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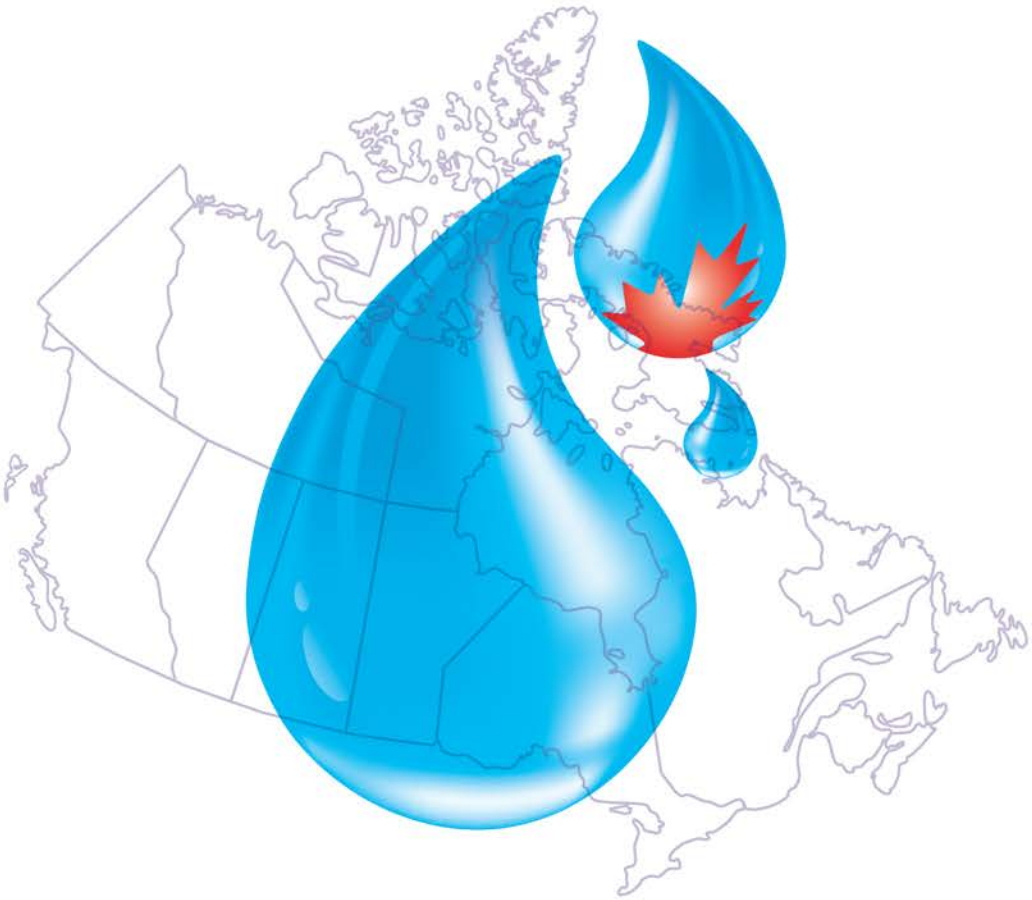
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Tetrachloroethylene



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Tetrachloroethylene

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

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Tetrachloroethylene

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for tetrachloroethylene in drinking water is 0.010 mg/L (10 µg/L).

2.0 Executive summary

Tetrachloroethylene is primarily a synthetic chemical. In Canada, it is mostly used as a solvent in the dry cleaning industry and as an intermediate in chemical synthesis. Information on its release in drinking water is primarily from reported spills. Tetrachloroethylene has not been produced in Canada since 1992; it is still being imported, primarily from the U.S.

This guideline technical document reviews and assesses all identified health risks associated with tetrachloroethylene in drinking water, incorporating all relevant routes of exposure from drinking water—namely, ingestion as well as inhalation and skin absorption from showering and bathing.

It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology in order to establish a maximum acceptable concentration that is protective of human health, measurable and achievable by both municipal and residential scale treatment technologies. Based on this review, the drinking water guideline for tetrachloroethylene has been established at a maximum acceptable concentration of 0.010 mg/L (10 µg/L).

2.1 Health effects

Tetrachloroethylene has repeatedly caused various types of cancers in experimental animals by inhalation and ingestion, including liver tumors in mice and leukemia in rats. The cancer risk assessment was based on liver tumors in mice. Studies on the carcinogenic effects of tetrachloroethylene in humans, including those from long term occupational exposures, are inconsistent, and available evidence is not sufficient to draw conclusions regarding cancer effects.

Various non-cancer health effects related to inhalation or ingestion of tetrachloroethylene were observed in humans and/or animals. These effects include neurological, liver, kidney and reproductive/developmental effects. The non-cancer risk assessment was based on neurological effects (color confusion) in humans, occurring at the lowest level of exposure.

Both cancer and non-cancer risk assessments were considered in the derivation of the MAC. The non-cancer risk assessment produces a MAC that is protective of human health from both cancer and non-cancer effects.

2.2 Exposure

Canadians can be exposed to tetrachloroethylene in the workplace or through its presence in air, drinking water, food and possibly through the use of specific consumer products. Exposure is mainly from air, particularly indoor air. Tetrachloroethylene is not frequently found in Canadian drinking water supplies, and its presence would normally be associated with a spill or

another point source of contamination. Because tetrachloroethylene is highly volatile, it is more frequently found in groundwater than in surface water. When present in drinking water, it may be absorbed through ingestion, inhalation and skin absorption.

2.3 Analysis and treatment

The establishment of a drinking water guideline must take into consideration the ability to both measure the contaminant and remove it from drinking water supplies. Tetrachloroethylene can be reliably measured in drinking water at the MAC.

At the municipal level, conventional treatment techniques are not effective for the removal of tetrachloroethylene. The best available technologies for removing tetrachloroethylene from drinking water are packed tower aeration and granular activated carbon. Taking into consideration currently available technologies, municipal treatment plants are expected to be able to consistently achieve concentrations below the MAC.

At the residential scale, there are certified point-of-use treatment devices available that can remove volatile organic chemicals (VOCs) such as tetrachloroethylene from drinking water to meet the MAC. They rely on adsorption (activated carbon) technologies and may be installed at the faucet (point-of-use) or at the location where water enters the home (point-of-entry). From a health perspective, point-of-entry systems are preferred for the removal of VOCs, because they provide treated water for bathing and laundry as well as for cooking and drinking. This will decrease the potential for VOC exposure through inhalation.

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.

Generally, tetrachloroethylene is not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily. However, the anaerobic conditions of groundwater increases biodegradation time of tetrachloroethylene, which is usually detected in groundwater in the vicinity of sites where there have been spills or other potential contamination with this compound.

The drinking water guideline is based on lifetime exposure (70 years) to tetrachloroethylene in drinking water. For drinking water supplies that occasionally experience short-term exceedances above the guideline values, it is suggested that a plan be developed and implemented to address these situations. For more significant, long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of water for drinking, showering, and bathing be considered.

3.1 Monitoring

Groundwater sources should be characterized to determine if tetrachloroethylene is present, especially if the land use history is unknown. Quarterly monitoring for tetrachloroethylene should be conducted for groundwater sources that are or may have been impacted by spills or other potential contamination with this compound. Authorities may consider reduced monitoring when it has been demonstrated that a previously contaminated site has been successfully remediated.

Although components and coatings for distribution system pipes are now required to meet standards that limit the leaching of contaminants, distribution pipes installed prior to the 1983 may leach tetrachloroethylene if a vinyl-toluene lining was used to rehabilitate the inside of

asbestos-cement pipes. Since this type of pipe lining was discontinued in 1983, it is generally not expected that tetrachloroethylene will be found in the distribution system. Quarterly monitoring for tetrachloroethylene should be undertaken in the areas of the distribution system where old asbestos-cement pipes with vinyl-toluene lining are located, specifically at locations with the maximum residence time (e.g., dead ends). Utilities that have baseline data indicating that tetrachloroethylene is not present within the distribution system may conduct less frequent monitoring. Jurisdictions may consider reduced sampling if an appropriate flushing protocol is in place.

In the event that monitoring data show elevated levels of tetrachloroethylene, 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

Tetrachloroethylene (C_2Cl_4; molecular mass 165.85 g/mol; Chemical Abstracts Service No. 127-18-4), also known as tetrachloroethene, perchloroethylene, PERC, PER, PCE and ethylene tetrachloride, is a clear, colourless, non-flammable liquid with an ether-like odour (ECETOC, 1999; WHO, 2000). The odour threshold for tetrachloroethylene in water has been reported as 0.3 mg/L by other agencies (ATSDR, 1997;WHO, 2003), although no primary reference has been found. The odour threshold for tetrachloroethylene in air is ≥0.77 ppm[1] (Leonardos et al., 1969; Nagata, 2003). At room temperature, tetrachloroethylene is a volatile liquid with a high vapour pressure (1.9 kPa at 20°C). Tetrachloroethylene has a melting point of −22°C and a boiling point of 121°C, with a density of 1.623 g/cm^3 (European Commission, 2005). Tetrachloroethylene is relatively insoluble in water (i.e., 150 mg/L at 25°C) (WHO, 2003) and has a low log octanol/water partition coefficient (2.53) (European Commission, 2005). With bioconcentration factors reported to range from 39 to 49, tetrachloroethylene is not expected to bioconcentrate in organisms or to biomagnify within food chains (U.S. EPA, 2012a).

In Canada, the predominant uses of tetrachloroethylene are as a solvent in the dry cleaning industry and as an intermediate in chemical synthesis (e.g., of fluorocarbons). Other uses for this solvent include processing and finishing in the textile industry, as an extraction solvent, as an anthelmintic, as a heat exchange fluid and in grain fumigation. In addition, tetrachloroethylene is used as an insulating fluid and cooling gas in electrical transformers and in paint removers, printing inks, adhesive formulations, paper coatings and aerosol formulations such as water repellents (Government of Canada, 1993; CPI, 2004; HSDB, 2007). Regulations concerning the use of tetrachloroethylene in Canadian dry cleaning operations and establishing reporting requirements on the importation, recycling, sale and use of tetrachloroethylene were adopted in 2003 and amended in 2011 (Environment Canada, 2011).

The manufacture of tetrachloroethylene in Canada ceased in 1992 (CPI, 2004). Import levels in 2013 were 10.4 kilotons (9.5 kilotonnes), and were primarily (97%) from the United States. Imports in 2009–2012 ranged from 7.7 to 12.3 kilotons (7.0 to 11.2 kilotonnes; International Trade Centre, 2014).

Tetrachloroethylene's entry into the environment is primarily from anthropogenic sources (Government of Canada, 1993), but there has been one report of marine algae that can naturally produce tetrachloroethylene (Abrahamsson et al., 1995). The majority (>97%) of anthropogenic tetrachloroethylene releases in Canada are to air, with <0.1% of releases in water. Releases to water have decreased over time, with the highest levels (annual average of 0.076 tonnes) observed between 1994 and 1996, decreasing to an annual average of 0.032 tonnes in 1997–2005, to an even lower annual average of 0.003 tonnes in 2006–2012. Air releases similarly decreased from an average annual release of 204 tonnes in 1994–2001 to 40.8 tonnes in 2002–2011. However, air releases increased between 2012 and 2014, averaging 101 tonnes per year (Environment Canada, 2015).

Tetrachloroethylene is distributed between environmental compartments by volatilization, precipitation and adsorption. The behaviour of tetrachloroethylene in the environment is affected by a number of processes, such as atmospheric photooxidation, volatilization and biotransformation. Once released in soil or water, tetrachloroethylene can accumulate in

[1] 1 ppm of tetrachloroethylene in air is equal to 6.78 mg/m^3 at standard ambient temperature (25°C) and pressure (100 kPa).

groundwater if not removed by degradation or evaporative processes (Government of Canada, 1993).

Tetrachloroethylene has the potential to volatilize from water and moist soil, with a Henry's Law constant of 1.8×10^{-2} atm-m^3/mol at 25°C (or a unitless value of 7.23×10^{-1}) (Gossett, 1987). Volatilization into the atmosphere is the dominant fate process for tetrachloroethylene in aquatic systems; 99.45% of tetrachloroethylene in water can be released into the atmosphere (Callahan et al., 1979; Schwarzenbach et al., 1979; Wakeham et al., 1983; Kaiser and Comba, 1986; ECETOC, 1999). Evaporation half-lives of less than 1 hour were observed in laboratory studies, but those from field measurements and theoretical considerations were higher, ranging from 2 to 10 days in rivers and from 10 to 30 days in lakes and ponds. Volatilization rates from groundwater are expected to be low, since both volatilization and biodegradation are greatly reduced (IPCS, 1984; ECETOC, 1999; U.S. EPA, 2012a).

Tetrachloroethylene is expected to evaporate rapidly from soil surfaces, as it has a high vapour pressure and moderately low adsorption to soil (Wilson et al., 1981). Soil adsorption of tetrachloroethylene depends on the partition coefficient, the organic carbon content of the soil, the type of release and the concentration of tetrachloroethylene in the liquid phase (Seip et al., 1986; Poulsen and Kueper, 1992). Based on experimental and estimated soil sorption coefficients of 209–1685, tetrachloroethylene has low to moderate mobility through soil (U.S. EPA, 2012a). Seip et al. (1986) determined that in sandy soil, tetrachloroethylene moves at almost the same rate as in water, but retention can occur in soils with higher organic carbon and clay contents. Migration of the chemical through soil is determined by the permeability and porosity of the soil as well as the amount of tetrachloroethylene released. It is assumed that tetrachloroethylene will be mobile in most soils and able to penetrate to depths where groundwater can be contaminated (Schwille, 1988; Poulsen and Kueper, 1992).

Microbial degradation of tetrachloroethylene has been shown to occur under anaerobic conditions, through microcosm and pilot-scale laboratory studies, but degradation under aerobic conditions has not been observed (Bouwer et al., 1981; Barrio-Lage et al., 1986; Fogel et al., 1986; Freedman and Gossett, 1989). Anaerobic degradation of tetrachloroethylene proceeds by reductive dechlorination to trichloroethylene, dichloroethylene and vinyl chloride, with microbial oxidation and dehalogenation leading to carbon dioxide and ethylene as end-products, respectively (Freedman and Gossett, 1989; Bradley, 2000).

5.0 Exposure

Canadians can be exposed to tetrachloroethylene present in air, drinking water and possibly food. In addition, certain segments of the population may be exposed through the use of specific consumer products or in occupational settings. Dry cleaning and metal degreasing are the two most important occupational activities by which humans are exposed to tetrachloroethylene; inhalation is the most important route of exposure in occupational settings (IARC, 1995). Although some exposure data are available, they are considered insufficient to justify modifying the default allocation factor for drinking water of 20%.

Based on exposure data used at the time of the Priority Substances List assessment for tetrachloroethylene, the total daily intake of tetrachloroethylene was estimated to range from 1.22 to 2.67 μg/kg body weight (bw) for each of the age groups in the general population of Canada. Drinking water ingestion contributed only a minor amount to the overall exposure, estimated at 0.002 to 0.06 μg/kg bw per day (<3%). Estimated contributions of food were 0.12–0.65 μg/kg bw per day (7 to 28%). The highest contributor to exposure was air, which provided >1.22 μg/kg

(>62%) of daily exposure, of which the majority (1.21 to 1.88 µg/kg per day) came from indoor air (Government of Canada, 1993).

5.1 Water

A limited number of studies have measured tetrachloroethylene concentrations in various Canadian water bodies. As was noted in the Priority Substances List assessment report for tetrachloroethylene, concentrations of tetrachloroethylene are typically low in surface water, with exceptions occurring when industrial or other point sources released the chemical into water bodies (Government of Canada, 1993).

Recent data on concentrations of tetrachloroethylene in drinking water obtained from several provinces (see Table 1) demonstrate that concentrations are typically below the level of detection in Canadian water supplies. No provinces detected tetrachloroethylene in more than 4% of all treated water samples. Only one treated sample from all provinces contained tetrachloroethylene at a concentration of > 10 µg/L. A small proportion (10/2560) of raw water samples in Ontario contained tetrachloroethylene at concentrations above 10 µg/L, but once the water was treated and distributed, all tetrachloroethylene concentrations in the province were below 2 µg/L.

Table 1. Concentrations of tetrachloroethylene in provincial water samples[a]

Province (water type), years	MDL (µg/L)	No. of samples	No. (%) of samples > MDL	Average concentration (µg/L)	Maximum concentration (µg/L)
Alberta[b], 2002–2007	NS	2353	NS	0.41	4.04
Saskatchewan (distributed water), 2002–2005	NS	4	NS	1	1
Ontario (raw water), 2002–2007	0.05	2560	151 (5.9%)	2.6[c]	23.1
Ontario (treated water), 2002–2007	0.05	2100	51 (2.4%)	0.33[c]	1.95
Ontario (distributed water), 2002–2007	0.05	2104	77 (3.7%)	0.28[c]	1.9
Quebec (distributed water), 2001–2005	0.03–1	2473	31 (1.3%)	0.55[c]	3.4
New Brunswick (municipal sources)[b], 1994–2007	NS	2532	9 (0.4%)	1.2[c]	7
New Brunswick (municipal distribution)[b], 1994–2007	NS	3294	12 (0.4%)	6.1[c]	54
New Brunswick (Crown sources)[b], 1994–2007	NS	4304	4 (0.09%)	1.02[c]	2
New Brunswick (Crown distribution)[b], 1994–2007	NS	359	0 (0%)	ND	ND

MDL, method detection limit; ND, not detected; NS, not specified

[a] Data obtained from Alberta Environment (2007), Ministère du Développement durable, de l'Environnement et des Parcs du Québec (2007), New Brunswick Department of Health (2007), OMOE (2007) and Saskatchewan Environment (2007).

[b] Data were provided as compiled results from various types (i.e., raw, treated, distributed)

[c] Average of detected samples only.

Tetrachloroethylene was used as a solvent in the application of vinyl coating to asbestos–cement pipes during their manufacture in the 1960s and 1970s. This type of lining material was

discontinued in the 1980s after the leaching of tetrachloroethylene into the drinking water was discovered (Larson et al., 1983).

5.2 Food

Limited data are available on the level of tetrachloroethylene in food products in Canada, but food is not considered to be a major exposure pathway (Government of Canada, 1993). Food surveys in the United States have estimated the average concentrations of tetrachloroethylene in dairy, meat, cereal, fruit, vegetable, fats and oil, and sugar composite food groups to be 6.6, 12.3, 14.7, 0.8, 0.4, 12.9 and 2.9 ng/g, respectively (Heikes, 1987; Daft, 1988). Based on these surveys, the average daily intake of tetrachloroethylene through food has been estimated to be 8.4 µg.

Proximity of supermarkets to dry cleaning facilities can affect the concentration of tetrachloroethylene in foods. This has been demonstrated for butter and margarine from stores near dry cleaning facilities, which had higher tetrachloroethylene concentrations when compared with samples collected from stores with no nearby dry cleaning facilities (Entz and Diachenko, 1988; Miller and Uhler, 1988). Concentrations of tetrachloroethylene in butter from grocery stores near dry cleaning facilities exceeded 1 ppm in some samples, whereas concentrations in butter from control grocery stores were mostly ≤ 0.05 ppm (Entz and Diachenko, 1988; Miller and Uhler, 1988).

5.3 Air

In Canada, the concentration of tetrachloroethylene in ambient (outdoor) air has been measured to range from 0.2 to 5 µg/m^3 in a national survey of 22 sites in 11 Canadian cities (Dann and Wang, 1992). In indoor air, the average concentration of tetrachloroethylene was measured to be 5.1 µg/m^3 in a pilot study of 757 randomly selected Canadian homes (Otson et al., 1992). In the United States, background concentrations of tetrachloroethylene lie in the low parts per trillion range in rural and remote areas and in the low parts per billion range in urban and industrial areas and areas near point sources of pollution (ATSDR, 1997). According to the European Commission (2005), the majority of measured concentrations of tetrachloroethylene in air in Europe are below 10 µg/m^3, but mostly below 1 µg/m^3.

Recent studies by Health Canada obtained indoor and outdoor air samples over a 24-hour period in Halifax, Nova Scotia (Health Canada, 2012), over 24-hour periods on 5 consecutive days (for 2 different years) in Windsor, Ontario (Health Canada, 2010b), and using both sampling schemes in Regina, Saskatchewan (Health Canada, 2010a). Geometric mean indoor air concentrations of tetrachloroethylene in the summer were 0.853 and 0.696 µg/m^3 in Windsor, 0.548 µg/m^3 for 24-hour samples in Regina and 0.257 µg/m^3 in Halifax; the concentrations in winter were 0.431 and 0.321 µg/m^3, 0.0426 µg/m^3 and 0.269 µg/m^3, respectively. Geometric mean outdoor air concentrations in the summer were 0.231 and 0.137 µg/m^3 in Windsor, 0.051 µg/m^3 for 24-hour samples in Regina and 0.062 µg/m^3 in Halifax; the cocentrations were 0.158 and 0.119 µg/m^3, 0.069 µg/m^3 and 0.053 µg/m^3, respectively, in winter. Personal air sampling was performed in the summer and winter of 2005 in Windsor, identifying exposure levels that were slightly higher than the indoor air concentrations (0.995 µg/m^3 in summer and 0.584 µg/m^3 in winter). The Regina study also investigated potential differences between smokers and non-smokers and found similar results for the two groups.

Certain activities result in an increase in personal exposure to tetrachloroethylene far above the outdoor concentrations. In a study of exposures to various volatile organic compounds (VOCs) during regular daily activities, seven volunteers (four males, three females) from four households had a mean personal air tetrachloroethylene exposure level of 8.5 µg/m^3 and a mean

outdoor air tetrachloroethylene exposure level of 1.2 μg/m^3. An increase in tetrachloroethylene exposure was observed in one subject who visited a dry cleaner for 10 minutes and brought laundered clothes home; this subject's wife also had increased exposure (both with a 12-hour time-weighted average exposure level of 50 μg/m^3). Another volunteer who used an engine carburetor cleaner for 2 hours also had elevated exposures (a 9-hour time-weighted average exposure level of 220 μg/m^3) (Wallace et al., 1989).

Indoor air concentrations can become elevated in residences co-located with dry cleaning facilities using tetrachloroethylene, as demonstrated by air measurements obtained in two New York City apartment buildings with dry cleaning carried out on the ground floor. Concentrations measured in indoor air ranged from 50 to 6100 μg/m^3, with mean concentrations ranging from 358 to 2408 μg/m^3. After the dry cleaning operation ceased, the concentrations in the apartments declined substantially, but still ranged from 10 to 800 μg/m^3 after 1 month (Schreiber et al., 2002).

Vapour intrusion is a process by which tetrachloroethylene and other VOCs from subsurface sources (e.g., soil or groundwater) move through dirt floors or crawlspaces, as well as through cracks or openings in building slabs or foundations, to be introduced inside buildings (U.S. EPA, 2012d). This process is another potential source of tetrachloroethylene in indoor air, particularly for buildings located on sites with high contamination of tetrachloroethylene in the soil or groundwater (McDonald and Wertz, 2007; U.S. EPA, 2012c).

A review of published data on personal air monitoring for tetrachloroethylene was performed to examine levels of exposure of U.S. workers to the chemical from different industries (dry cleaning, metal degreasing and other industries). The highest personal exposures came from the dry cleaning industry, where the mean tetrachloroethylene concentration was 59 parts per million (ppm) (range 0–4636 ppm, n = 1395), as well as in metal and plastics degreasing, where the mean tetrachloroethylene concentration has been measured to be 95 ppm (range 0–1800 ppm, n = 206). Lower concentrations were measured in other industries; for example, the measured mean air concentration in the production of leather products was 15 ppm (no range given, n = 71), and measurements in the printing industry gave a mean air concentration of 6 ppm (range 1.9–16 ppm, n = 22) (Gold et al., 2008).

5.4 Consumer products

Limited information is available on levels of tetrachloroethylene in Canadian consumer products, and no quantitative data are available on exposure levels from use of these products. However, in general, tetrachloroethylene can be found in some consumer products, such as spot removers, suede protectors, leather and shoe polish, adhesives, automotive chemicals, printing inks and paint removers (CAREX Canada, 2010).

5.5 Soil

Limited information is available regarding the levels of tetrachloroethylene in Canadian soil.

In Ontario, the upper 98th percentile concentrations of tetrachloroethylene in rural (n = 102) and urban (n = 59) parkland soils not impacted by pollution were found to be 1.1 and 0.87 ng/g, respectively (OMEE, 1994). Average concentrations were 0.2 and 0.18 ng/g, respectively.

Soils impacted by point sources of pollution can have higher concentrations of tetrachloroethylene. At an industrial site in Vancouver, British Columbia, tetrachloroethylene was found in soil at concentrations ranging from 0.006 to > 10 mg/kg (Golder Associates, 1989).

