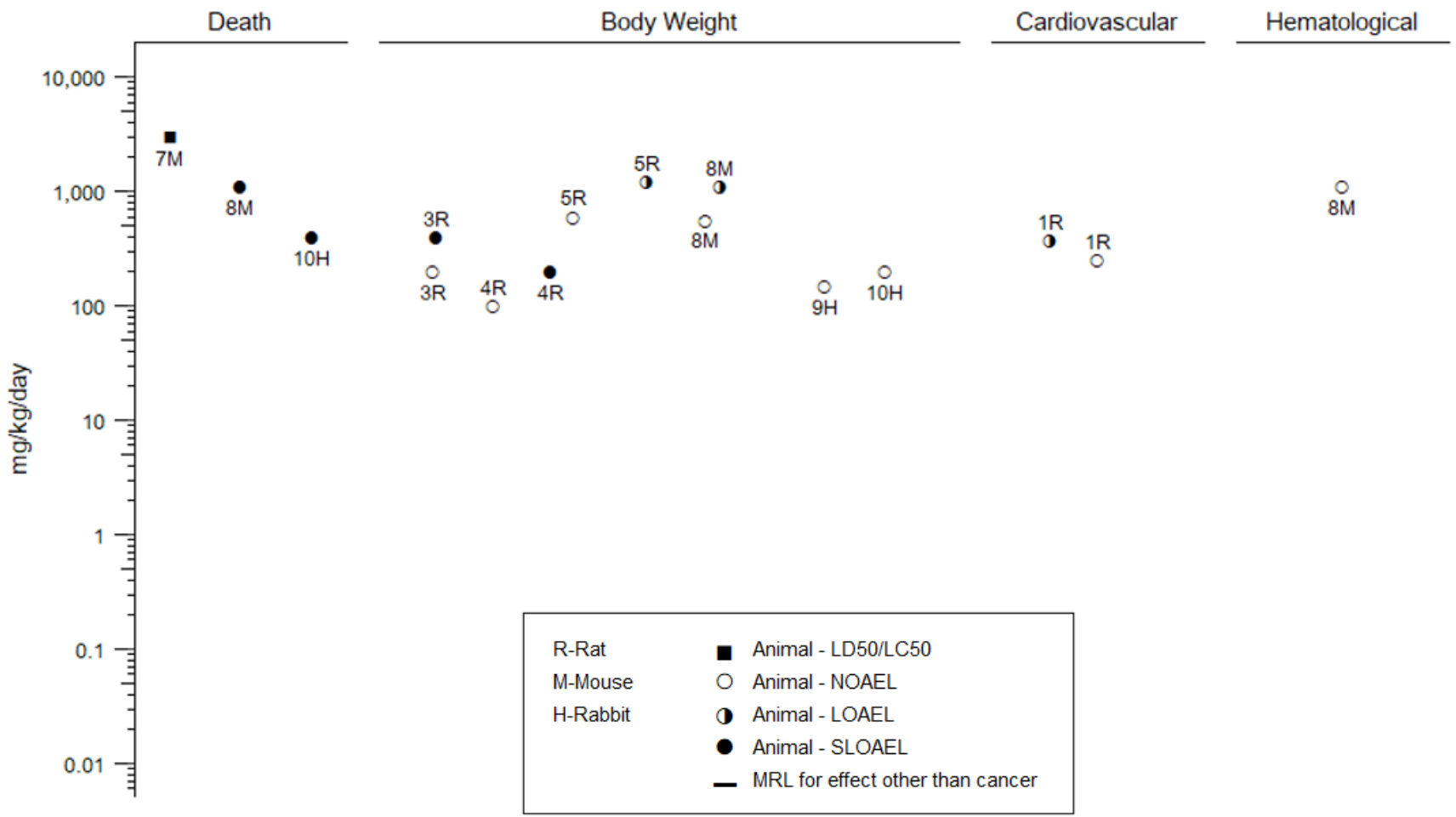

Figure 2-3. Levels of Significant Exposure to Carbon Disulfide – Oral
Acute (≤14 days)

