CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

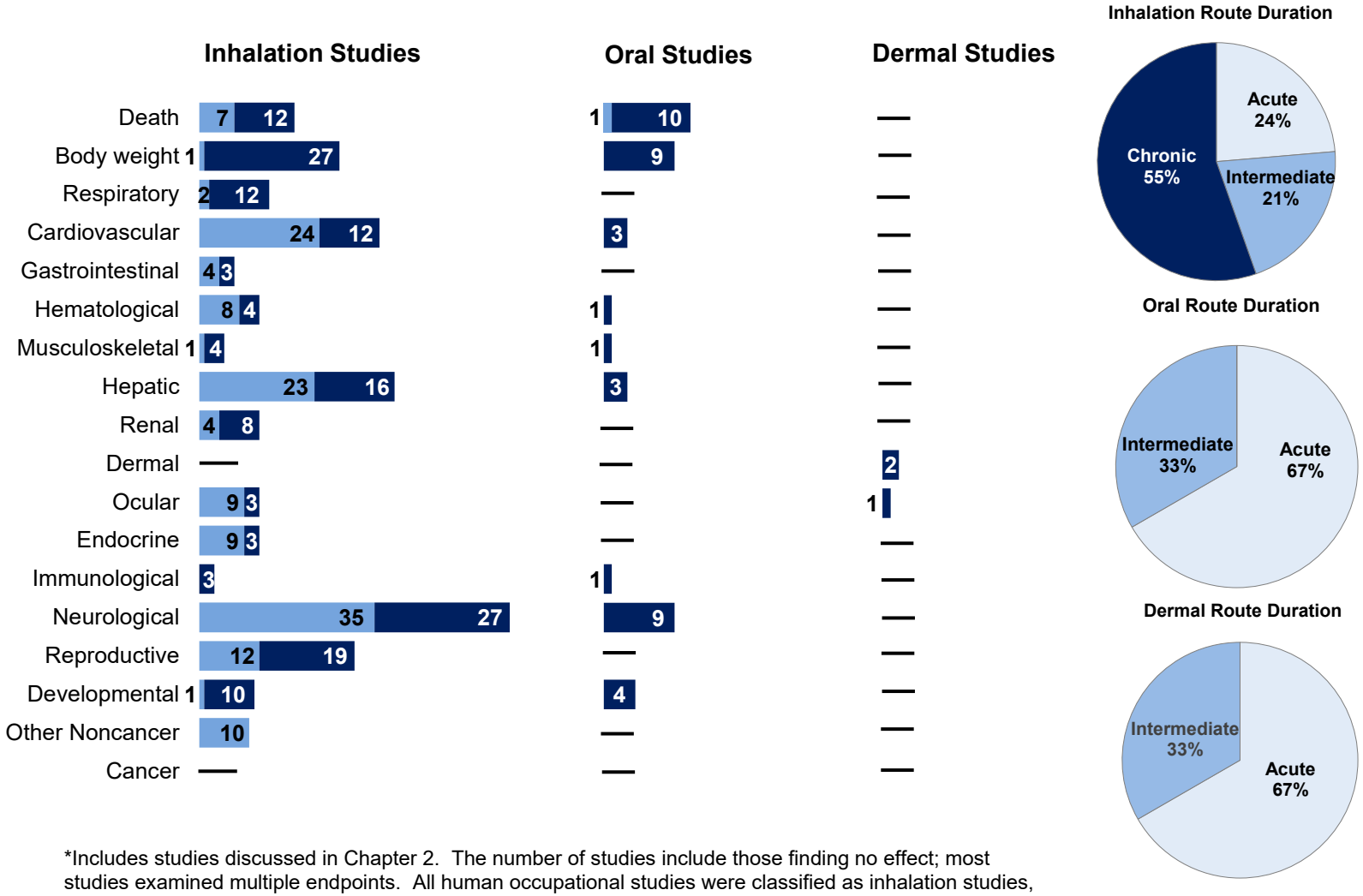
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to carbon disulfide that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of carbon disulfide. The number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

