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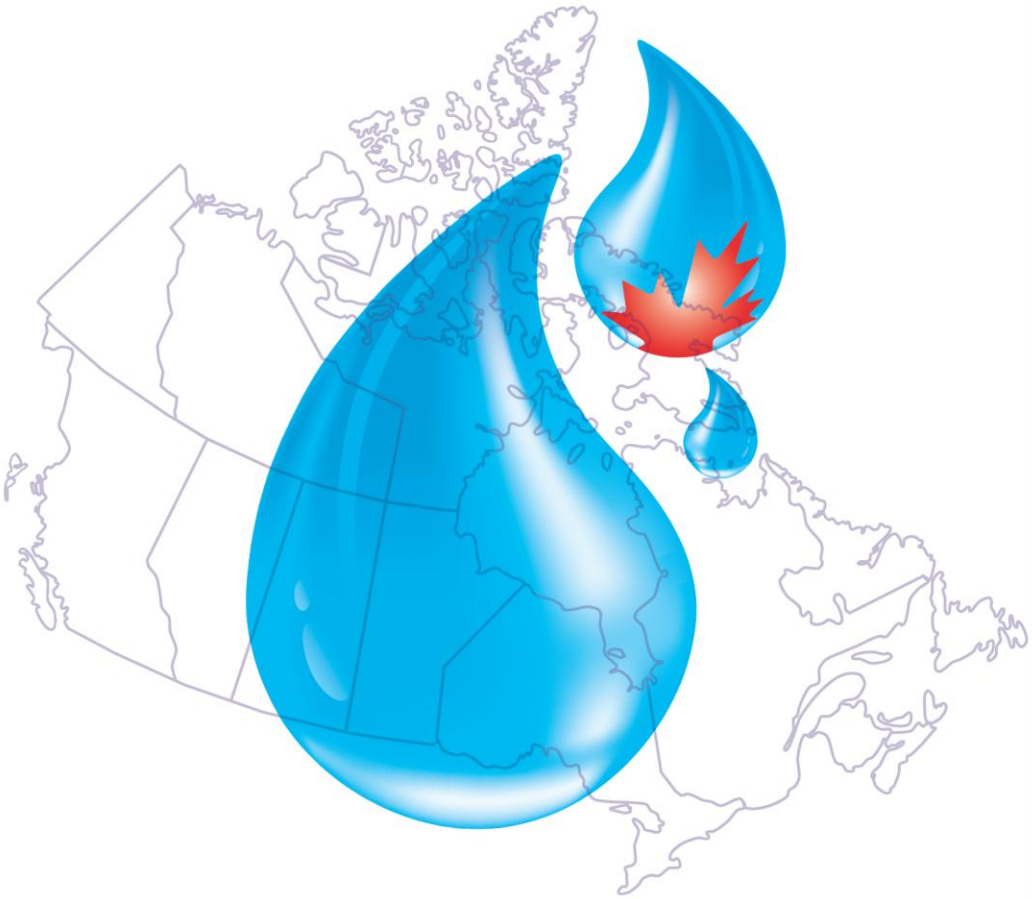
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Vinyl chloride



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Vinyl Chloride

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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March, 2013

Vinyl Chloride

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for vinyl chloride in drinking water is 0.002 mg/L (2 μg/L). Every effort should be made to maintain vinyl chloride levels in drinking water as low as reasonably achievable (or ALARA).

2.0 Executive summary

Vinyl chloride is primarily a synthetic chemical. It can enter drinking water through leaching from polyvinyl chloride (PVC) pipes, from industrial discharges from chemical and latex manufacturing plants, or as a result of the biodegradation of synthetic solvents. Only one PVC manufacturing facility currently exists in Canada.

This guideline technical document reviews and assesses all identified health risks associated with vinyl chloride 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 vinyl chloride has been established at a maximum acceptable concentration of 0.002 mg/L (2 μg/L).

2.1 Health effects

Vinyl chloride is classified as a human carcinogen, with sufficient evidence in both humans and animals. Vinyl chloride exposure has been linked with liver and neurological effects, in both humans (at occupational exposure levels) and animals. Liver cancer is the most serious endpoint that follows exposure from ingestion or inhalation of vinyl chloride.

The MAC has been established taking into consideration the most vulnerable population: Evidence from animal studies suggests that very young children (less than 5 weeks of age) may be twice as sensitive to the carcinogenic effects of vinyl chloride as adults. However, there are no human studies supporting these findings.

2.2 Exposure

The general population is primarily exposed to vinyl chloride from inhalation of ambient air and the ingestion of items packaged in PVC containers, which may leach vinyl chloride. Exposure can also occur from drinking water, from sources of contamination in the environment, or from leaching of PVC pipes in the distribution system. However, vinyl chloride is rarely detected in Canadian drinking water supplies. There are no Canadian data on vinyl chloride levels in sediment, sewage or consumer products. Canadians may also be exposed to vinyl chloride from drinking water through inhalation and dermal 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. Vinyl chloride can be reliably measured in drinking water at the MAC.

At the municipal level, conventional treatment techniques are not effective at removing vinyl chloride. The best available technology for removing vinyl chloride is packed tower aeration. Taking into consideration currently available technologies, municipal treatment plant are expected to be able to consistently achieve concentrations below the MAC.

At the residential level, although there are no treatment units currently certified to remove vinyl chloride, treatment devices using treatment technologies such as activated carbon may remove vinyl chloride below the MAC if two or more units are installed in series.

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.

Vinyl chloride is a human carcinogen, which means that exposure to any level in drinking water may increase the risk of cancer. Jurisdictions may establish more stringent limits than the MAC.

Generally, vinyl chloride 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, as vinyl chloride released to the ground does not adsorb onto soil, any that does not evaporate migrates readily to groundwater, where it is expected to remain for months to years. Vinyl chloride is usually only detected in groundwater in the vicinity of landfills and where there have been spills of vinyl chloride or chlorinated precursor compounds.

Vinyl chloride may also leach from polyvinyl chloride pipes used in the distribution and plumbing systems. To minimize levels of vinyl chloride from these systems, materials in contact with drinking water should be certified to ANSI/NSF Standard 61.

The drinking water guideline is based on lifetime exposure (70 years) to vinyl chloride from drinking water. For drinking water supplies that occasionally experience short-term exceedances above the guideline value, 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. For infants less than 5 weeks of age, who may be more sensitive to the health effects of vinyl chloride, concentrations in drinking water should be kept as low as reasonably achievable.

The guideline for a carcinogen is normally established at a level at which the increased cancer risk is "essentially negligible" when a person is exposed at that level in drinking water over a lifetime. In the context of drinking water guidelines, Health Canada has defined this term as a range from one new cancer above background levels per 100 000 people to one new cancer above background levels per 1 million people (i.e., 10^{-5}–10^{-6}). The estimated lifetime risk associated with ingestion of water containing vinyl chloride at the MAC is 5.0×10^{-5} which is above the range that is considered to represent "essentially negligible" risk. However, the MAC for vinyl chloride is a risk-managed value based on analytical achievability. Considering that it

exceeds the health-based value, every effort should be made to maintain vinyl chloride levels in drinking water as low as reasonably achievable (or ALARA).

3.1 Monitoring

Groundwater sources should be characterized to determine if vinyl chloride is present, especially if the land use history is unknown. Quarterly monitoring for vinyl chloride should be conducted for groundwater sources that are or may have been impacted by landfill leachate, spills of vinyl chloride or chlorinated VOCs.

Although newer pipes and components are required to meet standards that limit leaching of contaminants, polyvinyl chloride water mains manufactured prior to 1977 are prone to leaching vinyl chloride because they often contain higher concentrations of unpolymerized vinyl chloride monomer.

It is recommended that distribution systems with these older PVC pipes be monitored for vinyl chloride. Quarterly monitoring for vinyl chloride should be undertaken in the areas of the distribution system where older PVC pipes are located, specifically at locations with the maximum residence time (e.g., dead ends). Utilities that have baseline data indicating that vinyl chloride 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 vinyl chloride, it is suggested that a plan be developed and implemented to address these situations.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

4.1 Identity

Vinyl chloride (CH_2CHCl; Chemical Abstracts Service registry number 75-01-4) is a colourless, flammable, explosive gas with a boiling point of -13.4°C and high volatility, as indicated by its Henry's Law constant of 2.8 $kPa \cdot m^3/mol$ at 25°C and vapour pressure of 362.6 kPa at 20°C (U.S. EPA, 2000a). Vinyl chloride, also known as vinyl chloride monomer, chloroethene, monochloroethylene or ethylene monochloride, has a relative molecular weight of 62.5 (OEHHA, 2000; ATSDR, 2006). It is slightly soluble in water (1.1 g/L at 28°C) but highly soluble in fats and organic solvents. It polymerizes in light and in the presence of a catalyst. On combustion, it degrades to hydrogen chloride, carbon dioxide and traces of phosgene. Vinyl chloride has a pleasant, sweet odour at high concentrations (ATSDR, 2006; IARC, 2008). In air, 1 part per million (ppm) of vinyl chloride corresponds to 2.6 mg/m^3 at 25°C and one atm of pressure.

4.2 Major uses and sources

Vinyl chloride can primarily enter the environment through anthropogenic sources, and may also be formed naturally in soil (Keppler et al., 2002). It is now produced and used with stringent methods for containment and recovery. Vinyl chloride can enter drinking water through leaching of the entrapped monomer from polyvinyl chloride (PVC) pipe. Releases to the aquatic environment are primarily a result of industrial discharges from chemical and latex manufacturing plants (IARC, 1979). Vinyl chloride can also be formed in groundwater and the environment by biodegradation of synthetic solvents, such as trichlorethene, trichloroethane and tetrachloroethene (Parsons et al., 1984; OEHHA, 2000; ATSDR, 2006).

Between 1986 and 1999, Canadian industrial manufacturing capacity for vinyl chloride ranged between 373 and 550 kilotonnes per year, whereas production rates ranged between 270 and 439 kilotonnes per year (CIS, 1999). The closing of vinyl chloride manufacturing plants has decreased Canadian production of vinyl chloride since 2000: the Dow Chemical Company closed its vinyl chloride facility in Sarnia, Ontario, in the early 1990s and its facility in Fort Saskatchewan, Alberta, in 2006; BF Goodrich closed its Shawinigan, Québec, plant in 1993, and Royal Polymer closed its plant in Sarnia, Ontario, in 2009. Only one PVC manufacturing facility currently exists in Canada located in Niagara Falls, Ontario (Environment Canada, 2008).

In 1982, 86% of the Canadian production of vinyl chloride was used to manufacture polyvinyl chloride, 4% was used to manufacture 1,1,1-trichloroethane and 10% was exported (Environment Canada, 1985). However, between 1986 and 1999, production of PVC increased while the use of vinyl chloride for 1,1,1-trichloroethane became negligible and the quantity exported decreased. The importation of PVC into Canada rose from 73 to 440 kilotonnes per year during that same period. After 1993, nearly 100% of vinyl chloride produced in Canada was used in the manufacture of PVC (CIS, 1999). The majority of PVC demand in Canada was for the manufacture of pipe and fittings. Rigid PVC used for pipes and fittings contains little or no plasticizer when produced for potable water applications. As such, PVC is sometimes called rigid or unplasticized PVC (Richardson and Edwards, 2009).

PVC is used in electrical wire, insulation and cables, industrial and household equipment, medical supplies, food packaging materials, building and construction products and piping. In

addition, PVC is used as a raw material in the paper, glass, rubber and automotive industries. Vinyl chloride and polyvinyl chloride co-polymers are distributed and processed in a variety of forms, such as dry resins, plastisol, organosol and latex (U.S. EPA, 2000b). Concentrations of vinyl chloride monomer in PVC were reduced drastically between 1973 and 1975, ranging from 1 to 10 ppm (ECETOC, 1988). A wide variety of foods and drinks are packaged in containers or film made of polyvinyl chloride or vinyl chloride co-polymers, and residual vinyl chloride may migrate into food or beverages (ECETOC, 1988). Children's plastic toys, such as dolls, bath toys and squeeze toys are often manufactured with PVC. Vinyl chloride has also historically been detected in the interior of new cars (824 to 3120 μg/m^3) (IARC 1979). The vinyl chloride content in the smoke of USA-manufactured cigarettes and small cigars ranged from 5 to 27 ng per cigarette (mean concentration of 11.35 ng/cigarette) (Hoffmann et al., 1976).

A PVC manufacturing facility located in Niagara Falls (Thorold), Ontario, released 2489 million litres of wastewater per day to the river between 2005 and 2007 and reported a vinyl chloride concentration of 1.46 μg/L in the wastewater released to the river (Oxy Vinyl, 2008). According to National Pollutant Release Inventory data, the total amount of vinyl chloride released into surface water in 2007 was 0.001 tonnes (NPRI, 2007). Vinyl chloride was historically released to water in Sarnia, Ontario; however, the amount has decreased since 1998, and no vinyl chloride release to water has been reported in Sarnia since 2000, with the exception of 0.297 tonnes in 2003.

Historically, the amount of vinyl chloride released into air peaked at 44 tonnes in 1997 and has since been steadily decreasing. In 2007, 2.7 tonnes of vinyl chloride were emitted to the atmosphere by major Canadian industrial facilities; the largest vinyl chloride emissions in 2007 occurred in three Ontario cities: Thorold, Sarnia and Guelph. Releases were also regularly reported for Fort Saskatchewan, Alberta, before the 2006 closure of the vinyl chloride manufacturing plant there (NPRI, 2007).

Lesage et al. (1993) measured the vinyl chloride levels in leachate from a municipal solid waste landfill located in Guelph, Ontario: average vinyl chloride concentrations of 14 μg/L and 23 μg/L were found in samples (number not specified) collected in 1988 and 1989, respectively. In 2007, 0.538 tonnes of vinyl chloride were released to land, with releases occurring in Thorold, Ontario; Sarnia, Ontario; and Winnipeg, Manitoba (NPRI, 2007).

In a study conducted to investigate the potential for the production of vinyl chloride through natural soil processes, soil air and ambient air were analyzed for volatile chlorinated halocarbons. The concentrations of vinyl chloride in the soil air were significantly higher than those in ambient air, suggesting a natural formation in soil. Given that the vinyl chloride, trichloroethene and tetrachloroethene concentrations in ambient air were very low, the authors concluded that the significantly higher concentrations for vinyl chloride in soil air could not be attributed to ambient air contamination. The authors were able to produce vinyl chloride in the laboratory during follow up experiments using different pristine soils and model compounds. The authors proposed that vinyl chloride could be formed during the oxidative degradation of organic matter in soil, such as through a reaction between humic substances, chloride ions and an oxidant (ferric ions or hydroxyl radicals). The authors (Keppler et al., 2002) indicated that more detailed investigations are required to better understand the formation and significance of naturally produced vinyl chloride in soil.

4.3 Environmental fate

Vinyl chloride is not usually detected in groundwater. Possible sources to groundwater include landfill leachate as well as spills of vinyl chloride or chlorinated precursor compounds.

Vinyl chloride released to the soil does not adsorb onto soil particles; any that does not evaporate migrates readily to groundwater, where it can remain for months to years (Parsons et al., 1984). The half-life of vinyl chloride monomer at a concentration of 1 mg/L in open water at a 1 m depth is estimated to be 26 minutes, and 90% is lost by evaporation within 96 minutes (Verschueren, 1984).

Under aerobic conditions, vinyl chloride in samples taken from a shallow aquifer (groundwater) was readily degraded, with more than 99% being degraded after 108 days and approximately 65% being mineralized to carbon dioxide (Davis and Carpenter, 1990). Further, Bradley and Chapelle (2011) reported that even under hypoxic (initial dissolved oxygen concentrations about 0.1 mg/L) and nominally anoxic (dissolved oxygen minimum detection limit = 0.01 mg/L) conditions, first-order rates for vinyl chloride biodegradation (mineralization) were approximately 1 to 2 orders of magnitude higher in hypoxic groundwater sediment treatments and at least three times higher in hypoxic surface water sediment treatments than in the respective anoxic conditions.

Under anaerobic conditions, biodegradation of chlorinated compounds can result in vinyl chloride production. Vinyl chloride may be further degraded to less chlorinated and non-chlorinated ethenes, and possibly to carbon dioxide and ethane. However, these subsequent reactions often proceed at a slow rate under anaerobic conditions, and hence vinyl chloride may persist in groundwater (ATSDR, 2006). For example, Jacobs et al. (2007) reported that at some U.S. Superfund sites, vinyl chloride has been shown to persist for over 20 years. A pseudo-first order rate constant of 1.01×10^{-3} $(\text{months})^{-1}$ and a half-life of 57.2 years were estimated for the disappearance of vinyl chloride in water microcosms under anaerobic conditions without bioenhancement. However, anaerobic biodegradation has been shown to occur more rapidly under methanogenic or Fe(III)-reducing conditions (Bradley and Chapelle, 1996, 1997). Bradley and Chapelle (1996) reported that the addition of Fe(III) as Fe-EDTA to anaerobic aquifer microcosms resulted in rapid mineralization (15-34%) of [1,2-^{14}C]vinyl chloride to $^{14}CO_2$ within a period of 84 hours. Rates of vinyl chloride mineralization in Fe-EDTA-amended microcosms were comparable to those observed in aerobic microcosms (22-39% in 84 hours). The authors concluded that the addition of chelated Fe(III) may be an effective treatment for enhanced bioremediation of vinyl chloride contaminated ground water systems. In another study by Bradley and Chapelle (1997), the recovery of [1,2-^{14}C]VC radioactivity as $^{14}CO_2$ ranged from 5% to 44% in methanogenic microcosms and from 8% to 100% in Fe(III)-reducing microcosms for a 37 day period.

