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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 11

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The five interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the five committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bis-chloromethyl ether (interim reports 18 and 19a), chloromethyl methyl ether (interim reports 11, 18, and 19a), chlorosilanes (interim reports 18 and 19a), nitrogen oxides (interim reports 15, 18, and 19a), and vinyl chloride (interim reports 16, 18, and 19a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Sidney Green, Jr. (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim report 11 was overseen by Rakesh Dixit (MedImmune/AstraZeneca Biologics, Inc.), and interim reports 15, 16, 18, and 19a were overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional

procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke and Iris A. Camacho (both from EPA) and George Rusch (Risk Assessment and Toxicology Services). The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 11

National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the eleventh volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial

Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five expo-

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

sure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from

inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently Syracuse Research Corporation. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the committee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared ten reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011). This report is the eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

bis-Chloromethyl Ether[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory), Mark Follansbee (Syracuse Research Corporation), and Chemical Manager Ernest V. Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

bis-Chloromethyl ether (BCME) is a synthetic chemical that is a severe respiratory, eye, nose, and skin irritant that can lead to pulmonary edema and congestion, corneal necrosis, dyspnea, and death. Chronic occupational exposure has caused small-cell lung carcinoma, which has a histology distinct from smoking-associated lung cancer and a shorter latency period. The U.S. Environmental Protection Agency (EPA) classifies BCME as a human carcinogen based on sufficient human carcinogenicity data, and the Occupational Safety and Health Administration (OSHA) federal regulations limit its use, storage, and handling to controlled areas.

AEGL-1 values were not recommended for BCME because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals.

The AEGL-2 was based on a study in which rats were exposed for 7 h to BCME at a concentration of 0.7, 2.1, 6.9, or 9.5 ppm and hamsters were exposed for 7 h to BCME at 0.7, 2.1, 5.6, or 9.9 ppm, followed by lifetime observation (Drew et al. 1975). All groups of treated rats had increased lung-to-body weight ratios, indicative of respiratory lesions, which were considered irreversible because they were seen after lifetime observation. There also was an increased incidence of tracheal epithelial hyperplasia in rats and of pneumonitis in hamsters at 0.7 ppm, and both species had increased mortality and lung lesions

at ≥2.1 ppm. The lowest concentration tested was a lowest-observed-adverse-effect level (LOAEL) for irreversible respiratory-tract lesions, and an adjustment factor of 3 was applied to estimate a no-observed-adverse-effect level (NOAEL) of 0.23 ppm. This point-of-departure is supported by two other experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions. No data were available from which to determine the BCME concentration-time relationship to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 when extrapolating to shorter time points than 7 h and n = 1 when extrapolating to longer time points than 7 h. The 10-min values were not extrapolated because of unacceptably large inherent uncertainty; the 30-min value were adopted for the 10-min value to be protective of human health. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level from 129 exposures in rats and mice (Leong et al. 1981).

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were received 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm, and observed for a lifetime (Drew et al. 1975). After one exposure, rats and hamsters had slightly increased incidences of lung lesions, whereas three exposures produced lung lesions and increased mortality. This study was chosen because it had the highest BCME concentration that caused no mortality after lifetime observation. Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values, using n = 3 and n = 1 for durations shorter and longer, respectively, than 6 h. The 10-min values were set equal to the 30-min values to be protective of human health. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the no-observed-effect level (NOEL) for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, as the effects are unlikely to vary greatly among humans. AEGLs values are summarized in Table 1-1 below.

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure for 10 min to 8 h, as shown in Appendix B,

and in Table 1-2 below. The concentrations are similar to the AEGL-2 values for exposures ≤1 h, but are up to 5-fold lower than AEGL-2 values for exposures of 4-8 h. The carcinogenic end points were not considered appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, a direct comparison of BCME cancer risk and AEGL values is of unknown validity because the two sets of numbers are calculated using different methodologies (the cancer risk calculation involves a linear extrapolation from 25,600 days to 0.5 to 8 h whereas the calculation of AEGL values involves extrapolation from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods). The estimated cancer risks associated with the AEGL-2 and AEGL-3 values are shown in Table 1-2.

TABLE 1-1 Summary of AEGL Values for bis-Chloromethyl Methyl Ether

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR	NR	NR	NR	
AEGL-2 (disabling)	0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm[b] (0.21 mg/m^3)	0.028 ppm[b] (0.13 mg/m^3)	0.020 ppm[b] (0.095 mg/m^3)	NOAEL for irreversible lung lesions in rats and hamsters (Drew et al. 1975)
AEGL-3 (lethal)	0.23 ppm[b] (1.1 mg/m^3)	0.23 ppm[b] (1.1 mg/m^3)	0.18 ppm[b] (0.86 mg/m^3)	0.11 ppm[b] (0.52 mg/m^3)	0.075 ppm[b] (0.36 mg/m^3)	Lethality NOEL for rats and hamsters (Drew et al. 1975)

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).
[b]These concentrations are estimated to have a cancer risk greater than 1×10^{-4}, on the basis of an inhalation cancer slope factor derived by EPA (2002).

TABLE 1-2 Estimated Cancer Risks Associated with a Single Exposure to bis-Chloromethyl Ether

Exposure	10 min	30 min	1 h	4 h	8 h
BCME concentration:	Not calculated	0.069 ppm	0.035 ppm	0.0086 ppm	0.0043 ppm
Estimated cancer risk:		1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}
AEGL-2 value:	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
Estimated cancer risk:	Not calculated	8.0×10^{-5}	1.3×10^{-4}	3.3×10^{-4}	4.7×10^{-4}
AEGL-3 value:	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
Estimated cancer risk:	Not calculated	3.3×10^{-4}	5.1×10^{-4}	1.3×10^{-3}	1.7×10^{-3}

1. INTRODUCTION

BCME is a colorless, flammable liquid with a "suffocating" and irritating odor (O'Neil et al. 2001; NTP 2011). It is used industrially as a chloromethylating agent in the manufacture of ion-exchange resins, bactericides, pesticides, dispersing agents, water repellants, solvents for industrial polymerization reactions, and flame-proofing agents (O'Neil et al. 2001; NTP 2011). BCME is a contaminant (≤10%) of the related and similarly used chemical, chloromethyl methyl ether (CMME) (Langner 1977). BCME does not occur naturally, and human exposure by inhalation is limited to occupational settings. BCME is produced by saturating a paraformaldehyde solution with cold sulfuric acid and hydrochloric acid (HCl) (IARC 1974). A low yield (~0.01-0.001%) of BCME has been shown to form spontaneously from the commonly used chemicals HCl and formaldehyde; for example, mixtures of 500-5,000 ppm each of HCl and formaldehyde produced BCME at <0.5-179 ppb (Kallos and Solomon 1973; Frankel et al. 1974; Albert et al. 1982; Sellakumar et al. 1985).

BCME is hydrolyzed to HCl and formaldehyde upon contact with water, where it is believed to exist in equilibrium with its hydrolysis products, with about 20% of the original compound (Van Duuren et al. 1972). The BCME half-life in water is 10-60 seconds (sec) at 20°C (Van Duuren et al. 1972; Tou and Kallos 1974). In humid air, at ambient temperature and 81% relative humidity, BCME is more stable, having a half-life of 7-25 h depending on the surface coating of the container (Tou and Kallos 1974). Collier (1972) reported that BCME at 10 and 100 ppm was stable for at least 18 h in air with 70% relative humidity. Frankel et al. (1974) also found BCME was stable for 18 h in a Saran bag containing moist air (40% relative humidity, 24°C).

BCME vapor is a severe respiratory, eye, nose, and skin irritant, and has caused pulmonary edema and congestion, corneal necrosis, dyspnea, and blood-stained sputum in humans (O'Neil et al. 2001). BCME is an alkylating agent and has been shown to react in vitro with guanine and adenine of calf thymus DNA (Goldschmidt et al. 1975). BCME and CMME were recognized as potent human respiratory carcinogens in the early 1970s, prompting facilities to develop hermetically isolated systems for their use (Travenius 1982; Collingwood et al. 1987). In 1973, BCME and CMME were listed by OSHA as part of the first group of chemicals to be restricted by federal regulations because of their human carcinogenicity. The use, storage, and handling of preparations containing BCME at ≥0.1% (by weight or volume) must be in a controlled area (29 CFR 1910.1008 [1996]). BCME is classified as a human carcinogen by EPA, the American Conference of Governmental Hygienists (ACGIH), the International Agency for the Research on Cancer (IARC), and the National Institute of Occupational Safety and Health (NIOSH).

As of 1982, BCME is no longer produced as a commercial product in the United States. Small amounts may be produced or repackaged as a chemical intermediate or laboratory chemical, and it might be inadvertently released

during industrial operations (HSDB 2005). Five U.S. suppliers and three non-U.S. suppliers of BCME were identified in 2005 (ChemSources 2005). Selected chemical and physical properties of BCME are listed in Table 1-3.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Exposure to BCME at 100 ppm for 1-2 min might produce fatal lung injury, whereas a concentration of 100 ppm would incapacitate a person in a few seconds (Flury and Zernik 1931).

Thiess et al. (1973) reported a case of a chemical laboratory worker who died after being splashed from an explosive reaction formed when aluminum chloride was added to a reactor that contained BCME in methylene chloride. The worker developed severe conjunctival irritation, corneal opacity, facial-skin irritation, and second and third degree burns on parts of his body within hours of exposure. His optic nerve atrophied and he developed double pneumonia which progressed into pulmonary fibrosis that resulted in death. BCME concentrations were not measured.

TABLE 1-3 Chemical and Physical Data for bis-Chloromethyl Ether

Parameter	Value	Reference
Synonyms	BCME; bis-CME; chloromethyl ether; dichlorodimethyl ether; oxybis(chloromethane); dichloromethyl ether	NIOSH 2005
CAS registry no.	542-88-1	NIOSH 2005
Chemical formula	$(CH_2Cl)_2O$	NIOSH 2005
Structure	O(CCl)CCl	NIOSH 2005
Molecular weight	114.96	O'Neil et al. 2001
Physical state	Colorless liquid	O'Neil et al. 2001
Melting point	-41.5°C	HSDB 2005
Boiling point	106°C	O'Neil et al. 2001
Density (water = 1)	1.315 at 20/4°C	O'Neil et al. 2001
Vapor density	4.0 (air = 1)	HSDB 2005
Solubility in water	Decomposes to HCl and formaldehyde	O'Neil et al. 2001
Vapor pressure	30 mm Hg at 22°C	HSDB 2005
Flammability limits (volume % in air)	Flash point <23°C; estimated lower explosives limit = 6.5%; estimated upper explosives limit = 21.9%	AIHA 2000; NIOSH 2005
Conversion factors	1 mg/m^3 = 0.21 ppm; 1 ppm = 4.75 mg/m^3	HSDB 2005

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Awareness

BCME has a "suffocating" odor (O'Neil et al. 2001). A several-hour exposure to a concentration of BCME (specified only as <3 ppm) did not reach the threshold of perception, but caused severe eye damage several hours after exposure ceased (Travenius 1982). Leong et al. (1971) stated that BCME is a health risk at concentrations that do not produce sensory irritation.

