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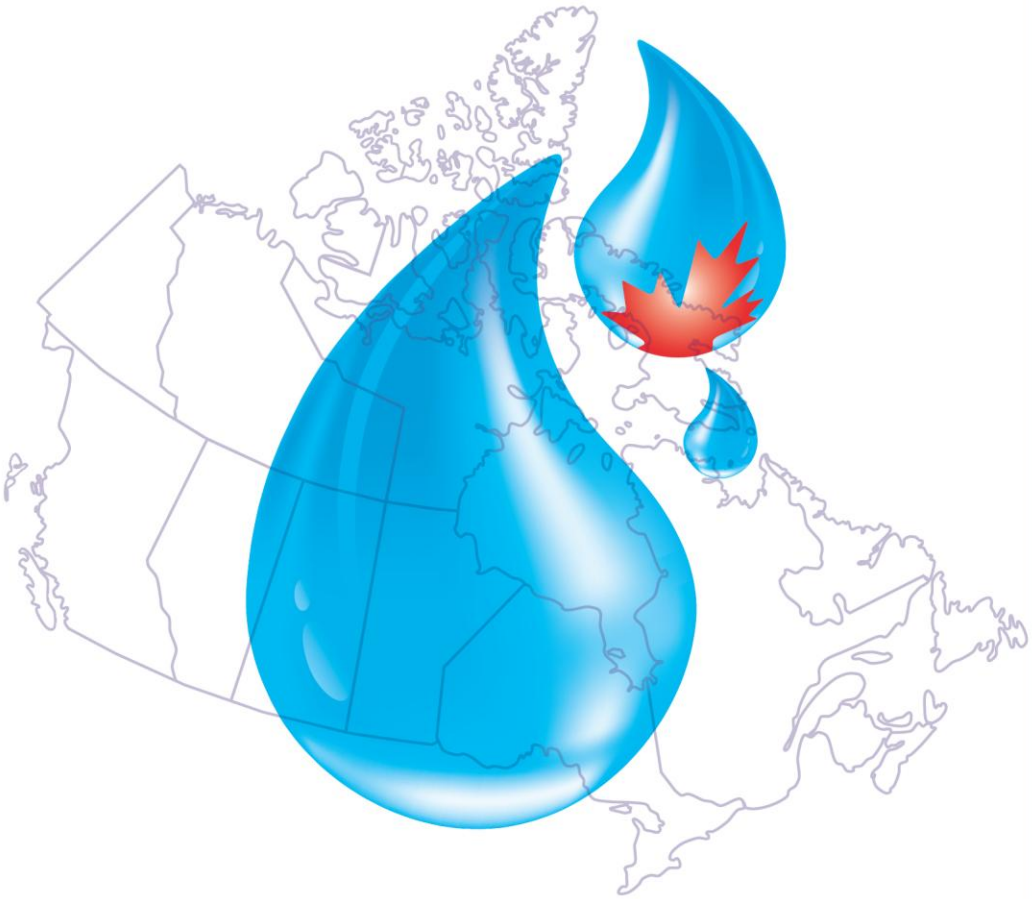
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

1,2-Dichloroethane



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Published by authority of the Minister of Health.

Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – 1,2-Dichloroethane

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Également disponible en français sous le titre :
Recommandations pour la qualité de l'eau potable au Canada : Document technique – Le 1,2-dichloroéthane

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

Pub. Number: 130473
Cat.: H144-13/3-2013E-PDF
ISBN: 978-1-100-23000-9

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1,2-Dichloroethane

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

Health Canada
Ottawa, Ontario

February, 2014

This document may be cited as follows:

Health Canada (2014). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — 1,2-Dichloroethane. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (Catalogue No H144-13/3-2013E-PDF).

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

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February, 2014

1,2-Dichloroethane

Part I. Overview and Application

1.0 Guideline

A maximum acceptable concentration (MAC) of 0.005 mg/L (5 µg/L) is established for 1,2-dichloroethane in drinking water.

2.0 Executive summary

1,2-dichloroethane (1,2-DCA) is a volatile organic compound that does not occur naturally in the environment. It hasn't been produced in Canada since 2006, but is still imported, primarily for use in the synthesis of vinyl chloride and other organic chemicals.

This guideline technical document reviews and assesses all identified health risks associated with 1,2-DCA 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. Based on this review, the guideline for 1,2-DCA in drinking water is a maximum acceptable concentration of 0.005 mg/L (5 µg/L).

2.1 Health effects

1,2-DCA is classified by Health Canada as a probable human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals. Animal studies have shown links between inhalation and/or ingestion of 1,2-DCA and various types of tumours in rats and mice. No conclusion of excess cancer linked to 1,2-DCA could be derived from the available studies in humans.

Various non-cancer health effects related to exposure to 1,2-DCA were observed in rodents, including immunological and renal effects, occurring at the lowest level of exposure. The non-cancer risk assessment was based on renal effects in rats.

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

2.2 Exposure

Canadians can be exposed to 1,2-DCA through its presence in air, drinking water, food and possibly through the use of specific consumer products or in occupational settings. Exposure is mainly from air, particularly indoor air. Because 1,2-DCA is highly volatile, its presence in water is usually associated with groundwater sources. 1,2-DCA is not frequently found in Canadian drinking water supplies. However, when present in drinking water, it may be absorbed through ingestion, inhalation and skin absorption.

2.3 Analysis and treatment

1,2-DCA can readily be detected and analysed in drinking water supplies using the general methods used for volatile organic compounds (VOCs), at levels below the MAC.

Conventional treatment methods have little effect in reducing VOC concentrations. Municipal-scale treatment technologies effective at removing 1,2-DCA include air stripping (preferably using packed tower aeration), and granular activated carbon adsorption. At the residential scale, certified point-of-use treatment devices as well as a limited selection of point-of-entry devices are currently available for the reduction of VOCs, including 1,2-DCA.

3.0 Application of the guideline

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

Generally, 1,2-DCA is not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily. As levels of 1,2-DCA in treated water are generally very low, water suppliers are not expected to monitor the concentrations of 1,2-DCA in drinking water supplies on a routine basis.

Groundwater sources should be characterized to determine if 1,2-DCA is present, especially if the land use history is unknown. Quarterly monitoring for 1,2-DCA is recommended for groundwater sources that are or may have been impacted by spills or other potential contamination with this compound. VOCs and organic solvents in contaminated land may permeate some drinking water pipes and adversely affect water quality. The problem of permeation is generally limited to plastic and non-metallic materials.

The drinking water guideline is based on lifetime exposure to 1,2-DCA from drinking water. For drinking water supplies that occasionally experience short-term exceedances above the MAC, 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 drinking water be considered.

Part II. Science and Technical Considerations

4.0 Identity, uses, sources and fate in the environment

4.1 Identity

1,2-Dichloroethane (1,2-DCA; Chemical Abstracts Service Registry No. 107-06-2), also known as ethylene dichloride, is a volatile organic compound (VOC) that is clear, colourless and oily and has a chloroform-like odour. The molecular formula of 1,2-DCA is $C_2H_4Cl_2$, and its molecular weight is 98.96 g/mol. Its conversion factor in air is 1 ppm = 4.05 mg/m^3 at 25°C (U.S. EPA, 2000). 1,2-DCA has a boiling point and melting point of 83.5ºC and −35.7ºC, respectively (Lide, 2011); at 20ºC, it has a density of 1.23 g/cm^3 and a vapour pressure of 8.53 kPa (WHO, 2003). Its water solubility is 8.69×10^3 mg/L at 20ºC (Verschueren, 2001), and it will readily move through soil based on a log soil sorption coefficient of 1.14–1.28 (OEHHA, 1999). 1,2-DCA has the potential to volatilize from water and moist soil (unitless Henry's Law constant 4.83×10^{-2} at 25ºC; U.S. EPA, 2011a). It has a log octanol/water partition coefficient of 1.48, indicating that it will partition into the lipid layer (OEHHA, 1999). 1,2-DCA is not expected to bioconcentrate in organisms or to be biomagnified within food chains because of its very low estimated bioconcentration factor of 3.78 (U.S. EPA, 2011a).

4.2 Major uses and sources

The predominant use of 1,2-DCA is as an intermediate for the synthesis of vinyl chloride monomer. It is also used in the manufacture of ethylene oxide, trichloroethane, trichloroethylene and perchloroethylene (OEHHA, 1999; Environment Canada, 2006). 1,2-DCA is also used as an analytical solvent in laboratories and in soaps and scouring compounds, wetting and penetrating agents, organic chemical synthesis, ore flotation, solvents, fumigants, pharmaceuticals, adhesives and glycol production (Lewis, 2001; Environment Canada, 2006).

In Canada, Dow Chemical Canada Inc. was the only recent manufacturer of 1,2-DCA, but with the 2006 closure of its chlor-alkali and 1,2-DCA plant in Fort Saskatchewan, Alberta, there are no facilities in Canada currently manufacturing this compound (Dow Chemical Canada Inc., 2006, 2007; Environment Canada, 2006). In Canada, the demand for 1,2-DCA has primarily been for the production of vinyl chloride monomer (Chemical Marketing Reporter, 1992; CIS, 2004a). Vinyl chloride monomer is no longer produced in Canada (CIS, 2004b; Dow Chemical Inc., 2007; Occidental Petroleum Corporation , 2013). From 2007 to 2009, the quantity of 1,2-DCA imported for use annually in Canada decreased from 147 to 114 tons (equivalent to approximately 133 to 103 tonnes; International Trade Centre, 2010).

There is no known natural source of 1,2-DCA in the environment. The presence of 1,2-DCA in the atmosphere is a result of direct releases from industrial activity, particularly during its production and during the production of vinyl chloride monomer (Environment Canada and Health Canada, 1994). Secondary sources include industrial emissions from various industries that use imported 1,2-DCA (e.g., pharmaceuticals, refineries, glycol production, laboratories). Long-range transport of 1,2-DCA in air from the United States and leachates from waste disposal sites are additional sources of release to the atmosphere (Environment Canada, 2006). Member companies of the Canadian Chemical Producers' Association have reported that emissions of 1,2-DCA have been reduced considerably since 1992, decreasing from 27.52 tonnes to 8.90, 4.83, 5.57 and 0.550 tonne in 2004, 2005, 2006 and 2007, respectively (CCPA, 2005, 2007). With the closure of Dow Chemical Canada Inc.'s manufacturing plant in Fort Saskatchewan in

2006, it is projected that emissions due to manufacturing will continue to decrease to levels of 0.061 tonne in 2012 (CCPA, 2007).

4.3 Environmental fate

Direct release by land disposal of liquid and solid wastes is responsible for the presence of 1,2-DCA in soil. Once 1,2-DCA is released to land, surface amounts may volatilize rapidly into the atmosphere or, as it is highly mobile in soil, leach into groundwater (Lesage et al., 1993; ATSDR, 2001). VOCs and organic solvents, including 1,2-dichloroethane, may permeate plastic and non-metallic drinking water pipes in contaminated soil and adversely affect water quality (Wilson and Norris, 1992).

Microbial degradation of 1,2-DCA is possible in water, but overall degradation occurs slowly, as a result of the short residence time of 1,2-DCA in water (Hill et al., 1976; U.S. EPA, 1982; Ellington et al., 1988; Jeffers et al., 1989). In aerobic conditions, some bacteria (e.g., *Ancylobacter aquaticus*, *Methylosinus trichosporium*, *Xanthobacter autotrophicus*) are capable of biodegrading 1,2-DCA as the sole carbon source in culture (Janssen et al., 1985; Oldenhuis et al., 1989; Van den Wijngaard et al., 1992). Studies on the anaerobic biodegradation of 1,2-DCA in aquatic environments are conflicting, likely because of the variability of microbial communities and oxidative and reductive conditions present in the substrates (Van der Zaan et al., 2009). For example, based on the chemical properties of 1,2-DCA, it has been theorized that its biodegradation can occur in anaerobic water (Saint-Fort, 1991); however, some experimental results have shown no degradation in anoxic sediment–water suspensions (Jafvert and Wolfe, 1987). Conversely, another study showed that concentrated cell suspensions of methanogenic (anaerobic) bacteria incubated at 37°C (or 55°C) for 24–96 hours reductively dechlorinated 1,2-DCA to ethylene, chloroethane and ethane, regardless of the substrate used (methanol, acetate or hydrogen/carbon dioxide) (Holliger et al., 1990). In water, residence time can vary depending on conditions. Bosma et al. (1998) reported biodegradation half-life of 1,2-DCA in groundwater ranging from less than a year up to 30 years. In aerobic and anaerobic water studies, biodegradation half lives of 100 days and 400 days were reported, respectively, however the studies lacked experimentation details (Capel and Larson,1995).

Microbial biodegradation is expected to be the primary transformation process for 1,2-DCA in sediment and soil under both aerobic and anaerobic conditions (ATSDR, 2001). Biodegradation of 1,2-DCA to carbon dioxide was achieved under controlled laboratory conditions using different soil types (i.e., sand, sandy clay, silty loam, clay and Lincoln fine sand) (Henson et al., 1988; Speitel and Closmann, 1991).

5.0 Exposure

Canadians can be exposed to 1,2-DCA through its presence in drinking water, air and possibly food. The main route of exposure for the general population is inhalation of air, particularly indoor air. Certain segments of the population may also be exposed in occupational settings or from specific consumer products. The limited exposure data available do not show drinking water to be a major source of exposure. However, they are not sufficient to modify the default proportion (20%) of the daily intake allocated to drinking water (floor allocation factor) in the calculation of the MAC (Krishnan and Carrier, 2013).

5.1 Water

In Canada, 1,2-DCA concentrations in the majority of samples recently obtained from drinking water supplies ranged from non-detected to 1 µg/L.

The mean concentrations of 1,2-DCA in undiluted effluents in Sarnia, Ontario, ranged from 2.5 µg/L (1989–1990) to 25 µg/L (1992) (Ontario Ministry of the Environment, 1992). 1,2-DCA was not detected in the effluent of the plant manufacturing the chemical in Alberta during 1991 and 1992 (AEC, 1992).

In Greater Vancouver, British Columbia, 1,2-DCA was measured in source waters at concentrations below 0.5 µg/L in samples taken in 2010 (detection limit was not specified; Greater Vancouver Regional District, 2010). In Victoria, 5-year results (2005–2010) showed that untreated source waters had concentrations of 1,2-DCA ranging from less than 0.005 to 0.5 µg/L (Capital Regional District, 2010). In 660 samples taken at First Nations communities province-wide in British Columbia (2006-2011), there were no positive detections for 1,2-DCA, where the detection limit was 1 µg/L (Health Canada, 2011b).

In Alberta, mean 1,2-DCA concentrations between 0.098 and 0.305 µg/L were measured in treated water from 2006 to 2010 (Alberta Environment, 2011).

In Saskatchewan (1992-2008), 1,2-DCA was found in raw water at concentrations ranging from 0.5 to 1 µg/L, with a mean concentration of 0.9 µg/L. For treated water, 1,2-DCA was found at concentrations ranging from 0.005 to 1 µg/L, with a mean concentration of 0.49 µg/L (detection limit was not specified; Saskatchewan Ministry of Environment, 2011).

In Ontario First Nations communities, there was only one detection of 1,2-DCA at 4 µg/L out of 938 samples taken between 2006 and 2010 (Health Canada, 2011a).

In Quebec (2005-2010), concentrations of 1,2-DCA were below the detection limit (ranging from 0.06 to 1 µg/L) in 3259 of 3263 samples taken from 201 distribution systems supplied by surface water; 1,2-DCA was detected at 0.1 µg/L in the remaining 4 samples (from 4 different systems; Ministère du Développement durable, de l'Environnement et des Parcs du Québec, 2011).

In New Brunswick (1996-2006), 1,2-DCA was not detected in 7570 samples from drinking water supplies and distribution sites. 1,2-DCA was only detected in a few samples: 3 samples ranged from 1 to 3.7 µg/L and 9 samples were below 1 µg/L (the limit of quantification was 1 µg/L; New Brunswick Department of Health, 2006).

In Nova Scotia, 1,2-DCA was not detected in 167 samples of drinking water taken at raw and treated water sites between 2005 and 2009 (Nova Scotia Department of Environment and Labour, 2011).

Out of 180 samples taken at First Nations communities in the Atlantic region between 2006 and 2010, there was only one exceedance of 10.4 µg/L for 1,2-DCA (Health Canada, 2011a)

In Yukon, 1,2-DCA was detected at concentrations of less than 1 µg/L in 7 samples of water supplies taken between 2004 and 2010 (Yukon Environmental Health, 2011).

5.2 Food

Food is not considered to be an important source of exposure to 1,2-DCA because of its low potential for bioaccumulation (IPCS, 1998).

Various surveys have shown that 1,2-DCA is detected at very low levels in food, or not at all. In studies conducted in Canada, the United States and Japan, commodities from market basket surveys had low numbers of positive samples for 1,2-DCA. When 1,2-DCA was detectable, food items such as cereal, butter or margarine, cake, ice cream and milk contained it

at low nanogram per gram levels (Daft, 1989, 1991; Heikes et al., 1995; Miyahara et al., 1995). 1,2-DCA was not detected in two surveys conducted between 1991 and 1992 of 34 food groups in Calgary (Alberta) and Windsor (Ontario) (Hughes et al., 1994). No recent data are available on 1,2-DCA residues in food in Canada (Canadian Food Inspection Agency, 2007).

5.3 Air

A greater proportion of 1,2-DCA is present in ambient air than in other environmental media, as a result of releases from its production, disposal or industrial use (IPCS, 1998).

Recent data (2004–2006) indicated that 1,2-DCA was detected in the air in outdoor urban and rural areas across Canada at concentrations ranging from 0.012 to 21.51 µg/m^3, with a mean concentration ranging from 0.027 to 2.882 µg/m^3 (Environment Canada, 2007). In an earlier survey across Canada (1988–1990), the levels of 1,2-DCA in ambient air ranged from non-detectable to a maximum of 2.78 µg/m^3 (12 cities; 23 sites; 1412 samples), with a overall mean concentration of 0.13 µg/m^3 (Environment Canada, 1992).

As part of a 2-year personal monitoring exposure study, levels of VOCs, including 1,2-DCA, were monitored on a 24-hour basis (with individual monitors) in indoor and outdoor areas for 5 days in Windsor, Ontario, during the winter and summer of 2005 and 2006. Geometric mean concentrations of 1,2-DCA both indoors and outdoors were significantly higher in the summer than in the winter (0.046–0.265 µg/m^3 in the summer, 0.045–0.105 µg/m^3 in the winter), and mean concentrations were also significantly higher indoors than outdoors (0.080–0.265 µg/m^3 indoors, 0.034–0.046 µg/m^3 outdoors; Health Canada, 2010a). A similar study conducted in Regina, Saskatchewan, found a comparable trend of higher 1,2-DCA levels indoors and in the summer (Health Canada, 2010b). In another indoor air survey conducted in Quebec in 2005, 1,2-DCA was found in 22 of 96 homes surveyed at minimum and maximum concentrations of 0.10 and 2.63 µg/m^3, respectively (Héroux et al., 2007). A residential air survey in Ottawa, Ontario, detected 1,2-DCA at concentrations below 0.03 µg/m^3 (Zhu et al., 2005).

