# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 14**

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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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 fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl

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

phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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 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 committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for BZ (interim reports 19a, 20a, and 21a), ethyl phosphorodichloridate (interim reports 20a and 21a), hexane (interim reports 17 and 21a), methanesulfonyl chloride (interim reports 20a and 21a), nitric acid (interim reports 15, 18, and 21a), propargyl alcohol (interim reports 16 and 19a), and vinyl acetate monomer (interim reports 18 and 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still, Occupational Toxicology Associates, 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 reports 15-21 was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was 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 Ernest Falke and Iris A. Camacho from EPA. 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

# Contents

# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 14**

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

This report is the fourteenth 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 and 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 exposure 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:

[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.

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 extrap-

olation 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 ($1 \times 10^{-4}$), 1 in 100,000 ($1 \times 10^{-5}$), and 1 in 1,000,000 ($1 \times 10^{-6}$) 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 recommenda-

tions 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 thirteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c). This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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

# 4

# Methanesulfonyl Chloride[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 effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Roberta Grant (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). 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).

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 concentrations 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

Methanesulfonyl chloride is a pale yellow liquid with an unpleasant odor. It is made commercially either by the chlorination of methyl mercaptan or by the sulfochlorination of methane. It is used as an intermediate in the pharmaceutical, photographic, fiber, dye, and agricultural industries. It is also used as a stabilizer, catalyst, curing agent, and chlorinating agent. Methanesulfonyl chloride causes severe ocular, dermal, and mucous membrane irritation. Chlorine gas and sulfur oxides are produced when it is heated until decomposition.

Data were insufficient to derive AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended.

Appropriate chemical-specific data were not available for deriving AEGL-2 values. In the absence of such data, chemicals with a steep concentration-response curve may be derived by dividing AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm (Pennwalt Corporation 1987).

A 4-h rat $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 15.5 ppm (Pennwalt Corporation 1987) was used as the point of departure for AEGL-3 values. Values were time scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h by log probit analysis (see Appendix E). However, the data and modeling results were considered inadequate to define an empirical value of n, but

indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. Uncertainty factors of 10 were applied to account for interspecies differences and intraspecies variability (total uncertainty factor of 100), because of the lack of information available to describe species differences in toxicity and interindividual variability. Although clinical signs and pathologic findings from the limited data set suggest contact irritation (partial eye closure, disturbed respiratory patterns, salivation, nose rubbing, blinking, nasal discharge, lacrimation, increased relative lung weight, pulmonary congestion, and corneal surface damage) and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. The 30-min AEGL-3 value was adopted as the 10-min value because of the added uncertainty of extrapolating a 4-h point of departure to a 10-min value.

AEGL values for methanesulfonyl chloride are presented in Table 4-1.

## 1. INTRODUCTION

Methanesulfonyl chloride is a pale yellow liquid with an unpleasant odor. It is made commercially either by the chlorination of methyl mercaptan or by the sulfochlorination of methane. It is used as an intermediate in the pharmaceutical, photographic, fiber, dye, and agricultural industries. It is also used as a stabilizer, catalyst, curing agent, and chlorinating agent. Methanesulfonyl chloride causes severe ocular, skin, and mucous membrane irritation. Chlorine gas and sulfur oxides are produced when methanesulfonyl chloride is heated to decomposition (Shertzer 2001). Methanesulfonyl chloride is shipped in 55 gallon drums; production in 1981 was "probably greater than $2.27 \times 10^6$ grams" (HSDB 2007). Chemical and physical data for methanesulfonyl chloride are presented in Table 4-2.

## 2. HUMAN TOXICITY DATA

Methanesulfonyl chloride is a strong irritant to the skin, eyes, mucous membranes, and respiratory tract and is corrosive. Its odor is described as unpleasant, although no information on an odor threshold was found (Shertzer 2001).

**TABLE 4-1** AEGL Values for Methanesulfonyl Chloride

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h | End Point (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1 (nondisabling)[a] | NR | NR | NR | NR | NR | Insufficient data. |
| AEGL-2 (disabling) | 0.40 ppm (1.9 $mg/m^3$) | 0.40 ppm (1.9 $mg/m^3$) | 0.21 ppm (0.98 $mg/m^3$) | 0.053 ppm (0.25 $mg/m^3$) | 0.026 ppm (0.12 $mg/m^3$) | One third of AEGL-3 values (NRC 2001). |
| AEGL-3 (lethal) | 1.2 ppm (5.6 $mg/m^3$) | 1.2 ppm (5.6 $mg/m^3$) | 0.62 ppm (2.9 $mg/m^3$) | 0.16 ppm (0.75 $mg/m^3$) | 0.078 ppm (0.37 $mg/m^3$) | 4-h $BMCL_{05}$ of 15.5 ppm in rats (Pennwalt Corporation 1987) |

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended because of insufficient data.
[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 values are without effect.

