Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 10

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 approximately 200 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 tenth volume in that series. AEGL documents for *N,N*-dimethylformamide, jet propellant fuels 5

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

and 8, methyl ethyl ketone, perchloromethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl 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 NAC 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 six 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 six committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for *N*,*N*-dimethylformamide (fourteenth interim report, 2006), jet propellant fuels 5 and 8 (seventeenth interim report, 2010), methyl ethyl ketone (twelfth and fifteenth interim reports, 2005 and 2008, respectively), perchloromethyl mercaptan (fifteenth interim report, 2008), phosphorus oxychloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), phosphorus trichloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), and sulfuryl chloride (sixteenth interim report, 2009): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), David Gaylor (Gaylor and Associates, LLC), 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), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Kenneth Still (Occupational Toxicology Associates, Inc.), and Bernard M. Wagner (New York University Medical Center [retired]).

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 the eleventh interim report was overseen by Rakesh Dixit

(MedImmune/AstraZeneca Biologics), and the twelfth interim report was overseen by David Gaylor (Gaylor and Associates, LLC). The review of the fourteenth, fifteenth, sixteenth, and seventeenth interim reports was 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 (Honeywell, Inc.). The committee also acknowledges Keegan Sawyer, 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), Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Orin Luke (senior program assistant), 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

Dedication

The subcommittee dedicates this series of reports to our late colleague
and co-founder of the Acute Exposure Guideline Levels program,
Dr. Paul Tobin,
whose 31 years of distinguished service with the
U.S. Environmental Protection Agency in the fields of chemistry,
toxicology and health-risk assessment contributed significantly to scientific
knowledge, to the development of the Acute Exposure Guideline Levels
program, and to the protection of public health and safety.

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

This report is the tenth 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 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:

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

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

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 are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are 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 subcommittee 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 nine reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b). This report is the tenth volume in that series. AEGL documents for *N*,*N*-dimethylformamide, jet propellant fuels 5 and 8, methyl ethyl ketone, perchlormethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl 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

7

Sulfuryl 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 min to 8 h. Three levels—AEGL-1, AEGL-2 and AEGL-3—are developed for each of five exposure periods (10 and 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 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, non-sensory 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 Robert Young (Oak Ridge National Laboratory) and Steven Barbee (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 concludes 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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Sulfuryl chloride, a colorless to light yellow liquid with a pungent odor, is used as chlorinating, sulfonating, and chlorosulfonating agent in organic synthesis. It is generally used in closed systems, thereby limiting exposure potential.

No information is available regarding exposure of humans to sulfuryl chloride. Because it decomposes to hydrochloric acid and sulfuric acid upon contact with water, it may assumed that exposure would result in notable irritation and corrosive action on the eyes and respiratory tract. Due to this decomposition, metabolism is irrelevant in the toxic response to sulfuryl chloride.

Inhalation exposure data in animals are limited to lethality studies in laboratory rats, all of which confirm toxic effects (dyspnea, ocular irritation, and respiratory tract irritation leading to pulmonary hemorrhage and death) consistent with severe irritation and /or corrosive activity. One-hour LC_{50} values of 59 to 242 ppm and a 4-h LC_{50} of 159 ppm have been reported for rats. There was some discrepancy regarding the lethal toxicity of sulfuryl chloride in rats exposed for one or four hours. However, all studies demonstrated that exposure of rats produces clinical signs of ocular and respiratory tract irritation, dyspnea, and body weight loss. Necropsy findings consistently indicated concentration-related pulmonary involvement. Although death may occur during exposure at higher concentrations, post-exposure observation has shown that lethality may be delayed for several days at lower concentrations.

Data were insufficient for development of AEGL-1 values. All exposure regimens in the rat studies resulted in effects that were considered of greater severity than those of the AEGL-1 tier. Specifically, signs of ocular and respiratory tract irritation in rats exposed for one hour to sulfuryl chloride concentrations as low as 31 ppm also exhibited pulmonary hemorrhage upon necropsy.

