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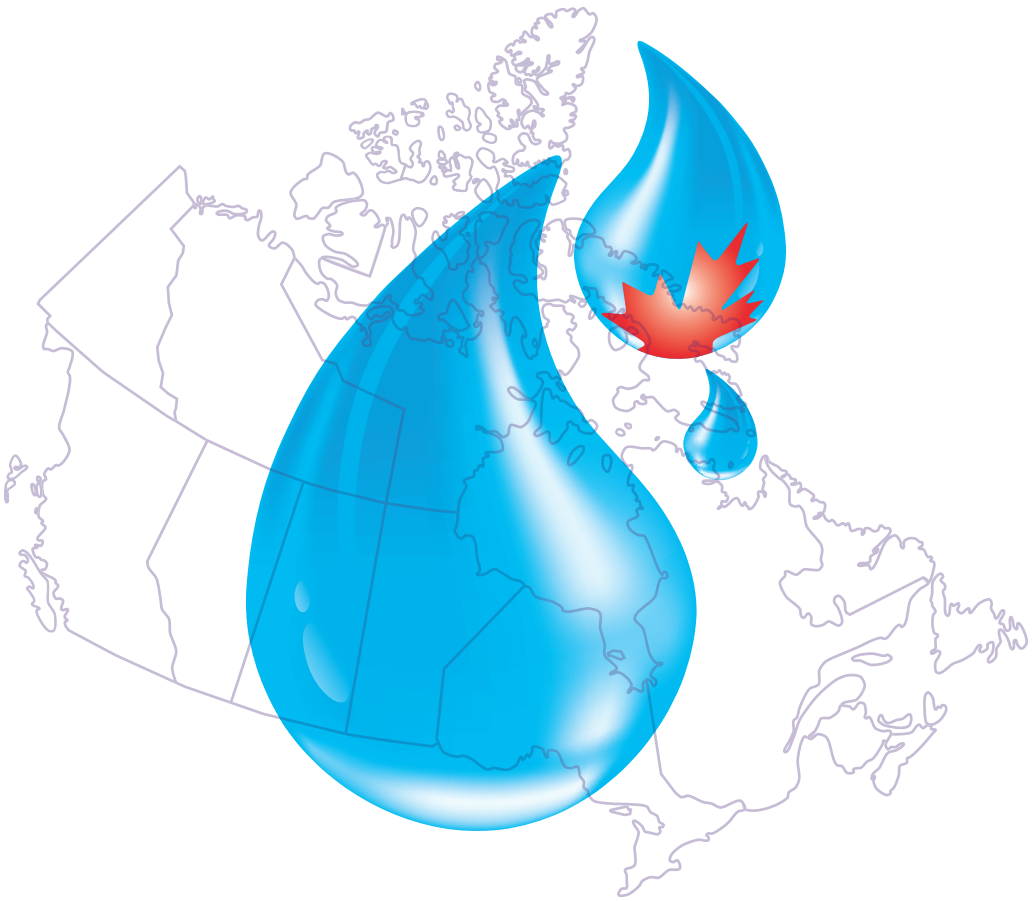
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Carbon Tetrachloride



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Published by authority of the
Minister of Health

Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Carbon Tetrachloride
is available on Internet at the following address: www.healthcanada.gc.ca

Également disponible en français sous le titre :
Recommandations pour la qualité de l'eau potable au Canada : Document technique Le tétrachlorure de carbone

This publication can be made available on request
in a variety of alternative formats.

For further information or to obtain additional copies, please contact:
Publications
Health Canada
Ottawa, Ontario K1A 0K9
Tel.: 613-954-5995
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Email: info@hc-sc.gc.ca

Cat.: H128-1/11-661E
ISBN: 978-1-100-18992-5

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Carbon Tetrachloride

Prepared by the
Federal-Provincial-Territorial Committee on Drinking Water
of the
Federal-Provincial-Territorial Committee on Health and the Environment

Ottawa, Ontario

November 2010

This document may be cited as follows:

Health Canada (2010). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Carbon Tetrachloride. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (Catalogue No. H128-1/11-661E).

The document was prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterquality

Table of Contents

Part I. Overview and Application 1

1.0 Guideline 1

2.0 Executive summary 1
- 2.1 Health effects 1
- 2.2 Exposure 1
- 2.3 Treatment 2

3.0 Application of the guideline 2

Part II. Science and Technical Considerations 3

4.0 Identity, use, and sources in the environment 3
- 4.1 Identity and uses 3
- 4.2 Environmental sources and fate 3

5.0 Exposure 4
- 5.1 Water 4
- 5.2 Air 5
- 5.3 Food 5
- 5.4 Multi-route exposure through drinking water 6

6.0 Analytical methods 8

7.0 Treatment technology 8
- 7.1 Municipal scale 8
  - 7.1.1 Activated carbon adsorption 9
  - 7.1.2 Air stripping 9
  - 7.1.3 Reverse osmosis 10
  - 7.1.4 Emerging treatment technologies 11
- 7.2 Residential scale 11

8.0 Kinetics and metabolism 13
- 8.1 Absorption 13
- 8.2 Distribution 13
- 8.3 Metabolism 14
- 8.4 Excretion 14

9.0 Health effects 15
9.1 Effects in humans 15
9.1.1 Acute and short-term toxicity 15
9.1.2 Epidemiology (non-cancer effects) 16
9.1.3 Epidemiology (cancer effects) 17
9.1.4 Developmental and reproductive effects 18
9.2 Effects on experimental animals and *in vitro* 18
9.2.1 Acute toxicity 18
9.2.2 Short-term exposure 20
9.2.3 Long-term exposure and carcinogenicity 23
9.2.4 Mutagenicity and genotoxicity 25
9.2.5 Reproductive and developmental toxicity 27
9.2.6 Mode of action 28

10.0 Classification and assessment 29
10.1 International Considerations 31

11.0 Rationale 32

12.0 References 33

Appendix A: List of acronyms 48

November 2010

Carbon Tetrachloride in Drinking Water

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for carbon tetrachloride in drinking water is 0.002 mg/L (2 µg/L).

2.0 Executive summary

Carbon tetrachloride is an ozone-depleting substance, and its production and consumption are controlled following an international agreement (the Montreal Protocol). It was phased out in Canada in 1996, but can still be imported for limited use in chemical production. In the environment, it is found mainly in air, primarily from direct releases to the atmosphere.

Health Canada recently completed its review of the health risks associated with carbon tetrachloride in drinking water. This Guideline Technical Document reviews and assesses all identified health risks associated with carbon tetrachloride in drinking water, incorporating multiple routes of exposure from drinking water, including ingestion and both inhalation and skin absorption from showering and bathing. It assesses new studies and approaches, and takes into consideration the availability of appropriate treatment technology. From this review, a guideline for carbon tetrachloride in drinking water is established as a maximum acceptable concentration (MAC) of 0.002 mg/L (2 µg/L).

2.1 Health effects

Carbon tetrachloride is classified as a possible human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals. However, there are major deficiencies in the available cancer studies. Animal studies suggest that the carcinogenicity of carbon tetrachloride is secondary to its hepatotoxic effects, indicating a possible threshold. As a result the MAC was established based on liver toxicity, and incorporating an additional uncertainty factor of 10 to accommodate for a lack of adequate chronic studies and evidence regarding the carcinogenic mode of action.

2.2 Exposure

Canadians can be exposed to carbon tetrachloride through its presence in air and drinking water. In addition, certain segments of the population may be exposed through the use of specific consumer products or in occupational settings. Because of its high volatility, concentrations of carbon tetrachloride are expected to be higher in drinking water from groundwater sources than in drinking water from surface water. Carbon tetrachloride is present in ambient air due to past and present releases resulting from production, disposal, or use. Recent surveys conducted on

carbon tetrachloride in indoor and outdoor air in Canada have shown that mean levels are below 1 $\mu g/m^3$. Exposure to carbon tetrachloride from food is not of concern because it is no longer used for grain fumigation in Canada, and its use in other countries is limited.

2.3 Treatment

Municipal treatment plants can reduce the levels of carbon tetrachloride in drinking water through granular activated carbon adsorption and air stripping. Oxidation and reverse osmosis membrane filtration may also be effective in the reduction of volatile organic compounds such as carbon tetrachloride from drinking water. At the residential scale, certified treatment devices (primarily point-of-use, some point-of-entry) are currently available for the reduction of volatile organic compounds such as carbon tetrachloride. Point-of-entry systems are preferred because they provide treated water for bathing and laundry as well as for cooking and drinking.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

Carbon tetrachloride is classified as a possible human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals. However, there are major deficiencies in the available cancer studies. The guidelines for carbon tetrachloride is based on a lifetime exposure from drinking water. Carbon tetrachloride is not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily.

Short-term exceedances above the guideline value are unlikely to have an effect on health. However, in the event that monitoring data show elevated levels on a yearly basis, it is suggested that a plan be developed and implemented to address these situations.

Part II. Science and Technical Considerations

4.0 Identity, use, and sources in the environment

4.1 Identity and uses

Carbon tetrachloride (CCl_4; relative molecular mass 153.82), also known as tetrachloromethane,is a colourless, nonflammable, heavy liquid with a sweet, aromatic, non-irritating odour (IPCS, 1999; Lide, 2005–2006). At room temperature, carbon tetrachloride is a volatile liquid with a boiling point of 76.5°C (ATSDR, 2005). Its odour thresholds are <64 mg/m^3 in air and 0.52 mg/L in water (Amoore and Hautala, 1983). It is a chlorinated solvent that is miscible with organic solvents, but it has poor solubility in water (800 mg/L at 20°C) (ATSDR, 2005). Carbon tetrachloride has an *n*-octanol/water partition coefficient (log K_{ow}) of 2.64, a high vapour pressure (12.2 kPa at 20°C; 15.36 kPa at 25°C), and high volatilization from water (Henry's law constant of 2.98 kPa·m^3/mol at 25°C) (IPCS, 1999; WHO, 2004a).

Carbon tetrachloride is considered one of several ozone-depleting substances (UNEP, 1994, 2002). An international agreement, the Montreal Protocol on Substances that Deplete the Ozone Layer, was reached in 1987 to control the production and consumption of certain ozone-depleting substances, including carbon tetrachloride. In Canada, carbon tetrachloride was phased out (100% elimination) in 1996 (Environment Canada, 2006a). However, it can still be imported for limited use as a feedstock in chemical production (CCME, 1999, 2001). According to Environment Canada (2006b), all other uses of carbon tetrachloride are prohibited in Canada. In the United States, although carbon tetrachloride is still manufactured, it has seen a decline in the amounts imported and exported (ATSDR, 2005).

In the past, carbon tetrachloride was used mainly as a feedstock for the production of chlorofluorocarbons (for refrigerant use). Because of its solvent properties, carbon tetrachloride was also used as a component of domestic cleaning fluids and as a degreaser in industry, while its non-flammable properties led to its past use in fire extinguishers. It was also used as a solvent for oils, fats, lacquers, varnishes, rubber waxes, and resins, as a grain fumigant, and as a dry cleaning agent, as well as in pharmaceutical products (ATSDR, 2005).

4.2 Environmental sources and fate

Most atmospheric carbon tetrachloride is a result of direct releases to the atmosphere (ATSDR, 2005). In the lower atmosphere (the troposphere), carbon tetrachloride is fairly stable and resists breakdown. As it diffuses to higher altitudes (the stratosphere, more than 20 km above the Earth's surface), it has been shown to undergo photodegradation in the presence of strong ultraviolet light (short wavelengths, 185–225 nm) to produce chlorine atoms and other chlorine species, which deplete ozone. According to estimates, the atmospheric lifetime (troposphere and stratosphere combined) of carbon tetrachloride ranges from 30 to 100 years, with 50 years as a reasonable average (ATSDR, 2005).

Carbon tetrachloride can be found in surface water as a result of industrial activities or from rainfall. In surface waters, volatilization is the principal route of loss, whereas no measurable degradation was seen as a result of photolysis, oxidation, or hydrolysis (Howard,

1990; CCME, 1999; ATSDR, 2005). Limited studies have shown that biodegradation occurs in the laboratory under both anaerobic and aerobic conditions (Howard, 1990). Despite its *n*-octanol/water partition coefficient of 2.64, bioaccumulation in fish is not expected to be significant because
of its short tissue lifetime in some species (IPCS, 1999).