**TABLE 4-2** Chemical and Physical Data for Methanesulfonyl Chloride

| Parameter | Value | References |
|---|---|---|
| Synonyms | Chloromethyl sulfone; mesyl chloride; methanesulfonic acid chloride; methyl sulfochloride | HSDB 2007 |
| CAS registry no. | 124-63-0 | HSDB 2007 |
| Chemical formula | $CH_3ClO_2S$ | HSDB 2007 |
| Molecular weight | 114.55 | HSDB 2007 |
| Physical state | Pale, yellow liquid | HSDB 2007 |
| Freezing point | -32°C | HSDB 2007 |
| Boiling point | 62°C @ 18mmHg | HSDB 2007 |
| Flash point | 110°C | Shertzer 2001 |
| Density/specific gravity | 1.4805 g/L @ 18°C | HSDB 2007 |
| Solubility in water | Insoluble; hydrolyzes slowly | HSDB 2007 |
| Vapor pressure | 3.09 mm Hg @ 25°C | HSDB 2007 |
| Conversion factors | 1 ppm = 4.68 $mg/m^3$<br>1 $mg/m^3$ = 0.21 ppm | |

## 3. ANIMAL TOXICITY DATA

### 3.1. Acute Toxicity

Groups of five male and five female Sprague-Dawley rats were exposed to methanesulfonyl chloride at 0, 20, 28, or 54 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (Pennwalt Corporation 1987). Whole-body exposure chambers were constructed of Perspex and had an internal volume of 115 L. Test atmospheres were generated by supplying methanesulfonyl chloride from a syringe driven by a syringe pump. The compressed air supply to the generator was dried, filtered, and oil free; flow rate was 25 L/min. Test atmospheres were analyzed five times per exposure by gas chromatography flame ionization detection, and were monitored for the presence of droplets of methanesulfonyl chloride at 1.5 and 3.5 h. The study followed Good Laboratory Practice and the guidelines of Organisation for Economic Cooperation and Development for assessing acute inhalation toxicity (OECD Test 403). Clinical signs observed during exposure in all groups included closing or partial closing of the eyes, wet fur around the mouth, hunched body posture, and disturbed respiratory patterns. Clinical signs during the observation period included lethargy and disturbances of the respiratory pattern. Respiratory effects persisted for several days in rats that survived. Lung-to-body weight ratio was increased in most decedents, and pulmonary congestion and damage to the corneal surface of the eyes were also found. A 4-h $LC_{50}$ (lethal concentration, 50% lethality) value of 25 ± 2.7 ppm, a $BMCL_{05}$ of 15.5 ppm, and $BMC_{01}$ (benchmark concentration with 1% response) of 17.4 ppm were calculated. Mortality data from this study are summarized in Table 4-3.

**TABLE 4-3** Mortality in Rats Exposed to Methanesulfonyl Chloride for 4 Hours

| | Mortality | | |
|---|---|---|---|
| Concentration (ppm) | Males | Females | Combined |
| 0 | 0/5 | 0/5 | 0/10 |
| 20 | 1/5 | 0/5 | 1/10 |
| 28 | 4/5 | 5/5 | 9/10 |
| 54 | 5/5 | 5/5 | 10/10 |
| $LC_{50}$ | | | 25 ppm |
| $BMC_{01}$ | | | 17.4 ppm |
| $BMCL_{05}$ | | | 15.5 ppm |

Source: Pennwalt Corporation 1987.

Groups of five male and five female Sprague-Dawley rats were exposed to methanesulfonyl chloride at 165, 174, or 300 ppm (analytic concentrations) for 1 h, followed by a 14-day observation period (Pennwalt Corporation 1986). Animal were exposed (whole body) in 100-L Plexiglas chambers. Test atmospheres were generated by placing methanesulfonyl chloride into a bubbler fitted with an impinger. A metered, dried air supply was delivered into the bubbler and the resulting vapor laden air stream was introduced into the exposure chamber; flow rate was 25-26 L/min. Concentrations of methanesulfonyl chloride were analyzed twice per exposure. The study followed Good Laboratory Practice and U.S. Department of Transportation guidelines. Clinical signs noted during exposure and within 5-h post-exposure included secretory and pulmonary responses (not otherwise specified) and decreased activity in all groups. Rats in the 300-ppm group had closed eyes and exhibited prostration. Signs of toxicity in this group during the observation period included secretory and pulmonary responses and generally poor condition until death on the afternoon following exposure. Survivors in the 165- and 174-ppm groups showed secretory and pulmonary effects through days 4-5; these signs were noted sporadically thereafter. Corneal irregularities and opacities were found in three of nine rats in the 165-ppm group and all eight rats in the 174-ppm group at the end of the observation period. An $LC_{50}$ value could not be calculated from the data; however, the investigators stated that the 1-h $LC_{50}$ is most likely in the range of 175 to 250 ppm. Mortality data from this study are summarized in Table 4-4.

