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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

2

Chloromethyl Methyl 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

Chloromethyl methyl ether (CMME) is a man-made chemical that is highly flammable, and causes severe irritation of the respiratory tract, eyes, nose, and skin. Chronic occupational exposure has caused small-cell lung carcinoma with histology distinct from that caused by cigarette smoke, and with a shorter latency period. The U.S. Environmental Protection Agency (EPA) classifies technical-grade CMME as a human carcinogen. Upon contact with water, CMME hydrolyzes completely and irreversibly to form hydrochloric acid, methanol, and formaldehyde. Technical-grade CMME contains 1-10% bis-chloromethyl ether (BCME) as a contaminant. Because humans are exposed only to technical-grade CMME (a great deal of effort is needed to remove "all" BCME from CMME), and the human and animal inhalation-exposure data all involved technical-grade CMME, the AEGL values derived in this document will address the toxicity and carcinogenicity of technical-grade CMME.

AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects.

AEGL-2 values for technical-grade CMME were based on an acute toxicity study in which rats and hamsters were exposed to CMME for 7 h at 12.5-225 ppm (contamination by BCME not given) and observed for 14 days (Drew et al. 1975). Toxic effects were not attributed to specific concentrations, but it was reported that animals that died, and to a lesser degree, animals that

survived, had increased relative lung weights, pulmonary congestion, edema, hemorrhage, and acute necrotizing bronchitis. Therefore, 12.5 ppm was considered the lowest-observed-adverse-effect level (LOAEL) for serious or irreversible lung lesions in both species (also a no-observed-effect level [NOEL] for lethality in rats), and was divided by 3 to obtain an estimated no-observed-adverse-effect level (NOAEL) of 4.2 ppm. No data were available from which to determine the CMME 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 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for 10-min value to be protective of human health (see Section 4.4.3.). An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because CMME caused a similar degree of lung toxicity in two animal species and is expected to cause similar toxicity in human lungs. A 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 intraspecies uncertainty factor of 3 also was used in the derivation of AEGL-2 values for BCME. A modifying factor of 1.7 was applied because the BCME content in technical-grade CMME in the key study was unknown. The modifying factor was obtained by assuming 10% contamination with BCME (the maximum reported) and accounting for the greater toxicity of BCME (the rat LC_{50} [lethal concentration, 50% lethality] was 55 ppm for CMME and 7 ppm for BCME in the key study) in the following calculation: $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

AEGL-3 values were based on the same study as the AEGL-2 values (Drew et al. 1975). The threshold for lethality from severe lung lesions, expressed as the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response), was approximately 18 ppm for hamsters and 19 ppm for rats; the lower value was used in the derivation. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al.(1986) equation described above for AEGL-2. An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was virtually 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. A 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. An intraspecies uncertainty factor of 3 also was used in the derivation of AEGL-3 values for BCME. A modifying factor of 1.7 was also applied because the content of BCME in technical-grade CMME in the key study was unknown. The AEGL values are summarized in Table 2-1.

TABLE 2-1 Summary of AEGL Values for Chloromethyl Methyl Ether

Level	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR[b]	NR	NR	NR	NR	
AEGL-2 (disabling)	0.60 ppm (2.0 mg/m^3)	0.60 ppm (2.0 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.30 ppm (0.98 mg/m^3)	0.22 ppm (0.72 mg/m^3)	Estimated NOAEL for serious or irreversible lung lesions in rats and hamsters (Drew et al. 1975)
AEGL-3 (lethal)	2.6 ppm (8.6 mg/m^3)	2.6 ppm (8.6 mg/m^3)	2.0 ppm (6.6 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.93 ppm (3.1 mg/m^3)	Lethality threshold for hamsters and rats (Drew et al. 1975)

[a]Data on odor threshold not found for CMME, but industrial experience indicates that 1.5 ppm is barely detectable and 23 ppm is easily detectable.
[b]Not recommended (no studies were available in which toxicity was limited to AEGL-1 effects).

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical-grade CMME contains 10% BCME, and that the carcinogenicity of "pure" BCME is 10-fold more potent than "pure" CMME (Van Duuren et al. 1968, 1969; Gargus et al. 1969; Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975), then it follows that technical-grade CMME has, at most, 9% of the carcinogenic activity of BCME. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values the estimates range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how valid the stated assumptions are to predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values as compared with extrapolating the carcinogenic potency from a lifetime study to a single exposure, the non-carcinogenic end points were considered to be more appropriate for deriving AEGLs for CMME.

1. INTRODUCTION

Technical grade CMME is a highly volatile, colorless, flammable liquid (CHRIS 1985). CMME vapor is severely irritating to the respiratory tract, eyes, nose, and skin, and exposure to high air concentrations causes sore throat, fever, chills, and difficulty breathing (Hake and Rowe 1963). The odor has been reported as barely detectable at 1.5 ppm and easily detectable at 23 ppm

(Wagoner et al. 1972), concentrations shown to cause lung lesions or mortality in animals. Technical-grade CMME contains 1-10% BCME as a contaminant, which is a more potent human carcinogen than CMME and is believed to be responsible for most or all of the carcinogenic activity of technical-grade CMME (Travenius 1982; HSDB 2010).

CMME decomposes so rapidly in aqueous solution that its half-life cannot be accurately measured. The half-life of CMME in pure water was estimated to be <1 seconds (sec) (Tou and Kallos 1974). In humid air (ambient temperature; 81% relative humidity), CMME and BCME were more stable, although the half-life depended on the surface coating of the container; the half-life was 7-25 h for BCME and 2.3 min to 6.5 h for CMME (Tou and Kallos 1974). It was reported that of the CMME decomposition products in water (methanol, formaldehyde, and hydrochloric acid [HCl]), the latter two can recombine to form BCME, and that vapors of HCl and formaldehyde, which are commonly used in industries and laboratories, can combine spontaneously in the air to form BCME (it has not been shown that CMME can be formed spontaneously in air or water). The hydrolysis of CMME is believed to be irreversible, whereas that of BCME is reversible, although the extent of conversion from CMME to BCME in water or air has not been well-characterized (Travenius 1982).

CMME does not occur naturally, and human exposure occurs in only occupational settings. CMME is usually prepared "in-house" by passing HCl through a mixture of formalin and methanol, and is used industrially in the manufacture of ion-exchange resins, bactericides, pesticides, dispersing agents, water repellants, solvents for industrial polymerization reactions, and flame-proofing agents (Van Duuren 1989; Budavari et al. 1996; Kirwin and Galvin 1993). CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine; nucleophilic displacement of the halogen-bearing carbon atom occurs readily and, therefore, CMME and BCME are referred to as alkylating agents. CMME and BCME react spontaneously with nucleophilic substrates, such as DNA, without enzymatic conversion (Burchfield and Storrs 1977).

CMME and BCME were recognized as potent human respiratory-tract carcinogens in the early 1970s by the U.S. industry, prompting facilities to develop hermetically isolated systems for their use (Travenius 1982; Collingwood et al. 1987). In 1973, BCME and CMME were listed by the Occupational Safety and Health Administration as part of the first 14 chemicals to be restricted by Federal regulations because of their human carcinogenicity, effective February 11, 1974 (39 Fed. Reg. 3756). Their use, storage, and handling must be in a controlled area (38 Fed. Reg. 10929). These regulations apply to all preparations containing CMME or BCME at ≥0.1% (by weight or volume). Subsequent studies examined the carcinogenicity of CMME and BCME in animals, although it has been practically impossible to assess the effect of CMME alone because, unless extraordinary measures are taken, it is contaminated with BCME.

In 1993, the U.S. International Trade Commission listed only one company producing CMME in the United States, although the amount produced or sold was not published to avoid disclosure of individual company operations (USITC 1994). The amount of CMME produced in situ during the production of other chemicals, and the companies involved, was not determined. The physical and chemical properties of CMME are listed in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No quantitative information was located regarding acute exposure to CMME in humans. The vapors are severely irritating and painful to the eyes and nose. Vapor concentrations that are rapidly fatal are "irrespirable" (term used in reference; no further explanation given) for humans, and illness or death that results from exposure to CMME will occur several days after exposure from lung edema or secondary pneumonia (Hake and Rowe 1963).

