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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 15

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Committee on Toxicology

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Division on Earth and Life Studies

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Preface

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

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

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

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the fifteenth volume

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

in that series. AEGL documents for ethyl mercaptan, methyl mercaptan, phenyl mercaptan, tert-octyl mercaptan, lewisite, methyl isothiocyanate, and selected monoisocyanates are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for ethyl mercaptan (interim reports 19a, 20a, and 21a), methyl mercaptan (interim reports 15, 19a, 20a, and 21a), phenyl mercaptan (interim reports 19a, 20a, and 21a), tert-octyl mercaptan (interim reports 19a, 20a, and 21a), lewisite (interim reports 19a and 21a), methyl isothiocyanate (interim reports 20a and 21a), and selected monoisocyantes (interim reports 20a, 20b, 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim reports was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review com-

ments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 15

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

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

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

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

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared fourteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013). This report is the fifteenth volume in that series. AEGL documents for ethyl mercaptan, methyl mercaptan, phenyl mercaptan, tert-octyl mercaptan, lewisite, methyl isothiocyanate, and selected monoisocyanates are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

Ethyl 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 Cheryl Bast (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Chemical Manager Iris Camacho (U.S. Environmental Protection Agency and National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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 concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Ethyl mercaptan is an odorous, colorless liquid. The disagreeable odor has been described as penetrating, persistent, and garlic- or leek-like, similar to decaying cabbage. It is found in illuminating gas, in "sour" gas in West Texas oil fields, and in petroleum distillates from which it may be separated by chemical or physical methods. It is used as an intermediate and starting material in the manufacture of plastics, insecticides, and antioxidants, and as an odorant to serve as a warning property for natural gas (O'Neil et al. 2006).

Ethyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis. Clinical signs of exposure are ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, and vomiting. Paralysis of locomotor muscles has also been observed. Its primary mechanism of action appears to be interference with cytochrome oxidase.

AEGL-1 values for ethyl mercaptan were based on a no-effect level of 10 ppm for respiratory changes associated with odor avoidance in rabbits exposed for 20 min (Shibata 1966a). Two uncertainty factors of 3 were applied to account for interspecies differences and intraspecies variability, and are considered sufficient because use of the full factor of 10 for either type of uncertainty would yield AEGL-1 values of 0.3 ppm or less, concentrations that are inconsistent with human data. A single AEGL-1 value was used across exposure durations

because prolonged exposure to ethyl mercaptan is unlikely to result in an enhanced effect.

The level of distinct odor awareness (LOA) for ethyl mercaptan is 1.4×10^{-4} ppm (see Appendix C for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. Because of its relatively high vapor pressure (442 mm Hg at 20°C) (NIOSH 2011), ethyl mercaptan has the potential to generate toxic air concentrations very quickly in the event of a spill. The LOA should help chemical emergency responders assess the public awareness of exposure to ethyl mercaptan from its odor.

No robust data on ethyl mercaptan consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for ethyl mercaptan were based on a 3-fold reduction in the AEGL-3 values. This calculation is considered an estimate of a threshold for irreversible effects and is appropriate because of the steep concentration-response curve for ethyl mercaptan toxicity.

AEGL-3 values are based on a calculated 4-h LC_{01} (lethal concentration, 1% lethality) of 2,250 ppm in mice (Fairchild and Stokinger 1958). The corresponding 4-h LC_{01} value for rats is 3,808 ppm. An intraspecies uncertainty factor of 3 was applied, and is considered sufficient because of the steepness of the lethality concentration-response curve which implies limited individual variability. An interspecies uncertainty factor of 3 was also applied because the limited data suggest that the mouse is the most sensitive species. Although an interspecies uncertainty factor of 10 might normally be applied because of the limited data, a total uncertainty factor of 30 would yield AEGL-3 values that are inconsistent with the total data set (the values would be in the range of AEGL-3 values for hydrogen sulfide [NRC 2010]). Furthermore, the 30-min AEGL-3 value would be 150 ppm, a value that is inconsistent with the finding that a single human exposed to ethyl mercaptan at 112 ppm for 20 min exhibited only a slightly irregular and decreased breathing rate (Shibata 1966b). Thus, the total uncertainty factor is 10. The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 4-h point of departure to a 10-min value.

AEGL values for ethyl mercaptan are presented in Table 1-1.

