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

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
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This project was supported by Contract No. W81K04-06-D-0023 and EP-W-09-007 between the National Academy of Sciences and the U.S. Department of Defense and the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-21987-7
International Standard Book Number-10: 0-309-21987-6

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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.

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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

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(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

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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

VOLUME 10

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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

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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.

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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

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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

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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

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4

Perchloromethyl Mercaptan[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

[1]This document was prepared by the AEGL Development Team composed of Claudia Troxel (Oak Ridge National Laboratory) and Zarena Post and Susan Ripple (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 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).

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

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

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

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

SUMMARY

Perchloromethyl mercaptan is an oily, yellow liquid with an unbearable, acrid odor and a reported odor threshold of approximately 0.001 ppm (Ruth 1986; ACGIH 1991; NIOSH 1996). Although it was used as a chemical warfare agent by the French in the 1915 battle of Champagne, wartime use was abandoned shortly thereafter because of the clear warning properties, the decomposition in the presence of iron and steel, and the easy removal of the vapor by charcoal (Prentiss 1937). Today, perchloromethyl mercaptan is used as an intermediate in the synthesis of dyes and phthalimide fungicides.

Data addressing human and animal toxicity following exposure to perchloromethyl mercaptan vapor are sparse. Only secondary sources described human data; case reports described respiratory and topical exposures to unquantified amounts of perchloromethyl mercaptan; and sources did not provide experimental details. Animal data addressing the lethal and nonlethal effects of perchloromethyl mercaptan were limited to rats, and studies addressing nonlethal effects were limited to repeat-exposure protocols.

Because there were no acute animal toxicity data appropriate for deriving an AEGL-1, the AEGL-1 is based on the repeat-exposure study by Knapp et al. (1987) in which rats were exposed 6 h/day, 5 days/week, for 2 weeks, to 0.02, 0.13, or 1.15 ppm. No effects were reported at 0.02 ppm, mild nasal epithelial changes were noted at 0.13 ppm, and mild nasal epithelial changes and pulmo-

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nary irritation (labored breathing, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema) were noted at 1.15 ppm. The AEGL-1 point of departure is based on mild nasal epithelial changes noted at 0.13 ppm, which represents a no-observed-adverse-effect level (NOAEL) for notable irritation. This concentration is also a NOAEL for pulmonary irritation. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species. No modifying factor was applied because the minor epithelial changes were noted in a repeat-exposure study; it is likely that the epithelial changes following a single exposure would have been less pronounced. The derived value was set equal at all AEGL time-points because the end point is a no-effect level for perchloromethyl mercaptan as a respiratory irritant.

Insufficient data are available to derive values consistent with the AEGL-2 definition. Studies that reported analytic exposure concentrations failed to describe adverse health effects consistent with an AEGL-2 end point. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

No deaths occurred in male and female rats exposed at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Company 1971). Therefore, 9 ppm represents a no-effect-level for mortality and was selected as the most appropriate basis for the AEGL-3 derivation, given the limited database. All exposed rats developed ocular and mucosal irritation within 5 min of initial exposure; dyspnea, gasping, and “acute depression” were also observed. Necropsy revealed inflamed oral and nasal mucosa. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues. This type of port-of-entry effect is not expected to vary greatly among individuals or among species. The intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve, which may be an indication of relatively little variation within a population.

The values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). Although the mechanism of action appears to be direct contact irritation, it is not appropriate to set the values equal across time because the irritation is no longer considered mild, but rather the AEGL-3 concentration represents a threshold for lethality. Therefore, the irritation is sufficiently severe that continued exposure would produce increased and likely irreversible damage. The value of n could

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not be empirically derived because of inadequate data. Therefore, the default values of n = 1 and 3 were used for extrapolating from shorter to longer and longer to shorter durations of exposure, respectively.

The derived AEGL values are listed in Table 4-1. All values are above the estimated odor threshold of 0.001 ppm; therefore, odor will not provide information on the extent of exposure. Perchloromethyl mercaptan is corrosive to the skin, and skin absorption may provide additional exposure (Stauffer Chemical Co. 1971).

I. INTRODUCTION

Perchloromethyl mercaptan is an oily, yellow liquid with an unbearable, acrid odor (ACGIH 1991; NIOSH 1996). Although it was used as a chemical warfare gas by the French in the battle of the Champagne in 1915, wartime use was abandoned shortly thereafter because of the strong warning odor, decomposition in the presence of iron and steel, and because the vapor could easily be removed by charcoal (Prentiss 1937). Today, perchloromethyl mercaptan is used as an intermediate in the synthesis of dyes and phthalimide fungicides (ACGIH 1991; Shertzer 2001). Production data for perchloromethyl mercaptan were not available. The physicochemical data on perchloromethyl mercaptan are presented in Table 4-2.

2. HUMAN TOXICITY DATA

2.1 Acute Lethality

Althoff (1973) published the case of a 15-year-old male laboratory assistant who was exposed to perchloromethyl mercaptan liquid and vapor when a flask was broken. Approximately 200 mL of perchloromethyl mercaptan spilled onto his clothing and onto the floor. He was taken to the hospital and admitted. Thirty-six hours following exposure, the patient died from massive hemorrhaging pulmonary edema and simultaneous heart, circulatory, and kidney failure from the resultant hypoxia. Damage noted during autopsy included partly hemorrhagic, necrotizing tracheobronchitis and bronchiolitis with numerous mucus obstructions, high-grade diffuse hemorrhagic lung edema, and extreme interstitial edema; and pleural discharge on both sides of the lungs.

