

Canadian Environmental Protection Act

Priority Substances List Assessment Report

Dichloromethane



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Priority Substances List
Assessment Report

Dichloromethane

Government of Canada
Environment Canada
Health Canada

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Synopsis

In Canada, approximately 13.2 kilotonnes of dichloromethane are used annually, in such applications as paint removal, as a blowing agent in foam production, and as a component in aerosols. Due to its volatility and the dispersive nature of its uses, the majority of dichloromethane used may be released into the environment, primarily the atmosphere. Dichloromethane has been measured in indoor air, outdoor air, and surface waters across Canada. It has also been detected in groundwaters in several provinces, often as a result of its disposal from landfills or waste-disposal sites.

Median levels of dichloromethane in Canadian surface waters exceeded the estimated effects threshold for the most sensitive aquatic species, a freshwater nematode. For wild mammals, exposure, estimated on the basis of worst-case conditions, was more than 10 times less than the estimated effects threshold.

Dichloromethane has a relatively short half-life and is present in low concentrations in the atmosphere, and therefore is not expected to contribute significantly to global warming or to depletion of stratospheric ozone.

Based upon estimates of total average daily intakes from indoor air; ambient air; drinking water, and food for various age groups in the general population, air (particularly indoor air) appears to be the most important source of exposure to dichloromethane in Canada. Based upon the weight of evidence of carcinogenicity in experimental animals, dichloromethane is classified as "probably carcinogenic to humans", i.e., as a substance for which there is believed to be some chance of adverse health effect at any level of exposure. For such substances, estimated exposure is compared to quantitative estimates of cancer potency to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure). For dichloromethane, such a comparison suggests that the priority for analysis of options to reduce exposure, based upon consideration of health risk only, would be low to moderate.

Based on these considerations, it has been concluded that dichloromethane occurs at concentrations that may be harmful to the environment, and that may constitute a danger in Canada to human life or health. It has been concluded that dichloromethane occurs at concentrations that do not constitute a danger to the environment on which human life depends.

1.0 Introduction

The Canadian Environmental Protection Act (CEPA) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as interpreted in section 11 of the Act, which states:

“...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions

- (a) having or that may have an immediate or long-term harmful effect on the environment;
- (b) constituting or that may constitute a danger to the environment on which human life depends; or
- (c) constituting or that may constitute a danger in Canada to human life or health.”

Substances assessed as "toxic" according to section 11 may be placed on Schedule 1 of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether dichloromethane is "toxic", as defined under CEPA, was based on the determination of whether it **enters** or may enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota to the extent that adverse **effects** could result.

For identification of data for determination of whether or not dichloromethane is "toxic" under the Act, evaluations of agencies such as the International Programme on Chemical Safety (WHO, 1984) and the United States Agency for Toxic Substances and Disease Registry (ATSDR, 1989, 1991) have been consulted where available and considered to be appropriate. Reviews of data on exposure and toxicity relevant to assessment of effects upon human health prepared under contract by Coad (1992) and the Midwest Research Institute (MRI, 1991), respectively, were also consulted in the preparation of the Supporting Documentation. For the background document prepared by MRI (1991), information was identified largely from previous reviews (U.S. EPA,

1985; Brandt and Okamoto, 1988; ATSDR, 1989) and on-line searches of TOXLINE (U.S. National Library of Medicine); the Hazardous Substances Data Bank (HSDB; U.S. National Library of Medicine); the National Technical Information Service (NTIS; U.S. Department of Commerce); the Registry of Toxic Effects of Chemical Substances (RTECS; U.S. National Institute for Occupational Safety and Health); the Scientific and Technical Information Network's Chemical Abstracts File; EMBASE (on-line version of *Excerpta Medica*); and Federal Research in Progress and TSCATS (TSCA test submissions). An SDI (selective dissemination of information) profile provided on-line (MEDLINE, NTIS) identification of both toxicological data and data relevant to the estimation of exposure of the general human population to dichloromethane. Data relevant to the assessment of whether dichloromethane is "toxic" to human health obtained after the completion of the health-related sections of this report (i.e., March 1993) were not considered for inclusion.

Data relevant to the assessment of whether dichloromethane is "toxic" to the environment were identified from on-line searches of a number of commercial databases, completed in November 1991 by McDonald Environmental Sciences Ltd. for Environment Canada. MI databases were searched without date restrictions, except for Chemical Abstracts, which was searched from 1987 to the present. The databases examined include AGRICOLA (U.S. National Agricultural Library); AQUAREF (Inland Waters Directorate, Environment Canada); AQUIRE (Aquatic Information Retrieval, Chemical Information Systems, Baltimore); BIOSIS Previews (BIOSIS, Philadelphia); CAB (Commonwealth Agricultural Bureau, Farnham Royal, U.K.); CESARS (Chemical Evaluation Search and Retrieval System, Department of Natural Resources, Michigan); CHEMICAL EXPOSURE (Science Applications International Corporation, Oak Ridge, TENN); CHEMNAME (Chemical Name Dictionary, Chemical Abstracts Service); CGRS (Chemical Regulations and Guidelines System, Fairfax, VA); CHEM-INTELL (Chemical Intelligence Services; London, U.K.); CODOC (Cooperative Documents Project, University of Guelph); ELIAS (Departmental Library, Environment Canada); ENVIROLINE (R.R. Bowker, New York); Environmental Bibliography (Environmental Studies Institute, Santa Barbara, CA); FATE RATE, Federal Register Abstracts (National Standards Association, Bethesda, MD); GEOREF (Geological Reference File, American Geological Institute); IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency); MEDLINE (U.S. National Library of Medicine, Bethesda, MD); MICROLOG (Micromedia Limited, Toronto); NAQUADAT/ENVIRODAT (Environment Canada); NRC PUBS (Publications of the National Research Council of Canada, Canada Institute for Scientific and Technical Information); NRTCR, NTIS (National Technical Information Service, Springfield, VA); PHYTOTOX (University of Oklahoma, Chemical Information Systems, Baltimore); Pollution Abstracts (Cambridge Scientific Abstracts, Bethesda, MD); RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health); Water Resources

Abstracts (U.S. Department of the Interior, Reston, VA); and TOXLINE (U.S. National Library of Medicine). Information relevant to preparation of the environmental sections that was obtained after June 23, 1993, was not considered for inclusion.

Although review articles were consulted where considered appropriate, all original studies that form the basis for the determination of "toxic" under CEPA have been critically evaluated by staff of Environment Canada (effects on the environment) and Health Canada (effects on human health). The following officials contributed to the preparation of this report:

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Critical evaluation of aspects related to the toxicokinetics of dichloromethane was provided by J. Withey of Health Canada. Quantitative estimation of carcinogenic potency based upon physiologically based pharmacokinetic modelling was performed by S. Bartlett and M. Walker, also of Health Canada, and reviewed (Supporting Documentation only) by K. Khanna (University of Montreal) and R.H. Reitz (Dow Chemical Company).

As part of the review and approvals process established by Environment Canada, the environmental sections of the Assessment Report were reviewed externally by J. Trevors (University of Guelph), N. Bunce (University of Guelph), and D. Mackay (University of Toronto). Following circulation and external peer review of the draft health-related sections of the Assessment Report and Supporting Documentation by A.G. Renwick (University of Southampton), R.J. Bull (Washington State University), P. Watts (BIBRA Toxicology International), L. Rhomberg (U.S. EPA; Assessment Report only), and T. Green (ICI Central Toxicology Laboratory), they were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The final Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

In this report, a Synopsis that will appear in the *Canada Gazette* is presented. In addition, an extended summary of the technical information critical to the assessment is presented in Section 2.0. The assessment of whether dichloromethane is "toxic" under CEPA is presented in Section 3.0. Supporting Documentation, in which the technical information is presented in greater detail, has also been prepared and is available upon request.

Copies of this Assessment Report and the unpublished Supporting Documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production and Uses

Dichloromethane (DCM), also known as methylene chloride, (CH_2Cl_2) [CAS Registry No. 75-09-2] is a clear, colourless liquid with a mildly sweet odour. It is a highly volatile and nonflammable liquid at room temperature. Dichloromethane has a molecular weight of 84.93 g/mol, a density of 1.326 g/mL at 20°C (Budavari *et al.*, 1989), reported vapour pressures of 43 and 46.5 kPa at 20°C (Anthony, 1979; Verschueren, 1983; Garc?a-Sánchez *et al.*, 1989), boiling points ranging between 39.75 and 40.1°C (Hawley, 1971; Budavari *et al.*, 1989), a log octanol/water partition coefficient (log K_{oc}) of 1.25 (WHO, 1984), and a Henry's Law constant of 227.9 Pa/m³/mol at 25°C (Ashworth *et al.*, 1988). It has a relatively high water solubility compared to other chlorinated hydrocarbons, with reported values ranging between 13 200 and 20 000 mg/L at 20°C (Anthony, 1979; Verschueren, 1983). Dichloromethane absorbs infrared radiation, predominantly wavelengths between 7 and 13 µm (Sadtler Research Laboratories, 1982).

Dichloromethane levels in air; water; soil, sediment, and tissues are most often determined by gas chromatography (GC) combined with mass spectrometry (MS), electron capture detection (ECD), or flame ionization detection (FID)[U.S. EPA 1982a, 1982b; Ferrario *et al.*, 1985; U.S. EPA, 1986, 1989a, 1989b, 1989c, 1989d; Dann and Wang, 1992; Golder Associates, 1989]. Reported detection limits are as low as 0.1 µg/m³ in air (Dann and Wang, 1992), 30.0 ng/L in water (Comba and Kaiser, 1983), and 5.0 µg/kg (dry weight) in soil (Golder Associates, 1989).