1. INTRODUCTION

Ethyl mercaptan is used as an intermediate and starting material in the manufacture of plastics, insecticides, and antioxidants, and as an odorant to serve as a warning property for natural gas (O'Neil et al. 2006).

Ethyl mercaptan is an odorous, colorless liquid. The disagreeable odor has been described as penetrating, persistent, and garlic- or leek-like, similar to decaying cabbage (O'Neil et al. 2006). It is found in illuminating gas, in "sour" gas in West Texas oil fields, and in petroleum distillates from which it may be separated by chemical or physical methods (O'Neil et al. 2006).

TABLE 1-1 AEGL Values for Ethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	No-effect level for respiratory changes associated with odor avoidance in rabbits (Shibata 1966a).
AEGL-2 (disabling)	150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)	3-fold reduction of AEGL-3 values.
AEGL-3 (lethal)	450 ppm (1,100 mg/m^3)	450 ppm (1,100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)	LC_{01} in mice (Fairchild and Stokinger 1958).

Abbreviation: LC_{01}, lethal concentration, 1% lethality.

Ethyl mercaptan is produced commercially by the reaction of sodium ethyl sulfate with potassium hydrosulfide, or catalytically from ethanol and hydrogen sulfide (O'Neil et al. 2006). The total production of methane, ethane, propane, butane, octane, nonane, decane, hexadecane, and miscellaneous thiols was 264,797,000 pounds in 1976, and an estimated 23,130 U.S. workers were exposed to ethyl mercaptan from 1972-1974 (NIOSH 1978).

The physical and chemical properties of ethyl mercaptan are presented in Table 1-2. Because of its relatively high vapor pressure (442 mm Hg at 20°C), ethyl mercaptan has the potential to generate toxic air concentrations very quickly in the event of a spill.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information concerning human lethality from acute exposure to ethyl mercaptan was found.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Odor Awareness

Katz and Talbert (1930) conducted two trials, each exposing six human subjects to a range of ethyl mercaptan concentrations via a nosepiece. The subjects described the odor as that of decayed cabbage and very disagreeable. A description of the odor intensity of ethyl mercaptan is presented in Table 1-3. No ocular or nasal irritation was reported in subjects exposed to ethyl mercaptan at concentrations up to 1,000 ppm for less than 10 seconds.

TABLE 1-2 Physical and Chemical Data for Ethyl Mercaptan

Parameter	Value	Reference
Synonyms	Ethanethiol; ethyl sulfhydrate; ethylthioalcohol thioethanol; thioethyl alcohol; mercaptoethane	HSDB 2011
CAS registry no.	75-08-1	HSDB 2011
Chemical formula	C_2H_5SH	HSDB 2011
Molecular weight	62.14	HSDB 2011
Physical state	Colorless liquid	O'Neil et al. 2006
Odor	Garlic-, leek-, or skunk-like	O'Neil et al. 2006; NIOSH 2011
Melting point	-147.8°C	HSDB 2011
Boiling point	35.1°C	HSDB 2011
Flash point	-48.3°C (closed cup)	HSDB 2011
Density/Specific gravity	0.8315 at 25°C	HSDB 2011
Solubility	15,603 mg/L at 25°C in water, soluble in acetone, dilute alkali, alcohol, ether, and petroleum naphtha	HSDB 2011
Saturated vapor concentration (neat)	7.0×10^5 ppm (1.8×10^6 mg/m^3) at 25°C	Calculated
Vapor pressure	442 mm Hg at 20°C	HSDB 2011
Incompatibility	Strong oxidizers	NIOSH 2011
Conversion factors in air	1 mg/m^3 = 0.39 ppm 1 ppm = 2.54 mg/m^3	NIOSH 2011

TABLE 1-3 Odor Intensity of Ethyl Mercaptan

		Concentration (ppm)	
Intensity	Description	Trial 1	Trial 2
0	No odor	2.1×10^{-5}	6.0×10^{-6}
1	Detectable	9.7×10^{-4}	2.6×10^{-4}
2	Faint	4.5×10^{-2}	1.1×10^{-2}
3	Median, easily noticeable	2.1×10^{0}	4.9×10^{-1}
4	Strong	9.7×10^{1}	2.1×10^{1}
5	Most intense	4.5×10^{3}	9.20×10^{2}

Source: Adapted from Katz and Talbert 1930.

