

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert
opinions of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
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IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

BIS(CHLOROMETHYL) ETHER AND CHLOROMETHYL METHYL ETHER

Bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) were considered by previous IARC Working Groups in 1973 and 1987 ([IARC, 1974, 1987a](#)). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

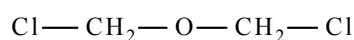
1.1.1 Bis(chloromethyl) ether

Chem. Abstr. Serv. Reg. No.: 542-88-1

Chem. Abstr. Serv. Name:

1,1'-Oxybis[1-chloromethane]

Formula: C₂H₄Cl₂O



Relative molecular mass: 115.0

Synonyms: BCME; Bis(chloromethyl) ether; chloromethyl ether (note: this name is sometimes used incorrectly for chloromethyl methyl ether)

Description: Colourless liquid, suffocating odour ([O'Neil, 2006](#))

Boiling point: 106 °C ([Lide, 2008](#))

Solubility: Miscible with ethanol and diethyl ether ([Lide, 2008](#))

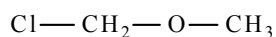
1.1.2 Chloromethyl methyl ether

Chem. Abstr. Serv. Reg. No.: 107-30-2

Chem. Abstr. Serv. Name:

Chloromethoxymethane

Formula: C₂H₅ClO



Relative molecular mass: 80.5

Synonyms: CMME; chloromethyl methyl ether; chloromethoxymethane; methyl chloromethyl ether; monochloromethyl ether; chlorodimethyl ether

Description: Colourless liquid ([O'Neil, 2006](#))

Boiling point: 59.5 °C ([Lide, 2008](#))

Solubility: Soluble in acetone, chloroform, diethyl ether, and ethanol ([Lide, 2008](#))

1.2 Uses

BCME and CMME are used primarily as chemical intermediates and alkylating agents. BCME is used as a laboratory reagent in the manufacture of plastics, ion-exchange resins, and polymers ([HSDB, 2003](#)). Historical uses of

Table 1.1 Estimated numbers of workers exposed to BCME and CMME in the European Union

Industry, occupational activity	
Manufacture of industrial chemicals	1000
Manufacture of fabricated metal products, except machinery and equipment	350
Wholesale and retail trade, and restaurants and hotels	600
Sanitary and similar services	300
TOTAL	2250

From [CAREX \(1999\)](#)

BCME include crosslinking of cellulose, preparation of styrene and other polymers, surface treatment of vulcanized rubber to increase adhesion, and manufacture of flame-retardant fabrics ([ATSDR, 1989](#)). CMME is used as an alkylating agent and industrial solvent to manufacture dodecylbenzyl chloride, water repellants, ion-exchange resins, and polymers, and as a chloromethylating reagent ([HSDB, 2003](#)).

Exposure to these chemicals is strictly regulated in the United States of America (USA) and worldwide. Small quantities of BCME and CMME are currently produced, to be used only in enclosed systems for the synthesis of other chemicals ([Brüske-Hohlfeld, 2009](#)).

1.3 Human exposure

1.3.1 Occupational exposure

The primary route of occupational exposure to BCME or CMME is through inhalation of vapours; however, the potential for exposure nowadays is low because these chemicals are no longer produced or sold in large quantities and most industrial operations with these chemicals are conducted in closed containers. The most likely source of exposure to BCME is during the production or use of chemicals in which it may be present as a contaminant or be formed inadvertently ([ATSDR, 1989](#)).

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens,

based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry ([Kauppinen et al., 2000](#)). [Table 1.1](#) presents the numbers of workers exposed to BCME and CMME in the EU by industry ([CAREX, 1999](#)).

From the US National Occupational Exposure Survey (1981–83) it was estimated that 14 workers (all laboratory personnel, including five women) were potentially exposed to BCME. No estimate of potential CMME exposure was reported ([NIOSH, 1984](#)).

1.3.2 Non-occupational exposure

The primary routes of potential human exposure to BCME and technical-grade CMME are inhalation and dermal contact. BCME is rapidly degraded in the environment and has not been detected in ambient air or water ([ATSDR, 1989](#)). According to the US Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of BCME and CMME have been into the air ([US EPA, 2003](#)).

2. Cancer in Humans

BCME and CMME were evaluated previously in *IARC Monograph* Volume 4 and in Supplement 7 ([IARC, 1974, 1987a](#)).

In a retrospective study of a small group of men exposed to BCME during the period 1956–1962, six cases of lung cancer were found among 18 workers in a testing laboratory. Five of these six men were moderate smokers, one was a non-smoker. Two further cases of lung cancer were seen in a group of 50 production workers. Five of these eight cases were oat-cell carcinomas. Duration of exposure had been six to nine years, while the period from first exposure to diagnosis was 8–16 years ([Thiess et al., 1973](#); [IARC, 1974](#)).