Dichloromethane is not produced in Canada, but is imported. The quantity of dichloromethane imported and used in Canada annually during the period from 1977 to 1990 ranged from 9 to 13.2 kilotonnes (Environment Canada, 1990). In Canada, it is primarily used as a paint remover (56.3 to 69.6%), as a blowing agent for foam production (16 to 29.7%), and as a component in aerosols (8.7 to 11.8%). Major global industrial applications of dichloromethane include use in paint removers, as a solvent for degreasing, as a blowing agent in foam production, for photoresistant stripping operations, in film processing, and as an extraction solvent for spice oleoresins, hops, and, to a limited extent, for the removal of caffeine from coffee (WHO, 1984; Edwards *et al.*, 1982a; U.S. EPA, 1985; ATSDR, 1991).

2.2 Entry into the Environment

There are no known natural sources of dichloromethane. The dispersive nature of its applications implies as much as 100% of the dichloromethane used may be released to the environment (Environment Canada, 1990). Entry may also occur during production, transportation, and storage, as well as from waste-disposal sites, industrial effluents, and in effluents of pulp- and paper-mill operations and water-treatment facilities (Turoski *et al.*, 1983; Kringstad and Lindstrom, 1984; U.S. EPA, 1985; Jackson *et al.*, 1985, 1991; Otson *et al.*, 1986; McBride *et al.*, 1989; Crume *et al.*, 1990). Quantitative estimates of releases of dichloromethane into the Canadian environment are limited to loadings from industrial effluents. In 1983, in effluents from several industries, including automotive-painting operations and steel manufacturing, and from sewage-treatment plants, dichloromethane was discharged into the Detroit River, Ontario, at rates of 0.03 to 0.31 kg/day (Comba and Kaiser; 1985). On the Canadian side of the St. Clair River in Ontario, where 18 industrial sources are estimated to release 1.7 billion litres of effluent and cooling water daily, levels of dichloromethane in effluent ranged up to 160 µg/L (ECIMOE, 1986).

Although relevant Canadian data have not been identified, in the United States it was estimated that in 1989, 30.7 million kg of dichloromethane were released into the air and 0.10 million kg into water, 0.75 million kg were injected into underground wells, and 0.67 million kg were sent to U.S. landfills and/or other treatment/disposal facilities (TRI, 1992). The total release of dichloromethane into the environment in the United States in 1989 was estimated to be 45.4 million kg (TRI, 1992).

Although similar data for Canada were not identified, dichloromethane was the most frequently detected organic contaminant in groundwater at waste disposal sites in the U.S. and the 11th most frequently detected in Germany (Kerndorff *et al.*, 1992).

2.3 Exposure-related Information

2.3.1 Fate

Dichloromethane has a high vapour pressure and Henry's Law constant, and so the atmosphere plays an important role in its distribution and ultimate fate. Photooxidation and photolysis of dichloromethane at sea level are expected to be minimal, whereas conditions in the upper troposphere will allow photooxidation to occur as a result of photochemically generated hydroxyl radicals. Levels in aquatic environments may be substantial, however, due to the relatively high solubility and low potential for hydrolysis of dichloromethane.

Lifetimes for dichloromethane in the troposphere have been estimated to be 109 days (Cox *et al.*, 1976) and 1 year (Singh *et al.*, 1979; Edwards *et al.*, 1982a); however, based on a recent model, half-lives over 3 Canadian cities (Windsor; Ontario; Edmonton, Alberta; and Resolute Bay, Northwest Territories) were estimated to range from 30 days to several years. These values vary with the potential of dichloromethane to photooxidize, which in turn is dependent on the concentration of hydroxyl radicals and the light intensity (which varies with season and latitude) in the region (Bunce, 1992). Migration of dichloromethane from the troposphere to the stratosphere was estimated to take between 5 and 10 years (Rowland, 1990). It is estimated that 2.0 to 2.5% of the dichloromethane released to the troposphere enters into the stratosphere (Singh *et al.*, 1979; Edwards *et al.*, 1982b) where high energy irradiation is available, thereby increasing the potential for photolysis and photooxidation (NAS, 1978). Dichloromethane in the troposphere may also return to earth via precipitation. Based upon global estimates, approximately 0.08% of dichloromethane in the troposphere is washed out annually by precipitation (Edwards *et al.*, 1982a, 1982b).

Dichloromethane is not expected to undergo hydrolytic cleavage in aqueous media under natural conditions (Chodola *et al.*, 1989; Howard, 1990). Mabey and Mill (1978) estimated a half-life of 704 years for the hydrolysis of dichloromethane in water. The potential for hydrolysis appears to increase under conditions of high pH and elevated temperatures (Chodola *et al.*, 1989).

Based on its high vapour pressure and water solubility, dichloromethane is expected to be highly mobile in most soils. Dichloromethane adsorbs strongly to peat moss, less strongly to bentonite clay, only slightly to dolomitic limestone, and not at all to sand (Dilling *et al.*, 1975). The absorption and adsorption of dichloromethane to soils is highly dependent on soil type, moisture level, and temperature (Koo *et al.*, 1990). The soil adsorptive coefficient (K_{oc}) calculated on the basis of water solubility was relatively low, at 18.8 (Kenaga, 1980).

Dichloromethane may be biodegraded in aqueous media by aerobic and anaerobic bacteria common in soil and sludge. Degradation proceeds rapidly to completion within hours to weeks, depending on the microbiota present, depth and type of medium, and environmental conditions. Under aerobic conditions (activated sludge reactor), 99.5% of 180 mg/L dichloromethane was degraded in 48 hours (Stover and Kincannon, 1983). Eighty percent of 0.5 mg/L dichloromethane was degraded in a sandy loam soil surface within 3 weeks (Davis and Madsen, 1991). Acclimated microbes enhanced degradation rates (Klecka, 1982; Henson *et al.*, 1988; Bhattacharya and Parkin, 1988; Davis and Madsen, 1991). By-products of the biodegradation of dichloromethane include carbon dioxide and chloride ion (Brunner *et al.*, 1980; Klecka, 1982; Davis and Madsen, 1991).

The potential of dichloromethane to bioaccumulate has been examined in few studies. Based on the octanol/water partition coefficient, calculated bioconcentration factors (BCF) for freshwater fish were low (i.e., 0.8 [Neely *et al.*, 1974] and 2.3 [Veith *et al.*, 1979]), which indicates that the potential for bioaccumulation and biomagnification in aquatic life is very low. Similarly, little or no bioaccumulation or biomagnification is expected in terrestrial organisms.

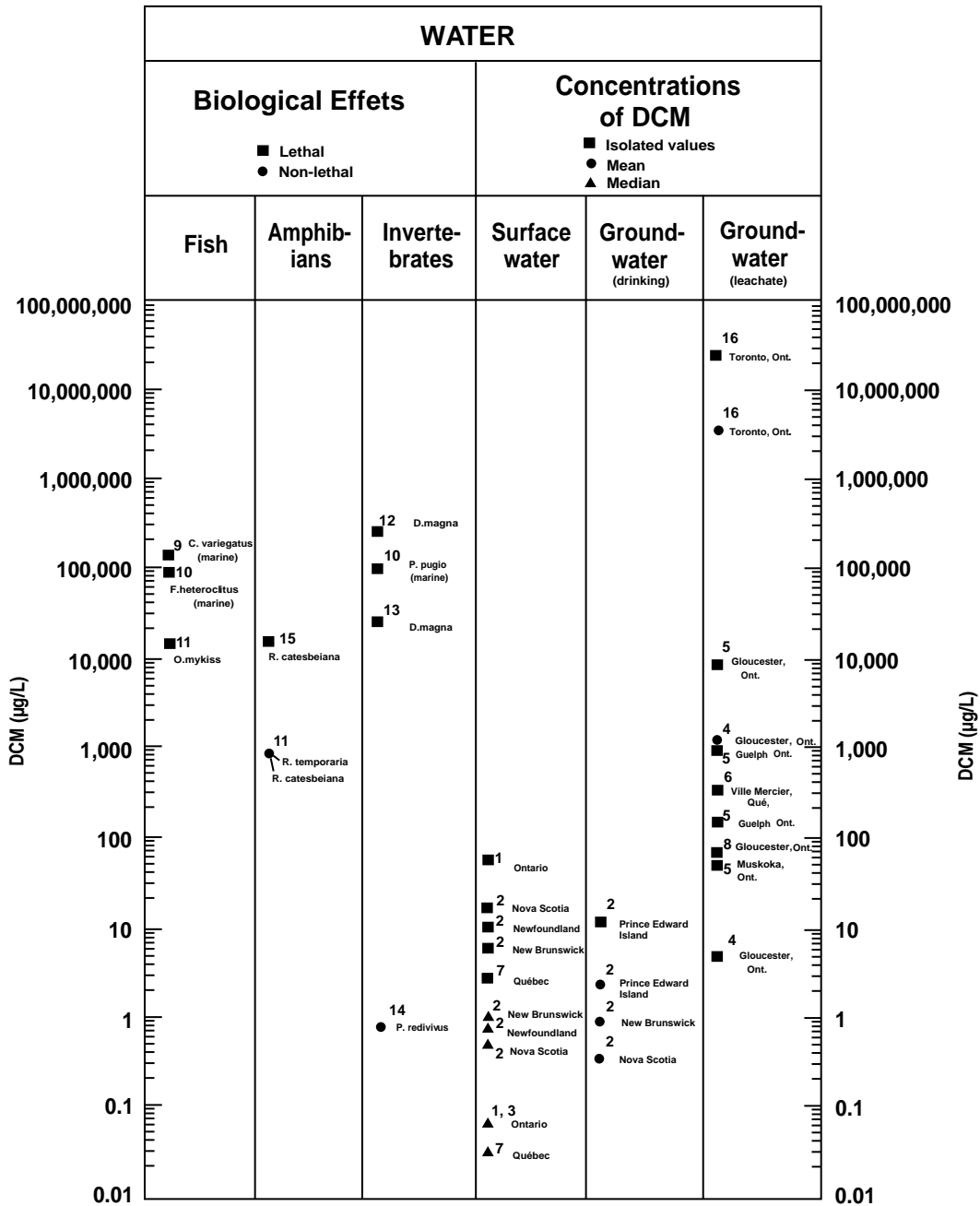
2.3.2 Concentrations

Dichloromethane has been detected in ambient and indoor air; surface water; groundwater, drinking water; and food; however, relevant data on levels in soil, sediment, biota, or human breast milk were not identified. In Figure 1, the available data on levels in surface and groundwater are summarized.

