Environmental and Workplace Health

Priority Substances List Assessment Report for Carbon Disulfide

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2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties

Synonyms for carbon disulfide (disulphide) include carbon bisulfide, carbon sulfide and dithiocarbonic anhydride. Carbon disulfide, which has the chemical formula CS_2, is an extremely volatile and flammable liquid. Structurally, it is a linear molecule, comprising two sulfur atoms double-bonded to a carbon atom (S = C = S). Technical-grade carbon disulfide has a strong, unpleasant odour due mainly to traces of organic sulfur compounds (BUA, 1993). The Chemical Abstracts Service (CAS) registry number for carbon disulfide is 75-15-0, and the Registry of Toxic Effects of Chemical Substances (RTECS) registry number is FF6650000 (HSDB, 1993). Values for physical and chemical properties of carbon disulfide are presented in Table 1. The conversion factor for carbon disulfide used in this report is 1 ppm = 3.125 mg/m^3.

Table 1 Physical and chemical properties of carbon disulfide[1]

Parameter	Value	Reference
Molecular weight	76.1 g/mol	Merck Index, 1989
Density	1.2632 g/mL @ 20°C	Merck Index, 1989
Melting point	-111.6°C	Merck Index, 1989
Boiling point	46.5°C @ 101.3 kPa	Merck Index, 1989
Vapour pressure	48.210 kPa @ 25°C	Riddick *et al.*, 1986
Water solubility	2100 mg/L @ 20°C	Riddick *et al.*, 1986
Henry's law constant	1748 Pa·m^3/mol @ 25°C	DMER and AEL, 1996
Solubility in organic solvents	miscible	Beauchamp *et al.*, 1983
Log K_{oc}	1.79	Howard, 1989; DMER and AEL, 1996
Log K_{ow}	2.14	Martiska and Bekarek, 1990

1 See Environment Canada (1999a) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.

2.2 Entry characterization

2.2.1 Production, importation, exportation and use

In 1996, 3.1 kilotonnes of carbon disulfide were manufactured for commercial purposes in Canada (Environment Canada, 1997c). Camford Information Services (1995) reported Canadian domestic production of 10.9 kilotonnes in 1993, down from 25 kilotonnes in 1976. The much lower production figure in recent years reflects the closure in 1995 in Canada of the rayon and cellulose fibre industry, which had been the major user of carbon disulfide.

In 1996, 1473 kg of carbon disulfide were imported into Canada as a specialty chemical. There have been no further imports reported since then (Environment Canada, 1997c).

Exports of carbon disulfide from Canada reached nearly 1.2 kilotonnes in 1996 (Environment Canada, 1997c).

Nearly 1.7 kilotonnes of carbon disulfide were used in Canada in 1996 as a precursor in the manufacture of xanthates, which are used as flotation agents in mineral refining processes (Environment Canada, 1997c). Carbon disulfide is also used to produce drilling mud additives to dissolve waxes that interfere with the efficiency and yields of oil and gas wells and in the manufacture of rubber curing accelerators, which are used in the production of rubber tires for vehicles (Camford Information Services, 1995). Carbon disulfide had also been used as an active ingredient of certain pest control products, but the registration of carbon disulfide in these pesticides was suspended as of December 31, 1984 (PMRA, 1997).

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2.2.2 Sources and releases

2.2.2.1 Natural sources

Carbon disulfide is released into the environment from a wide variety of natural sources. Soils, marshes and coastal regions tend to be the largest biogenic sources. Production of carbon disulfide from soil and plants occurs naturally from the metabolic action of soil bacteria and plants during the growing season. Increases in soil moisture, temperature, organic content and light resulted in a direct increase in the rate of production from soil (Staubes *et al.*, 1987). Up to 35 000 tonnes of carbon disulfide may be added to the Canadian environment annually from this natural source alone (Environment Canada, 1980). Caron and Kramer (1994) identified several species of freshwater algae that produced significant amounts of carbon disulfide. Although no estimate of the magnitude of this contribution to the total was made, median concentrations for several species of algae ranged between 93.8 and 268.4 ng carbon disulfide/L culture medium. In cases where abiotic weathering of sulfide ores is occurring, significant concentrations of carbon disulfide have been measured in the air at or near the surface. It is estimated that up to 2280 tonnes of carbon disulfide per year could be released globally as a result of the weathering of sulfide minerals (Stedman *et al.*, 1984). Carbon disulfide is also produced by forest and grass fires and by volcanoes, which are more intermittent by nature.

A great deal of uncertainty exists about the magnitude of the contribution of carbon disulfide in the environment derived from natural and anthropogenic sources. This uncertainty is largely due to differences in the methods used by various authors to calculate releases from the various natural sources. The rate at which carbon disulfide is released from natural sources is subject to climatic and temporal variations, unlike industrial releases, which are more likely to be continuous. Older estimates place the annual amount of carbon disulfide released worldwide from natural sources at 4-5 times the amount released from human or industrial activities (Turco *et al.*, 1980; Khalil and Rasmussen, 1984; Steudler and Peterson, 1984). More recently, Chin and Davis (1993) and Pham *et al.* (1995) modelled scenarios suggesting that the majority of carbon disulfide may be produced through human activity, rather than naturally. They estimated that the major source of carbon disulfide derives from industrial emissions (58%), while the oceans contribute about 34%, and the remainder comes from terrestrial sources.

2.2.2.2 Anthropogenic sources

Data on the amounts of carbon disulfide released in Canada as a result of industrial activity were obtained from the N ational Pollutant Release Inventory (NPRI, 1996b) and from a survey carried out

under the authority of Section 16 of CEPA (Environment Canada, 1997c). This information, which is summarized in Table 2, indicates that between 2120 and 2465 tonnes of carbon disulfide were released from Canadian industrial sources in 1996. Nearly all of this was emitted into the atmosphere from 10 facilities in the gas sector; nine of these are in Alberta, and one in Saskatchewan. Total reported releases from all other industrial sources - including commercial manufacture, distribution and use of carbon disulfide - are less than 100 tonnes. There were no transfers of carbon disulfide for off-site disposal; however, one company reported that 0.5 tonnes were disposed of by deep-well injection (Environment Canada, 1997c).

Table 2 Summary of major anthropogenic releases in Canada (NPRI, 1996; Environment Canada, 1997c)

Type of source	Number of sources	1996: NPRI (1996b) (tonnes/year)	1996: Environment Canada (1997c) (tonnes/year)
Large-scale gas/oil plant	10	2465	1991
Paper manufacturer	1	-	1.5
Chemical company	5	-	1.6
Manufacturing	1	-	25.6

In addition to these releases, there are unreported releases, including those from small facilities not meeting the reporting criteria of more than 1000 kg of carbon disulfide per year. Individual sour gas and oil wells that dispose of waste solution gas (gas produced along with oil) by burning in flares form one of the largest groups of non-reporting facilities (Strosher, 1996; AEUB, 1997). There are about 10 500 of these small facilities currently operating in Alberta, and virtually all of them produce some amount of solution gas. Of these, about 4000 use gas flaring as a means of disposal. The total amount of flared gas in Alberta is estimated to be as much as 2340 x 106 m^3/year, and the highest reported concentration of carbon disulfide measured in one flare was 482 mg/m^3. Thus, total releases of carbon disulfide from these sources may be as high as 1128 tonnes (2340 x 10^6 m^3 flared gas/year x 482 mg carbon disulfide/m^3) (Strosher, 1996; AEUB, 1997).

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

In air, carbon disulfide is primarily degraded through photo-oxidation by reactions with hydroxyl (OH) radicals and by a secondary route involving triplet oxygen ($O(^3P)$). With a hydroxyl radical concentration of 5 x 10^5 radicals/cm^3, a half-life of about 5.5-15 days is calculated from rate constants between 1.1 x 10^{-12} and 2.9 x 10^{-12} cm^3/molecule per second (BUA, 1993). Wine *et al.* (1981) likewise estimated that photo-oxidation in the troposphere results in a half-life in air of 7-14 days. Reaction products include carbonyl sulfide (COS) and sulfur dioxide (SO_2). Carbonyl sulfide has a much longer lifetime (2 years) than carbon disulfide in the atmosphere.

Photolysis of carbon disulfide by radiation at wavelengths above 290 nm occurs in the troposphere. An atmospheric lifetime of 11 days (half-life of 7.7 days) was calculated assuming 12 hours of sunlight (Peyton *et al.*, 1976). Wood and Heicklen (1971) demonstrated that direct photolysis of carbon disulfide at 313 nm produces reaction products similar to those of the photo-oxidation reaction - that is, carbon monoxide (CO), carbonyl sulfide, sulfur dioxide plus an unidentified polymeric material. Wet deposition from the atmosphere is probably a minor removal process, because carbon disulfide is interacted only weakly with water (Lovejoy, 1989).

The overall reactivity-based half-life of carbon disulfide in air, as estimated for ChemCAN4 steady-state

fugacity modelling, is about 1 week (Section 2.3.1.6) (DMER and AEL, 1996).

