Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Bis(Chloromethyl) Ether and Chloromethyl Methyl Ether

Government of Canada | Gouvernement du Canada
Environment Canada | Environnement Canada
Health Canada | Santé Canada

Canada

CANADA'S GREEN PLAN

Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Bis(CHLOROMETHYL) ETHER AND CHLOROMETHYL METHYL ETHER

Government of Canada
Environment Canada
Health and Welfare Canada

Also available in French under the title:
Loi canadienne sur la protection de l'environnement
Liste des substances d'intérêt prioritaire
Rapport d'évaluation
Oxybis(chlorométhane) et
oxyde de chlorométhyle et de méthyle

CANADIAN CATALOGUING IN PUBLICATION DATA

Main entry under title:

Bis(chloromethyl) ether and chloromethyl methyl ether

(Priority substances list assessment report)
Issued also in French under title: Oxybis (chlorométhane) et oxyde chlorométhyle et de méthy1e.
At head of title: Canadian Environmental Protection Act.
Includes bibliographical references.
ISBN 0-662-20377-1
DSS cat. no. En40-215/8E

1. Chloromethyl group -- Toxicity testing. 2. Methyl ether -- Toxicity testing. 3. Environmental monitoring – Canada. I. Canada. Environment Canada. II. Canada. Health and Welfare Canada. III. Series.

TD196.C5B5 1993 363.73’84 C93-099468-X

Catalogue No. En 40-215/8E
ISBN 0-662-20377-1
BEAUREGARD PRINTERS LIMITED

TABLE OF CONTENTS

Synopsis

Data gathered under the authority of Section 16 of CEPA indicate that bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are not currently used or produced in Canada. If these substances were to enter the environment, they would both be rapidly broken down by hydrolysis and photo-oxidation. Data were not found concerning concentrations of BCME and CMME in the ambient environment in Canada.

Based on the fate of these substances in the environment and the lack of exposure, there is no reason to suspect that adverse effects on aquatic and terrestrial organisms would occur. For the same reason, these substances are not considered to be associated with depletion of stratospheric ozone or with global warming, and are not expected to contribute significantly to ground level ozone formation.

Bis(chloromethyl) ether and technical grade CMME [which contains bis(chloromethyl) ether] have been demonstrated to cause cancer in experimental animals and in humans. These substances are, therefore, considered to be "non-threshold toxicants" (substances for which there is believed to be some chance of adverse health effects at any level of exposure). For such substances, where data permit, estimated exposure is compared to quantitative estimates of cancer potency to characterize risk and provide guidance in establishing priorities for further action under CEPA. For BCME and CMME, such values would be expected to be extremely low owing to the lack of exposure in the general environment.

Based on these considerations, the federal Minister of the Environment and the federal Minister of National Health and Welfare have concluded that the substances BCME and CMME are not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment or to the environment on which human life depends. However, if these non-threshold toxicants were to enter the Canadian environment (as a consequence of their commercial use), they may constitute a danger in Canada to human life and health. Therefore, BCME and CMME are considered to be "toxic" as defined under Paragraph 11(c) of the *Canadian Environmental Protection Act.*

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the federal Minister of the Environment and the federal Minister of National Health and Welfare 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 requires both Ministers to assess these substances and determine whether they are "toxic" as defined under 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 that are assessed as "toxic" according to Section 11 may be placed on Schedule I of the Act. Consideration can then be given to possible development of regulations, guidelines, or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are "toxic", as defined in CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota to levels that could cause harmful **effects**. Both BCME and CMME are considered in this report since technical grade CMME contains small amounts (1 to 8%) of BCME (Travenius, 1982; ATSDR, 1989). Unless otherwise noted in this Assessment Report, "CMME" refers to technical grade CMME which contains small amounts of BCME as a contaminant.

Data relevant to the assessment of whether either BCME or CMME are "toxic" under CEPA were identified through evaluation of existing review documents (ASTDR, 1989; Durkin *et al.*, 1975; U.S. EPA, 1980; 1987; and 1991) supplemented with information from published reference texts and literature identified through on-line searches of databases conducted between April and November, 1991 These databases included: AQUIRE, AQUALINE, AQUAREF, BIOSIS Previews, CAS ONLINE, CAB, CCINFO, Chemical Evaluation Search and Retrieval System (CESARS), Cooperative Documents Project (CODOC), Chemical Hazard Response Information System (CHRIS), DOBIS, Environment Canada Departmental Library Catalogue (ELIAS), ENVIROLINE, Federal Register, Hazardous Substances Data Bank (HSDB), Integrated Risk Information System (IRIS) (U.S. EPA, 1991), MEDLINE, MICROLOG, Pollution

Abstracts, Registry of Toxic Effects of Chemical Substances (RTECS), TOXLINE, TOXLIT, and TRI (TOXNET). Reviews of the environmental fate and effects, and effects on human health of these substances were prepared under contract by Monenco Consultants Ltd., and Cambridge Environmental Inc. (Croy and DeVoto, 1991), respectively. In addition, a number of officials within federal and provincial governments were asked to provide any available (unpublished) monitoring data on the levels of these substances in the Canadian environment, including drinking water. Data relevant to the assessment of the effects of BCME and CMME on the environment and human health obtained after June 1992 were not considered for inclusion.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether BCME and CMME are "toxic" under CEPA have been critically evaluated by the following Environment Canada staff (entry, and environmental exposure and effects) and Health and Welfare Canada staff (human exposure and effects on human health):