Earlier indoor air analyses were performed in approximately 750 residences across all provinces in Canada (1991-1992) for various VOCs; 1,2-DCA was generally not detected, except in dwellings in one area where it was detected at a mean value of 0.11 µg/m^3 with a maximum value of 1.7 µg/m^3 (Fellin et al., 1992).

5.4 Consumer products

No information was found on the amounts of 1,2-DCA currently in consumer products in Canada. In the past, 1,2-DCA could be found in household products such as adhesives and cleaners (Wallace et al., 1987); however, its use in these products has been discontinued for some time (Environment Canada and Health Canada, 1994; ATSDR, 2001).

5.5 Soil

The relevance of available exposure levels in soil may be limited, as production of 1,2-DCA was terminated in Canada in 2006. In Canada, 1,2-DCA was not detected in soil samples from residential and parkland locations in southern Ontario in 1987 (Golder Associates, 1987). Levels of 1,2-DCA in leachate from a chemical plant in Sarnia, Ontario, were 6100 µg/L before treatment with activated charcoal, 910 µg/L after treatment and 64 µg/L in the leachate from the township ditch (King and Sherbin, 1986). 1,2-DCA was not detected in sediment (detection limit 0.01 µg/kg) downstream of two facilities that manufactured the compound in Canada (Oliver & Pugsley, 1986; AEC, 1989).

5.6 Multi-route exposure through drinking water

Owing to 1,2-DCA's physicochemical properties, inhalation and dermal absorption during bathing and showering may serve as important routes of exposure.

To assess the overall exposure to 1,2-DCA in drinking water, the relative contribution of each exposure route was assessed using a multiroute exposure assessment approach (Krishnan and Carrier, 2008). Contributions developed through this approach are expressed in litre-equivalents (L-eq) per day. Both the dermal and inhalation routes of exposure for a VOC are considered significant if they contribute at least 10% of the drinking water consumption level (Krishnan and Carrier, 2008).

5.6.1 Dermal exposure

According to the literature review by U.S. EPA (1985), dermal absorption may contribute significantly to the total exposure of 1,2 -DCA. To evaluate the significance of the dermal route of exposure for 1,2-DCA, tier 1 of the multiroute exposure assessment was used to determine whether this route of exposure contributes a minimum of 10% of the drinking water consumption level (i.e., 10% of 1.5 L = 0.15 L). For a tier 1 goal of 0.15 L-eq, the skin permeability coefficient (K_p) for 1,2-DCA should be higher than 0.024 cm/h (Krishnan and Carrier, 2008). As the experimental K_p for 1,2-DCA is 0.259 cm/h (Frasch and Barbero, 2009), which is greater than 0.024 cm/h, dermal exposure to 1,2-DCA via bathing or showering is considered significant. Tier 2 of the assessment was then used to calculate the litre-equivalent value for dermal absorption, using the following equation (Krishnan and Carrier, 2008):

$$\begin{aligned}\text{Dermal exposure (L-eq)} &= K_p \times t \times F_{abs} \times A \times C_f \\ &= 0.259\ \text{cm/h} \times 0.5\ \text{h} \times 0.7 \times 18\,000\ \text{cm}^2 \times 0.001\ \text{L/cm}^3 \\ &= 1.63\ \text{L-eq}\end{aligned}$$

where:

- K_p is the skin permeability coefficient of 0.259 cm/h (Frasch and Barbero, 2009);
- t is the duration of the shower or bath, assumed to be 0.5 h;
- F_{abs} is the fraction of dose absorbed, assumed to be 0.7, based on Krishnan (2003a,b);
- A is the area of skin exposed, assumed to be 18 000 cm^2 for adults; and
- C_f is the conversion factor from cm^3 to litres.

5.6.2 Inhalation exposure

A two-tier assessment was also used to evaluate the significance of the inhalation route of exposure to 1,2-DCA. Similar to the approach used for dermal exposure, tier 1 of the assessment determines whether the inhalation of 1,2-DCA during showering or bathing is likely to contribute at least 10% of the drinking water consumption level. According to the equation below, for a tier 1 goal of 0.15 L-eq, the average ratio of air to water 1,2-DCA concentration factor ($F_{air:water}$) should be greater than 0.00063 (Krishnan and Carrier, 2008). Using the estimated Henry's Law constant (K_{aw}) obtained from the U.S. Environmental Protection Agency's EPI Suite™ program (U.S. EPA, 2011a), the $F_{air:water}$ value for 1,2-DCA was determined by means of the following equation developed by Krishnan (2004):

$$F_{air:water} = 0.61 \times K_{aw} / [1 + (80.25 \times K_{aw})]$$
$$= 0.61 \times 4.83 \times 10^{-2} / [1 + (80.25 \times 4.83 \times 10^{-2})]$$
$$= 0.00604$$

where:

- 0.61 is the transfer efficiency from water to air (McKone and Knezovich, 1991);
- K_{aw} is the Henry's Law constant (dimensionless) of 4.83×10^{-2} at 25°C (U.S. EPA, 2011a); and
- 80.25 is the ratio of the volume of air in an average bathroom (6420 L) to the average volume of water (80 L) used during the showering/bathing event (Krishnan, 2004).

As the $F_{air:water}$ value for 1,2-DCA is greater than 0.00063, exposure to 1,2-DCA via inhalation from bathing or showering is considered to be significant. Tier 2 of the assessment calculates what the inhalation exposure in litre-equivalents would be, using the following formula (Krishnan, 2004):

$$\text{Inhalation exposure (L-eq)} = F_{air:water} \times Q_{alv} \times t \times F_{abs}$$
$$= 0.00604 \times 675 \text{ L/h} \times 0.5 \text{ h} \times 0.7$$
$$\approx 1.43 \text{ L-eq}$$

where:

- $F_{air:water}$ is the ratio of air to water 1,2-DCA concentrations, as calculated above;
- Q_{alv} is the adult alveolar ventilation rate, assumed to be 675 L/h;
- t is the exposure duration of the shower or bath, assumed to be 0.5 h; and
- F_{abs} is the fraction absorbed, assumed to be 0.7, based on Krishnan (2003a,b).

5.6.3 PBPK approach for multiroute exposure assessment

A human physiologically based pharmacokinetic (PBPK) model based on Sweeney et al. (2008) was used to estimate the litre-equivalent (L-eq) contributions from dermal and inhalation exposure to 1,2-DCA when showering and bathing. Using the external doses generated from the human PBPK model (see Sections 8.5 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 2.06 and 0.68 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 1,2-DCA in drinking water was estimated to be 4.2 L-eq (rounded).

5.6.4 Conclusion for multiroute exposure assessment

This multiroute exposure assessment is a conservative approach used to estimate the contribution of both the dermal and inhalation routes towards total exposure. Using the two-tier approach, the litre-equivalent were calculated as 1.63 L-eq for the dermal route and 1.43 L-eq for the inhalation route. Assuming one showering or bathing event per day and adding these values

to the standard Canadian drinking water consumption rate of 1.5 L/day, this results in a total daily exposure of 4.6 L-eq (rounded from 4.56 L-eq).

In data-rich situations, the PBPK approach can be used to calculate the L-eq value, which uses a robust, chemical-specific model that compares estimates of relevant dose metrics for inhalation and dermal exposures to those for ingestion from drinking water. The results from the two-tier approach are supported by the PBPK approach, which resulted in litre-equivalent exposures of 2.06 L-eq for the dermal route and 0.68 L-eq for the inhalation route, which when added to the standard Canadian drinking water consumption rate of 1.5 L/day also results in a total litre-equivalent daily exposure of 4.2 L-eq (rounded from 4.24 L-eq). Because of the chemical-specific nature of the estimates calculated using the PBPK approach, the L-eq value of 4.2 L-eq/day calculated from the PBPK approach was used to calculate the MAC.

6.0 Analytical methods

The United States Environmental Protection Agency (U.S. EPA, 2010) currently has three approved analytical methods (502.2 rev. 2.1, 524.2 rev. 4.1 and 524.3 ver. 1.0) for measuring 1,2-DCA in drinking water. 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, which employs purge and trap capillary gas chromatography with electrolytic conductivity detector (ELCD) and photoionization detector (PID) in series, has a method detection limit (MDL) of 0.03 µg/L. Method 524.2 revision 4.1 includes purge and trap of the samples, and desorption of the trapped sample components into a capillary gas chromatography column interfaced to a mass spectrometer (MS). Depending on the GC column and GC/MS interface used, the method has an MDL range of 0.02 - 0.06 µg/L (U.S. EPA, 1995, 2009a). Method 524.3 is an updated version of method 524.2 and has a detection limit of 0.025 µg/L. The advantages of this 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, 2009b).

The current U.S. EPA practical quantitation level (PQL) for 1,2-DCA is 5 µg/L. When established, this level was considered the lowest concentration that could be reliably achieved within specified limits of accuracy and precision (U.S. EPA, 1987). Recently, as part of the U.S. EPA's 6-year review, an assessment of the analytical data for 1,2-DCA from the performance evaluation and proficiency testing studies was conducted. The U.S. EPA reported 90% passing rates for laboratories analysing samples at the current PQL. The agency determined that the assessment data supported the reduction of the PQL and estimated a lower possible PQL in the range of 0.3 to 0.6 µg/L. EPA retained 0.5 µg/L as an estimated quantitation level (EQL) for 1,2-DCA which is an estimate of the possible lower bound for a PQL and take into consideration laboratory analytical limits nationwide (U.S. EPA, 2003b, 2009a, 2009d,).

In addition, two equivalent standard methods, SM 6200B and SM 6200C, can be used for the analysis of 1,2-DCA in drinking water. These methods are based on purge and trap capillary gas chromatography followed by mass spectrometry detection, or a photoionization detector in series with an electrolytic conductivity detector, respectively. Method SM 6200B has a MDL of 0.055 µg/L and SM 6200C has a MDL of 0.074 µg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately, are 0.22 µg/L and 0.296 µg/L for methods

SM 6200B and SM 6200C respectively (APHA et al. 2005).

7.0 Treatment technology

7.1 Municipal scale

Conventional water treatment techniques (coagulation, sedimentation, filtration and chlorination) have generally been found to have a little or no effect in reducing concentrations of VOCs, in drinking water (Love and Eilers, 1982; Robeck and Love, 1983; Lykins et al., 1984; Lykins and Clark, 1994). Conventional treatment processes were reported to achieve 1,2-DCA reductions ranging from 0 to 29%; however, the observed reductions may be partially attributed to incidental volatilization during the treatment process (Love et al., 1983; AWWA, 1991; U.S. EPA, 1991a; Health and Welfare Canada, 1993; Lykins and Clark, 1994).

The U.S. EPA has identified packed tower aeration (PTA) and granular activated carbon (GAC) as the best available technologies (BATs) for 1,2-DCA removal in drinking water and the agency considers a 99% reduction to be achievable under all anticipated conditions (U.S. EPA 1991b). Small system compliance technologies include: GAC, PTA, diffused aeration, multi-stage bubble aeration, tray aeration, and shallow tray aeration (U.S. EPA, 1998).

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

7.1.1 Activated carbon adsorption

Activated carbon is used in the water treatment processes either as GAC or as powder activated carbon (PAC). The adsorption capacity of activated carbon to remove VOCs is affected by a variety of factors such as competition from other contaminants, preloading with natural organic matter (NOM), temperature, and the physical/chemical properties of the VOCs and the carbon media (Speth, 1990; AWWA, 1991). The PAC application, most suitable for conventional treatment systems treating surface waters, may remove occasional low concentrations of VOCs down below the guideline value when it is applied at the treatment plant, allowing sufficient contact time and a proper mixing. PAC adsorption is found to be less efficient than GAC adsorption for VOC removal largely due to: (1) its use in coagulation/sedimentation basins where the adsorption sites can be blocked due to floc formation; (2) the fact that it will not have the necessary time to reach its maximum adsorption capacity; and (3) the fact that the equilibrium liquid-phase concentration (concentration gradient driving force) decreases during the adsorption process. Greater concentrations of VOCs are typically found in groundwater where GAC adsorption is the most commonly used process (Snoeyink, 1990). In the GAC process, as water passes through the GAC contactor, the contaminants diffuse into the adsorbent granules and accumulate on the inner surface within the pores. The GAC column allows more complete contact between water and the media, greater adsorption efficiency, and greater process control than PAC. The GAC process is used at small water treatment systems due to its simplicity and ease of operation (Snoeyink, 1990; U.S. EPA, 1998).

The choice of GAC application for removing VOCs from drinking water supplies involves the following process design consideration: carbon usage rate, empty bed contact time (EBCT), pretreatment of the raw water, contactor configuration and method of GAC replacement or regeneration. During the operation time, and depending on a variety of factors discussed above, organic contaminants will “breakthrough” the carbon bed. Initial breakthrough is defined

as the time when the contaminant concentration in the effluent exceeds the treatment objective. In systems with multiple beds, the individual beds can be operated beyond the time of initial breakthrough, provided the blended effluent is still below the guideline value. Ultimately, the GAC is regenerated or replaced. The replacement and/or regeneration of exhausted media are important economic considerations in achieving the MAC.

Common operating problems when using GAC adsorption contactors can include biological growth and the concurrent increase in heterotrophic plate counts in the effluent, and clogging and fouling of the carbon adsorber by suspended solids (AWWA, 1991). Operating considerations may include a need to ensure a proper backwash, maintain the bed depth and bed density after backwashing and control the flow rate. To prevent the bed from clogging, pretreatment of the water before it enters the GAC contactor is often required (Snoeyink, 1990; Speth, 1990; AWWA, 1991; Crittenden et al., 2005).

Full-scale studies of GAC adsorber and GAC filter-adsorber (sand/GAC) have demonstrated that both systems were effective in removing VOCs from surface water. Of the two system types, a GAC adsorber is typically optimal since the GAC bed is deeper and provides greater EBCT. The increased EBCT also reduces the impact of NOM preloading. In one study, a GAC adsorber reduced influent concentrations of up to 24 µg/L of 1,2-DCA to far below 5 µg/L using an average hydraulic loading rate of 0.9 gpm/ft^2 (2.2 m/h), an average EBCT of 20.4 minutes and a bed life of approximately 100 days (Lykins et al., 1984, 1994). Pilot scale results indicated that influent concentrations of 8 µg/L and 2 µg/L of 1,2-DCA were both reduced to 0.1 µg/L, using GAC depths of 0.8 and 0.9 meters, and EBCTs of 20 and 11 minutes, respectively (Love and Eilers, 1982).

Mathematical model predictions using equilibrium data have been used to estimate full-scale GAC performance for the reduction of 1,2-DCA in drinking water (Adams and Clark, 1991; Lykins and Clark, 1994). The estimated carbon-usage rate to reduce an influent concentration of 100 µg/L of 1,2-DCA to an effluent concentration of 5 µg/L is 1.05 lb/1000 gal (0.13 kg/m^3), a hydraulic loading rate of 4 gpm/ft^2 (9.8 m/h), an EBCT of 15 minutes, and a bed life of 40 days (Lykins and Clark, 1994).

7.1.2 Air stripping: packed tower aeration

Air stripping treatment technology is widely used to reduce the concentration of VOCs, such as 1,2-DCA, in drinking water (Dyksen et al. 1984; Cummins and Westrick, 1990; U.S. EPA, 1991a; Dzombak et al., 1993; WHO, 2011; 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 drinking water. PTA application allows for greater air-to-water ratios than other aeration systems (diffuser aerator, multiple tray aerator, spray aerator, mechanical aerator). In PTA, the contaminated water flows downward by gravity over a bed of packing material, while air is introduced into the tower below the packed bed and flows upward countercurrent to the water flow. As PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to reduce the contaminant concentrations prior to discharge into the atmosphere may be necessary (Crittenden et al. 1988; Adams and Clark, 1991).

Several factors affect the stripping rate of VOCs: air-to-water ratio; available area of mass transfer; 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 et al. 2005). Although the PTA process is effective, site considerations such zoning, column height and noise restrictions should be considered. Where the installation of a PTA system is restricted other means of treatment may have to be considered (Dyksen, 2005). Diffused aeration, multi-stage bubble aerators, tray aeration, and shallow tray aeration have been identified as alternate air stripping treatment technologies for the reduction of 1,2-DCA in drinking water for small systems (U.S. EPA, 1998).

A common operating problem is scaling and fouling of the column. The main causes of fouling are calcium carbonate and/or calcium sulphate scale, iron oxidation and microbial growth. Methods to prevent the fouling of the column include pH suppression of the influent, using 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, such as the use of a corrosion inhibitor, may also be required to reduce corrosive properties of the water due to increased dissolved oxygen from the aeration process. Environmental conditions, such as water temperature, may impact the packed tower performance. Although temperatures below freezing can cause operational issues, contact between water and air in PTA will result in a change in the air temperature until it approaches the water temperature. The temperature influences both the Henry's Law constant and the rate of mass transfer coefficient of the contaminant. These parameters impact the size of the equipment and the removal efficiency of the VOCs (Crittenden et al., 2005).

Full-scale data demonstrated that PTA, using an air-to-water ratio of 120, an air stripper length of 24 ft (7.3 meters), a packed column diameter of 4.5 ft (1.4 meters) and a hydraulic loading rate of 17.3 gpm/ft^2 (42.2 m/h), was capable of reducing an influent groundwater concentration of 80 µg/L of 1,2-DCA to less than 1 µg/L (AWWA, 1991).

The installation of a full scale 60 ft (18 m) air stripping tower reduced the influent concentrations of 11.0 µg/L and 5.1 µg/L, found in two wells, to 1.3 µg/L in the finished water. No information was provided on the operational conditions of the PTA systems (Querishi and Ulrich, 2007).

According to Crittenden et al. (1988), typical full-scale design parameters for the reduction of 1,2-DCA include an air-to-water ratio of 150.6, an air stripper length 10.2 meters, packed column diameter of 4.5 meters. Under these conditions, a 99% reduction of 1,2-DCA could be achieved in drinking water with an influent concentration of 100 µg/L to a final concentration of 1 µg/L.

Diffused aeration generally achieves lower removal efficiencies and has higher power requirements than PTA systems. The efficiency of the process is dependent on several factors, including diffuser type, air-to-water ratio, depth of the water in the contact chamber, detention time and water temperature. Diffused aeration performance data for 1,2-DCA indicates a reduction in the range of 42 - 77% (Love and Eilers 1982; U.S. EPA, 1990; 1991a).