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

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

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

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



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

6.2 IDENTIFICATION OF DATA NEEDS

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

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

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

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

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

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

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

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

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

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

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

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

Reproductive. There are limited and inconsistent human data that indicate that chronic-duration inhalation exposure to carbon disulfide can affect the reproductive system in both males and females. In males, sperm morphology, hormone levels, and libido have been altered by occupational exposure to carbon disulfide in some studies (Guo et al. 2016; Vanhoorne et al. 1994; Wägar et al. 1981); however, there is no evidence of impaired fertility (NIOSH 1983; Vanhoorne et al. 1994). Additional well-conducted, longitudinal occupational studies could help re-evaluate inconsistencies in male reproductive findings, especially if they are well-controlled for key confounders including known risk factors for altered male reproductive performance or fertility (e.g., smoking, alcohol intake, parity of partner, time since last ejaculate, etc.) or use of medication to treat fertility or erectile dysfunction. In females, self-reported menstrual irregularities have been associated with occupational exposure to carbon disulfide (Cai and Bao 1981; Zhou et al. 1988), although more serious effects, such as increased miscarriage, stillbirth,

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

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

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

Biomarkers of Exposure and Effect. Methods for detecting carbon disulfide or its metabolites in exhaled breath, blood, urine, and tissues are available. The most sensitive biomarker for carbon disulfide that correlates best with external exposure is urinary levels of the metabolite, TTCA (Beauchamp et al. 1983; Campbell et al. 1985; Drexler et al. 1994). However, certain vegetables (e.g., cabbage, Brussels sprouts) can increase levels of TTCA, resulting in detection of TTCA in unexposed individuals with high dietary intakes (Simon et al. 1994; Kivistö 2000). Therefore, in persons who eat large amounts of these vegetables, measurements of urinary TTCA may overestimate carbon disulfide exposure. Studies

designed to better quantify community baseline levels could help correct for nonworkplace exposure sources.

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

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

Comparative Toxicokinetics. Both human and animal data indicate that the target organs for carbon disulfide are similar across species (Cohen et al. 1958; DeMatteis and Seawright 1973; Dutkiewicz and Baranowska 1967; Freundt et al. 1975; McKee et al. 1943; Soucek 1957; Teisinger and Soucek 1949; Toyama and Kusano 1953). There are no studies that directly compare the toxicokinetics across species. Most of the animal studies on toxicity endpoints have used high doses. The studies in rats, mice, and rabbits have generally been consistent in their conclusions regarding the pharmacokinetics of carbon

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

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

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

Production, Import/Export, Use, Release, and Disposal. The TRI lists data on the releases of carbon disulfide to air, water, and soil from U.S. industrial sources (TRI22 2024). Data are available on emissions from natural sources such as oceans (Lennartz et al. 2021). U.S. production volumes and import/export data are available from the Chemical Data Reporting (CDR); however, companies will often declare import and export volumes as CBI (EPA 2022c). Disposal methods include liquid injection incineration, rotary kiln incineration, and fluidized bed incineration (EPA 1981b; UNEP 1985); however, data on the efficiency of these methods are lacking. This information will be useful in identifying the media of concern for human exposure and populations at risk of adverse health effects from exposure to carbon disulfide.

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

Bioavailability from Environmental Media. Carbon disulfide is absorbed following inhalation of contaminated ambient air (Soucek 1957; Teisinger and Soucek 1949) and from dermal contact with contaminated soils or water (ATSDR 2023; Helasova 1969). Data are lacking on the bioavailability of carbon disulfide following ingestion of contaminated soils and groundwater or foods grown with contaminated water. This information would be useful in determining the importance of these routes of exposure.

Food Chain Bioaccumulation. BCF values of <6 and <60 were measured in fish (NITE 1988) and a value of 8.9 was estimated from a regression-based method. Based on these data, carbon disulfide does not significantly bioaccumulate in aquatic organisms. No information was available on the bioaccumulation of carbon disulfide in organisms at other trophic levels in aquatic environments. Monitoring for the accumulation of carbon disulfide in organisms from several trophic levels would be useful in estimating the levels of carbon disulfide to which humans are exposed through dietary intake.

Exposure Levels in Environmental Media. Studies of background levels of carbon disulfide in air have been conducted (Carroll 1985; Conley et al. 2005; Cooper and Saltzman 1993; EPA 2023c; Logue et al. 2010, 2011; Rosenbaum et al. 1999; Zhu et al. 2005), but site-specific concentration data for ambient

air, drinking water, and biota, particularly at hazardous waste sites, are lacking. These data would be helpful in estimating the exposure of the general population as well as those living near hazardous waste sites. The sites with highest concentrations of carbon disulfide need to be determined. In addition, estimates of human intake from various media would be helpful in assessing human exposure for carbon disulfide for populations living near hazardous waste sites.

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

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

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

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

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2023) database.