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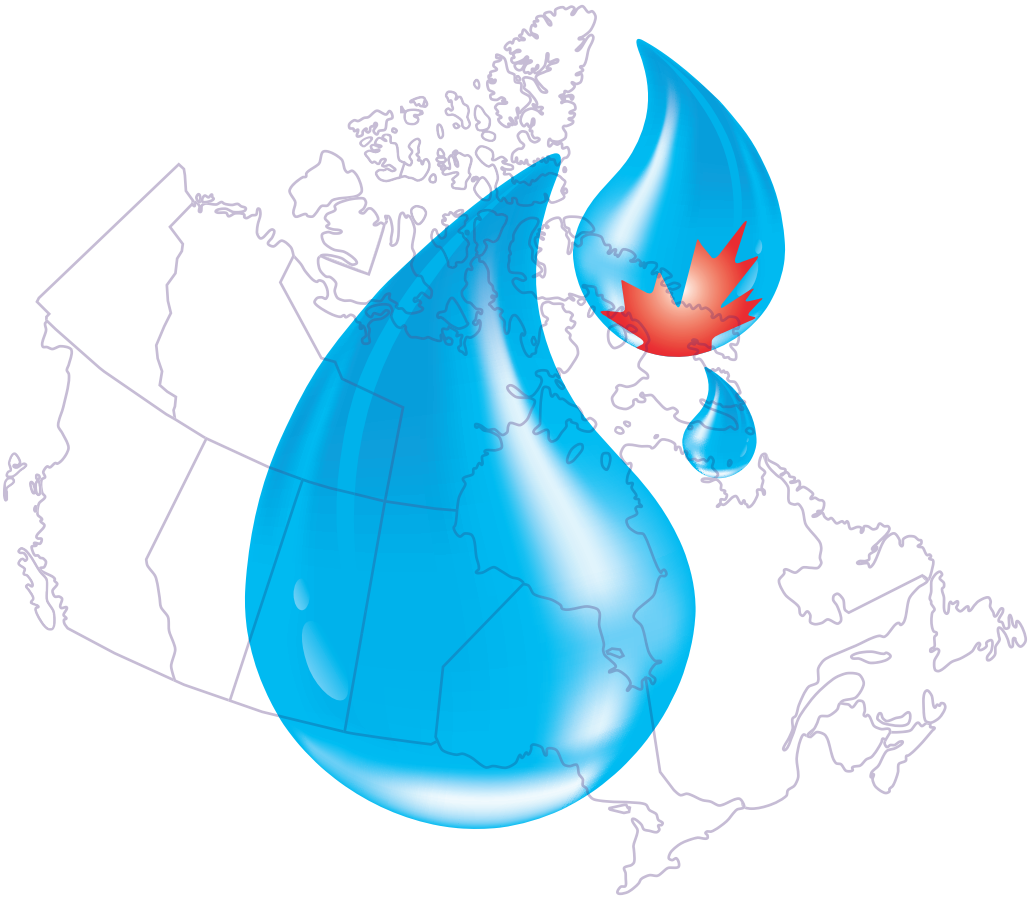
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Dichloromethane



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Publications
Health Canada
Ottawa, Ontario K1A 0K9
Tel.: 613-954-5995
Fax: 613-941-5366
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Dichloromethane

Prepared by the
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of the
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Any questions or comments on this document may be directed to:

Water, Air and Climate Change Bureau
Healthy Environments and Consumer Safety Branch
Health Canada
269 Laurier Avenue West, Address Locator 4903D
Ottawa, Ontario
Canada K1A 0K9

Tel.: 613-948-2566
Fax: 613-952-2574
E-mail: water_eau@hc-sc.gc.ca

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March, 2011

Dichloromethane in Drinking Water

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for dichloromethane in drinking water is 0.05 mg/L (50 µg/L).

2.0 Executive summary

Dichloromethane is a halogenated aliphatic hydrocarbon that does not occur naturally in the environment. It is no longer produced in Canada but is still imported, primarily for use as a paint stripper, a blowing agent for foam production and a component in aerosols.

This Guideline Technical Document reviews and assesses all identified health risks associated with dichloromethane 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.

Health Canada recently completed its review of the health risks associated with dichloromethane in drinking water. This review, and the resulting Guideline Technical Document, assesses all identified health risks, taking into account new studies and approaches, and incorporates appropriate uncertainty factors. Based on this review, the guideline for dichloromethane in drinking water is a maximum acceptable concentration of 0.05 mg/L.

2.1 Health effects

Dichloromethane 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 dichloromethane exposure and various types of tumours in rats and mice. Such links have not been found in humans, based on studies conducted on workers exposed to dichloromethane for many years.

Because current scientific literature seems to indicate that cancer is only expected after high levels of exposure, both cancer and non-cancer endpoints were considered in the derivation of the MAC. The non-cancer approach was used in this assessment, based on histopathological changes in the liver of rats, and produces a MAC that is protective of human health from both cancer and non-cancer effects.

2.2 Exposure

Canadians can be exposed to dichloromethane through its presence in air, food and drinking water, as well as through the use of specific consumer products or in occupational settings. Exposure is more frequently associated with air and consumer products. Because dichloromethane is highly volatile, its presence in water is usually associated with groundwater sources. Dichloromethane 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

Dichloromethane can be readily detected and analysed in drinking water supplies to levels well below the MAC. Some studies have shown more dichloromethane in treated water than in raw water samples, suggesting it may be formed during the chlorination process; however, it is not considered to be a disinfection by-product.

Conventional drinking water treatment is not effective at removing volatile organic compounds such as dichloromethane. The treatment technologies effective at removing dichloromethane include air stripping (preferably using packed tower aeration), and activated carbon adsorption. At the residential scale, there is no drinking water treatment device certified to remove dichloromethane, although treatment devices using activated carbon filters may be effective for the reduction of dichloromethane.

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.

Although dichloromethane may be formed during the chlorination process, it is not considered to be a disinfection by-product. As levels of dichloromethane in treated water are generally very low, water suppliers are not expected to monitor the concentrations of dichloromethane in drinking water supplies on a routine basis. Generally, dichloromethane is not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily.

The drinking water guideline is based on lifetime exposure to dichloromethane 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, use and sources in the environment

Dichloromethane (CAS Registry No. 75-09-2), also known as methylene chloride, methylene dichloride and methylene bichloride, is a halogenated aliphatic hydrocarbon (ATSDR, 2000). It is a clear, colourless liquid with a mildly sweet odour and is highly volatile and non-flammable at room temperature. The molecular formula for dichloromethane is CH_2C1_2 and its molecular weight is 84.933 g/mol (Lide, 2008). Dichloromethane's boiling and melting points are 40°C and -95°C, respectively (O'Neil et al., 2006; Lide, 2008). At 25°C, it has a vapour pressure of 57.8 kPa (Mackay et al., 2006), a density of 1.3163 g/mL (Lide, 2008), a log octanol/water partitition coefficient of 1.25, and a unitless Henry's Law constant of 0.25 (U.S. EPA, 2000). The water solubility of dichloromethane is 18 650 mg/L at 25°C (Mackay et al., 2006), which is high relative to other chlorinated compounds (Spiker and Morris, 2001).

The odour threshold of dichloromethane in air ranges between 155 and 622 ppm[1] (Ruth, 1986). The predicted water odour threshold is 9.1 mg/L (Amoore and Hautala, 1983). No taste threshold for dichloromethane in drinking water has been identified.

Dichloromethane is no longer produced in Canada (CPI, 2000). From 1977 to 1990, the quantity of dichloromethane imported and used in Canada ranged annually from 9 to 13.2 kilotonnes (Environment Canada, 1990); however, usage of pure dichloromethane, recycled dichloromethane and dichloromethane contained in formulations has declined from 7.4 kilotonnes (kt) in 1995 to 7.1 kt in 1998, a 4% decline over 3 years (Environment Canada, 2004a). Dichloromethane is used in a wide variety of consumer products. It is used as an industrial solvent and as a paint stripper. It may also be found in some aerosol and pesticide products and is used in the manufacture of photographic film (ATSDR, 2000). In Canada it is primarily used as a paint stripper, a blowing agent for foam production and a component in aerosols (Environment Canada, 2007). Major global industrial applications of dichloromethane include use in paint removers, foam production and film processing, as a solvent for degreasing and extraction of spice oleoresins, hops and caffeine, and for photoresistant stripping operations (IPCS, 1996; ATSDR, 2000).

Dichloromethane does not occur naturally in the environment. Since dichloromethane has a high vapour pressure and Henry's Law constant, it tends to volatilize from water and soil into the atmosphere (ATDSR, 2000). The atmosphere plays an important role in the distribution and environmental fate of dichloromethane. Although the photooxidation and photolysis of dichloromethane at sea level is minimal, conditions in the upper troposphere allow for photooxidation to occur where dichloromethane is degraded by reacting with photochemically produced hydroxyl radicals with a lifetime of 6 months (IPCS, 1996). A high sorption partition coefficient (log K_{oc}) of 1.4 (Mackay et al., 2006) suggests that dichloromethane will be highly mobile in soil, and therefore may leach into groundwater (ATSDR, 2000). In the aquatic environment, hydrolysis and photolytically induced degradation is slow compared with evaporation from surface water (IPCS, 1996); however, aerobic and anaerobic biotransformation of dichloromethane may serve as important fate processes in water (ATDSR, 2000). In Canada in 2006, 246 tonnes of dichloromethane were released to the atmosphere. This amount represented a 20% decrease from that released in 2005, and an 89% decrease since the data were first reported

[1]Conversion factor in air: 1 ppm = 3.47 mg/m^3 at 25°C and 760 mm Hg

in 1994. No releases have been recorded for land since 2001 and water since 2003 (Environment Canada, 2008).

Volatilization and aerobic–anaerobic biotransformation serve as important processes involved in the removal of dichloromethane from water (ATSDR, 2000). The half-life of dichloromethane volatilization from water has been reported to be 21 minutes in an experimental study where 200 mL of a 1-mg/L aqueous solution of dichloromethane was placed in a Pyrex beaker and stirred at 200 rpm (Dilling et al., 1975); however, actual volatilization from natural waters will depend on temperature and other factors (Dilling et al., 1975; U.S. EPA, 1979).

5.0 Exposure

Canadians can be exposed to dichloromethane through its presence in air, food and drinking water. In addition, certain segments of the population may be exposed through the use of specific consumer products or in occupational settings. The main route of exposure to dichloromethane for the general population is via inhalation of air, particularly indoor air, or from use of consumer products (Environment Canada and Health Canada, 1993; ATSDR, 2000). Although some exposure data are available, they are not sufficient to modify the default proportion (20%) of the daily intake allocated to drinking water (allocation factor) in the calculation of the MAC.

5.1 Water

Dichloromethane enters the aquatic environment through industrial and municipal waste water discharges and has been detected in ground and surface water at hazardous waste disposal sites (IPCS, 1996; IARC, 1999; ATSDR, 2000). Water chlorination might also increase the concentration and frequency of occurrence of dichloromethane in drinking water supplies (U.S. EPA, 2006), but chlorination results in a greater generation of trihalomethanes than dichloromethane (Gyunter et al., 1985), and dichloromethane is generally not considered to be a disinfection by-product. Some surveys of both raw and treated water have measured dichloromethane at higher concentrations and at a greater frequency of detection in treated water than in raw water (NAS, 1977; Gyunter et al., 1985; Otson et al., 1982; Otson, 1987). However, laboratory studies have not identified the formation of dichloromethane subsequent to various types of disinfection (Lykins and Koffskey, 1986; Koffskey and Lykins, 1987). Since dichloromethane has a low tendency to adsorb to soil (Dilling et al., 1975; Dobbs et al., 1989; ATSDR, 2000), there is a potential for it to occur in groundwater. Also, because volatilization is restricted in groundwater, dichloromethane concentrations are often higher in groundwater than in surface water.

The majority of samples recently obtained from drinking water supplies in Canada had dichloromethane concentrations below the detection limit. Dichloromethane was found in some water supplies in quantifiable concentration. Approximately 5% of groundwater and surface samples obtained in Quebec from 2001 to 2005 contained dichloromethane concentrations above 1 µg/L., with maximum values of 290 and 170 µg/L in groundwater and surface water, respectively, and average concentrations of 2.6 µg/L in groundwater, 1.5 µg/L in surface water, and 1.9 µg/L in all samples (Ministère de l'Environnement du Québec, 2006). In New Brunswick, dichloromethane was detected in less than 1% of samples obtained from 1994 to 2004; the maximum concentration of dichloromethane measured in water was 32 µg/L, and the average was below the limit of quantification, which varied from 1.0 to 2.0 µg/L (New

Brunswick Department of Health and Wellness, 2004). Results of monitoring in Alberta from 1999 to 2004 indicated that the average concentration of dichloromethane in drinking water was less than the sample detection limit of 2 µg/L, with a maximum concentration of 25.17 µg/L (Alberta Environment, 2004). The maximum and average concentrations of dichloromethane measured in drinking water in Nova Scotia in 2001 were 14 µg/L and 1.84 µg/L, respectively (Nova Scotia Department of Environment and Labour, 2004). In Ontario from 1999 to 2004, maximum measured concentrations of dichloromethane in drinking water were 4.5 and 2 µg/L in water coming from groundwater and surface water, respectively; average concentrations were measured at 0.5 µg/L in water coming from both groundwater and surface water (Ontario Ministry of the Environment, 2004). Dichloromethane was detected in 4.5% of samples obtained in Saskatchewan from 1994 to 2001, with a maximum of 2.5 µg/L and an average of 0.8 µg/L (Saskatchewan Department of Environment, 2004).

5.2 Food

Limited information exists on the levels of dichloromethane in food in Canada. Dichloromethane is used for solvent extraction in spices, hops, coffee and tea. Maximum residue limits legislated by the Food and Drug Regulations in Canada are 30 ppm in spice extracts, 22,000 ppm (2.2%) in hop extracts and 10 ppm in decaffeinated coffee and tea (Health Canada, 2004). A Canadian study performed before the implementation of the maximum residue limit in spices found concentrations of solvent residues in 34 spice oleoresins from three manufacturers that ranged from 1 to 83 ppm (Page and Kennedy, 1975). At a large decaffeinating plant in the USA in 1978, monthly average residual levels of dichloromethane in decaffeinated coffee beans were reported to range from 0.32 to 0.42 ppm (115–295 samples) (Cohen et al., 1980), while residue levels were lower (range = 0.01–0.1 ppm) in a study performed by the U.S. Food and Drug Administration of decaffeinated coffee beans from a major coffee processor (U.S. FDA, 1985).

Using data on dichloromethane residue levels in table-ready foods from the U.S. FDA's Total Diet Program (no reliable Canadian data were available), Long et al. (1994) estimated that food contributes 0.7–2% of the total daily intake of dichloromethane for Canadians. The foods found to contain the highest concentrations of dichloromethane in the U.S. total diet study were cereals, butter, cheese, margarine, processed foods and peanut butter.