2.2. Nonlethal Toxicity

The odor of perchloromethyl mercaptan has been described as unbearable, acrid, and disagreeable (ACGIH 1991; NIOSH 1996). Secondary sources reported an odor threshold of 0.001 ppm (reported as 0.0075 mg/m^3) (Ruth 1986)

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TABLE 4-1 Summary of AEGL Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm ([0.099 mg/m^3)	Nasal epithelial changes in rats exposed at 0.13 ppm for 6 h /d, 5 d/wk, for 2 weeks (Knapp et al. 1987)
AEGL-2 (disabling)	0.53 ppm (4.0 mg/m^3)	0.37 ppm (2.8 mg/m^3)	0.30 ppm (2.3 mg/m^3)	0.077 ppm (0.59 mg/m^3)	0.037 ppm (0.28 mg/m^3)	One-third of the AEGL-3 values
AEGL-3 (lethality)	1.6 ppm (12 mg/m^3)	1.1 ppm (8.4 mg/m^3)	0.90 ppm (6.8 mg/m^3)	0.23 ppm (1.7 mg/m^3)	0.11 ppm (0.84 mg/m^3)	No mortality in rats exposed at 9 ppm for 1 h (Stauffer Chemical Co. 1971)

TABLE 4-2 Chemical and Physical Data on Perchloromethyl Marcaptan

Parameter	Value	Reference
Synonyms	Clarisit (war gas); methane sufenyl chloride; PCM; perchloromethanethiol; thrichloromethylsulfenyl chloride	ACGIH 1991
CAS registry no.	594-42-3	ACGIH 1991
Chemical formula	CCl_3SCl	ACGIH 1991
Molecular weight	185.87	ACGIH 1991
Physical state	Liquid	ACGIH 1991
Color	Yellow	ACGIH 1991
Boiling point	147-148°C	Shertzer 2001
Density (air = 1)	6.414	Shertzer 2001
Solubility	Insoluble in water; soluble in ether	ACGIH 1991
Vapor pressure	65 torr at 70ºC 3 mmHg at 20ºC	ACGIH 1991 Shertzer 2001
Specific gravity (water = 1)	1.7 at 20ºC	ACGIH 1991
Conversion factors	1 ppm = 7.60 mg/m^3 1 mg/m^3 = 0.132 ppm	Farr and Kirwin 1994

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and an "olfactory threshold" of 0.24 ppm (reported as 1.8 mg/m^3) (Izmerov et al. 1982). Flury and Zernik (1931) reported severe eye, mouth, and chest irritation in humans following exposure to low (unspecified) concentrations of perchloromethyl mercaptan. A 19-year-old male accidentally exposed ("in the face") to an unknown concentration of perchloromethyl mercaptan experienced irritation of the conjunctiva and respiratory tract mucosa and developed extensive bronchopneumonia within 20 h (Spácilová 1971). He was treated with antibiotics, oxygen, and "cardiotonics", and recovered within 14 days. Prentiss (1937) stated that perchloromethyl mercaptan caused lacrimation at 1.3 ppm (reported as 0.010 mg/L) was intolerable at 9.2 ppm (0.070 mg/L) and was lethal at 390 ppm (3.0 mg/L) after 10 min (no original citations or details provided).

The National Institute for Occupational Safety and Health (NIOSH) conducted a combined environmental and medical evaluation of a chemical plant in which workers were potentially exposed to Folpet, Captan, phthalimide, tetrahdrophthalimide, perchloromethyl mercaptan, carbon tetrachloride, carbon disulfide, mercaptan, and chlorine (Burroughs and Hora 1982). Unfortunately, NIOSH investigators were unable to measure perchloromethyl mercaptan air samples because of an inadequate analytic method. The conclusion of the investigation was that the acute symptoms reported by workers were nonspecific and not necessarily related to occupational exposure, "although the most commonly reported symptoms involved eye irritation, which is typical of exposure to Captan and Folpet."

2.3. Developmental and Reproductive Effects

No human developmental and reproductive toxicity data on perchloromethyl mercaptan were found in the open literature.

2.4. Genotoxicity

No human genotoxicity data on perchloromethyl mercaptan were found in the open literature.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of perchloromethyl mercaptan.

2.6. Summary

Data addressing toxicity following perchloromethyl mercaptan exposure in humans are sparse. Following exposure to an unknown concentration of perchloromethyl mercaptan vapor and skin contact with the liquid, one fatality oc-

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curred due to massive hemorrhagic pulmonary edema, accompanied by simultaneous heart, circulatory, and kidney collapse (Althoff 1973).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Vernot et al. (1977) determined the 1-h lethal concentration to 50% of the exposed population (LC_{50}) for perchloromethyl mercaptan in rats. Groups of five male or five female Sprague-Dawley rats were exposed to various concentrations of perchloromethyl mercaptan (individual concentrations not given) for 1 h in an exposure chamber (in either bell jar or large desiccators). The 1-h LC_{50} values were calculated by probit analysis of the data and were 11 ppm (95% confidence interval [C.I.]: 10-13) for male rats and 16 ppm (95% C.I.: 13-22) for female rats. When averaged, the 1-h LC_{50} for male and female Sprague-Dawley rats (combined) is 13 ppm.

Groups of 10 Sprague-Dawley rats (five males and five females) were exposed to perchloromethyl mercaptan vapor at concentrations of 9, 18, 124, 382, 822, or 2,342 ppm for 1 h in a 32-liter (L) positive pressure chamber (concentrations given in report as 0.066, 0.133, 0.940, 2.900, 6.250, and 17.800 mg/L/h) (Stauffer Chemical Co. 1971). The vapor was generated using a midget impinger. It is not clear from the text of the original report whether exposure concentrations were nominal or measured. Animals were observed for clinical signs of toxicity and mortality during the exposure and for 14-days thereafter. All animals exhibited eye and mucosa irritation within 5 min of initial exposure, and dyspnea, gasping, and "acute depression" ensued. Mortality occurred in all test groups by 24 h postexposure except for the 9-ppm group (Table 4-3). Necropsy of animals that died revealed pulmonary edema, heart and liver congestion, and inflammation of the pericardial and peritoneal membranes and upper gastrointestinal tract. Oral and nasal mucosa were inflamed at all exposure concentrations. Corneal opacity was present in animals exposed at 124 ppm and greater. The authors calculated a 1-h LC_{50} of 13 ppm (reported as 0.1 mg/L/h).