Groups of three rats were exposed to nominal concentrations of methanesulfonyl chloride at 2,145 ppm for up to 45 min, 29 ppm for 6 h, or 132 ppm for 6 h, followed by a 14-day observation period (TerHaar 1978). Chamber temperatures were 24-26°C. No further experimental details were provided. Methanesulfonyl chloride was described as a severe tissue irritant, capable of causing necrosis on any tissue it contacts. Results and observations of this study are presented in Table 4-5.

Oral $LD_{50}$ values for methanesulfonyl chloride of approximately 175 mg/kg and 200 mg/kg were determined for rats and mice, respectively (TerHaar 1978). Deaths occurred immediately after dosing, except for two mice that survived a dose near the $LD_{50}$. Hematuria developed in surviving rats. No additional details were presented.

**TABLE 4-4** Mortality in Rats Exposed to Methanesulfonyl Chloride for 1 Hour

| | Mortality | | |
|---|---|---|---|
| Concentration (ppm) | Males | Females | Combined |
| 165 | 1/5 | 0/5 | 1/10 |
| 174 | 1/5 | 1/5 | 2/10 |
| 300 | 5/5 | 5/5 | 10/10 |

Source: Pennwalt Corporation 1986.

**TABLE 4-5** Mortality and Clinical Signs in Rats Exposed to Methanesulfonyl Chloride

| Concentration (ppm) | Duration | Mortality | Time to Death | Clinical Signs (when first observed) |
|---|---|---|---|---|
| 2,145 | 45 min | 3/3 | 1 dead in 30 min<br>1 dead in 40 min<br>1 dead in 45 min | Blinking and nose rubbing (1 min), salivation (4 min), dyspnea and piloerection (5 min), lacrimation and clear nasal discharge (10 min). |
| 29 | 6 h | 0/3 | — | Blinking (1 min), nose rubbing (2 min), piloerection (5 min), vasodilation (15 min). |
| 132 | 6 h | 3/3 | 2 dead in 20-h post-exposure<br>1 dead in 3-d post-exposure | Blinking and nose rubbing (1 min), dyspnea and piloerection (10 min), clear nasal discharge (15 min), lacrimation and salivation (25 min), wheezing (265 min). |

Source: TerHaar 1978.

### 3.2. Developmental and Reproductive Toxicity

No data on the developmental and reproductive toxicity of methanesulfonyl chloride were available.

### 3.3. Genotoxicity

In the presence of exogenous metabolic activation (S9 mix), methanesulfonyl chloride induced chromosome aberrations in vitro in Chinese hamster ovary (CHO) cells (Sipi et al. 1997). Without metabolic activation, no response was observed.

### 3.4. Chronic Toxicity and Carcinogenicity

No data on the chronic toxicity or carcinogenicity of methanesulfonyl chloride were available.

### 3.5. Summary

Animal toxicity data are limited. Clinical signs, including ocular and nasal irritation, respiratory difficulty, nasal discharge, wheezing, and corneal opacities, are consistent with severe irritation. Methanesulfonyl chloride induced chromosome aberrations in CHO cells only in the presence of metabolic activation. No data on the developmental, reproductive, chronic, or carcinogenic effects of methanesulfonyl chloride were available.

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism and Disposition

No information was available on the metabolism and disposition of methanesulfonyl chloride.

### 4.2. Mechanism of Toxicity

No information was available on the mechanism of toxicity of methanesulfonyl chloride.

### 4.3. Structure-Activity Relationships

Methanesulfonyl chloride ($CH_3ClO_2S$) is structurally similar to thionyl chloride ($Cl_2OS$) and sulfuryl chloride ($Cl_2O_2S$). However, thionyl chloride and sulfuryl chloride readily hydrolyze to $SO_2$ and HCl whereas methanesulfonyl chloride hydrolyzes very slowly. The health effects of these three compounds are similar but their mechanism of toxicity is likely different. Although data are limited, it appears that the effects of thionyl chloride and sulfuryl chloride result from their hydrolysis products rather than from exposure to the parent compounds; in contrast, because methanesulfonyl chloride is hydrolyzed very slowly, the effects likely result from exposure to the parent compound (EPA 2006; NRC 2011).