The low boiling point, high vapour pressure and low water solubility of vinyl chloride indicate that any vinyl chloride released to surface water will migrate rapidly to air. In waters containing photosensitizers, such as humic materials, sensitized photodegradation may also be important removal pathway (ATSDR, 2006).

When released to the atmosphere, vinyl chloride is expected to be removed by reaction with photochemically generated hydroxyl radicals (half-life of 1–2 days) liberating reaction products such as hydrochloric acid, formaldehyde, formyl chloride, acetylene, chloroacetaldehyde, chloroacetylchloranil, and chloroethylene epoxide (ATSDR, 2006).

5.0 Exposure

The general population is primarily exposed to vinyl chloride from inhalation of ambient air and the ingestion of items packaged in PVC containers, from which vinyl chloride can leach

(ATSDR, 2006). Canadian data on vinyl chloride levels in sediment or sewage were not located. No published quantitative data on vinyl chloride exposure from plastic toys are available.

5.1 Water

In a national survey of 30 Canadian water treatment facilities conducted in 1979, vinyl chloride was detected at < 1 µg/L in one sample each of treated and raw water collected in the months of November and December but was not present in samples collected in August or September (Otson et al., 1982).

In Alberta, out of 1622 samples collected since January 1, 2000, only two detections of vinyl chloride were reported from provincial parks treated drinking water; both detections (0.11 and 0.5 µg/L) were at or near the method detection limit (MDL), with the "largest" MDL in the data being 1.0 µg/L (Alberta Environment, 2009).

In New Brunswick, vinyl chloride was not detected in any drinking water supplies from 1994 to 2008 (New Brunswick Department of Environment, 2009).

In Nova Scotia, testing was conducted between March 2002 and April 2008 in 47 of 85 municipal drinking water treatment facilities; a total of 202 "non-detect" results for vinyl chloride were reported, which included 102 raw and 100 treated samples. The MDL ranged from 0.17 µg/L to 1 µg/L (Nova Scotia Department of Environment, 2009).

In Quebec, during the period of 2001–2009, 4824 samples from 276 distribution systems (mostly serving more than 5000 people) were analysed for vinyl chloride. In total, 4807 results (99.6%) were reported as being below the MDL, which ranged between 0.02 and 0.6 µg/L, depending on the laboratory; 17 samples contained vinyl chloride at levels ranging between 0.04 and 3.0 µg/L, with a mean of 0.75 µg/L (Ministère du Développement durable, de l'Environnement et des Parcs du Québec, 2009).

In Saskatchewan, during the period of 1996–2008, no vinyl chloride was detected in 25 samples from the distribution system (MDL ranged from 0.4 to 1 µg/L) (Saskatchewan Ministry of Environment, 2009).

The First Nations and Inuit Health Branch of Health Canada reported vinyl chloride sampling results for both raw and treated water from four provinces (Health Canada, 2009). In British Columbia, no vinyl chloride was detected in 10 raw water samples (MDL ranged from 0.5 to 1 µg/L) for the period of 2002–2008; however, vinyl chloride was detected in 2 of 920 treated samples at 0.61 and 0.54 µg/L. For Alberta, from 2004 to 2008, vinyl chloride was not detected in 177 treated drinking water samples; however, it was detected in 1 of 30 raw water samples at a level below 2 µg/L (MDL ranged from 0.2 to 2 µg/L). In Ontario, vinyl chloride was not detected in 424 raw water samples (MDL of 0.2 µg/L); however, 1 detection (0.5 µg/L) out of 1072 samples was reported for treated drinking water during the period of 2001–2009. Finally, in Manitoba, from 2001 to 2009, no vinyl chloride was detected in 460 samples of raw water (MDL ranged from 0.2 to 2 µg/L); however, 7 samples of treated drinking water out of 700 contained vinyl chloride at levels ranging from 0.9 to 1.6 µg/L.

Environment Canada (1998) monitored vinyl chloride levels in surface waters and groundwaters in eastern Canada (Nova Scotia, Prince Edward Island, Newfoundland and New Brunswick). Between 1985 and 1988, vinyl chloride levels were measured in lakes (n = 86), ponds (n = 17), reservoirs (n = 29) and rivers and streams (n = 50). The average vinyl chloride concentration in each of these surface water systems was below the MDL of 5 µg/L (Environment Canada, 1998). In 141 groundwater samples from various locations throughout the provinces, vinyl chloride levels were below the MDL of 5 µg/L in all samples (Environment Canada, 1998).

5.1.1 Leaching from polyvinyl chloride pipes

Currently, PVC and chlorinated PVC (CPVC) plastic pipes and components are used for conveying potable water. In the polymerization process, some of the vinyl chloride monomers are retained in the plastic pipe matrix (PVC or CPVC) as a residue and may be released into the air or water (WHO, 2004; Richardson and Edwards, 2009). In early field investigation (Dressman and McFarren, 1978) and experimental studies (Banzer, 1979; Ando and Sayato, 1984) demonstrated the ability of residual vinyl chloride to migrate from water distribution PVC pipes into the water flowing through them. The extent of leaching is determined by the vinyl chloride concentrations in the pipe material. In the field study, the highest vinyl chloride concentrations (1.4 µg/L) consistently occurred in water from pipes manufactured in 1975 whereas the lowest level (0.03 µg/L) was found in the pipes manufactured in 1966 (Dressman and McFarren, 1978). The amount of vinyl chloride migrating from rigid PVC pipes into drinking water was found to be directly proportional to the residual level of vinyl chloride in the pipe itself. Older PVC pipes (pre-1977) may contain vinyl chloride in concentrations up to 600 mg/kg, and have been shown to leach vinyl chloride into drinking water (Beardsley and Adams, 2003).

There are several solutions to address vinyl chloride leaching from the pre-1977 PVC pipes that are still in use today, including replacement of pipes, use of drinking water treatment devices and implementation of flushing protocol. Beardsley and Adams (2003) determined that the development and implementation of an appropriate flushing protocol is a practical approach to reduce exposure from vinyl chloride in these pipes. PVC is generally used for cold water applications for distribution system and premise plumbing pipes and components (i.e., fittings). The National Plumbing Code of Canada (NPC) allows the use of PVC only for cold water plumbing applications (NRCC, 2010). CPVC has higher heat resistance and greater mechanical stability from the chlorination process. Under the NPC, CPVC is permitted for use in both hot and cold water applications (NRCC, 2010). It is also important to note that the NPC has required that all plastic pipe meet the Canadian Standards Association's (CSA) standard for plastic pipes (CSA, 2009). The CSA standard was revised in 1990 to include a leaching test for vinyl chloride into drinking water. The CSA B137 series of standards for thermoplastic pressure piping currently requires that PVC and CPVC pipes and components (e.g. tubing and fittings), used for drinking water applications, comply with the requirements of NSF/ANSI Standard 61 (CSA, 2009). In order for PVC and CPVC products and materials to be certified to NSF/ANSI Standard 61, they must contain 3.2 mg/kg or less residual vinyl chloride monomer in the product wall, which is equivalent to 0.2 µg/L of vinyl chloride diffused into water. This acceptance criterion is the single product allowable concentration (SPAC), which is derived using the contaminant regulatory values from the U.S. EPA and Health Canada (one tenth of the regulatory value of 2 µg/L) (NSF/ANSI, 2012). Pipes and components meeting NSF/ANSI Standard 61 would be expected to leach very low concentrations of vinyl chloride into drinking water.

Richardson and Edwards (2009) investigated the leaching and accumulation of vinyl chloride from static segment/fragment reactors from PVC and CPVC piping used in drinking water applications. Although the results indicated that the newer PVC reactors leached faster and accumulated higher concentrations than CPVC, the levels of vinyl chloride concentrations leached from PVC and CPVC reactors were very low. The results from this study are presented in greater detail in section 7.1.5.

When PVC pipes were exposed to sunlight at maximum ambient temperatures of 35ºC the pipes were found to release more than 2.5 µg/L of vinyl chloride into the water. In the

absence of sunlight, no vinyl chloride was released which indicates that environmental conditions such heat and UV light can adversely affect vinyl chloride release (Al Malack and Sheikheldin, 2001).

5.2 Food

Vinyl chloride has been shown to migrate from PVC packaging to bottled drinking water. Benfenati et al. (1991) found that progressive migration of vinyl chloride from the bottle to the water occurred at a rate of 0.001 µg/L per day. Vinyl chloride levels of 0.013–0.083 µg/L (mean of 0.048 µg/L) were measured in Italian drinking water bottled in PVC (Benfenati et al., 1991).

There is very little information on concentrations of vinyl chloride in food. The leaching of vinyl chloride from wet food packaging materials is low; however, vinyl chloride is soluble in alcohols and mineral oil. The Canadian *Food and Drug Regulations* prohibit the sale of any food packaged in materials that leach detectable residues of vinyl chloride monomer, as determined by an analytical method with a detection limit of 50 µg/kg (Government of Canada, 2011). Vinyl chloride intake via food and drinks has been estimated to be 0.1 µg/day (Purchase et al., 1985).

5.3 Air

In Alberta, 24-hour average concentrations of vinyl chloride at the perimeter of a vinyl chloride plant from 1979 to 1984 were 12.9 µg/m^3 (5 ppb) 86–98% of the time; 12.9–23.2 µg/m^3 (5–9 ppb) 0.3–4.9% of the time; 25.8–77.4 µg/m^3 (10–30 ppb) 0.1–6.5% of the time; and 77.4 µg/m^3 (30 ppb) 0.3–2.4% of the time (Environment Canada, 1986). The general public may be exposed to small amounts of vinyl chloride from inhalation of ambient air in urban areas, typically in the order of 5 µg/day per person (ECETOC, 1988), with higher amounts in the vicinity of vinyl chloride and PVC plants.

Of 2560 samples collected at 47 sites in Canada in 2002, vinyl chloride was generally not detected (< 0.05 µg/m^3) in 24-hour samples (Environment Canada, 2004). A maximum 24-hour concentration of 0.7 µg/m^3 was reported for Sarnia, Ontario; Sarnia is an urban area with a known industrial point source. Based on annual outdoor air data from Montreal, Quebec, the average 24-hour vinyl chloride concentration was 0.02 µg/m^3 for 2001 and 2002 (four sites, eight samples) (Environment Canada, 2002).

National Air Pollution Surveillance Network stations measured concentrations of vinyl chloride in ambient air across Canada (Environment Canada, 2006). Between 2003 and 2006, nearly 99% of all average vinyl chloride concentrations for both rural (4379 of 4447 samples) and urban centres (7787 of 7879 samples) were reported to be below the MDL of 0.02 µg/m^3.

Health Canada measured vinyl chloride levels inside 100 non-smoking homes in Windsor, Ontario, from 2005 to 2006 (Stocco et al., 2008). The mean indoor vinyl chloride concentration was 0.062 µg/m^3 in the summer and 0.028 µg/m^3 in the winter. Outdoor levels of vinyl chloride were lower than indoor levels in summer and winter. The mean exposure concentration was determined to be 0.01 µg/m^3 in winter and < 0.001 µg/m^3 in summer (Stocco et al., 2008).

In a study by Dawson and McAlary (2009), vinyl chloride was detected in 7% of a total of 1684 North American homes sampled; concentrations up to 1.3 µg/m^3 were detected (with reporting limits ranging from 0.01 to 1.3 µg/m^3).

In the United States, indoor air concentrations of vinyl chloride in houses close to landfills have reached concentrations of up to 1 mg/m^3 and have exceeded the maximum reported concentration in outdoor air for areas adjacent to the landfills. A California monitoring program that collected 500 samples at two outdoor and four indoor sites downwind of a landfill

reported that the 120 samples containing the highest vinyl chloride concentration (25 μg/m^3) were taken inside homes (Little et al., 1992). An average vinyl chloride concentration of 4 ppb (10.4 μg/m^3) and a maximum of 9.3 ppb (24.2 μg/m^3) were measured in over 500 samples from 69 homes near a co-disposal landfill site in California, while concentrations over the site ranged from 83 to 12,800 ppm (216–33,280 mg/m^3) (Stephens et al., 1986).

5.4 Soil

To establish local background conditions, the Ontario Ministry of the Environment measured the vinyl chloride concentration in soil samples collected from sites with no known point sources (OME, 1997). A vinyl chloride concentration of 0.003 μg/g was determined to be the typical background level in Ontario for agricultural and all other land uses, based on the 90th percentile concentration measured in soil samples.

5.5 Multi-route exposure through drinking water

A human physiologically based pharmacokinetic (PBPK) model based on Clewell et al. (2001, 2004) was developed to extrapolate the results from two high-dose oral exposure studies in rats (Feron et al., 1981; Til et al. 1991) to humans exposed to low concentrations of vinyl chloride in drinking water. The model was also used to estimate the litre-equivalent (L-eq) contributions from dermal and inhalation exposure to vinyl chloride when showering and bathing. Using the external doses generated from the human PBPK model (see Sections 8.4 and 10.1), litre-equivalent contributions from dermal and inhalation exposure 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 dermal and inhalation routes of exposure with the internal dose from ingestion, the litre-equivalent contributions for dermal and inhalation exposure were determined to be 1.9 L-eq and 0.4 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 vinyl chloride in drinking water was estimated to be 3.8 L-eq. This litre-equivalent daily exposure was used in both the cancer and non-cancer risk assessments in Section 10.

6.0 Analytical methods

The U.S. Environmental Protection Agency (EPA) currently has three approved analytical methods (Method 502.2 Revision 2.1, Method 524.2 Revision 4.1 and Method 524.3 Version 1.0) for the analysis of vinyl chloride in drinking water (U.S. EPA, 2003, 2009a). These methods are general methods for the identification and measurement of purgeable volatile organic compounds (VOCs). The methods use purge and trap procedures, followed by a capillary gas chromatography (GC) column to separate the analytes. After an elution from the GC column, the analytes are identified by different detection techniques.

Method 502.2 Revision 2.1 uses a purge and trap capillary GC column equipped with photoionization detectors (PID) and electrolytic conductivity detectors (ELCD) in series. The method's MDL will vary depending on the GC column used and ranges from 0.02 to 0.04 μg/L for the PID and from 0.01 to 0.18 μg/L for the ELCD.

Method 524.2 Revision 4.1 uses a capillary GC column interfaced with a mass spectrometer (MS). The method has MDL values between 0.04–0.17 μg/L, depending on the GC column and the interface used between the GC and MS (U.S. EPA, 1995).

Method 524.3 version 1.0, approved in 2009, uses the GC-MS technique and has a detection limit of 0.029 µg/L for vinyl chloride. 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, 2009a).

Two Standard Methods can also be used for the analysis of vinyl chloride in drinking water (APHA et al., 2005). These methods, SM 6200B and SM 6200C, are based on purge and trap capillary GC followed by MS detector or PID and ELCD in series, respectively. Method SM 6200B has an MDL of 0.12 µg/L, and SM 6200C has an MDL of 0.025 µg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately using these methods, are 0.48 µg/L and 0.1 µg/L for methods SM 6200B and SM 6200C, respectively.

A recent study investigating the factors affecting the leaching of vinyl chloride from PVC and CPVC piping used in drinking water applications reported an MDL of 0.0045 µg/L using GC-MS in SIM mode (Richardson and Edwards, 2009).

However, the practical quantitation level (PQL) for U.S. EPA-approved methods is 2 µg/L and is based on the capability of laboratories to measure vinyl chloride within reasonable limits of precision and accuracy at the time of regulation. Current PQL assessments are based on two approaches: (1) the lowest value for which 75% of laboratories can quantitate within prescribed accuracy limits based on actual performance data, if the data is sufficient; or (2) multiplying the upper levels of the MDLs to account for the variability inherent to test methods and instruments used for analyses, when data is insufficient. In establishing the PQL, the U.S. EPA considers and prefers the laboratory performance data for methods approved at the time of the review over the MDL approach (U.S. EPA, 2009d).

In the second 6-year review of existing National Primary Drinking Water Regulations, the U.S. EPA determined that there was insufficient proficiency testing data to derive PQLs (U.S. EPA 2009d). Therefore, the U.S. EPA used two other sources to derive an estimated quantitation level (EQL): a minimum reporting level (MRL) approach and an MDL multiplier approach based on the approved analytical methods. The EQL is an estimate of the possible lower bound for a PQL. It is based on statistical analysis of proficiency test results for a method or the MRL from the dataset. The MRLs represent laboratory analytical limits for a large pool of laboratories in the U.S. Using the MRLs of more than 139,000 records collected from 1998 to 2005, the U.S. EPA established an EQL of 0.5 µg/L for vinyl chloride, reporting that a high percentage of the samples achieved a MRL of 0.5 µg/L.

Applying a multiplier of 10 to the upper bounds of the MDL for each of the two approved analytical methods (502.2 and 524.2), resulted in a possible PQL range of 1.7 to 1.8 µg/L. These values were slightly below the current PQL of 2 µg/L (U.S. EPA, 2009d). Ultimately, the U.S. EPA chose not to modify the existing PQL, because the data could not support the adoption of a lower value (U.S. EPA, 2009d).

There is no equivalent centralised program for the collection and rigorous statistical analysis of analytical data in Canada. As such, establishing a PQL for Canadian laboratories is not possible.