Most of the carbon tetrachloride released into soil as a result of spills, runoff, or leaching will rapidly volatilize and thus will be present in the air (IPCS, 1999). Experimental studies showed a short half-life (5 days using silt loam and sandy loam) in both sterile and non-sterile soils (Anderson et al., 1991). Based on its soil adsorption coefficient (K_{oc} of 71), carbon tetrachloride is not expected to bind significantly to soil and therefore should move readily through soil (IPCS, 1999; OEHHA, 2000; ATSDR, 2005). As a result, carbon tetrachloride may leach from soil into groundwater (Letkiewicz et al., 1983).

5.0 Exposure

Canadians can be exposed to carbon tetrachloride through its presence in air and drinking water. In addition, certain segments of the population may be exposed through the use of specific consumer products or in occupational settings. Although some exposure data are available, they are not sufficient to modify the default allocation factor for drinking water of 20%.

5.1 Water

Owing to its high volatilization from water, carbon tetrachloride concentrations are normally low in surface water (≤ 1 µg/L). However, in groundwater systems where volatilization and biodegradation are limited, concentrations may be higher if contamination has occurred in the vicinity and leaching has taken place.

Concentrations of carbon tetrachloride have been measured in various water sources at limited locations across Canada. In Québec, carbon tetrachloride was detected in 10 distribution systems at a maximum concentration of 1 µg/L between the years 2001 and 2005 (Tremblay and Robert, 2005).

In Ontario, carbon tetrachloride levels above 0.5 µg/L have very rarely been detected. In over 5700 analysis carried out over the period 2004–2009, levels above 0.5 µg/L were found in only two instances with the highest being 1.2 µg/L (Ontario Ministry of the Environment, 2010). Carbon tetrachloride was not detected in raw or treated groundwater or surface water from First Nations water supplies sampled in southern and northern Ontario during various years between 1996 and 2004 (Health Canada, 2005).

In Saskatchewan, carbon tetrachloride was not detected (detection limit 1 µg/L) in raw water, wells, or treated water sampled between 1992 and 2005 (Saskatchewan Environment, 2005).

5.2 Air

Carbon tetrachloride is present in ambient air due to past and present releases resulting from production, disposal, or use (ATSDR, 2005). Recent surveys conducted on carbon tetrachloride in indoor and outdoor air in Canada have shown that mean levels are below 1 μg/m^3.

Ambient air sampled at 17 rural and 40 urban sites across Canada (2004–2005), for a total of 6992 samples, showed an overall mean level of 0.60 μg/m^3 (range 0.34–1.02 μg/m^3) (Dann, 2006). Similar outdoor air levels were seen in a 2005 local survey of backyards of 48 homes in Windsor, Ontario, during the winter (range 0.47–0.72 μg/m^3; overall mean 0.60 μg/m^3) and summer (range 0.48–0.70 μg/m^3; overall mean 0.59 μg/m^3) (Health Canada, 2006a).

Simmonds et al. (1998) measured global atmospheric concentrations (lower troposphere) of carbon tetrachloride at five coastal monitoring stations around the world from 1978 to 1996. Peak levels were seen during 1989–1990, at 104.4 ppt (0.653 μg/m^3). Less recent data from 1976 showed levels in North America ranging from 0.33 to 0.99 μg/m^3, with a mean level of 0.86 μg/m^3 (IPCS, 1999). Similar levels (0.87 μg/m^3) were seen in the northern hemisphere between 1979 and 1981 (IPCS, 1999). Shah and Heyerdahl (1988) reported an average concentration of carbon tetrachloride of 0.168 ppb (1.1 μg/m^3) in ambient air in the United States based on 4913 ambient air samples taken at various sites, and these levels have since been decreasing.

Member companies of the Canadian Chemical Producers' Association have reported that since 1992, emissions of carbon tetrachloride in Canada have been reduced by over 99%; the emissions went from 58.190 tonnes in 1992 down to 0.024 tonnes in 2004 (CCPA, 2006).

According to ATSDR (2005), carbon tetrachloride also appears to be a common contaminant of indoor air; the sources of exposure appear to be building materials or products, such as cleaning agents, used in the home. However, it should be noted that carbon tetrachloride has been eliminated from production, import, and export in Canada, and is on a list of restricted substances under the Canadian Environmental Protection Act (CEPA). Sources in Canada are therefore expected to be limited.

Indoor air levels were sampled in 48 homes in Windsor, Ontario, during the winter and summer of 2005 (Health Canada, 2006a). In winter, the concentration of carbon tetrachloride ranged from 0.035 to 3.31 μg/m^3, with an overall mean value of 0.60 μg/m^3; in summer, concentrations ranged from 0.24 to 7.30 μg/m^3, with an overall mean of 0.72 μg/m^3.

In the United States, typical indoor air concentrations of 1 μg/m^3 were reported for 600 homes sampled in several states (Wallace, 1986), whereas slightly higher mean levels (2.6 μg/m^3) were seen in another study in which 2120 indoor air samples were taken (although carbon tetrachloride was detected in less than half the samples) (Shah and Heyerdahl, 1988).

5.3 Food

Data on the residues of carbon tetrachloride in Canadian food commodities were not available. In the past, carbon tetrachloride was used in agriculture as a grain fumigant; as a result, residues occurred in grain and food products such as bread prepared using the fumigated grain. In Canada, the Pest Management Regulatory Agency (PMRA, 2006) no longer supports the use of

ozone-depleting chemicals such as carbon tetrachloride as formulants in pesticides; as a result, no new pesticide registrations or renewals will be issued for products containing them. Since carbon tetrachloride is no longer used for grain fumigation in Canada, and its use in other countries is limited, exposure to carbon tetrachloride via this route is not of concern.

No significant amount of carbon tetrachloride was found in food in the United States (U.S. FDA, 2003; ATSDR, 2005). In a total diet study summary from 1991 to 2001 (U.S. FDA, 2003), carbon tetrachloride residues were rarely detected. Detected concentrations of carbon tetrachloride ranged from 0.0040 to 0.0310 mg/kg. As a result, food does not represent a significant source of carbon tetrachloride exposure.

5.4 Multi-route exposure through drinking water

No studies have been located that measure human exposure from inhalation of carbon tetrachloride volatilized from tap water as a result of activities such as showering and bathing (IPCS, 1999). However, owing to carbon tetrachloride's high volatility, exposure by inhalation and through the skin during bathing and showering may also serve as important routes of exposure. Tancrède et al. (1992) studied the volatilization of various volatile organic compounds (VOCs) from tap water from household activities such as showering and found that at a temperature of 25°C, the fraction of volatilized carbon tetrachloride was approximately 40% and increased to over 70% when the temperature increased to either 33°C or 42°C (an ~50% increase in volatilization).

To assess the overall exposure to carbon tetrachloride in drinking water, the relative contribution of each exposure route is assessed through a multi-route exposure assessment approach (Krishnan, 2004). Contributions developed through this approach are expressed in litre equivalents (L-eq) per day. Both the dermal and inhalation routes of exposure for a VOC are considered significant if they contribute at least 10% of the drinking water consumption level (Krishnan, 2004).

Dermal exposure

To determine whether dermal exposure represents a significant route of exposure for carbon tetrachloride, tier 1 of the multi-route exposure assessment determines whether or not this route of exposure contributes a minimum of 10% of the drinking water consumption level (i.e., 10% of 1.5 L = 0.15 L). For a tier 1 goal of 0.15 L-eq, the skin permeability coefficient (K_p) for VOCs should be higher than 0.024 cm/h. Since the K_p for carbon tetrachloride of 0.16 cm/h is greater than 0.024 cm/h, exposure to carbon tetrachloride via dermal absorption from bathing or showering is considered significant. Tier 2 of the assessment is then used to calculate the L-eq value, using the following equation (Krishnan, 2004):

$$\text{Dermal L-eq} = K_p \times t \times F_{abs} \times A \times C_f$$

$$\text{Dermal L-eq} = 0.16 \text{ cm/h} \times 0.5 \text{ h} \times 0.7 \times 18000 \text{ cm}^2 \times 0.001 \text{ L/cm}^3$$

$$\approx 1.0 \text{ L-eq/day}$$

where:

- K_p is the skin permeability coefficient of 0.16 cm/h (Krishnan, 2004);
- t is the duration time of the shower or bath assumed to be 0.5 h;
- F_{abs} is the fraction of dose absorbed assumed to be 0.7 (Krishnan, 2003a,b);
- A is the area of skin exposed assumed to be 18000 cm^2 for adults; and
- C_f is the conversion factor from cm^3 to litres.

Inhalation exposure

A two-tier assessment was also used to evaluate the inhalation route of exposure. Similar to the approach used for dermal exposure, tier 1 of the assessment determines whether inhalation of carbon tetrachloride during bathing or showering is likely to contribute at least 10% of the drinking water consumption level. For a tier 1 goal of 0.15 L-eq, the air to water concentration ($F_{air:water}$) value for VOCs should be greater than 0.00063. Using the estimated Henry's law constant obtained from the U.S. EPA EPI Suite program (U.S. EPA, 2000), the $F_{air:water}$ value for carbon tetrachloride was determined to be 0.0075. Since the $F_{air:water}$ value is greater than 0.00063, exposure to carbon tetrachloride via inhalation from bathing or showering is considered to be significant. Tier 2 of the assessment calculates what the L-eq should be as a function of using the following formula (Krishnan, 2004):

$$\text{Inhalation L-eq} = F_{air:water} \times Q_{alv} \times t \times F_{abs}$$

$$\text{Inhalation L-eq} = 0.0075 \times 675\ \text{L/h} \times 0.5\ \text{h} \times 0.7$$
$$= 1.77\ \text{L-eq/day}$$
$$\approx 1.8\ \text{L-eq/day}$$

where:

- $F_{air:water}$ is the ratio (partitioning) of air to water concentrations of carbon tetrachloride;
- Q_{alv} is the adult alveolar ventilation rate assumed to be at 675 L/h;
- t is the time of exposure duration assumed to be 0.5 h; and
- F_{abs} is the fraction absorbed, 0.7 (based on Krishnan, 2003a,b).

It should be noted that this multi-route exposure assessment is a conservative approach used to estimate the contribution that both the dermal and inhalation routes of exposure make towards total exposure. Using physiologically based pharmacokinetic (PBPK) modelling to estimate the L-eq contributions to the total daily dose from the dermal and inhalation pathways does not take into account exposure to carbon tetrachloride metabolites. Therefore, the approach does not place any "toxicological" weight on a particular route of exposure due to metabolite production.

Using the above approach, the L-eq/day exposure was calculated as 1.0 L-eq/day for the dermal route and 1.8 L-eq/day for the inhalation route. Adding these values to the standard Canadian drinking water consumption rate of 1.5 L/day results in a total litre-equivalent daily exposure of 4.3 L-eq/day.

6.0 Analytical methods

Several analytical methods can be used to measure carbon tetrachloride in drinking water, including purge and trap gas chromatography with photoionization and electrolytic conductivity detection or mass spectrometry detection. Carbon tetrachloride can also be measured using liquid–liquid extraction followed by gas chromatography with electron capture detection.

The U.S. EPA has approved three analytical methods for the analysis of carbon tetrachloride in drinking water (U.S. EPA, 2002).

- EPA Method 502.2 Revision 2.1 employs purge and trap capillary gas chromatography with electrolytic conductivity detectors, and has a method detection limit (MDL) range of 0.01–0.02 µg/L.
- EPA Method 524.2 Revision 4.1 uses purge and trap capillary gas chromatography with mass spectrometry detection, and has an MDL range of 0.08–0.21 µg/L.
- EPA Method 551.1 uses liquid–liquid extraction and gas chromatography with linearized electrolytic conductivity detectors and has an MDL range of 0.002–0.006 µg/L (U.S. EPA, 1995). A detection limit range is cited, as multiple detection limits are possible due to variability in reagents, instrumentation, and/or laboratory analyst performance.

In 1985, the U.S. EPA established a practical quantitation limit (PQL) of 5 µg/L for carbon tetrachloride, which was considered the lowest level that could be reliably achieved within specified limits of accuracy and precision (U.S. EPA, 1985). Although the U.S. EPA has not officially adopted a lower PQL, it has identified carbon tetrachloride as a possible candidate for
a PQL revision and indicated that more recent data would support selecting a PQL ranging between 2.1 and 2.5 µg/L (U.S. EPA, 2003a).