2.3.1.2 Water

With a Henry's law constant of 1748 Pa×m^3/mol at 20°C and a vapour pressure of 48.2 kPa at 20°C, the major fate process for carbon disulfide released into water is volatilization, with a half-life ranging between 11 minutes in water (saturated solution) and 2.6 hours in a model river (Peyton *et al.*, 1976; Howard, 1989). Carbon disulfide is resistant to hydrolysis in water within the biological pH range (4-10), with a hydrolysis half-life extrapolated to pH 9 of 1.1 years (Peyton *et al.*, 1976). Its predicted rate of biodegradation in water is negligible compared with its rate of volatilization from surface water (ATSDR, 1996). The mean degradation half-life used for fugacity modelling by DMER and AEL (1996) (Section 2.3.1.6) of 5500 hours (7.4 months) was based on the estimate of biodegradation half-life by Abrams *et al.* (1975).

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2.3.1.3 Sediment

Owing to its low affinity for sorption to organic substances (organic carbon/water partition coefficient [log K_{oc}] = 1.79), very little carbon disulfide is likely to partition to or remain in sediment. One study indicated that the soil/sediment microorganism *Thiobacillus thiorapus* (grown aerobically, incubated anaerobically) was able to metabolize carbon disulfide to produce carbonyl sulfide and hydrogen sulfide (Smith and Kelly, 1988). Thus, some biodegradation is expected to occur. The estimated mean reactivity half-life used for fugacity modelling (Section 2.3.1.6) was 5500 hours (7.4 months), based on the estimate of biodegradation half-life by Abrams *et al.* (1975).

2.3.1.4 Soils

No estimates of a half-life for carbon disulfide in soil were identified in the literature. Aerobic degradation of carbon disulfide has been observed with a strain of *Thiobacillus thiorapus*. This particular strain was able to hydrolytically oxidize carbon disulfide sequentially to carbonyl sulfide and hydrogen sulfide; all the carbon was released as carbon dioxide, followed by oxidation of the sulfide to sulfate (Smith and Kelly, 1988). For soil, DMER and AEL (1996) used a mean degradation half-life of 5500 hours for their fugacity modelling (Section 2.3.1.6), based on the estimate of biodegradation half-life by Abrams *et al.* (1975). In the natural environment, carbon disulfide is highly mobile in soil (log K_{oc} = 1.79) and is subject to rapid volatilization, so it is unlikely to remain in soil long enough to undergo significant biodegradation.

2.3.1.5 Biota

Carbon disulfide is expected to have little or no tendency to bioaccumulate or biomagnify in biota, owing to its relatively low octanol/water partition coefficient (log K_{ow}) value (2.14) and rapid metabolism in most animals (Beauchamp *et al.*, 1983).

2.3.1.6 Environmental distribution

Fugacity modelling was carried out to provide an overview of key reaction, intercompartment and advection (movement out of a system) pathways for carbon disulfide and its overall distribution in the environment (DMER and AEL, 1996). A steady-state, non-equilibrium EQC model (Level III fugacity modelling) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Values for input parameters were as follows: molecular weight, 76.1 g/mol; water solubility, 2100 mg/L; vapour pressure, 48 210 Pa; log K_{ow}, 2.14; Henry's law constant, 1748 Pa×m^3/mol; half-life in air, 170 hours; half-life in water, soil and sediment, 5500 hours. Modelling was based on an assumed default emission rate of 1000 kg/hour into a region of 100 000 km^2, which includes a 10 000-km^2 ar ea of surface water (20 m deep). The height of the atmosphere is 1000 m. Sediments and soils have an organic carbon content of 4% and 2% and a depth of 1 cm and 10 cm, respectively. The estimated percent distribution predicted by this model is not affected by the assumed emission rate.

Modelling indicates that carbon disulfide partitions differently depending on the medium to which it is released. For example, if emitted into air, 99.8% of the carbon disulfide is present in air; if emitted into soil, the fraction in air is reduced to 73%, with most of the rest in soil. When carbon disulfide is

released to water, it is present primarily in water (85%) and, to a lesser extent, in air (15%) (DMER and AEL, 1996). Thus, while the predicted distributions suggest that little intermedia transport will occur when carbon disulfide is discharged to air, release to each of soil and (to a lesser extent) water has the potential for substantial transport of carbon disulfide to air.

If reliable data on discharge quantities are available, the average environmental concentrations within a given region of Canada can be predicted by models. Such modelling was done using the ChemCAN4 Level III fugacity model, which includes in its assumptions the dimensions and environmental parameters for various contiguous regions of Canada. The region modelled was southern Alberta, the region of Canada for which total releases are the largest, and the only region of Canada for which monitoring data removed from point sources are available (Section 2.3.2.1). The chemical-specific properties and degradation rates were the same as those used with the EQC model described above. Based on the total industrial releases of carbon disulfide in this region reported for 1995 in the National Pollutant Release Inventory of 1861 tonnes, exclusively to air (NPRI, 1996a), the Level III fugacity modelling predicted approximate concentrations of carbon disulfide of 1.1 x 10^{-2} µg/m^3 in ambient air, 2 x 10^{-5} µg/L in water, 5 x 10^{-8} µg/g in soil, 4 x 10^{-7} µg/g in terrestrial plants and 3 x 10^{-7} µg/g in terrestrial animals. These values likely represent an underestimate of actual concentrations in this region, however, since releases from natural sources and advective inputs from outside of the region were not considered.

2.3.2 Environmental concentrations

There are very few available data on environmental levels of carbon disulfide. In large measure, this reflects its widespread use as a desorbing solvent in conventional sampling and analysis for other volatile organic chemicals (VOCs). In addition, carbon disulfide binds very strongly to activated carbon, commonly used to trap VOCs, with the result that recoveries are poor. While sensitive and specific methods to monitor carbon disulfide in environmental media exist (see, for example, Phillips, 1992), these have not been widely applied.

2.3.2.1 Ambient (outdoor) air

The most extensive Canadian data on ambient levels of carbon disulfide are from the Alberta Government/Industry Acid Deposition Research Program, in which a number of substances in ambient air were determined continuously over 2 years at a remote site and at two sites in the vicinity of a sour gas processing plant (carbon disulfide is a minor component of the waste gases emitted from the processing of sour gas). Carbon disulfide was not detected in the majority of samples at all three sites - e.g., in 85-90% of samples at the remote site - and was detected somewhat more frequently at the sour gas sites. Based on extensive data from conventional gas chromatography, combined with some limited data collected over an 8-minute sampling period using a sensitive cryofocusing technique, the mean and maximum levels are estimated to have been higher at the sites near the sour gas plant (0.61 and 88 µg/m^3, respectively, at an upwind site, and 1.40 and 156 µg/m^3, respectively, at a downwind site) than at the remote site (0.51 and 12.5 µg/m^3, respectively) (Legge *et al.*, 1990a, 1990b).

Table 3 Average maximum air concentrations derived from ISC 3 model predictions (The, 1998)

Receptor location	Averaging period	Maximum concentration (µg/m^3)
10 km	Annual	0.8
10 km	24-hour	14.3
10 km	1-hour	113.6
1 km	Annual	0.4
1 km	1-hour	114.3

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A local air dispersion modelling study was conducted by The (1998), using the ISC 3 view plume dispersion model to predict the concentration of carbon disulfide in the air downwind from another gas processing site. This single source reported a release of 1287 tonnes to the atmosphere in 1995, the largest release reported for Canada that year (NPRI, 1996a). The maximum concentrations in ambient air that were predicted by the air dispersion model are presented in Table 3. From this table, it can be seen that the highest calculated concentration in air 1 km downwind (a 1-hour average) was about 114 $\mu g/m^3$. The 24-hour average maximum ground-level concentration 10 km downwind was 14.3 $\mu g/m^3$.

The results of other modelling studies suggest that levels near smaller sour gas wells are somewhat less than those near larger wells. Based on concentrations of carbon disulfide measured in flare gases from a sour gas facility in central Alberta, in combination with plume dispersion modelling, Strosher (1996) predicted the maximum ground-level concentration at 2.02 $\mu g/m^3$ for a daily average and 0.16 $\mu g/m^3$ for an annual average.

Carbon disulfide levels were also elevated on the site of Prospec Chemicals, Fort Saskatchewan, Alberta, which uses the compound on-site as a feedstock for xanthates. In monitoring of ambient air outside of the property line (at the point of impingement predicted by dispersion modelling) during the summer of 1997, monthly average concentrations of carbon disulfide ranged from 3 to 6 $\mu g/m^3$, and hourly maximum concentrations were between 56 and 100 $\mu g/m^3$ (Fu, 1997; Weiss, 1998).

2.3.2.2 Indoor air

In a very small study of levels of carbon disulfide in New York City air, carbon disulfide was detected in all of the nine indoor air samples, at a mean concentration (0.63 $\mu g/m^3$) that was not significantly higher than the mean level in six outdoor air samples (0.30 $\mu g/m^3$) (Phillips, 1992).