Environment Canada	Health and Welfare Canada
D. Boersma	S. Basavaraj
C. Fortin	I. Caldwell
S. Walker	R.G. Liteplo
	M.E. Meek

In this report, a synopsis concerning BCME or CMME that will appear in the *Canada Gazette* is presented. Section 2.0 is an extended summary of the technical information that is critical to the assessment. The assessment of whether BCME or CMME are "toxic" is presented in Section 3.0. A Supporting Document that presents the technical information in greater detail has also been prepared.

As part of the review and approvals process established by Environment Canada, the environmental sections of this Assessment Report were peer reviewed by the following scientists: Dr. Derek Muir (Fisheries and Oceans Canada, Winnipeg, Manitoba) and Dr. Keith Solomon (Centre for Toxicology, Guelph, Ontario). Sections related to the assessment of effects on human health were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada. The entire Assessment Report was reviewed and approved by the Environment Canada/Health and Welfare Canada CEPA Management Committee.

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

Commercial Chemicals Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec
K1A 0H3

Environmental Health Centre
Room 104
Health and Welfare Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Bis(Chloromethyl) Ether - Bis(chloromethyl) ether (BCME) is an a-chloroalkyl ether with the Chemical Abstracts Service (CAS) registry number 542-88-1; the molecular formula $C_2H_4C1_20$; and the structural formula $ClCH_2OCH_2Cl$ (Sittig, 1981; U.S.EPA, 1980). Synonyms for BCME include: chloro(chloromethoxy) methane, sym-dichloro-dimethyl ether, dimethyl-1, 1'-dichloroether, oxybis(chloromethane), dichloromethyl ether, and bichloromethyl ether (Sax, 1984; Verschueren, 1983).

Bis(chloromethyl) ether is a colourless, volatile liquid with a "suffocating" odour (Sittig, 1981; Verschueren, 1983). No experimental values for the vapour pressure of BCME were found in the literature. There are no experimental values for water solubility and Henry's Law Constant for BCME, as this substance hydrolyses very rapidly in water (see Subsection 2.3.1). This substance is miscible with most organic solvents (Weast, 1984). Analytical methods used to quantify BCME involve gas chromatography/mass spectrometry or gas chromatography with electron capture detection (Collier, 1972; Evans *et al.,* 1975; Frankel and Black, 1976).

Chloromethyl Methyl Ether - Chloromethyl methyl ether (CMME) is an a-chloroalkyl ether with the CAS registry number 107-30-2; the molecular formula C_2H_5ClO; and the structural formula CH_3OCH_2C1 (Sittig, 1981; U.S. EPA, 1980). Synonyms for CMME include: chloromethoxymethane, dimethylchloro ether, monochlorodimethyl ether, and methoxymethyl chloride (Sax, 1984; Verschueren, 1983; Sittig, 1981). Technical grade CMME contains from 1 to 8% BCME (Travenius, 1982). Available data for CMME permit evaluation only of the technical grade material (referred to as "CMME", unless otherwise specified).

Chloromethyl methyl ether is a colourless liquid with an "irritating" odour (Verschueren, 1983). No experimental values for the vapour pressure of CMME were found in the literature. There are no experimental values for water solubility and Henry's Law Constant for CMME as this substance is hydrolyzed very rapidly in water (Radding *et al.,* 1977; Verschueren, 1983). This substance is soluble in most organic solvents (Weast, 1984). Analytical methods used to quantify CMME include gas chromatography with electron-capture detection (Kallos *et al.,* 1977; Langhorst *et al.,* 1981; Sittig, 1981).

Information provided in response to a Notice published under Section 16(1) of CEPA indicated that there was no commercial activity involving more than one kilogram of either BCME or CMME in Canada during 1990 or 1991 (Environment Canada, 1992). However, each of these compounds was reported to be used in Canada between 1984 and 1986 (Canada Gazette, 1991).

Since the early 1980s, industrial use of both BCME and CMME in the United States has been restricted to specific intermediate chemical reactions (Travenius, 1982).

2.2 Entry into the Environment

Neither BCME or CMME occurs naturally in the environment. However, BCME can be formed as a by-product when formaldehyde reacts with chloride ions in an acidic medium (Travenius, 1982). Moderate to high concentrations (mg/L or mg/m^3) of the reactants are required to produce low concentrations (µg/L) of BCME (Tou and Kallos, 1974; Travenius, 1982; Kallos and Tou, 1977).

Information showing that CMME may be formed as a by-product during the production of other industrial chemicals was not found.

It was reported in the Toxic Release Inventory (U.S. EPA, 1990) that less than 1 kg of BCME and 50 kg of CMME were released to the atmosphere in the United States from industrial producers and users during 1989. No releases were reported in other media (water, soil, underground injection).