A few studies have examined the potential of dichloromethane to bioaccumulate in freshwater fish. Based on dichloromethane's octanol–water partition coefficient, estimated bioconcentration factors (BCF) for freshwater fish range from 1.83 to 6.0 (U.S. EPA, 2000; Mackay et al., 2006), which is considered to be low (Franke et al., 1994), suggesting that the potential for bioaccumulation and biomagnification in aquatic life is low. Similarly, it is expected that little or no bioaccumulation or biomagnification will occur in terrestrial organisms (Environment Canada and Health Canada, 1993). Actual measurements of dichloromethane levels in oysters and clams from Lake Pontchartrain in Louisiana by Ferrario et al. (1985) found mean levels of 7.8 and 27 ppb for oysters and clams, respectively.

In a survey of 182 samples of retail bottled water purchased in Canada, dichloromethane was detected in four samples. The average concentration in samples where dichloromethane was detected, which were all bottled spring waters, was 59 µg/L, with a range of 22 to 97 µg/L (Page et al., 1993).

5.3 Air

The atmosphere is the major environmental sink for dichloromethane due to its high vapour pressure and Henry's Law constant. Indoor and ambient air are the greatest sources of dichloromethane for the Canadian general population; Long et al. (2004) estimated that >90% of the daily dichloromethane exposure may be coming from a combination of the two air sources.

Concentrations of dichloromethane in ambient air from 22 locations across Canada (1991–1992) ranged from 0.5 to 9.9 $\mu g/m^3$, with a national mean value of 1.7 $\mu g/m^3$ and an isolated maximum value of 311.3 $\mu g/m^3$ for Saint John, New Brunswick (Dann, 1993). Median dichloromethane concentrations in air in 2001 were less than 0.5 $\mu g/m^3$ for the majority of urban areas (Calgary, Edmonton, Regina, Windsor, Sarnia, London, Kitchener, Hamilton, Peterborough, Ottawa, Saint John and St. John's), between 0.5 and 1 $\mu g/m^3$ for Vancouver, Winnipeg, Oakville, Toronto and Montreal, and between 1.5 and 2 $\mu g/m^3$ for Kingston. During the period from 1990 to 2001, average dichloromethane concentrations in urban sites decreased from approximately 2.0 $\mu g/m^3$ to <1.0 $\mu g/m^3$ (Environment Canada, 2004b).

Indoor air concentrations of dichloromethane generally exceed those in ambient air as indicated in the results of a study by Zhu et al. (2005), in which various volatile organic chemicals were measured in indoor and outdoor air for 75 residential homes in Ottawa during the winter of 2002–2003. Dichloromethane concentrations in indoor and outdoor air were 0.06–408.37 $\mu g/m^3$ (mean = 14.98 $\mu g/m^3$) and 0.06–3.49 $\mu g/m^3$ (mean = 0.32 $\mu g/m^3$), respectively.

5.4 Consumer products

Consumer exposures to aerosol formulations may involve high peak exposures. A study by Dow Chemical USA (1975) reported the indoor air concentrations of dichloromethane when three different aerosol products (i.e. aerosol air freshener, deodorant and hair spray) were used for >15 minutes in a small unventilated room, which would represent a worst-case scenario for the use of these products. Peak dichloromethane concentrations of approximately 500 ppm were measured, with an average 15-minute time-weighted average (TWA) of 102 ppm. However, since the use of these products is generally very short in duration, the total exposure to dichloromethane is considered to be low.

The use of aerosol spray paints involves much longer spraying times, which can lead to higher exposures. Exposures to dichloromethane were measured by Stevenson et al. (1978) after simulated heavy use of paint aerosols containing 30% dichloromethane in a test room that was ventilated only after spraying. Peak dichloromethane concentrations of up to 900 ppm were reported, which resulted in an 8-hour TWA of 10 ppm.

Exposure to paint strippers containing dichloromethane may also occur in the home. Exposures have been estimated on the basis of U.S. investigations of household solvent products (U.S. EPA, 1990). Estimated exposure levels ranged from <10 ppm to a few short-term exposures of 4000 to 6000 ppm. However, the majority of the concentration estimates were found to be <500 ppm.

5.5 Soil

The principle source of dichloromethane in soil is the disposal of dichloromethane products and containers in landfill sites. It has been estimated that approximately 12% of the dichloromethane released to the environment is to soil (ATSDR, 2000). Data on the levels of dichloromethane in soil are restricted to contaminated sites and no data on levels in sediment at Canadian sites have been identified (Environment Canada and Health Canada, 1993). Levels of

dichloromethane in sediment from Lake Pontchartrain near New Orleans, Louisiana, ranged from not detectable to 3.2 ppb wet weight (Ferrario et al., 1985).

In soil, biodegradation occurs under both aerobic and anaerobic conditions (Davis and Madsen, 1991; ATSDR, 2000). However, since dichloromethane has a low tendency to adsorb to soil (Dilling et al., 1975; Dobbs et al., 1989; ATSDR, 2000), there is a potential for it to occur in groundwater.

5.6 Multi-route exposure through drinking water

Exposure to dichloromethane in drinking water was previously assessed using ingestion as the only route of exposure. Owing to dichloromethane's physicochemical properties, exposure by inhalation and dermal absorption during bathing or showering may also be important routes of exposure. To date, no studies have assessed exposure to individuals bathing or showering in water containing dichloromethane.

To assess the overall exposure to dichloromethane in drinking water, the relative contribution of each exposure route is assessed through a multi-route exposure assessment approach (Krishnan, 2004; Krishnan and Carrier, 2008). A physiologically based pharmacokinetic (PBPK) model developed for Health Canada was also used to calculate the relative contributions of each exposure route (Hamelin et al., 2009). Contributions developed through these approaches are expressed in litre-equivalents (L-eq) per day. Both the dermal and inhalation routes of exposure for a volatile organic chemical are considered significant if they contribute to at least 10% of the drinking water consumption level (Krishnan, 2004; Krishnan and Carrier, 2008).

5.6.1 Two-tiered approach for multi-route exposure assessment

5.6.1.1 Dermal exposure

To determine whether dermal exposure represents a significant route of exposure for dichloromethane, tier 1 of the multi-route exposure assessment determines 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). According to the equation below, for a tier 1 goal of 0.15 L-eq, the skin permeability coefficient (K_p) for dichloromethane should be higher than 0.024 cm/h (Krishnan, 2004; Krishnan and Carrier, 2008). Tier 1 of the assessment is used to calculate the K_p for dichloromethane, using the following equation (Bogen, 1994; WHO, 2000):

$$\begin{aligned} \text{Log } K_p &= -0.812 - 0.0104\ MW + 0.616 \log K_{ow} \\ &= -0.812 - (0.0104 \times 84.93) + (0.616 \times 1.25) \\ &= -0.925 \\ K_p &= 0.119 \text{ cm/h} \end{aligned}$$

where:

- MW is the molecular weight of 84.93 g/mol; and
- $\log K_{ow}$ is the log of the experimental n-octanol–water partition coefficient (1.25).

Since the K_p for dichloromethane of 0.119 cm/h is greater than 0.024 cm/h, exposure to dichloromethane via dermal absorption from bathing and/or showering is considered significant.

Tier 2 of the assessment is then used to calculate the litre-equivalent value, using the following equation (Krishnan, 2004; Krishnan and Carrier, 2008):

$$\begin{aligned} \text{Dermal L-eq} &= K_p \times t \times F_{abs} \times A \times C_f \\ \text{Dermal L-eq} &= 0.119 \text{ cm/h} \times 0.5 \text{ h} \times 0.7 \times 18\,000 \text{ cm}^2 \times 0.001 \text{ L/cm}^3 \\ &= 0.75 \text{ L-eq/day} \\ &\approx 0.8 \text{ L-eq/day} \end{aligned}$$

where:

- K_p is the skin permeability coefficient of 0.119 cm/h, as calculated above (tier 1);
- 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;
- A is the area of skin exposed, assumed to be 18 000 cm^2 for adults; and
- C_f is the conversion factor from cubic centimetres (cm^3) to litres (L).

5.6.1.2 Inhalation exposure

A two-tier assessment was also used to evaluate the inhalation route of exposure. Similar to the approach used for dermal exposure, tier 1 of the assessment determines whether the inhalation of dichloromethane during bathing or showering 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 air-to-water dichloromethane concentration ($F_{air:water}$) value should be greater than 0.00089 (Krishnan, 2004; 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, 2000), the $F_{air:water}$ value for dichloromethane was determined by means of the following equation developed by Krishnan (2004):

$$\begin{aligned} F_{air:water} &= \frac{0.59 \times K_{aw}}{1 + (80.25 \times K_{aw})} \\ &= \frac{0.59 \times 0.25}{1 + (80.25 \times 0.25)} \\ &= 0.0070 \end{aligned}$$

where:

- K_{aw} is the average estimated unitless Henry's Law constant at 25ºC of 0.25 (U.S. EPA, 2000);
- 0.59 is 59% transfer efficiency for dichloromethane (Hamelin et al., 2009); 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 or bathing event (Krishnan, 2004).

Since the $F_{air:water}$ value is greater than 0.00089, exposure to dichloromethane via inhalation from bathing or showering is considered to be significant. Tier 2 of the assessment calculates what the litre-equivalents should be based on the following formula (Krishnan, 2004):

$$\text{Inhalation L-eq} = F_{air:water} \times Q_{alv} \times t \times F_{abs}$$
$$= 0.0070 \times 675 \text{ L/h} \times 0.5 \text{ h} \times 0.7$$
$$= 1.65 \text{ L-eq/day}$$

where:

- $F_{air:water}$ is the ratio (partitioning) of air-to-water dichloromethane concentrations (0.0070, as calculated above);
- Q_{alv} is the adult alveolar ventilation rate, assumed to be 675 L/h;
- t is the exposure duration, assumed to be 0.5 h; and
- F_{abs} is the fraction absorbed, assumed to be 0.7, based on Krishnan (2003a, 2003b) and DiVincenzo and Kaplan (1981).

5.6.2 PBPK approach for multi-route exposure assessment

A human PBPK model was developed to properly extrapolate the results of a high-dose mouse inhalation study to scenarios where humans would be exposed to low concentrations of dichloromethane in drinking water (Hamelin et al., 2009). The human PBPK model was also used to estimate the daily contribution of a 30-minute shower to the internal generation of metabolites from dichloromethane. The litre-equivalent exposure was calculated to be 0.58 L-eq/day for the dermal route and 1.96 L-eq/day for the inhalation route (Hamelin et al., 2009). Further information on the PBPK model is provided in sections 8.5 and 10.1.

5.6.3 Conclusion for multi-route exposure assessment

This multi-route exposure assessment is a conservative approach used to estimate the contribution that both the dermal and inhalation routes of exposure make towards total exposure. Using the two-tier approach, the litre-equivalent exposure was calculated as being 0.8 L-eq for the dermal route and 1.65 L-eq/day for the inhalation route. Adding these values to the standard Canadian drinking water consumption rate of 1.5 L/day results in a total litre-equivalent daily exposure of 4.0 L-eq (rounded from 3.95 L-eq). The results from the two-tier approach are supported by the PBPK approach, which resulted in litre-equivalent exposures of 0.58 L-eq/day for the dermal route and 1.96 L-eq/day 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 4.0 L-eq (rounded from 4.04 L-eq). Therefore, a value of 4.0 L-eq/day is used to calculate the MAC.

6.0 Analytical methods

The U.S. Environmental Protection Agency (U.S. EPA) currently has two approved analytical methods (Method 502.2 Revision 2.1 and Method 524.2 Revision 4.1) for the analysis of dichloromethane in drinking water (U.S. EPA, 2002). Method 502.2 Revision 2.1, which employs purge-and-trap capillary gas chromatography (GC) with a photoionization detector

(PID) and an electrolytic conductivity detector (ELCD) placed in series, has a method detection limit (MDL) in the range of 0.01–0.02 μg/L, depending on the GC column used. 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 allows MDL values in the range of 0.03–0.09 μg/L (U.S. EPA, 1995a). Multiple values for the MDL result from variability in reagents, instrumentation and/or laboratory analyst performance (U.S. EPA, 2003).

The U.S. EPA practical quantitation limit (PQL), based on the capability of laboratories to measure the concentration of dichloromethane within reasonable limits of precision and accuracy, is currently 5 μg/L (U.S. EPA, 1992). In the U.S. EPA's 6-year review, based on information from analytical methods most widely used in Water Supply studies to analyse dichloromethane, the U.S. EPA has estimated that the PQL for dichloromethane could possibly be lowered to approximately 0.55 μg/L (U.S. EPA, 2002a).

In addition, two methods from Standard Methods (APHA et al., 2005), SM 6200B and SM 6200C, can be used for the analysis of dichloromethane in drinking water. These methods are based on purge-and-trap capillary gas chromatography followed by MS detector or PIDs and ELCDs in series, respectively. Method SM 6200B has a MDL of 0.099 μg/L and SM 6200C has a MDL of 0.068 μg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately using these methods, are 0.396 μg/L and 0.272 μg/L for methods SM 6200B and SM 6200C, respectively (APHA et al., 2005).

7.0 Treatment technology

Following a U.S. survey of drinking water supplies which found dichloromethane in 8% of finished water and 1% of raw water samples, it has been suggested that dichloromethane can be formed during the chlorination treatment process (NAS, 1977). Water chlorination might increase the concentration and frequency of occurrence of dichloromethane in drinking water supplies (U.S. EPA, 2006), but chlorination results in a greater generation of trihalomethanes than dichloromethane (Gyunter et al., 1985).

7.1 Municipal scale

Conventional water treatment techniques (coagulation, sedimentation, filtration and chlorination) have been found to have a little or no effect in reducing concentrations of volatile organic compounds (VOCs) in drinking water (Love and Eilers, 1982; Love et al., 1983; Lykins and Clark, 1994).

Although the solubility of dichloromethane in water is relatively high, incidental removal of dichloromethane may occur as a result of volatilization in open basins (Health and Welfare Canada, 1993).

Due to the volatile organic nature of dichloromethane, there are two existing treatment technologies that public water systems can use: air stripping and granular activated carbon (GAC) adsorption (U.S. EPA, 1987, 1992, 1995b). The U.S. EPA has identified packed tower aeration (PTA) as a best available technology (BAT) for dichloromethane removal in drinking water below the U.S. EPA Maximum Contaminant Level of 5 μg/L (U.S. EPA, 1992). Removal of volatile chlorinated aliphatic hydrocarbons similar to dichloromethane by packed tower aeration is estimated to be from 90% to 99% effective (U.S. EPA, 1985).

The selection of an appropriate treatment process for a specific water supply will depend on the characteristics of the raw water supply and the operational condition of the specific treatment method.