Mean atmospheric levels of dichloromethane at 22 locations across Canada (1991-1992) ranged from 0.5 $\mu\text{g}/\text{m}^3$ in the Longwoods Conservation Area, Ontario to 9.9 $\mu\text{g}/\text{m}^3$ in Saint John, New Brunswick (Dann, 1993). The national mean value was approximately 1.7 $\mu\text{g}/\text{m}^3$, with an isolated maximum value of 311.3 $\mu\text{g}/\text{m}^3$ reported for Saint John, New Brunswick (Dann, 1993). Similarly, the overall mean concentration of dichloromethane was 2.6 $\mu\text{g}/\text{m}^3$ (range not reported), in samples of ambient air taken in 1989 from 17 urban sites in Canada Environment Canada, 1991a). Mean concentrations at 16 sites sampled in additional national surveys conducted between 1988 and 1990 ranged from 1.0 $\mu\text{g}/\text{m}^3$ in Halifax to 6.2 $\mu\text{g}/\text{m}^3$ in Vancouver (Environment Canada, 1991b).

In general, mean concentrations of dichloromethane in indoor air are higher than those in ambient air. Based upon preliminary results, the mean concentration in indoor air in 757 homes across Canada was 16.3 $\mu\text{g}/\text{m}^3$ (maximum = 1 690 $\mu\text{g}/\text{m}^3$), although complete experimental details were not provided in the published account (Otson *et al.*, 1992). Mean levels of dichloromethane in samples of indoor air (ground floor) in a small survey in Metro Toronto were similar, ranging from 9.1 $\mu\text{g}/\text{m}^3$ (12 homes sampled in 1986) to 26.9 $\mu\text{g}/\text{m}^3$ (6 homes sampled in 1987) [Chan *et al.*, 1990].

Median levels (and range of reported values) of dichloromethane in surface water, based upon data at 264 sites across Canada included in a national database (NAQUADAT/ENVIRODAT, 1991) and other sources (Ayotte, 1987; Kaiser and Comba, 1992) are: Ontario, 0.05 $\mu\text{g}/\text{L}$ (non-detectable to 57 $\mu\text{g}/\text{L}$); Quebec, 0.03 $\mu\text{g}/\text{L}$ (non-detectable to 2.7 $\mu\text{g}/\text{L}$); New Brunswick, 1.05 $\mu\text{g}/\text{L}$ (non-detectable to 6.7 $\mu\text{g}/\text{L}$); Nova Scotia, 0.4 $\mu\text{g}/\text{L}$ (non-detectable to 13.9 $\mu\text{g}/\text{L}$); and Newfoundland, 0.71 $\mu\text{g}/\text{L}$ (non-detectable to 10.3 $\mu\text{g}/\text{L}$).



1. Kaiser and Comba, unpublished 1992
2. NAQUADAT/ENVIRODAT 1991
3. Kaiser et al. 1983
4. Jackson et al. 1985
5. Lesage et al. 1989
6. Pakdel et al. 1992

7. Ayotte 1987
8. Jackson et al. 1991
9. Heitmuller et al. 1981
10. Burton and Fisher 1990
11. Black et al. 1982
12. LeBlanc 1980

13. McCarty 1979
14. Samoiloff et al. 1980
15. Birge et al. 1980
16. Ladanowski et al. 1993

NOTE: aquatic organisms are freshwater species unless otherwise noted

Figure 1. Range of dichloromethane (DCM) concentrations in Canadian waters and concentrations causing adverse effects to biota.

The highest reported level of dichloromethane in groundwater in Canada was 25 g/L in the Weston area of northwest Toronto, measured approximately 20 years after release of the compound from a ruptured underground storage tank (Ladanowski *et al.*, 1993). Initially, levels in groundwater samples taken from a landfill site in Gloucester; Ontario, that had received organic wastes for many years ranged from non-detectable to 10 400 µg/L, with a mean value at one site of 1 081 µg/L (Jackson *et al.*, 1985). These levels were reduced to 4 to 60 µg/L after 6 years (Jackson *et al.*, 1991; Lesage *et al.*, 1990). Levels of dichloromethane in leachate from a landfill site in Guelph, Ontario, were 131 and 1 008 µg/L in 1988 and 1989, respectively, and 577 µg/L at a site in the Muskokas (Lesage *et al.*, 1989). In Ville Mercier; Quebec, groundwater (estimated to cover an area of 10 to 15 km²) contaminated with dichloromethane at concentrations up to approximately 300 µg/L is treated and discharged to the environment (Pakdel *et al.*, 1992). Figure 1 depicts a range of reported levels of dichloromethane in groundwaters across Canada.

Levels of dichloromethane in samples collected from groundwater used as a source for drinking water in the provinces of Nova Scotia and Prince Edward Island ranged between 0.1 and 11.0 µg/L (NAQUADAT/ENVIRODAT, 1991).

Levels of dichloromethane in municipal drinking water supplies in Newfoundland, Nova Scotia, New Brunswick, and Prince Edward Island have been determined in a survey of samples taken over the period from 1985 to 1988 (Environment Canada, 1989a, 1989b, 1989c, 1989d, 1989e). The data collected in 1988 are based upon the most sensitive detection limit (0.05 µg/L) of the available studies. Mean concentrations ranged from 0.2 µg/L in both New Brunswick and Nova Scotia to 2.6 µg/L in New Brunswick (Environment Canada, 1989b, 1989c). These concentrations are similar to those reported for the earlier period from 1985 to 1987 (Coad, 1992).

Identified data on levels of dichloromethane in soil in Canada are restricted to contaminated sites. No data on levels in sediment at Canadian sites were identified. Levels of dichloromethane in sediment from Lake Pontchartrain, New Orleans, Louisiana, were 1.5 and 3.2 ng/g wet weight (Ferrario *et al.*, 1985).

No data on levels of dichloromethane in Canadian biota were identified. Levels in biota are not expected to be high, based on the physical and chemical properties of dichloromethane (e.g., log K_{ow} of 1.25 [WHO, 1984]) and the low calculated BCF values. Mean levels in the tissue of oysters and clams from Lake Pontchartrain, New Orleans, Louisiana, were between 4.5 and 27 ng/g wet weight (Ferrario *et al.*, 1985).

Data on levels of dichloromethane in foods in Canada are very limited. Since the 1980s, levels of dichloromethane in table-ready foods have been monitored in the Total Diet Program of the U.S. Food and Drug Administration (Heikes and Hopper, 1986; Heikes, 1987a, 1987b; Daft, 1988); they are summarized in a recent report

(Heikes, 1990). Although exact dates were not clearly specified, sampling is believed to have been conducted in the mid-1980s. Levels in ready-to-eat cereals and butter were the highest (95 and 84 $\mu\text{g}/\text{kg}$, respectively), followed by cheese (45 $\mu\text{g}/\text{kg}$), margarine (27 $\mu\text{g}/\text{kg}$), processed foods (34 $\mu\text{g}/\text{kg}$), and peanut butter (19 $\mu\text{g}/\text{kg}$).

2.4 Toxicokinetics

There are two pathways for the metabolism of dichloromethane in various species examined to date. One pathway involves the cytochrome P-450 mixed-function oxidase (MFO) system, leading to formation of carbon monoxide (CO) and elevated levels of carboxyhemoglobin in blood; metabolism via this pathway occurs in the microsomal fraction of several organs, including the liver, kidney, and lung. Based upon studies with metabolic inhibitors, significant amounts of carbon dioxide (CO_2) also appear to be produced by this pathway. The other identified pathway, which is catalyzed by a soluble glutathione-S-transferase (GST) enzyme, leads to production of formaldehyde and the subsequent formation of CO_2 *in vivo* (Green, 1989). In addition to being metabolized to both CO and CO_2 , dichloromethane is exhaled unchanged.

Data on the metabolism of dichloromethane in humans and other species have been acquired in recent studies to serve as a basis for physiologically based pharmacokinetic (PBPK) modelling.

Assays of GST in cytosol prepared from liver samples of 4 species, including mice, rats, hamsters, and humans, were exposed to concentrations of dichloromethane from 6.7 mM to 100 mM. The activity of GST was highest in mouse liver, intermediate in rat liver, and lowest in human and hamster liver. Values of K_m and V_{max} were obtained by computer optimization. Again, the values of K_m and V_{max} in mice were greater than the values calculated on the basis of results in human samples.

In additional *in vitro* studies conducted by Reitz *et al.* (1989), samples of liver cytosol from humans, F344 rats, B6C3F₁ mice, and Syrian Golden hamsters were assayed at 40 mM dichloromethane. Cytosol from lung tissue was also assayed. The levels of GST activity were highest in the mouse-liver cytosol (25.9 nmol product formed/min/mg protein). GST activity was lower in cytosols of the rat and hamster. Activity in cytosol preparations from 4 humans ranged from 0.0 to 3.03 nmol product formed/min/mg protein. The reaction rates in cytosol prepared from lung tissue was highest in the mouse (7.3 nmol product formed/min/mg protein), with lower rates in rats (1.0) and humans (0.37). No GST activity was detectable in cytosol prepared from hamster lungs.