2.3 Exposure-related Information

2.3.1 *Fate*

Bis(chloromethyl) ether and CMME hydrolysis rapidly in water. At 20°C, half-lives in water of 38 seconds for BCME and <1 second for CMME have been reported (U.S. EPA, 1980; Tou *et al.*, 1974; Radding *et al.*, 1977). Although BCME may be degraded by oxidation, the extremely rapid hydrolysis of BCME in an aqueous medium precludes any oxidative degradation of this substance from taking place in aquatic systems (Callahan *et al.*, 1979). Bis(chloromethyl) ether is hydrolyzed to formaldehyde and hydrogen chloride (ASTDR, 1989). Chloromethyl methyl ether is hydrolyzed to hydrogen chloride, methanol, and formaldehyde (Travenius, 1982).

Owing to their rapid hydrolysis in an aqueous medium, the volatilization of BCME and CMME from surface water is likely to be insignificant. Callahan *et al.* (1979) suggested that BCME could volatilize rapidly from an aquatic system only if it were discharged in a water-immiscible solvent that had a high vapour pressure. Once in the atmosphere, these substances would be degraded by photo-oxidation or hydrolysis. Cupitt (1980) reported atmospheric half-lives of <2.9 days for BCME and <3.9 days for CMME. Tou and Kallos (1974) reported half-lives for atmospheric hydrolysis as >1 day for BCME and between 0.0024 (Nichols and Merritt, 1973) and 0.27 days for CMME, in humid air. At low humidity levels, however, BCME may be degraded by oxidative as well as hydrolytic pathways (Callahan *et al.*, 1979).

In air, the decomposition products for BCME include hydrogen chloride, formaldehyde, and chloromethylformate, while those for CMME include chloromethyl and methyl formate (Cupitt, 1980).

Very little information was found concerning the behaviour of BCME or CMME in soil. For BCME, Mabey *et al.* (1982) calculated a log organic carbon partition coefficient (log $K_{??}$) of 1.2. On the basis of this value, BCME appears to have minimal

potential to adsorb to soil. However, it is also unlikely that BCME and CMME are mobile in soil as both compounds are hydrolyzed rapidly in an aqueous environment. No information on the biodegradation of either BCME or CMME in soil was identified.

The high rates of hydrolysis preclude any possibility of BCME or CMME bioaccumulating in organisms.

2.3.2 *Concentrations*

No data on levels of BCME or CMME in the ambient Canadian environment or in industrial effluents were identified.

2.4 Effects-related Information

2.4.1 *Experimental Animals and* In Vitro

Bis(chloromethyl) ether and CMME are acutely toxic following inhalation, oral, or dermal exposure. The LC_{50} for the exposure (by inhalation) of experimental animals to BCME ranges from 5.3 ppm (25 mg/m^3) to 10.3 ppm (48 mg/m^3) (Drew *et al.*, 1975; Union Carbide, 1968; Leong *et al.*, 1971). The LD_{50} for the oral administration of BCME to rats was 0.21 mL/kg body weight (b.w.) (278 mg/kg b.w.) (Union Carbide, 1968). The LC_{50} for the exposure (by inhalation) of rats and hamsters to CMME was 55 ppm (182 mg/m^3) and 65 ppm (215 mg/m^3), respectively (Drew *et al.*, 1975). It should be noted that since CMME contains between 1 to 8% BCME, the toxic effects produced by CMME may be due, at least in part, to BCME.

Information is limited on the toxicological effects produced following short-term exposure of experimental animals to BCME or CMME. The repeated exposure by inhalation of male rats or hamsters to 1 ppm (4.7 mg/m^3) BCME over periods of up to 30 days, produced a marked reduction in survival, hyperplastic changes within the trachea and bronchus, and subarachnoid haemorrhage, compared to unexposed controls (Drew *et al.*, 1975). In male rats exposed (duration not specified) by inhalation to 10 ppm (33 mg/m^3) CMME, there was a reduction in survival in addition to alterations in lung/body weight ratios, and regenerative hyperplasia of the bronchial epithelium, compared to unexposed controls (Drew *et al.*, 1975).

Studies on the toxicological effects produced following long-term inhalation exposure to BCME and CMME have been restricted primarily to limited carcinogenesis bioassays in mice, rats, and hamsters. Following exposure (inhalation) of male mice to 5 mg/m^3 BCME over a period of 82 days, there was a marked reduction in survival, and increased incidence of pulmonary tumors (adenomas) compared to unexposed controls (26/47 versus 20/49, respectively). The statistical significance of this increase, however, was not specified (Leong *et al.*, 1971). The number of lung tumors per animal in the BCME-exposed mice was slightly higher than in unexposed controls (5.2 versus 2.2, respectively). In male mice exposed to 1, 10, or 100 ppb (0.0047, 0.047, or 0.47 mg/m^3) BCME over a period of 6 months, there was a reduction in survival (compared to unexposed controls), although after 6 months, a significant increase in the incidence of

pulmonary adenomas was observed only in surviving mice exposed to the highest concentration (Leong *et al.,* 1981).