7.1.1 Air stripping

Air-stripping treatment technology is commonly used to reduce the concentration of VOCs in drinking water (Cummins and Westrick, 1990; U.S. EPA, 1991; WHO, 2004; Dyksen, 2005). An air-stripping process brings water and air into contact, which allows the transfer of dissolved 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, the PTA provides an optimum system for the removal of VOCs from water as it allows for greater air-to-water ratios than other aeration systems. In the PTA column the contaminated water flows downward by gravity over a bed of packed media, while the air is introduced into the tower below the packed bed and flows upward countercurrent to the water flow. As the PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to reduce the contaminant concentrations before discharge into the atmosphere may be necessary (Crittenden et al., 1988; Adams and Clark, 1991).

Several factors affect the rate of stripping the VOCs from water: the air-to-water (A:W) ratio, available area of mass transfer (including packing depth), hydraulic loading rate, the temperature of the water and air, and the physical and chemical properties of the contaminant (AWWA, 1991; MWH, 2005a; Dyksen et al., 2005). The PTA process is effective, but relatively expensive to build and maintain, and thus may not be appropriate for small water treatment utilities. Where the installation of PTA treatment system is not feasible, 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 dichloromethane in drinking water for small systems (U.S. EPA, 1998).

A common operating problem is the 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 PTA influent, using scale inhibitors, or iron removal before 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 approaches, 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 affect the packed tower performance. Contact between the water and the air in PTA column typically allows the air temperature to approach that of the water. The temperature influences both the Henry's Law constant and the rate of mass transfer coefficient of the contaminant. These parameters affect the size of the equipment and the removal efficiency of the VOCs (MWH, 2005a).

A pilot plan PTA system designed to operate with a loading rate greater than 8340 $lb/ft^2/h$ (11.3 $kg/m^2/s$)**,** demonstrated that modifying the packing depth or the A:W ratio increased the removal efficiency of dichloromethane in contaminated groundwater. Using A:W ratios of 20 and 30 resulted in a reduction of the influent concentrations in the range of 46–193 μg/L to effluent concentrations in the range of 1.7–13.6 μg/L, and influent concentrations in the range of 95–214 μg/L to effluent concentrations in the range of 2.1–15.5 μg/L, respectively. Under these conditions, removal reduction rates in the range of 96.3–92.9% and 97.8–92.8% for

dichloromethane were achieved, respectively, for those A:W ratios. The samples were evaluated at a stripper length of 15 feet (4.6 metres). An additional increase of the stripper length to 30 feet (9.14 metres) and using an A:W ratio of 20 was capable of reducing an influent concentration from 226 μg/L to an effluent concentration of 1.5 μg/L, achieving 99.3% removal reduction of dichloromethane in contaminated water (Bilello et al., 1984). Another pilot study (Ball and Edwards, 1992) demonstrated removal efficiencies for dichloromethane from influent levels of 67 μg/L to below the detection limit of 1 μg/L, using an A:W ratio in the range of 30–100, a packing height of 1.22 m, and a liquid loading rate of 6.48 kg/m^2/s. Using the confirmation of the input parameters from this pilot study, the authors developed and optimized design parameters for a full-scale air stripping tower to achieve a treatment objective of 92.6% removal of dichloromethane. A packed tower column designed with a packed depth of 5.49 metres, liquid loading rate of 18.2 kg/m^2/s and an A:W ratio of 35 could reduce dichloromethane from an influent concentration of 67 μg/L to an effluent concentration of 5 μg/L (Ball and Edwards, 1992).

Modelling studies by Crittenden et al. (1988) and Adams and Clark (1991) estimated that a 99% removal efficiency and an effluent concentration of 1 μg/L of dichloromethane could be achieved in the treated water. According to Crittenden et al. (1988), typical full-scale plant air-stripping design parameters for reduction of dichloromethane include an A:W ratio of 71.6, an air stripper length of 8.72 m, a packed column diameter of 3.39 m and a flow rate of 8.17 ML/d. Under these conditions, a 99% reduction of dichloromethane could be achieved in drinking water with an influent concentration of 100 μg/L resulting in an effluent concentration of 1 μg/L.

After an evaluation of the cost of PTA and GAC adsorption technologies for the control of selected organic compounds in water, Adams and Clark (1991) indicated that the cost effective PTA design parameters for the reduction of DCM include an A:W ratio of 55 and a packing depth of 11.52 m or an A:W ratio of 40 and a packing depth of 15.33 m. Under these estimated conditions a 99% reduction of dichloromethane could be achieved from an influent level of 100 μg/L to an effluent level of 1 μg/L. These evaluations indicate that, in most cases, the use of PTA for the reduction of dichloromethane in drinking water is more cost effective than GAC alone, even when subsequent treatment of the tower off-gas using GAC is required (Adams and Clark, 1991).

7.1.2 Activated carbon adsorption

Activated carbon is used in the water treatment process 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 pH, competition from other contaminants, preloading with natural organic matter (NOM), and the physical and chemical properties of the VOC and carbon (Speth, 1990). According to Singley et al. (1979) and Love and Eilers (1982), PAC adsorption is less efficient than GAC adsorption for VOC removal. The PAC application, most suitable for conventional treatment systems, may remove occasional low concentrations of organic contaminants when it is applied at the right location (to provide a good mixing and sufficient contact time) in the surface water treatment process.

Greater concentrations of VOCs are found in groundwater and for its continuous removal the GAC adsorption is the commonly used process (Snoeyink, 1990). The process uses a contactor packed with granular activated carbon and as the water passes through the GAC contactor, the contaminants diffuse to the adsorbent granules and accumulate on its surface. Packing the carbon in columns allows more complete contact between the water and the media,

greater adsorption efficiency and greater process control than PAC. The GAC process is the most widely used for small water treatment systems due to its simplicity and ease of operation (Snoeyink, 1990; U.S. EPA, 1998).

Design considerations for employing GAC application include an empty bed contact time (EBCT), bed depth, hydraulic loading rate and organic loading rates. During the operation time and depending on a variety of factors, such as the specific VOC or mixture of VOCs to be removed, organic contaminant will "break through" the carbon bed, which is defined as the time when the contaminant concentration in the effluent exceeds the treatment objective. The replacement and regeneration of exhausted media are important economic considerations in achieving the contaminant treatment goal.

Common operating problems when using GAC adsorption contactors include biological growth and the concurrent increase in heterotrophic plate counts in the effluent, and clogging and fouling of the carbon adsorber by chemical and bacterial precipitants. Operating considerations 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; MWH, 2005b).

Data from full-scale testing demonstrated that two GAC adsorbers operating in series with a flow rate of 20 gpm (0.1 ML/day), a surface loading rate of 0.25 gpm/ft^2 (0.62 m/h), a total EBCT of 262 minutes and carbon usage rate of 3.9 lb/1000 gallons (0.47 kg/m^3) were capable of reducing dichloromethane concentrations of 21 mg/L to an effluent concentration of 1 μg/L (O'Brian et al., 1981). Another full-scale study demonstrated that two downflow pressure GAC contactors operating in parallel were able to reduce an influent dichloromethane concentration in the range of 40–45 μg/L to less than 1μg/L. Operating conditions of these GAC adsorbers, designed for the reduction of several VOCs in groundwater, included a flow rate of 900 gpm (4.9 L/day), a surface loading rate of 5.7 gpm/ft^2 (13.7 m/h) and an EBCT of 12 minutes (Anon., 1981a, 1981b; Hess et al., 1981b). A study examining the efficiency of full-scale systems using GAC for removal of organic contaminants in drinking water, suggested that dichloromethane was barely adsorbed (Koffskey et al., 1983). Data from another full-scale GAC system reported that an average low influent concentration of 0.2 μg/L did not show a decrease of dichloromethane in the effluent (Lykins et al., 1984). However, both studies made no firm conclusions regarding the adsorbability of dichloromethane by GAC due to analytical issues such as the low influent concentrations (detection limit of 0.1 μg/L) and the possible contamination of samples due to its use as an analytical reagent for non-volatile analysis.

Adams and Clark (1991) estimated the cost-effective design parameters for liquid-phase GAC treatment of dichloromethane in drinking water. The estimated carbon-usage rate to reduce an influent dichloromethane concentration of 100 μg/L to an effluent concentration of 5 μg/L was 5.1346 lb/1000 gallons (0.615 kg/m^3), an EBCT of 40 minutes and a bed life of 22 days. Under these conditions, a 95% reduction of dichloromethane in drinking water may be achievable. According to Adams and Clark (1991), poorly adsorbed organic compounds such as dichloromethane would exhibit higher GAC usage rate (shorter bed life) in the presence of more strongly adsorbed organic contaminant, as a result of competitive adsorption and displacement.

7.1.3 Combination of packed tower aeration and granular activated carbon

Aeration technologies with a combination of GAC adsorption could be extremely effective for producing water with low effluent levels of VOC concentration (Robeck and Love,

1983; McKinnon and Dyksen, 1984). The aeration step reduces the organic load to the adsorbent and may remove compounds competing for adsorption sites and, in addition, can significantly extend carbon bed life (Hess et al., 1981a; Stenzel and Gupta, 1985; U.S. EPA, 1991). The common operational problems existing with PTA system and GAC adsorption contactors should be considered when this combined technology is employed.

Combining an air-stripping tower and a series of three gravity flow carbon adsorbers was capable of reducing an influent dichloromethane concentration of 503 μg/L to an effluent concentration of less than 1 μg/L (McIntyre et al., 1986). The PTA design parameters included a hydraulic loading rate of 8.2 L/m^2/s; an air-to-water ratio of 200, tower diameter of 1.2 m and packing depth of 7.3 m. The adsorbers were designed to operate in down-flow mode, each containing 3,630 kg of activated carbon and having a bed depth of 1.4 m. The EBCT for each contactor was 15 minutes at the design hydraulic loading rate of 2 L/m^2/s.

7.1.4 Emerging treatment technologies

Other drinking water treatment technologies for removal of dichloromethane have been developed, but are still in the research-scale evaluation. Some emerging treatment technologies include the following:

- *Advanced oxidation processes (AOPs)* – These processes use appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts to generate highly reactive radicals such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants. In a pilot-scale study, the concentration of dichloromethane was not detected (no detection limits were stated) after 30 minutes of treatment time, using a UV dose of 160 W/L, with a combination of a hydrogen peroxide (H_2O_2) dose of 150 mg/L per min. An influent concentration of dichloromethane in the contaminated groundwater was in the range of 2–3.0 mg/L (Hager et al., 1987).
- *High energy electron beam (E beam)* – This technique involves injecting high-energy electrons into an aqueous solution of contaminants to form highly reactive species such as aqueous electrons, hydrogen atoms and hydroxyl radicals, which mineralize the organic molecules. Pilot-scale experiments were capable of reducing three different influent concentrations of dichloromethane from 9.08, 41.6 and 108 mg/L to effluent concentrations of 0.77, 6.6 and 28.5 mg/L, respectively, and showed a percentage removal of 91.6%, 84.17% and 73.7%, respectively, while increasing the required dose of treatment (Mak et al., 1997).
- *Steam stripping* – This is a separation process that uses differences in the thermodynamic properties of the liquid. Steam is used as a stripping gas to remove VOCs from the water. A pilot-scale study using a two-pass treatment process conducted for contaminated groundwater with an influent concentration of 9700 mg/L achieved an effluent concentration of <1 mg/L dichloromethane (Landanowski et al., 1992).
- *Biodegradation* – Some microorganisms could use dichloromethane as a sole carbon and energy source for growth (Bruner et al., 1980) and could mineralize it to harmless end products such as a carbon dioxide, water and chloride (Klecka, 1982). A field-scale application of biological treatment techniques has proven effective for the biodegradation of dichloromethane in groundwater (Flathman et al., 1992).
- *Membrane pervaporation* – Pervaporation is a process in which a liquid stream containing two or more contaminants is placed in contact with one side of a non-porous polymeric membrane while a vacuum or gas purge is applied to the other side. The components in the liquid stream sorb into the membrane, permeate through it and evaporate into the

vapour phase. Laboratory experiments that used hollow-fibre-type pore-filling Laurylacrylate grafted membranes showed good separation performance for the removal of dichloromethane from water (Yamaguchi et al., 2001).

- *Electrochemical decomposition* – Chemical changes (decomposition) occur at electrodes in contact with an electrolyte when an electric current is passed through. Laboratory studies reported that a copper (Cu) metal-powder column electrode decomposed 20 mg/L of dichloromethane in an aqueous solution with 100% decomposition occurring at a low flow rate (Sonoyama et al., 2001).

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 (treatment device) may be an option for reducing dichloromethane concentrations in drinking water. Although no certified residential treatment devices are currently available for the reduction of dichloromethane from drinking water, treatment devices using activated carbon filters may be effective for the reduction of dichloromethane. 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, because they provide treated water for bathing and laundry as well as for cooking and drinking.

Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of dichloromethane. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations.

Health Canada does not recommend specific brands of drinking water treatment devices, but strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2007):

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

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

8.0 Kinetics and metabolism

8.1 Absorption

Dichloromethane is absorbed through the gastrointestinal tract, lungs and skin. Animal data indicate that dichloromethane in water becomes rapidly absorbed across the gastrointestinal tract, then becomes detected in the bloodstream soon after ingestion. The amount of dichloromethane measured in the upper gastrointestinal tract of mice gavaged with 10 or 50 mg/kg body weight (bw) of dichloromethane in water and rats gavaged with 50 or 200 mg/kg bw of dichloromethane in water rapidly declined over time, particularly in the first 40 minutes after administration. A similar decrease was observed in the lower gastrointestinal tract for mice, but less than 2% of the gavage dose was found in the lower gastrointestinal tract in rats. Blood samples obtained from rats and mice 10 minutes after a gavage dose of dichloromethane indicated high concentrations of the solvent in the blood (Angelo et al., 1986a, 1986b).

DiVincenzo and Kaplan (1981) estimated that 69% to 75% of inhaled dichloromethane was absorbed across the surface of human lungs. During the first hour of inhalation exposure to dichloromethane in humans, rapid uptake occurred, with dichloromethane blood concentrations of 0.2 mg/L in subjects exposed to 50 ppm in air and 0.6 mg/L in subjects exposed to 100 to 200 ppm (DiVincenzo and Kaplan, 1981). Increased physical activity caused an increase in the amount of dichloromethane absorbed through the inhalation route in humans (Åstrand et al., 1975). With continued inhalation exposure, a plateau in the net uptake of dichloromethane in blood appears to occur after 2 hours of inhalation in rats (McKenna et al., 1982) or before the end of a 7.5-hour exposure period in humans (DiVincenzo and Kaplan, 1981); the time period appears to be independent of concentration.