Toxicity studies on sulfuryl chloride were conducted primarily to assess lethality. All nonlethal exposures in these studies resulted in respiratory tract damage (necrosis, hemorrhage) that was detectable at the end of the 3 to14-day post-exposure observation periods. Lethality threshold estimates (e.g., LC_{01}, $BMCL_{05}$) from all studies resulted in exposure concentrations that were less than the nonlethal concentrations in the respective studies. Therefore, it was not possible to determine a data-driven estimate of the threshold for AEGL-2 severity effects. Because lethality threshold estimates tended to be less than nonlethal experimental exposures and because of the apparent steep exposure-response curve for sulfuryl chloride, AEGL-2 values were estimated by a three-fold reduction of the AEGL-3 values (NRC 2001).

A 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the POD for deriving AEGL-3 values. Although this is a somewhat more conservative approach than use of an LC_{01} (70.6 ppm) as an estimate of the lethality threshold, its selection may be justified by the known respiratory tract damage observed from nonlethal exposures and the potential uncertainty regarding latent-occurring health effects (including lethality beyond the 3 to 14-day observation periods of the animal studies). Because the effects of sulfuryl chloride appear to be contact tissue damage resulting from the degradation products (sulfuric acid and hydrochloric acid) not resulting from metabolic processes and because rodents will receive a greater dose to target tissues than would humans, the uncertainty factor for interspecies variability was limited to 3. An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional uncertainty was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to 55 ppm was not lethal (Kelly and Stula 1983). The exposure concentration-exposure 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 (ten Berge et al. 1986). In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Results of gentoxicity assays of sulfuryl chloride are equivocal and no carcinogenicity bioassays have been conducted. The AEGL values for sulfuryl chloride are summarized in Table 7-1.

1. INTRODUCTION

Sulfuryl chloride, a colorless to light yellow liquid with a pungent odor, is used as chlorinating, sulfonating, and chlorosulfonating agent in organic synthesis of such chemicals as chlorophenol and chlorothymol (O'Neil et al. 2001). Approximately 10,000 to 20,000 metric tons of sulfuryl chloride were produced worldwide in 2001 (OECD 2005).

The chemical and physical data on DMF are presented in Table 7-2.

TABLE 7-1 Summary of AEGL Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3	Data insufficient for derivation of AEGL-2 threshold. Due to steep exposure-response relationship, AEGL-2 values estimated as one-third reduction of AEGL-3 values (NRC 2001)
AEGL-3 (Lethality)	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3	$BMCL_{05}$ of 70.1 ppm estimated as lethality threshold in rats following 4-h exposure to sulfuryl chloride (DuPont 1982; Kelly and Stula 1983)

TABLE 7-2 Chemical and Physical Data for Sulfuryl Chloride

Parameter	Value	Reference
Synonyms	Sulfuryl dichloride; sulfonyl chloride; sulphuric acid dichloride; sulfuric oxychloride	IUCLID 2000; O'Neil et al. 2001
CAS Registry No.	7791-25-5	O'Neil et al. 2001
Chemical formula	Cl_2O_2S	O'Neil et al. 2001
Molecular weight	134.96	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Boiling/melting point	69.3°C/-54.1°C	O'Neil et al. 2001
Density	1.67 g/cm^3 at 20°C	OECD 2005
Solubility in water	Hydrolyzes in water	O'Neil et al. 2001
Vapor pressure	148 hPa at 20°C	OECD 2005
Conversion factors in air	1 mg/m^3 = 0.18 ppm 1 ppm = 5.51 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding lethality in humans following inhalation exposure to sulfuryl chloride.

2.2. Nonlethal Toxicity

No information was available regarding the nonlethal effects of sulfuryl chloride in humans. No odor threshold or odor detection limits were available for sulfuryl chloride.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data were available regarding sulfuryl chloride.

2.4. Genotoxicity

No human genotoxicity data were available.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of sulfuryl chloride in humans.

2.6. Summary

There are no human exposure data regarding inhalation of sulfuryl chloride.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

In a Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983), groups of 10 male Crl:CD7 rats (7-8 weeks old, 233-274g) were exposed (head-only) to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four

hours. The rats were observed for 14 days post exposure. All exposed rats exhibited red nasal discharge lasting up to two days post exposure. Rats surviving the exposures exhibited severe weight loss for one to two days post exposure. The response of exposure groups are summarized in Table 7-3. The estimated 4-h LC_{50} was reported as 159 ppm. A lethality threshold estimate (4-h LC_{01}) of 70.6 ppm was independently estimated using the method of Litchfield and Wilcoxon (1949) (see Appendix B).