7.1.3 Combination of aeration and granular activated carbon

Generally, the use of GAC after air stripping is intended to reduce the release of VOCs into the atmosphere. However, several articles have indicated that combining aeration technologies and GAC into a two-step treatment train is very effective for achieving low finished water concentrations of VOCs (Robeck and Love, 1983; McKinnon and Dyksen, 1984; Stenzel and Gupta, 1985; U.S. EPA, 1991a). In a municipal-scale treatment plant combining these processes, air stripping was used for the bulk reduction of VOCs from water, and activated carbon was used in the second step to further reduce residual VOC concentrations below the

detection limit of 0.1 µg/L (Robeck and Love, 1983). The air stripping process preceding liquid-phase GAC adsorption can also extend carbon bed life (Hess et al., 1981; Stenzel and Gupta, 1985; U.S. EPA, 1991a). The common operational problems existing with PTA systems and GAC adsorption contactors are similar and should be considered when these combined technologies are employed. However, no information specific to the effectiveness of the process for reduction of 1,2-DCA was available in the literature.

7.1.4 Membrane filtration

The performance of reverse osmosis (RO) systems depends on a variety of factors, including pH, turbidity, iron and manganese concentrations in the raw water, membrane type, molecular weight cutoff, as well as the structure and chemical characteristics of the compounds (AWWA, 1991; Fronk and Lykins, 1998). A pretreatment of the feed water is required to prevent scaling and fouling of the RO membranes. Pilot scale experiments demonstrated that thin film composite membranes were more effective for removing chlorinated ethanes from drinking water than cellulose acetate and polyamide membranes. A selected membrane was capable of achieving up to 71% reduction of 1,2-DCA in spiked groundwater. No information was provided on the concentration of 1,2-DCA in the feed water (Lykins et al., 1988; Fronk and Lykins, 1998). Typically, high pressure membranes are not considered for VOCs such as 1,2-DCA because of cost and energy issues.

7.1.5 Advanced oxidation processes

Advance oxidation processes refer to the use of combinations of chemical oxidants, ultraviolet (UV) light and catalysts (e.g., O_3/H_2O_2, O_3/UV; UV/ H_2O_2; UV/TiO_2; O_3/UV/TiO_2; O_3 oxidation at elevated pH) to generate highly reactive radicals such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants. In a pilot-scale study, a concentration of 16.0 mg/L of 1,2-DCA in contaminated groundwater was reduced to below the detectable level (no detection limit was stated) after 30 minutes treatment with a UV dose of 160 watts/L, combined with a hydrogen peroxide (H_2O_2) dose of 150 mg/L/min (Hager et al., 1987). The formation of by-products from the oxidation and/or advanced oxidation of 1,2-DCA or other inorganic or organic compounds in the source water should be considered when using these processes.

7.1.6 Emerging treatment technologies

New drinking water treatment technologies for 1,2-DCA are being studied but are still primarily in the experimental stage and/or have no published information on the effectiveness of full-scale application. These include:

- Cascade crossflow stripping: The flow directions of the water and the air in this process are at right angles. Experimental data has shown a higher stripping efficiency for 1,2-DCA and a lower pressure drop for this process in comparison to the traditional countercurrent air stripping (Harrison et al., 1993; Verma et al., 1994). A pilot scale cascade crossflow study indicated a capability of reducing an influent concentration of 1.15 mg/L of 1,2-DCA to 0.008 mg/L, using an air-to-water ratio of 135 and an hydraulic loading rate of 18.9 kg/m^2/s. Parallel experiments conducted with a countercurrent configuration column achieved a finished water concentration of 0.087 mg/L, when conducted at comparable operating conditions (Verma et al., 1994).
- Membrane Air-Stripping - Air-stripping of VOCs with microporous polypropylene hollow fibre membranes has been introduced as an alternative method to PTA; however,

no information was found on the removal of 1,2-DCA specifically (Semmens et al., 1989; Castro and Zander, 1995).

- Bioreactors have been used for treatment of contaminants such as petroleum hydrocarbons, monoaromatic hydrocarbons, chlorinated aliphatics and aromatics in groundwater. The most commonly used bioreactors for groundwater include: trickling filters, upflow fixed-film reactor and fluidized bed reactor (Langwaldt and Puhakka, 2000). Laboratory experiments, using two fixed bed reactors, achieved up to 90% degradation and mineralization of 1,2-DCA in feed concentrations in the range of 20-25 mg/L (Stucki et al., 1992).

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for decreasing 1,2-DCA concentrations in drinking water.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International/ American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2014):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- QAI (www.qai.org);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained directly from the SCC (2014).

Treatment devices to remove 1,2-DCA from untreated water (such as a private well) can be certified either specifically for 1,2-DCA removal or for the removal of VOCs as a group. Certified devices for the reduction of 1,2-DCA from drinking water, rely on an adsorption (activated carbon) and reverse osmosis technologies.

For a drinking water treatment device to be certified to NSF/ANSI Standards 53 for the reduction of 1,2-DCA alone, the device must be capable of reduction an average influent concentration of 0.015 mg/L to a maximum of 0.005 mg/L. For a drinking water treatment device to be certified to NSF/ANSI Standards 53 by surrogate testing, the device must be capable of reduction of an influent concentration of 0.088 mg/L 1,2-DCA to a maximum product water concentration of 0.0048 mg/L (NSF/ANSI, 2013a).

RO systems are intended for point-of-use installation only. This system requires larger quantities of influent (incoming) water to obtain the required volume of drinking water, as the systems reject (waste) part of the influent water. A consumer may need to pretreat the influent water to reduce the fouling and extend the service life of the membrane. For a drinking water treatment device to be certified to NSF/ANSI Standards 58 by surrogate testing, the device must

be capable of a 95% reduction of 1,2-DCA, from an influent concentration of 0.088 mg/L to a maximum of 0.0048 mg/L (NSF/ANSI, 2013b).

A number of residential treatment devices from various manufacturers are available that can remove 1,2-DCA from drinking water to concentrations below 5 µg/L. Filtration systems may be installed at the faucet (point-of-use) or at the location where water enters the home (point-of entry). Point-of-entry systems are preferred for VOCs such as 1,2-DCA, because they provide treated water for bathing and laundry as well as for cooking and drinking. This will reduce the potential for 1,2-DCA exposure through inhalation and dermal absorption. Certified point-of-use treatment devices as well as a limited selection of point-of-entry devices are currently available for the reduction of VOCs, including 1,2-DCA. In the case where certified point-of-entry treatment devices are not available for purchase, systems can be designed and constructed from certified materials. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the water it produces to verify that the treatment device is effective. Devices can lose removal capacity through usage and time and need to be maintained and/or replaced. Consumers should follow the manufacturer's instructions regarding the expected longevity of the components in their treatment device.

8.0 Kinetics and metabolism

8.1 Absorption

1,2-DCA is readily absorbed by both humans and experimental animals through the lungs, the gastrointestinal tract and the skin.

Although no studies have been conducted with humans, some accidental, intentional or occupational exposures resulting in adverse effects (e.g., central nervous system effects) have been reported in case studies and have substantiated the absorption of 1,2-DCA following ingestion, dermal contact and inhalation (NIOSH, 1976).

Ingested 1,2-DCA is absorbed rapidly and extensively in laboratory animals. Peak blood levels were attained within 10–20 minutes of dosing when single oral 1,2-DCA doses of 25, 50 and 150 mg/kg body weight (bw) in corn oil were administered to male Sprague-Dawley rats (Spreafico et al., 1980) and male Osborne-Mendel rats (Reitz et al., 1982).

Several studies investigated the effect of the vehicle (water versus corn oil) on the uptake of 1,2-DCA from the gastrointestinal tract in male Wistar and F344 rats exposed via gavage (Withey et al., 1983; Saghir et al., 2006). Results showed that when 1,2-DCA was administered in water, peak blood levels were reached up to 3 times faster than when it was administered in corn oil.

1,2-DCA is also readily absorbed in experimental animals following inhalation, although it takes slightly longer to reach peak concentrations in blood following inhalation compared with ingestion. Peak blood levels were reached within 2–3 hours of continuous inhalation exposure when rats were exposed to 150 ppm in air (male Osborne-Mendel: 8–9 µg/mL blood; Reitz et al., 1980; 1982) and to 50 and 250 ppm in air (male Sprague-Dawley: 1.34 µg/mL and 29.36 µg/mL blood; Spreafico et al., 1980) and remained steady at those levels until after exposure was ended at 6 hours.

Dermal absorption of 1,2-DCA has been demonstrated in *in vivo* studies involving mice, guinea pigs and male Fischer rats (Tsuruta, 1975; Jakobson et al., 1982; Morgan et al., 1991) and in *in vitro* studies involving humans and/or guinea pigs (Tsuruta, 1977; Frasch and Barbero, 2009).

Absorption of 1,2-DCA *in vivo* was demonstrated in a study by Morgan et al. (1991), in which male Fischer rats were dermally (shaved and occluded) exposed to 2 mL of various concentrations (neat, and three different aqueous solutions: one-third, two-third or saturated) of 1,2-DCA for 24 hours. Rapid absorption was seen with the aqueous solutions as peak blood levels were reached within 2 hours of exposure, and then decreased to near control levels by 24 hours, due to the depletion of the chemical in the exposure cell. Of the three aqueous solutions, the saturated solution caused the highest blood concentration, showing that blood levels were directly related to the degree of saturation. Volumes of 1,2-DCA aqueous solution absorbed after 24 hours ranged from 0.24 to 0.32 mL, and exposure concentrations ranged from 6738 µg/mL (saturated) to 2270 µg/mL (one-third saturated). In contrast, blood levels for the neat solution continued to increase during the 24 hour exposure, possibly due to equilibrium not being reached; blood levels reached 135 µg/mL but only half (1.1 mL) was absorbed into the skin.

Jakobson et al. (1982) also monitored uptake via the blood when guinea pigs were exposed dermally (shaved and occluded) to 1 mL of 1,2 DCA for up to 12 hours. Increased blood concentrations were observed throughout the entire exposure period, except for a marked decrease after 30 minutes for a brief period (30 minutes). Blood concentrations reached approximately 20 µg/mL at 12 hours and decreased non-linearly once exposure ended. In contrast, Tsuruta (1975) exposed mice to 0.5 mL of 1,2-DCA to a small shaved abdominal area for a period of only 15 minutes, because in this period no biotransformation was expected. Analysis showed that a total of 2078 µg of 1,2-DCA was dermally absorbed with 96% of 1,2-DCA being retained in the whole body analysis, and 4% being found in exhaled breath. The percutaneous absorption rate was calculated 479.3 nmoles/min/cm^2 of skin. Tsuruta (1977) also conducted an *in vitro* experiment using excised skin of rats exposed to 1 mL of 1,2-DCA for 1, 2 or 3 hours, and calculated a lower percutaneous rate of 169 nmoles/min/cm^2.

In vitro dermal exposure to 1,2-DCA using skin samples of hairless guinea pigs and humans resulted in absorption with comparable permeability coefficients of 0.295 and 0.259 cm/h (guinea pigs and humans, respectively; Frasch and Barbero, 2009).

8.2 Distribution

Although no information on the distribution of 1,2-DCA in humans is available, reported adverse health effects and the presence of 1,2-DCA in exhaled breath or in various organs following accidental, intentional or occupational exposure suggest that 1,2-DCA is widely distributed in the body. Once absorbed by the oral and inhalation routes in experimental animals, 1,2-DCA is widely distributed to all major organs, including crossing the blood–brain and placental barriers.

8.2.1 Humans

Luznikov et al. (1985) detected 1,2-DCA in various organs (spleen, stomach, liver and kidney) following autopsies of humans that were acutely poisoned (orally) with 1,2-DCA. Metabolites such as 2-chloroethanol and chloroacetic acids were also detected at low levels. Inhalation of 1,2-DCA caused central nervous system effects in workers (NIOSH, 1976), suggesting that 1,2-DCA is capable of crossing the blood–brain barrier. 1,2-DCA was also detected in breast milk of nursing women and in the breath of these women (1 hour after leaving the worksite where they were exposed) (Urusova, 1953; U.S. EPA, 1980).

8.2.2 Experimental animals

Radioactivity from [^{14}C]1,2-DCA was widely distributed in the major organs of rats within 48 hours after a single oral administration of 150 mg/kg bw in corn oil or a 6-hour exposure to 150 ppm in air (Reitz et al., 1982). The highest amount of radioactivity was present in the liver and kidney, less radioactivity was detected in the forestomach, lung, spleen and stomach and the least amount was found in the carcass.

1,2-DCA was also found in various tissues (blood, liver, lung, adipose tissue, brain, kidney and spleen) of Sprague-Dawley rats following a single oral administration of 25, 50 or 150 mg/kg bw or a 6-hour exposure to 50 and 250 ppm in air (Spreafico et al., 1980). Following oral administration, concentrations of 1,2-DCA peaked within 10 minutes in the liver and within 45–60 minutes in the adipose tissue. The peak concentration in the adipose tissue was 5 times higher (for the two highest oral doses) than that seen in the liver. Following inhalation, the lowest level of 1,2-DCA was detected in the lung, whereas the adipose tissue had the highest level, which was 8–9 times higher than that from oral exposure. As the inhalation exposure increased 5-fold (from 50 to 250 ppm), there was a 20- to 30-fold increase in the concentration of 1,2-DCA in the various tissues (adipose, blood, lung and liver).

1,2-DCA was shown to cross the placental barrier. 1,2-DCA was detected in fetuses in an inhalation study in which groups of pregnant Sprague-Dawley rats were exposed to vapour concentrations of 1,2-DCA ranging from 153 to 1999 ppm for 5 hours on day 17 of gestation (Withey and Karpinski, 1985). Mean fetal concentrations and maternal blood concentrations of 1,2-DCA increased linearly with increasing exposure levels. Payan et al. (1995) also detected 1,2-DCA in fetuses in a developmental study involving Sprague-Dawley rats exposed either by gavage or by inhalation.

In the absence of dermal studies in laboratory animals, ATSDR (2001) suggested that the distribution pattern of 1,2-DCA may resemble that following oral exposure and inhalation, as 1,2-DCA is well absorbed dermally and distribution was not found to be route dependent.

8.3 Metabolism

No information on the metabolism of 1,2-DCA in humans were found in the literature. In animal studies, 1,2-DCA has been shown to be extensively metabolized. 1,2-DCA is metabolized via two competing metabolic pathways: a microsomal oxidative pathway and a glutathione (GSH) conjugation pathway.

8.3.1 Humans

No studies were found in the literature regarding the metabolism of 1,2-DCA in humans following oral, inhalation or dermal exposure (ATSDR, 2001). However, results from an *in vitro* study using human liver microsomes conducted by Guengerich et al. (1991) indicate that the human cytochrome P450 2E1 seems to be a major (and, possibly, the principal) human catalyst responsible for the oxidation of 1,2-DCA.

8.3.2 Experimental animals

1,2-DCA is readily and extensively metabolized in rats and mice. Metabolism of 1,2-DCA occurs primarily in the liver (Spreafico et al., 1979; Sweeney et al., 2008).

Based on various studies conducted *in vivo* and *in vitro*, two different pathways have been proposed for the biotransformation of 1,2-DCA (IPCS, 1995; OEHHA, 1999; ATSDR, 2001; Gwinn et al., 2011):

1) Microsomal oxidative pathway (also known as cytochrome P450–mediated and mixed-function oxidase pathway): In this pathway, in a reaction catalysed by cytochrome P450 enzymes, 1,2-DCA forms an unstable reactive intermediate (gem-chlorohydrin), which then forms 2-chloroacetaldehyde. 2-Chloroacetaldehyde can undergo different paths: it can bind to cellular macromolecules (deoxyribonucleic acid [DNA] or proteins) or it can be further biotransformed to one of the three following metabolites:
   i) 2-chloroacetic acid (a urinary metabolite), which can also be further metabolized to carbon dioxide (an exhaled metabolite) or (via GSH) to *S*-carboxymethyl-glutathione;
   ii) 2-chloroethanol (formed by reduction with alcohol dehydrogenase), which can also be reconverted to 2-chloroacetaldehyde; or
   iii) *S*-carboxymethyl-glutathione (further metabolism, which includes conjugation with GSH and reduction with alcohol dehydrogenase, leads ultimately to the urinary metabolites thiodiacetic acid [also called thiodiglycolic acid] and/or thiodiacetic acid sulfoxide).
2) Direct conjugation or GSH conjugation pathway (also known as GSH-dependent cytosolic pathway): The second metabolic pathway for 1,2-DCA involves direct conjugation with GSH (catalysed by glutathione transferase [GST]) to form *S*-(2-chloroethyl)-glutathione, a half sulphur mustard. *S*-(2-Chloroethyl)-glutathione can undergo several biotransformations:
   i) metabolism to ethylene (ethene) in the presence of GSH); or
   ii) non-enzymatic conversion to a glutathione episulfonium ion, which is an alkylating agent. This alkylating agent can then:
      - form adducts with DNA, ribonucleic acid (RNA) or proteins;
      - react with water to form *S*-(2-hydroxyethyl)glutathione; or
      - react with GSH to form *S*,*S*′-ethene bis glutathione, which is further converted to *S*,*S*′-ethene bis L-cysteine, a urinary metabolite.

Both pathways involve GSH, which in general is used for the detoxification process; however, with 1,2-DCA, GSH may also take on another role, one of bioactivation, such as the formation of a half sulphur mustard, which is an alkylating agent (Jean and Reed, 1992).

The microsomal oxidative pathway (cytochrome P450) is a high-affinity pathway with a low capacity (Gargas et al., 1986a) and is predominant at lower concentrations. However, it becomes saturated at relatively low concentrations of 1,2-DCA (D'Souza et al., 1987). Conversely, the GST-mediated pathway has a lower affinity but a higher capacity (Gargas et al., 1986a) and, based on various studies, is predominant at higher concentrations. At high concentrations of 1,2-DCA, the oxidative pathway is overwhelmed and causes a greater proportion of the dose to be biotransformed through the GST-mediated pathway (U.S. EPA, 1985; Gwinn et al., 2011). Gwinn et al. (2011) reported that saturation of the oxidative pathway may occur when 1,2-DCA blood levels reach 5–10 µg/mL, which represents doses of approximately 150 ppm for rat inhalation studies and 25 mg/kg bw for rat oral studies (based on Spreafico et al., 1980; Reitz et al., 1982). As a result of saturation, the percentage of excreted urinary metabolites decreases, whereas increases are seen in levels of unchanged 1,2-DCA in blood and exhaled breath.

The metabolites formed (half sulphur mustard and glutathione episulphonium ion) via the GSH pathway may be mostly responsible for the DNA damage, mutagenicity and carcinogenicity of 1,2-DCA (U.S. EPA, 1985; Gwinn et al., 2011).

Pretreatment of Sprague-Dawley rats with disulfiram (an inhibitor of aldehyde dehydrogenase and, to a lesser extent, microsomal mixed-function oxidase activities) followed by exposure to 50 ppm 1,2-DCA in air for 7 hours resulted in a higher blood concentration (5-fold increase) of unchanged 1,2-DCA compared with rats treated only with 50 ppm 1,2-DCA. The pretreated rats also eliminated a higher amount of unchanged 1,2-DCA in the breath, and, as a result, less was excreted as urinary metabolites (Cheever et al., 1990).