No studies have measured the penetration of dichloromethane-containing water across human skin under typical conditions; however, dermal penetration of solvents containing high concentrations of dichloromethane has been studied. Dermal penetration rates for liquid dichloromethane are dependent on skin characteristics (thickness, vascularity, age, chemical composition), the surface area of exposed skin and exposure duration (Stewart and Dodd, 1964). Dichloromethane is considered to be lipophilic, and therefore absorption probably occurs through the stratum corneum (McDougal et al., 1986). Experimental studies indicate that absorption of dichloromethane across human skin occurs more slowly than through the lung (Stewart and Dodd, 1964). However, a PBPK model suggested that the internal dose from dermal exposure of two unprotected hands for 8 hours (reference states exposure to high dichloromethane vapour concentrations, but does not specify a numerical concentration) may be greater than the internal dose resulting from inhalation exposure to 25 ppm for an 8-hour shift (OSHA, 1997). A study by McDougal et al. (1986) suggests that dermal absorption of dichloromethane vapour in rats is more rapid than in humans, and permeability constants were consistent over three different air concentrations (30 000, 60 000, and 100 000 ppm), with the mean calculated as 0.28 cm/h.

8.2 Distribution

Dichloromethane and [^{14}C]dichloromethane-derived radioactivity have been measured in various organs (liver, kidney, lungs, brain, muscle) and adipose tissues in rats exposed to radiolabelled dichloromethane via inhalation and ingestion, but concentrations in the tissues declined after exposure was ceased (Carlsson and Hultengren, 1975; McKenna et al., 1982; Angelo et al., 1986a, 1986b). In a study where rats were exposed to 557 ppm of dichloromethane by inhalation for 1 hour, white adipose tissue was the largest store for dichloromethane 1 hour after exposure, but dichloromethane concentrations in this tissue decreased more rapidly than in

the liver, kidneys, adrenal glands and brain (Carlsson and Hultengren, 1975). In mice, radiolabelled dichloromethane inhaled for 10 minutes (10 µL, 461.3 mg/kg bw of intake) was quickly distributed, with high concentrations of dichloromethane occurring in brain white matter, body fat, blood, liver and kidney immediately after exposure; after 30 minutes distribution was apparent in tissues with high rates of cell turnover or protein synthesis (Bergman, 1979). In an autopsy of a 47-year-old worker in a paint-stripping factory that died from accidental overexposure, dichloromethane concentrations of 150 mg/L in blood, 2 mg/L in urine, 122 mg/kg in brain, 99 mg/kg in fat, 44 mg/kg in liver, 20 mg/kg in lung, 15 mg/kg in kidney and 5.6 mg/kg in gastric contents were measured (Goullé et al., 1999). Dichloromethane was detected in the same organs, as well as the heart (Kim et al., 1996) and spleen (Leikin et al., 1990), in autopsies of other individuals who died from accidental occupational overexposures to dichloromethane.

Maternal exposure to dichloromethane may lead to distribution of dichloromethane and its metabolites to the fetus and nursing infants. In pregnant Sprague–Dawley rats exposed to approximately 500 ppm of dichloromethane in air, both dichloromethane and carbon monoxide (a metabolite) were found in fetal blood (Anders and Sunram, 1982). Blood, fetal membrane and fetal concentrations of dichloromethane were higher in women exposed to average concentrations of 25 ppm of dichloromethane in an industrial rubber manufacturing facility than in non-exposed workplace controls. Dichloromethane was also measured in breast milk 5–7 hours after the beginning of an exposure period, but the concentration was minimal 17 hours postexposure (Vosovaja et al., 1974).

8.3 Metabolism

The process of metabolism for dichloromethane is similar for all routes of exposure. The majority of metabolism of dichloromethane takes place in the liver and the lungs, with the liver being the predominant organ of metabolism (Andersen et al., 1987); however, oxidative metabolism may also occur in other tissues (Sweeney et al., 2004).

Dichloromethane metabolism occurs via two pathways. The mixed-function oxidase (MFO) pathway is dependent on microsomal cytochrome P450 2E1 (CYP2E1), which metabolizes dichloromethane to carbon monoxide (CO) and carbon dioxide (CO_2) (Starr et al., 2006), with dichloromethanol and formyl chloride as intermediates (Kubic and Anders, 1978). The second metabolic pathway for dichloromethane involves cytosolic glutathione S-transferase (GST) enzymes that metabolize dichloromethane to carbon dioxide following the formation of formaldehyde, formic acid, and the glutathione conjugate intermediates *S*-(chloromethyl)-glutathione, *S*-(hydroxymethyl)glutathione, and *S*-formylglutathione (Ahmed and Anders, 1976; 1978; Reitz, 1990; Green, 1997).

Although dichloromethane may be metabolized by the two pathways concurrently, animal studies have identified that the MFO pathway is a high-affinity pathway with a low capacity and is therefore predominant at lower exposure levels, while the GST pathway has a lower affinity yet has a higher capacity and is therefore predominant at higher exposure levels (Gargas et al., 1986). The enzymes in the MFO pathway can become saturated, leading to a lack of a dose-related increase in the production of carboxyhemoglobin (COHb) at high exposures (Rodkey and Collison, 1977), which will result in greater metabolism of dichloromethane down a secondary pathway. Since the MFO pathway can become saturated, chronic high exposures to dichloromethane are likely to lead to metabolism primarily via the GST pathway.

For rats exposed to 50 ppm of dichloromethane by inhalation for 6 hours, the steady-state COHb concentration was measured at 3% (percent of carbon monoxide saturation measured in blood samples), while the steady-state concentration for rats exposed to either 500 or 1500 ppm

was 10–13% (McKenna et al., 1982). The absence of a significant difference in COHb concentrations in rats exposed to 500 or 1500 ppm was indicative of saturation of the MFO pathway at these concentrations.

In humans, levels of COHb in the blood following exposure to dichloromethane via inhalation or ingestion were repeatedly higher than pre-exposure concentrations. In a variety of different human experiments, exposures of 500 to 1000 ppm of dichloromethane for 1 to 2 hours resulted in elevations in COHb saturation in all 11 subjects (Stewart et al., 1972). A 56-year-old woman who died approximately 25 days after ingesting a paint remover containing dichloromethane had a COHb concentration of 9% in blood 1 hour postingestion, and a peak concentration of 12.1% 36 hours after ingestion (Hughes and Tracey, 1993). COHb concentrations of 9% in rats gavaged once with 527 mg/kg bw dichloromethane (Wirkner et al., 1997) indicate that there are metabolic similarities between animals and humans.

Polymorphisms in the GST theta 1 (GSTT1) enzyme, one of the enzymes involved in the GST pathway, occur in humans. Individuals that are homozygous for the wild-type gene (i.e., no mutations) have complete metabolic activity, while heterozygotes or those with no copies of the gene have decreased or no ability to metabolize dichloromethane (Haber et al., 2002). Depending on the ethnic group, approximately 10–64% of the American population have no copies of the GSTT1 gene (Nelson et al., 1995).

GST activity is greater in mice than in rats or humans. This is supported by higher levels of GSTT1 and GST theta 2 (GSTT2) in mouse tissues than in rats or humans (Reitz et al., 1989; Mainwaring et al., 1996). *In vivo* data also indicate rates of GST metabolism are higher in mice than in rats. In rats exposed to 500 ppm, the majority of dichloromethane was metabolized, whereas at concentrations of 1000, 2000 and 4000 ppm, concentrations at which the MFO pathway was saturated, little additional metabolism took place. In the mouse, however, metabolism still occurred after the MFO pathway was saturated, which was interpreted to indicate metabolism was occurring via a secondary pathway (Green et al., 1986). In addition, the amount of dichloromethane or its metabolites that became incorporated into the DNA of lung or liver tissue was 2–4 times greater in mice than in rats when animals were exposed to a concentration of 4000 ppm, which would have led to the GST pathway as the primary metabolic pathway (Green et al., 1988).

8.4 Excretion

Excretion of dichloromethane does not vary with the route of exposure. The primary route of excretion for dichloromethane is expired air, with urine as a secondary route. In adults exposed to 100 or 200 ppm by inhalation for 2 or 4 hours, dichloromethane concentrations in breath decreased exponentially after exposure, with a drop from 20 ppm 1 minute postexposure, to approximately 5 ppm after 30 minutes, and <1 ppm after 5 hours (DiVincenzo et al., 1972). After 2-hour exposures, the average measurement of dichloromethane in 24-hour urine collection samples was 22.6 µg in subjects exposed to 100 ppm and 81.5 µg in those exposed to 200 ppm.

In a gavage study, the total excretion of radiolabelled dichloromethane or metabolites (measured as either CO, CO_2 or dichloromethane) in expired air during the 48-hour period after a single dose to rats of 1 or 50 mg/kg bw of radiolabelled dichloromethane in aqueous solution was 78% and 90%, respectively (McKenna and Zemple, 1981). Urine was the other major route of excretion, with 2% of the radiolabel in the low-dose group and 5% in the high-dose group being excreted by this route. In rats inhaling 50, 500, or 1500 ppm of radiolabelled dichloromethane, the majority of the radiolabelled parent compound or its metabolites were exhaled (McKenna et al., 1982). For the 50-, 500- and 1500-ppm groups, 58%, 71%, and 79% of the radioactivity was

exhaled, respectively; urinary excretions accounted for 7.2–8.9% of the absorbed dose and faecal excretion accounted for 1.9–2.3% of the absorbed dose. No volatile compounds in the urine contained radiolabelled carbon; therefore, McKenna et al. (1982) hypothesized that the metabolites, rather than the parent compound, were excreted in urine.

Pulmonary excretion of dichloromethane, CO and CO_2 was observed within 30 minutes postexposure in mice and rats that were dosed daily by gavage for 14 days with 50 mg/kg bw in water (mice and rats), 200 mg/kg bw in water (rats), or 500 or 1000 mg/kg bw in corn oil (mice) (Angelo et al., 1986a, 1986b). In these two studies, exhaled dichloromethane levels were greater than exhaled metabolite levels for all doses, species and time periods, and exhaled CO_2 levels were greater than the CO levels.

As the concentration of dichloromethane exposure increases, the percentage of dichloromethane exhaled as metabolites decreases. In rats exposed to 50 ppm dichloromethane for 6 hours, 5% of exhaled dichloromethane was exhaled as the parent compound, while rats exposed to 500 and 1500 ppm exhaled 30% and 55% as dichloromethane, respectively (McKenna et al., 1982). Similar results were observed via gavage. For all time periods in rats and for most time periods in mice, the percentage of dichloromethane exhaled as metabolites was greater in animals dosed by gavage with 50 mg/kg bw dichloromethane in water than those dosed at higher concentrations of dichloromethane in either corn oil or water (Angelo et al., 1986a, 1986b). In rats that were given 1 or 50 mg/kg bw of dichloromethane in water via gavage, the amount of dichloromethane in the expired air increased from 12% to 72% with the increase in dose (McKenna and Zempel, 1981).

The majority of dichloromethane and its metabolites are excreted after exposure. The total amount of dichloromethane or metabolites excreted from any route within 48 hours after a single gavage dose of 1 or 50 mg/kg bw was 92% and 96% of the initial dose, respectively (McKenna and Zempel, 1981).

8.5 PBPK models

In human health risk assessment for dichloromethane, PBPK modelling is useful because no appropriate toxicity data are available for humans ingesting dichloromethane in drinking water, ingestion studies in animals are limited and the differences between GST metabolites generated at high and low concentrations are not linear. Information from PBPK models has been used to account for saturation of the MFO pathway, which results in reduced uncertainty in risk assessments for dichloromethane.

The majority of PBPK models for dichloromethane are based on a model by Andersen et al. (1987). This model allows for exposure estimates for dichloromethane via either the inhalation or ingestion routes, and groups body tissues into lung, fat and liver, as well as richly perfused and slowly perfused compartments, with metabolism occurring in the lung and liver compartments. Various adjustments have been made to the model by different investigators, so that the model meets the objectives for different studies.

For the purpose of this risk assessment, PBPK modelling was used to perform mouse-to-human, high-to-low dose and exposure route extrapolations (Hamelin et al., 2009). The mouse model was based on the Andersen et al. (1987) model and then refined using the Marino et al. (2006) model. The Andersen et al. (1987) model was also used as the basis for the human model, and was refined using the David et al. (2006) model. The external concentrations of dichloromethane associated with an excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6}, as calculated from the NTP (1986) study, were used in the mouse PBPK model to calculate the internal dose

(measured as liver metabolites generated by the GST enzyme in the liver, and the area under the curve for liver dichloromethane concentrations) associated with each of the risk levels. These internal doses associated with each of the risk levels were the inputs into the human PBPK model, and the external doses to humans that would generate the internal doses were calculated. This resulted in an external human dose in drinking water that would be associated with an excess cancer risk in humans of 10^{-4}, 10^{-5} and 10^{-6}, when daily exposure to drinking water occurs via ingestion of 1.5 L of water and via inhalation and dermal exposures from a 30-minute shower.

Many other PBPK models have been developed for dichloromethane. Models have been used to extrapolate experimental results from rats to humans (Portier and Kaplan, 1989; Andersen et al., 1991; Reitz et al., 1996) and from mice to humans (Reitz, 1990; Andersen and Krishnan, 1994; El-Masri et al., 1999; Marino et al., 2006). Intraspecies variability has also been incorporated into PBPK models by factoring in variation in DCM metabolism due to genetic differences in the GSTT1 enzyme (El-Masri et al., 1999; Jonsson and Johanson, 2001), various levels of activity (Dankovic and Bailer, 1994; Jonsson and Johanson, 2001; Jonsson et al., 2001), and variances in pharmacokinetic, physiological and biochemical inputs into the model (Portier and Kaplan, 1989; Sweeney et al., 2004). Models have also been developed to determine equivalent target tissue doses between the inhalation and oral routes of exposure (Reitz, 1990; Andersen et al., 1991; Reitz et al., 1996), and to determine how metabolite production varies between low and high doses (Andersen et al., 1987; Andersen and Krishnan, 1994; El-Masri et al., 1999; Jonsson and Johanson, 2001; Jonsson et al., 2001).

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute toxicity

Acute effects in humans after exposure to dichloromethane by ingestion have been reported after accidental poisoning events or attempted suicides. A 38-year-old man who ingested 0.57–1.14 L (1–2 Imperial pints) of Nitromors, a paint stripper containing high concentrations of dichloromethane (exact composition of product is unknown, but ATSDR [2000] estimated the exposure to be the equivalent of 9000 to 18 000 mg/kg bw of dichloromethane), became unconscious for 14 hours. Tachypnoea, hemoglobinuria, metabolic acidosis, edema and ulcerations of the vocal cords and epiglottis, decreased responsiveness and gastrointestinal hemorrhage were observed, and skin was blistered in areas that were likely to be in contact with spilled liquid (Roberts and Marshall, 1976). This individual eventually recovered, but ulcers that developed in the jejunum became diverticula. In another case, a 56-year-old female ingested approximately 300 mL of Nitromors (Hughes and Tracey, 1993). Consciousness was regained in the patient after approximately 14 hours, and a peak in carboxyhemoglobin (COHb) of 12.1% was observed 36 hours post-exposure. After 3 weeks, the individual died, with serious adverse effects observed in kidneys, lungs, pancreas and upper gastrointestinal tract. Case studies for five males and one female that ingested 25 to 350 mL of dichloromethane (reported by OEHHA [2000] to range from 384 to 4794 mg/kg bw) indicated that multiple patients experienced abdominal pain, caustic injury of skin and internal tissues, high or low blood pressures, fever, leukocytosis, tachypnea, respiratory failure and coma (Chang et al., 1999). The two individuals with the highest exposure both experienced renal failure. In the only individual whose injuries were fatal, COHb concentrations were measured to be 35%.