The American Public Health Association has three equivalent standard methods for the analysis of carbon tetrachloride in water. SM 6200B and SM 6200C are based on purge and trap capillary gas chromatography followed by mass spectrometry or electrolytic conductivity detection, respectively. SM 6200B has an MDL of 0.042 µg/L, and SM 6200C has an MDL of 0.022 µg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately, using these methods are 0.168 µg/L and 0.088 µg/L for methods SM 6200B and SM 6200C, respectively. SM 6232 uses liquid–liquid extraction followed by gas chromatography and mass spectrometry detection. A MDL is not reported for this method, due to the possibility of variations in the characteristics of the gas chromatographic system used and interferences present in the solvent (APHA et al., 2005).

7.0 Treatment technology

7.1 Municipal scale

Municipal water filtration plants that rely on conventional treatment techniques (coagulation, sedimentation, filtration, and chlorination) have generally been found to be

ineffective in reducing concentrations of VOCs in drinking water (Love et al., 1983; Robeck and Love, 1983). Two common treatment technologies reported to be effective for the reduction of carbon tetrachloride in drinking water include granular activated carbon (GAC) adsorption and air stripping (Love et al., 1983; U.S. EPA, 1985, 1991a,b; AWWA, 1991; Lykins and Clark, 1994). To a lesser degree, oxidation and reverse osmosis membrane filtration may also be effective in the reduction of VOCs from drinking water.

The selection of an appropriate treatment process for a specific water supply will depend on many factors, including the characteristics of the raw water supply and the operational conditions of the specific treatment method. These factors should be taken into consideration to ensure that the treatment process selected is effective for the reduction of carbon tetrachloride in drinking water.

7.1.1 Activated carbon adsorption

GAC adsorption is widely used to reduce the concentration of VOCs in drinking water. A removal efficiency of 99% (U.S. EPA, 1985, 2003b; Lykins and Clark, 1994) to achieve effluent concentrations below 1 µg/L is considered feasible for carbon tetrachloride under reasonable operating conditions (O'Brian et al., 1981; Lykins et al., 1984; AWWA, 1991).

Full-scale data demonstrated that the use of GAC operating with a flow rate of 40 gallons per minute (0.22 ML/day), a total empty bed contact time (EBCT) of 130 min, and a carbon usage rate of 11.6 lb/1000 gallons (1.4 kg/m^3) was capable of reducing influent carbon tetrachloride concentrations of 72.9 mg/L to an effluent concentration of below 1 µg/L (O'Brian et al., 1981). Another treatment facility operating with a flow rate of 0.23 million gallons per day (0.87 ML/day) and using a downflow GAC adsorber with an EBCT of 35 min and a carbon depth of 9 ft. (2.7 m) reported that influent concentrations of carbon tetrachloride of 6 µg/L could be reduced to below 1 µg/L (AWWA, 1991).

Adams and Clark (1991) estimated the cost-effective design parameters for liquid-phase GAC treatment of carbon tetrachloride in drinking water. The estimated carbon usage rate to reduce an influent carbon tetrachloride concentration of 100 µg/L to an effluent concentration of 5 µg/L was 0.25/1000 gallons (0.03 kg/m^3) using an EBCT of 15 min and a bed life of 168 days. Under these conditions, a 95% reduction of carbon tetrachloride in drinking water may be achievable.

The adsorption capacity of activated carbon to remove VOCs is affected by a variety of factors, such as concentration, pH, competition from other contaminants, preloading with natural organic matter, contact time, and the physical/chemical properties of the VOC and carbon (Speth and Miltner, 1990). GAC filtration effectiveness is also a function of the EBCT, flow rate, and filter run time.

7.1.2 Air stripping

Air stripping is commonly used to reduce the concentration of VOCs in drinking water (Cummins and Westrick, 1990; U.S. EPA, 1991b; WHO, 2004b; Dyksen, 2004). Although various air stripping equipment configurations exist, packed tower aeration (PTA) is recognized as the most effective method for the reduction of carbon tetrachloride in drinking

water. Removal efficiencies of 99% (U.S. EPA, 1985, 2003b) to obtain effluent concentrations of 1 µg/L are considered to be achievable using PTA.

Design considerations for PTA include the temperature of the air and water, physical and chemical characteristics of the contaminant, air to water ratio, contact time, and available area for mass transfer (Adams and Clark, 1991; U.S. EPA, 1991b; Crittenden et al., 2005; Dyksen, 2004). PTA provides an optimum system for the removal of VOCs from water, as it allows for greater air to water ratios than with traditional diffused aeration systems. As PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to reduce the contaminant concentrations prior to discharge may be necessary (Crittenden et al., 1988; Adams and Clark, 1991).

Typical and model-generated PTA designs for the removal of commonly occurring VOCs have been reported by several authors (Crittenden et al., 1988; Adams and Clark, 1991). According to Crittenden et al. (1988), typical full-scale plant (>8.17 ML/day) air stripping design parameters for reduction of carbon tetrachloride include an air to water ratio of 6.2, an air stripper length of 13.7 m, and a packed column diameter of 1.5 m. Under these conditions, a 99% reduction of an influent carbon tetrachloride concentration of 100 µg/L to an effluent concentration of 1 µg/L in drinking water could be achieved.

After an evaluation of the cost of PTA and GAC adsorption for the control of selected organic compounds in water, Adams and Clark (1991) indicated that the cost-effective PTA design parameters for plants ranging in size from 1 to 100 ML/day include an air to water ratio of 20 and a packing depth of 31.5 ft. (9.6 m) for reduction of carbon tetrachloride. Under these estimated conditions, a 99% reduction of an influent carbon tetrachloride level of 100 µg/L to an effluent level of 1 µg/L could be achieved. According to the authors, the PTA treatment technology appears to be more cost-effective than liquid-phase GAC treatment for the contaminant, even when vapour-phase GAC treatment of the stripping tower off-gas is required.

Alternative air stripping treatment technologies that have been identified as potential methods for the reduction of carbon tetrachloride in drinking water include diffused aeration, multi-stage bubble aerators, tray aeration, and shallow tray aeration. These technologies may be particularly useful for small systems where the installation of GAC or PTA treatment is not feasible (U.S. EPA, 1998).

Combining PTA and GAC into a two-step treatment train has been suggested as the most effective method for achieving low effluent levels of VOCs. In a municipal-scale treatment plant combining these processes, air stripping is used for the bulk reduction of VOCs in the water, and activated carbon is used in the second step to further reduce the residual VOC concentrations (McKinnon and Dyksen, 1984; Stenzel and Gupta, 1985; U.S. EPA, 1991b). In addition, the use of air stripping preceding GAC can significantly extend carbon bed life.

7.1.3 Reverse osmosis

Reverse osmosis has shown some promise for its potential to remove VOCs from drinking water (Clark et al., 1988). Bench-scale investigations demonstrated that selected reverse osmosis membranes were capable of reducing 70–100% of the carbon tetrachloride concentration in water (Fronk et al., 1990; Lykins and Clark, 1994; WHO, 2004b).

The ability of reverse osmosis to remove other synthetic organic chemicals has been found to be dependent on a variety of system components, including type of membrane, flux, recovery, solubility of the organic chemical, charge, and molecular weight (Taylor et al., 2000).

7.1.4 Emerging treatment technologies

There are several emerging treatment technologies for the removal of carbon tetrachloride from drinking water, including the following:

1. *High-energy electron beam (E Beam):* This technique involves injecting high-energy electrons into an aqueous solution of contaminants following the formation of highly reactive species such as aqueous electrons, hydroxyl radicals, and hydrogen radicals, which mineralize the organic molecules. Pilot-scale experiments were capable of reducing influent concentrations of carbon tetrachloride of 133, 848, and 8490 µg/L to effluent concentrations of 3.38, 6.15, and 174 µg/L, respectively, with respective percentage removals of 97.5, 99.3, and 98.0 (Mak et al., 1997).
2. *Pervaporation:* This technique involves the removal of VOCs by permeating the liquid through a membrane and then evaporating the VOC into the vapour phase. Although it is considered an emerging technology for treatment of water contaminated with VOCs, no information was found on the removal of carbon tetrachloride specifically (Lipski and Cote, 1990; Uragami et al., 2001).
3. *Membrane air stripping:* Air stripping of VOCs with microporous polypropylene hollow fibre membranes has been introduced as an alternative method to PTA (Semmens et al., 1989; Castro and Zander, 1995). Pilot-scale studies demonstrated up to 85% reduction of carbon tetrachloride and greater mass transfer coefficients with than with the use of traditional air stripping towers (Zander et al., 1989).

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment of municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing carbon tetrachloride concentrations in drinking water.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2009):

- CSA International (www.csa-international.org);

- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Treatment devices to remove carbon tetrachloride from untreated water (such as a private well) can be certified for either the removal of carbon tetrachloride alone or the removal of a variety of VOCs, including carbon tetrachloride. Treatment devices are designed to be installed at the faucet (point-of-use) or at the location where water enters the home (point-of-entry). Point-of-entry systems are preferred for VOCs such as carbon tetrachloride because they provide treated water for bathing and laundry as well as for cooking and drinking. Only treatment devices certified for the removal of VOCs can verify that a final concentration of less than 1.8 µg/L of carbon tetrachloride is achieved; treatment devices certified specifically for carbon tetrachloride removal can only verify that they would meet a final concentration of 5 µg/L, which is above the maximum acceptable concentration (MAC) of 0.002 mg/L.

For a drinking water treatment device to be certified to NSF/ANSI Standard 53 (Drinking Water Treatment Units — Health Effects) for the removal of carbon tetrachloride, the device must be capable, in surrogate qualification testing, of reducing the concentration by more than 98% from an influent (challenge) concentration of 0.078 mg/L to a maximum final (effluent) concentration of less than 0.0018 mg/L (NSF/ANSI, 2009a). Treatment devices that are certified to remove VOCs under NSF/ANSI Standard 53 are generally based on activated carbon adsorption technology. Reverse osmosis systems certified to NSF/ANSI Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) may also be certified for the reduction of VOCs to achieve a final concentration of less than 0.0018 mg/L (NSF/ANSI, 2009b). These devices, however, are applicable only for point-of-use treatment.

A number of residential treatment devices from various manufacturers are available that can remove carbon tetrachloride from drinking water to concentrations below 1.8 µg/L. Certified point-of-use treatment devices as well as a limited selection of point-of-entry devices are currently available for the reduction of VOCs, including carbon tetrachloride. In the case where certified point-of-entry treatment devices are not available for purchase, systems can be designed and constructed from certified materials. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the water it produces to verify that the treatment device is effective. Devices will lose removal capacity through usage and time and need to be maintained and/or replaced. Consumers should read the manufacturer's recommendations to verify the expected longevity of the components in their treatment device.

8.0 Kinetics and metabolism

8.1 Absorption

Carbon tetrachloride is readily absorbed from the gastrointestinal tract into the systemic circulation in animals. In rats, 80–86% of an orally administered dose of ^{14}C-labelled carbon tetrachloride was excreted in the expired air within 10–18 h (Paul and Rubinstein, 1963; Marchand et al., 1970). The type of vehicle used and the mode of administration have been shown to influence the oral absorption rate in experimental studies. Although carbon tetrachloride was rapidly and extensively absorbed from the gastrointestinal tract of fasted rats when administered in water or as an Emulphor aqueous emulsion, corn oil markedly delayed its oral absorption (Kim et al., 1990a). Studies in rats comparing the pharmacokinetics of carbon tetrachloride after gastric infusion and bolus gavage show that peak blood carbon tetrachloride concentrations were higher after bolus dosing than after infusion over 2 h (Sanzgiri et al., 1995). Although no quantitative studies were found regarding absorption in humans after oral exposure to carbon tetrachloride, numerous case studies of accidental or intentional ingestion of carbon tetrachloride suggest that absorption of carbon tetrachloride from the gastrointestinal tract in humans is likely to be extensive (ATSDR, 2005).

Animal studies indicate that carbon tetrachloride is readily absorbed from the lung into the systemic circulation. In monkeys exposed to 46 ppm carbon tetrachloride for up to 5 h, an average of 30% of the total amount inhaled was absorbed (McCollister et al., 1951). Following inhalation exposure of mice to 5 µL ^{14}C-labelled carbon tetrachloride for 10 min, uptake was determined to be 84% of the administered dose (Bergman, 1979). Rapid absorption of carbon tetrachloride from the lung was observed in rats exposed to 100 or 1000 ppm for 2 h (Sanzgiri et al., 1995). Immediately following exposure of rats, mice, and hamsters to 20 ppm carbon tetrachloride vapour for 4 h, the initial body burdens of ^{14}C-labelled carbon tetrachloride equivalents were 12.1, 1.97, and 3.65 µmol, respectively (Benson et al., 2001). Although there is little quantitative information on the absorption of inhaled carbon tetrachloride in humans, it is likely readily absorbed as there are numerous cases of human toxicity following exposure to carbon tetrachloride vapour (ATSDR, 2005).

