

Bis(chloromethyl)ether (BCME); CASRN 542-88-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR BCME

File First On-Line 09/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	message	07/01/1991
Carcinogenicity Assessment (II.)	yes	09/26/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bis(chloromethyl)ether (BCME)
CASRN — 542-88-1

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bis(chloromethyl)ether (BCME)
CASRN — 542-88-1

The health effects data for bis(chloromethyl) ether were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. For additional information on the health effects of this chemical, interested parties are referred to the EPA documentation listed below.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Chloroalkyl Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-030.

Agency Work Group Review — 03/28/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Bis(chloromethyl)ether (BCME) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bis(chloromethyl)ether (BCME)

CASRN — 542-88-1

Last Revised — 09/26/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk

Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — A; human carcinogen

Basis — Statistically significant increases in lung tumors (oat cell carcinomas) observed in six studies of exposed workers and bioassay data from rats and mice.

II.A.2. Human Carcinogenicity Data

Sufficient. There are six studies of workers exposed to BCME in which statistically significant increases in lung tumors were found (Figuroa et al., 1973; Sakabe, 1973; Thiess et al., 1973; Albert et al., 1975; Lemen et al., 1976; Pasternack et al., 1977). In four studies, workers were primarily exposed to CMME (technical-grade chloromethyl methyl ether) with 1-8% of BCME as a contaminant in the remaining two studies, workers were exposed to BCME alone. All six studies found statistically significant increases in the incidence of lung carcinomas, predominantly of the oat-cell type which is generally not associated with smoking. The observed numbers of lung carcinomas were much higher in workers exposed to BCME alone than in workers exposed to both BCME and CMME. The age range in the studies was from 35-54 years, with latency periods of 8-16 years. Despite a lack of information on study designs and analytical techniques, the consistent finding of a high incidence of oat-cell carcinoma of the lung in similar age groups after an appropriate latency period in all studies provides sufficient qualitative evidence of the carcinogenicity of BCME in humans. The data, however, were not considered to be adequate for use in quantitative risk estimation.

II.A.3. Animal Carcinogenicity Data

Sufficient. Kuschner et al. (1975) conducted an inhalation study of male Sprague-Dawley rats exposed to BCME at 0.1 ppm 6 hours/day, 5 days/week for 10, 20, 40, 60, 80, or 100 days, then observed for the remainder of their lifetimes. There was a marked increase in the incidence of several types respiratory tract tumors at this low dose in the treated animals as compared with the controls. There was also a log-normal distribution of cancer induction time, with a median of 440 days; The cancer incidence shows a sigmoidal curve with time.

Several other investigators have demonstrated the ability of BCME to induce respiratory tumors by the inhalation route. Leong et al. (1971) reported a 34% increase in tumor incidence in A/Heston mice exposed 6 hours/day, 5 days/week for 6 months to CMME vapors at either 1 ppm or 2 ppm with 0.3-2.6% BCME as an impurity. Drew et al. (1975) reported a skin tumor on 1/25 Sprague-Dawley rat after one exposure to 0.7 ppm and a nose tumor on 1/50 Syrian golden hamster after three exposures to 1 ppm of BCME; both tumors occurred more than 1 year after exposure.

BCME is a potent complete skin carcinogen in mice, producing both papillomas and squamous cell carcinomas (Van Duuren et al., 1969). Pulmonary tumors in newborn ICR Swiss mice have been induced by s.c. injection of BCME (Gargus et al., 1969).

II.A.4. Supporting Data for Carcinogenicity

BCME is a direct-acting mutagen for *Salmonella typhimurium* (Nelson, 1976). BCME decreases the latency period of benzo[a]pyrene-initiated tumors, but does not affect tumor yield (Van Duuren et al., 1968).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 2.2E+2 per (mg/kg)/day

Drinking Water Unit Risk — 6.2E-3 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1.6E-2 ug/L
E-5 (1 in 100,000)	1.6E-3 ug/L
E-6 (1 in 1,000,000)	1.6E-4 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Based on inhalation data in II.C.2.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The unit risk should not be used if the water concentration exceeds 1.6 ug/L, since above this concentration the unit risk may not be appropriate.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

This oral estimate is derived from inhalation data. BCME is not likely to be found in water since it rapidly hydrolyzes.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 6.2E-2 per (ug/cu.m)

Extrapolation Method — Linerarized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1.6E-3 ug/cu.m
E-5 (1 in 100,000)	1.6E-4 ug/cu.m
E-6 (1 in 1,000,000)	1.6E-5 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — respiratory tract tumors
 Test animals — rat/Sprague-Dawley, male
 Route — inhalation
 Reference — Kuschner et al., 1975

-----Dose-----		
Number of 6-hour, 0.1-ppm Exposures	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	0/240
10	0.000270	1/41
20	0.000541	3/46
40	0.00105	4/18
60	0.00184	4/18
80	0.00347	15/34
100	0.00373	12/20

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Tumor types observed were neuroepitheliomas, malignant olfactory tumors (unclassified), ganglioneuroepitheliomas, squamous cell carcinomas of the turbinates and gingiva, poorly differentiated epithelial tumors of the nose, nasal cavity adenocarcinomas, and squamous cell carcinomas and adenocarcinomas of the lung.