Wilby (1969) exposed three individuals to ethyl mercaptan at 12 concentrations representing a 100-fold range. An odor recognition threshold was determined for each subject on the basis of three trials. The mean odor-threshold concentration for ethyl mercaptan was 4.0×10^{-4} ppm, with a standard deviation of 2.6×10^{-4} ppm and a coefficient of variation of 0.65. No other effects were noted.

Blinova (1965) conducted a series of experiments whereby a total of nine human subjects inhaled ethyl mercaptan through a mask connected to a 1,000-L chamber in which a known concentration of ethyl mercaptan had been established. No other information on atmosphere generation or analytic methods was provided. The concentration range of minimum perceptible odor was 2.2×10^{-3} to 1.1×10^{-2} ppm, and the range of imperceptible odor (olfactory fatigue) was reported as 1.8×10^{-3} to 7.2×10^{-3} ppm. Other experimental protocols and results from this study are summarized in Table 1-4.

NIOSH (1978) cites an Italian study wherein humans (no details provided) experienced olfactory fatigue and mucosal irritation during experimental exposure to ethyl mercaptan at 4 ppm (1 mg/m^3) for 3 h/day for 5 days. These effects were transient with cessation of exposure. Subjects exposed at 0.4 ppm did not experience these effects (Gobbato and Terribile 1968). This Italian-language study provides support for the effect levels reported by Blinova (1965).

Amoore and Hautala (1983) reported an odor threshold of 7.6×10^{-4} ppm for ethyl mercaptan. This value is the geometric mean calculated from reliable published odor threshold values.

Nagata (2003) reported an odor threshold of 8.7×10^{-6} ppm for ethyl mercaptan. This value was determined by a validated method and included a butanol standard for comparison. Therefore, it is considered most appropriate for calculation of the level of distinct odor awareness (LOA).

TABLE 1-4 Effects of Ethyl Mercaptan in Humans

Concentration (ppm)	Duration	Subjects	Effects
4.0	3 h/d for 10 d	1 female	Odor, olfactory fatigue, mucosal irritation
0.4	3 h/d for 10 days (one month after above exposure)	1 female	None
4.0	3 h/d for 5 d	2 subjects (sex not reported)	Odor, olfactory fatigue, mucosal irritation
4.0	3 h/d for 5 d (one month after above exposure)	2 subjects (sex not reported)	Same as above, but less pronounced
0.4	3 h/d for 5 d	2 subjects (sex not reported)	None
0.4	3 h/d for 5 d (one month after above exposure)	2 subjects (sex not reported)	None

Source: Blinova 1965.

The LOA for ethyl mercaptan is 1.4×10^{-4} ppm (see Appendix C for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure to ethyl mercaptan from its odor; however, the potential for odor fatigue should also be considered (Shertzer 2012).

2.2.2. Case Report

Twenty-eight male and two female high school students (16- to 18-years old), whose classroom was connected by a door to a chemical storeroom, were accidentally exposed to ethyl mercaptan vapor during morning classes (Pichler 1918). The class was dismissed approximately 1 h after the students began complaining about a bad odor emanating from the adjacent room. Ten students (eight male and two female) complained of dull headache, general discomfort, and abdominal pain, and three students vomited and had diarrhea. All symptoms resolved by the afternoon, and the students reportedly slept normally that night. The class met in the same room the next day for 3 h. Even though the classroom and storeroom had been ventilated, eight of the students with symptoms the previous day developed headaches, but to a lesser degree. Two of the students did not return to school for several days. Examination of one male student showed "changes" around the eyes and a palpable liver, and protein, erythrocytes, and a few leukocytes were detected in the urine. There were no epithelial cells or casts in the urine and the other urinary parameters returned to normal within 5-6 weeks. It was estimated that 3 g of ethyl mercaptan had vaporized in 325-m^3 rooms resulting in an approximate concentration of 4 ppm.

2.2.3. Experimental Study

Shibata (1966b) exposed two adult men to ethyl mercaptan at 50 ppm for 20 min and one adult man to 112 ppm for 20 min. Respiration frequency, pulse rate, and blood pressure were monitored continuously for 10 min before and throughout exposure. In one subject exposed at 50 ppm, breathing frequency decreased immediately with exposure and returned to the pre-exposure inhalation rate after termination of exposure. The second subject exposed at 50 ppm experienced no change in breathing rate. The subject exposed at 112 ppm had a slightly irregular and decreased breathing rate. Minute volume and tidal volume increased in all three subjects. Pulse rate increased slightly in only one subject (50 ppm), and there was no effect on blood pressure and no electrocardiographic abnormalities in any subject. The only subjective response was odor recognition only during the first few breaths, suggesting that olfactory fatigue and accommodation occurred.