Tetrachloroethylene was also measured in sediments of water bodies that were affected by point sources of tetrachloroethylene. Samples of river sediment from the St. Clair River, which was selected as a sampling site due to its proximity to industrial sources, contained tetrachloroethylene at concentrations ranging from 0.006 to 0.029 mg/kg (OMOE, 1987). Tetrachloroethylene concentrations of 5.9–29 μg/kg were observed in two of five urban sediment samples obtained in Sarnia, Ontario (Marsalek, 1986). No measurements of tetrachloroethylene in unpolluted sediments in Canadian bodies of water were found.

5.6 Multiroute exposure through drinking water

Owing to tetrachloroethylene's physicochemical properties, inhalation and dermal absorption during bathing and showering may serve as important routes of exposure.

To assess the overall exposure to tetrachloroethylene in drinking water, the relative contribution of each exposure route can be assessed using a multiroute exposure assessment approach (Krishnan and Carrier, 2008). 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 and Carrier, 2008).

A human physiologically based pharmacokinetic (PBPK) model—based on Gearhart et al. (1993), and including a showering component based on Reitz et al. (1996) and Rao and Brown (1993)—was used to estimate the contributions in L-eq from dermal and inhalation exposures to tetrachloroethylene when showering and bathing, in a manner consistent with the Krishnan and Carrier (2008) approach. The Rao and Brown (1993) model was based on blood tetrachloroethylene concentrations measured in subjects who were exposed by showering and therefore accounts for exposure to tetrachloroethylene both dissolved in the water and vaporized into the air. Using the external doses generated from the human PBPK model (see Sections 8.5 and 10), litre-equivalent contributions from dermal and inhalation exposures during showering or bathing were estimated by running the human PBPK model for a 30-minute bathing scenario. By comparing the internal doses generated from the dermal and inhalation routes of exposure with the daily internal dose estimates from ingestion, the daily litre-equivalent contributions for dermal and inhalation exposures were determined to be 1.21 and 3.45 L-eq, respectively. When added to the standard Canadian drinking water consumption rate of 1.5 L/day, the total litre-equivalent daily exposure to tetrachloroethylene in drinking water was estimated to be 6.2 L-eq (rounded).

6.0 Analytical methods

The U.S. Environmental Protection Agency (U.S. EPA) currently has four approved analytical methods for the analysis of tetrachloroethylene in drinking water (U.S. EPA, 2002).

Method 502.2 Revision 2.1, which uses purge and trap capillary gas chromatography (GC) with photoionization detectors and electrolytic conductivity detectors in series, has a method detection limit (MDL) range of 0.02–0.05 μg/L. Method 524.2 Revision 4.1, which uses purge and trap capillary GC with mass spectrometry (MS) detection, has an MDL range of 0.05–0.14 μg/L. Method 524.3 Version 1.0 measures VOCs in drinking water. The method uses the GC-MS technique and has a detection limit of 0.036 μg/L for tetrachloroethylene. The advantages of the method include an optimization of the purge and trap parameters, an option for use of selected ion monitoring (SIM) and the use of solid acid preservatives (U.S. EPA, 2009). Method 551.1 Revision 1.0, employing liquid–liquid extraction and GC with electron capture detectors,

has MDLs of 0.002 µg/L and 0.008 µg/L when methyl tertiary-butyl ether (MTBE) or pentane is used as the extraction solvent, respectively (U.S. EPA, 1995).

The current U.S. EPA practical quantitation level (PQL), based on the capability of laboratories to measure the concentration of tetrachloroethylene within reasonable limits of precision and accuracy, is 5 µg/L (U.S. EPA, 1991b). However, an assessment of the analytical data for tetrachloroethylene from performance evaluation and proficiency testing studies was recently conducted as part of the U.S. EPA's second 6-year review to re-evaluate PQLs (U.S. EPA, 2009). The U.S. EPA reported greater than 90% passing rates for laboratories analyzing samples, suggesting that the current PQL could be lower. This analysis included several studies with spiked concentrations below the current PQL. Applying a multiplier of 10 to the upper levels of the MDL of the three approved analytical methods (502.2, 524.2 and 551.1) resulted in a possible PQL range of 0.08–1.4 µg/L (U.S. EPA, 2009, 2010). The U.S. EPA's review indicated that the PQL could be lowered to approximately 0.5 µg/L (U.S. EPA, 2010).

In addition, three Standard Methods, SM 6200B, SM 6200C and SM 6232, can be used for the analysis of tetrachloroethylene in drinking water. Methods SM 6200B and SM 6200C are based on purge and trap capillary GC followed by MS detectors or photoionization detectors and electrolytic conductivity detectors in series, respectively. SM 6200B has an MDL of 0.047 µg/L, and SM 6200C has an MDL range of 0.013–0.014 µg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately using these methods, are 0.188 µg/L and 0.056 µg/L for methods SM 6200B and SM 6200C, respectively (APHA et al., 2005). SM 6232 uses liquid–liquid extraction followed by GC with electron capture detectors. An MDL is not reported for this method due to its high dependency on the characteristics of the GC system used, solvent to water ratio and interferences present in the solvent (APHA et al., 2005).

ASTM International lists method D5790 for the analysis of tetrachloroethylene in drinking water. This method uses purge and trap capillary GC with MS detection (ASTM, 1999) and has an MDL of 0.25 µg/L (NEMI, 1995).

7.0 Treatment technology and distribution system considerations

7.1 Municipal scale

Municipal drinking water treatment plants that rely on conventional treatment techniques (coagulation, sedimentation, filtration and chlorination) have generally been found to be ineffective (0–29%) in decreasing concentrations of VOCs in drinking water (Love et al., 1983; Robeck and Love, 1983). Some incidental removal of VOCs may occur as a result of volatilization in open basins (Health and Welfare Canada, 1993). U.S. EPA (1991b) reported granular activated carbon (GAC) adsorption and packed tower aeration (PTA) as the best available technologies (BATs) for the reduction of tetrachloroethylene concentrations in drinking water. These treatment technologies have proven effective for the reduction of an influent concentration of tetrachloroethylene in the range of 30–500 µg/L to an effluent concentration of below 1 µg/L (Love and Eilers, 1982; Chrobak et al., 1985; Reijnen et al., 1985; Hand et al., 1988; AWWA, 1991; Lykins and Clark, 1994; Dyksen et al., 1995).

Various advanced oxidation processes (AOPs), such as ozonation in combination with hydrogen peroxide, have also been found to be effective treatment methods for tetrachloroethylene (Aieta et al., 1988; Zeff, 1991; Dyksen et al., 1992; Topudurti, 1993; Hirvonen et al., 1996b; Karimi et al., 1997; Hirvonen et al., 1998).

The selection of an appropriate treatment process for a specific water supply will depend on many factors, including the characteristics of the raw water and the operational conditions of the specific treatment method.

7.1.1 Activated carbon adsorption

Activated carbon is used in water treatment processes either as GAC or as powdered activated carbon (PAC). The adsorption capacity of activated carbon to remove VOCs is affected by a variety of factors, such as competition from other contaminants, preloading with natural organic matter (NOM), temperature, the physicochemical properties of the VOCs and the carbon media (Speth, 1990; AWWA, 1991). The PAC application, most suitable for conventional treatment systems treating surface waters, may decrease occasional low concentrations of VOCs, including tetrachloroethylene, when it is applied at the treatment plant, allowing sufficient contact time and a proper mixing. In conventional treatment plants, the common points of PAC application are at the plant intake, during the rapid mix process and in the filter influent. Sufficient contact time, a function of the characteristics and the concentration of the contaminant to be adsorbed, is necessary (Najm et al., 1991). In general, PAC adsorption is found to be less efficient than GAC adsorption for VOC removal largely due to its use in coagulation/ sedimentation basins where the adsorption sites can be blocked due to floc formation; the fact that it will not have the necessary time to reach its maximum adsorption capacity; and the fact that the equilibrium liquid-phase concentration (concentration gradient driving force) decreases during the adsorption process. A full-scale study demonstrated that PAC application was capable of decreasing an influent tetrachloroethylene concentration of 0.7 µg/L to 0.3 µg/L, with an applied PAC dose of 7.1 mg/L (Singley et al., 1979).

Higher concentrations of VOCs are found in groundwater. For the continuous removal of VOCs from groundwater, GAC adsorption is a commonly used process (Snoeyink, 1990). The process uses a contactor packed with GAC. As the water passes through the GAC contactor, the contaminants diffuse to the adsorbent granules and accumulate on their surfaces (Crittenden et al., 2005). Packing the carbon in columns allows more complete contact between the water and the media, greater adsorption efficiency and greater process control than with PAC (Snoeyink, 1990).

The choice of GAC application for removing VOCs from drinking water supplies involves the following process design considerations: carbon usage rate, empty bed contact time (EBCT), pretreatment of the raw water, contactor configuration and method of GAC replacement or regeneration. During the operation time, and depending on a variety of factors discussed above, organic contaminants will “breakthrough” the carbon bed. Initial breakthrough is defined as the time when the contaminant concentration in the effluent exceeds the treatment objective. In systems with multiple beds, the individual beds can be operated beyond the time of initial breakthrough, provided the contaminant concentration in the blended effluents still meets the treatment objectives. Once the GAC is exhausted, it is removed from the contactor and replaced with fresh or regenerated GAC. For practical reasons, PAC is not recovered and reactivated; thus, its carbon use rate can be high when compared with that of GAC (Chowdhury et al., 2013). The regeneration and/or replacement of exhausted media are important economic considerations in achieving the contaminant treatment goal.

Common operating problems when using GAC adsorption contactors include biological growth and the increase in heterotrophic plate counts in the effluent, clogging and fouling of the carbon bed by chemical and bacterial precipitants (AWWA, 1991). Operating considerations include the needs to ensure a proper backwash, maintain the bed depth and bed density after backwashing and control the flow rate. To prevent clogging of the bed, pretreatment of the water

prior to the GAC contactor is often required (Snoeyink, 1990; Speth, 1990; Crittenden et al., 2005).

An influent tetrachloroethylene concentration in the range of 30–194 µg/L could be decreased to below 1 µg/L in drinking water under reasonable operating conditions (Love and Eilers, 1982; Chrobak et al., 1985; Hand et al., 1988; U.S. EPA, 1990; AWWA, 1991; Dyksen et al., 1995). Operational data from a municipal-scale GAC treatment facility indicate that an influent concentration of tetrachloroethylene of 30 µg/L can be decreased to below 1 µg/L using a single contactor with a hydraulic loading rate of 2.56 gpm/ft^2 (6.2 m/h) and an EBCT of 12.7 minutes, resulting in a carbon use rate of 0.0167 kg/m^3 (kilograms of GAC per cubic metre of water treated; Hand et al., 1988). Other full-scale results demonstrated that two GAC contactors in parallel mode with a hydraulic loading rate of 7.1 gpm/ft^2 (17.3 m/h) each and an EBCT of 10.5 minutes were capable of decreasing a tetrachloroethylene concentration of 194 µg/L to less than 1 µg/L with a carbon use rate of 102 lb GAC per million gallon of treated water (0.0122 kg /m^3; Chrobak et al., 1985). A survey of treatment plants using GAC for the removal of tetrachloroethylene in the United States found that influent concentrations ranging from 5 to 150 µg/L could be decreased to below 1 µg/L under a variety of operating conditions (AWWA, 1991; Dyksen et al., 1995).

The GAC process is the most widely used for small water treatment systems due to its simplicity and ease of operation (Snoeyink, 1990).

7.1.2 Air stripping: packed tower aeration

Air stripping treatment technology is widely used to decrease the concentrations of VOCs in drinking water (Dyksen et al., 1984; Cummins and Westrick, 1990; U.S. EPA, 1991a; Dzombak et al., 1993; Dyksen, 2005; WHO, 2011). An air stripping process brings water and air into contact, allowing the transfer of volatile contaminants from the water to the air, as the driving force of the process is the contaminant concentration gradient between the two phases.

Although various air stripping equipment configurations exist, the U.S. EPA considers PTA as the best technology, achieving 99% removal of VOCs from drinking water (U.S. EPA, 1991b). PTA provides an optimum system for the removal of VOCs from water, as it allows for greater air-to-water ratios than other aeration systems. In the PTA column, the contaminated water flows downward by gravity over a bed of packed material, while the air is introduced into the tower below the packed bed and flows upward countercurrent to the water flow. As the PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to decrease the contaminant concentrations prior to discharge into the atmosphere may be necessary (Crittenden et al., 1988; Adams and Clark, 1991).

Several design factors affect the stripping rate of VOCs: air-to-water ratio; available area of mass transfer, hydraulic loading rate, temperature of the water and air, and physical and chemical properties of the contaminant (AWWA, 1991; Crittenden et al., 2005; Dyksen, 2005). Diffused aeration, multistage bubble aerators, tray aeration and shallow tray aeration have been identified as alternative air stripping treatment technologies for the removal of tetrachloroethylene in drinking water for small systems (U.S. EPA, 1998).

A common operating problem is scaling and fouling of the column. The main causes of fouling are calcium carbonate and/or calcium sulphate scale, iron oxidation and microbial growth. Methods to prevent the fouling of the column include pH suppression of the influent, use of scale inhibitors or iron removal prior to the PTA application (U.S. EPA, 1984; Dyksen, 2005). Algal growth can also be a problem in locations where light could be introduced into the tower. Post treatment, such as the use of a corrosion inhibitor, may also be required to reduce corrosive

properties of the water due to increased dissolved oxygen from the aeration process. Environmental conditions, such as water temperature, may impact the packed tower performance. Although temperatures below freezing can cause operational issues, contact between water and air in PTA will result in a change in the air temperature until it approaches the water temperature. The temperature influences both the Henry's Law constant and the rate of mass transfer coefficient of the contaminant. These parameters impact the size of the equipment and the removal efficiency of the VOCs (Crittenden et al., 2005).

Using PTA, an influent tetrachloroethylene concentration in the range of 60–500 µg/L could be decreased to below 1 µg/L in drinking water under reasonable operating conditions (Reijnen et al., 1985; Hand et al., 1986, 1988; AWWA, 1991; Dyksen et al., 1995). Full-scale PTA data indicates that an influent flow rate of 8.1 ML/day with a concentration of tetrachloroethylene of 60 µg/L can be decreased to 0.4 µg/L using an air-to-water ratio of 61, an air stripper length of 7.5 m, hydraulic loading rate of 15.5 $kg/m^2/s$, and a packed column diameter of 2.4 m (Hand et al., 1988). Influent concentrations as high as 500 µg/L have been decreased to below 1 µg/L using an air-to-water ratio of 35, an air stripper length of 7.3 m, a hydraulic loading rate of 27.2 gpm/ft^2 (66.3 m/h) and a packed column diameter of 2.3 m (Dyksen et al., 1995). Results of a survey conducted on full-scale drinking water treatment plants indicated that PTA is commonly capable of decreasing influent concentrations of tetrachloroethylene of up to 170 µg/L to levels below 1 µg/L in the finished water under a variety of operating conditions (Reijnen et al., 1985; AWWA, 1991).

Generally, diffused aeration achieves lower removal efficiencies and has higher power requirements than PTA systems (AWWA, 1991). Typical diffused aeration performance ranges from 73% to 95% removal of tetrachloroethylene (U.S. EPA, 1984, 1991a). A pilot-scale diffused aeration study indicated that influent concentrations of tetrachloroethylene can be decreased from 636 µg/L to less than 1 µg/L using an air-to-water ratio of 16 and a contact time of 10 minutes (Love and Eilers, 1982).

Cost evaluations of systems ranging from 1 to 100 ML/day were conducted by Adams and Clark (1991). These evaluations indicate that, in most cases, the use of PTA for the removal of tetrachloroethylene in drinking water is more cost effective than the use of GAC, even when vapour-phase GAC treatment of the stripping tower off-gas is required.

7.1.3 Combination of packed tower aeration and granular activated carbon

PTA technology combined with liquid-phase GAC adsorption has the potential to be effective for producing water with low effluent levels of VOCs. In a municipal-scale treatment plant combining these processes, air stripping was used for the bulk removal of VOC from water, and activated carbon adsorption was used in the second step to further decrease the residual VOC concentrations (McKinnon and Dyksen, 1984; Stenzel and Sen Gupta, 1985). In addition, the use of an air stripping process preceding liquid-phase GAC adsorption can extend the carbon bed life. A packed tower column combined with a GAC adsorber demonstrated that an influent concentration of tetrachloroethylene of 100 µg/L could be decreased to less than 1 µg/L using an air-to-water ratio of 90 and a packing height of 3.0 m (AWWA, 1991). No information was provided on the operational conditions of the GAC adsorber used in this study.

7.1.4 Ozonation

The reaction kinetics of ozonation are generally not considered to be favourable for the treatment of tetrachloroethylene in drinking water due to slow reaction rates and the need to achieve low effluent concentrations (Dyksen et al., 1992; Hirvonen et al., 1996b). However, pilot-

scale studies have demonstrated that a 60–75% removal of tetrachloroethylene is achievable using ozone doses between 6 and 9 mg/L (Fronk, 1987; Zeff, 1991).

7.1.5 Advanced oxidation processes

AOP refers to the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (ozone/hydrogen peroxide, ozone/UV, UV/hydrogen peroxide, UV/titanium dioxide, ozone/UV/titanium dioxide, ozone oxidation at elevated pH) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Physical and chemical properties of the water matrix have a major impact on AOPs. Water quality parameters that may impact the effectiveness of the AOPs are alkalinity of the water, pH, NOM, reduced metal ions (iron and manganese) and turbidity. The primary advantage of AOPs is their capability to completely convert the organic compounds into carbon dioxide and mineral acids (Crittenden et al., 2005), whereas the adsorption processes and the air stripping techniques transfer the contaminants from one phase to another phase and may require additional treatment (Glaze and Kang, 1988; Topudurti, 1993; Crittenden et al., 2005). Pilot-scale studies indicated that an in-line ozone/hydrogen peroxide process was capable of decreasing an influent tetrachloroethylene concentration of 18.6 µg/L to an effluent concentration of 1 µg/L using an applied ozone dose of 6.0 mg/L, a hydrogen peroxide to ozone ratio of 0.5 and a contact time of 3 minutes (Dyksen et al., 1992). Other full-scale data demonstrated that the use of an ozone/hydrogen peroxide process was effective in decreasing an influent tetrachloroethylene concentration of 10 µg/L to below 1 µg/L using an ozone dose of 4.7 mg/L and a hydrogen peroxide to ozone ratio of 0.57 (Karimi et al., 1997). Results from both studies suggest that the ozone dosage appears to have a greater impact on the removal of tetrachloroethylene than the contact time of the reaction. Similarly, full-scale data demonstrated that a combined UV/hydrogen peroxide/ozone oxidation process was capable of decreasing an influent tetrachloroethylene concentration of 7 µg/L to less than 1 µg/L (Zeff, 1991).

Full-scale AOPs using UV radiation and hydrogen peroxide oxidation treatment have been assessed for the removal of tetrachloroethylene. Medium-pressure UV lamps and hydrogen peroxide doses of 15–70 mg/L decreased an influent concentration of tetrachloroethylene in the range of 70–150 µg/L to below 1 µg/L in the treated water (Topudurti, 1993). Field-scale results, reported by Hirvonen et al. (1998), showed that low-pressure mercury lamps and hydrogen peroxide doses of 83–138 mg/L could decrease an influent concentration of tetrachloroethylene in the range of 76–139 µg/L to an effluent concentration of below 0.5 µg/L.

Specific operational issues should be considered when using each of the above-described AOP technologies. The common operating issues related to the use of UV radiation are UV lamp replacement, regular removal of the suspended particles that coat the quartz tubes housing the UV lamps and ensuring low levels of colour and turbidity of the water. The application of a UV/hydrogen peroxide process requires a high initial dosage of hydrogen peroxide in order to efficiently utilize the UV light to produce hydroxyl radicals, which results in a high effluent hydrogen peroxide concentration in the finished water. Other operating concerns when using ozone/hydrogen peroxide and UV/ozone include the stripping of the VOCs from the ozone contactor.

The formation of by-products from the oxidation and/or advanced oxidation of tetrachloroethylene or other inorganic or organic compounds in the source water should be considered when using these processes. AOPs produce reactive peroxy organic radicals, which undergo radical chain reactions and result in a variety of oxygenated by-products. The typical by-

products produced by AOPs are aldehydes, ketones and carboxylic compounds. The presence of by-products may require additional treatment following AOPs and/or process optimization to minimize by-product formation.

The formation of low concentrations of trichloroacetic acid (TCA) (0.1 µg/L) and dichloroacetic acid (DCA) in the range of 1–6 µg/L from the UV/hydrogen peroxide oxidation of tetrachloroethylene has been observed in the treated water (Hirvonen et al., 1996a, 1998). However, the reported concentrations of these compounds were below the World Health Organization (WHO) drinking water guidelines of 200 µg/L for TCA and 50 µg/L for DCA (WHO, 2011). Health Canada's guideline for total haloacetic acids in drinking water is 80 µg/L.

Other studies found that with the exception of assimilable organic carbon (AOC) and bromate, no by-products were produced following ozone/hydrogen peroxide oxidation. The average concentration of an AOC of 53.5 µg/L in the groundwater was increased to about 239 µg/L in the treated water. An influent bromide concentration of 0.21 mg/L resulted in an effluent bromate concentration in the range of 0.029–0.11 mg/L (Karimi et al., 1997). The formation of bromate was found to be dependent on the applied ozone dosage.

7.1.6 Reverse osmosis

Reverse osmosis technology has shown some promise for its potential to remove tetrachloroethylene from drinking water (U.S. EPA, 1991a). Bench-scale investigations demonstrated that influent concentrations of tetrachloroethylene ranging from 6 to 153 µg/L were decreased up to 92% using thin film composite membranes (Lykins et al., 1988). The ability of reverse osmosis to remove synthetic organic chemicals has been found to be dependent on a variety of system components, including type of membrane, flux, recovery, synthetic organic chemical solubility, charge and molecular weight (Taylor et al., 2000).

7.1.7 Emerging and other treatment technologies

New drinking water treatment technologies for tetrachloroethylene are being developed but are still primarily in the experimental stage and/or have no published information on the effectiveness of full-scale application. Some of the emerging technologies are as follows:

<u>Layered upflow carbon adsorption</u>

- Alternative GAC contactor configurations have shown some success for the removal of tetrachloroethylene in drinking water at decreased carbon usage rates. A pilot-scale layered upflow carbon absorber was capable of decreasing a tetrachloroethylene concentration of 13 µg/L to below 5 µg/L in the finished water, with an EBCT of 6 minutes and a carbon usage rate of 0.010 kg/m^3 (Munz et al., 1990).

<u>Membrane technologies</u>

- *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 80% decrease of tetrachloroethylene concentrations and greater mass transfer coefficients than with the use of traditional air stripping towers (Zander et al., 1989).
- *Nanofiltration*: Laboratory-scale studies examining the effectiveness of various nanofiltration membrane characteristics demonstrated an average 93% removal of tetrachloroethylene with an influent concentration of 400 µg/L in synthetic water (Ducom and Cabassud, 1999).

- *Pervaporation*: Pervaporation has been considered as an emerging polymeric membrane-based technology for the removal of organic contaminants from water. Pervaporation requires dense and selective membranes and the separation is based on the relative solubility and diffusivity of each component in the membrane material (Khayet and Matsuura, 2004). In pervaporation, one side of the membrane is in contact with the contaminated water, while the other side is exposed to a vacuum. The process includes sorption of the contaminant onto the membrane, permeation through the membrane and evaporation into the vapour phase. However, no information was found specifically related to the removal of tetrachloroethylene from water (Lipski and Cote, 1990; Uragami et al., 2001).
- *Vacuum membrane distillation*: The vacuum membrane distillation process uses porous and hydrophobic membranes that act only as support for the vapour–liquid interface (Khayet and Matsuura, 2004). The liquid stream vaporizes on the feed side of the membrane; the vapour diffuses through the membrane pores and is condensed outside the membrane. Mass transfer through the membrane is improved by applying a vacuum on the permeate side (Couffin et al., 1998). Couffin et al. (1998) reported that the vacuum membrane distillation process appears to be a promising treatment technology for the removal of low concentrations of tetrachloroethylene from water.

Other AOPs

- A pilot-scale photocatalytic oxidation system was capable of decreasing influent concentrations of tetrachloroethylene from 125 µg/L to 5 µg/L in the finished water. The oxidation system utilized UV radiation with a titanium dioxide semiconductor combined with the addition of 70 mg/L of hydrogen peroxide and 0.4 mg/L of ozone (Topudurti et al., 1998).
- The Fenton oxidation reaction, based on strong oxidizing (OH·) radicals produced by the reaction of hydrogen peroxide with iron sulphate, is also an effective process for the degradation of tetrachloroethylene in water. Laboratory experiments demonstrated 95% degradation of tetrachloroethylene with a high initial concentration of 162 mg/L. The formation of by-products such as TCA should be considered when using AOPs such as Fenton oxidation (Yoshida et al., 2000).
- Use of a high-energy electron beam (e-beam) has been shown to be an effective process for the destruction of tetrachloroethylene in aqueous solutions at a large scale. An energy dose in the range of 299-776 krad was required to achieve a 99% removal of tetrachloroethylene in an aqueous solution with a pH of 7 (initial concentration ranging from 0.1 to 4.5 mg/L) (Cooper et al., 1993).