2.2. Nonlethal Toxicity

No short-term quantitative studies were located describing nonlethal effects of CMME exposure in humans. CMME vapor was reported to be very irritating and painful to the eyes and nose at 100 ppm, but exposure duration was not specified (Hake and Rowe 1963). One U.S. manufacturer set an in-house threshold limit value (TLV) of 1 ppm for CMME in the early years of its use, presumably because its odor was not detected or was not irritating at <1 ppm (Weiss 1992). This Michigan plant did not have an elevated incidence of respiratory-tract cancer in an industry-wide study by Collingwood et al. (1987). However, a 1-h exposure to CMME at1 ppm is presently considered dangerous to human health according to an in-house exposure standard of a large chemical company (Rohm & Haas, personal communication, February 1998).

Chronic occupational exposure to CMME resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), and weight loss (NIOSH 1988). Several long-term occupational exposure studies described nonlethal toxic end points; however, respiratory tract cancer was the principal focus of these studies. Leong et al. (1971) indicated that CMME (and BCME) are a health risk at concentrations that do not produce sensory irritation.

2.2.1 Odor Threshold and Awareness

Industrial experience indicates that the odor of CMME is undetectable at 0.5 ppm, barely detectable at 1.5 ppm, easily detectable at 23 ppm, and strong at 100 ppm (Wagoner et al. 1972; AIHA 2000). Another source indicated that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm (Travenius 1982).

TABLE 2-2 Physical and Chemical Data for Chloromethyl Methyl Ether

Parameter	Value	Reference
Synonyms	Chloromethoxymethane; chloromethyl ether; monochloromethyl ether; chlorodimethyl ether; CMME	Budavari et al. 1996
CAS registry no.	107-30-2	IARC 1974
Chemical formula	CH_3OCH_2Cl	Budavari et al. 1996
Structure	C(OC)Cl	
Molecular weight	80.51	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Melting point	-103.5°C	Verschueren 1996
Boiling point	59°C at 760 mm	Budavari et al. 1996
Density		
Vapor	2.8 (air = 1)	CHRIS 1985
Liquid	1.0605 at 20/4°C (water = 1); 1.074 at 20/4°C (water = 1)	IARC 1974 Kirwin and Galvin 1993
Solubility in water	Decomposes in water (half-life <0.5 sec) to methanol, formaldehyde, and HCl	Nelson 1976; Travenius 1982
Vapor pressure	122 mm Hg at 20°C; 260 mm Hg at.20°C	IPCS 1998; HHMI 1995
Flammability/ explosive limits	4.5-22.8 (estimated)	AIHA 2000
Conversion factors	1 mg/m^3 = 0.304 ppm 1 ppm = 3.29 mg/m^3	Verschueren 1996

The data were not adequate to derive the level of distinct odor awareness per the guidance given by van Doorn et al. (2002).

2.2.2. Accidents

Accidental industrial exposure to "rather high" concentrations of CMME caused sore throat, fever, and chills, and the person was not able to work for 8 days, at which time recovery appeared complete (Hake and Rowe 1963). Another subject who received "very slight exposure" had difficulty breathing for several days (Hake and Rowe 1963).

2.3. Neurotoxicity

No studies reporting neurotoxic effects of CMME in humans were located.

2.4. Developmental and Reproductive Toxicity

No studies on the developmental or reproductive effects in humans were located.

2.5. Genotoxicity

The incidence of chromosomal aberrations was greater in the peripheral lymphocytes of workers exposed to CMME or 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 dose of BCME exposure during the last 3 months (Sram et al. 1985).

Zudova and Landa (1977) cytogenetically scored 22 peripheral lymphocytes/person in 2 workers exposed for 2 years to CMME and BCME. Exposed workers had an average of 6.7% aberrant cells compared with 2% in the controls. Blood samples taken from 10 workers after their holidays (length not defined) had only 3.1% aberrant cells.

CMME was cytotoxic (inhibited scheduled DNA synthesis) in human lymphocytes treated for 4 h with CMME at 10^{-2} M (97-99% pure), although the cytotoxicity was reversed in the presence of metabolic activation with rat liver phenobarbital-induced S-9 mix (Perocco et al. 1983). CMME (10^{-2} to 10^{-3} M or 5 microliters per milliliters [µL/mL]) also increased in vitro DNA repair in the presence of metabolic activation, seen by increased incorporation of tritiated thymidine (Perocco and Prodi 1981; Perocco et al. 1983).

2.6. Carcinogenicity

EPA has designated technical-grade CMME (and BCME) as Group A ("human carcinogen") on the basis of an increased incidence of respiratory-tract cancer in exposed workers (EPA 2005a). This was supported by evidence of respiratory-tract tumors in mice, rats, and hamsters exposed by inhalation (EPA 2005a). The American Conference of Industrial Hygienists has classified CMME as a "suspected human carcinogen" (Class A2), has assigned no values for a TWA or short-term exposure limit (STEL), and suggests that "it may be desirable to monitor exposures on the basis of BCME (TLV = 0.001 ppm)" (ACGIH 1991). International Agency for the Research on Cancer (IARC) places technical-grade CMME in Group 1 ("sufficient evidence for carcinogenicity to humans and to animals") (IARC 1987). In epidemiologic studies, there was a

clear trend of an increasing incidence of lung cancer with increasing dose (longer and/or more intense exposure).

Several studies showed that the incidence of cancer peaked about 15-20 years post-exposure (Weiss 1982; Maher and DeFonso 1987). Exposed humans had elevated rates of respiratory-tract cancer, but not of other types of cancer. The cases occurred at a younger age than lung cancer in the general population, especially among nonsmokers. The cancer histology was most frequently small-cell carcinoma, with a high fraction of them being oat-cell carcinoma, in contrast to lung cancer caused by cigarette smoking, which is predominantly squamous-cell carcinoma (Weiss and Boucot 1975). The air concentrations of CMME in the workroom were almost never measured, although Travenius (1982) has estimated that they might have been 1-10 ppm, because higher concentrations would have been intolerable.

2.6.1. Case Reports

A nonsmoking German research chemist exposed for 2 years to high concentrations of CMME and BCME died 12 years later (at age 45) of heart circulation failure as a result of pulmonary adenocarcinoma cachexia (Reznik et al. 1977). A 42-year old chemist exposed to CMME and BCME by inhalation for 7 years died from extensive pulmonary carcinoma (Bettendorf 1977). The air concentrations of CMME or BCME were not given in either report.

2.6.2. Epidemiologic Studies

Langner (1977) reported CMME air concentrations of 0-12 ppm, with a mean of 0.7 ppm, from 230 measurements taken in 1957 at a U.S. anion exchange plant. CMME concentrations became progressively lower as processing and engineering controls were implemented to reduce exposure. The CMME contained 7-10% BCME. No excess respiratory-tract cancer or oat-cell lung cancer was found in workers during the plant's 27 years of operation.

Industrial workers exposed for months to years to CMME (containing BCME) had a dose-related increase in chronic bronchitis, although the exposure concentrations were not available (Weiss and Boucot 1975; Weiss 1976, 1977). There was no effect on the worker's ventilatory function, as measured by the forced vital capacity (FVC) and the 1-sec forced expiratory volume (FEV_1), suggesting the large airways were normal. The small airways did appear to be affected, because the end-expiratory flow rate was below predicted values in a dose-related manner. Cigarette smoking acted synergistically with CMME to produce chronic bronchitis and small-airway disorders among the workers (however, there was an inverse relationship between smoking and the induction of lung cancer by CMME; see Section 2.5.1.). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not described).

In 1972, four workers at a California chemical plant (Diamond Shamrock Co., Redwood City) with 100-200 workers involved in anion-exchange resin production (exposed to CMME and BCME) died from lung cancer and two more workers developed lung cancer (Donaldson and Johnson 1972; Fishbein 1972). The concentration of CMME or BCME in the air was not specified. One of the workers that died, a 32-year old male, worked at the plant for only 2 years. Subsequent analysis of exfoliated cells of the sputum of the workers found no difference in metaplasia or atypia between in-plant workers not involved in CMME/BCME production and controls (Lemen et al. 1976). A significant association was found between abnormal cytology and exposure to CMME/BCME for more than 5 years (34% of anion-exchange workers vs. 11% of controls). In conjunction with the cytology survey, a retrospective cohort study of 136 men who worked at the plant for at least 5 years (mean was 10 years) was initiated. Five cases of bronchogenic cancer (three deaths) were found, compared with 0.54 cases expected (in white, age-matched men from Connecticut). The mean age at diagnosis was 47 years, and the predominant histology was small cell-undifferentiated carcinoma. The majority had smoked cigarettes.

Workers exposed at least 6 months to low concentrations of CMME (containing 4-5% BCME) in a workplace in France from 1959-1971 did not have increased rates of respiratory-tract cancers (Schaffer et al. 1984). The actual concentrations of CMME in the air were not specified. The authors speculated that an increased cancer incidence might not have been found because a limited number of people were included in the study (670, of which 168 were exposed to CMME), and the observation period might have been too short.

