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PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Carbon Disulfide

Canada

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Environment Canada
Health Canada

May 2000

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List of Acronyms and Abbreviations

BMC	benchmark concentration
BMC_{05}	concentration associated with a 5% increase in the benchmark endpoint
BMCL	lower 95% confidence limit for the BMC
$BMCL_{05}$	lower 95% confidence limit for the BMC_{05}
BMR	benchmark risk level
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act,* 1999
CFC	chlorofluorocarbon
CI	confidence interval
CTV	Critical Toxicity Value
EC_{50}	median effective concentration
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HDL-C	high-density lipoprotein cholesterol
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDL-C	low-density lipoprotein cholesterol
LOAEL	Lowest-Observed-Adverse-Effect Level
mRNA	messenger ribonucleic acid
NOEL	No-Observed-Effect Level
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
RR	relative risk
RTECS	Registry of Toxic Effects of Chemical Substances
SMR	standardized mortality ratio
TC	Tolerable Concentration
TTCA	2-thiothiazolidine-4-carboxylic acid
VOC	volatile organic chemical

SYNOPSIS

Carbon disulfide is commercially produced in Canada, with annual production of about 3 kilotonnes. It is mainly used as a precursor in the manufacture of xanthates, which are used as flotation agents in mineral refinery processes. Releases into the environment from human activities occur primarily as a result of its production as a by-product in oil and gas processing in Canada. Additional industrial releases result from its use in the chemical industry and tire manufacturing. Virtually all anthropogenic and natural releases are to air. Carbon disulfide is also produced naturally by several types of soil, sediment and aquatic microorganisms, vegetation, forest and grass fires and volcanoes. Worldwide, at least 40% and possibly as much as 80% of releases are a result of natural or biogenic activity.

Carbon disulfide is ubiquitous throughout the environment. It has been detected in air, water, sediment and soil; however, it is found primarily in air. The highest concentrations of carbon disulfide in Canadian air have been measured near industrial sources, in particular near natural gas processing plants and sites with sulfur-containing natural gas flares. Carbon disulfide is removed from the air primarily by reaction with hydroxyl radicals, resulting in a half-life of 1–2 weeks. This half-life in air makes it a candidate for long-range transport; however, it is rapidly diluted to natural background levels. Carbon disulfide is rapidly metabolized by organisms and does not bioconcentrate or biomagnify.

As carbon disulfide is mainly released to and detected in air, this is a critical compartment in the assessment of risk to the environment. In situations where carbon disulfide-containing effluents are released to surface waters, biota in water may be exposed. Selected assessment endpoints are, therefore, terrestrial plants and animals and freshwater organisms. Carbon disulfide is of moderate to low toxicity to aquatic biota.

Based on concentrations measured in air and surface water in Canada and on the Estimated No-Effects Values derived from experimental data for terrestrial and aquatic biota, it is unlikely that organisms are exposed to harmful levels of carbon disulfide in the Canadian ambient environment.

Carbon disulfide is not likely to contribute significantly to depletion of stratospheric ozone, ground-level ozone formation or climate change.

Available data upon which to base estimates of human exposure to carbon disulfide in Canada are extremely limited; however, air appears to be the major route of exposure for members of the general population. Airborne exposures are estimated to be elevated for populations in the vicinity of industrial point sources in Canada. Based on the results of epidemiological studies of workers exposed to carbon disulfide and supporting data from experiments conducted on animals, the nervous system appears to be the critical target for carbon disulfide-induced toxicity, manifested most often as reduced conduction velocity in the peripheral nerves and impaired performance in psychomotor testing. Other effects for which there is considerable weight of evidence in humans exposed to carbon disulfide include alterations in serum lipids and blood pressure that are associated with increased risk of heart disease, damage to the blood vessels of the retina and (with higher exposures) increased mortality from heart disease. The estimated mean airborne exposure to carbon disulfide for the general population, and for populations in the vicinity of point sources, is considerably less than a Tolerable Concentration derived on the basis of a benchmark concentration for reduced peroneal

motor nerve conduction velocity in a population of viscose rayon workers exposed to carbon disulfide. A Tolerable Concentration is the level to which it is believed a person may be exposed daily over a lifetime without deleterious effect.

Based on the information available, it is concluded that carbon disulfide is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends, or that constitute or may constitute a danger in Canada to human life or health. Therefore, carbon disulfide is not considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

The evaluation of options under CEPA 1999 to reduce exposure is not considered to be a priority at this time. However, this is based on current use patterns; thus, future releases of this compound should continue to be monitored to ensure that exposure does not increase to any significant extent.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act,* 1999 (CEPA, 1999) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health in Canada. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as are defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing carbon disulfide provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Carbon disulfide is widely used in Canada to produce carbon tetrachloride, rayon, rubber chemicals and cellulose films. It has been used as a fungicide and fumigant. It has been found in a variety of industrial effluents — leather tanning, paint and ink, organics and plastics, pulp and paper. Chronic exposure to low levels of carbon disulfide has resulted in effects on the nervous system among workers and in animals. People living near sources of industrial emissions can be exposed to higher than background levels of the substance. An assessment is needed of the risk to the environment and public health from exposure to carbon disulfide.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. A document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0. March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Commercial Chemicals Evaluation Branch web site at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to assessment of potential effects on the environment (prior to May 1998) and human health (prior to August 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether carbon disulfide is "toxic" under CEPA have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

The environmental sections of this Assessment Report were prepared by D.S. Caldbick, Environment Canada. Sections of the Assessment Report and the supporting documentation (Environment Canada, 1999a) related to the environmental assessment of carbon disulfide were reviewed by the following members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

B. Dowsley, Ecological Services for Planning
L. Fu, Alberta Environmental Protection
J. Headley, National Hydrology Research Institute, Environment Canada
B. Scott, National Water Research Institute, Environment Canada

Environmental sections of the Assessment Report and supporting documentation (Environment Canada, 1999a) were also reviewed by external reviewers:

L. Brownlee, Environment Canada
K. Kaiser, National Water Research Institute, Environment Canada
E. Moran, Chemical Manufacturers Association, USA
C. Williams, CRW Consulting Inc.

Supporting sections and documentation of this Assessment Report related to human health were prepared by the following staff of Health Canada:

M.E. Meek
R. Newhook
M. Walker

Sections of the supporting documentation on genotoxicity were reviewed by D. Blakey of the Environmental and Occupational Toxicology Division of Health Canada.

In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by:

H. Drexler, Technical University at Aachen
S. Gabos, Alberta Health
D. Graham, Vanderbilt University Medical Center
R. Henrich, Akzo Nobel Chemicals Inc.
W. Valentine, Vanderbilt University Medical Center
M. Vanhoorne, State University of Ghent

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analyses were considered in written review by staff of the Information Department of BIBRA International and by H. Kappus, Humboldt University, as well as at a panel meeting of the following members, convened by Toxicology Excellence in Risk Assessment (TERA), on May 17, 1999, in Ottawa, Ontario:

R. Bornschein, University of Cincinnati
J. Christopher, California Environmental Protection Agency
H. Clewell III, ICF Kaiser International
M. Dourson, TERA
M. Prince, National Institute of Occupational Safety and Health
W. Valentine, Vanderbilt University Medical Center

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (October 23 to December 22, 1999) (Environment Canada and Health Canada, 1999b). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and their responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
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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.

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).

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.

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).

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 National 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

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

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).

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 2340×10^6 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 (2340×10^6 m^3 flared gas/year $\times$ 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 5×10^5 radicals/cm^3, a half-life of about 5.5–15 days is calculated from rate constants between 1.1×10^{-12} and 2.9×10^{-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 $Pa \cdot m^3/mol$ 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).