Short-term inhalation of very high concentrations of dichloromethane has resulted in groin pain (Fairfax et al., 1996), abdominal pain (Miller et al., 1985), organ congestion (Kim et al., 1996), metabolic acidosis (Leiken et al., 1990), elevated liver enzymes (Miller et al., 1985; Leiken et al., 1990), acute tubular necrosis (Miller et al., 1985) and a variety of adverse effects on the central nervous system (Memon and Davidson 1981; Miller et al., 1985; Leiken et al., 1990; Fairfax et al., 1996; Nager and O'Connor, 1998) and cardiopulmonary system (Leiken et al., 1990; Nager and O'Connor, 1998).

Clinical studies have also measured neurobehavioural effects in humans after acute exposures to dichloromethane. Adult volunteers inhaled 200 ppm of dichloromethane, 70 ppm of carbon monoxide, or no carbon monoxide or solvents for 4 hours (Putz et al., 1979); exposure to either carbon monoxide or dichloromethane resulted in a COHb concentration of approximately 5%. After exposure to either carbon monoxide or dichloromethane, significant impairments in visual peripheral performance (after 1.5 hours of exposure), tracking performance (after 2 hours of exposure), and auditory performance (after 3 hours of exposure) were detected. After 3 hours of exposure, tracking and visual peripheral performance was significantly worse for dichloromethane exposure than for carbon monoxide exposure; no similar observations were made for auditory impairments. Critical flicker frequency, auditory vigilance and psychomotor performance were also affected after female volunteers were exposed to approximately 300, 500 or 800 ppm of dichloromethane via the inhalation route for more than 3 hours (Winneke, 1974).

9.1.2 Subchronic and chronic toxicity and carcinogenicity

Studies on the effects of subchronic or chronic exposure to dichloromethane in humans are limited; most of these involve chronic exposures in occupational settings. The most useful epidemiology studies for the purpose of assessing chronic health effects and carcinogenicity associated with dichloromethane are the prospective and retrospective cohort studies of occupationally exposed workers. In these cohort studies, chronic exposure to dichloromethane was not associated with any consistent increases in mortality due to any cancer or non-cancer causes. Increases in mortality from hypertensive disease, accidental deaths, pancreatic cancer and biliary or liver cancer were associated with occupational exposures to dichloromethane in some published studies, but the increases were no longer significant after longer follow-up periods and were not observed in more than one cohort. The weight-of-evidence of occupational studies therefore indicates that there is a low likelihood that dichloromethane exposure is associated with increased risk of any type of cancer in humans.

Male employees of Eastman Kodak that worked in areas where dichloromethane exposure occurred for at least 1 year between 1964 and 1970 were followed through 1994 (Friedlander et al., 1978; Hearne and Friedlander, 1981; Hearne et al., 1987, 1990; Hearne and Pifer, 1999). Workers were divided into groups based on cumulative exposure levels in all studies except the first two studies (Friedlander et al., 1978; Hearne and Friedlander, 1981). Eight-hour time-weighted average (TWA) exposures ranged from <1–520 ppm from 1946 to 1965, <1–300 ppm from 1966 to 1985 and <1–100 ppm from 1986 to 1994. In the initial Kodak study, Friedlander et al. (1978) examined death from a variety of causes. The only significant non-cancer increase in mortality was observed in hypertensive disease when study subjects were compared with Kodak controls ($p \leq 0.05$). However, when only employees that had been exposed for at least 20 years by 1964 were examined, the elevated levels of hypertension were no longer observed. In follow-up studies, subjects were followed for an additional 4 years (Hearne and Friedlander, 1981), 8 years (Hearne et al., 1987) or 12 years (Hearne et al., 1990), with no significantly elevated levels of deaths occurring in the overall cohort or in any exposure groups in the latter two studies. In the

most recent study, the cohort was followed until 1994 (Hearne and Pifer, 1999), and there were still no elevated levels of mortality from any non-cancer cause when compared with New York State or Kodak controls. Throughout the series of studies, the only excess in cancer mortality that approached statistical significance was for pancreatic cancer. In the initial Kodak study (Friedlander et al., 1978), five deaths from pancreatic cancers were observed (expected n = 4.7). The first follow-up study (Hearne et al., 1981), which followed a smaller group from the original study (workers that were more likely to be exposed) for four additional years, reported three deaths from pancreatic cancer in the total cohort (expected n = 2.36). The cohort exposed for 20+ years had two deaths from pancreatic cancers (expected n = 1.34). None of the excesses were significant (all *p*-values > 0.05). In the next study (Hearne et al., 1987), deaths from pancreatic cancers approached a significant excess when eight deaths from the disease were observed (expected n = 3.1), of which four cases were reported to be in the highest exposure and longest latency groups. The *p* -value for this observation was greater than 0.01, which was Hearne et al.'s (1987) threshold for cancers that had not previously been observed in animals. However, this excess had achieved significance at $p < 0.05$ (Mirer et al., 1988). When the cohort was followed until 1988, no more deaths from pancreatic cancers had occurred in the cohort, but the eight deaths were still in excess of the expected amount (expected n = 4.2) (Hearne et al., 1990). The study did not indicate whether the *p* -value in this scenario was <0.05, since the investigators were again looking for statistical significance at $p = 0.01$. In the most recent follow-up investigation (Hearne and Pifer, 1999), no new cases of deaths from pancreatic cancer were observed in the original cohort; therefore, the standardized mortality ratio (SMR) had decreased and the elevated number of cases was not significant (observed n = 8, expected n = 5.1, SMR = 155, 95% confidence interval [CI] = 67–306). No dose–response relationship was observed, with four of the deaths in the <400 ppm-years group, and two cases each in the 800–1199 and >1200 ppm-years groups (Hearne and Pifer, 1999).

The Hoechst Celanese Celriver Plant cohort in Rock Hill, South Carolina, included 1271 male and female employees that worked in the cellulose triacetate (CTA) preparation or extrusion areas of the facility for at least 3 months between 1 January 1954 and 1 January 1977. The cohort was followed through 1990 (Ott et al., 1983b, 1983d; Lanes et al., 1990, 1993; Soden, 1993). Time-weighted (8-hour) average dichloromethane exposures for exposed employees were measured to range from below detectable limits to 1700 ppm (Lanes et al, 1990), with median measured values of 140 ppm in low-exposure jobs, 280 ppm in moderate-exposure jobs, and 475 ppm in high-exposure jobs (Ott et al., 1983a). However, employees were not divided into exposure groups for these studies, with the exception of the hematological and electrocardiogram investigations. Throughout the series of studies, the only increase in non-cancer mortality that was significant at more than one time period was for accidental deaths. Accidental deaths were significantly increased in males in the initial study (SMR = 2.5, $P < 0.05$; Ott et al., 1983b) and in the first follow-up (SMR = 1.64, 95% CI = 1.05–2.47; Lanes et al., 1990), but in the most recent follow-up study (Lanes et al., 1993), the number of deaths from accidents remained higher than expected, but the increase was no longer significant (SMR = 1.51, 95% CI = 0.97–2.28). Attempts were made to determine whether exposure to dichloromethane was related to measurable changes in the liver, heart or nervous system of cohort members (Ott et al., 1983c; Soden, 1993). Changes in bilirubin, serum alanine transaminase (ALT) and aspartate transaminase (AST), hemoglobin, and hematocrit were associated with dichloromethane exposure in certain groups in the initial study (Ott et al., 1983c), but no significant differences in blood chemistry parameters related to liver function were observed in exposed and control workers in a more recent study (Soden, 1993). No significant differences in electrocardiogram (ECG)

measurements were observed between workers exposed to dichloromethane and non-exposed workers (Ott et al., 1983d), and responses to a health history questionnaire indicated there were similar cardiac and neurological symptoms in exposed and non-exposed workers (Soden, 1993). The initial mortality study (Ott et al., 1983b) did not identify any significant excess in frequency of cancers in employees. In the follow-up to the initial study (Lanes et al., 1990), a total of four deaths from biliary or liver cancer was observed, which when compared with county controls was a significant excess (SMR = 5.75, 95% CI = 1.82–13.78). In the later follow-up study (Lanes et al., 1993), no new deaths from biliary and liver cancers were observed and the excess was no longer significant (SMR = 2.98, 95% CI = 0.81–7.63). However, analysis of only the workers employed at the facility for more than 10 years and that had a latency of at least 20 years since first exposure, a category into which all four cases fell, resulted in a significant excess of cancers (SMR = 5.83, 95% CI = 1.59–14.92). Since employees were not divided into groups based on levels of exposure, it is not possible to determine whether there was an exposure-related increase. Lanes et al. (1990) suggested that one of the workers that died of biliary cancer would have had low cumulative exposure to dichloromethane, while the other two would probably have had substantial cumulative exposure to dichloromethane, and no exposure information was provided for the individual that died from liver cancer.

The Hoechst Celanese Amcelle Plant cohort in Cumberland, Maryland, consisted of 3211 workers employed at the facility for a minimum of 3 months between 1970 and 1981, and were monitored until 31 December 1989 (Gibbs et al., 1996). Maximum concentrations of dichloromethane measured by air sampling in the late 1960s were 1250 ppm, whereas in the years before the facility was closed the maximum exposures to employees were 300 ppm. Employees were classified into exposure groups based on their work history and industrial hygiene air sampling data. No significant increases in death from any non-cancer cause were found in workers at any exposure level. When exposure length was analysed in the high-exposure group, an apparent inverse relationship was observed between duration of exposure and deaths from ischemic heart disease. Non-significant increases in prostate and cervical cancer deaths were observed when the various exposure groups were compared with county controls; but when length of exposure and latency were considered, increases were significant. A non-significant increase in prostate cancer mortality was observed in males in the high-exposure (SMR = 179.2, 95% CI = 95.4–306.4), low-exposure (SMR = 140.3, 95% CI = 64.2–266.4) and non-exposed (SMR = 104.4, 95% CI = 21.5–305.1) categories. Significant increases in death from prostate cancer were observed in highly exposed male workers with at least 20 years since initial exposure (SMR = 208.4, $p < 0.05$) or those with a latency period of 20 years and at least 20 years of exposure (SMR = 290.9, $P < 0.05$). Deaths from cancers of the cervix were elevated in females, but not significantly, with very wide confidence intervals due to low incidences of the disease (high exposure: SMR = 540.2, 95% CI = 13.5–3010.3, one case; low exposure: SMR = 296.4, 95% CI = 96.2–691.7, five cases; non-exposed: SMR = 702.0, 95% CI = 17.5–3911.3, one case). Mortality from cervical cancer became significantly increased in women in the low-exposure category with a latency period of at least 20 years (SMR = 802.2, $p < 0.01$) (Gibbs et al., 1996).

A number of case-control studies have investigated whether there is an increased risk of different types of cancers due to exposure to dichloromethane. Case-control studies were suggestive of possible increased risks of breast cancer (Cantor et al., 1995), central nervous system tumours (Cocco et al., 1999) and astrocytic brain cancer (Heineman et al., 1994) due to dichloromethane exposure. A cohort study of aircraft maintenance workers, which was primarily concerned with trichloroethylene exposure but also observed the effect of a wide variety of other chemicals, was suggestive of an association between dichloromethane exposure and death from

multiple myeloma (Spirtas et al., 1991). In the follow-up to that study, there was still an elevated risk of mortality from multiple myeloma in dichloromethane-exposed workers, but the risk was no longer significant (Blair et al., 1998). The risk of developing liver or biliary tract cancer was explored in workers in a variety of work areas and with exposure to many different chemicals, but development of these cancers was not associated with dichloromethane (Bond et al., 1990).

9.1.3 Developmental and reproductive toxicity

No epidemiological studies have explored developmental and reproductive effects of dichloromethane via ingestion. All developmental and reproductive toxicity studies are based on exposed workers, except for one population-based study. Associations between parental dichloromethane exposure and measures of reproductive or developmental toxicity were not consistently observed in the investigations.

Bell et al. (1991) performed a study to determine whether dichloromethane levels in ambient air affected weight at birth. Birth certificates were obtained for all births between 1976 and 1987 in the county within New York State where Kodak Park is located; once multiple births, infants <750 g in weight and non-white infants were excluded from the study, a total of 91 302 subjects remained. Using a model to predict average annual concentrations of dichloromethane at the ground level in the different census tracts in the county, census tracts were classified as high (50 µg/m^3), moderate (25 µg/m^3), low (10 µg/m^3) or no exposure. No significant differences in birth weight were observed between the no-exposure category and any other exposure categories.

Some investigators have assessed the effects of occupational dichloromethane exposure on semen and sperm. Kelly (1988) summarized case reports of four men with dermal and inhalation exposures to dichloromethane who had genito-urinary and abdominal complaints and indicated that all semen samples obtained from the subjects had motile sperm counts of <20 million/mL, which is considered to be the reference value by WHO (WHO, 1999). The suggestion from this study, which had a small number of subjects (n = 8), that inhalation exposure inhibited sperm production has not yet been supported by other epidemiological studies (Wells et al., 1989; Lemasters et al., 1999). Epidemiology studies performed in Sweden and Finland investigated the associations between paternal and maternal occupational exposures and miscarriage. Levels of exposure were not considered in any of the studies. Lindbohm et al. (1984) used job title and type of workplace, obtained from censuses, to determine the potential for exposure to various classes of chemicals for women and husbands of women who were listed in the Finnish Hospital Discharge Register as having given birth, a miscarriage or an induced abortion between 1973 and 1976; the study was later updated for women meeting these requirements between 1973 and 1982 (Lindbohm et al., 1991). In the first study, there was no increase in miscarriages in women who were assumed to be exposed to solvents, or whose husbands were assumed to be exposed to solvents (Lindbohm et al., 1984); the solvent category was not divided further, so no results were available specifically for dichloromethane. In the second study (Lindbohm et al., 1991), the solvent class was subdivided, and dichloromethane was included in the categories of solvents used in manufacturing rubber products (along with 1,1,1-trichloroethane) and those used in the manufacture of drugs (along with chloroform). Paternal exposure to solvents used in rubber product manufacturing (odds ratio [OR] = 1.9, 95% CI = 1.2–2.8), but not to those used in drug manufacturing (OR = 0.5, 95% CI = 0.2–1.7), was associated with a significant increase in spontaneous abortions (Lindbohm et al., 1991). A significantly increased risk in spontaneous abortions was also associated with fathers who were

rubber product workers (OR = 1.5, 95% CI = 1.1–2.2). Maternal exposures were not investigated in the latter study.