Technical-grade CMME (unspecified BCME content) was used in the production of anion exchange resins in a factory (Rohm & Haas) in Chauny, France, from 1958 to December 31, 1986 (Gowers et al. 1993). The air concentrations of CMME in the factory were not measured, but concentrations of BCME were monitored from 1979 to 1984 with personal and stationary air-sampling devices. Approximate annual concentrations of BCME were 0.6-4.4 ppb, with an overall weighted average of 1.7 ppb. After standardization for age, workers with jobs involving exposure to CMME (258 men) had a greater incidence of lung cancer than nonexposed workers (945 men) in the same plant (rate ratio [RR] = 5.0; 95% confidence interval [CI] = 2.0-12.3) and a greater incidence than an external reference population (RR = 7.6; 95% CI = 4.3-13.5). Increased cumulative exposure was associated with an increased incidence of cancer but not with the time from first exposure to diagnosis, which was about 13 years. Exposed workers developed cancer an average of 10.5 years earlier than nonexposed workers. Of the cancers in exposed cases, 10/11 were small-cell, mostly oat-cell, carcinomas whereas in the nonexposed group only 1/8 cancers were small-cell carcinomas (16-33% were reported in the external reference population). Smoking history was not known, but reportedly a large fraction of the workers smoked. The observed-to-expected lung cancer ratio

decreased as the exposure concentrations decreased over the years. The cancer cases found while exposure to BCME was monitored were probably due to previous, much higher exposures before engineering controls were put into place in 1984.

The three cases of lung cancer (men aged 33-39) among about 45 workers who worked in the production of CMME (0.5-4% BCME) in one building of a large Philadelphia chemical plant (Rohm & Haas, about 2,500 employees) in 1962 prompted studies of cancer in potentially exposed workers. Air concentrations of CMME or BCME were not measured but were estimated retrospectively on a scale of 0-6, where 0 was "essentially" no exposure. Figueroa et al. (1973) studied a group of 125 men, some of whom were exposed to CMME in this Philadelphia plant. Of the 125 workers, 96 were current cigarette smokers, 13 were nonsmokers, 10 smoked cigars or pipes only, and six were former smokers (Weiss and Boucot 1975). Fourteen of the 125 men were lost to the study because their employment was terminated. Fourteen cases of lung cancer developed in men aged 33-55 from 1962 to 1971; these men were exposed 3-14 years with one exception (uncertain duration; possibly one year). Thirteen cancers were oat-cell carcinomas, and one was of unknown histologic type. Three of the 13 cancers occurred in nonsmokers. The workers were periodically examined (chest photofluorogram and questionnaire) between 1963 and 1968, during which time four cancers developed in men aged 35-54 years (88 men were in this age group), which was a roughly an 8-fold increase in incidence of cancer over the control group. Brown and Selvin (1973) asserted that the actual increase was 44-fold, and that Figueroa et al. (1973) had used an inappropriate control group (too old) and that all 111 men (not just the 88 men between ages 35-54) should have been included.

A 10-year prospective study of this same cohort of 125 men from January 1963 to December 1972 revealed a strong dose-response relationship for bronchogenic cancer (all small-cell carcinomas) among the men exposed for at least 3 months (Weiss and Boucot 1975; Weiss 1980). The exposed workers had symptoms, such as dose-related chronic bronchitis, and the end-expiratory flow rate was below predicted values in a dose-related manner (Weiss 1977). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not recorded). Significantly increased risk occurred only among men with moderate or heavy exposure; these workers had an inverse relationship between smoking and the incidence of lung cancer (Weiss and Boucot 1975; Weiss 1976, 1977; Weiss et al. 1979). This finding is in marked contrast to other industrial carcinogens (e.g., asbestos, uranium), where cancer was rarely induced without smoking being a cofactor (Travenius 1982). It is unknown how or whether chronic cigarette smoking was inhibiting development of cancer from CMME/BCME, but Weiss (1980) postulates that the additional or altered viscosity secretions or increased thickness of the mucous covering the bronchial epithelium of the cigarette smokers might protect the workers by chemically neutralizing or separating the CMME hydrolysis products from the lung epithelium.

A retrospective study conducted from 1973-June 1974 in the same Philadelphia plant involved workers (669 men) exposed to CMME from 1948-1972 (DeFonso and Kelton 1976). They had a statistically significant (3.8-fold) increase in lung cancer compared with unexposed workers (1,616 men). Dose-response relationships were evident for the incidence of lung cancer and the duration or intensity of exposure. There was no correlation between age at first exposure and the time from the first exposure to death, the latter being from 8.3 to 25.2 years for men whose exposures began in their late twenties. An additional 9-year follow-up of essentially this same group of men, as well as summer and short-term employees (737 exposed; 2,120 unexposed) also showed a dose-related increase in the incidence of respiratory-tract cancer in exposed workers (32 observed [obs], 11.5 expected [exp]; obs/exp = 2.79, $p < 0.01$) (Maher and DeFonso 1987). At the lowest doses, there was no increase in cancer risk (obs/exp = 1.02) whereas at the highest doses the risk was >10-fold. Most of the cases of respiratory-tract cancer (20/32) had a latency period of 10-20 years. Cancer risk was not adjusted for smoking because complete information was unavailable, although exposed and nonexposed workers had similar smoking habits. The incidence of respiratory-tract cancer decreased in parallel (after an induction period) with the decreased exposure of the workers to CMME and BCME as workplace engineering controls were adopted.

These findings agree with those of Weiss (1982) who studied a cross-section of 125 men employed at this Philadelphia plant in 1963, and followed them from January 1963 to December 1979. Weiss (1982) showed that there was a small "epidemic" of respiratory-tract cancer, including 14 cases of lung cancer and two cases of laryngeal cancer compared with two cases of lung cancer among 34 unexposed men (0.51 expected). This epidemic peaked 15-19 years after the onset of exposure and began to subside thereafter (as workplace exposure decreased). The standard mortality ratio (SMR) for lung cancer was determined to be 8.45 (white Philadelphia males as reference). Almost all the cases (13/14) of lung cancer were small-cell carcinomas (one was large-cell); the two laryngeal cancers were squamous cell carcinomas. The latency period ranged from 10 to 23 years. All the cancer cases occurred in men with moderate to heavy exposure. CMME was first used at the plant in 1948; 24 years later, the SMR was no longer statistically increased.

The lung mortality patterns of 1,794 employees (all men; <10 females were excluded) exposed to CMME (2-8% BCME) from 1948 to 1972 at six U.S. companies (accounting for the vast majority of U.S. exposure) were examined by Albert et al. (1975) and Pasternack et al. (1977). The control group was nonexposed men working in the companies during the same time. No CMME/BCME exposure concentrations were available. About 98% of the workers were white; race was not considered in the analysis. The age-adjusted rates for noncancer death and for overall cancer death were comparable in control and exposed men, whereas the age-adjusted respiratory tract cancer death rate was 2.5-fold greater in the exposed workers (1.48 in the exposed group and 0.59 in the control group). Of the 22 respiratory-tract cancer cases in

the exposed workers, 20 were bronchogenic, one was laryngeal, and the other mediastinal. At one of the firms (company 2, probably Rohm & Haas in Philadelphia, PA), where at least 5 years had elapsed since the first exposure, a clear dose-response between exposure and respiratory-tract cancer rate was obtained. All 19 respiratory-tract cancer deaths were seen in workers with heavy exposure, and occurred at an early age of onset (77% occurring before age 55, as compared with 43% in U.S. white males). Smoking histories of the workers were not considered in the analysis.

Collingwood et al. (1987) conducted a 7-year (1973-1980) follow-up of workers at the six companies above, and the seventh major producer of CMME in the United States was included for follow-up from 1953 to 1980. At company 7, 26% of the workers were female. Overall, 96% of the workers were male and 97% were white. This study showed that respiratory-tract cancer mortality was increased only at company 2 (obs = 32; SMR = 430) and company 7 (obs = 9; SMR = 603), although the sex of the workers was not specified. There was a significant exposure-response relationship with cumulative time-weighed exposure. Of the 32 respiratory-tract cancer deaths with verifiable cell type, oat-cell carcinoma accounted for the highest proportion (38%) among exposed workers, whereas adenocarcinoma accounted for the highest proportion (31%) in nonexposed workers.