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 thioparus*. 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 $Pa \cdot m^3/mol$; 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 area 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 1.1×10^{-2} µg/m^3 in ambient air, 2×10^{-5} µg/L in water, 5×10^{-8} µg/g in soil, 4×10^{-7} µg/g in terrestrial plants and 3×10^{-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/m³)
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

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 µg/m³. The 24-hour average maximum ground-level concentration 10 km downwind was 14.3 µg/m³.

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 µg/m³ for a daily average and 0.16 µg/m³ 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 µg/m³, and hourly maximum concentrations were between 56 and 100 µg/m³ (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 µg/m³) that was not significantly higher than the mean level in six outdoor air samples (0.30 µg/m³) (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 between 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).

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 µg/m^3 for 6 hours) and no visual injury seen at the single measured concentration tested for this effect (1.0×10^7 µg/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/m³ (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 µg/m³ 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 µg/m³ 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 significance 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 Co-operation 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 EC_{50} 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} cm³/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm³/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).

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):

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

where:

- $t_{carbon\ disulfide}$ is the lifetime of carbon disulfide (10 days),
- t_{CFC-11} is the lifetime of CFC-11 (60 years),
- M_{CFC-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/cm^2 per atmosphere, default) and
- S_{CFC-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 neurotoxic exposures/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).

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 Tolonen, 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.

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).

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.

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; Lukáš, 1979; Maroni *et al.*, 1979; Colombi *et al.*, 1981; Gagnaire *et al.*, 1986; 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.

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 carbon disulfide is 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.

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.

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, nearly all carbon disulfide is released to air. Therefore, terrestrial organisms living near industrial sources are chosen as assessment endpoints, as these organisms are the most likely to have the highest potential for exposure and effects. Despite the fact that nearly all releases of carbon disulfide are to the atmosphere, there are releases to water. Since aquatic organisms close to discharge points could also be affected, they are also selected as assessment endpoints.

3.1.1.1 Terrestrial organisms

Toxicity test results are available for terrestrial plants, invertebrates and vertebrates, all of which can be exposed to carbon disulfide in the atmosphere. The most sensitive organism identified in these studies was the mouse, and effects data for this organism were used for the risk characterization for terrestrial organisms.

3.1.1.2 Aquatic organisms

Toxicity test results are available for algae, *Daphnia*, an amphibian and several fish species. The most sensitive organism identified in these tests was the invertebrate, *Daphnia magna*, and effects data for this species were used for the risk characterization for aquatic organisms. Aquatic invertebrates are key consumers in the aquatic food web and are themselves consumed by other species of invertebrates and by vertebrates.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial organisms

The hyperconservative EEV for terrestrial organisms is 156 µg/m^3, the maximum concentration measured in air over an 8-minute period, downwind from a gas plant.

The CTV for terrestrial organisms is 6.9×10^5 µg/m^3, the 1-hour LC_{50} for mice exposed to carbon disulfide via inhalation. Dividing this CTV by an application factor of 100 (to account for the conversion of an LC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 6.9×10^3 µg/m^3.

The hyperconservative quotient (EEV/ENEV), comparing a short-term (acute) exposure value with an estimate of long-term (chronic) effects, can be calculated as follows:

$$\text{Quotient} = \frac{156\ \mu g/m^3}{6.9 \times 10^3\ \mu g/m^3}$$

$$= 0.023$$

Since this hyperconservative quotient is less than 1, it is very unlikely that carbon disulfide causes adverse effects on populations of terrestrial organisms in Canada.

3.1.2.2 Aquatic organisms

The conservative EEV for aquatic biota is 3.9 µg/L (the maximum concentration of carbon disulfide measured in Lake Ontario in 1981). This value is believed to be conservative, because emissions of carbon disulfide to the environment have decreased significantly since the early 1980s. Although a higher exposure value (25 µg/L) was reported, this value was not chosen as the EEV, since it was associated with a chemical plant that is now closed and hence does not represent current concentrations in surface waters.

The CTV is 2.1×10^3 µg/L, the 48-hour LC_{50} for the most sensitive aquatic invertebrate, *Daphnia magna*. Dividing this CTV by a factor of 100 (to account for the conversion of an LC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions and a somewhat limited toxicity data set) (Environment Canada, 1997a) gives an ENEV of 21 µg/L.

The conservative quotient (EEV/ENEV) can be calculated as follows:

$$\text{Quotient} = \frac{3.9\ \mu g/L}{21\ \mu g/L}$$

$$= 0.19$$

Since this quotient is less than 1, it is unlikely that carbon disulfide causes adverse effects on populations of aquatic organisms in Canada.

A summary of the risk quotient derivations is provided in Table 4.

3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this assessment, the principal one being the lack of recent ambient concentration data in most Canadian media. The EEV for air, the principal environmental compartment of concern, was, however, based on monitoring data in areas where the largest Canadian releases occur. Furthermore, it represents a maximum value over a very short time period (8 minutes). It is very unlikely that environmental concentrations resulting from pulsed releases of carbon disulfide would be underestimated by this value. The EEV for air is furthermore supported by the modelling study of The (1998) and by monitoring data near other similar sources.

It should also be noted that since the substance was first proposed as a priority for assessment, the majority of Canadian industrial users of carbon disulfide have either ceased operation or improved emission controls. Consequently, the ambient concentrations of carbon disulfide in the various environmental compartments near such industrial sources in Canada would likely be lower than the values presented in the literature. In the case of surface waters, for example, the values obtained for carbon disulfide from the literature are at least 12 years old; as most releases from industrial sources have decreased since then, these older values likely represent a conservative exposure scenario for surface water.

Regarding effects of carbon disulfide on terrestrial and aquatic organisms, uncertainty surrounds the extrapolation from available acute toxicity data to prediction of long-term ecosystem effects. For wildlife, and especially small mammals, inhalation exposure in laboratory animals was used as a surrogate for actual exposure in the field. While the aquatic toxicity data set included studies on organisms from a variety of ecological niches and taxa, there are no chronic studies available for invertebrates

TABLE 4 Summary risk quotients for carbon disulfide for CEPA 1999 64(a)

Environmental Compartment	Estimated Exposure Value EEV	Critical Toxicity Value CTV	Application Factor AF	Estimated No-Effects Value ENEV	Conservative or Hyperconservative Risk Quotient (EEV/ENEV)
Terrestrial organisms	156 µg/m^3	1-hour LC_{50} 6.9×10^5 µg/m^3	100	6.9×10^3 µg/m^3	0.023
Aquatic organisms	3.9 µg/L	48-hour LC_{50} 2.1×10^3 µg/L	100	21 µg/L	0.19

or fish. To account for these uncertainties, conservative application factors were used in the environmental risk analysis to derive ENEVs.

Despite some data gaps regarding the environmental effects and exposure of carbon disulfide, the data available at this time are considered adequate to assess the environmental risk of carbon disulfide in Canada.

3.2 CEPA 1999 64(b): Environment on which life depends

The calculations shown in Section 2.4.2 imply that carbon disulfide is not likely to contribute significantly to climate change or the depletion of stratospheric ozone, but it does have the potential to contribute somewhat to ground-level ozone formation. The magnitude of this effect would depend upon the concentration of carbon disulfide in the atmosphere, and the concentration of carbon disulfide in Canadian air is very low relative to the concentrations of volatile organic compounds that are responsible for ozone formation. Consequently, the contribution of carbon disulfide to ground-level ozone formation is not expected to be significant. Based on the above, the atmospheric effects of carbon disulfide are not expected to be significant. It is proposed at this time that carbon disulfide not be considered "toxic" as defined under CEPA 1999 Paragraph 64(b).