Dermal absorption of liquid carbon tetrachloride has been demonstrated in mice, guinea pigs, and rats (Tsuruta, 1975; Jakobson et al., 1982; Morgan et al., 1991); however, dermal absorption of carbon tetrachloride vapour is low. In monkeys, dermal exposure to ^{14}C-labelled carbon tetrachloride vapour for 4 h resulted in negligible amounts of radioactivity in blood and expired air (McCollister et al., 1951). In humans, carbon tetrachloride can be absorbed through the skin, although not to the extent of absorption via the inhalation and oral routes of exposure (ATSDR, 2005). Dermal absorption was significant in volunteers who immersed their thumbs in liquid carbon tetrachloride for 30 min (Stewart and Dodd, 1964).

8.2 Distribution

Animal studies indicate that, once absorbed, carbon tetrachloride is distributed to all major organs as a function of blood flow and fat content of the tissues, with highest concentrations in the fat, liver, kidney, brain, lung, bone marrow, and adrenals (McCollister et al., 1951;

Dambrauskas and Cornish, 1970; Marchand et al., 1970; Bergman, 1983; Paustenbach et al., 1986a; Sanzgiri et al., 1997; Benson et al., 2001). Sanzgiri et al. (1997) compared the uptake and distribution of carbon tetrachloride administered to rats by inhalation, gastric infusion, and oral bolus dosing. Carbon tetrachloride levels in all tissues were much lower in the gastric infusion group than in the oral bolus or inhalation group. For all three groups, carbon tetrachloride concentrations in fat increased slowly but progressively, reaching higher levels than in other tissues and remaining elevated for a much longer time. The liver had the highest carbon tetrachloride levels of all non-lipid tissues following oral bolus dosing; in contrast, carbon tetrachloride levels were lower in the liver than in any other organ in the gastric infusion group. These results suggest that the oral bolus dose likely exceeded the capacity of first-pass hepatic and pulmonary elimination (Sanzgiri et al., 1997). Quantitative studies on the distribution of carbon tetrachloride in humans are not available.

8.3 Metabolism

Carbon tetrachloride metabolism occurs primarily in the liver, although it may also occur in other tissues. In rats and mice, cytochrome P450 (CYP) 2E1 is primarily responsible for the bioactivation of carbon tetrachloride (Raucy et al., 1993; Wong et al., 1998). Studies in human liver microsomes have shown that CYP2E1 is the major human enzyme responsible for carbon tetrachloride activation at lower, environmentally relevant levels (Zangar et al., 2000). This isoenzyme catalyses the reductive dechlorination of carbon tetrachloride, forming the reactive trichloromethyl radical ($CCl_3\cdot$). Under anaerobic conditions, this radical can bind to lipids and proteins, react with hydrogen to produce chloroform ($CHCl_3$), dimerize to form hexachloroethane, or undergo further reduction, producing carbon monoxide (Uehleke et al., 1973; Wolf et al., 1977). Aerobically, the trichloromethyl radical can react with oxygen, forming the trichloromethylperoxyl radical ($CCl_3OO\cdot$). This highly reactive radical may initiate lipid peroxidation or may react further, producing phosgene ($COCl_2$) (Mico and Pohl, 1983; Pohl et al., 1984). Carbon dioxide is formed by the hydrolytic dechlorination of phosgene (Shah et al., 1979).

8.4 Excretion

Carbon tetrachloride is excreted primarily in exhaled air, in the faeces, and, to a lesser extent, in the urine. In animal studies, excretion of carbon tetrachloride and its metabolites has been shown to vary by species, dose, and route of exposure. Reynolds et al. (1984) orally administered a range of doses of ^{14}C-labelled carbon tetrachloride to rats and then monitored the recovery of carbon tetrachloride and its metabolites in exhaled breath, liver, urine, and faeces for 24 h. At the lowest dose (0.1 mmol/kg), less than half of the dose was recovered in the breath: 28% as carbon dioxide, 19% as carbon tetrachloride, and <1% as chloroform. In contrast, at doses of 0.3 mmol/kg or higher, the majority of the dose (71–89%) was recovered in exhaled breath as carbon tetrachloride. Efficient first-pass removal of the lowest dose of carbon tetrachloride by the liver likely diminished the amount of carbon tetrachloride available for pulmonary clearance. As the dose of carbon tetrachloride increased, the fraction of the dose recovered as metabolites decreased, indicating that the metabolic capacity for carbon

tetrachloride was saturated or impaired. Of total metabolites recovered in 24 h, the largest proportion were recovered as exhaled carbon dioxide (50–86%). A significant proportion of total metabolites was also recovered in the faeces (7–30%) and as chloroform in exhaled breath (0.3–19%); smaller fractions were recovered in the urine (2.7–9.7%) and liver (1.9–4.3%) (Reynolds et al., 1984).

Benson et al. (2001) exposed rats, mice, and hamsters to 20 ppm ^{14}C-labelled carbon tetrachloride vapour by inhalation for 4 h. In the 48 h following exposure, 65–83% of the initial body burden of ^{14}C activity was eliminated in exhaled breath as carbon dioxide and VOCs. Rats exhaled approximately 3 times as much radioactivity as VOCs (61%) than as carbon dioxide (22%), whereas mice and hamsters exhaled approximately equal amounts of radioactivity as VOCs and carbon dioxide (30–39%). Rats eliminated less than 10% of the initial body burden of carbon tetrachloride equivalents in urine and faeces combined, whereas mice and hamsters eliminated >20% in urine and faeces (Benson et al., 2001). In an earlier study by Paustenbach et al. (1986b), rats were repeatedly exposed to 100 ppm ^{14}C-labelled carbon tetrachloride vapour for 1–2 weeks. Of the total radioactivity excreted in the 64–108 h following exposure, 32–59% was excreted in expired air as carbon tetrachloride, less than 2% was excreted in expired air as carbon dioxide, 32–62% was excreted in the faeces, and 4–8% was excreted in the urine (Paustenbach et al., 1986b). Based on a PBPK model developed to describe these results, a small amount of the initially metabolized carbon tetrachloride was directly converted to carbon dioxide and rapidly eliminated; however, the vast majority of metabolized carbon tetrachloride became bound in compartments and was slowly eliminated in the faeces and urine (Paustenbach et al., 1988).

There is little quantitative information available on the elimination of carbon tetrachloride in humans; however, unchanged carbon tetrachloride has been detected in the expired air following oral, inhalation, and dermal exposures (Stewart et al., 1961, 1963; Stewart and Dodd, 1964).

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute and short-term toxicity

Acute exposure to carbon tetrachloride has been shown to cause central nervous system depression and gastrointestinal effects such as nausea and vomiting. The liver and kidneys have been shown to be the most sensitive target organs of carbon tetrachloride toxicity (ATSDR, 2005).

A number of historical cases of poisoning by oral exposure to carbon tetrachloride have been reported in the literature, with lethalities occurring over a wide range of doses (approximately 43–450 mg/kg bw) (Phelps and Hu, 1924; Umiker and Pearce, 1953; Guild et al., 1958). Acute exposure to carbon tetrachloride via inhalation has also been shown to cause various adverse effects, such as headaches and dizziness in workers exposed to 250 ppm for 4 h (Norwood et al., 1950), decreased serum iron in volunteers exposed to up to 50 ppm

for 1–3 h (Stewart et al., 1961), and gastrointestinal irritation, nausea, proteinuria, and increased hepatic bilirubin in workers exposed to up to 200 ppm for 3 h (Barnes and Jones, 1967).

Alcohol consumption has been shown to increase the severity of acute carbon tetrachloride toxicity (ATSDR, 2005). Norwood et al. (1950) reported the death of one man with a history of alcoholism (after a 15-min exposure to 250 ppm carbon tetrachloride) due to liver, kidney, and lung failure. In addition, Folland et al. (1976) reported several cases of hepatic and renal injury among workers in an isopropyl alcohol packaging plant following accidental exposure to carbon tetrachloride. The most severe case exhibited acute renal failure and required dialysis.

Gastrointestinal effects (nausea, dyspepsia) at 20–50 ppm, central nervous system depression at 40 ppm, and narcosis at 80 ppm were found in humans occupationally exposed via inhalation for 2–3 months (Heimann and Ford, 1941; Elkins, 1942; Kazantzis and Bomford, 1960). Hepatic (fat accumulation) and renal (swelling) effects were also observed in workers after short-term (<3 h) exposure to 200 ppm carbon tetrachloride, similar to findings following acute exposure (Barnes and Jones, 1967).

Six male volunteers per group were exposed to carbon tetrachloride vapour (3 times, 4 weeks apart) at concentrations of 49 ppm for 70 min, 11 ppm for 180 min, and 10 ppm (64.1 mg/m^3) for 180 min. At 49 ppm, all subjects were able to detect a sweetish odour. A decrease in serum iron concentration in two subjects was the only adverse effect observed at the highest dose. Carbon tetrachloride was detected in exhaled breath at all three exposure levels (Stewart et al., 1961). It is estimated that the threshold for central nervous system effects in humans is probably in the range of 20–50 ppm for an 8-h workday (ATSDR, 2005).

9.1.2 Epidemiology (non-cancer effects)

The effect of carbon tetrachloride on hepatic function following occupational exposure via inhalation was examined in a cross-sectional study of chemical plant workers. Historical personal monitoring data were used to categorize the exposed group into low, medium and high exposure groups. Alcohol consumption data were collected from control and exposed groups, and were found to be equivalent among groups. Multivariate analysis of serum levels of alanine transaminase, aspartate transaminase, alkaline phosphatase and gamma-glutamyl transferase showed significant differences between exposed and control groups, however there were no significant differences between different exposure categories. Univariate analyses identified increases in only alkaline phosphatase and gamma-glutamyl transferase within the exposed group, and these did not show a significant dose-response. Although there was no evidence of significant clinical effects on the liver function of workers exposed to carbon tetrachloride, it is possible that some of the effects seen in liver function enzymes were due to carbon tetrachloride exposure. No evidence of any change in liver function was observed in a follow-up study conducted 3 years after the initial study (Tomenson et al., 1995).

No adverse effects on endocrine, cardiovascular, haematological, or musculoskeletal systems have been reported in the literature following dermal exposure to carbon tetrachloride in humans (ATSDR, 2005).

9.1.3 Epidemiology (cancer effects)

A case–control study was carried out in Montréal to estimate the association between 293 workplace substances (including carbon tetrachloride) and several types of cancer. Population subgroups were categorized according to ethnicity in an attempt to account for the effect of differing genetic or cultural characteristics that may have confounded the relationship between cancer and occupation. Approximately 4% of the population (firefighters, mechanics, and electricians) had been exposed to carbon tetrachloride mainly via inhalation. Elevated risks were observed for rectal cancer in all subjects (odds ratio [OR] = 2.0, 90% confidence interval [CI] = 1.2–3.3) and for bladder cancer in one ethnic subgroup (OR = 1.6, 90% CI = 0.9–2.8) (Siemiatycki, 1991).

Deaths due to cancer were analysed in 330 laundry and cleaning workers exposed dermally and via inhalation to carbon tetrachloride, trichloroethylene, and tetrachloroethylene. Eighty-seven deaths due to cancer were observed compared with the expected 67.9, indicating an increase in cancer risk. A significant increase in malignant neoplasms of the lung and cervix was observed, in addition to a slight increase in the incidence of leukaemia and liver cancer. Confounding factors such as exposure to multiple compounds and lack of adequate controls were noted in this study (Blair et al., 1979). Following investigation based on three occupational studies, associations between carbon tetrachloride and an increased risk of non-Hodgkin lymphoma and/or multiple myeloma were suggested, but were not statistically powerful and were observed in females only (Blair et al., 1990, 1998; IARC, 1999).

A nested case–control study within a cohort of workers from a large rubber and tire manufacturing plant was performed to examine the relationship between exposure to 24 solvents (including carbon tetrachloride) and the risk of cancer. The cohort study consisted of 6678 male plant workers (either active or retired), with a control group consisting of a 20% age-stratified random sample of the cohort (n = 1350) and cases composed of persons with fatal stomach cancer (n = 30), lung cancer (n = 101), prostate cancer (n = 33), lymphosarcoma (n = 9), or lymphatic leukaemia (n = 10). Lymphatic leukaemia was significantly related to carbon tetrachloride exposure (OR = 15.3). Lymphosarcoma showed similar but weaker associations with carbon tetrachloride exposure. Overlapping chemical exposures (strong associations with carbon disulphide were also noted for these two cancer types) limit the ability to draw conclusions regarding carbon tetrachloride exposure and cancer (Wilcosky et al., 1984).