Workers were exposed to CMME/BCME in a chemical factory (Rohm & Haas) in Chauny, France, where CMME was used in making anion-exchange resins since 1958. Air concentrations of BCME were measured from 1979 to 1984 (Gowers et al. 1993). The annual average air concentration of BCME was 0.6-4.4 ppb. The highest BCME concentration corresponds to CMME concentrations of 0.044-0.44 ppm, if BCME represents 1-10% of the CMME in the air. Although respiratory-tract cancer rates were increased, the workers were not examined after a sufficient latency period and the cancer cases observed were probably due to earlier, substantially higher exposures.

In a group of 318 Shanghai workers (212 men, 106 women) exposed to CMME (containing unknown amounts of BCME) for at least 1 year between 1958 1981, there were 16 cancer deaths, of which 12 were lung cancer (Hsueh et al. 1984). The air concentrations of CMME were not specified and smoking histories of the workers were not reported. Taking into account the age, sex, and calendar-year specific mortality, the SMR for all cancer was 485, and for lung cancer was 2,296, whereas the proportional mortality ratio (PMR) was 219 for all cancer and 855 for lung cancer. All cancer deaths occurred in male workers; it is unclear whether this was due to different exposures. Illness occurred after 2-18 years of exposure, the average exposure was 10.5 years. Histologic examination of the cancers indicated that 70% were undifferentiated cell type carcinomas (Hsueh et al. 1984).

A study of 276 men working in CMME production (BCME content unknown) at a factory in South Wales between 1948 and 1980 showed an increased incidence of lung cancer but not other cancers compared with a local unexposed population of 295 men (McCallum et al. 1983). Measurements of

CMME were not taken, but the author indicated that exposure "may have been high." The rate of cancer deaths was related to total exposure duration and average exposure rate, and total dose, but the authors stated that "the degree of exposure appeared to be more important than the duration of exposure in determining carcinogenicity." The incidence of cancer decreased after the manufacturing process was changed to decrease CMME exposure. In another factory in the United Kingdom (northeastern England), where air CMME concentrations were "estimated to be low" an increase in cancer rate was not found (McCallum et al. 1983). The first case of lung cancer was diagnosed about 13 years after production began. Smoking histories of the men were not available.

Wu (1998) reported that air concentrations of CMME at a chemical plant in Shanghai, China, between 1977 and 1978 were 1.2-59 ppm, and might have been much higher previously (Wu 1988). These measurements are inconsistent with the report by Travenius (1982) that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm; the reason for the discrepancy is unknown but might be partly due to analytic differences in air-concentration measurements. Of the Chinese workers exposed to CMME for at least 1 year (534 men and 381 women) from the 1950s through 1981, 15 died of lung cancer compared with 0.97 death expected based on Shanghai death rates (SMR = 1,546; 95% CI = 944-2,531). The mortality incidence from lung cancer was reportedly related to the amount of CMME exposure but was unrelated to cigarette smoking. Histologic analysis of the lung cancers indicated 8/11 were undifferentiated cell cancers and 3/11 were squamous cell cancers. The average age of death was 50 years (range: 32-64 years), which was 10 years younger than the age of death from cancer in the general Shanghai population. No details of any adverse human health effects besides cancer, the method used to analyze air concentrations, or the degree of contamination by BCME were provided.

2.7. Summary

No quantitative information was located regarding acute exposure to CMME in humans, although anecdotal reports indicate that the vapors are severely irritating and painful to the eyes and nose. No short-term studies were located describing nonlethal effects of CMME exposure in humans. Chronic exposure to CMME has resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), weight loss, and death from lung cancer.

A number of studies in the United States and abroad (Japan, China, United Kingdom, and France) have described occupational exposure to CMME and BCME that was associated with an increased incidence of lung cancer. The lung cancer occurred approximately 10 years earlier than in the general population (who would most likely get it from cigarette smoking), was of a histologic type distinct from that induced by cigarette smoking, and showed a dose-response when exposures were estimated semi-quantitatively. In the few rare reports in

which air concentrations of CMME were determined, exposure durations were insufficient or inadequate follow-up was conducted to allow the relationship between exposure and cancer development to be quantified.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of 6 rats (strain not specified) exposed for 2-4 h to CMME at 100-10,000 ppm experienced marked irritation to the mucous membranes at concentrations (Hake and Rowe 1963). A 30-min exposure to 2,000 ppm or a 4-h exposure to 100 ppm was "dangerous to life." Death was usually from chemical pneumonia several days or weeks after exposure. Details of the specific concentrations, exposure durations, and accompanying animal responses were not given.

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content specified) using approximately 8-week old male Sprague-Dawley rats. CMME vapor was generated by bubbling air through or passing it over liquid CMME before introduction into 128-L or 1.3-m^3 exposure chambers; concentration was measured every half hour. Rats were exposed to CMME for 7 h at 12.5-225 ppm (see Table 2-3) and the observation period was 14 days. The number of animals was not specified but appeared to be more than 10 per concentration. Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations (SD) in the lung-to-body weight ratio; the ratio for controls was approximately 0.6. A value of 0.9 was considered to be elevated, because previous studies in the same laboratory showed it provides an objective criterion for the evaluation of lung damage for irritants. Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and to a lesser degree in surviving animals. No statements were made about the incidence of lung lesions in the 12.5-ppm group, so this possibility cannot be ruled out even though no significant changes in lung-to-body weight ratio were found. The LC_{50} was graphically estimated by the authors to be 55 ppm.

Drew et al. (1975) exposed 25 male Sprague-Dawley rats daily for 30 days to technical grade CMME at 1.0 or 10.0 ppm (BCME content specified). The exposure duration was not stated but was likely 6 h/day. (Several studies were described in the same report, including other single-exposure studies that used exposure durations of 7 h/day and a multiple-exposure study in which exposure was for 6 h/day; therefore, 6 h/day was assumed for the 30-day exposure study). In the 10 ppm group, rats began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight

TABLE 2-3 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Rats after Single 7-Hour Exposure to Chloromethyl Methyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Rats with Increased Lung-to-Body Weight Ratio (%)[a]	Estimated LC_{50}[b]
225	100[c]	80	55 ppm
141	100	80	
70	100	90	
54	43	67	
42	225 (25)[d]	55	
26	110 (10)[d]	20	
12.5	0	0	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} value were estimated graphically by the study authors.
[c]All rats died after 4 h of exposure.
[d]The mortality percentage in the paper appeared to be typographic errors; suggested values are in parentheses.
Source: Adapted from Drew et al. 1975.

ratios (up to 2.2 vs. 0.6 for controls), 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia. Of the rats exposed to CMME at 1.0 ppm, one died on exposure day 16 and one on day 22. The cause of death was not specified. Of the survivors, five were killed at the end of the last exposure; four had normal lungs and one had slight bilateral hemorrhage. Five more rats were killed 2 weeks later, and the remaining 13 rats were observed for their lifetime. No effects on weight gain occurred in the treated rats. The rats that were observed for their lifetimes had minimal mucosal effects; two had regenerative hyperplasia, one had squamous metaplasia of the bronchial epithelium, and one had squamous metaplasia of the trachea. No tumors or effects on lung-to-body weight ratios were reported.

3.1.2. Hamsters

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content specified) in male Syrian golden hamsters (~6 weeks old). CMME vapor was generated by bubbling air through or passing it over liquid CMME before introduction into 28-L or 1.3-m^3 exposure chambers; concentrations were measured every half hour. Hamsters were exposed to CMME for 7 h at 12.5-225 ppm (see Table 2-4) and observed for 14 days. The number of animals was not specified but appeared to be more than 10 per concentration. Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations in the lung-to-body weight ratio. Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necro-

tizing bronchitis were evident in lungs of animals that died and to a lesser degree in surviving animals. The LC_{50} was graphically estimated by the authors to be 65 ppm.

3.2. Nonlethal Toxicity

3.2.1. Mice

Using an upper-respiratory-tract screening technique (Alarie 1966) with A/Heston male mice, Leong et al. (1971) reported slight irritation in mice exposed to CMME at 40 ppm (0.3-2.6% BCME) for 60 sec. No further details of the experiment were provided; however, in this 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.

No deaths occurred in A/Heston male mice exposed for 6 h to CMME 14.6-100 ppm (0.3-2.6% BCME) within 14 days of exposure (Leong et al. 1971). No further details of the study were provided.

3.3. Neurotoxicity

No studies were found that assessed the neurotoxicity of CMME in animals.

3.4. Developmental and Reproductive Toxicity

No studies were found that assessed the developmental or reproductive effects of CMME in animals.