Travenius (1982) reported that the highest tolerable concentration of BCME in air is 5 ppm. BCME was found to be distinctly irritating at 3 ppm (Flury and Zernik 1931).

The data were not adequate to derive a level-of-distinct-odor awareness according to the guidance of van Doorn et al. (2002).

2.2.2. Occupational Exposure

Thirteen accidental exposures to unknown concentrations of BCME occurred from leaking pipes or vessels in a German chemical plant (Thiess et al. 1973). Two of the exposures resulted in severe chemical burns of the cornea that did not completely heal, and some local skin burning. The other 11 exposures were milder, resulting in short-term irritation of the upper respiratory tract, headaches, and nausea. It was not reported whether there was simultaneous exposure to other airborne chemicals.

An overall 8-h time-weighted average concentration for BCME of 0.34 ppb (quarterly range of 0.01-3.1 ppb) was measured for seven workers in an anion exchange plant between 1972 and 1975 (Langner 1977). CMME containing up to 10% BCME was used in closed systems of the plant. No cases of oat-cell respiratory cancer were reported in workers at the plant over its 27 years of operation.

Unwin and Groves (1996) detected BCME at concentrations of 0.03-15.4 ppb at three industrial plants in the United Kingdom. Air samples were taken near reaction vessels where BCME formation was anticipated, and from the continuous online air sampling system. No irritation or other toxicity were reported in the workers, although health effects were not specifically addressed in the study.

Studies in which BCME exposure was associated with respiratory cancer are described in Section 2.5.

2.3. Neurotoxicity

No studies reporting neurotoxic effects of BCME in humans were found.

2.4. Developmental/Reproductive Effects

No developmental or reproductive human studies with BCME were found.

2.5. Genotoxicity

The incidence of chromosomal aberrations was greater in the peripheral lymphocytes of workers exposed to BCME during the manufacture of ion-exchange resins than in control workers (Sram et al. 1983, 1985). The frequency of aberrations was not related to the years of exposure (1-10 years), but was related to the calculated BCME exposure during the last 3 months.

An 11-fold increase in the frequency of transformed cells occurred in human lung WI-38 cells cultured with BCME at 0.008-25 milligrams per milliliter (mg/mL) in the presence of exogenous activation (Styles 1978). Human neonatal foreskin fibroblasts had a 3-14 fold increase in anchorage-independent cells after incubation with BCME at 0.1-8 micrograms per milliliter (μg/mL) (Kurian et al. 1990).

DNA repair was increased in human skin fibroblasts exposed to BCME at ≥0.16 μg/mL, although the quantitative response was not provided (Agrelo and Severn 1981).

2.6. Carcinogenicity

BCME is classified as a human carcinogen by EPA, ACGIH, IARC, and NIOSH. EPA (2002) places BCME in classification A ("human carcinogen") on the basis of sufficient human carcinogenicity data. ACGIH (1991) places BCME in group A1 ("confirmed human carcinogen"), IARC (1987) places it in Group I ("sufficient evidence of carcinogenicity in humans"), and NIOSH (2005) states that BCME is a carcinogen, with no further classification.

2.6.1. Case Reports

Reznik et al. (1977) reported a case of a chemist who developed bronchial adenocarcinoma and died 12 years after over 2 years of work on an experiment in which BCME and CMME were reaction byproducts. Air concentrations of BCME or CMME were unknown but the chemical reaction with triphenyl hydroxymethyl phosphonium chloride was conducted "on a scale of 1-2 mol."

Three workers from a small BCME manufacturing facility in the United Kingdom died from lung cancer (Roe 1985). The exposure concentrations and the total number of men exposed were not given, but it was stated that "between 5 and 8 individuals were employed at any one time on a process involving a chloromethylation stage." The ages of the men at diagnosis were 35-40 years.

Two of the 3 men had oat-cell carcinoma, and the third had anaplastic squamous-cell carcinoma.

Two cases of small-cell lung cancer were attributed to BCME exposure in a Japanese manufacturing facility (Fujio et al. 1986). BCME concentration was not reported. Each case involved a male smoker of approximately 50 years old. One worker was exposed to BCME for 2 years and the other for 8 years. The latter worker died within a year after diagnosis despite treatment with radiation and chemotherapy; the other worker seemingly recovered.

2.6.2. Epidemiologic Studies

In 1972, four workers at a California chemical plant (Diamond Shamrock Co., Redwood City) with 100-200 workers exposed to BCME from anion-exchange resin production died from lung cancer, and two more workers developed lung cancer (Donaldson and Johnson 1972; Fishbein 1972). The ages of the workers at death were 31-48. The concentration of BCME in the air was not reported. One of the workers that died, a 32-year old man, worked at the plant only 2 years. Subsequent cytologic analysis of exfoliated cells in the sputum of 125 current white male employees found a significant association between abnormal cytology (metaplasia and atypia) and exposure to BCME for more than 5 years (34% of anion-exchange workers vs. 11% of controls), whereas there was no difference between in-plant workers not involved in anion-exchange resin production and controls (Lemen et al. 1976). In concert with this cytology survey, a retrospective cohort study of 136 men who worked in the plant for 5 or more years between Jan. 1, 1955 and Mar. 31, 1972 (mean exposure was 10 years) was conducted. During this 17-year period, nine workers died: five from heart disease, one from lymphosarcoma, and three from bronchogenic cancer. Two more workers were diagnosed with bronchogenic cancer. The five cases among 136 workers represented a 9-fold increase in lung cancer from the expected mortality rate of 0.54 cases in white, age-matched men from Connecticut. The histologic type of carcinoma in four of five cases was small-cell undifferentiated carcinoma (the fifth case was large-cell undifferentiated carcinoma). The mean latency period was 15 years and the mean age of the cancer patients was 47 years, the majority of whom were smokers. The majority (>60%) of the workers were followed for less than 10 years after exposure, suggesting that the actual cancer incidence might have been greater.

Five of 32 workers exposed to unreported concentrations of BCME in a Japanese dyestuff factory for 4-7 years during 1955-1970 died of lung cancer, compared with the expected incidence of 0.024 (Sakabe 1973). One of the five cases was confirmed as being of the oat-cell carcinoma type. The latency period was 8-14 years after initial exposure. The men were smokers and their ages were 37-47 at the time of death. A subsequent epidemiologic study of this and a second Japanese dyestuff factory where BCME was manufactured and used

between 1960 and 1968, found a total of 13 cases of lung cancer among 35 exposed men at the two factories (Nishimura et al. 1990). The overall mean exposure period was 7.2 years, the latency period was 13.5 years, and age at death was 46.1 years. The histologic types of the eight cases not previously described by Sakabe (1973) were: small-cell carcinoma in five cases, adenoma in three cases, and large-cell carcinoma in one case.

In a retrospective study for years 1956-1962, Thiess et al. (1973) reported that six of 18 testing facility workers and two of 50 production workers developed lung cancer after 6-9 years of exposure to BCME at unknown concentrations. Most of the workers were smokers. The tumor latency period was 8-16 years. Five of the eight cases were diagnosed as oat-cell carcinomas.

Air concentrations of BCME, but not CMME, were measured in a factory in Chauny, France, that used CMME to produce anion exchange resins (because BCME is more stable) (Gowers et al. 1993). This study is described in greater detail in the technical support document for CMME (see Chapter 2 of this report). For 1979-1984, mean yearly concentrations of BCME were found to be 0.6-4.4 ppb (1.7 ppb, overall weighted average) by mass spectrometry of personal and stationary air samples (n = 96-175 per year). Workers exposed previously to much higher BCME concentrations had an increased incidence of lung cancer with small-cell histology relative to nonexposed workers.

Xue et al. (1988) reported the results of an epidemiologic investigation of lung cancer incidence in a cohort of 915 workers (534 men, 381 women) in 11 plants in China that produced or used "chloromethylether (CME)." It was not clear whether exposure was to BCME or CMME or both. The concentration of chloromethyl in the air was not measured. Between 1958 and 1981, there were 32 mortalities, 15 from lung cancer. Of the 11 cases evaluated histologically, eight were undifferentiated cell carcinoma and three were squamous cell carcinoma. The average age at death was 49.7 (32-64), and the mean interval from beginning of exposure to diagnosis was 9.86 years (2-20). Calculation of standard mortality ratios using various reference cohorts showed that the excess of deaths from all causes and all cancers were from increased lung cancer mortality. The number of lung cancer cases increased with exposure severity, which was estimated from the degree of irritation, job description, and duration of exposure. Heavy smoking was associated with increased lung cancer.

2.7. Summary

No quantitative human studies of BCME were found in which the exposure duration, concentration, and corresponding observed effects were reported. BCME caused severe eye damage and workers developed lung tumors from exposure concentrations that did not produce sensory irritation. The lung cancers had a shorter latency period and histology distinct from tumors from cigarette smoking. BCME is one of the most potent known human (and animal) carcinogens, and is classified as a human carcinogen by EPA, ACGIH, IARC,

and NIOSH. No human developmental or reproductive toxicity studies of BCME were found. An increased incidence of chromosomal aberrations was found in peripheral lymphocytes of workers exposed to BCME, and BCME induced cell transformation and DNA repair in vitro. A summary of semi-quantitative inhalation exposure studies of BCME is provided in Table 1-4.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

In a range-finding study, a 4-h exposure to a nominal concentration of BCME at 7.8 ppm caused death in one of six male albino rats on day 14, and 15.6 ppm caused deaths in all six test rats on days 2, 4, and 7 (Union Carbide 1968; Smyth et al. 1969). The LC_{50} (lethal concentration, 50% lethality) was reported to be 10.26 ppm. Animals that died had lung hemorrhage and blood in the intestines, and survivors had morphologic lung changes described as "consolidated" or "greatly enlarged" areas. Exposure to "substantially" saturated vapor (~40,000 ppm at saturation) caused irritation and prostration by 3 min, and killed six of six rats within 8 min (Union Carbide 1968).