A second case–control analysis was performed to evaluate the association of lymphocytic leukemia mortalities in 11 male workers and exposure to rubber industry solvents. Carbon tetrachloride (OR = 14.8) and carbon disulphide (OR = 8.7) showed the strongest associations with leukaemia mortality; however, due to small sample size and multi-solvent exposures, no conclusive associations between individual solvents and leukaemia mortality can be inferred (Checkoway et al., 1984).

A nested case–control study (Bond et al., 1986) of 308 lung cancer deaths in a cohort of chemical workers showed no association with exposure to carbon tetrachloride (OR < 1).

Although several epidemiological studies have explored a possible association between carbon tetrachloride and the incidence of cancer, these studies are all characterized by mixed exposures and a lack of carbon tetrachloride exposure data. Consequently, IPCS (1999) has concluded that any contribution from carbon tetrachloride cannot be reliably identified.

9.1.4 Developmental and reproductive effects

The effect of public drinking water contamination on birth outcomes was evaluated in an area of northern New Jersey by using the Birth Defects Registry data from 1985 to 1988 (including 80 958 live births and 594 fetal deaths) (Bove et al., 1995). Positive associations were found between exposure to >1 ppb carbon tetrachloride in drinking water and term low birth weight (OR = 2.26; 90% CI = 1.52–3.36), small for gestational age (OR = 1.75; 90% CI = 1.31–2.32), central nervous system defects (OR = 3.80; 90% CI = 1.14–10.63) and neural tube defects (OR = 5.39; 90% CI = 1.12–18.95). The authors concluded that this study did not resolve whether the drinking water contaminants caused the adverse birth outcomes, because drinking water databases were developed primarily for regulatory and enforcement purposes and are limited in their use for exposure assessment. Interpretation of this study is difficult due to simultaneous exposure to multiple chemicals in the drinking water, and the small number of cases observed; in the group exposed to >1 ppb carbon tetrachloride, only three cases of central nervous system defects and two cases of neural tube defects were observed.

No association was found between small for gestational age babies and exposure to carbon tetrachloride in 3418 out of 3946 women in Germany who had been exposed while pregnant (86.6%). The ORs for carbon tetrachloride in low- and moderate-exposure groups were 1.2 (95% CI = 0.6–2.7) and 2.4 (95% CI = 0.2–25.2), respectively, compared with 1.0 for the no-exposure group (Seidler et al., 1999).

Croen et al. (1997) investigated the association between maternal proximity to hazardous waste sites in California and selected congenital malformations using data from two population-based case control studies. No association was found between conotruncal heart defects or oral cleft defects and maternal residential proximity to sites contaminated with carbon tetrachloride.

9.2 Effects on experimental animals and *in vitro*

9.2.1 Acute toxicity

The acute toxicity of carbon tetrachloride has been widely studied in animals. In acute oral studies in rats, LD_{50} values of 4.7 mL/kg (equivalent to 7500 mg/kg bw; Pound et al., 1973), 6.4 mL/kg (equivalent to 10 200 mg/kg bw; McLean and McLean, 1966), and 10 054 mg/kg bw (Dashiell and Kennedy, 1984) have been reported.

In a study by Korsrud et al. (1972), single oral doses of carbon tetrachloride in corn oil were administered to male Wistar rats at 0, 0.001, 0.005, 0.025, 0.075, 0.125, 0.250, 0.750, or 2.50 mL/kg bw. The rats were killed 18 h after dosing. At 0.025 mL/kg bw (equivalent to 39.9 mg/kg bw) and above, liver weight and fat, serum urea, and serum enzyme activities were increased. In a second experiment, single oral doses of 0, 0.0125, 0.0250, 0.0500, or 0.1000 mL/kg bw in corn oil were administered to rats that were again sacrificed 18 h subsequent

to exposure. Histopathological evidence of liver damage was seen in all treated animals and included loss of basophilic stippling of the cytoplasm, fat, and hydropic degeneration, with occasional single-cell necrosis at the highest dose level (Korsrud et al., 1972).

Kim et al. (1990b) investigated the effect of oral dosing vehicles on the acute hepatotoxicity of carbon tetrachloride . Male Sprague-Dawley rats were administered carbon tetrachloride (0, 10, 25, 50, 100, 250, 500, or 1000 mg/kg bw) by gavage in corn oil, as the undiluted chemical, as an aqueous emulsion, or in water (10 and 25 mg/kg bw doses only). Dose-dependent increases in serum enzyme levels and histopathological changes were observed with each vehicle; however, hepatotoxicity was consistently less pronounced in groups given carbon tetrachloride in corn oil than in other vehicle groups. The lowest-observed-adverse-effect level (LOAEL) for carbon tetrachloride given in corn oil (25 mg/kg bw) was higher than that when carbon tetrachloride was given in the other vehicles (10 mg/kg bw) (Kim et al., 1990b).

The acute inhalation toxicity of carbon tetrachloride has also been studied in animals. Svirbely et al. (1947) reported a LC_{50} value of 9526 ppm (60 mg/L) for male and female Swiss mice following a 7-h inhalation exposure (8-h observation period). Adams et al. (1952) reported 100% mortality of Wistar rats following single inhalation exposures to 19 000 ppm carbon tetrachloride for 2.2 h, 12 000 ppm for 4 h, and 7300 ppm for 8 h. Exposure of male rats to 3000 ppm for 0.1 h, 800 ppm for 0.5 h, and 50 ppm for 7 h caused no adverse effects. In the same study, rats were repeatedly exposed to carbon tetrachloride for 7 h per day. At 10 ppm, 13 exposures in a 17-day period caused fatty degeneration of the liver, which increased in extent and severity with increasing concentration. Cirrhosis was also observed at 200 and 400 ppm following 10 exposures in a 12- to 13-day period.

Brondeau et al. (1983) exposed male Sprague-Dawley rats to carbon tetrachloride by inhalation at concentrations of 259, 531, 967, and 1459 ppm for 4 h. Twenty-four hours post-exposure, serum glutamate dehydrogenase activity was increased at the lowest concentration. At the higher exposure levels, serum activities of sorbitol dehydrogenase (SDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were also increased. In a study by Boyd et al. (1980), male Swiss mice were exposed by inhalation to carbon tetrachloride concentrations of 0.46 or 0.92 mmol/L for 1 h, 1.84 mmol/L for 12 min, or 3.68 mmol/L for 2 min. All exposures produced marked Clara cell lesions in the lung and hepatic necrosis.

Acute toxicity following dermal exposure to carbon tetrachloride has also been observed in animals. LD_{50} values of >9.4 mL/kg were reported for rabbits and guinea pigs following a single dermal exposure to carbon tetrachloride (Roudabush et al., 1965). In guinea pigs, centrilobular hydropic change and necrosis were observed in the liver 16 h after dermal application of 1 mL carbon tetrachloride to a 3.1-cm^2 area of skin (Kronevi et al., 1979). A dose of 0.5 mL applied to the skin of guinea pigs (3.1 cm^2) resulted in 25% mortality within 14 days; 65% mortality was reported 21 days following application of 2.0 mL (Wahlberg and Boman, 1979).

9.2.2 Short-term exposure

Several studies have investigated the effect of short-term oral exposure to carbon tetrachloride on animals. In a study by Bruckner et al. (1986), five male Sprague-Dawley rats (300–350 g) per dose level were administered carbon tetrachloride by gavage in corn oil (0, 20, 40, or 80 mg/kg bw/day) for 5 consecutive days, allowed 2 days without dosing, and dosed once daily for 4 additional days. In a second study, five rats (200–250 g) per dose level were gavaged with 0, 20, 80, or 160 mg/kg bw/day according to the same dosing schedule. In both studies, one group of rats at each dosage level was sacrificed 1, 4, and 11 days after initiation of dosing. Single doses of 20 and 40 mg/kg bw had no apparent toxic effects after 1 day. Significant increases in serum enzyme levels and hepatic vacuolization were observed 1 day after single doses of 80 and 160 mg/kg bw; hepatic necrosis was also observed at 160 mg/kg bw. Progressively severe hepatotoxicity at each dosage level was observed over the 11-day period.

In a subchronic experiment by Bruckner et al. (1986), carbon tetrachloride was administered to 15–16 male Sprague-Dawley rats per dose group by gavage in corn oil (0, 1, 10, or 33 mg/kg bw/day), 5 days per week for 12 weeks. At the end of the 12-week dosing period, 7–9 rats per group were sacrificed; the remaining animals were sacrificed 13 days after the last dose. The lowest dose (1 mg/kg bw/day) had no apparent adverse effects. At 10 mg/kg bw/day, serum SDH levels were modestly increased and mild centrilobular vacuolization was seen in the liver. Marked hepatotoxicity was observed at the highest dose (33 mg/kg bw/day). Serum levels of SDH, ornithine-carbamyl transferase, and ALT were significantly increased during the 12-week dosing period, but returned to normal within 13 days after the last dose. In rats sacrificed after 12 weeks, hepatic lesions observed included vacuolization, bile duct hyperplasia, periportal fibrosis, lobular distortion, parenchymal regeneration, hyperplastic nodules, and single-cell necrosis. The severity of the fibrosis and bile duct hyperplasia observed in rats sacrificed 13 days after the last dose was similar to that seen in rats sacrificed after 12 weeks. The no-observed-adverse-effect level (NOAEL) was 1 mg/kg bw/day and the LOAEL was 10 mg/kg bw/day, based on increased serum SDH levels and mild centrilobular vacuolization observed at this dose.

Koporec et al. (1995) investigated the effect of oral dosing vehicles on the subchronic hepatotoxicity of carbon tetrachloride in rats. Carbon tetrachloride was administered to Sprague-Dawley rats at doses of 0, 25, or 100 mg/kg bw/day by gavage in either corn oil or a 1% Emulphor aqueous emulsion, 5 times per week for 13 weeks. Dose-dependent increases in serum SDH and ALT activities were observed for both vehicle groups. The incidence and severity of hepatic histopathological changes were dose dependent, however no differences between vehicle groups were observed. The majority of rats in the 25 mg/kg bw/day groups exhibited only minimal to slight vacuolation. At 100 mg/kg bw/day, hepatic lesions observed included vacuolation, cytomegaly, nodular hyperplasia and necrosis.

Smialowicz et al. (1991) administered carbon tetrachloride to male Fischer 344 rats by gavage in corn oil at 0, 5, 10, 20, or 40 mg/kg bw/day for 10 consecutive days. Rats were sacrificed 2 days following the last treatment. Relative liver weight was increased at 40 mg/kg bw/day. Increased serum levels of AST and ALT were observed at 20 and 40 mg/kg bw/day. Histopathological examination of livers showed minimal to moderate vacuolar degeneration

at all doses other than the control. Minimal to mild hepatocellular necrosis was observed at 10 mg/kg bw/day and above.

In a study by Allis et al. (1990), 24 male F344 rats per dose group were administered carbon tetrachloride by gavage in corn oil (0, 20, or 40 mg/kg bw/day), 5 days per week for 12 weeks. Six rats from each dose level were sacrificed at 1, 3, 8, and 15 days post-exposure. At 1 day post-exposure, significant, dose-dependent increases in relative liver weight and serum levels of AST, ALT, and LDH were observed at both dose levels. Serum levels of alkaline phosphatase and cholesterol were significantly increased at the highest dose. At both doses, hepatic lesions observed included hepatocellular vacuolar degeneration, mild necrosis, and cirrhosis; cirrhosis was more severe at the higher dose. Recovery from the hepatotoxic effects was relatively rapid, with serum enzyme levels returning to normal and necrosis no longer evident at 8 days post-exposure. Cirrhosis and vacuolar degeneration were still evident at 15 days post-exposure, but had decreased in severity.

Hayes et al. (1986) administered carbon tetrachloride to 20 male and 20 female CD-1 mice per dose level by gavage in corn oil at 0, 625, 1250, or 2500 mg/kg bw/day for 14 days. A dose-dependent decrease in body weight was observed in male mice. Mortality was dose dependent, and females appeared less sensitive than males. Serum levels of lactate dehydrogenase (LDH), ALT and AST were significantly increased at all doses other than the control in both sexes; serum alkaline phosphatase levels were significantly increased at the highest dose only. Liver weights were significantly increased at all doses other than the control in males and females. In addition, the reported LD_{50} of carbon tetrachloride for mice (12 000–14 000 mg/kg bw) was confirmed by administration of carbon tetrachloride to 10 CD-1 mice of each sex, at a dose of 14 000 mg/kg, by corn oil gavage.