2.3.2.3 Surface water and groundwater

Data on levels of carbon disulfide in Canadian surface water are limited to southern Ontario. Background levels at remote sites in Ontario, largely due to biogenic production, range between about 0.005 and 0.4 µg/L (Caron and Kramer, 1994). In Lake Ontario, in 1981, a median concentration of 0.4 µg/L and a maximum of 3.9 µg/L were measured (Kaiser *et al.*, 1983). The authors considered that the lower levels seen in the open lake were likely due to biogenic activity, while the elevated levels were due mainly to the influence of nearby urban/industrial areas (Scott, 1998). The highest measured concentration in Canadian surface water, 25.0 µg/L, was associated with a chemical plant on Thompson Creek in the Niagara region that has since closed (Kaiser and Comba, 1983).

In seawater, Lovelock (1974) reported concentrations in the open Atlantic of 0.52 and 0.78 ng/L off the coast of Ireland and 5.4 ng/L in stagnant bay water near Ireland. Leck and Rodhe (1991) measured levels of carbon disulfide in the open Baltic and North seas between 0.83 and 1.18 ng/L. Kim and Andreae (1987) reported carbon disulfide concentrations in surface waters in the North Atlantic ranging bet ween 0.01 and 4.6 ng/L.

2.3.2.4 Drinking water

Very few data on the levels of carbon disulfide in Canadian drinking water supplies were identified. In a 1982-1983 survey of raw and treated water samples from 10 Ontario municipalities, carbon disulfide was frequently detected at low levels in each of spring, summer and winter samplings. Concentrations over the three seasons ranged from non-detectable to trace levels in most cities, from non-detectable to 0.2 µg/L in Cornwall and from non-detectable to 0.3 µg/L in Hamilton (Otson, 1987, 1996). No other Canadian data were identified.

2.3.2.5 Soil and sediment

The available data on concentrations of carbon disulfide in soils are quite limited. In a 1985-1986 study of background sites in the general vicinity of petrochemical refinery facilities west of Toronto, Ontario, carbon disulfide was detected at one of five sites in Port Credit at 0.000 11 µg/g, but not at any of six sites from Oakville/Burlington (Golder Associates, 1987). The same report also summarized the results of a 1987 survey of organic compounds in surface soils in background areas in the same

municipalities, in which carbon disulfide was reportedly detected at three of 30 urban residential and parkland sites in Port Credit, Oakville and Burlington, at concentrations of 0.10, 0.10 and 0.14 µg/g (Golder Associates, 1987). However, the latter results are of uncertain validity, as the reported levels were near the method detection limit (0.10 µg/g), and the values were not corrected for the observed contamination of the method blank.

In 1988, carbon disulfide was measured in sediment suspensions taken from Lake Ontario, near Burlington, Ontario, and in Harp Lake, near Huntsville, Ontario. Caron and Kramer (1994), using a sulfur-specific gas chromatographic method, were able to detect 5.9 ng carbon disulfide/L in Lake Ontario sediment and 9.7 ng carbon disulfide/L in Harp Lake sediments.

No other quantitative Canadian data were identified.

2.3.2.6 Biota

No information was identified in the literature regarding the levels of carbon disulfide in biota in Canada.

2.3.2.7 Food

No data were identified on the levels of carbon disulfide in Canadian foods. Carbon disulfide was previously registered as a fumigant for use on stored grain, but this registration was withdrawn in 1984. There are currently no registered food uses for carbon disulfide in Canada (Warfield, 1996). For certain pesticides, such as dithiocarbamates, carbon disulfide is produced during their metabolism in plants and in soil. Carbon disulfide is also known to be a metabolite produced by plants from naturally occuring sulfur compounds (Section 2.2.2.1). However, no information was accessed with which to quantitatively characterize the potential for exposure to carbon disulfide in Canada from these sources (Ballantine, 1998; Moore 1999).

The results of a number of food surveys from the United States in which the levels of carbon disulfide were determined have been published (Heikes and Hopper, 1986; Daft, 1987, 1988, 1989; Heikes, 1987). However, the results of these studies are considered to be of limited relevance to characterizing exposure to carbon disulfide in foods in Canada, because they appear to have been conducted before the use of carbon disulfide as a grain fumigant was cancelled and/or were conducted using insensitive methodology.

2.3.2.8 Consumer products

A variety of sulfur compounds are components of tobacco smoke. Horton and Guerin (1974) analysed the mainstream smoke from seven samples of commercial and experimental cigarettes and a single cigar and marijuana cigarette. They reported that each of these products delivered approximately 2 µg of carbon disulfide per cigarette/cigar smoked

2.3.3 Human tissues and fluids

No data were identified on levels of carbon disulfide in biological materials from the general population in Canada. However, carbon disulfide and/or its metabolite 2-thiothiazolidine-4-carboxylic acid (TTCA) have been measured at part-per-billion levels in virtually all samples of breath, blood, urine or breast milk of subjects from other countries with no known occupational exposure in a number of studies (Pellizzari *et al.*, 1982; Phillips, 1992; Brugnone *et al.*, 1994). This provides support for the data on levels in environmental media, which indicate that humans have environmental exposure to carbon disulfide. It should be noted, however, that at least some of the carbon disulfide and/or TTCA may have arisen from exposure to other chemicals of which they are known to be metabolites, such as disulfiram, captan or dithiocarbamate fungicides, and that TTCA is present naturally in brassica vegetables (Simon *et al.*, 1994, and references therein).

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2.4 Effects characterization

2.4.1 Ecotoxicology

The toxic mode of action of carbon disulfide varies from species to species. In microorganisms, carbon disulfide may interfere with the general metabolism of a nitrifier species or with the primary oxidative reactions. In higher life forms, it is suggested that metabolic reactions of carbon disulfide follow two distinctly different pathways: it can form dithiocarbamates, which are metal chelating, or it can form elemental sulfur during oxidative desulfurization in the liver (Beauchamp *et al.*, 1983). Acute toxicity is confined mainly to neurotoxic effects.

The following sections present a summary of the most sensitive endpoints found for terrestrial and aquatic organisms. More extensive descriptions of environmental effects are provided in Environment Canada (1999a).

2.4.1.1 Terrestrial organisms

Mammals appear to have relatively high tolerance to short-term or acute exposure to carbon disulfide (Crookes *et al.*, 1993). While no tests on wild mammals were found in the literature, effects on laboratory mammals have been extensively studied. In a flow-through inhalation study using mice, an approximate 1-hour LC_{50} for vapour exposure of 220 ppm (690 mg/m^3) was estimated by Gibson and Roberts (1972). This was the most sensitive result identified from the literature (see Section 2.4.4.1).

Taylor and Selvidge (1984) studied the effects of gaseous carbon disulfide on bush beans (*Phaseolus vulgaris*) in a closed system, with three replicate exposures, and reported no effect on transpiration or photosynthesis at any of the measured concentrations tested (0.42×10^6 to 5.6×10^6 $\mu g/m^3$ for 6 hours) and no visual injury seen at the single measured concentration tested for this effect (1.0×10^7 $\mu g/m^3$). In a previous study to assess the internal flux of carbon disulfide and other gases from leaf surface to leaf interior, Taylor *et al.* (1983) found that carbon disulfide had the lowest flux rate for all three plant species and all of the reduced sulfur gases tested. This may account in part for its relatively low toxicity compared with that of other sulfur gases, since flux to the interior of a leaf is the major determinant of the ability of a compound to cause leaf injury.

Few other studies on plants were identified in the literature; however, the effects on seeds from the use of carbon disulfide as a fumigant were examined by two separate investigators (Kamel *et al.*, 1975; Verma, 1991). The most sensitive species was seed of the wheat plant, Giza 135 variety. Grains with a 15% moisture content suffered a 55% reduction in germination when exposed to a concentration of 5.05×10^8 µg carbon disulfide/m^3 (Kamel *et al.*, 1975). In general, seeds with higher moisture content were more sensitive. Overall, it can be stated that a concentration of carbon disulfide of 2.53×10^8 $\mu g/m^3$ for a 24-hour exposure could be considered safe for wheat seed when the moisture content does not exceed 15%.

It has been found that carbon disulfide fumigation affects all life stages of invertebrates with varying degrees of toxicity (Crookes *et al.*, 1993). The most sensitive test result was a 7-day LC_{50} value of 1.1×10^6 $\mu g/m^3$ for the mite, Lepidoglyphus destructor (Barker, 1982). Further studies in invertebrates are listed in Table A.3 in Environment Canada (1999a).

In one 5-day study of the effects of carbon disulfide on the nitrification of ammonium in soils using sealed containers, Bremner and Bundy (1974) reported nearly complete inhibition of nitrification at nominal concentrations as low as 0.5 µg/g. The ecological signif icance of this result is uncertain, however, because concentrations in test soils were not measured, and the effect nearly disappeared when the test duration was increased to 14 days.