### 4.4. Other Relevant Information

#### 4.4.1. Species Variability

No information on species variability from inhalation exposure to methanesulfonyl chloride was available. However, clinical signs are consistent with contact irritation. Therefore, effects are not expected to vary widely between species. The limited data suggest no difference in acute oral lethality between rats and mice (TerHaar 1978).

#### 4.4.2. Susceptible Populations

No information on populations especially sensitive to methanesulfonyl chloride toxicity was available. However, clinical signs are consistent with contact irritation. Therefore, effects are not expected to vary widely among individuals.

### 4.4.3. Time Scaling

AEGL values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis of the data (see Appendix E) yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square goodness-of fit-test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1.

## 5. DATA ANALYSIS FOR AEGL-1

### 5.1. Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values for methanesulfonyl chloride were available.

### 5.2. Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values for methanesulfonyl chloride were available.

### 5.3. Derivation of AEGL-1 Values

No human or animal data were available for derivation of AEGL-1 values for methanesulfonyl chloride. Therefore, no AEGL-1 values are recommended.

## 6. DATA ANALYSIS FOR AEGL-2

### 6.1. Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values for methanesulfonyl chloride were available.

### 6.2. Animal Data Relevant to AEGL-2

No animal data relevant to development of AEGL-2 values for methanesulfonyl chloride were available.

### 6.3. Derivation of AEGL-2 Values

Appropriate chemical-specific data for deriving AEGL-2 values were not available. In the absence of such data, chemicals with a steep concentration-response curve may be derived by dividing AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm (Pennwalt Corporation 1987). AEGL-2 values are presented in Table 4-6, and calculations are presented in Appendix A.

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values for methanesulfonyl chloride were available.

### 7.2. Animal Data Relevant to AEGL-3

A 4-h $BMCL_{05}$ of 15.5 ppm and $BMC_{01}$of 17.4 ppm (Pennwalt Corporation 1987) was calculated from a well-conducted acute inhalation study with rats (see Appendix D). A 1-h rat study was also available (Pennwalt Corporation 1986); however, the data did not allow for the calculation of an $LC_{50}$ value, although the investigators stated that the 1-h $LC_{50}$ is most likely in the range of 175 to 250 ppm. Ocular and nasal irritation, piloerection, and vasodilation were observed within the first 15 min of exposure in rats exposed to methanesulfonyl chloride at 29 ppm for 6 h, but no deaths occurred (TerHaar 1978).

### 7.3. Derivation of AEGL-3 Values

The 4-h rat $BMCL_{05}$ of 15.5 ppm (Pennwalt Corporation 1987) was used as the point of departure for calculating AEGL-3 values. Values were scaled

across time using the equation $C^n \times t = k$, with n = 1, on the basis of the time-scaling analysis in Section 4.4.3. The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty of extrapolating a 4-h point of departure to a 10-min value. Uncertainty factors of 10 were applied to account for inter-species differences and intraspecies variability (total uncertainty factor of 100), because of the lack of information available to describe species differences in toxicity and interindividual variability. Although clinical signs and pathologic finding from the limited data set suggest contact irritation (partial eye closure, disturbed respiratory patterns, salivation, nose rubbing, blinking, nasal discharge, lacrimation, increased relative lung weight, pulmonary congestion, and corneal surface damage) and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. AEGL-3 values for methanesulfonyl chloride are presented in Table 4-7, and calculations are presented in Appendix A.

AEGL-3 values are considered adequately protective. If the study by TerHaar (1978) is used to calculate values, a point of departure of 29 ppm for a 6-h exposure would be chosen on the basis of no mortality, although severe irritation was present. Time scaling and applying the uncertainty factors described above yields higher AEGL-3 values of 3.5 ppm for the 10-min and 30-min durations, 1.7 ppm for 1 h, 0.44 ppm for 4 h, and 0.22 ppm for 8 h.

## 8. SUMMARY OF AEGLS

### 8.1. AEGL Values and Toxicity End Points

AEGL values for methanesulfonyl chloride are presented in Table 4-8. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were derived by taking one-third of the AEGL-3 values, and AEGL-3 values were based on a 4-h rat $BMCL_{05}$ value (Pennwalt Corporation 1987).