In male rats exposed (by inhalation) to 1, 10, or 100 ppb (0.0047, 0.047, or 0.47 mg/m^3) BCME over a period of 6 months, there was an increase in the incidence of "tumors of the respiratory tract" at the highest concentration (102/111 in BCME-exposed group versus 0/112 in unexposed controls); 94% of which were tumors of the olfactory neural tissue (esthesioneuroepitheliomas)(Leong *et al.,* 1981). In male rats exposed to 0.1 ppm (0.47 mg/m^3) BCME for periods ranging up to 20 weeks, there was an increase in the incidence of nasal esthesioneuroepitheliomas and squamous cell carcinomas of the lung with increasing periods of exposure; the incidence of carcinomas of the lung in animals exposed over a 20-week period was 8/30. Survival was reduced by approximately 24% in animals exposed to BCME over periods of 16 and 20 weeks (Kuschner *et al.,* 1975).

In male mice exposed (by inhalation) to 2 ppm (6.6 mg/m^3) CMME over a period of 101 days, the incidence of "pulmonary tumors" was not greater than in unexposed controls, although the number of lung tumors per animal in the CMME-exposed group was slightly higher than in the controls (3.1 versus 2.2, respectively) (Leong *et al.,* 1971). In male rats exposed to 1 ppm (3.3 mg/m^3) CMME for virtually their entire lives, the incidence of tracheal metaplasia and bronchial hyperplasia was greater than in unexposed controls; two tumors of the respiratory tract (an esthesioneuroepithelioma and lung squamous cell carcinoma) were observed in CMME-exposed animals, while none was reported in unexposed controls (Laskin *et al.,* 1975). In male hamsters exposed to 1 ppm (3.3 mg/m^3) CMME for virtually their entire lives, the incidence of tracheal metaplasia and bronchial hyperplasia was increased compared to unexposed controls. One lung adenocarcinoma and a tracheal squamous papilloma were observed in two animals exposed to CMME (information on tumor incidence in controls was not presented) (Laskin *et al.,* 1975*).*

The incidence of pulmonary adenomas was greater in mice observed for six months after receiving a single subcutaneous injection of 12.5 µL/kg b.w. (16.6 mg/kg b.w.) BCME, or 125 µL/kg b.w. (132.5 mg/kg b.w.) CMME than in mice that received vehicle alone. There were, however, no effects on growth or survival of the animals (Gargus *et al*., 1969). In female rats administered BCME (3 mg) or "laboratory purified" CMME (3 mg) subcutaneously once a week for approximately 300 days (though the dose and schedule of administration were modified owing to the corrosive effects of BCME around the site of injection), there was an increase in the incidence of tumors (though the statistical significance was not specified) at the site of injection for BCME but not for "laboratory purified" CMME, compared to that in the control group administered vehicle alone (van Duuren *et al.,* 1969). However, in a subsequent study (van Duuren *et al.,* 1972) in which "laboratory purified" CMME (300 µg/animal) was administered once a week to female mice for their entire lives, the number of mice with sarcomas at the site of injection was 0/30 in the (vehicle) control and 10/30 in the (laboratory-purified) CMME-exposed groups. In mice, the incidence of tumors (mainly fibrosarcomas) at the site of injection was increased following 32 subcutaneous injections of 0.3 mg BCME

compared to that in a control group administered vehicle alone (Zajdela *et al.,* 1980). The incidence of squamous cell carcinomas of the skin in female mice that received 2 mg of BCME (applied dermally) or solvent, i.e., benzene, alone (controls) three times a week for 325 days was 12/20 and 0/20, respectively. "Laboratory purified" CMME (2 mg), however, was not carcinogenic in this skin tumor bioassay. In two-stage skin tumor carcinogenesis bioassays in which several substances were examined, BCME and CMME had "weak" tumor-initiating activity (van Duuren *et al.,* 1969; Zajdela *et al.,* 1980).

The genotoxicity of BCME and CMME has been examined in a variety of limited *in vitro* bioassays (Anderson and Styles, 1978; Mukai and Hawryluk, 1973; Agrelo and Severn, 1981; Styles, 1978; Kurian *et al.,* 1990; Goldschmidt *et al.,* 1975; Shooter, 1975; Perocco *et al.,* 1983). The weight of evidence from these investigations in which a range of endpoints was examined indicates that both BCME and CMME are genotoxic. Available studies, however, are limited and generally, poorly documented.

No other relevant information was identified concerning the reproductive, developmental, immunological, or neurological toxicity of BCME or CMME in experimental animals or in humans.

2.4.2 *Humans*

In several case reports and series, the occurrence of lung cancer, several of which were small (oat) cell cancers, has been reported in workers exposed to BCME (Roe, 1985; Sakabe, 1973) or both compounds (Reznick *et al.,* 1977). In addition, there have been a number of epidemiological studies of populations occupationally exposed to BCME or CMME.

In 136 workers employed at a chemical plant in California where BCME was used in the production of ion-exchange resins (Lemen *et al.,* 1976) and in a population of 35 BCME-exposed workers employed at two dye stuff factories in Japan (Nishimura *et al.,* 1990), the standardized mortality ratios for lung cancer were 9.3 and 21, respectively. The average age of appearance of or death due to a lung cancer was 47 and 46 years, respectively, and the average latency period was 10 years and 13.5 years, respectively.