2.4.1.2 Aquatic organisms

Van Leeuwen *et al.* (1985) studied the toxic effects on several aquatic species, from algae to the guppy (*Poecilia reticulata*). Under controlled conditions in a sealed container to prevent evaporative loss, the most sensitive species was *Daphnia magna*, with a 48-hour LC_{50}, tested according to Organisation for Economic Cooperation and Development (OECD) test guideline 202, of 2.1 mg/L. At higher concentrations, 3 mg/L and above, reduced hatching and developmental effects, particularly notochord deformities, were observed in the frog, *Microhyla ornata* (Ghate, 1985). The most sensitive fish species studied was the guppy, with a 96-hour LC_{50} of 4 mg/L (van Leeuwen *et al.*, 1985). The 96-hour EC50 for the green alga, *Chlorella pyrenoidosa*, was 21 mg/L, based on inhibition of growth (van Leeuwen *et al.*, 1985). Further data are presented in Table A.3 in Environment Canada (1999a).

2.4.2 Abiotic atmospheric effects

Calculations were made to determine if carbon disulfide has the potential to contribute to depletion of stratospheric ozone, the formation of ground-level ozone or climate change (Bunce, 1996).

Since carbon disulfide is non-halogenated, its Ozone Depletion Potential (ODP) is 0, and it will therefore not contribute to the depletion of stratospheric ozone (Bunce, 1996).

The Photochemical Ozone Creation Potential (POCP) of carbon disulfide, relative to that of the reference compound, ethene, which has a value of 100, was conservatively estimated to be 35 (Bunce, 1996), based on the following formula:

$POCP = (k_{carbon\ disulfide}/k_{ethene}) \times (M_{ethene}/M_{carbon\ disulfide}) \times 100$

where:

- $k_{carbon\ disulfide}$ is a conservative estimate of the rate constant for the reaction of carbon disulfide with OH radicals (8.0×10^{-12} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28 g/mol) and
- $M_{carbon\ disulfide}$ is the molecular weight of carbon disulfide (76.1 g/mol).

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Although this POCP is somewhat elevated, the magnitude of any effect will depend on the concentration of carbon disulfide in the atmosphere. Except in proximity to strong point sources, average annual concentrations of carbon disulfide in ambient air are low relative to typical annual concentrations reported by Dann and Summers (1997) for the volatile organic compounds with similar POCPs that contribute most to the formation of ground-level ozone. Therefore, the contribution of carbon disulfide to ground-level ozone formation is not expected to be significant.

Gases involved in climate change strongly absorb infrared radiation of wavelengths between 7 and 13 µm, enabling them to trap and re-radiate the Earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Worst-case calculations were made to determine if carbon disulfide has the potential to contribute to climate change (Bunce, 1996). Quantitative data on infrared absorption strength are not available. Therefore, the worst-case calculations assumed the same infrared absorption strength as for a reference compound (CFC-11). The Global Warming Potential (GWP) for carbon disulfide, relative to that of the reference compound, CFC-11, which has a GWP of 1, was calculated to be 0.001, based on the following formula (Bunce, 1996):

$GWP = (t_{carbon\ disulfide}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{carbon\ disulfide}) \times (S_{carbon\ disulfide}/SCFC\text{-}11)$

where:

- $t_{carbon\ disulfide}$ is the lifetime of carbon disulfide (10 days),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{carbon\ disulfide}$ is the molecular weight of carbon disulfide (76.1 g/mol),
- $S_{carbon\ disulfide}$ is the infrared absorption strength of carbon disulfide (2389/cm2 per atmosphere, default) and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

As this estimate is less than 1% of the GWP of the reference compound, carbon disulfide is not considered to be involved in climate change (Bunce, 1996).

Carbon disulfide may also have an indirect impact on climate change and stratospheric ozone depletion through its main atmospheric transformation product, carbonyl sulfide, but the magnitude of this impact is considered to be small (Environment Canada, 1999a).

2.4.3 Humans

Owing to the relatively extensive database in humans, the epidemiological data have been emphasized in characterizing the hazard associated with exposure to carbon disulfide; information from studies in animals contributes primarily to assessment of biological plausibility and understanding of the mode of action.

2.4.3.1 Acute effects

In a number of early reports of poisoning following pulmonary exposure to 500-1000 ppm (1560-3125 mg/m^3) carbon disulfide, a range of psychiatric disturbances was reported, while concentrations of approximately 5000 ppm (15 625 mg/m^3) resulted in central nervous system depression, coma, respiratory paralysis and death. In several case reports, ingestion of approximately 18 g caused neurological signs, cyanosis, peripheral vascular collapse and hypothermia, followed by death due to central nervous system depression and respiratory paralysis within a few hours (HSE, 1981).

2.4.3.2 Effects of long-term exposure

The majority of the available epidemiological studies are of workers in the viscose rayon industry, in which workers are exposed to airborne carbon disulfide, along with lesser quantities of hydrogen sulfide, at several stages during the process of manufacturing viscose rayon fibres. The following discussion is limited principally to studies in which information on the exposure levels associated with the effects observed in the study population was provided.

2.4.3.2.1 Effects on the nervous system

Neurophysiological effects on both the peripheral and central nervous systems, as well as behavioural and neuropathological effects, have been reported in a number of cross-sectional studies of workers exposed to carbon disulfide in the viscose rayon industry. The most common observations are of effects on the peripheral nervous system, most often characterized by reduced conduction velocity in the motor and, in some instances, sensory nerves, and generally most pronounced in the more distal portions of the nervous system (e.g., in the lower limbs).

These findings are exemplified by an early neurophysiological study of male Finnish viscose rayon workers with long-term exposure to carbon disulfide and hydrogen sulfide at 31-94 mg/m^3 (with higher peak and historical levels) compared with unexposed paper mill workers (Seppäläinen and Tolonen, 1974). In exposed workers as a whole, there were significant reductions in motor nerve conduction velocities of the deep peroneal, posterior tibial and ulnar nerves and in slow motor fibre conduction velocities in the deep peroneal and ulnar nerves. Findings were comparable in workers who were currently exposed and in those removed from exposure for a number of years.

Effects on peripheral nervous system conduction were also associated with lower exposures to carbon disulfide in a well-conducted study of white male workers in a U.S. viscose rayon plant (Johnson *et al.*, 1983). After excluding data from workers with possible neuro toxic ex posures/conditions and adjusting for age, exposed workers had significantly reduced maximum motor nerve conduction velocity and amplitude ratio of muscle action potentials following peroneal nerve stimulation and reduced maximum sensory nerve conduction velocity and increased discrete amplitude of the nerve action potential in the sural nerve. These differences were observed primarily in the workers who were most highly exposed at the time of the study, with median personal air levels of 24 mg/m^3, although conduction velocities in both nerves were slightly lower in workers with moderate (median 13 mg/m^3) and low (median 3 mg/m^3) exposures. Based on area samples, exposures were stable over more than 20 years prior to the study. In contrast to the findings for nerves in the legs, none of the neurophysiological variables in the ulnar nerve was associated with carbon disulfide exposure. In behavioural testing of this population, there were no remarkable findings in psychological, psychomotor, cognitive-perceptual or vision testing, although exposed workers reported symptoms of neurobehavioural ailments significantly more frequently (Putz-Anderson *et al.*, 1983).

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In another study in which exposures were well characterized, there were significant reductions in motor nerve conduction velocity of the peroneal nerve, after adjustment for potential confounders (age, weight, height, glucose tolerance, and cigarette and alcohol consumption), in workers exposed to

carbon disulfide (median 13 mg/m^3) in personal air and in sensory nerve conduction velocity of the sural nerve in workers from those departments with high exposure compared with workers from departments with low exposure (Reinhardt *et al.*, 1997a). The authors questioned the significance of these results, based primarily on the lack of effects on other neurophysiological parameters and the lack of significant dose-response among exposed workers. However, it is considered that the changes observed by Reinhardt *et al.* (1997a) represent a compound-related effect. While Reinhardt *et al.* (1997a) argued that the reductions in motor nerve conduction velocity should be preceded by a decreased amplitude of the action potential and a prolonged distal motor latency, it is noted that reductions in conduction velocity of the same nerves were not accompanied by alterations in these neurophysiological parameters in the study by Johnson *et al.* (1983); indeed, this pattern is expected based on the fact that carbon disulfide acts specifically on the axon. In addition, the equivocal nature of the findings for the sural nerve is consistent with the general pattern of increased susceptibility of the longest and largest- diameter axons to the neurotoxic effects of carbon disulfide in exposed humans and animals (Section 2.4.4.2.1). Finally, although there was no dose-response among the exposed workers, there was a significant dose-response when the control workers were included in the analysis.

The results of several other studies confirm that exposure to carbon disulfide at mean concentrations of 15-<30 mg/m^3 is associated with reductions in motor and sensory nerve conduction velocity in the peripheral nerves, most often in the lower limbs, although exposures were not well characterized in most of these studies (Vasilescu and Florescu, 1980; Sandrini *et al.*, 1983; Hirata *et al.*, 1996; Takebayashi *et al.*, 1998).

