CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

The general population is primarily exposed to carbon disulfide from inhalation of ambient air. Data for 2022 showed average concentrations of carbon disulfide at various monitoring stations in the United States ranging from below detectable limits to 2.17 µg/m^3 (0.694 ppb), with maximum values of 12.2 µg/m^3 (3.90 ppb). Much higher levels are often detected under occupational exposure settings such

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

1.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

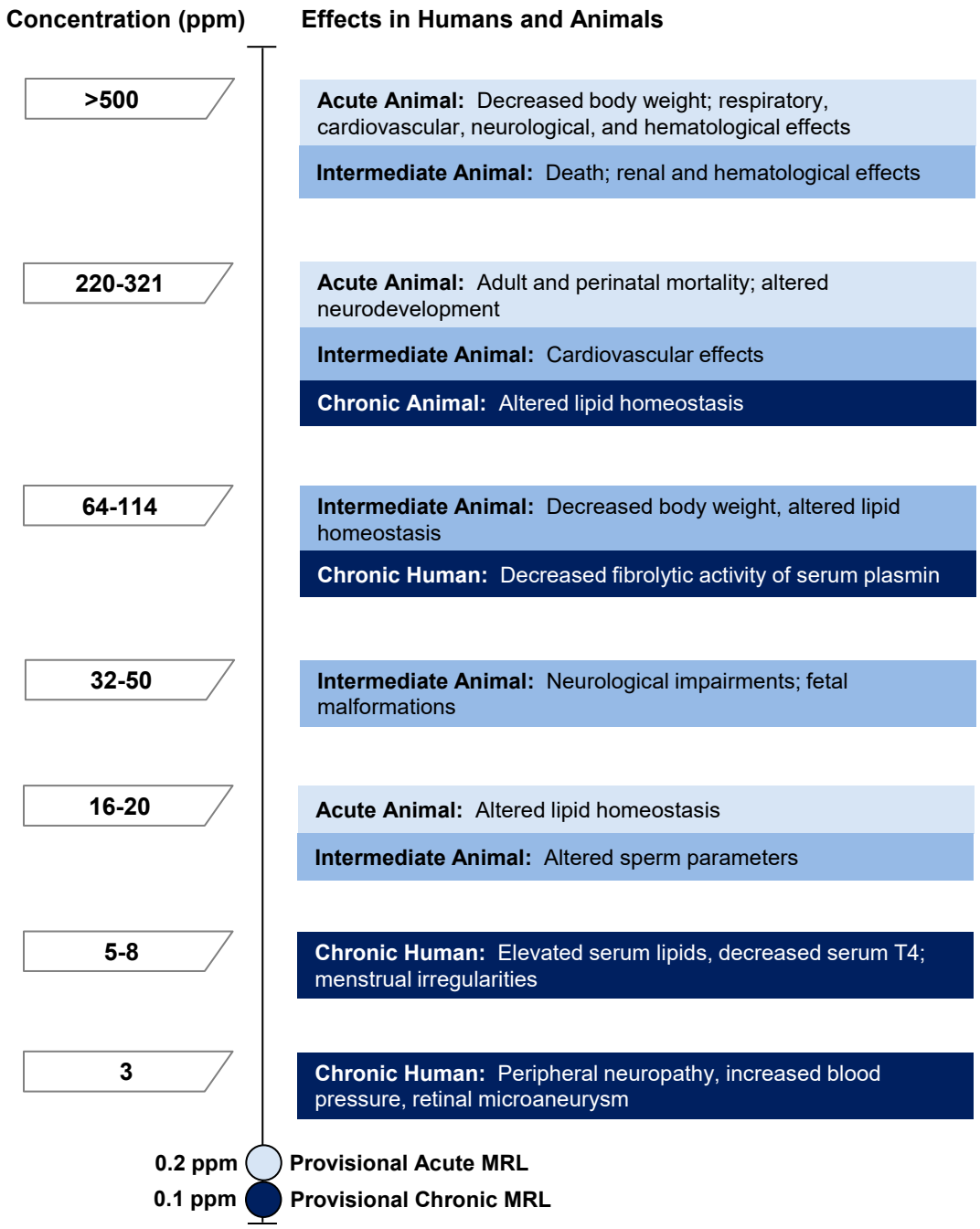
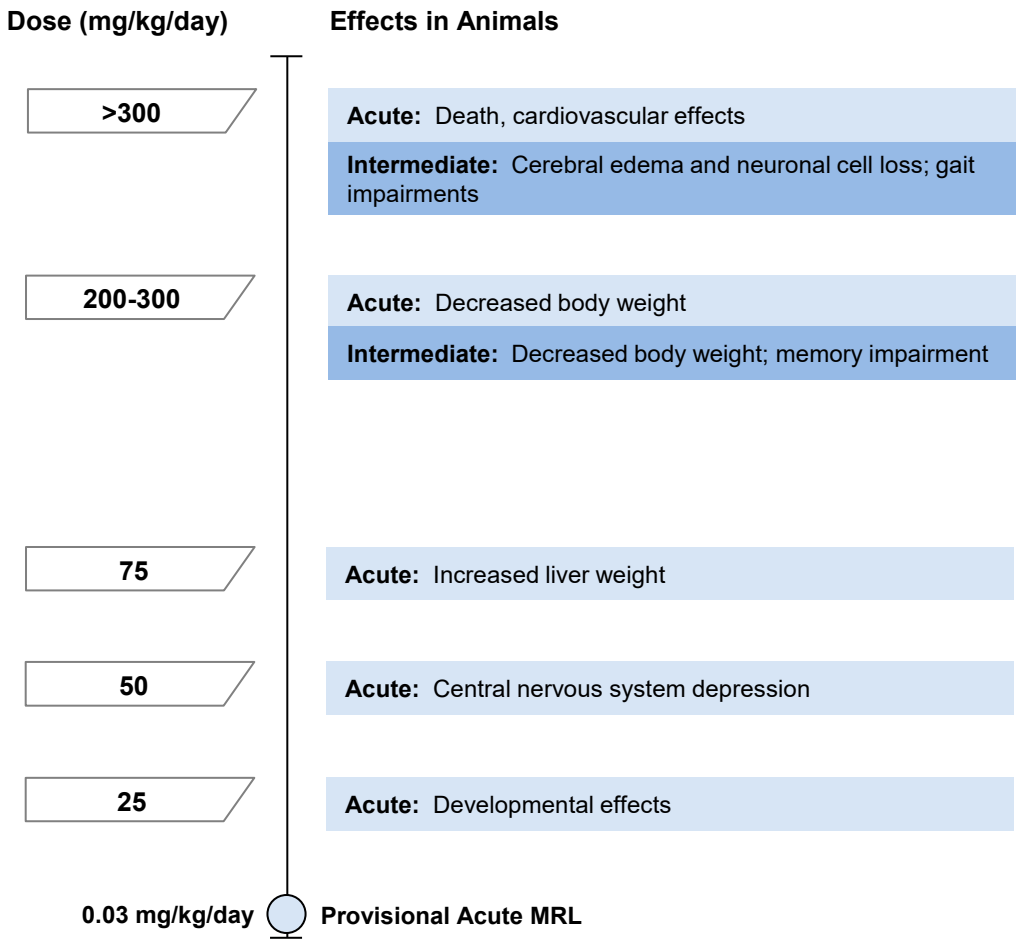