TABLE 1-4 Summary of Human Exposure Data with Defined Concentrations to bis-Chloromethyl Ether

Exposure Concentration	Exposure Duration	Results (Reference)
0.01-3.1 ppb	≤27 years	No effects from occupational exposure (Langner 1977)
0.03-15.4 ppb	Years	No effects reported at three industrial plants (Unwin and Groves 1996)
0.6-4.4 ppb	Years	No sensory effects reported; workers developed oat-cell carcinoma but were previously exposed to much higher BCME levels (Gowers et al. 1993)
<3 ppm	Unknown (short-term)	Did not reach the threshold of perception but caused severe eye damage several hours after exposure ceased (Travenius 1982)
3 ppm	Unknown (short-term)	Distinctly irritating (Flury and Zernik 1931)
5 ppm	Unknown (momentary)	Highest "tolerable" concentration (Travenius 1982)
100 ppm	Few seconds	Would incapacitate a person (Flury and Zernik 1931)
100 ppm	1-2 min	Might produce fatal lung injury (Flury and Zernik 1931)

In another study, all 12 test rats died after 3 min of inhaling air saturated with BCME (~40,000 ppm) (Zeller and Hoffmann 1973). The animals had mucous membrane irritation, milky opacity of the cornea, narcosis, and dyspnea.

Drew et al. (1975) conducted three sets of experiments to evaluate the inhalation toxicity of BCME in male Sprague-Dawley rats. The acute lethality of BCME was determined using ~8-week old rats (10/concentration). Rats were exposed for 7 h to BCME at 0.94-74 ppm and observed for 14 days. BCME vapor was generated by bubbling air through or passing it over liquid BCME before it was introduced into 128-L or 1.3-m^3 exposure chambers; air concentrations of BCME were measured every half-hour spectrophotometrically after coupling with 4-(*p*-nitrobenzyl) pyridine. Lungs were removed from each animal and damage was measured as an increase of three standard deviations in the lung-to-body weight ratio. The ratio for controls was approximately 0.6. A value of 0.9 was considered elevated for rats. (Previous studies with irritants in the same laboratory showed that this ratio was an objective indicator of lung damage.) As shown in Table 1-5, the 14-day LC_{50} was estimated graphically to be ~7 ppm. All animals given BCME at ≥9 ppm died within 14 days, most on the first post-exposure day. The rats had extensive lung damage, including congestion, edema, and hemorrhage and a dose-related increase in the incidence of lung-to-body weight ratio.

In a related experiment, Drew et al. (1975) examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, or 9.5 ppm in rats (25/concentration; 50 controls) observed for their lifetimes. Results were reported in terms of percentage of findings per number of observations, as shown in Table 1-6, although it was not clear how the "number of observations" was determined, relative to the original 25 or 50 animals per dose group. At concentrations of 2.1 ppm and greater, rats had severe life shortening (first death during week 2), weight loss, and elevated lung-to-body weight ratios, and as lung edema, congestion, and hemorrhage. Histopathologic findings included increased incidences of tracheal and bronchial hyperplasia (often with nuclear atypia) and squamous metaplasia compared with controls. Animals exposed to BCME at 0.7 ppm had respiratory pathologic changes similar to those of controls, although there was an increase in the incidence of tracheal epithelial hyperplasia (67% vs. 36% in controls) and increased lung-to-body weight ratios.

In their third experiment, Drew et al. (1975) subjected groups of 50 rats to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm. Results were reported in terms of percentage of findings per number of observations, as shown in Table 1-7. All groups that received 3, 10, or 30 exposures had increased mortality compared with controls and dose-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia. Additional findings in rats that received 1 or 10 exposures included bronchoalveolar squamous metaplasia (incidences of 1/29 and 5/43, respectively), cuboidal transformation of the alveolar epithelium (4/29 and 7/43, respectively), and alveolar squamous metaplasia (0/29 and 3/43, respectively). One rat that died 570 days after three exposures had an ulcerating squamous skin cell carcinoma. Central nervous

system effects and extreme irritability were seen after 10 or 30 exposures: subarachnoid hemorrhage was seen microscopically in 24% of the rats given 30 exposures, and in 17% of the rats given 10 exposures.

TABLE 1-5 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Rats after Single 7-Hour Exposure to bis-Chloromethyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Rats with increased lung-to-body weight ratio (%)[a]	Estimated LC_{50}[b]
74	100	100	7 ppm
19	100	100	
9	100	100	
7.3	60	90	
6.2	30	100	
4.6	0	100	
0.94	0	40	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} value was estimated graphically by the study authors.
Source: Adapted from Drew et al. 1975.

TABLE 1-6 Median Lifespan, Lung-to-Body Weight Ratio, and Histopathologic Findings in Rats after Single 7-Hour Exposure to bis-Chloromethyl Ether

Concentration (ppm)	Median Lifespan (d)	Increased Lung-to-Body Weight Ratio[a] (%)	Histopathologic Findings in Lung Mucosa (%) (based on number observations [obs])[b]
9.5	2	93	Specific lesions not quantified; respiratory lesions similar to those at 2.1 ppm but with higher incidence; seen only in rats that survived >2 d
6.9	2	88	
2.1	36	100	Tracheal [obs = 6]: hyperplasia (100), squamous metaplasia (17) Broncheal [obs = 13]: hyperplasia (100), with atypia (28); squamous metaplasia (62)
0.7	420	96	Increased tracheal epithelial hyperplasia (67% vs. 36% in controls;[c] incidence not stated)
Control	462	0	Tracheal [obs = 35]: hyperplasia (31)[c], squamous metaplasia (11); Broncheal [obs = 48]: hyperplasia (50), with atypia (6); squamous metaplasia (27)

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]Report does not state how the "number of observations" was determined, relative to the original 25 animals per dose group and 50 controls.
[c]The incidence of epithelial hyperplasia in controls is reported by Drew et al. (1975) as 36% on page 66 and as 31% on page 64 (see Table 3) of the reference.
Source: Adapted from Drew et al. 1975.

TABLE 1-7 Median Lifespan and Histopathologic Findings in Rats after Multiple 6-Hour Exposures to bis-Chloromethyl Ether at 1 ppm

Number Exposures	Median Lifespan (d)	Histopathologic Findings in the Lung Mucosa (%) (based on number of observations [obs])[a]
30	23	Tracheal [obs = 35]: hyperplasia (89), with atypia (11); squamous metaplasia (37); Broncheal [obs = 41]: hyperplasia (95), with atypia (27); squamous metaplasia (66), with atypia (7)
10	21	Tracheal [obs = 23]: hyperplasia (70), with atypia (52); squamous metaplasia (13) Broncheal [obs = 45]: hyperplasia (80), with atypia (47); squamous metaplasia (58)
3	168	Tracheal [obs = 23]: hyperplasia (52), with atypia (22) squamous metaplasia (26); Broncheal [obs = 34]: hyperplasia (62), with atypia (26); squamous metaplasia (41), with atypia (3)
1	457	Tracheal [obs = 22]: hyperplasia (27), with atypia (18) Broncheal [obs = 39]: hyperplasia (41), with atypia (5); squamous metaplasia (23)
Control	462	Tracheal [obs = 35]: hyperplasia (31), squamous metaplasia (11); Broncheal [obs = 48]: hyperplasia (50), with atypia (6); squamous metaplasia (27)

[a]Report does not state how the "number of observations" was determined, relative to the original 50 animals per dose group.
Source: Adapted from Drew et al. 1975.

An RD_{50} (50% decrease in the respiratory rate) value of 145 ppm for BCME was calculated in 8-week old male Crl-CD rats treated head-only for 15 min (Gardner et al. 1985). The BCME exposure concentrations and corresponding mean decreases in respiration rate were 14.4 ppm (14%), 32.5 ppm (16%), 49.8 ppm (37%), 82.8 ppm (55%), 125 ppm (47%), and 233 ppm (62%). The rats (4/dose) were exposed in a body plethysmograph and each rat was its own control. The maximal respiratory inhibition was achieved after 4 min of exposure. During the 5-min post-exposure period, the respiration rate improved but did not return to pretreatment rates. All rats exhibited lacrimation after exposure, and the rats exposed to BCME at 125 and 233 ppm had red nasal discharge. During the 48-h post-treatment observation period, severe weight loss and mortality occurred at ≥82.8 ppm (mortality: 2/4, 2/4, and 1/4 at 82.8, 125, and 233 ppm, respectively). Gardner et al. (1985) also evaluated the respiratory inhibition caused by seven other tumorigens to determine if there was a correlation between sensory irritation potential and nasal tumorigenic potential; no correlation was found.

3.1.2. Mice

Strain A/Heston male mice exposed for 6 h to BCME at 2.7-10.6 ppm had a 14-day LC_{50} of 5.3 ppm (95% confidence limit: 3.7-7.6 ppm) but no respiratory tract irritation (Leong et al. 1971). No further details of the study were provided.

3.1.3. Hamsters

Drew et al. (1975) examined the inhalation toxicity of BCME using male Syrian golden hamsters (~6 weeks old). The generation and measurement of BCME vapor, as well as the evaluation of lung damage was conducted as in the rat studies (see Section 3.1.1.), except that a lung-to-body weight ratio of 0.8 was considered elevated for hamsters. In an acute lethality experiment, hamsters (10/concentration) were exposed for 7 h to BMCE at 0.94-74 ppm and observed for 14 days. Mortality was increased at ≥4.6 ppm, and the 14-day LC_{50} was 7 ppm. All animals given BCME at ≥9 ppm died within 14 days. Animals had concentration-dependent increases in relative lung weights and damaged lungs (congestion, edema, and hemorrhage). The results are summarized in Table 1-8.

TABLE 1-8 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Hamsters Exposed to bis-Chloromethyl Ether for 7 Hours

Concentration (ppm)	Mortality at 14 d (%)	Increased Lung-to-Body Weight Ratio[a] (%)	Estimated LC_{50}[b]
74	100	100	7 ppm
19	100	100	
9	100	100	
7.3	60	90	
6.2	10	90	
4.6	10	100	
0.94	0	10	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} values were estimated graphically by the study authors.
Source: Adapted from Drew et al. 1975.