8.4 Excretion

There is little quantitative information on the elimination of 1,2-DCA in humans. However, in one occupational study, 1,2-DCA was detected in exhaled air of women exposed through inhalation and dermal contact. In experimental animal studies, 1,2-DCA has been shown to be extensively metabolized and rapidly eliminated from the body. The primary route of excretion for 1,2-DCA is urinary in the form of non-volatile metabolites. Smaller amounts of unmetabolized 1,2-DCA are excreted through the lungs.

In a study in which Osborne-Mendel rats received radiolabelled 1,2-DCA as a single oral dose of 150 mg/kg bw in corn oil or as a 6-hour inhalation exposure of 150 ppm (Reitz et al., 1982), the total excretion of radiolabelled 1,2-DCA or its metabolites was approximately 96% during the 48-hour period following exposure. During this frame, 29% of the body burden was eliminated as unchanged 1,2-DCA in expired air following oral dosing, whereas only 2% was eliminated when exposure was by inhalation. The distribution pattern of the non-volatile urinary metabolites was similar between both routes of exposure, with 84–86% of excretion in urine, 7–8% exhaled as carbon dioxide and 2% in faeces. The urinary metabolites were characterized as mainly thiodiacetic acid (67–68%) and thiodiacetic acid sulphoxide (26–29%) following exposure by both routes.

Mitoma et al. (1985) also conducted oral material balance studies with rats and mice. During pretreatment, male B6C3F1 mice were orally dosed with 38 and 150 mg/kg bw/day for 4 weeks, whereas male Osborne-Mendel rats received unlabelled 1,2-DCA at doses of 25 and 100 mg/kg bw/day for 4 weeks. After the pretreatment, mice and rats were administered a single oral dose of radiolabelled 1,2-DCA and were observed in metabolism cages for 48 hours. 1,2-DCA was extensively metabolized. Of the total radioactivity excreted in the 48 hours following exposure, 11.5% was excreted unchanged in breath, 8% was exhaled as carbon dioxide and 69% was excreted in the excreta (primarily urine) in rats. In mice, 7.7% was excreted unchanged in breath, 18% as carbon dioxide and 82% in the excreta. Urinary metabolites were identified as *S*-carboxymethylcysteine, thiodiacetic acid and chloroacetic acid; the urinary metabolite patterns were similar in rats and mice.

In another study, Payan et al. (1993) investigated the effect of increasing doses on the excretion of metabolites. Male Sprague-Dawley rats were given a single oral dose of radiolabelled 1,2-DCA in mineral oil (doses ranged from 0.125 to 8.08 mmol/kg bw), and urine samples were collected over a 24-hour period. The percentage of administered radioactivity excreted in the urine decreased (from 63% to 7.4%) with increasing dose of 1,2-DCA. Thiodiglycolic acid was identified as the main urinary metabolite, and the remaining metabolites were other thioether compounds. The authors suggested that the decrease in radioactivity from 0.125 to 4.04 mmol/kg bw could be due to saturation of the metabolism or to a defect of gastrointestinal absorption, rather than a result of renal toxicity. Changes in clinical chemistry related to the kidney were observed in rats dosed with 8.08 mmol/kg bw, but not at the lower doses (0.125–4.04 mmol/kg bw).

After groups of rats were exposed for 2 years to 50 ppm 1,2-DCA in air, Cheever et al. (1990) dosed a subgroup of rats with a single radiolabelled dose of 1,2-DCA at 150 mg/kg bw and examined the metabolism for 24 hours. Of the total radioactivity administered to rats, 34–43% was recovered in the urine as metabolites, 27–40% in exhaled breath as unchanged 1,2-DCA and 0.1% as carbon dioxide. Urinary metabolites were identified as thiodiglycolic acid (54–71%), thiodiglycolic acid sulphoxide (18–33%) and chloroacetic acid (0.3–4%), and the remaining 12% of the radioactive metabolites were unidentified.

There is little quantitative information on the elimination of 1,2-DCA in humans. However, unchanged 1,2-DCA has been detected in exhaled air of women exposed through inhalation and dermal contact in the workplace; the levels in exhaled air decreased over time (Urusova, 1953).

8.5 Physiologically based pharmacokinetic (PBPK) modelling

Several PBPK models have been developed to describe the kinetics of 1,2-DCA in rats (Gargas et al., 1986b; D'Souza et al., 1987, 1988; Environ, 2004; Sweeney et al., 2008). The description of 1,2-DCA metabolism in the liver, lung and extrahepatic tissues has evolved as new models have been developed and is one of the major differences between models.

D'Souza et al. (1987, 1988) developed a five-compartment PBPK model that simulated the kinetics of 1,2-DCA along with its metabolites in the body. The compartments included lung, liver, fat and grouped compartments representing richly perfused tissues (e.g., kidney and spleen) and slowly perfused tissues (e.g., muscles and skin). The model accounted for exposure via inhalation and ingestion, and the liver and lung were considered to be the only organs where metabolism took place. As discussed in Section 8.3, 1,2-DCA is metabolized by two different pathways, a microsomal oxidative pathway (a saturable pathway) and a GSH conjugation pathway; both pathways are reflected in the model. The model also reflected the depletion of GSH levels with exposure to high 1,2-DCA concentrations; the GSH is then resynthesized, with levels surpassing baseline levels and eventually return to normal. The model was validated for mice and rats using oral and inhalation exposure routes.

Two more recent PBPK models for 1,2-DCA refined the model by D'Souza et al. (1987, 1988). Environ (2004) modified the model to include a revised oral absorption rate and also revised the constant for the time delay for resynthesis of GSH following depletion. Another modification was made to reflect different levels of GSH protein in the lungs versus the liver. The model was validated with experimental data (using inhalation and oral data sets for rats and mice). Sweeney et al. (2008) further refined the structure of the PBPK model of Environ (2004) to include two compartments for the gastrointestinal tract (to better describe absorption of 1,2-DCA, particularly when dosed in oil), a separate compartment for kidneys and extrahepatic metabolism in slowly perfused tissues, kidney and other richly perfused tissues. Sweeney et al. (2008) also revised the time delay constant for the GSH resynthesis by using a lower value than that used by Environ (2004). The model was validated using data on intravenous, gavage and inhalation doses in rats from 13 studies.

Owing to the absence of pharmacokinetic data in humans, the PBPK models have not been validated for humans. In the absence of a validated human model, a model that is considered to be reasonably representative of potential human metabolism of 1,2-DCA was developed (Nong, 2012). Because the rat model could be appropriately scaled to mice without requiring optimization and human metabolism was considered by looking at differences between rodents and humans in metabolism for similar chemicals metabolized by the same enzymes. Although this approach is not as scientifically strong as the application of a fully validated

human model, the approach is still considered optimal to using a default approach of allometric scaling to extrapolate from rats to humans.

Health Canada (Nong, 2012) reproduced the two most recent models (Environ, 2004; Sweeney et al., 2008) and validated the models using inhalation data from animal studies by Gargas et al. (1986b) and Igwe et al. (1986) and oral data from D'Souza et al. (1988). Application of the Health Canada model to extrapolate from an inhalation study in rodents (Nagano et al., 2006) to ingestion in water by humans for the cancer dose–response assessment is presented in Section 10.1.

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute toxicity

Acute incidental exposure of humans, either by ingestion or by inhalation, to 1,2-DCA has been shown to cause adverse health effects on the central nervous system, liver, kidney, immune system, lung and cardiovascular system, as well as produce deaths in some cases. Dermal contact has been shown to cause severe dermatitis, along with various central nervous system effects; however, these effects may have been a combined effect from dermal contact with and inhalation exposure to 1,2-DCA.

Ingestion of 1,2-DCA has been shown to be toxic to humans. Several case reports of accidental or intentional ingestion of 1,2-DCA have been documented and reviewed in the literature (NIOSH, 1976; U.S. EPA, 1985; IPCS, 1995). Although not all cases of ingestion were fatal, the majority were (NIOSH, 1976; U.S. EPA, 1987b). The onset of symptoms was usually delayed and occurred within 30 minutes to up to 3 hours following exposure; in a few cases, however, symptoms occurred after only a few minutes (NIOSH, 1976; U.S. EPA, 1985). The symptoms included nausea, vomiting, diarrhoea, epigastric pain or tenderness and central nervous system effects (e.g., headache, sleepiness, dizziness, dilated pupils, rapid pulse and unconsciousness). In the case of fatalities, the onset of death was shown to occur between 5 hours and 6 days following ingestion and was due to circulatory or respiratory failure (U.S. EPA, 1985). Damage (tissue congestion, cellular degeneration, necrosis and haemorrhagic lesions) to the liver, kidney, stomach, intestines, spleen, lung, cardiovascular system (heart) and brain and hyperaemia were seen among fatalities (NIOSH, 1976; U.S. EPA, 1985). IPCS (1998) estimated a lethal oral dose of 1,2-DCA in humans to be between 20 and 50 mL, whereas U.S. EPA (1985) and NIOSH (1976) reported it to be as low as 8 mL.

Similar symptoms to those seen following ingestion were observed in individuals exposed by inhalation (nausea, vomiting, epigastric pain or tenderness and central nervous system effects) in occupational settings. In several case reports, however, the acute exposure was fatal; these individuals became unconscious, and death, which was generally attributed to respiratory and circulatory failure, followed. Damage to the liver, kidneys and lungs was also observed, and there were several reports of increases in white blood cells (leukocytosis) and serum bilirubin levels (NIOSH, 1976).

Dermal contact with 1,2-DCA has been shown to cause severe dermatitis in several case reports (Wirtschafter and Schwartz, 1939; NIOSH, 1976). In a few of these case reports, workers handling or splashed with 1,2-DCA also experienced nausea, vomiting, epigastric pain and central nervous system effects (NIOSH, 1976); however, these effects may have been a combined effect from dermal contact with and inhalation exposure to 1,2-DCA.

9.1.2 Subchronic and chronic toxicity

NIOSH (1976) and U.S. EPA (1985) reported that repeated inhalation exposures of industrial workers to 1,2-DCA have produced symptoms similar to those produced by acute exposure, such as headaches, anorexia, nausea, vomiting, epigastric pain, irritation of the eyes and respiratory tract, and effects on the liver and kidney. Only a few cases have resulted in fatalities.

A large number of workers (approximately 1600) in the southern United States were hired in 1994 for cleanup of a hazardous leak originating from an underground and underwater pipeline that was used to store and transport 1,2-DCA (Bowler et al., 2003). Most workers were not provided personal protective equipment and as such were exposed to contaminated water (wet clothes, feet and skin), mud, dirt and dust; many complained of symptoms such as abdominal and chest pain, nausea, vomiting, headaches, rashes and tremors. Over half of the cleanup workers were evaluated by occupational physicians, approximately 400 of whom had complained of adverse health and neurological effects. From these, 221 workers were referred to undergo a full neuropsychological evaluation by the principal author; after screening, however, only 137 were retained for the final analysis. The duration of exposure of these workers varied between 1 and 420 months (mean 28 months, median 13 months). According to the authors, the results suggested a significant relationship between 1,2-DCA "exposure and adverse health symptoms and neuropsychological impairment." Bowler et al. (2003) also found a significant level of emotional dysfunction and vision impairment among those tested. It should be noted that exposure levels were unknown and that a number of workers who were tested were involved in legal proceedings for which their attorneys had requested these health evaluations.

In a preliminary study abstract, neuropsychological effects (lower scores related to divided attention and problem solving in addition to intellectual and memory functioning) were seen in a small subgroup (n = 7) of cleanup workers (most exposed) from the aforementioned Bowler et al. (2003) study who were evaluated separately by Ruffalo et al. (2000).

9.1.3 Carcinogenicity

There are no epidemiological studies concerning exclusive exposure to 1,2-DCA. One epidemiological study examined populations exposed to groundwater drinking water sources and with various contaminants, including 1,2-DCA. Because other chemical exposures were not accounted for, no conclusion of excess cancer could be drawn for 1,2-DCA exposure. Most of the other available human exposure studies were occupational exposure studies involving 1,2-DCA, either used in production or a by-product of the process.

An ecological study in Iowa, which investigated the cancer incidences in municipalities (with populations between 1000 and 10 000) supplied only with groundwater, examined various VOCs and metals (Isacson et al., 1985). Although the results are suggestive of an association between 1,2-DCA and cancer of the colon and rectum, especially in males, no definitive conclusion can be drawn because of the extremely low levels of certain chemicals including 1,2-DCA in the finished water. The authors pointed out that these chemicals are "merely indicators of the groundwater supplies most susceptible to anthropogenic contaminants." As a result, the authors could not conclude which specific water quality variables were responsible for the risk of human cancer and stated that further epidemiological research to characterize the water supplies was needed.

In a case–control study of 230 men exposed occupationally to gasoline vapours and related combustion products (including complex mixtures) in Denmark, an elevated risk of breast cancer was observed, especially in men exposed for over three months (OR = 2.2), and in men

less than 40 years of age when they were first hired (OR = 3.7) (Hansen, 2000). The risk was also elevated when a lag time of 10 years was considered: in men exposed for over three months (OR = 2.5); and in men less than 40 years of age when they were first hired (OR = 5.4). However, 1,2-DCA is a volatile compound found in gasoline and is reported to be present at less than 0.1%. Since these men were exposed to multiple chemicals and mixtures, study limitation prevented the separation of effects from each compound on the risk of male breast cancer. Although the authors suggested that gasoline (vapours and combustion products) may play a role on breast cancer, no causal association could be confidently shown, and as such further studies were proposed.

In the following cohort and case-control studies, the risk of developing brain, stomach, pancreatic, lymphopoietic and haematopoietic tumours, multiple myeloma, and leukemia was explored in workers employed in a variety of plants (petrochemical, chlorohydrin and ethylene oxide production plants) with exposure to many different chemicals (including 1,2-DCA), but development of these cancers was not associated with 1,2-DCA, although some studies were suggestive of an association, possibly in combination with other chemicals.

In a retrospective cohort mortality study (1941-1979) in petrochemical workers (7595 men) in Texas (Union Carbide), workers were exposed to many chemicals, including 1,2-DCA, which was produced in the plant (Waxweiler et al., 1983). An excess risk of death due to brain tumours among one group (hourly workers) of the petrochemical workers when 22 deaths were observed (expected n=10.7, SMR 206). In workers after 15 years since initial hire, significant increases in SMR for mortality due to brain tumours were observed in conjunction with the duration of exposure: less than 10 years of employment (SMR=147, 95% CI = 48-342), between 10-19 years (SMR=357, 95% CI = 116-832) and over 20 years (SMR=377, 95% CI=158-411). Given that workers were exposed to multiple chemicals, the authors were unable to identify a specific carcinogenic agent or another non-occupational cause. In order to further investigate, a case–control study nested within their cohort study was conducted by Leffingwell et al. (1983). In this case–control study, no reference was made to 1,2-DCA as a possible cause of brain tumours. In addition, the authors concluded that "no significant differences between cases and controls were apparent in duration of exposure to" any of the 10 chemicals with the greatest apparent risk associated with brain tumours (1,2-DCA was not included in this short list). At least four cases (excluding maintenance workers) were exposed to 1,2-DCA, one of 505 chemicals reviewed by the authors.

Union Carbide also independently initiated their own cohort and case–control studies on this same population of petrochemical workers. The cohort study (1941-1977) found a borderline significant excess of death due to brain tumours among hourly workers employed for 6 months or more (10 observed versus 5 expected; SMR 200, $p<.05$), (Austin and Schnatter, 1983a). Although there was an excess of death due to malignant brain tumours in the overall plant population (12 observed versus 7.42; SMR 162), it was not statistically significant. When the latency period was analysed in hourly workers with more than 6 months employment, the number of deaths due to brain tumours observed compared to expected increased; after 10 years or more since initial hire, the SMR was 248 ($p>.05$), and after 20 years or more, the SMR was 337. Although elevated cases of death due to brain cancer was found in this subgroup of hourly workers, the authors discuss various observations that either suggest an occupational cause or negate it (e.g. two case-control studies that failed to find an association), and ultimately conclude that there is not enough evidence to link the brain tumours in hourly workers to occupational factors.

In a follow-up study, these workers were followed for an additional 6 years (Teta et al., 1991) during which an additional 5 deaths due to brain tumours (1 benign and 4 malignant) were observed (expected n = 3.4, SMR = 147). However, even with the longer follow-up period, the authors were unable to identify any workplace factor to explain the excess deaths related to brain tumours. The associated case–control study (Austin and Schnatter, 1983b), primarily concerned with the cause of brain tumours, also failed to find a causal association between workplace exposure to various chemicals, including 1,2-DCA, and brain tumours.

A cohort study (1952–1977) of a Texas fuel additive (tetraethyl lead) plant where several chemicals, including 1,2-DCA, were used in the manufacture of the fuel additive or produced at the plant, was undertaken to investigate several cases of multiple myeloma and deaths related to brain tumours (Sweeney et al., 1986). Overall, a slight increase (not significant) was seen in deaths due to malignant tumours (38 observed versus 36.95 expected; standardized mortality ratio = 103; 90% confidence interval = 77–135) which was, in part, related to slight increases in the number of deaths due to brain tumours (4 observed versus 1.88 expected), as well as various other tumours. Exposure data was not reported due to incomplete work history records, however an industrial hygiene survey conducted in 1980 indicated that the levels of 1,2-DCA (as well as a few other chlorinated compounds) to which workers were exposed were below the standards set by the U.S. Occupational Safety and Health Administration and U.S. National Institute for Occupational Safety and Health. Other limitations of the study included small sample size, small number of deaths and low power for detecting excess risk of mortality from various cancers including rate causes of death. The authors concluded overall that "no statistically significant increases in site-specific mortality from malignancies were observed, including multiple myeloma and brain tumors."

In a cohort study of ethylene oxide production workers, an excess in mortality due to stomach cancer (3 observed versus 0.4 expected) and leukaemia (2 observed versus 0.14 expected) as well as diseases of the circulatory system was observed in the full-time exposed subcohort (Hogstedt et al., 1979). 1,2-DCA was one of the primary by-products in the processes involved in the production of ethylene oxide. The authors could not seem to pinpoint any particular chemical in the production process that was responsible for the cancers; however, they hypothesized that ethylene oxide and 1,2-DCA, along with possibly two other chemicals, ethylene chlorohydrin and ethylene, might be responsible. Hogstedt et al. (1979) point out that further studies and a longer follow-up period might help clarify the risks associated with the production of ethylene oxide.

In a cohort study of men employed in a chlorohydrin production unit of Union Carbide, excess deaths from pancreatic cancer (SMR = 492) and lymphopoietic and haematopoietic cancers (SMR = 294) were observed (Benson and Teta, 1993). In this production unit, several chemicals were used as raw materials, were produced in the unit or were by-products of the process (1,2-DCA was one of the main by-products). Based on their records, several of the employees who died from pancreatic cancer had overexposure to or injuries from 1,2-DCA in the work unit. Although the authors were unable to identify the causative agent or agents, they were suggestive of an association between 1,2-DCA (based on its known toxicity and probable exposure of employees), possibly in combination with other chlorinated hydrocarbons, and death from these cancers.