In another experiment, Hayes et al. (1986) administered carbon tetrachloride to 20 male and 20 female CD-1 mice per dose group by gavage in corn oil (0, 12, 120, 540, or 1200 mg/kg bw/day) for 90 days. Increases in liver and spleen weights and serum levels of LDH, ALT, AST and alkaline phosphatase were observed at all dose levels in both sexes. Histopathological examination of the liver showed evidence of hepatotoxicity in all treated mice. Hepatic lesions including necrosis, chronic hepatitis, hepatocytomegaly, and fatty change were evident at all doses other than the control and tended to increase in severity at higher doses. A NOAEL was not obtained in this study.

Guo et al. (2000) administered carbon tetrachloride to eight female B6C3F1 mice per dose by gavage in corn oil at doses of 0, 50, 100, 500, or 1000 mg/kg bw/day for 14 days. Liver weight was significantly increased at all doses other than the control. Histopathological examination of the liver showed hydropic changes and necrosis. Significant increases in serum ALT levels were observed at all dose levels other than the control. Carbon tetrachloride was immunotoxic at all doses other than the control, causing a decrease in humoral immune response, compromising the mononuclear phagocyte system, and decreasing host resistance to pathogenic bacteria.

Condie et al. (1986) conducted a subchronic study in mice comparing the effects of different gavage vehicles on carbon tetrachloride hepatotoxicity. Carbon tetrachloride was

administered to 12 male and 12 female CD-1 mice by gavage in either corn oil or 1% Tween-60 (0, 1.2, 12, or 120 mg/kg bw/day), 5 days per week for 90 days. Liver weights and liver to body weight ratios were increased at the high dose in both sexes with both vehicles. In mice receiving the corn oil vehicle, increases in serum enzyme activities (ALT, AST, LDH) were observed in the mid-dose groups, and substantial increases were seen in the high-dose groups. Significant increases in serum enzyme activities occurred only in the high-dose groups of mice that received carbon tetrachloride in Tween-60. Hepatocytomegaly was observed at the middle dose in mice receiving corn oil and in mice at the high dose with both vehicles. Moderate fat accumulation was observed at the middle dose in the livers of mice receiving corn oil only. Hepatic necrosis was observed in male mice at the middle and high doses with corn oil and at the high dose only with Tween-60. In female mice, necrosis was observed at the high dose with both vehicles. Necrosis and fatty infiltration were seen more frequently in male and female mice receiving carbon tetrachloride in corn oil. Fibrosis was detected at the high dose in both sexes with both vehicles. The NOAEL was 1.2 mg/kg bw/day when corn oil was used as the vehicle and 12 mg/kg bw/day when Tween-60 was used.

The toxicity of carbon tetrachloride following short-term inhalation exposure has also been studied in animals. Prendergast et al. (1967) exposed groups of Long-Evans or Sprague-Dawley rats (15 per group), Hartley guinea pigs (15 per group), squirrel monkeys (3 per group), New Zealand albino rabbits (3 per group), and beagle dogs (2 per group) to carbon tetrachloride by inhalation, either continuously (6.1 or 61 mg/m^3) for 90 days or repeatedly (515 mg/m^3) 8 h per day, 5 days per week, for 6 weeks. In animals exposed to 6.1 mg/m^3 continuously, no visible signs of toxicity were seen, and all animals survived the exposure period. All species except the rat showed decreased body weight gain. Following continuous exposure to 61 mg/m^3, three guinea pigs died on days 47, 63, and 71. All species showed decreased body weight gain, and all monkeys experienced hair loss and emaciation. In all species, liver changes observed included fatty changes associated with mononuclear cell infiltrates, fibroblastic proliferation, collagen deposition, hepatic cell degeneration and regeneration, and lobular alteration; these changes were more severe in rats and guinea pigs. After repeated exposure to 515 mg/m^3, one monkey died after the 7th exposure, and three guinea pigs died after the 20th, 22nd, and 30th exposures. Body weight loss was seen in all species except the rat. All species exhibited pulmonary interstitial inflammation or pneumonitis. Histopathological examination showed fatty changes in the livers of all species. In the livers of guinea pigs, fibrosis, bile duct proliferation, hepatocellular degeneration and regeneration, focal inflammatory cell infiltration, lobular alteration, and early portal cirrhosis were also observed.

In a short-term inhalation study, BDF1 mice and F344 rats (10 per sex per group) were exposed to carbon tetrachloride by whole-body inhalation (0, 10, 30, 90, 270, or 810 ppm) 6 h per day, 5 days per week, for 13 weeks. In male mice, body weight gain was decreased at 30 ppm and above, and decreased haemoglobin levels and increased mean platelet volume were observed at the highest dose (810 ppm). In female mice, decreased haemoglobin, haematocrit, and red blood cells were observed at the two highest doses. In mice of both sexes, increased liver enzymes in the blood were observed at 90 ppm and above. Microscopic examination showed slight to moderate dose-related changes in the liver, even at the lowest dose level in

males. At higher dose levels, more severe changes, described as collapse, deposit of ceroid, proliferative ducts, increase in mitosis, pleomorphism, and foci, were observed. In rats, a decrease in body weight gain was observed at the highest dose (810 ppm). Haematological changes were observed at 90 ppm and above in male rats and at 30 ppm and above in females. Increased liver enzymes in the blood and urinalysis changes were observed in male rats at 270 ppm and above and in females at 90 ppm and above. Microscopic examination showed slight to marked liver changes at all dose levels, including fatty change, cytological alterations, deposition of ceroid, proliferative ducts, increase in mitosis, pleomorphism, cirrhosis, and foci. At the two highest doses, vacuolar change of tubules, hyaline degeneration of the glomeruli, and protein casts were seen in the kidney (Japan Bioassay Research Centre, 1998).

A short-term inhalation study by Nagano et al. (2007) examined the subchronic toxicity of carbon tetrachloride in groups of 10 F344 rats and BDF1 mice (of both sexes) exposed to 0, 10, 30, 90, 270 or 810 ppm (v/v) of carbon tetrachloride vapour for 13 weeks (6 h/d and 5 d/wk). In the high exposure groups at 270 and 810 ppm, altered cell foci in the livers of both rats and mice, and fibrosis and cirrhosis in the rat liver were observed. Hematoxylin and eosin-stained altered cell foci of rats were recognized as glutathione-S-transferase placental form (GST-P) positive foci, which are preneoplastic lesions of hepatocarcinogenesis. The most sensitive endpoint of carbon tetrachloride-induced toxicity was fatty change with large droplets in rats of both sexes and male mice, and cytoplasmic globules in male mice, as well as increased relative liver weight in male rats. Those endpoints were manifested at 10 ppm and the LOAEL was determined as 10 ppm for the hepatic endpoints in rats and mice. Enhanced cytolytic release of liver transaminases into plasma in rats and mice and its close association with hepatic collapse in mice were observed at medium and high levels of inhalation exposure. Hematotoxicity and nephrotoxicity were observed in both rats and mice, but those toxicities were manifested at higher exposure concentrations than hepatotoxicity. A 6 hour inhalation exposure of rats and mice to 10 ppm carbon tetrachloride vapour corresponds to a daily uptake of 13 and 29 mg/kg bw, respectively, assuming a volume of 561 mL/min/kg bw for rats (Mauderly et al., 1979) and 1,239 mL/min/kg bw for mice (Guyton, 1947) and a lung absorption ratio of 100% for both rats and mice.

9.2.3 Long-term exposure and carcinogenicity

In long-term studies, hepatotoxicity and the development of liver tumours have been reported in mice, rats, and hamsters following oral and inhalation exposure to carbon tetrachloride.

Della Porta et al. (1961) administered carbon tetrachloride to 10 female and 10 male Syrian golden hamsters by gavage in weekly doses of 6.25–12.5 µL (equivalent to approximately 100–200 mg/kg bw/week) for 30 weeks. The livers of the nine animals dying during the treatment period and one female dying 11 weeks after treatment showed post-necrotic cirrhosis with regenerative hyperplastic nodules. All animals dying 13–24 weeks after treatment (two females) or sacrificed 25 weeks after treatment (three females and five males) had one or more liver cell carcinomas. No control groups were used in this study; however, the authors indicated that no liver cell tumours were observed in historical control groups.

Carbon tetrachloride was used as a positive control in National Cancer Institute carcinogenicity bioassays of chloroform and trichloroethylene. Doses of 47 and 94 mg/kg bw (males) and 80 and 159 mg/kg bw (females) were administered daily by gavage in corn oil 5 days per week to groups of 50 male and 50 female Osborne-Mendel rats for 78 weeks. Surviving rats were sacrificed at 110 weeks. Carbon tetrachloride treatment caused marked hepatotoxicity with resultant fibrosis, bile duct proliferation, and regeneration. A decrease in survival was also observed in treated rats. An increased incidence of hepatocellular carcinoma and neoplastic nodules was seen at both doses in both sexes. In the same study, doses of 1250 mg/kg bw and 2500 mg/kg bw were administered daily by gavage in corn oil 5 days per week to groups of 50 male and 50 female B6C3F1 mice for 78 weeks. Surviving mice were sacrificed at 90 weeks. Only 14% of treated mice survived to 78 weeks, and less than 1% survived to 90 weeks, compared with 66% of untreated controls surviving to 90 weeks. Hepatocellular carcinomas were found in almost all (>98%) treated mice, including those dying before termination of the test (NCI, 1976a,b).

In an inhalation study, groups of 50 male and 50 female BDF1 mice and F344 rats were exposed to 0, 5, 25, or 125 ppm carbon tetrachloride 6 h per day, 5 days per week, for 104 weeks. In mice, a significant decrease in survival was observed at 25 and 125 ppm. Decreases in body weight gain, as well as changes in haematology, blood biochemistry, including liver enzymes, and urinalysis were also observed at the two highest doses. In male mice, protein casts in the kidney and liver changes, including deposit of ceroid, cyst, and degeneration, were observed at 25 and 125 ppm. In the spleen, there was an increase in haemosiderin deposit at 25 ppm, and extramedullary haematopoeisis was observed at 125 ppm. In female mice, changes in the liver included deposit of ceroid, thrombus, necrosis, degeneration, and cyst at 25 and 125 ppm. At 25 ppm, an increased deposit of haemosiderin of the spleen was observed, whereas at 125 ppm, deposit of ceroid of the ovary was seen. The incidence of hepatocellular adenomas was significantly increased at 25 and 125 ppm in males and at 5 and 25 ppm in females. The incidence of hepatocellular carcinomas was significantly increased at 25 and 125 ppm in male and female mice. The incidence of pheochromocytomas of the adrenal gland was increased in male mice at 25 and 125 ppm and in female mice at 125 ppm (Japan Bioassay Research Centre, 1998; Nagano et al., 1998).

In rats, survival was significantly decreased at the highest dose, and body weight gain was decreased at the two highest doses. Changes in haematology, blood biochemistry, including liver enzymes, and urinalysis were observed at 25 ppm; changes in the nitrate and protein levels in the urine were also observed at 5 ppm. Liver changes observed in both sexes at the two highest doses included fatty change, deposit of ceroid, fibrosis, granulation, and cirrhosis. In males at all doses other than the control, an increased deposit of haemosiderin in the spleen was observed. Chronic nephropathy (progressive glomerulonephrosis) was observed in females at 25 ppm and in both sexes at 125 ppm. At 125 ppm, deposit of ceroid and granulation of the lymph nodes were observed in both sexes. The incidence of hepatocellular adenomas and hepatocellular carcinomas was significantly increased at 125 ppm in both sexes (Japan Bioassay Research Centre, 1998; Nagano et al., 1998).

Results of chronic studies in rodents exposed orally or by inhalation indicate that hepatic tumours were induced at hepatotoxic doses. The carcinogenicity of carbon tetrachloride appears to be secondary to its hepatotoxic effects, which suggests that a threshold for carbon tetrachloride carcinogenicity may exist.

9.2.4 Mutagenicity and genotoxicity

A range of *in vitro* and *in vivo* assays has been performed to assess the possible genotoxic effects of carbon tetrachloride. DNA- or chromosome-damaging effects have been evaluated in bacteria, fungi, yeast, insects, rodents, and humans.

Negative results have been reported for the majority of mutagenicity assays with carbon tetrachloride in bacteria. Owing to the volatility of carbon tetrachloride, in some cases the use of unsealed vessels may have resulted in false negatives. In addition, carbon tetrachloride requires metabolic activation, and reactive metabolites produced by exogenous activation systems may not be able to cross cell membranes and reach DNA.