In a five-year observational study of 125 workers exposed to CMME, four cases of lung cancer were diagnosed, representing an eight-fold higher incidence than that in a control group ($n = 2804$) with similar smoking history. In a retrospective follow-up, a total of 14 cases were identified, all of whom had been working in the production of CMME. In the latter group, three men were non-smokers. Duration of exposure had been 3–14 years. Histological analysis revealed that 12 of the 14 cases were oat-cell carcinomas ([Figueroa et al., 1973](#); [IARC, 1974](#)). This cohort was further reported on ([Weiss & Boucot, 1975](#); [Weiss et al., 1979](#); [Weiss, 1982](#), [Weiss & Nash, 1997](#)) with confirmatory results (Table 2.1, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-20-Table2.1.pdf>).

Several additional case-reports ([Bettendorf, 1977](#); [Reznik et al., 1978](#); [Roe, 1985](#); [Nishimura et al., 1990](#)) and epidemiological studies from the USA ([Collingwood et al., 1987](#)), the United Kingdom ([McCallum et al., 1983](#)) and France ([Gowers et al., 1993](#)) demonstrated that workers exposed to CMME and/or BCME have an increased risk for lung cancer. Among heavily exposed workers, the relative risks were ten-fold or more. An increase in risk was observed with duration of exposure and with cumulative exposure. Histological evaluation indicated that exposure resulted primarily in small-cell type lung cancer ([Weiss & Boucot, 1975](#)). The highest relative risks appeared to occur 15–19 years after first exposure ([Weiss, 1982](#)), and latency was

shortened among workers with heavier exposure ([Weiss & Figueroa, 1976](#); [Pasternack & Shore, 1981](#)).

3. Cancer in Experimental Animals

3.1 BCME

Studies on the carcinogenesis of BCME in rats, mice and hamsters after inhalation, skin application, and subcutaneous or intra-peritoneal injection have been reviewed in previous IARC Monographs ([IARC, 1974, 1987b](#)). The results of adequately conducted carcinogenicity studies are summarized in [Tables 3.1, 3.2, 3.3, 3.4](#). There were no additional studies reported in the literature since *IARC Monographs Supplement 7* ([IARC, 1987b](#)).

BCME was tested for carcinogenicity by inhalation exposure in five studies with rats, one study with mice and two studies with hamsters; by skin application in two studies with mice; by subcutaneous injection in one study with rats and three with mice; and by intra-peritoneal injection in one study with mice.

Exposure to BCME by inhalation caused an increased incidence of rare malignant tumours of the nose (esthesioneuroepitheliomas and squamous-cell carcinomas of the nasal mucosa) and squamous-cell carcinomas of the lung in male rats ([Kuschner et al., 1975](#); [Leong et al., 1981](#); [Albert et al., 1982](#); [Sellakumar et al., 1985](#)) and of lung adenomas in male mice ([Leong et al., 1981](#)). Skin application of BCME resulted in an increased incidence of skin papillomas in male and female mice ([Van Duuren et al., 1969](#); [Zajdela et al., 1980](#)) and of squamous-cell carcinomas of the skin in female mice ([Van Duuren et al., 1969](#)). Intra-peritoneal injection caused increased incidences of sarcomas at the site of injection in female mice ([Van Duuren et al., 1975](#)). Subcutaneous injection of BCME caused strongly increased incidences of lung adenomas

Table 3.1 Carcinogenicity studies in experimental animals exposed to bis(chloromethyl) ether by inhalation