TABLE 2-4 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Hamsters after Single 7-Hour Exposure to Chloromethyl Methyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Hamsters with Increased Lung-to-Body Weight Ratio[a]	Estimated LC_{50}[b]
225	100[c]	90	65 ppm
141	70	80	
70	60	100	
54	33	63	
42	0	60	
26	0	10	
12.5	0	0	

[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.
[c]Two hamsters died during the exposure period.
Source: Adapted from Drew et al. 1975.

3.5. Genotoxicity

F344 rats given the maximum tolerated concentration of CMME (concentration not stated) had a slight but not statistically definitive increase in micronuclei of the bone marrow, but had negative results in the hypoxanthine phosphoribosyl-transferase (HPRT) specific locus assay of lung fibroblasts (Heddle et al. 1991).

CMME (5-10 mg) was weakly mutagenic in *Drosophila melanogaster* larvae (Filippova et al. 1967). Viral transformation of SA7/SHE cells was enhanced by CMME at 10 μg/mL in the absence of metabolic activation (Casto 1981).

CMME (purity unknown) was mutagenic (approximately 2-fold increase in revertants) in *Salmonella typhimurium* TA98 when tested at a concentration of 1.0 μL/2,000 cm^3 in the absence of metabolic activation (Norpoth et al. 1980). CMME was found to be mutagenic in *Escherichia coli* and *S. typhimurium* by Mukai and Hawryluk (1973), although experimental details were not provided.

Technical grade CMME (12.5 or 25 μmols) did not induce DNA, RNA, or protein synthesis in the epidermis of mice treated dermally with CMME, as measured by radiolabeled thymidine, cytidine, and leucine (Slaga et al. 1973). However, when higher amounts of CMME were applied (50 or 125 μmols) followed by the promoter croton oil, a "marginal" initiating effect was seen (Slaga et al. 1973).

3.6. Carcinogenicity

Fifty A/Heston male mice were exposed to CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 21 weeks (total of 101 exposures), after which they were sacrificed (Leong et al. 1971). Exposure was in 100-L acrylate plastic chambers, and the CMME vapor was generated by metering liquid CMME into the airstream entering the exposure chamber; the analytic concentration of the CMME inside the chamber was not measured. There was no effect on mortality, body weight, or the appearance of the mice throughout the study. 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. The incidence and frequency of lung adenomas was increased slightly in the CMME-exposed mice; 50% of the CMME-treated mice had tumors compared with 41% of the controls, and the mean number of adenomas per tumor-bearing animal was 3.1 for the treated mice and 2.2 for the controls. It was not stated whether other parts of the respiratory system were examined for tumors. Microscopically, the tumor cells from control animals were uniform in size and shape whereas tumor cells from the treated animals were less well-defined and frequently formed papillary structures in the surrounding lung tissues. The carcinogenic affect of CMME could not be definitively established from this study because of the small amount of contaminating BCME (Leong et al. 1971).

In a lifetime inhalation study conducted by Laskin et al. (1975), 74 male Sprague-Dawley rats and 90 Syrian golden hamsters were given CMME at 1 ppm for 6 h/day, 5 days/week. There was no effect on mortality or body weight gain in either species. Histologic examination of the respiratory-tract mucosa of the rats showed a marked increase in the incidence of tracheal squamous metaplasia and bronchial hyperplasia compared with controls (74 sham exposed), as well as one squamous-cell carcinoma of the lung (with metastasis to the kidneys) and one esthesioneuroepithelioma of the olfactory epithelium. Additionally, one animal had an undifferentiated pituitary tumor that was probably not related to treatment. The treated hamsters had few mucosal differences from the 80 sham exposed controls, although they had more peripheral bronchoalveolar changes, including metaplasia and alveolar cell atypia (nuclear abnormality). One exposed hamster had a lung adenocarcinoma and one had a tracheal squamous papilloma (0 in controls).

3.7. Summary

There was one major study of the acute toxicity of CMME in rats and hamsters, where the LC_{50} based on a 7-h exposure and 2-week observation period was about 55 ppm for rats and 65 ppm for hamsters (Drew et al. 1975). Death was not immediate, and usually resulted from pneumonia. Rats given 30 exposures to CMME at 1.0 or 10.0 ppm (probably for 6 h/day) had premature mortality and lung hyperplasia or metaplasia (Drew et al. 1975). Mice exposed to CMME at 2 ppm for 6 h/day for 21 weeks had a slight increase in lung tumors (Leong et al. 1971). Rats and hamsters exposed to CMME at 1 ppm for 6 h/day, 5 days/week for a lifetime had increased incidences of respiratory-tract tumors (Leong et al. 1971; Laskin et al. 1975).

Rats and mice appeared to be able to tolerate (no apparent irritation or effects on demeanor) concentrations of CMME or BCME greater than those producing carcinogenicity or toxicity (>1 ppm).

No studies were found that assessed developmental or reproductive effects of CMME on animals. CMME was genotoxic in *S. typhimurium* in the absence of metabolic activation, and caused a slight increase in bone marrow micronuclei in F344 rats and mutations in *D. melanogaster* larvae (Filippova et al. 1967; Mukai and Hawryluk 1973; Norpoth et al. 1980; Sram et al. 1983; Heddle et al. 1991).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was found in the literature regarding CMME metabolism. CMME hydrolyzes completely and irreversibly in water to form HCl, methanol, and formaldehyde. HCl and formaldehyde can form BCME, although the kinetics of the conversion from CMME to BCME have not been defined

(Travenius 1982). It is unknown if CMME or its hydrolysis products are further metabolized in vivo. Consistent with its in situ hydrolysis, the respiratory tract is the primary site of technical grade CMME toxicity and carcinogenicity in humans and animals. It is unknown to what extent the CMME hydrolysis products, metabolites, or any potentially-formed BCME are responsible for the toxicity and carcinogenicity of CMME.

4.2. Mechanism of Toxicity

The mechanism of CMME toxicity has not been elucidated. Several investigators have suggested that CMME is a direct-acting carcinogen that causes radiomimetic injury (Drew et al. 1975; Travenius 1982). CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine (Burchfield and Storrs 1977). Nucleophilic displacement of the halogen-bearing carbon atom should occur readily and, therefore, CMME is an alkylating agent. It has been shown to react with DNA (Burchfield and Storrs 1977). However, in other in vitro studies, CMME did not form any isolable discrete base-alkylation products detected 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).

4.3. Structure Activity Relationships

The chemical most related to technical grade CMME in its behavior is BCME. 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 by inhalation (Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975) and dermal application and subcutaneous injection (Gargus et al. 1969; Van Duuren et al. 1968, 1969). CMME odor, however, is more readily detected than BCME odor (Rohm & Haas, personal communication, February 1998).

Burchfield and Storrs (1977) reported that when 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. Ocular irritation, however, 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 that there is not a great deal of variability in CMME acute toxicity between species; the 7-h LC_{50} for rats and hamsters was 55 and 65 ppm, respectively.

4.4.2. Susceptible Populations

No studies were found that identified populations susceptible to CMME toxicity.

4.4.3. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for CMME. 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 30-480 minutes, n = 3 and n = 1 were used to extrapolate to shorter and longer durations, respectively, than the exposure duration in the key study. The 10-min values were not extrapolated because the National Advisory Committee determined that extrapolating from ≥4 h to 10 min has unacceptably large inherent uncertainty, so the 30-min value was adopted for 10-min value to be protective of human health. AEGL-1 values were not derived.

4.4.4. Concurrent Exposure Issues

Because commercially available CMME is contaminated with 1-10% BCME, exposure to CMME inevitably involves simultaneous exposure to BCME. No studies were found to determine the effect of varying the BCME contamination on CMME toxicity or carcinogenicity. However, since BCME is a more potent toxicant and carcinogen than CMME, its degree of contamination is expected to have an effect on CMME toxicity and carcinogenicity.

4.4.5. Neoplastic Potential by Other Routes of Exposure

CMME also has been shown to have carcinogenic potential by routes other than inhalation. Purified CMME (99.5%) was not a complete carcinogen or a promoter when applied topically (0.1 or 1 mg; 2% solution in benzene) to the skin of female ICR/Ha Swiss mice three times per week for 325 days, but did act like a tumor initiator (papillomas or squamous carcinomas) when a single application was given 2 weeks before the promoter croton resin (Van Duuren et al. 1968, 1969). When purified CMME (99.5%) was injected subcutaneously in female Sprague-Dawley rats (1-3 mg/wk for 301 days), 14/20 animals developed nodules at the injection site and 1/20 developed fibrosarcoma; no lesions developed in the controls (Van Duuren et al. 1968, 1969). Female ICR/Ha Swiss mice given weekly subcutaneous injections of CMME (99.5% pure) at 300 μg in Nujol (0.1 mL) over their lifetime developed sarcomas at the injection site (10/30 compared with 0/30 controls) (Van Duuren at al. 1972). A single

subcutaneous injection of CMME (0.3-2.6% BCME) at 125 µL/kg (0.17 mg/kg) in peanut oil was given to newborn ICR Swiss mice (1-3 days old; 48 females, 51 males). Treated mice were killed after 6 months, and necropsy showed a slightly increased incidence and multiplicity of pulmonary adenomas (incidence of 17% for treated and 14% for controls; multiplicity of 0.21 for treated and 0.14 for controls), which the study author stated might have been from the contaminating BCME (Gargus et al. 1969).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No appropriate human studies were found.