2.5 Effects-related Information

2.5.1 *Experimental Animals and In Vitro*

Acute exposure of laboratory animals to dichloromethane by inhalation has resulted in effects upon the liver, heart, and central nervous system (WHO, 1984). Reported LC₅₀s in mice range from 49 g/m³ (6 hours) to 92 g/m³ (20 minutes), while LC₅₀s in rats range from 52 g/m³ (6 hours) to 200 g/m³ (15 minutes). The acute oral toxicity appears to be similar in mice and rats, with LD₅₀s of 1.6 and 1.6 to 2.3 g/kg bw, respectively.

Short-term exposure of experimental animals to dichloromethane by inhalation or orally has resulted in various effects on the central nervous system, liver, eyes, kidneys, spleen, brain, and lungs. The lowest concentration at which effects have been observed in short-term studies following inhalation of dichloromethane is that reported by Weinstein and Diamond (1972), in which increases in hepatic triglycerides and mild changes in the liver (fatty change but no necrosis) were observed in mice following continuous exposure for up to 10 weeks to 100 ppm (347 mg/m³). [There was only one dose group in this study.]

Species exposed to dichloromethane in investigations of sub-chronic toxicity include monkeys, dogs, rats, mice, and gerbils, with observed effects being dependent on exposure regimens. Effects following continuous exposure are more severe than those for intermittent exposures. The lowest concentrations at which effects have been observed in experimental animals exposed to dichloromethane by inhalation in sub-chronic studies are 25 and 100 ppm (87 and 347 mg/m³) in early studies in several species reported by Haun *et al.* (1972). In rats continuously exposed to 25 ppm, "nonspecific" renal tubular degenerative and regenerative changes were observed. In mice exposed continuously to 100 ppm, effects on liver microsomal cytochrome content and fat staining of the liver were reported; concentrations of carboxyhemoglobin in the blood of monkeys and dogs were also elevated following continuous exposure to this concentration (Haun *et al.*, 1972).

It should be noted that compound-related effects have not been observed in more recent, well-documented studies in which rats and mice were exposed intermittently to concentrations as high as 2 100 ppm (7 287 mg/m³) 6 hrs/day, 5 days/week for 13 weeks (NTP, 1986). At 4 200 ppm (14 574 mg/m³), rats had mild to minimal lung changes; hydropic degeneration of the liver was observed in mice exposed to this concentration.

Only one chronic inhalation study has been conducted in mice (NTP, 1986; see also Mennear *et al.*, 1988). In this bioassay, 50 male and 50 female B6C3F₁ mice were exposed to 0, 2 000, or 4 000 ppm (0, 6 940 or 13 880 mg/m³) dichloromethane in air for 6 hours/day, 5 days/week, for 102 weeks. Increased incidences of cytologic

degeneration of the liver were observed in both males and females in the high-dose group. Increased incidences of both benign and malignant lung tumours were observed in both males and females. The incidences of alveolar/bronchiolar carcinomas in male mice were 2/50, 10/50, and 28/50 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the female mice, the incidences were 1/50, 13/48, and 29/48 for the control, 2 000 ppm, and 4 000 ppm groups, respectively. The incidences of alveolar/bronchiolar adenomas in male mice were 3/50, 19/50, and 24/50 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the female mice, the incidences were 2/50, 23/48, and 28/48 for the control, 2 000 ppm, and 4 000 ppm groups, respectively. The combined incidence of adenomas and carcinomas in the lungs of males was 5/50, 27/50, and 40/50 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the females, the combined incidence was 3/50, 30/48, and 41/48, respectively. Incidences of hepatocellular adenomas or hepatocellular carcinomas (combined) were increased in males in the high-dose group and all exposed groups of females. In male mice, the incidences of hepatocellular carcinomas were 13/50, 15/49, and 26/49 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the female mice, the incidences were 1/50, 11/48, and 32/48 for the control, 2 000 ppm, and 4 000 ppm groups, respectively. In male mice, the incidences of hepatocellular adenomas were 10/50, 14/49, and 14/49 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the female mice, the incidences were 2/50, 6/48, and 22/48 for the control, 2 000 ppm, and 4 000 ppm groups, respectively. The combined incidence of hepatocellular adenomas and carcinomas in male mice was 22/50, 24/49, and 33/49 for the control, 2 000 ppm, and 4 000 ppm groups, respectively; for the females, the combined incidence was 3/50, 16/48, and 40/48, respectively. There were also dose-related increases in the numbers of mice bearing multiple lung or liver neoplasms. It was concluded that there was "clear evidence of carcinogenicity of dichloromethane for male and female B6C3F₁ mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms" (NTP 1986).

The results of this bioassay (NTP, 1986) are similar to those reported more recently at the U.S. National Institute of Environmental Sciences, in an experiment in which the same strain of (female) mice were exposed to 2 000 ppm dichloromethane under various regimens. Increases in lung and liver neoplasia occurred in the absence of overt cytotoxicity and under circumstances in which there was no demonstrable sustained enhanced cell proliferation. The results indicated that dichloromethane was a more potent inducer of lung than of liver tumorigenesis (Anderson and Maronpot, 1993; Foley *et al.*, 1993; Kari *et al.*, 1993).

In the NTP bioassay (NTP, 1986; see also Mennear *et al.*, 1988), 50 male and 50 female Fischer 344/N rats were exposed to 1 000, 2 000 or 4 000 ppm (3 470, 6 940 or 13 880 mg/m³) dichloromethane for 6 hours/day, 5 days/week for 2 years. Increased incidences of benign mammary-gland lesions (adenomas and fibroadenomas) occurred in males and females (male: 0/50, 0/50, 2/50, 5/50; female: 5/50, 11/50, 13/50, 23/50

for the 0, 1 000, 2 000 and 4 000 ppm groups, respectively). The incidence of malignant mammary-gland neoplasms was not increased in females (2/50, 2/50, 2/50, 0/50) and none was observed in males. Integumentary system tumours "in the area of the mammary chain" occurred with a positive trend in males (subcutaneous tissue fibroma or sarcoma: 1/50, 1/50, 2/50, 5/50). The combined incidence of all tumours in the mammary area in males was 1/50, 1/50, 4/50, and 9/50. NTP concluded that "...there was some evidence of carcinogenicity of dichloromethane for male F344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland. There was clear evidence of carcinogenicity of dichloromethane for female F344/N rats as shown by increased incidences of benign neoplasms of the mammary gland."

Burek *et al.* (1984) reported the results of a 2-year inhalation study in Sprague-Dawley rats exposed to 0, 500, 1 500 or 3 500 ppm (0, 1 735, 5 205, or 12 145 mg/m³). While the incidence of benign tumours of the mammary gland in females was not increased, the total number of benign mammary tumours per group was increased in an exposure-related manner. Results were similar in males in the groups exposed to 1 500 and 3 500 ppm (5 205 and 12 145 mg/m³). Hepatic vacuolization consistent with fatty change and other manifestations of liver toxicity were seen at all doses. (There was a significant increase in the mortality of females only during the 18th to the 24th month of exposure to 3 500 ppm but no exposure-related changes in body weight in any group.)

An additional study, in which rats were exposed under similar conditions to concentrations of 0, 50, 200, or 500 ppm (0, 173.5, 696, or 1 735 mg/m³) dichloromethane for up to 2 years, was reported by Nitschke *et al.* (1988a). The incidence of both hepatocellular cytoplasmic vacuolization (consistent with fatty change) and multinucleated hepatocytes was significantly increased in females at 500 ppm. The authors stated that there was no difference between exposed and control rats in the number of benign and/or malignant neoplasms; however, there was a significant (although not dose-related) increase in the incidence of benign mammary tumours in females at 200 ppm. Although there was an increase in the number of benign mammary tumours per tumour-bearing rat in females at 500 ppm, these data were not statistically analyzed.

Although there was a non-significant increase in total malignant tumours in Sprague-Dawley rats exposed to 100 ppm for 104 weeks in an additional study by Maltoni *et al.* (1988), these results contribute little to the weight of evidence for carcinogenicity, since the incidence of individual tumour types was not reported.

Concurrent with the study in rats, Burek *et al.* (1984) exposed Syrian Golden hamsters to 0, 500, 1 500, and 3 500 ppm dichloromethane (0, 1 735, 5 205, and 12 145 mg/m³) for up to 2 years. During the latter part of the study, the mortality in females at

1 500 and 3 500 ppm was decreased; this appeared to be related to the decreased incidence and severity of amyloidosis (a naturally occurring, geriatric pathologic alteration) in exposed animals. All hamsters had some hemosiderin in the liver; the authors considered this to be a slight exposure-related effect in the liver of male (but not female) hamsters exposed to 3 500 ppm for 6 or 12 months. There were no significant differences between exposed and control groups of males with regard to total number of animals with a tumour, the number with a benign tumour; or the number with a malignant tumour. A significant increase in the total number of benign tumours occurred in females at 3 500 ppm, but this was considered to be secondary to the increased survival of this group. There was no discussion of specific tumour types in the report of this study.

The lowest-effect-level in these studies (for non-neoplastic effects) following chronic exposure by inhalation to dichloromethane was, therefore, that reported in the investigations conducted by Burek *et al.* (1984) and Nitschke *et al.* (1988a). The no-adverse-effect-level for hepatic effects in female rats was considered to be 200 ppm, based on observation of cytoplasmic vacuolation consistent with fatty change and multinucleated hepatocytes at the next highest dose level (500 ppm).