7.1.8 Distribution system

A vinyl-toluene lining used in the 1960s and 1970s to minimize the corrosion of asbestos-cement pipes (primarily in New England) was a source of tetrachloroethylene in drinking water. However, use of this type of lining material was discontinued after it was discovered that tetrachloroethylene leached into the drinking water (Larson et al., 1983). Tetrachloroethylene was added to thin the resin used to line the inside of pipes prior to spraying. Leaching of tetrachloroethylene was observed when insufficient time was allowed for the resin to dry (cure) after its application. The highest tetrachloroethylene concentrations measured (up to 3500 µg/L) were most often found in dead-ends or in areas of low flow in the distribution system. Remedial actions taken to decrease tetrachloroethylene concentrations included the removal or replacement

of lined pipes, the flushing of distribution systems and the installation of bleeders. Moreover, concentrations in water were found to decrease as the pipes aged (Larson et al., 1983).

Drinking water contamination incidents resulting from permeation of organic chemicals in soil through water piping and piping components have been reported in the literature (Glaza and Park, 1992; Bromhead, 1997; Goodfellow et al., 2002; Ong et al. 2008).

Plastic pipes and piping components are durable and have a good resistance to chemicals, such as chlorine, used in the water treatment. However, plastic pipes and piping components may come in contact with contaminated soils as a result of leaks from underground storage tanks, chemical spills, and improper disposal of used chemicals. These contaminants may pose serious threats to the longevity and structural integrity of plastic pipes and elastomeric gaskets and can affect the water quality in the distribution system.

A survey (2004) of water utilities on permeation incidents involving plastic pipes and elastomeric gasket provided information on utilities' experience. Of the 151 water utilities in the US and Canada that responded to the survey, 70% reported using plastic pipes. Polyvinyl chloride (PVC) and polyethylene (PE) pipes accounted for 18% and 0.18% of the mains, respectively. The survey also reported that ductile iron (DI) pipes accounted for 16% of the mains. Generally, permeation incidents involving potable water distribution pipes are rarely reported. The survey reported 6 water main permeation incidents; three of these incidents involved gasoline, one involved a chlorinated solvent and two were associated with unknown chemicals. The pipe materials involved in permeation incidents were PVC (4), asbestos cement (1) and cast iron (1). A case reported a cast iron pipe with lead joints exposed to chlorinated solvents. Concentrations of tetrachloroethylene were detected in the soil and groundwater (1,560 mg/kg and 0.44 mg/L, respectively) but not in the drinking water. Plastic service connections were used by 49% of the utilities, with PVC and PE accounting for 5% and 6%, respectively. In addition, the survey reported that of the 44 service connection incidents of permeation, two involved chlorinated solvents and DI pipes with styrene butadiene rubber gaskets. In an incident of permeation involving tetrachloroethylene and ductile iron pipes with styrene butadiene rubber gaskets, ranges of concentrations of tetrachloroethylene were 0.04–3.6 mg/kg in the contaminated soil, 0.9–15.4 mg/L in the groundwater and not detectable to 6.6 µg/L in the potable water (Ong et al., 2008).

Bromhead (1997) reported permeation incidents of tetrachloroethylene with polyethylene service pipes at contaminated locations in Rotterdam, Netherlands. Of the 143 water samples, 98% had tetrachloroethylene concentrations between <0.05 and 10 µg/L, and 2% had concentrations above 10 µg/L, with a maximum of 14.4 µg/L after 8 hours of stagnation.

7.2 Residential

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to 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 decreasing tetrachloroethylene concentrations in drinking water.

A number of residential treatment devices from various manufacturers are available that can remove tetrachloroethylene from drinking water to concentrations below 5 µg/L. Filtration systems may be installed at the faucet (point-of-use) or at the location where water enters the home (point-of-entry). From a health perspective point-of-entry systems are preferred for VOCs such as tetrachloroethylene because they provide treated water for bathing and laundry as well as for cooking and drinking. Certified point-of-use treatment devices are currently available for the removal of VOCs, including tetrachloroethylene. 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 can lose their removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations.

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, 2015):

- CSA Group (www. csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca – available in French only); and
- International Association of Plumbing and Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (2015).

Treatment devices to remove tetrachloroethylene from untreated water (e.g., a private well) can be certified for either the removal of tetrachloroethylene alone or the removal of a variety of VOCs, including tetrachloroethylene.

Treatment devices that are certified to remove tetrachloroethylene or VOCs under NSF/ANSI Standard 53 are generally based on activated carbon adsorption technology. For a drinking water treatment device to be certified to NSF/ANSI Standard 53 (Drinking Water Treatment Units—Health Effects) for the reduction of tetrachloroethylene concentrations, the device must be capable of reducing an average influent concentration of 0.015 mg/L to a maximum finished effluent concentration of 0.005 mg/L or less (NSF/ANSI, 2011). Treatment devices certified for the reduction of organic chemicals included in NSF/ANSI Standard 53 by surrogate testing must be capable of reducing the concentration of tetrachloroethylene by greater than 99% from an influent (challenge) concentration of 0.081 mg/L to a maximum final (effluent) concentration of less than 0.001 mg/L (NSF/ANSI, 2011).

Reverse osmosis systems certified to NSF/ANSI Standard 58 (RO) may also be certified for the reduction of tetrachloroethylene concentrations to achieve a final concentration of less than 0.001 mg/L (NSF/ANSI, 2012). Reverse osmosis systems should only be installed at the point of use as the water they have treated may be corrosive to internal plumbing components.

8.0 Kinetics and metabolism

8.1 Absorption

Experimental absorption of tetrachloroethylene via the ingestion route has not been measured in humans; however, a poisoning case study in which tetrachloroethylene was measured in blood after being ingested by a 6-year-old boy (Koppel et al., 1985) indicated that tetrachloroethylene was absorbed following oral exposure.

Initial uptake of tetrachloroethylene via inhalation is rapid in humans, but declines as blood and body tissues become saturated (Fernandez et al., 1976; Monster, 1979). In six male volunteers exposed by inhalation to tetrachloroethylene at concentrations of 72 and 144 ppm, absorption was > 90% at the beginning of exposure and fell to approximately 50% after 8 hours (Monster, 1979). Steady-state levels of tetrachloroethylene in blood were reached after 50–100 minutes in five subjects exposed by inhalation to 100 ppm, and retention was 78–89% (Benoit et al., 1985). Another study found that peak tetrachloroethylene levels in venous blood were measured at the end of a 6-hour inhalation exposure to 1 ppm and declined thereafter (Chiu et al., 2007). Absorption of tetrachloroethylene by inhalation is also substantial in experimental animals (Schumann et al., 1980; Dallas et al., 1994).

Dermal absorption of tetrachloroethylene is less extensive than that via the ingestion and inhalation routes. Percutaneous absorption of tetrachloroethylene can occur in humans when skin is exposed to the compound in liquid form (Stewart and Dodd, 1964; Aitio et al., 1984; Kezic et al., 2001), but dermal absorption of tetrachloroethylene in vapour form is negligible compared with absorption following inhalation exposure (Riihimaki and Pfaffli, 1978). Stewart and Dodd (1964) suggested that dermal absorption of tetrachloroethylene is unlikely to be hazardous under normal working conditions. Dermal absorption of liquid tetrachloroethylene has been measured in mice (Tsuruta, 1975), rats (Tsuruta, 1977) and guinea pigs (Bogen et al., 1992), and absorption of tetrachloroethylene vapour was explored in mice (Tsuruta, 1989). Rats have shown a skin uptake of 3.5% following dermal exposure to tetrachloroethylene vapour at a concentration of 12 500 ppm (McDougal et al., 1990).

8.2 Distribution

Although no studies have measured the distribution of tetrachloroethylene in humans following oral exposure, distribution of tetrachloroethylene is not expected to be dependent on the route of exposure, as demonstrated in rats (Pegg et al., 1979).

Only a small fraction (~1–4%) of inhaled and ingested tetrachloroethylene has been observed to remain in the carcass of rats (Pegg et al., 1979; Frantz and Watanabe, 1983). The majority of the tetrachloroethylene that is stored tends to be distributed to fatty tissues, which reflects tetrachloroethylene's lipophilicity. Tissues with the highest concentrations of tetrachloroethylene are those with higher lipid content in both humans (Lukaszewski, 1979; Levine et al., 1981; Garnier et al., 1996) and experimental animals (Savolainen et al., 1977; Pegg et al., 1979). For example, tissue analyses of humans following fatal inhalation exposures showed the highest tetrachloroethylene concentrations in the liver, brain and kidney and the lowest concentrations in the lung tissue (Lukaszewski, 1979; Levine et al., 1981; Garnier et al., 1996), consistent with the lipophilic properties of tetrachloroethylene. Similarly, the highest concentrations of tetrachloroethylene in exposed rats were found in fat, kidneys and liver, and the lowest concentrations were in lung, heart and adrenals (Savolainen et al., 1977; Pegg et al., 1979). Some discrepancies were found related to storage in the brain, as tetrachloroethylene was not detected in the brain in one study (Pegg et al., 1979), but was detected in the brain in another study (Savolainen et al., 1977), with higher concentrations in the cerebrum than in the cerebellum.

Tetrachloroethylene is also distributed to tissues of relevance for developing humans and animals. After exposure of pregnant rats to tetrachloroethylene, the compound was measured in fetal blood and amniotic fluid (Ghantous et al., 1986; Szakmáry et al., 1997). Tetrachloroethylene has also been found in breast milk in humans (Bagnell and Ellenberger, 1977; Schreiber et al., 2002) and experimental animals (Byczkowski and Fisher, 1994), with partitioning to breast milk

likely higher in animals than in humans due to differences in milk fat content (Byczkowski and Fisher, 1994).

8.3 Metabolism

The metabolism of tetrachloroethylene in experimental animals and humans has been thoroughly reviewed by Anders et al. (1988), Lash and Parker (2001) and U.S. EPA (2012c).

The majority of inhaled tetrachloroethylene does not undergo metabolism in humans and is excreted unchanged (Monster, 1979; Benoit et al., 1985; Chiu et al., 2007). For the minor amount of the compound that is metabolized, there are two major pathways for transformation. In both humans and experimental animals, tetrachloroethylene undergoes mainly oxidative metabolism and will proceed to reductive metabolism once the enzymes associated with oxidative metabolism are saturated (Lash and Parker, 2001).

Oxidative metabolism is driven by cytochrome P450 (CYP) enzymes, with CYP2E1 as the major relevant isoform for tetrachloroethylene metabolism (Lash and Parker, 2001). The primary site for oxidative metabolism is the liver, with smaller amounts of metabolism occurring in other organs. Although renal metabolism is relevant to rats (Cummings et al., 1999), the role of renal metabolism is less clear in humans, as the human kidney expresses some CYP isoforms, but not CYP2E1 (Cummings et al., 2000). The major end products of oxidative metabolism are TCA, carbon monoxide, carbon dioxide and—primarily in rats—oxalic acid. Reaction of tetrachloroethylene with CYP2E1 first results in a tetrachloroethylene–iron oxide intermediate, which can then generate 1,1,2,2-tetrachloroethylene oxide (a hypothesized epoxide), oxalic acid and trichloroacetyl chloride. The epoxide is thought to generate trichloroacetyl chloride, ethanedioyl chloride (which eventually can be metabolized to carbon monoxide and carbon dioxide) and chloral hydrate, and reaction of the epoxide with microsomal epoxide hydrase forms oxalic acid. The major metabolite, TCA, is formed from trichloroacetyl chloride. There is conflicting evidence stating that DCA, the major metabolite from the glutathione transferase (GST) pathway, might be generated from TCA by conversion in gut microflora; however, the primary source of DCA is thought to be from the GST pathway (U.S. EPA, 2012c).

The second pathway for metabolism, the GST pathway, becomes predominant when tetrachloroethylene levels are high enough for saturation of CYP2E1; however, it can still operate prior to the saturation of the oxidative pathway (Chiu and Ginsberg, 2011). Saturation of oxidative metabolism occurs in humans at inhalation exposures of approximately $\geq$ 100 ppm, as metabolite excretion measured in workers in industrial and dry cleaning settings was shown to plateau at higher concentrations (Ikeda, 1977; Ohtsuki et al., 1983; Seiji et al., 1989); however, there are still uncertainties regarding the extent of GST metabolism in humans (Chiu and Ginsberg, 2011). Although the GST pathway is responsible for less tetrachloroethylene metabolism at low exposure levels, it is still considered of importance, because it produces several reactive metabolites.

Through glutathione conjugation, further biotransformation and processing occur; GST mediates this production of water-soluble compounds for excretion (U.S. EPA, 2012c). Conjugation begins primarily in the liver, where GST converts tetrachloroethylene to *S*-(1,2,2-trichlorovinyl) glutathione (TCVG), and early products of the metabolism—including TCVG and the product it generates with the catalysts gamma-glutamyltransferase and dipeptidases, *S*-(1,2,2-trichlorovinyl) cysteine (TCVC)—travel to the kidney; however, a smaller amount of metabolism also occurs in the kidney (Lash et al., 1998; U.S. EPA, 2012c). *N*-Acetyl transferase can catalyze the conversion of TCVC to the excretory product *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine (NAcTCVC), but other enzymes can lead to the production of the reactive metabolites TCVC

sulphoxide (via flavin monooxygenase-3 and CYP) or the unstable 1,2,2-trichlorovinylthiol (via β-lyases). DCA, the major end-product of the GST pathway, can be formed from the latter reactive metabolite (U.S. EPA, 2012c).

Variability in tetrachloroethylene metabolism has been studied in human populations. Some variability in metabolism may be related to ethnicity, as demonstrated by studies showing lower levels of urinary TCA and higher exhalation of tetrachloroethylene in Chinese workers compared with Japanese workers (Seiji et al., 1989) and in Asians compared with Caucasians (Jang and Droz, 1997). It has been suggested that variations in the oxidative and reductive metabolic pathways due to genetic polymorphisms in populations may be responsible for the differences in metabolism of tetrachloroethylene among individuals and ethnic groups (Lash et al., 2007; U.S. EPA, 2012c).

Although the conversion of tetrachloroethylene to TCA is the main route of metabolism in humans, rats and mice, species differences in the metabolism of tetrachloroethylene have been identified. Mice metabolize tetrachloroethylene more extensively than rats, and rats metabolize it more extensively than humans (Schumann et al., 1980; Völkel et al., 1998; Lash and Parker, 2001). Moreover, although saturation of oxidative metabolism occurs at similar levels in rats and humans, oxidative metabolism does not become saturated in mice, as demonstrated by the continued increase in blood TCA concentrations at inhalation exposure levels of up to 400 ppm (Odum et al., 1988).

8.4 Excretion

For humans and experimental animals, many quantitative studies have shown that the majority of tetrachloroethylene is eliminated unmetabolized in exhaled air, regardless of the route of exposure (Yllner, 1961; Daniel, 1963; Fernandez et al., 1976; Monster, 1979; Pegg et al., 1979).

Tetrachloroethylene exhibits a multiphasic elimination curve in humans, with a rapid phase followed by slower phases (Fernandez et al., 1976; Monster, 1979). The rapid phase likely represents the elimination of tetrachloroethylene from the blood immediately after exposure, and the slow phase is indicative of elimination from adipose tissue (Monster, 1979). Pulmonary excretion was estimated from modelling to occur in three different phases: a rapid phase of elimination from blood vessel-rich tissues (brain, heart, hepatoportal system, kidneys, endocrine glands); a slower elimination from muscle, skin and blood vessel-poor tissues (connective tissue, lung tissue); and a very slow elimination from adipose tissues (Guberan and Fernandez, 1974). Quantitative estimates of the rapidity of elimination in humans vary, with empirical studies demonstrating half-lives of 12–16, 30–40 and 55 hours, depending on where along the concentration curve they were calculated (20, 50 and 100 hours, respectively) (Monster, 1979), and 79 minutes (Benoit et al., 1985) and a model providing an estimate of 71.5 hours (Guberan and Fernandez, 1974); this phenomenon is likely representative of the different phases of elimination from different tissues. Calculated half-lives in rats ranged from 6.94 to 7.43 hours (Pegg et al., 1979). Elimination occurs more rapidly via exhalation than via urinary excretion, as demonstrated by elimination half-lives of 65 hours and 144 hours, respectively (Ikeda, 1977, as calculated from data from Stewart et al., 1970). Men appear to eliminate tetrachloroethylene more rapidly than women, with half-lives of urinary metabolites of 123 hours in males and 190 hours in females, estimated from occupational exposures (Ikeda and Imanura, 1973); however, this differed from rats, where there were no differences in elimination half-lives between males and females (Ikeda and Imanura, 1973). Elimination over a short time period is also more pronounced

in individuals with lower body weights than in those with higher body weights (Monster et al., 1983).

Tetrachloroethylene can also be excreted in breast milk, as demonstrated in a case study. Breast milk concentrations in a woman exposed to tetrachloroethylene while visiting her husband at a dry cleaning establishment were 1 mg/dL 1 hour after her visit and 0.3 mg/dL 24 hours afterwards; the blood concentration of tetrachloroethylene measured 2 hours after her exposure was 0.3 mg/dL (Bagnell and Ellenberger, 1977).

The majority of tetrachloroethylene (80–100%) is excreted unchanged via exhalation in humans (Monster, 1979; Benoit et al., 1985; Chiu et al., 2007); however, in animals—particularly mice—metabolism is greater (Yllner, 1961; Daniel, 1963; Pegg et al., 1979; Schumann et al., 1980), leading to levels of unchanged tetrachloroethylene in breath as low as 12% in mice (Schumann et al., 1980). Only minor amounts of metabolites are excreted in humans exposed by inhalation to 72–200 ppm (Fernandez et al., 1976; Monster, 1979), with slightly higher levels in rats exposed by gavage to 1–9000 mg/kg bw per day for up to 12 administrations or by inhalation to 10–600 ppm for 6 hours (Daniel, 1963; Pegg et al., 1979; Schumann et al., 1980) and much higher levels in mice exposed by gavage to 100–1000 mg/kg bw per day for up to 12 administrations or by inhalation to 10–600 ppm for 6 hours (Schumann et al., 1980).

The major metabolite in humans is TCA (Völkel et al., 1998), which is excreted in urine (Monster, 1979; Birner et al., 1996; Völkel et al., 1998; Schreiber et al., 2002; Chiu et al., 2007); however, studies demonstrate that only ≤ 1–3% of tetrachloroethylene intake is excreted as TCA (Monster, 1979; Chiu et al., 2007). The half-life of TCA has been measured at 45.6–65 hours in urine (Monster et al., 1983; Völkel et al., 1998) and 75–90 hours in blood (Monster, 1979; Monster et al., 1983), and the highest excretion has been measured to occur 24–48 hours after exposure (Fernandez et al., 1976). TCA excretion is more rapid in experimental animals than in humans (Völkel et al., 1998). Other metabolites that have been measured in human urine after tetrachloroethylene exposure include NAcTCVC (Birner et al., 1996; Völkel et al., 1998; Schreiber et al., 2002) and trichloroethanol (Monster, 1979; Birner et al., 1996; Schreiber et al., 2002); however, the latter compound is not expected to be a metabolite of tetrachloroethylene and might therefore result from simultaneous trichloroethylene exposures or be an analytical artifact (U.S. EPA, 2012c). DCA has been detected in the urine of rats, but not humans (Völkel et al., 1998).

8.5 Physiologically based pharmacokinetic models

In human health risk assessment for tetrachloroethylene, physiologically based pharmacokinetic (PBPK) modelling is useful, because no appropriate toxicity data are available for humans ingesting tetrachloroethylene in drinking water, ingestion studies in experimental animals are limited and the metabolite generation over low to high parent compound exposures is non-linear. Several PBPK models have been developed for tetrachloroethylene; a detailed critical review of available models was performed by Clewell et al. (2005).

The basic structure of these models is based primarily on the initial Ramsey and Andersen (1984) styrene model, which compartmentalizes organs into liver, fat, rapidly perfused tissues and slowly perfused tissues. A separate kidney compartment was also included in many of the models (Gearhart et al., 1993; Covington et al., 2007; Qiu et al., 2010; Chiu and Ginsberg, 2011), and some models (Rao and Brown, 1993; Dallas et al., 1994; Qiu et al., 2010) included a brain compartment to enable prediction of tetrachloroethylene concentrations in target tissues in neurological studies. Although several earlier models either did not simulate metabolism (Rao and Brown, 1993) or predicted only overall tetrachloroethylene metabolism (Bois et al., 1996; Reitz et

al., 1996), generation of TCA via the oxidative pathway has been included in models for rats (Chiu and Ginsberg, 2011), mice (Gearhart et al., 1993; Fisher et al., 2004; Sweeney et al., 2009; Chiu and Ginsberg, 2011) and humans (Gearhart et al., 1993; Covington et al., 2007; Chiu and Ginsberg, 2011). GST metabolism has been considered in only two models (Sweeney et al., 2009; Chiu and Ginsberg, 2011), wherein urinary concentrations of NAcTCVC and DCA were predicted in rats, mice and humans. The models were designed for exposures from the injection, inhalation and/or ingestion routes, and one model included exposure to tetrachloroethylene via both dermal and inhalation routes from bathing and showering (Rao and Brown, 1993). Monte Carlo simulation components have also been added to some models (Gearhart et al., 1993; Bois et al., 1996; Covington et al., 2007) to consider distributions of values for some of the model parameters (e.g., the ventilation over perfusion ratio, blood flows, volumes, partition coefficients and metabolism values).

The model by Gearhart and colleagues (1993) was used as the basis for the PBPK model developed to facilitate rodent to human and inhalation to ingestion extrapolation estimates for this assessment (Nong, 2013). The model quantitatively accounts for differences in metabolism between animals and humans. Minor adjustments to the model were applied using physiological and metabolic parameters from Reitz et al. (1996) and Clewell et al. (2005). Health Canada's model (Nong, 2013) allows for the estimation of concentration and area under the concentration–time curve (AUC) for tetrachloroethylene in the blood, liver and kidney; rates of metabolism in liver and kidney; and concentration and AUC of TCA in blood. The model, however, does not allow for estimates of TCA levels in tissues. Moreover, a brain compartment was not added to the model, as the blood–brain partition coefficient is similar to that for blood–liver and blood–kidney, and liver and kidney tetrachloroethylene concentrations and AUCs have been demonstrated to be appropriate proxies for brain levels (Dallas et al., 1994). The model was also extrapolated to describe pregnancy kinetics using similar assumptions as for the Fisher et al. (1989) model for trichloroethylene. The model also incorporated elements from Rao and Brown (1993) to allow for estimates of tetrachloroethylene exposure via the dermal (in liquid form—a conservative estimate because it is more highly absorbed than tetrachloroethylene in vapour form, which will form some of the exposure in bathing) and inhalation (in vapour form) routes from bathing and showering, which were used to calculate the litre-equivalent values (see Section 5.6). The Health Canada model (Nong, 2013) was validated using data for mice (Odum et al., 1988), rats (Dallas et al., 1994; Reitz et al., 1996) and humans (Fernandez et al., 1976; Monster, 1979; Rao and Brown, 1993; Völkel et al., 1998), with exposures from the ingestion (Gearhart et al., 1993; Dallas et al., 1994), inhalation (Fernandez et al., 1976; Monster, 1979; Odum et al., 1988; Dallas et al., 1994; Reitz et al., 1996; Völkel et al., 1998) and dermal (Rao and Brown, 1993) routes.

9.0 Health effects

9.1 Effects in humans

A large number of studies have been conducted to investigate the effects of tetrachloroethylene on human health. Only the most relevant information from these studies is included in this section. An in-depth authoritative review of the effects of tetrachloroethylene on human health was recently performed by U.S. EPA (2012b), which is readily available and can be consulted for further details on individual studies.

9.1.1 Acute toxicity

The discussion in this section focuses primarily on several controlled dosing studies that investigated the acute toxicity of tetrachloroethylene, rather than on case studies of accidental or intentional overexposure that tend to have weak exposure estimates.

Tetrachloroethylene may exert toxicity as an irritant and neurotoxic substance upon acute inhalation exposure. Transient self-reported symptoms, including mild eye and nasal irritation, dizziness, light-headedness, speech difficulties and nausea, were observed in clinical studies of short-term exposure to tetrachloroethylene by inhalation at levels of 100 and 200 ppm (Stewart et al., 1961, 1970). However, these studies did not include controls; studies comparing exposed groups with controls (Stewart et al., 1977) or using non-exposed days in subjects as controls (Stewart et al., 1981) did not find any differences in these symptoms between exposed and control groups. Various neurophysiological and neurobehavioural effects were also observed. The neurophysiological effects included changes in electroencephalogram wave amplitude and frequency at 100 ppm that were consistent with drowsiness and anesthesia (Stewart et al., 1981); changes in peak latencies of visually evoked potentials (Altmann et al., 1990, 1992) and visual contrast sensitivity (Altmann et al., 1990) at 50 ppm; and difficulties in obtaining normal scores in balance tests at 100 ppm (Stewart et al., 1970) and > 200 ppm (Stewart et al., 1961). Decrements in coordination and vigilance tests were observed at > 50 ppm in some acute studies (Stewart et al., 1977, 1981; Altmann et al., 1992), but not all of them (Stewart et al., 1970).