5.2. Summary of Animal Data Relevant to AEGL-1

No appropriate animal studies were found. The mouse respiratory-inhibition study of Leong et al. (1971) had an exposure duration that was too short (60 sec), and the resulting decrease in the breathing rate was not quantified.

5.3. Derivation of AEGL-1

AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Concentrations that caused AEGL-1 effects also caused toxicity within or exceeding the severity of AEGL-2 effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No appropriate human data were found.

6.2. Summary of Animal Data Relevant to AEGL-2

The following studies were considered for derivation of AEGL-2 values:

- The study in which male A/Heston mice exposed for 6 h to CMME at 14.6-100 ppm (0.3-2.6% BCME) had no deaths within 14 days of exposure (Leong et al. 1971). The presence of toxic effects in the animals was not investigated.

- The rat and hamster 7-h LC_{50} studies (Drew et al. 1975). Rats were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h and observed for 14 days; the number of animals tested was not stated but appeared to be 10 or more per concentration. Increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in the lungs of animals that died and to a lesser degree in animals surviving to 14 days. It was assumed that some of these effects occurred at the lowest test concentration of 12.5 ppm. An adjustment factor of 3 could be applied to the LOAEL of 12.5 ppm to estimate a NOAEL of 4.2 ppm for lung lesions in both species.
- The 30-day exposure study in which male rats were exposed to CMME at 1 ppm (content of BCME not specified; see Section 3.1.1.) for 6 h/day, 5 days/week (Drew et al. 1975). Two rats died (on exposure days 16 and 22), although it is unknown if the deaths were treatment related. One of five rats sacrificed immediately after exposure had slight hemorrhage and several rats retained for lifetime study had lung hyperplasia or squamous metaplasia but no tumors.
- Lifetime exposure study of male rats and hamsters to CMME at 1 ppm for 6 h/day, 5 days/week (Laskin et al. 1975). Mortality and body weight gain were unaffected. Rats had an increased incidence of tracheal squamous metaplasia and bronchial hyperplasia, and two had respiratory-tract tumors. Hamsters had an increased incidence of bronchoalveolar metaplasia and alveolar cell atypia, and one had lung adenocarcinoma and another had tracheal squamous papilloma.
- The study in which male mice were exposed to CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 101 exposures over 21 weeks, after which they were killed (Leong et al. 1971). CMME had no effect on mortality, body weight, or demeanor but had a slightly increased incidence and frequency of lung adenomas.

6.3. Derivation of AEGL-2

AEGL-2 values were based on an acute toxicity study in which rats and hamsters were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h and observed for 14 days (Drew et al. 1975). Toxic effects were not attributed to specific concentrations, but it was stated that animals that died had increased relative lung weights, pulmonary congestion, edema, hemorrhage, and acute necrotizing bronchitis. These effects were found to a lesser degree in surviving animals. Therefore, 12.5 ppm was considered the LOAEL for serious or irreversible lung lesions in both species, and was also a NOEL for lethality in rats. An estimated NOAEL of 4.2 ppm for serious or irreversible lung lesions in both species was obtained by dividing the LOAEL by an adjustment factor of 3. No data were available from which to determine the CMME 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 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for the 10-min values to be protective of human health (see Section 4.4.3.). A total uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because CMME caused a similar degree of lung toxicity in two animal species, and is expected to cause similar toxicity in human lungs. A 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. An intraspecies uncertainty factor of 3 was also used in the derivation of AEGL-2 values for BCME. A modifying factor of 1.7 was also applied because the BCME content in technical grade CMME in the key study was unknown. The modifying factor was obtained by assuming contamination with 10% BCME (the maximum reported) and accounting for its greater toxicity (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study), as follows: [0.1 × (55 ppm ÷ 7 ppm)] + [0.9 × 1] = 1.7. The resulting AEGL-2 values are shown in Table 2-5; calculations are detailed in Appendix A. The analytic detection limit of CMME in the air is <1 ppb; the AEGL-2 values are well above the detection limit.

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent a carcinogen than "pure" CMME (Gargus et al. 1969; Van Duuren et al. 1968, 1969; Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975), then it follows that technical CMME at most has 19% of the carcinogenic activity of BCME. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values are estimated range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in the methods used for deriving AEGL values and for extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for deriving AEGLS for CMME.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No appropriate human studies were available.

TABLE 2-5 AEGL-2 Values for Chloromethyl Methyl Ether

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.0 mg/m^3)	0.60 ppm (2.0 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.30 ppm (0.98 mg/m^3)	0.22 ppm (0.72 mg/m^3)

7.2. Summary of Animal Data Relevant to AEGL-3

The following studies were considered relevant for the development of AEGL-3 values:

- Study by Hake and Row (1963) in which rats exposed for 30-min to CMME at 2,000 ppm (purity unknown) or for 4-h to 100 ppm died from chemical pneumonia several days or weeks after exposure. Further study details were not provided.
- Study by Drew et al. (1975) that reported 7-h LC_{50} values of 55 ppm for rats and 65 pm for hamsters. Concentration-related increases in relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were found in all groups of treated animals that died and were found to a lesser degree in surviving animals.
- Study of male Sprague-Dawley rats exposed for 30 consecutive days to technical grade CMME at 10.0 ppm for 6 h/day (Drew et al. 1975). Rats began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight ratios, 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia.
- Study by Leong et al. (1971) of male mice exposed to technical grade CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 101 exposures over 21 weeks. No effect on mortality rates, body weight, or demeanor were observed, but there was a slightly increased incidence (50% vs. 41% in controls) and multiplicity (3.1 vs. 2.2 for the controls) of lung adenomas. The morphology of the tumor cells in control and treated animals differed.
- Lifetime study in which male rats and hamsters exposed to technical grade CMME at 1 ppm (6 h/day, 5 days/week) had no differences in mortality or body weight gain compared with controls, but had an increased incidence of pulmonary squamous metaplasia and hyperplasia (Laskin et al. 1975). Two rats (of 74) and two hamsters (of 90) developed respiratory tract tumors (0 in controls).

7.3. Derivation of AEGL-3

AEGL-3 values were based on the LC_{50} study in which rats and hamsters exposed for 7 h to CMME at 12.5-225 ppm (content of BCME not given) had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis (Drew et al. 1975). The effects occurred in animals that

died and, to a lesser degree, in animals that survived. Assuming n = 20 for all dose groups, a $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) was calculated using the long/probit model from EPA's Benchmark Dose Software, Version 1.3.2 (EPA 2005b). The $BMCL_{05}$ was approximately 18 ppm for hamsters and 19 ppm for rats; the lower value of 18 ppm was used for derivation of AEGL-3 values. (Alternatively, if it is assumed that n = 10 for all test concentrations, the $BMCL_{05}$ is 15 ppm for rats and 16 ppm for hamsters, and if n = 30 for all test concentrations the $BMCL_{05}$ is 20 ppm for rats and 19 ppm for hamsters.) Increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were found in animals that died and, to a lesser degree, in animals that died. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al. (1986) equation $C^n \times t = k$ and n = 1 or n = 3, as described above for AEGL-2 values. An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was virtually 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. A 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 intraspecies uncertainty factor of 3 was also used in the derivation of AEGL-3 values for BCME. As for AEGL-2, a modifying factor of 1.7 was also applied because the content of BCME in technical grade CMME in the key study was unknown. The resulting AEGL-3 values are shown in Table 2-6; calculations are detailed in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for technical grade CMME and their relationship to one another are shown in Table 2-7. No data were available to determine the concentration-time relationship for CMME toxic effects. Scaling across time for 30-480 min was performed using the equation $C^n \times t = k$, with n = 3 and n = 1 to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study. The 10-min values were not extrapolated because the National Advisory Committee determined that extrapolating from ≥4 h to 10 min has unacceptably large inherent uncertainty. The 30-min values were adopted for 10-min values to be protective of human health.