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Lifetime Kuschner et al. (1975)	0.1 ppm, 6 h/d, 5 d/wk, 70 rats/group. In addition, rats received 10, 20, 40, 60, 80 or 100 6-h exposures, with 50, 50, 20, 20, 50, 30/group, respectively 240 rats served as controls	Nose Esthesioneuroepitheliomas: 0/50, 1/50, 2/20, 2/20, 9/50, 3/30 Malignant olfactory tumours: 0/50, 0/50, 0/20, 0/20, 0/50, 1/30 Ganglioneuroepitheliomas: 0/50, 0/50, 0/20, 0/20, 1/50, 0/30 Squamous cell carcinomas: 0/50, 0/50, 0/20, 0/20, 1/50, 0/30 Poorly differentiated epithelial tumours: 0/50, 1/50, 1/20, 0/20, 1/50, 1/30 Nasal cavity adenocarcinomas: 1/50, 10/50, 0/20, 0/20, 1/50, 1/30 Lung Squamous cell carcinomas: 0/50, 0/50, 0/20, 2/20, 3/50, 8/30 Adenocarcinomas: 0/50, 0/50, 1/20, 0/20, 0/50, 0/30	NR	Purity NR Tumour incidence NR for controls
Rat, SPF Sprague-Dawley (M) Lifetime Leong et al. (1981)	0, 1, 10, 100 ppb 6 h/d, 5 d/wk for 6 mo 120/group	Esthesioneuroepitheliomas of the nose: 0/112, 0/113, 0/111, 96/111* Lung adenomas: 0/112, 0/113, 0/111, 4/111 [§]	* $P < 0.05$ [§] $P = 0.059$	Purity NR Esthesioneuroepitheliomas were malignant tumours, several of which invaded the cribriform plate into the brain and metastasized to the regional lymph nodes and/or the lungs.
Rat, Sprague-Dawley (M) Lifetime Albert et al. (1982)	Premixed HCHO, 14.7 ppm + HCL, 10.6 ppm 6 h/d, 5 d/wk 99/group Air-sham controls, 50/group	Papillomas of the nasal mucosa: 0/50, 3/99 Squamous cell carcinomas of the nasal mucosa: 0/50, 25/99	[NS] [$P < 0.0001$]	Purity NR Weight gains in the exposed group lower than in the controls. All exposed animals had died by 100 wk.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Lifetime Sellakumar et al. (1985)	HCl alone, 10.0 ppm; HCHO alone, 14.8 ppm; premixed HCHO, 15.2 ppm + HCl, 9.9 ppm; non premixed HCHO, 14.9 ppm + HCl, 9.7 ppm 6 h/d, 5 d/wk 100/group	Nasal cancers Squamous cell carcinomas: 0/99, 38/100, 45/100, 27/100 Adenocarcinomas: 0/99, 0/100, 1/100, 2/100 Mixed carcinomas: 0/99, 1/100, 0/100, 0/100 Fibrosarcomas: 0/99, 1/100, 1/100, 0/100 Esthesioneuroepitheliomas: 0/99, 0/100 1/100, 0/100	Nasal cancers Premixed vs HCHO: P < 0.025 Non-premixed vs HCHO: NS	Purity NR Both combined exposures and HCHO exposure alone had a marked decreasing effect on body weight after 16 wk. Mortality was higher in the premixed group after 32 wk of exposure. The concentrations of BCME in the premixed HCl-HCHO chamber varied between 0.1 and 0.4 ppb. It was noted that alkylating agents other than BCME could have been formed by the interaction of HCHO and HCl and that, since the average amount of BCME in the exposure chamber of the premixed HCl-HCHO was less than 1 ppb, BCME may not have been the only agent responsible for the induction of tumours.
Mouse, Strain A/Heston (M) 27 wk Leong et al. (1971)	0 and 1.0 ppm (0.005 mg/L) 6 h/d, 5 d/wk; total of 82 exposures. Controls exposed to filtered air 50/group	Lung adenomas: 20/49, 26/47 Lung adenoma multiplicity: 2.2, 5.2	NS NR	Industrial grade (purity NR) Exposures resulted in loss of body weight and higher mortality
Mouse, Ha/ICR (M) Lifetime Leong et al. (1981)	0, 1, 10, 100 ppb 6 h/d, 5 d/wk for 6 mo 144–157/group	Lung adenomas: 6/157, 4/138, 2/143, 7/144 Lung adenocarcinomas: 4/157, 3/138, 1/143, 3/144 Lung adenomas in mice that survived beyond the initial 6 mo exposure period: 9/86, 5/45, 3/37, 8/27*	*P < 0.05	Purity NR There was an exposure concentration-related effect on cumulative mortality. Deaths began at approximately 1 mo of exposure, plateau-ing between 6 and 8 mo for exposed groups and 11 mo for the controls. Control and exposed mice developed an ascending urinary tract infection that was considered the direct cause of death.

d, day or days; h, hour or hours; HCl, hydrochloric acid; HCHO, formaldehyde vapours; M, male; mo, month or months; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

Table 3.2 Carcinogenicity studies in mice exposed to bis(chloromethyl) ether by intra-peritoneal injection

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR/Ha Swiss (F) 424–456 d Van Duuren <i>et al.</i> (1975)	0 (control) or 0.02 mg BCME in 0.05 mL nujol (purified paraffin oil) once weekly injection 50/group	Sarcoma (at injection site): 0/30, 4/30	$P < 0.05$, χ^2 test	Purity NR

d, day or days; F, female, NR, not reported

Table 3.3 Carcinogenicity studies in mice exposed to bis(chloromethyl) ether by skin application