For CMME, in prospective (cohort) studies of 125 employees of a chemical plant in the United States (Weiss, 1976; 1982), 737 "exposed" and 2120 "unexposed" workers at a chemical plant in Philadelphia (Maher and DeFonso, 1987) and 2460 "exposed" and 3692 "unexposed" workers at seven industrial facilities (Collingwood *et al.,* 1987), the standardized mortality ratios for lung cancer were 20, 2.8, and 3, respectively. In the study reported by Weiss (1982), the standardized mortality ratios for deaths due to lung cancer peaked 15 to 19 years from the onset of exposure; similarly, Maher and DeFonso (1987) reported that the greatest increase in deaths due to cancer of the respiratory tract occurred approximately 10 to 20 years after first exposure.

For BCME, exposure was not assessed in any of the available epidemiological studies; however, a relationship between qualitative measures of exposure to CMME and

lung cancer was observed in the only two studies in which it was examined (Collingwood *et al.*, 1987; Maher and DeFonso, 1987).

Sram *et al.* (1983) reported that the proportion of peripheral lymphocytes with chromosomal aberrations (breaks, exchanges) isolated from 77 workers exposed to BCME and CMME was approximately twofold higher than that observed in lymphocytes isolated from 25 non-exposed controls. Except for information on whether the workers were smokers, which did not influence the results, no other relevant information was provided in this published account.

2.4.3 *Ecotoxicology*

No studies were found that investigated the toxicity of either BCME or CMME to aquatic or terrestrial organisms.

No information on the effects of BCME or CMME on the ozone layer or global warming was found. In view of their relatively short atmospheric lifetime, however, effects of these substances on the ozone layer or global warming are not anticipated.

3.0 Assessment of "Toxic" Under CEPA

3.1 CEPA 11(a) Environment

From 1990 to 1991, in Canada, there was no commercial activity involving more than one kilogram of BCME or CMME and it is highly unlikely that these compounds would be formed from other substances that may be present in the environment. Both substances are readily degraded by hydrolysis in aqueous media or by photo-oxidation in the atmosphere and, therefore, are not likely to accumulate within living organisms. No data were found concerning concentrations of these substances in the ambient environment in Canada. Because of their extremely short residence time, it is believed that levels in the environment are extremely low (if they exist at all), and there is no exposure that could potentially arise from the past use of these substances in Canada. Therefore, even though there is a complete absence of data concerning the environmental toxicity of these substances, as previously noted, there is no reason to suspect that adverse effects due to BCME or CMME could occur in organisms living in the Canadian environment.

Therefore, on the basis of available data, BCME and CMME are not considered to be "toxic" as defined under Paragraph 11(a) of the *Canadian Environmental Protection Act.*

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

The short persistence of BCME and CMME in the atmosphere and the extremely low levels of release preclude these substances from contributing to ozone layer depletion, global warming, or photochemical smog formation.

Therefore, on the basis of available data, BCME and CMME are not considered to be "toxic" as defined under Paragraph 11(b) of the *Canadian Environmental Protection Act.*

3.3 CEPA 11(c) Human Life or Health

In all of the five cohorts of exposed workers conducted to date, an association has been observed between lung cancer and exposure to either BCME (Lemen *et al.*, 1976; Nishimura *et al.*, 1990) or CMME (Weiss, 1976; Maher and DeFonso, 1987; Collingwood *et al.*, 1987). The type of lung cancer [predominantly small (oat) cell carcinomas], the standardized mortality ratios, the latency periods (10 to 24 years), and the average age of appearance of cancer (35 to 55 years) in populations exposed either to BCME or CMME have been remarkably consistent. The type and incidence of lung cancer in individuals exposed to BCME or CMME [predominantly small (oat) cell carcinomas, occurring in relatively young individuals after short latency periods] is distinct from that caused by tobacco. Tobacco is one of the potential confounders in such

studies, where lung tumors are predominantly squamous cell carcinomas, occurring after long latency periods in individuals more than 60 years of age (Weiss, 1976; Pasternack *et al.*, 1977). Moreover, in the study in which tobacco smoking was most extensively addressed, involving a population of workers exposed to CMME, the incidence of lung cancer was inversely related to the use of tobacco (Weiss, 1980). The association between exposure to either BCME or CMME and lung cancer is strong, with standardized mortality ratios ranging up to 21 (Nishimura *et al.*, 1990) and 20 (Weiss, 1982), respectively. For CMME, there is also evidence of a positive relationship between a qualitative measure of exposure and mortality due to lung cancer. In two studies on occupationally exposed individuals, the standardized mortality ratios for deaths due to lung cancer peaked 10 to 20 years from the onset of exposure (Weiss, 1982; Maher and DeFonso, 1987). Furthermore, observation of an association between occupational exposure to BCME and CMME and the development of lung cancer is plausible, based on the results of early, rather limited carcinogenesis bioassays and on available data on the genotoxicity of BCME and CMME. Increases in the incidence of tumors predominantly of the respiratory tract were observed in studies of exposed animal species.