Several studies have been conducted to elucidate the possible mechanisms of carcinogenesis of inhaled dichloromethane in rats and mice. Green (1989) described a histological/histochemical investigation of the effects of dichloromethane upon F344 rats and B6C3F₁ mice following exposure to 2 000 or 4 000 ppm (6 940 or 13 880 mg/m³) for 1 or 10 days. The most significant observations were liver growth and a marked lesion in the Clara cells of mice. This lesion, observed after a single exposure, involved extensive vacuolation or balloon degeneration of the Clara cells, which had largely recovered after 10 days of exposure. Clara cells damaged by exposure to dichloromethane no longer contained cytochrome P-450 iso-enzymes as determined using polyclonal antibodies. Using microsomes prepared from whole-lung homogenates, the metabolism of dichloromethane to CO was reduced by 50%, suggesting that 50% of the cytochrome P-450 responsible for metabolizing dichloromethane is found in the Clara cells, which comprise only 5% of the total cell types in the mouse lung. Assay of the glutathione-S-transferases with dichloromethane, chlorodinitrobenzene, or antibodies indicated that these enzymes were not affected either in Clara cells or whole-lung homogenates. After 10 days of exposure to dichloromethane, the cells recovered, as did the iso-enzymes of cytochrome P-450, with the exception of the one responsible for the metabolism of dichloromethane. On a whole-lung basis, the metabolism of dichloromethane remained reduced by 50%. Green (1989) concluded that Clara cells damaged in this way are at increased risk and may well be the population of cells from which tumours develop.

The studies by Green (1989) were continued, and reported by Foster *et al.* (1992), who attempted to correlate metabolic with pathological events in mice exposed to dichloromethane for longer periods. In an experiment designed to duplicate the 1986 NTP protocol, male B6C3F₁ mice were exposed to 4 000 ppm (13 880 mg/m³) dichloromethane for 6 hours/day, 5 days/week for up to 13 weeks. The major initial morphological effect in lungs was acute Clara cell damage, which was observed after one exposure and appeared to resolve after 5 exposures. After 2 days of no exposure, the lesion in the Clara cell reappeared following renewed exposure, but the severity of the lesion diminished over the duration of the study, which correlated with the activity of cytochrome P-450 monooxygenase. The authors concluded that the developing tolerance of the Clara cell to dichloromethane might be due to the inactivation of a cytochrome P-450 isozyme. The metabolism of dichloromethane by glutathione-S-transferase remained virtually unaltered throughout the study'.

Casanova *et al.* (1992) attempted to determine whether formaldehyde derived from dichloromethane could form DNA-protein cross-links in the liver or lungs of B6C3F₁ mice and Syrian Golden hamsters. Mice and hamsters were exposed to 4 000 ppm (13 880 mg/m³) dichloromethane for 6 hours on 2 successive days. DNA-protein cross-links were detected in the liver in mice, but not in the lung of mice, or the liver or lung of hamster. The authors (citing Green, 1989; and Foster *et al.*, 1992), suggested that the failure to detect DNA-protein cross-links in mouse lung might be attributed to their formation in Clara cells, which may comprise only 5% of the total population of lung cells. The metabolic incorporation of ¹⁴C derived from [¹⁴C]dichloromethane into DNA suggested a higher turnover rate for mouse than hamster lung cells. The difference in turnover rates in liver was not as noticeable.

Maltoni *et al.* (1986, 1988), exposed 50 male and 50 female Swiss mice to 100 or 500 mg dichloromethane/kg bw/day by gavage for 4 to 5 days/week. Excess mortality occurred in both male and female mice at both dose levels after 36 weeks of exposure; as a result, exposure was terminated after 64 weeks. A dose-related increase in the incidence of pulmonary adenomas was observed in males. This increase was not significant when the total number of pulmonary tumours was evaluated without considering the mortality rate. When mortality was taken into account, the incidence of pulmonary tumours was significantly greater ($p < 0.05$) than that in controls in males exposed to the higher dose level that died in the period ranging from 52 to 78 weeks, "whether or not the pulmonary tumours were considered as cause of death" (Maltoni *et al.*, 1986).

1. In 1972, Haun *et al.*, reported that continuous exposure of mice to 100 ppm dichloromethane for 4 to 12 weeks decreased the hepatic cytochrome P-450 content (Haun *et al.*, 1972, in U.S. EPA [1985]).

Serota *et al.* (1986a) exposed B6C3F₁ mice to concentrations of dichloromethane in their drinking water equivalent to 0, 60, 125, 185, or 250 mg/kg bw/day for 2 years. At the highest-dose, there was a slight increase in the number of small lung masses in females, which was not associated with any remarkable pathology. The incidence of liver carcinomas in the males was higher than that in one of the control groups but was not significant when compared to the other control group or to the combined control groups². The authors considered the no-observed-effect-level (NOEL) to be 185 mg/kg bw/day, based upon toxicological and non-neoplastic histopathological effects (lung masses, changes in hepatocellular staining consistent with increase in fat content).

Maltoni *et al.* (1986, 1988) exposed groups of 50 male and 50 female Sprague-Dawley rats to dichloromethane by stomach tube at doses of 100 or 500 mg/kg bw/day. Excess mortality occurred in both male and female rats at the higher dose level after 36 weeks of exposure; as a result, exposure was terminated after 64 weeks. At 100 mg/kg bw/day, body weight was decreased. In females, there was a nonsignificant increase in malignant mammary tumours, due mainly to an increased incidence of adenocarcinomas.

Serota *et al.* (1986b) conducted a 2-year study in which F344 rats were administered concentrations of dichloromethane in their drinking water equivalent to doses of 0, 5, 50, 125, and 250 mg/kg bw/day. Small but significant decreases in body-weight gain and water consumption in both sexes were noted at 125 and 250 mg/kg bw/day. At an interim sacrifice after 78 weeks of exposure, both sexes had increased incidences of hepatic changes, consisting of foci/areas of cellular alteration and fatty change; these changes occurred at all doses except 5 mg/kg bw/day. Although there were small increases in "hepatocellular tumours" in the females exposed to 50 or 250 mg/kg bw/day, they were not considered to be meaningful, due to the absence of a comparable increase in females administered 125 mg/kg bw/day and the low incidence in female controls in this bioassay compared to historical controls. The authors cited a NOEL of 5 mg/kg bw/day for both sexes, based upon toxicological and non-neoplastic histopathological effects on the liver.

The lowest-reported-effect-level for non-neoplastic effects in adequately documented investigations following chronic exposure by ingestion of dichloromethane is, therefore, 50 mg/kg bw/day in F344 rats, at which fully reversible cellular proliferation and partially reversible fatty change in the livers were observed (lowest-observed-effect-level (LOEL) = 50 mg/kg bw/day; NOEL = 5 mg/kg bw/day) [Serota *et al.*, 1986b].

2. Unbalanced group size allocation based upon Weibull model, to optimize definition of any dose-response curve at lower doses in presence of anticipated high background levels of liver tumours in control males (Serota *et al.*, 1986a).

Dichloromethane is clearly mutagenic in short-term tests in bacteria and yeast and there is some evidence for chromosomal damage in mammalian cells *in vitro*. Results from *in vivo* studies are mixed and inconclusive; however, chromosomal damage observed consistently in lung, blood, and bone-marrow cells following inhalation of dichloromethane is consistent with the hypothesis that the carcinogenicity of dichloromethane (particularly in the lung) is due to its genotoxicity (or that of its metabolites) [Westbrook-Collins *et al.*, 1989; Allen *et al.*, 1990].

Available data on the developmental toxicity of dichloromethane following inhalation are restricted to studies in which groups of animals have been exposed to only one concentration, all exceeding 500 ppm (1 735 mg/m³) [Schwetz *et al.*, 1975; Leong *et al.*, 1975; Hardin and Manson, 1980; Bornschein *et al.*, 1980]. In all of these investigations, only minor effects were observed in the offspring at doses that induced minor maternal toxicity. In the only multigeneration study of reproductive toxicity identified, in rats exposed to up to 1 500 ppm (5 205 mg/m³) dichloromethane for over 2 generations, there were no effects on any reproductive parameters (Nitschke *et al.*, 1988b).

In general, evidence of behavioural effects has not been observed at concentrations less than approximately 500 ppm (1 735 mg/m³) in rats. Effects on enzymes and neurotransmitters in the brain have been reported in several species of animals exposed to lower concentrations of dichloromethane; however, in the absence of reported functional or pathological effects, the significance of these observations is unclear (Savolainen *et al.*, 1981, in ATSDR, 1991; Mattsson *et al.*, 1990; Briving *et al.*, 1986; Karlsson *et al.*, 1987; Rosengren *et al.*, 1986; Bornschein *et al.*, 1980).

2.5.2 Humans

In case reports of poisonings with dichloromethane, effects on the central nervous system have been predominant (Rioux and Meyers, 1988). In short-term studies in which volunteers were exposed to (at most) 500 ppm (1 735 mg/m³) repeatedly for periods up to 5 weeks, behavioural effects were not observed (Stewart *et al.*, 1973, in Brandt and Okamoto, 1988).

The potential carcinogenicity of dichloromethane in occupationally exposed populations has been investigated in several epidemiological studies, the most extensive of which was that of a cohort of dichloromethane-exposed male workers from the Eastman Kodak Company in Rochester (Hearne *et al.*, 1990).

Exposure of the workers in this cohort was estimated based on results of air sampling and job records from the period 1944 to 1988. Exposure estimates for about 160 job codes were derived from more than 1 200 area and 900 full-shift, job-specific, breathing-zone samples, collected over 40 years. As well, information from

4 300 individual occupational assignments was abstracted from personnel records, and an index of career exposure was developed. The mortality of the cohort was compared to both the general population of upstate New York men and male Kodak workers who were not exposed to dichloromethane.