One-hour LC_{50} values (Table 7-4) for sulfuryl chloride indicating a gender-related variability in lethal response have been reported (Bayer AG 1993a; IUCLID 2000). No experimental details were available regarding these values.

An acute inhalation exposure experiment conducted by Western Research Center (Stauffer Chemical Company 1969) provided lethality data for rats exposed to sulfuryl chloride for one hour. In this study, groups of 10 rats (200 g, gender and strain not specified) were exposed to sulfuryl chloride at concentrations of 0.240, 0.394, 0.600, 1.110, 1.400, or 2.180, mg/l (equivalent to 43, 71, 108, 200, 252, and 392 ppm). Rats in all exposure groups exhibited dyspnea and hyperactivity. Exposures at "larger doses" exhibited heavy nasal and pulmonary discharges that were expelled from the mouth. Nasal irritation increased with exposure concentration. Necropsy at 14 days following the 0.240 mg/l (43 ppm) exposure revealed necrosis and erythema in the nasal passages. The lethality data are summarized in Table 7-5.

TABLE 7-3 Toxicity of Sulfuryl Chloride in Male Rats Following a Single 4-h Head Only Inhalation Exposure

Exposure in ppm (mean ± s.d)	Exposure concentration range (ppm)	Mortality
84.4 ± 7.7	80-103	0/10
134 ± 39.9	70-110	2/10 (1 During exposure and 1 within 24 h)
155 ± 19.9	135-195	8/10 (6 During exposure; 2 within 24 h)
207 ± 23.4	172-240	7/10 (All died during exposure)
273 ±16.5	225-294	10/10 (All during exposure)

Source: DuPont 1982.

TABLE 7-4 Inhalation Toxicity in Rats Exposed to Sulfuryl Chloride

Gender	Lethality Value	Source
Male	1-h LC_{50} = 131 ppm	Bayer AG 1993a; IUCLID 2000
Female	1-h LC_{50} = 242 ppm	Bayer AG 1993a; IUCLID 2000

TABLE 7-5 Lethality in Rats Following 1-h Inhalation Exposure to Sulfuryl Chloride

Exposure concentration (ppm)	Mortality ratio	Time-to-death
43	0/10	–
71	8/10	1-18 h
108	8/10	1-16 h
200	10/10	1-10 h
252	10/10	1-5 h
392	10/10	1-5 h

Source: Stauffer Chemical Company 1969.

In a later study, a 1-h LC_{50} of 0.33 mg/L (~59.4 ppm) for male and female rats (200 g, strain, age not specified) was reported by Western Research Center (Stauffer Chemical Company 1970). Purity of the test article was specified as "> 1% < 100%". Results of this study are shown in Table 7-6. Exposed rats exhibited concentration-related increased severity of lacrimation, erythema around the eyes and ears, salivation, and dyspnea. All dead rats exhibited grossly hemorrhagic lungs with severe erythema of the gastrointestinal tract. Rats in the low-dose groups also exhibited areas of pulmonary hemorrhage. Total post-exposure observation time was not specified although it may be inferred that the rats were observed for at least 72 h.

3.2. Nonlethal Toxicity

3.2.1. Rats

In the study reported by Kelly and Stula (1983), male Sprague-Dawley rats (10/group) exposed head-only to a nonlethal exposure of 84.4 ppm sulfuryl chloride exhibited reddish exudate around the eyes and nostrils. Notable body weight loss for two days following exposure was also reported for these rats. The rats were observed for up to 14 days post exposure. No gross or histopathologic findings were reported.