**TABLE 4-6** AEGL-2 Values for Methanesulfonyl Chloride

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 0.40 ppm (1.9 mg/m$^3$) | 0.40 ppm (1.9 mg/m$^3$) | 0.21 ppm (0.98 mg/m$^3$) | 0.053 ppm (0.25 mg/m$^3$) | 0.026 ppm (0.12 mg/m$^3$) |

**TABLE 4-7** AEGL-3 Values for Methanesulfonyl Chloride

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 1.2 ppm (5.6 mg/m$^3$) | 1.2 ppm (5.6 mg/m$^3$) | 0.62 ppm (2.9 mg/m$^3$) | 0.16 ppm (0.75 mg/m$^3$) | 0.078 ppm (0.37 mg/m$^3$) |

**TABLE 4-8** AEGL Values for Methanesulfonyl Chloride

| | Exposure Duration | | | | |
|---|---|---|---|---|---|
| Classification | 10 min | 30 min | 1 h | 4 h | 8 h |
| AEGL-1 (nondisabling)[a] | NR | NR | NR | NR | NR |
| AEGL-2 (disabling) | 0.40 ppm (1.9 mg/m$^3$) | 0.40 ppm (1.9 mg/m$^3$) | 0.21 ppm (0.98 mg/m$^3$) | 0.053 ppm (0.25 mg/m$^3$) | 0.026 ppm (0.12 mg/m$^3$) |
| AEGL-3 (lethal) | 1.2 ppm (5.6 mg/m$^3$) | 1.2 ppm (5.6 mg/m$^3$) | 0.62 ppm (2.9 mg/m$^3$) | 0.16 ppm (0.75 mg/m$^3$) | 0.078 ppm (0.37 mg/m$^3$) |

Abbreviations: NR, not recommended because of insufficient data.
[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 values are without effect.

### 8.2. Comparison with Other Standards and Guidelines

There are no other standards or guidelines for methanesulfonyl chloride.

### 8.3. Data Adequacy and Research Needs

There are no human data on methanesulfonyl chloride, and animal data are limited. Additional acute inhalation toxicity studies in other species would be helpful.

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## APPENDIX A

## DERIVATION OF AEGL VALUES FOR METHANESULFONYL CHLORIDE

### Derivation of AEGL-1 Values

Data are insufficient to derive AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended.

### Derivation of AEGL-2 Values

AEGL-2 values were derived by taking one-third of the respective AEGL-3 values, because there inadequate data to derive AEGL-2 values. This approach is justified by the steep concentration-response for this chemical (NRC 2001).

10-min AEGL-2: 1.2 ppm ÷ 3 = 0.40 ppm

30-min AEGL-2: 1.2 ppm ÷ 3 = 0.40 ppm

1-h AEGL-2: 0.62 ppm ÷ 3 = 0.21 ppm

4-h AEGL-2: 0.16 ppm ÷ 3 = 0.053 ppm

8-h AEGL-2: 0.078 ppm ÷ 3 = 0.026 ppm

### Derivation of AEGL-3 Values

Key study: Pennwalt Corporation. 1987. Methanesulfonyl Chloride, Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Report No. PWT 45/861670. Huntingdon Research Centre. February 23, 1987 (as cited in Arkema 2007).

Toxicity end point: 4-h rat $BMCL_{05}$ of 15.5 ppm

Time scaling: AEGL values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square

| | |
|---|---|
| | goodness-of-fit test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. $(15.5 \text{ ppm})^1 \times 4 \text{ h} = 62 \text{ ppm-h}$ |
| Uncertainty factors: | 10 for interspecies differences<br>10 for intraspecies variability<br>Total uncertainty factor of 100 |
| 10-min AEGL-3: | Set equal to the 30-min value of 1.2 ppm |
| 30-min AEGL-3: | $C^1 \times 0.5 \text{ h} = 62 \text{ ppm-h}$<br>C = 124 ppm<br>124 ppm ÷ 100 = 1.2 ppm |
| 1-h AEGL-3: | $C^1 \times 1 \text{ h} = 62 \text{ ppm-h}$<br>C = 62 ppm<br>62 ppm ÷ 100 = 0.62 ppm |
| 4-h AEGL-3: | C = 15.5 ppm<br>15.5 ppm ÷ 100 = 0.16 ppm |

8-h AEGL-3: $C^1 \times 8\ h = 62\ ppm\text{-}h$
$C = 7.75\ ppm$
$7.75\ ppm \div 100 = 0.078\ ppm$

## APPENDIX B

## ACUTE EXPOSURE GUIDELINE LEVELS FOR METHANESULFONYL CHLORIDE

### Derivation Summary

### AEGL-1 VALUES

Data were insufficient for deriving AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended for this chemical.