2.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies of human exposure to ethyl mercaptan were not available.

2.4. Genotoxicity

Genotoxicity studies of human exposure to ethyl mercaptan were not available.

2.5. Carcinogenicity

Carcinogenic studies of human exposure to ethyl mercaptan were not available.

2.6. Summary

Data on human exposure to ethyl mercaptan are limited. Case reports of deaths from accidental exposure to ethyl mercaptan were not available. Nonlethal toxicity data include a case report where high school students accidentally exposed to ethyl mercaptan experienced reversible dull headache, general discomfort, abdominal pain, vomiting, and diarrhea. Other data included odor-detection (identification) and olfactory-fatigue data but no accompanying health effects information, and a study showing slight changes in breathing rate in three individuals exposed to ethyl mercaptan for 20 min. Atmospheric generation and exposure concentration parameters were not described in detail for any of the human studies. Data on developmental and reproductive toxicity, genotoxicity, and carcinogenicity in humans were not available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

Fairchild and Stokinger (1958) exposed groups of 10 Swiss-derived male mice (body weight 25-28 g) to ethyl mercaptan at 2,600, 3,150, 3,573, 4,438, or 4,832 ppm for 4 h, followed by a 15-day observation period. Vapor generation was achieved by either bubbling a stream of nitrogen gas through a midget fritted-glass bubbler, which contained liquid ethyl mercaptan, or by passage of nitrogen into a borosilicate glass nebulizer containing the ethyl mercaptan. Target concentrations were maintained in an 18-L glass chamber by varying the ratio of volume flow of compressed air and compressed nitrogen. Ethyl mercaptan concentrations during exposure periods were measured by absorption of vapors in

either isopropyl alcohol or acetone containing an excess of silver nitrate and titrating the uncombined silver amperometrically. Chamber concentrations during tests were uniform after the first 30 min; mean variation for all exposures was approximately 4%. Clinical signs included increased respiration and restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of a prone position, and mild to heavy sedation. Animals exposed to "maximal lethal concentrations" typically died from respiratory arrest during exposure or shortly after removal from the chamber. Animals exposed to "minimal lethal concentrations" typically died while in a semiconscious condition of "long duration". Surviving animals often remained in a semiconscious state of sedation and lethargy for 4- to 6-h post-exposure before showing signs of recovery. An LC_{50} value (lethal concentration, 50% lethality) of 2,770 ppm, LC_{05} value (lethal concentration, 5% lethality) of 2,498 ppm, and LC_{01} value of 2,250 ppm were calculated by the method of Litchfield and Wilcoxon (1949). A BMC_{01} (benchmark concentration with 1% response) of 1,921 ppm and $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 1,545 ppm were also calculated. Mortality data are summarized in Table 1-5.

3.1.2. Rats

Fairchild and Stokinger (1958) exposed groups of five or six Wistar-derived male rats (body weight 180-220 g) to ethyl mercaptan at 2,600, 3,150, 3,573, 4,438, 4,832, 4,868, 5,100, or 5,125 ppm for 4 h, followed by a 15-day observation period. Vapor generation and test chamber analysis is similar to that described for studies in mice (see Section 3.1.1). Clinical signs included increased respiration and restlessness (hyperactivity), incoordinated movement, staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of a prone position, and mild to heavy sedation. Animals exposed to "maximal lethal concentrations" typically died from respiratory arrest during exposure or shortly after removal from the chamber. Animals exposed to "minimal lethal concentrations" typically died while in a semiconscious condition of "long duration". Surviving animals often remained in a semiconscious state of sedation and lethargy for 4- to 6-h post-exposure before showing signs of recovery. An LC_{50} value of 4,420 ppm, LC_{05} value of 4,120 ppm, and LC_{01} value of 3,808 ppm were calculated by the method of Litchfield and Wilcoxon (1949). Mortality data are summarized in Table 1-5.

Fairchild and Stokinger (1958) also administered ethyl mercaptan by oral gavage or intraperitoneal injection to Wistar-derived male rats, followed by 15-day observation periods. An oral LD_{50} (lethal dose, 50% mortality) of 682 mg/kg and an intraperitoneal LD_{50} of 226 mg/kg were reported.