7.0 Treatment technology and distribution system considerations

Vinyl chloride is typically found in groundwater in the vicinity of landfills and where there have been spills of vinyl chloride or chlorinated precursor compounds. As such, it is important to characterize these groundwater sources in order to select the appropriate treatment

for removal of vinyl chloride. The selection of an appropriate treatment process will depend on many factors, including the characteristics of the raw water supply and the source and concentration of vinyl chloride.

7.1 Municipal scale

Municipal water filtration plants that rely on conventional treatment techniques (coagulation, sedimentation, filtration and chlorination) are generally ineffective in reducing concentrations of VOCs, such as vinyl chloride, in drinking water (Love and Eilers, 1982; Love et al., 1983; Lykins and Clark, 1994). Two common treatment technologies reported to be effective for the reduction of most VOCs in drinking water are aeration and adsorption.

Vinyl chloride is a gas under ambient environmental conditions. It has a relatively low solubility in water and a low capacity to adsorb to particulate matter and sediment. Volatilization is the most rapid process for the removal of vinyl chloride from surface waters (IPCS, 1999). Its high Henry's Law constant (2.8 $kPa \cdot m^3/mol$ at 25°C) suggests that vinyl chloride would be very amenable to removal by air stripping (U.S. EPA, 1985a; Crittenden et al., 1988; Haarhoff and Cleasby, 1990). The U.S. EPA has identified packed tower aeration (PTA) as the best available technology (BAT) for vinyl chloride removal from drinking water and considers a 99.9% reduction to be achievable under all anticipated conditions (U.S. EPA, 1985a, 2009c). WHO (2011) states that vinyl chloride levels of 1 µg/L are achievable using air stripping.

Small system compliance technologies for the removal of vinyl chloride in drinking water include granular activated carbon (GAC), PTA, diffused aeration, multistage bubble aeration, tray aeration and shallow tray aeration (U.S. EPA, 1998, 2009c). The PTA process is effective, but the equipment is relatively expensive to build and maintain, and it may not be appropriate for small water treatment utilities.

Vinyl chloride has been reported as a degradation product of the microbial reductive dechlorination of chlorinated hydrocarbons such as tetrachloroethene and trichloroethene (IPCS, 1999; Bradley, 2000).

Vinyl chloride is primarily of concern as a potential contaminant from some older grades of PVC pipes, mainly manufactured prior to 1977 (Flournoy et al., 1999; Carroll and Eckstein, 2001; Beardsley and Adams, 2003; MDNR, 2006).

7.1.1 Air stripping and PTA

Air stripping treatment technology is commonly used to reduce the concentration of VOCs in drinking water (Cummins and Westrick, 1990; U.S. EPA, 1991; Dyksen, 2005). An air stripping process brings water and air into contact, allowing the transfer of volatile contaminant from the water to the air, as the driving force of the process is the contaminant concentration gradient between the two phases.

A variety of configurations exist with respect to air stripping equipment; however, PTA provides an optimum system for the removal of VOCs from water, as it allows for greater air to water ratios compared with other aeration systems. In the PTA column, the contaminated water flows downward by gravity over a bed of packing material, while the air is introduced into the tower below the packed bed and flows countercurrent to the water flow. Several factors affect the rate of stripping of the VOCs from water: the air to water ratio; the available area of mass transfer; the hydraulic loading rate; the temperature of the water and air; and the physical and chemical properties of the contaminant (AWWA, 1991; Crittenden et al., 2005; Dyksen, 2005). As the PTA transfers VOCs from water to air, treatment of the stripping tower off-gas may be

necessary to reduce the contaminant concentrations prior to discharge into the atmosphere (Crittenden et al., 1988; Adams and Clark, 1991).

A common operating problem is the scaling and fouling of the packing material of the column. The main causes of fouling are calcium carbonate or calcium sulphate scale, iron oxidation and microbial growth. Methods to prevent the fouling of the column include pH suppression of the PTA influent, the use of scale inhibitors or iron removal prior to the PTA application (ESE, 1984; Dyksen, 2005). Algal growth can also be a problem in locations where light could be introduced into the tower. Post-treatment processes, such as the use of a corrosion inhibitor, may also be required to reduce the corrosive properties of the water as a result of increased dissolved oxygen from the aeration process. Environmental conditions, such as water temperature, may have an impact on the packed tower performance. Contact between the water and the air in PTA column leads the air temperature typically to approach the water temperature. The temperature influences both the Henry's Law constant and the rate of mass transfer. These parameters affect the size of the column and the efficiency of removal of the VOCs (Crittenden et al., 2005).

A study using a full-scale PTA system indicated that an average influent vinyl chloride concentration of 8.4 µg/L can be reduced to below 0.3 µg/L using an air to water ratio of 61, a design hydraulic loading rate of 29.8 gpm/ft^2 (20.1 kg/m^2/s), an air stripper length of 7.5 meters, and a packed column diameter of 2.4 meters (Hand et al., 1988).

U.S. EPA pilot studies conducted at more than 30 water treatment sites showed that PTA achieved > 99% VOC removals. As vinyl chloride is more easily removed by aeration than are other VOCs included in the studies, the U.S. EPA concluded that PTA systems designed using reasonable engineering practices could achieve 99.9% removal of vinyl chloride (U.S EPA, 2009c). Pilot-scale data have demonstrated removal efficiencies of 99.9% and 99.5% using air to water ratios of 20 and 5, respectively. No information was provided on the influent concentrations (ESE, 1984).

After an evaluation of the cost of PTA technology for the control of selected organic compounds in drinking water, Adams and Clark (1991) indicated that the cost-effective PTA design parameters for the reduction of vinyl chloride include an air to water ratio of 5 and a packing depth of 6.9 m. Under these estimated conditions, a 99% reduction of vinyl chloride could be achieved, from an influent level of 100 µg/L to a level of 1 µg/L in the finished water.

Spray aeration and air-lift pumping are identified as alternative air stripping treatment technologies for the reduction of vinyl chloride in drinking water, achieving > 99.0% and 97.0% reductions, respectively (U.S. EPA, 1985b).

7.1.2 Granular activated carbon

The U.S. EPA identified GAC as an effective technology for the removal of VOCs from drinking water, with the exception of vinyl chloride. Study reports showed that the adsorption of vinyl chloride by GAC is a sporadic and erratic process and that vinyl chloride cannot be effectively removed (U.S. EPA, 1987a, 1987b; Hand et al., 1988 Lykins and Clark, 1994). A carbon adsorption isotherm for vinyl chloride has not been reported in the literature.

A pilot-scale study reported an erratic pattern for the treatment of vinyl chloride by GAC adsorption (U.S. EPA, 1987b). Data from the study demonstrated that a series of four 30-inch (0.76 m) GAC columns was capable of reducing vinyl chloride concentrations of up to 19 µg/L to a concentration below 0.5 µg/L in the finished water, achieving 810, 1250, 2760 and 2050 bed volumes for an empty bed contact time of 6, 12, 19 and 25 minutes, respectively.

Adams and Clark (1991) estimated cost-effective design parameters for liquid-phase GAC treatment of VOCs, including vinyl chloride, in drinking water. The estimated carbon usage rate to reduce an influent vinyl chloride concentration of 100 µg/L to a finished water concentration of 1 µg/L was 2.94 lb/1000 gallons (0.35 kg/m^3), with an empty bed contact time of 30 minutes and a bed life of 28 days.

GAC adsorption with a combination of aeration technologies could be extremely effective for producing water with low VOC concentrations in the finished water (Robeck and Love, 1983; McKinnon and Dyksen, 1984). The aeration step reduces the organic load to the adsorbent and may remove compounds competing for adsorption sites (Stenzel and Gupta, 1985). In addition, this step can significantly extend carbon bed life (Hess et al., 1981a; McKinnon and Dyksen, 1984).

The U.S. EPA (1998) identified GAC as a small system compliance technology for the removal of vinyl chloride in drinking water. GAC is the most widely used technology for small systems due to the general ease of use, practicality and affordability. Generally, small systems use closed GAC systems which have a higher treatment efficacy.

7.1.3 Ozonation and advanced oxidation processes

Ozonation and advanced oxidation processes (AOPs) have been reported to be effective for the reduction of vinyl chloride concentrations in drinking water, although data from full-scale systems were not available for these treatment methods (Lykins and Clark, 1994; Schwammlein and Leitzke, 1995; Zhong et al., 2002). AOPs refer to the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts 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 to be treated, such as alkalinity, pH, natural organic matter, iron and manganese, and turbidity, have a major impact on AOPs, as they scavenge hydroxyl radicals or absorb UV light used to produce the radicals (Crittenden et al., 2005).

In pilot plant ozone (O_3) tests, removal efficiency for vinyl chloride in groundwater in the range of 70–100% was observed with O_3 doses of 2–6 mg/L. Concentrations in the influent and in the finished water were not identified (Clark et al., 1988). Other pilot-scale tests conducted with O_3/hydrogen peroxide (H_2O_2), UV/ O_3 and UV/ H_2O_2 showed that all three processes achieved greater than 97% removal of vinyl chloride in groundwater under a variety of operating conditions. The results demonstrated reduction of an influent concentration in the range of 4–25 µg/L to a concentration below 0.5 µg/L (Schwammlein and Leitzke, 1995).

The performance of AOPs for the treatment of contaminated groundwater with chlorinated ethenes, including vinyl chloride, has been reported in non-peer-reviewed paper. The pilot-scale application of ozone/hydrogen peroxide treatment was reported to be effective for the treatment of an influent vinyl chloride concentration of 900 µg/L to levels below 0.5 µg/L in the finished water with an ozone dose of 32.2 mg/L (Bowman, 2003).

The formation of by-products, including disinfection by-products, from the oxidation and/or advanced oxidation of vinyl chloride or other inorganic or organic compounds in the source water should be considered when using these processes. The types and concentrations of by-products formed will be dependent on the source water quality, concentrations of the oxidants and the reaction contact time. Dowideit and von Sontag (1998) and von Gunten (2003) identified hydroxymethylhydroperoxide, formyl chloride and formic peracid as the by-products formed during ozonation of vinyl chloride in water. Another drawback of the use of AOPs such as

ozone/hydrogen peroxide and ozone/ultraviolet is the formation of bromate in waters containing bromide ion (Fronk et al., 1987; Crittenden et al., 2005). The presence of by-products may require additional treatment following AOPs and/or process optimization to minimize by-product formation.

7.1.4 Emerging technologies

New experimental technologies have been shown to have potential for removing VOCs, including vinyl chloride, but there is not sufficient information available at present to fully evaluate the technologies:

- *Catalytic hydrodehalogenation*: Catalytic hydrodehalogenation processes (replacement of halide by hydrogen), using hydrogen gas and palladium catalyst supported on alumina or GAC, have been evaluated for the treatment of chlorinated ethenes in contaminated water (Marques et al., 1994; Shreir and Reinhard, 1995). In a laboratory experiment using 0.5 g of 0.5% palladium on alumina and 0.1 atm H_2, vinyl chloride at an initial concentration of 1 mg/L in spiked tap water was completely hydrodehalogenated within 10 minutes at room temperature. The presence of nitrite, nitrate and sulphate ions caused a minor decrease in the rate of the hydrodehalogenation reaction. The presence of sodium bisulphide resulted in deactivation of the palladium catalyst (Shreir and Reinhard, 1995).
- *Pervaporation*: Although the use of membranes for the pervaporation extraction of VOCs has been applied primarily in wastewater treatment, this technique also has been studied for the removal of VOCs from groundwater (Jian and Pintauro, 1997; Uragami et al., 2001; Peng et al., 2003). Pervaporation is a membrane process in which a liquid stream containing VOCs is placed in contact with one side of an organophilic polymer membrane while a vacuum or gas purge is applied to the other side. The contaminants in the liquid stream adsorb into the membrane, diffuse through it and evaporate into the vapour phase.

7.1.5 Distribution system materials: PVC/CPVC

In the polymerization process, some of the vinyl chloride monomers are retained in the product matrix as a residue and may be released into the air or water.

The migration of vinyl chloride monomer from PVC pipes, mainly manufactured prior to 1977, was reported to be a possible source of vinyl chloride in drinking water (Flournoy et al., 1999; Carroll and Eckstein, 2001; Beardsley and Adams, 2003; MDNR, 2006). A study examining PVC pipes from the dead-end water distribution lines installed between 1960 and 1977 reported vinyl chloride levels in the range from non-detectable to 9.4 µg/L, the maximum being 25 µg/L (MDL of 0.1 µg/L) (Beardsley and Adams, 2003). As stated in section 5.1.1, plastic pipes and components used for potable water applications must now comply with NSF/ANSI Standard 61 which ensures minimal leaching of vinyl chloride into drinking water (CSA, 2009; NSF, 2012; NRCC, 2010).

Several studies have investigated the factors affecting the rate of leaching and the accumulation of vinyl chloride from PVC and CPVC piping used in drinking water applications (Al-Malack et al., 2000; Al-Malack and Sheikheldin, 2001; Al-Malack, 2004; Richardson and Edwards, 2009; Walter et al., 2011). Static laboratory experiments conducted with PVC reactors (PVC locally manufactured in Saudi Arabia) indicated that vinyl chloride at 2.5 µg/L accumulated in extracted (double-distilled) water after 30 days of exposure to 45°C; vinyl chloride at 2.3 µg/L accumulated in extracted water after 14 days of exposure to direct UV

radiation at an intensity of 218 mW/cm^2 and a temperature of 25°C (Al-Malack, 2004); vinyl chloride at > 2.5 µg/L was detected in extracted water after 30 days of exposure to direct solar radiation (Al-Malack and Sheikheldin, 2001); and vinyl chloride at concentrations up to 2.1 µg/L was detected in both reactors with groundwater (total dissolved solids 2670 mg/L) and chlorinated drinking water (total dissolved solids 160 mg/L) after 17 days of exposure to 45°C. The MDL for all experiments was 0.6 µg/L.

Laboratory experiments compared the leaching rate and the accumulation of vinyl chloride, in drinking water from static PVC and CPVC fragment/segment reactors and from in-use consumer water lines (Richardson and Edwards, 2009; Walter et al., 2011). The pipes were provided by different U.S. manufacturers and were certified to NSF International/American National Standards Institute (NSF/ANSI) Standard 61 for potable water applications. A 2-year laboratory study using static new schedule 40 PVC segment reactors filled with chlorinated tap water reported vinyl chloride concentrations below the detection limit until day 63 (limit of quantification [LOQ] of 0.095 µg/L). An equilibrium concentration of approximately 0.3 µg/L was reported on day 715 (LOQ of 0.006 µg/L; Walter et al., 2011).

In a short-term (4 days) laboratory study, all new pipes (schedule 40 PVC, schedule 80 CPVC and SDR11 CPVC) provided by different manufacturers showed detectable levels of vinyl chloride in chlorinated tap water in the range of 0.011–0.025 µg/L at day 4 of the experiments (LOQ of 0.006 µg/L). The authors reported no statistically significant differences in vinyl chloride levels between the types of piping (PVC vs. CPVC). However, variations in vinyl chloride levels were seen between different pipe manufacturers (Walter et al., 2011).

In order to investigate the effect of pipe age on leaching rate, Richardson and Edwards (2009) conducted laboratory experiments with new and aged PVC/CPVC segment reactors (schedule 40 PVC, schedule 80 CPVC and schedule 80 PVC). Laboratory experiments were conducted on new PVC/CPVC segment reactors with no biofilm or with biofilm artificially grown for 11 months, both present and subsequently removed. Based on the graphical representation of the experimental data, on day 7 of the experiment, reactors with artificially grown biofilm had estimated vinyl chloride levels of 0.009 µg/L in the PVC reactors and 0.007 µg/L in the CPVC reactors. In the reactors where the biofilm was removed, vinyl chloride levels were detected but not quantifiable in the PVC reactors and were estimated to be 0.009 µg/L in the CPVC reactors. In both new PVC and CPVC reactors, vinyl chloride levels were > 0.014 µg/L and < 0.008 µg/L, respectively (limit of detection [LOD] of 0.0045 µg/L; Richardson and Edwards, 2009).

Richardson and Edwards (2009) concluded that a faster accumulation of vinyl chloride occurred in 15-year-old PVC segment reactors compared with 2-year-old PVC loop segment reactors, regardless of whether biofilm was present or removed. In laboratory experiments conducted with 2-year-old schedule 40 PVC loop segment reactors and chlorinated tap water, vinyl chloride levels were approximately 0.0072 µg/L on day 3. By day 7 of the experiments, vinyl chloride concentrations were in the range of 0.01–0.012 µg/L when the biofilm was intact and 0.01–0.014 µg/L when the biofilm was removed. Experiments conducted with 15-year-old schedule 80 PVC segment reactors filled with chlorinated tap water showed vinyl chloride levels of 0.0057 µg/L (biofilm intact) and 0.0086 µg/L (biofilm removed) by the second hour. By day 7 of the experiments, vinyl chloride concentrations reached levels > 0.10 µg/L for reactors with biofilm intact and > 0.12 µg/L for those with biofilm removed (LOD of 0.0045 µg/L; Richardson and Edwards, 2009). According to the authors, the faster leaching rate for a 15-year-old pipe, whose surface had a rust colour, may be caused by damage to the pipe structure. The authors also

noted that PVC pipe segments with natural biofilm removed (2-year-old and 15-year-old PVC) leached vinyl chloride at rates slightly higher than those with biofilm intact.