Although a few positive results have been reported, the majority of *Salmonella typhimurium* reversion assays of carbon tetrachloride have been negative with and without metabolic activation (McCann et al., 1975; Uehleke et al., 1977; Barber et al., 1981; De Flora, 1981; De Flora et al., 1984; Brams et al., 1987; Araki et al., 2004). Increased reversion frequency was observed in *Escherichia coli* strains WP2uvrA/pKM101 and WP2/pKM101, with and without activation (Araki et al., 2004). Negative results were reported for the Ara forward mutation assay in *S. typhimurium* strains BA13 and BAL13, as well as for SOS induction in *S. typhimurium* strain TA1535/psK1002 and *E. coli* strain PQ37 (Brams et al., 1987; Nakamura et al., 1987; Roldán-Arjona et al., 1991). Carbon tetrachloride did not induce differential DNA repair in *E. coli* strains K-12 343/113 (Hellmér and Bolcsfoldi, 1992). Induction of differential DNA repair was observed in *E. coli* strains WP2, WP67, and CM871 when sealed plates were used without activation; however, assays using sealed plates with activation, as well as spot tests without activation, were negative (De Flora et al., 1984).

Induction of mitotic, intrachromosomal, and interchromosomal recombination was observed in various strains of the yeast *Saccharomyces cerevisiae* exposed to toxic concentrations of carbon tetrachloride (Callen et al., 1980; Schiestl et al., 1989; Galli and Schiestl, 1995, 1996; Brennan and Schiestl, 1998). Carbon tetrachloride did not induce aneuploidy in *S. cerevisiae* (Whittaker et al., 1989). Assays in the mould *Aspergillus nidulans* were weakly positive for forward mutation and positive for somatic segregation at cytotoxic concentrations (Gualandi, 1984; Benigni et al., 1993).

Mixed results have been obtained from *in vitro* genotoxicity assays in mammalian cells. Carbon tetrachloride did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes (Selden et al., 1994); however, weakly positive results were reported for UDS in human lymphocytes exposed to cytotoxic doses of carbon tetrachloride (Perocco and Prodi, 1981). Increases in DNA single-strand breaks were observed in rat hepatocytes and mouse lymphoma cells exposed to cytotoxic concentrations of carbon tetrachloride (Sina et al., 1983; Garberg et al., 1988; Beddowes et al., 2003). Negative results were reported for induction of DNA damage in human lymphocytes (Tafazoli et al., 1998). In one study, chromosomal aberrations were

detected at anaphase following exposure of Chinese hamster ovary (CHO) cells to carbon tetrachloride; however, the results of other assays using CHO cells, ovine lymphocytes, human lymphocytes, and rat hepatocyte cell line RL1 were negative for chromosomal aberrations (Coutino, 1979; Dean and Hodson-Walker, 1979; Garry et al., 1990; Loveday et al., 1990; Šiviková et al., 2001). Carbon tetrachloride did not increase the frequency of sister chromatid exchange (SCE) in CHO cells or human lymphocytes; however, SCE was induced in ovine lymphocytes following exposure to carbon tetrachloride for 48 h (Garry et al., 1990; Loveday et al., 1990; Šiviková et al., 2001). Carbon tetrachloride also induced aneuploidy in Chinese hamster V79 lung cells (Önfelt, 1987). Micronucleus formation was induced by carbon tetrachloride in ovine lymphocytes, as well as in human lymphocytes from one of two donors (Tafazoli et al., 1998; Šiviková et al., 2001). Carbon tetrachloride induced micronuclei in human lymphoblastoid cell lines MCL-5, which expresses human cDNA for CYP1A2, 2A6, 3A4, 2E1, and microsomal epoxide hydrolase, and h2E1, which expresses cDNA for human CYP2E1 (Doherty et al., 1996).

The majority of *in vivo* genotoxicity assays with carbon tetrachloride have been negative. Although some positive results have been reported, these effects were observed only at cytotoxic doses. In studies in *Drosophila melanogaster*, no sex-linked recessive mutations were induced following exposure of males to carbon tetrachloride in the diet or by injection prior to mating (Foureman et al., 1994). There was no UDS in hepatocytes isolated from male Fischer 344 rats 2–48 h following carbon tetrachloride exposure by gavage (Mirsalis and Butterworth, 1980; Mirsalis et al., 1982). However, in a study by Craddock and Henderson (1978), UDS was observed 17 h after oral exposure of female Wistar rats to carbon tetrachloride. The authors suggested that the DNA damage may have been caused by an indirect process, such as DNase activity resulting from lysosomal damage (Craddock and Henderson, 1978). In most studies, no DNA damage was observed in mice or rats following carbon tetrachloride treatment by gavage or injection (Schwarz et al., 1979; Stewart, 1981; Bermudez et al., 1982; Barbin et al., 1983; Brambilla et al., 1983). Positive results have been reported for DNA damage in the liver of CD-1 mice; however, DNA damage was observed only at doses also resulting in liver necrosis (Gans and Korson, 1984; Sasaki et al., 1998). No increases in chromosomal aberrations, SCE, or micronuclei were detected in the liver of male F344 rats orally exposed to carbon tetrachloride at 1600 mg/kg bw by gavage 4–72 h prior to sacrifice (Sawada et al., 1991). In several studies, micronuclei were not induced in the bone marrow or peripheral blood of CD-1 or BDF1 mice treated with carbon tetrachloride at doses up to 3000 mg/kg bw (Morita et al., 1997; Suzuki et al., 1997; Crebelli et al., 1999).

Although results of *in vivo* genotoxicity assays were largely negative, carbon tetrachloride has been shown to produce an increase in DNA adducts following exposure *in vivo*. Covalent binding of reactive carbon tetrachloride metabolites to liver DNA and nuclear proteins was detected following treatment of mice, rats, and hamsters with carbon tetrachloride (Castro et al., 1989). Carbon tetrachloride treatment also resulted in an increase in lipid peroxidation induced DNA adducts. Following injection of F344 rats with carbon tetrachloride, an increase in hydroxynonenal-deoxyguanosine adducts has been observed in the liver, forestomach, lung,

and colon (Chung et al., 2000; Wacker et al., 2001). Increases in malondialdehyde-DNA adducts have also been observed in the liver of Sprague-Dawley rats and liver and kidney of Syrian golden hamsters treated with carbon tetrachloride by gavage (Chaudhary et al., 1994; Wang and Liehr, 1995). DNA adducts have also been detected in mammalian cells following exposure to carbon tetrachloride *in vitro*. In rat hepatocytes treated with carbon tetrachloride, a dose-dependent increase in malondialdehyde-deoxyguanosine adducts was observed, and increased 8-oxo-deoxyguanosine adducts were detected at the highest dose, which was also cytotoxic (Beddowes et al., 2003). *In vitro*, it has been demonstrated that reactive carbon tetrachloride metabolites are able to covalently bind to guanine, cytosine, and thymine, producing the altered bases 2,6-diamino-4-hydroxy-5-formamidopyrimidine, 5-hydroxycytosine, and 5-hydroxy-methyluracil (Castro et al., 1997). Increased covalent binding of carbon tetrachloride metabolites to calf thymus DNA has also been demonstrated following *in vitro* metabolic activation (DiRenzo et al., 1982).

In summary, while the genotoxicity data are not fully conclusive, there is some evidence that carbon tetrachloride exerts a weak genotoxic effect, likely secondary to cytotoxicity.

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental effects of carbon tetrachloride have been studied in rats and mice. In an inhalation study by Adams et al. (1952), rats were exposed to 5, 10, 25, 50, 100, 200, or 400 ppm carbon tetrachloride for 7 h per day, 5 days per week, for 24–29 weeks. At 200 ppm, the weight of the testes was decreased, and some tubules showed complete atrophy of the germinal elements. Moderate to marked degeneration of the germinal elements of the testes was observed at 400 ppm (Adams et al., 1952). In a multigenerational study, groups of male and female rats were exposed to 50, 100, 200, or 400 ppm carbon tetrachloride by inhalation, 8 h per day, 5 days per week, for up to 10.5 months. A decrease in fertility was observed at 200 and
400 ppm; however, since both sexes were exposed, it not clear whether this was due to effects on the males or females (Smyth et al., 1936).

In a study by Alumot et al. (1976), male and female rats were fed fumigated mash with a residual carbon tetrachloride concentration of up to 200 ppm (10–18 mg/kg bw) for 2 years. There was no effect on fertility, litter size and weight, or pup mortality. Oral administration of carbon tetrachloride to pregnant B6D2F1 mice at 82.6 or 826 mg/kg bw/day for 5 days beginning on gestation day 1, 6, or 11 had no effect on maternal body weight, liver and kidney weight, or pregnancy. No malformations or effects on pup weight or crown–rump length were observed, and development of the pups was normal (Hamlin et al., 1993).

Narotsky et al. (1997a) administered carbon tetrachloride to pregnant Fischer 344 rats by gavage at dose levels of 0, 25, 50, or 75 mg/kg bw/day on gestation days 6–15 in either corn oil or an aqueous vehicle. No maternal or developmental toxicity occurred at 25 mg/kg bw/day. Full litter resorption was observed at 50 and 75 mg/kg bw/day with both vehicles, and the incidence of full litter resorption was significantly greater at 75 mg/kg bw/day with corn oil than with the aqueous vehicle. No effects on gestation length, pre- or postnatal survival, or pup morphology were observed in the surviving litters (Narotsky et al., 1997a). When a single dose of carbon

tetrachloride (150 mg/kg bw) was administered to pregnant Fischer 344 rats on gestation day 6, 7, 8, 10, or 12, full litter resorption was observed in 36–72% of dams treated on gestation days 6–10; none was seen in dams treated on gestation day 12. No developmental toxicity was observed in the surviving litters (Narotsky et al., 1997b).

Inhalation exposure of pregnant Sprague-Dawley rats to 330 or 1000 ppm carbon tetrachloride for 7 h per day on gestation days 6–15 caused maternal hepatotoxicity and significant reductions in food consumption and maternal body weight. There was no effect on conception rate, number of implantations, litter size, or number of resorptions. No gross anomalies were observed; however, significant reductions in fetal body weight and crown–rump length were observed at both concentrations, and the incidence of sternebral anomalies was significantly increased at 1000 ppm (Schwetz et al., 1974).

9.2.6 Mode of action

In humans and laboratory animals, the major effect of exposure to carbon tetrachloride is hepatotoxicity, including fatty degeneration, necrosis, fibrosis, and cirrhosis. Hepatic tumours are also observed in rodents following chronic exposure to carbon tetrachloride. The mechanism of carbon tetrachloride carcinogenicity may involve both genotoxic and non-genotoxic processes. Hepatic tumours occur at doses higher than those inducing hepatotoxicity; therefore, the carcinogenicity of carbon tetrachloride may be secondary to its toxic effects (ATSDR, 2005).

The liver is particularly sensitive to carbon tetrachloride toxicity due to high levels of CYP2E1, the enzyme primarily responsible for the bioactivation of carbon tetrachloride to reactive metabolites (Raucy et al., 1993; Wong et al., 1998; Zangar et al., 2000). Carbon tetrachloride is bioactivated to form the trichloromethyl radical, which can react with oxygen, forming the trichloromethyl peroxyl radical (Pohl et al., 1984). Carbon tetrachloride-induced hepatic toxicity has been studied extensively, but similar cellular damage would be expected in other tissues with high levels of CYP2E1 (ATSDR, 2005).

Reactive carbon tetrachloride metabolites mediate hepatic injury by two initial processes: haloalkylation and lipid peroxidation (Weber et al., 2003). Haloalkylation of cellular macromolecules such as nucleic acids, proteins, and lipids can lead to impairment of cellular processes. Metabolism of carbon tetrachloride *in vitro* by rat liver microsomes and *in vivo* leads to covalent binding of trichloromethyl radicals to lipids (Link et al., 1984); lipid haloalkylation is involved in the early phases of impaired lipid secretion by the Golgi apparatus, which can lead to fatty degeneration (Poli et al., 1990). Covalent binding of reactive carbon tetrachloride metabolites to DNA and nuclear proteins in livers of rats, mice, and hamsters has also been detected (Castro et al., 1989).