A 4-h LC_{100} value of 34 ppm (given as 260 mg/m^3) was reported for rats (Izmerov et al. 1982). No other details were provided.

Gage (1970) conducted a series of experiments in which Alderley Park specific-pathogen-free rats were exposed to perchloromethyl mercaptan at 0.5, 2, 10, or 100 ppm in a glass desiccator with wire mesh separating the animals. The appropriate nominal concentration was produced by injecting perchloromethyl mercaptan at a known rate into a metered flow of air using a controlled fluid-feed atomizer, but analytic chamber concentrations were not determined during the exposures. When nominal concentrations were less than 100 ppm, perchloromethyl mercaptan was mixed with acetone. In an acute exposure ex-

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periment, four male rats were exposed at 100 ppm for 1 h. The animals exhibited severe respiratory difficulty, and all died. Postmortem examination revealed pulmonary edema. In another experiment, four male rats were exposed to perchloromethyl mercaptan in acetone for 6 h at 10 ppm. Animals developed lethargy and respiratory difficulty, and three animals died. Necropsy again revealed pulmonary edema. In a series of short-term exposures, four male rats exposed to perchloromethyl mercaptan in acetone 20 times at 2 ppm for 6 h (time between exposures not stated) had initial respiratory difficulty. No animals died. Pulmonary congestion was noted during postmortem examination (conducted the day after the last exposure). In another experiment, four male and four female rats were exposed to perchloromethyl mercaptan in acetone at 0.5 ppm for 20 exposures over 6 h (time between exposures not stated). No signs of toxicity were noted, and all organs were found to be normal during necropsy conducted on the day after the last exposure. The protocol used by Gage was confounded by several factors, including the lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations.

3.1.2. Mice

A 2-h LC_{50} value of 38.9 ppm (reported as 296 ± 43 mg/m^3) and a 3-h LC_{50} of 9 ppm were reported for mice following inhalation exposure to perchloromethyl mercaptan (Althoff 1973; Izmerov et al. 1982). No further details were provided. Mice inhaling approximately 46 ppm for 15 min (reported as 0.35 mg/L) died from pulmonary edema within 1-2 days of exposure (Flury and Zernick 1931).

TABLE 4-3 Mortality of Sprague-Dawley Rats Exposed to Perchloromethyl Mercaptan for 1 h

Concentration		Mortality After Exposure					
ppm	mg/L/h	1 h	2 h	6 h	12 h	24 h	48 h
9	0.066	0/10	0/10	0/10	0/10	0/10	0/10
18	0.133	0/10	0/10	2/10	6/10	7/10	7/10
124	0.940	1/10	9/10	10/10	—	—	—
382	2.900	10/10	7/10	10/10	—	—	—
822	6.250	10/10	10/10	—	—	—	—
2,342	17.800	10/10	10/10	—	—	—	—

Source: Stauffer Chemical Co. 1971.

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3.1.3. Cats

Cats exposed to perchloromethyl mercaptan at approximately 46 ppm for 15 min (reported as 0.35 mg/L) died from pulmonary edema within 1-2 days of exposure (Flury and Zernick 1931).

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of 15 male and female Sprague-Dawley rats were exposed to "cumulative" mean air concentrations of 0, 0.02, 0.13, or 1.15 ppm (reported as 0, 0.13, 1.0, or 8.7 mg/m^3) for 6 h/day, 5 days/week, for 2 weeks (Knapp et al. 1987). At 1.15 ppm, signs consisted of haircoat stains, dyspnea, tremors, and reduced body-weight gain. Necropsy revealed increased lung weight, pulmonary edema, and increased mucous secretion, and microscopic examination of the lungs found alveolitis, interstitial fibroplasia, and perivascular edema. Mild nasal epithelial changes (not further described) were noted in animals exposed at 0.13 and 1.15 ppm.

Groups of 18 male and 18 female Sprague-Dawley CD rats were exposed to perchloromethyl mercaptan vapor in the air at measured concentrations of 0, 0.014, 0.079, or 0.580 ppm (reported as 0, 0.11, 0.60, or 4 mg/m^3) for 6 h/day, 5 days/week, for a total of 70 to 72 exposure days (Knapp and Thomassen 1987). The exposures were conducted in 1.0-m^3-inhalation exposure chambers. No animals died from the exposure, and no exposure-related effects were noted in hematology or clinical chemistry parameters. Exposure-related effects were observed in the high-concentration group. Clinical signs consisted of increased incidences of salivation in males and increased sneezing in males and females starting on test days 18 and 59, respectively. High-concentration-group females had a time-related decrease in absolute body weight starting at week 1 and continuing throughout the study (−6-12% compared with controls). The controls had a total body-weight gain of 64%. Necropsy of the high-concentration groups at study termination revealed increased absolute lung weight and lung weight relative to body weight and brain weight in males (+9%, +16%, and +10%, respectively) and increased lung weight relative to body weight in females (+15%) compared with controls. Other effects noted in animals from the high-concentration group included gross mucus in the trachea in 4 of 18 males and in 2 of 18 females. Microscopic findings of acute inflammation and hypertrophy, and hyperplasia of respiratory nasal epithelium in males and females were reported. Residues of purulent or serum exudate were noted in all males and in 13 of 18 females in the 0.580-ppm group and in one male and one female exposed at 0.079 ppm. The only exposure-related pulmonary lesion was mild-to-minimal focal subacute interstitial pneumonia in five males and one female from the high-concentration group.

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As discussed in Section 3.1.1, Gage (1970) conducted a series of experiments in which Alderley Park specific-pathogen-free rats were exposed to perchloromethyl mercaptan at 100, 10, 2, or 0.5 ppm for various time periods. No deaths occurred in the four male rats exposed at 2 ppm or in the four male or female rats exposed at 0.5 ppm for 20 exposures over 6 h (time between exposures not stated). In the 2-ppm group, initial respiratory difficulty was reported, and pulmonary congestion was noted during postmortem examination. No clinical signs of toxicity or remarkable necropsy findings were reported for rats in the 0.5-ppm group. It should be reemphasized that the protocol used by Gage was compromised by several factors, including the lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations.