An investigation of women working in laboratories at a Swedish university between 1968 and 1979 did not demonstrate an increased risk of miscarriages in workers exposed to dichloromethane (Axelsson et al., 1984). However, a borderline significant increase in miscarriages (OR = 2.3, 95% CI = 1.0–5.7, $p = 0.06$) was observed in women exposed to dichloromethane who worked in Finnish pharmaceutical factories from 1973 to 1980 for at least 1 week during their first trimester (Taskinen et al., 1986). When the women exposed to dichloromethane were divided based on frequency of exposure, women who were exposed once or more per week had a higher risk of miscarriage than those who were exposed less frequently than once per week, but the risks were not significantly increased in either group when compared with non-exposed workers.

A study conducted in The Netherlands examined whether occupation as a hairdresser was related with prolonged time to pregnancy, or an increased incidence of spontaneous abortions, low birth weight, pre-term birth or major malformations (Kersemaekers et al., 1997). Two study periods, 1986–1988 and 1991–1993, were used because the use of dichloromethane and certain dye formulations was restricted in this country's industry in 1990. No significant differences in time to pregnancy, birth weight, premature births or major malformations were observed in either study period when compared with controls. A non-significant increase in miscarriages was observed during the 1986–1988 study period (OR = 1.6, 95% CI = 0.8–1.6), but not in the later study period (OR = 0.9, 95% CI = 0.7–1.1).

9.2 Effects on experimental animals

The target system for toxicity in animals exposed to high concentrations of dichloromethane for short periods of time is the central nervous system. High concentrations of dichloromethane can also irritate tissues upon contact. The target organ in animals exposed to lower levels of dichloromethane in subchronic and chronic studies is the liver. Dichloromethane exposures also caused renal and neurotoxic effects in animals, and pulmonary effects have occurred in animals exposed via inhalation. Liver, lung and mammary gland tumours were also associated with exposures to dichloromethane, primarily when animals were exposed by inhalation.

9.2.1 Acute toxicity

Several oral acute-duration toxicity studies have been performed for dichloromethane. However, the studies are not representative of human exposure because the dosages were given in single bolus doses, and concentrations were much higher than what would be found in drinking water.

Animals exposed to a single high dose of dichloromethane via either inhalation (5000 to 50 000 ppm) or ingestion (337 to 3825 mg/kg bw) have displayed central nervous system depression, alterations in neuromuscular and sensorimotor test results and other adverse effects on the nervous system, cardiac arrhythmia and other adverse effects on the cardiovascular system, decreased body weight, hemorrhaging of gastrointestinal organs, congestion and edema of organs and liver cell necrosis (Aviado, 1975; Taylor et al., 1976; Laham et al., 1978; Morris et al., 1979; Alexeeff and Kilgore, 1983; Marzotko and Pankow, 1987; Kitchin and Brown, 1989; Berman et al., 1995; Moser et al., 1995). Eye irritation and histological changes to eyes occurred with ocular exposure in New Zealand white rabbits (Ballantyne et al., 1976).

Kimura et al. (1971) determined that oral LD_{50} values for Sprague-Dawley rats did not differ greatly with age, except in newborns. LD_{50} values were similar for 14-day-old rats (2400 mg/kg bw), young adult rats (2100 mg/kg bw) and older adult rats (3000 mg/kg bw); the LD_{50} for newborns was stated to be <1300 mg/kg bw because lower concentrations could not be accurately measured. Other oral LD_{50} values reported in the literature (for mice and rats) ranged from 1405 to 3373 mg/kg bw (Laham et al., 1978; Berman et al., 1995; Dhillon and Von Burg, 1995).

9.2.2 Short-term exposure

Only one subchronic animal study used drinking water as the medium of exposure for dichloromethane. A study by Kirschman et al. (1986) exposed Fischer 344 rats and B6C3F1 mice (20 per sex per concentration) to dichloromethane in drinking water at concentrations of 0%, 0.15%, 0.45% and 1.5% (corresponding to 0, 166, 420 and 1200 mg/kg bw per day in male rats; 0, 209, 607 and 1469 mg/kg bw per day in female rats; 0, 226, 587 and 1911 mg/kg bw per day in male mice; and 0, 231, 586 and 2030 mg/kg bw per day in female mice) for 90 days. Decreased body weights were observed in male rats exposed to 420 mg/kg bw per day, female rats exposed to 1469 mg/kg bw per day, and medium- and high-dose mice from week 6 until the end of the study. Mean serum ALT levels were elevated in treated male rats and both serum ALT and AST levels were elevated in high-dose female rats, which suggests liver damage. Similar changes were not observed in mice. No histological changes were apparent in rodent livers after 1 month of exposure, but changes did occur after 3 months. In the high-exposure group, female rats had increases in focal granuloma, pigmentation in the central, lobular and Kupffer cells, and eosinophilic cytoplasmic bodies. Hepatocyte vacuolation was observed in male and female rats treated with dichloromethane at all doses. A greater incidence of fatty changes in cells in the central lobule of the liver were observed in medium-dosed male mice, and mononuclear infiltration in the liver was slightly increased in high-dose male mice. Kidney weights were elevated in female rats after 1 and 3 months of exposure to 1469 mg/kg bw per day of dichloromethane, and dose-related decreases in urinary pH were observed in all treated rats. No similar effects were observed in mice in the same study. Statistical significance for all of the above observed effects was not reported by the authors (Kirschman et al., 1986).

Maltoni et al. (1988) administered dichloromethane to Sprague-Dawley rats and Swiss mice (50 per sex per dose) via gavage in olive oil at dose levels of 0, 100 and 500 mg/kg bw per day, 4–5 days per week for 64 weeks. The study was initially supposed to last for 2 years, but significant excess mortality was observed in male rats exposed to 500 mg/kg bw per day and male and female mice exposed to 100 and 500 mg/kg bw per day via the gavage route; therefore, the study was terminated early. Decreased body weight was observed beginning at 36–40 weeks in male and female mice and continued throughout the study, but no effect was observed in rats. A non-significant increase in the incidence of malignant mammary tumours (primarily adenocarcinomas) was observed in female rats in the high-dose group. Pulmonary tumours increased in a dose-related manner in male mice, but the increase was not significantly greater than controls until the investigators took mortality into account, at which point an increase was observed in the group subjected to 500 mg/kg bw per day.

Condie et al. (1983) reported no significant changes in body weight in a study in which male CD-1 mice (number of mice per group not given) were exposed to doses of 0, 133, 333 and 665 mg/kg bw per day by gavage in corn oil for 14 consecutive days. Minimal to slight hepatic centrilobular cytoplasmic vacuolation appeared to be dose-related in the study. No mice in the low-exposure group had vacuole formation, and cytoplasmic vacuolation was minimal in three

animals in each of the medium- and high-dose groups and slight in one animal in the high-dose group. No changes were observed in levels of serum creatinine, blood urea nitrogen (BUN) or ALT and no histopathological effects were observed in kidney tissue. However, uptake of p-aminohippurate by renal cortical slices was significantly inhibited in all exposed groups when compared with controls; the authors stated this was a more sensitive indicator of kidney damage than clinical chemistry and histopathological changes.

In a range-finding study by the NTP (1986), Fischer 344 rats and B6C3F1 mice (10 per sex per concentration) were exposed to dichloromethane in air at concentrations of 0, 525, 1050, 2100, 4200 and 8400 ppm for 6 hours per day, 5 days per week, for 91 days. Mean body weights in the highest exposure group were lower for male and female rats and female mice when compared with controls. Significantly lower liver-to-lipid weight ratios were reported for male and female rats exposed to 8400 ppm, female rats exposed to 4200 ppm and female mice exposed to 8400 ppm. Foreign-body pneumonia developed in four male and six female rats in the highest exposure group, although similar effects were not observed in mice.

Two different subchronic studies have measured the effects of dichloromethane on the brains of Mongolian gerbils. In the first study by Rosengren et al. (1986), the gerbils were continuously exposed by inhalation to 210 ppm (for 3 months), 350 ppm (for 10 weeks) or 700 ppm (for 7 weeks); exposure of all groups except the 210-ppm group was ended early due to elevated mortality, and results from the 700-ppm group were not published. Significant increases in the weight of the cerebral sensory motor cortex were observed in the 350-ppm group. Significant differences were also observed in the 350-ppm group in the concentration of S-100 protein (a marker for brain damage-related astroglial cell increases after brain injury) and GFA protein (a marker for brain damage-related astroglial fibre increases after brain injury) per wet weight in the frontal cerebral cortex and sensorimotor cerebral cortex. A decrease in DNA concentration per wet weight was significant in the hippocampus of gerbils in the 210- and 350-ppm groups, and in the cerebellar hemispheres in the 350-ppm group only. The changes observed in the study may have been due to cell loss in these areas of the brain (Rosengren et al., 1986). In the second study, gerbils were continuously exposed to 210 ppm of dichloromethane in air for 90 days. Significant decreases in glutamate, phosphoethanolamine and γ-aminobutyric acid were observed in the frontal cerebral cortex, while in the cerebellar posterior vermis, significant increases were detected in levels of glutamine and γ-aminobutyric acid (Briving et al., 1986). The investigators of the study also indicated that these amino acids are part of the neurotransmitters group. Although these two studies identified changes to gerbil brains after continuous exposure to dichloromethane, a study of Fisher 344 rats exposed to 50, 200 or 2000 ppm by inhalation 6 hours per day, 5 days per week, for 91 days did not measure any significant changes in neurobehavioural outcomes (lacrimation, grip strength, cortical flicker fusion, auditory brainstem responses, somatosensory evoked potentials, caudal nerve action potentials), gross pathology or histopathology. A significant difference in flash-evoked potentials was observed in the 2000-ppm group when compared with controls, but the difference was no longer significant when body weight and body temperature were taken into account (Mattsson et al., 1990).

9.2.3 Long-term exposure and carcinogenicity

Dichloromethane was administered to Fischer 344 rats (85 per sex per dose) in drinking water at doses of approximately 0, 5, 50, 125 and 250 mg/kg bw per day (actual mean intake of 0, 6, 52, 125 and 235 mg/kg bw per day in males and 0, 6, 58, 136 and 263 mg/kg bw per day in females) for 104 weeks (Serota et al., 1986a). Slight (but significantly different from controls) decreases in body weights and body weight gains were observed throughout the study in both

sexes in the groups exposed to 125 and 250 mg/kg bw per day. Small but statistically significant decreases in food consumption occurred in the first 13 weeks of the study in both males and females in the 125- and 250-mg/kg bw per day groups, and a decrease in water consumption in the same groups. Several changes in hematological and clinical chemistry parameters were noted, but they were of limited biological relevance and within the range of historical values. A variety of histological changes were observed in the liver. A dose-related trend was seen in the increase in incidence of foci and areas of cellular alteration in both sexes, with the increase being significant in males and females in all exposure groups except for the group exposed to 5 mg/kg bw per day. The no observed adverse effect level (NOAEL) for this study for liver lesions, the most sensitive effect in this study, was 6 mg/kg bw per day. Tumour development was observed in the study, but only became significant at doses higher than those that led to liver lesions. The incidence of combined liver neoplastic nodules and hepatocellular carcinomas in treated females was increased significantly in groups treated with approximately 50 mg/kg bw per day (n = 4, adjusted $p = 0.0176$) and 250 mg/kg bw per day (n = 6, adjusted $p = 0.0012$), and in the female recovery group treated with 269 mg/kg bw per day for 78 weeks (n = 2, adjusted $p = 0.0402$). The increase in the group subjected to approximately 125 mg/kg bw per day was not significant, and Serota et al. (1986a) did not consider any of the significant cancer observations to be biologically relevant because the incidence of the tumours in controls was lower than expected. Males treated with dichloromethane tended to have lower incidences of these carcinomas than the control groups.

In a similar study involving mice, Serota et al. (1986b) administered dichloromethane to B6C3F1 mice (50 per sex per dose) in drinking water at target dose levels of 0, 60, 125, 185 and 250 mg/kg bw per day for 24 months. Actual mean daily consumption was 0, 61, 124, 177 and 234 mg/kg bw per day in males and 0, 59, 118, 172 and 238 mg/kg bw per day in females. No differences between controls and exposed mice were observed for mortality rates, organ weights, gross pathology or clinical observations. Histological effects were studied in a wide variety of tissues, but the only treatment-related effects observed were morphological changes consistent with an increase in fat content in the liver, which were observed in males and females in the groups receiving approximately 250 mg/kg bw per day. An increase in combined hepatocellular adenomas and carcinomas was observed in males, but there was no dose-related trend and the observation was not significant when compared with controls. The only significant observation indicated by Serota et al. (1986b) was an increase in hepatocellular carcinomas in high-dose males when compared with one of the control groups, but not both. The investigators also stated that the number of small lung masses was slightly increased in higher-dose females, but significance of findings and specific dose groups were not indicated.

NTP (1986) conducted a study in which dichloromethane was administered by the inhalation route for 6 hours per day, 5 days per week, for 102 weeks to Fischer 344 rats and B6C3F1 mice (50 per sex per concentration) at concentrations of 0, 1000, 2000 and 4000 ppm for rats, and at concentrations of 0, 2000 and 4000 ppm for mice. Female rats and mice exposed to 4000 ppm and male mice exposed to both concentrations had a significantly lower survival rate than did controls. Rats were observed to be restless and pawed at eyes and muzzles when exposed to concentrations of 4000 ppm. Histological changes were observed in the livers of rats and mice of both sexes, some of which increased in a dose-dependent manner. Histological changes were also observed in mouse testicles, ovaries, kidneys, stomach and spleen. There were significant increases or exposure-related trends in certain types of tumours in both rats and mice; the most relevant increases were for mammary fibroadenomas and adenomas (female rats exposed to 1000, 2000 and 4000 ppm and male rats exposed to 4000 ppm), alveolar and bronchiolar

adenomas and carcinomas (female and male mice exposed to 2000 and 4000 ppm), and liver adenomas and carcinomas (female and male mice exposed to 2000 and 4000 ppm). NTP (1986) concluded there was some evidence of carcinogenicity in male Fischer 344 rats, and clear evidence of carcinogenicity in female Fischer 344 rats and male and female B6C3F1 mice.

Maltoni et al. (1988) exposed Sprague-Dawley rats to 0 ppm (60 female breeder rats in one control group, 158 males and 149 females of an unspecified age in the other control group), 60 ppm (60 males and 69 females, exposure beginning as embryos) and 100 ppm (54 females) of dichloromethane via inhalation for 4–7 hours per day for either 104 or 15 weeks; rats in the embryo group were also exposed transplacentally. No excess mortality or changes in body weight were observed. An increased incidence of malignant tumours (of any type) per 100 animals was observed in rats exposed to 100 ppm, but the increase was not significant. A slight non-significant increase in the percentage of malignant mammary tumours in female rats exposed during gestation and for 15 weeks after parturition was observed. Maltoni et al. (1988) in this study also attempted to assess the effects of daily exposure to dichloromethane via gavage in mice and rats, but the study was ended after 64 weeks due to high levels of mortality, and therefore the investigators were not able to assess the effects of chronic exposure to dichloromethane via gavage (a summary of the gavage portion of the study is presented in Section 9.2.2).