The long-term effect of single 7-h exposures to BCME at 0.7, 2.1, 5.6, or 9.9 ppm was examined in hamsters (25/concentration) by Drew et al. (1975). The animals were observed for their lifetimes. The study results were reported in terms of percentage of findings per number of observations, as shown in Table 1-9. At concentrations of ≥2.1 ppm, animals had severe life shortening (first death during week 4), weight loss, and high lung-to-body weight ratios, as well as lung edema, congestion, and hemorrhage and tracheal and bronchial hyperplasia (often atypical). The incidence of the mucosal histopathologic changes was tabulated for only the 2.1-ppm exposure group, although the study also reported that four of five hamsters exposed at 5.6 ppm had squamous metaplasia of the tracheal epithelium. Animals exposed to BCME at 0.7 ppm had respiratory pathologic changes similar to those of controls, although there was an increase in the incidence of pneumonitis (67% vs. 23% in controls), and a few animals had bronchial hyperplasia (two animals with atypia), alveolar squamous metaplasia, and bronchoalveolar metaplasia.

TABLE 1-9 Median Lifespan, Lung-to-Body Weight Ratio, and Histopathoglogic Findings in Hamsters Exposed to bis-Chloromethyl Ether for 7 Hours

Concentration (ppm)	Median Lifespan (d)	Increased Lung-to-Body Weight Ratio[a] (%)	Histopathologic Findings in the Lung Mucosa (%) (as of number of observations [obs])[b]
9.9	4	68	Not specified
5.6	16	100	Not tabulated; stated 4/5 animals examined had tracheal epithelium squamous metaplasia
2.1	68	100	Tracheal [obs = 17]: hyperplasia (76), with atypia (18) Broncheal [obs = 12]: hyperplasia (58), with atypia (33)
0.7	657	100	Not tabulated; reported increased pneumonitis (67% vs. 23% in controls; incidences not given), and few animals had bronchial hyperplasia (± atypia), alveolar or bronchoalveolar metaplasia.
Control	675	0	Tracheal [obs = 23]: hyperplasia (18) Broncheal [obs = 25]: hyperplasia (4)

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]Report does not state how the "number of observations" was determined, relative to the original 25 animals per dose group.
Source: Adapted from Drew et al. 1975.

Groups of 50 hamsters were exposed 1, 3, 10, or 30 times to BCME for 6 h at 1 ppm (Drew et al., 1975). The study results were reported in terms of percentage of findings per number of observations, but it was not clear how the "number of observations" was determined relative to the initial 50 animals/group. All groups receiving 3, 10, or 30 exposures had increased mortality compared with controls. Treated hamsters had generally concentration-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia (with and without atypia), with minor increases evident after a single exposure (see Table 1-10). Several other findings were reported in the 1-, 3-, and 10-exposure groups. Animals given 10 exposures had bronchoalveolar metaplasia (4/26; one atypical), bronchoalveolar squamous metaplasia with atypia (1/26), and atypical alveolar epithelium (4/26). One hamster given three exposures had turbinate mucosa metaplasia, and one hamster that died 756 days after three exposures had an early nasal esthesioneuroepithelioma. Animals exposed once had bronchoalveolar metaplasia (1/24), atypical alveolar epithelium (1/24), and one animal that died after 1,000 days had an undifferentiated malignant nose tumor. Central nervous system effects and extreme irritability were seen in animals given 10 or 30 exposures; subarachnoid hemorrhage was seen microscopically in 8% of the hamsters given 30 exposures.

TABLE 1-10 Median Lifespan and Histopathologic Findings in Hamsters Exposed to bis-Chloromethyl Ether at 1 ppm for 6 Hours

Number Exposures	Median Lifespan (d)	Histopathologic Findings in the Lung Mucosa (%) (as of number of observations [obs])[a]
30	42	Tracheal [obs = 18]: hyperplasia (67), with atypia (6); squamous metaplasia (44) Broncheal [obs = 10]: hyperplasia (60), with atypia (40)
10	137	Tracheal [obs = 30]: hyperplasia (70), with atypia (33); squamous metaplasia (20) Broncheal [obs = 30]: hyperplasia (50), with atypia (20); squamous metaplasia (7)
3	471	Tracheal [obs = 39]: hyperplasia (21), with atypia (13) Broncheal [obs = 40]: hyperplasia (20), with atypia (8); squamous metaplasia (0), with atypia (0)
1	620	Tracheal [obs = 31]: hyperplasia (16), with atypia (3); squamous metaplasia (3) Broncheal [obs = 40]: hyperplasia (13), with atypia (3)
Control	675	Tracheal [obs = 23]: hyperplasia (18) Broncheal [obs = 25]: hyperplasia (4)

[a]Report does not state how the "number of observations" was determined, relative to the original 50 animals per dose group.
Source: Adapted from Drew et al. 1975.

3.2. Nonlethal Toxicity

3.2.1. Rats

Three multiple-exposure rat studies in which carcinogenicity was an end point are detailed in Section 3.5.1. (Kuschner et al. 1975; Leong et al. 1975, 1981; Dulak and Snyder 1980).

3.2.2. Mice

In an upper respiratory tract screening assessment (Alarie 1966) with strain A/Heston male mice, 60-sec exposure to BCME was nonirritating at concentrations as high as 10.6 ppm (Leong et al. 1971). No further details of the experiment were given. However, in the screening technique, mice are typically placed in body plethysmographs and a decrease in their breathing rate during the 60-sec exposure or during the ensuing 15-min observation period is considered indicative of irritation.

Two multiple-exposure carcinogenicity studies conducted by Leong et al. (1971, 1981) are summarized in Section 3.5.2.

3.2.3. Hamsters

A multiple-exposure study of BCME in hamsters (Kuschner et al. 1975) is described in Section 3.5.3.

3.3. Developmental and Reproductive Effects

No studies were found assessing developmental or reproductive effects of BCME on animals.

3.4. Genotoxicity

BCME was mutagenic in *Salmonella typhimurium* TA100, but not in TA1535, TA1538, or TA98 in a plate incorporation assay when tested at a concentration of 20 μg/plate, with activation (Anderson and Styles 1978). Another laboratory found that exposure to BCME at 0.5 μL per 2,000 cm^3 in the absence of metabolic activation was weakly mutagenic in *S. typhimurium* TA1535 (Norpoth et al. 1980). BCME was found to be mutagenic in *Escherichia coli* and *S. typhimurium* by Mukai and Hawryluk (1973), but experimental details were not provided.

A 6.6-fold increase in the frequency of transformed cells occurred in BHK-21 cells cultured with BCME at 0.008-25 mg/mL in the presence of exogenous activation (Styles 1978).

Chromosome aberrations were not induced in the bone marrow cells of Sprague-Dawley rats examined 5 days after being exposed by inhalation to BCME at 1-100 ppb for 6 h/day, 5 days/week for 6 months (Leong et al. 1981).

DNA synthesis was inhibited in the epidermis of mice for up to 24 h after dermal exposure to BCME at 9 or 18 μmols, as detected by radiolabeled thymidine, cytidine, or leucine administered after treatment. RNA synthesis was increased maximally after 12 h (Slaga et al. 1973).

Goldschmidt et al. (1975) showed that BCME binds to DNA at guanine and adenine residues in vitro. However, in other in vitro studies, BCME did not form any isolable discrete base-alkylation products (assessed by thin-layer chromatography) and had no effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al. 1969, 1972).

3.5. Chronic Toxicity and Carcinogenicity

3.5.1. Rats

Male Sprague-Dawley rats (70) were exposed to BCME at 0.1 ppm for 6 h/day, 5 days/week, for their lifetimes (Kuschner et al. 1975). Animals were exposed in a 1.3-m^3 chamber, and air concentrations of BCME were measured at 30-min intervals using the coupling agent 4-(*p*-nitrobenzyl) pyridine. Because mortality was high (43% after 80 exposures [16 weeks]), additional groups of rats were exposed to BCME at 0.1 ppm for a total of 10, 20, 40, 60, 80, or 100 exposures and observed until death (20-50 animals per concentration). A control group of 240 rats was included, but only the mortality results were given for this group. The lungs were examined microscopically, and the nose was also examined once the first nasal tumor was found. Twenty animals from the chronic study were removed after 80 exposures and added to the limited-exposure 80-exposure group to determine cancer incidence.

Rats given ≥80 exposures had shortened lifespan and deceased weight gain. In the limited-exposure study, mortality after 80 exposures was about half of that in the initial chronic study, for unknown reasons. Animals given 10-100 exposures had 40 nasal and lung cancers; 17 nasal esthesioneuroepitheliomas, 13 lung squamous-cell carcinomas, four poorly differentiated nasal-epithelial tumors, two nasal adenocarcinomas, and one each of lung adenocarcinoma, malignant olfactory tumor, ganglioneuroepithelioma, and nasal squamous-cell carcinoma. Only one rat (100 exposures) had both cancer types. The median induction time for all tumors was 440 days, and it was determined that there was a probability of ≤1% of developing a tumor before exposure for 210 days. When the survival cutoff of 210 days was used, a clear concentration-response relationship was seen in animals given 10-100 exposures. The shortest number of exposures that resulted in cancer was 10. In that case, a nasal adenocarcinoma was found in one rat that died after 652 days. It is possible that some early nasal tumors were missed because the nose was not dissected in animals that died

early in the study. Information on controls was not provided by Kuschner et al. (1975), but the incidence of cancer was given as 0/240 in the EPA (2002) Integrated Risk Information System (IRIS) carcinogenicity risk assessment. The limited-exposure study results, summarized in Table 1-11, were used by EPA (2002) to derive a cancer slope factor and unit risk for BCME (see Appendix B).