In contrast, there was little indication of effects on the peripheral nervous system in a small study of Italian viscose rayon workers who had been exposed to slightly lower carbon disulfide levels - i.e., mostly less than 10 mg/m^3 (Cirla and Graziano, 1981). In this study, motor nerve conduction velocity of the peroneal nerve was non-significantly slower in exposed workers than in well-matched controls. Based on needle electromyography and neurological examinations, five out of 50 exposed subjects had peripheral nerve impairment, compared with only two out of 50 controls. There were no significant differences in the results of neuropsychological testing of intelligence, performance and memory conducted on half of the subjects.

In several studies in which exposures were substantially higher, effects on the peripheral nervous system were more pronounced, as indicated by reductions in the motor and sensory nerve conduction velocities of a wider range of nerves (including those in the upper limbs) and/or alterations in other peripheral neurophysiological variables (Gilioli *et al.*, 1978; Ruijten *et al.*, 1993; Chu *et al.*, 1995; Vanhoorne *et al.*, 1995). In the subset of these studies in which subgroup analyses were conducted, there was an exposure-response relationship, with reductions in peroneal motor nerve conduction velocity among exposed workers being related to the exposure concentrations (Gilioli *et al.*, 1978; Vanhoorne *et al.*, 1995) or most pronounced in workers engaged in tasks that would most likely have entailed the heaviest exposure to carbon disulfide (Chu *et al.*, 1995).

Chu *et al.* (1996) reported histopathological findings in a male viscose rayon worker exposed to a time-weighted average concentration of 125-209 mg/m^3, with clinical and neurophysiological signs of peripheral neuropathy. The results of sural nerve biopsy revealed ultrastructural changes similar to those in the peripheral nervous system of animals exposed to carbon disulfide (axonal degeneration with disorganized neurofilaments) (Section 2.4.4.2.1).

In four studies, workers with long-term exposure to approximately 30-90 mg carbon disulfide/m^3 (often with higher historical exposures) performed significantly more poorly than unexposed workers on a variety of neurobehavioural tests, most often on psychomotor tests of motor speed or dexterity (Hänninen, 1971; Cassitto *et al.*, 1978; Hänninen *et al.*, 1978; De Fruyt *et al.*, 1998). The evidence that such effects are associated with lower exposures is conflicting, although there were no remarkable differences in the results of extensive neurobehavioural testing in workers exposed to similar or slightly higher levels of carbon disulfide in several well-described studies (Cirla and Graziano, 1981; Putz-Anderson *et al.*, 1983; Reinhardt *et al.*, 1997b; Takebayashi *et al.*, 1998); however, there were significant increases in the frequency of reported central nervous system symptoms in some of these studies (Cirla and Graziano, 1981; Putz-Anderson *et al.*, 1983; Takebayashi *et al.*, 1998).

There was no clear evidence of effects on the results of electroencephalography conducted on workers exposed to carbon disulfide (Seppäläinen and Tolonen, 1974; Gilioli *et al.*, 1978; Chrostek Maj and Czeczotko, 1995b; Sinczuk-Walczak and Szymczak, 1997), although this endpoint has not been extensively investigated.

In epidemiological studies of more specific effects on the nervous system, exposure to mean levels of carbon disulfide in the range of 15-30 mg/m^3 was associated with vestibular alterations (Merluzzi *et*

al., 1981), changes in the wave pattern of brainstem auditory evoked potentials (Hirata *et al.*, 1992b) and effects on the dopaminergic system (Wasilewska *et al.*, 1989; Stanosz *et al.*, 1994b; Yang *et al.*, 1996). However, in all of these studies, the group sizes were fairly small, and there was often historical exposure to higher levels.

2.4.3.2.2 Mortality from cardiovascular disease

Excess mortality from cardiovascular disease, most often ischemic heart disease, has been reported in a number of occupational cohorts exposed to carbon disulfide.

In an early prospective study, Hernberg *et al.* (1970, 1971, 1973; Tolonen *et al.*, 1975) reported a significant excess of deaths from coronary heart disease over the first 5 years in 343 workers exposed to carbon disulfide in a Finnish viscose rayon plant, compared with a well-matched group of workers from a paper mill (14 exposed, three control deaths, relative risk [RR] 4.8, $p < 0.007$). There were also significant increases in indicators of cardiovascular morbidity (non-fatal myocardial infarction, chest pain) and of risk factors for coronary heart disease (increased blood pressure). The workers had been exposed to airborne concentrations of carbon disulfide of 31-94 mg/m^3 during the period when the study was initiated, although short-term and historical exposures were much higher. After these results were reported, exposures were reduced to less than 31 mg/m^3, and the majority of the cohort was removed from exposure. In a subsequent (13-year) follow-up (Tolonen *et al.*, 1979; Hernberg and Tolo nen, 1981; Nurminen *et al.*, 1982), there was still a significant excess of deaths from coronary heart disease, but this was entirely due to the almost fivefold excess in the initial 5 years.

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Cardiovascular mortality was significantly greater in the most highly exposed workers in a cohort of 2939 male workers at a U.K. viscose rayon factory (Sweetnam *et al.*, 1987). Among spinners with at least 10 years of employment in the industry, who were considered to have the highest continuous exposures, mortality was significantly in excess for all causes, ischemic heart disease (73 deaths, standardized mortality ratio [SMR] 172, $p < 0.001$) and other circulatory diseases combined (33 deaths, SMR 165, $p < 0.01$), compared with the general population. There was also a significant excess of mortality from ischemic heart disease in non-process fitters, although this was based on a small number of deaths (nine deaths, SMR 290, $p < 0.01$). A significant trend between mortality from ischemic heart disease among long-term older workers and cumulative exposure score or exposure score over the last 2 years was observed. These patterns were not evident in workers who had left employment or those with less than 10 years of exposure. Based on a report of an earlier follow-up, levels in the spinning department frequently exceeded 63 mg/m^3 (Tiller *et al.*, 1968). While there was concomitant exposure to hydrogen sulfide, the excess of mortality from ischemic heart disease was similar among workers with high-level exposure to carbon disulfide alone or to both compounds.

Findings were similar in a larger cohort of 10 418 male workers employed for at least 1 year at one of four U.S. viscose rayon plants (MacMahon and Monson, 1988). In workers with the greatest exposure (based on their job titles - principally spinners and cutters), there was a significant excess of mortality from arteriosclerotic heart disease compared with the general population (242 deaths, SMR 124, $p < 0.01$); this occurred principally in workers with 15 or more years of exposure. No data were presented on exposures to carbon disulfide or other chemicals, nor on other known risk factors for heart disease.

In a historical cohort study of 3322 Dutch male viscose rayon workers, mortality from circulatory diseases was significantly increased among the 1434 workers exposed to carbon disulfide compared with the general population (Swaen *et al.*, 1994). Among workers from the bleaching and spinning departments, who had continuous exposure to carbon disulfide, there was a significant excess of mortality from cardiovascular diseases (103 deaths, SMR 126, 95% confidence interval [CI] 1.03-1.54) and a non-significant excess from ischemic heart disease (65 deaths, SMR 125, 95% CI 0.96-1.62). Among these workers, mortality from cardiovascular diseases and ischemic heart disease was inversely related to cumulative exposure, although this was estimated from personal air samples collected late in the study period, and historical exposures were most likely higher. The risk for cardiovascular disease was reported to be most pronounced 20-30 years after the first exposure. In contrast to the results of other studies (Hernberg and Tolonen, 1981; Sweetnam *et al.*, 1987), the risk for cardiovascular mortality did not decrease after termination of exposure. No information was available on other risk factors for heart disease, but there was no excess of cardiovascular diseases in unexposed workers, who were considered to be similar to the exposed workers in terms of lifestyle.

Mancuso (1981) conducted a historical cohort study of more than 9000 males and females employed at a U.S. viscose rayon plant. In the 26-year follow-up, there was significant excess mortality from coronary heart disease among males (453 deaths, SMR 111.2, 95% CI 101.2-121.9). There were no

quantitative exposure data, but the SMRs for coronary heart disease increased with increasing duration of exposure and were significantly increased in male workers employed for more than 10 years in those tasks for which exposure was considered high (spinning and twisting, maintenance and mechanics). In females, findings were similar but less pronounced and generally not statistically significant.

Among a historical cohort of 2291 Polish viscose rayon workers who had been diagnosed with chronic carbon disulfide poisoning, there were significant excesses of deaths from diseases of the circulatory system (359 deaths, SMR 139, 95% CI 125-154), including ischemic heart disease (122 deaths, SMR 137, 95% CI 114-164) and cerebrovascular disease (60 deaths, SMR 188, 95% CI 143-242), and a non-significant excess of mortality from arteriosclerosis among males (73 deaths, SMR 120, 95% CI 94-151) (Peplonska *et al.*, 1996). Results were similar among women but were based on few cases and were often not statistically significant. Exposures to carbon disulfide, although apparently heavy, were poorly characterized.

Several other epidemiological studies of cardiovascular mortality among populations exposed to carbon disulfide in the workplace were identified, but each is considered to contribute less to the weight of evidence for this effect, as a consequence of one or more of small numbers of deaths, limited statistical power and poor characterization of exposure (Lyle, 1981; Wilcosky and Tyroler, 1983; Liss and Finkelstein, 1994, 1996).