In general, acute studies do not seem to support liver and kidney effects after short-term exposure, except in extreme cases of high-level accidental overexposure. These effects were limited to serum biomarkers of liver damage (Saland, 1967) and mild chemical hepatitis (Stewart, 1969) after extremely high occupational exposures and transient renal failure and tubular necrosis after ingestion (Choi et al., 2003). At lower exposure levels (20–200 ppm), no effects on biomarkers of liver and kidney damage were observed (Stewart et al., 1961, 1970, 1977, 1981).

Mortality from short-term exposures to tetrachloroethylene has been reported in cases of extreme accidental overexposure by inhalation. Although none of the case reports present estimated inhalation levels, concentrations of tetrachloroethylene in various tissues were listed. These tissue levels included 66 mg/L in blood and 31–79 mg/kg in heart, lung and brain in a 2-year-old boy (Garnier et al., 1996). In two adult workers, tissue concentrations were measured at 44 mg/L in blood, 3 mg/kg in lung and 360 mg/kg in brain (Lukaszewski, 1979); and 4.5 mg/L in blood and 69–240 mg/L in brain, kidney and liver (Levine et al., 1981).

9.1.2 Subchronic and chronic toxicity and carcinogenicity

The subchronic and chronic health effects associated with tetrachloroethylene exposure in humans have been investigated primarily in occupational settings and in limited studies of non-occupational exposure through contamination of drinking water or indoor air. In these studies, investigations of non-cancer effects focused primarily on the nervous system, with a few studies also considering hepatic, renal and immunological effects. Associations between tetrachloroethylene exposure and a variety of types of cancer have also been investigated.

9.1.2.1 Neurological effects

Various studies have investigated subjective neurological symptoms and objective measures of neurophysiological, neurobehavioural and neuroendocrine effects of tetrachloroethylene in workers and the general public. The studies of general public exposure examined several cohorts. The first was a cohort of adults who had been previously exposed to tetrachloroethylene in drinking water—both prenatally and until the age of 5 years—when it was

leached from the vinyl lining of asbestos–concrete pipes (Getz et al., 2012). Exposed participants in Schreiber et al. (2002) and Storm and Mazor (2004) were adult and child apartment dwellers whose residences were located in buildings containing dry cleaning facilities; the larger cohort from the New York State Department of Health (Getz et al., 2012) and Storm et al. (2011) was gathered in a similar manner, but was composed of different subjects. Another cohort with residential exposures was a group of adults exposed by living in a neighbourhood containing dry cleaning facilities. The majority of occupationally exposed cohorts were composed of dry cleaners (Lauwerys et al., 1983; Seeber, 1989; Cai et al., 1991; Ferroni et al., 1992; Nakatsuka et al., 1992; Cavalleri et al., 1994; Echeverria et al., 1995; Gobba et al., 1998), of which only two contained the same participants (Cavalleri et al., 1994; Gobba et al., 1998). One additional occupationally exposed cohort was a group of workers in a daycare centre that was located in a building containing dry cleaning facilities (Schreiber et al., 2002). Children of dry cleaners were also investigated in one study (Perrin et al., 2007).

Neurophysiological effects observed in the studies involved visual function, with decrements in colour vision and contrast sensitivity being the two effects that were primarily noted. The effects of tetrachloroethylene exposure on colour vision were investigated in the cohort of adults exposed in drinking water prenatally and until 5 years of age (Getz et al., 2012) and in inhalation studies of individuals with current exposures (Nakatsuka et al., 1992; Cavalleri et al., 1994; Gobba et al., 1998; Schreiber et al., 2002; New York State Department of Health, 2010; Storm et al., 2011), with most using the Lanthony desaturated 15 hue panel (a test that requires participants to arrange coloured caps according to colour similarity) for testing. The weight of evidence suggests an association between tetrachloroethylene exposure and decrements in colour discrimination. Significantly higher (i.e., worse) colour confusion index (CCI) scores were observed in adults exposed to tetrachloroethylene in drinking water early in life (at all exposure levels using the Farnsworth desaturated 15 hue panel, but only for estimated exposure concentrations of $\geq$ 40 µg/L using the Lanthony panel) (Getz et al., 2012). Adults occupationally exposed by inhalation to mean tetrachloroethylene levels of 4.35–7.27 ppm (Cavalleri et al., 1994; Gobba et al., 1998) also had significantly elevated CCI scores. A trend towards higher CCI scores, but without statistical significance, was measured in people living in apartment buildings containing dry cleaning facilities with mean and median daytime exposure concentrations of 1198 and 620 µg/m^3, respectively (Schreiber et al., 2002). The majority of the decrements in colour vision that were observed were in the yellow–blue spectrum, which is the spectrum that is expected to be affected by exposure to solvents (Iregren et al., 2002). A dose-response relationship was observed (Cavalleri et al., 1994; Gobba et al., 1998; Getz et al., 2012); furthermore, temporality is suggested by increases in CCI scores in a group of workers whose exposure was measured to be higher (geometric mean level of 4.35 ppm) in a 2-year follow-up (Gobba et al., 1998). Despite these positive observations, no difference in colour vision was observed between exposed and unexposed workers in a study of dry cleaners exposed to geometric mean time-weighted average concentrations of 15.3 ppm (men) and 10.7 ppm (women) (Nakatsuka et al., 1992) or in daycare workers located in a building containing a dry cleaning facility, with a mean exposure concentration of 2150 µg/m^3 (Schreiber et al., 2002). These studies, however, might have had a decreased ability to detect changes in colour vision, because the version of the hue panel used in the Nakatsuka (1992) study (the non-desaturated version of the Lanthony 15 hue panel) has a lower ability to detect more subtle decrements in colour vision, and exposure levels in the Schreiber et al. (2002) study were very low for occupational exposures. Despite these minor inconsistencies, the epidemiological weight of evidence tends to indicate that colour vision deficits occur in humans exposed to tetrachloroethylene at occupationally and

environmentally relevant exposure levels. These effects might be sustained over time, as was demonstrated in adults whose exposure occurred prenatally and in early childhood (Getz et al., 2012). Moreover, no improvement in CCI score was observed after 2 years in workers whose geometric mean exposure levels dropped from 2.95 to 0.66 ppm (Gobba et al., 1998).

The second neurophysiological effect that was explored for tetrachloroethylene was contrast sensitivity. In adults exposed at a young age to tetrachloroethylene in drinking water, contrast sensitivity was decreased at intermediate and high spatial frequencies, but significance was reached only at the highest frequency and was restricted to the high-exposure group (estimated concentrations of ≥ 40 µg/L) (Getz et al., 2012). Changes in contrast sensitivity were significant at all spatial frequencies in apartment dwellers and daycare operators who were exposed to tetrachloroethylene (at geometric mean concentrations of 1198 and 2150 µg/m^3, respectively) from dry cleaning facilities within the building (Schreiber et al., 2002). The analysis of residential exposures, however, included test scores for both adults and children; reanalysis identified no effects on contrast sensitivity when looking solely at adults, and effects on visual contrast sensitivity tests in children might have been affected by diagnosed developmental delay and attention deficit disorder (Storm and Mazor, 2004). A more recent study of apartment dwellers observed a trend of fewer adults and—to an even greater extent—children reaching maximum visual contrast sensitivity scores at multiple spatial frequencies with increasing indoor air exposure (geometric mean concentrations of 11.6 µg/m^3 in low exposed adults, 477.9 µg/m^3 in high exposed adults, 12.4 µg/m^3 in low exposed children and 335.8 µg/m^3 in high exposed children) (Storm et al., 2011). The validity of these results, however, is limited by differing characteristics of individuals in the high-exposure category that could affect visual contrast sensitivity scores, including minority status, lower education levels and lower income levels.

Various neurobehavioural and neuropsychological effects were investigated in the cohort of adults who had been exposed to tetrachloroethylene in drinking water during childhood. A neurobehavioural battery was administered to a small subset of the initial study population, which identified significant but inconsistent decrements in memory and attention/executive function (Janulewicz et al., 2012). Exposed subjects had decreased scores in one memory test (delayed recall in the Wechsler memory test, but not in others); furthermore, impacts on attention were identified in only one part of the Trail Making Test, but these effects lost significance when adjusted for sex and education (Janulewicz et al., 2012). Due to a limited number of participants in the neurobehavioural battery, comparisons were made solely between exposed and unexposed participants (and no average exposure estimates were provided); however, a greater sample size in other studies within this cohort allowed for division of participants by exposure subgroups to identify trends in effects. Slight increases in a tendency towards risky behaviour (likelihood for regular smoking, drinking or use of various drugs in adolescence or recently) were observed, particularly in the highest tertile of exposure (estimated cumulative prenatal plus postnatal exposures of ≥ 77.6 g) (Aschengrau et al., 2011). An increase in self-reported behavioural and learning disorders did not demonstrate a dose-response relationship, and borderline significance observed in the low-exposure group (estimated cumulative exposures of < 10 g prenatally and < 66.7 g postnatally, corresponding to 40 µg/L) was lost when adjustment for maternal age, race, education, sex, prematurity and low birth weight was performed (Janulewicz et al., 2008). Weak associations were observed between exposure and self-reported mental illness, with a significantly increased risk of bipolar disorder in the highest tertile (but with no dose-response relationship, as a higher risk was observed in the lowest tertile than in the middle tertile), an increase of borderline significance in post-traumatic stress disorder in the highest tertile that was lost when adjusted, and a non-significant increase in schizophrenia that could not be analyzed by

tertile due to the low incidence of the disease (Aschengrau et al., 2012). No exposure estimates were provided for any of the tertiles. Therefore, the Aschengrau et al. (2012) findings were not sufficient to confirm those of a preliminary study of schizophrenia in a study with a large number of participants in Israel, which found a significantly increased risk of being diagnosed with schizophrenia in subjects whose parent's occupation was dry cleaning (as identified on subjects' birth certificates; therefore, no exposure levels were provided) (Perrin et al., 2007).

Table 2. Neurobehavioural test results for populations exposed via inhalation

Neurobehavioural function	Test	Results
Attention, vigilance and executive function	Continuous performance test	- Significantly prolonged response (Altmann et al., 1995)
	Simple reaction time	- Significantly prolonged response (Altmann et al., 1995) - Significantly prolonged response (Ferroni et al., 1992) - No effect (Lauwerys et al., 1983)
	Trail making test	- No effect (Echeverria et al., 1995)
	Shape comparison	- Significantly prolonged response (Ferroni et al., 1992)
	Choice reaction	- Significantly lower score (Seeber, 1989) - No effect (Lauwerys et al., 1983)
	Perceptual functions (digit recognition)	- Significantly prolonged response (Seeber, 1989)
Attention and short-term memory	Visual retention test	- Significantly fewer correctly identified (Altmann et al., 1995)
	Visual reproduction test	- Significantly lower score with lifetime exposure, but not 3-year or current exposure (Echeverria et al., 1995)
	Pattern memory test	- Significantly lower score with lifetime and 3-year exposure, but not current exposure; prolonged response time with lifetime and current exposure (Echeverria et al., 1995)
	Pattern recognition test	- Significantly lower score with lifetime exposure, but not 3-year or current exposure (Echeverria et al., 1995)
	Digit span test	- No effect (Echeverria et al., 1995) - Significantly lower score (with or without cancellation task) (Seeber, 1989)
Visuospatial and visuomotor	Finger tapping test	- No effect on right or left; difference for alternating, but not significant ($p < 0.1$ but not $p < 0.05$) (Altmann et al., 1995)
	Visual–motor tracking	- No effect (Altmann et al., 1995)
	Digit symbol test	- No effect (Echeverria et al., 1995) - No effect (Ferroni et al., 1992) - Significantly lower score (Seeber, 1989)

Neurobehavioural effects were also investigated in populations exposed through inhalation, from either residential (Altmann et al., 1995) or occupational (Lauwerys et al., 1983; Seeber, 1989; Ferroni et al., 1992; Echeverria et al., 1995) exposures. Detailed results from specific tests can be found in Table 2. Differences between exposed and unexposed groups were observed at a median concentration of 1.36 mg/m^3 (Altmann et al., 1995) in those residentially

exposed. Higher levels were required for effects to be observed in occupational studies. Responses were observed at median levels of 15 ppm (Ferroni et al., 1992) and at average concentrations of 83.4 and 363.8 mg/m^3 (Seeber, 1989), but dose-response relationships were not observed in either study. In the study by Echeverria et al. (1995), effects were observed—typically with a dose-response relationship—in the lifetime or 3-year cumulative exposure groups (exposure quantification not published for these groups), but not at current exposures of up to 41.8 ppm. No effects were observed at a mean level of 20.8 ppm in an additional study (Lauwerys et al., 1983). The weight of evidence from these epidemiological studies suggests that tetrachloroethylene exposure at elevated levels might be associated with adverse effects on attention, vigilance and executive function, as well as on attention and short-term memory function, but not on visuomotor or visuospatial function.

Three studies considered the effects of chronic tetrachloroethylene exposure on subjective neurological symptoms by administering questionnaires that focused on symptoms that could possibly be related to disturbances of the nervous system (e.g., dizziness and fainting, drunkenness, forgetfulness, loss of concentration, increased excitability). Significantly higher prevalence of self-reported neurological symptoms was observed in two of these studies in workers exposed by inhalation to a geometric mean level of 19.9 ppm (Cai et al., 1991) and average concentrations of 83.4 and 363.8 mg/m^3 (Seeber, 1989), but no dose-response relationships were observed. Although the prevalence of neurological signs was increased in workers exposed to a mean level of 20.8 ppm in the third study (Lauwerys et al., 1983), these increases were not significant. Furthermore, in the one study in which a clinical examination was administered by a physician, no differences were observed between exposed (geometric mean level of 19.9 ppm) and unexposed workers (Cai et al., 1991).

In an attempt to identify neuroendocrine effects of tetrachloroethylene, Ferroni et al. (1992) measured prolactin levels in female dry cleaning workers. Basal serum prolactin levels were significantly elevated during the proliferative phase of the menstrual cycle in tetrachloroethylene-exposed women (median level of 15 ppm); however, no dose-response relationship was observed. Other phases of the menstrual cycle were not discussed. The authors postulated that this effect might suggest that pituitary function is affected by tetrachloroethylene.

Of the endpoints discussed in this section, two studies (Cavalleri et al., 1994; Echeverria et al., 1995) were considered to be most relevant for the risk assessment. The reason for this decision is outlined in Section 9.5.2. A more in-depth description of these two studies is included below.

The first study (Cavalleri et al., 1994) investigated the effect of occupational exposure on colour vision by dividing 35 workers from 12 dry cleaning shops around Modena, Italy, into high-exposure (dry cleaners; mean 8-hour time-weighted average exposure level of 7.27 ppm) and moderate-exposure (ironers; mean 8-hour time-weighted average exposure level of 4.8 ppm) groups. Although breathing zone air samples were obtained for all participants, exposure was measured only during one workshift (which was considered to be representative of other days). Exposed workers had been exposed to tetrachloroethylene for an average of 8.8 years at the time of testing. The same number of controls (matched to exposed subjects based on sex, age, and alcohol and cigarette consumption) was gathered from workers unexposed occupationally or vocationally to solvents or other substances toxic to eyes. Exposed and control participants were excluded if they consumed more than an average alcohol intake of 50 g/day, smoked more than 30 cigarettes/day or had visual acuity of less than 6/10 with lenses. Testing was performed under standard conditions using the Lanthony desaturated 15 hue panel by a technician who was blinded to the exposure level and workers' tasks. Only three workers received a perfect score on the test,

which was significantly less than the 13 controls that performed the test perfectly. Mean CCI score was significantly higher (worse) than controls in dry cleaners, but not in ironers; therefore, the no-observed-adverse-effect concentration (NOAEL) for the workers was 4.8 ppm. A multivariate analysis confirmed that the effect was most likely due to tetrachloroethylene and not other characteristics that can affect CCI score (e.g., age, alcohol, smoking). One weakness of the study was that some overlap in exposure occurred between the two exposure groups (range of exposures: ironers, 0.52–11.28 ppm; dry cleaners, 0.38–31.19 ppm); however, the authors also found a significant correlation between workers' time-weighted average exposure levels and their CCI scores, further supporting a dose-response relationship. An additional weakness with the use of the study in a dose-response assessment is that the significant association between tetrachloroethylene and CCI scores is lost upon exclusion of the three workers with the highest exposure levels (> 12.5 ppm) (Cavalleri et al., 1994; Benignus et al., 2009).

The second study that was considered further in the risk assessment was of 65 dry cleaners with no previous central nervous system problems who had worked in 1 of 23 shops in the Detroit, Michigan, area for at least 1 year (Echeverria et al., 1995). Workers were assigned to low-exposure (n = 24), moderate-exposure (n = 18) or high-exposure (n = 23) groups based on an industrial hygiene walkthrough. Breath samples were obtained from participants, and 15-minute breathing zone samples were obtained from one low-, medium- and high-exposed participant in 19 of the shops; the air sampling results identified average exposure levels of 0.6, 12.1 and 41.8 ppm, respectively, in wet transfer shops and of 0, 4.3 and 11.4 ppm, respectively, in dry-to-dry shops. In addition to current exposures, chronic and 3-year indices of exposure were estimated by summing the product of duration of employment and job title over 3 years or a lifetime. Controls were considered to be participants in the low-exposure group and were matched with highly exposed participants on education and age. Neurobehavioural testing of participants was performed on the 1st or 2nd day of the work week using a battery of tests (Profile of Mood States, Digit Span, Visual Reproductions Subtest, Wechsler Memory Scale, Neurological Evaluation Scale [NES] Pattern Memory, NES Pattern Recognition, Trail Making Test, NES Symbol-Digit Substitution Test and a vocabulary test). Regression models considered the potential effect of other variables on test results, including age, years of education, verbal skill, frequency of alcohol consumption, hours of sleep, fatigue, mood, symptoms, medication, and current or previous occupational or avocational exposure to neurotoxicants. Associations between tetrachloroethylene exposures and tests were found for the Visual Reproductions Subtest (lifetime index), Pattern Memory (lifetime and 3-year indices) and NES Pattern Recognition (lifetime index). No associations with tetrachloroethylene exposure were found for the other tests, and no associations were identified on any of the tests for current tetrachloroethylene exposures.

9.1.2.2 Other non-cancer effects

Studies in dry cleaners have suggested that chronic inhalation exposure to tetrachloroethylene may be associated with damage to the liver, as demonstrated by elevated serum gamma-glutamyltransferase activity (Gennari et al., 1992; Brodkin et al., 1995) and alterations in the liver parenchyma observed using ultrasonography (Brodkin et al., 1995). However, other studies in similar populations did not demonstrate changes in levels of enzymes potentially indicative of liver damage (Lauwerys et al., 1983; Cai et al., 1991).

Adverse effects of tetrachloroethylene on kidney tubules are also suggested by occupational epidemiology studies. Elevated levels of urinary retinol binding protein (RBP) were observed in two studies (Mutti et al., 1992; Verplanke et al., 1999); although the levels were within normal ranges in the Verplanke et al. (1999) study, a significant increase in the incidence

of abnormal RBP levels was reported by Mutti et al. (1992). No effect on RBP level was observed in one study with a smaller sample size (Lauwerys et al., 1983). Data to support the potential for tubular effects come from observations of proteinuria in occupationally exposed populations. Decreased integrity of the proximal tubule brush border was suggested by increases in brush border antigens and tissue non-specific alkaline phosphatase (ALP) (Mutti et al., 1992). Elevated urinary concentrations of β2μ-globulin (Mutti et al., 1992) and lysozyme (Franchini et al., 1983; Vyskocil et al., 1990) in dry cleaners were suggestive of decreased reabsorption in renal tubules; it should be noted, however, that two other studies—albeit with smaller sample sizes—did not note significant increases in urinary β2μ-globulin (Lauwerys et al., 1983; Vyskocil et al., 1990). β2-glucuronidase levels were also significantly increased in female dry cleaning shop workers (Franchini et al., 1983). No effects were observed on urinary levels of *N*-acetyl-β-D-glucosaminidase (Solet and Robins, 1991; Mutti et al., 1992; Verplanke et al., 1999; Trevisan et al., 2000) or alanine aminopeptidase (Verplanke et al., 1999).

The limited data available suggest that immunological and hematological effects are possible following tetrachloroethylene exposure, as noted by alterations in serum immunoglobulin E and circulating leukocytes, in addition to many other markers (Andrys et al., 1997; Lehmann et al., 2001, 2002; Emara et al., 2010). Studies of respiratory effects (Delfino et al., 2003a, 2003b; Tanios et al., 2004) and connective tissue effects (e.g., scleroderma) (Hinnen et al., 1995; Goldman, 1996; Lacey et al., 1999; Garabrant et al., 2003; Maître et al., 2004) are limited and inconsistent; thus, no firm conclusions can be drawn for these endpoints.

9.1.2.3 Cancer

The potential for tetrachloroethylene to cause cancer has been examined mostly in occupational studies within the dry cleaning industry, but also in studies pertaining to drinking water. Studies of exposure to tetrachloroethylene via leaching from vinyl linings in pipes have revealed significant increases in leukemia in highly exposed individuals (i.e., participants with exposure levels ≥ 90th percentile) (Aschengrau et al., 1993). Several analyses of this population also suggest that exposure to tetrachloroethylene may be associated with breast cancer in highly exposed women (Aschengrau et al., 1998, 2003; Vieira et al., 2005; Gallagher et al., 2011), but observed increases were not significant in most of the studies and only of borderline significance in one of the studies (Gallagher et al., 2011). Other cancers examined were not associated with tetrachloroethylene exposure, including bladder, kidney and colon–rectum cancer (Aschengrau et al., 1993; Paulu et al., 1999). A study in a different population revealed tetrachloroethylene-related increases in high-grade non-Hodgkin's lymphoma with or without Burkitt's lymphoma among females exposed to concentrations above 5 ppb (5 μg/L) in drinking water (Cohn et al., 1994); however, the relative influence of trichloroethylene on these results is unclear due to the high degree of correlation between both chemicals in the study population.

Other community-based studies of contaminated water (containing many chemicals, including tetrachloroethylene) have noted increases in bladder cancer (Mallin, 1990) and mortality from liver cancer (Lee et al., 2003), whereas another reports no effects on liver cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma or leukemia (Vartianinen et al., 1993). Other studies have noted a positive association between childhood leukemia and access to water potentially contaminated with chlorinated compounds, including tetrachloroethylene (Cutler et al., 1986; Lagakos et al., 1986); however, when likelihood of exposure to the contaminated wells was considered, no increase in risk was observed (Costas et al., 2002). The aforementioned studies involved co-exposure to various other chemicals, including trichloroethylene; thus, it is

not possible to decipher whether these effects were caused directly by tetrachloroethylene exposure or by exposure to other chemicals.

As individuals working in the dry cleaning industry are primarily exposed to tetrachloroethylene, studies of dry cleaners can provide useful information on the carcinogenicity of tetrachloroethylene. These studies have noted increases in the incidence of or mortality from lung cancer (Brownson et al., 1993; Calvert et al., 2011), bladder cancer (Brown et al., 1987), tongue cancer (Calvert et al., 2011), oesophagus cancer (Calvert et al., 2011) and renal cell carcinoma (McCredie and Stewart, 1993; Mandel et al., 1995) in dry cleaners or in individuals classified as being exposed to dry cleaning solvents. Non-significant effects for laryngeal and oesophageal cancers (Vaughan et al., 1997) have also been reported. Other studies—based primarily on census data, cancer registries and other similar databases—that grouped dry cleaners into broader occupational categories have reported increases in the incidence of lung cancer (Andersen et al., 1999; Pohlabeln et al., 2000; Travier et al., 2002; Ji and Hemminki, 2005; Pukkala et al., 2009; Seldén and Ahlborg, 2011), liver cancer (Lynge and Thygesen, 1990; Pukkala et al., 2009), breast cancer (Band et al., 2000), kidney cancer (Ji et al., 2005), upper aerodigestive and pharynx cancer (Ji and Hemminki, 2005), stomach cancer (Pukkala et al., 2009), cervix uteri cancer (Pukkala et al., 2009), oral cancer (Pukkala et al., 2009), leukaemia (Morton and Marjanovic, 1984; Travier et al., 2002), non-Hodgkin's lymphoma (Seldén and Ahlborg, 2011) and Hodgkin's disease (Andersen et al., 1999). However, similar studies have also reported no excess risk of liver and kidney cancer (Lynge et al., 1995) and non-Hodgkin's lymphoma (Cano and Pollán, 2001).