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Data on levels of carbon disulfide in environmental media to serve as the basis for development of estimates of population exposure in Canada are limited to a small number of surveys of ambient air conducted at few locations in Canada or in the United States and limited Canadian surveys in drinking water and soil in which carbon disulfide was seldom detected. Meaningful probabilistic exposure assessment is precluded, therefore. In this section, mean deterministic estimates of environmental intake from air, water and soil by members of the general population of Canada have been derived. These are followed by consideration of mean estimates of potential airborne exposures by populations in the vicinity of point sources in Canada, based on the very limited available data.

Point estimates of total daily intake of carbon disulfide by six age groups of the general population of Canada were developed (Table 5), primarily to determine the relative contributions from various media. These estimates indicate that intake from environmental exposure to carbon disulfide is virtually all from inhalation. That air is the principal route of exposure is supported by the results of the EQC and ChemCAN4 fugacity modelling, which indicate that virtually all of the carbon disulfide released to air (industrial releases in Canada are almost entirely to air) will tend to

TABLE 5 Estimated mean intakes of carbon disulfide for the general population of Canada

	Mean intake of carbon disulfide (µg/kg-bw per day)					
	0–0.5 years[1]	**0.5–4 years[2]**	**5–11 years[3]**	**12–19 years[4]**	**20–59 years[5]**	**60+ years[6]**
Outdoor air[7]	0.01	0.02	0.02	0.01	0.01	0.01
Indoor air[8]	0.15	0.33	0.26	0.15	0.13	0.11
Drinking water[9]	0.007	0.003	0.002	0.001	0.001	0.001
Soil[10]	1×10^{-7}	2×10^{-7}	7×10^{-8}	2×10^{-8}	1×10^{-8}	1×10^{-8}
Total intake (not food or cigarettes)	0.17	0.36	0.28	0.16	0.14	0.12
Intake by cigarette smokers[11]	—	—	—	0.67	0.57	0.57

[1] Assumed to weigh 7.5 kg, breathe 2.1 m^3 of air per day, drink 0.8 L of water used in the preparation of powdered infant formula per day and ingest 30 mg of soil per day (EHD, 1998).

[2] Assumed to weigh 15.5 kg, breathe 9.3 m^3 of air per day, drink 0.7 L of water per day and ingest 100 mg of soil per day (EHD, 1998).

[3] Assumed to weigh 31.0 kg, breathe 14.5 m^3 of air per day, drink 1.1 L of water per day and ingest 65 mg of soil per day (EHD, 1998).

[4] Assumed to weigh 59.4 kg, breathe 15.8 m^3 of air per day, drink 1.2 L of water per day and ingest 30 mg of soil per day (EHD, 1998).

[5] Assumed to weigh 70.9 kg, breathe 16.2 m^3 of air per day, drink 1.5 L of water per day and ingest 30 mg of soil per day (EHD, 1998).

[6] Assumed to weigh 72.0 kg, breathe 14.3 m^3 of air per day, drink 1.6 L of water per day and ingest 30 mg of soil per day (EHD, 1998).

[7] Based on the mean concentration of carbon disulfide in ambient (outdoor) air (0.30 µg/m^3) at six randomly selected sites in New York, N.Y. (Phillips, 1992; Section 2.3.2.2), assuming three of 24 hours are spent outdoors daily (EHD, 1998).

[8] Based on the mean concentration of carbon disulfide in nine samples of indoor air (0.63 µg/m^3) from a hospital office room in New York, N.Y. (Phillips, 1992; Section 2.3.2.2), assuming that 21 of 24 hours are spent indoors daily (EHD, 1998).

[9] Based on the average concentration of carbon disulfide over three seasons (0.065 µg/L) reported in treated drinking water samples from a 1982–1983 survey of 10 Ontario municipalities (<0.1 µg/L) (Otson, 1987, 1996). In calculating the mean, a value of one-half the detection limit (0.05 µg/L) was assigned to samples that did not contain detectable levels of carbon disulfide.

[10] Based on analysis of a limited number of samples of urban soils removed from point sources in a 1985–1986 survey conducted in Port Credit and in Oakville/Burlington, in which carbon disulfide was detected at one of five sites in Port Credit at 0.000 11 µg/g (Golder Associates, 1987). In calculating the mean, a value of one-half the detection limit (0.000 015 µg/g) was assigned to samples that did not contain detectable levels of carbon disulfide.

[11] Based on the approximate content of carbon disulfide in mainstream smoke from cigarettes reported by Horton and Guerin (1974) (2 µg/cigarette) and consumption of 20 cigarettes per day, the approximate number smoked by regular Canadian smokers aged 15 years or older as of 1995 (Kaiserman, 1997).

remain in that compartment. (However, it is noted that the atmospheric concentrations predicted by the ChemCAN4 fugacity modelling are an order of magnitude or more lower than those measured in ambient air in a number of studies throughout the world. This may reflect the combined contribution of natural sources, local anthropogenic sources and advective inputs from outside of the region to the levels measured.) Exposure from ingestion of drinking water and soil appears to be negligible in comparison with that from air. Based on the absence of registered

uses for carbon disulfide on food and the results of the fugacity modelling for southern Alberta, which predicted that very low levels of the compound ($<1 \times 10^{-6}$ µg/g) will accumulate in biota (Section 2.3.1.6), it was assumed that exposure via food will be negligible. For smokers, it is estimated that cigarette smoking can increase the intake of carbon disulfide severalfold.

It is also known that concentrations of carbon disulfide in ambient air are elevated in the vicinity of some point sources in Canada (Section 2.3.2.1). Based on the range of mean concentrations measured in the vicinity of natural gas processing (1.40 µg/m^3 — Legge *et al.*, 1990b) and xanthate production facilities (3–6 µg/m^3 — Fu, 1997; Weiss, 1998) in Canada, average exposures by inhalation near such facilities may be increased between two- and 10-fold over those for the general population.

3.3.2 Hazard characterization

The data most relevant to hazard characterization are those from epidemiological studies of populations exposed to carbon disulfide in the workplace. In this section, the available data for those effects that are potentially critical (i.e., effects on the nervous and cardiovascular systems) are evaluated in the context of the traditional criteria for causality for epidemiological studies. (While the epidemiological data regarding the association between exposure to carbon disulfide and damage to the retinal capillaries [Section 2.4.3.2.4] would satisfy some of the criteria for causality, such effects are considered to be of uncertain clinical significance. The weight of evidence for the remaining categories of effects discussed in Sections 2.4.3.2 and 2.4.4.2, including carcinogenicity, genotoxicity and reproductive, developmental and other systemic or organ system effects, is considered inadequate.)

Effects on the nervous system, including neurophysiological, behavioural and pathological effects, were reported in a large number of cross-sectional studies of viscose rayon workers (Section 2.4.3.2.1). The most common findings were reduced conduction velocity in the motor and sensory nerves, generally most pronounced in the more distal portions of the nervous system (e.g., in the lower limbs). There are also a small number of reports of impaired performance on neuropsychological testing, most often on psychomotor tests of motor speed or dexterity, in workers exposed to relatively high levels of carbon disulfide. Hence, there is evidence of both consistency and specificity for these effects on the nervous system.