3.2.2. Other Species

Seven rats, seven guinea pigs, and two dogs were exposed to perchloromethyl mercaptan at a nominal concentration of 1 ppm for 8 h/day, 5 days/week, for 3 months (Hazleton Laboratories 1952). For numerous reasons, this study can be used only to provide descriptive data. The materials and methods and the results sections of the study report were mostly illegible (poor copy quality). It appeared that the laboratory had difficulty with the instrumentation used to deliver the perchloromethyl mercaptan to the exposure chamber. The (legible) summary section failed to discuss or mention control animals, suggesting that control animals were not assigned. At least one of the dogs had parasitic infestation and findings suggestive of bronchopneumonia; the guinea pigs that died appeared to have had pneumonia with septicemia, and the surviving guinea pig had signs of a chronic infection. The study authors suggested that the irritative effects of perchloromethyl mercaptan led to increased susceptibility to secondary infections. However, it is not clear that these infections were not already present prior to or at the start of exposures. The data for all the animals are presented together below.

In summary, six of seven guinea pigs died within the first 3 weeks of exposure. Signs included lacrimation, rhinorrhea, lethargy, and increased respiration. Guinea pigs that died had pneumonia with septicemia, and the surviving guinea pig developed fibrotic lungs and liver findings consistent with a chronic infection. Neither of the dogs died as a result of their exposure. The dogs developed lacrimation, rhinorrhea, nausea and retching, coughing and sneezing, diarrhea, and occasional blood-stained stools. (Note that at least one of the dogs had a parasitic infection.) Microscopic examination of the lungs of one of the dogs revealed bronchiolitis with possible bronchopneuomonia. Clinical signs in rats were not summarized. Microscopic examination of the lungs revealed thin alveolar walls with a hyaline-like appearance, and in some areas, the alveolar walls ruptured and formed emphysematous blebs.

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3.3. Developmental and Reproductive Effects

No developmental and reproductive toxicity data on perchloromethyl mercaptan were found in the available literature.

3.4. Genotoxicity

Perchloromethyl mercaptan was mutagenic in a number of in vitro assays, including *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with or without metabolic activation (Stauffer Chemical Company 1982a), the DNA-polymerase-deficient *Escherichia coli* (pol A_1- strain) without metabolic activation (Rosenkranz and Leifer 1980), inhibition of DNA synthesis (via DNA polymerase β inhibition) in isolated bovine liver nuclei (Dillwith and Lewis 1980), induction of mutations at the thymidine kinase locus in cultured L5178Y mouse lymphoma cells with or without metabolic activation (Stauffer Chemical Company 1983a), and induction of morphologic transformations in the BALB/3T3 morphologic transformation assay (Stauffer Chemical Company 1982b). Perchloromethyl mercaptan failed to increase chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells with or without metabolic activation, and there was no increase in micronuclei in the bone marrow of mice in a micronucleus assay (Stauffer Chemical Company 1983b, 1984).

3.5. Carcinogenicity

No data were found in the literature concerning the carcinogenic potential of perchloromethyl mercaptan in animals.

3.6. Summary

A summary of lethal and nonlethal data is presented in Table 4-4. Acute lethality data were available for rats: 1-h inhalation LC_{50} values for perchloromethyl mercaptan vapor were 13 ppm for males and females combined (Stauffer Chemical Co. 1971) and 11 ppm for males and 16 ppm for females for an average of 13.5 ppm for males and females combined (Vernot et al. 1977). Although a 3-h LC_{50} value of 9 ppm and a 2-h LC_{50} value of 39 ppm were reported in mice, these values were published in a secondary source and did not provide any original citation or experimental details (Stauffer Chemical Co. 1971, as cited in Althoff 1973; Eastman Kodak Co. 1979; Izmerov et al. 1982).

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TABLE 4-4 Summary of Inhalation Data in Laboratory Rats

Concentration (ppm)	Exposure Time	Effect	Reference
		Lethal Effects	
18	1 h	Lowest empirical exposure causing mortality (7/10) (males and females); deaths resulting from pulmonary edema, heart and liver congestion, inflammation of upper gastrointestinal tract and pericardial and peritoneal membranes	Stauffer Chemical Co. 1971
11	1 h	Calculated LC_{50} (males)	Vernot et al. 1977
16	1 h	Calculated LC_{50} (females)	Vernot et al. 1977
13	1 h	Calculated LC_{50} (average of males and females)	Vernot et al. 1977
		Nonlethal Effects	
9	1 h	Eye and mucosa irritation, dyspnea, gasping, "acute depression" (severity of signs not defined), inflamed mouth, and nasal mucosa	Stauffer Chemical Co. 1971
0.13	6 h/d, 5 d/wk, for 2 wk	Mild nasal epithelial changes	Knapp et al. 1987
1.15	6 h/d, 5 d/wk, for 2 wk	Haircoat stains, labored breathing, tremors, decreased birth weight., increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and mild nasal epithelial changes	
0.58	6 h/d, 5 d/wk, for 70-72 d	Salivation (day 18) and sneezing (day 59) Mild changes, including decreased female birth weight, increased male and female lung weight relative to body weight, mucous in trachea, respiratory nasal epithelium changes, and focal subacute interstitial pneumonia	Knapp and Thomassen 1987

Data addressing nonlethal effects in animals following perchloromethyl mercaptan exposure are small. Clinical signs in rats surviving a 1-h exposure at 9 ppm included eye and mucosa irritation, dyspnea, gasping, and "acute depression" (Stauffer Chemical Co. 1971). The severity of those signs at this concentration and at the higher concentrations (which resulted in mortality) was not provided; no control group was included. A 2-week repeat-exposure study reported numerous findings in rats exposed at 1.15 ppm, including clinical signs (haircoat stains, labored breathing, tremors, and decreased body weight) and gross and microscopic lung changes (increased lung weight, pulmonary edema,

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increased mucous secretion, alveolitis, and interstitial fibroplasia) (Knapp et al. 1987). Mild nasal epithelial changes were observed in rats repeatedly exposed at 0.13 or 1.15 ppm (Knapp et al. 1987). Minimal effects were observed in rats exposed subchronically at 0.580 ppm; these effects included reduced body weight, increased lung weight, mucous in the trachea, respiratory nasal epithelial changes (acute inflammation and hypertrophy and hyperplasia of respiratory nasal epithelium), residues of purulent serous exudate, and focal subacute interstitial pneumonia (Knapp and Thomassen 1987). No such changes were observed in rats that inhaled 0.014 or 0.079 ppm for 70 to 72 days (Knapp and Thomassen 1987). The descriptive data provided by Gage (1970) and Hazleton Laboratories (1952) are of little use because the protocols used were fundamentally compromised by several factors.