The observed association of lung cancer [predominantly small (oat) cell carcinomas] and occupational exposure to either BCME or CMME, therefore, fulfils the traditional criteria (i.e., consistency, strength, specificity, temporal relationship, exposure-response relationship, and plausibility and supporting experimental data) for assessment of causality in epidemiological studies. Consequently, on the basis of the available data, BCME and CMME have been classified in Group I ("Carcinogenic to Humans") of the classification scheme developed for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (Health and Welfare Canada, 1989).

Owing to the lack of available information on concentrations in several environmental media to which humans are exposed, it is not possible to quantitatively estimate the total daily intake of BCME or CMME by the general population of Canada. It is also not appropriate to estimate intake on the basis of fugacity modelling, owing to the lack of commercial activity reported for these compounds. Consequently, estimates of total daily intake cannot be compared to quantitative estimates of cancer potency to characterize risk and provide guidance in establishing priorities for further action under CEPA. Such values would be expected to be extremely low owing to the lack of reported use of these compounds in Canada and their rapid degradation in the general environment.

On the basis of available data, BCME and technical grade CMME have been classified as being "Carcinogenic to Humans" and are therefore considered to be "toxic" as defined under Paragraph 11(c) of the *Canadian Environmental Protection Act*.

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.

3.4 Conclusion

On the basis of available data, neither BCME or CMME are considered to be "toxic" as defined under Paragraphs 11(a) and 11(b) of the *Canadian Environmental Protection Act* but both are considered to be "toxic" as defined under Paragraph 11(c) of the *Canadian Environmental Protection Act.*

4.0 References

Agrelo, C.E. and B.J. Severn, "A Simplified Method for Measuring Scheduled and Unscheduled DNA Synthesis in Human Fibroblasts", *Toxicol., 21:* 151-158 (1981).

Anderson, D. and J.A. Styles, "The Bacterial Mutation Test", *Br. J. Cancer., 37:* 924-930 (1978).

ATSDR (Agency for Toxic Substances and Disease Registry), "Toxicological Profile for Bis(Chloromethyl) Ether", U.S. Public Health Service, 65 pp. (PB90-168691) (1989).

Callahan, M.A., M.W. Slimak, N.W. Gabel, I.P. May, C.F. Fowler, J.R. Freed, P. Jennings, R.L. Durfee, F.C. Whitmore, B. Maestri, W.R. Mabey, B.R. Holt, and C. Gould, "Water-related Environmental Fate of 129 Priority Pollutants, Volume II: Halogenated Aliphatic Hydrocarbons, Halogenated Ethers, Monocyclic Aromatics, Phthalate Esters, Polycyclic Aromatic Hydrocarbons, Nitrosamines, and Miscellaneous Compounds", Office of Water Planning and Standards, Office of Water and Waste Management, U.S. Environmental Protection Agency, Washington, D.C., EPA-440/4-79-029b, NTIS No. PB80-204381, 673 pp. (1979).

Canada Gazette, "CEPA Domestic Substances List", Department of the Environment, Supplement, Canada Gazette, Part I, (January 26, 1991).

Collier, L., "Determination of bis-Chloromethyl Ether at the ppb Level in Air Samples by High-resolution Mass Spectroscopy", *Environ. Sci. Technol.,* 6(10): 930-932 (1972).

Collingwood, K.W., B.S. Pasternack, and R.E. Shore, "An Industry-wide Survey of Respiratory Cancer in Chemical Workers Exposed to Chloromethyl Ethers", *J. Natl. Cancer Inst., 78: 1127-1136(1987).*

Croy, R.G. and E. DeVoto, "Bis(Chioromethyl) Ether and Chloromethyl(Methyl) Ether: A Review of Environmental Behavior and Health Effects", prepared for Priority Substances Section, Health Protection Branch, Department of National Health and Welfare, Ottawa (1991).

Cupitt, L.T., "Fate of Toxic and Hazardous Materials in the Air Environment. Atmospheric Chemistry and Physics Lab", U.S. Environmental Protection Agency, Research Triangle Park, NC, EPA-600/3-80-084, NTIS No. PB80-221948, 35 pp. (1980).

Drew, R.T., S. Laskin, M. Kuschner, and N. Nelson, "Inhalation Carcinogenicity of Halo Ethers I. The Acute Inhalation Toxicity of Chloromethyl Methyl Ether and bis(Chloromethyl) Ether", *Arch. Environ. Health., 30:* 61-69 (1975).

Durkin, P.R., P.H. Howard, and J. Saxena, "Investigation of Selected Potential Environmental Contaminants. Haloethers", Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C., EPA 68-1-2996, NTIS No. PB-246356, 178 pp. (1975).

Environment Canada, "Results of the Chloroalkyl Ethers Notice", Use Patterns Section, Commercial Chemicals Branch (1992).

Evans, K.P., A. Mathias, N. Mellor, R. Silvester, and A.E. Williams, "Detection and Estimation of bis(Chloromethyl) Ether in Air by Gas Chromatography-High Resolution Mass Spectrometry", *Anal. Chem., 47(6):* 821-824 (1975).

Frankel, L.S. and R.F. Black, "Automatic Gas Chromatographic Monitor for the Determination of Parts-per-billion Levels of bis(Chloromethyl) Ether", *Anal. Chem., 48(4):* 732-737 (1976).