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR/Ha Swiss (F) 540 d Van Duuren et al. (1969)	BCME as an initiator			> 99% pure When BCME was used as a promoter or carcinogen, the experiment was terminated at 325 d due to ulcers, cancers and poor condition of the animals.
	Single application of 1.0 mg BCME in 0.1 mL benzene followed 14 d later by 0.025 mg PE in 0.1 mL acetone 3 × /wk. Controls received 0.025 mg PE in 0.1 mL acetone 3 × /wk. 20/group	Skin papillomas: 2/20, 5/20 Skin squamous cell carcinomas: 0/20, 2/20	[NS] [NS]	
	BCME as a promoter			
	Single application of 0.15 mg B[a]P in 0.1 mL benzene followed 14 d later by 2.0 mg BCME in 0.1 mL benzene 3 × /wk for 325 d. Controls received a single application of 0.15 mg B[a]P in 0.1 mL benzene. 20/group	Skin papillomas: 0/20, 13/20 Skin squamous cell carcinomas: 0/20, 12/20	[P < 0.0001] [P < 0.0001]	
	BCME as a carcinogen			
	2 mg BCME in 0.1 mL benzene 3x weekly. Controls received 0.1 mL benzene 3 × /wk. 20/group	Skin papillomas: 0/20, 13/20 Skin squamous cell carcinomas: 0/20, 12/20	[P < 0.0001] [P < 0.0001]	
Mouse, XVIIInc./Z (M) 590 d Zajdela et al. (1980)	Single application of 1.0 mg BCME in 80 µl benzene followed by 2.0 µg TPA in 80 µl acetone 3 × /wk for 42 wk. Controls received 2.0 µg TPA in 80 µl acetone 3 × /wk for 42 wk 28/group	Skin: Papillomas: 4/28, 12/28 Carcinomas: 0/28, 3/28 Tumour multiplicity: 1.0, 1.3.	[significant] NS NR	98.9% pure

B[a]P, benzo[a]pyrene; d, day or days; F, female; M, male; NR, not reported; NS, not significant; PE, phorbol ester; TPA, 12-O-tetradecanoylphorbol-13-acetate, wk, week or weeks

Table 3.4 Carcinogenicity studies in experimental animals exposed to bis(chloromethyl) ether by subcutaneous injection

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (F) 515 d Van Duuren et al. (1969)	3 mg BCME in 0.1 mL nujol (purified paraffin oil) once/wk for 114 d, reduced to 1 mg BCME in 0.1 mL nujol weekly for unspecified time and later reduced to 1 mg BCME in 0.1 mL nujol 3 × /mo. Vehicle control: 0.1 mL nujol weekly for 300 d 20/group	Skin fibromas: 0/20, 2/20 Skin fibros arcomas: 0/20, 5/20	[NS] [<i>P</i> < 0.05]	> 99% pure BCME dosage was reduced because of corrosive effects at injection site. By 300 d the treatment was discontinued because the animals were in poor condition with substantial weight loss and ulceration around the injection site.
Mouse, Newborn ICR Swiss (M, F) 6 mo Gargus et al. (1969)	Single injection of 50 µl of 0.05% BCME solution in peanut oil when 24–72 h old (dose, 12.5 µl/kg bw BCME) Vehicle controls: 50 µl of peanut oil (25 mL/kg bw) 50/treated groups, 20–30/control groups	Lung adenomas: 2/30, 25/50 (M); 5/20, 20/50 (F) Lung adenomas/animal: 0.07, 0.82 (M); 0.25, 0.46 (F)	[<i>P</i> < 0.05] (M) NR	Industrial grade (purity unspecified) One papilloma and one fibrosarcoma developed at the site of injection in two BCME-treated mice; such tumours did not occur in control mice.
Mouse, ICR/Ha Swiss (F) 371 d (BCME)–458 d (controls) Van Duuren et al. (1975)	0 (control) or 0.3 mg in 0.05 mL nujol Single injection, once/wk 50/group	Skin sarcomas: 1/50, 21/50	<i>P</i> < 0.01	Purity unspecified Animals sacrificed because of poor survival (median survival was 260 d in treated mice vs 443 d for vehicle controls)
Mouse, XVIIInc./Z (M, F) 549 d Zajdela et al. (1980)	Vehicle control: 20 µl nujol (purified paraffin oil), 32 injections over 42 wk 30/group (M) BCME 0.3 mg in 20 µl nujol 32 injections over 42 wks 30/group/sex	Skin fibrosarcomas: 0/30, 12/27 (M); 10/24 (F)	<i>P</i> < 0.0001 <i>P</i> < 0.0001 (vs male control group)	98.9% pure No female control group

bw, body weight; d, day or days; h, hour or hours; F, female; M, male; mo, month or months; NR, not reported; NS, not significant, vs, versus; wk, week or weeks

Table 3.5 Carcinogenicity studies in mice exposed to chloromethyl methyl ether by skin application