Long-term (2 years) laboratory experiments using schedule 40 PVC and schedule 80 CPVC fragment reactors (no biofilm) investigated the impact of temperature on the leaching rate of vinyl chloride in the water. Based on the graphical representation of the experimental data, vinyl chloride concentrations were below the detection limit in all PVC and CPVC reactors incubated at 4°C. Vinyl chloride levels were estimated to be 0.1 to < 0.16 µg/L at 22°C, 0.07 to < 0.12 µg/L at 37°C and > 0.1 µg/L at 52°C for PVC reactors; and < 0.05 µg/L at 37°C and 0.04 to < 0.06 µg/L at 52°C for CPVC reactors. Henry's Law constants were applied to calculate the vinyl chloride concentrations in the water at the different temperatures (Richardson and Edwards, 2009).

In order to investigate the effect of mixed-species biofilm coverage on biotic reactors, experiments were conducted with schedule 40 PVC and schedule 80 CPVC fragment reactors with biofilm, with killed biofilm (soaked in formaldehyde), with scraped biofilm and without biofilm. The biofilms were artificially grown on new pipe fragments and stored at 22°C for more than 2 years. Richardson and Edwards (2009) reported quantifiable vinyl chloride levels in the range of 0.124–0.158 µg/L (LOD of 0.045 µg/L) for all PVC reactors, regardless of whether biofilm was present, killed or scraped. Vinyl chloride levels were below the detection limit for all CPVC with the exception of the reactor with biofilm. In this case, the levels were above the detection limit, but not quantifiable.

In summary, the results from static -pipe segment/fragment reactors indicated that the quantity of vinyl chloride leached from newer PVC reactors is higher than that from CPVC reactors in term of leaching rate and equilibrium concentrations (Richardson and Edwards, 2009).

In order to assess the vinyl chloride concentrations in tap water resulting from PVC and CPVC pipes, field samples were collected from 15 consumer homes. Vinyl chloride at concentrations in the range of 0.011–0.023 µg/L (LOQ of 0.006 µg/L) was detected in 3 of the 15 consumers' tap water samples. These homes had small-diameter CPVC pipes (<1") and were connected to chlorinated municipal water supplies (Walter et al., 2011). The age of two of the pipes were established (6 and 21 years), whereas the third pipe's age was unknown. Flushing of the pipes did not result in any differences in vinyl chloride concentrations before or after flushing in these homes. The study suggested that the chlorine residual in the water may contribute to vinyl chloride accumulation in the distribution system via disinfection by-product reactions (Walter et al., 2011). This fact is supported by laboratory experiments conducted with CPVC and copper pipe reactors. CPVC reactors with chlorinated tap water accumulated higher levels of vinyl chloride (levels not reported) than did reactors with dechlorinated water. Copper pipe reactors, which eliminated vinyl chloride accumulation via leaching, showed detectable levels of vinyl chloride in chlorinated water and not detectable levels of vinyl chloride in dechlorinated water by the 101st hour (4 days). After 2 months of the experiments, all reactors with dechlorinated water showed levels below the detectable level, whereas two of the triplicate samples with chlorinated water showed detectable levels up to 0.01 µg/L (LOQ of 0.006 µg/L) (Walter et al., 2011).

Another study reported no detectable levels of vinyl chloride in the raw water (MDL of 0.013 µg/L). However, average (and maximum) vinyl chloride concentrations of 0.04 µg/L (0.48 µg/L) and 0.014 µg/L (0.25 µg/L) were reported in treated and distributed water, respectively (Chung et al., 1997).

Several studies reported the formation of chloroacetaldehyde (CAA) and chloroacetic acid as a result of the reaction between the vinyl chloride migrating from the PVC pipes and the chlorine residual in the water (Ando and Sayato, 1984; Wolf et al., 1987; IPCS, 1999).

7.2 Residential scale

It is not generally recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. However, the migration of vinyl chloride monomer from PVC pipes manufactured mainly prior to 1977 was reported to be a possible source of vinyl chloride in drinking water distribution systems. In such cases, as well as where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing vinyl chloride concentrations in drinking water.

There is little information in the published literature regarding the effectiveness of GAC treatment technology at the residential scale and no certified residential treatment devices are currently available for the reduction of vinyl chloride in drinking water. However, one study conducted on treatment devices using activated carbon filters demonstrated that they may be effective for the reduction of vinyl chloride concentrations. The authors reported that countertop-style carbon filters were capable of reducing levels of vinyl chloride monomer of approximately 13 µg/L to levels well below 2 µg/L (Carroll and Eckstein, 2001). Carbon filters may be installed at the faucet (point of use) or at the location where water enters the home (point of entry). Point-of-entry systems are preferred for VOCs, because they provide treated water for bathing and laundry as well as for cooking and drinking. Some point-of-entry or point-of-use treatment technologies such as activated carbon may remove vinyl chloride from the drinking water below the MAC if two or more units are installed in series. No drinking water treatment device is certified specifically for vinyl chloride removal at this time, as vinyl chloride is not currently included in any ANSI/NSF treatment standard.

Before a treatment device is installed, the water should be tested to determine general water chemistry and to verify the concentration of vinyl chloride. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Products that use adsorption technology can lose removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the adsorption media in their treatment device as per the manufacturer's recommendations and service it when required.

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/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, 2011).

- CSA International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);

- Quality Auditing Institute (www.qai.org); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

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

As noted previously, low levels of vinyl chloride may leach from some PVC/CPVC pipes used in drinking water systems and is best controlled by specification of material quality. The NPC requires that all plastic pipes used for cold water applications for distribution system and premise plumbing pipes and components (i.e., fittings) meet the CSA standard for plastic pipes. The standard requires that PVC and CPVC pipes and components (e.g., tubing and fittings), used for drinking water applications, comply with the requirements of NSF/ANSI Standard 61 (CSA, 2009). NSF/ANSI Standard 61 (Drinking Water System Components—Health Effects) ensures that materials meet health-based leaching requirements and are safe for use in potable water applications. This standard evaluates PVC and CPVC products and materials for the concentration of residual vinyl chloride monomer in the product wall. Products and materials must contain 3.2 mg/kg or less residual vinyl chloride monomer in the product wall (equivalent to 0.2 µg/L or less in the drinking water) in order to be certified to NSF/ANSI Standard 61 (NSF/ANSI, 2012).

8.0 Kinetics and metabolism

8.1 Absorption

8.1.1 Experimental animals

In rats, vinyl chloride is readily absorbed via oral and inhalation routes of exposure and is rapidly distributed throughout the body. After gastric intubation of male Wistar rats with 10 mL of aqueous solutions containing vinyl chloride at concentrations of 2.26–2.82 mg/mL (total dose 22.6–28.2 mg/animal), peak blood concentrations (6 to > 40 µg/mL) were found in less than 10 minutes, and absorption was almost complete (Withey, 1976; Feron et al., 1981). One dose of 450 mg/kg body weight (bw) administered orally to rats resulted in 98.7% absorption from the gastrointestinal tract (Green and Hathway, 1977).

Dermal absorption of vinyl chloride gas is not likely to be significant, as only 0.031% and 0.023% of the total vinyl chloride doses (7000 ppm and 800 ppm, respectively) were absorbed by male Rhesus monkeys, and the majority of the dose was exhaled (Hefner et al., 1975a).

8.1.2 Humans

Inhalation of vinyl chloride at concentrations of 7.5, 15, 30 and 60 mg/m^3 for six hours resulted in rapid pulmonary absorption and retention of 40% in five young, healthy adult males voluntarily exposed, independent of the concentration (Krajewski et al., 1980).

8.2 Metabolism

The metabolism of vinyl chloride has been quantitatively estimated in humans from gas uptake experiments whereby after initial absorption of vinyl chloride, continued absorption is mainly attributed to metabolism. When exposing young men to vinyl chloride at concentrations of 7.5, 15, 30 and 60 mg/m^3 by gas mask for six hours, Krajewski et al. (1980) reported that the retention of vinyl chloride was found to be independent of the inhaled concentration and did not

change with increasing vinyl chloride concentrations, suggesting that exposure to vinyl chloride up to 60 mg/m^3 did not cause saturation of the major metabolic pathway.

The fate of vinyl chloride in the animals appears to be dose dependent (Watanabe and Gehring, 1976), which is primarily due to the linear kinetics of the metabolic pathway for vinyl chloride at low doses. The metabolism of vinyl chloride has been shown to follow Michaelis-Menten kinetics in rats, with enzyme saturation occurring following exposure to approximately 100 ppm in air or between 1 and 100 mg/kg bw/day for a single gavage dose (Hefner et al. 1975b; Watanabe et al. 1976a).

The vinyl chloride metabolic pathway occurs through mixed-function oxidase cytochrome P450 2E1 (CYP2E1) both *in vitro*, with cell isolates of the microsomal fraction (S9) from rats (Kappus et al., 1976; Guengerich and Shimada, 1991; el Ghissassi et al., 1998) and humans (Guengerich et al., 1991) and with the human B-lymphoblastoid cell line (Chiang et al., 1997), and *in vivo*, with rats (Watanabe et al., 1976a, 1976b) and Rhesus monkeys (Buchter et al., 1980). Liver toxicity (vacuolization of the centrilobular parenchyma) increases in parallel with P450 liver content in rats after vinyl chloride inhalation exposure to 50 000 ppm for 6 hours (Reynolds et al., 1975).

Inhibition of vinyl chloride metabolism in rat and human microsomes was observed when vinyl chloride exposure occurred in the presence of diethyldithiocarbamate, a CYP2E1 selective inhibitor (Guengerich et al., 1991; el Ghissassi et al., 1998). Pretreatment of Sprague-Dawley rats with a general mixed-function oxidase blocker (SKF-525A) impeded the metabolism of inhaled vinyl chloride at a concentration of 1000 ppm (Hefner et al., 1975b).

Enzymatic transformation of vinyl chloride for excretion results in the generation of polar intermediates (Antweiler, 1976; Kappus et al., 1976; Rannug et al., 1976). The two major metabolites of vinyl chloride in the liver are the highly reactive and short-lived chloroethylene oxide (CEO) and CAA (Whysner et al., 1996; el Ghissassi et al., 1998), a highly reactive α-halocarbonyl compound which results from a rapid rearrangement of CEO (Pessayre et al.; 1979; Whysner et al., 1996; el Ghissassi et al., 1998). These two metabolites are detoxified mainly through glutathione (GSH) conjugation (Leibman, 1977; Tarkowski et al., 1980; Jedrychowski et al., 1985) which is supported by the observation of decreased non-protein sulfhydryl concentrations when exposed to high concentrations of vinyl chloride (Tarkowski et al., 1980; Jedrychowski et al., 1985), and by the excretion of GSH-conjugated metabolites in the urine of rats following exposure to vinyl chloride (Hefner et al., 1975b; Watanabe et al., 1976c). CAA may also combine directly or enzymatically with GSH by way of glutathione transferase (GST) to form S-formylmethylglutathione. S-formylmethylglutathione can act directly with GSH-derived cysteine to form N-acetyl-S-(2-hydroxyethyl)cysteine which is another major urinary metabolite of vinyl chloride (Green and Hathway, 1975). The GSH conjugates are then hydrolysed, resulting in excretion of cysteine conjugates in the urine (Hefner et al., 1975b). The two major metabolites identified in the urine of rats following exposure to vinyl chloride are N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid (Watanabe et al., 1976b).

8.3 Distribution and excretion

Vinyl chloride is distributed rapidly throughout the body, but poorly retained due to rapid metabolism and elimination (OEHHA, 2000; ATSDR, 2006).

In rats exposed to 4.5–70 ppm ^{14}C-labelled vinyl chloride for five hours, vinyl chloride was found to bind in the largest proportion in the liver, followed by the small intestine, kidney, lung and spleen; this organ distribution is supported by the lipophilicity of vinyl chloride, as

indicated by its low octanol:water partition coefficient of 1.62 (U.S. EPA, 2000a). Monkeys acutely exposed by the skin to ^{14}C-labelled vinyl chloride gas also had detectable ^{14}C activity in the bile, liver and kidney, however, no appreciable amount of activity was detected in other tissues (Hefner et al., 1975a; Bolt et al., 1980).

In an experiment in which rats were given single oral doses (by gavage) of 0.05, 1.0, 20.0 or 100 mg/kg bw of ^{14}C-labelled vinyl chloride dissolved in corn oil, the percentage of the dose exhaled within 72 hours as unchanged vinyl chloride was 1.4%, 2.1%, 41.4 and 66.6%, respectively. Excretion in urine was 68.3%, 59.3%, 22.6 and 10.8%, respectively. $^{14}CO_2$ in expired air accounted for 9.0%, 13.3%, 4.8% and 2.5%, respectively. A proportion of 0.47–2.39% was unabsorbed and excreted unchanged in the faeces. The liver was found to retain the maximum percentage of activity at all dose levels, 3–5 times the percentage found in muscle, lungs or fat (Watanabe and Gehring, 1976).

Alderley Park rats (Wistar-derived strain) exposed to vinyl chloride at 1–450 mg/kg bw pulmonarily excreted unchanged vinyl chloride after 3–4 hours, whereas polar metabolites and labelled carbon dioxide continued to be excreted for 3 days (Green and Hathway, 1977).

When Sprague-Dawley rats were exposed to > 100 ppm (260 mg/m^3) vinyl chloride in air for 5 hours, 69% of the absorbed dose was excreted as metabolites within 24 hours in urine via the kidney (Watanabe et al., 1976b; OEHHA, 2000). An additional 1.7% was found in the urine 24–48 hours later (Bolt et al., 1976). The half-life for urinary excretion in rats was about 4 hours. The blood concentration fell rapidly after removal of vinyl chloride from the air (Withey, 1976).

Intravenous injection of vinyl chloride (250 µg of ^{14}C-labelled vinyl chloride per kg in N-(β-hydroxyethyl) lactamide) was reportedly almost entirely exhaled (99%) after 1 hour by rats (Green and Hathway, 1975).

Deoxyribonucleic acid (DNA) adducts were found in various tissues (testis, kidney, spleen, lung, liver, lymphocytes) after exposing rats to 500 ppm vinyl chloride in air, suggesting the migration of CEO via the bloodstream after liver metabolism (Guichard et al., 1996; Barbin, 1999). No ethenoguanine or 7-(oxoethyl)-guanine adducts were found in brains of rats exposed to 1100 ppm vinyl chloride for 4 weeks (Morinello et al., 2002a). However, in this same study, an increase of adducts in weanling rats was found (Morinello et al., 2002a).

Regardless of route of administration, as the dose of vinyl chloride increases, so does the proportion of the dose (unmetabolized) that is exhaled; however, the proportion of the dose that is excreted in the urine and faeces decreases with increasing dose (Green and Hathway, 1975; Hopkins, 1979).

8.4 PBPK modeling

Several PBPK models have been developed for vinyl chloride. Clewell et al. (1995) developed a PBPK model to refine the vinyl chloride risk calculation for animal to human extrapolations based on pharmacokinetic information. To illustrate the pharmacokinetics of vinyl chloride, four compartments were necessary for the model: liver, fat, and highly and poorly vascularized tissues, with the liver being the site of metabolism and the target tissue in which angiosarcoma of the liver (ASL) arises (Clewell et al., 1995). Further biotransformation of CEO, resulting in carbon dioxide generation, glutathione depletion and binding of reactive metabolic products to macromolecules in the liver, was also included in the model. The risk estimate for vinyl chloride exposure was found to be consistent across species, routes and media of exposure, showing agreement between the results and risk evaluation methods.

Clewell et al. (2001, 2004) further refined their PBPK model to include the glutathione dynamic and age extrapolations, based on CYP2E1 enzyme maturation and body weight–clearance capacity; the refined model also takes into account each life stage with cumulative exposure to 1 µg/kg bw per day over a lifetime. Blood concentrations of the parent compound were found to be the highest very early in life (< 6 months old) and then decrease in early childhood. The plateau reached in adulthood can be explained by rapid maturation of CYP2E1 after 6 months of age and changes in body weight–clearance capacity (Clewell et al., 2004).

Other PBPK models for vinyl chloride include those by Gentry et al. (2003), Chiu and White (2006) and Yoon et al. (2007). The Gentry et al. (2003) model examines differences in blood and tissue dose metrics between a mother and foetus (human) during pregnancy and lactation. This model adds fetal liver, fetal blood and other fetal tissue compartments to the adult model to account for transfers through the placenta and breast milk, as well as differences between adult and fetal enzyme activity. The vinyl chloride concentrations in fetal blood were predicted to be similar to concentrations in the mother's blood during gestation, however, during lactation, blood concentrations in the neonate were predicted to be much lower. Concentrations of vinyl chloride and CEO in the liver were not predicted. Owing to the lack of a developed CYP2E1 enzyme system, Gentry et al. (2003) concluded that fetal exposure to reactive metabolites of vinyl chloride is expected to be negligible. However, there is some evidence that transplacental exposure can result in carcinogenicity in rat studies, and the half-life of CEO may be long enough for this reactive metabolite to cross the placenta after being generated in maternal tissues (Rice, 1981). The Chiu and White (2006) human PBPK model incorporates fewer parameters and assumes that all vinyl chloride metabolism occurs in the liver via first-order kinetics. This model was found to duplicate the Clewell et al. (2001) model for extrapolation between oral and inhalation exposure to vinyl chloride; however, as it assumes first-order kinetics for metabolism, it is appropriate for use only in the dose range in which metabolism is approximately linear. A model by Yoon et al. (2007), validated in Sprague-Dawley rats, considered the effect of extrahepatic CYP2E1 on PBPK modeling results. The results of the modeling indicated that extrahepatic CYP2E1 metabolism did not contribute significantly to the results considering only liver metabolism, indicating that PBPK models only considering liver metabolism are appropriate for the risk assessment of vinyl chloride.