TABLE 1-11 Median Lifespan and Respiratory Cancers in Rats after Limited Exposures to bis-Chloromethyl Ether at 0.1 ppm

		Number of Rats			
Number of Exposures	Median Lifespan (wk)	At start	At ≥210 d	At ≥210 d with cancer (%)	Cancer Types (number of affected animals)
100	50	30	20	12 (60.0)	Nose: ENE (3), unclassified malignant tumor (1), PD epithelial tumor (1) Lung: squamous-cell carcinoma (8)
80	43	30 + 20[a]	34	15 (44.1)	Nose: ENE (9), squamous-cell carcinoma (1), ganglioneuroepithelioma (1), PD epithelial tumor (1) Lung: squamous-cell carcinoma (3)
60	61	20	18	4 (22.2)	Nose: ENE (2) Lung: squamous-cell carcinoma (2)
40	71	20	18	4 (22.2)	Nose: ENE (2), PD epithelial tumor (1) Lung: adenocarcinoma (1)
20	69	50	46	3 (6.5)	Nose: ENE (1), PD epithelial tumor (1), adenocarcinoma (1)
10	69	50	41	1 (2.4)	Nose: adenocarcinoma (1)
0	66	240	NR[b]	NR[b]	NR[b] (none)

[a]Twenty animals from the chronic-exposure study were removed after 80 exposures and added to this group to determine cancer incidence.
[b]The incidence of rats with respiratory cancers was not specified in the study, but was reported as 0/240 in EPA (2002).
Abbreviations: ENE, esthesioneuroepithelioma; NR, not reported; PD, poorly differentiated.
Source: Adapted from Kuschner et al. 1975.

Leong et al. (1975, 1981) attempted to determine whether there is a non-tumorigenic or NOEL for BCME inhalation in rodents. Groups of 120 male rats (Sprague-Dawley Specific Pathogen-free) were exposed to BCME at 0, 1, 10, or 100 ppb for 6 h/day, 5 days/week for 6 months (129 exposures), followed by lifetime observation. Some animals were sacrificed after 6 months for pulmonary exfoliative cytologic examination on day 1 of the post-exposure period, and cytogenetic evaluation of bone marrow chromosomes on day 5 postexposure. Tests were performed in a 3.7-m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump and the BCME concentration was measured at least once daily. Parameters assessed included periodic and terminal body weights, gross and microscopic pathology, organ weights, hematology (packed cell volume, mean hemoglobin concentration, red- and white-blood-cell count, and differential white-blood-cell count). No treatment-related non-neoplastic gross or microscopic changes, effects on hematology, organ weights, bone marrow cell chromosome integrity, or pulmonary exfoliated cells were seen in any group of rats. Neither respiratory tumors nor increased mortality occurred in rats or mice exposed to BCME at 1 or 10 ppb. Rats exposed to BCME at 100 ppb, however, had increased (tumor-related) mortality starting at the seventh experimental month (1 month postexposure) and all died or were euthanized by the nineteenth experimental month. Most of the 100-ppb rats developed esthesioneuroepitheliomas (96/111; 86.5%), of which four also had pulmonary adenoma. The tumors were frequently found 2-7 months postexposure, with the first case occurring during the sixth month of exposure. Many of the animals had a distended gastrointestinal-tract lumen secondary to the nasal obstruction and subsequent mouth breathing.

Male Sprague-Dawley rats (number not specified) were exposed by inhalation to BCME at 0.1 ppm for 30 exposures (6 h/day, 5 days/week) with lifetime follow-up (Dulak and Snyder 1980). Approximately 35% of the animals died with respiratory tract tumors, which were first observed 350 days after exposure.

3.5.2. Mice

A/Heston male mice (47) were exposed to BCME at 1 ppm for 6 h/day, 5 days/week, for 82 times over 27 weeks, after which they were sacrificed (Leong et al. 1971). Testing was performed in 100-L acrylate plastic chambers, and BCME vapor was generated by metering liquid BCME into the airstream entering the exposure chamber; the analytic concentration inside the chamber was not measured. The lungs of all the treated animals, as well as the 49 control males (exposed to filtered room air for 28 weeks) were examined histologically. Compared with untreated controls, the BCME-exposed mice had an increased incidence (55% vs. 41% for controls) and multiplicity (5.2 vs. 2.2 for controls)

of lung adenomas. These mice had body weight loss, respiratory distress, and 37/50 died during the exposure period. Gross necropsy revealed 27/47 animals with lung tumors and 11/47 with pinpoint hemorrhages or patchy consolidation in the lungs.

Leong et al. (1981) exposed groups of 144-157 male Ha/ICR mice to BCME at 0, 1, 10, or 100 ppb for 6 months (129 exposures) followed by lifetime observation to determine whether there is a non-tumorigenic or no-observable-effect level for BCME inhalation. Animals were exposed for 6 h/day, 5 days/week, in a 3.7-m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump and the chamber BCME concentration was measured at least once daily. Parameters assessed included periodic body weights and terminal gross and microscopic pathology. All groups had ascending urinary tract infections, which "may have been aggravated by exposure to BCME." No treatment-related toxic or neoplastic effects were seen in mice exposed at 1 or 10 ppb. However, when mice that died prematurely from urinary tract infections were excluded from analysis, the 100-ppb group had increased mortality and incidence of pulmonary adenomas (8/27 vs. 9/86 for controls). No nasal tumors were seen. Leong et al. (1981) concluded that "10 and 1 ppb appear to be the no-observable-effect-levels for a 6-month exposure period."

3.5.3. Hamsters

Male Syrian golden hamsters (100) were exposed to BCME at 0.1 ppm for 6 h/day, 5 days/week, for their lifetimes (Kuschner et al. 1975). Mortality was increased after 20 weeks and one hamster that received 334 exposures developed an undifferentiated lung carcinoma and died on day 501 (Kuschner et al. 1975).

3.5.4. Carcinogenicity by Other Exposure Routes

BCME is also shown to be a carcinogen by other routes of exposure. Application of BCME (2 mg in 0.1 mL benzene) to the skin of female ICR/Ha Swiss mice three times per week for 325 days caused papillomas in 13 of 20 mice, 12 of which became squamous-cell carcinomas (Van Duuren et al. 1968, 1972). A single dermal application of BCME (1 mg in 0.1 mL benzene) had no effect, but when followed by promotion with acetone/phorbol esters, papilloma developed in five of 20 mice, two of which progressed to squamous-cell carcinoma (Van Duuren et al. 1972). Other investigators also showed that BCME (1 mg applied dermally) was a potent tumor initiator in mice (Slaga et al. 1973; Zajdela et al. 1980). Newborn ICR-Swiss mice (50/sex) injected subcutaneously with BCME at 0.0125 mg/kg in peanut oil had a 45% incidence

and 0.64 multiplicity of pulmonary adenomas at the 6-month sacrifice, and two mice developed papilloma or fibrosarcoma at the injection sites (Gargus et al. 1969). The vehicle control had a 15% incidence and 0.14 multiplicity of lung tumors. Female Sprague-Dawley rats (20) injected with BCME subcutaneously once weekly for 300 days at 1 or 3 mg in Nujol developed local fibromas (2/20) and fibrosarcomas (5/20), but there was no increase in distal tumors or any tumors in rats injected with the solvent only (Van Duuren et al. 1969). ICR/HA Swiss mice (Van Duuren et al. 1975) and XVIInc/Z mice (Zajdela et al. 1980) injected subcutaneously with 0.3 mg of BCME in Nujol once weekly for over a year developed a high incidence (~40%) of sarcomas at the injection site. Van Duuren et al. (1975) also found one sarcoma (1/50 mice) in the Nujol-only controls, and Zajdela et al. (1980) found pulmonary adenomas in 7of 57 mice. Female ICR/HA Swiss mice that received weekly intraperitoneal injections of BCME (0.0.02 mg in 0.05 mL of Nujol) for 537 days developed local sarcomas (4/30) and had a decreased median survival time; no sarcomas were found in the Nujol-treated or untreated controls (Van Duuren et al. 1975).

3.6. Summary

Rats and mice had no apparent irritation from exposure to BCME at concentration greater than those producing carcinogenicity or toxicity. The LC_{50} of BCME for rats and hamsters, based on a 7-h exposure and 2-week observation period, was about 7 ppm for both species (Drew et al. 1975). An examination of the long-term effects of a single 7-h exposure of BCME at 0.7-9.5 ppm in rats and hamsters showed that some pathologic changes of the respiratory system occurred at even the lowest concentration, although overt treatment-related toxicity and increased mortality occurred at concentration of ≥2.1 ppm (tracheal epithelial hyperplasia in rats and pneumonitis in hamsters) (Drew et al. 1975). Rats and hamsters given 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm had generally exposure-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia, and mortality was increased with ≥3 exposures (Drew et al. 1975). Rats, mice, and hamsters exposed by inhalation to BCME at 0.1 ppm for as few as 10 six-hour exposures developed respiratory tumors or had shortened lifetimes (Kuschner et al. 1975; Leong et al. 1975, 1981; Dulak and Snyder 1980). No treatment-related non-neoplastic or neoplastic effects were seen in rats or mice exposed to BCME at 1 or 10 ppb for 6 h/day for 6 months (Leong et al. 1975, 1981). No studies were located assessing developmental or reproductive effects of BCME in animals. BCME was mutagenic in several strains of *S. typhimurium*, increased the transformation frequency of BHK-21 cells, inhibited DNA synthesis, and was shown to bind DNA, but did not induce chromosome aberrations in rat bone marrow.

Summaries of BCME single-exposure and multiple-exposure animal studies are presented in Table 1-12 and Table 1-13, respectively.

TABLE 1-12 Animal Studies of Single Exposure to bis-Chloromethyl Ether

Species	Exposure Duration	Concentration (ppm)	Effects (Reference)
Rat	4 h	7.8, 15.6	14-d LC_{50} = 10.26 ppm; 1/6 died at 7.8 ppm (day 14) and 6/6 died at 15.6 ppm (day 2, 4, 7). Decedents had lung hemorrhage and blood in the intestines. Survivors had morphologic lung changes ("consolidated" or "greatly enlarged" areas) (Union Carbide 1968; Smyth et al. 1969).
Rat	3 min 8 min	Saturated (~40,000)	Irritation and prostration; 6/6 died (Union Carbide 1968).
Rat	3 min	Saturated (~40,000)	12/12 died; mucous membrane irritation, milky opacity of the cornea, narcosis, and dyspnea (Zeller and Hoffmann 1973).
Rat	7 h	0.94,4.6, 6.2, 7.3, 9, 19, 74	14-d LC_{50} = 7 ppm; 100% mortality at ≥9 ppm (most on day 2). Extensive lung congestion, edema, and hemorrhage, and increased lung-to-body weight ratio (Drew et al. 1975).
Rat	7 h	0.7, 2.1, 6.9, 9.5	At 0.7 ppm, increase in tracheal epithelial hyperplasia; at >2.1 ppm, shortened lifespan, weight loss, increased lung-to-body weight ratio, lung edema, congestion, hemorrhage, tracheal and bronchial hyperplasia (+ nuclear atypia), and squamous metaplasia (Drew et al. 1975).
Rat	15 min	14.4, 32.5, 49.8, 82.8, 125, 233	Lacrimation at all concentrations; RD_{50} = 145 ppm (calculated); red nasal discharge at ≥125 ppm; severe weight loss and increasing mortality at ≥82.8 ppm (48 h after exposure) (Gardner et al. 1985).
Mouse	6 h	2.7-10.6	14-d LC_{50} = 5.3 ppm; no respiratory-tract irritation (Leong et al. 1971).
Mouse	60 sec	≤10.6	No decrease in breathing rate during exposure or 15-min observation period (Leong et al. 1971).
Hamster	7 h	0.94, 4.6, 6.2, 7.3, 9, 19, 74	14-d LC_{50} = 7 ppm; mortality increased at ≥4.6 ppm; increased relative lung weights and damaged lungs (congestion, edema, and hemorrhage) (Drew et al. 1975).
Hamster	7 h	0.7, 2.1, 5.6, 9.9	At 0.7 ppm, increased pneumonitis and some alveolar changes; at ≥2.1 ppm, shortened lifespan, weight loss, increased lung-to-body weight ratio, lung edema, congestion, hemorrhage, and tracheal and bronchial hyperplasia (often atypical) (Drew et al. 1975).