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR/Ha Swiss (F) 540 d Van Duuren et al. (1969)	CMME as an initiator 0.1 mg CMME in 0.1 mL benzene (low dose) or 1.0 mg CMME in 0.1 mL benzene (high dose) followed 14 d later by 0.025 mg PE in 0.1 mL acetone 3 × /wk Controls received 0.025 mg PE in 0.1 mL acetone 3 × /wk	Skin papillomas: 2/20 (control), 7/20 (low dose), 5/20 (high dose) Skin squamous cell carcinomas: 0/20, 4/20, 1/20	[<i>P</i> = 0.06, low dose] [<i>P</i> = 0.053, low dose]	> 99.5% pure Treatment with CMME was discontinued at 325 d but animals were maintained and observed for the entire duration of the experiment. CMME probable initiator of skin papillomas and carcinomas combined.
	CMME as a promoter Single application 0.15 mg B[a]P in 0.1 mL benzene followed 14 d later by 2 mg CMME in 0.1 mL of benzene 3 × /wk. Controls received a single application of 0.15 mg B[a]P in 0.1 mL benzene	Skin papillomas: 0/20, 1/20 Skin squamous cell carcinomas: 0/20, 0/20	[NS] [NS]	
	CMME as a carcinogen 2 mg CMME in 0.1 mL benzene 3x weekly. Controls received 0.1 mL benzene 3 × /wk	Skin papillomas: 0/20, 0/20 Skin squamous cell carcinomas: 0/20, 0/20	[NS] [NS]	

B[a]P, benzo(a)pyrene; d, day or days; F, female; PE, phorbol ester; wk, week or weeks

Table 3.6 Carcinogenicity studies in experimental animals exposed to chloromethyl methyl ether (CMME) by subcutaneous injection

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague Dawley (F) 515 d Van Duuren <i>et al.</i> (1969)	Vehicle control: nujol 0.1 mL/wk for 300 d Treated: 3 mg CMME in 0.1 mL Nujol/wk for 300 d 20/group	Skin fibrosarcomas: 0/20, 1/20 Skin fibromas: 0/20, 0/20	[NS] [NS]	Treatment discontinued at 300 d due to local reaction at injection site
Mouse, Newborn ICR Swiss (M, F) 6 mo Gargus <i>et al.</i> (1969)	Single injection when 24–72 h old Vehicle controls: 50 µl peanut oil (25 mL/kg bw) Treated: 50 µl of CMME solution (125 µl/kg bw CMME) in peanut oil 48–51/treated groups 20–30/control groups	Lung adenomas: 2/30, 9/51 (M); 5/20, 8/48 (F) Lung adenomas/animal: 0.07, 0.23 (M); 0.25, 0.18 (F)	[NS] NR	99.7% pure
Mouse, Newborn ICR/Ha Swiss (F) 685 d Van Duuren <i>et al.</i> (1972)	Vehicle controls: 0.05 mL nujol Treated: 300 µg CMME in 50 µl nujol once/wk for life 30/group	Skin sarcomas: 0/30, 10/30	[$P < 0.01$]	Technical grade (purity NR)

bw, body weight; d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NS, not significant; NR, not reported; wk, week or weeks

in male mice ([Gargus et al., 1969](#)), of sarcomas and fibrosarcomas at the site of injection in male and female mice, and of fibrosarcomas in female rats ([Van Duuren et al., 1969](#); [Van Duuren et al., 1975](#); [Zajdela et al., 1980](#)).

3.2 CMME

Studies on the carcinogenesis of CMME administered to mice, rats and hamsters by inhalation, skin application and subcutaneous injection have been reviewed in previous *IARC Monographs* ([IARC, 1974, 1987b](#)). The results of adequately conducted carcinogenicity studies are summarized in [Tables 3.5, 3.6](#). There were no additional studies reported in the literature since the previous *IARC Monograph* ([IARC, 1987b](#)).

CMME was tested for carcinogenicity by inhalation exposure in one study in rats, one in mice and one in hamsters; by skin application in one study in mice; and by subcutaneous injection in one study in rats and two in mice.

Technical grade CMME induced skin sarcomas in female mice following subcutaneous injection ([Van Duuren et al., 1972](#)). In a skin-painting study in female mice, CMME was found to be a probable initiator of skin papillomas and carcinomas combined ([Van Duuren et al., 1969](#)).

4. Other Relevant Data

4.1 Toxicokinetics and toxicity

BCME and CMME belong to the group of chloroalkyl ethers. In water and aqueous biological fluids these substances are rapidly hydrolysed to form hydrochloric acid, methanol and formaldehyde ([Nichols & Merritt, 1973](#); [NTP, 2005](#)).

The toxic effects of BCME are restricted to the epithelial tissue where exposure occurs, and

this is consistent with the short half-life of BCME in aqueous media ([ATSDR, 1989](#)).

4.2 Genetic and related effects

Studies on the genotoxicity and cytotoxicity of BCME and CMME are limited and yielded mixed results ([IARC, 1987b](#)). [These studies are generally poorly documented.]

Both BCME and CMME are powerful alkylating agents ([Van Duuren et al., 1968](#); [Van Duuren & Van Duuren, 1988](#); [Van Duuren, 1989](#)) that are mutagenic in bacteria ([Mukai & Hawryluk, 1973](#); [Anderson & Styles, 1978](#); [IARC, 1987b](#)). [The Working Group noted that the test systems used may not be optimal for investigating effects of rapidly hydrolysing material. Specifically, since BCME and CMME are short-lived alkylating agents, tests that favour hydrolysis of the compound before it enters the cell may yield misleading results.]