Perchloromethyl mercaptan was generally mutagenic in standard in vitro test systems. No data were found regarding the potential for perchloromethyl mercaptan exposure to cause developmental and reproductive toxicity or to increase carcinogenic risk.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Mechanism of Toxicity

Althoff (1973) postulated that two mechanisms of action could be responsible for the toxicity of perchloromethyl mercaptan: one is the direct damage to tissues resulting from contact with the hydrolysis product hydrochloric acid:

$$CCl_3\text{-}S\text{-}Cl + H_2O \rightarrow CCl_3\text{-}SOH + HCl,$$

and the other is inactivation of key enzymes by the reaction of perchloromethyl mercaptan with biologic functional groups, such as amino, hydroxyl, carboxyl, sulfhydryl, or histidyl groups:

$$R\text{-}NH_2 + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}NH\text{-}R + HCl \text{ or } R\text{-}OH + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}O\text{-}R + HCl.$$

Because perchloromethyl mercaptan is insoluble in water, large amounts of HCl are not likely to be produced. This fact explains the deeper lung damage after HCl exposure compared with the relatively mild upper-respiratory-tract damage observed in animals exposed to perchloromethyl mercaptan.

4.2. Structure-Activity Relationships

Structure-activity relationships were not used in the derivation of inhalation exposure guidelines for perchloromethyl mercaptan. Although acute toxic-

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ity data are available for methyl mercaptan, the potency of perchloromethyl mercaptan is greater than that of methyl mercaptan. In rats, the highest nonlethal concentration of perchloromethyl mercaptan is 9 ppm for 1 h, and the 1-h LC_{50} is reported to be 11, 13, or 16 ppm. In comparison, the highest nonlethal concentration of methyl mercaptan in rats is 400 ppm for 4 h, with a 4-h LC_{50} value of 675 ppm in rats and 1,664 ppm in mice (EPA 2008). Therefore, the two chemicals are sufficiently different to preclude useful structure-activity relationship comparison.

4.3. Concentration-Exposure Duration Relationship

The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically acting vapors and gases. The authors subjected the individual animal data sets to probit analysis with exposure duration and exposure concentration as independent variables. An exponential function ($C^n \times t = k$), where the value of n ranged from 0.8 to 3.5 for different chemicals was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90% of the values of n range between n = 1 and n = 3. Consequently, these values were selected as the reasonable lower and upper bounds of n. A value of n = 1 is used when extrapolating from shorter to longer time periods because the extrapolated values represent the most conservative approach in the absence of other data. Conversely, a value of n = 3 is used when extrapolating from longer to shorter time periods because the extrapolated values are more conservative in the absence of other data.

5. DATA ANALYSIS FOR AEGL-1 VALUES

5.1. Human Data Relevant to AEGL-1

Ruth (1986) reported an odor threshold of 0.001 ppm, while Izmerov et al. (1982) reported an “olfactory threshold” value in humans of 0.24 ppm. No further information was provided. The odor of perchloromethyl mercaptan is said to be unbearable, acrid, and disagreeable (ACGIH 1991; NIOSH 1996). Prentiss (1937) reported lacrimation at a concentration of 1.3 ppm, but no original citations or experimental details were provided.

5.2. Animal Data Relevant to AEGL-1

There were no acute animal data appropriate for deriving an AEGL-1. Although one study reported eye and mucosa irritation in rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, the severity of the signs was not provided, and the report stated that dyspnea, gasping, and signs of acute depression

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were also observed (Stauffer Chemical Co. 1971). Other nonlethal data are from repeat-exposure studies. Exposure of rats to perchloromethyl mercaptan for 6 h/day, 5 days/week, for 2 weeks at 0.02 ppm failed to elicit any measurable changes; exposure at 0.13 ppm resulted only in mild nasal epithelial changes (not further defined); exposure at 1.15 ppm resulted in objective clinical signs of intoxication (haircoat stains, labored breathing, tremors, reduced body-weight gain, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema in the lungs and mild epithelial changes in the nose) (Knapp et al. 1987). No exposure-related changes were observed in rats inhaling perchloromethyl mercaptan at 0.014 or 0.079 ppm for 6 h/day, 5 days/week, for a total of 70 to 72 exposure days (Knapp and Thomassen 1987).

5.3. Derivation of AEGL-1 Values

Because there were no acute animal toxicity data appropriate for deriving an AEGL-1, the AEGL-1 is based on the repeat-exposure study by Knapp et al. (1987) in which rats were exposed to perchloromethyl mercaptan at 0.02, 0.13, or 1.15 ppm for 6 h/day, 5 days/week, for 2 weeks. No effects were reported at 0.02 ppm, mild nasal epithelial changes were noted at 0.13 ppm, and mild nasal epithelial changes and pulmonary irritation (labored breathing, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema) were noted at 1.15 ppm. The AEGL-1 point of departure is mild nasal epithelial changes noted at a concentration of 0.13 ppm, which represents a NOAEL for notable irritation. This concentration is also a NOAEL for pulmonary irritation. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues. This type of port-of-entry effect is not expected to vary greatly among individuals or among species, respectively. No modifying factor was applied because the minor epithelial changes were noted in a repeat-exposure study; the epithelial changes following a single exposure probably would have been less pronounced. The derived value was set equal at all AEGL time points because the end point is a no-effect level for irritation.