**AEGL-2 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 0.40 ppm (1.9 mg/m$^3$) | 0.40 ppm (1.9 mg/m$^3$) | 0.21 ppm (0.98 mg/m$^3$) | 0.053 ppm (0.25 mg/m$^3$) | 0.026 ppm (0.12 mg/m$^3$) |

Data adequacy: Sparse data set for methanesulfonyl chloride. For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm.

**AEGL-3 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 1.2 ppm (5.6 mg/m$^3$) | 1.2 ppm (5.6 mg/m$^3$) | 0.62 ppm (2.9 mg/m$^3$) | 0.16 ppm (0.75 mg/m$^3$) | 0.078 ppm (0.37 mg/m$^3$) |

Key reference: Pennwalt Corporation. 1987. Methanesulfonyl Chloride, Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Report No. PWT 45/861670. Huntingdon Research Centre. February 23, 1987 (cited in Arkema 2007).

Test species/Strain/Number: Rat, strain not specified, 10/sex/concentration

Exposure route/Concentrations/Durations: Inhalation; 20, 28, and 54 ppm for 4 h

Effects: Clinical signs of irritation in all test groups.

| Concentration (ppm) | Mortality |
|---|---|
| 0 | 0/10 |
| 20 | 1/10 |
| 28 | 9/10 |
| 54 | 10/10 |
| $LC_{50}$ | 25 ppm |
| $BMC_{01}$ | 17.4 ppm |
| $BMCL_{05}$ | 15.5 ppm |

*(Continued)*

**AEGL-3 VALUES** Continued

End point/Concentration/Rationale: 4-h $BMCL_{05}$ of 15.5 ppm (see Appendix D), considered threshold for lethality.

Uncertainty factors/Rationale: No information available to describe species differences in toxicity or interindividual variability. Although clinical signs and pathologic findings from the limited data set suggest contact irritation and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity.
Total uncertainty factor: 100
Interspecies: 10
Intraspecies: 10

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: AEGL-3 values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square goodness-of-fit test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 4-h point of departure to a 10-min value.

Data adequacy: Sparse data set. AEGL-3 values are considered protective. If the study by TerHaar (1978) is used to calculate values, a point of departure of 29 ppm for a 6-h exposure would be chosen on the basis of no mortality, although severe irritation was present. Time scaling and applying the uncertainty factors described above yields higher AEGL values of 3.5 ppm for the 10- and 30-min durations, 1.7 ppm for 1h, 0.44 ppm for 4 h, and 0.22 ppm for 8 h.