Gargus, J.L., W.H. Reese, and H.A. Rutter, "Induction of Lung Adenomas in Newborn Mice by bis(Chloromethyl) Ether", *Toxicol. Appl. Pharmacol., 15:* 92-96 (1969).

Goldschmidt, B.M., B.L. van Duuren, and K. Frenkel, "The Reaction of ^{14}C-labelled bis(Chloromethyl) Ether with DNA", *Proc. Am. Assoc. Cancer Res., 16:* 66 (1975).

Health and Welfare Canada, "Derivation of Maximum Acceptable Concentrations and Aesthetic Objectives for Chemicals in Drinking Water", In: *Guidelines for Canadian Drinking Water Quality - Supporting Documentation,* Environmental Health Directorate, Bureau of Chemical Hazards (1989).

Kallos, G.J. and J.C. Tou, "Study of Photolytic Oxidation and Chlorination Reactions of Dimethyl Ether and Chlorine in Ambient Air", *Environ. Sci. Technol., 11*(12): 1101-1105(1977).

Kallos, G.J., W.R. Albe, and R.A. Solomon, "On-column Reaction Gas Chromatography for Determination of Chloro-methyl Methyl Ether at One Part-per-billion Level in Ambient Air", *Anal. Chem., 49*(2): 1817-1820 (1977).

Kurian, P., S. Nesnow, and G.E. Milo, "Quantitative Evaluation of the Effects of Human Carcinogens and Related Chemicals on Human Foreskin Fibroblasts", *Cell Biol. Toxicol., 6:* 171-184 (1990).

Kuschner, M., S. Laskin, R.T. Drew, V. Cappiello, and N. Nelson, "Inhalation Carcinogenicity of Alpha Haloethers III. Lifetime and Limited Period Inhalation Studies with bis(Chloromethyl) Ether at 0.1 ppm", *Arch. Environ. Health., 30:* 73-77 (1975).

Langhorst, M.L., R.G. Meicher, G.J. Kallos, "Reactive Adsorbent Derivative Collection and Gas Chromatographic Determination of Chloromethyl Methyl Ether in Air", *Am. Ind. Hyg. Assoc. J., 42*(1): 47-55 (1981).

Laskin, S., R.T. Drew, V. Cappiello, M. Kuschner, and N. Nelson, "Inhalation Carcinogenicity of Alpha Halo Ethers II. Chronic Inhalation Studies with Chloro Methyl Methyl Ether", *Arch. Environ. Health., 30:* 70-73 (1975).

Lemen, R.A., W.J. Johnson, J.K. Wagoner, V.E. Archer, and G. Saccomanno, "Cytologic Observation and Cancer Incidence Following Exposure to BCME", *Ann. N.Y. Acad. Sci., 271:* 71-80(1976).

Leong, B.K.J., H.N. MacFarland, and W.H. Reese, "Induction of Lung Adenomas by Chronic Inhalation of bis(Chloromethyl) Ether", *Arch. Environ. Health., 22:* 663-666 (1971).

Leong, B.K.J., R.J. Kociba, and G.C. Jersey, "A Lifetime Study of Rats and Mice Exposed to Vapors of bis(Chloromethyl) Ether", *Toxicol. Appl. Pharmacol., 58:* 269-281(1981).

Mabey, W.R., J.H. Smith, R.T. Podoll, H.L. Johnson, T. Mill, T.W. Chou, J. Gates, I.W. Partridge, H. Jaber, and D. Vandenberg, "Aquatic Fate Processes Data for Organic Priority Pollutants", Monitoring and Data Support Division (WH 553), Office of Water Regulations and Standards, U.S. Environmental Protection Agency, Washington, D.C., EPA 440/4-81-014, 407 pp. (1982).

Maher, K.V. and L.R. DeFonso, "Respiratory Cancer Among Chloromethylether Workers", J. *Natl. Cancer Inst., 78:* 839-843 (1987).

Mukai, F.H. and I. Hawryluk, "Mutagenicity of Some Halo-ethers and Halo-ketones", *Mutat. Res., 21:* 228 (1973).

Nichols, R.W. and R.F. Merritt, "Brief Communication: Relative Solvolytic Reactivities of Chloromethyl Ether and bis(Chloromethyl) Ether", *J. Nat. Cancer Inst., 50:* 1373-1374 (1973).

Nishimura, K., K. Miyashita, Y. Yoshida, M. Kuroda, M. Matsumoto, K. Matsumoto, S. Takeda, and I. Hara, "An Epidemiological Study of Lung Cancer Among Workers Exposed to bis(Chloromethyl) Ether", *Jpn. J. Ind. Health., 32:* 448-453 (1990).

Pasternack, B.S., R.E. Shore, and R.E. Albert, "Occupational Exposure to Chloromethylethers", *J. Occup. Med., 19:* 741-746 (1977).

Perocco, P., S. Bolognesi, and W. Alberghini, "Toxic Activity of 17 Industrial Compounds on Human Lymphocytes Cultured *in vitro", Toxicol. Lett., 16:* 69-76 (1983).

Radding, S.B., B.R. Holt, J.L. Jones, D.H. Liu, T. Mill, and D.G. Hendry, "Review of the Environmental Fate of Selected Chemicals", Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C., EPA 560/5-77/003, 147 pp. (1977).