Although no significant excess risk of bladder cancer was observed in case–control studies including dry cleaning workers (Smith et al., 1985; Lynge et al., 1995; Zheng et al., 2002), an association between tetrachloroethylene exposure and bladder cancer has been considered consistent because of observations from three large cohorts of dry cleaning workers with several follow-up periods (Guha et al., 2012). A significant increase in the incidence of bladder tumours was observed in Nordic dry cleaners (44% increase), with a higher increase (69%) in workers from Denmark and Norway, the countries with better job classification data in the study (Lynge et al., 2006). Interviews with these participants or their family members identified that the greatest excesses were observed in support staff in small dry cleaning shops (120%) and owners of combined laundry and dry cleaning shops (92%). A significant increase (of 159%) in mortality from bladder and other urinary cancer was observed in workers from four U.S. cities (San Francisco/Oakland, California; Chicago, Illinois; Detroit, Michigan; and New York City, New York), but only in subjects who had worked in multiple shops, some of which had predominant use of solvents other than tetrachloroethylene (Calvert et al., 2011). In the third cohort, composed of dry cleaners from St. Louis, Missouri, only slight increases (of 30%) in mortality from bladder tumours were observed over the entire follow-up period, and these increases were not significant (Blair et al., 2003). No cases of bladder cancer were observed in the smaller, predominantly tetrachloroethylene-exposed cohort. Risk of bladder tumours did not increase with longer exposure periods in one of the studies (Lynge et al., 2006) and actually appeared to decrease with duration of exposure in another (Blair et al., 2003), but the majority of cases were observed in workers exposed for longer than 5 years in the third cohort (Calvert et al., 2011). Other occupational studies encompassing exposure to various substances but investigating the specific effects of tetrachloroethylene exposure have reported no effects on renal cell carcinoma (Dosemeci et al., 1999), lymphoma (Mester et al., 2006; Miligi et al., 2006; Seidler et al., 2007) or cancer in general (Anttila et al., 1995), as well as no increase in childhood leukemia from

maternal exposure (Shu et al., 1999; Infante-Rivard et al., 2005). However, effects on multiple myeloma (Spirtas et al., 1991) and renal cell carcinoma (Schlehofer et al., 1995) were noted.

Thus, the current epidemiological data suggest that tetrachloroethylene may be involved in carcinogenic outcomes. However, the number of studies that also demonstrate a lack of association between tetrachloroethylene exposure and cancer, coupled with limitations such as exposure to other potentially carcinogenic solvents and absence of exposure analysis for tetrachloroethylene, make it difficult to draw firm conclusions. As cancers were inconsistently observed at various sites, it is difficult to draw any conclusions on the carcinogenicity of tetrachloroethylene in humans based on these studies. The cancer endpoint that has been considered to be the most consistent across studies is bladder cancer (Guha et al., 2012); however, the lack of thorough exposure assessments in these studies combined with an absence of bladder tumours in experimental animal studies prevents the inclusion of this tumour type in the dose-response assessment.

9.1.3 Reproductive and developmental toxicity

The potential effects of occupational exposure to tetrachloroethylene on reproductive and developmental toxicity have been examined in a number of case–control and cohort studies. Overall, an increased risk of spontaneous abortion was reported for some of the studies (Hemminki et al., 1980; Kyyronen et al., 1989; Olsen et al., 1990; Windham et al., 1991; Doyle et al., 1997), although others have reported negative findings for tetrachloroethylene-induced pregnancy loss (Ahlborg, 1990; Lindbohm et al., 1990; Eskenazi et al., 1991; Aschengrau et al., 2009a), including one study that investigated paternal exposure (Eskenazi et al., 1991). Exposure to tetrachloroethylene via soil vapours was not associated with lower birth weight or fetal growth restrictions, but a non-significant association related to cardiac defects was noted (Forand et al., 2012).

A limited number of community-based studies have evaluated the potential reproductive and developmental toxicity of tetrachloroethylene through exposure from drinking water. In an area of Massachusetts affected by leaching of tetrachloroethylene from vinyl-lined pipes, pregnancy outcomes were evaluated in a cohort of pregnant women exposed to concentrations ranging from 1.5 to 80 µg/L (most highly contaminated areas were flushed until levels were below 40 µg/L) in comparison with an unexposed control group. These investigations revealed non-significant associations between exposure to tetrachloroethylene and congenital anomalies such as neural tube defects and oral clefts (Aschengrau et al., 2009b). Moreover, no associations between tetrachloroethylene exposure and birth weight (Aschengrau et al., 2008), gestational duration (Aschengrau et al., 2008) or pregnancy loss (Aschengrau et al., 2009a) were observed. Several factors limited the findings from these studies, including the fact that tetrachloroethylene concentrations in water were estimated using a leaching transport model and that details related to water consumption and bathing habits could not be included because of poor recall; moreover, there is a possibility of underreporting of the pregnancy losses. One study in a population in northern New Jersey exposed to various chemicals through drinking water noted increases in oral cleft defects when tetrachloroethylene levels were above 10 ppb (10 µg/L) (Bove et al., 1995); however, the relevance of this is unknown, since it is not possible to elucidate which of the chemicals could have resulted in the effect. Many other chemicals were considered in this study, including trichloroethylene, 1,1,1-trichloroethane, *trans*-1,2-dichloroethylene, 1,1-dichloroethylene, carbon tetrachloride, 1,2-dichloroethane, benzene, dichloromethane, vinyl chloride, chlorobenzene, dichlorobenzenes, trichlorobenzenes, chlordane and polychlorinated biphenyls.

Other epidemiological studies related to neurodevelopmental endpoints, including those that investigated the effects of tetrachloroethylene in populations exposed via drinking water *in utero* and until 5 years of age (Janulewicz et al., 2008, 2012; Aschengrau et al., 2011, 2012; Getz et al., 2012) and in children exposed from indoor air in apartment buildings containing a dry cleaning facility (Schreiber et al., 2002; Storm and Mazor, 2004; New York State Department of Health, 2010; Storm et al., 2011), are summarized in Section 9.1.2.1. That section also discusses a study investigating the effects of tetrachloroethylene on prolactin levels in occupationally exposed women (Ferroni et al., 1992), which could have reproductive repercussions.

9.2 Effects on experimental animals

A large number of studies have investigated the effects of tetrachloroethylene on the health of animal models. Only the most relevant information from these studies is discussed in the following sections.

9.2.1 Acute toxicity

Tetrachloroethylene is of low acute oral toxicity. Oral median lethal doses (LD_{50} values) in rats range from 2.4 to 13.0 g/kg bw (Pozzani et al., 1959; Smyth et al., 1969; Withey and Hall, 1975; Hayes et al., 1986), and values for mice range from 6.4 to 9.6 g/kg bw (Dybing and Dybing, 1946; Wenzel and Gibson, 1951; Bandman, 1990). Tetrachloroethylene-related deaths occurred at most exposure levels in rats exposed to 2445–5163 ppm and mice exposed to 2328–3786 ppm for 4 hours via inhalation, with 100% mortality in the 5163 ppm rat group and 2971 and 3786 ppm mouse groups (NTP, 1986). Symptoms preceding death after high exposures included tremors, ataxia and central nervous system depression in rats (Hayes et al., 1986) and hypoactivity and anaesthesia in mice (NTP, 1986).

The nervous system was the most commonly researched organ system in acute toxicity studies with tetrachloroethylene. Neurobehavioural effects were the neurological effects observed at the lowest concentrations in oral and inhalation studies, with the lowest gavage effect (anticonvulsion) occurring at ≥ 50 mg/kg bw (Chen et al., 2002). Changes in motor activity occurred at ≥ 150 mg/kg bw by ingestion and at ≥ 90 ppm by inhalation (Kjellstrand et al., 1985; Moser et al., 1995), with a tendency for increased arousal at lower doses and lower activity at higher doses in one of the studies (Moser et al., 1995). The circadian rhythm of motor activity was also increased in rats intraperitoneally injected with higher doses (Motohashi et al., 1993). Other neurobehavioural effects observed at higher doses included decreased righting ability (Moser et al., 1995); abnormal gait, increased landing foot splay and inability to grasp grip strength devices (Moser et al., 1995); decreased equilibrium and coordination (Umezu et al., 1997); and suppressed learned behaviour (Warren et al., 1996). Of the non-neurobehavioural effects, autonomic effects—including altered pupil response, lacrimation and salivation—were those observed at gavage doses of ≥ 150 mg/kg bw (Moser et al., 1995). At the lowest inhalation exposure level of 200 ppm (6 hours/day for 4 days), neurochemical measures of toxicity, including reduction in brain ribonucleic acid (RNA) and glutathione content and increased cholinesterase activity, were observed (Savolainen et al., 1977). Other neurological effects observed at higher doses included changes to the shape and amplitude of waveforms for visually evoked potentials, cerebellar flash-evoked potentials and somatosensory evoked potentials (Mattsson et al., 1998), electroencephalogram-confirmed anaesthesia (Mattsson et al., 1998) and decreased sensory perception (Chen et al., 2002).

Only a few studies investigated acute effects on other organ systems after tetrachloroethylene exposure. Renal effects observed after intraperitoneal injection included

hydropic degeneration and necrosis in tubules of mice (Klaassen and Plaa, 1966) and calcification in tubules in dogs (Klaassen and Plaa, 1967), with the lowest median effective dose (ED_{50}) of 14 mmol/kg bw, equivalent to 2322 mg/kg bw, as measured by phenolsulphonphthalein retention, in the dogs. The same studies reported hepatic effects of vacuolation of hepatocytes in both mice and dogs and liver and hepatocyte enlargement, cellular infiltration and slight necrosis in mice; again, the dogs were more sensitive, with ED_{50} values of 7.2 mmol/kg bw (1194 mg/kg bw), as measured by serum alanine transaminase (ALT) levels. Immunotoxicity was also observed, which manifested as decreased bactericidal activity and increased mortality from streptococcal pneumonia in mice exposed by inhalation to 50 ppm for 3 hours (Aranyi et al., 1986) and as enhanced allergic reactions (measured by increases in passive cutaneous anaphylaxis after antigen challenge) in mice exposed to ≥ 0.01 mg/kg bw via intraperitoneal injection (Seo et al., 2012). Cardiotoxic effects observed in rabbits, cats and dogs injected with tetrachloroethylene included ventricular arrhythmias, increased myocardial vulnerability to premature ventricular contractions, bigeminy and tachycardia; rabbits had the lowest threshold for effects, which was 10 mg/kg bw (Kobayashi et al., 1982).

9.2.2 Short-term exposure

Many studies investigated the effects of tetrachloroethylene on various organ systems over subacute and subchronic durations. Exposures in these studies were mainly via oral gavage and inhalation, with a few studies of intravenous or intraperitoneal injection. No studies exposed experimental animals to tetrachloroethylene by drinking water.

9.2.2.1 Clinical and serological indicators of health

Adverse clinical outcomes were observed after high subacute and subchronic exposures to tetrachloroethylene. Increased mortality in rats and mice occurred at 1000 mg/kg bw in a gavage study (Philip et al., 2007) and at ≥ 1600 ppm in inhalation studies (NTP, 1986). Decreases in body weight gain were consistently observed in both sexes of various species of mice and rats at doses of ≥ 5 mg/kg bw via gavage (Hayes et al., 1986; Chen et al., 2002) and at inhalation exposures of ≥ 75 ppm (Kjellstrand et al., 1984; NTP, 1986; JISA, 1993; Wang et al., 1993). Hematology and clinical chemistry were not explored in most subacute or subchronic studies, but exposure of mice to 3000 mg/kg bw per day by gavage for 15 days resulted in lower levels of hemoglobin, red blood cells, hematocrit (Ebrahim et al., 2001), blood glucose and gluconeogenic enzymes and increases in hexokinase, aldolase and phosphoglucoisomerase enzymes (Ebrahim et al., 1996); these parameters returned to normal with antioxidant administration. Hematological and clinical chemistry changes were also reported in mice and rats after inhalation of ≥ 609 ppm, but further details on the effects were not provided by the authors (JISA, 1993).

9.2.2.2 Neurological effects

Neurological effects were investigated in several subacute and subchronic studies of exposure to tetrachloroethylene. Animals were exposed via gavage in oil, by inhalation and by intraperitoneal injection.

Whole brain weight (absolute and/or relative) was decreased in female (but not male) rats gavaged with 1400 mg/kg bw per day (Hayes et al., 1986) and in rats and gerbils exposed to 320 ppm via inhalation (Kyrklund et al., 1988), with no effects observed at lower levels (Hayes et al., 1986). At inhalation concentrations of ≥ 320 ppm, the weights of certain brain sections (frontal cerebral cortex and brain stem) were also decreased in gerbils and rats (Rosengren et al., 1986).

Studies also looked at the impact of tetrachloroethylene on brain biochemistry—including protein, amino acid, deoxyribonucleic acid (DNA), phospholipid, cholesterol and fatty acid content, and levels of neurotransmitters and cell marker proteins—in rodents exposed by inhalation only. Of these effects, altered brain amino acid content was observed at the lowest level, with effects on glutamine and taurine levels observed at ≥ 120 ppm in gerbils and rats (Briving et al., 1986). Other effects were observed at higher exposure levels. Decreased DNA and protein concentrations were found in specific brain sections (cerebral cortex, cerebellum and brain stem) of rats and gerbils (Rosengren et al., 1986; Karlsson et al., 1987). Cholesterol and phospholipid levels, as well as a change in their ratio, tended to be decreased in gerbils and male rats (Kyrklund et al., 1987, 1990), but not at tetrachloroethylene levels as low as 120 ppm (Kyrklund et al., 1984). Fatty acid patterns in the cerebral cortex and hippocampus were also changed in gerbils and rats, with a tendency towards elongation and desaturation of fatty acids, resulting in greater levels of very long chain polyunsaturated fatty acids (Kyrklund et al., 1987). Results for cell marker proteins were variable, with increases in S-100 in several brain lobes (hippocampus, anterior and posterior cerebellum, and occipital cerebral cortex) and a decrease in the frontal cerebral cortex in gerbils (Rosengren et al., 1986), but decreases in S-100 and glial fibrillary acid in the cerebral cortex, hippocampus and brain stem of rats (Wang et al., 1993). Finally, a significant decrease in acetylcholine level and a decrease in dopamine level that was dose related but not significant at any individual tetrachloroethylene doses were also observed in male rats exposed by inhalation (Honma et al., 1980).

The only subacute or subchronic study to investigate neurophysiological effects noted changes to midlatency components of visual cortex flash-evoked potentials in rats exposed by inhalation to 800 ppm (Mattsson et al., 1998).

The neurobehavioural effects that were observed at the lowest level in gavage studies were antinociception and anticonvulsive effects (for myoclonic twitch and forearm clonus) in male rats exposed to ≥ 5 mg/kg bw per day by gavage for 8 weeks (Chen et al., 2002). Although the adversity of these effects is unclear, the high dose in this study (50 mg/kg bw per day) demonstrated more clearly undesirable outcomes, with a lower level of motor activity and rearing. The most sensitive effect in inhalation studies was also related to motor activity, but with an increase in motor activity over controls in mice exposed to 225 ppm for 16 hours/day (and other higher exposure levels, but for shorter time periods, resulting in the same 24-hour time-weighted average concentration[2]) for 30 days (Kjellstrand et al., 1984). Because lower activity was observed at lower doses and higher activity was observed at higher doses,[3] the effect on activity was opposite to that observed in acute studies. The circadian rhythm of motor activity was also increased at higher doses in the Kjellstrand et al. (1984) study. Some evidence of weak neuromuscular effects was demonstrated in rats, as significant increases were observed only in an overall neuromuscular domain score and not in the results of individual tests (for gait score, righting reflex, forelimb and hindlimb grip strength, and landing foot splay) (Moser et al., 1995), and grip strength was unchanged in another study (Mattsson et al., 1998).

Neurological effects also occurred in rodents that were exposed for short durations as developing fetuses or pups. Mice exposed to tetrachloroethylene at oral gavage doses as low as 5 mg/kg bw per day for 7 days, as of postnatal day 10, exhibited hyperactive behaviour later in

[2] 450 ppm for 8 hours/day, 900 ppm for 4 hours/day, 1800 ppm for 2 hours/day and 3600 ppm for 1 hour/day.

[3] The exposures in the Kjellstrand et al. (1984) study linearly adjust to a 24-hour time-weighted average concentration of 150 ppm. Given that 1 ppm of tetrachloroethylene in air is equivalent to 6.78 mg/m^3, and using the default assumption that 1 mg/m^3 in air provides a dose of 1.33 mg/kg bw per day to mice (Health Canada, 1994), the daily dose is estimated at 1353 mg/kg bw per day.

development (i.e., at 60 days of age, but not 17 days) (Fredriksson et al., 1993). Altered behaviour was also reported in rats exposed *in utero* (Nelson et al., 1980; Szakmáry et al., 1997). Moreover, a study with mice exposed to tetrachloroethylene, chloroform and bromoform via drinking water throughout pregnancy, weaning and development noted behavioural changes that are relevant to autism in male (but not female) offspring (Guariglia et al., 2011). As a result of *in utero* exposure, no changes in brain fatty acids were observed (Kyrklund and Haglid, 1991); however, decreases in acetylcholine and dopamine levels have been reported (Nelson et al., 1980). These studies suggest that tetrachloroethylene may target the nervous system, leading to altered behaviour later in development.

9.2.2.3 Hepatic effects

Increases in absolute and relative liver weights were observed in many studies, with more consistent effects in mice, particularly at lower doses. Exposures of mice resulted in consistent increases at doses as low as 100 mg/kg bw per day in oral gavage studies (Schumann et al., 1980; Ebrahim et al., 1996) and 9 ppm by inhalation (Kjellstrand et al., 1985; Odum et al., 1988; Kyrklund et al., 1990). In rats, liver weight increases were observed at ≥ 1000 mg/kg bw per day by gavage in two studies (Hayes et al., 1986; Goldsworthy and Popp, 1987), but another study did not demonstrate effects at 1000 mg/kg bw per day (Schumann et al., 1980); similarly, inhalation studies demonstrated effects at 320 ppm (Kyrklund et al., 1988), but not at 200 or 400 ppm (Odum et al., 1988). Liver weight effects were somewhat, but not completely, reversible after cessation of exposure (Kjellstrand et al., 1984; Kyrklund et al., 1990).

Biochemical indicators of hepatic effects were also observed in several studies. The most sensitive effects were increases in liver triglycerides at ≥ 100 mg/kg bw per day by gavage (Buben and O'Flaherty, 1985) and a reversible increase in plasma butyrylcholinesterase activity in mice exposed to ≥ 37 ppm by inhalation (Kjellstrand et al., 1984). Other effects at higher levels included an increase in enzymes associated with glycolysis and a decrease in those associated with gluconeogenesis (Ebrahim et al., 1996) and increases in ALT (referred to in older studies as serum glutamate–pyruvate transaminase) (Philip et al., 2007) and glucose-6-phosphatase activity (Buben and O'Flaherty, 1985).

Various morphological and histological changes were observed in animals exposed to tetrachloroethylene via gavage or inhalation for up to 90 days. The lowest effect in animals exposed via gavage was hepatocyte hypertrophy at ≥ 100 mg/kg bw per day (Buben and O'Flaherty, 1985), which was also observed in an inhalation study (Odum et al., 1988). In one inhalation study with the lowest exposure levels (≥ 9 ppm continuous exposure), liver discolouration, hepatocyte hypertrophy, vacuolization and accumulation of inflammatory cells were observed[4] (Kjellstrand et al., 1984). These effects were also observed in other studies, albeit at higher exposure levels (liver discoloration: Buben and O'Flaherty, 1985; JISA, 1993; Philip et al., 2007; vacuolization and infiltration of inflammatory and immune cells: NTP, 1986; Odum et al., 1988). Effects observed at higher levels included hepatocyte degeneration (Buben and O'Flaherty, 1985; Ebrahim et al., 1996; Philip et al., 2007) and necrosis (Ebrahim et al., 1996); central enlargement (JISA, 1993); peroxisome proliferation, lipid accumulation and changes in mitochondria levels (Odum et al., 1988); clumped cytoplasm and karyorrhexis (disintegrating nucleus) (Buben and O'Flaherty, 1985); and bile stasis (NTP, 1986). Of the aforementioned effects, only hepatocyte hypertrophy was observed in rats, and it occurred at higher doses than in

[4] The study mentioned that these effects occurred in exposed mice, but because the actual data for these effects were not presented in the study, it is difficult to identify whether the incidence and severity were actually significantly greater than in controls at exposures as low as 9 ppm.

mice. Additional effects that occurred in rats included hepatic congestion (NTP, 1986), hepatic foci (Story et al., 1986) and altered staining affinity of hepatocytes (Schumann et al., 1980).

9.2.2.4 Renal effects

Tetrachloroethylene increased absolute and relative kidney weights in some gavage studies at ≥ 400 mg/kg bw per day, with male rats appearing more sensitive than female rats and with effects occurring at lower doses in rats than in mice (Hayes et al., 1986; Green et al., 1990; Ebrahim et al., 1996; Jonker et al., 1996). Conversely, no increase in relative or absolute kidney weight was observed in another gavage study (Goldsworthy and Popp, 1987) or in any inhalation studies (Odum et al., 1988; Green et al., 1990).

Biochemical changes related to kidney effects have been investigated in gavage studies only, and primarily in rats, with the most sensitive effect of proteinuria (increases in urinary excretion of albumin, RBP and α2-microglobulin and transient increase in *N*-acetylglutamate [NAG]) at ≥ 500 mg/kg bw per day (Bergamaschi et al., 1992; Jonker et al., 1996). At higher doses, increased urinary volume and alterations in levels of urinary ALP, NAG, glucose, gamma-glutamyl transpeptidase, lactate dehydrogenase (LDH), aspartate transaminase (AST) and ALT (Green et al., 1990; Jonker et al., 1996) were observed. In mice, an increase in renal glycolytic enzymes and decrease in renal gluconeogenic enzymes were observed (Ebrahim et al., 1996), but tetrachloroethylene did not appear to have any effect on levels of blood urea nitrogen (BUN) (Philip et al., 2007) or renal catalase (Odum et al., 1988).

Renal morphological and histological changes occurring after subacute and subchronic exposure to tetrachloroethylene primarily affected the proximal tubule, with the majority of effects noted in rats. Protein (hyaline) droplet accumulation was the effect observed at gavage doses of ≥ 500 mg/kg bw per day (Green et al., 1990; Bergamaschi et al., 1992), but not in an inhalation study (Green et al., 1990); the effects were sometimes observed in females, but they occurred earlier and more severely in males (Bergamaschi et al., 1992). Renal peroxisome proliferation was observed in rats and male mice at ≥ 200 ppm (Odum et al., 1988) and in mice exposed to 1000 mg/kg bw per day by gavage (Goldsworthy and Popp, 1987). Other renal tubular effects observed at higher exposure levels, and predominantly in male rats, included necrosis (Goldsworthy et al., 1988), regeneration (Goldsworthy et al., 1988), cellular proliferation (Goldsworthy et al., 1988), tubular casts (Green et al., 1990) and vacuolation and karyomegaly (enlarged nuclei) in female rats (Jonker et al., 1996). In mice, reported changes included karyomegaly in the renal tubule epithelium (NTP, 1986), unspecified changes to proximal tubules (JISA, 1993) and hypercellular effects in the glomerulus (Ebrahim et al., 1996).

9.2.2.5 Effects on other organs and systems

Two subacute studies investigated the immunotoxicity of tetrachloroethylene. Tetrachloroethylene was considered to enhance allergic reactions due to dose-dependent increases in passive cutaneous anaphylaxis in mice with mean intakes of 0.07 µg/day and 7.2 µg/day[5], via drinking water prior to an antigen challenge (Seo et al., 2012). No increase in susceptibility to respiratory infection was observed in mice exposed to 25 ppm via inhalation (Aranyi et al., 1986).

Lung congestion was observed in male and female rats exposed to 1600 ppm, but not lower levels, via inhalation for 13 weeks (NTP, 1986).

[5] Body weights for mice in this study were not stated; however, assuming a body weight of 0.03 kg (from Health Canada, 1994), the doses are 2.3 and 240 µg/kg bw per day.

9.2.3 Long-term exposure and carcinogenicity

No long-term studies have investigated the adverse effects of tetrachloroethylene from exposure in drinking water. Although a few experiments have exposed animals via gavage, the vast majority of studies of tetrachloroethylene in animals have relied on inhalation exposure.