## APPENDIX C

## CATEGORY PLOT FOR METHANESULFONYL CHLORIDE

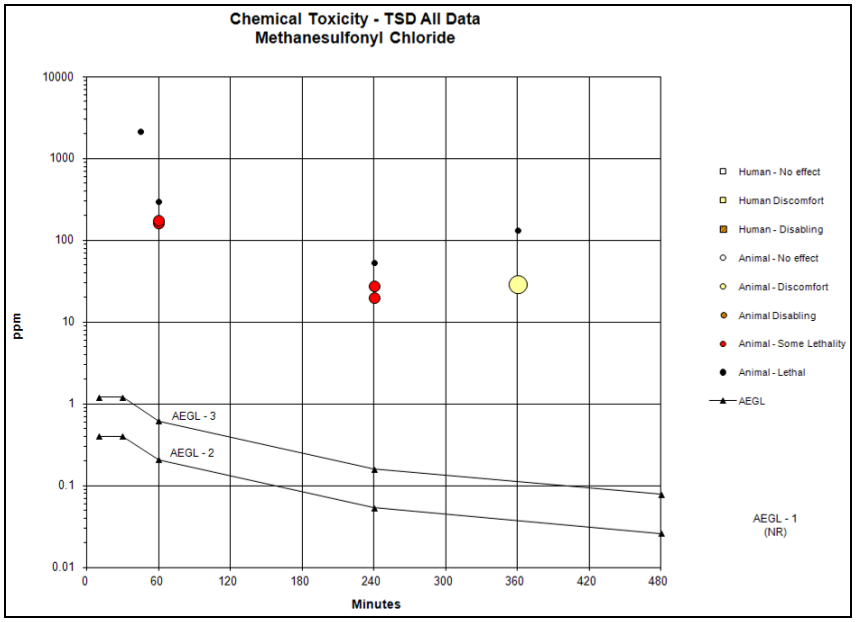


**FIGURE C-1** Category plot of animal data and AEGL values for methanesulfonyl chloride.

**TABLE C-1** Data Used in the Category Plot for Methanesulfonyl Chloride

| Source | Species | Sex | No. Exposures | ppm | Minutes | Category | Comments |
|---|---|---|---|---|---|---|---|
| NAC/AEGL-1 | | | | NR | 10 | AEGL | |
| NAC/AEGL-1 | | | | NR | 30 | AEGL | |
| NAC/AEGL-1 | | | | NR | 60 | AEGL | |
| NAC/AEGL-1 | | | | NR | 240 | AEGL | |
| NAC/AEGL-1 | | | | NR | 480 | AEGL | |
| NAC/AEGL-2 | | | | 0.40 | 10 | AEGL | |
| NAC/AEGL-2 | | | | 0.40 | 30 | AEGL | |
| NAC/AEGL-2 | | | | 0.21 | 60 | AEGL | |
| NAC/AEGL-2 | | | | 0.053 | 240 | AEGL | |
| NAC/AEGL-2 | | | | 0.026 | 480 | AEGL | |

*(Continued)*

**TABLE C-1** Continued

| Source | Species | Sex | No. Exposures | ppm | Minutes | Category | Comments |
|---|---|---|---|---|---|---|---|
| NAC/AEGL-3 | | | | 1.2 | 10 | AEGL | |
| NAC/AEGL-3 | | | | 1.2 | 30 | AEGL | |
| NAC/AEGL-3 | | | | 0.62 | 60 | AEGL | |
| NAC/AEGL-3 | | | | 0.16 | 240 | AEGL | |
| NAC/AEGL-3 | | | | 0.078 | 480 | AEGL | |
| Pennwalt Corporation 1987 | Rat | Both | 1 | 20 | 240 | SL | Mortality (1/10); clinical signs, pulmonary function changes for several days; relative lung weight increase in decedents; damage to corneal surface of eyes |
| | Rat | Both | 1 | 28 | 240 | SL | Mortality (9/10) |
| | Rat | Both | 1 | 54 | 240 | 3 | Mortality (10/10) |
| Pennwalt Corporation 1986 | Rat | Both | 1 | 165 | 60 | SL | Mortality (1/10); secretory and pulmonary effects through days 4-5; corneal irregularities (3/9 survivors) |
| | Rat | Both | 1 | 174 | 60 | SL | Mortality (2/10); secretory and pulmonary effects through days 4-5; corneal irregularities (8/8 survivors) |
| | Rat | Both | 1 | 300 | 60 | 3 | Mortality (10/10); |
| TerHaar 1978 | Rat | | 1 | 2,145 | 45 | 3 | Mortality (3/3) |
| | Rat | | 1 | 29 | 360 | 1 | Blinking, nose rubbing, piloerection, vasodilation (3 exposed rats) |
| | Rat | | 1 | 132 | 360 | 3 | Mortality (3/3) |

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

## APPENDIX D

## BENCHMARK DOSE CALCULATIONS FOR METHANESULFONYL CHLORIDE

Probit Model (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Wed Jul 11 10:33:08 2007

BMDS MODEL RUN - 4-hour study

The form of the probability function is:

P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -8.60752
Slope = 2.6668

**Asymptotic Correlation Matrix of Parameter Estimates**

| | Background | Intercept |
|---|---|---|
| Background | 1 | -1 |
| Intercept | -1 | 1 |

(***The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

**Analysis of Deviance Table**

| Model | Log (likelihood) | No. Parameters | Deviance Test | DF | P-value |
|---|---|---|---|---|---|
| Full model | -6.50166 | 4 | | | |
| Fitted model | -6.50166 | 2 | 3.41848e-009 | 2 | 1 |
| Reduced model | -27.7259 | 1 | 42.4485 | 3 | <0.0001 |

AIC: 17.0033

**Parameter Estimates**

| Variable | Estimate | Standard Error | 95.0% Wald Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Confidence Limit | Upper Confidence Limit |
| Background | 0 | NA | | |
| Intercept | -24.1018 | 7.1988 | -38.2112 | -9.99242 |
| Slope | 7.61759 | 2.27204 | 3.16448 | 12.0707 |

NA: indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

**Goodness of Fit**

| | | Scaled | | | |
|---|---|---|---|---|---|
| Dose | Estimated Probability | Expected | Observed | Size | Residual |
| 0.0000 | 0.0000 | 0.000 | 0 | 10 | 0.000 |
| 20.0000 | 0.1000 | 1.000 | 1 | 10 | -0.000 |
| 28.0000 | 0.9000 | 9.000 | 9 | 10 | -0.000 |
| 54.0000 | 1.0000 | 10.000 | 10 | 10 | 0.000 |