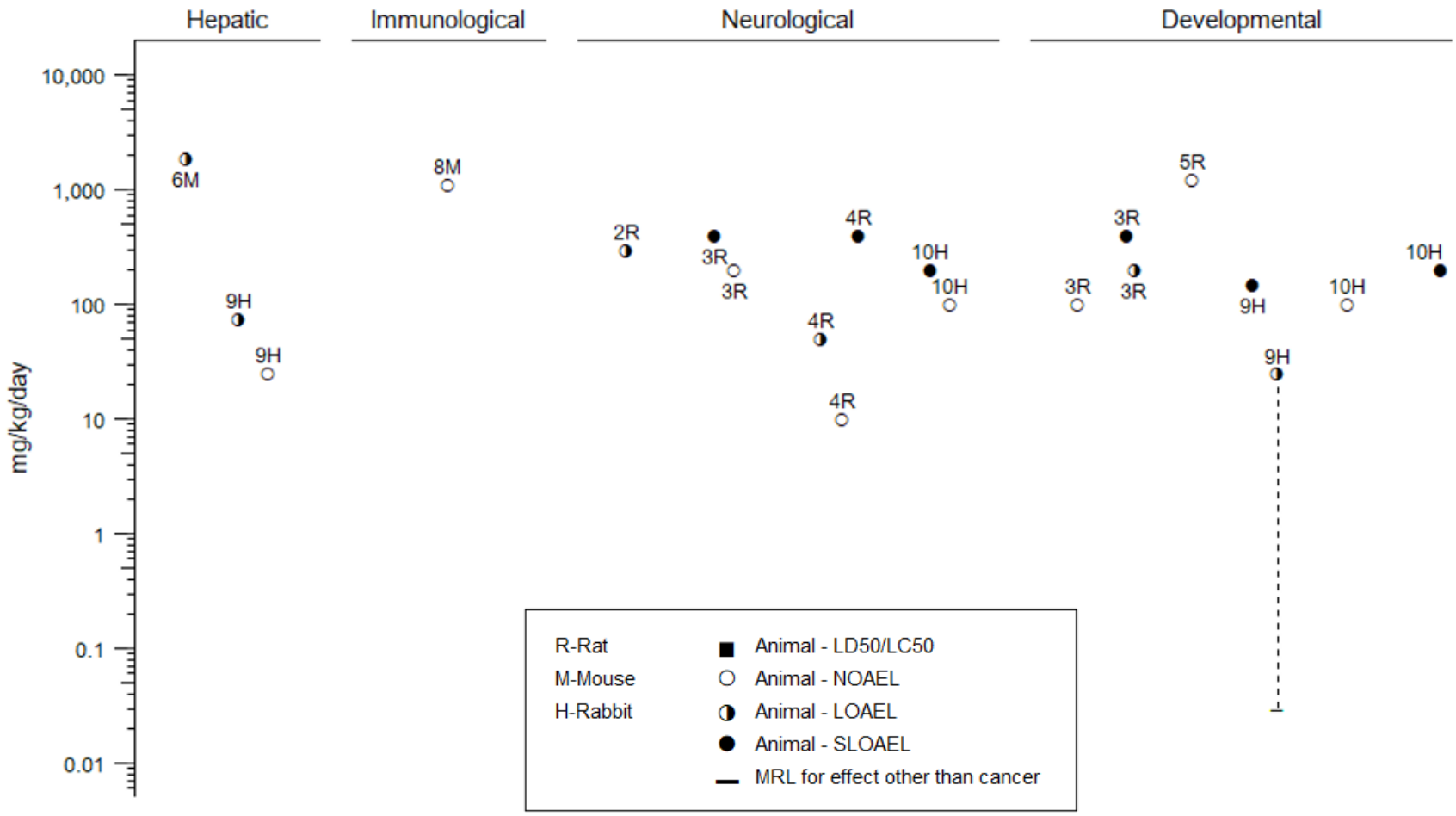

Figure 2-3. Levels of Significant Exposure to Carbon Disulfide – Oral
Intermediate (15–364 days)