Health Canada (2011) developed a PBPK model based on the one developed by Clewell et al. (2001, 2004) to facilitate animal to human and high dose to low dose extrapolations for vinyl chloride. The model was updated to include a dermal component so that it could be used to estimate the contribution of showering and bathing to vinyl chloride exposure. The model was validated using pharmacokinetic data from animals (Feron et al., 1981; Til et al., 1983) and humans (Buchter et al., 1978) exposed to vinyl chloride. Non-cancer effects (liver toxicity) and tumour progression (DNA adducts, mutations) have been shown to result from CEO generation; therefore, the appropriate dose metric with which to estimate cancer and non-cancer risks corresponds to the quantity of vinyl chloride metabolites produced divided by the liver volume.

Data from both Feron et al. (1981) and Til et al. (1991) were used for PBPK modeling by Health Canada. The external doses from these studies were inputted into the rat PBPK model to determine the cumulative lifetime internal dose of vinyl chloride metabolites generated per litre of liver for several liver tumour endpoints in both male and female rats. During the modeling, vinyl chloride oral uptake was designated as zero-order (independent of concentration) and spread out over a 24-hr period; this ensured that saturation of the metabolic pathways was avoided, thus generating a maximum value of the dose metric which is conservative with respect

to what may actually occur during an oral dose. This approach, coupled with the use of the same liver metabolic processes for both inhalation and oral inputs, increases the confidence in dose metrics derived from oral inputs. It also addresses concerns of reduced confidence in dose metrics derived from oral studies compared to those derived from inhalation studies (as indicated experimental data). Using the multistage cancer model from the U.S. EPA's benchmark dose (BMD) software, BMDS (U.S. EPA, 2010), the internal concentrations of vinyl chloride metabolites associated with an excess lifetime cancer risk of 10^{-4}, 10^{-5} and 10^{-6} in male and female rats were estimated for several cancer endpoints in order to determine the most appropriate point of departure (POD) for use in the human PBPK model. The cumulative lifetime internal dose of vinyl chloride metabolites associated with combined liver tumours (neoplastic nodules, hepatocellular carcinoma [HCC] and ASL) was determined as the most appropriate POD to use in the human PBPK model to estimate the external human doses associated with each risk level for a lifetime (70 years) exposure. The external human doses generated by the model represent the levels in drinking water that would be associated with an excess lifetime cancer risk in humans of 10^{-4}, 10^{-5} and 10^{-6}, when daily exposure to drinking water occurs through ingestion (1.5 L-eq/day) as well as through inhalation (0.4 L-eq/day) and dermal (1.9 L-eq/day) exposures from a 30-minute bathing scenario.

The estimated L-eq contribution from dermal exposure likely represents an over estimate since the PBPK model accounts for exposure to both the liquid and gas phases of vinyl chloride during a bathing event. Based on the physical/chemical properties of vinyl chloride and human physiological characteristics, the PBPK model estimated an inhalation absorption of 33%; a dermal absorption of 94% was estimated for the liquid phase (that is water containing solubilised vinyl chloride) which represents the majority of the L-eqs for the dermal route and the gas phase was determined as contributing a negligible amount of L-eqs given its very low absorption by the skin. This is a conservative approach used in the absence of published data on the proportion of solubilised vinyl chloride that could be present during showering or bathing; Health Canada determined that this conservative approach is appropriate to estimate the L-eq contribution from dermal exposure.

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute effects

Vinyl chloride is a narcotic agent, and loss of consciousness can occur from exposure to high concentrations (25 000 mg/m^3). Acute exposure to high concentrations in air also causes central nervous system depression, with symptoms of dizziness, light-headedness, nausea, headache, irritability, poor memory, tingling sensations, weight loss, irritation of the respiratory tract and chronic bronchitis (IARC, 2008). Autopsies of several vinyl chloride workers who died following exposure to high levels revealed congestion of the liver, spleen and kidney (Cook et al., 1971).

9.1.2 Chronic effects and cancer epidemiology

The association of vinyl chloride with the risk of death from liver angiosarcoma (ASL; cancer of the liver blood vessels) reached public attention after the discovery of three cases in a vinyl chloride plant (Creech and Johnson, 1974). Tumours of the respiratory tract, digestive system, cardiovascular system and other sites from vinyl chloride exposure have been reported in

a few controversial studies; however, the risk of ASL has been demonstrated by many investigators to increase with the exposure length and intensity, the latency period, the year of employment (before 1970) and age at first exposure (Simonato et al., 1991; Mundt et al., 2000; Wong et al., 2002; Bosetti et al., 2003; Lewis et al., 2003). Other cancers, such as brain and lung cancer, lymphoma and HCC, have been sparsely observed (Monson et al., 1975; Waxweiler et al., 1976; Pirastu et al., 1990; Simonato et al., 1991; Wong et al., 1991) and their causal relationship with vinyl chloride remains controversial.

In the 1970s, the International Agency for Research on Cancer (IARC) coordinated a European multicentre study within Italy, Norway, Sweden and the United Kingdom with 14 351 individuals from 19 factories to investigate the relationship between exposure to vinyl chloride and liver cancer as well as cancer risks for sites other than the liver. IARC (1979) concluded that vinyl chloride could be associated with HCC, brain tumours, lung tumours and malignancies of lymphatic and haematopoietic tissues. The data, analysed by Simonato et al. (1991), revealed a nearly 3-fold increase in liver cancer deaths: 24 observed compared with 8.4 expected (standardized mortality ratio [SMR] = 286; 95% confidence interval [CI] = 186–425). The excess deaths from liver cancer were clearly associated with the elapsed time since the first exposure, duration of employment and quantitative exposure scenarios based on job titles (ranked level: ≤ 50, 50–499, ≥ 500 ppm; and cumulative estimates: 0–1999, 2000–5999, 6000–9999, ≥ 10 000 ppm-years). No statistically significant excess mortality was reported for the cancers at sites other than the liver due to exposure to vinyl chloride. A further analysis by Ward et al. (2001) followed up on an additional 8 years of mortality and cancer incidence and reported that mortality from all causes was lower than expected, whereas cancer mortality was close to expected. A total of 53 deaths from primary liver cancer (SMR = 2.40; 95% CI = 1.80-3.14) and 18 cases of liver cancer were reported which included 37 angiosarcomas (ASL), 10 HCCs, and 24 other liver cancers; a clear exposure response relationship was reported for all liver cancers, ASL, and HCC. Bosetti et al. (2003) confirmed the relationship between liver cancer and vinyl chloride exposure, however, showed that the increasing trend for HCC was appreciably less pronounced than for ASL, and that the relative risk for HCC was statistically significant only in the highest category of cumulative exposure. Again, no association was found with other cancer types.

The North American multicentre cohort of vinyl chloride workers has been followed by various investigators, with a focus on the plants in Calvert City and Louisville, Kentucky (Creech and Johnson, 1974; Monson et al., 1975; Waxweiler et al., 1976; Lewis and Rempala, 2003; Lewis et al., 2003). Monson et al. (1975) were the first to find increased deaths from all cancers, particularly of the liver, biliary tract (SMR = 11.0) and brain (SMR = 4.2), but also of the lung (SMR = 1.6) and lymphatic tissue (SMR = 1.5). In a follow-up based on cumulative estimates ranking workers within exposure groups ≤ 100, 100–400, 400–1000 and ≥ 1000 ppm multiplied by the number of months worked, Lewis and Rempala (2003) confirmed the high occurrence of liver and brain cancer among workers from the Louisville plant. Deaths from total liver cancer and ASL were strongly related to vinyl chloride exposure intensity ($P < 0.001$). Wong et al. (1991) analysed data, including from the Louisville plant, for 10 173 men exposed to vinyl chloride for at least 1 year before 1973 at 37 plants in the United States. This represents the largest group of vinyl chloride workers in North America. The study confirmed that workers exposed to vinyl chloride experienced a significant excess mortality due to ASL (15 deaths), cancer of the liver (unspecified type) and biliary tract (SMR = 641) and cancer of the brain and central nervous system (23 deaths compared with 12.8 expected; SMR = 180). However, half of

the cases of brain cancer came from two plants that were manufacturing only PVC. Only the deaths from liver cancer showed increased occurrence by length of exposure and by latency period since first exposure and decreasing trends by age at first exposure. The study did not find any excess in respiratory cancer or lymphatic and haematopoietic cancers. Lewis et al. (2003) separated the Louisville cases from the large U.S. vinyl chloride workers cohort and found that liver cancer mortality remained high compared to the total U.S. cohort (SMR = 400 and 359, respectively), but brain cancer deaths increased dramatically (SMR = 229 and 142, respectively). Another follow-up to December 31, 1995, by Mundt et al. (2000) added the number of deaths after a latency period of 20–50 years. Again, the cancer risk was higher for workers employed earlier (SMR = 499 before 1950) and longer (SMR = 434 for 30 years or more). Liver and biliary tract cancer deaths were still in excess, although slightly decreased since the 1980s; brain cancer deaths were no longer different from the controls.

Data from nine United Kingdom vinyl chloride plants involving 7717 workers employed between 1940 and 1974 found only two cases of ASL (Fox and Collier, 1977). A follow-up including 5498 workers from this study added 10 years of latency and discerned exposure categories based on job titles and length of employment (Jones et al., 1988). A significant increase of deaths from liver cancer (SMR = 567) was reported among autoclave workers with the highest vinyl chloride exposure; out of 11 observed deaths, 2 were expected, and 7 of the 11 deaths were largely attributable to ASL (SMR = 1842).

Pirastu et al. (1990) conducted a mortality study on 5946 vinyl chloride and PVC workers from nine Italian plants. Analysis of the data from 253 deaths (death certificates, clinical and pathological information) confirmed the carcinogenic action of vinyl chloride, with 14 liver cancers, but no other cancers were reported in any of the other suggested target organs (i.e., lung, lymphopoietic tissues, brain). The cancers were observed in various job titles that exposed workers to different concentrations; however, these levels were not specified by the authors. Of the 14 liver cancers, seven were ASL and two were HCC. Later, Pirastu et al. (2003) updated the mortality and occupational history for an Italian plant in Porto Marghera until 1999. Cumulative exposures were determined on the basis of job- and time-specific exposure estimates, and classified into six exposure categories (0–735, 735–2379, 2379–5188, 5188–7531 and 7531–9400 ppm–years) with employment as an autoclave worker (ever/never) also considered in the analyses. Clinical and pathological data which gave the best diagnosis were used to identify cases of liver angiosarcoma and hepatocellular carcinoma. With regional rates as a reference, mortality in the cohort for all causes (SMR, 0.75; 90% CI, 0.68–0.83) and all cancers (SMR, 0.94; 90% CI, 0.81–1.09) was lower than expected. For all causes, the analysis by time since leaving employment and adjusted for latency showed that the SMR in the first year after leaving employment was 2.76 (90% CI, 1.94–3.91). Mortality rates for liver angiosarcoma (six cases) increased with latency and cumulative exposure, however, no cases were associated with duration of employment of less than 12 years, latency of less than 10 years or cumulative exposure of less than 2379 ppm–years. Mortality rates for hepatocellular carcinoma (12 cases) and liver cirrhosis (20 cases) showed a similar pattern. For this cohort, Mastrangelo et al. (2003, 2008) confirmed that an increase in deaths from liver cancer was associated with vinyl chloride inhalation exposure.

Boffetta et al. (2003) analysed the data from six studies of the U.S. and European cohorts. They found a low incremental average SMR from the studies for liver cancer other than ASL (SMR = 1.35; 95% CI = 1.04–1.77). Of the six studies, only four were still positive for liver cancer when ASL was excluded. Moreover, no association between brain cancer or lymphatic

and haematopoietic neoplasms and vinyl chloride exposure was found, contrary to the findings of Theriault and Allard (1981) and Wong et al. (1991).

Laplanche et al. (1992) analysed data from a French prospective cohort study by the French National Institute of Health and Medical Research (INSERM) representing 1100 exposed and 1100 unexposed subjects. Diseases of the respiratory system did not differ between the two groups (relative risk [RR] = 1.1; 95% CI = 0.7–1.8); however, 3 cases of ASL and 14 cases of Raynaud's disease were found among the exposed group, and 1 case of Raynaud's disease was noted among non-exposed subjects.

Data from male workers employed for at least 1 year during the period 1950–1992 in Taiwan were analysed by Wong et al. (2002). Being employed when younger than 30 years of age increased the risk of death (SMR = 2.24). Those employed before 1970 were 5 times more likely to develop liver cancer (unspecified type) than the general population. No increased risk was found for longer employment duration or for development of brain tumours. The study confirmed an increased mortality from cancer (SMR = 1.30), with the liver as the main target organ (SMR = 1.78).

Based on five registry sources from the United Kingdom, including the national cancer registry and death certificates, no non-occupational cases of ASL among residents within 10 km of a vinyl chloride industrial site were found (Elliott and Kleinschmidt, 1997). Of the 52 cases of ASL registered during 1979–1986, only 11 were within 10 km of a vinyl chloride industrial site. From those 11 cases, 10 had been employed in a vinyl chloride plant, whereas the remaining case was thought to be a misclassified ASL diagnosis.

Infante et al. (2009) reported two cases of ASL in hairdressers and barbers who used hairsprays containing vinyl chloride as a propellant over a period of 4 to 5 years between 1966 and 1973. The peak exposure for Case 1 (hairdresser) was estimated to range from 129 to 1234 ppm, with a 8-hour time weighted- average (TWA) vinyl chloride exposure estimated to have ranged from 70 to 1037 ppm (median TWA estimated at 228 ppm); estimates for Case 1 were dependant on the products used (% vinyl chloride varied based on product used), the length of time of spraying the product, and the number of estimated air exchanges per hour. For Case 2 (barber), atmospheric levels of vinyl chloride from a 22 second spray in a room with 4 air exchanges were estimated to range from 129 ppm at the outset to approximately 40 ppm after 40 minutes had elapsed, with an average exposure of 70 ppm over the 40 minute period. The authors concluded that to their knowledge this represents the first literature reports of ASL cases identified among hairdressers and barbers who used hair sprays containing vinyl chloride as a propellant.

9.1.3 Non-cancer endpoint epidemiology

The liver remains the primary target organ of vinyl chloride for non-cancer endpoints (U.S. EPA, 2000b). Occupational exposure to high levels of vinyl chloride (2400 ppm-month) is an independent risk factor for the development of liver fibrosis (cirrhosis) (Hsiaos et al., 2004). Impaired liver functions with evidence of porphyria, liver enlargement, hepatocyte hypertrophy and fibrosis were observed by many authors in workers exposed to vinyl chloride for a variable, but considerable, amount of time (Gedigk et al., 1975; Lilis et al., 1975; Popper and Thomas, 1975; Berk et al., 1976; Doss et al., 1984).

Vinyl chloride tank cleaners were exposed to vinyl chloride at concentrations of hundreds of parts per million, producing a wide range of effects, including Raynaud-like syndrome, acroosteolysis (bone resorption in the fingers and toes), thrombocytopenia, scleroderma-like

dermatitis, thyroid insufficiency, damage to the liver (steatohepatitis), spleen and lungs, as well as functional disturbances of the central nervous system (Cook et al., 1971; Lilis et al., 1975; ECETOC, 1988; U.S. EPA, 2000b). An effect of vinyl chloride on coronary heart disease was not found, but a direct relationship between vinyl chloride exposure and development of arterial hypertension was observed (Kotseva, 1996). Ho et al. (1991) revealed an increase of glutamic pyruvic transaminase concentrations before and after the occurrence of liver dysfunction in workers exposed to vinyl chloride levels ranging from 1 to 21 ppm.

9.1.4 Mutagenicity/genotoxicity

Accidental and occupational exposures to vinyl chloride and its metabolites have been associated with chromosomal aberrations and gene mutations in humans. A single acute exposure to vinyl chloride in air after an environmental accident in Germany led to slight increases in chromatid breaks, acentric fragments, dicentrics and translocations in peripheral blood lymphocytes in 27 exposed individuals compared with those unexposed (Hüttner and Nikolova, 1998). However, the exposure did not produce any significant chromosomal abnormalities in the HPRT locus of lymphocytes, measured immediately or 2 years later, compared with 29 non-exposed individuals (Becker et al., 2001).

Mutations of both pro-carcinogenic genes p53 (A:T mis-sense mutations) and ras, leading to the expression of altered p53 and $p21^{ras}$ proteins (Trivers et al., 1995), were detected in tumour samples from workers who developed ASL and HCC after being occupationally exposed to vinyl chloride in the United States, France and Taiwan (Marion et al., 1991; De Vivo et al., 1994; Weihrauch et al., 2000, 2001, 2002). A dose–response relationship was observed between vinyl chloride exposure and the mutation of p53 and ras (Smith et al., 1998). Further, chronic occupational exposure to 1.3–16 ppm vinyl chloride resulted in sister chromatid exchange and chromosomal aberrations such as DNA breaks in a group of 52 workers (Sinués et al., 1991) and in another group of 57 workers exposed to an average of 2 ppm vinyl chloride with occasional excursions of up to 1000 ppm (Purchase et al., 1985).