AEGL-1 values are presented in Table 4-5.

TABLE 4-5 AEGL-1 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)

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6. DATA ANALYSIS FOR AEGL-2 VALUES

6.1. Human Data Relevant to AEGL-2

No available human data were appropriate for an AEGL-2 derivation for perchloromethyl mercaptan.

6.2. Animal Data Relevant to AEGL-2

Acute animal toxicity data appropriate for use in an AEGL-2 derivation were sparse. Although rats survived a 1-h exposure to perchloromethyl mercaptan at 9 ppm, the severity of the reported clinical signs (eye and mucosa irritation, dyspnea, gasping, and acute depression) was not provided for the various exposure concentrations (Stauffer Chemical Co. 1971). In addition, exposure at 9 ppm was close to the calculated LC_{50} of 13 ppm. The inhalation study conducted by Gage (1970) reported initial respiratory difficulty in rats exposed 20 times at 2 ppm for 6 h. However, the protocol used by Gage was confounded by several factors including lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations. Therefore, the descriptive data provided by Gage are of little use.

Rats exposed to perchloromethyl mercaptan for 6 h/day, 5 days/week, for 2 weeks, at 0.13 ppm developed mild nasal epithelial changes, while rats exposed at the next higher concentration (1.15 ppm) developed severe effects, including haircoat stains, labored breathing, tremors, decreased body weight, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, and interstitial fibroplasia (Knapp et al. 1987). In a subchronic toxicity study, rats exposed at 6 h/day, 5 days/week, for 70-72 days developed only minimal effects at the highest exposure concentration (0.58 ppm) (Knapp and Thomassen 1987). Clinical signs were not present until later in the study (salivation on day 18; sneezing on day 59). Other effects noted in the high-exposure group compared with the controls included reductions in female body weight (−12%), increased lung weight in males and females (relative to body weight, approximately +15%), mucous in trachea in 4 of 18 males and 2 of 18 females, and respiratory nasal epithelium changes in males and females (acute inflammation and hypertrophy and hyperplasia). Residues of purulent or serum exudate were noted in all males and in 13 of 18 females in the 0.580-ppm group. The only exposure-related pulmonary lesion was mild-to-minimal focal subacute interstitial pneumonia in 5 of 18 males and in 1 of 18 females.

6.3. Derivation of AEGL-2 Values

Insufficient data are available to derive values consistent with the AEGL-2 definition. Studies that reported analytic exposure concentrations failed to de-

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scribe adverse health effects consistent with an AEGL-2 end point. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

AEGL-2 values are presented in Table 4-6.

7. DATA ANALYSIS FOR AEGL-3 VALUES

7.1. Human Data Relevant to AEGL-3

No available human data were appropriate for an AEGL-3 derivation. Human data were limited to case reports describing exposures to unquantified concentrations of perchloromethyl mercaptan; it is likely these accidents involved both skin and respiratory tract contract with the material (Spácilová 1971; Althoff 1973).

7.2. Animal Data Relevant to AEGL-3

No mortality was observed in rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Co. 1971). All exposed rats exhibited clinical signs of eye and mucosa irritation, dyspnea, gasping, and acute depression within 5 min of exposure, and necropsy revealed that the mouth and nasal mucosa were inflamed. On the basis of the mortality in this study, the calculated 1-h LC_{50} was 13 ppm (males and females combined). Vernot et al. (1977) reported 1-h LC_{50} values of 11 ppm for male rats and 16 ppm for female rats. A 4-h LC_{50} of 25 ppm was also reported in rats, and a 2-h LC_{50} value of 38.9 ppm (reported as 296 ± 43 mg/m^3) and a 3-h LC_{50} value of 9 ppm were reported in mice following inhalation exposure to perchloromethyl mercaptan (Althoff 1973; Izmerov et al. 1982). However, no original citations or experimental details were provided to support these values.

7.3. Derivation of AEGL-3 Values

No mortality was observed in male and female rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Company 1971). Therefore, 9 ppm represents a no-effect-level for mortality and was selected as the most appropriate basis for the AEGL-3 derivation, given the limited database. All exposed rats developed ocular and mucosal irritation within 5 min of initial exposure; dyspnea, gasping, and “acute depression” were also observed. Necropsy revealed inflamed mouth and nasal mucosa.

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A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species. The intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve, which may be an indication of relatively little variation within a population.

The values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). Although the mechanism of action responsible for death appears to be direct contact irritation in the lung, it is not appropriate to set the values equal across time because the irritation is no longer considered mild, but rather the concentration represents the threshold for lethality. Therefore, the irritation is severe enough that continued exposure would result in increased damage. The value of n could not be empirically derived because of inadequate data. Therefore, the default values of n = 1 and 3 were used for extrapolating from shorter to longer and longer to shorter exposure periods, respectively.

AEGL-3 values are presented in Table 4-7.

8. SUMMARY OF AEGLs VALUES

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for perchloromethyl mercaptan is presented in Table 4-8. All values are above the estimated odor threshold of 0.001 ppm; therefore, odor will not provide information on the extent of exposure. Perchloromethyl mercaptan is corrosive to the skin and skin absorption may provide additional exposure (Stauffer Chemical Co. 1971).