The three major lifetime studies in rodents exposed rats and mice (50 of each sex per group) to tetrachloroethylene at various concentrations. The first inhalation study exposed F344 rats to 0, 200 or 400 ppm and B6C3F1 mice to 0, 100 or 200 ppm, both for 6 hours/day, 5 days/week, for 103 weeks (NTP, 1986), and the other exposed F344 rats to 0, 50, 200 or 600 ppm and Crj:BDF1 mice to 0, 10, 50 or 250 ppm for 6 hours/day, 5 days/week, for 104 weeks (JISA, 1993). The ingestion study exposed animals by gavage in corn oil, for 71 weeks (with observation until 110 weeks) for Osborne-Mendel rats and for 78 weeks (with observation until 90 weeks) for B6C3F1 mice (NCI, 1977). Dose levels in all groups were changed throughout the study, leading to respective time-weighted average doses of 471 and 474 mg/kg bw per day in low-dose male and female rats, 941 and 949 mg/kg bw per day in high-dose male and female rats, 536 and 386 mg/kg bw per day in low-dose male and female mice and 1072 and 772 mg/kg bw per day in high-dose male and female mice, respectively. This ingestion study is considered inconclusive, because high incidences of respiratory disease and mortality were observed in exposed groups, leading to the early termination of the study; therefore, the NTP (1986) and JISA (1993) studies hold more weight in the dose-response assessment.

9.2.3.1 Clinical and serological indicators of health

General health effects were observed after lifetime tetrachloroethylene exposure in all three studies. Body weight gains were inhibited in both rats and mice in two of the lifetime studies (NCI, 1977; JISA, 1993), but not in the NTP (1986) study; furthermore, feed consumption was decreased in both rats and mice in the JISA (1993) study. Animals exposed to tetrachloroethylene tended to have decreased survival when compared with controls in all three studies. The effects appeared to be dose related, with more highly dosed animals having higher mortality levels and earlier deaths (NCI, 1977; NTP, 1986; JISA, 1993). Clinical signs in animals exposed via gavage included hunched appearance and stained fur in both rats and mice, body sores and irritation, alopecia and hunched appearance in mice, and salivation in rats (NCI, 1977).

Haematological and biochemical effects were also measured in the JISA (1993) study. Mean corpuscular haemoglobin levels were increased in high-dose female rats and mice, but decreased in high-dose male mice. Mean cell volume and platelet counts were also decreased in male mice exposed to 250 ppm. Red blood cell count and hematocrit levels were increased in the high-dose group in both male and female mice. In low-dose female mice, the segmented neutrophil ratio was increased and lymphocyte ratio was decreased. Triglyceride levels were decreased in high-dose female rats and high-dose male mice, and glucose level reduction was observed in high-dose male mice; however, total protein and total cholesterol levels were increased in the high-dose male mice. LDH activity was increased in male and female mice. Although potassium concentrations were increased in high-dose female rats, they were decreased in high-dose female mice; calcium concentrations were increased in high-dose female mice, and chloride concentrations were decreased in high-dose male and female mice (JISA, 1993). Additional biochemical effects that were measured were indicators of hepatic and renal effects; therefore, these results will be described in the sections related to those organ systems.

9.2.3.2 Neurological effects

Although the three lifetime studies did not investigate more subtle neurological effects in study animals, they did examine brain tissues for gross and histological abnormalities. No adverse effects were noted in the NCI (1977) study. Relative brain weights were increased in high-dose male and female mice in the JISA (1993) study. Furthermore, vitreous deposits in the brain were significantly increased in 50 ppm male mice, but not in the high dose males (JISA, 1993). The NTP (1986) study identified a significantly positive dose-related trend in the increase in gliomas in male rats exposed to 200 and 400 ppm; however, the incidence of gliomas in each dose group was not elevated over control (NTP, 1986).

9.2.3.3 Hepatic effects

The only study to report changes in liver weight was the JISA (1993) study. Both absolute and relative liver weights were increased in female rats exposed to 50 and 600 ppm (but not 200 ppm, and no effects were observed in male rats). Increases in both absolute and relative liver weights were observed in male mice exposed to 250 ppm, but only relative liver weight was increased in female mice exposed to 250 ppm (JISA, 1993).

Among the lifetime studies, only JISA (1993) considered biochemical effects. Effects on blood levels of hepatic indicators were observed, with an increase in ALT and levels in high-dose male rats and female mice and mid- and high-dose female rats and male mice; increases in AST in mid-dose males and high-dose females, and total bilirubin and ALP in high-dose males and females were also observed in mice (JISA, 1993).

Hepatic effects were more prevalent in mice than in rats. No adverse effects were observed in rats in two of the studies (NCI, 1977; NTP, 1986). In the third study, the NOAEL for hepatic effects was 50 ppm, with increases in spongiosis hepatitis in males at ≥ 200 ppm and decreases in granulation in females at ≥ 200 ppm that were dead or dying (JISA, 1993). In 600 ppm male rats, hyperplasia was also increased, but not significantly. Although there were no significant increases in tumours, two cases of hepatocellular adenoma were observed (compared with zero in all other groups).

Non-neoplastic histological observations in the livers of mice were made in all three of the lifetime studies. Angiectasis and central degeneration were observed in males and females exposed to 250 ppm (as well as males scheduled for dissection only) (JISA, 1993). Central degeneration was also significantly increased in males and females exposed to 250 ppm. Necrosis occurred in males exposed to 250 ppm (JISA, 1993), males exposed to ≥ 100 ppm and females exposed to 200 ppm (NTP, 1986). Cell proliferation, in the form of foci of altered cells, was observed only in three males in the high-dose gavage group (NCI, 1977), and not in the other studies. The lowest-observed-adverse-effect level (LOAEL) for non-neoplastic effects, based on necrosis in male mice in the NTP (1986) study, was 100 ppm.

Tumours were also observed in mice in the three lifetime studies. Hepatocellular adenomas and carcinomas were increased in mice in all of the studies, with a significantly positive trend. Hepatocellular carcinomas had also metastasized to other organs in one study (NTP, 1986). A positive trend in haemangioendothelioma was also observed in male mice in one study (JISA, 1993).

9.2.3.4 Renal effects

The effect of tetrachloroethylene on kidney weights was inconsistent. Both absolute and relative kidney weights were increased in male rats exposed to ≥ 200 ppm, and relative kidney weight was increased in female rats exposed to ≥ 200 ppm and in male and female mice exposed

to 250 ppm, but a decrease in absolute kidney weight was observed in male mice exposed to 250 ppm (JISA, 1993).

Biochemical effects were measured only in the JISA (1993) study. In this study, inconsistent kidney-relevant effects were observed in the blood, with BUN level increases in mid-dose female mice and decreases in high-dose male rats (JISA, 1993).

Non-neoplastic effects were observed in the kidneys of rats and mice, with the majority of effects observed in the proximal tubule. Nuclear enlargement was observed primarily in the proximal tubule in all rat and mouse exposure groups in the NTP (1986) study and in male rats exposed to ≥ 200 ppm, female rats exposed to 600 ppm and male and female mice exposed to 250 ppm (as well as low-dose males scheduled for dissection) in the JISA (1993) study. Other proximal tubule effects included atypical dilation in all high-dose groups (JISA, 1993); degeneration, necrosis and regeneration in epithelium, inflammatory cell infiltration, fibrosis and focal mineralization in male and female rats (NCI, 1977); and hyperplasia in a small number of rats (NTP, 1986). Nephropathy was observed in the majority of male and female rats and mice exposed by gavage (NCI, 1977), and nephrosis occurred in female mice exposed by inhalation in the NTP (1986) study. Casts were also observed in the kidneys of dosed male mice and high-dose female mice in the NTP (1986) study. The NOAEL for renal effects in the JISA (1993) study was 50 ppm, with nuclear enlargement occurring at 250 ppm; the LOAEL in the NTP (1986) study was 100 ppm for the same effect.

A slight increase in renal neoplasms (no statistical significance reported) was observed in male rats in one of the studies. In the NTP (1986) study, tubular cell adenomas and adenocarcinomas (combined) were observed in 2% of controls, 6% of low-dose rats and 8% of high-dose rats.

9.2.3.5 Effects on other organs and systems

Evidence of immunotoxicity was observed in the JISA (1993) study. Splenic enlargement occurred in male and female rats of all exposure groups, and absolute and relative spleen weights were increased in 250 ppm male mice. Extramedullary hematopoiesis was decreased in male rats exposed to 200 ppm (but not higher) that were scheduled for dissection; conversely, it was increased in male and female mice exposed to the highest dose, as well as in low-dose female mice.

The relative weight of adrenal glands was increased in high-dose male mice in the JISA (1993) study. Moreover, hyperplasia was increased in the adrenal medulla in dosed male rats and in the adrenal cortex of high-dose female rats in the NTP (1986) study.

Effects on the gastrointestinal tract were observed in animals exposed via inhalation. These effects included forestomach ulcers in male rats exposed to 400 ppm (NTP, 1986) and decreased stomach ventriculus hyperplasia in male and female mice exposed to 250 ppm that were scheduled for dissection, as well as the 10 ppm male mice scheduled for dissection (JISA, 1993).

Tetrachloroethylene adversely affected teeth and the skeletal system in mice in the JISA (1993) study. Effects observed were dysplasia of teeth in ≥ 50 ppm male mice and increased osteosclerosis in 250 ppm female mice.

Non-neoplastic respiratory tract effects were observed, but only in the inhalation studies. Some of these effects included increased lung weight in female rats and male and female mice (JISA, 1993); reduction in cellular changes in respiratory epithelium in female rats and male and female mice and in olfactory epithelium in male and female mice (JISA, 1993); nasal cavity thrombosis in rats (NTP, 1986) and unspecified blood clots in male rats (JISA, 1993); and lung

congestion in male mice (NTP, 1986). Cardiovascular effects were also observed, but were limited to an increase in relative heart weight in female mice exposed to 200 ppm (JISA, 1993).

Tetrachloroethylene exposure was also associated with neoplastic effects in various organ systems that have not been described in the previous sections. An increase in the incidence of mononuclear cell leukaemia (*MCL*) was observed in male and female rats in the NTP (1986) study, with significance measured both in increases over control in all exposed groups and in a positive trend. In earlier stages of the disease, infiltration was primarily limited to the liver sinusoids and interfollicular pulp of the spleen, but as the disease advanced, infiltration affected most organs and tissues (NTP, 1986). *MCL* also showed a significant trend in male and female mice and a significant increase in high-dose male mice in the JISA (1993) study. Increases in mammary fibroadenomas were observed in one study in female rats in the lowest exposure group (50 ppm), but not in higher dose groups (JISA, 1993). A significant positive trend was observed in pheochromocytomas of the adrenal gland in male rats (NTP, 1986), Harderian (lacrimal) gland adenomas in male mice and hemangioendothelioma in all organs—including the spleen—in male and female mice (JISA, 1993). Nasal squamous cell metaplasia was also observed in dosed male rats in one study (NTP, 1986).

9.2.4 Reproductive and developmental toxicity

Animal studies of reproductive and developmental effects have focused primarily on the inhalation route of exposure, with limited evidence of effects via oral exposure. Three studies have addressed reproductive and/or developmental effects of tetrachloroethylene exposure via the oral route. These studies had few doses and endpoints; thus, only limited conclusions can be drawn. Exposure of pregnant rats to ≥ 900 mg/kg bw per day by oral gavage on gestation days 6–19 resulted in increased resorption and postnatal death, as well as increased cases of microphthalmia/anophthalmia in offspring (Narotsky and Kavlock, 1995). The two other ingestion studies (Fredriksson et al., 1993; Guariglia et al., 2011) identified neurobehavioural effects in mice that were exposed prenatally to ≥ 5 mg/kg bw per day; these studies were discussed in Section 9.2.2.2.

Studies of exposure to tetrachloroethylene by inhalation throughout gestation do not suggest teratogenicity at doses as high as 500 ppm in rabbits and 900 ppm in rats (Nelson et al., 1980; Hardin et al., 1981; Carney et al., 2006). However, several studies have reported incomplete or delayed ossification of rats and mice exposed *in utero* (Schwetz et al., 1975; Szakmáry et al., 1997; Carney et al., 2006). Adverse neurological effects have been observed after intrauterine exposure, with dams exposed by inhalation (Nelson et al., 1980; Kyrklund and Haglid, 1991; Szakmáry et al., 1997), as discussed in Section 9.2.2.2. Inhalation studies suggest that tetrachloroethylene exposure during gestation may increase cases of resorption as well as decrease fetal weight (Schwetz et al., 1975; Szakmáry et al., 1997). A multigenerational study in rats exposed to 1000 ppm resulted in reduced live births, increased pup mortality during lactation, as well as reduced growth with and without pup exposure, thus confirming *in utero* effects (Tinston, 1995). When unexposed females were mated with exposed males, no effects were observed, thus suggesting no paternal effects of exposure in offspring (Tinston, 1995). However, one study noted increased sperm abnormalities in mice following exposure to 500 ppm tetrachloroethylene for 7 hours/day over 5 consecutive days, although this effect was not observed in rats (Beliles, 2002).

Overall, studies suggest that exposure to tetrachloroethylene during gestation can affect survival of offspring and may be involved in alterations in ossification. Inhalation exposure through gestation or early in development may also be linked to neurological effects in adulthood.

9.3 Genotoxicity

9.3.1 In vitro findings

The genotoxicity of tetrachloroethylene and most of its metabolites has been investigated *in vitro*. Overall, studies do not suggest that tetrachloroethylene is genotoxic. However, metabolites of tetrachloroethylene may be involved in genotoxic outcomes.

Tetrachloroethylene did not increase mutation rates in the thymidine kinase locus of L5178Y/TK$^{+/-}$ mouse lymphoma cells at any dose tested (6.25, 12.50, 25, 50 and 100 nL/mL) with and without metabolic activation with S9, despite increased mutations observed in positive controls (NTP, 1986). Gene mutations were also not observed in bacterial systems, including *Escherichia coli* and *Salmonella typhimurium*, in the absence of metabolic activation or in the presence of standard S9 (Greim et al., 1975; Bartsch et al., 1979; Hardin et al., 1981; Kringstad et al., 1981; Haworth et al., 1983; Connor et al., 1985; Shimada et al., 1985; NTP, 1986; Milman et al., 1988; Warner et al., 1988; Roldan-Arjona et al., 1991; DeMarini et al., 1994; Watanabe et al., 1998; Emmert et al., 2006). However, exposure of bacterial cells with enhanced metabolic activity resulted in a clear dose-response relationship, suggesting the role of metabolic activation in tetrachloroethylene genotoxicity (Vamvakas et al., 1989a).

Studies of additional genotoxic endpoints also do not suggest tetrachloroethylene genotoxicity. Chromosomal aberrations were not observed in Chinese hamster ovary cells exposed to tetrachloroethylene at concentrations of 17, 34.1, 68.1 and 136.3 µg/mL with and without S9 metabolic activation (the highest concentration was not tested in the presence of standard S9) (NTP, 1986). Micronuclei induction was not affected by tetrachloroethylene exposure (125–250 µg/mL) in a Chinese hamster lung cell line in the absence of metabolic activation. However, a marginal increase (non-statistically significant) in micronuclei was observed at a lower dose of 75 µg/mL in the presence of S9 (Matsushima et al., 1999). Experiments in various metabolically competent human lymphoblastoid cell lines resulted in increased micronuclei induction at concentrations as low as 5, 1 and 1 mM for the AHH-1, H2E1 and *MCL*-5 cell lines, respectively (Doherty et al., 1996). Exposure of the *MCL*-5 cell line at tetrachloroethylene concentrations of 0, 0.01, 0.05, 0.1, 0.25, 0.5, 1.0 and 2.0 mM over 24 hours resulted in a dose-dependent induction of micronuclei (White et al., 2001). Exposure to tetrachloroethylene via vapours dissolved in culture medium (with a peak concentration in the culture medium of approximately 63 ppm) resulted in dose-dependent increases in micronuclei induction in Chinese hamster ovary cells (Wang et al., 2001). Tetrachloroethylene did not induce sister chromatid exchanges or DNA strand breaks in cultured human blood cells exposed to up to 5 mM (approximately 830 mg/L) tetrachloroethylene, a concentration that induced 40% cell death (Hartmann and Speit, 1995). Analysis of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells gave negative results for both assays (Sofuni et al., 1985; Galloway et al., 1987). An additional study in Chinese hamster ovary cells using concentrations of up to 164 µg/mL showed no increase in sister chromatid exchanges in the presence and absence of standard S9 (NTP, 1986). Tetrachloroethylene exposure was not associated with unscheduled DNA synthesis, as measured in cultured human lymphocytes, human fibroblasts and rat/mouse hepatocytes. One study that examined unscheduled DNA synthesis in human fibroblasts exposed to concentrations ranging from 0.1 to 5.0 µL/mL reported increased DNA synthesis at low doses that was similar to that observed in positive controls, whereas highly exposed cells were not affected (although cytotoxicity was high) (Beliles et al., 1980).

Studies have investigated the genotoxicity of tetrachloroethylene metabolites, including TCA, DCA and chloral hydrate; limited information is available on other metabolites. Some of

these metabolites were shown to exhibit genotoxic activity. Overall, TCA did not induce mutation in *S. typhimurium* with and without metabolic activation (Shirasu et al., 1976; Waskell, 1978; Nestmann et al., 1980; Rapson et al., 1980; Moriya et al., 1983; DeMarini et al., 1994; Nelson et al., 2001; Kargalioglu et al., 2002). Studies in cultured mammalian cells revealed no induction of DNA strand breaks in mouse and rat hepatocytes, Chinese hamster ovary cells or human lymphoblastic cell lines (Chang et al., 1992; Plewa et al., 2002). Weak mutagenic effects of TCA were observed at a cytotoxic concentration of 3000 µg/mL in mouse lymphoma cells (Harrington-Brock et al., 1998). The genotoxicity of DCA varied across studies. Studies in mammalian systems have revealed increased mutation rates and chromosomal aberrations in a mouse lymphoma cell line, whereas studies in bacterial systems have shown increased mutation frequency in *S. typhimurium* (DeMarini et al., 1994; Giller et al., 1997; NTP, 2007). Overall, chloral hydrate tested positive in bacterial mutation tests (Haworth et al., 1983; Ni et al., 1994; Beland, 1999) with and without metabolic activation, as well as in the mouse lymphoma assay for mutagenicity at the *Tk* locus (Harrington-Brock et al., 1998). Clastogenic effects, including induction of micronuclei in Chinese hamster cells (Degrassi and Tanzarella, 1988; Parry et al., 1990; Lynch and Parry, 1993; Seelbach et al., 1993) and mouse lymphoma cells (Nesslany and Marzin, 1999) and aneuploidy in human lymphocytes (Vagnarelli et al., 1990; Sbrana et al., 1993) and various other mammalian cell systems (Furnus et al., 1990; Natarajan et al., 1993; Warr et al., 1993; Harrington-Brock et al., 1998) were observed. Few studies examined additional metabolites, including trichloroacetyl chloride, tetrachloroethylene epoxide and trichloroethanol. Trichloroacetyl chloride was mutagenic in *S. typhimurium* when exposed in the vapour phase (DeMarini et al., 1994), but not in the liquid phase (Reichert et al., 1983). Tetrachloroethylene epoxide was mutagenic in *S. typhimurium*, but not in *E. coli*. Finally, no evidence of mutagenicity was found for trichloroethanol (Waskell, 1978; Bignami et al., 1980; DeMarini et al., 1994). Additional metabolites, including TCVC, TCVG and NAcTCVC, observed upon glutathione conjugation were positive in bacterial screening assays with *S. typhimurium* (Vamvakas et al., 1987, 1989a; Dreessen et al., 2003).

9.3.2 In vivo findings

In vivo investigations of tetrachloroethylene provide some support for genotoxicity, although the majority of studies reported negative findings. Positive results for frameshift mutagenicity were observed using the *S. typhimurium* strain TA98 implanted into the peritoneal cavity of male and female CD-1 mice exposed to tetrachloroethylene by inhalation at 100 and 500 ppm (7 hours/day for 5 days) (Beliles et al., 1980). However, positive results were found at the low dose only in males and high dose only in females. No significant effects on chromosomal aberrations were observed in rats exposed to 100 or 500 ppm (7 hours/day for 5 days) (Beliles et al., 1980). Oral and inhalation exposures to radiolabelled tetrachloroethylene in mice (10 or 600 ppm by inhalation for 6 hours measured at 6, 24, 48 and 72 hours post-exposure and 500 mg/kg bw by oral gavage measured at 1, 6, 12, 24 and 48 hours post-exposure) did not induce DNA binding, whereas binding to protein and RNA increased (Schumann et al., 1980). Low levels of tetrachloroethylene binding to DNA were detected in mouse liver 22 hours after intraperitoneal injection of 1.4 mg/kg bw (Mazzullo et al., 1987). Exposure of ddY mice to a single intraperitoneal injection of tetrachloroethylene at 1000 or 2000 mg/kg bw resulted in increased micronucleus induction in hepatocytes that was exclusively observed after partial hepatectomy (Murakami and Horikawa, 1995). Micronucleus induction was not observed in peripheral blood reticulocytes in this study. Tetrachloroethylene did not induce DNA strand breaks in kidney of male F344 rats following a 7-day oral gavage exposure to tetrachloroethylene at 1000 mg/kg bw

(Potter et al., 1996). One study reported marginal increases in DNA strand breaks in liver, but not in kidney, of CD-1 mice exposed to two doses (24 hours apart) of 1000 or 2000 mg/kg bw by gavage, 3 hours after the second dose (Cederberg et al., 2010). However, the significance of these results has been disputed after reanalyses of the data using more conservative statistical approaches, which indicated that these results may not represent significant increases (Lillford et al., 2010; Lovell, 2010). Exposure of NMRI mice to tetrachloroethylene at 4–8 mmol/kg bw by intraperitoneal injection increased DNA single strand breaks in liver and kidney that were reversible within 24 hours post-exposure, but no effects were observed in lung (Walles, 1986). Single intraperitoneal injections of up to 1000 mg/kg bw in male Fischer rats caused no increase in 8-hydroxydeoxyguanosine (8-OH-dG) levels within liver, lymphocytes or urine; however, this exposure level caused high toxicity (Toraason et al., 1999). Only negative findings for induction of sex-linked recessive lethal mutations and chromosomal aberrations through exposure by feeding, inhalation and injection have been reported in *Drosophila melanogaster* (Beliles et al., 1980; Valencia et al., 1985; NTP, 1986).

A limited number of studies have evaluated the genotoxicity of tetrachloroethylene metabolites *in vivo*. Genotoxic outcomes of TCA exposure varied across studies. Some studies of oral exposure demonstrated genotoxicity in mouse liver (Nelson and Bull, 1988; Nelson et al., 1989; Hassoun and Dey, 2008) and induction of micronuclei and chromosomal aberrations in bone marrow of mice (Bhunya and Behera, 1987) at doses as low as 22 mmol/kg bw. However, negative findings for liver, stomach and duodenum epithelial DNA strand breaks (Nelson et al., 1989; Chang et al., 1992) in mice upon oral exposure at a dose as high as 1630 mg/kg bw have also been reported. Oral exposure of mice to DCA has been shown to result in liver DNA strand breaks (Nelson and Bull, 1988; Nelson et al., 1989; Hassoun and Dey, 2008) in most of the studies that have investigated these endpoints and micronuclei in erythrocytes (Fuscoe et al., 1996). Experiments with chloral hydrate suggest that it may be involved in aneuploidy through spindle poisoning. Several studies indicate that chloral hydrate can induce DNA strand breaks in liver of mice and rats upon oral exposure (Nelson and Bull, 1988), micronuclei in mouse bone marrow and spermatids upon intraperitoneal injection (Russo and Levis, 1992; Russo et al., 1992; Allen et al., 1994; Marrazzini et al., 1994; Nutley et al., 1996; Beland, 1999) and aneuploidy in mouse secondary spermatocytes and bone marrow erythrocytes upon intraperitoneal injection (Miller and Adler, 1992; Marrazzini et al., 1994). Increased frequency of micronucleus formation and sister chromatid exchange in lymphocytes was observed in infants after a single exposure to chloral hydrate as a sedative at 50 mg/kg bw (Ikbal et al., 2004). *In vivo* experiments on additional metabolites were not available.

Tetrachloroethylene exposure was not clastogenic in human lymphocytes of exposed factory workers according to sister chromatid exchange tests and examination for chromosomal aberrations at concentrations ranging from 70 to 1500 mg/m^3 (Ikeda et al., 1980). This finding is further supported by an additional study that reported negative results for sister chromatid exchanges in peripheral lymphocytes of occupationally exposed individuals (Seiji et al., 1990). No evidence of oxidative DNA damage, as measured by 8-OH-dG in leukocytes and urinary 8-OH-dG was found in female dry cleaners relative to unexposed launderers (Toraason et al., 2003).

9.4 Mode of action

An in-depth mode of action (MOA) analysis was performed (Health Canada, 2013) according to guidelines set out in the International Life Sciences Institute/International Programme on Chemical Safety conceptual frameworks for the evaluation of cancer and non-

cancer endpoints (IPCS, 2007). Results of the assessment for MOAs potentially relevant to the major endpoints considered in Section 10 are summarized here.