Gene polymorphism has reportedly affected vinyl chloride workers in Taiwan and China. An increase in sister chromatid exchanges and micronuclei was observed in exposed workers and in individuals expressing specific alleles. For example, the homozygous individuals bearing the c2c2 allele of the CYP2E1 gene ($P < 0.05$) or the variant allele Arg399Gln of the DNA repair gene XRCC1 ($P < 0.05$) had more micronuclei (Wong et al., 2003; Ji et al., 2010). The variant allele c2c2 of CYP2E1 reportedly metabolizes vinyl chloride at a higher rate, thus generating more CEO per time unit (Wong et al., 2003). A significant increase in liver fibrosis incidence was reported among CYP2E1 c2c2 allele carriers in a group of 320 vinyl chloride workers employed in five different vinyl chloride factories in Taiwan (Hsieh et al., 2007). Fucic et al. (1996) demonstrated that the chromosomal damage was reversible after occupational exposure levels dropped below 1 ppm in vinyl chloride plants. However, sister chromatid exchanges were persistent and detected up to 10 years after the last occupational exposure to levels higher than 1 ppm (Fucic et al., 1996).

Chiang et al. (1997) reported that 16 µM of CEO or CAA for 24 hours induced similar mutation frequencies of the HPRT locus in human B-lymphocytes, but that CAA was more cytotoxic (cell proliferation assay). When plotted as a function of relative survival, CEO induced mutations at a rate similar to that of vinyl chloride, but 6 times higher than that of CAA. The authors concluded that CEO is responsible for larger deletions and for most of the mutations induced by vinyl chloride exposure (Chiang et al., 1997).

9.1.5 Reproductive and developmental toxicity

No adverse reproductive effects were reported in workers exposed to vinyl chloride (Hemminki et al., 1984), although an increase in total birth malformations in populations employed in the vinyl chloride industry has been suggested by a few investigators (Infante et al., 1976; Theriault et al., 1983). An association between parental occupational exposure to vinyl chloride and fetal loss has also been suggested (RR = 1.8) (Infante et al., 1976; Waxweiler et al., 1976), but exposures were not measured.

Theriault et al. (1983) investigated the incidence of birth defects in infants born between 1966 and 1979 to residents of Shawinigan, Quebec, a town where a vinyl chloride polymerization plant had been in operation since 1943. The incidence of birth defects (observed 159 vs. expected 107) was significantly higher in Shawinigan than in any or all of the matched control towns with no potential exposure to vinyl chloride. The incidence rate peaked in March and was lowest in September, which corresponded to variation in atmospheric levels of vinyl chloride at the time of the first 3 months of pregnancy (vinyl chloride monomer was not detected in air samples taken between December and February). No such variations were observed in the control communities. However, there was no excess of stillbirths in Shawinigan. As several other industries emitted pollutants into the atmosphere in Shawinigan, these observations remain inconclusive.

9.1.6 Children's sensitivity

Evidence from animal studies suggests that very young children may be particularly sensitive to the carcinogenic effects of vinyl chloride (see Section 9.2.6). The rate of cell division in the brain, liver and kidney is much higher in the first 2 years of life than in later childhood, making the liver more sensitive to DNA adduction and hepatocarcinogenesis from vinyl chloride exposure during this time (Ginsberg, 2003). A second growth peak for the liver may occur around the age of 6, indicating that children this age may also be sensitive to vinyl chloride (Ginsberg, 2003).

9.2 Effects in experimental animals and *in vitro*

9.2.1 Acute effects

Prodan et al. (1975) reported that inhalation exposure to high concentrations of vinyl chloride for two hours has a narcotic effect described by phases of excitement, tranquillity and then death. The most sensitive experimental animals were mice, with 70% mortality at 107 mg/L, followed by rats, with 23% mortality at 375 mg/L, guinea pigs, with 75% mortality at 600 mg/L, and rabbits, with 50% mortality at 600 mg/L, corresponding to median lethal doses (LD_{50}s) of 27 419, 47 640, 236 215 and 263 215 ppm for the four species, respectively.

9.2.2 Subchronic exposure

Administration of vinyl chloride monomer dissolved in soybean oil by gavage to groups of Wistar rats (30 per group) at doses of 0, 30, 100 or 300 mg/kg bw per day, 6 days/week, for 13 weeks did not result in adverse effects at the 30 mg/kg bw per day level. A dose-related increase in relative liver weight was observed at the two highest dose levels; however, the increase was statistically significant only at 300 mg/kg bw per day (Feron et al., 1975).

Inhalation exposure of guinea pigs, rats, rabbits and dogs to 50 ppm (130 mg/m^3), 100 ppm (260 mg/m^3), 200 ppm (540 mg/m^3) or 500 ppm (1300 mg/m^3vinyl chloride for 7

hours/day, 5 days/week, for 26 weeks did not induce any adverse effects at 50 ppm, in terms of appearance, growth, haematology, liver weight and mortality; however, rats exposed to 100 ppm had increased liver weights, one of the more sensitive indicators of hepatotoxicity (Torkelson et al., 1961). Exposure to 200 ppm resulted in increased relative liver weight in male and female rats, but there was no biochemical or microscopic evidence of liver damage; rabbits exhibited histological changes (characterized as granular degeneration and necrosis with some vacuolization and cellular infiltration) in the centrilobular area of the liver. No effects were observed in guinea pigs or dogs exposed to 200 ppm. Histopathological lesions of the liver (centrilobular granular degeneration) and increased organ weight occurred in rats exposed to 500 ppm.

9.2.3 Long-term exposure and carcinogenicity

Vinyl chloride administered by inhalation or ingestion induces neoplasms at multiple sites in several species of animals. In the rat, mouse and hamster, it has induced hepatic haemangiosarcomas (equivalent to ASL in humans), Zymbal gland tumours, nephroblastomas, pulmonary and mammary gland tumours and forestomach papillomas.

The minimum dose at which compound-related tumours were induced by inhalation (4 hours/day, 5 days/week) was 10 ppm (26 mg/m^3) for 52 weeks for rats, 50 ppm (130 mg/m^3) for 30 weeks for mice and 500 ppm (1300 mg/m^3) for 30 weeks for hamsters (Maltoni et al., 1981). When vinyl chloride in PVC powder was administered orally to rats, the minimum effective dose of vinyl chloride (causing liver tumours) was 1.7 mg/kg bw per day (Til et al., 1991).

The first experimental data on the carcinogenic effects of vinyl chloride in rats were published by Viola et al. (1971). Male Wistar rats exposed by inhalation to very high doses (30 000 ppm) for 4 hours daily, 5 days/week, for 12 months, developed skin, lung and osteochondroma tumours. Moreover, general central nervous system degeneration, specifically degeneration of granular cells, Purkinje cells and the cerebellum was observed in 3-month-old rats.

The most comprehensive carcinogenesis bioassays relevant to the assessment of risk associated with the ingestion of vinyl chloride are those of Maltoni et al. (1981), Feron et al. (1981) and Til et al. (1983, 1991). Groups of 40 male and 40 female (80 per group) 13-week-old Sprague-Dawley rats received gastric intubations of 0, 3.33, 16.65 or 50 mg/kg bw per day of vinyl chloride dissolved in olive oil, 4–5 times per week for 52 weeks, followed by an extended observation period (Maltoni et al., 1981). At 136 weeks, no hepatic angiosarcomas were observed in low-dose and control rats. No dose–response relationship was observed in the induction of other tumours in these animals. Two nephroblastomas (one in each sex), one Zymbal gland tumour, one thymic angiosarcoma and one intraabdominal angiosarcoma were observed in the 50 mg/kg bw per day group; two Zymbal gland carcinomas (one in each sex) and three nephroblastomas (two in males and one in females) were observed in rats administered 16.65 mg/kg bw per day. Seventeen incidences of ASL (eight in males and nine in females) were found in the 50 mg/kg bw per day group; 10 ASLs (four in males and six in females) occurred in rats administered the 16.65 mg/kg bw per day dose (Maltoni et al., 1981).

In another experiment by Maltoni et al. (1981), vinyl chloride doses of 0.003, 0.3 or 1.0 mg/kg bw per day were administered by stomach tube to 10-week-old rats (75 of each sex per group), 5 days/week for 59 weeks. At 136 weeks, no exposure-related liver or kidney tumours were observed in low-dose or control animals. ASL was found in 1/74 males and 2/75 females administered 1.0 mg/kg bw per day and in 1/73 females administered 0.3 mg/kg bw per

day, however, these increased incidences were not statistically significant. When Sprague-Dawley rats were exposed to high inhalation concentrations (above 10 000 ppm) for 4 hours daily, 5 days/week, for 52 weeks, ASL, Zymbal gland carcinoma, forestomach tumours and neuroblastomas increased significantly. Mammary gland tumours developed at 5 ppm and above in female rats, whereas nephroblastomas occurred in males at 100–2500 ppm. (Maltoni et al., 1981).

In a rat lifespan carcinogenicity study (Feron et al., 1981), Wistar rats were exposed to a mixture of vinyl chloride monomer and PVC powder via the diet. Groups of 60–80 rats of each sex were fed vinyl chloride at doses of 0, 1.7, 5.0 or 14.1 mg/kg bw per day; as a positive control, vinyl chloride dissolved in soybean oil (300 mg/kg bw) was also administered by gavage, 5 days/week. The experiment was terminated once 75% mortality was observed in the control group (135 weeks for males and 144 weeks for females). Hepatic and lung angiosarcomas were observed in males (27/55, 27/59, 6/56) and females (2/59, 9/57, 29/54) in the three highest dose groups (5.0, 14.1, 300 mg/kg bw per day), respectively, but not in the low-dose group or controls. Males at the 5.0 and 14.1 mg/kg bw per day doses developed 3 times more angiosarcomas than females. HCC and an increased incidence of foci of cellular alteration were observed at the lowest level (1.7 mg/kg bw per day). Also, centrilobular degeneration, necrosis and mitochondrial damage were noted in hepatic parenchyma.

Til et al. (1983) did a follow-up study, under the same conditions, except at lower doses and with 1% PVC instead of the 10% used by Feron et al. (1981); the results are described in Til et al. (1991). Oral vinyl chloride doses of 0.017, 0.17 and 1.7 mg/kg bw per day (corresponding to 0.014, 0.13 and 1.3 mg/kg bw per day when only absorbed vinyl chloride is considered) were administered to groups of 100 males and 100 females for 149 weeks except for the high-dose group, which consisted of 50 males and 50 females. An increased incidence of liver nodules was the only neoplastic response in rats administered 0.17 mg/kg bw per day, but both HCC (three per sex) and ASL (1/49 males, 2/49 females) were observed at the highest dose (1.7 mg/kg bw per day), with only the incidence of HCC in males being significantly different from that of the controls (Til et al., 1983, 1991). No ASL was observed at the 1.7 mg/kg bw per day level in the original study (Feron et al., 1981). Non-neoplastic results in the liver, such as increased cellular alteration, polymorphism and cyst formation, were observed in the highest exposure group for males (1.7 mg/kg bw per day). However, basophilic foci were observed in the lowest exposure groups (0.017 and 0.17 mg/kg bw per day) for females (Til et al., 1983, 1991); these are not considered as a precursor of hepatocellular tumour formation, as they arise at a different location (U.S. EPA, 2000b). The no-observed-adverse-effect level (NOAEL) for tumour induction in rats was estimated by the authors to be 0.13 mg/kg bw per day (Til et al., 1983, 1991).

The only carcinogenic bioassay in which vinyl chloride was administered to rats in drinking water is the unpublished work of Evans et al. (ECETOC, 1988). Groups of male and female (150 per group) Wistar rats received vinyl chloride in drinking water at concentrations of 0, 2.5, 25 or 250 mg/L (equivalent to daily intakes of approximately 0, 0.12, 1.2 or 12 mg/kg bw per day for males and 0, 0.22, 2.2 or 22 mg/kg bw per day for females) for up to 152 weeks, except for males and females of the highest dose group, which received the dose for 115 and 101 weeks, respectively. In rats receiving the highest dose, there was a significantly higher incidence of ASL (8/50 males, 8/49 females) and hepatomas (HCC) (3/50 males, 3/49 females). Only 1 of the 47 males developed hepatic angiosarcomas in the 25 mg/L dose group. There was no dose–response relationship in the development of kidney and brain tumours in these animals.

In a reproductive and developmental toxicity study on Sprague-Dawley rats (Thornton et al., 2002), an increase in liver weight was observed at 10, 100 and 1100 ppm in all F_0 rats and at 100 and 1100 ppm in F_1 male rats exposed by inhalation under the conditions described in Section 9.2.5. In maternal rats exposed to 100 ppm, the kidney relative to body weight ratio was statistically significantly increased, while in the 1100 ppm exposed group, the organ relative to body weight ratios for both kidney and liver were statistically significantly increased.

Female CD-1 and B6C3F1 mice, Fischer-344 rats and Golden Syrian hamsters were exposed to fixed concentrations of vinyl chloride (50, 100 and 200 ppm, respectively) for 6 hours daily, 5 days/week, for 6, 12, 18 and 24 months (Drew et al., 1983). When exposed after 8 months of age, all animals showed a decrease in their length of survival. Every species developed at least three types of cancer, including ASL, mammary gland adenocarcinomas, HCC, lung carcinomas and stomach adenomas. Vinyl chloride induced ASL in all three species (Maltoni et al., 1984).

Different authors have reported different cancer type incidences among mammalian species. Drew et al. (1983) found a 4- to 5-fold higher incidence of cancer than did Maltoni et al. (1981). Nevertheless, this could be explained by younger age of exposure and longer exposure period in the study by Drew et al. (1983). Accordingly, Bi et al. (1985) and Lee et al. (1978) found an increased occurrence of lung sarcoma in Wistar rats exposed to 100 and 3000 ppm vinyl chloride in air (6 hours daily, 6 days/week, for 18 months), although at a lower incidence than ASL; lung sarcoma was not found in mice, however, mammary gland carcinoma, adenocarcinoma or carcinoma has been reported in mice but not in rats (Lee et al., 1978; Drew et al., 1983).Animals exposed at a young age developed more cancers (Lee et al., 1978; Drew et al., 1983; Maltoni et al., 1984; Bi et al., 1985). Swiss mice appear to be more sensitive than B6C3F1 mice, as they reportedly develop lung carcinomas after 6 months of exposure, suggesting an interspecies variability. Both strains developed ASL and mammary gland carcinomas (Maltoni et al., 1984). In hamsters, the highest incidence of cancer was reported for those exposed for their first 12 months of age compared with those exposed after 12 months of age (Drew et al., 1983). Rats exposed after 12 months of age failed to develop vinyl chloride–related neoplasms, whereas a shorter latency of 6 months resulted in a significant increase in mammary gland adenocarcinomas, HCC and ASL. Rats were the only species that developed Zymbal gland carcinomas, nephroblastomas or neuroblastomas, and HCC; however, the HCC response did not seem to correlate with the dose. Hamsters did not develop mammary carcinomas, lung adenomas or hepatomas (Maltoni et al., 1984; Whysner et al., 1996); however, they were the only species to develop acoustic duct epithelial tumours (Maltoni et al., 1984). Apart from the latter result, mice and hamsters are not known to develop any additional tumours not reported in rats (Maltoni et al., 1984). Increasing the exposure for more than a year in rats or 6 months in mice and hamsters generally did not significantly increase the development of cancer if the exposure began early in life (Drew et al., 1983).

9.2.4 Mutagenicity/genotoxicity

DNA etheno adducts, naturally occurring in bacteria and animals, can be formed and detected in mammals (mouse, rat, monkey, human, hamster) *in vivo* and in bacteria and yeast *in vitro* if vinyl chloride is pre-incubated with a mammalian microsomal system (Bartsch et al., 1975; Laib and Bolt, 1977; Swenberg et al., 1992, 2000; Dogliotti, 2006).

9.2.4.1 In vitro

The Ames test indicated that vinyl chloride and its metabolites are mutagenic (Rannug et al., 1974; Bartsch et al., 1975). Mutations increase with dose and with increasing time of exposure (Malaveille et al., 1975; Bartsch et al., 1976, 1979; IARC, 1979; ECETOC, 1988). The addition of liver human and rat S9 activation system fractions (Rannug et al., 1974; Bartsch et al., 1975; Bartsch et al., 1975; Malaveille et al., 1975; Sabadie et al., 1980), either pre-incubated or not with P450 inducers (phenobarbital, 3-methylcholanthrene or Aroclor 1254), and a reduced nicotinamide adenine dinucleotide phosphate (NADPH) generating system stimulated the mutagenicity of vinyl chloride in *Salmonella typhimurium* strains TA1530, TA1535 and G-46 (Malaveille et al., 1975; Loprieno et al., 1976.

Rat hepatic microsomes co-exposed to CEO directly or generated after incubation with vinyl chloride and polyadenosine or polycytidylic acid (artificial cytidine) reportedly form ribonucleic acid (RNA) adducts (Laib and Bolt, 1977, 1978; Guengerich and Watanabe, 1979). CEO and CAA produce adducts that induce transversions (A↔T) but mainly transitions (GC→AT) in *S. typhimurium* and in key mammalian genes, such as p53 and k-ras (Matsuda et al., 1995; Barbin, 2000; Gros et al., 2003). CEO alone was found to be much more potent than CAA in inducing reverse mutations in *S. typhimurium* (Malaveille et al., 1975; Loprieno et al., 1976; Bartsch et al., 1979) and in *Escherichia coli* strains A3, A11, A23, A58, A88, A446 and A46 (Barbin et al., 1985; Perrard, 1985) at concentrations as low as 0.1 mM for 1 hour. The addition of epoxide hydrolase and glutathione *S*-transferase *in vitro*, which eliminates CEO, has been shown to inhibit the binding of CAA and CEO to DNA (Guengerich et al., 1979; Guengerich and Shimada, 1991).