In a 14-day inhalation exposure study, groups of 10 male Sprague-Dawley rats were exposed to sulfuryl chloride (17, 55, or 166 mg/m^3, equivalent to 3.1, 9.9, or 29.9 ppm) for 6 h/day, 5 days/week (Kelly and Stula 1983). The highest concentration caused excessive weight loss after two exposures and was reduced to 100 mg/m^3 (19.8 ppm) which resulted in the death of two rats after only 8 exposures. Fourteen-day exposure to the lower concentrations was not lethal but produced a concentration-related increase in blood urea nitrogen and histopathologic evidence of respiratory tract damage. Exposure to the lowest dose also exacerbated naturally occurring murine pneumonitis.

TABLE 7-6 Lethality of Rats Exposed to Sulfuryl Chloride for 1 h

Exposure concentration	Mortality ratio	Time to death
0.174 mg/l (31.3 ppm)	0/10	–
0.346 mg/l (62.3 ppm)	6/10	16-72 h
0.695 mg/l (125.1 ppm)	10/10	8-12 h

Source: Stauffer Chemical Company 1970.

3.3. Developmental/Reproductive Effects

Information was not available regarding the developmental/reproducetive toxicity of sulfuryl chloride.

3.4. Genotoxicity

Sulfuryl chloride was negative in an Ames test with *Salmonella typhimurium* TA 100 (up to 4000 µg/plate) with and without metabolic activation (Bayer AG 1993b). In another assay (Bayer AG 1989) with *Salmonella typhimurium* TA 100, there was a significant dose-dependent increase in the number of revertants with no metabolic activation. However, tests with strains TA98, TA 1535, and TA 1537 were negative with and without activation (Bayer AG 1989).

3.5. Carcinogenicity

Information was not available regarding the carcinogenicity of sulfuryl chloride.

3.6. Summary

Toxicity data for sulfuryl chloride are limited to lethality studies in rats. One-hour LC_{50} values for rats ranged from 59-242 ppm. The 1-h LC_{50} estimates from one study (Bayer 1987) suggested a gender-related sensitivity in lethality; 1-h LC_{50} of 131 and 242 ppm for male and females, respectively. A 4-h LC_{50} of 159 ppm was reported for male rats. Because sulfuryl chloride decomposes to hydrochloric acid and sulfuric acid upon contact with water, it may be assumed that much of its toxicity is attributable to corrosive activity of these products on contacted tissues (e.g., respiratory tract). Exposure of test animals to nonlethal concentrations of sulfuryl chloride was associated with signs of ocular and respiratory irritation, body weight loss, and respiratory tract damage. There is a notable discrepancy among the available toxicity data; results of the Stauffer Chemical Company 1-h exposure studies appear to suggest much greater toxicity for sulfuryl chloride than do data from other studies.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was available regarding the metabolism of sulfuryl chloride. Substantial decomposition to sulfuric acid and hydrochloric acid upon contact with moisture (e.g., respiratory tract epithelial surfaces) is expected based upon the chemical properties of sulfuryl chloride.

4.2. Mechanism of Toxicity

No experimental data were available regarding the mechanism of toxicity of sulfuryl chloride. Corrosive activity and subsequent damage to epithelial tissue would be expected from the decomposition products of sulfuric acid and hydrochloric acid.

4.3. Structure-Activity Relationships

Structure-activity relationships were not utilized for AEGL development. Sulfur chloride (S_2Cl_2) is sufficiently different from sulfuryl chloride in its water solubility (less soluble), its degradation products (hydrochloric acid, sulfur, and sulfur dioxide for sulfur chloride versus hydrochloric acid and sulfuric acid for sulfuryl chloride), and acute toxicity (animal data indicate that sulfur chloride is notably less toxic than sulfuryl chloride). Acute inhalation exposure toxicity data in animals show that sulfuryl chloride is notably more toxic than its degradation products.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human exposure data are available with which to develop AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

There were no data with which to develop AEGL-1 values for sulfuryl chloride.