2.4.3.2.3 Cardiovascular morbidity and risk factors for cardiovascular disease

In a number of cross-sectional studies, associations have been reported between exposure to carbon disulfide and clinical measures that are established risk factors for heart disease, including blood pressure and serum cholesterol. In addition, there are reports of increases in overt manifestations of coronary heart disease, such as angina and coronary electrocardiographs, in workers exposed to carbon disulfide.

In a well-conducted study, Egeland *et al.* (1992) observed a significant association between increases in serum levels of low-density lipoprotein cholesterol (LDL-C) and diastolic blood pressure and increasing exposure to carbon disulfide (and a non-significant one for total cholesterol) among male workers exposed to median levels of 3-24 mg/m^3 at a U.S. viscose rayon plant, compared with unexposed workers at three synthetic textile plants, and after adjustment for potential confounders. There was no association between exposure and high-density lipoprotein cholesterol (HDL-C), triglyceride, blood glucose or systolic blood pressure. The levels of LDL-C, total cholesterol and diastolic blood pressure were significantly greater in the high-exposure group than in the low-exposure workers. (Patterns were generally similar in comparison with the unexposed workers.) The results of area sampling indicated that exposures were stable for more than 20 years prior to the study. The authors estimated that the higher LDL-C concentrations in the high-exposure group corresponded to an increased risk of coronary heart disease of 26% and noted that this was similar to the 24% increase in ischemic heart disease mortality among workers that had job assignments similar to the high-exposure group in a cohort study at four U.S. rayon textile plants, including the plant studied here (MacMahon and Monson, 1988).

Similar results were reported in a study of 237 Polish women exposed to levels of carbon disulfide in the same range (i.e., 16-22 mg/m^3) in viscose fibre production (Stanosz *et al.*, 1994a). Exposed women had significantly increased levels of total cholesterol and LDL-C and a significantly reduced level of HDL-C compared with a control group of female textile workers of similar age. Effects on these blood lipids were confined to women aged 40-55 and to those with greater than 10 years of exposure. No subgroup analyses by exposure level were conducted.

These findings are supported by two studies of viscose rayon workers (Wronksa-Nofer and Laurman, 1987; Vanhoorne *et al.*, 1992) in which exposure to carbon disulfide at levels generally in excess of 31 mg/m^3 was associated with significant increases in serum cholesterol and LDL-C and decreases in HDL-C and, in the latter study (which adjusted for several potential confounders), with increases in blood pressure. However, it should be noted that there was no significant association between total cholesterol and exposure to similar levels of carbon disulfide in the prospective study by Hernberg *et al.* (1970).

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In contrast to the above studies, findings were negative in two investigations in which exposure levels were slightly less than those for the U.S. workers studied by Egeland *et al.* (1992). In a well-conducted study of German male viscose rayon workers exposed to a median personal airborne concentration of

13 mg/m ^{3} (Drexler *et al.*, 1995), there was no association between various measures of exposure (exposure category, levels in personal air or TTCA levels in urine) and blood pressure or blood levels of cholesterol, LDL-C, HDL-C, triglycerides, apolipoproteins, electrolytes or glucose. HDL-C and apoliprotein levels were associated with duration of employment in jobs with exposure, but this was also observed in the controls, and the authors suggested that this was the result of long-term shift work. Similarly, Cirla and Graziano (1981) reported no significant differences in blood pressure or serum levels of blood lipid and lipoproteins between workers exposed to mean carbon disulfide levels of 5-20 mg/m^3 and controls who were well matched for age and a series of lifestyle factors.

Results of some other studies in this area are considered to contribute little to the weight of evidence for effects of carbon disulfide on cardiovascular risk factors, as a consequence of lack of dose-response and/or inconsistency of results with those observed in the more reliable studies described above (Franco *et al.*, 1981, 1982; Krstev *et al.*, 1992; Chrostek Maj and Czeczotko, 1995a).

There is also evidence from cross-sectional studies of overt toxicity to the cardiovascular system, most often reported as an increased frequency of angina or non-fatal myocardial infarction or of abnormal electrocardiograph (Hernberg *et al.*, 1970; Sugimoto *et al.*, 1978; Cirla and Graziano, 1981; Albright *et al.*, 1984; Kamal *et al.*, 1991; Vanhoorne *et al.*, 1992; Bortkiewicz *et al.*, 1997; Kuo *et al.*, 1997). However, the increases were often non-significant and were based on small numbers of cases, and there is no clear dose-response across studies (although exposures were poorly characterized in most of these investigations).

2.4.3.2.4 Effects on the eye

Exposure to carbon disulfide at levels greater than 31 mg/m^3 was associated with damage to the retinal capillaries, in the form of microaneurysms or hemorrhages, in a number of cross-sectional studies (Sugimoto *et al.*, 1976, 1977, 1978; Tolonen *et al.*, 1976; Karai *et al.*, 1983; Vanhoorne *et al.*, 1996). However, there appears to be considerable variation in the susceptibility to this effect among populations, and there is no clear evidence that exposure to lower levels of carbon disulfide is associated with retinopathy (Albright *et al.*, 1984; Sugimoto *et al.*, 1984, 1992; Omae *et al.*, 1998). In addition, such effects are of uncertain clinical significance, although it has been suggested that they could possibly be early indicators of more serious damage to the ocular, vascular or nervous system (Vanhoorne *et al.*, 1996).

The association of exposure to carbon disulfide with other effects on the eye has not been extensively investigated. There are two reports of effects on colour vision in viscose rayon workers with current or historical exposures to carbon disulfide at levels greater than 31 mg/m^3 (Raitta *et al.*, 1981; Vanhoorne *et al.*, 1996), while colour vision was not affected in workers exposed to median levels of 3-24 mg/m^3 (Albright *et al.*, 1984). In these populations, there were no other effects on measures of vision, including visual acuity, visual field, eye motility, depth perception and pupillary reaction (Raitta *et al.*, 1974; Albright *et al.*, 1984; Vanhoorne *et al.*, 1996).

2.4.3.2.5 Carcinogenicity

In those epidemiological studies in which mortality from non-cardiovascular causes was presented, there was no consistent excess of mortality from all cancers combined or from cancers at any specific site (Lyle, 1981; Mancuso, 1981; Wilcosky *et al.*, 1984; Nurminen and Hernberg, 1985; MacMahon and Monson, 1988; Swaen *et al.*, 1994; Liss and Finkelstein, 1996; Peplonska *et al.*, 1996). However, exposures were poorly characterized (if at all), and the number of cancer deaths at any given site was small or modest in all of these studies, many of which were designed specifically to investigate the association between exposure to carbon disulfide and mortality from cardiovascular diseases.

2.4.3.2.6 Effects on reproduction and development

With the exception of several reports of reduced libido and/or impotence in male workers exposed to (mostly) high concentrations of carbon disulfide in the viscose rayon industry (Cirla *et al.*, 1978; Cirla and Graziano, 1981; Wägar *et al.*, 1981; Vanhoorne *et al.*, 1994), there is no clear evidence of effects on human reproduction and development. Semen quality, fertility and pregnancy outcomes were not associated with exposure of male viscose rayon workers to carbon disulfide in the better documented of the available studies (Meyer, 1981; Selevan *et al.*, 1983; Vanhoorne *et al.*, 1994). The potential effects of carbon disulfide on female reproduction have not been adequately investigated, although there are two reports of an increased frequency of abnormal menstrual duration and pain/bleeding in populations of female Chinese viscose rayon workers (Cai and Bao, 1981; Zhou *et al.*, 1988). Two early Finnish reports (Hemminki *et al.*, 1980; Hemminki and Niemi, 1982) of an increased frequency of

spontaneous abortions associated with maternal or paternal employment in the viscose rayon industry were not confirmed in several subsequent studies, some of which were of inherently stronger design, although in all cases the number of abortions was small (Cai and Bao, 1981; Selevan *et al.*, 1983; Zhou *et al.*, 1988; Lindbohm *et al.*, 1991).

No reports of developmental effects associated with exposure to carbon disulfide were identified.

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2.4.3.2.7 Other effects

There are a number of epidemiological investigations of the association between exposure to carbon disulfide and a variety of other effects, most often alterations in circulating levels of thyroid hormones (Cirla *et al.*, 1978; El-Sobkey *et al.*, 1979; Cirla and Graziano, 1981; Wägar *et al.*, 1981; Albright *et al.*, 1984; Vanhoorne *et al.*, 1993; Takebayashi *et al.*, 1998), gonadotropins (Cirla *et al.*, 1978; Wägar *et al.*, 1981, 1983; Vanhoorne *et al.*, 1993), adrenal and/or testicular hormones (Cavalleri *et al.*, 1967; Wink, 1972; Wägar *et al.*, 1981; Takebayashi *et al.*, 1998) and increases in the prevalence of diabetes or decreased glucose tolerance (Goto and Hotta, 1967; Goto *et al.*, 1971; Hernberg *et al.*, 1971; Candura *et al.*, 1979; Cirla and Graziano, 1981; Franco *et al.*, 1981, 1982; Egeland *et al.*, 1992; Chrostek Maj and Czeczotko, 1995a; Drexler *et al.*, 1995). However, the findings in the available studies of these effects were inconsistent and, in some instances, contradictory and have often not been confirmed in those studies in which the study design was stronger and/or the reporting was more detailed.