9.4.1 Hepatocellular adenomas and carcinomas

Mutagenicity and other genotoxicity MOAs were considered for tetrachloroethylene. As described in Section 9.3, the weight of evidence from *in vivo* and *in vitro* studies demonstrates that tetrachloroethylene and its major metabolite, TCA, are not genotoxic. The genotoxicity of other metabolites of tetrachloroethylene was considered in the assessment. Data were limited for other metabolites acting via oxidative metabolism. Increased DNA strand breaks were observed in a dose-related manner in a single *in vivo* study of chloral hydrate (Nelson and Bull, 1988); however, the increase was significant only in the highest dose group, and not at lower doses, at which hepatocellular adenomas and carcinomas from chloral hydrate exposure were observed. Hepatocellular tumours from chloral hydrate exposure are therefore not considered to be due to mutagenicity. Oxidative metabolism of tetrachloroethylene is expected to produce a small amount of an epoxide (tetrachloroethylene oxide), which would be suspected to be reactive due to the electrophilicity of chloroalkene epoxides. Studies of this epoxide are limited to *in vitro* exposure; although the metabolite is genotoxic in bacterial systems (Kline et al., 1982), it is difficult to identify the relevance of this effect at the low levels that would be produced by metabolism of tetrachloroethylene. Metabolites via the GST pathway were also considered for their genotoxicity. Studies of DCA identified DNA strand breaks (Nelson et al., 1989; Hassoun and Dey, 2008) and positive gene mutation (Leavitt et al., 1997) observed at doses lower than those causing hepatocellular tumours. For other GST metabolites, only *in vitro* studies were performed, and these identified the mutagenicity of TCVG (Vamvakas et al., 1989a; Dreessen et al., 2003), TCVC (Green and Odum, 1985; Dekant et al., 1986; Vamvakas et al., 1989b; Dreessen et al., 2003) and NAcTCVC (Vamvakas et al., 1987). These data suggest that genotoxicity from tetrachloroethylene and its oxidative metabolites is not likely to be a relevant MOA, but that the mutagenicity of GST metabolites is a plausible MOA for hepatic tumours. Further support for this is provided by quantitative results of the PBPK model, as the pattern of increase of GST—and not oxidative—metabolites matches the pattern of significant increases in hepatocellular tumours. Although this MOA would not be presumed to be relevant to humans, as the GST metabolism of tetrachloroethylene in humans is considered to be minor, it cannot be completely ruled out, as even low exposures to the genotoxic metabolites could play a role in tumour development.

Epigenetic change, specifically changes in DNA methylation, was considered as a potential MOA for carcinogenicity. The MOA involves the decrease in global DNA methylation, which leads to an increase in the messenger RNA and protein synthesis of proto-oncogenes (e.g., *c-myc*, *c-jun* and/or the growth promoting hormone IGF-II), resulting in cell proliferation. Data specific to tetrachloroethylene are lacking, but DCA and TCA have been shown to induce hypomethylation of DNA and proto-oncogenes in mouse liver (Tao et al., 2000, 2004; Ge et al., 2001; Pereira et al., 2001, 2004). The exposure levels in these few studies, however, have been higher than those that are associated with hepatocellular tumours in mice. This endpoint is therefore plausible, but further research is required to identify whether the MOA is quantitatively relevant to hepatocellular tumours induced by tetrachloroethylene or its metabolites, particularly at levels that are the same as or lower than those in the carcinogenicity bioassays.

Another MOA that was considered for hepatocellular tumours was peroxisome proliferation. Peroxisome proliferation is involved in fatty acid metabolism (Feige et al., 2006). Various chemicals can activate peroxisome proliferator-activated receptor alpha (PPARα), but once this activation occurs, the pathway is independent of the chemical. As a by-product of the

fatty acid metabolism, oxidative stress occurs, which results in indirect DNA damage. Oxidative stress then results in the activation of NF-κB, a negative regulator of apoptosis, leading to a perturbation of hepatocyte growth. This can result in selective clonal expansion and tumour development (Corton, 2010).

Although increases in markers of PPARα activation were observed in tetrachloroethylene-exposed mice (Goldsworthy and Popp, 1987; Odum et al., 1988), the exposure levels at which these effects were observed were higher than those at which hepatocellular tumours were observed. This discrepancy is potentially related to study design in the PPARα activation marker studies, as no studies have been performed at levels lower than those used in the carcinogenicity studies. Philip et al. (2007) noted an additional weakness in this endpoint, which is that CYP4A expression was not sustained for as long as 2 weeks; however, palmitoyl coenzyme A (CoA) oxidase activity increases were sustained for as long as 28 days (Odum et al., 1988), and no similar studies of longer duration have been performed. A lack of data on oxidative stress and hepatocyte growth perturbation also decreases the ability to identify whether peroxisome proliferation is a main MOA for tetrachloroethylene.

The major metabolite of tetrachloroethylene, TCA, has been considered to be a peroxisome proliferator. The most commonly used marker for PPARα in animal (primarily mouse) studies was palmitoyl CoA oxidase activity. TCA exposure consistently resulted in increased activity in this marker at exposure levels as low as 19 mg/kg bw per day (Austin et al., 1995; Parrish et al., 1996; DeAngelo et al., 2008), except in a study of short duration (1 week), in which 400 mg/kg bw per day was required for this activity (Laughter et al., 2004); these levels are lower than those at which hepatocellular adenomas and carcinomas were observed. The other markers of this effect were less studied and occurred at higher exposure levels. Markers of oxidative stress (8-OH-dG and thiobarbituric acid reactive substances [TBARS] activity) and hepatocyte growth perturbation (hepatocyte proliferation and centrilobular hepatocyte hypertrophy) were not as well studied and tended to occur at higher levels than tumours. The TCA data therefore provide a clear improvement in certainty of the MOA when compared with tetrachloroethylene, as PPARα activation is measured at lower levels than tumour induction; confidence in this MOA for TCA could be strengthened if measures of oxidative stress and hepatocyte growth perturbation were measured at levels lower than those associated with hepatocellular tumours.

The observation of peroxisome proliferation in rats can also provide some additional support for the peroxisome proliferation MOA. Rats, in which no increased incidence of hepatocellular tumours was observed, had lower levels of activation of PPARα for both tetrachloroethylene (Odum et al., 1988) and TCA (Mather et al., 1990; DeAngelo et al., 1997).

These analyses indicate that a peroxisome proliferation MOA is potentially plausible for tetrachloroethylene-induced hepatocellular tumours; however, there are key data gaps, which prevent the confident identification of peroxisome proliferation as a main MOA. There is stronger evidence that TCA exposure leads to hepatocellular tumours via a peroxisome proliferation MOA, but there are again limitations in the existing data. However, the weight of evidence supporting tetrachloroethylene's activity via this MOA, with TCA being a toxic moiety, is stronger than for other MOAs. If the data are considered sufficiently supportive of tetrachloroethylene acting by a peroxisome proliferation MOA, a threshold approach could be used for risk assessment. This is because a peroxisome proliferation MOA is most likely a threshold effect, since low concentrations of tetrachloroethylene—and therefore low internal doses of TCA—activate the PPARα receptor only at low levels, leading to inadequate signalling to generate increased peroxisome levels. If tetrachloroethylene were considered to act via a peroxisome proliferation

MOA, the human relevance of hepatocellular tumours could also be considered to be limited. Lower levels of TCA are generated in humans than in animals; therefore, higher exposures to tetrachloroethylene would be required to generate sufficient levels of TCA. Moreover, quantitative and qualitative toxicodynamic differences in PPARα activation appear to occur between experimental animals and humans. Humans exhibit ≥ 10-fold lower PPARα expression than mice and rats, and activation of the receptor triggers different gene targets, with an absence of induction of liver cell proliferation and suppression of apoptosis (Corton, 2010). PPARα activators are used as a human therapeutic agent for hyperlipidemia; the therapeutic effect in humans appears to be separate from the proliferating effect (Fidaleo, 2009). Peroxisome proliferation does not occur and liver tumours are not developed in mice transplanted with human PPARα and exposed to peroxisome proliferators (Corton, 2010). In support of this, only one clinical trial has ever identified a potential for an increase in cancer deaths (associated with clofibrate), but these observations diminished with follow-up (Klaunig et al., 2003); however, these trials have low power to identify hepatic tumours, and treatment was halted in participants demonstrating liver toxicity, which precludes the ability to make conclusions about the carcinogenicity of these therapeutic agents (Guyton et al., 2009). In general, the adverse effects of peroxisome proliferators are considered to be of limited relevance to humans.

Recent studies of known peroxisome proliferators, however, suggest that activation of PPARα might be a necessary but insufficient step in tumorigenesis. A study in PPARα-null mice exposed to di(2-ethylhexyl) phthalate, a peroxisome proliferator, identified rates of liver tumour development that were similar to those for wild-type mice with active PPARα receptors, indicating that the tumours occurred independently of PPARα activation (Ito et al., 2007; Guyton et al., 2009). Moreover, activation of PPARα via constitutive expression in transgenic mice resulted in similar hepatic responses in rodents activated with the model peroxisome proliferator Wy-14,643 (including activation of acyl CoA, palmitoyl CoA, CYP4A and cell cycle genes and decreases in triglycerides and fatty acids that were quantitatively similar to those observed with the ligand-induced peroxisome proliferation), but did not develop the expected preneoplastic lesions (Yang et al., 2007). Guyton et al. (2009) also demonstrated that there is a lack of correlation between the PPARα activation potency of a compound and its potency in hepatic tumorigenesis. These observations suggest that PPARα activation and other key events discussed in this section are not completely sufficient for liver tumour development, and additional unknown key events might play a role in the hepatocarcinogenesis of peroxisome proliferators. The previous conclusion that peroxisome proliferators are of limited human relevance is weakened considering the absence of knowledge of these additional key events (Guyton et al., 2009).

A final MOA that was considered for hepatocellular tumours was cytotoxicity resulting from oxidative stress, which can lead to regenerative proliferation. Few data exist for this MOA, but chronic studies have identified hepatotoxicity, including hepatocellular degeneration and necrosis, resulting from tetrachloroethylene exposure (NTP, 1986; JISA, 1993). Mice administered high doses (3 g/kg bw per day) of tetrachloroethylene for 15 days demonstrated these effects, which were reduced in animals that were subsequently exposed to antioxidants (Ebrahim et al., 1996), providing support for the effects being due to oxidative stress. In an *in vitro* study, similar effects were observed, with tetrachloroethylene exposure causing significant elevations in TBARS production in rat hepatocytes, which was modulated when co-exposures with vitamin E occurred (Costa et al., 2004). Although these studies indicate that tetrachloroethylene exposure likely results in oxidative stress and that neutralizing the oxidant activity reduces hepatocyte necrosis and degeneration, there are no studies demonstrating that the

hepatocellular tumours produced as a result of tetrachloroethylene exposure progress from the hepatic necrosis and degeneration. If a longer-term study with co-exposures to tetrachloroethylene and antioxidants were performed, this might give a better indication as to whether the antioxidants would reduce or prevent the occurrence of hepatocellular tumours, which could lend support to or allow for the rejection of oxidative stress–related cytotoxicity as a relevant MOA. Studies on TCA and DCA indicate that oxidative stress occurs in the liver in mice at ≥ 7 mg/kg bw per day (Larson and Bull, 1992; Austin et al., 1996; Parrish et al., 1996; Hassoun and Dey, 2008; Hassoun et al., 2010; Hassoun and Cearfoss, 2011; Cearfoss and Hassoun, 2012; Hassoun and Al-Dieri, 2012), which tends to be below levels causing cell proliferation (Carter et al., 1995; Snyder et al., 1995; Ge et al., 2001; DeAngelo et al., 2008).

9.4.2 Mononuclear cell leukaemia

Limited data exist on the MOA of *MCL*. Although several different MOAs (increased growth hormones leading to proliferation of splenocytes, inhibition of apoptosis leading to cell cycle changes in natural killer cells, immunosuppression leading to decreased elimination of tumour cells and genotoxicity leading to increased mutation of splenocytes) were considered in the analysis, none had adequate data to allow for proper assessment of the plausibility of each of the MOAs or their human relevance. No data could be found related to the effects of tetrachloroethylene or its metabolites on large granular lymphocytes or their precursors. However, high levels of chloral hydrate, a minor intermediate metabolite of tetrachloroethylene, were found to induce micronuclei and sister chromatid exchange in peripheral blood lymphocytes (further delineation of cell types was not mentioned) in infants (Ikbal et al., 2004). Fischer 344 rats are prone to *MCL* and have high background rates of the disease; however, the incidence of the disease was clearly above historical control rates in tetrachloroethylene-exposed rats (NTP, 1986; JISA, 1993), and exposure to tetrachloroethylene also resulted in a dose-related increase in severity of *MCL* in female rats and in decreased tumour development latency in male and female rats (NTP, 1986).

Without knowledge of potential MOAs for tetrachloroethylene, it is difficult to assess the human relevance of rat *MCL*. In rats, *MCL* is first observed in the spleen; therefore, this is considered to be the organ of origin (Stromberg and Vogtsberger, 1983; Stromberg et al., 1990). The evidence that *MCL* development is drastically reduced in splenectomized F344 rats (Moloney and King, 1973) provides further support to this hypothesis. The bone marrow was affected by *MCL* only late in the progression of the disease in rats, and a smaller percentage of rats have bone marrow involvement (Stromberg and Vogtsberger, 1983). Haematopoiesis is different between rats and humans, as extramedullary haematopoiesis occurs in the spleen in rats (Stefanski et al., 1990). In humans, the spleen is a site of haematopoiesis in foetuses and neonates, but bone marrow becomes the primary site for haematopoiesis very early in life. Although haematopoietic stem cells can migrate to the spleen when increased blood cells are required (e.g., in infection, inflammation and diseases affecting the bone marrow), this is not a typical site for haematopoiesis (Kim, 2010). Because of these haematopoietic differences between rats and humans, *MCL* in rats might not be relevant to humans if the MOA for *MCL* is found to be related to haematopoiesis; however, because there is no indication as to whether this might be a relevant MOA, the human relevance of *MCL* in rats cannot currently be discounted.

Many similarities (in the cellular phenotype, clinical, haematological and serum chemistry and pathological characteristics) exist for *MCL* in rats and the large granular lymphocyte leukaemia associated with natural killer cells in humans (Thomas et al., 2007). Although some epidemiological studies have considered associations between tetrachloroethylene exposure and

leukaemia, it is difficult to assess the associations. Participants in the community-based studies were exposed to a variety of chemicals, and the occupational studies considering leukaemia were based on census data and cancer registries; therefore, exposure assessment is limited to the identification of individuals who have reported working in the dry cleaning industry. Moreover, the assessments do not typically distinguish between different types of leukaemia.

9.4.3 Neurotoxicity

Limited data exist on the potential MOAs for tetrachloroethylene-associated neurotoxicity; however, because the effects have been clearly identified in environmental and occupational epidemiological studies, the effects can be considered relevant to humans, despite a lack of MOA data. The MOA of tetrachloroethylene is presumably most closely related to parent compound effects, rather than effects of metabolites (Bale et al., 2011); therefore, decreased tetrachloroethylene metabolism in humans compared with experimental animals does not lessen the likelihood of an effect in humans.

Some evidence exists to indicate that tetrachloroethylene might have effects on dopamine activity, which might have an effect on colour discrimination and contrast sensitivity, effects that were observed in epidemiological and acute controlled dosing studies. Decreased release of dopamine can result in decreases in transmission of nerve signals to the retina, which can result in decrements in visual abilities (Gralewicz and Dyzma, 2005). Although there have not been any direct measures of altered dopamine levels after tetrachloroethylene exposure, other data indirectly suggest that this might occur. Increases in dopamine levels can lead to inhibition of glutamate release, resulting in the activation of gamma-aminobutyric acid (GABA)–producing neurons, which can cause tremors (Gralewicz and Dyzma, 2005). No changes were measured in glutamate or GABA uptake in gerbils exposed to a single exposure level of tetrachloroethylene (Briving et al., 1986), but the anti-convulsive effects observed in rats (Chen et al., 2002) might suggest a decrease in dopamine levels. Dopamine also inhibits the release of prolactin; therefore, the increases in plasma prolactin levels in female dry cleaners (Ferroni et al., 1992) could be an indication of decreased dopamine levels. However, more conclusive evidence of the effects of tetrachloroethylene on dopamine levels is required before this MOA can be confirmed. There is also some evidence that tetrachloroethylene might disrupt the function of voltage- and ligand-gated ion channels. In general, tetrachloroethylene and other related solvents tend to increase inhibitory receptor function and decrease excitatory receptor function, resulting in the inhibition of current (Bale et al., 2011). These changes are expected to affect neurobehavioural responses in the cognitive domain—particularly if the changes occur in the hippocampus—and visual function (Bale et al., 2011). Changes to cholinergic system function are suspected to affect memory and cognition, as demonstrated in Alzheimer's disease research (Mufson et al., 2008). The specific receptors that affect visual function have not been completely elucidated, but one hypothesis is that increased activation of the *N*-methyl-D-aspartate–glutamate receptor system, likely via increase of agonist neurotransmitters such as glutamate, results in changes to visually evoked potentials (Bale et al., 2011). This hypothesis is supported by evidence that the agonist *N*-methyl-D-aspartate decreases the F2 amplitude in rats, similar to tetrachloroethylene, but that *N*-methyl-D-aspartate antagonists do not change visual evoked potentials (Bale et al., 2005a). Several different ion channels have been found to be disrupted by tetrachloroethylene in *in vitro* studies. Tetrachloroethylene increases the activation and decreases the inactivation of voltage-sensitive calcium channels (Bushnell et al., 2005; Shafer et al., 2005), resulting in shifts in a hyperpolarizing direction. A concentration-dependent inhibition of human and rat neuronal nicotinic acetylcholine receptors has also been observed for tetrachloroethylene (Bale et al.,

2005b). Although there are no data for the effects of tetrachloroethylene on *N*-methyl-D-aspartate, GABA or glycine receptors, data for compounds that potentially act by similar modes of action (toluene, trichloroethylene and ethanol) can be used to predict tetrachloroethylene activity on these receptors. In general, these compounds tend to inhibit excitatory (e.g., *N*-methyl-D-aspartate) receptors and potentiate inhibitory (e.g., GABA and glycine) receptors (Bushnell et al., 2005).

As mentioned above, the hippocampus controls cognition and memory; therefore, changes directly to this area of the brain could impact the neurobehavioural domains that were affected in exposed humans. One hypothesized MOA that could affect cognition is demyelination of the hippocampus (Bale et al., 2011). Fatty acid changes in the brains of gerbils, including in the hippocampal region, were potentially indicative of changes to the myelin sheath (Kyrklund et al., 1984, 1987).

9.5 Dose-response assessment

An extended summary of the cancer and non-cancer dose-response assessments is presented in Sections 9.5.1 and 9.5.2, respectively, as a supplement to the discussions in Section 10. Several endpoints were considered for each assessment (Health Canada, 2013), but those that were most relevant to the assessment (based on consistency of observations among studies, increased incidence of effects at lower doses and demonstrated relevance to humans) are discussed in detail in these sections.

As described in Section 8.5, a PBPK model was developed for use in both the cancer and non-cancer risk assessments for tetrachloroethylene. This is because quantitative differences in metabolism exist when comparing humans with rodents, and saturation of the oxidative pathway in high-dose studies results in a plateau in the generation of oxidative metabolites while driving the metabolism to the GST pathway. Linear extrapolation from high-dose studies in rodents to low-dose human exposures might not be representative of the actual risk of exposure to drinking water containing low concentrations of tetrachloroethylene. For this reason, internal dose metrics are more appropriate for use in risk assessments of tetrachloroethylene.

The species-relevant models were applied to studies that were deemed to be relevant for the dose-response assessment to allow for the estimation of various internal dose metrics at each of the exposure levels reported in the studies. Wherever possible, benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were obtained for relevant internal dose metrics using the U.S. EPA Benchmark Dose Software (BMDS Version 2.2 R67) (U.S. EPA, 2011a). BMDS was also used to calculate cancer slope factors for each of the internal dose metrics, which allowed for the estimation of excess cancer risks of 10^{-4}, 10^{-5} and 10^{-6} for these dose metrics. To extrapolate from these internal dose metrics to external oral doses of concern in humans, the human PBPK model was applied.

9.5.1 Dose-response assessment for carcinogenic endpoints

As described in Section 9.2.3, four cancer types have been identified in chronic bioassays in mice and rats. Two of the tumour types, splenic haemangioendothelioma in male mice (observed in JISA, 1993) and renal tubular adenomas and adenocarcinomas in male rats (observed in NTP, 1986) were initially considered, but were eventually excluded from the dose-response assessment for two reasons: (1) the observations were not replicated in other studies or in other sexes and species within the same study; and (2) the incidence of tumours was low in the studies and only slightly above background, with no significant increase in any dose over controls when

using pair-wise comparisons. The two remaining cancer types, hepatocellular adenoma and carcinoma (combined) and *MCL*, were the main focus of the dose-response assessment, which is described below.

Hepatocellular adenomas and carcinomas were observed in mice in both chronic inhalation studies. In both males and females, significant increases were observed at high doses in the JISA (1993) study and at both doses in the NTP (1986) study, and the trends were significantly positive for both studies. The NCI (1977) study, in which significant increases in the tumours were observed in both dose groups, can also be used as qualitative support of the effect via the oral route, but the study was not considered quantitatively in the dose-response assessment due to the shortened duration of the study and dose levels that varied over time. As discussed in Section 9.4, although multiple MOAs were considered, none was found to be the sole causative factor for hepatocellular tumours. MOAs of peroxisome proliferation from the TCA metabolite and cytotoxicity are suspected to be predominant, with the greatest weight of evidence for peroxisome proliferation. If tumours in mice were due to peroxisome proliferation or cytotoxicity, a threshold dose-response assessment approach could be considered relevant, because preventing the PPARα activity or the development of hepatocellular degeneration and necrosis could be expected to prevent the occurrence of later key events in the MOA pathway, including the development of hepatocellular tumours. The more conservative linear low-dose extrapolation is presented together with the threshold approach, because although the weight of evidence most strongly supports a threshold approach and refutes mutagenicity, there is inadequate evidence to firmly conclude whether either peroxisome proliferation or cytotoxicity is the MOA responsible for these tumours. Moreover, the role of mutagenicity in these tumours cannot be completely ignored, because minor metabolites from the GST pathway have displayed genotoxicity in assays. Although there is not absolute certainty regarding the MOA of tetrachloroethylene for hepatocellular tumours, there is a much stronger weight of evidence to support the threshold approach than for the use of linear low-dose extrapolation for the assessment of hepatocellular tumours.

Elevated levels of *MCL* were observed in male and female rats in both chronic inhalation studies. These increases were significant for both dose groups in the NTP (1986) study and in high-dose males in the JISA (1993) study; although no significant increase was observed through pair-wise comparisons for female rats in the latter study, a significantly positive exposure–response trend was reported. F344 rats, the strain in which the *MCL* occurred, have high background rates of the disease. The increase was still considered to be an increase over background rates, because *MCL* levels in exposed rats were clearly higher than those in both concurrent and historical controls, shorter latency periods for *MCL* development occurred in exposed rats and dose-related increases in disease severity were observed. This conclusion is further supported by other judgements of the relevance of tetrachloroethylene to *MCL*. Pathologists from the NTP (1986) study concluded that there was “clear evidence of carcinogenicity” for tetrachloroethylene in male F344 rats, based on *MCL* and renal tubular neoplasms, and “some evidence of carcinogenicity” in female F344 rats, based on *MCL* alone. Moreover, using a weight-of-evidence approach to analyze the incidence of *MCL* in rats from the NTP (1986) study, Thomas et al. (2007) concluded that *MCL* was definitively associated with tetrachloroethylene exposure, a classification that was given to only 5 of the 34 substances studied by NTP (1986) that had increased *MCL*. The relevance of rat *MCL* to humans has been questioned (Caldwell, 1999; Ishmael and Dugard, 2006). Although rat *MCL* is potentially of limited relevance to humans, the disease is similar to the rare human natural killer large granular lymphocyte leukaemia (Thomas et al., 2007). Very little is known about the MOA of *MCL* in rats;

however, the weight of evidence related to physiological differences between humans and rats and the weak associations between tetrachloroethylene exposure and leukaemia in humans support the lack of human relevance for this endpoint. For this reason, the dose-response assessment for *MCL* was performed, but is considered to hold a lessened weight in the overall risk assessment, because the dose-response relationship in genetically predisposed rats might not be quantitatively relevant to humans without this genetic predisposition (Ishmael and Dugard, 2006).

Results for the cancer dose-response modelling for tetrachloroethylene exposure are presented in Table 3. Hepatic oxidative metabolism rate was selected as the most relevant dose metric for hepatocellular tumours, because the generation of oxidative metabolites in the liver is likely most closely associated with the tumours. Because the MOA for *MCL* is unknown, the most appropriate dose metric cannot be selected, so the most conservative dose metric (TCA concentration in blood) was selected. Although none of the models had adequate fit with the data for hepatocellular tumours from the JISA (1993) study, the value calculated for the NTP (1986) study is considered to be appropriate, as external points of departure (PODs) for other internal dose metrics were similar for the two studies, with the NTP (1986) results being slightly more conservative.