5.3. Derivation of AEGL-1

The lowest concentrations tested in available animal studies were associated with evidence of respiratory tract damage. No exposure-response data are

available to differentiate AEGL-1 type effects from those that may progress to more serious effects. The continuum of toxic responses is likely a function of the corrosive action of the sulfuryl chloride degradation products, hydrochloric and sulfuric acid. The sulfur chloride concentrations at which the corrosive activity of these products becomes more than minor irritation is unclear. Therefore, AEGL-1 values are not recommended (Table 7-7).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human exposure data were available with which to develop AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Rats exposed to 0.174 mg/l (31.3 ppm sulfuryl chloride for one hour exhibited signs of toxicity consistent with contact irritation and respiratory tract damage (lacrimation, erythema around the eyes and ears, salivation, dyspnea, and pulmonary hemorrhage) (Stauffer Chemical Company 1970). Reddish exudate around the eyes and nostrils was also observed in rats exposed to 84.4 ppm (lowest concentration tested) for four hours (DuPont 1982; Kelly and Stula 1983). Neither of these exposures were associated with lethality. Overall, the animal data clearly showed evidence of pulmonary damage in the absence of lethality. In addition, body weight losses were reported for rats at nonlethal concentrations. Repeated (3.1 or 9.9 ppm for 6 h/day, 5 days/week) nonlethal exposures exacerbated naturally occurring murine pneumonitis (Kelly and Stula 1983).

6.3. Derivation of AEGL-2

The reviewed toxicity studies were conducted primarily to assess lethality. Lethality threshold estimates (e.g., LC_{01}, $BMCL_{05}$) from all studies resulted in exposure concentrations that were less than the nonlethal concentrations in the respective studies. However, all nonlethal exposures resulted in respiratory tract damage (necrosis, hemorrhage) that was detectable at the end of the 3 to 14-day post-exposure observation periods. Because lethality threshold estimates tended to be less than nonlethal experimental exposures and because of the apparent steep exposure-response curve for sulfuryl chloride, AEGL-2 values (Table 7-8) were estimated by a three-fold reduction of the AEGL-3 values (NRC 2001).

TABLE 7-7 AEGL-1 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: not recommended; insufficient data.

TABLE 7-8 AEGL-2 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human exposure data were available with which to develop AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Lethality data in animals are limited to rats. In acute inhalation studies conducted at Haskell Laboratory (DuPont 1982; Kelly and Stula 1983), rats were exposed (head-only) to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four hours. Exposure to 84.4 ppm was without lethality and provided a 4-h LC_{50} of 159 ppm. Stauffer Chemical Company (1970) reported a 1-h LC_{50} value of 59 ppm and Bayer (1987) reported 1-h LC_{50} values of 131 ppm and 242 ppm for male and female rats, respectively. A 4-h $BMCL_{05}$ of 70.1 ppm (EPA 2005) and an LC_{01} of 70.6 ppm (Litchfield and Wilcoxon 1949) were derived from the 4-h exposure-response data of the DuPont (Kelly and Stula 1983) study.

7.3. Derivation of AEGL-3

The 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the point-of-departure for deriving AEGL-3 values (Appendix B). This is a more conservative approach than use of the LC_{01} (70.6 ppm) as an estimate of the lethality threshold using these data. This may be justified by the known respiratory tract damage observed in nonlethal exposures and the potential uncertainty regarding latent-occurring health effects, including lethality, beyond the observation periods utilized in the animal studies. The Haskell Laboratory studies were used for AEGL

development in preference to alternate data sets because they contained greater detail than other reports, utilized nose-only exposures, and specified purity of the test article. The interspecies uncertainty factor was limited to 3 because the effects of sulfuryl chloride consist of contact tissue damage of degradation products (sulfuric acid and hydrochloric acid), and not from metabolites, and because rodents will receive a greater dose to target tissues than would humans. An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional adjustment was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to at least two 6-h exposures to 29.9 ppm followed by up to seven additional 6-h exposures to 19.8 ppm were not lethal (Kelly and Stula 1983). In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001). Because of uncertainties in extrapolating from the 4-h experimental durations upon which the $BMCL_{05}$ is based to a 10-min AEGL exposure period, the 10-min AEGL-3 value was set equivalent to the 30-min value (NRC 2001). AEGL-3 values for sulfuryl chloride are presented in Table 7-9 and their derivation shown in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for sulfuryl chloride are summarized in Table 7-10. The AEGL-3 values are based upon a lethality threshold ($BMCL_{05}$ of 70.1 ppm) estimated from 4-h exposure data in rats. The available lethality studies in rats utilized post exposure observation periods up to 14 days and, therefore, accounted to some extent for the latency in lethal response to chemicals causing pulmonary damage via corrosive activity. Date were insufficient for determining a threshold for AEGL-2 severity effects. Therefore, the AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values. Because all exposure concentrations tested produced effects greater than AEGL-1 severity, AEGL-1 values were not developed and are not recommended. A comparison of the AEGL values to the available animal toxicity data (Appendix D) reveals that all AEGL concentrations are well below those causing any effects in animals.