Chi-square = 0.00; DF = 2; P-value = 1.0000

Benchmark Dose Computation
Specified effect = 0.05

Risk Type = Extra risk
Confidence level = 0.95
BMD = 19.0685
BMDL = 15.5113

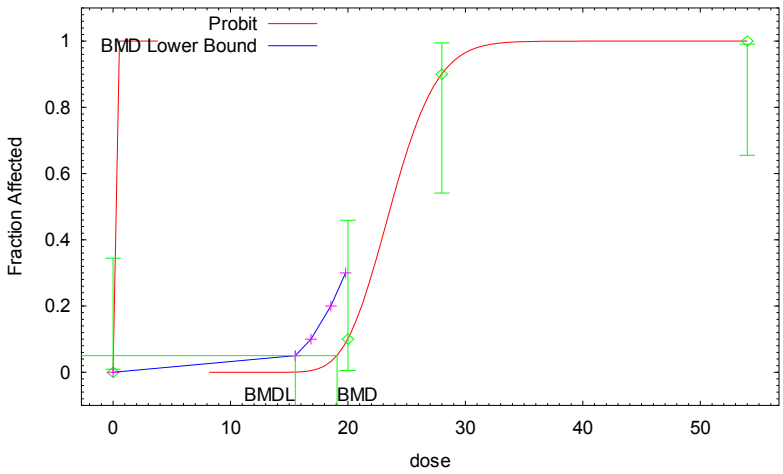


**FIGURE B-1** Probit model with 0.95 confidence level.

## APPENDIX E

## CALCULATION OF THE TIME-SCALING EXPONENT 'n'

**Log Probit Analysis of Full Dataset:**

Filename: Methanesulfonyl chloride time scaling
Date: 09 February 2012 Time: 16:05:18

| Sequence No. | Concentration (ppm) | Minutes | Exposed | Responded |
|---|---|---|---|---|
| 1 | 165 | 60 | 10 | 1 |
| 2 | 174 | 60 | 10 | 2 |
| 3 | 300 | 60 | 10 | 10 |
| 4 | 20 | 240 | 10 | 1 |
| 5 | 28 | 240 | 10 | 9 |
| 6 | 54 | 240 | 10 | 10 |
| 7 | 29 | 360 | 3 | 0 |
| 8 | 132 | 360 | 3 | 3 |

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/$m^3$, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 48.83
Degrees of freedom = 5
Probability Model = 2.40E-09

Ln(Likelihood) = -20.30

B 0 = -2.3058E+01 Student t = -1.1494
B 1 = 2.5164E+00 Student t = 1.3933
B 2 = 3.5681E+00 Student t = 1.3718

Variance B 0 0 = 4.0242E+02
Covariance B 0 1 = -3.5556E+01
Covariance B 0 2 = -5.1770E+01
Variance B 1 1 = 3.2617E+00
Covariance B 1 2 = 4.4695E+00
Variance B 2 2 = 6.7650E+00

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.705
Lower limit (95% CL) = 0.296
Upper limit (95% CL) = 1.114

**Log Probit Analysis of Reduced Dataset:**

Filename: Methanesulfonyl chloride time scaling
Date: 09 February 2012 Time: 16:07:06

| Sequence No. | Concentration (ppm) | Minutes | Exposed | Responded |
|---|---|---|---|---|
| 1 | 165 | 60 | 10 | 1 |
| 2 | 174 | 60 | 10 | 2 |
| 3 | 300 | 60 | 10 | 10 |
| 4 | 20 | 240 | 10 | 1 |
| 5 | 28 | 240 | 10 | 9 |
| 6 | 54 | 240 | 10 | 10 |

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/$m^3$, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 0.01
Degrees of freedom = 3
Probability Model = 1.00E+00

Ln(Likelihood) = -4.05

B 0 = -8.3259E+01 Student t = -3.5083
B 1 = 7.6810E+00 Student t = 3.5633
B 2 = 1.1669E+01 Student t = 3.7691

Variance B 0 0 = 5.6320E+02
Covariance B 0 1 = -5.1013E+01
Covariance B 0 2 = -7.3391E+01
Variance B 1 1 = 4.6466E+00
Covariance B 1 2 = 6.6254E+00
Variance B 2 2 = 9.5856E+00

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.658
Lower limit (95% CL) = 0.611
Upper limit (95% CL) = 0.705