TABLE 1-13 Animal Studies of Multiple Exposures to bis-Chloromethyl Ether

Species	Exposure Duration	Concentration (ppm)	Effects (Reference)
Rat	1 × 6 h 3 × 6 h 10 × 6 h 30 × 6 h	1	1 exposure: alveolar changes 3 or more exposures: increased mortality; tracheal and bronchial hyperplasia and squamous metaplasia; central nervous system effects; extreme irritability 10 or 30 exposures: subarachnoid hemorrhage (Drew et al. 1975)
Rat	6 h/d, 5 d/wk, 6 mo (129 exp.)	0.001, 0.01, 0.1	No effects at 1 or 10 ppb. At 100 ppb, increased death from month 7; all died or were killed by month 19; some had pulmonary adenoma; most had esthesioneuroepitheliomas (Leong et al. 1975, 1981).
Rat	6 h/d, 5 d/wk for life	0.1	High mortality (43% after 80 exposures [16 wk]); discontinued after 80 exposures (Kuschner et al. 1975).
Rat	10 × 6 h 20 × 6 h 40 × 6 h 60 × 6 h 80 × 6 h 100 × 6 h	0.1	≥80 exposures had shortened lifespan and deceased weight gain; using survival cutoff of 210 days, concentration-response in tumor incidence from 10-100 exposures, primarily nasal esthesioneuroepithelioma and lung squamous cell carcinoma (Kuschner et al. 1975).
Rat	6 h/d, 5 d/wk, 6 wk (30 exp.)	0.1	Approximately 35% mortality from respiratory-tract tumors, first observed 350 days after beginning exposure (Dulak and Snyder 1980).
Mouse	6 h/d, 5 d/wk, 6 mo (129 exp.)	0.001, 0.01, 0.1	No effects at 1 or 10 ppb. At 100 ppb, increased mortality and incidence of pulmonary adenoma when mice that died early from urinary tract infections excluded (Leong et al. 1975, 1981).
Mouse	6 h/d, 5 d/wk, 27 wk (82 exp.)	1	74% mortality; body weight loss; respiratory distress; lung hemorrhages or patchy consolidation; lung adenomas (Leong et al. 1971).
Hamster	1 × 6 h 3 × 6 h 10 × 6 h 30 × 6 h	1	1 exposures: alveolar changes; one undifferentiated nasal tumor 3 or more exposures: increased mortality; tracheal and bronchial hyperplasia; squamous metaplasia 10-30 exposures: central nervous system effects; irritability 30 exposures: subarachnoid hemorrhage (Drew et al. 1975).
Hamster	6 h/d, 5 d/wk for life	0.1	1/100 developed undifferentiated lung carcinoma after 334 exposures and died on day 501 (Kuschner et al. 1975).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was found in the literature regarding BCME metabolism. BCME is hydrolyzed within 10-60 sec in water to form HCl and formaldehyde, with about 20% of the original compound remaining at equilibrium (Van Duuren et al. 1972; Van Duuren 1980). Consistent with its in situ hydrolysis, the respiratory tract is the primary site of BCME toxicity and carcinogenicity after inhalation, and the skin is the target organ after dermal application and subcutaneous injection in humans and animals.

Whether BCME or its hydrolysis products are metabolized in vivo, or to what extent any such metabolites contribute to its toxicity and carcinogenicity, is unknown.

4.2. Mechanism of Toxicity

The mechanism of BCME toxicity and carcinogenicity has not been determined. The chemical structure of BCME predicts that it would be an alkylating agent, which is consistent with its ability to react in vitro with the guanine and adenine of calf thymus DNA (Goldschmidt et al. 1975), its mutagenicity in the Ames test, and its carcinogenicity in animals and humans. This is inconsistent, however, with other in vitro studies in which BCME did not form any isolable discrete base-alkylation products detected by thin-layer chromatography, or have any effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al. 1969, 1972).

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4.3. Structure-Activity Relationships

The chemical most related to BCME is CMME. BCME was more toxic and carcinogenic than technical grade CMME in all studies, although CMME

odor was more readily detected (Rohm and Haas, personal communication, Feb. 1998). Comparison of LC_{50} values for CMME and BCME in rats and hamsters (55-65 ppm for CMME; 7 ppm for BCME) indicates that BCME is more acutely toxic by inhalation than CMME (Drew et al. 1975). Animal carcinogenesis studies indicate that BCME is at least 10-fold more potent a carcinogen than CMME, both by inhalation (Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975) and by dermal application and subcutaneous injection (Van Duuren et al. 1968, 1969; Gargus et al. 1969).

It has been reported that the higher carcinogenic potency of BCME compared with CMME is not due to the potential of cross-linking DNA strands by BCME (Burchfield and Storrs 1977). The reason is that the reactive groups of a bifunctional alkylating agent should be able to reach across approximately 8Å, and the distance between the reactive halogens in BCME is too short for cross-linking to be likely or possible.

When the chlorine and oxygen atoms are separated in structurally-related chloroethers by two or more carbon atoms (e.g., bis(β-chloroethyl) ether), the alkylating power and carcinogenicity are greatly reduced (Burchfield and Storrs 1977), whereas eye irritation seems to be unaffected by chain length (Kirwin and Galvin 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The study by Drew et al. (1975) indicated little variability in the acute toxicity of BCME between species. The 7-h LC_{50} for both rats and hamsters was 7 ppm. A similar 6-h LC_{50} of 5.3 ppm for mice was reported by Leong et al. (1971).

4.4.2. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for BCME-related toxic effects. ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 and AEGL-3 values for durations of 30-480 min (AEGL-1 values were not derived), scaling across time was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points than the exposure duration in the key study. Extrapolations were not used to determine 10-min values because the National Advisory Committee judged that extrapolation from ≥4 h to 10 min has unacceptably large inherent uncertainty. The 30-min value is adopted for 10-min value to be protective of human health.

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No studies were identified that could be used to develop AEGL-1 values. BCME has poor warning properties, and has caused severe eye damage in humans several hours after exposure at concentrations that were not perceived (<3 ppm) (Travenius 1982).

5.2. Animal Data Relevant to AEGL-1

No relevant studies were found because toxicity exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation. A decrease in the breathing rate of A/Heston male mice, indicative of respiratory irritation, was not observed after inhalation of BCME at concentrations up to 10.6 ppm for 60 sec, although mortality was observed at that concentration after a 6-h exposure (LC_{50} of 5.3 ppm) (Leong et al. 1971).

5.3. Derivation of AEGL-1

AEGL-1 values are not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals.

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were located that were appropriate for derivation of AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

The studies considered relevant for derivation of AEGL-2 values included the following:

- The 14-day LC_{50} study of Drew et al. (1975), in which male Sprague-Dawley rats and Syrian golden hamsters were exposed to BCME at 0.94-74 ppm for 7 h and observed for 14 days. At the lowest test concentration of 0.94 ppm, no mortality occurred, and both species had increased lung-to-body weight ratios (40% of rats and 10% of hamsters), lung congestion, edema, and

hemorrhage. An adjustment factor of 3 was used to estimate an NOAEL of 0.31 ppm for lung lesions, which could be a point-of-departure for developing AEGL-2 values.

- The Drew et al. (1975) study which examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, and 9.5 ppm in rats and 0.7, 2.1, 5.6, and 9.9 ppm in hamsters. At 0.7 ppm, both species had increased lung-to-body weight ratios (96% rats; 100% hamsters), and there was an increased incidence of tracheal epithelial hyperplasia in rats (67% vs. 36% in controls) and of pneumonitis in hamsters (67% vs. 23% in controls). The respiratory lesions were considered irreversible because they were seen after lifetime observation. At ≥2.1 ppm, both species had increased mortality and lung lesions. The lowest-observed-adverse-effect level (LOAEL) of 0.7 ppm can be divided by an adjustment factor of 3 to estimate a NOAEL of 0.23 ppm for lung lesions as a point-of-departure for developing AEGL-2 values.
- The single-exposure scenario of the Drew et al. (1975) study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures of BCME at 1 ppm followed by lifetime observation. After one exposure, rats and hamsters had slightly increased incidences of alveolar, tracheal, or bronchial transformation. An adjustment factor of 3 was used to estimate a NOAEL of 0.33 ppm for lung lesions, which could be a point-of-departure for developing AEGL-2 values.
- The respiratory inhibition study in which male Crl-CD rats were exposed head-only for 15 min to BCME at 14-233 ppm (Gardner et al. 1985). Lacrimation occurred at all test concentrations and exposure to ≥82.8 ppm caused severe weight loss and mortality during the 48-h observation period. AEGL-2 values could be based on exposure for 15 min to 14.4 ppm, which caused 14% respiratory inhibition and lacrimation, which could impede the ability to escape. However, 14 ppm might cause toxicity exceeding the severity of AEGL-2, on the basis of reports that the highest tolerable BCME air concentration for humans is 5 ppm (Travenius 1982), and that BCME was distinctly irritating at 3 ppm (Flury and Zernik 1931) (no exposure durations were specified in the two references).