In most instances when subgroups of the study populations were analysed separately, the reductions in nerve conduction velocities were most pronounced in those workers with exposure to the highest concentrations, those employed in tasks that were considered to entail the highest exposures or those with the greatest cumulative exposures (Gilioli *et al.*, 1978; Johnson *et al.*, 1983; Chu *et al.*, 1995; Vanhoorne *et al.*, 1995). Considering the most reliable studies as a whole, there was an apparent gradient in response across studies, with reductions in the nerve conduction velocities of a wider range of nerves, including those in the upper limbs, observed in the most highly exposed populations, compared with effects only on the lower limbs in populations with exposure to moderate or low concentrations, and no significant effects on conduction velocities in the least exposed populations (Seppäläinen and Tolonen, 1974; Cirla and Graziano, 1981; Johnson *et al.*, 1983; Sandrini *et al.*, 1983; Vanhoorne *et al.*, 1995; Hirata *et al.*, 1996; Reinhardt *et al.*, 1997a). In addition, effects on peripheral nerve conduction velocity were generally observed at lower levels than were other effects on the nervous system, particularly the psychomotor effects, both within and between studies (Cassitto *et al.*, 1978; Hänninen *et al.*, 1978; Cirla and Graziano, 1981; Johnson *et al.*, 1983; Putz-Anderson *et al.*, 1983; Vanhoorne *et al.*, 1995; Reinhardt *et al.*, 1997a, 1997b; De Fruyt *et al.*, 1998). Hence, there is evidence of a dose–response relationship for effects on peripheral nerve conduction velocity and other parts of the nervous system, both within and across studies. With respect to temporality,

results are conflicting; although there is little information, reductions in nerve conduction velocity in workers who were removed from exposure for a number of years were less pronounced (often non-significant) than in workers who were currently exposed in some studies (Hirata *et al.*, 1996), but not in others (Seppäläinen and Tolonen, 1974; Sandrini *et al.*, 1983). However, the lack of temporality is not unexpected in light of the limited capacity of the peripheral nervous system to regenerate.

The effects reported on the peripheral nervous system are supported by the results of studies of animals exposed subchronically or chronically by inhalation, in which nerve conduction velocity in the peripheral nerves or spinal cord was consistently reduced, accompanied by histopathological lesions and biochemical changes similar to those induced by certain other compounds that cause axonopathy (e.g., 2,5-hexanedione, the neurotoxic metabolite of hexane) (Section 2.4.4.2.1). Similar histopathological alterations, accompanied by clinical and neurophysiological signs of peripheral neuropathy, were also reported in a worker exposed to relatively high levels of carbon disulfide (Chu *et al.*, 1996). In several studies in rats, exposure to carbon disulfide also affected performance in neurobehavioural testing or altered levels of catecholamines in the brain or adrenals (Section 2.4.4.2.1). (Although impaired performance in certain behavioural tests was evident in animals at earlier time points and at lower levels than histopathological or neurophysiological effects, in contrast to the results of epidemiological studies, the changes observed [i.e., ataxia, leg splay, decreased hind limb grip strength, etc.] are consistent with dysfunction of the distal segments of motor neurons.) While the exact mechanism of action is not yet known, there is considerable evidence that the axonal degeneration that underlies the neuropathy may be the result of covalently cross-linked masses of neurofilaments occluding axonal transport at the nodes of Ranvier (Section 2.4.5).

Excess mortality from coronary heart disease has been observed in a number of cohorts of viscose rayon workers exposed to carbon disulfide. While there was inadequate account taken of factors known to affect heart disease (e.g., smoking) in most of these studies, there were consistent excesses in all of the more powerful investigations (Hernberg *et al.*, 1970; Mancuso *et al.*, 1981; Sweetnam *et al.*, 1987; MacMahon and Monson, 1988; Swaen *et al.*, 1994; Peplonska *et al.*, 1996). The strength of the association was moderate to high, with relative risks ranging from 1.1 to 4.8. There was evidence of a dose–response relationship in most of the studies in which it was examined, although exposure was not well characterized in any of the investigations, and this was based principally on rather crude measures — i.e., often restricted to those workers with a long duration of exposure or those in the most highly exposed jobs (Mancuso, 1981; Sweetnam *et al.*, 1987; MacMahon and Monson, 1988; Swaen *et al.*, 1994). The excesses were generally much less pronounced following elimination or reduction of exposure (e.g., by retirement or transfer to jobs that entailed less exposure) (Hernberg and Tolonen, 1981; Sweetnam *et al.*, 1987), thereby satisfying the criterion of temporality.

The results of cross-sectional studies of cardiovascular morbidity or of clinical measures known to be related to risk from heart disease are generally consistent with the reported excesses of mortality from coronary heart disease. In a number of cross-sectional studies, occupational exposure to carbon disulfide was associated with clinical changes that increase the risk of heart disease, including increases in blood pressure and in serum levels of total cholesterol and LDL-C and with decreases in serum levels of HDL-C. (Potential confounders, such as age and smoking, were accounted for in most of these studies.) In those studies where internal comparisons were made, these effects were related to the extent of exposure (i.e., associated with exposure level, or restricted primarily to subpopulations with the longest duration of exposure) (Egeland *et al.*, 1992; Vanhoorne *et al.*, 1992; Stanosz *et al.*, 1994a). However, while these effects were fairly consistently absent in less exposed populations and present in moderately or heavily exposed

populations, the available data are not entirely consistent in this regard. For example, increases in total cholesterol were observed in some studies (Wronska-Nofer and Laurman, 1987; Vanhoorne *et al.*, 1992), but not in others with similar exposure levels (Hernberg *et al.*, 1971). Similarly, decreases in HDL-C were not observed in the high-exposure group studied by Egeland *et al.* (1992) but were present in a similarly exposed population of Polish workers (Stanosz *et al.*, 1994a). In the German workers studied by Drexler *et al.* (1995, 1996), cumulative exposure was inversely related to systolic blood pressure (i.e., the opposite direction to that observed in other studies) and to HDL-C levels (not affected in other populations with exposure to such low levels — i.e., median 13 mg/m^3). There have been some reports of increases in overt manifestations of coronary heart disease, such as angina and coronary electrocardiograph, in workers exposed to carbon disulfide; in the available studies, however, there was often no precise information on the extent of exposure, and the increases were often non-significant and/or based on small numbers of cases.

Thus, exposure of occupational populations to carbon disulfide has been associated with increased risks for coronary heart disease at a number of levels of manifestation, including mortality, morbidity and risk factors, providing a coherent picture. There is little information relevant to temporality for effects other than mortality, although Toyama and Sakurai (1967) observed that an initial significant difference in total serum cholesterol in Japanese viscose rayon workers disappeared in a second survey, conducted after airborne concentrations had been reduced severalfold. The biological plausibility of these findings is supported by the results of studies in animals, in which chronic exposure of rats to high levels of airborne carbon disulfide consistently altered lipid metabolism, resulting in increased serum levels of cholesterol and other blood lipids and exacerbating the atherogenic effects of a lipid-rich diet (Section 2.4.4.2.1). Hence, the traditional criteria for causality for associations observed in epidemiological studies are fulfilled, at least in part, for cardiovascular effects associated with exposure to carbon disulfide.

The weight of evidence for effects on the nervous system, which meets most of the traditional criteria for causality in epidemiological studies (including consistency, specificity, dose–response relationship, coherence and biological plausibility), is clearly the strongest from among the various types of effects observed in epidemiological studies that might have been considered critical. (Further, while the effects on the nervous system do not appear to meet the criterion of temporality, this is expected, given the limited capability of the nervous system for regeneration.) While the weight of evidence for effects on the cardiovascular system meets several of the criteria for causality, there are several inconsistencies in the dose–response across studies, and potential modes of action have not been as well elucidated as for the reductions in peripheral nerve conduction velocity. Further, there is a high background prevalence of heart disease, and it is affected by a number of other factors, with the result that the dose–response curve is shallow and variable, limiting the ability to detect a compound-related effect more than is the case for a specific effect such as nerve conduction velocity. Effects on the peripheral nerve conduction velocity have also been fairly consistently observed at concentrations that are lower than those at which other effects were observed, and, as noted in the next section, this effect also yields a lower benchmark concentration (BMC) than for cardiovascular risk factors.