Mutations in the yeast *Saccharomyces pombe* increased with time of exposure (5–60 minutes) to vinyl chloride at 16–48 mM concentrations only in the presence of an exogenous activation system from mouse liver microsomes (Loprieno et al., 1976).

9.2.4.2 In vivo

RNA adducts with adenosine (Laib and Bolt, 1977; Guengerich et al., 1979) and cytidine (Laib and Bolt, 1978) were found in rats exposed by inhalation to vinyl chloride at 50 ppm for 5 hours. The RNA products were reported to decrease with time after exposure (Bolt et al., 1980). The more common adduct, albeit not mutagenic, is 7-(2-oxoethyl)-guanosine, with 98% occurrence (Bolt et al., 1986) in rats exposed to vinyl chloride (Swenberg et al., 1992). It is followed in lower proportion by the persistent miscoding inducers N^2,3-ethenoguanosine and 3,N^4-ethenocytosine, both representing ~1% each, and 1,N^6-ethenoadenosine, which rarely occurs at less than 1% (Fedtke et al., 1990; Basu et al., 1993). When 10-day-old neonatal rats and their mothers were exposed for 4 days to 600 ppm vinyl chloride, high 7-(2-oxoethyl)-guanosine and N^2,3-ethenoguanosine levels were revealed by GC and high-performance liquid chromatography, respectively (Fedtke et al., 1990). The N^2,3-ethenoguanosine accumulation in liver of rats was linear between 10 and 1100 ppm (Morinello et al., 2002a) and increased with exposure time from 2 to 8 weeks when rats were exposed to 500 ppm (Guichard et al., 1996). No difference was noted between the amount of N^2,3-ethenoguanosine in hepatocytes and non-parenchymal cells in the liver, but weanling rats had 2–3 times the amount of adducts compared with adults in the same conditions (Morinello et al., 2002a). Moreover, 3,N^4-ethenocytosine and 1,N^6-ethenoadenosine were found in livers of rats exposed for 2 years to 250 mg/L vinyl chloride in their drinking water, but no data were given in relation to non-exposed rats (Green and Hathway, 1978).

In rats, the AT→TA mutation was found at codon 61 of the ha-ras gene after exposure by inhalation to 500 ppm of vinyl chloride for 8 hours/day for 33 days, leading to liver tumours (Marion and Boivin-Angele, 1999; Boivin-Angele et al., 2000), and not at codon 13, as found in humans with ASL. Indeed, ha-ras and ki-ras are involved in rat hepatocyte and human sinusoidal cell growth activation, respectively. Moreover, none of the codons 12, 13 or 61 that are associated with human vinyl chloride carcinogenicity were mutated in rat ASL (Marion and Boivin-Angele, 1999; Barbin, 2000; Boivin-Angele et al., 2000). AT base pair transversion caused by 1,N^6-ethenoadenosine in the p53 gene was associated with rat and human ASL after exposure to vinyl chloride (Boivin-Angele et al., 2000), revealing consistency between species. No difference was observed between the amount of 3,N^4-ethenocytosine in rats exposed for 4 weeks and allowed to recover for 1 week compared with the ones killed immediately (Morinello et al., 2002a). Alderley Park rats exposed by inhalation to 1500 ppm vinyl chloride for 6 hours daily for 5 days had a bone marrow cell chromatid gap frequency similar to that of rats exposed to the same regime for 3 months (Anderson and Richardson, 1981). However, only two rats per dose group were used.

Drosophila exposed by inhalation to vinyl chloride at 30–10 000 ppm for 3–17 days had increased mature sperm recessive lethal mutations, but no chromosomal aberrations were observed (Verburgt and Vogel, 1977). However, no dominant lethal effects were observed up to gestational days 12–14 after exposure of male CD-1 mice to vinyl chloride at 10 000 ppm for 4 hours daily for 5 days or at 5000 ppm for 4 hours daily, 5 days/week, for 10 weeks (Himeno et al., 1983). Female NMR mice and female Chinese hamsters exposed by inhalation to vinyl chloride at 500 ppm for 5 days and at 12 500 ppm for 6 hours, respectively, had increased single strand breaks (Basler and Rohrborn, 1980; Walles and Holmberg, 1984).

9.2.5 Reproductive and developmental toxicity

No significant embryotoxic, fetotoxic or teratogenic effects were observed in groups of pregnant CF-1 mice, Sprague-Dawley rats or New Zealand White rabbits exposed 7 hours/day via inhalation to vinyl chloride at doses of 50 or 500 ppm on days 6–15 of gestation (mice) or at doses of 500 or 2500 ppm on days 6–15 (rats) or days 6–18 (rabbits) of gestation (John et al., 1981). Maternal toxicity, such as higher death rate, decreased feed consumption and increased liver weight, was observed in mice and rats exposed to 500 ppm and 2500 ppm, respectively. Fetal effects consisted of delayed skeletal development in mice and an increase in the incidence of ureter dilation in rats after exposure to a maternally toxic dose (John et al., 1981).

The dose–response changes in the reproductive system of rats exposed to vinyl chloride were evaluated by Bi et al. (1985). Wistar rats were exposed chronically for 6 hours daily, 6 days/week, for 3, 6, 12 or 18 months to air concentrations of 0, 10, 100 and 1000 ppm. The authors observed a significant dose–response decrease in testis weight at 100 and 1000 ppm, accompanied by perturbations in the spermatogenesis process, including fusion of spermatids and swelling and necrosis of seminiferous tubule cells, with the severity of these effects directly related to the vinyl chloride concentration. According to Heywood and James (1978), approximately 20% of rats fed under normal conditions developed testicular atrophy. Sokal et al. (1980) exposed rats to vinyl chloride at 50, 500 and 20 000 ppm for 10 months. Degeneration of the seminiferous tubule cells and perturbations in spermatogenesis were reported; however, these effects did not increase in a dose-responsive fashion at higher concentrations. The fertility of the males, the capacity to generate offspring and the reversible potency of vinyl chloride were not

examined. Based on these two studies, further research is needed to determine a clear relationship between vinyl chloride and reproductive effects.

A more recent vinyl chloride inhalation investigation on embryo-fetal development and reproduction in rats was carried out by Thornton et al. (2002). Four groups of F_0 rats were subchronically exposed to vinyl chloride. Males and females (120 of each sex) were exposed for a 10-week pre-mating period and a 3-week mating period, followed by continued exposure for males and 20 days of exposure for gestational females to 0, 10, 100 or 1100 ppm for 6 hours/day. Thirty pups of each sex were selected from each of the four groups. The F_1 generation was also exposed to the same conditions. F_0 and F_1 animals were examined twice daily for toxic effects. Physical evaluation of F_1 and F_2 pups was done on lactation days 0, 4, 7, 14, 21 or 25. Macroscopic and microscopic examinations of the reproductive organs were executed at weaning for 15 male and 15 female F_1 and F_2 pups. Then, sperm quality was analysed for F_0 and F_1 animals of each of the four groups. Supporting John et al. (1981), this study revealed no alteration of embryo-fetal development, teratogenicity or reproduction in the four groups of vinyl chloride–exposed rats. Body weight, pregnancy rates, postmortem observations, uterine status, feed consumption and duration of gestation were all unaffected during the pre-mating, mating and post-mating periods. The reproductive organs did not show any signs of adverse effects, including sperm motility, number and morphology (Thornton et al., 2002). In the F_1 pups, the live birth index was lower for the 1100 ppm group (0.98), whereas the viability was lower for the 10 and 100 ppm groups (0.89 and 0.88, respectively). Still, the authors stated that historic data supported these results. For the F_2 litter, the authors found a reduced pup number in the 1100 ppm group compared with the F_2 controls; however, an increased viability was reported for the F_2 litter exposed to 10, 100 and 1100 ppm. No dose–response relationship for birth rate was seen after vinyl chloride exposure (Thornton et al., 2002). The authors determined a no-observed-adverse-effect concentration (NOAEC) of 1100 ppm for embryo-fetal development and reproduction in rats.

9.2.6 Juvenile sensitivity

Rodent studies have shown that animals less than 4 weeks old appear to be more susceptible to the formation and persistence of DNA adducts induced by vinyl chloride (Grosse et al., 2007). Morinello et al. (2002a) found that concentrations of N^2,3-ethenoguanine were 2- to 3-fold higher in weanlings than in adults exposed for the same amount of time. The available data indicate that the cancer risk from a relatively short-term exposure in juveniles is approximately equal to the risk from long-term exposure in adults; several other genotoxic carcinogens have shown similar results (Ginsberg, 2003).

Laib et al. (1989) , using radiolabelled vinyl chloride, found an 8-fold increase in the amount of DNA alkylation in the liver of young rats compared with adult rats; this increase was attributed to increased levels of DNA synthesis per cell in younger rats.

Maltoni and Cotti (1988) examined the effect of age at the start of exposure on vinyl chloride toxicity by exposing rat breeders (13 weeks old at the start of the experiment) and offspring (12 days old at the start of the experiment) to vinyl chloride for 104 weeks. Another group of rat offspring was exposed for 15 weeks; all rats were observed until their death. The incidence of hepatocarcinomas was highest in the two groups of offspring; the incidence of ASL was highest in the offspring exposed for 104 weeks. Neuroblastomas, by contrast, occurred with the highest frequency in rats exposed for 104 weeks, regardless of starting age. The authors concluded that the incidence of hepatocarcinomas was influenced by the age at the start of

exposure, ASL was influenced by both age at the start of exposure and duration of exposure and neuroblastomas were influenced only by the duration of exposure.

Cogliano et al. (1996) reviewed data on early-life exposures to vinyl chloride. They concluded that the cancer risk from a brief early-life exposure (weeks 1–5 for a rat) is approximately equal to that from chronic exposure to the same concentration in air beginning at maturity, but that the specific effects from early-life and full-life exposures may be different.

The U.S. EPA (2000b) reviewed data on early-life and adult cancer potencies based on studies with repeated exposures of juvenile (from birth to 5 weeks of age) and adult animals (from 13 to 52 weeks after birth) to genotoxic carcinogens, including vinyl chloride. Based primarily on the Maltoni and Cotti (1988) study, the median ratios of juvenile to adult cancer potencies for ASL from vinyl chloride exposure ranged from 9.8 to 29 (geometric mean = 14); the ratios for hepatoma ranged from 32 to 58 (geometric mean = 47). For other cancers resulting from vinyl chloride exposure, there was no clear trend towards higher cancer risks in juveniles compared with adults.

9.3 Mode of action

Primary liver cancer or, more specifically, liver angiosarcoma (ASL; a cancer of the liver blood vessels) is the most severe endpoint that follows oral (food or water) or inhalation exposure to vinyl chloride, based on consistencies between epidemiological and experimental animal studies (Albertini et al., 2003).

The first key event in vinyl chloride–induced toxicity is the formation of the oxidized metabolites CEO and CAA by hepatocyte CYP2E1 (Bolt, 1986; Barbin and Bartsch, 1989; Albertini et al., 2003). Metabolites migrate by a cell to cell passage mechanism from hepatocyte P450 sites to the sinusoidal cells (Morinello et al., 2002b), where ASL originates.

The second key event is the generation of DNA adducts (IPCS, 1999; Holt et al., 2000). Highly reactive CEO is the major metabolite involved in their formation. The mode of action is supported by the fact that the toxicokinetics of the metabolite production, dependent on the activity level of CYP2E1 and the conjugation with glutathione catalyzed by glutathione S-transferase, are correlated to the adduct formation (IPCS, 1999; U.S. EPA, 2000b). This second key event is characterized by the persistence of the DNA adducts. Sinusoidal cells express DNA repair enzymes at lower levels than do hepatocytes (metabolism site), which may explain their higher amount of DNA etheno adducts (Swenberg et al., 1999; Holt et al., 2000; U.S. EPA, 2000b; Morinello et al., 2002a). After 4 weeks of exposure of rats to vinyl chloride at 1100 ppm, recovery for 5 days significantly lowered the amount of N^2,3-ethenoguanosine in rat hepatocytes, but not in non-parenchymal cells, compared with the animals sacrificed immediately after exposure (Morinello et al., 2002a). Differences in the time of repair were observed between the three common DNA adducts in rats following exposure to vinyl chloride at 600 ppm for 4 hours daily over 5 days; a longer repair time was observed with 3,N^4-ethenocytosine and 1,N^6-ethenoadenosine (Swenberg et al., 1992; Dosanjh et al., 1994;OEHHA, 2000; Dogliotti, 2006).

The third key event is the formation of mutations specific to vinyl chloride (Bolt, 2005). The etheno adducts, which are the more persistent, but also the least numerous (~2%), lead to base pair transition and transversion mutations in cell growth regulator genes (Swenberg et al., 2000). In fact, rare A→T transversions in the p53 gene have been found in three out of six ASL cases in vinyl chloride workers (Hollstein et al., 1994), and a linear trend in mutant p53 expression as a function of workers' exposure intensity was found (Marion and Boivin-Angele, 1999; Wong et al., 2002; Luo et al., 2003). This mutation is chemical specific, as it is not found

in Thorotrast (a radioactive thorium dioxide solution)-induced ASL and is uncommon in sporadic ASL (Barbin, 2000). Vinyl chloride workers with ASL have prominent ki-ras activating GC→AT transition mutations at codon 13 (Marion et al., 1991; De Vivo et al., 1994; Marion and Boivin-Angele, 1999). Vinyl chloride also produces sister chromatid exchanges, clastogenicity and micronuclei in humans (U.S. EPA, 2000b).

The fourth key event is the effect of genotoxicity on loss of cell cycle regulation and tumour progression (IARC, 2008). Worker exposure intensities were associated with p53 and Asp13-p21-ki-ras mutant protein expression levels (De Vivo et al., 1994; Trivers et al., 1995; Weihrauch et al., 2000, 2001; Luo et al., 2003). The biological plausibility is supported by the association of the p53 and ras mutations with ASL and HCC development in vinyl chloride workers (Weihrauch et al., 2000). DNA methylation of $p23^{INK4A}$, a gene that inhibits cell cycle progression, was also observed in a cohort of vinyl chloride workers with HCC (Weihrauch et al., 2001).

The vinyl chloride non-cancerous mode of action is not as clearly defined as the cancerous process (U.S. EPA, 2000b).

10.0 Classification and assessment

Vinyl chloride has been classified by IARC, the U.S. Department of Health and Human Services and the U.S. EPA as a known human carcinogen (Group 1 carcinogen), with sufficient evidence of cancer in both humans and animals. Health Canada classifies vinyl chloride as a Group 1 carcinogen (carcinogenic to humans). This is consistent with the classifications established by IARC and the U.S. EPA.

The effects of vinyl chloride exposure have been studied in humans and experimental animals, with similar outcomes reported in all species. Liver and neurological effects have been observed consistently in workers as well as several animal species exposed to vinyl chloride over different exposure durations. Neurological effects have been observed only following inhalation exposures; however, liver effects have been reported following both medium- and long-term inhalation and long-term oral exposures. The sensitivity of the liver to vinyl chloride exposure is supported by the mode of action, as outlined in Section 8.5. The key factors supporting the liver as the main target organ for cancer and non-cancer effects from vinyl chloride exposure are the prevalence of mixed-function oxidase activity, specifically CYP2E1, in the liver and the generation of highly reactive metabolites, which have been shown to bind to DNA as a result of vinyl chloride metabolism.

Health Canada has considered both cancer and non-cancer endpoints in deriving a guideline value. The results from both the cancer and non-cancer risk assessment approaches are described below.

10.1 Cancer risk assessment

The association between occupational exposure to vinyl chloride and the development of ASL is one of the best characterized cases of chemical-induced carcinogenicity in humans. ASL is an extremely rare tumour type in the general population; in fact, primary liver cancer of all types (including ASL) is uncommon in Canada, with an estimated 2,000 new cases for 2012 among an estimated total of 186,400 new cases of all cancers (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2012). With the emergence of vinyl chloride manufacturing, most of the reported ASL cases in North America have been associated with

occupational vinyl chloride exposure. The association of vinyl chloride with ASL in numerous epidemiological studies has been supported by findings in rats, mice and hamsters exposed to vinyl chloride through the oral and inhalation routes. Animal data were used for estimating the cancer potency of vinyl chloride in humans, as exposure data deficiencies in the current vinyl chloride occupational exposure studies prevent their use for risk assessment. A PBPK model was used to determine the liver concentration of the active vinyl chloride metabolites, as it allows for a more pharmacologically relevant estimation of the cancer risk than default models incorporating body surface area correction or allometric scaling, which are adjusted for by the model. The most appropriate dose metric generated by the PBPK model was identified to be the amount of vinyl chloride metabolites produced (per litre of liver tissue per day) that interact directly with DNA in both animals and humans.