In one study, reaction of BCME with DNA *in vitro* did not affect the melting temperature or the buoyant density of the DNA, nor did it yield isolatable products upon reaction with purines or DNA, as did other alkylating agents ([Van Duuren et al., 1972](#)). In another study, BCME was shown to bind to calf-thymus DNA at guanine and adenine residues ([Goldschmidt et al., 1975](#)).

In vitro, CMME enhanced virus-induced transformation of Syrian hamster embryo cells ([Casto, 1983](#); [IARC, 1987b](#)) and elicited unscheduled DNA synthesis, reflecting its activity as a DNA-damaging agent, in cultured human lymphocytes ([Perocco et al., 1983](#)).

BCME did not cause chromosomal aberrations in bone-marrow cells of rats exposed to vapours for six months ([Leong et al., 1981](#); [IARC, 1987b](#)) but it did induce unscheduled DNA synthesis ([Agrelo & Severn, 1981](#); [IARC, 1987b](#)) and cell transformation ([Kurian et al., 1990](#)) in cultured human fibroblasts.

A slight increase in the incidence of chromosomal aberrations was observed in blood

lymphocytes of workers exposed to BCME or CMME during the preparation of ion-exchange resins ([Srám *et al.*, 1983](#); [IARC, 1987b](#)).

4.3 Mechanistic considerations

The limited experimental studies on BCME and CMME preclude a detailed understanding of a mechanism of action, but sufficient information is available to support a genotoxic mode of action. [Bernucci *et al.* \(1997\)](#) outlined some possible steps in the process by which BCME and CMME may contribute to carcinogenesis. Similar to other alkylating agents, the observed formation of DNA adducts and resultant mutations are likely key steps in their mechanism of carcinogenicity. However, very little is known regarding their covalent interaction with DNA.

The hydrolysis products of BCME are formaldehyde and hydrochloric acid (HCl). Since formaldehyde is carcinogenic in animals and humans (see the *Monograph* on Formaldehyde in this volume), at least some of the carcinogenic potential of BCME may be due to this degradation product. However, the difference in carcinogenic potency between the two compounds (BCME being much more potent than formaldehyde) would indicate that this cannot be the sole mechanism of carcinogenicity.

BCME, formaldehyde and HCl could interact synergistically within the cell. Exposure of rats to mixtures of formaldehyde and HCl by inhalation resulted in little change in the frequency of nasal tumours compared with exposure to formaldehyde alone. However, one animal developed an esthesioneuroepithelioma, a very rare tumour that is characteristic of BCME exposure ([Albert *et al.*, 1982](#); [Sellakumar *et al.*, 1985](#)).

4.4 Synthesis

BCME is among the most potent animal and human carcinogens known. The fact that BCME and CMME are powerful alkylating agents provides moderate to strong evidence that they operate by a genotoxic mechanism of action. This mechanism is likely to be similar to that of other strong alkylating agents, involving modification of DNA and resultant mutations.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of bis(chloromethyl)ether and chloromethyl methyl ether (technical grade). Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade) cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of bis(chloromethyl)ether.

There is *limited evidence* in experimental animals for the carcinogenicity of chloromethyl methyl ether.

There is moderate to strong evidence that bis(chloromethyl)ether and chloromethyl methyl ether, powerful alkylating agents, operate by a genotoxic mechanism. This mechanism is likely to be similar to that of other strong alkylating agents, involving modification of DNA and resultant mutations.

Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade) are *carcinogenic to humans (Group 1)*.

References

- Agrelo CE & Severn BJ (1981). A simplified method for measuring scheduled and unscheduled DNA synthesis in human fibroblasts. *Toxicology*, 21: 151–158. doi:10.1016/0300-483X(81)90125-6 PMID:7281203
- Albert RE, Sellakumar AR, Laskin S *et al.* (1982). Gaseous formaldehyde and hydrogen chloride induction of