TABLE 1-5 Mortality in Mice and Rats Exposed to Ethyl Mercaptan for 4 Hours

Concentration (ppm)	Mice	Rats
2,600	4/10	0/5
3,150	7/10	0/5
3,573	10/10	0/5
4,438	10/10	1/5
4,832	10/10	4/6
4,868	–	2/5
5,100	–	5/5
5,125	–	2/6
LC_{01}	2,250 ppm	3,808 ppm
LC_{05}	2,498 ppm	4,120 ppm
LC_{50}	2,770 ppm	4,420 ppm

Source: Adapted from Fairchild and Stokinger 1958.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of three to five male Holtzman or Sprague-Dawley rats (weighing 285-325 g) were individually exposed in a 4-L glass desiccator to ethyl mercaptan at concentrations of 2.7-3.8% (approximately 27,000-38,000 ppm) for 15 min or less (Zieve et al. 1974). The target concentrations were achieved by injecting the required amount of ethyl mercaptan through a rubber septum in the lid of the chamber. The concentration of ethyl mercaptan in the chamber atmosphere was not analyzed, rather concentrations were calculated from the dose injected. A CD_{50} value (concentration causing coma induction in 50% of animals, as measured by complete loss of the righting reflex) of 3.3% (33,000 ppm) was determined. No rats lost the righting reflex at ethyl mercaptan concentrations of about 3.0% (30,000 ppm), but all rats lost the righting reflex at about 3.7% (37,000 ppm). The rats exhibited a brief excitement phase before becoming "groggy". At the CD_{50}, the excitement phase lasted about 2 min, the groggy and lethargic phase lasted about 1 min, and finally frank coma ensued within 1 to 2 min. At lower concentrations, the excitement and pre-coma phases were prolonged and at higher concentrations, the entire sequence occurred more quickly. When rats were removed from exposure immediately after becoming comatose, the coma generally did not last more than 30 min and the rats appeared and remained alert and active on recovery. Blood concentrations of ethyl mercaptan found in comatose animals were greater than 200 nmoles/mL; however, there was no clear concentration-response relationship between inhaled concentrations and blood levels.

No mortality was observed in rats exposed head only to ethyl mercaptan at 991 ppm for 4 h or in rats exposed whole body at 27 ppm for 4 h (Shertzer 2012).

3.2.2. Rabbits

Shibata (1966a) exposed groups of two male rabbits (weighing 3 kg) to ethyl mercaptan at 10, 100, or 1,000 ppm by breathing mask for 20 min. Breathing rate (measured by observed thorax movement) and minute expiratory volume (measured by wet spirometry) were monitored throughout the exposure periods. Tidal volume was then calculated by dividing the minute expiratory volume by the breathing rate. At 100 and 1,000 ppm, respiratory rate and expiratory volume were decreased and tidal volume was increased. Approximate changes in respiratory function parameters (estimated from graphs) at the end of the exposure period in the 1,000-ppm group were: 20% decrease in expiratory volume, 40% decrease in respiratory rate, and 40% increase in tidal volume. Approximate changes in the 100 ppm group were: 10% decrease in expiratory volume, 10% decrease in respiratory rate, and 20% increase in tidal volume. The respiratory changes in rabbits at 1,000 and 100 ppm for 20 min are suggestive of odor avoidance. At 10 ppm, respiratory rate and ventilation rate showed unstable fluctuation and tidal volume was increased slightly during the last half of the exposure period. All respiratory indicators returned to pre-exposure levels by the end of the 35-min observation period, except for the respiratory rate of animals exposed at 1,000 ppm, which was still decreased by approximately 25%. The changes in breathing rate and tidal volume in rabbits exposed to ethyl mercaptan at 100 ppm or higher for 20 min are similar to the effects reported in the human study by the same investigator (Shibata 1966b). However, the authors note (Shibata 1966b, translated by OPPT):

> It is difficult to compare the rabbit study and human study. The rabbit's body weight is about one-twentieth that of humans and the expiratory volume is about one-ninth that of humans; therefore, rabbit's expiratory volume per body weight is greater than humans, which indicates that the rabbit's inspiratory volume is about twice as much as that of humans if they are exposed to the same concentration of gas. Therefore rabbits would be affected more than humans. The differences in respiratory center sensitivity of rabbits and humans should also be considered as well.