TABLE 4-6 AEGL-2 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.53 ppm (4.0 m^3)	0.37 ppm (2.8 m^3)	0.30 ppm (2.3 m^3)	0.077 ppm (0.59 m^3)	0.037 ppm (0.28 m^3)

TABLE 4-7 AEGL-3 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	1.6 ppm (12 m^3)	1.1 ppm (8.4 m^3)	0.90 ppm (6.8 m^3)	0.23 ppm (1.7 m^3)	0.11 ppm (0.84 m^3)

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TABLE 4-8 Summary of AEGL Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm ([0.099 mg/m^3)
AEGL-2 (disabling)	0.53 ppm (4.0 mg/m^3)	0.37 ppm (2.8 mg/m^3)	0.30 ppm (2.3 mg/m^3)	0.077 ppm (0.59 mg/m^3)	0.037 ppm (0.28 mg/m^3)
AEGL-3 (lethality)	1.6 ppm (12 mg/m^3)	1.1 ppm (8.4 mg/m^3)	0.90 ppm (6.8 mg/m^3)	0.23 ppm (1.7 mg/m^3)	0.11 ppm (0.84 mg/m^3)

The AEGL-1 values were based on mild nasal epithelial changes in rats from a repeat-exposure study. This end point represents a NOAEL for notable discomfort. Data were insufficient to derive AEGL-2 values; therefore, the AEGL-2 values were obtained by dividing the AEGL-3 values by 3. The AEGL-3 values were based on a no-effect level for lethality. At the no-effect level for increased mortality, exposed animals developed eye and mucosa irritation, dyspnea, gasping, and acute depression, and necropsy revealed inflamed oral and nasal mucosa.

One way to evaluate the AEGL values in context of existing empirical data is presented in Figure 4-1. For this plot, the toxicity response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: no effects; discomfort; disabling; lethal, and partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The concentrations often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 4-1 plots the perchloromethyl mercaptan AEGL values along with the existing acute animal toxicity data in terms of the categories assigned to them. From this plot, it is evident that the AEGL values are below any exposure concentration in animals resulting in adverse effects and, therefore, should be protective of human health.

8.2. Comparisons with Other Standards

Published standards and guidance levels for perchloromethyl mercaptan are listed in Table 4-9.

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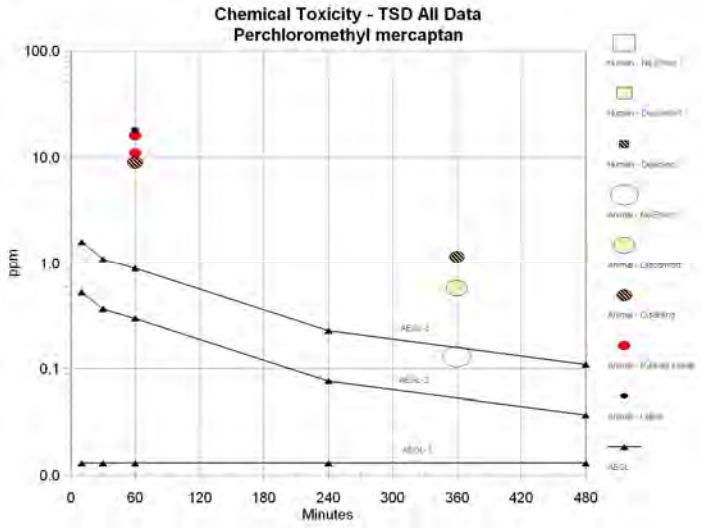

FIGURE 4-1 Category plot of animal toxicity data compared with AEGL values.

TABLE 4-9 Extant Standards and Guidelines for Perchloromethyl Mercaptan

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm
AEGL-2	0.53 ppm	0.37 ppm	0.30 ppm	0.077 ppm	0.037 ppm
AEGL-3	1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm
IDLH (NIOSH)[a]		10 ppm			
TLV-TWA (ACGIH)[b]					0.1 ppm
PEL-TWA (OSHA)[c]					0.1 ppm
REL-TWA (NIOSH)[d]					0.1 ppm
MAK (Germany)[e]					Not established; insufficient data
MAC (The Netherlands)[f]					($0.01 mg/m^3$ = 0.01 ppm)

[a]IDLH (immediately dangerous to life or health, National Institute of Occupational Safety and Health) (NIOSH 1996; 2005) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for perchloromethyl mercaptan is based on the statement by Prentiss (1937) that perchloromethyl mercaptan is about one-sixth as toxic as phosgene; the phosgene IDLH is 2 ppm.

[b]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 1991, 2008) is the time-weighted average

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concentration for a normal 8-h workday and a 40-h workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[c]PEL-TWA (permissible exposure limits–time-weighted average, Occupational Health and Safety Administration) (OSHA) (29 CFR 1910.1000 [1996]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.
[d]REL-TWA (recommended exposure limits–time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.
[e]MAK (maximale Argeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2007) is analogous to the ACGIH TLV-TWA.
[f]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is analogous to the ACGIH TLV-TWA.

8.3. Data Quality and Research Needs

Data addressing human and animal toxicity following exposure to perchloromethyl mercaptan vapors were very limited. Human data were generally limited to case reports describing exposures to an unquantifiable amount of perchloromethyl mercaptan, secondary sources, and/or sources in which the experimental details were not provided. Further studies addressing the acute lethal and nonlethal effects of perchloromethyl mercaptan in animals would be of utility, since available animal data were limited to rats, and studies addressing nonlethal effects were limited to repeat-exposure protocols. No data were available addressing the potential for perchloromethyl mercaptan exposure to cause developmental or reproductive effects or neoplasia.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PERCHLOROMETHYL MERCAPTAN

Derivation of AEGL-1

Key study:	Knapp et al. 1987
Toxicity end point:	Mild nasal epithelial changes representing a NOAEL for notable discomfort following exposure of rats at 0.013 ppm for 6 h/day, 5 days/week, for 2 weeks.
Time-scaling:	Values were set equal across time because the effects are those of mild irritation.
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Calculations:	Point of departure/uncertainty factors 0.13/10 = 0.013
10-min, 30-min, 1 h, 4 h, and 8 h AEGL-1:	0.013 ppm for all time points

Derivation of AEGL-2

Key study:	AEGL-3 divided by 3; see AEGL-3 derivation
Toxicity end point:	AEGL-3 divided by 3; see AEGL-3 derivation
Time-scaling:	AEGL-3 divided by 3; see AEGL-3 derivation
Uncertainty factors:	AEGL-3 divided by 3; see AEGL-3 derivation
Calculations:	AEGL-3 values divided by 3
10-min. AEGL-2:	1.6 ppm/3 = .53 ppm
30-min AEGL-2:	1.1 ppm/3 = 0.37 ppm
1-h AEGL-2:	0.90 ppm/3 = 0.30 ppm