2.4.4 Experimental animals and in vitro

2.4.4.1 Acute toxicity

The LC_{50} for male mice exposed for 60 minutes to carbon disulfide by inhalation was reported to be approximately 220 ppm (690 mg/m^3) (Gibson and Roberts, 1972), whereas no mortality occurred in rats exposed to as much as 790 ppm (2470 mg/m^3) for 15 hours, although neurological effects were observed (HSE, 1981). The oral LD_{50} for mice (sex unspecified) over a 24-hour period was 3020 mg carbon disulfide/kg-bw. Single oral doses of up to 1260 mg/kg-bw did not cause any deaths or overt toxicity in rats, and only minimal lesions (i.e., some pulmonary congestion and hemorrhage) were noted at autopsy (HSE, 1981; ATSDR, 1996).

2.4.4.2 Repeated exposure

2.4.4.2.1 Inhalation

Most of the available studies in animals have addressed the effects of carbon disulfide on the nervous system. In general, the results of these studies provide neurophysiological, histopathological, neurochemical and behavioural support for the effects on the nervous system observed in workers exposed to carbon disulfide (Section 2.4.3.2.1).

In numerous studies, subchronic or chronic exposure of rats to carbon disulfide levels of between 800 and 2500 mg/m^3 has been associated with reductions in the nerve conduction velocity in the peripheral nerves or spinal cord (Seppäläinen and Linnoila, 1976; Knobloch *et al.*, 1979; Lukás, 1979; Maroni *et al.*, 1979; Colombi *et al.*, 1981; Gagnaire *et al.*, 19 86; Rebert and Becker, 1986; Herr *et al.*, 1998). In a number of these studies, this effect was accompanied in later stages by neurological impairment and atrophy of the hind limbs and was only partially reversible upon cessation of exposure. In rats exposed to carbon disulfide, hydrogen sulfide or both in approximate proportion to their concentrations in the workplace, reductions in peripheral nerve conduction velocity were observed only in those exposed to carbon disulfide, and there was no interaction between the compounds (Gagnaire *et al.*, 1986). These reductions in nerve conduction velocity have also been observed in the central nervous system and in the optic pathway, as indicated by increased latencies and decreased amplitudes of somatosensory-, visual-or brainstem auditory-evoked potentials in rats exposed to 2500 mg carbon disulfide/m^3 for periods of 11-15 weeks (Rebert and Becker, 1986; Hirata *et al.*, 1992a). In the latter study, there was also a transient increase in the latency of some components of the brainstem auditory-evoked potential at 625 mg/m^3 (Hirata *et al.*, 1992a). Bokina *et al.* (1976, 1979) observed deviations in visual-evoked potentials in rabbits exposed for 6 weeks to 0.2 or 2.0 mg/m^3, but these results cannot be critically evaluated, owing to limitations in their reporting. However, it is noted that this endpoint was affected

only at much higher levels (i.e., 2500 mg/m^3) in the (well-reported) study in rats by Rebert and Becker (1986).

The reductions in nerve conduction velocity observed in animal studies are accompanied by characteristic histopathological lesions in the axon. In a number of studies, rats exposed to between 800 and 2500 mg carbon disulfide/m^3 for between 3 and 15 months developed an axonopathy in the peripheral nerves and/or spinal cord (Juntunen *et al.*, 1974, 1977; Maroni *et al.*, 1979; Gottfried *et al.*, 1985; Opacka *et al.*, 1985, 1986; Valentine *et al.*, 1997; Sills *et al.*, 1998). The distal portions of the largest and longest myelinated axons (which are the most rapidly conducting axons) are affected first. Structural changes proceed through the development of large axonal swellings composed of disorganized masses of neurofilaments proximal to the nodes of Ranvier, followed by axonal atrophy and Wallerian-like degeneration proximal and distal to the swellings, respectively. These features are characteristic of giant neurofilament axonopathies induced by other compounds, such as 2,5-hexanedione, the neurotoxic metabolite of hexane (Graham *et al.*, 1995).

Neurobehavioural effects have been observed in a number of studies in rats. Neuromuscular effects, most notably reductions in grip strength and gait alterations, were observed following 2-4 weeks of exposure to 1600 and 2500 mg/m^3. Gait was also significantly affected after 13 weeks of exposure to 160 mg/m^3, although the test values were usually within the normal range (Moser *et al.*, 1998). Exposure to between 610 and roughly 800 mg/m^3 or greater inhibited avoidance behaviour in short-term studies (Goldberg *et al.*, 1964a, 1964b) and affected some measures of locomotor activity in chronic studies (Frantik, 1970; Opacka *et al.*, 1984). In those studies that included a recovery period, these neurobehavioural effects were reversible.

Short-term exposure of rats to relatively high levels of carbon disulfide (2000 mg/m^3) was associated with alterations in catecholamine levels in the brain and adrenals, most often increases in dopamine and its metabolites (Magos and Jarvis, 1970; Caroldi *et al.*, 1984, 1985). This appeared to be the combined result of increased synthesis and decreased conversion of dopamine.

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The sequence of neurotoxic effects of carbon disulfide was elucidated in a recent collaborative study at the U.S. National Institute for Environmental Health Sciences. In this study, in which rats were exposed to 160, 1600 or 2500 mg/m^3, 6 hours per day, 5 days per week, for up to 13 weeks, neurofilament protein cross-linking in the spinal cord was observed as early as 2-4 weeks at all exposure levels (Valentine *et al.*, 1997, 1998). (Chemical cross-linking of neurofilament proteins by a derivative of carbon disulfide is postulated to be the mechanism of its peripheral neurotoxicity [Section 2.4.5].) Other early indicators were increased expression of nerve growth factor receptor mRNA in the sciatic nerve (an indicator of alterations in the axon-Schwann cell relationship) (Toews *et al.*, 1998) and gait abnormalities (Moser *et al.*, 1998). By 4 weeks, the neuromotor alterations progressed to the point where there were reductions in grip strength of the hind limbs and forelimbs (Moser *et al.*, 1998). Axonal swelling and degeneration (Sills *et al.*, 1998) and electrophysiological alterations (Herr *et al.*, 1998) in the peripheral nerves and/or spinal cord occurred only in the later stages of the study and at the two highest dose levels.

The effect of carbon disulfide on lipid metabolism has been extensively studied. In several studies, exposure of rats to between 230 and 1700 mg/m^3 for periods of between 6 and 15 months resulted in significant increases in serum levels of cholesterol (and often phospholipids and triglycerides). This appears to have resulted from increased hepatic synthesis and, perhaps, reduced degradation of cholesterol to bile acids (Wronska-Nofer, 1972, 1973, 1977; Wronska-Nofer *et al.*, 1980). The content of total cholesterol and cholesterol esters in the aorta was significantly increased in rats and rabbits as a result of subchronic or chronic exposure to 1000 mg carbon disulfide/m^3 (Wronska-Nofer and Parke, 1978; Wronska-Nofer *et al.*, 1978, 1980), accompanied by increases in the rates of transfer and synthesis of cholesterol in the aorta wall in rats (Wronska-Nofer and Parke, 1978). Exposure to 1000 mg carbon disulfide/m^3 exacerbated the effect of an atherogenic diet on the levels of lipids in the serum, heart or walls of the coronary blood vessels (Wronska-Nofer *et al.*, 1978, 1980).

There is only limited evidence of other effects induced by inhalation of carbon disulfide. In the collaborative National Institute for Environmental Health Sciences study, subchronic exposure to 160-2500 mg/m^3 did not cause histopathological lesions in a range of organs (brain, heart, aorta, lung and female reproductive tract), with the exception of the peripheral nervous system and spinal cord (Sills *et al.*, 1998).

However, there are a number of reports in which elevated exposure to levels of several hundred mg/m^3

or greater affected renal histopathology in mice and rabbits or hepatic metabolism in rats and mice (ATSDR, 1996).

2.4.4.2.2 Oral

While it has often been assumed that the cardiovascular effects of carbon disulfide are secondary to its arteriosclerotic effects, the results of several studies in rats suggest that these may be the result of a direct effect on the heart. Short-term exposure of restrained and anesthetized rats to between 126 and 253 mg/kg-bw per day had a cardiodepressive effect on electrophysiological and mechanical parameters and decreased left ventricular contractility, increased blood pressure and caused electrocardiograph alterations indicative of myocardial ischemia following administration of epinephrine or norepinephrine (Hoffmann and Klapperstück, 1990; Hoffmann and Müller, 1990; Klapperstück *et al.*, 1991). However, in conscious unrestrained normotensive rats, the highest dose did not alter mean arterial blood pressure or heart rate, although it significantly reduced body weight (Hoffmann and Klapperstück, 1990).