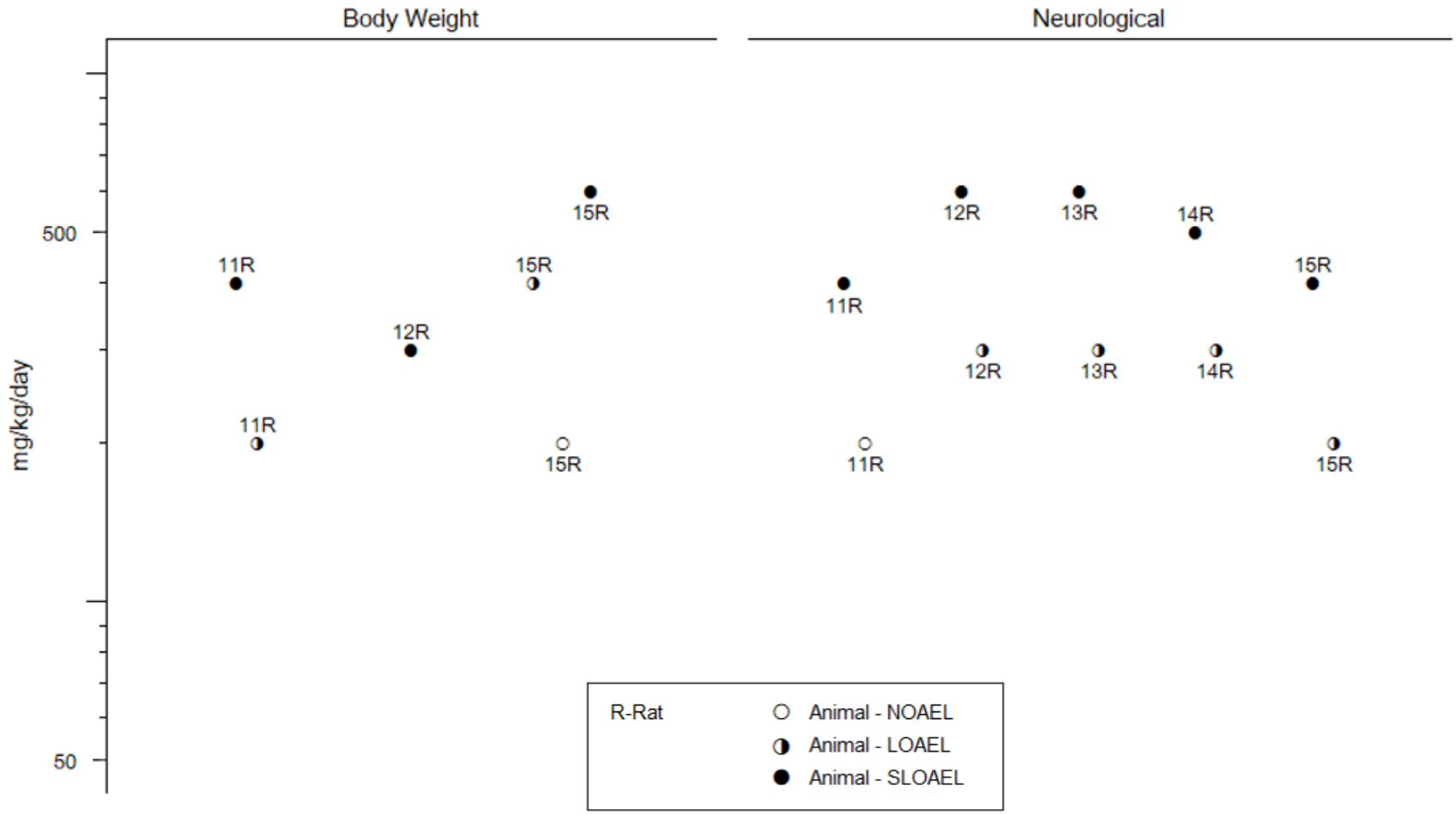

Table 2-3. Levels of Significant Exposure to Carbon Disulfide – Dermal

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 oral 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). Another 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. 2021). 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.

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, evaluate 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)

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
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 Angina 1967/1968 1972 SBP, DBP 1967/1968 1972 Abnormal ECG 1967/1968	 ↔ (workers versus referents) ↑ (workers versus referents) ↑ (workers versus referents) ↑ (workers versus referents) ↑ (workers versus referents) ↑ (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[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 Abnormal ECG 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) ↔ (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] SBP DBP	↔ (workers versus referents) ↔ (workers versus referents) ↓ (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 (Goën 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 free radical, mediated lipid peroxidation is an early effect of low-density lipoprotein (LDL) cholesterol oxidation caused by many oxidants, that it could indicate long-term inhalation exposure to carbon disulfide results in oxidative modifications of LDL cholesterol, and that it plays 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 arteriosclerotic 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 Plasminogen	 ↓ (workers versus referents) ↓ (duration of exposure) ↓ (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 (Goën 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 by 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. 1977a). 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 gamma-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 by 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 transaminase; AST = aspartate transaminase; CEI = cumulative exposure index; GGT = gamma-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. 1977a) 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 year) 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 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 are a presumed target of carbon disulfide toxicity in humans following inhalation exposure based on moderate evidence in humans.

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 ocular 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 Ophthalmology

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)
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)

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

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
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)
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)

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

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
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)
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 ophthalmological or histopathological changes to the eye were reported 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, eye irritation, attributed to direct contact with carbon disulfide vapor, was reported in female rats exposed to 502 ppm in air for 6 hours/day up to 49 days (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 including 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	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)

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
	*Last 3 years <19 ppm **Last 12 years <19 ppm	Serum Free-T4	↔ (workers versus referents)
		Serum T3	↔ (workers versus referents)
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 carbon disulfide and noise is a 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 up to 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.

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 neurofilament 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. 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 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 wives of 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 and 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, 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' 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 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 postimplantation 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 postimplantation 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 postimplantation 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 are 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 (Goën 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.

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*

		Results		
		Activation		
Species (test system)	Endpoint	With	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

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

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
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
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

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

Species (exposure route)	Endpoint	Results	Reference
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).