In contrast, no increased risk of cancer (pancreatic, lymphopoietic and haematopoietic) was seen in Dow Chemical ethylene and propylene chlorohydrin production plant workers (Olsen et al., 1997). Different factors may explain the differences between these two cohort studies, including differences in first employment dates, sample size, intensity of exposure,

production processes (enclosed in building versus enclosed process), different levels of exposure, different follow-up periods for the cohorts, and possible confounding factors. However, as suggested by the authors, an additional follow up period of 5 to 10 years might be useful for comparison purposes to the study by Benson and Teta (1993) which had a longer follow-up period to account for the latency period associated with the cancers.

9.1.4 Genotoxicity

9.1.4.1 In vitro

Information is limited regarding the genotoxic effects of 1,2-DCA in human cells *in vitro*.

Gene mutations were induced with 1,2-DCA exposure in two human lymphoblastoid cell lines (Crespi et al., 1985). Results showed that 1,2-DCA was more mutagenic (about 25-fold more) in the AHH-1 cell line (100–1000 µg/ml) than in the TK6 cell line (500–1000 µg/ml) owing to a greater GST activity (5-fold) in the AHH-1 line.

Chromosomal damage (micronuclei formation) was induced with 1,2-DCA exposure (1–5 mmol/L) in three metabolically competent human cell lines: AHH-1, h2E1 and MCL5 (Doherty et al., 1996). Because these three cell lines, which are genetically engineered, are able to express metabolizing enzymes, the use of 9000 × *g* rat liver supernatant (S9) is not needed.

DNA damage occurred in isolated human lymphocytes (with S9 metabolic activation) in an alkaline comet assay at 1,2-DCA concentrations of 2–6 mmol/L (Tafazoli et al., 1998).

9.1.4.2 In vivo

Data in the literature on the genotoxic effects of 1,2-DCA in humans are limited to one study by Cheng et al. (2000). Through blood sampling, sister chromatid exchange frequency was determined in 51 men working in vinyl chloride manufacturing, with low to moderate amounts of 1,2-DCA exposure, and 20 workers assumed to have no exposure. This study found that smoking and exposure to 1,2-DCA at concentrations of about 1 ppm in air were associated with increased sister chromatid exchange frequency. However, study limitations prevent the separation of the effects from smoking, vinyl chloride exposure and 1,2-DCA exposure on sister chromatid exchange frequency.

9.1.5 Reproductive and developmental toxicity

No epidemiological studies have been conducted with regards to reproductive and developmental outcomes associated with exposure to 1,2-DCA specifically. Several studies have been conducted for chemical exposures that included 1,2-DCA; however, because the populations or workers may have been exposed to multiple contaminants, it is difficult to isolate effects related to exposure to 1,2-DCA alone.

A limited occupational study reports on an increased rate of premature births in female workers (54 females) and in wives of male workers (44 males) working in a Chinese synthetic fibre factory where 1,2-DCA was used (0.4–384 ppm); however, workers were also exposed to other chemicals (Zhao et al., 1989).

In a cross-sectional study looking at the effects of public drinking water contamination on birth outcomes in northern New Jersey, the list of contaminants included 1,2-DCA (Bove et al., 1995; Bove, 1996). The authors found an increased prevalence of cardiac defects from drinking water exposure levels greater than 1 µg/L (odds ratio = 2.11), which increased (odds ratio = 2.81) when the results were recategorized according to detected versus non-detected 1,2-DCA. It should be noted, however, that the population was also exposed to other contaminants, such as chlorinated solvents and trihalomethanes, and that these results are only suggestive and need to be interpreted with caution, as suggested by an ATSDR (2001) review.

Croen et al. (1997) investigated whether an association existed between maternal residential proximity to hazardous waste sites, specifically National Priorities List sites, and the incidence of selected congenital malformations, such as neural tube defects, based on data from a California population-based case–control study. An increase in the incidence of neural tube defects was found in offspring of residents living in a census tract (i.e., counties divided into subdivisions for census purposes) with a National Priorities List site that was contaminated with 1,2-DCA (crude odds ratio = 2.8, 95% confidence interval = 1.0–7.2). However, this neural tube defect risk decreased (odds ratio = 1.7) for maternal residence within 1.6 km of a National Priorities List site. Although they reported risks for single chemicals, the authors acknowledged that waste sites contain several chemical contaminants, and, as a result, residents may also be exposed to several chemicals.

9.2 Effects on experimental animals

9.2.1 Acute toxicity

The 6-hour median lethal concentration (LC_{50}) of 1,2-DCA in female mice was 1050 mg/m^3 (Gradiski et al., 1978). In rats (different strains), the LC_{50} varied between 4000 and 6600 mg/m^3 over an exposure period of 6–7 hours (Spencer et al., 1951; Bonnet et al., 1980). The oral median lethal dose (LD_{50}) for CD-1 mice was 489 and 413 mg/kg bw for males and females, respectively (Munson et al., 1982). The oral LD_{50} ranged from 680 to 770 mg/kg bw for rats (McCollister et al., 1956; Smyth et al., 1969) and was 860 mg/kg bw for rabbits (RTECS, 2006). The dermal LD_{50} was 3.89 ml/kg for rabbits (Smyth et al., 1969).

In laboratory animals, following acute inhalation exposures, 1,2-DCA produced central nervous system effects, irritation of the lung and adverse effects on the adrenal glands, liver and kidney (Spencer et al., 1951; McCollister et al., 1956).

A recent study by Hotchkiss et al. (2010) demonstrated histopathological changes to the olfactory (nasal) epithelium in Fischer 344 rats (both sexes) exposed to 1,2-DCA at 200, 600 or 2000 ppm for 4 hours or at 100 and 150 ppm for 8 hours. No histopathological changes were seen in rats exposed to 50 ppm for either 4 or 8 hours. At 2000 ppm, increased mean adrenal gland and kidney weights (both relative and absolute) as well as changes in relative liver weights were seen in both sexes, which were accompanied by morphological alterations in both the kidney and liver. Bronchoalveolar lavage did not reveal any significant effects. Neurobehavioural effects were also measured using functional observational battery tests (during pretreatment and on days 1, 8 and 15) with another group of rats exposed to 0, 200, 600 and 2000 ppm for 4 hours. Effects related to central nervous system depression were seen at the two highest doses only on day 1. Pathological examination on day 15 revealed a regeneration (repair) of the nasal epithelium, indicating an adaptive or repair response when comparing results seen directly after exposure to 4 hours in the first half of the study. Based on the central nervous system depression endpoint observed on day 1, the authors established a no-observed-effect concentration (NOEC) of 200 ppm for behavioural neurotoxicity. The authors also established an overall no-observed-effect concentration (NOEC) of 50 ppm for up to 8 hours in Fischer 344 rats (both sexes), based on neuropathology observed in the most sensitive tissue identified (nasal epithelium).

Transitory lung injury, seen as changes in lung tissue, congestion, oedema and interstitial inflammatory changes, was observed in 80 male Wistar rats given a single dose of 1,2-DCA by gavage in sunflower oil at 136 mg/kg bw and sacrificed at various times (days 1, 5, 15 and 30) after exposure (Salovsky et al., 2002). 1,2-DCA was also shown to increase lipid peroxidation

(as seen by increased levels of malondialdehyde, a marker of lipid peroxidation, in lung homogenate) on day 1, which indicates early cell damage or cytotoxicity in lung tissues.

An investigation of acute immunotoxicity was performed after single 3-hour inhalation exposures to target concentrations of 0, 2.5, 5 and 10 ppm in female CD-1 mice and 0, 100 or 200 ppm in male Sprague-Dawley rats (Sherwood et al., 1987). A significant increase in mortality from streptococcal pneumonia occurred in mice exposed to 5 and 10 ppm, and a significant decrease in the amount of *Klebsiella pneumoniae* rendered non-viable in lungs occurred in high-dose mice, but not in rats. No other immunotoxic effects, including changes in amounts or viability of alveolar macrophages or T- and B-cell function in regions distant to the lungs, were observed.

9.2.2 Short-term exposure

Inflammation (multifocal to diffuse) of minimal severity of the mucosa and submucosa of the forestomach was observed at 100 mg/kg bw/day in Sprague-Dawley rats (10 of each sex) administered 1,2-DCA by gavage in corn oil for 10 consecutive days. At the highest dose (300 mg/kg bw/day), mortality was significant in both sexes (10/10 females and 8/10 males). At the highest dose, apart from an observation of diffuse reddening of the lungs, no histopathological examinations were performed because of protocol limitations (Daniel et al., 1994).

In an assessment of immunotoxicity, groups of male CD-1 mice (n = 48 for controls and n = 32 for each exposure group) were administered 1,2-DCA in the drinking water for 90 days at concentrations of 0, 0.02 , 0.20 and 2.0 mg/ml (equivalent to 0, 3, 24 and 189 mg/kg bw/day) (Munson et al., 1982). Decreased water consumption was seen at the two highest doses. Although a concentration-dependent decrease in growth rate was observed, only a slight suppression of humoral immunity (not statistically significant) was seen at the high dose. This is in contrast to the range-finding study, in which male CD-1 mice (10–12 per dose) were administered 1,2-DCA by gavage at 0, 4.9 or 49 mg/kg bw/day for 14 days (Munson et al., 1982). Suppression of humoral (statistically significant and dose related) and cell-mediated immunity (slight but statistically significant and not dose related) was seen in treated mice. In addition, a significant reduction (30%) in leukocyte count was observed in high-dose mice. The authors attempted to explain the differences in immune response in both studies as partly due to a higher level of immunocompetent cells resulting from bolus doses (gavage) versus continuous exposure (drinking water) and to the induction of its "own metabolism over the longer exposure period, effectively reducing the amount of chemical reaching the immune cells" (Munson et al., 1982).

In a 13-week drinking water study, NTP (1991) investigated strain and species susceptibility to 1,2-DCA exposure using three strains of rats (F344/N, Sprague-Dawley and Osborne-Mendel) and one strain of mice (B6C3F1). Rats (10 of each sex per strain per dose) and mice (10 of each sex per dose) were exposed to 1,2-DCA in drinking water at 0, 500, 1000, 2000, 4000 or 8000 mg/L (equivalent to estimated doses of 0, 49–82, 86–126, 146–213, 259–428 and 492–727 mg/kg bw/day in rats and 0, 244–249, 448–647, 781–1182, 2478–2710 and 4207–4926 mg/kg bw/day in mice). Differences in susceptibility between rat strains were not apparent at the drinking water concentrations used; increased kidney and liver (absolute and/or relative) weights, decreased weight gain and decreased water consumption (up to 50–60% due to palatability at the higher concentrations) were seen in all strains of rats and at most doses. No deaths were reported in rats. No treatment-related lesions were observed in rats exposed by drinking water, with the exception of female F344/N rats, which displayed a dose-related

incidence of mild kidney lesions (renal tubular regeneration[1] of minimal severity) at 1000 mg/L and above. Mild renal tubular regeneration[2] was also observed in many control and dosed rats from the other strains (both sexes), as well as in male F344 rats. Clinical chemistry showed increases at concentrations of 2000 mg/L and above, although not consistent, in blood urea nitrogen in male rats (all three strains; no biochemical analysis was performed on females or on mice), which did not persist past day 45 of the study. Although 1,2-DCA had no effect on absolute or relative weight of the thymus, a significant decrease in leukocytes was observed at high doses (8000mg/L) on day 3 (F344 rats) and days 7 and 45 (Sprague-Dawley rats).

According to the authors, mice usually drink more water than rats on a milligram per kilogram body weight basis; as a result, mice received a considerably higher estimated daily intake (up to approximately 8–10 times) than rats in the drinking water study (NTP, 1991). At the highest dose (8000 mg/L), no deaths were seen in male mice, whereas 9 of the 10 female mice died during the study. Decreased mean body weights and increased kidney and liver weights (absolute and/or relative) were also seen in both sexes of dosed mice. In addition, male mice had a significant increase in kidney lesions, including mild and mild to moderate renal tubular regeneration at the two highest doses (4000 and 8000 mg/L) and karyomegaly, dilatation, protein casts and mineralization at the highest dose (8000 mg/L).

For the purpose of comparing the effects of toxicity between continuous exposure (drinking water study) and bolus exposure (gavage study), additional groups of F344/N rats (10 of each sex per dose) were administered 1,2-DCA in corn oil by gavage at dose levels of 0, 30, 60, 120, 240 or 480 mg/kg bw/day in males and 0, 18, 37, 75, 150 or 300 mg/kg bw/day in females on 5 days per week for 13 weeks (NTP, 1991). These doses were calculated to be within the range of those delivered to rats in the drinking water studies above. 1,2-DCA was more toxic to F344 rats when administered by gavage compared with drinking water. The authors suggested that it may be due to saturation of the metabolic pathway and increased levels of 1,2-DCA in the blood. The gavage study caused mortalities in both sexes (all the males at the two highest doses, especially at the highest dose, at which all males died within 1 week, and 9 out of 10 females at the highest dose). Necrosis of the cerebellum was seen in three males at 240 mg/kg bw/day and in three females at 300 mg/kg bw/day. In addition, a significant increase ($p < 0.05$) in hyperplasia and inflammation of the forestomach was observed in male rats (240 mg/kg bw/day), whereas only a slight increase was seen in high-dose males and female rats. Although a statistically significant increase in necrosis of the thymus was observed in both male and female rats at the highest dose, the authors attributed it to stress in animals that died or were killed moribund. Increases in liver and kidney weights (relative and absolute) were also seen in male and female rats in the gavage study, in the absence of histological evidence of lesions.

NTP (1991) established no-observed-effect levels (NOELs) of 120 mg/kg bw/day for male rats and 150 mg/kg bw/day for female rats in the gavage study, and 2000 mg/L for male mice due to kidney lesions and 4000 mg/L for female mice due to mortality in the drinking water study. OEHHA (1999) determined an oral no-observed-adverse-effect level (NOAEL) of

1 Tubular regeneration according to ATSDR (2001) is "indicative of previous tubular injury with subsequent repair."

2 NTP (1991) reports that "regenerative lesions of the rat kidney are commonly seen and are associated with chronic progressive nephropathy, which occurs in most strains of albino rats. The incidence and severity of progressive nephropathy are sex dependent; in general, male rats are more susceptible than females, with the earliest lesions appearing at about 3 months of age based on Goldstein et al. (1988)",

500 mg/L[1] based on mild renal lesions (tubular regeneration) in female F344 rats observed in the drinking water study. In contrast, ATSDR (2001) established 500 mg/L[2] as the lowest-observed-adverse-effect level (LOAEL) for kidney effects in female rats because it considered the increases in kidney weight as an "early-stage adverse effect" to the renal lesions that occurred at and above 1000 mg/L.

Increases in organ weights, specifically kidney and liver weights, were also observed in a 90-day study conducted by Daniel et al. (1994), in which Sprague-Dawley rats (10 of each sex per dose) were administered 1,2-DCA in corn oil by gavage at doses of 0, 37.5, 75.0 and 150 mg/kg bw/day. In females, increases in relative kidney weight were seen at the two highest doses, and increases in relative liver weight were seen at the highest dose. Males at the two highest doses had a significant increase in relative kidney, liver and brain weights ($p \leq 0.05$), and males at the highest dose had a significant increase in relative testes and adrenal weights. Decreased body weight gain and total feed consumption were also observed in high-dose males. There were also changes in haematological parameters in both sexes at the highest dose and in males (significant decrease in haemoglobin and haematocrit values) at the middle dose. No effects were seen at the lowest dose. As a result, the authors set the NOAEL at 37.5 mg/kg bw/day.

Changes in liver, kidney and/or brain weights were also observed at the highest dose in another 90-day oral study in which groups of Wistar rats (10 of each sex per dose) received 1,2-DCA in olive oil at a dose of 0, 10, 30 or 90 mg/kg bw/day (Van Esch et al., 1977). However, no histopathological changes were observed in the tissues examined. Although haematocrit values were also increased in females at 10 mg/kg bw/day and above, no dose–response relationship was observed. A NOEL of 30 mg/kg bw/day was identified by the authors. Van Esch et al. (1977) also conducted a 2-week range-finding study with male rats in which all rats gavaged with the highest dose (300 mg/kg bw/day) died before the end of the experiment. Fatty degeneration of the liver was observed in those rats. Increased haematocrit values (in the absence of a dose–response relationship) were also seen in low- and mid-dose males rats. The authors found the haematocrit effects in both studies to be questionable.

In a subchronic inhalation study, rats (15 of each sex per dose), guinea pigs (8 of each sex per dose) , rabbits (1 female and 2 males per dose) and monkeys (2 males per dose) were exposed to 1,2-DCA vapour at concentrations of 400 and 100 ppm for 7 hours per day, 5 days per week, for 6 months (Spencer et al., 1951). Severe effects, including hepatotoxicity and death, were observed in rats and guinea pigs exposed at the 400 ppm level. No adverse effects were observed in any of the four species exposed to 100 ppm. An additional 15 rats of each sex and 8 guinea pigs of each sex were exposed to 200 ppm for 30 and 36 weeks, respectively; no adverse effects were seen in rats, but liver effects (slight parenchymatous degeneration with some vacuolization) were seen in guinea pigs.

Hofmann et al. (1971) exposed various laboratory animals (cats, rabbits, guinea pigs and rats) repeatedly to 500 ppm for 6 hours per day, 5 days per week, for 6 weeks. All animals died,

1 NTP (1991) estimated that 500 mg/L in female F344 rats was equivalent to a daily intake of 58 mg/kg bw/day, which is the value that Health Canada used for the NOAEL. OEHHA (1999) calculated 500 mg/L as 45.3 mg/kg bw/day. They derived this estimate from NTP (1991) data showing that 8000 mg/L was equivalent to a daily intake of about 500–725 mg/kg bw/day, but used the higher number (725 mg/kg bw/day) to derive the value for 500 mg/L.
2 ATSDR (2001) reported the same value as that listed in the study from NTP (1991) where 500 mg/L was estimated as equivalent to a daily intake of about 58 mg/kg bw/day

with the exception of the cats. Liver, kidney, heart and lung effects were observed. Laboratory animals were also exposed to 100 ppm with no deaths reported.

9.2.3 Long-term exposure and carcinogenicity

In long-term studies, tumours (benign and malignant) have been reported at multiple sites in mice and rats following oral and inhalation exposure to 1,2-DCA.

In an inhalation study, a dose-dependent increase in the incidence of various benign and malignant tumours was observed in male and female rats and female mice, whereas no significant positive trend was observed in male mice (Nagano et al., 2006). In this 104-week inhalation study, groups of F344 rats (50 of each sex per dose) were exposed to concentrations of 0, 10, 40[1] and 160 ppm, and groups of BDF1 mice (50 of each sex per dose) to concentrations of 0, 10, 30 and 90[2] ppm, for 6 hours per day, 5 days per week.