Table 3. Summary of dose-response modelling results for cancer endpoints

Endpoint, species (reference)	POD	Dose metric	Dose-response model	External POD (mg/kg bw per day)
Hepatocellular tumours, male mice (JISA, 1993)	10^{-5}	Hepatic oxidative metabolism rate	All models were rejected based on lack of fit; no external POD	
	10^{-6}			
	BMD_{10}			
	$BMDL_{10}$			
Hepatocellular tumours, male mice (NTP, 1986)	10^{-5}		Multistage	0.000 2
	10^{-6}			0.000 02
	BMD_{10}			6.2
	$BMDL_{10}$			1.7
MCL, male rats (JISA, 1993)	10^{-5}	TCA concentration in blood	Multistage	0.000 4
	10^{-6}			0.000 04
Stage 3 *MCL*, male rats (NTP, 1986)	10^{-5}		Multistage	0.000 4
	10^{-6}			0.000 04

These results indicate that a "*de minimis*" (essentially negligible) excess cancer risk of 10^{-5} is 0.0002 mg/kg bw per day for hepatocellular tumours and 0.0004 mg/kg bw per day for *MCL*. Because the weight of evidence for tetrachloroethylene tends to suggest that a non-mutagenic mode of action is predominant for hepatocellular tumours, the threshold approach can also be used for the risk assessment. Using this approach, the tolerable daily intake (TDI) is calculated by identifying the most appropriate POD and dividing by relevant uncertainty factors. Relevant PODs for the threshold approach for tetrachloroethylene are the BMD_{10} of 6.2 mg/kg bw per day and the $BMDL_{10}$ of 1.7 mg/kg bw per day.

9.5.2 Dose-response assessment for non-cancer endpoints

For effects other than cancer, a TDI can be derived by considering all studies and selecting the critical effect that is most relevant or occurs at the lowest dose, selecting a dose (or POD) at which the critical effect either is not observed or would occur at a relatively low incidence (e.g.,

10%) and reducing this dose by an uncertainty factor to reflect the differences between study conditions and conditions of human environmental exposure.

The non-cancer risk assessment is based on neurotoxicity. Neurotoxic endpoints have been demonstrated to be relevant to humans in epidemiological studies performed in environmental and occupational settings and in acute controlled dosing studies; furthermore, the effects are more conservative than those for other non-cancer endpoints (hepatic, renal and reproductive/developmental effects). Neurotoxicity was observed in experimental animal studies, and these were initially considered in the dose-response assessment, but the epidemiological studies are more relevant to humans and demonstrate neurotoxicity at lower levels than in the animal studies. The non-cancer risk assessment is thus based on human studies. Most of the studies were excluded from the dose-response assessment process, for the following reasons:

- characteristics of control groups, including socioeconomic status, were different from exposed (Schreiber et al., 2002; New York State Department of Health, 2010; Storm et al., 2011);
- no control group was included (Gobba et al., 1998);
- only a single exposure group was included, precluding measurement of dose-response relationships (Ferroni et al., 1992; Altmann et al., 1995);
- exposure estimates were limited to concentrations in water, with no estimates of water intake for the participants (Janulewicz et al., 2008, 2012; Aschengrau et al., 2011, 2012; Getz et al., 2012);
- exposures were acute and higher than in other studies (Stewart et al., 1961, 1970, 1977, 1981; Altmann et al., 1990, 1992); or
- adverse effects were absent (Nakatsuka et al., 1992), limited to subjective symptoms (Lauwerys et al., 1983; Cai et al., 1991) or occurred in groups with low exposure but not high exposure (Seeber, 1989).

After excluding these studies, only two remained for consideration in the dose-response assessment. The first study (Cavalleri et al., 1994) demonstrated a NOAEL of 4.8 ppm for colour confusion—considered to be an adverse effect—as decreases in CCI scores were not significant in ironers (the lower exposure group, with an average exposure level of 4.8 ppm). A multivariate analysis confirmed that the effect was most likely due to tetrachloroethylene and not other characteristics that can affect CCI score (e.g., age, alcohol, smoking). Health Canada calculated $BMDL_{10}$ values using the summary statistics for CCI scores (average and standard deviation for the CCI score and exposure for controls, ironers and dry cleaners), which resulted in a BMD_{10} of 7.2 ppm and a $BMDL_{10}$ (using a 95% lower confidence limit) of 6.6 ppm using the power model (it should also be noted that using a benchmark response level of 1 standard deviation resulted in a similar BMDL of 6.7 ppm using this approach). One weakness of the study was that some overlap in exposure occurred between the two exposure groups (range of exposures, dry cleaners: 0.38–31.19 ppm; ironers: 0.52–11.28 ppm); however, the authors also found a significant correlation between workers' time-weighted average exposure levels and their CCI scores, further supporting a dose-response relationship. Using these regression data, Health Canada calculated a BMD_{10} of 10.1 ppm and a $BMDL_{10}$ of 8.1 ppm using a linear model. However, for the latter approach, no controls were plotted in the graph presented in the original paper. Because of this weakness, the $BMDL_{10}$ from the former modelling approach was used as the relevant POD for neurological endpoints. The regression approach also identified that the association was driven primarily by three workers with exposures > 12.5 ppm, presenting a weakness in the use of the study in the dose-response assessment, as the association between the CCI score and

tetrachloroethylene exposure levels was no longer significant when these subjects were removed from the analysis (Cavalleri et al., 1994; Benignus et al., 2009).

The other study that was not excluded was the neurobehavioural study of dry cleaners performed by Echeverria et al. (1995). Although this study can be used to qualitatively support the Cavalleri et al. (1994) study, it was not included in the quantitative dose-response assessment because associations between exposure and neurobehavioural (visuospatial and visuomotor) effects were observed only for the 3-year or lifetime indices and not for current exposure levels. The only exposure data provided in the study were for current exposures—which were also limited, because they were based on 15-minute samples from a subsample of participants—and no associations were observed between current exposure levels and neurobehavioural effects. Because details of participants' exposure were provided only for the current exposures, for which there were no significant changes, the exposure indices from the Echeverria et al. (1995) study cannot be used for performing quantitative dose-response assessments. This would not impact the dose-response assessment, as the current exposure levels in the Echeverria et al. (1995) study were higher than those in the Cavalleri et al. (1994) study; therefore, the Cavalleri et al. (1994) study would still have driven the risk assessment, even if the Echeverria et al. (1995) study were considered quantitatively.

PBPK modelling was performed using the NOAEL and $BMDL_{10}$ values from Cavalleri et al. (1994) to extrapolate from inhalation exposures to equivalent oral doses. Because the parent compound is suspected to be the toxic moiety for neurological effects and peak exposure levels for solvents are often more relevant for neurological effects, the relevant dose metrics were the daily peak and average concentrations of tetrachloroethylene. No brain compartment was included in the PBPK model, but partitioning coefficients for tetrachloroethylene in brain are similar to those in kidney (Dallas et al., 1994); therefore, the daily peak and average concentrations of tetrachloroethylene in the kidney were used as proxies for brain values. Peak and average concentrations of tetrachloroethylene in blood were also considered. Results of this modelling are summarized in Table 4. Peak exposures to tetrachloroethylene are thought to be most closely associated with adverse neurological effects; therefore, a POD of 4.7 mg/kg bw per day was selected.

Table 4. Dose-response modelling for neurological effects from Cavalleri et al. (1994)

Point of departure	Measure	Peak in blood	Peak in kidney[a]	Average in blood	Average in kidney
NOAEL	Internal dose	0.23 mg/L	1.18 mg/L	0.087 mg/L	0.44 mg/L
	External dose	3.4 mg/kg bw per day	3.4 mg/kg bw per day	1.3 mg/kg bw per day	1.3 mg/kg bw per day
$BMDL_{10}$	Internal dose	0.32 mg/L	1.62 mg/L	0.119 mg/L	0.602 mg/L
	External dose	4.7 mg/kg bw per day	4.7 mg/kg bw per day	1.7 mg/kg bw per day	1.7 mg/kg bw per day

[a] In the absence of a brain compartment in the PBPK model, kidney was used as a proxy for brain exposure, as described above.

The TDI derived for neurological endpoints is also considered to be protective of hepatic, renal and reproductive/developmental non-cancer effects. These endpoints were also considered in a detailed dose-response assessment, using the most conservative results from animal studies as

the PODs and applying the PBPK model to extrapolate between species and routes of exposure (Health Canada, 2013). Using $BMDL_{10}$ values (using a 95% lower confidence limit) for liver necrosis and liver degeneration in mice and kidney tubule nuclear enlargement in rats (NTP, 1986; JISA, 1993), the TDIs for liver and kidney effects were calculated as 176 µg/kg bw per day and 52 µg/kg bw per day, respectively. For reproductive and developmental endpoints, a PBPK model to estimate rat foetal exposures to tetrachloroethylene was developed; however, due to a lack of data on the pharmacokinetics of the compound in pregnant women, the model could not be used for extrapolation to humans. Using default assumptions to extrapolate from experimental animals to humans and from inhalation to ingestion, the TDI for reproductive and developmental effects based on decreased foetal weight in rats (Carney et al., 2006) was 210 mg/kg bw per day. The PBPK model was applied to estimate foetal exposure, and comparisons with other non-cancer endpoints were made using internal dose metrics; foetal tetrachloroethylene exposure levels at the POD were estimated to be on the same order of magnitude as those for kidney effects. The TDI for neurological effects was more conservative than the other non-cancer endpoints, and the effects have been directly observed at relevant concentrations in the human population; therefore, neurological effects were considered as the most relevant non-cancer endpoint for the tetrachloroethylene risk assessment.

Immunological effects were not considered in the dose-response assessment. Although enhanced allergic reactions were observed in mice exposed to doses as low as 2 µg/kg bw per day (Seo et al., 2012), the study involved passively sensitizing mice prior to exposure, which leads to difficulties in including the study in a quantitative dose-response assessment. This factor, combined with some study limitations, led to the exclusion of this study for further consideration in the non-cancer risk assessment.

10.0 Classification and assessment

Tetrachloroethylene was classified as a Group III carcinogen (possibly carcinogenic to humans) in the Priority Substances List Assessment Report (Government of Canada, 1993). The International Agency for Research on Cancer (IARC) recently classified tetrachloroethylene as probably carcinogenic to humans (Group 2A), based on limited evidence in humans and sufficient evidence in experimental animals (IARC, 2014). Although carcinogenicity studies concerning tetrachloroethylene have largely focused on the inhalation route of exposure, carcinogenicity has also been reported following oral exposure. The NTP (1986) and JISA (1993) inhalation studies provide the best data for assessment of the risk of tumour development. Linear extrapolation from high-dose studies in rodents to low-dose human exposures might not be representative of the actual risk of exposure to drinking water containing low concentrations of tetrachloroethylene. This is because quantitative differences in metabolism exist when comparing humans with rodents, and saturation of the oxidative pathway in high-dose studies results in a plateau in the generation of oxidative metabolites while driving the metabolism to the GST pathway. For this reason, external dose is not considered to be the appropriate metric for use in risk assessments based on high-dose exposures, and internal dose metrics should be used instead. As described in Sections 8.5 and 9.5, a PBPK model was developed for use in both the cancer and non-cancer risk assessments for tetrachloroethylene. The species-relevant models were applied to studies that were deemed to be relevant for the dose-response assessment to allow for the estimation of various internal dose metrics at each of the exposure levels reported in the studies. Summaries of the approaches for the most relevant health-based values (HBVs) for cancer and non-cancer effects are presented in Sections 10.1 and 10.2, respectively.

10.1 Cancer risk assessment

Detailed results for the cancer dose-response modelling for tetrachloroethylene exposure are presented in Table 3 in Section 9.5.1. As described in the aforementioned section, hepatocellular tumours are the most relevant endpoint for the cancer risk assessment. The default approach for cancer risk assessment for mutagenic compounds (or for compounds that cannot be excluded as being mutagenic) is to perform linear extrapolation to estimate exposure levels that would result in excess risk levels in the range of 10^{-5} to 10^{-6} (1 in 100 000 to 1 in 1 000 000). The weight of evidence for tetrachloroethylene more strongly supports a non-genotoxic mechanism for hepatocellular tumours; therefore, the TDI approach is considered an appropriate replacement for the default approach for calculation of the HBV for tetrachloroethylene in drinking water. The mouse PBPK model described in Section 8.5 was applied to estimate internal dose metrics in mice from the NTP (1986) and JISA (1993) studies. Benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were then calculated for the internal dose metrics using the U.S. EPA Benchmark Dose Software (BMDS Version 2.2 R67) (U.S. EPA, 2011a). Hepatic oxidative metabolism rate was selected as the most relevant dose metric for hepatocellular tumours, because the generation of oxidative metabolites in the liver is assumed to be most closely associated with the tumours. After obtaining the internal dose BMDs, the human PBPK model was applied to estimate the oral exposures that would be associated with the internal dose levels. The external BMD_{10} of 6.2 mg/kg bw per day and $BMDL_{10}$ of 1.7 mg/kg bw per day were obtained from the NTP (1986) study, using a multistage model. To calculate the TDI, the $BMDL_{10}$ is divided by uncertainty factors to account for inter- and intraspecies variability; only the pharmacodynamic component of the interspecies uncertainty factor (2.5) is used because pharmacokinetic differences between mice and humans were already quantitatively accounted for with the application of the PBPK model. The default uncertainty factor of 10 for intraspecies variability was applied. Finally, an uncertainty factor of 10 was also applied to reflect the fact that the assessment was being performed for a threshold carcinogen, as described in Ritter et al. (2007). The extra level of protection provided by this additional uncertainty factor is also supported by the fact that the specific mode of action of tetrachloroethylene-induced tumours has not been confirmed. Using the $BMDL_{10}$ value, a TDI can be calculated as follows:

$$\text{TDI} = \frac{1.7 \text{ mg/kg bw per day}}{250}$$

$$= 0.0068 \text{ mg/kg bw per day}$$

where:

- 1.7 mg/kg bw per day is the external dose associated with the $BMDL_{10}$ (using a 95% lower confidence limit) from NTP (1986), as presented in Table 3; and
- 250 is the uncertainty factor (×10 for intraspecies variability; ×2.5 for the pharmacodynamic portion of the interspecies uncertainty factor; and ×10 for the severity of the effect of carcinogenicity)

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.0068 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{}$$

$$= \frac{0.0068 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{6.2 \text{ L-eq/day}}$$

$$= 0.0154 \text{ mg/L}$$

$$\approx 0.015 \text{ mg/L (15 µg/L)}$$

where:

- 0.0068 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 6.2 L-eq/day is the daily volume of water consumed by an adult, accounting for multiroute exposure (as described in Section 5.6)

10.2 Non-cancer risk assessment

For effects other than cancer, a TDI can be derived by considering all studies and selecting the critical effect that is most relevant or occurs at the lowest dose, selecting a dose (or POD) at which the critical effect either is not observed or would occur at a relatively low incidence (e.g., 10%) and reducing this dose by an uncertainty factor to reflect the differences between study conditions and conditions of human environmental exposure.

The non-cancer risk assessment is based on neurotoxicity. Neurotoxic endpoints have been demonstrated to be relevant to humans in epidemiological studies performed in environmental and occupational settings and in acute controlled dosing studies; furthermore, the effects are more conservative than those for other non-cancer endpoints (hepatic, renal and reproductive/developmental effects). Neurotoxicity was observed in experimental animal studies, and these were initially considered in the dose-response assessment, but the epidemiological studies are more relevant to humans and demonstrate neurotoxicity at lower levels than the animal studies. The non-cancer risk assessment is thus based on human studies.

As described in Section 9.5.2, a NOAEL of 4.8 ppm for colour confusion was obtained from the key study from the neurological assessment (Cavalleri et al., 1994). Health Canada calculated a BMD_{10} of 7.2 ppm and a $BMDL_{10}$ (using a 95% lower confidence limit) of 6.6 ppm using the power model. PBPK modelling was performed using the $BMDL_{10}$ value to extrapolate from inhalation exposures to equivalent oral doses. Because the parent compound is suspected to be the toxic moiety for neurological effects and peak exposure levels for solvents are often more relevant for neurological effects, the most relevant dose metric was the peak concentrations of tetrachloroethylene. No brain compartment was included in the PBPK model, but partitioning coefficients for tetrachloroethylene in brain are similar to those in kidney (Dallas et al., 1994); therefore, the peak concentrations of tetrachloroethylene in the kidney were used as a proxy for brain values. The external oral dose associated with the $BMDL_{10}$ was 4.7 mg/kg bw per day.

A 1000-fold uncertainty factor is recommended for the neurological endpoint. The full default uncertainty factor of 10 was applied for intraspecies variability to represent differences in pharmacokinetics and pharmacodynamics within the population, because the PBPK model did not account for variability in either of these factors within the human population. An uncertainty factor of 10 for database deficiency is also applied. Due to limitations in the human neurotoxicity database, the selection of the key study for the endpoint was based on the quality of the study

rather than the effect observed at the lowest level. Adverse neurological effects were observed at lower concentrations than those in the Cavalleri et al. (1994) study, but these studies could not be used in the dose-response assessment because they presented exposed participants as a single exposure group or there were differences in characteristics of exposed and control participants that could affect study results. Moreover, the database deficiency uncertainty factor is also applied with the use of an occupational exposure study because the "healthy worker effect" can potentially bias study results by diluting or quantitatively reducing the adverse effects observed.

The third uncertainty factor is a value of 10 to extrapolate from a less than lifetime exposure. Average duration of exposure for participants in the Cavalleri et al. (1994) study was 8.8 years. Although adverse effects were already observed despite a less than lifetime exposure, longer durations could have lowered the exposure levels at which the effects were observed.

The TDI for neurological effects of tetrachloroethylene can be calculated as follows:

$$\text{TDI} = \frac{\text{4.7 mg/kg bw per day}}{1000}$$

$$= \text{0.0047 mg/kg bw per day}$$

where:

- 4.7 mg/kg bw per day is the external dose associated with the $BMDL_{10}$ (using a 95% lower confidence limit) from Cavalleri et al. (1994), as described above; and
- 1000 is the uncertainty factor (×10 for intraspecies variability; ×10 for database deficiency; and ×10 to represent a less than lifetime exposure, as described above).

Using this TDI, the HBV can be calculated as follows:

$$\text{HBV} = \frac{\text{0.0047 mg/kg bw per day} \times \text{70 kg} \times 0.2}{\text{6.2 L-eq/day}}$$

$$= \text{0.0106 mg/L}$$

$$\approx \text{0.010 mg/L (10 µg/L)}$$

where:

- 0.0047 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 6.2 L-eq/day is the daily volume of water consumed by an adult, accounting for multiroute exposure (as described in Section 5.6).

10.3 Comparison of cancer and non-cancer assessments

The HBV for the non-cancer assessment, which was 0.010 mg/L using human neurological data, is more conservative than the HBV for hepatocellular tumours of 0.015 mg/L. Moreover, there is much greater confidence in the human relevance of neurological effects than

that of liver tumours at environmentally relevant exposure levels for tetrachloroethylene. The HBV of 0.010 mg/L that was derived using human neurological data is therefore considered to be sufficiently protective of the carcinogenic effects of tetrachloroethylene.

10.4 International considerations

This section presents the various drinking water guidelines and standards from other international organizations. Variation in these limits can be attributed simply to the year of assessment, or to differing policies and approaches including the choice of key study, as well as the use of different consumption rates, body weights, and allocation factors.

WHO (2003) established a drinking water guideline of 40 µg/L (originally published in 1996) based on a no-observed-adverse-effect level (NOAEL) for hepatotoxic effects from a 6-week gavage study in mice (Buben and O'Flaherty, 1985) and a 90-day drinking water study in rats (Hayes et al., 1986). The Australian drinking water guideline is 50 µg/L, based on the same two studies (NHMRC and NRMMC, 2011).

Tetrachloroethylene is currently regulated in the United States under the National Primary Drinking Water Regulations. The maximum contaminant level (MCL) of 0.005 mg/L is designed to be protective of liver problems and increased risk of cancer, with a maximum contaminant level goal (MCLG) of 0 mg/L (U.S. EPA, 2012e). The U.S. EPA is considering regulating tetrachloroethylene along with up to 15 other VOCs that are known or suspected to cause cancer as a group, under the new Drinking Water Strategy (U.S. EPA, 2011b). This group of VOCs will be the first group of contaminants to be addressed under this new strategy. The U.S. EPA also recently performed an Integrated Risk Information System assessment for tetrachloroethylene. They calculated an oral reference dose of 6 µg/kg bw per day based on the average value for two separate neurological endpoints (Cavalleri et al., 1994; Echeverria et al., 1995), and the concentration in drinking water associated with a 10^{-6} excess risk was estimated as 20 µg/L based on hepatocellular adenomas and carcinomas from the JISA (1993) study (U.S. EPA, 2012c).

The Office of Environmental Health Hazard Assessment of the California EPA (OEHHA, 2001) derived a non-regulatory public health goal of 0.06 µg/L for tetrachloroethylene based on hepatocellular carcinomas in mice (NCI, 1977; NTP, 1986) and mononuclear cell leukaemia in rats (NTP, 1986).

11.0 Rationale

Tetrachloroethylene is primarily used as a solvent in the dry cleaning industry and as a chemical intermediate, with exposures of the general public primarily coming from indoor and outdoor air. Entry into the environment is primarily from anthropogenic sources, and tetrachloroethylene's presence in drinking water can result from spills.

The effects of tetrachloroethylene have been studied in humans and experimental animals, with neurological effects being observed in all species. The cancers repeatedly observed in animals (hepatocellular adenomas and carcinomas in mice and mononuclear cell leukaemia in rats) have not been observed in humans with occupational or environmental exposure to tetrachloroethylene. The weight of evidence for the MOA for these animal tumours suggests that they do not likely result from mutagenic activity.

Given the volatility of tetrachloroethylene, a multiroute exposure assessment was performed using PBPK modelling in order to determine any additional exposure by dermal or inhalation exposure during showering or bathing. This multiroute exposure was used in both the cancer and non-cancer risk assessments.

PBPK modelling was used to calculate the BMD for neurological effects based on the internal dose of tetrachloroethylene in humans occupationally exposed to the compound in air. The HBV for tetrachloroethylene obtained from this approach was 0.01 mg/L (10 µg/L). This value is lower than the HBV for hepatocellular tumours of 0.015 mg/L (15 µg/L), which was calculated based on the rate of tetrachloroethylene metabolism in the liver. The HBV for neurological effects is therefore sufficiently protective of both potential cancer and non-cancer effects resulting from exposure to tetrachloroethylene in drinking water.

A MAC of 0.010 mg/L (10 µg/L) is established for tetrachloroethylene in drinking water, as it is protective of potential health effects, can be reliably measured by available analytical methods and is achievable by municipal and residential scale treatment technologies.

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 is deemed necessary.

12.0 References

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Appendix A: List of acronyms

8-OH-dG	8-hydroxydeoxyguanosine
ALP	alkaline phosphatase
ALT	alanine transaminase
ANSI	American National Standards Institute
AOC	assimilable organic carbon
AOP	advanced oxidation process
AST	aspartate transaminase
AUC	area under the concentration–time curve
BMDL	lower confidence limit of the benchmark dose
BMD	benchmark dose
BMDL	lower confidence limit of the benchmark dose
BMDS	Benchmark Dose Software
BUN	blood urea nitrogen
bw	body weight
CCI	colour confusion index
CoA	coenzyme A
CYP	cytochrome P450
DCA	dichloroacetic acid
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
ED_{50}	median effective dose
GABA	gamma-aminobutyric acid
GAC	granular activated carbon
GC	gas chromatography
gpm	gallons per minute
GST	glutathione *S*-transferase
HBV	health-based value
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
L-eq	litre-equivalent
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MCL	maximum contaminant level (U.S.)
MCL	mononuclear cell leukaemia
MCLG	maximum contaminant level goal (U.S.)
MDL	method detection limit
MOA	mode of action
MS	mass spectrometry
NAcTCVC	*N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine
NAG	*N*-acetylglutamate
NES	Neurological Evaluation Scale
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
NSF	NSF International

PAC	powdered activated carbon
PBPK	physiologically based pharmacokinetic
POD	point of departure
PPARα	peroxisome proliferator-activated receptor alpha
ppm	parts per million
PQL	practical quantification level
PTA	packed tower aeration
RBP	retinol binding protein
RNA	ribonucleic acid
S9	9000 × *g* supernatant fraction from rodent liver homogenate
SCC	Standards Council of Canada
TBARS	thiobarbituric acid reactive substances
TCA	trichloroacetic acid
TCVC	*S*-(1,2,2-trichlorovinyl) cysteine
TCVG	*S*-(1,2,2-trichlorovinyl) glutathione
TDI	tolerable daily intake
U.S. EPA	United States Environmental Protection Agency
UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organization