Reznick, G., W.W. Wagner, and Z. Atay, "Lung Cancer Following Exposure to bis(Chloromethyl) Ether: A Case Report", *J. Environ. Pathol. Toxicol., 1:* 105-111 (1977).

Roe, F.J.C., "Chloromethylation: Three Lung Cancer Deaths in Young Men", *The Lancet., 2:* 268 (1985).

Sakabe, H., "Lung Cancer Due to Exposure to bis(Chloromethyl) Ether", *Ind. Health., 11:* 145-148 (1973).

Sax, N.I., *Dangerous Properties of Industrial Materials,* 6th Edition, Van Norstrand Reinhold Co., Toronto, Ont., 3124 pp. (1984).

Shooter, K.V., "Assays for Phosphotriester Formation in the Reaction of Bacteriophage R17 with a Group of Alkylating Agents", *Chem.-Biol. Interactions., 11:* 575-588 (1975).

Sittig, M., *Handbook of Toxic and Hazardous Chemicals,* Noyes Publications, Park Ridge, NJ, 729 pp. (1981).

Sram, R.J., I. Samkova, and N. Hola, "High-dose Ascorbic Acid Prophylaxis in Workers Occupationally Exposed to Halogenated Ethers", *J. Hyg. Epidemiol. Microbiol. Immunol.,27:* 305-318(1983).

Styles, J.A., "Mammalian Cell Transformation *in vitro", Br. J. Cancer., 37:* 931-936 (1978).

Tou, J.C. and G. J. Kallos, "Kinetic Study of the Stabilities of Chloromethyl Methyl Ether and bis(Chloro-methyl) Ether in Humid Air", *Anal. Chem., 46(12):* 1866-1869 (1974).

Tou, J.C., L.B. Westover, and L.F. Sonnabend, "Kinetic Studies of bis(Chloromethyl) Ether Hydrolysis by Mass Spectrometry", *J. Phys. Chem., 78*(11): 1096-1098 (1974).

Travenius, S.Z.M., "Formation and Occurrence of bis(Chloromethyl) Ether and its Prevention in the Chemical Industry", *Scand. J. Work Environ. Health, 8(Suppl. 3):* 1-86 (1982).

Union Carbide, "Summary of Acute Toxicity and Irritancy Studies of bis(Chloromethyl) Ether", Union Carbide Corp., Danbury, CT, Report 31-85, 5 pp. (1968).

U.S. EPA (Environmental Protection Agency), *Ambient Water Quality Criteria for Chloroalkyl Ethers,* Environmental Criteria and Assessment Office, Office of Water Regulations and Standards, Criteria and Standards Division, Washington, D.C., EPA-440/5-80-030, NTIS No. PB81-117418, 98 pp. (1980).

U.S. EPA (Environmental Protection Agency), *Health and Environmental Effects Document for Haloethers,* Environmental Criteria and Assessment Office, ECAO-CIN-GO14 (1987).

U.S. EPA (Environmental Protection Agency), *Toxic Chemical Release Inventory Data Base for 1989,* National Library of Medicine and the U.S. Environmental Protection Agency, Washington, D.C. (1990).

U.S. EPA (Environmental Protection Agency), *Integrated Risk Information System (IRIS),* "Data Summary for bis(Chloromethyl) Ether and Chloromethyl(Methyl) Ether" (1991).

van Duuren, B.L., A. Sivak, B.M. Goldschmidt, C. Katz, and S. Melchionne, "Carcinogenicity of Halo-ethers", *J. Natl.. Cancer Inst., 43:* 481-486 (1969).

van Duuren, B.L., C. Katz, B.M. Goldschmidt, K. Frenkel, and A. Sivak, "Carcinogenicity of Haloethers. II. Structure-activity Relationships of Analogues of bis(Chloromethyl) Ether", *J. Natl. Cancer Inst.,* 48:1431-1439 (1972).

Verschueren, K., *Handbook of Environmental Data on Organic Chemicals,* 2nd Edition, Van Nostrand Reinhold Co., Toronto, Ont. 1310 pp., (1983).

Weast, R.C., *CRC Handbook of Chemistry and Physics,* 65th Edition, CRC Press Inc., Boca Raton, FL, 2290 pp. (1984).

Weiss, W., "Chloromethyl Ethers, Cigarettes, Cough and Cancer", *J. Occup. Med., 18:* 194-199 (1976).

Weiss, W., "The Cigarette Factor in Lung Cancer due to Chloromethyl Ethers", *J. Occup. Med., 22:* 527-529 (1980).

Weiss, W., "Epidemic Curve of Respiratory Cancer due to Chloromethyl Ethers", *J. Natl. Cancer Inst., 69:* 1265-1270(1982).

Zajdela, F., A. Croisy, A. Barbin, C. Malaveille, L. Tomatis, and H. Bartsch, "Carcinogenicity of Chloroethylene Oxide, an Ultimate Reactive Metabolite of Vinyl Chloride, and bis(Chloromethyl) Ether after Subcutaneous Administration and in Initiation Promotion Experiments in Mice", *Cancer Res., 40:* 352-356 (1980).