Fairchild and Stokinger (1958) instilled ethyl mercaptan (0.1mL) into the conjunctival sac of the right eye of one male New Zealand white rabbit. The left eye served as a control. Slight to moderate irritation was observed and resolved within 48 h.

3.3. Repeated-Exposure Study

Shibata ((1966a) exposed four male rabbits (weighing 3 kg) to ethyl mercaptan at 1,000 ppm by breathing mask for 20 min/day for 9 days in a 10-day period. No significant treatment-related effects on urinary sulfate, urine volume, erythrocyte or leukocyte counts, or body weight were found.

3.4. Developmental and Reproductive Toxicity

Developmental or reproductive toxicity studies of animal exposure to ethyl mercaptan were not available.

3.5. Genotoxicity

Ethyl mercaptan was negative in an Ames *Salmonella typhimurium* assay (Hazleton Laboratories 1984). It was positive in a sister-chromatid-exchange assay in cultured Chinese hamster ovary cells with or without metabolic activation (Hazleton Laboratories 1984), and in a forward mutation assay in cultured mouse lymphoma cells without activation (Hazleton Laboratories 1983).

3.6. Carcinogenicity

Carcinogenicity studies of ethyl mercaptan in animals were not available.

3.7. Summary

Animal toxicity data for ethyl mercaptan are limited. Lethality studies are available for rats and mice, and suggest a steep concentration-response curve for ethyl mercaptan. For example, lethality was 40% and 100% in rats exposed for 4 h to ethyl mercaptan at 2,600 ppm and 3,573 ppm, respectively. The 4-h LC_{50} value for rats was 4,420 ppm, and the 4-h LC_{01} value was 3,808 ppm. In mice, the 4-h LC_{50} value was 2,770 ppm, and the 4-h LC_{01} value was 2,250 ppm (Fairchild and Stokinger 1958). Clinical observations were indicative of central nervous system depression and respiratory arrest, and included changes in respiration, restlessness (hyperactivity), incoordinated movement, staggering gait, muscular weakness, skeletal muscle paralysis, light to severe cyanosis, and coma. Coma-induction data also suggest a steep concentration-response curve for ethyl mercaptan. No coma-induction was observed in rats exposed at 30,000 ppm for up to 15 min, but coma was induced in 50% of rats exposed at 33,000 ppm and 100% of rats exposed at 37,000 ppm (Zieve et al. 1974). The limited genotoxicity data are equivocal. No reproductive or developmental toxicity data or carcinogenicity studies were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Snow (1957) demonstrated that ethyl mercaptan was rapidly absorbed and distributed evenly throughout the body tissues of mice and guinea pigs after oral or subcutaneous administration. Excretion occurred mainly via the kidney as inorganic sulfate. Organic metabolites, ethyl methyl sulfone, and an unidentified product accounted for 10-20% of the sulfur excreted in the urine. There was little fecal excretion, but approximately 14% of the dose was excreted in the breath. It was hypothesized that oxidation converted the thiol to the sulphide and then to the sulfone.

Ethyl mercaptan is a metabolite of the human body and is excreted in the breath of normal individuals; patients with advanced liver disease excrete it at higher concentrations. Chen et al. (1970) measured ethyl mercaptan in the breath of normal subjects and in patients with liver cirrhosis or in hepatic coma after fasting and after ingestion of methionine (8-12 g),. Concentrations in the breath were 1.1-12.3 ng/L in seven normal, fasting subjects, and increased about 1.5-fold after daily ingestion of methionine for 7 days. In cirrhotic patients, the average ethyl mercaptan concentration was 11.5 ng/L. After ingestion of methionine, there was no significant increase in the amount of ethyl mercaptan in the breath of patients with liver disease.

4.2. Mechanism of Toxicity

Ethyl mercaptan acts similar to hydrogen sulfide and cyanide by interrupting electron transport through inhibition of cytochrome oxidase. Ethyl mercaptan decreased Na,K-ATPase in the rat brain (Foster et al. 1974). Vahlkamp et al. (1979) investigated the effects of ethyl mercaptan in vitro in isolated rat hepatocytes, isolated mitochondria from rat liver and brain, and submitochondrial particles from ox heart. Ethyl mercaptan inhibited gluconeogenesis and ureogenesis from various substrates in rat hepatocytes, decreased cellular ATP content, and caused an increase in the reduction state of mitochondria. It also inhibited respiration in rat liver mitochondria with several substrates, in the presence of ADP and phosphate or in the presence of an uncoupling agent, and inhibited respiration in rat brain mitochondria. In submitochondrial particles of ox heart, ethyl mercaptan inhibited electron transfer between cytochrome *c* and oxygen, and purified cytochrome *c* oxidase was inhibited by ethyl mercaptan in a non-competitive manner.