The human equivalent dose was calculated from the animal dose, assuming surface area equivalence. The animal dose was calculated from the air concentration (0.1 ppm or 0.479 mg/cu.m.), an assumed breathing rate (0.283 cu.m./day) for 500-g rats (assumed), and from the number of exposures in each group. Although the median life span of these animals (ranging from 483 to 497 days in the control and lowest two treated groups) was shorter than other Sprague-Dawley colonies reported in the literature (Anver et al., 1982), the response is still considered to represent a lifetime incidence. Since the animals were allowed to live until natural death occurred, a correction factor for estimating the lifetime incidence from less than lifetime studies was not applied here, whereas the Ambient Water Quality Criteria Document (U.S. EPA, 1980) made such a correction. The customary 5/7 adjustment to convert from 5 to 7 days/week exposure in such studies was similarly unnecessary since the actual number of days of exposure was provided by the authors. Also, a mistake was found in the criteria document unit risk calculations, which were a factor of 10 too high. The effect of these adjustments is to reduce the unit risks by a factor of about 45 from that reported in the Ambient Water Quality Criteria Document (U.S. EPA, 1980).

The unit risk should not be used if the air concentration exceeds $1.6E-1$ ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Tumor incidence was shown to be dose-dependent in rats based on a time- related exposure pattern. Human data do not corroborate the risk estimate. Control data were pooled, not run concurrently.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1980, 1986

The 1980 Ambient Water Quality Criteria Document for Chloroalkyl Ethers has received agency and external review. The 1986 evaluation of the potential carcinogenicity of bis(chloromethyl)ether has received limited review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 07/23/1986, 05/04/1988

Verification Date — 05/04/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Bis(chloromethyl)ether (BCME) conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Bis(chloromethyl)ether (BCME)
CASRN — 542-88-1

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Chloroalkyl Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-030.

VI.C. Carcinogenicity Assessment References

Albert, R.E., B.S. Pasternack, R.E. Shore, M. Lippmann, N. Nelson and B. Ferris. 1975. Mortality patterns among workers exposed to chloromethyl ethers - A preliminary report. *Environ. Health Perspect.* 11: 209-214.

Anver, M.R., B.J. Cohen, C.P. Lattuada and S.J. Foster. 1982. Age-associated lesions in barrier-reared male Sprague-Dawley rats: A comparison between hap: (SD) and CrI:COBS(R)CD(SD) stocks. *Exp. Aging Res.* 8(1):3-24.

Drew, R.T., S. Laskin, M. Kuschner and N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. *Arch. Environ. Health.* 30: 61-69.

Figuroa, W.G., R. Raszkowski and W. Weiss. 1973. Lung cancer in chloromethyl methyl ether workers. *New Engl. J. Med.* 288: 1096-1097.

Gargus, J.L., W.H. Reese, Jr. and H.A. Rutter. 1969. Induction of lung adenomas in newborn mice by bis(chloromethyl)ether. *Toxicol. Appl. Pharmacol.* 15: 92-96.

Kuschner, M., S. Laskin, R.T. Drew, V. Cappiello and N. Nelson. 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.

Lemen, R.A., W.M. Johnson, J.K. Wagoner, V.E. Archer and G. Saccomanno. 1976. Cytologic observations and cancer incidence following exposure to BCME. *Ann. NY Acad. Sci.* 271: 71-80.

Leong, B.K.J., H.N. Macfarland and W.H. Reese, Jr. 1971. Induction of lung adenomas by chronic inhalation of bis(chloromethyl)ether. *Arch. Environ. Health.* 22: 663-666.

Nelson, N. 1976. The chloroethers - occupational carcinogens: A summary of laboratory and epidemiology studies. *Ann. NY Acad. Sci.* 271: 81-90.

Pasternack, B.S., R.E. Shore and R.E. Albert. 1977. Occupational exposure to chloromethyl ethers. A retrospective cohort mortality study (1948-1972). *J. Occup. Med.* 19: 741-746.

Sakabe, H. 1973. Lung cancer due to exposure to bis(chloromethyl)ether. *Ind. Health.* 11: 145-148.

Thiess, V.A.M., W. Hey and H. Zeller. 1973. Zur Toxikologie von Dichlordimethylather - Verdacht auf kanzerogene Wirkung auch beim Menschen. *Zbl. Arbeitsmed.* 23: 97-102.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Chloroalkyl Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-030. NTIS PB 81-117418.

U.S. EPA. 1986. Evaluation of the Potential Carcinogenicity of Bis(Chloromethyl)Ether. Draft RQ Document. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. July 8.

Van Duuren, B., B. Goldschmidt, C. Katz, et al. 1968. Alpha-Haloesters: A new type of alkylating carcinogen. *Am. Med. Assoc. Arch. Environ. Health.* 16: 472-476.

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

VII. Revision History

Substance Name — Bis(chloromethyl)ether (BCME)

CASRN — 542-88-1

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
07/01/1991	I.B.	Inhalation RfC message on-line
12/03/2002	I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Bis(chloromethyl)ether (BCME)

CASRN — 542-88-1

Last Revised — 09/26/1988

- 542-88-1
- BCME
- Bis(chloromethyl)ether
- BIS-CME
- CHLORO(CHLOROMETHOXY)METHANE
- CHLOROMETHYL ETHER
- DICHLORDIMETHYLAETHER
- 1,1'-DICHLORODIMETHYL ETHER
- sym-DICHLORO-DIMETHYL ETHER
- sym-DICHLOROMETHYL ETHER
- DIMETHYL-1,1'-DICHLOROETHER
- ETHER, BIS(CHLOROMETHYL)
- METHANE, OXYBIS(CHLORO-
- OXYBIS(CHLOROMETHANE)
- RCRA WASTE NUMBER P016
- UN 2249