Lipid peroxidation can be initiated by the trichloromethyl peroxyl radical and results in the destruction of polyunsaturated fatty acids, particularly membrane phospholipids. This affects the permeabilities of mitochondrial, endoplasmic reticulum, and plasma membranes, impairing cellular functions dependent on membrane integrity (Weber et al., 2003). Lipid peroxidation also results in the formation of reactive aldehydes, such as 4-hydroxynonenal and malondialdehyde, which can bind to proteins and DNA (Weber et al., 2003). 4-Hydroxynonenal and malondialdehyde protein adducts have been detected in the livers of rats treated with carbon

tetrachloride (Hartley et al., 1999). Increased levels of 4-hydroxynonenal-deoxyguanosine adducts have also been observed in the liver DNA of carbon tetrachloride-treated rats (Chung et al., 2000; Wacker et al., 2001).

Several studies have suggested that the increased cytosolic calcium concentrations observed following carbon tetrachloride exposure may play a central role in the induction of cytotoxicity. Prolonged elevation of cytosolic calcium may activate calcium-dependent hydrolytic enzymes capable of causing irreversible cellular injury or death. Early studies showed that carbon tetrachloride exposure was associated with decreased calcium storage by the endoplasmic reticulum, and that this effect correlated well with decreased calcium pump activity (Long and Moore, 1986). More recently, carbon tetrachloride exposure has also been shown to inhibit calcium pumps in the mitochondria and plasma membrane (Hemmings et al., 2002).

The carcinogenicity of carbon tetrachloride appears to be secondary to its hepatotoxic effects, which suggests that a threshold for carbon tetrachloride carcinogenicity may exist. There is evidence that the mechanism involves both genotoxic and non-genotoxic processes. The ability of reactive carbon tetrachloride metabolites to bind to DNA (Castro et al., 1989) indicates that carbon tetrachloride is potentially genotoxic. However, the results of most *in vivo* studies in animals suggest that genotoxic effects occur only at cytotoxic doses. Since lipid peroxidation products such as 4-hydroxynonenal and malondialdehyde also have the ability to form adducts with DNA (Chaudhary et al., 1994; Chung et al., 2000; Wacker et al., 2001), the genotoxic effect of carbon tetrachloride may be indirect, secondary to lipid peroxidation. Carbon tetrachloride may also cause cancer by a non-genotoxic mechanism involving regenerative hyperplasia. Hepatic necrosis stimulates cellular regeneration; the resulting increase in cell proliferation increases the possibility that unrepaired DNA damage will become fixed mutations, possibly resulting in an initiated preneoplastic cell (ATSDR, 2005).

10.0 Classification and assessment

Carbon tetrachloride has been classified in Group IIIC (Health Canada, 1994), possibly carcinogenic to humans, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in experimental animals. Although Health Canada's previous guideline was based on carcinogenesis, the carcinogenicity of carbon tetrachloride now appears to be secondary to its hepatotoxic effects in animal studies, suggesting that a threshold may exist. This is consistent
with the classifications established by the International Agency for Research on Cancer of Group 2B (IARC, 1999), possibly carcinogenic to humans, based on inadequate evidence in humans, but sufficient evidence in animals, and by the U.S. EPA of Group B2 (IRIS, 1991), probably carcinogenic to humans, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in experimental animals. The U.S. Department of Health and Human Services has determined that carbon tetrachloride may reasonably be anticipated to be a carcinogen (ATSDR, 2005).

Epidemiological studies suggesting an association between carbon tetrachloride exposure and cancer were confounded by many factors, including exposure to other substances in drinking water or in industrial settings, lack of adequate control groups, and lack of statistical significance

of effects. These studies are therefore inadequate to infer a causal relationship between carbon tetrachloride and cancer in humans (IPCS, 1999).

Studies in animals have shown an increased incidence of hepatic tumours in rats, mice, and hamsters following oral or inhalation exposure to carbon tetrachloride. IPCS (1999) has indicated that many genotoxicity assays have been conducted with carbon tetrachloride. On the basis of available data, carbon tetrachloride can be considered as a non-genotoxic compound. Carbon tetrachloride induces hepatomas and hepatocellular carcinomas in mice and rats, however the doses inducing hepatic tumours are higher than those inducing cell toxicity. Despite evidence of the carcinogenicity of carbon tetrachloride in animals, there are numerous deficiencies identified
in the cancer studies (e.g., inappropriate routes of exposure, poor dose response, excessive mortality, inadequate sample size). Consequently, the TDI approach is considered appropriate to calculate the guideline for carbon tetrachloride in drinking water. In addition, the carcinogenicity of carbon tetrachloride appears to be secondary to its hepatotoxic effects, suggesting that a threshold may exist. There is evidence that the mechanism of carbon tetrachloride carcinogenicity involves both genotoxic and non-genotoxic processes. The ability of reactive carbon tetrachloride metabolites and lipid peroxidation products to bind to DNA indicates potential for genotoxicity. However, results of most *in vivo* studies in animals suggest that genotoxic effects may be secondary to cytotoxicity. Carbon tetrachloride may also cause cancer by non-genotoxic mechanisms involving regenerative hyperplasia.

As there are no adequate long-term studies on carbon tetrachloride, the subchronic rat study by Bruckner et al. (1986) was chosen as the most appropriate study for risk assessment. The subchronic rodent studies conducted by Condie et al. (1986), Hayes et al. (1986), and Allis et al. (1990) support the choice of the Bruckner et al. (1986) study, as similar hepatotoxic effects were observed in these studies at similar doses. It should be noted that carbon tetrachloride was administered to rats as a single oral bolus in corn oil in Bruckner et al. (1986), which does not represent the typical exposure scenario in humans. Sanzgiri et al. (1995) demonstrated that carbon tetrachloride was significantly more hepatotoxic when administered as a single oral bolus than when it was administered by gastric infusion over a period of 2 hours. Furthermore, Bruckner et al. (1986) dosed the rats with carbon tetrachloride soon after the beginning of their light/inactive period, which has since been shown to result in increased susceptibility to carbon tetrachloride hepatotoxicity. This effect is likely related to restricted food intake during the inactive period, as fasting is known to increase CYP2E1 activity and potentiate carbon tetrachloride hepatotoxicity (Bruckner et al., 2002). Given the experimental evidence suggesting that the dosing regimen and timing used in the Bruckner et al. (1986) study may have influenced the observed toxicity, the guideline derived from this study is based on a conservative approach.

The TDI for carbon tetrachloride is calculated as follows:

$$\text{TDI} = \frac{0.71 \text{ mg/kg bw/day}}{1000}$$

$$= 0.000\,71 \text{ mg/kg bw/day}$$

$$= 0.71 \text{ µg/kg bw/day}$$

where:

- 0.71 mg/kg bw/day is the adjusted NOAEL; a NOAEL of 1 mg/kg bw/day determined from Bruckner et al. (1986) was multiplied by 5/7 to correct for a dosing schedule of 5 days per week; and
- 1000 is the uncertainty factor (×10 for interspecies variability; ×10 for intraspecies variability; ×10 for major database deficiencies, including lack of adequate chronic studies and evidence regarding carcinogenic mode of action in animals).

Using this TDI, the maximum acceptable concentration (MAC) for carbon tetrachloride in drinking water is derived as follows:

$$\text{MAC} = \frac{0.000\,71 \text{ mg/kg bw/day} \times 70 \text{ kg} \times 0.20}{4.3 \text{ L-eq/day}}$$

$$= 0.0023 \text{ mg/L}$$

$$= 0.002 \text{ mg/L (rounded)}$$

where:

- 0.000 71 mg/kg bw/day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.20 is the default allocation factor for drinking water in the absence of adequate exposure data from all exposure media; and
- 4.3 L-eq/day is the daily volume of water consumed by an adult, which accounts for the following multi-route exposure: 1.0 L-eq/day from dermal absorption, and 1.8 L-eq/day from inhalation.

A quantitative cancer risk assessment was conducted by Health Canada (2006b) to estimate the unit risks associated with hepatocellular carcinomas and adenomas in rats and mice from two studies (Weisburger, 1977; Nagano et al., 1998). Concentrations of carbon tetrachloride in drinking water yielding risks of 1×10^{-5} and 1×10^{-6} range from 1.0 to 30 µg/L and 0.1 to 3.0 µg/L, respectively. Health Canada's confidence in these estimated unit risks is low due to the quality of the studies and the lack of fit of the Nagano et al. (1998) data to the statistical model applied. This further supports the choice of the TDI approach as the most appropriate approach for developing a MAC for carbon tetrachloride in drinking water.

10.1 International Considerations

The current U.S. EPA maximum contaminant level (MCL) for carbon tetrachloride is 5 µg/L (U.S. EPA, 1998b) based on the carcinogenic potential of carbon tetrachloride. The U.S. EPA approach calculated the geometric mean of the upper limit unit risk estimates (3.7×10^{-6}) from data from four animal studies, and selected this mean as the unit risk corresponding to drinking water containing 1 µg/L. A human water consumption of 2 L/d and a human body weight of 70 kg were used to derive a slope factor of 1.3×10^{-1} (mg/kg bw/d)$^{-1}$ from the above unit risk (U.S. EPA, 1984, 1989).

The WHO established a drinking water guideline of 4.0 µg/L based on a NOAEL of 1 mg/kg from Bruckner et al. (1986) for hepatotoxic effects in rats. The guideline value is based on 10% allocation of the TDI to drinking water and assuming a 60 kg adult drinking 2 litres of water per day. WHO reported this value to be lower than the range of values associated with lifetime upperbound excess cancer risks of 10^{-4}, 10^{-5} and 10^{-6} calculated by linear extrapolation (WHO, 2004a).

The California EPA has developed a public health goal (PHG) of 0.1 µg/L (or 0.1 ppb) for carbon tetrachloride in drinking water (OEHHA, 2000). The PHG is based on an increased incidence of hepatocellular carcinomas in mice, an estimated cancer potency of 1.8×10^{-1} (mg/kg bw/day)$^{-1}$ and a *de minimis* theoretical excess individual cancer risk level of 10^{-6}. California's current drinking water standard for carbon tetrachloride is 0.5 µg/L. The California Department of Health Services (DHS) adopted this standard, referred to as the state maximum contaminant level (MCL), in 1988.

The Australian drinking water guideline for carbon tetrachloride is 3 µg/L based on a NOAEL of 1.2 mg/kg body weight per day for hepatotoxicity in mice. The guideline value is based on 10% allocation of the TDI to drinking water and assuming a 70 kg adult drinking 2 litres of water per day (NHMRC, 2004).

11.0 Rationale

Although carbon tetrachloride is no longer produced in Canada, Canadians may be exposed to carbon tetrachloride through air and drinking water due to its continued presence in the environment. Carbon tetrachloride is unlikely to pose a concern from surface water sources because of its high volatility, but may be a problem from groundwater. Carbon tetrachloride's high volatility indicates that inhalation and dermal absorption during bathing and showering may also serve as important routes of exposure. As a result, this assessment incorporates a multi-route exposure approach.

Carbon tetrachloride is classified as a possible human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals. This is consistent with the classifications established by both IARC and the U.S. EPA. A TDI approach was chosen to derive the Maximum Acceptable Concentration for carbon tetrachloride in drinking water, because of the major deficiencies in the available cancer studies, and because animal studies suggest that the carcinogenicity of carbon tetrachloride is secondary to its hepatotoxic effects, indicating a possible threshold. Consequently, the MAC of 0.002 mg/L is established based on

hepatotoxicity (observed increase in SDH activity and mild hepatic centrilobular vacuolization in a subchronic rat study), and incorporates an additional uncertainty factor of 10 to accommodate for database deficiencies.

This MAC is achievable by available treatment technology at both the municipal and residential scales, and measurable by available analytical methods. As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change to the guideline that it deems necessary.

12.0 References

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Appendix A: List of acronyms

ALT	alanine aminotransferase
ANSI	American National Standards Institute
AST	aspartate aminotransferase
bw	body weight
cDNA	complementary deoxyribonucleic acid
CHO	Chinese hamster ovary
CI	confidence interval
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
EBCT	empty bed contact time
EPA	Environmental Protection Agency (United States)
GAC	granular activated carbon
K_{oc}	soil adsorption coefficient
K_{ow}	*n*-octanol/water partition coefficient
K_p	skin permeability coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
L-eq/day	litre equivalents per day
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MDL	method detection limit
ML	million litres
NOAEL	no-observed-adverse-effect level
NSF	NSF International
OR	odds ratio
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PQL	practical quantitation limit
PTA	packed tower aeration
SCC	Standards Council of Canada
SCE	sister chromatid exchange
SDH	sorbitol dehydrogenase
TDI	tolerable daily intake
UDS	unscheduled DNA synthesis
VOC	volatile organic compound