As a result of the electron transfer blockage, oxidative phosphorylation and aerobic metabolism are compromised, peripheral tissue P_{O2} increases, and the unloading gradient for oxyhemoglobin decreases. High concentrations of oxyhemoglobin are thus found in the venous return, resulting in flushed skin and mucous membranes. Lactic acidemia occurs as a result of the increased demand placed on glycolysis.

4.3. Structure-Activity Relationships

Rat lethality data suggest that the acute toxicity of ethyl mercaptan is much less than that of methyl mercaptan (approximately 6-fold lower) or hydrogen sulfide (approximately 10-fold lower) (see Table 1-6). For example, the 4-h LC_{50} value for ethyl mercaptan was 4,420 ppm, whereas the corresponding values for methyl mercaptan and hydrogen sulfide were 675 ppm and 444 ppm, respectively (Tansy et al. 1981).

TABLE 1-6 Comparative Toxicity of Selected Mercaptans

Compound	Rat Intraperitoneal LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	4-h Inhalation LC_{50} (ppm) Rats	Mice	Reference
Hydrogen sulfide	–	–	444	–	Tansy et al. 1981
Methyl mercaptan	–	–	675	1,664	Horiguchi 1960 (mice); Tansy et al. 1981 (rats)
Ethyl mercaptan	*226*	*682*	*4,420*	*2,770*	Fairchild and Stokinger 1958
Propyl mercaptan	515	1,790	7,200	4,010	Fairchild and Stokinger 1958
Isobutyl mercaptan	917	7,168	>25,000	>25,000	Fairchild and Stokinger 1958
tert-Butyl mercaptan	590	4,729	22,200	16,500	Fairchild and Stokinger 1958
n-Butyl mercaptan	399	1,500	4,020	2,500	Fairchild and Stokinger 1958
n-Hexyl mercaptan	396	1,254	1,080	528	Fairchild and Stokinger 1958
Phenyl mercaptan	9.8	46.2	33	28	Fairchild and Stokinger 1958
Benzyl mercaptan	373	493	>235	178	Fairchild and Stokinger 1958
tert-Octyl mercaptan	12.9	83.5	51 (males)	47 (males)	Fairchild and Stokinger 1958

4.4. Concurrent Exposure Issues

Because cyanide, hydrogen sulfide, methyl mercaptan, and ethyl mercaptan are all cytochrome oxidase inhibitors, an interaction might be possible if individuals were simultaneously exposed to two or more or more of these chemicals (Smith 1991). Such interactions could result in lower lethal exposure concentrations for ethyl mercaptan.

Ethyl mercaptan may also have a role in facilitating the toxic effects of ammonia and fatty acids relative to hepatic failure in humans (Zieve et al. 1974).

4.5. Species Differences

Because of the limited data available on ethyl mercaptan, a definitive assessment of species variability is not possible. However, the data suggest that mice are approximately 1.6-fold more sensitive than rats to lethality from inhalation exposure to ethyl mercaptan.

4.6. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate to empirically derive a chemical-specific scaling exponent for ethyl mercaptan. So, temporal scaling was performed using default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations. See Appendix A.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

One of two adult males exposed to ethyl mercaptan at 50 ppm for 20 min had decreased respiratory frequency (Shibata 1966b). Mucosal irritation occurred in one female exposed at 4 ppm for 3 h/day for 10 days and in two males exposed at 4 ppm for 3 h/day for 5 days (Blinova 1965); no effects were reported at 0.4 ppm. These findings are supported by the study of Gobbato and Terribile (1968). That study reported that mucosal irritation and olfactory fatigue returned to normal after cessation of exposure.

5.2. Animal Data Relevant to AEGL-1

Rabbits exposed to ethyl mercaptan at 100 or 1,000 ppm for 20 min exhibited decreased respiratory rate and expiratory volume, indicative of odor avoidance, but no significant effects was observed at 10 ppm (Shibata 1966a).