Short-term administration of 300 mg carbon disulfide/kg-bw per day to mice was not hepatotoxic but reduced the hepatic microsomal cytochrome P-450 content and the activities of several associated monooxgenases (Masuda *et al.*, 1986).

While short-term exposure of mice to between 138 and 1102 mg/kg-bw per day altered thymus weight, it was not immunotoxic, as indicated by white blood cell differentials, spleen weight and natural killer cell activity (Keil *et al.*, 1996).

2.4.4.2.3 Carcinogenicity

No adequate cancer bioassays of carbon disulfide have been conducted. The data available are confined to a single screening study of lung tumour induction in mice (Adkins *et al.*, 1986). It is not possible to assess the carcinogenicity of carbon disulfide to animals based on this limited database.

2.4.4.2.4 Genotoxicity

The results of in vitro studies have provided little evidence that ca rbon disulfide i s genotoxic. In several studies in bacteria, carbon disulfide did not induce point mutations in Salmonella typhimurium or in Escherichia coli, both with and without metabolic activation (Hedenstedt *et al.*, 1979; Belisles *et al.*, 1980; Donner *et al.*, 1981; Haworth *et al.*, 1983). In studies of mammalian cells exposed to carbon disulfide in the presence of metabolic activation, there were small and/or equivocal increases in chromatid gaps in human lymphocytes (Garry *et al.*, 1990), in unscheduled DNA synthesis in diploid WI-38 cells derived from human embryonic lung tissue (Belisles *et al.*, 1980) and in sister chromatid exchanges in human lymphocytes (Garry *et al.*, 1990). In human sperm exposed to carbon disulfide in vitro, there was a significant increase in the frequency of chromosomal aberrations and in the frequency of chromosomal breaks (Le and Fu, 1996).

In male and female rats inhaling 63 or 125 mg carbon disulfide/m^3, 7 hours per day for 1 or 5 days, there was no significant increase in the frequency of chromosomal aberrations in bone marrow cells (Belisles *et al.*, 1980). In contrast, Vasil'eva (1982) reported that oral exposure to carbon disulfide induced chromosomal aberrations and polyploid cells in the bone marrow of female rats and in rat embryos exposed on days 10-13 of gestation. It is difficult to assess the validity of these findings, as the reporting was brief (e.g., the statistical significance was often not indicated) and the effective dose was not reported, except to indicate that it was one-tenth of the LD_{50}.

When male rats were exposed to 63-125 mg carbon disulfide/m^3, 7 hours per day for 5 days, there was no significant increase in dominant lethal mutations, nor was there a dose-related increase in sperm abnormalities in rats or mice exposed according to the same protocol (Belisles *et al.*, 1980), although lack of an effect on sperm abnormalities in positive control rats suggests that there was a problem with the test methods in this study.

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2.4.4.2.5 Effects on reproduction and development

In a small number of studies, exposure of male rats to 1875 mg/m^3 (but not to 1090 mg/m^3), 5 hours per day, 5 days per week, for several weeks affected copulatory behaviour, reducing times to mount

and ejaculate. There were no clear effects on sperm counts, circulating levels of reproductive hormones or testicular histology (Tepe and Zenick, 1984; Zenick *et al.*, 1984).

In the sole study of female reproduction identified (WIL Research Laboratories, Inc., 1992), there were no effects on estrous cycling, mating index or fertility index in rats exposed to up to 1560 mg carbon disulfide/m^3, 6 hours per day, before and during mating and throughout gestation. This dose adversely affected maternal weight and weight gain and increased pup mortality, decreased pup viability and decreased live litter size, but development of pups was otherwise unaffected. There were no effects at 780 mg/m^3, except for a small increase in the length of gestation (also at 1560 mg/m^3), which was within the range of historical controls.

The developmental toxicity of inhaled carbon disulfide in rats has been investigated in a number of studies. In an early series of investigations in rats by Tabacova and colleagues, inhalation of 100 or 200 mg/m^3 for several hours daily during gestation was reported to be fetotoxic and cause malformations, most often club foot and hydrocephalus (Tabacova *et al.*, 1978, 1983), while 10 mg/m^3 reduced postnatal survival, delayed the development of postnatal milestones and impaired motor coordination (Tabacova *et al.*, 1981). Behavioural effects, most often reduced exploratory activity in open field tests, were also reported at levels between 0.03 and 200 mg/m^3 (Hinkova and Tabacova, 1978; Tabacova *et al.*, 1978, 1981, 1983). Exposure over two generations appeared to result in greatly increased sensitivity to the teratogenic effects of carbon disulfide, causing malformations at as little as 0.03 mg/m^3 in the second generation, compared with 100 mg/m^3 in the first (Tabacova *et al.*, 1983). However, it is difficult to evaluate the validity of these findings. The studies are generally only briefly reported, and important information (e.g., concerning maternal toxicity) is often not provided. There is also some inconsistency in the findings; for example, Tabacova *et al.* (1981) reported that *in utero* exposure to as little as 0.03 mg/m^3 increased motor activity in open field tests, whereas it was impaired in their other studies. Moreover, the results of subsequent studies, most of which are better reported, have generally failed to confirm the teratogenic findings reported by Tabacova and colleagues, although it should be noted that some of the studies conducted by these investigators differed somewhat in their design (e.g., exposure over two generations). In utero exposure of rats to levels of 1250 or 2500 mg/m^3 did not induce a significant increase in the incidence of club foot, although it did cause maternal and fetal toxicity and minor skeletal anomalies (Saillenfait *et al.*, 1989). (There was no effect at 625 mg/m^3.) In another study (Belisles *et al.*, 1980; Hardin *et al.*, 1981), there was no evidence of embryo/fetotoxicity or of teratogenicity in rats exposed to levels (63 or 125 mg/m^3) similar to those that induced malformations in the studies by Tabacova *et al.* (1978, 1983). However, there is some weak support for the behavioural effects reported by Tabacova and colleagues (Hinkova and Tabacova, 1978; Tabacova *et al.*, 1978, 1981, 1983) from a small study by Lehotzky *et al.* (1985), in which the latency of a conditioned avoidance response was significantly lengthened by *in utero* exposure to concentrations of 10-2000 mg/m^3, although there was no clear dose-response.

In rabbits, inhalation of 1875 or 3750 mg carbon disulfide/m^3 during organogenesis decreased fetal body weight and increased post-implantation losses. Significant increases in visceral and skeletal malformations were also observed at the higher, maternally toxic, dose level (PAI, 1991). In another study, there was no evidence of embryo/fetotoxicity or teratogenicity in rabbits exposed to much lower concentrations (63 or 125 mg/m^3) prior to and during gestation (Belisles *et al.*, 1980; Hardin *et al.*, 1981). However, it is difficult to assess the validity of these results, owing to mortality among the dams from causes that were apparently unrelated to the chemical exposure.

There was no compound-related increase in malformations, and no clear evidence of embryo- or fetotoxicity, in rats exposed orally to maternally toxic doses of carbon disulfide (between 100 and 600 mg/kg-bw per day) during the period of organogenesis. Fetal body weights were decreased in rats exposed to 200 mg/kg-bw per day and more (Jones-Price *et al.*, 1984a). In contrast, in rabbits gavaged with 25, 75 or 150 mg/kg-bw per day in a similar study, carbon disulfide was embryo- and fetotoxic at all dose levels, although this was accompanied by maternal toxicity at the two highest doses. The highest dose also induced significant increases in the frequency of malformed fetuses (Jones-Price *et al.*, 1984b).

2.4.5 Toxicokinetics and mode of action

Carbon disulfide can be metabolized in the liver by the cytochrome P-450 monooxygenase system to an unstable oxygen intermediate that either spontaneously generates atomic sulfur, carbonyl sulfide and carbon dioxide or hydrolyzes to form atomic sulfur and monothiocarbonate, yielding carbonyl sulfide and carbon dioxide in breath and inorganic sulfates and organosulfur compounds in urine. Alternatively, dithiocarbamates are formed in humans and animals by reaction with amino acids; conjugation of carbon disulfide or carbonyl sulfide with endogenous glutathione forms TTCA and

2-oxythiazolidine-4-carboxylic acid, respectively, which are excreted in urine (ATSDR, 1996).

As reviewed by Graham *et al.* (1995), it has been postulated that the axonal degeneration that underlies the central-peripheral neuropathy caused by carbon disulfide is the result of the reaction of carbon disulfide and carbonyl sulfide with protein amino groups to yield initial adducts (dithiocarbamate derivatives). The adducts decompose to an electrophile (isothiocyanate and isocyanate, respectively), which in turn reacts with protein nucleophiles on the neurofilaments to cause protein cross-linking. (However, it is noted that, although the metabolites resulting from carbonyl sulfide have been identified, the production of protein cross-links via this pathway has not yet been demonstrated.) Progressive cross-linking of the neurofilament occurs during its transport along the axon, and covalently cross-linked masses of neurofilaments may occlude axonal transport at the nodes of Ranvier, ultimately resulting in axonal swelling and degeneration.

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