In an inhalation study, Burek et al. (1984) administered dichloromethane to Sprague-Dawley rats and Golden Syrian hamsters (129 rats per sex per concentration and 107–109 hamsters per sex per concentration) at concentrations of 0, 500, 1500 and 3500 ppm for 6 hours per day, 5 days per week, for 2 years. Statistically significant increases in mortality were observed in female rats in the 3500-ppm exposure group from 18–24 months. A significant increase in absolute and mean relative liver weights in male rats and in mean relative liver weights in female rats exposed to 3500 ppm was observed at the 18-month interim kill, but not at other time periods. Significantly increased histological changes were observed in the livers of rats and hamsters in all treatment groups. Significant increases in histological changes were also observed in the spleen (male rats exposed to 3500 ppm), kidney (male rats exposed to 1500 and 3500 ppm and all female rat exposure groups) and adrenal gland (all male hamsters exposure groups and female hamsters exposed to 1500 and 3500 ppm). An exposure-dependent increase in the number of benign mammary tumours per tumour-bearing rat was observed. In male rats, the mammary tumours appeared to increase in an exposure-related manner, but to a lesser extent than that in females. A significant increase in salivary gland sarcomas was observed in male rats exposed to 3500 ppm (which increased in an exposure-dependent manner), but the authors stated that a viral infection of the salivary gland that occurred across all exposure groups may have contributed to disease incidence. Female hamsters exposed to dichloromethane at 3500 ppm had a significantly increased incidence of total benign tumours, but this observation was thought to be due to increased survival rates in this group (Burek et al., 1984).

Dichloromethane was administered to Sprague-Dawley rats (90 males and 108 females per dose) by inhalation at concentrations of 0, 50, 200 and 500 ppm for 6 hours per day, 5 days per week, for 20 months for males (termination was early due to early onset of geriatric changes) and 24 months for females (Nitschke et al., 1988a). A significant increase in histopathological changes in the liver was observed in females exposed to 500 ppm for the entire study, and also in females exposed to 500 ppm of dichloromethane for the first half of the study and air for the second half, but not in females exposed to 500 ppm for the latter half of the study only. The number of palpable mammary masses per tumour-bearing rat was significantly increased in female rats exposed to 500 ppm. A significant increase in the number of rats with benign

mammary tumours was observed in females exposed to 200 ppm, but not in other exposure groups. No significant effects of dichloromethane exposure were noted in male rats.

9.2.4 Genotoxicity

Mixed results, in both *in vitro* and *in vivo* studies, have been obtained for dichloromethane genotoxicity. Genotoxicity of dichloromethane has been especially characterized with respect to the induction of mutations, interaction with DNA, and effects on chromosomes (clastogenicity). Additional reviews of the genotoxicity associated with dichloromethane are provided in other reports (WHO, 1993; IARC, 1999; OEHHA, 2000). Although some positive findings were observed, these occurred mostly in assays using prokaryotic cells and not typically in mammalian cells.

9.2.4.1 In vitro *findings*

Tests in bacterial assays are generally positive, which indicates genotoxicity in prokaryotes. Studies have reported positive results for dichloromethane in the Ames test in some strains of *Salmonella typhimurium* (TA 98, 100, 1535), indicating that it has the potential to cause DNA mutations (Jongen et al., 1981; Nestmann et al., 1981; Green, 1983; Osterman-Golkar et al., 1983; Hughes et al., 1987; Kundu et al., 2004). Despite these positive findings, it should be noted that other strains of *S. typhimurium* (TA 97, 1537, 1538) have produced negative results in the Ames test.

The activation of *S. typhimurium* by dichloromethane is mediated by GST enzymes (DeMarini et al., 1997). Transfection of rat glutathione transferase 5-5 into *S. typhimurium* TA1535 resulted in stronger mutagenic reactions from dichloromethane than the original test strain (Thier et al., 1993; Oda et al., 1996).

Salmonella typhimurium tested positive for mutagenic activity in the Ara test (Roldán-Arjona and Pueyo, 1993). Test results in *Escherichia coli* have proven negative for the streptomycin locus test, but positive for reverse mutation and forward mutations (Osterman-Golkar et al., 1983; Zielenska et al., 1993). Dichloromethane also tested positive for enhancement of viral transformation in hamster embryo cells, indicating a capacity to cause DNA damage within a cell (Hatch et al., 1983).

Investigation of the effect of dichloromethane on mammalian cells has only demonstrated weak evidence of genotoxicity. Chinese hamster cells tested weakly positive for sister chromatid exchange (SCE) and chromosomal aberrations upon exposure to dichloromethane, indicating a potential clastogenic ability (Jongen et al., 1981). However, these results were not consistent with another study that reported a negative SCE test result in hamster ovary cells at doses ranging from 2 to 15 µL/mL (Thilagar and Kumaroo, 1983).

9.2.4.2 In vivo *findings*

Given the volatile nature of dichloromethane, many genotoxic reports from *in vivo* studies are based on an inhalation route of exposure, although additional studies have reported exposure by gavage. In general, several mammalian species have tested negative or very weakly positive for unscheduled DNA synthesis, including Alpk:AP male rats, Fischer 344 male rats, and B6C3F1 male mice (Trueman and Ashby, 1987; Lefevre and Ashby, 1989; Mirsalis et al., 1989). Tests for DNA single-strand breaks were positive in mouse and rat hepatocytes at very high doses, but negative in hamster and human hepatocytes (Graves et al., 1995). In contrast to mice, rats have also tested negative for single-strand breaks in hepatocyte DNA upon inhalation of

4000 ppm of dichloromethane, indicating a difference in species sensitivity, possibly due to differences in rates of metabolism by GST (Graves et al., 1994).

Clastogenicity results from SCE experiments in mice have also yielded mixed results. Positive results were obtained after exposure to high doses (4000–8000 ppm) in bone marrow cells, lung cells and erythrocytes (Allen et al., 1990). In contrast, single injections of dichloromethane ranging from 100 to 2000 mg/kg bw in C57B1/6J mice showed no chromosomal damage for both SCE and chromosomal aberration assays (Westbrook-Collins et al., 1990). Positive results have been reported for the micronucleus tests in B6C3F1 mouse erythrocytes at doses of 4000–8000 ppm (Allen et al., 1990), but exposure to 1250–4000 mg/kg bw produced negative results in C57BL/6J/Alpk mouse bone marrow (Sheldon et al., 1987). The sex-linked recessive lethal assay also tested negative in *Drosophila* at doses approaching anaesthesia (Kramers et al., 1991).

9.2.5 Reproductive and developmental toxicity

In the only relatively recent reproductive or developmental study where dichloromethane exposure was via the oral route, dichloromethane was administered in corn oil to Fischer 344 rats by gavage at concentrations of 0 mg/kg bw per day (21 treated, 15 pregnant), 337.5 mg/kg bw per day (16 treated, 13 pregnant) and 450 mg/kg bw per day (17 treated, 14 pregnant) on gestational days 6 to 19 (Narotsky and Kavlock, 1995). No adverse effects were noted in reproductive and developmental endpoints. Maternal toxicity (decreased weight gain during the first 10 days of exposure, increased extrauterine weight gains, rales, nasal congestion and vocalization) was observed in dams exposed to 450 mg/kg bw per day, but not those exposed to 337.5 mg/kg bw per day.

When male Swiss-Webster mice (20 per concentration) inhaled 0, 100, 150 or 200 ppm of dichloromethane for 2 hours per day, 5 days per week, for 6 weeks and were subsequently mated with female mice, no significant differences were observed in reproductive or developmental endpoints. The percentage of mated females producing litters was lower in mice exposed to 150 and 200 ppm than in controls or those exposed to 100 ppm, but not significantly so. No increases in testicular lesions were observed (Raje et al., 1988).

In a two-generation study, male and female Fischer 344 rats (30 per sex per concentration per generation) were exposed to 0, 100, 500 or 1500 ppm of dichloromethane in air for 6 hours per day, 5 days per week, beginning 13–14 weeks before mating and continuing until euthanization (exposure was halted in females from gestational day 21 to 4 days after parturition) (Nitschke et al., 1988b). No adverse exposure-related observations were made in F_0, F_1 or F_2 rats. Another study from the same laboratory (Nitschke et al., 1985) having a similar study design, with exposure of the parent generation for 14 weeks before mating and the F_1 generation for 17 weeks before mating, did not result in exposure-related changes in clinical observations, physical appearance, body weight, survival, litter size or histopathological indicators.

Adverse developmental effects were observed in Sprague-Dawley rats (30 control and 19 exposed dams) and Swiss–Webster mice (30 control and 13 exposed dams) exposed by inhalation to 1225 ppm, the only concentration of dichloromethane used in the study, for 7 hours per day during gestational days 6–15 (Schwetz et al., 1975). Significant increases in incidence of renal pelvis dilation and delayed ossification of sternebrae were observed in rat pups, and an increased incidence of an extra centre of ossification in the sternum of mice pups was observed. In the dams, a significant increase in body weight was observed in mice but not rats, and increases in absolute but not relative liver weight were observed in both rats and mice.

Long-Evans rats (15 pregnant dams per treatment group in each of two experiments) were exposed to 0 or 4500 ppm of dichloromethane in air before gestation, during pregnancy or both and observed for adverse maternal effects and teratogenicity (Hardin and Manson, 1980) or neurobehavioural effects throughout life (Bornschein et al., 1980). The only significant adverse embryotoxic effect observed was decreased body weight in rats whose mothers were exposed during pregnancy. Maternal toxicity was documented as increases in absolute and relative liver weights in rats exposed during pregnancy, but not in those exposed only before breeding (Hardin and Manson, 1980). Neurobehavioural effects were observed at several different periods during the offsprings' lives, including alterations in activity levels and longer time for adaptation to test environments (Bornschein et al., 1980).

Maternal exposure to dichloromethane can result in fetal exposure to both dichloromethane and its metabolites, including carbon monoxide (Anders and Sunram, 1982). Fetal carbon monoxide exposure can cause adverse effects on fetal development (Longo, 1977). However, fetal exposure to dichloromethane has only been found to cause adverse effects on development at the highest concentrations used in the animal studies.

9.3 Mode of action

Two different pathways of metabolism for dichloromethane exist in both animals and humans. While metabolism can occur by both pathways concurrently, the MFO pathway (cytochrome P450 [CYP]-mediated), which results in endogenous production of CO and CO_2, is a high-affinity and low-capacity pathway and is the predominant pathway at lower concentrations; however, this pathway becomes saturated at elevated substrate concentrations (approximately 500 ppm through inhalation, and no data on saturation was found for ingestion). Conversely, the GST-mediated pathway, which results in the production of formaldehyde, has a low affinity for dichloromethane, but since it has a high capacity, it is predominant at high concentrations (Green, 1997; Slikker et al., 2004; Starr et al., 2006).

Cancer in animals is thought to be associated with the GST pathway, and not the MFO pathway. Comparisons of patterns of tumour development in 2-year animal studies to predicted rates of metabolite generation for the two different pathways are supportive of this hypothesis. Using PBPK models, the estimated amount of dichloromethane metabolized via the MFO pathway for mice exposed to 250 mg/kg bw per day in drinking water (highest dose group in Serota et al., 1986b) or 2000 or 4000 ppm by inhalation (the two treatment groups for mice in NTP, 1986) was relatively similar for all three groups, whereas the amount of dichloromethane metabolized via the GST pathway was very low in mice exposed to dichloromethane in drinking water, higher in mice exposed by inhalation to 2000 ppm and highest in mice exposed by inhalation to 4000 ppm. Tumour incidence follows the same patterns as GST-mediated metabolite production rate (Andersen et al., 1987; Reitz et al., 1990, 1991). The exact mechanism by which the GST pathway contributes to tumorigenesis is still unknown. Tumour production is non-linear, which is probably due to the fact that exposure to high concentrations of dichloromethane are required to saturate the MFO pathway and result in the increase in tumours (Slikker et al., 2004; Starr et al., 2006).

The GST pathway is more predominant in metabolism in mice than in rats or humans, which supports the observation that tumours were most common in mice. GSTT1-1 mRNA and protein levels are lower in humans than in mice and rats (Slikker et al., 2004), and greater production of metabolites via the GST pathway in mice appears to be more than an order of magnitude higher than in the rat, hamster or human (Green, 1997). Conversely, rates of

metabolism via the MFO pathway were similar for mice, rats, hamsters and humans (Green, 1997).

The exact mechanism by which the GST pathway and its resulting metabolites cause carcinogenicity in mice has not yet been determined (Starr et al., 2006). Some evidence implicates the *S*-(chloromethyl)glutathione intermediate formed in the GSTT1-1-catalyzed bioactivation of dichloromethane, which has been demonstrated in laboratory studies using *S*-(acetoxymethyl)glutathione as a surrogate because *S*-(chloromethyl)glutathione is highly labile (Thier et al., 1993; Marsch et al 2001; 2004). Alternatively, a suspected mode of action for dichloromethane-associated lung and liver tumours in mice is the endogenous formaldehyde production that occurs in the GST-mediated pathway. Support for the formaldehyde metabolite as the potential contributor to tumours is provided by the fact that increased DNA-protein crosslinks in liver and RNA–formaldehyde adducts in lungs of mice were caused by both dichloromethane and formaldehyde (Slikker et al., 2004). The formaldehyde and DNA-protein crosslink production observed in mice was not observed in human hepatocytes *in vitro*. Similarly, *in vitro* studies have demonstrated single-strand breakage in DNA in mouse, but not human, hepatocytes (Slikker et al., 2004).

In the parent compound form, dichloromethane does not appear to be genotoxic in mammalian cells *in vitro*, but there is some evidence that it is in some prokaryotes (ECETOC, 1988b; Green, 1997). It cannot be ruled out that the reactive intermediate of the CYP2E1-mediated pathway (formyl chloride) may also play a role in tumorigenesis (Environment Canada and Health Canada, 1993). However, the pattern of tumour development in animal studies and the results of mechanistic studies suggest that GST-mediated metabolism is more relevant to tumour development.

Studies have found tumours in mice exposed to high concentrations of dichloromethane via inhalation, and possibly via ingestion. Because humans produce less GST metabolites than mice, they may have a lower risk of developing tumours. This is because high exposures produce a non-linear increase in the amount of GST metabolites over low exposures, and less GST metabolites are produced when exposure is via ingestion than via inhalation. However, the potential for humans exposed to dichloromethane in drinking water to develop cancer cannot be discounted.