Concomitant exposures were noted. The authors estimated that, in general, the ratio of dichloromethane: 1,2-dichloropropane: 1,2-dichloroethane was 17:2:1; however, the concentrations of these various compounds at some machines were equal. Workers were also regularly exposed (in less significant amounts) to methanol, ethanol, isopropanol, butanol, 2-methoxyethanol, and cyclohexane.

Follow-up was essentially complete (99%). The principal confounding factor for lung carcinoma and ischemic heart disease was cigarette smoking. Data on smoking habits, available for ~ 75% of the subjects and obtained from medical records and a 1986 mail survey, indicated that the proportion of cohort members who used tobacco products was similar to that reported for the general population and for other Kodak employees (Hearne *et al.*, 1990). Overall mortality from 1964 to 1988 (n = 238) was significantly decreased compared to both control populations. Based on comparison of the cohort to both the general population and the industrial referent group, there were non-significant deficits in observed:expected ratios for lung cancer; liver cancer, and ischemic heart disease. This study had 90% power to detect relative risks of 1.7 and 1.3 for lung cancer and ischemic heart disease, respectively; the power was inadequate for liver cancer (80% probability of identifying a relative risk of 5.4). Deaths from other malignant neoplasms (digestive system, genitourinary, lymphatic, and hematopoietic tissue) were lower (non-significant) than expected, based upon the 2 control populations.

In an historical cohort study conducted at Dow Chemical, the mortality of workers exposed to dichloromethane (and methanol and acetone) was compared to that of the population of York County, South Carolina, where 95% of the cohort members resided (Ott *et al.*, 1983a, 1983b; Lanes *et al.*, 1990). There was excess mortality for cancer of the buccal cavity and pharynx (observed:expected = 2:0.87), liver and biliary passages (observed:expected = 4:0.70) and melanoma (observed:expected = 2:0.88). A deficit in mortality was observed for cancer of the respiratory system, breast, and pancreas. It should be noted, however; that vital status of the cohort was identified only through the national death index and records of the Social Security Administration, and may have been underestimated by 10 to 20%.

A significant increase in breast and gynecological cancers was observed in a small cohort of men and women employed in a lamp manufacturing plant, but use patterns of, and exposure to, dichloromethane (and trichloroethylene) were not known

(Shannon *et al.*, 1988). Based on an historical cohort study at a Dow Chemical manufacturing site, there was no excess mortality overall or due to cancer in workers exposed to dichloromethane and numerous other chemicals (Olsen *et al.*, 1989).

In a case-control study in a chemical-production facility, there was no association between exposure to dichloromethane and liver and biliary tract cancer (Bond *et al.*, 1990, in MRI, 1991). Based on a limited case-control study (Osorio *et al.*, 1986, in MRI, 1991) of female cosmetologists, it was concluded that an observed excess of lung cancer was attributable to cigarette smoking.

2.5.3 Ecotoxicology

The acute and chronic toxicity of dichloromethane in aquatic species has been investigated in numerous studies. Only a few studies on the effects of dichloromethane in terrestrial biota have been identified, however. The following discussion focuses on those studies of adequate quality in species sensitive to dichloromethane. Levels of dichloromethane that induced adverse effects in aquatic biota are presented in Figure 1.

The lowest concentration of dichloromethane inducing an adverse effect was that for the ubiquitous free-living freshwater nematode, *Panagrellus redivivus*. A chronic (4-day) exposure to 0.9 µg/L inhibited completion of the fourth larval stage (L4) to adult moult and resulted in a considerable reduction in the adult population. Lethal mutations to the b7 X-linked gene also occurred at concentrations as low as 0.849 µg/L (Samoiloff *et al.* 1980; Samoiloff, 1992).

The lowest 48-hour LC₅₀ in other invertebrate species was 27 mg/L for *Daphnia magna* in its first instar stage (McCarty, 1979). In *D. magna* and the marine grass shrimp (*Palaemonetes pugio*), 48-hour LC₅₀s were 220 and 108.5 mg/L, respectively (LeBlanc, 1980; Burton and Fisher, 1990).

The 96-hour EC₅₀ in adult fathead minnow (*Pimephalas promelas*) exposed to dichloromethane in a flow-through system was 99.0 mg/L (impairment of swimming ability); the 96-hour LC₅₀ was 193.0 mg/L (Alexander *et al.*, 1978). In other studies with the fathead minnow, the blue gill sunfish (*Lepomis macrochirus*), and the marine fish, sheepshead minnow (*Cyprinodon variegatus*), 96-hour LC₅₀s were within the range of 220 to 502 mg/L (Buccafusco *et al.*, 1981; Heitmuller *et al.*, 1981; Geiger *et al.*, 1986; Dill *et al.*, 1987). A 48-hour LC₅₀ of 97.0 mg/L was reported for the killifish (*Fundulus heteroclitus*) [Burton and Fisher, 1990], while the 96-hour no-observed-effect-concentration (NOEC) for the sheepshead minnow was 130 mg/L (Heitmuller *et al.*, 1981). In a partial, life-cycle toxicity study (embryo to larval stage) in rainbow trout (*Oncorhynchus mykiss*), the LC₅₀ was 13.2 mg/L and the lowest-observed-effect-level (LOEL) for teratogenic effects was 5.5 mg/L (Black *et al.*, 1982).

An LC₅₀ of 16.9 mg/L was reported for the frog (*Rana temporaria*), in a partial life-cycle toxicity study (embryo to larval stage) [Black *et al.*, 1982]. In other frog, toad, and salamander species, embryo/larvae LC₅₀s ranged from 17.8 to > 48 mg/L (Birge *et al.*, 1980; Black *et al.*, 1982). Lowest-observed-effect-concentrations (LOECs) [LC₁₀s] of 981 µg/L and 822 µg/L were reported for *R. catesbeiana* and *R. temporaria*, respectively (Birge *et al.*, 1980; Black *et al.*, 1982).

The few identified studies on the effects of dichloromethane on aquatic plants were considered inadequate.

Dichloromethane inhibited enzymatic activity (β-glucosidase, β-acetyl-glucosaminidase, phosphatase, and phosphodiesterase) of soil microbes at a concentration of 10 µg/g (dry weight), and decreased the ATP content of the soil by 80 to 85% (Kanazawa and Filip, 1986, 1987). Dichloromethane inhibited CO₂ production from freshwater sediment with a reported 7-day EC₅₀ of 11.7 µL/g ww (15.6 mg/g) [Trevors, 1985]. Gas production was inhibited in anaerobic sludge reactors at levels as low as 2.5 mg/L (Stuckey *et al.*, 1980); however, metabolic rates in sludge acclimated to dichloromethane for 1 to 2 weeks were not reduced relative to non-acclimated sludge (Klecka, 1982).

Although dichloromethane is not registered as a pest-control product in Canada, it has been used as an effective insect fumigant in other countries. Twenty-four hour LD₅₀s were 129.9 and 81.28 mg/L for the fumigation of *Sitophilus oryzae* and *Trilobolium castaneum*, respectively (Rajendran and Mathu, 1981).

Data on the toxicity of dichloromethane in birds are limited to 2 studies in chick embryos. In one study, the LD₅₀ was 14.1 mg/egg following the injection of dichloromethane, dissolved in ethanol, into the yolk of White Leghorn Chicken eggs (Verrett *et al.*, 1980). Similarly, Elovaara *et al.* (1979) reported that the LD₅₀ for an injection of dichloromethane dissolved in olive oil into the air space of White Leghorn Chicken eggs was greater than 100 µmol/egg (> 8.5 mg dichloromethane/egg). There was no evidence of teratogenicity in either study (Verrett *et al.*, 1980; Elovaara *et al.*, 1979).

Information on the effects of dichloromethane on terrestrial plants was limited to 3 studies on seed germination. Immersion of oat and pigweed seeds for 24 hours in dichloromethane inhibited seed germination (Brewer and Wilson, 1975). Soybean seeds were unaffected by immersion in dichloromethane for 5 hours (Ellis *et al.*, 1976, 1977); however, seed germination was enhanced for the light-sensitive Grand Rapids lettuce seeds following immersion in dichloromethane for 10 minutes to 12 hours (Rao *et al.*, 1976).

3.0 Assessment of “Toxic” under CEPA

3.1 CEPA 11(a): Environment

Dichloromethane is used in Canada primarily as a paint remover, a blowing agent for foam production, and as a component of aerosols. Because it is highly volatile, releases to the Canadian environment are most often in the form of emissions to the atmosphere, although release within industrial effluent also occurs. Spills of dichloromethane have also been significant sources of release. Dichloromethane has been measured in air and in surface and groundwaters in several provinces across Canada.

The most sensitive aquatic species identified was that of the freshwater nematode, *Panagrellus redivivus*, which occurs throughout Canada and the world. Inhibition of larval moulting of the fourth larval stage to the adult stage occurred at levels as low as 0.9 µg/L. This sublethal effect occurs during a sensitive period in the development of the male and female reproductive system and would decrease population growth of this species. Levels of dichloromethane in surface water exceeded this effect threshold at 28% of 264 sites in 5 provinces in Canada.

To estimate exposure of wildlife to dichloromethane, a worst-case exposure scenario was developed for mink (*Mustela vison*), an opportunistic carnivore, along the St. Clair River. This site was chosen because levels of dichloromethane in surface water were the highest recorded across Canada and data on levels in air were available for a nearby rural site (Walpole Island). The main route of exposure is oral (Table 1). In the absence of toxicological data for wildlife, an effects threshold has been estimated based upon the results of toxicity studies on laboratory rodents. The LOEL reported for hepatic effects following chronic exposure by ingestion of dichloromethane was 50 mg/kg bw/day in rats; the NOEL was 5 mg/kg bw/day. Assuming a factor of 10 to account for interspecies variation and extrapolation of results from a laboratory to field situation, the estimated effects threshold is 0.5 mg/kg bw/day. The estimated worst-case exposure scenario is more than 10 times less than this effects threshold. Therefore, dichloromethane is not anticipated to cause effects to mammalian wildlife.