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Carbon Disulfide



Neurological Effects. Neurological effects are a commonly evaluated and reported endpoint in occupational cohorts exposed to carbon disulfide, particularly peripheral neuropathy. At low concentrations (<10 ppm), the most frequently reported, objective, and quantifiable endpoint is impaired nerve conduction velocity (Hirata et al. 1996; Kim et al. 2000; Johnson et al. 1983; Ruijten et al. 1990, 1993; Seppalainen and Tolonen 1974; Vanhoorne et al. 1995; Yoshioka et al. 2017). Peripheral neuropathy may be reversible at low concentrations but is reportedly persistent at higher concentrations (Seppalainen and Tolonen 1974; Yoshioka et al. 2017). Overt polyneuritis or polyneuropathy are common findings among isolated occupational cases with very high exposure levels (≥100 ppm), including impaired nerve conduction, subjective complaints, decreased pain sensitivity, tremors, and abnormal movements resembling early Parkinsonism (Chapman et al. 1991; Chu et al. 1995; Lancranjan et al. 1972; Peters et al. 1988; Vasilescu 1976). Acute psychosis has also been reported in workers exposed to very high levels, ranging as high as 300–800 ppm; however, reported cases are pre-1940, prior to modern industrial hygiene practices (DOL 1940; Gordy and Trumper 1938, 1940; Paluch 1948; Vigliani 1950). Numerous inhalation studies in animals indicate that the peripheral nervous system, spinal cord, and optic nerve are sensitive targets, although tested exposure concentrations are often much higher than levels experienced by the average modern worker (Section 2.15). There is some evidence of hearing loss associated with inhalation exposure to carbon disulfide in conjunction with noise exposure in both humans and animals (Carreres Pons et al. 2017; Chalansonnet et al. 2020; Chang et al. 2003; Venet et al. 2017). Oral data are limited, but reported overt clinical signs in animals at high doses include incoordination and gait impairments, lethargy, ataxia, tremor, paralysis, and convulsions (Gao et al. 2014; Liu et al. 2023, 2024; NCTR 1984a, 1984b; Song et al. 2009; Wang et al. 2016). Findings were associated with impaired caudal nerve conduction (Liu et al. 2024). One study in rats reported impairments in learning and memory, cerebral edema, and neuronal loss in the cortex and hippocampus (Wang et al. 2017).

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

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

Ophthalmological Effects (Ocular). Increased prevalence of retinal microaneurysms has been reported in several cohorts of viscose rayon workers from multiple countries, including the United States, Belgium Korea, and Japan (Kim et al. 2000; NIOSH 1984a; Sugimoto et al. 1976, 1977; Vanhoorne et al. 1996). However, a large longitudinal cohort study from Finland did not observe this effect, despite much higher historical exposure levels. No ophthalmological changes were observed in an intermediate-duration inhalation study in rats and mice (Phillips 1983a, 1983b, 1983c). While ocular irritation was noted in animals exposed to higher concentrations (Holson 1992), this finding was attributed to direct ocular contact with carbon disulfide vapor. Therefore, systematic review was restricted to ocular effects related to ophthalmological changes.

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

Male Reproductive Effects. A few studies provide evidence of potential associations between self-reported impairments in male sexual function and occupational exposure to carbon disulfide (Cirla et al. 1978; Vanhoorne et al. 1994; Wägar et al. 1981). However, there is no evidence of impaired fertility in male workers exposed to carbon disulfide (NIOSH 1983; Vanhoorne et al. 1994). Animal studies reported altered mating behaviors in male rats following inhalation exposure to carbon disulfide at concentrations much higher than levels experienced by the average worker (Tepe and Zenick 1984;

Zenick et al. 1984). There is inconsistent evidence for damage to sperm and/or for alterations to male reproductive hormones in available human and animal studies (Section 2.16).

Developmental Effects. Data in humans are limited to a single study that did not observe an association between occupational exposure during pregnancy and congenital malformations (Zhou et al. 1988). In animals, developmental effects (increased postimplantation loss/fetal resorptions, decreased fetal body weight, decreased neonatal viability, fetal malformations) have been observed in both rats and rabbits following inhalation exposure during gestation (Denny and Gerhart 1991; Holson 1992; Tabacova and Balabaeva 1980; Tabacova et al. 1978, 1983; Saillenfait et al. 1989). Postnatal exposure was associated with increased perinatal mortality, delayed reflex ontology, and impaired neurodevelopment (Lehotzky et al. 1985). Similar developmental effects occurred in rats and rabbits in oral gestational exposure studies; in oral studies, rabbits were distinctly more sensitive compared to rats (NCTR 1984a, 1984b). However, another oral study in rats did not observe adverse developmental effects under similar conditions (Tsai et al. 2000).

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

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of acute- and chronic-duration inhalation MRLs for carbon disulfide. As illustrated in Figure 1-3, the most sensitive endpoints in animals appear to hepatic effects (specifically altered lipid homeostasis) as well as the male reproductive, developmental, and neurological effects. In humans, neurological, cardiovascular, and ocular (ophthalmological) effects appear to be the most sensitive targets of carbon disulfide toxicity following occupational exposure. While workers may be exposed via multiple routes, inhalation is assumed to be the predominant route of exposure. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

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

Available data indicate that the neurological, cardiovascular, ocular (ophthalmological), hepatic (altered lipid homeostasis), and male reproductive systems and the developing organism appear to be the most sensitive targets of carbon disulfide inhalation exposure.

Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively.

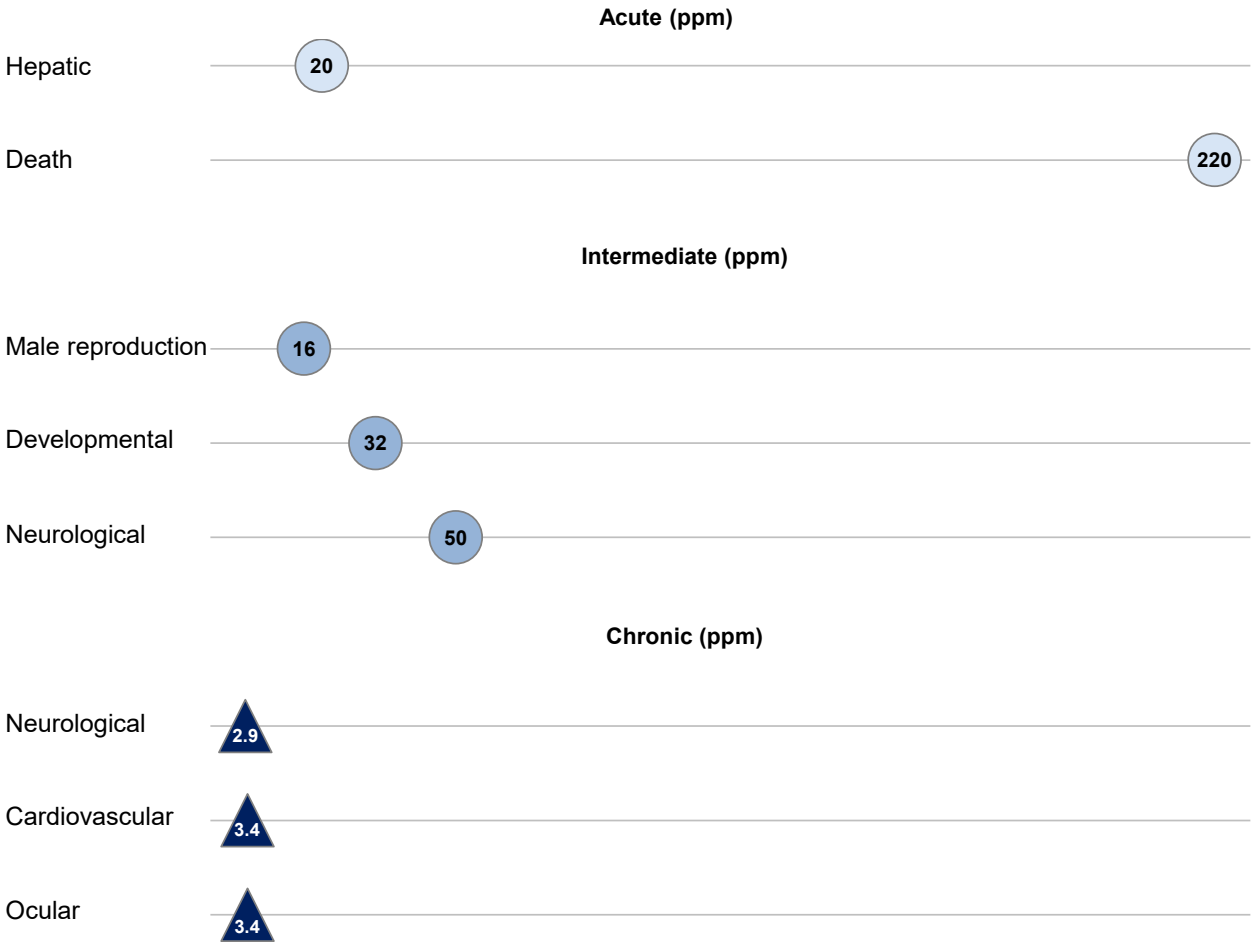


Figure 1-4. Summary of Sensitive Targets of Carbon Disulfide – Oral

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

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

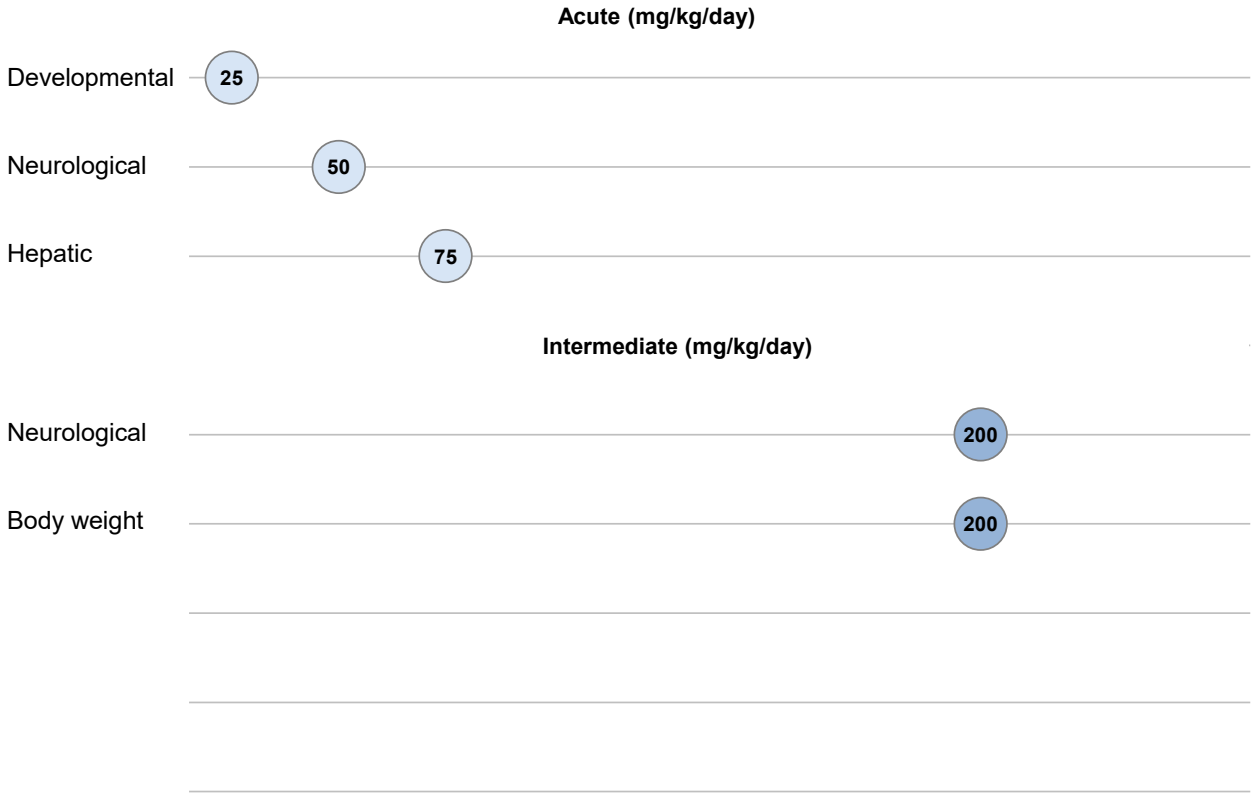


Table 1-1. Provisional Minimal Risk Levels (MRLs) for Carbon Disulfide[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**Acute**	**0.2 ppm** (0.6 mg/m^3)	Increased total lipid levels in hepatic microsomal fraction	$LOAEL_{HEC}$	16 ppm	UF: 90	Freundt et al. 1974b
	Intermediate	None	–	–	–	–	–
	Chronic	**0.1 ppm** (0.3 mg/m^3)	Impaired peripheral nerve conduction	Weighted $median_{ADJ}$[b]	0.957 ppm	UF: 10	Cirla and Graziano 1981; Godderis et al. 2006; Hirata et al. 1996; Johnson et al. 1983; Kim et al. 2000; Reinhardt et al. 1997a; Yoshioka et al. 2017
Oral	**Acute**	**0.03 mg/kg/day**	Increased resorptions per litter	LOAEL	25 mg/kg/day	UF: 1,000	NCTR 1984b
	Intermediate	None	–	–	–	–	–
	Chronic	None	–	–	–	–	–

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

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