TABLE 7-9 AEGL-3 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3

TABLE 7-10 AEGL Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3
AEGL-3 (Lethality)	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3

NR: not recommended; insufficient data.

8.2. Comparisons with Other Standards and Guidelines

No standards or guidelines are currently available for sulfuryl chloride.

8.3. Data Adequacy and Research Needs

Human exposure data for sulfuryl chloride were unavailable. The currently available toxicity information for sulfuryl chloride is limited to data from acute lethality studies and one repeated exposure study in rats. Due to the known degradation of sulfuryl chloride to hydrochloric acid and sulfuric acid, the toxic effects are qualitatively predicable. The available lethality data in rats were sufficient for development of AEGL-3 values although there are apparent discrepancies among the available data sets. Exposure-response data were insufficient for assessing with confidence a point-of departure for AEGL-2 severity effects. It may be assumed that the continuum of the toxic response from irritation to lethality may be attributed to sulfuryl chloride-induced respiratory tract damage but the precise exposure at which this occurs is uncertain. Data were insufficient for deriving AEGL-1 values.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR SULFURYL CHLORIDE

Derivation of AEGL-1 for Sulfuryl Chloride

Data were insufficient for developing AEGL-1 values for sulfuryl chloride. All exposure regimens in the available studies resulted in effects greater than those consistent with AEGL-1.

Derivation of AEGL-2 for Sulfuryl Chloride

Lethality thresholds (e.g., LC_{01}, $BMCL_{05}$, one-third of LC_{50}) estimated from the Stauffer Chemical (1969, 1970) and from the DuPont studies (DuPont 1982; Kelly and Stula 1983) reports were less than the respective nonlethal exposures reported in these studies. For this reason and because exposure-response data were insufficient for determination of a threshold for AEGL-2 severity effects, derivation of AEGL-2 values by a three-fold reduction of AEGL-3 values was considered appropriate. The resulting AEGL-2 values are:

10-min AEGL-2:	4.7 ppm
30-min AEGL-2:	4.7 ppm
1-h AEGL-2:	3.7 ppm
4-h AEGL-2:	2.3 ppm
8-h AEGL-2:	1.2 ppm

Derivation of AEGL-3 Sulfuryl Chloride

Key studies:

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine. E. I. du Pont de Nemours and Co., Inc.

Kelly, D.P., and E.F. Stula. 1983. Acute and subacute inhalation toxicity of sulfuryl chloride in rats. Toxicologist 3(1):62 [Abstract 248].

Critical effect:	$BMCL_{05}$ of 70.1 ppm estimated as lethality threshold in rats following 4-h exposure to sulfuryl chloride.
Time scaling:	$C^n \times t = k$ where $n = 1$ or 3. In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).
Uncertainty factors:	Total uncertainty factor adjustment was 10. Interspecies: The effects of sulfuryl chloride are mediated by contact tissue damage resulting from the degradation of sulfuryl chloride to sulfuric acid and hydrochloric acid and not the result of metabolic processes. In addition, rodents will receive a greater dose to target tissues than would humans. Therefore, the uncertainty factor for interspecies variability was limited to 3. Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents and for individuals with compromised respiratory function.
Calculations:	$(70.1 \text{ ppm})^1 \times 4 \text{ h} = 280.4 \text{-ppm-h}$ $(70.1 \text{ ppm})^3 \times 4 \text{ h} = 1{,}377{,}888 \text{ ppm}^3\text{-h}$
10-min AEGL-3	Due to uncertainties in extrapolating from the 4-h POD to 10-min exposure duration, the 10-min AEGL-3 is set equivalent to the 30 min AEGL-3 (14 ppm)
30-min AEGL-3	$C^3 \times 0.5 \text{ h} = 1{,}377{,}888 \text{ ppm}^3\text{-h}$ $C^3 = 2{,}755{,}777 \text{ ppm}^3\text{-h}$ $C = 140$ ppm UF application: 140 ppm/10 = 14 ppm