- nasal cancer in the rat. *J Natl Cancer Inst*, 68: 597–603. PMID:6951075
- Anderson D & Styles JA (1978). The bacterial mutation test. Six tests for carcinogenicity. *Br J Cancer*, 37: 924–930. doi:10.1038/bjc.1978.134 PMID:354673
- ATSDR (1989) *Toxicological Profile for bis(Chloromethyl) Ether (Final Report)*. NTIS Accession No. PB90–168691. Atlanta, GA: Agency for Toxic Substances and Disease Registry, pp. 76
- Bernucci I, Turrini D, Landi MT (1997). [Bis-chloromethyl ether and carcinogenesis of alkylating agents] *Med Lav*, 88: 347–355. PMID:9489299
- Bettendorf U (1977). Gewerblich induzierte lungenkarzinome nach inhalation alkylierender verbindungen (bischloromethylather). *Zentralbl Arbeitssch Prophyl*, 27: 140–143.
- Brüske-Hohlfeld I (2009). Environmental and occupational risk factors for lung cancer. *Methods Mol Biol*, 472: 3–23. doi:10.1007/978-1-60327-492-0_1 PMID:19107427
- CAREX (1999) *Carex: industry specific estimates – Summary*. Available at http://www.ttl.fi/en/chemical_safety/carex/Documents/5_exposures_by_agent_and_industry.pdf. Accessed 12/12/2011
- Casto BC (1983). Comparison of the sensitivity of rodent and human cells to chemical carcinogens using viral transformation, DNA damage, and cytotoxicity assays. *Basic Life Sci*, 24: 429–449. PMID:6305332
- Collingwood KW, Pasternack BS, Shore RE (1987). An industry-wide study of respiratory cancer in chemical workers exposed to chloromethyl ethers. *J Natl Cancer Inst*, 78: 1127–1136. PMID:3473253
- Figueroa WG, Raszkowski R, Weiss W (1973). Lung cancer in chloromethyl methyl ether workers. *N Engl J Med*, 288: 1096–1097. doi:10.1056/NEJM197305242882104 PMID:4348988
- Gargus JL, Reese WH Jr, Rutter HA (1969). Induction of lung aenomas in newborn mice by bis(chloromethyl) ether. *Toxicol Appl Pharmacol*, 15: 92–96. doi:10.1016/0041-008X(69)90136-7 PMID:5798736
- Goldschmidt BM, van Duuren BL, Frenkel K (1975). The Reaction of 14C-labelled bis(Chloromethyl) Ether with DNA. *Proc Am Assoc Cancer Res*, 16: 66
- Gowers DS, DeFonso LR, Schaffer P *et al.* (1993). Incidence of respiratory cancer among workers exposed to chloromethyl-ethers. *Am J Epidemiol*, 137: 31–42. PMID:8382005
- HSDB (2003) *Hazardous Substances Data Bank*. Bethesda, MD: National Library of Medicine. [<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>]
- IARC (1974). Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents. *IARC Monogr Eval Carcinog Risk Chem Man*, 4: 1–286.
- IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1987b). Genetic and related effects: An updating of selected IARC monographs from Volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 6: 1–729. PMID:3504843
- Kauppinen T, Toikkanen J, Pedersen D *et al.* (2000). Occupational exposure to carcinogens in the European Union. *Occup Environ Med*, 57: 10–18. doi:10.1136/oem.57.1.10 PMID:10711264
- Kurian P, Nesnow S, Milo GE (1990). Quantitative evaluation of the effects of human carcinogens and related chemicals on human foreskin fibroblasts. *Cell Biol Toxicol*, 6: 171–184. doi:10.1007/BF00249592 PMID:2361190
- Kuschner M, Laskin S, Drew RT *et al.* (1975). Inhalation carcinogenicity of alpha halo ethers. III. Lifetime and limited period inhalation studies with bis(chloromethyl) ether at 0.1 ppm. *Arch Environ Health*, 30: 73–77. PMID:1115531
- Leong BKJ, Kociba RJ, Jersey GC (1981). A lifetime study of rats and mice exposed to vapors of bis(chloromethyl) ether. *Toxicol Appl Pharmacol*, 58: 269–281. doi:10.1016/0041-008X(81)90432-4 PMID:7245201
- Leong BKJ, Macfarland HN, Reese WH Jr (1971). Induction of lung adenomas by chronic inhalation of bis (chloromethyl) ether. *Arch Environ Health*, 22: 663–666. PMID:5574007
- Lide DR, editor (2008) *CRC Handbook of Chemistry and Physics*. 89th ed., Boca Raton, FL: CRC Press, pp. 3–50, 3–106.
- McCallum RI, Woolley V, Petrie A (1983). Lung cancer associated with chloromethyl methyl ether manufacture: an investigation at two factories in the United Kingdom. *Br J Ind Med*, 40: 384–389. PMID:6226309
- Mukai FH & Hawryluk I (1973). Mutagenicity of Some Halo-ethers and Halo-ketones. *Mutat Res*, 21: 228
- NTP (2005). NTP 11th Report on Carcinogens. *Rep Carcinog*, 11: 1–A32. PMID:19826456
- Nichols RW & Merritt RF (1973). Relative solvolytic reactivities of chloromethyl ether and BIs(chloromethyl) ether. *J Natl Cancer Inst*, 50: 1373–1374. PMID:4712596
- NIOSH (1984) *National Occupational Exposure Survey (1981–83)*. Cincinnati, OH: US Department of Health and Human Services [<http://www.cdc.gov/noes/noes3/empl0003.html>]
- Nishimura K, Miyashita K, Yoshida Y *et al.* (1990). [An epidemiological study of lung cancer among workers exposed to bis(chloromethyl) ether] *Sangyo Igaku*, 32: 448–453. doi:10.1539/joh1959.32.448 PMID:1962826
- O’Neil MJ, editor (2006) *The Merck Index*, 14th Ed., Whitehouse Station, NJ, Merck & Co., Inc., pp. 355, 520.
- Pasternack BS, Shore RE (1981). *Lung cancer following exposure to chloromethyl ethers*. In: *Proceedings of the International Conference on Critical Current Issues*