6.3. Derivation of AEGL-2

The AEGL-2 values are based on the lowest LOAEL (0.7 ppm) for irreversible respiratory lesions in rats and hamsters (Drew et al. 1975), which was divided by 3 to estimate a NOAEL of 0.23 ppm. This point-of-departure is supported by two other single-exposure experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions. No data were available from which to determine the BCME concentration-time relationship in order to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the

exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 for exposure durations shorter than 7 h and n = 1for exposure durations longer than 7 h. However, such extrapolation was not performed for the 10-min values because of unacceptably large inherent uncertainty; instead, the 30-min AEGL values were adopted for the 10-min values to be protective of human health (see Section 4.2.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship (such as BCME), as the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level after 129 exposures to BCME in rats and mice (6 h/day, 5 days/week) (Leong et al. 1981). The AEGL-2 values are shown in Table 1-14. Analytic methods are able to routinely detect concentrations of BCME below 1 ppb in the air (Collier 1972; Blease et al. 1989).

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure to BCME for 30 min to 8 h, as shown in Appendix B. For exposures of 30 min and 1 h, the BCME concentrations predicted to cause a 1×10^{-4} cancer risk are similar to the 30-min and 1-h AEGL-2 values. For exposures of 4-8 h, BCME concentrations calculated to cause a 1×10^{-4} cancer risk are up to 5-fold lower than the AEGL-2 values. The noncarcinogenic end points were considered more appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, a direct comparison of BCME cancer risk and AEGL values is of unknown validity because different methods are used to calculate the two sets of numbers (cancer risk calculation uses a linear extrapolation from 25,600 days to 0.5 to 8 h whereas AEGL values were extrapolated from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods).

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No appropriate human studies were available.

7.2. Animal Data Relevant to AEGL-3

The following studies were considered relevant for AEGL-3 derivation:

TABLE 1-14 AEGL-2 Values for bis-Chloromethyl Ether

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)

- The 14-day LC_{50} study by Drew et al. (1975), in which male Sprague-Dawley rats and Syrian golden hamsters were exposed to BCME at 0.94-74 ppm for 7 h and observed for 14 days. All dose groups of both species had increased lung-to-body weight ratios and extensive lung lesions, including congestion, edema, and hemorrhage. AEGL-3 values could be derived using the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 3.7 ppm for hamsters and 4.2 for rats. BMC_{01} [benchmark concentration with 1% response] values were 4.1 and 4.7 ppm, respectively, which were obtained using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2 (EPA 2005).
- The study by Drew et al. (1975), which examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, and 9.5 ppm in rats and 0.7, 2.1, 5.6, and 9.9 ppm in hamsters. At 0.7 ppm, rats had increased incidences of lung lesions but mortality was comparable to controls, whereas at ≥2.1 ppm, both species had increased mortality, weight loss, and lung lesions. The first deaths occurred during week 2 in rats and week 4 in hamsters. Exposure to BCME for 7 h to 0.7 ppm could be considered a NOEL for lethality.
- The single-exposure scenario of the study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures of BCME at 1 ppm followed by lifetime observation (Drew et al. 1975). Rats and hamsters had slightly increased incidences of lung lesions after one exposure, whereas increased mortality and lung lesions were observed after three exposures. Exposure for 6 h to 1 ppm could be considered a NOEL for lethality.
- The respiratory inhibition study in which male Crl-CD rats were exposed head-only for 15 min to BCME at 14.4, 32.5, 49.8, 82.8, 125, or 233 ppm (Gardner et al. 1985). Lacrimation occurred at all test concentrations, and exposure at ≥82.8 ppm caused severe weight loss and mortality during the 48-h observation period. AEGL-3 values could be based on exposure for 15 min to 49.8 ppm, which caused 37% respiratory inhibition and was the NOEL for increased mortality. This study has the drawback of an insufficient observation period, which could have missed treatment-related deaths.
- The acute lethality study in which an LC_{50} of 5.3 ppm was obtained for A/Heston male mice given BCME at 2.7-10.6 ppm for 6 h and observed for 14 days (Leong et al. 1971). Data were not provided to be able determine a $BMCL_{05}$ or BMC_{01}, although an adjustment factor of 3 could be applied to the LC_{50} to estimate 1.8 ppm as an estimated NOEL for lethality from a 6-h exposure. However, 1.8 ppm is similar to 2.1 ppm, which caused lethality from a single 7-h exposure in a lifetime observation study (Drew et al. 1975).

7.3. Derivation of AEGL-3

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm followed by lifetime observation (Drew et al. 1975). Rats and hamsters had slightly increased incidences of lung lesions after one exposure, whereas increased mortality occurred after three exposures. This study was chosen because it had the highest concentration of BCME that was shown to not cause lethality after lifetime observation. The 7-h $BMCL_{05}$ of 4.2 ppm for rats and 3.7 ppm for hamsters exceeded a concentration (2.1 ppm) that caused mortality in rats and hamsters from a single 7-h exposure in a lifetime observation study (Drew et al. 1975). Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values, using n = 3 and n = 1 to for durations shorter and longer, respectively, than 6 h. The 10-min AEGL values were set equal to the 30-min values to be protective of human health (see Section 4.4.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in human and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship (such as BCME), as the effects are unlikely to vary greatly among humans. The resulting AEGL-3 values are shown in Table 1-15.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals.

The AEGL-2 values were based on a study in which rats and hamsters were exposed for 7 h to BCME at 0.7-9.5 and 0.7-9.9 ppm, respectively, followed by lifetime observation (Drew et al. 1975). The lowest concentration tested of 0.7 ppm was a LOAEL for irreversible respiratory lesions, and an adjustment factor of 3 was applied to estimate a NOAEL of 0.23 ppm. This point-of-departure is supported by two other experiments by Drew et al. (1975) in which BCME caused irreversible or serious lung lesions. No data were available to determine the BCME concentration-time relationship, and AEGL-2 values for time periods other than 7 h were calculated using the ten Berge et al. (1986) equation $C^n \times t = k$, with n = 3 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for the 10-

TABLE 1-15 AEGL-3 Values for bis-Chloromethyl Ether

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

min values to be protective of human health (see Section .2.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level in a study of rats and mice exposed to BCME 6 h/day, 5 days/week, for a total of 129 exposures (Leong et al. 1981).

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm, followed by lifetime observation (Drew et al. 1975). After one exposure, rats and hamsters had slightly increased incidences of lung lesions, whereas three exposures caused lung lesions and increased mortality. This study was chosen because it had the highest concentration of BCME that was shown to not cause lethality after lifetime observation. Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans.

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure for 30 min to 8 h, as shown in Appendix B. For exposures of 30 min and 1 h, the BCME concentrations predicted to cause a 1×10^{-4} cancer risk are similar to the 30-min and 1-h AEGL-2 values. For exposures of 4-8 h, BCME concentrations calculated to cause a 1×10^{-4} cancer risk are up to 5-fold lower than the AEGL-2 values. The noncarcinogenic end points were considered more appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, the validity of comparing cancer risk and AEGL values is unknown because different methods are used to calculate the two sets of values

(the cancer-risk calculation involves a linear extrapolation from 25,600 days to 0.5 to 8 h whereas AEGL values were extrapolated from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods).

A summary of the AEGL values for BCME is shown in Table 1-16.

8.2. Comparison with Other Standards and Criteria

The existing standards and guidelines for BCME are shown in Table 1-17. OSHA, NIOSH, Germany, Austria, and Sweden have no permissible limits for BCME because it is a human carcinogen. A TLV-TWA of 0.001 ppm was adopted by the ACGIH and the Belgium based on the carcinogenic potential of BCME.

A large chemical manufacturer in Philadelphia has developed internal Emergency Response Planning Guideline (ERPG) values (1-h exposure) for BCME of 1 ppb for the ERPG-2 and 100 ppb for ERPG-3 (no ERPG-1) (Rohm and Haas, personal communication, Feb. 1998).

8.3. Data Quality and Research Needs

No studies of BCME had defined exposures and responses that fell within the scope of AEGL-1 severity. Perhaps a more sensitive, molecular-based assay could be developed to detect subclinical respiratory toxicity.

Adequate single-exposure animal studies were available for derivation of AEGL-2 and AEGL-3 values. The AEGL-2 and AEGL-3 values were each supported by several studies with rats and hamsters. However, no relevant human studies were available that adequately documented exposures to BCME (time and concentration).

TABLE 1-16 Summary of AEGLs Values for bis-Chloromethyl Ether

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR	NR	NR	NR
AEGL-2	0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm[b] (0.21 mg/m^3)	0.028 ppm[b] (0.13 mg/m^3)	0.020 ppm[b] (0.095 mg/m^3)
AEGL-3	0.23 ppm[b] (1.1 mg/m^3)	0.23 ppm[b] (1.1 mg/m^3)	0.18 ppm[b] (0.86 mg/m^3)	0.11 ppm[b] (0.52 mg/m^3)	0.075 ppm[b] (0.36 mg/m^3)

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).
[b]These concentrations are estimated to have a cancer risk greater than 1×10^{-4}, on the basis of an inhalation cancer slope factor derived by EPA (2002).

TABLE 1-17 Extant Standards and Guidelines for bis-Chloromethyl Ether

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR	NR	NR	NR
AEGL-2	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
AEGL-3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
ERPG-1 (AIHA)[b]			Not derived		
ERPG-2 (AIHA)			0.1 ppm		
ERPG-3 (AIHA)			0.5 ppm		
PEL-TWA (OSHA)[c]					No value[c]
REL-TWA (NIOSH)[d]					No value[d]
TLV-TWA (ACGIH)[e]					0.001 ppm
MAK (Germany)[f]					No value[f]
OELV-LLV (Sweden)[g]					No value[g]
VLEP (Belgium)[h]					0.001 ppm

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).

[b]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2000, documented 9/1/87).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing effects other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. An ERPG-1 was not derived because of insufficient data.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for BCME is based on animal data, and was intended to be below 0.21 ppm, which was calculated to have a 1×10^{-4} excess cancer risk, and 0.7 ppm, which caused serious respiratory lesions in animals.

ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for BCME is based on animal lethality data.

[c]OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (54 Fed. Reg. 2931[1989]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week. A numeric value was not assigned, but OSHA identifies BCME as an occupational carcinogen and workplace exposure is regulated by law (29 CFR 1910.1006 [1996]).

[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA. A numeric value was not assigned, but NIOSH considers BCME to be an occupational carcinogen subject to Federal regulation (29 CFR 1910.1006 [1996]), and recommends that exposure to it be limited to the lowest feasible concentrations.