While the populations of viscose rayon workers in which effects on the nervous system were observed had concomitant exposure to carbon disulfide and hydrogen sulfide, the available evidence indicates that the effects on peripheral nerve conduction velocity were due to carbon disulfide alone. In these studies, concentrations of hydrogen sulfide were typically much less than concentrations of carbon disulfide. In addition, the results of a large number of

studies in animals have confirmed that carbon disulfide reduces peripheral nerve conduction velocity and have documented the associated histopathological and ultrastructural changes in the axons of the peripheral nerves (Section 2.4.4.2.1). In one study, motor tail nerve conduction velocity in rats was reduced by exposure to carbon disulfide but was not affected by hydrogen sulfide alone, nor did hydrogen sulfide modify the effect of carbon disulfide in combined exposures (Gagnaire *et al.*, 1986). Subchronic exposure of Sprague-Dawley rats to up to 114 mg hydrogen sulfide/m^3 (a concentration that reduced body weights) did not affect neuropathology in routine histopathological examination or in examination of teased fibres from the muscular and sural branches of the tibial nerve (CIIT, 1983).

3.3.3 Exposure–response analyses

Concentrations of carbon disulfide in the viscose rayon industry are known to have declined substantially over the several decades encompassed by the available epidemiological studies (Price *et al.*, 1997), and the results of the epidemiological studies suggest that some effects on the nervous system (e.g., reductions in peripheral nerve conduction velocity) are not completely reversible. In addition, it is clear that exposures vary considerably between sites at a given workplace and between job titles (Vanhoorne and Grosjean, 1985). Consequently, the studies that are most relevant to characterization of exposure–response are those in which exposures and/or processes were reported to have remained the same for many years and those in which personal monitoring data were collected.

Based principally on the results of studies that meet these criteria, effects on the nervous system that occurred at the lowest concentrations in humans were reductions in conduction velocity in the peripheral motor or sensory nerves, which were observed in several studies of viscose rayon workers with long-term exposure to carbon disulfide. There is also fairly consistent evidence of effects on the results of neurobehavioural testing in such populations, but such effects have not been observed at levels as low as those associated with alterations in peripheral nerve conduction velocity, and the exposure–response has been less well characterized.

It is not possible at present to identify a quantitative relationship between a given decrease in nerve conduction velocity and an expected degree of loss of function. However, it is noted that nerve conduction velocity is a relatively crude indicator of effects of carbon disulfide on the nerves, because function is not impaired until axonal degeneration has actually occurred, in contrast to agents that produce demyelination or have a direct effect on conduction. An additional concern is that, although the effect is measured in the peripheral nervous system, because carbon disulfide produces a central-peripheral distal axonopathy, it is likely that the long axons of the central nervous system are also affected. Further, there is only limited capability for regeneration in the peripheral nervous system, and even less in the central nervous system. In short, while reduced nerve conduction velocity by itself may not produce an adverse health outcome, it is indicative of, and a precursor of, other changes that clearly are adverse; given the limited reversibility of this effect, a precautionary approach is warranted. Consequently, the critical effect for the characterization of exposure–response is defined as a statistically significant, compound-related decrease in peripheral nerve conduction velocity.

The lowest levels associated with the reductions in peripheral nerve conduction velocity in exposed humans are very similar among the key studies, ranging from 13 to <31 mg/m^3 (Johnson *et al.*, 1983; Vanhoorne *et al.*, 1995; Hirata *et al.*, 1996; Reinhardt *et al.*, 1997a). Those levels without significant effect in the key studies are also very similar, ranging from <10 to 13 mg/m^3 (Cirla and Graziano, 1981; Johnson *et al.*, 1983); in both studies, however, there were reductions in nerve conduction velocity, albeit not statistically significant, in the peroneal and/or sural nerves even at these concentrations.

However, in only one of the available epidemiological studies in which there was an association between exposure to carbon disulfide and reductions in peripheral nerve conduction velocity was the exposure of the study population adequately characterized to permit quantitative exposure–response analyses — i.e., in the study reported by Johnson *et al.* (1983). In the remaining key studies, the analysis was limited to a comparison of exposed versus control workers (Hirata *et al.*, 1996; Reinhardt *et al.*, 1997a), or, when subgroup analyses were presented, these were limited to broad categories with respect to exposure (Vanhoorne *et al.*, 1995). In addition, the design of the study by Johnson *et al.* (1983) was among the strongest of the available studies — it was conducted on a sizable population, for which a range of exposure levels were well characterized using personal sampling and for which exposures had been stable for more than 20 years; the analyses controlled for a number of potential confounders; and the study also included examination of other manifestations of effects on the nervous system, including peripheral nervous system symptoms and neurobehavioural testing.

Based on the results of the study by Johnson *et al.* (1983), a BMC for the association between exposure to carbon disulfide and effects on peripheral nerve conduction has been calculated as a measure of exposure–response.

All of the response variables in the data were of a continuous nature, thus complicating the BMC calculation. With continuous data, there is not usually a clear distinction between normal and adverse responses. Crump (1995) suggested a method for developing BMCs in such cases. This method involves directly defining an abnormal response by specifying a cut-off within the unexposed population that separates continuous responses into normal and abnormal categories. In other words, responses that are observed to be more extreme than the cut-off are considered abnormal. This effectively reduces the continuous endpoint to a quantal endpoint. The BMC is then chosen as the concentration at which the risk of an abnormal response is increased by a specified quantity. The mean observed response may then be modelled as a function of other confounding factors (such as age, weight and height). This method of computing BMCs was applied to the data from the study of workers exposed to carbon disulfide by Johnson *et al.* (1983).

The original study data[1] from the population studied by Johnson *et al.* (1983) were used to calculate the BMC. The data file contained measurements on 165 exposed and 245 unexposed workers. The measurements consisted of indicators (i.e., response variables) relating to ischemic heart disease and the peripheral nervous system as well as potential confounding information.[2] Exposures were represented as either current job exposures to carbon disulfide in parts per million (ppm), cumulative exposure in ppm-months or average exposure (ppm), defined as a worker's cumulative exposure divided by the duration of exposure.

Following Johnson *et al.* (1983) and Price *et al.* (1996), workers were eliminated from the nervous system analysis if they were diabetic, showed excessive alcohol consumption (≥35 units) or had high blood lead levels (≥40 µg/dL). These conditions can cause peripheral neuropathy and therefore potentially mask an exposure effect. Following Egeland *et al.* (1992), workers were eliminated from the blood pressure analysis if they used antihypertensive drugs, from the fasting glucose analysis if they

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[1] The cooperation of the Chemical Manufacturers Association in the provision of these data is gratefully acknowledged.

[2] For ischemic heart disease: total serum cholesterol, LDL-C, HDL-C, triglyceride, fasting glucose, systolic and diastolic blood pressure. For peripheral nerve conduction: maximal motor conduction velocity, distal latency and amplitude ratio of the ulnar and peroneal nerves, and sensory conduction velocity, distal latency and discrete amplitude ratio of the sural nerve. For confounders: age, height, weight, race, body mass index, education, current smoking status, current alcohol consumption, blood lead level, hemoglobin concentration, pulse rate and diabetes.

used hypoglycemic drugs and from the lipoprotein analysis if they used corticosteroids or lipid-lowering or thyroid medications.

Stepwise regression was performed to determine which confounding variables (including the three exposure measures — current, cumulative and average) could be used to explain the response variables. For those responses showing a significant relationship with exposure, BMCs were calculated using the following procedure.