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4-h AEGL-2: 0.23 ppm/3 = 0.077 ppm

8-h AEGL-2: 0.11 ppm/3 = 0.037 ppm

Derivation of AEGL-3

Key study: Stauffer Chemical Co. 1971

Toxicity end point: No lethality in rats exposed to 9 ppm for 1 h

Time-scaling: $C^n \times t = k$ (default of n = 1 for shorter to longer exposure periods and n=3 for longer to shorter exposure periods)

Uncertainty factors: 3 for interspecies variability
3 for intraspecies variability
Combined uncertainty factor of 10

Calculations: $(C/\text{uncertainty factors})^n \times t = k$
$[(9 \text{ ppm})/10]^1 \times 1 \text{ h} = 0.9 \text{ ppm-h}$
$[(9 \text{ ppm})/10]^3 \times 1 \text{ h} = 0.729 \text{ ppm-h}$

10-min AEGL-3: $C^3 \times 0.167 \text{ h} = 0.729 \text{ ppm-h}$
$C^3 = 4.365 \text{ ppm}$
$C = 1.63 \text{ ppm} = 1.6 \text{ ppm}$

30-min AEGL-3: $C^3 \times 0.5 \text{ h} = 0.729 \text{ ppm-h}$
$C^3 = 1.458 \text{ ppm}$
$C = 1.13 \text{ ppm} = 1.1 \text{ ppm}$

1-h AEGL-3: $C^1 \times 1 \text{ h} = 0.729 \text{ ppm-h}$
$C^1 = 0.729 \text{ ppm-h}$
$C = 0.90 \text{ ppm}$

4-h AEGL-3: $C^1 \times 4 \text{ h} = 0.9 \text{ ppm-h}$
$C^1 = 0.225 \text{ ppm}$
$C = 0.225 \text{ ppm} = 0.23 \text{ ppm}$

8-h AEGL-3: $C^1 \times 8 \text{ h} = 0.9 \text{ ppm-h}$
$C^1 = 0.1125 \text{ ppm}$
$C = 0.1125 \text{ ppm} = 0.11 \text{ ppm}$

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APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR PERCHLOROMETHYL MERCAPTAN

Derivation Summary for Perchloromethyl Mercaptan

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm

Reference:
Knapp, H.F., S.M. MacAskill, G.M. Zwicker, and G.L. Sprague. 1987. Effects in rats of repeated inhalation exposure to perchloromethyl mercaptan. Toxicologist 7(1):191[Abstact 762].

Test species/Strain/Number: Rat/Sprague-Dawley/15 per exposure group

Exposure route/Concentrations/Durations:
Inhalation at 0.02, 0.13, 1.15 ppm for 6 h/d, 5 d/wk, for 2 wk

Effects:
0.02 ppm: no effects
0.13 ppm: mild nasal epithelial changes
1.15 ppm: clinical signs of haircoat stains, labored breathing, tremors, and reduced body weight gain; necropsy revealed increased lung weight, pulmonary edema, and increased mucous secretion; microscopic examination found alveolitis, interstitial fibroplasia, and perivascular edema in the lungs and mild epithelial changes in the nose

End point/Concentration/Rationale: NOAEL for notable discomfort of 0.13 ppm for 6 h/day

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among species

Intraspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals, and the steep dose-response curve may be an indication of little variation within a population; (no deaths were observed in rats exposed at 9 ppm but 7 of 10 died at 18 ppm [Stauffer Chemical Company 1971]).

Modifying factor: No modifying factor was applied because the minor epithelial changes were noted in a repeated exposure study; it is likely that the epithelial changes following a single exposure would have been less pronounced.

Animal-to-human dosimetric adjustment: Not applicable

(Continued)

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AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm

Time scaling: The derived value was set equal at all AEGL time-points because the end point is a no-effect level for irritation.

Data adequacy: No acute toxicity data were available for use in the derivation of the AEGL-1; therefore, the AEGL-1 values are based on a NOAEL from a repeat-exposure study.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.53 ppm	0.37 ppm	0.30 ppm	0.077 ppm	0.037 ppm

Reference: See “Data adequacy” below.

Test species/Strain/Sex/Number: See “Data adequacy” below.

Exposure route/Concentrations/Durations: See “Data adequacy” below.

Effects: See “Data adequacy” below.

End point/Concentration/Rationale: See “Data adequacy” below.

Uncertainty factors/Rationale: See “Data adequacy” below.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time-scaling: See “Data adequacy” below.

Data adequacy: No acute toxicity data were available for use in the derivation of the AEGL-2. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-3 values are divided by 3 (see AEGL-3 derivation).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Reference: Stauffer Chemical Company. 1971. Initial Submission: Acute Inhalation Test with Perchloromethyl Mercaptan in Rats. Report No. T-1683. Stauffer Chemical Company, Westport, CT. Submitted by ICI Americas Inc., to U.S. Environmental Protection Agency, August 28, 1992. EPA Document No. 88-920006928. 7 pp.

Test Species/Strain/Number: Rat/Sprague-Dawley/5 per exposure group

Exposure route/Concentrations/Durations:
Inhalation at 9, 18, 124, 382, 822, or 2,342 ppm for 1 h

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Effects:

Concentration (ppm):	Mortality
9	0/10
18	7/10
124	10/10
382	10/10
822	10/10
2,342	10/10

End point/Concentration/Rationale: Exposure at 9 ppm for 1 h did not result in mortality; all exposed rats exhibited clinical signs of eye and mucosa irritation, dyspnea, gasping, and acute depression; necropsy revealed that the mouth and nasal mucosa were inflamed.

Uncertainty factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among species.

Intraspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals; also supported by the steep dose-response curve, which may be an indication of little variation within a population.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time-scaling: $C^n \times t = k$, where n = 3 for extrapolation from longer to shorter durations and n = 1 for extrapolation from shorter to longer durations.

Data adequacy: The AEGL-3 value was based on a concentration not causing lethality and should be protective of human health.

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