In male rats at the highest dose, a statistically significant increase was observed for the incidence of fibroadenomas of the mammary gland (7/49) and for the combined incidence of adenomas and fibroadenomas (7/50) of the mammary gland; both incidences showed significant positive trends and also exceeded the maximum tumour incidence of historical control data. Incidences of mesotheliomas of the peritoneum and of subcutaneous fibroma in male rats also showed significant positive trends, but the incidences were not statistically significant. The incidences of mesotheliomas of the peritoneum (5/50 at the highest dose) and subcutaneous fibromas (12/50 and 15/50 at the mid- and high-doses, respectively) did, however, exceed the maximum tumour incidences of historical control data.

In female rats at the highest dose, a significant increase was observed for the incidences of subcutaneous fibromas (5/50) and of fibroadenomas (13/50) and adenomas (11/50) of the mammary gland, with the incidences showing significant positive trends and also exceeding historical control data. In the mammary gland, the incidence of adenocarcinomas, the combined incidence of adenomas and fibroadenomas and the combined incidence of adenomas, fibroadenomas and adenocarcinomas showed significant positive trends. The combined incidences of adenomas and fibroadenomas as well as adenomas, fibroadenomas and adenocarcinomas in the mammary gland were not statistically significant at the middle dose (11/50 and 11/50), but were significant at the highest dose (22/50 and 25/50, respectively), with both incidences at the middle and highest doses exceeding historical control data. The incidence of mammary gland adenocarcinomas (5/50), although increased, was not statistically significant at the highest dose, but exceeded historical control data.

In male mice, a statistically significant increase (without a dose–response relationship) in the incidence of liver haemangiosarcomas was seen at the two highest doses (6/50 and 5/50, respectively), but the incidence at the highest dose did not exceed the maximum tumour incidence of historical control data, nor was a positive trend observed. According to the authors, this tumour was not likely to be associated with exposure to 1,2-DCA. In female mice, tumours of the lung, uterus, mammary gland and liver all showed significant positive trends. At the highest dose, a non-significant increase was observed in the incidences of mammary gland adenocarcinomas (6/50), hepatocellular adenomas (6/50), endometrial stromal polyps in the

1 Nagano et al. (2006) estimated for rats (both sexes) that a 6-hour inhalation exposure to "40 ppm corresponded to a daily [1,2-DCA] uptake of 33 mg/kg body weight, assuming a minute volume of 561 ml/min and a lung absorption ratio of [1,2-DCA] of 100%."

2 In female mice, Nagano et al. (2006) estimated that a 6-hour inhalation exposure to 90 ppm corresponded to a daily [1,2-DCA] uptake of "165 mg/kg body weight, assuming a minute volume of 1,239 ml/min and a lung absorption ratio of [1,2-DCA] of 100%."

uterus (6/50) and bronchiolo-alveolar adenomas of the lung (8/50) and in the combined incidence of bronchiolo-alveolar adenomas and carcinomas of the lung (11/50), with the incidences showing significant positive trends and also exceeding historical control data. A slight increase (not statistically significant) in bronchiolo-alveolar carcinoma was seen at the highest dose, showing a positive trend; however, it did not exceed historical control data.

No significant differences were seen in the survival rates of treated rats or male mice compared with controls. Female mice had a lower survival rate, especially mid-dose females (survival rate of 38%), which was related to a significant increase in malignant lymphomas that the authors did not consider treatment related. No significant exposure-related changes in the incidence of non-neoplastic lesions or in any haematological, blood chemistry or urinary parameters occurred in any of the exposed animals (Nagano et al., 2006).

In contrast to the above inhalation study, no significant increase in the incidence of any type of tumour was found in Sprague-Dawley rats (90 of each sex per group) or Swiss mice (90 of each sex per dose group; 115 males and 134 females in controls) exposed to 1,2-DCA at 5, 10, 50 or 150 ppm for 7 hours per day, 5 days per week, for 78 weeks and observed until spontaneous death (Maltoni et al., 1980). The highest-dose group was originally exposed to 250 ppm, but the concentration was reduced after a few days due to severe toxicity to the animals. Control groups for mice and one group for rats (90 of each sex) were housed in a nearby room, whereas another control group for rats (90 of each sex) was housed in an exposure chamber with the same conditions as the other exposed animals. One of the drawbacks of the study included the dosing period of 78 weeks, which did not cover the lifetime of the rodents. In addition, survival was low in rats (dosed and controls) at 104 weeks (average 27.3%; lower in males than in females) and in mice at 78 weeks (average 45.9%; lower in males than in females). The authors did not report the number of rats surviving at 78 weeks or the number of mice surviving at 104 weeks. As a result, no comparison could be made between species for the same time period. In summary, survival in both species was variable (no dose–response relationship) in all groups, including control groups. The highest survival rate occurred in the low-dose rats at 104 weeks. According to ATSDR (2001), "only a small number of surviving animals were at risk for late-developing tumors."

The apparent discrepancies between the results from the two inhalation studies may be related to several factors, such as length of study, survival rates and early deaths, and different strains of rats and mice used. It should be noted that both inhalation studies exposed high-dose rats to similar concentrations, whereas the highest-dosed mice from the Nagano et al. (2006) study were exposed to lower concentrations of 1,2-DCA than those from the Maltoni et al. (1980) study.

In a gavage study conducted by the U.S. National Cancer Institute (NCI, 1978), tumours were observed in both rats and mice exposed to 1,2-DCA. From preliminary studies, NCI determined the maximum tolerated dose (MTD) and one-half the MTD, which became the high and low doses, respectively, in the study (NCI, 1978, 1979). Using these doses, 1,2-DCA in corn oil was administered by gavage on 5 consecutive days per week for 78 weeks to groups of Osborne-Mendel rats (50 of each sex per dose) and to groups of B6C3F1 mice (50 of each sex per dose). In addition, 20 animals were given no treatment (untreated controls), 20 animals were dosed with the vehicle alone for each dose and sex group (matched vehicle control) and 60 animals of each sex were in pooled controls from concurrent experiments. After treatment, rats were observed for a further period of 32 weeks or less, whereas mice were observed for only 12–13 weeks. The selected doses were inappropriate and necessitated several changes in the administered dosages during the 78 weeks of the study; doses were adjusted up after week 7 and

then down after week 17 due to severe toxicity. In addition, starting in week 36, dosing was stopped for 1 week every 4 weeks until the end of the dosing period at week 78. As a result, time-weighted average doses were calculated: male and female rats received doses of 47 and 95 mg/kg bw/day; male mice, 97 and 195 mg/kg bw/day; and female mice, 149 and 299 mg/kg bw/day.

Multiple tumours were induced in both species. In rats receiving the higher dose, there was a statistically significant increase in the incidence of squamous cell carcinomas of the forestomach (9/50) in males and of adenocarcinomas of the mammary gland (18/50) in females. Significantly higher incidences of haemangiosarcomas of the circulatory system (9/50, 7/50) and fibromas of the subcutaneous tissue (5/50, 6/50) were observed in male rats at both doses (47 and 95 mg/kg bw/day), respectively. In male mice, there was a statistically significant increase in the incidence of alveolar/bronchiolar adenomas (15/48) at the higher dose. Although there was a statistically significant increase in the incidence of hepatocellular carcinomas in high-dose male mice, historical controls also showed a high incidence variability. In female mice, there was a statistically significant increase in the incidences of alveolar/bronchiolar adenomas (7/50, 15/48) mammary adenocarcinomas (9/50, 7/48) and endometrial tumours (5/49, 5/47) at both doses (149 and 299 mg/kg bw/day), respectively.

Early deaths of rats were seen during the study. Survival rates were affected in rats (both sexes), with 25 out of 50 (50%) high-dose males dead by week 55 and 42 out of 50 (84%) dead by week 75; in high-dose females, 25 out of 50 (50%) were dead by week 57 and 40 out of 50 (80%) by week 75. Low-dose rats had better survival—52% of males lived at least 82 weeks, and 50% of females at least 85 weeks. In addition, pneumonia was present in a high percentage of rats, including controls, whereas only a few cases were seen in mice. Survival was also severely affected in high-dose female mice (72% died between weeks 60 and 80), which NCI (1978) suggested "may have been tumor-related as 25/36 (69 percent) had one or more tumors." Conversely, 50% of high-dose males survived at least 84 weeks. Ward (1980) reported that "the statistics were not age-adjusted for early toxicity owing to toxicity, so that the induced tumors actually occurred in incidences higher than those in the statistical tables of the study." In general, Ward (1980) seemed to attribute the early deaths not to cancer, but rather to lesions caused by 1,2-DCA, which also included pneumonia; the author suggested that the chemical exposure may also have made the animals more susceptible to the pulmonary lesions, resulting in death. Weight was also affected during the study; in high-dose rats, weight depression averaged 12% by week 50, whereas in high-dose female mice, the depression was greater than 20% (Ward et al., 1980). According to Hooper et al. (1980), early deaths may lead to an underestimation of carcinogenicity, as most tumours occur later in the lifespan of a laboratory animal and thus may not yet have been manifested.

As part of a larger study, Sprague-Dawley rats (50 of each sex) were exposed to 1,2-DCA by inhalation at 0 or 50 ppm for 7 hours per day, 5 days per week, for 2 years (Cheever et al., 1990). No effects on body and liver weights or survival rate were observed. No significant increase in tumours was seen; however, only one low dose of 1,2-DCA was studied. In this same study, rats were also exposed to 50 ppm 1,2-DCA along with 0.05% disulphiram (known to inhibit aldehyde dehydrogenase and microsomal mixed-function oxidase activities) in the diet (Cheever et al., 1990). As a result, a significant increase in the number of tumours in both sexes (hepatic, testicular and mammary) was observed. With the combined treatment, blood levels of unchanged 1,2-DCA were higher (5-fold increase), levels of metabolites were decreased and no change was observed in the amount of hepatic DNA adduct formation.

As part of a 1-year initiation/promotion drinking water study, male B6C3F1 mice (35 per dose) exposed to 835 or 2500 mg/L (equivalent to approximately 167 or 500 mg/kg bw/day1) of 1,2-DCA alone in drinking water had no increased incidence of lung or liver tumours over controls (Klaunig et al., 1986). Mice initiated with diethylnitrosamine and then treated with 1,2-DCA (same dose levels) also did not show an increased incidence of lung or liver tumours over initiated controls. Three mice died in the high-dose initiated group. Drinking water intake was significantly decreased in treated high-dose mice with or without initiation, and body weight was lower (not statistically significantly) in all treated mice. Limitations of the study included the small number of mice per dose (10 per dose were sacrificed at week 24 as part of the protocol, leaving 25 per dose), the less than lifetime exposure, the lack of an observation period following exposure and the histological examination of only the liver, lung and kidney.

Two other studies by different routes of exposure showed that 1,2-DCA could induce an increase in tumours at sites remote from the point of application (e.g., lung and stomach). One study was a pulmonary tumour bioassay in which mice were dosed intraperitoneally with 1,2-DCA in tricaprylin, and the other was a skin application study using a promoter, phorbol myristate acetate (Theiss et al., 1977; Van Duuren et al., 1979).

The types of tumours observed in rats and mice in long-term carcinogenicity studies are summarized in Tables 1 and 2, respectively.

Table 1: Summary table of tumour types in rats in long-term studies

Parameter	NCI (1978)	Maltoni et al. (1980)	Nagano et al. (2006)
Route	Gavage	Inhalation	Inhalation
Treatment period	78 weeks, 5 days/week	78 weeks, 7 h/day, 5 days/week	104 weeks, 6 h/day, 5 days/week
Observation period	High dose: 15–23 weeks Low dose: 32 weeks	Until spontaneous death or up to 70 weeks	None
Rat strain	Osborne-Mendel	Sprague-Dawley	F344
Dose	0, 47, 95 mg/kg bw (TWA)	0, 5, 10, 50, 150[a] ppm	0, 10, 40, 160 ppm
Adjusted dose	0, 24, 48 mg/kg bw[b]	0, 1.6, 3.2, 16, 48 mg/kg bw[b]	0, 12, 50, 200 mg/kg bw[c]
Number of animals	50 of each sex per dose; 20 untreated controls; 20 vehicle controls; 60 pooled vehicle controls	90 of each sex per dose (2 control groups)	50 of each sex per dose
Presence of tumours	Yes	No	Yes

1 Based on default assumptions from the Health Canada (1994) dose conversion table (Appendix E), where 1 mg/L equals 0.20 mg/kg bw/day in mice.

Parameter	NCI (1978)	Maltoni et al. (1980)	Nagano et al. (2006)
Males			
Survival rate (%)	V: 50 (72 weeks) U: 50 (87 weeks) L: 52 (82 weeks) H: 16 (75weeks)	At 104 weeks: 13.3–17.8, 50, 14.4, 18.9, 11.1	At 104 weeks: 74, 70, 64, 74
Mammary gland			Fibroadenomas (160 ppm: SS, PT, E) Combined fibroadenomas and adenomas (160 ppm: SS, PT, E)
Peritoneum			Mesothelioma (160 ppm: NS, PT, E)
Skin	Subcutaneous fibromas (47, 95 mg/kg: SS)		Subcutaneous fibromas (40, 160 ppm: NS, PT, E)
Forestomach	Squamous cell carcinomas (95 mg/kg: SS)		
Circulatory system	Haemangiosarcomas (47, 95 mg/kg: SS)		
Females			
Survival rate (%)	V: 50 (88 weeks) U: 50 (106 weeks) L: 50 (85 weeks) H: 20 (75 weeks)	At 104 weeks: 24.4–40, 53.3, 28.9, 32.2, 23.3	At 104 weeks: 70, 82, 74, 76
Mammary gland	Adenocarcinomas (95 mg/kg: SS)		Adenomas (160 ppm: SS, PT, E) Fibroadenomas (160 ppm: SS, PT, E) Adenocarcinomas (160 ppm: NS, PT, E) Combined adenomas and fibroadenomas (40 ppm: NS, PT, E; 160 ppm: SS, PT, E) Combined adenomas, fibroadenomas and adenocarcinomas (40 ppm: NS, PT, E; 160 ppm: SS, PT, E)
Skin			Subcutaneous fibromas (160 ppm: SS, PT, E)

E: exceeded historical control data; H: high dose; L: low dose; NS: not significant; PT: positive trend (according to Peto's test); SS: statistically significant; TWA: time-weighted average; U: untreated controls; V: vehicle controls; W: within range of historical control data

[a] The dose was originally set at 250 ppm; however, due to severe toxicity, it was adjusted down to 150 ppm after a few days.
[b] Based on daily doses calculated and extrapolated over the animals' lifetime in the experiment (based on Hooper et al., 1980).
[c] Dose equivalency estimated using a PBPK model (Nong, 2012).

Table 2: Summary table of tumour types in mice in long-term studies

Parameter	NCI (1978)	Maltoni et al. (1980)	Nagano et al. (2006)
Route	Gavage	Inhalation	Inhalation
Treatment period	78 weeks, 5 days/week	78 weeks, 7 h/day, 5 days/week	104 weeks, 6 h/day, 5 days/week
Observation period	12-13 weeks	Until spontaneous death	None
Mouse strain	B6C3F1	Swiss	BDF1
Dose	Males: 0, 97, 195 mg/kg bw (TWA) Females: 0, 149, 299 mg/kg bw (TWA)	0, 5, 10, 50, 150[a] ppm	0, 10, 30, 90 ppm
Adjusted dose	Males: 0, 60, 120 mg/kg per day Females: 0, 92.5, 185.0 mg/kg /day[b]	0, 56, 11, 56, 171.mg/kg per day[b]	0, 54, 162, 486 mg/kg bw[c]
Number of animals	50 of each sex per dose; 20 untreated controls or vehicle controls; 60 pooled vehicle controls	90 of each sex per dose; control group: 115 males and 134 females)	50 of each sex per dose
Presence of tumours	Yes	No	Yes
Males			
Survival rate (%)	V: 55 (90 weeks) U: 55 (less than 74 weeks) L: 52 (less than 74 weeks) H: 50 (84weeks) & 42 (91 weeks)	At 78 weeks: 36.6, 28.9, 37.8, 33.3, 28.9	At 104 weeks: 78, 65, 70, 74
Lung	Bronchiolo-alveolar adenomas (195 mg/kg bw: SS)		
Liver	Hepatocellular carcinomas (195 mg/kg bw: SS, but historical controls had high incidence variability)		Haemangiosarcomas (30 ppm: SS, E; 90 ppm: SS, W, no dose–response relationship)

Parameter	NCI (1978)	Maltoni et al. (1980)	Nagano et al. (2006)
Females			
Survival rate (%)	V: 80 (90 weeks) U: 80 (91 weeks) L: 68 (91 weeks) H: 28 (60-80 weeks)	At 78 weeks: 56.8, 75.6, 55.6, 54.4, 48.9	At 104 weeks: control: 69; L: 56; M: 38; H: 52
Mammary gland	Adenocarcinomas (149, 299 mg/kg bw: SS)		Adenocarcinomas (90 ppm: NS, PT, E)
Lung (bronchiolo-alveolar)	Adenomas (149, 299 mg/kg bw: SS)		Adenomas (90 ppm: NS, PT, E) Carcinoma (90 ppm: NS, PT, W) Combined adenomas and carcinomas (90 ppm: NS, PT, E)
Liver			Hepatocellular adenomas (90 ppm: NS, PT, E)
Uterus	Endometrial tumours (combined stromal polyps and sarcomas) (149, 299 mg/kg bw: SS)		Endometrial stromal polyps (90 ppm: NS, PT, E)

E: exceeded historical control data; H: high dose; L: low dose; M: middle dose; NS: not significant; PT: positive trend (according to Peto's test); SS: statistically significant; TWA: time-weighted average; U: untreated controls; V: vehicle controls; W: within range of historical control data

[a] The dose was originally set at 250 ppm; however, due to severe toxicity, it was adjusted down to 150 ppm after a few days.
[b] Based on daily doses calculated and extrapolated over the animals' lifetime in the experiment (based on Hooper et al., 1980).
[c] Dose equivalency estimated using a PBPK model (Nong, 2012).

9.2.4 Genotoxicity

Using a wide range of endpoints, 1,2-DCA has been shown to be genotoxic in a variety of *in vitro* assays (in mammalian, eukaryotic and prokaryotic cells) and *in vivo* studies (rodent and *Drosophila* sp.), with positive findings for DNA damage, gene mutations and chromosomal aberrations. The genotoxicity of 1,2-DCA, both *in vitro* and *in vivo*, is affected by how the chemical is administered; more DNA damage occurs when 1,2-DCA is administered over a short period of time and at high concentrations than when administered over a long period at low concentrations (Reitz et al., 1982; Storer et al., 1984; Baertsch et al., 1991; IARC, 1999; ATSDR, 2001; Gwinn et al., 2011).

9.2.4.1 In vitro

In mammalian cell assays, genetic mutations were detected in Chinese hamster ovary cells exposed to 1,2-DCA (Tan and Hsie, 1981; Zamora et al., 1983).