First, the regression was obtained of exposure and all other significant confounders on the response:

$$\gamma = \underline{\beta}' \underline{x} + \gamma d \qquad (1)$$

where γ is the response, d is exposure, $\underline{x}$ is a vector of confounding variables and $\underline{\beta}$ and γ are parameters estimated in the regression. For the purpose at hand, the response y is thought of as the mean response as a function of exposure. That is, $y = \mu(d)$.

Next, the responses were discretized following the method of Crump (1995), modified to use excess risk rather than additional risk. In this method, it is assumed that a proportion, P_0, of the control group will be abnormal. This proportion is chosen to be small (e.g., 5% or 1%) so that most unexposed individuals will not be abnormal. This is equivalent to choosing a cut-off level x_0, above which a response in the control group would be considered abnormal. The probability of a response in the unexposed population being abnormal is given by

$$P(0) = P\left\{x > x_0 \,\middle|\, x \sim N(\mu(0),\sigma)\right\} = 1 - \Phi\left\{\frac{x_0 - \mu(0)}{\sigma}\right\} = P_0 \qquad (2)$$

where Φ is the normal cumulative density function (i.e., $\Phi(z)$ is the probability that a standard normal variable is *less* than z), μ is the mean response as a function of exposure and σ is the standard deviation, assumed to be constant for all exposures. As a consequence, equation 2 says that, knowing x_0, P_0 can be calculated from normal tables, and vice versa. For this analysis, P_0 is specified as either 1% or 5%. Given P_0 (and hence x_0), the probability of a response being abnormal at dose d is given by

$$P(d) = P\left\{x > x_0 \,\middle|\, x \sim N(\mu(d),\sigma)\right\} = 1 - \Phi\left\{\frac{x_0 - \mu(d)}{\sigma}\right\} \qquad (3)$$

The BMC is computed by setting the excess risk equal to BMR, the specific benchmark risk level; that is,

$$\frac{P(\mathrm{BMC}) - P(0)}{1 - P(0)} = \mathrm{BMR} \qquad (4)$$

By solving equation 2 for x_0, substituting into equation 3 and then substituting equations 2 and 3 into 4, it can be shown that solving equation 4 for BMC is equivalent to solving

$$\mu(\mathrm{BMC}) - \mu(0) = M \cdot \sigma \qquad (5)$$

for BMC, with

$$M = \Phi^{-1}(1 - P_0) - \Phi^{-1}(1 - P_0 - (1 - P_0) \cdot \mathrm{BMR})$$

and μ defined by equation 1. This effectively reduces the continuous endpoint to a quantal endpoint; the BMC_{05} is chosen as the concentration at which the excess risk of an abnormal response is 5%.

Note that this argument assumes that larger responses are adverse. Blood pressure is an example of a case where a larger response is adverse, since higher blood pressure levels are associated with an increased risk of heart disease. If smaller responses are more severe, such as with nerve conduction velocities, where slower velocities are detrimental, a similar argument would hold and equation 5 would be identical, except that M would be replaced by $-M$.

The BMC was calculated by substituting equation 1 into 5, with $y = \mu(d)$ and solving for BMC. The $\underline{\beta}' \underline{x}$ terms cancel, and the BMC is given by

$$\text{BMC} = \frac{-M \cdot \sigma}{\gamma} \qquad (6)$$

Finally, BMCL, the lower bound on the BMC, was obtained using a standard formula in linear regression for the lower bound on an inverse prediction (i.e., when the response is known and the exposure is estimated by equation 6). This formula can be found in, for example, Neter *et al.* (1989). BMCs computed on the basis of cumulative exposures were converted to a daily exposure in ppm by dividing by 12.2 years, which is the average exposure duration of exposed workers in the cohort.

The stepwise regression indicated that, of the nervous system outcomes, maximum motor conduction velocity for the peroneal nerve and sensory conduction velocity for the sural nerve were significantly related to all three exposure measures. If given the choice, the stepwise model would choose average exposure for peroneal motor nerve conduction velocity and cumulative exposure for sural sensory nerve conduction velocity. Average exposure was chosen to model both outcomes, however, since the model including cumulative exposure fit the sural sensory nerve conduction velocity data nearly as well (r^2 of 0.166 versus r^2 of 0.158 for average exposure), and since using average exposure gives a more accurate estimate of ambient exposure for each worker (i.e., the cumulative exposure was divided by employment duration for each worker, as opposed to dividing the final BMC by the average employment duration for the entire exposed cohort). Sural distal latency was significantly related to current exposure; when one large outlier was removed (a value of 39.1, whereas the median sural distal latency for the cohort was 4.2), however, the relationship with exposure was no longer significant. As a result, sural distal latency was not utilized for BMC calculation. Among the risk factors for heart disease, LDL-C was significantly related to current exposure.

The variables selected for inclusion in the linear regression models by the stepwise procedure were age, height, race and average exposure for the maximum motor conduction velocity of the peroneal nerve; age, height, weight and average exposure for the sensory conduction velocity of the sural nerve; and age, current exposure, weight and height for LDL-C. For each of peroneal motor nerve conduction velocity, sural sensory nerve conduction velocity and LDL-C, the corresponding contributing variables were input into the linear regression in equation 1, and the resulting parameter estimates were obtained.

BMC_{05}s were calculated by applying equation 6 with *M* equal to either 0.77 for a 1% adverse response rate or 0.35 for a 5% adverse response rate, σ equal to the standard error and γ equal to the regression coefficient for exposure. The resulting values are presented in Table 6. For an abnormal response based on the 5th percentile of the control population (i.e., a 5% adverse response), the $BMCL_{05}$s (the lower 95% confidence limits for the BMC_{05}s) were 6.3 ppm (20 mg/m^3) for peroneal motor nerve conduction velocity and 9.9 ppm (31 mg/m^3) for sural sensory nerve conduction velocity. (While serum LDL-C was also significantly associated with exposure to carbon disulfide, it is noted that the weight of evidence for cardiovascular effects is not as great as for effects on the nervous system, and the BMC calculated for this endpoint was greater than those for the peroneal motor nerve conduction velocity, in any case [Table 6].) The BMC_{05} point estimates are quite similar to the lower bounds. The BMC_{05}s and $BMCL_{05}$s estimated for a 1% adverse response are approximately twofold higher than those for a 5% adverse response.

Based on the $BMCL_{05}$ estimated for a 5% adverse response for the most sensitive response variable — i.e., peroneal motor nerve conduction

TABLE 6 Final BMC_{05}s and $BMCL_{05}$s for selected outcome variables

Outcome	1% adverse response		5% adverse response	
	BMC_{05} (ppm)	**$BMCL_{05}$ (ppm)**	**BMC_{05} (ppm)**	**$BMCL_{05}$ (ppm)**
Peroneal motor nerve conduction velocity	16.3	14.9	7.6	6.3
Sural sensory nerve conduction velocity	25.9	23.7	12.1	9.9
Low-density lipoprotein cholesterol	20.9	19.2	9.8	8.1

velocity[3] at 6.3 ppm (20 mg/m^3) — a Tolerable Concentration (TC) has been derived as follows:

$$TC = \frac{20\ mg/m^3 \times 8/24 \times 5/7}{50}$$

$$= 0.10\ mg/m^3$$

$$= 100\ \mu g/m^3$$

where:

- 20 mg/m^3 is the $BMCL_{05}$ estimated for a 5% adverse response for peroneal motor nerve conduction velocity based on the original data from the cross-sectional study of U.S. viscose rayon workers with long-term exposure to carbon disulfide reported by Johnson *et al.* (1983)
- 8/24 and 5/7 are the factors to convert exposure during 8 hours per work day and 5 days per work week, respectively, to continuous exposure
- 50 is the uncertainty factor (×10 for intraspecies [interindividual] variation[4]; ×5 to account for potential for effects on neurobehavioural development, since limited available data, although inadequate to serve as a basis for developing a TC, indicate that the developing offspring may be more sensitive to the neurological effects of carbon disulfide). While neurobehavioural endpoints in animals were consistently affected by lower concentrations of carbon disulfide in developing offspring (Hinkova and Tabacova, 1978; Tabacova *et al.*, 1981, 1983; Lehotzky *et al.*, 1985) than in adults (Goldberg *et al.*, 1964a, 1964b; Frantik, 1970; Opacka *et al.*, 1984; Moser *et al.*, 1998), limitations in the available data preclude the development of a data-derived uncertainty factor to account for this difference, as a consequence of such factors as the variety of endpoints examined, inadequate dose spacing and inadequate reporting of some of the studies. This source of uncertainty is discussed further in Section 3.3.5. An additional uncertainty factor to account for less than lifetime exposure was not considered necessary, in light of the long duration of exposure for the population on which the TC is based (mean of 12.2 years),

[3] A TC calculated on the basis of the No-Observed-Effect Level (NOEL) of 13 mg/m^3 from the same study would be quite similar.

[4] Available quantitative data are insufficient to replace default values for the components of this uncertainty factor with data-derived values (see IPCS, 1994). For example, knowledge regarding the respective contributions of the parent compound and oxidative metabolites to the critical effect is inadequate (Section 2.4.5). In addition, the metabolism of carbon disulfide is not fully known, particularly in humans, and there are potential sensitive subpopulations that would not have been included in the occupational epidemiological studies (e.g., the elderly [because of the age-related decrease in nerve conduction velocity, this group would have less reserve] and diabetics [who are prone to polyneuropathy]).

the lesser association of peroneal motor nerve conduction velocity with cumulative exposure in the regression analysis and the limited life span of neurofilaments as they traverse the axon (approximately 3–8 months). An uncertainty factor was also not incorporated for inadequacies in the available data for some other effects (e.g., cancer, reproductive), because available data indicate that the critical effect is likely to be limiting.

A Tolerable Intake for oral exposure to carbon disulfide has not been derived, owing to the limitations of the available data. There are no epidemiological or controlled studies of humans exposed to carbon disulfide via the oral route. The data concerning the toxicity to animals, which are limited to the results of short-term investigations of specialized endpoints in small groups of rats or mice exposed to one or two dose levels and single well-conducted and well-reported developmental toxicity studies in rats and rabbits, are considered inadequate to support exposure–response analyses for oral exposure to carbon disulfide. However, it is noted that a Tolerable Intake derived on the basis of the Lowest-Observed-Adverse-Effect Level (LOAEL) for developmental toxicity of 25 mg/kg-bw per day in the study in rabbits conducted by Jones-Price *et al.* (1984b) would be almost identical to one that might be derived by taking into account the volume of air inhaled and the body weights for various age classes of the Canadian population (EHD, 1998), from the TC presented above.

3.3.4 Human health risk characterization

The mean airborne concentrations of carbon disulfide used to estimate exposure of the general population of Canada are 0.63 µg/m^3 in indoor air and 0.30 µg/m^3 in outdoor air. Assuming that people spend on average 21 hours indoors and 3 hours outdoors each day (EHD, 1998), they would be exposed to a time-weighted average concentration of 0.58 µg/m^3. This concentration is 172-fold less than the TC derived above. The mean concentrations of carbon disulfide measured in air in limited available studies in the vicinity of point sources in Canada ranged from 1.4 to 6 µg/m^3, while the maximum 24-hour average concentration predicted in dispersion modelling of the largest anthropogenic source in Canada was 14 µg/m^3. These concentrations are 7- to 71-fold less than the TC.

3.3.5 Uncertainties and degree of confidence in human health risk characterization

There is a high degree of uncertainty inherent in the mean estimates of the intake of carbon disulfide in air, the likely principal medium of exposure, due to the paucity of monitoring data for both outdoor and indoor air. The estimated intakes from air are based on the results of a very small U.S. survey of levels in outdoor and indoor air from a single geographic location. While the low levels measured in ambient air in this study are supported by other available data, all of the available studies are extremely limited, inasmuch as they were conducted at very few locations, for very short time periods and often using methods that were not sufficiently sensitive to reliably detect carbon disulfide at ambient levels. The same limitations apply to the extremely limited data that exist on the levels of carbon disulfide in the vicinity of point sources in Canada. Moreover, how the monitoring stations in these studies were situated with respect to the point of impingement of the point source emissions was not often reported, nor were the size and location of local human populations. Finally, there are very few data on levels of carbon disulfide in indoor air.

There is also some uncertainty introduced by the lack of current, representative monitoring data for food. Although carbon disulfide is no longer registered for food applications in Canada and the results of fugacity modelling suggest that it does not accumulate to an appreciable degree in terrestrial plants and animals, it is known to be a soil and plant metabolite of some thiocarbamate pesticides applied to fruit crops. Carbon disulfide is also known to be a metabolite produced by plants and soil organisms from naturally occuring sulfur compounds. However,

no information was accessed with which to quantitatively estimate the potential for exposure to carbon disulfide in Canada from these sources (Ballantine, 1998; Moore, 1999).

There is, however, a fair degree of certainty that drinking water and soil contribute only negligible amounts to the total exposure to carbon disulfide. Based on data from a limited survey of treated drinking water and a very small survey of soils from non-contaminated areas, even the upper range of estimated intakes via these media, calculated by assuming that carbon disulfide was present at the detection limit in samples in which it was not detected (the vast majority), is orders of magnitude lower than those from indoor or outdoor air. Furthermore, these estimates are consistent with what is known concerning anthropogenic releases in Canada (i.e., almost entirely to air), the physical/chemical properties of carbon disulfide and the results of fugacity modelling (i.e., it is not expected to partition to soil).

The overall degree of confidence in the population exposure estimates is, therefore, low, owing principally to the scarcity of data on levels of carbon disulfide in air, the principal medium of exposure. To a lesser extent, uncertainty arises from the lack of knowledge concerning the contribution of food to total environmental exposure, particularly the possible role of dithiocarbamate pesticides and naturally occuring sulfur compounds as a source of general population exposure.

The degree of confidence in the available data regarding the effects of exposure to carbon disulfide is moderate.

There is a fair degree of confidence in the results of the critical study by Johnson *et al.* (1983), which was part of a large, well-designed investigation in which a wide range of endpoints (including those that have historically been associated with exposure to carbon disulfide) was examined in a sizable population, and for which a range of exposures and potential confounders was fairly well characterized. Further, there is consistent support for the critical effect (i.e., reduced peripheral nerve conduction velocity) identified in this study from the results of other rigorously conducted epidemiological studies in which exposure levels were relatively low (as for the study by Johnson *et al.*, 1983) and from the results of studies in animals for both the nature and plausible mechanism of action of the critical effect. However, while the exposure characterization in the critical study was based on personal monitoring of a population for whom a large majority had had the same work assignment for the duration of their employment, it is noted that the personal monitoring was conducted only over a few days at the time of the study and on a minority of the study population. Further, in the exposure–response analyses in the original paper by Johnson *et al.* (1983), as well as in this assessment, each worker was assigned the mean concentration in personal air for his job task, while it is known that the range of measured concentrations for some job categories was quite wide, more than two orders of magnitude (Egeland *et al.*, 1992).