1-h AEGL-3	$C^3 \times 1$ h = 1,377,888 ppm^3-h C^3 = 1,377,888 ppm^3-h C = 111 ppm UF application: 111 ppm/10 = 11 ppm
4-h AEGL-3	$C^1 \times 4$ h = 280.4 ppm-h C = 70 ppm UF application: 70 ppm/10 = 7.0 ppm
8-h AEGL-3	$C^1 \times 8$ h = 280.4 ppm-h C = 35 ppm UF application: 35 ppm/10 = 3.5 ppm

APPENDIX B

LC_{50} AND BENCHMARK DOSE CALCULATIONS FOR SULFURYL CHLORIDE

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc.

Rats (male); all exposure concentrations expressed in ppm

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
84.400	0/10	0 (2.60)	2.81	-0.21	0.0002
134.000	2/10	20.00	30.77	-10.77	0.0544
155.000	8/10	80.00	51.23	28.77	0.3314
207.000	7/10	70.00	85.30	-15.30	0.1866
273.000	10/10	100 (97.40)	96.75	0.65	0.0013

Values in parentheses are corrected for 0 or 100% Total = 0.5739

LC_{50} = 153.718 (133.380 - 177.158)*
Slope = 1.32 (1.19 - 1.47)*
*These values are 95% confidence limits

Total animals = 50
Total doses = 5
Animals/dose = 10.00
Chi-square = total chi-square × animals/dose = 5.7391
Table value for chi-square with 3 degrees of freedom = 7.8200

LC_{84} = 203.516
LC_{16} = 116.105
FED = 1.15
FS = 1.11
A = 1.08

Probit Model $Revision: 2.1
$ Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\SO2CL2.(d)
Gnuplot Plotting File: C:\BMDS\SO2CL2.plt
Mon Nov 27 11:22:45 2006

Exposure	Expected Lethal Dose Values (ppm)
$LC_{0.1}$	47.752
$LC_{1.0}$	70.619
$LC_{5.0}$	93.383
LC_{10}	105.974
LC_{25}	127.633
LC_{50}	153.718
LC_{75}	185.134
LC_{90}	222.972
LC_{99}	334.600

Benchmark Dose: $BMCL_{05}$ Rat lethality data DuPont 1982; Kelly and Stula 1983).

BMDS MODEL RUN

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 = 5
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 = -14.2564
Slope = 2.83606

Asymptotic Correlation Matrix of Parameter Estimates
(*** 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)

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Intercept	-17.8499	4.6632
Slope	3.54497	0.917185

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-16.1167			
Fitted model	-19.3819	6.53043	3	0.08847
Reduced model	-34.4972	36.761	4	< .0001
AIC: 42.7638				

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
84.4000	0.0168	0.168	0	10	-0.4128
134.0000	0.3131	3.131	2	10	-0.7709
155.0000	0.5115	5.115	8	10	1.825
207.0000	0.8542	8.542	7	10	-1.381
273.0000	0.9791	9.791	10	10	0.462

Chi-square = 6.22
DF = 3
P-value = 0.1015

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 96.6681
BMDL = 70.1015

APPENDIX C

TIME SCALING CALCULATIONS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, *t* = exposure duration, and *k* = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (*k*) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where *n* represents a chemical specific, and even a toxic end point specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t. Ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of *n* ranged from 0.8 to 3.5 among this group of chemicals. Hence, it was shown that the value of the exponent (*n*) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect end point. Haber's Rule is the special case where $n = 1$. As the value of *n* increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve. In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values for sulfuryl chloride was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

APPENDIX D

ACUTE EXPOSURE GUIDELINES FOR SULFURYL CHLORIDE

Derivation Summary for Sulfuryl Chloride

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: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Data Adequacy: Data were insufficient for developing AEGL-1 values. Test exposures in all available studies resulted in greater than AEGL-1 effects (respiratory tract damage) in animals.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
4.7 ppm	4.7 ppm	3.7 ppm	2.3 ppm	1.2 ppm

Reference: NA

Test Species/Strain/Sex/Number: NA

Exposure Route/Concentrations/Durations: inhalation (see AEGL-3)

Effects: NA; estimated as one-third of AEGL-3

End Point/Concentration/Rationale: Due to inadequate data and uncertainties regarding a definitive threshold for AEGL-2 level effects, the AEGL-2 values were estimated as one-third of the AEGL-3.