PBPK modeling allows for the calculation of excess cancer risks based on the estimation of internal dose of vinyl chloride liver metabolites in humans exposed to vinyl chloride through drinking water. PBPK modeling accounted for metabolic differences between animals and humans as well as metabolic differences between high and low exposure levels. Both the Feron et al. (1981) and Til et al. (1991) studies were used for cancer risk assessment, given the appropriate route of exposure used (oral ingestion), the adequate sample sizes and appropriate duration of exposure (lifetime). The external doses from these studies were inputted into the rat PBPK model to determine the daily internal doses of vinyl chloride metabolites generated per litre of liver tissue for several of the reported cancer endpoints in both male and female rats. These daily internal doses were then analysed using the multistage cancer model from BMDS (U.S. EPA, 2010) to determine the most appropriate point of departure to input into the human PBPK model. The cumulative lifetime internal doses of vinyl chloride liver metabolites associated with an excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6} for combined liver cancers (neoplastic nodules, HCC and ASL) in male and female rats were determined as the most appropriate inputs into the human PBPK model to estimate the external human doses associated with each risk level for a lifetime (70 years) exposure. The external human doses associated with an excess risk of combined liver cancers of 10^{-4}, 10^{-5} and 10^{-6} were estimated as 4.19×10^{-4}, 4.19×10^{-5} and 4.19×10^{-6} mg/kg bw per day, respectively; these doses were derived from an oral human slope factor of 0.24 $(\text{mg/kg bw per day})^{-1}$.

The cancer risk estimates for combined liver cancers in females from Feron et al. (1981) resulted in the most conservative cancer risk estimate; therefore, combined female liver tumours were chosen as the key endpoint for cancer risk assessment. Although neoplastic nodules may not necessarily progress to malignancy, including this endpoint avoids any potential underestimation of the total cancer risk from vinyl chloride exposure. The combined liver tumour endpoint is also protective of lung angiosarcoma, as the estimated risks for lung angiosarcoma were lower than those for combined liver tumours , and animals displaying this cancer endpoint in the Feron et al. (1981) study also had ASL, suggesting metastases from the liver.

Evidence from animal studies suggests that very young children may be more sensitive to the carcinogenic effects of vinyl chloride due to increased DNA adduct formation and liver tumour incidence observed in animals under five weeks of age exposed to vinyl chloride compared to animals exposed after maturity (see Sections 9.1.6 and 9.2.6). In reviewing cancer potency data from early-life and adult exposures to vinyl chloride, the U.S. EPA (2000b) has suggested that that the full lifetime cancer risk for vinyl chloride can be approximated by adding the risks from exposures in early life and adulthood since, for example, the incidence of angiosarcoma following after short-term, early-life exposure is approximately equal to that

following long-term exposure starting after maturity. As a result, the U.S EPA (2000b) concluded that continuous lifetime exposure from birth would approximately double cancer risk, and recommended that if continuous exposure to vinyl chloride were to occur from birth, a twofold increase should be applied to the adult slope factor in order to protect young children who may be more sensitive to vinyl chloride exposure.

Although early-life data in humans is lacking, many of the factors likely to be responsible for early-life sensitivity in animals also pertain to humans. Such factors include rapid cell division during early life as well as dosimetric considerations such as increased water intake per unit body weight and more rapid blood flow to liver. As a result, the approach used in this document is consistent with that of the U.S. EPA, and an additional 2-fold uncertainty factor is applied to protect young children if exposure to vinyl chloride were to occur from birth.

The concentrations of vinyl chloride in drinking water representing a lifetime excess combined liver cancer risk of 10^{-6} and 10^{-5} in adult humans exposed to 3.8 L-eq of water daily (see Section 8.4) are 0.08 and 0.8 µg/L, respectively. These concentrations are higher than the values of 0.013 and 0.13 µg/L calculated using traditional linear extrapolation with allometric scaling. Given the animal evidence of early-life sensitivity to vinyl chloride, if lifetime exposure was to occur from birth, then the above concentrations for adults should be divided by two to protect young children whom may be more sensitive to vinyl chloride. Therefore, the resulting health-based values (HBVs) for vinyl chloride in drinking water representing a lifetime excess combined liver cancer risk of 10^{-6} and 10^{-5} for early life exposure are 0.04 and 0.4 µg/L, respectively.

The results that incorporate metabolite generation rates (from PBPK modeling) are considered to represent a more reasonable estimate of human risk from exposure to vinyl chloride than simple linear extrapolation with the incorporation of an allometric scaling factor to account for metabolic differences between rats and humans.

10.2 Non-cancer risk assessment

The most appropriate study for a non-cancer risk assessment is Til et al. (1991), as it represents a well-controlled study with a large sample size as well as an appropriate duration and route of exposure (orally through the diet). The most appropriate endpoint is liver cell polymorphism, as it represents an effect in the liver that is sensitive to both inhalation and oral exposures to vinyl chloride (ATSDR, 2006). Liver cell polymorphism is not considered a precursor to carcinogenicity, as it is an effect observed in both the nucleus and cytoplasm of the liver cells and therefore is considered to be a toxic effect rather than a carcinogenic effect (Schoental and Magee, 1957, 1959; Afzelius and Schoental, 1967, U.S. EPA, 2000b). Additionally, the lowest-observed-adverse-effect level (LOAEL) and NOAEL for liver cell polymorphism in both sexes of rats from the Til et al. (1991) study represent the lowest doses identified in the literature for any chronic effect resulting from vinyl chloride exposure.

PBPK modeling was used to determine an external human dose corresponding to an external NOAEL of 0.13 mg/kg bw per day for combined moderate and severe liver cell polymorphism in female rats from Til et al. (1991); female rats were found to be more sensitive than males possibly due to a higher internal dose received. Using a rat PBPK model, the internal dose of vinyl chloride metabolites in the liver resulting from exposure to 0.13 mg/kg bw per day was determined as 2.85 mg/L of liver tissue per day. This internal dose was then inputted into the human PBPK model in order to determine a human external dose required (when consuming 1.5 L of drinking water per day for 70 years) to generate the same concentration of liver

metabolites; the resulting human external dose corresponding to an internal daily dose 2.85 mg/L of liver metabolites was determined as 0.224 mg/kg bw per day.

Using the human external dose derived above as the most appropriate point of departure, the tolerable daily intake (TDI) for vinyl chloride can be calculated as follows:

$$\text{TDI} = \frac{0.224 \text{ mg/kg bw per day}}{25}$$
$$= 0.009 \text{ mg/kg bw per day}$$

where:

- 0.224 mg/kg bw per day is the human external dose for combined moderate and severe liver cell polymorphism derived through PBPK modeling as described above; and
- 25 is the uncertainty factor (×2.5 for interspecies toxicodynamic variability [see below] and ×10 for intraspecies variability).

The interspecies uncertainty factor can be divided in two components: a toxicokinetic (delivered dose) component (4.0) and a toxicodynamic (differential tissue sensitivity) component (2.5) (IPCS, 2005). PBPK modeling accounts for differences in the toxicokinetics between animals and humans; as a result, the toxicokinetic component of the interspecies uncertainty factor (4.0) can be removed from the TDI calculation. As the toxicodynamic variation (relating to tissue sensitivity) between animals and humans for vinyl chloride is not well known, the toxicodynamic portion of the interspecies uncertainty factor was retained for determining the TDI. Retention of the toxicodynamic portion of variation between animals and humans is further supported by the uncertainty surrounding the basic mode of action for non-cancer liver effects as well as the limited evidence of human susceptibility to non-cancer liver effects from occupational exposure to vinyl chloride.

Using the above TDI, a health-based value (HBV) for vinyl chloride in drinking water can be derived as follows:

$$\text{HBV} = \frac{0.009 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{3.8 \text{ L-eq/day}}$$
$$= 0.033 \text{ mg/L}$$
$$\approx 0.03 \text{ mg/L (30 µg/L)}$$

where:

- 0.009 mg/kg bw per day is the TDI as derived above;
- 70 kg is the average body weight of an adult;
- 0.20 is the proportion of the daily intake allocated to drinking water; this is a default value, as there are insufficient data to calculate the actual value; and
- 3.8 L-eq/day is the daily volume of water consumed by an adult, accounting for multiple routes of exposure from showering and bathing, as determined in Section 8.4.

10.3 Comparison of cancer and non-cancer risk assessments

In Section 10.1, the concentrations of vinyl chloride in drinking water associated with a lifetime excess risk of combined liver tumours of 10^{-6} and 10^{-5} were determined as 0.08 and 0.8 µg/L, respectively, for exposure during adulthood; if exposure was to occur from birth, these concentrations are to be reduced to 0.04 and 0.4 µg/L, respectively. Using a TDI approach in Section 10.2, a health-based value that is protective of liver cell polymorphism (moderate and severe) was determined to be 30 µg/L. As the cancer risk assessment resulted in a more conservative value for vinyl chloride in drinking water compared with that generated by the non-cancer approach, the cancer risk assessment approach was determined as the most appropriate approach for developing the maximum acceptable concentration (MAC) in drinking water.

10.4 International considerations

The U.S. EPA maximum contaminant level (MCL) for vinyl chloride in drinking water is 0.002 mg/L (2 µg/L) based on liver cancer. The U.S. EPA (2000b) extrapolated its cancer slope factors as well as a non-cancer inhalation reference concentration (RfC) and oral human reference dose (RfD) from the Clewell et al. (1995) PBPK model. For the cancer risk assessment, the U.S. EPA used the data from the Feron et al. (1981) study to derive an a human oral cancer slope factor of 0.72 per mg/kg bw/day for total liver cancers (liver angiosarcoma, hepatocellular carcinoma and neoplastic nodules) resulting from continuous lifetime exposure during adulthood. A twofold increase to 1.4 per mg/kg bw/day is recommended to account for continuous lifetime exposure starting at birth. For the non-cancer assessment, the integration of the rat NOAEL of 0.13 mg/kg bw per day for induction of non-cancer cell polymorphism (Til et al., 1983, 1991) generated a rat target tissue concentration of 3 mg of metabolites/L of liver (U.S. EPA, 2000b). Assuming a consumption of 2 L water per day, 70 kg person, the PBPK-derived human dose given orally that would generate the same target tissue concentration (TTC) equal to 0.09 mg/kg bw per day, resulting in an RfD of 0.003 mg/kg bw per day.

The WHO (2004) drinking water quality guideline of 0.3 µg/L is based on the U.S. EPA (2000b) oral slope factor and a 10^{-5} cancer risk. A concentration of vinyl chloride in drinking water of 0.5 µg/L was calculated as being associated with an upper-bound excess risk of liver tumours of 10^{-5} for lifetime exposure beginning at adulthood. However, with uncertainty regarding differences in sensitivity during early life exposure and the assumption by the U.S. EPA (2000b) that continuous lifetime exposure from birth would double cancer risk, the WHO divided the level for adults by a 2-fold uncertainty factor and rounded up to 0.3 µg/L to arrive at its drinking water guideline value.

The California EPA (OEHHA, 2000) established a non-regulatory public health goal (PHG) of 0.05 µg/L for vinyl chloride in drinking water. The PHG is based on an inhalation cancer slope factor of 0.27 $(\text{mg/kg bw per day})^{-1}$ for lung cancer observed in mice from an inhalation study by Drew et al. (1983). A value of 3 µg/L was calculated based on non-cancer effects of vinyl chloride based on liver cell polymorphism and hepatic cysts in male and female rats. The non-cancer PHG incorporates a 100-fold uncertainty factor and a water exposure rate of 7.1 L/day that includes 5.1 L-equivalents to account for exposure by inhalation and dermal exposure from bathing or showering. California's current drinking water standard (MCL) for vinyl chloride is 0.5 µg/L, which was adopted in 1989.

The Australian Drinking Water Guideline for vinyl chloride of less than 0.0003 mg/L (0.3 µg/L) is based on considerations of health effects (cancer) and the limit of determination (NHMRC, 2004).

11.0 Rationale

Vinyl chloride has been classified as a human carcinogen (Group 1 carcinogen) with sufficient evidence of cancer in both humans and animals. Entry into drinking water may result from industrial discharges to source water from chemical and latex manufacturing or from leaching of the entrapped monomer from polyvinyl chloride pipe. Vinyl chloride may also be formed in groundwater and the environment through the biodegradation of synthetic solvents such as trichlorethylene, trichloroethane and tetrachloroethylene.

The effects of vinyl chloride exposure have been studied in humans and animals, with similar outcomes reported in all species. Liver and neurological effects have been observed consistently in workers as well as several animal species exposed to vinyl chloride over different exposure durations. Liver cancer is the most serious endpoint that follows oral (food or water) or inhalation exposure to vinyl chloride, based on consistencies between epidemiological and experimental animal studies. Although many other tumour types have been reported in animals following vinyl chloride exposure, there is little consistency in the observed tumour types across species.

Given the volatility of vinyl chloride, a multi-route exposure assessment was performed using PBPK modeling in order to determine any additional exposure by dermal or inhalation exposure during showering or bathing. Additional litre-equivalent (L-eq) exposures of 1.9 L-eq from dermal exposure and 0.4 L-eq from inhalation exposure during showering or bathing were determined from the human PBPK model and were added to the Canadian drinking water ingestion rate of 1.5 L/day, resulting in a total estimated L-eq daily exposure of 3.8 L-eq. This daily exposure was used in both the cancer and non-cancer risk assessments.

PBPK modeling was used to calculate excess cancer risks based on the internal dose of vinyl chloride metabolites in humans exposed to vinyl chloride through drinking water. Evidence from animal studies suggests that very young children (less than 5 weeks of age) may be more sensitive to the carcinogenic effects of vinyl chloride than adults; in fact, current scientific evidence suggests a 2-fold increased sensitivity if children under the age of 5 weeks are exposed to vinyl chloride. Therefore, the concentrations representing "essentially negligible" lifetime risk of combined liver tumours in children less than 5 weeks of age would range from 0.04 to 0.4 µg/L. Health Canada has defined this term as a range from one new cancer above background levels per 100 000 people to one new cancer above background levels per 1 million people (i.e., 10^{-5} to 10^{-6}). This level is protective of both potential cancer and non-cancer effects resulting from exposure to vinyl chloride in drinking water.

Air stripping and packed tower aeration are municipal-scale treatment processes, which can remove vinyl chloride from drinking water to level below 1 µg/L. Alternative processes, such as ozonation and advance oxidation processes, have been reported to be effective for the reduction of vinyl chloride from drinking water to below 0.5 µg/L.

There are no certified residential treatment devices currently available for the reduction of vinyl chloride from drinking water. However, a study conducted on treatment devices using activated carbon filters demonstrated that they may be effective for the reduction of vinyl chloride to levels below 2 µg/L. Health Canada recommends that PVC pipes used in the distribution of drinking water be certified to NSF/ANSI Standard 61, which limits the leaching of vinyl chloride based on a harmonized regulatory limit of 2 µg/L.

A MAC of 0.002 mg/L (2 µg/L) for vinyl chloride is established based on the following considerations:

- The MAC must be measurable. The U.S. EPA has established a PQL of 0.002 mg/L, based on the ability of laboratories to measure vinyl chloride within reasonable limits of precision and accuracy using approved methods. There is no similar process in place to establish a PQL specific to Canada.
- The MAC must be achievable at reasonable cost. Municipal scale treatment technologies can consistently remove vinyl chloride from drinking water to 0.5 µg/L, which is below the MAC of 2 µg/L. At the residential level, although there are no treatment units currently certified to remove vinyl chloride, it is expected that the use of two or more treatment devices using technologies such as activated carbon would remove vinyl chloride below the MAC.
- NSF/ANSI Standard 61 limits leaching of vinyl chloride into drinking water by ensuring materials meet a SPAC of 0.0002 mg/L (0.2 µg/L) or less (NSF/ANSI, 2012). The SPAC is established at one tenth the regulatory value for drinking water, as harmonized between the U.S. and Canada.

In considering both treatment achievability and the health risks associated with vinyl chloride exposure from drinking water, the Federal-Provincial-Territorial Committee on Drinking Water has established a MAC of 0.002 mg/L (2 µg/L). The estimated lifetime risk associated with ingestion of water containing vinyl chloride at the MAC is 5.0×10^{-5} which is above the range that is considered to represent "essentially negligible" risk. This value is based on analytical achievability; as it exceeds the health-based value for the protection of young children, every effort should be made to maintain vinyl chloride levels in drinking water as low as reasonably achievable (or ALARA).

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.

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Appendix A: List of acronyms

ALARA	as low as reasonably achievable
ANSI	American National Standards Institute
AOP	advanced oxidation process
ASL	angiosarcoma of the liver
bw	body weight
CAA	chloroacetaldehyde
CEO	chloroethylene oxide
CI	confidence interval
CPVC	chlorinated polyvinyl chloride
CSA	Canadian Standards Association
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ELCD	electrolytic conductivity detector
EPA	Environmental Protection Agency (U.S.)
EQL	estimated quantitation limit
GAC	granular activated carbon
GC	gas chromatography
GSH	glutathione
HBV	health-based value
HCC	hepatocellular carcinoma
IARC	International Agency for Research on Cancer
LD_{50}	median lethal dose
LOD	limit of detection
LOQ	limit of quantification
MDL	method detection limit
MRL	minimum reporting level
MS	mass spectrometer/spectrometry
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NOAEL	no-observed-adverse-effect level
NPC	National Plumbing Code
NSF	NSF International
PBPK	physiologically based pharmacokinetic
PID	photoionization detector
POD	point of departure
PQL	practical quantification limit
PTA	packed tower aeration
PVC	polyvinyl chloride
RNA	ribonucleic acid
RR	relative risk
SCC	Standards Council of Canada
SIM	selected ion monitoring
SMR	standardized mortality ratio
SPAC	single product allowable concentration
TDI	tolerable daily intake

UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organization