TABLE 2-6 AEGL-3 Values for Chloromethyl Methyl Ether

10 min	30 min	1 h	4 h	8 h
2.6 ppm (8.6 mg/m^3)	2.6 ppm (8.6 mg/m^3)	2.0 ppm (6.6 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.93 ppm (3.1 mg/m^3)

AEGL-1 values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects. AEGL-2 and AEGL-3 values were based on an acute toxicity study in which rats and hamsters were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h. A concentration of 12.5 ppm was considered the LOAEL for serious or irreversible lung lesions in both species, and was a NOEL for lethality in rats. An estimated NOAEL of 4.2 ppm for serious or irreversible lung lesions in both species was obtained by dividing the LOAEL by an adjustment factor of 3. For both the AEGL-2 and AEGL-3, an uncertainty factor of 10 was used (3 for interspecies and 3 for intraspecies variability), a modifying factor of 1.7 was applied because the BCME content in technical grade CMME in the key study was unknown, and scaling across time was performed using the ten Berge et al (1986) equation $C^n \times t = k$, with n = 1 or n = 3.

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent as a carcinogen than "pure" CMME (which is suggested by experimental data), then technical CMME has 19% of the carcinogenic activity of BCME at most. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values compared with extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for deriving AEGL values.

8.2. Comparison with Other Standards and Guidelines

Numeric standards for exposure to technical grade CMME were not established by the Occupational Health and Safety Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), or the American Conference of Governmental Industrial Hygienists (ACGIH) because of its known human carcinogenicity. The ACGIH has developed a Threshold Limit Value - Time Weighted Average (TLV-TWA) of 0.001 ppm for the related chemical BCME, and suggests that exposure to CMME could be monitored on the basis of the BCME TLV-TWA. Because studies have shown that BCME is more toxic and a more potent carcinogen than CMME, limiting CMME exposures to 0.001 ppm might be protective of CMME toxicity and carcinogenicity as well.

OSHA regulates occupational exposure to CMME under 29 CFR 1910.1006, which discusses control of exposures through the required use of engineering controls, work practices, and personal protective equipment, including respirators. NIOSH and ACGIH recommend that worker exposure be carefully controlled and reduced to the lowest achievable levels. Germany and Sweden also consider CMME a human carcinogen in their workplace exposure guidelines. The American Industrial Hygiene Association (AIHA 2000) has developed Emergency Response Planning Guidelines (ERPGs) for CMME. An ERPG-1 was not considered appropriate because CMME odor is easily noticed at 23 ppm and is strong at 100 ppm (Wagoner et al. 1972), which is above the LC_{50} values of 55 ppm for rats and 65 ppm for hamsters (Drew et al. 1975). The ERPG-2 of 1.0 ppm was selected because it was 10-fold lower than a concentration that did not produce a significant increase in the lung-to-body ratio of rats from a single 7-h exposure (Drew et al. 1975). The ERPG-3 of 10 ppm was chosen because it was below the maximum no-effect level of 12.5 ppm for pulmonary edema from a single 7-h exposure to CMME in rats and hamsters (Drew et al. 1975). The EPRG-3 value of 10 ppm was greater than the 1-h AEGL-3 value of 2 ppm. The values were based on the same study and no-effect level, but the AEGL-3 value was divided by an uncertainty factor of 10, adjusted for BCME content, and scaled across time.

A large chemical manufacturer in Philadelphia developed internal 1-h ERPG values for technical grade CMME of 0.01 ppm for ERPG-2 and 1 ppm for ERPG-3 (no ERPG-1); the respective ERPG values for BCME are 10-fold lower (Rohm & Haas, personal communication, February 1998). A TLV of 0.001 ppm was listed under "Health Hazards" by the Chemical Hazard Response Information System (CHRIS 1985).

The existing standards and guidelines for CMME are shown in Table 2-8.

8.3. Data Adequacy and Research Needs

No human or animal studies were found with defined exposures and responses that fell within the scope of AEGL-1 effects. CMME was toxic to animals and humans at concentrations below those leading to irritation and below the odor-detection level.

Appropriate single-exposure animal studies with AEGL-2 and AEGL-3 end points were few, and no useful (quantitative) human studies were available. However, two species were tested in the key study and had a similar response, and the lung is the target organ in animals and humans.

The BCME content of the CMME used in the key study should have been specified. Data quantifying the effect of BCME contamination on CMME toxicity are needed, and could be used to refine the modifying factor to account for the variability in BCME content of CMME in the AEGL derivations.

TABLE 2-8 Extant Standards and Guidelines for Chloromethyl Methyl Ether

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm
AEGL-3	2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm
ERPG-1 (AIHA)[a]			Not appropriate		
ERPG-2 (AIHA)			1.0 ppm		
ERPG-3 (AIHA)			10 ppm		
PEL-TWA (OSHA)[b]					No value[b]
REL-TWA (NIOSH)[c]					No value[c]
TLV-TWA (ACGIH)[d]					No value[d]
MAK (Germany)[e]					No value[e]
OELV-LLV (Sweden)[f]					No value[f]

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association (AIHA 2000).
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 other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
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 protection action.
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.
[b]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Safety and Health Administration [54 Fed, Reg. 2931[1989]) is 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 CMME as an occupational carcinogen and workplace exposure is regulated by 29 CFR 1910.1006.
[c]REL-TWA (recommended exposure limit–time-weighted average, National Institute for Occupational Safety and Health (NIOSH 2005) is analogous to the ACGIH TLV-TWA. A numeric value was not assigned, but NIOSH considers CMME to be an occupational carcinogen subject to OSHA regulation (29 CFR 1910.1006), and recommends that exposure to it be reduced to the lowest feasible concentrations.
[d]TLV-TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists (ACGIH 2004) 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. CMME was classified as carcinogenicity category A2 ("suspected human carcinogen"). No numeric value was assigned, but ACGIH (1991) recommends that worker exposure by all routes be controlled and kept as low as achievable, and suggests the exposures be monitored on the basis of the BCME TLV of 0.001 ppm.

[e]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], German Research Association). (DFG 2002) is analogous to the ACGIH TLV-TWA. A value was not developed but CMME was classified as a human carcinogen (Category 1), which applies to technical CMME that can be contaminated with ≤7% BCME.
[f]OELV-LLV (occupational exposure limit value-level limit value), Swedish Work Environmental Authority 2005). A value was not developed; CMME is classified as Group A, a substance that may not be handled.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CHLOROMETHLYL METHYL ETHER

Derivation of AEGL-1 Values

AEGL-1 values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects.

Derivation of AEGL-2 Values

Key study:	Drew et al. 1975
Toxicity end points:	4.2 ppm was NOAEL for serious or irreversible respiratory lesions in rats and hamsters. NOAEL obtained by dividing the LOAEL of 12.5 ppm by an adjustment factor of 3.
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 $(4.2 \text{ ppm}/17)^3 \times 7 \text{ h} = 0.106 \text{ ppm}^3\text{-h}$ $(4.2 \text{ ppm}/17)^1 \times 7 \text{ h} = 1.73 \text{ ppm}^3\text{-h}$
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	1.7 because BCME content in technical grade CMME in the key study was unknown. Calculated by assuming 10% BCME (the maximum contamination reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55 \text{ ppm} \div 7 \text{ ppm})] + [0.9 \times 1] = 1.7$.

Calculations:

10-min AEGL-2	Set equal to 30-min value because of uncertainty in extrapolating a 7-h exposure to 10 min.
30-min AEGL-2:	$C^3 \times 0.5$ h = 0.106 ppm^3-h C = 0.60 ppm [2.0 mg/m^3]
60-min AEGL-2:	$C^3 \times 1$ h = 0.106 ppm^3-h C = 0.47 ppm [1.5 mg/m^3]
4-h AEGL-2:	$C^3 \times 4$ h = 0.106 ppm^3-h C = 0.30 ppm [0.98 mg/m^3]
8-h AEGL-2:	$C^1 \times 8$ h = 1.73 ppm-h C = 0.22 ppm [0.72 mg/m^3]

Derivative of AEGL-3 Values

Key study:	Drew et al. 1975
Toxicity end point:	NOEL of 18 ppm for lethality from extreme lung irritation in hamsters ($BMCL_{05}$)
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 $(18 \text{ ppm}/17)^3 \times 7$ h = 8.31 ppm^3-h $(18 \text{ ppm}/17)^1 \times 7$ h = 7.41 ppm-h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	1.7 because BCME content in technical grade CMME in the key study was unknown. Calculated by assuming 10% BCME (the maximum contamination reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): [0.1 × (55 ppm ÷ 7 ppm)] + [0.9 × 1] = 1.7.