[e]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2007) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. BCME was classified as carcinogenicity category A1 ("confirmed human carcinogen").

[f]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft -German Research Association (DFG 2002) is defined analogous to the ACGIH TLV-TWA. A value was not developed but BCME was classified as a human carcinogen (category 1).

[g]OELV-LLV (Occupational Exposure Limit Value - Level Limit Value) (Swedish Work Environment Authority 2005) is defined analogous to the ACGIH TLV-TWA. A value was not developed but BCME is classified as Group A, a carcinogenic substance that may not be handled.

[h]VLEP [Occupational Exposure Limit (valeurs limites d'exposition professionnelle)] (Ministry of Employment and Work, Belgium 2002) is defined analogous to the ACGIH TLV-TWA. BCME was classified as a carcinogenic substance.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR bis-CHLOROMETHYL ETHER

Derivation of AEGL-1 Values

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals.

Derivation of AEGL-2 Values

Key study:	Drew et al. 1975
Toxicity end point:	0.23 ppm was NOAEL for irreversible respiratory lesions in rats and hamsters
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min $(0.23 \text{ ppm}/10)^3 \times 7 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $(0.23 \text{ ppm}/10)^1 \times 7 \text{ hr } 0.16 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-2:	Set equal to 30-min value because of uncertainty in extrpolating a 7-h exposure to 10 min
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $C = 0.055 \text{ ppm } [0.26 \text{ mg/m}^3]$
60-min AEGL-2:	$C^3 \times 1 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $C = 0.044 \text{ ppm } [0.21 \text{ mg/m}^3]$
4-h AEGL-2:	$C^3 \times 4 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$

	C = 0.028 ppm [0.13 mg/m^3]
8-h AEGL-2:	$C^1 \times 8$ hr = 0.16 ppm-h C = 0.020 ppm [0.095 mg/m^3]

Derivation AEGL-3 Values

Key study:	Drew et al. (1975)
Toxicity end point:	NOEL of 1 ppm for lethality from lung lesions.
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min values $(1.0 \text{ ppm}/10)^3 \times 6 \text{ h} = 6.0 \times 10^{-3}$ ppm^3-h $(1.0 \text{ ppm}/10)^1 \times 6 \text{ h} = 0.60$ ppm-h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Calculations:	
10-min AEGL-2:	Set equal to 30-min value because of uncertainty in extrapolating a 6-h exposure to 10 min
30-min AEGL-3:	$C^3 \times 0.5$ h = 6.0×10^{-3} ppm^3-h C = 0.23 ppm [1.1 mg/m^3]
60-min AEGL-3:	$C^3 \times 1$ h = 6.0×10^{-3} ppm^3-h C = 0.18 ppm [0.86 mg/m^3]
4-h AEGL-3:	$C^3 \times 4$ hr = 6.0×10^{-3} ppm^3-h C = 0.11 ppm [0.52 mg/m^3]
8-h AEGL-3:	$C^1 \times 8$ h = 0.60 ppm-h C = 0.075 ppm [0.36 mg/m^3]

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR BIS-CHLOROMETHYL ETHER

Cancer Assessment

A cancer assessment of BCME was performed by EPA (2002) on the basis of data from Kuschner et al. (1975). That study is summarized in Section 3.5.1.

The inhalation unit risk for BCME was calculated to be 6.2×10^{-2} per $\mu g/m^3$, using the linearized multistage procedure, extra risk (EPA 2002). The concentration of BCME corresponding to a lifetime risk of 1×10^{-4} is calculated as follows:

$$(1 \times 10^{-4}) \div [6.2 \times 10^{-2} (\mu g/m^3)^{-1}] = 1.6 \times 10^{-3} \mu g/m^3$$

To convert a 70-year exposure to a 24-h exposure, one multiplies by the number of days in 70 years (25,600 days). The concentration of BCME corresponding to a 1×10^{-4} risk from a 24-h exposure is:

$$(1.6 \times 10^{-3} \mu g/m^3)(25{,}600 \text{ days}) = 40.96 \mu g/m^3 \ (0.041 \text{ mg/m}^3 \text{ or } 0.0086 \text{ ppm})$$

To account for uncertainty about the variability in the stage of the cancer process at which BCME or its metabolites act, a multistage factor of 6 is applied (Crump and Howe 1984):

$$(40.96 \mu g/m^3) \div 6 = 6.83 \mu g/m^3 \ (0.0068 \text{ mg/m}^3 \text{ or } 0.0014 \text{ ppm})$$

If the exposure is reduced to a fraction of a 24-h period, the fractional exposure (f) becomes (1/f) × 24 h (NRC 1985). Extrapolation to 10 min was not calculated because of unacceptably large inherent uncertainty. Because the animal dose was converted to an air concentration that results in an equivalent human inhaled dose for the derivation of the cancer slope factor, no reduction in the exposure concentrations is made to account for interspecies variability.

A comparison of the AEGL-2 and AEGL-3 values for BCME with the estimated concentration associated with a cancer risk of 1×10^{-4} is shown below. For risks of 1×10^{-5} and 1×10^{-6}, the 1×10^{-4} values are reduced 10-fold or 100-fold, respectively. Also shown are the estimated cancer risks for the AEGL-2 and AEGL-3 values, obtained by assuming a linear relationship between exposure concentration and cancer risk.

TABLE B-1 Estimated Cancer Risks Associated with a Single Exposure to bis-Chloromethyl Ether

Exposure Duration	10 min	30 min	1 h	4 h	8 h
BCME concentration:	Not calculated	0.069 ppm	0.035 ppm	0.0086 ppm	0.0043 ppm
Estimated cancer risk:		1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}
AEGL-2 value:	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
Estimated cancer risk:	Not calculated	8.0×10^{-5}	1.3×10^{-4}	3.3×10^{-4}	4.7×10^{-4}
AEGL-3 value:	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
Estimated cancer risk:	Not calculated	3.3×10^{-4}	5.1×10^{-4}	1.3×10^{-3}	$1.7 \times x\ 10^{-3}$

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR bis-CHLOROMETHYL ETHER

Derivation Summary

AEGL-1 VALUES

30 min	30 min	1 h	4 h	8 h
Not Recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals)				
Reference: Not applicable				
Test species/strain/number: Not applicable				
Exposure route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
End point/Concentration/Rationale: Not applicable				
Uncertainty factors/Rationale: Not applicable				
Modifying factor: Not applicable				
Animal-to-human dosimetric adjustment: Not applicable				
Time scaling: Not applicable				
Data quality and support for AEGL-1 values: Values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects.				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)
Reference: 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(2):61-69.				
Test species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; 25/test concentration/species				
Exposure route/Concentrations/Durations: Inhaled BCME at 0.7, 2.1, 6.9, or 9.5 ppm (rats) or 0.7, 2.1, 5.6, or 9.9 ppm (hamsters) for 7 h. Lifetime observation.				
Effects: At 0.7 ppm, both species had increased lung-to-body weight ratios; rats had increased incidence of tracheal epithelial hyperplasia, and hamsters had increased incidence of pneumonitis. Respiratory lesions were considered irreversible because they were found after lifetime observation. At ≥2.1 ppm, both species had increased mortality and lung lesions.				

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)

End point/Concentration/Rationale: A NOAEL of 0.23 ppm for irreversible respiratory lesions in rats and hamsters was estimated by applying an adjustment factor of 3 to LOAEL of 0.7 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lungs.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for deriving AEGLs for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values below 0.010 ppm, the NOEL in a study of rats and mice exposed to BCME for 6 h/day, 5 days/week, for a total of 129 exposures (Leong et al. 1981).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time saling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter to longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.2.).

Data quality and support for AEGL-2 values: Adequate data were available to develop values. The estimated NOAEL of 0.23 ppm was supported by two other single-exposure experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

Reference: 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(2):61-69.

Test species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; 50/test concentration/species

Exposure route/Concentrations/Durations: Inhalation of BCME at 1 ppm for 6 h/day for 1, 3, 10, or 30 days. Lifetime observation.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

Effects: Slightly increased incidences of lung lesions in rats and hamsters after single exposure; lung lesions and increased mortality with ≥3 exposures.

End point/Concentration/Rationale: A single exposure of 1 ppm for 6 h was the NOEL for lethality from lung lesions.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for deriving AEGLs for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter to longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.2.).

Data quality and support for AEGL-3 values: The database was sufficient to develop AEGL-3 values. The key study was chosen because it had the highest concentration of BCME that did not cause lethality after lifetime observation; another study by the same authors found a lethality NOEL of 0.7 ppm (7 h) for rats and hamsters after lifetime observation. A 7-h LC_{50} study using rats and hamsters (Drew et al. 1975) was not used because it yielded a $BMCL_{05}$ of 4.2 ppm for rats and 3.7 ppm for hamsters, which exceed 2.1 ppm, the concentration that caused mortality in rats and hamsters after a single 7-h exposure to BCME in a lifetime observation study (Drew et al. 1975).

APPENDIX D

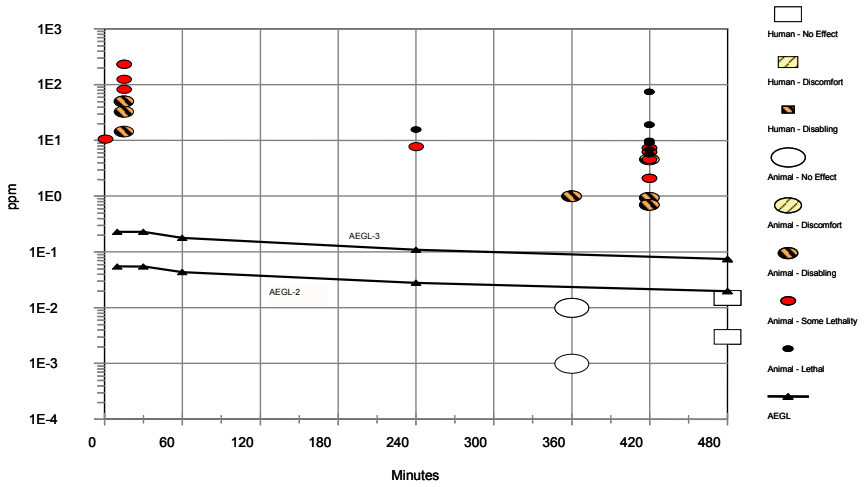

FIGURE D-1 Category plot for bis-chloromethyl ether. Multiple-exposure studies were not included in the plot except for Leong et al. (1975, 1981).