

Bis(chloroethyl)ether (BCEE); CASRN 111-44-4

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 BCEE

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	message	10/01/1991
Carcinogenicity Assessment (II.)	yes	03/31/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Bis(chloroethyl)ether (BCEE)
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Not available at this time.

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

Substance Name — Bis(chloroethyl)ether (BCEE)
CASRN — 111-44-4

The health effects data for bis(chloroethyl)ether have been reviewed by the RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. For additional information on 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 Criteria and Standards Division, Washington, DC. EPA 440/5-80-030. NTIS PB81-117418/AS.

U.S. EPA. 1987. Health Effects Assessment for Bis(2-chloroethyl)ether. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-88/023.

Agency Work Group Review — 07/17/1991

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(chloroethyl)ether (BCEE) 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(chloroethyl)ether (BCEE)
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Last Revised — 03/31/1987

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 — B2; probable human carcinogen

Basis — Positive carcinogenicity results in two strains of mice and evidence of mutagenicity

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

BCEE was marginally sarcomatogenic at s.c. injection sites in female ICR/Ha mice (Van Duurren et al., 1968). Innes et al. (1969) administered BCEE by gavage to two hybrid mouse strains, (C57Bl/6 x C3H/Anf)F1 and (C57Bl/6 x AKR)F1. Groups of 18 mice/sex/strain began treatment with 100 mg/kg at 7 days of age. At 4 weeks, after weaning, exposure was continued through the diet. Concentrations in diet were calculated so as to deliver the maximally tolerated dose (300 ppm), and treatment was continued for 18 months. Increased evidence of hepatomas were noted in male and female (C57Bl/6 x C3H/Anf)F1 mice and in male (C57Bl/6 x AKR)F1 mice.

By contrast to the above, Theiss et al. (1977) saw no increases in pulmonary tumors in strain A mice given repeated i.p. injections of BCEE. Futhermore, an NCI study (for which statistical

analyses were not available) indicated that BCEE was not carcinogenic for Charles River rats by the oral route (Ulland et al., 1973; U.S. EPA, 1980).

II.A.4. Supporting Data for Carcinogenicity

BCEE is a direct-acting mutagen producing base pair exchange mutations in *E. coli*, *S. typhimurium*, and *B. subtilis* (Shirasu et al., 1975). Vapor-phase exposure of *Salmonella* frameshift mutant strains TA1538 and TA98 also resulted in a weak positive response (Fishbein, 1977). BCEE is mutagenic in *S. cerevisiae* (Fishbein, 1977) but did not induce heritable translocations in mice (Jorgenson et al., 1977). BCEE is structurally related to bis(chloromethyl)ether (BCME), a human carcinogen.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.1E+0 per (mg/kg)/day

Drinking Water Unit Risk — 3.3E-5 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)	3E+0 ug/L
E-5 (1 in 100,000)	3E-1 ug/L
E-6 (1 in 1,000,000)	3E-2 ug/L

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

Tumor Type: hepatomas

Test animals: mouse/(C57B1/6 x C3H/AnF)F1, male

Route: gavage followed by diet

Reference: Innes et al., 1969

Administered Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	8/79
39	2.94	14/16

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

The tumor incidence in control mice is derived from pooling the tumor incidence of four untreated control groups (8/63) and one treated (gavaged with gelatin suspension) control group (0/16).

The unit risk should not be used if the water concentration exceeds 3E+2 ug/L, since above this concentration the unit risk may not be appropriate.

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

A small number of animals was treated at only one dose.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk 3.3E-4 per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

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

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

The inhalation risk estimates were calculated from the oral exposure data in Section II.B.2.

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

The unit risk should not be used if the air concentration exceeds 3E+1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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

See II.B.4.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1980

The 1980 Ambient Water Quality Criteria Document for Chloroalkyl Ethers received extensive peer and public review.

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

Agency Work Group Review — 07/23/1986

Verification Date — 07/23/1986

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(chloroethyl)ether (BCEE) 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.

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(chloroethyl)ether (BCEE)
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VI.A. Oral RfD References

None

VI.B. Inhalation RfC 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 Criteria and Standards Division, Washington, DC. EPA 440/5-80-030. NTIS PB81-117418/AS.

U.S. EPA. 1987. Health Effects Assessment for Bis(2-chloroethyl)ether. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-88/023.

VI.C. Carcinogenicity Assessment References

Fishbein, L. 1977. Potential industrial carcinogens and mutagens. U.S. EPA, Office of Toxic Substances, EPA 560/5-77-005. Washington, DC.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. Natl. Cancer Inst.* 42: 1101-1114.

Jorgenson, T.A., C.J. Rushbrook, G.W. Newell and R.G. Tardiff. 1977. Study of mutagenic potential of bis(2-chloroethyl) and bis(2-Chloroisopropyl)ethers in mice by the heritable translocation test. *Toxicol. Appl. Pharmacol.* 41: 196.

Shirasu, Y., M. Moriya, K. Kato and T. Kada. 1975. Mutagenicity screening of pesticides in microbial systems. *Mutat. Res.* 31: 268.

Theiss, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisburger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. *Cancer Res.* 37: 2717.

Ulland, B., E.K. Weisburger and J.H. Weisburger. 1973. Chronic toxicity and carcinogenicity of industrial chemicals and pesticides. *Toxicol. Appl. Pharmacol.* 25: 446.

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.

Van Duuren, B.L., B.M. Goldschmidt, C. Katz, L. Langseth, G. Mercado and A. Sivak. 1968. Alpha-haloethers: A new type of alkylating carcinogen. *Arch. Environ. Health.* 16: 472.

VII. Revision History

Substance Name — Bis(chloroethyl)ether (BCEE)
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Date	Section	Description
10/01/1991	I.B.	Inhalation RfC message on-line

Date	Section	Description
12/03/2002	I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Bis(chloroethyl)ether (BCEE)

CASRN — 111-44-4

Last Revised — 03/31/1987

- 111-44-4
- BCEE
- beta,beta'-DICHLOROETHYL ETHER
- Bis(chloroethyl)ether
- BIS(2-CHLOROETHYL) ETHER
- BIS(beta-CHLOROETHYL) ETHER
- CHLOREX
- 1-CHLORO-2-(beta-CHLOROETHOXY)ETHANE
- CHLOROETHYL ETHER
- CLOREX
- DCEE
- 2,2'-DICHLOORETHYLEETHER
- 2,2'-DICHLOR-DIAETHYLAETHER
- 2,2'-DICHLORETHYL ETHER
- beta,beta-DICHLORODIETHYL ETHER
- DICHLOROETHER
- DICHLOROETHYL ETHER
- DI(2-CHLOROETHYL) ETHER
- 2,2'-DICHLOROETHYL ETHER
- DI(beta-CHLOROETHYL)ETHER
- sym-DICHLOROETHYL ETHER
- DICHLOROETHYL OXIDE
- 2,2'-DICLOROETILETERE
- DWUCHLORODWUETYLOWY ETER
- ENT 4,504
- ETHANE, 1,1'-OXYBIS(2-CHLORO-
- ETHER, BIS(2-CHLOROETHYL)
- ETHER DICHLORE
- 1,1'-OXYBIS(2-CHLORO)ETHANE

- OXYDE DE CHLORETHYLE
- RCRA WASTE NUMBER U025
- UN 1916