Calculations:

10-min AEGL-3:	Set equal to 30-min value because of uncertainty in extrapolating a 7-h exposure to 10 min.
30-min AEGL-3:	$C^3 \times 0.5$ h = 8.31 ppm^3-hr C = 2.6 ppm [8.6 mg/m^3]
60-min AEGL-3:	$C^3 \times 1$ h = 8.31 ppm^3-h C = 2.0 ppm [6.6 mg/m^3]
4-h AEGL-3:	$C^3 \times 4$ h = 8.31 ppm^3-h C = 1.3 ppm [4.3 mg/m^3]
8-h AEGL-3:	$C^1 \times 8$ h = 4.2 ppm-h C = 0.93 ppm [3.1 mg/m^3]

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHRLOMETHYL METHYL ETHER

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

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 adequacy: AEGL-1 values for technical grade CMME were not derived because there were no studies in which toxicity was limited to AEGL-1 effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm

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; number not specified but appeared to be 10 or more per concentration.

Exposure route/Concentrations/Durations: Inhalation of 12.5-225 ppm for 7 h; observed for 14 d

Effects: Concentration-related increases in relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and, to a lesser degree, in animals surviving to 14 d (also assumed at 12.5 ppm). Mortality rates were:

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm

CMME (ppm)	Rats (%)	Hamsters (%)
225	100[a]	100[a]
141	100	70
70	100	60
54	43	33
42	225 (25)[b]	0
26	110 (10)[b]	0
12.5	0	0
	LC_{50} = 55 ppm (from reference) $BMCL_{05}$ = 19 ppm (probit analysis, if *n* = 20)	LC_{50} = 65 ppm (from reference) $BMCL_{05}$ = 18 ppm (probit analysis, if n = 20)

[a]The lung-to-body weight ratio was greater than the control mean plus 3 standard deviations.
[b]Appear to be typographic errors in the reference; suggested values are in parentheses.

End point/Concentration/Rationale: NOAEL of 4.2 ppm for serious or irreversible lung lesions in rats and hamsters, estimated by applying an adjustment factor of 3 to the LOAEL of 12.5 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because CMME caused a similar degree of lung toxicity in two animal species, and is expected to cause similar toxicity in human lungs.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

Modifying factor: 1.7 used because the BCME content in technical grade CMME in the key study was unknown; obtained by assuming 10% BCME (the maximum reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

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 4.4.3.).

Data adequacy: The key study was adequate and the two test species had similar results. The key study did not state the number of animals per concentration, which did not affect the AEGL-2 derivation.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm

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; number not given but appeared to be 10 or more per concentration.

Exposure route/Concentrations/Durations: Inhalation of 12.5-225 ppm for 7 h; observed for 14 d.

Effects: Concentration-related increases in relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and, to a lesser degree, in animals surviving to 14 d (also assumed at 12.5 ppm). Mortality rates were:

CMME (ppm)	Rats (%)	Hamsters (%)
225	100[a]	100[a]
141	100	70
70	100	60
54	43	33
42	225 (25)[b]	0
26	110 (10)[b]	0
12.5	0	0
	LC_{50} = 55 ppm (from reference) $BMCL_{05}$ = 19 ppm (probit analysis, if n = 20)	LC_{50} = 65 ppm (from reference) $BMCL_{05}$ = 18 ppm (probit analysis, if n = 20)

[a]The lung-to-body weight ratio was greater than the control mean plus 3 standard deviations.
[b]Appear to be typographic errors in the reference; suggested values are in parentheses.

End point/Concentration/Rationale: NOEL of 18 ppm for lethality from extreme lung irritation in hamsters ($BMCL_{05}$).

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because the NOEL for lethality was virtually 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 chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm

Modifying factor: 1.7 used because the BCME content in technical grade CMME in the key study was unknown; obtained by assuming 10% BCME (the maximum reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

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 4.4.3.).

Data adequacy: The key study was adequate and the two test species had similar results. The key study did not state the number of animals per concentration. This could have slightly affected the calculated $BMCL_{05}$ and AEGL-3 values. If it is assumed that n = 10 for all test concentrations, the $BMCL_{05}$ is 15 ppm for rats and 16 ppm for hamsters, and if n = 30, the $BMCL_{05}$ is 20 ppm for rats and 19 ppm for hamsters.

APPENDIX C

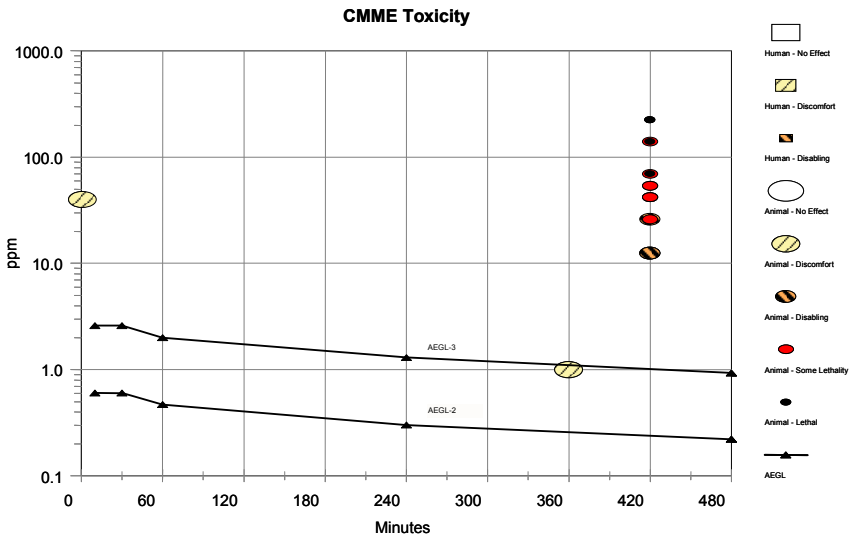

FIGURE C-1 Category plot of animal toxicity data compared with AEGL values. Multiple-exposure studies are not included in the plot.

APPENDIX D

CANCER ASSESSMENT OF CHLOROMETHYL METHYL ETHER AND bis-CHLOROMETHYL ETHER (BCME)

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME. EPA (2002) performed a cancer assessment of the related compound BCME using data from Kuschner et al. (1975). The calculated inhalation unit risk for BCME was 6.2×10^{-2} per $\mu g/m^3$, using the linearized multistage procedure, extra risk (EPA 2005b). 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). 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 of exposure concentrations is made to account for interspecies variability. The calculated concentration of BCME associated with a 1×10^{-4} cancer risk is shown in Table D-1 for a single exposure of 10 min to 8 h. For a 1×10^{-5} and 1×10^{-6} risk, the 1×10^{-4} values are reduced 10-fold or 100-fold, respectively.

If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent a carcinogen than "pure" CMME (which is suggested by experimental data), then technical-grade CMME has 19% of the carcinogenic activity of BCME at most ([90% of technical-grade CMME with 10% BCME activity] + [10% of technical grade CMME with 100% BCME activity]). Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the CMME concentration associated with a 1×10^{-4} cancer risk for a given exposure duration can be

calculated by dividing the respective BCME concentration by 0.19, as shown in Table D-1. Also presented in the table is the cancer risk for the AEGL-2 and AEGL-3 concentrations from a single exposure for 30 min to 8 h. The risk for the AEGL-2 values ranges from 1.7×10^{-4} for a 30-min exposure to 9.6×10^{-4} for an 8-h exposure. The predicted carcinogenic risk for the AEGL-3 values is greater, ranging from 7.4×10^{-4} for a 30-min exposure to 4.1×10^{-3} for an 8-h exposure. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values compared with extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for driving the AEGL values for CMME.

TABLE D-1 Estimated Cancer Risks Associated with a Single Exposure Chloromethyl Methyl Ether or 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		1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
CMME, containing 10% BCME[a]					
Concentration	Not calculated	0.36 ppm	0.18 ppm	0.045 ppm	0.023 ppm
Estimated cancer risk		1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
AEGL-2 value	0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm
Estimated cancer risk	Not calculated	1.7×10^{-4}	2.6×10^{-4}	6.7×10^{-4}	9.6×10^{-4}
AEGL-3 value	2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm
Estimated cancer risk	Not calculated	7.4×10^{-4}	1.1×10^{-3}	2.9×10^{-3}	4.1×10^{-3}

[a]Assumes BCME is a 10-fold more potent carcinogen than CMME.