1,2-DCA did not induce cell transformation in mouse BALB/c-3T3 cells without exogenous metabolic activation (Tu et al., 1985; Milman et al., 1988). 1,2-DCA enhances the transformation of Syrian hamster embryo cells by simian adenovirus (Hatch et al., 1983) and transformed ChH10T1/2 clone 8 mouse embryo cells to neoplastic cells (Schultz et al., 1992). 1,2-DCA weakly induced mitotic crossing over in *Saccharomyces cerevisiae* (Simmon, 1980).

Through Ames testing, 1,2-DCA was positive in Ames tests gene mutation in *Salmonella typhimurium* (*S. typhimurium*) with S9 metabolic activation, (Rannug et al., 1978; Nestmann et al., 1980; Barber et al., 1981) but yielded mixed results without metabolic activation. (Brem et al., 1974; Kanada and Uyeta, 1978; Rannug and Beije, 1979; Cheh et al., 1980; van Bladeren et

al., 1981; Moriya et al., 1983; Buijs et al., 1984; Strobel and Grummt, 1987; Milman et al., 1988; Roldan-Arjona et al., 1991; Oda et al., 1996).

Mutation assays gave inconsistent responses when *Escherichia coli* (*E. coli*) was exposed to 1,2-DCA (Brem et al., 1974, King et al., 1979, Moriya et al., 1983), and a negative response in a mouse peritoneal host media assay with *E. coli* was observed (King et al., 1979). DNA alkylation with *S. typhimurium* (S9) was induced with 1,2-DCA (Reitz et al., 1982).

9.2.4.2 In vivo

DNA damage was induced in the stomach, kidney, bladder, lung, brain and bone marrow cells of male CD-1 mice (Sasaki et al., 1998), in the liver of rats (Kitchin and Brown, 1994) and in the liver of male B6C3F1, BALB/c and CD-1 mice (Storer and Conolly, 1983; Storer et al., 1984; Taningher et al., 1991; Sasaki et al., 1998). DNA damage (breaks) was detected in B6C3F1 mouse liver following exposure by intraperitoneal injection and oral administration, but was not detected following inhalation exposures to 1,2-DCA (Storer and Conolly, 1983; Storer et al., 1984). Studies in rats have shown that DNA alkylation and other DNA damage occur at 1,2-DCA exposures of 134 mg/kg bw (oral), 150 mg/kg bw (gavage) and 150 ppm (inhalation) (Reitz et al., 1982; Kitchin and Brown, 1994).

DNA binding studies showed positive results in the forestomach of C57BL mice (Hellman and Brandt, 1986), in the kidney of C57BL mice (Hellman and Brandt, 1986), in the kidney of Wistar rats (Prodi et al., 1986) and in the liver, lung and stomach of BALB/c mice and Wistar rats (Prodi et al., 1986).

Chromosomal damage (e.g., sister chromatid exchange) has been induced in mice bone marrow cells by exposure to 1,2-DCA (Giri and Que-Hee, 1988). Gene mutations were slightly induced in the mouse spot test (Gocke et al., 1983).

1,2-DCA failed to induce the formation of micronuclei in mouse peripheral erythrocytes (Armstrong and Galloway, 1993; Sasaki et al., 1994) and in mouse bone marrow cells (King et al., 1979; Jenssen and Ramel, 1980; Crebelli et al., 1999).

The metabolism of 1,2-DCA is largely responsible for the genotoxicity of the chemical. An *in vivo* study in B6C3F1 mice indicated that metabolites produced by the GSH pathway of metabolism were primarily the cause of genotoxicity (Storer and Conolly, 1985). The alternate pathway of metabolism of 1,2-DCA, microsomal oxidation, resulted in metabolites, such as 2-chloroethanol and 2-chloroaldehyde, that did not induce hepatic DNA damage in mice. When this oxidative pathway was chemically inhibited, there was a significant increase in mouse hepatic DNA damage (4 hours following an intraperitoneal 1,2-DCA dose of 200 mg/kg bw).

The DNA covalent binding index was evaluated by Baertsch et al. (1991) in female F344 rats exposed by inhalation to 1,2-DCA at 4400 ppm for a few minutes (peak) compared with those exposed to 80 ppm for 4 hours (constant low). In liver DNA, the different exposure regimens resulted in markedly different covalent binding index values of 69 and 1.8 for “peak” and “constant low,” respectively. In the lungs, the respective values were 31 and 0.9. The effect was approximately 35 times greater after peak exposure, suggesting that acute exposure to highly concentrated 1,2-DCA may pose a greater genotoxic hazard than exposure at a lower level for a longer period.

Somatic, sex-linked and lethal genetic mutations have been observed in *Drosophila melanogaster* exposed to 1,2-DCA (Nylander et al., 1978; King et al., 1979; Romert et al., 1990; Kramers et al., 1991; Ballering et al., 1993; Rodriguez-Arnaiz, 1998; Chroust et al., 2001, 2007).

9.2.5 Reproductive and developmental toxicity

In general, maternal toxicity (and mortality in several studies) was observed in the absence of developmental toxicity when rats and rabbits were exposed to 1,2-DCA orally or by inhalation. No mouse studies were located in the literature. No reproductive effects were seen in rats in a one-generation inhalation study or in mice in a modified multigeneration drinking water study.

9.2.5.1 Developmental effects

Maternal toxicity (decreased body weight gain and two deaths) in the absence of developmental toxicity was observed when Sprague-Dawley rats were exposed to 1,2-DCA for 6 hours per day at 300 ppm on days 6–20 of gestation (Payan et al., 1995). No other significant effects were seen at the lower doses of 150, 200 and 250 ppm.

In another developmental toxicity study, groups of pregnant Sprague-Dawley rats (16–30 per dose) were exposed to 1,2-DCA at 0, 100 or 300 ppm for 7 hours per day on days 6–15 of gestation (Rao et al., 1980). Severe maternal mortality (10/16 died) was observed at the high dose; as a result, no fetuses were available for examination. Only one surviving high-dose rat was pregnant; all the implantation sites were resorbed. At 100 ppm, no effects were seen in the females or in the fetuses.

Rao et al. (1980) also exposed groups of pregnant New Zealand White rabbits to 1,2-DCA at 0, 100 or 300 ppm for 7 hours per day on days 6–18 of gestation. Maternal mortality was also observed at both exposure levels (4/21 and 3/19 at 100 and 300 ppm, respectively). Malformations were observed in one fetus from the 300 ppm group, and skeletal alterations were seen in one fetus exposed to 100 ppm. No other significant effects were observed.

1,2-DCA was administered orally in corn oil at concentrations of 0, 1.2, 1.6, 2.0 or 2.4 mmol/kg per day (corresponds approximately to 0, 119, 158, 199 and 238 mg/kg bw/day) to groups of pregnant female Sprague-Dawley rats on days 6–20 of gestation (Payan et al., 1995). Maternal toxicity (decreased body weight gain) was observed at the two highest doses in the absence of developmental toxicity.

Zhao et al. (1984, 1989) exposed groups of female rats to 1,2-DCA at concentrations of 24.8 and 207 mg/m^3 for 6 hours per day for the period from 2 weeks before mating until gestation day 20. At the highest dose, the incidence of preimplantation loss (31.0%) was significantly higher compared with controls (10.2%), and the male pup weights were statistically lower compared with controls. No gross skeletal or visceral malformations were detected. Maternal data were not reported. No other additional details were supplied in the summary of the study as reported in Zhao et al. (1997).

9.2.5.2 Reproductive effects

In a one-generation study, no adverse effects were found on fertility or reproductive indices (including survival) of the offspring of Sprague-Dawley rats exposed to 1,2-DCA for 6 hours per day, 5 days per week, at 0, 25, 75 or 150 ppm for 60 days prior to mating and then for 7 days per week until gestation day 20 (Rao et al., 1980). Exposure was stopped between gestation day 21 and postpartum day 4 to allow for delivery and rearing of the first litter, after which exposure was then continued. Females were then bred again after approximately 28 days to deliver a second litter. Each litter was sacrificed after 21 days; no histopathological changes were found.

No effects on gestation, fertility, viability or lactation indices were observed in a modified multigenerational study in which ICR Swiss mice were exposed to 1,2-DCA at 0, 0.03,

0.09 or 0.29 mg/mL (designed to yield doses of 0, 5, 15 or 50 mg/kg bw/day) in drinking water (Lane et al., 1982). A teratology component, which was conducted on the fetuses of F_{1c} and F_{2b} generations (day 18 of gestation), failed to show any teratogenic effects.

As part of a 2-year study in which rats were fed mash fumigated with 1,2-DCA at concentrations in feed of 250 and 500 ppm, reproductive and fertility effects were examined (Alumot et al., 1976). Male fertility was not affected, and, in general, 1,2-DCA did not produce any effect on reproductive parameters in males or females.

As part of a larger study, male Sprague-Dawley rats exposed to 1,2-DCA at 153, 304 or 455 ppm for 7 hours per day, 5 days per week, for 30 days showed no adverse testicular effects (no weight changes or lesions) (Igwe et al., 1986). In this same study, another groups of rats was also exposed to the same concentrations of 1,2-DCA along with 0.15% disulphiram (known to inhibit aldehyde dehydrogenase and microsomal mixed-function oxidase activities) in the diet. At the two highest doses of combined exposure, decreased relative testes weight and testicular effects (enlargement at 304 ppm and atrophy at 455 ppm) were observed.

As part of a larger study, Sprague-Dawley rats (50 of each sex) were exposed to 1,2-DCA by inhalation at 0 or 50 ppm for 7 hours per day, 5 days per week, for 2 years (Cheever et al., 1990). Testicular lesions were observed (24% compared with 10% in controls), but there was no significant increase in testicular tumours. However, when rats were also co-exposed to 0.05% disulphiram in the diet, a significant increase in the number of interstitial cell tumours of the testes was observed (11 for 1,2-DCA/disulphiram; 3 for 1,2-DCA alone; 3 for disulphiram alone; 2 for controls).

9.2.6 Mode of action

Tumour formation is the most severe endpoint that follows exposure to 1,2-DCA in animals. An increase in tumours was observed across species (mice and rats) and sexes, via inhalation (Nagano et al., 2006), oral (NCI, 1978), intraperitoneal (Theiss et al., 1977) and dermal (Van Duuren et al., 1979) routes of administration. Although mechanistic data for these tumours are limited, which precludes a thorough mode of action analysis, some discussion of potential modes of action is presented in this section. The discussion focuses primarily on tumours that have occurred via multiple routes of exposure and/or in multiple species or sexes, namely mammary adenomas, fibroadenomas and carcinomas; subcutaneous fibromas; bronchiolo-alveolar adenomas and carcinomas; and hepatocellular adenomas and carcinomas.

The potential mode of action with the most data related to tumorigenicity of 1,2-DCA is mutagenicity. As described in Sections 9.1.4 and 9.2.4, mutagenicity is associated more with reactive metabolites formed from GSH conjugation than with the parent compound; therefore, the first key event in this mode of action of 1,2-DCA is the formation of the metabolites by two different pathways, both involving GSH (see Section 8.3 for further details). Metabolism appears to operate with the same mechanisms across strains (Sweeney et al., 2008) and species (U.S. EPA, 1985), albeit at different rates and saturation levels. Although data for other dihalogenated compounds suggest that metabolic rates in humans are lower than those in rodents (Kim and Guengerich, 1990), no metabolism data exist for humans to confirm this for 1,2-DCA.

The second key event in the mutagenic mode of action is the generation of DNA adducts and subsequent mutations. Of the known GSH metabolites, *S*-(2-chloroethyl)-glutathione becomes rearranged into an episulphonium ion (Guengerich et al., 1987), and this, along with chloroacetic acid, can bind to macromolecules, such as DNA, RNA, proteins and non-protein thiols (IARC, 1999). The main adduct, *S*-[2-(N^7-guanyl)ethyl]-glutathione, modifies the nitrogen ring of guanine and adenine by binding N^7 and N^1, respectively (Guengerich et al., 1987;

Ballering et al., 1994). These lesions lead to miscoding, non-coding and misrepair of the DNA (Ballering et al., 1994). However, there are no data for 1,2-DCA to identify whether these lesions tend to be repaired or whether other changes (e.g., cell cycle changes) result in replication of the DNA damage and subsequent tumour development. As outlined in Section 9.2.4, mutagenicity has been identified *in vivo* in lung and liver tissue in rats and mice, but no investigations have been performed specifically in mammary or subcutaneous tissue.

Although the mutagenicity of 1,2-DCA and, particularly, its GSH pathway metabolites is apparent, data exist to suggest alternative non-mutagenic modes of action for certain tumour types. For example, for several tumour types (including various mammary and subcutaneous tumours), rats appeared to be more sensitive than mice in both the Nagano et al. (2006) and NCI (1978) studies. PBPK model data demonstrate that rats have lower rates of metabolism than mice, and therefore higher levels of the parent compound along with lower levels of the reactive conjugated metabolites (Nong, 2012), which suggests that the parent compound could be the toxic moiety for these tumour types. Because the parent compound tends to be less mutagenic than its metabolites, this might support a non-mutagenic mode of action. Further data to support this hypothesis can be obtained from a study in which rats were exposed to 1,2-DCA in conjunction with disulphiram, an inhibitor of aldehyde dehydrogenase and mixed-function oxidase activities, where a significant increase in hepatic and mammary gland tumours was observed when compared with rats exposed solely to 1,2-DCA (Cheever et al., 1990). These tumour increases might be associated with the parent compound, because the authors also identified that co-exposure to 1,2-DCA and disulphiram resulted in increased blood concentrations of the parent compound paired with decreased blood concentrations of metabolites, and there were no differences in DNA adduct formation compared with rats exposed to 1,2-DCA alone. Further support for a potential non-mutagenic mode of action for certain tumour types comes from their distance from organs with the highest levels of GST metabolism; because GST metabolites are highly reactive, it would be expected that the largest numbers of tumours would occur in tissues with higher levels of metabolism (e.g., liver and lung).

Based on the above discussion, broad-level hypotheses can be drawn about potential modes of action for the relevant tumour types. Subcutaneous and mammary gland tumours are located remotely from primary GST metabolizing tissues, presented earlier and at higher rates in rats than in mice and occurred at higher rates in rats exposed to 1,2-DCA in combination with disulphiram compared with exposure to 1,2-DCA alone; therefore, these tumours potentially appear to arise primarily from some non-mutagenic mechanism. An absence of mechanistic data prevents any further hypotheses about the specific non-genotoxic mode of action that might be associated with the development of these tumours from 1,2-DCA; however, mammary tumours are frequently a result of endocrine disruption (Russo and Russo, 1996). Conversely, bronchoalveolar and hepatocellular tumours developed in mice but not rats and originated in tissues with high levels of GST metabolism, suggesting that a mutagenic mode of action might be responsible for these tumours. Alternative non-mutagenic modes of action should not be ruled out for these tumour types, as there is some evidence that they could still play a role in tumour propagation. For example, cytotoxicity accompanied by evidence of lipid peroxidation was observed in lungs of rats exposed to 1,2-DCA *in vivo* (Salovsky et al., 2002) and in rat hepatocytes exposed *in vitro* to *S*-(2-chloroethyl)-DL-cysteine, an episulphonium ion–forming metabolite of 1,2-DCA (Webb et al., 1987); cell proliferation occurring in response to cytotoxicity could result in tumours through a non-genotoxic mechanism (Cohen and Arnold, 2011). Furthermore, an increase in hepatic neoplastic nodules was observed in male rats with co-exposure to 1,2-DCA and disulphiram, which occurred when there was an increase in the parent

compound, decrease in metabolites and no change in hepatic covalent bonding (Cheever et al., 1990).

It is not possible to identify the human relevance of any of these tumour types due to a lack of data on later key events in the mode of action for these tumours. Furthermore, epidemiological data are limited and not specific to 1,2-DCA, which precludes assessment of tumour consistency between rodents and humans.

Minimal data were found on which to base hypotheses on potential modes of action of relevant non-cancer effects of 1,2-DCA. [^{3}H]Thymidine incorporation was inhibited in the kidney in male mice after acute exposure to 1,2-DCA, but whether this was due to DNA damage or cytotoxicity has not been elucidated (Hellman and Brandt, 1986).

10.0 Classification and assessment

The International Agency for Research on Cancer (IARC, 1987, 1999) has classified 1,2-DCA as Group 2B, possibly carcinogenic to humans, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in experimental animals. 1,2-DCA has also been classified as a probable human carcinogen in Group B2 by the U.S. EPA (2009c), based on sufficient evidence in animals and inadequate or no evidence in humans.

These classifications are based on an increased incidence of tumours as a result of oral exposure in the following organs: lung (mice), mammary glands (mice and rats), forestomach (male rats), haemangiosarcomas (male rats), uterus (mice) and skin (rats); and a non-significant increase in liver tumours (male mice), which occurred above levels observed in historical controls. Positive results were also seen in both *in vitro* and *in vivo* genotoxicity studies. In humans, the available epidemiological studies associated with exposure to 1,2-DCA are limited, and none dealt specifically with 1,2-DCA, as workers or populations were also exposed concurrently to other chemicals. As such, no conclusion of excess cancer linked to 1,2-DCA could be derived for the epidemiological studies.

The non-neoplastic effects of 1,2-DCA have also been studied in experimental animals, with different outcomes reported between short- and long-term studies. Changes in liver and kidney weights were commonly seen as the result of short-term exposure to 1,2-DCA via oral and inhalation routes. Mild kidney lesions were also seen in male mice and female rats given 1,2-DCA in drinking water in a short-term study. As a result, the most sensitive non-carcinogenic adverse effect resulting from oral dosing of 1,2-DCA appears to be kidney lesions. In contrast, most chronic studies did not reveal any significant increases in tumours in the kidney or liver; rather, tumours were found in other organs/tissues, such as mammary glands, lungs, skin, forestomach, peritoneum, uterus and circulatory system in rats and/or mice.

Because of these differences in response between subchronic and chronic exposure and their target organs, both non-carcinogenic and carcinogenic approaches were considered in this risk assessment. The results from both the cancer and non-cancer risk assessment approaches are described in Sections 10.1 and 10.2, respectively.

10.1 Cancer risk assessment

As discussed in Section 9.2.3, rats and mice developed benign and malignant tumours following chronic oral (NCI, 1978) and inhalation (Nagano et al., 2006) exposure, with some consistency in tumour types between species and exposure routes. Significantly increased tumour types that were consistent across species and exposures included mammary tumours (in female rats and mice exposed by either route and in male rats exposed by inhalation) and subcutaneous

fibromas (after inhalation in male and female rats and after oral gavage in male rats). Furthermore, mice exposed by both routes of exposure developed hepatocellular tumours (in females exposed via inhalation and in males exposed by gavage), endometrial tumours (in females exposed by both routes) and bronchiolo-alveolar tumours (in females exposed by both routes and in males exposed orally). Mode of action data for 1,2-DCA are limited to investigations of toxicokinetics and genotoxicity; therefore, there are inadequate data to rule out the human relevance of these tumour types. Of the two chronic studies that produced tumours in rodents, the study by Nagano et al. (2006) exposed animals for a longer duration and maintained consistency in dosing levels and schedules, which led to its selection as the key study for the cancer assessment. Because animals were exposed via the inhalation route in this study, a PBPK model was used to extrapolate from the inhalation to the oral route of exposure.