Table 1
Estimated Worst-case Scenario for Total Daily Exposure
of Mink in the St. Clair River

Exposure Route	Environmental Levels ^a	Daily Rate of Consumption (per kg bw) ^b	Daily Intake (µg/kg bw/d)
Air	1.6 µg/m ³	0.55 m ³ /d	0.9
Surface water	57 µ/L	0.1 L/d	5.7
Biota (fish)	131.1 µg/kg	155 g/d	20.7
Total	-	-	27.3

- a. The level in air is the maximum level measured in a rural environment - Walpole Island, Ontario; the level in surface water is the maximum level measured in the St. Clair River, Ontario; the level in fish is based on a calculated BCF of 2.3 and the above concentration in water.
- b. Inhalation rate from Stahl (1967); drinking rate from Calder and Braun (1983); ingestion rate from Nagy (1987), assuming a diet of 75% fish.

On the basis of available information, dichloromethane is entering into the Canadian environment in significant quantities, but does not, in general, result in concentrations that would be expected to cause adverse effects to terrestrial wildlife; however, there are limited data suggesting that concentrations of dichloromethane in water may be sufficient to cause adverse effects to some aquatic organisms, notably certain freshwater nematodes. It is concluded that dichloromethane can cause harm to the environment.

3.2 CEPA 11(b): Environment on Which Human Life Depends

The troposphere is an important sink for dichloromethane. The tropospheric half-life of this compound is estimated to be as little as 30 days, however, and is dependent on the concentration of hydroxyl radical and the light intensity. A small amount of dichloromethane may also be washed out via precipitation. Due to the low concentration of dichloromethane, its short lifetime in the troposphere, and the expected long period for migration into the stratosphere (5 to 10 years), it is estimated that 2.0 to 2.5% of released dichloromethane may enter the stratosphere, where destruction is expected to be rapid. Dichloromethane is therefore expected to have a low ozone-depleting potential. Dichloromethane absorbs in the infrared region (7 to 13 µm range), but is generally present at low concentrations in the atmosphere, and has a relatively short half-life. It is therefore expected that dichloromethane will not contribute significantly to global warming.

On the basis of available data, dichloromethane is not involved in the depletion of stratospheric ozone, nor is it significantly involved in the formation of ground-level ozone or global warming. It has been concluded that dichloromethane is not entering the environment in quantities or under conditions that may constitute a danger to the environment on which human life depends.

3.3 CEPA 11(c): Human Life or Health

Population Exposure

Estimates of the average daily intake of dichloromethane via different routes by the Canadian population are summarized in Table 2. Estimated intake from indoor air is more than an order of magnitude greater than that from ambient air, food, or drinking water. Total daily intakes for the general population are estimated to range from 3.96 to 6.62 $\mu\text{kg bw/day}$.

Effects

Although there is no consistent, convincing evidence of excess mortality due to cancer associated with occupational exposure to dichloromethane in epidemiological studies conducted to date, because of their limitations the available data are considered inadequate to assess the carcinogenicity of dichloromethane in humans.

Based on the most extensive of the bioassays in animal species conducted to date (NTP, 1986), it has been concluded that there is "clear evidence" of the carcinogenicity of dichloromethane for male and female B6C3F₁ mice exposed to concentrations up to 4 000 ppm (13 880 mg/m^3), based on increased incidences of alveolar/bronchiolar neoplasms (adenomas, carcinomas) and of hepatocellular neoplasms (adenomas, carcinomas). There was also "clear evidence" of the carcinogenicity of dichloromethane for female F344/N rats and "some evidence" in male F344/N rats exposed to up to 4 000 ppm, based on increased incidence of benign neoplasms of the mammary gland.

Interpretation of the results of an additional study, in which there was an exposure-related increase in the incidence of benign mammary tumours in female Sprague-Dawley rats exposed to up to 3 500 ppm (12 145 mg/m^3), was complicated by high mortality in the females and a viral infection of the salivary glands in males (Burek *et al.*, 1984). In continuation of this work by Nitschke *et al.* (1988), there were no dose-related increases in the incidence of tumours in rats exposed to up to 500 ppm (1 735 mg/m^3), although there was a significant increase in benign mammary tumours in females exposed to 200 ppm (694 mg/m^3). The incidence of tumours was not increased in Syrian Golden hamsters exposed to up to 3 500 ppm (12 145 mg/m^3) [Burek *et al.*, 1984].

Table 2
Estimated Daily Intake of Dichloromethane by the Canadian Population

Route of Exposure ^a	Estimated Dichloromethane Intake ($\mu\text{g}/\text{kg}$ bw/day) of Various Age Groups				
	0-6 mo ^b (not breastfed)	7 mo-4yr ^c	5-11 yr ^d	12-19 yr ^e	20+ yr ^f
Ambient Air ^g	0.04-0.30	0.06-0.04	0.07-0.46	0.06-0.38	0.05-0.34
Indoor Air ^h	3.88	5.22	6.04	5.00	4.46
Total Air	3.92-4.18	5.28-5.62	6.11-6.50	5.06-5.38	4.51-4.80
Drinking Water ⁱ	0.01-0.07	0-0.04	0-0.03	0-0.02	0-0.01
Food ^j	0.03	0.11	0.09	0.05	0.05
Total Intake	3.96-4.28	5.39-5.77	6.20-6.62	5.11-5.45	4.56-4.86

- a. Available data are insufficient to serve as a basis for calculation of intakes from Soil.
- b. Assumed to weigh 7 kg, breathe 2 m³ of air per day, drink 0.2 litres of water per day and to consume on a daily basis: 0.73 g butter, 0.02 g margarine, 0.06 g processed cheddar cheese, 0.11 g cheese, 1.07 g cereal (corn), 0.16 g peanut butter and peanuts, 0 g canned luncheon meats, 0 g coffee, 1.5 g cookies, and 0 g shellfish (EHI, 1992).
- c. Assumed to weigh 13 kg, breathe 5 m³ of air per day, drink 0.2 litres of water per day, and to consume on a daily basis: 7.06 g butter, 2.65 g margarine, 3.59 g processed cheddar cheese, 2.56 g cheese, 3.42 g cereal (corn), 2.98 g peanut butter and peanuts, 0.88 g canned luncheon meats, 6.48 g coffee, 18.87 g cookies, and 0.28 g shellfish EHD, 1992).
- d. Assumed to weigh 27 kg, breathe 12 m³ of air per day, drink 0.3 litres of water per day, and to consume on a daily basis: 12.94 g butter, 6.13 g margarine, 4.92 g processed cheddar cheese, 3.18 g cheese, 5.37 g cereal (corn), 6.08 g peanut butter and peanuts, 0.97 g canned luncheon meats, 11.99 g coffee, 26 g cookies, and 0.64 g shellfish (EHD, 1992).
- e. Assumed to weigh 57 kg, breathe 21 m³ of air per day, drink 0.5 litres of water per day and to consume on a daily basis: 16.67 g butter; 8.34 g margarine, 6.43 g processed cheddar cheese, 5.66 g cheese, 3.40 g cereal (corn), 6.60 g peanut butter and peanuts, 2.2 g canned luncheon meats, 83.95 g coffee, 23.08 g cookies, and 1.0 g shellfish (EHD, 1992).
- f. Assumed to weigh 70 kg, breathe 23 m³ of air per day, drink 0.4 litres of water per day and to consume on a daily basis: 13.61 g butter; 6.23 g margarine, 3.81 g processed cheddar cheese, 8.33 g cheese, 1.82 g cereal (corn), 3.52 g peanut butter and peanuts, 2.10 g canned luncheon meats, 347.77 g coffee, 15.58 g cookies, and 1.93 g shellfish (EHD, 1992).
- g. Assumed to spend 4 hours/day outdoors (EHD, 1992) and based on a range of mean concentrations of dichloromethane in Canada from 0.9 $\mu\text{g}/\text{m}^3$ to 6.2 $\mu\text{g}/\text{m}^3$ (Environment Canada, 1991b).
- h. Assumed to spend 20 hours/day indoors (EHD, 1992) and based on a mean concentration of 6.3 $\mu\text{g}/\text{m}^3$ reported in preliminary results of a national survey in Canadian homes (Otson *et al.*, 1992); data from a smaller, less representative survey (Chan *et al.*, 1990) not incorporated.
- i. Based on mean concentrations of dichloromethane in drinking water in Canada, ranging from 0.2 $\mu\text{g}/\text{litre}$ in New Brunswick and Nova Scotia to 2.6 $\mu\text{g}/\text{litre}$ in New Brunswick (Environment Canada, 1989a, 1989b, 1989c).
- j. Based on levels of dichloromethane of 84 $\mu\text{g}/\text{kg}$ in butter; 27 $\mu\text{g}/\text{kg}$ in margarine, 71 $\mu\text{g}/\text{kg}$ in cheddar cheese (not specified if processed), 45 $\mu\text{g}/\text{kg}$ in cheese, 95 $\mu\text{g}/\text{kg}$ in ready-to-eat cereals (corn cereal intake used for exposure assessment), 19 $\mu\text{g}/\text{kg}$ in peanut butter, 34 $\mu\text{g}/\text{kg}$ in processed foods (intake for canned luncheon meats used for exposure assessment), 4.6 $\mu\text{g}/\text{kg}$ in coffee (mean of 3 concentrations reported), 1.6 $\mu\text{g}/\text{kg}$ in chocolate chip cookies, and 5 $\mu\text{g}/\text{kg}$ in fried breaded shrimp (Heikes, 1990); concentrations in other foodstuffs assumed to be 0. Available data are insufficient to serve as a basis for calculation of intakes from mothers' milk and it was assumed, therefore, that infants consume prepared foodstuffs. Mean consumption of individual foodstuffs by Canadians described in EHD (1992).