Uncertainty Factors/Rationale: Total uncertainty factor: See AEGL-3

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: See AEGL-3

Data Adequacy: Nonlethal exposure of rats to sulfuryl chloride produced effects of respiratory irritation and pulmonary damage, dyspnea, and body weight loss. Estimated lethality thresholds were less than experimental exposures that were not lethal. Therefore, the AEGL-2 values were derived as one-third of the AEGL-3 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
14 ppm	14 ppm	11 ppm	7.0 ppm	3.5 ppm

References:

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc.

Kelly, D.P., and E.F. Stula. 1983. Acute and subacute inhalation toxicity of sulfuryl chloride in rats. Toxicologist 3(1):62 [Abstract 248].

Test Species/Strain/Sex/Number:10 male Crl:CD7 rats (7-8 weeks old, 233-274g)

Exposure Route/Concentrations/Durations: Inhalation (head-only) exposure to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four hours; 14-day observation

Effects:

Exposure Conc. (ppm)	Mortality
84.4	0/10
134	2/10
155	8/10
207	7/10
273	10/10

End Point/Concentration/Rationale: The 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the point-of-departure for deriving AEGL-3 values. Although a somewhat more conservative approach than use of the LC_{01} (70.6 ppm), it may be justified by the known respiratory tract damage observed for nonlethal exposures and the potential for latent-occurring health effects, including lethality, beyond the 3 to 14-day observation periods utilized in the animal studies.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: The interspecies uncertainty factor was limited to 3 because contact tissue damage results from the degradation products (sulfuric acid and hydrochloric acid) and not metabolism processes, and because rodents will receive a greater dose to target tissues than would humans.

Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional uncertainty was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to 55 ppm was not lethal (Kelley and Stula 1983).

Modifying Factor: None applied

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
14 ppm	14 ppm	11 ppm	7.0 ppm	3.5 ppm

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Data Adequacy: Toxicity data were available for only one species, although the mode of action is likely very similar across species. Data were sufficient for AEGL-3 development.

APPENDIX E: CATEGORY PLOT FOR SULFURYL CHLORIDE

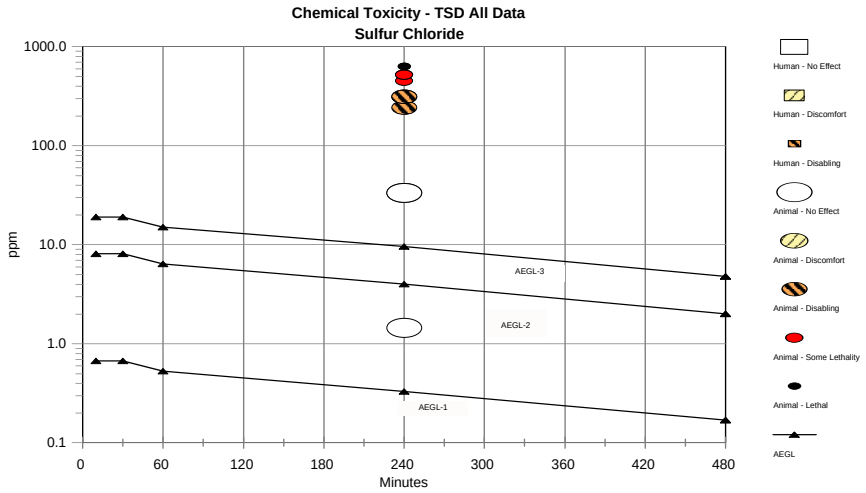

FIGURE 7-1 Category plot for sulfuryl chloride.