10.0 Classification and assessment

Dichloromethane has been classified in Group II “probably carcinogenic to humans” by Health Canada (Environment Canada and Health Canada, 1993), based on an increased incidence of lung and liver tumours in mice, benign mammary tumours in rats and a borderline increase in liver tumours in female rats, and also on *in vitro* mutagenicity and *in vivo* genotoxicity. However, it was stated that “there are clear species differences in the putatively carcinogenic pathway of metabolism of dichloromethane, which are consistent with the hypothesis that humans are likely to be less sensitive than some species of experimental animals in this regard” (Environment Canada and Health Canada, 1993). The International Agency for Research on Cancer (IARC, 1999) classified dichloromethane as Group 2B, possibly carcinogenic to humans, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in experimental animals.

In the past two decades, new PBPK models have identified that hepatic cancer findings in rodents exposed to high concentrations of dichloromethane may not be expected to occur in

humans exposed to low concentrations of dichloromethane. Because there is some debate over whether it is more appropriate to develop the guideline for dichloromethane based on a non-cancer endpoint or a cancer endpoint, Health Canada has considered both approaches for the purpose of deriving the current guideline value. The results from both approaches were compared, and the most conservative approach was used to derive the guideline.

10.1 Cancer risk assessment

Significant observations of cancers were made in rats and mice exposed to high concentrations of dichloromethane by inhalation. However, epidemiological evidence to date suggests that there is no strong or consistent increase in risk of cancer from exposure to dichloromethane. Drinking water and gavage studies in rats and mice provide little evidence for the carcinogenicity of dichloromethane through the oral route, except possibly in mice, a species known to have greater rates of metabolism of dichloromethane via the GST pathway. The most common tumours observed in these studies occurred in the liver, lung and mammary gland. The only clear dose-response relationships observed between dichloromethane exposure and tumour development were in alveolar and bronchial adenoma or carcinoma and liver adenoma or carcinoma in mice (NTP, 1986). Liver adenoma and carcinoma (combined) in male mice was selected as the key endpoint because it was the most relevant endpoint, as well as the endpoint occurring at the lowest level of exposure.

Although the NTP (1986) study provides the best data for the derivation of a guideline based on tumour development, the results of linear extrapolation using data from this study would not be representative of the actual risk to humans from exposure to drinking water containing low concentrations of dichloromethane. Results of chronic animal studies where rodents were exposed to dichloromethane suggest that dichloromethane exposure results in tumour development only when the MFO pathway has become saturated. Since saturation of the MFO pathway is not expected to occur after exposure to dichloromethane at typical concentrations in drinking water, and since the GST-dependent metabolic route is less active in humans than in animals, excess cancer risk levels derived by linear extrapolation would be higher than the true level of risk in humans, and would lead to an unnecessarily conservative drinking water guideline. For this reason, external dose is not considered to be the appropriate metric for use in cancer risk assessment, and internal dose should be used instead.

PBPK modelling was used to calculate excess cancer risks based on the internal dose of dichloromethane metabolites in humans exposed to dichloromethane in drinking water. PBPK modelling accounted for the use of an inhalation study instead of an ingestion study, metabolic differences between animals and humans, and metabolic differences between high and low exposure levels (Hamelin et al., 2009). The external concentrations of dichloromethane associated with an excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6}, as calculated from the NTP (1986) study, were used in the mouse PBPK model to calculate the internal dose (measured as liver metabolites generated by the GST enzyme in the liver, and the area under the curve for liver dichloromethane concentrations) associated with each of the risk levels. These internal doses associated with each of the risk levels were the inputs into the human PBPK model, and from which the external doses to humans that would generate the internal doses were calculated. This resulted in an estimated external human dose in drinking water that would be associated with an excess cancer risk in humans of 10^{-4}, 10^{-5} and 10^{-6} when daily exposure to drinking water occurs via ingestion of 1.5 L of water and via inhalation (1.65 L-eq) and dermal (0.8 L-eq) exposures from a 30-minute shower.

PBPK modelling results indicate that a "de minimis" (essentially negligible) excess cancer risk of 10^{-6} is associated with exposure to water containing 0.169 mg/L (169 µg/L) of dichloromethane (Hamelin et al., 2009). This concentration of dichloromethane is much higher than the value of 5.2 µg/L calculated using linear extrapolation only without using a PBPK model to account for metabolic differences between mice and humans and high and low exposures. The results that incorporate metabolite generation rates are considered to be a more reasonable estimate of human risk from exposure to dichloromethane than simple linear extrapolation.

10.2 Non-cancer risk assessment

For effects of dichloromethane 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 reducing 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 classified as a Group II carcinogen by Health Canada, this approach was considered for dichloromethane because of the evidence of low generation of carcinogenic metabolites of dichloromethane in low-level exposures in humans. In addition, it is possible that a guideline based on a cancer effect might not be sufficient to prevent adverse non-cancer effects.

The liver is the target organ for chronic, non-neoplastic adverse effects due to dichloromethane exposure. Several chronic animal studies identified exposure-related histological changes in the liver. However, a small number of inhalation studies noted adverse effects in other organ systems of animals chronically exposed to dichloromethane. No adverse effects on other organ systems were mentioned in the ingestion or gavage studies.

Only two 2-year ingestion studies have been published for dichloromethane; one study was performed in rats (Serota et al., 1986a) and the other in mice (Serota et al., 1986b). The most sensitive endpoint was for histopathological changes in the liver, which were observed in groups of rats exposed to ≥50 mg/kg bw per day, and in a mouse group exposed to a dose of 250 mg/kg bw per day. The NOAEL used for the basis of this risk assessment is 6 mg/kg bw per day, because statistically significant increases in the incidence of foci and areas of cellular alteration occurred in male and female rats that ingested >6 mg/kg bw per day (Serota et al., 1986a).

Although a NOAEL was identified in the critical study, the benchmark dose (BMD) approach was used to derive a point of departure, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the 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 method was therefore used to estimate a dose at which the critical effect either would not be observed or would occur at a relatively low incidence, based on the histopathological data of the critical study by Serota et al (1986a). Specifically, the incidence of liver foci or areas of alteration in male rats was 27/36 (75%), 25/40 (63%), 22/34 (65%), 35/38 (92%), 34/35 (97%), and 40/41 (98%) at doses of 0, 0, 6, 52, 125 and 235 mg/kg bw per day, respectively, and in female rats was 17/31 (55%), 17/36 (47%), 12/29 (41%), 30/41 (73%), 34/38 (89%), and 31/34 (92%) at doses of 0, 0, 6, 58, 136 and 263 mg/kg bw per day, respectively.

Using the data from this dosing regimen, the BMD and its lower 95% confidence limit

(BMDL) corresponding to a 10% increase in extra risk of liver foci and areas of cellular alteration over background were calculated using the U.S. EPA Benchmark Dose Software (U.S. EPA, 2009). The multistage model provided an acceptable goodness-of-fit (p = 0.27 of rejecting the model) for the incidence of liver foci and areas of cellular alteration in male rats, which was the most sensitive sex for this outcome in the Serota et al. (1986a) study. The BMD_{10} for male rats was 6.4 mg/kg bw per day, while the $BMDL_{10}$ (the lower 95% confidence limit on the BMD_{10}) was 4.2 mg/kg bw per day. This means that the excess risk at 4.2 mg/kg bw per day is estimated with 95% confidence to be less than 10%.

Although there have been many studies of dichloromethane that have been performed using the inhalation route of exposure, there is an incomplete database for the ingestion of dichloromethane. While lifetime bioassays have exposed rats and mice to dichloromethane in drinking water for 2 years, no multi-generational studies exist for the ingestion route, and reproductive and developmental studies have been performed on only one species (rat). Because of the incomplete database, an additional uncertainty factor of 3 was applied. While there are inadequate data to rule out the potential for dichloromethane to be a threshold carcinogen, a separate non-threshold cancer risk assessment was performed, which identified that the risk of developing cancer due to exposure to dichloromethane at concentrations typically found in the environment is negligible. In addition, the critical effect in the key study (development of liver foci and areas of cellular alteration) is a precursor for the critical carcinogenic effect used in the cancer risk assessment (hepatocellular adenoma and carcinoma); therefore, preventing the development of these toxic liver effects may preclude the development of hepatocellular carcinomas. For these reasons, an extra uncertainty factor for carcinogenic potential was not applied.

No information on the mode of action for dichloromethane related to histopathological changes in the liver could be found; therefore, chemical-specific adjustment factors cannot be used to replace uncertainty factors, and interspecies data derived from PBPK modelling cannot be incorporated into the non-cancer assessment. The TDI for dichloromethane is calculated as follows:

$$\text{TDI} = \frac{\text{4.2 mg/kg bw per day}}{300} = \text{0.014 mg/kg bw per day}$$

where:

- 4.2 mg/kg bw per day is the $BMDL_{10}$ calculated from the Serota et al. (1986a) rat study, based on an increase in the development of foci and alterations in the liver that is 10% above background levels; and
- 300 is the uncertainty factor (×10 for interspecies variability, ×10 for intraspecies variability and ×3 to account for database deficiencies, including a limited number of developmental drinking water studies).

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

$$\text{MAC} = \frac{\text{0.014 mg/kg bw per day} \times \text{70 kg} \times 0.20}{\text{4.0 L-eq/day}}$$

$= 0.049$ mg/L
≈ 0.05 mg/L (50 µg/L)

where:

- 0.014 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.20 is the proportion of the daily intake allocated to drinking water; this is a default value since there are insufficient data to calculate the actual value; and
- 4.0 L-eq/day is the daily volume of water consumed by an adult, accounting for multi-route exposure.

10.3 Comparison of cancer and non-cancer risk assessment

As described in Section 10.1, the concentration of dichloromethane in drinking water associated with an excess cancer risk of 10^{-6} is 0.169 mg/L. The MAC calculated using the TDI approach, as demonstrated in Section 10.2, is 0.05 mg/L. Since the MAC would be more conservative using the TDI approach, it is the approach chosen to develop the MAC. Despite the classification of dichloromethane as a probable human carcinogen (Environment Canada and Health Canada, 1993) and possible human carcinogen (IARC, 1999), cancer effects are negligible at a drinking water concentration of 0.05 mg/L, and protecting against toxic liver effects may prevent hepatocellular carcinomas from occurring. A MAC of 0.05 mg/L for dichloromethane would be protective of both cancer and non-cancer effects.

10.4 International considerations

Other organizations have set guidelines or regulations pertaining to the concentration of dichloromethane in drinking water. Existing guidelines/limits established are 20 µg/L (WHO, 2003), 5 µg/L (U.S. EPA, 2006), 4 µg/L for Australia (NHMRC, 2004) and 4 µg/L for California (OEHHA, 2000), respectively. Differences between these limits are primarily due on whether the organization based their derivation on unit risk for carcinogenicity (California EPA, U.S. EPA), or on hepatotoxicity endpoints with a TDI approach (WHO, Australia NHMRC). Within the organizations that used a TDI approach, variability is based on selection of different uncertainty factors, different allocation factors and different default body weights.

In deriving its public health goal for dichloromethane in drinking water, the California Environmental Protection Agency (OEHHA, 2000) used a daily water consumption equivalent of 6.0 L-eq/day. This was based on an estimated daily water ingestion rate of 2.2 L/day and an estimated 3.8 L-eq/day for dermal and inhalation equivalents from showering, bathing, flushing toilets and other household activities using dichloromethane-contaminated water. No other organizations calculated potential exposures via inhalation or dermal routes for drinking water.

PBPK models have been used in the risk assessment for dichloromethane by other organizations. Some examples of these include the derivation of an excess cancer risk by the U.S. EPA for their IRIS risk assessment (U.S. EPA, 1995c; DeWoskin et al., 2007) and maximum contaminant level in drinking water (OEHHA, 2000), and the derivation of the public health goal for dichloromethane in drinking water by the California EPA (OEHHA, 2000).

11.0 Rationale

Since dichloromethane is volatile, it will persist in groundwater for longer periods than in surface water. Dichloromethane's physicochemical properties indicate that inhalation and dermal

exposure during bathing and showering may also serve as important routes of exposure. As a result, this assessment incorporates a multi-route exposure approach.

Dichloromethane is classified by Health Canada as a probable human carcinogen, based on inadequate evidence of carcinogenicity in humans, but sufficient evidence in animals. The IARC considers dichloromethane to be a possible human carcinogen. However, the literature seems to indicate that cancer is only expected after high levels of exposure that would saturate one of the metabolic pathways (MFO pathway). Consequently, both cancer and non-cancer endpoints were considered in the derivation of the MAC.

Animal studies have shown links between dichloromethane exposure and various types of tumours in both rats (mammary fibroadenoma and adenoma) and mice (alveolar and bronchial adenoma and carcinoma, and liver adenoma and carcinoma). Epidemiological studies do not demonstrate a strong or consistent increase in tumours in workers exposed to dichloromethane for many years. PBPK modelling was performed to account for pharmacokinetic differences between animals and humans, between high exposures and low exposures and between routes of exposure.

A health-based value for dichloromethane in drinking water of 0.169 mg/L (169 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 in the liver of rats. A health-based value for dichloromethane in drinking water of 0.05 mg/L (50 µg/L) can be derived based on these observed effects. The lower of the two calculated health-based values (0.05 mg/L) is selected as the MAC, as it is protective for both cancer and non-cancer endpoints. The MAC can be measured by available analytical methods and is achievable by municipal-scale treatment technologies. No certified residential treatment devices are currently available for the reduction of dichloromethane from drinking water, but treatment devices using activated carbon filters may be effective for the reduction of dichloromethane.

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

12.0 References

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Appendix A: List of Acronyms

ALT	alanine transaminase
AST	aspartate transaminase
BAT	best available technology
BUN	blood urea nitrogen
CI	confidence interval
CO	carbon monoxide
CO_2	carbon dioxide
COHb	carboxyhemoglobin
CTA	cellulose triacetate
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
ECG	electrocardiogram
F_{abs}	fraction absorbed
$F_{air:water}$	air to water dichloromethane concentration
GAC	granular activated carbon
GST	glutathione transferase
GSTT1	glutathione transferase theta 1
GSTT2	glutathione transferase theta 2
K_{aw}	Henry's Law constant
K_{oc}	sorption partition coefficient
K_{ow}	n-octanol-water partition coefficient
K_p	skin permeability coefficient
L-eq/d	litre-equivalent per day
LD_{50}	lethal dose in 50% of test animals
MAC	maximum acceptable concentration
MDL	method detection limit
MFO	mixed-function oxidase
NOAEL	no observable adverse effect level
NOM	natural organic matter
OR	odds ratio
PBPK	physiologically based pharmacokinetic
ppm	parts per million
PQL	practical quantitation limit
PTA	packed tower aeration
RNA	ribonucleic acid
SCE	sister chromatid exchange
TDI	tolerable daily intake
TWA	time-weighted average
VOC	volatile organic compound