For the cancer dose–response assessment, the Sweeney et al. (2008) PBPK model was applied to estimate relevant oral exposure levels from the Nagano et al. (2006) inhalation study. The assessment focused on rats, because they appear to be more sensitive than mice to 1,2-DCA exposures. The PBPK model was used to estimate the lifetime average daily concentration of 1,2-DCA in blood in rats from inhalation following the exposure scheme used by Nagano et al. (2006). Blood concentration was used as the dose metric, because it presumably has a closer relationship to the tumours of interest than tissue concentrations for any of the compartments that comprise the PBPK model. Furthermore, the parent blood concentration was chosen over hepatic metabolite generation rates and levels, as it remains unclear whether tumour formation results from a specific metabolite or multiple metabolites. The conjugated metabolites generated from the glutathione pathway were considered as a potential dose metric for this risk assessment since these metabolites have been found to be the mutagenic moiety for 1,2-DCA; however, the evidence listed in Section 9.2.6 contributed to the selection of the parent compound. Evidence that mammary gland tumours were significantly increased in rats when metabolism was slowed and greater levels of the parent compound were present (Cheever et al., 1990) suggests that the parent compound might be the more relevant moiety for PBPK modelling. Furthermore, the development of mammary tumours was of greater importance in rats than mice, and PBPK simulations for the key study indicated that rats had higher internal exposures to the parent compound while mice generated more metabolites. Although there are not adequate data to conclusively identify blood concentrations of the parent compound as the best dose metric, the approach was also applied because it was more conservative than using metabolite generation estimates.

After estimating the internal dose metrics for each of the concentrations in the Nagano et al. (2006) study, benchmark dose (BMD) modelling was performed using the software BMDS Version 2.2 (U.S. EPA, 2011c). As discussed in Section 9.2.6, there are data suggestive of a non-mutagenic mode of action for certain types of tumours, but key events have not been delineated for the non-mutagenic modes of action; therefore, a mutagenic mode of action must be assumed until further data are gathered, which necessitates the derivation of cancer slope factors from the multistage model. The most sensitive endpoint was identified to be combined mammary adenoma, fibroadenoma and adenocarcinoma in female rats; because there are inadequate mode of action data for 1,2-DCA to discount the human relevance of mammary tumours, this was selected as the critical effect for the dose–response assessment. Using the multistage cancer slope factor for all combined mammary tumours, the internal dose metrics associated with risk levels of 10^{-4}, 10^{-5} and 10^{-6} were estimated to be 0.0027, 0.000 27 and 0.000 027 mg/L per day, respectively.

To extrapolate from the internal dose in animals to the external dose in humans, two approaches were considered. The first involved extrapolating to external dose in rats and applying an allometric scaling using the equation $(0.35 \text{ kg}/70 \text{ kg})^{¼}$, where 0.35 kg and 70 kg represent the default body weights of rats and humans, respectively (Health Canada, 1994). The second approach involved using a human PBPK model, as discussed in Section 8.5. The approaches resulted in similar values, with the PBPK approach being slightly more conservative than the allometric scaling approach. Because the application of the PBPK model allows for the incorporation of expected kinetics of 1,2-DCA in humans, whereas the allometric scaling approach provides a generic consideration of kinetic differences between animals and humans that is not chemical-specific, the PBPK approach is the basis for the assessment. The external doses for humans as estimated using both approaches are listed in Table 3.

Table 3: Calculation of the external dose using different scenarios for three estimated risk levels

Estimated risk level	Internal dose metrics	External dose (allometric scaling approach)		External dose (PBPK approach)
	Rats (mg/L per day)	Rats (mg/kg bw/day)	Humans[a] (mg/kg bw/day)	Humans (mg/kg bw/day)
10^{-6}	0.000 027	0.002	0.0005	0.0003
10^{-5}	0.000 27	0.019	0.005	0.003
10^{-4}	0.002 7	0.187	0.05	0.03

[a] Estimated using an allometric scaling approach rather than using 1,2-DCA-specific kinetic data.

Using the kinetic-adjusted human external dose with the corresponding risk, a health-based value (HBV) for 1,2-DCA in drinking water can be derived using the formula below; HBVs corresponding to each risk level are listed in Table 4. HBVs were based on the PBPK approach, but the allometric scaling approach was also included for comparison.

$$\text{HBV} = \frac{\text{X mg/kg bw/day} \times 70 \text{ kg}}{\text{4.2 L-eq/day}}$$

where:

- X mg/kg bw/day is the dose associated with the corresponding risk (see Table 3);
- 70 kg is the average body weight of an adult; and
- 4.2 L-eq/day is the daily volume of water consumed by an adult, accounting for multiroute exposure, as determined in Section 5.6.4.

Table 4: HBV based on the three different estimated risk levels

Estimated risk level	HBV (mg/L)
10^{-6}	0.005
10^{-5}	0.05
10^{-4}	0.5

In summary, health-based values for cancer endpoints range from 0.005 to 0.5 mg/L (5 to 500 µg/L), which correspond to estimated risk levels of 10^{-6} to 10^{-4} in humans.

The parent compound was used to estimate corresponding external human doses based on its mode of action. Using the rate of hepatic metabolite formation instead would have resulted in less protective drinking water limits (i.e., 1.3, 0.13 and 0.013 mg/L for lifetime exposure risk levels of 10^{-4}, 10^{-5} and 10^{-6}, respectively).

10.2 Non-cancer risk assessment

For effects of 1,2-DCA exposure other than cancer, a tolerable daily intake (TDI) can be derived by considering all studies and selecting the critical effect that occurs at the lowest dose, selecting a dose (or point of departure) at which the critical effect is either not observed or would occur at a relatively low incidence (e.g., 10%) and adjusting this dose by an uncertainty factor to reflect the differences between study conditions and conditions of human environmental exposure. Although the TDI approach is not typically used when assessing chemicals that are considered carcinogens, this approach was considered for 1,2-DCA because of the evidence of adverse effects in short-term studies.

The most appropriate study for a non-cancer risk assessment is the subchronic study by NTP (1991), as it represents a well-conducted study looking at appropriate routes of exposure, such as drinking water (and includes several different strains of rats and one strain of mice) and oral gavage (including one strain of rats). Both renal and immunological endpoints were considered in the dose–response assessment.

The NTP (1991) study showed some indications of progression of adverse kidney effects in rodents. Significant increases in relative and absolute kidney weights occurred in most exposed females of all strains and species and in many male exposure groups, particularly those with highest levels of exposure. Moreover, increases in blood urea nitrogen—a potential indicator of increased glomerular filtration rate, but one that can also be affected by dehydration and other factors (Schnellmann, 2008)—were observed in male rats (no biochemical analysis was performed on females or on mice), albeit inconsistently, and not persisting past day 45 of the study. Finally, renal tubular regeneration was present in male and female rats and mice in all drinking water studies. Although these effects were reported as not being dose related (without data being presented) for most of the strains, and NTP (1991) stated that "regenerative lesions of the rat kidney are commonly seen and are associated with chronic progressive nephropathy, which occurs in most strains of albino rats," the endpoint was considered for this dose–response assessment because dose-related increases in tubular regeneration occurred in female F344 rats and male B6C3F1 mice. Because no rodents were sacrificed prior to the end of the study, the types of lesions that might have preceded the regeneration are unknown. Male B6C3F1 mice had additional renal lesions that were significantly increased in the highest dose, including karyomegaly, dilatation, protein casts and mineralization.

Although not as pervasive throughout the NTP (1991) study as renal outcomes, adverse immunological effects warranted consideration in the dose–response assessment. Exposure to 1,2-DCA had no effect on absolute or relative weight of the thymus, but a significant decrease in leukocytes was observed at high doses in the drinking water studies on day 3 (F344 rats) and days 7 and 45 (Sprague-Dawley rats), and a significant increase in thymal necrosis occurred in high-dose male and female F344 rats exposed via gavage. Further support for the potential for 1,2-DCA to be immunotoxic was observed as decreases in leukocyte count and cell-mediated and humoral immunity in male mice (Munson et al., 1982), as well as decreased bactericidal activity and increased susceptibility to mortality from streptococcal pneumonia in female mice (Sherwood et al., 1987).

The BMD approach was used to calculate points of departure for tubular regeneration and thymal necrosis. Although NOAELs could be identified in the critical study, the BMD approach was used to derive a point of departure because it is calculated based on data from the entire dose–response curve for the critical effect rather than from a single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). The BMD and its lower 95% confidence limit (BMDL) corresponding to a 10% increase in extra risk were calculated for each of the adverse effects using the U.S. EPA BMD software (U.S. EPA, 2011c). The BMD_{10}, $BMDL_{10}$, selected model and measure of acceptability of goodness of fit for each endpoint are presented in Table 4. The most conservative of the values, which was a $BMDL_{10}$ of 78 mg/kg bw/day associated with renal tubular regeneration in female F344 rats exposed by drinking water, was used as the point of departure for the non-cancer risk assessment.

Table 5: Results of BMD analysis

Endpoint	Sex, strain, species, (route of administration)	Model with best fit	*P*-value	BMD_{10} (mg/kg bw/day)	$BMDL_{10}$ (mg/kg bw/day)
Renal tubular regeneration	Female F344 rats (drinking water)	Weibull	0.8273	142	78
	Male B6C3F1 mice (drinking water)	Quantal-linear	0.967	212	146
Necrosis of thymus	Female F344 rats (gavage)	Log-logistic and Weibull	1	268[a]	135[a]
	Male F344 rats (gavage)	Log-logistic	1	217	140

[a] Values presented are averages for log-logistic and Weibull because the data fit these two models equally well.

The overall database for 1,2-DCA is incomplete. There have been more studies conducted with 1,2-DCA by the inhalation route of exposure than by the oral route, including drinking water; however, this is not a major limitation of the database, as a PBPK model can be applied to perform inhalation to oral extrapolations. Only one of the lifetime bioassays (inhalation) exposed rats and mice to 1,2-DCA for 2 years, whereas the other long-term assays (oral and inhalation) exposed laboratory animals for only 78 weeks or less. The database for developmental and reproductive toxicity studies was limited. A multigenerational (modified)

drinking water study was conducted only in mice, and a one-generation study in rats exposed animals only by inhalation. Most developmental toxicity studies have been conducted by the inhalation route with both rats and rabbits, and only one developmental toxicity study was conducted in drinking water using rats only. In addition, several of these developmental studies were administered at doses that caused significant maternal toxicity in the form of maternal mortality, which indicates that the doses chosen were too high. An additional uncertainty factor of 10 was used to account for the incompleteness of the database.

The TDI for 1,2-DCA is calculated as follows:

$$\text{TDI} = \frac{78 \text{ mg/kg bw/day}}{1000}$$

$$= 0.078 \text{ mg/kg bw/day}$$

where:

- 78 mg/kg bw/day is the $BMDL_{10}$ for renal tubular regeneration in female F344 rats exposed by ingestion of drinking water in the NTP (1991) study (as derived above); and
- 1000 is the uncertainty factor: ×10 for interspecies variability, ×10 for intraspecies variability and ×10 for database deficiencies to account for incomplete developmental and reproductive data, and for extrapolation from a subchronic study (Ritter et al., 2007).

Using this TDI, the HBV for 1,2-DCA in drinking water for non-cancer effects is derived as follows:

$$\text{HBV} = \frac{0.078 \text{ mg/kg bw/day} \times 70 \text{ kg} \times 0.20}{4.2 \text{ L-eq/day}}$$

$$= 0.26 \text{ mg/L (260 µg/L)}$$

where:

- 0.087 mg/kg bw/day is the TDI, as derived above;
- 70 kg is the average body weight of an adult;
- 0.20 is the default allocation factor for drinking water; it is used as a "floor value," since drinking water is not a major source of exposure to 1,2-DCA, and there is evidence of the widespread presence of 1,2-DCA in one of the other media (i.e., air; Krishnan and Carrier, 2013); and
- 4.2 L-eq/day is the total daily exposure contribution from drinking water for an adult, accounting for multiroute exposure, as determined in Section 5.6.4.

10.3 Comparison of cancer and non-cancer risk assessments

The concentration of 1,2-DCA in drinking water associated with a lifetime excess risk of mammary tumours (combined) of 10^{-6} is determined as 0.005 mg/L for exposure during a lifetime. The non-cancer HBV is calculated as 0.26 mg/L. As the cancer risk assessment resulted in a more conservative value for 1,2-DCA in drinking water compared with that generated by the

non-cancer approach, the cancer risk assessment was determined to be the most appropriate driver of the MAC in drinking water. Based on an estimated lifetime excess risk of cancers of 10^{-6}, a MAC of 0.005 mg/L (5 µg/L) for 1,2-DCA would be protective of both cancer and non-cancer effects.

10.4 International considerations

Risk assessments conducted by various agencies (U.S. EPA, IARC, WHO, California EPA and National Health and Medical Research Council of Australia) have chosen haemangiosarcomas in male rats from the NCI (1978) study as the basis for their cancer risk estimates. However, many weaknesses were seen in this gavage study, including the length of the study (less than 2 years), low survival rates and dosing issues.

The current U.S. EPA maximum contaminant level (MCL) for 1,2-DCA was set at 0.005 mg/L (5 µg/L) based on analytical feasibility (U.S. EPA, 1987a). In a 2010 Federal Register that announced the review of the existing drinking water standards, the U.S. EPA decided not to revise the MCL at that time (U.S. EPA, 2010). However, the U.S. EPA is considering regulating 1,2-DCA along with up to 15 other VOCs that are known or suspected to cause cancer as a group, under the new Drinking Water Strategy (U.S. EPA, 2011d). This group of VOCs will be the first group of contaminants to be addressed under this new strategy. It should be noted that 1,2-DCA is not listed as part of the Contaminant Candidate List 3 from the U.S. EPA (2011b). The U.S. EPA (2009c) has classified 1,2-DCA as a probable human carcinogen (Class B2). It derived a slope factor of 0.091 $(\text{mg/kg bw/day})^{-1}$ for cancer risk associated with exposure to 1,2-DCA (U.S. EPA, 1991c) based on the incidence of haemangiosarcoma in male rats (NCI, 1978) using a linear multistage procedure with time-to-death analysis.

The World Health Organization (WHO, 2003) established a drinking water guideline of 0.03 mg/L (or 30 µg/L) based on the NCI (1978) 78-week study by applying a linear multistage model based on the incidence of haemangiosarcoma in male rats. This guideline value is associated with a lifetime upper-bound excess cancer risk of 10^{-5}.

The California Department of Health Services has set an MCL for 1,2-DCA of 0.5 µg/L (CDHS, 2005). The California Environmental Protection Agency has established a public health goal (PHG) of 0.0004 mg/L (0.4 µg/L) for 1,2-DCA in drinking water (OEHHA, 1999). The PHG is based on an increased incidence of haemangiosarcomas in male rats (from the long-term gavage study conducted by NCI, 1978), an estimated cancer potency value of 0.047 $(\text{mg/kg bw/day})^{-1}$ and a *de minimis* theoretical excess individual cancer risk level of 10^{-6}.

The Australian drinking water guideline for 1,2-DCA is set at 0.003 mg/L (NHMRC, 2004) and is based on the WHO (2003) calculation of excess risk; however, Australia has established a more conservative value associated with the lifetime upper-bound excess cancer risk of 10^{-6}, rather than the 10^{-5} risk level as established by WHO (2003).

11.0 Rationale

1,2-DCA is no longer produced in Canada, but can be imported for use. Based on its physicochemical properties, and laboratory tests results, 1,2-DCA has been shown to be very volatile and, as a result, will tend to evaporate fairly rapidly from surface waters. However, this may not be the case in groundwater, where 1,2-DCA may persist for longer periods. Because it is

a VOC, the contribution from inhalation and dermal exposure during bathing and showering was also estimated using a multiroute exposure approach.

1,2-DCA is classified by Health Canada and the U.S. EPA as a probable human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals, whereas IARC considers 1,2-DCA to be a possible human carcinogen (Group 2B). However, the literature seems to indicate that cancer may be expected only after high levels of exposure that would saturate one of the metabolic pathways (cytochrome P450 pathway), as is the case with similar chemicals, such as DCM. As a result, both cancer and non-cancer endpoints were considered in the derivation of the MAC.

Several animal studies have shown an association between exposure to 1,2-DCA and an increased incidence of various tumour types (benign and malignant tumours in either rats or mice: mammary glands, lungs, uterus, peritoneum, liver, skin and circulatory system) at both the site of application and distant sites. In addition, 1,2-DCA has been shown to be genotoxic based on available *in vitro* and *in vivo* studies, supporting a conclusion that 1,2-DCA is possibly a genotoxic carcinogen. Although there are epidemiological studies on exposure to 1,2-DCA and cancer, all involved concurrent exposures to other chemicals.

A health-based value for 1,2-DCA in drinking water of 0.005 mg/L (5 µg/L) can be derived based on the cancer risk assessment. This assessment assumes a *de minimis* excess cancer risk level of 10^{-6}, which is considered to be essentially negligible. The most sensitive non-cancer endpoint was for histopathological changes (tubular regeneration) in the kidneys of female rats. A health-based value for 1,2-DCA in drinking water of 0.26 mg/L (260 µg/L) can be derived based on the non-cancer risk assessment. The lower of the two calculated health-based values (0.005 mg/L) is selected as the MAC, as it is protective for both cancer and non-cancer endpoints.

Consequently, a MAC of 0.005 mg/L (5 µg/L) for 1,2-DCA is established based on the following considerations:

- It falls within the range considered to present an "essentially negligible" risk;
- The MAC can be measured by available analytical methods and is achievable by municipal and residential treatment technologies; and
- A number of residential treatment devices are available that can remove 1,2-DCA to 5 µg/L or less in drinking water.

As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change(s) to the guideline that it deems necessary.

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Appendix A: List of acronyms

1,2-DCA	1,2-dichloroethane
ANSI	American National Standards Institute
BMD	benchmark dose
BMDL	lower confidence limit of the benchmark dose
bw	body weight
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
GAC	granular activated carbon
GSH	glutathione
GST	glutathione *S*-transferase
HBV	health-based value
IARC	International Agency for Research on Cancer
K_p	skin permeability coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
L-eq	litre-equivalent
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MCL	maximum contaminant level
MDL	method detection limit
MTD	maximum tolerated dose
NCI	National Cancer Institute (U.S.)
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NSF	NSF International
NTP	National Toxicology Program (U.S.)
PAC	powdered activated carbon
PBPK	physiologically based pharmacokinetic
PHG	public health goal
ppm	parts per million
PQL	practical quantification limit
PTA	packed tower aeration
RNA	ribonucleic acid
SCC	Standards Council of Canada
TDI	tolerable daily intake
UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organization