There are 2 adequate studies in which dichloromethane was administered in drinking water to B6C3F₁ mice (Serota *et al.*, 1986a) and F344 rats (Serota *et al.*, 1986b) at concentrations equivalent to doses of up to 250 mg/kg bw/day for 2 years. In male mice, there was a borderline increase in hepatic carcinomas. The incidence of liver tumours was increased in female rats, although it was noted that the incidence in concurrent controls was unusually low, and there was no clear dose-response relationship.

In the most extensive bioassays in experimental animals exposed to dichloromethane conducted to date, therefore, there have been increases in the incidence of benign and malignant tumours in the lungs of both male and female mice, benign (females only) and malignant tumours in the liver (both male and female) of mice, and benign mammary tumours in male and female rats. There has also been a borderline increase in malignant liver tumours in female rats. Dichloromethane has been mutagenic *in vitro* and genotoxic in some studies *in vivo*. Therefore, dichloromethane has been classified in Group II ("Probably Carcinogenic to Humans") of the classification scheme for this end-point developed for the "Determination of 'Toxic' under paragraph 11(c) of the *Canadian Environmental Protection Act*" (EHD, 1992). It is recognized, however, 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.

For substances classified in Group II, to characterize risk and provide guidance in establishing priorities for further action under the Act (i.e., analysis of options to control exposure), wherever possible, the estimated daily total intake by the general population or concentrations in relevant environmental media in Canada are compared to quantitative estimates of the carcinogenic potency (referred to as the Exposure/ Potency Index or EPI). Potency is expressed as the concentration or dose that induces a 5% increase in the incidence of tumours considered to be associated with exposure (TD_{0.05}). For dichloromethane, the TD_{0.05}s have been determined by multi-stage modelling of the incidence of pulmonary adenomas and carcinomas (combined) and hepatic adenomas and carcinomas (combined) in male and female mice in the most extensive bioassay conducted to date by inhalation (NTP, 1986), the route by which the general population is principally exposed. The resulting values for the TD_{0.05}s range from 94 ppm (326 mg/m³) for adenomas and carcinomas (combined) of the lung in females to 1 030 ppm (3 574 mg/m³) for adenomas and carcinomas (combined) of the liver in males³.

3. Since available data indicate that dichloromethane is not a direct-acting carcinogen, a surface area: body weight correction has not been incorporated.

Wherever possible and considered appropriate, information on pharmacokinetics, metabolism, and mechanisms of carcinogenicity is incorporated into the quantitative estimates of potency derived from studies in animals to provide relevant scaling of potency for human populations. As indicated by the results of available bioassays, there are clear species differences in the carcinogenicity of dichloromethane with increases in benign and malignant tumours of the liver and lung being observed in mice, benign tumours of the mammary gland in rats, and no increase in tumours in hamsters exposed to concentrations of 2 000 to 4 000 ppm (6 940 to 13 880 mg/m³) dichloromethane. Moreover; consistent with the species differences in carcinogenicity, short-term exposure of rats and mice to dichloromethane caused a degenerative lesion in the Clara cells (the main cytochrome P-450-containing cells) in the lungs but no morphological effects in the liver of mice; there were no effects in the liver and lungs of rats following similar exposure (Green, 1989). It was further determined that the damaged Clara cells no longer contained cytochrome P-450 iso-enzymes but that glutathione-S-transferases were not affected. DNA-protein cross-links have been detected in the livers but not in the lungs of mice exposed by inhalation to dichloromethane, although the latter observation may have been attributable to lack of separation of the Clara cells from the remaining cells in the lung.

Results of available *in vitro* and *in vivo* studies are consistent with the hypothesis that variations in the carcinogenic potential of dichloromethane in different species and at different doses are related principally to differences in the rates and proportion of metabolism by 1 of 2 identified pathways of metabolism, namely the GST pathway. Rates of metabolism by the other pathway (MFO), namely oxidation by cytochrome P-450, appear to be similar in rats, mice, hamsters, and humans. In contrast, the rates of glutathione conjugation in both the liver and lungs of mice are high in comparison with rats, hamsters, and humans. Glutathione conjugation appears to be an important pathway in mice at high-dose levels, when the oxidative pathway is saturated. (The cytochrome P-450 pathway appears to be saturable *in vivo* at relatively low levels of exposure [< 500 ppm; 1 735 mg/m³] in both rats and mice.)

It should be noted, however, that some of the available data appear to be inconsistent with the hypothesis that variations in the carcinogenic potential of dichloromethane in different species are related principally to differences in the rates of metabolism by the GST pathway. For example, dichloromethane has been mutagenic in *S. typhimurium* and other organisms exposed *in vitro* to dichloromethane in the absence of metabolic activation (e.g., Dillon, 1990; Zeiger; 1990), although it is possible that the GST pathway may have been present in the exposed organisms. In addition, species differences in the genotoxicity of dichloromethane are not entirely consistent with those observed in the available bioassays for carcinogenesis. (For example, increases in sister chromatid exchanges have been observed by some investigators in Chinese Hamster Ovary cells exposed to dichloromethane *in vitro* [Jongen et al., 1981; Thilager and Kumaroo, 1983].)

It should also be noted that, although activity of the GST pathway correlates well with the observed carcinogenicity across the few species examined, it does not preclude the possibility of the contribution of other metabolites (e.g., formyl chloride) to carcinogenicity.

Since the majority of the available data is consistent with the hypothesis that interspecies variations in carcinogenicity are attributable to variations in rates of metabolism by the GST pathway, "PBPK modified $TD_{0.05S}$ " have been developed, taking into account interspecies variations in the rates of metabolism, by PBPK modelling of the delivered dose for the putatively carcinogenic pathway (GST) [Andersen *et al.*, 1987]⁴. It should be noted, however; that the results of such modelling can vary considerably, depending upon the estimates for physiological parameters incorporated. Kinetic and metabolic constants used in the modelling were determined in *in vivo* studies in a range of species, including a small number of human volunteers exposed to several different dose levels of dichloromethane, and in *in vitro* studies of the tissues of several experimental animal species and humans (Reitz *et al.*, 1988, 1989; Andersen *et al.*, 1987, 1991). (It should be noted, however, that although the V_{max} and K_m for the MFO pathway in humans are based on the studies in human volunteers, the KF (first-order rate constant for metabolism of dichloromethane by GST in liver) for the GST pathway is based on scaling of the KF value determined *in vivo* in mice by the "velocity substrate ratio" observed *in vitro* in mouse versus human liver tissue.) [A more detailed discussion is presented in an Appendix to the Supporting Documentation.]

The "PBPK modified $TD_{0.05S}$ " were then determined by multi-stage modelling of the incidence of pulmonary adenomas and carcinomas (combined) and hepatic adenomas and carcinomas (combined) in male and female mice in the NTP bioassay versus amortized delivered dose by the GST pathway. The resulting values of the "PBPK modified $TD_{0.05S}$ " range from 645 ppm (2 238 mg/m^3) for adenomas and carcinomas (combined) of the lung in females to 4 106 ppm (14 248 mg/m^3) for adenomas and carcinomas (combined) of the liver in males. These values are 4 to 7 times greater than those estimated on the basis of direct modelling of the relationship between administered doses and tumour incidence and within the same range as those estimated on the basis of direct modelling of the increase in benign mammary tumours observed in male and female rats in the NTP (1986) bioassay and in female rats by Nitschke *et al.* (1988a).

4. Although a PBPK model that also incorporates internal exposure to CO in the liver based on data in rats was presented by Andersen *et al.* (1991), it has not been used in this assessment, owing to the need for estimation of internal doses for both the liver and lungs of mice.

By far, the principal route of exposure of the general population in Canada to dichloromethane is inhalation, constituting between 97.4 and 98.7% of the total estimated intake for various age groups. Based on the incidence of tumours in mice in the NTP (1986) bioassay versus delivered dose determined by the PBPK model of Andersen *et al.* (1987), the exposure/carcinogenic potency indices range from 0.1×10^{-6} to 7.2×10^{-6} , assuming that 1 ppm is equal to 3.47 mg/m^3 dichloromethane and that the general population is exposed to a mean concentration of $2.6 \text{ }\mu\text{g/m}^3$ in ambient air and $16.3 \text{ }\mu\text{g/m}^3$ in indoor air. Based on these EPIs, the priority for further action (i.e., analysis of options to reduce exposure) is considered to be low to moderate.

Since dichloromethane has been classified as being "probably carcinogenic to humans", it has been concluded that this substance may enter the environment in quantities or under conditions that may constitute a danger in Canada to human life or health.

This approach is consistent with the objective that exposure to non-threshold toxicants should be reduced wherever possible and obviates the need to establish an arbitrary "de minimis" level of risk for determination of "toxic under CEPA.

4.0 Recommendations

In assessing the entry, exposure and effects of dichloromethane on human health and the environment, several data gaps have been identified. It is thus recommended that additional data be obtained in the following areas:

- (i) the levels, frequency of occurrence, and the potential for dichloromethane to migrate into ecosystem compartments from landfill and waste-disposal sites (high priority);
- (ii) the ambient levels of dichloromethane in soil, sediment, and biota in the Canadian environment (moderate priority);
- (iii) the effects of dichloromethane in soil and sediment on organisms within these media (moderate priority);
- (iv) the levels of dichloromethane in groundwater and the effects of dichloromethane to groundwater biota (moderate priority);
- (v) confirmation by other investigators of the rate constants for pathways of metabolism of dichloromethane in various species (high priority);
- (vi) information on the mechanisms of induction of the tumours in rodents exposed to dichloromethane, and their relevance to humans (high priority).

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