- in *Environmental Health Hazards*. Chwat M, Dror K, editors. Tel-Aviv, Israel, pp. 76–85.
- Perocco P, Bolognesi S, Alberghini W (1983). Toxic Activity of 17 Industrial Compounds on Human Lymphocytes Cultured in vitro. *Toxicol Lett*, 16: 69–76. doi:10.1016/0378-4274(83)90012-7 PMID:6836616
- Reznik G, Wagner HH, Atay Z (1978). Lung cancer following exposure to bis(chloromethyl)ether: a case report. *J Environ Pathol Toxicol*, 1: 105–111. PMID:722181
- Roe FJ (1985). Chloromethylation: three lung cancer deaths in young men. *Lancet*, 2: 268 doi:10.1016/S0140-6736(85)90308-3 PMID:2862432
- Sellakumar AR, Snyder CA, Solomon JJ, Albert RE (1985). Carcinogenicity of formaldehyde and hydrogen chloride in rats. *Toxicol Appl Pharmacol*, 81: 401–406. doi:10.1016/0041-008X(85)90411-9 PMID:4082190
- Šrám RJ, Samková I, Holá N (1983). High-dose ascorbic acid prophylaxis in workers occupationally exposed to halogenated ethers. *J Hyg Epidemiol Microbiol Immunol*, 27: 305–318. PMID:6227657
- Thiess AM, Hey W, Zeller H (1973[Verdacht auf kanzerogene Wirkung auch bei Menschen]). *Zur Toxicologie von Dichlordimethyläther*, 23: 97–102.
- US EPA; United States Environmental Protection Agency (2003) *Toxics Release Inventory Program (TRI)*
- Van Duuren BL (1989). Comparison of potency of human carcinogens: vinyl chloride, chloromethylmethyl ether and bis(chloromethyl)ether. *Environ Res*, 49: 143–151. doi:10.1016/S0013-9351(89)80059-3 PMID:2526731
- Van Duuren BL, Goldschmidt BM, Langseth L *et al.* (1968). Alpha-haloethers: a new type of alkylating carcinogen. *Arch Environ Health*, 16: 472–476. PMID:5652981
- Van Duuren BL, Goldschmidt BM, Seidman I (1975). Carcinogenic activity of di- and trifunctional α -chloro ethers and of 1,4-dichlorobutene-2 in ICR/HA swiss mice. *Cancer Res*, 35: 2553–2557. PMID:1149050
- Van Duuren BL, Katz C, Goldschmidt BM *et al.* (1972). Carcinogenicity of halo-ethers. II. Structure-activity relationships of analogs of bis(chloromethyl)ether. *J Natl Cancer Inst*, 48: 1431–1439. PMID:5030957
- Van Duuren BL, Sivak A, Goldschmidt BM *et al.* (1969). Carcinogenicity of halo-ethers. *J Natl Cancer Inst*, 43: 481–486. PMID:5805453
- Van Duuren BL, Van Duuren SB 1988. *Chemistry, reactivity and carcinogenicity of chloro ethers*. In: *Chemical carcinogens*. Politzer P, Martin FJ, editors. New York, NY: Elsevier, pp. 114–176.
- Weiss W (1982). Epidemic curve of respiratory cancer due to chloromethyl ethers. *J Natl Cancer Inst*, 69: 1265–1270. PMID:6958903
- Weiss W & Boucot KR (1975). The respiratory effects of chloromethyl methyl ether. *JAMA*, 234: 1139–1142. doi:10.1001/jama.1975.03260240043024 PMID:171460
- Weiss W & Figueroa WG (1976). The characteristics of lung cancer due to chloromethyl ethers. *J Occup Med*, 18: 623–627. PMID:966095
- Weiss W, Moser RL, Auerbach O (1979). Lung cancer in chloromethyl ether workers. *Am Rev Respir Dis*, 120: 1031–1037. PMID:228573
- Weiss W & Nash D (1997). An epidemic of lung cancer due to chloromethyl ethers. 30 years of observation. *J Occup Environ Med*, 39: 1003–1009. doi:10.1097/00043764-199710000-00012 PMID:9343765
- Zajdela F, Croisy A, Barbin A *et al.* (1980). 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. PMID:7356519