There is also additional uncertainty arising because the critical effect (i.e., reduced conduction velocity in the peripheral nerves) is a somewhat crude indicator of effects on the nervous system, being secondary to axonal damage. Moreover, it is likely that similar effects are occurring in the long axons of the central nervous system (indeed, Hirata *et al.* [1992a] observed effects on latency of some components of the brainstem auditory-evoked potential in rats at exposure levels that were slightly lower than those that affected peripheral nerve conduction velocity), although this has not been as well studied as the peripheral nervous system.

Finally, there is considerable uncertainty introduced by the limitations of the available database, particularly with respect to the effects of carbon disulfide on neurobehavioural development. While the available data in animals consistently indicate that the developing offspring is more sensitive to the neurotoxicity of carbon disulfide than the adult (there are no data regarding neurobehavioural effects in humans exposed *in utero*), the degree of the difference in sensitivity is not at all clear, as a consequence of the variety of endpoints that have been examined, the

inconsistency in the concentrations that have been employed and the inadequate reporting in a number of the key studies. Consequently, these data are inadequate to serve as a basis for developing a TC. (Although the confidence in these studies, which were conducted in one laboratory and were poorly reported in some cases, is low, research into the effects of carbon disulfide on neurobehavioural development is considered an important area for further work, given the very low effect levels reported in some of these studies. In particular, while there are a number of developmental studies [Section 2.4.4.2.5], neurobehavioural endpoints have been evaluated in only a few of these, and there is a need for a well-conducted multigeneration study in which neurobehavioural endpoints are evaluated, in order to confirm the results reported by Tabacova *et al.* [1983].) While the available data concerning other effects of exposure to carbon disulfide (e.g., reproductive effects) are also inadequate, it is noted that these are unlikely to be limiting, since it appears that they are associated with exposures that are greater than those for the critical neurological effects.

3.4 Conclusions

CEPA 1999 64(a): Based on available data, it has been concluded that carbon disulfide is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Therefore, carbon disulfide is not considered to be "toxic" as defined in Paragraph 64(a) of CEPA 1999.

CEPA 1999 64(b): Based on available data, it has been concluded that carbon disulfide is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, carbon disulfide is not considered to be "toxic" as defined in Paragraph 64(b) of CEPA 1999.

CEPA 1999 64(c): Based on available data, it has been concluded that carbon disulfide is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, carbon disulfide is not considered to be "toxic" as defined in Paragraph 64(c) of CEPA 1999.

Overall conclusion: Based on critical assessment of relevant information, carbon disulfide is not considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Since carbon disulfide is not considered to be "toxic" as defined in Section 64 of CEPA 1999 investigation of options to reduce exposure under CEPA is not considered a priority at this time. However, this is based upon current use patterns; thus, future releases of this compound should continue to be monitored to ensure that exposure does not increase to any significant extent. Available data indicate that anthropogenic releases of carbon disulfide into the environment in Canada at present are virtually all from the processing of gas and oil.

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APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether carbon disulfide is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches of the following databases for the period 1980–1996: APILIT (American Petroleum Institute), Aqualine (Water Research Centre, Buckinghamshire), ARET (Accelerated Reduction/Elimination of Toxics, Environment Canada), BIODEG (Syracuse Research Corp.), BIOLOG, BIOSIS (Biosciences Information Services), CAB (Commonwealth Agriculture Bureaux), CCINFO (Canadian Centre Information, Canadian Centre for Occupational Health and Safety), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources), CHEMFATE (Syracuse Research Corp.), CHEMINFO (Canadian Centre for Occupational Health and Safety), CHRIS (Chemical Hazards Release Information System), CPI Profile (Camford Information Services), Current Contents (Institute for Scientific Information), DATALOG (Syracuse Research Corp.), Domestic Substances List (Environment Canada), ELIAS (Environmental Library Integrated Automated System, Environment Canada library), ENVIRODAT (Environment Canada), Enviroline (R.R. Bowker Publishing Co.), Environmental Abstracts, Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara), Envirosource (Environment Canada), GEOREF (Geo Reference Information System, American Geological Institute), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRL (Information Retrieval Limited [Life Sciences]), IRPTC (International Register of Potentially Toxic Chemicals, Geneva), Life Sciences (Cambridge Scientific Abstracts), MSDS (Material Safety Data Sheets, Canadian Centre for Occupational Health and Safety), NATES (National Analysis of Trends in Emergencies System, Environment Canada), National Emission Inventory (Canadian Chemical Producers Association), Northern Info Network, NPRI (National Pollutant Release Inventory, Environment Canada), NTIS (National Technical Information Service, U.S. Department of Commerce), Pesticide Registrant Survey (Environment Canada and Agriculture Canada), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute of Occupational Safety and Health), Toxline (U.S. National Library of Medicine), TRI87-94 (Toxic Chemical Release Inventory, Office of Toxic Substances, U.S. Environmental Protection Agency), USEPA-ECOTOX (including AQUIRE; U.S. Environmental Protection Agency), USEPA-National Catalog (U.S. Environmental Protection Agency) and WASTEINFO (Waste Management Information Bureau, American Energy Agency).

A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997b). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them on carbon disulfide if they met the trigger quantity of 1000 kg of carbon disulfide per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the environmental effects of carbon disulfide. Data obtained after May 1998 were not considered in this assessment unless they were critical data received during the 60-day public review of the report (October 23 to December 22, 1999).

Health assessment

To identify effects-related data relevant to the preparation of the health assessment of carbon disulfide as a Priority Substance, literature searches were conducted in December 1995 using the strategy of searching by the name, carbon disulfide, or its CAS registry number, 75-15-0, in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), EMICBACK (backfile of EMIC, Environmental Mutagen Information Center database, Oak Ridge National Laboratory), ETICBACK (backfile of ETIC, Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENETOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health). The name, registry number and major synonyms were searched in the Toxline database (U.S. National Library of Medicine; 1965–1984 and 1995) and in Toxline Plus on CD-ROM (1985–July 1995). In addition to information identified from these sources, unpublished reports of reproductive and developmental studies in rats and rabbits, respectively (PAI, 1991; WIL Research Laboratories, Inc., 1992), and the original data from a U.S. study of health effects in a population of workers exposed to carbon disulfide (Johnson *et al.*, 1983; Egeland *et al.*, 1992) were kindly provided by the Chemical Manufacturers Association.

To identify data relevant to the estimation of exposure of the general population to carbon disulfide, literature searches were conducted, using the strategy of searching by the name, carbon disulfide, its CAS registry number, 75-15-0, and major synonyms in the following databases: Amicus (National Library of Canada), BIOSIS (Biosciences Information Services), CAB Abstracts (Commonwealth Agriculture Bureaux), CISTIMON (Canadian Institute for Scientific and Technical Information list of monographs, National Research Council of Canada), ELIAS (Environmental Library Integrated Automated System, Environment Canada library), Enviroline (R.R. Bowker Publishing Co.), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara), Food Science and Technology Abstracts, Microlog (Canadian Research Index, Government Publications, Micromedia Ltd.) and Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine). Information on exposure is also included in some of the toxicology sources noted above, especially HSDB, Toxline and Toxline Plus.

Data relevant to health effects published after December 1995 were identified using the strategy of searching by the name, carbon disulfide, or its CAS registry number, 75-15-0, through an SDI (Selective Dissemination of Information) profile run twice yearly in the following databases: Canadian Research Index, CCRIS, Dialog, EMIC and GENETOX, and by searches of the CD-ROM updates of Medline (monthly) and Toxline Plus (quarterly).

In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August of 1996 for data relevant to exposure and/or effects. The Pest Management Regulatory Agency was contacted in April 1998 and in July 1999 for information relevant to the characterization of potential exposure to carbon disulfide from the application of thiocarbamate pesticides to food crops.

Data relevant to the assessment of whether carbon disulfide is “toxic” to human health obtained after August 1999 have not been included.