5.3. Derivation of AEGL-1 Values

AEGL-1 values for ethyl mercaptan were based on a no-effect level of 10 ppm for respiratory changes associated with odor avoidance in rabbits exposed for 20 min (Shibata 1966a). Two uncertainty factors of 3 were applied to account for interspecies differences and intraspecies variability. These values are sufficient because a full factor of 10 for either uncertainty would yield AEGL-1 values of 0.3 ppm or less, concentrations that are inconsistent with human data. A single AEGL-1 value was used for all exposure durations because prolonged exposure to ethyl mercaptan is not expected to result in an enhanced effect. AEGL-1 values for ethyl mercaptan are presented in Table 1-7, and calculations are presented in Appendix A.

The AEGL-1 value of 1 ppm may appear to be too low in the context of the acute lethality information on ethyl mercaptan (see Table 1-6). However, the respiratory effects on which the AEGL-1 values are based appear be the result of odor avoidance rather than evidence of early effects that lead to lethality. In this case, comparison with LOA values is more applicable than a comparison with 4-h LC_{50} values in rats. The LOA for ethyl mercaptan is 1.4×10^{-4} ppm. The LOA for the related chemical methyl mercaptan (1.9×10^{-2} ppm) is greater than the LOA for ethyl mercaptan, which supports AEGL-1 values for ethyl mercaptan (1 ppm) being lower than the AEGL-1 values for methyl mercaptan (11 pm, see Chapter 2). Even though ethyl mercaptan has an extremely unpleasant odor, olfactory desensitization or olfactory fatigue may occur at high concentrations. Therefore, odor and symptoms of irritation may not adequately provide warning of high concentrations of ethyl mercaptan (Shertzer 2012).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Ten students complained of dull headache, general discomfort, and abdominal pain, and three students vomited and had diarrhea after accidentally being exposed to ethyl mercaptan at school (Pichler 1918). However, no definitive information on concentration or duration of exposure were available.

6.2. Animal Data Relevant to AEGL-2

No animal data on ethyl mercaptan relevant for deriving AEGL-2 values were available.

TABLE 1-7 AEGL-1 Values for Ethyl Mercaptan

10 min	30 min	1 h	4 h	8 h
1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)

6.3. Derivation of AEGL-2 Values

No relevant inhalation data on ethyl mercaptan consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values were based on a one-third reduction in the AEGL-3 values, which this is considered an estimate of a threshold for inability to escape and is considered appropriate because of the steep concentration-response curve for ethyl mercaptan (see Table 1-5; NRC 2001). The AEGL-2 values are supported by the 15-min no-effect level of 30,000 ppm for loss of righting reflex in rats reported by by Zieve et al. (1974), and a 20-min no-effect level of 112 ppm reported for a single human (Shibata 1966b). AEGL-2 values for ethyl mercaptan are presented in Table 1-8, and calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on ethyl mercaptan relevant to AEGL-3 values were available.

7.2. Animal Data Relevant to AEGL-3

A 4-h LC_{50} value of 2,770 ppm, LC_{05} value of 2,498 ppm, and LC_{01} value of 2,250 ppm were calculated for mice, and a 4-h LC_{50} value of 4,420 ppm, LC_{05} value of 4,120 ppm, and LC_{01} value of 3,808 ppm were calculated for rats (Fairchild and Stokinger 1958).

7.3. Derivation of AEGL-3

The LC_{01} of 2,250 ppm in mice exposed to ethyl mercaptan for 4 h (Fairchild and Stokinger 1958) was used to derive AEGL-3 values. The mouse data were chosen over the rat data because mice are more sensitive (LC_{01}, LC_{05}, and LC_{50} estimates were lower in mice than in rats; see Table 1-5) and because more mice were tested.

An intraspecies uncertainty factor of 3 was considered sufficient to account for intraindividual variability because of the steep concentration-response curve for lethality (see Table 1-5), which implies limited individual variability. An interspecies uncertainty factor of 3 was also be applied because the limited data suggest that the mouse is the most sensitive species (see Section 4.5). Although an interspecies uncertainty factor of 10 might normally be applied because of the limited data, a total uncertainty factor of 30 would yield AEGL-3 values approaching or equivalent to the AEGL-3 values for hydrogen sulfide. For example, if a total uncertainty factor of 30 is applied, an 8-h

TABLE 1-8 AEGL-2 Values for Ethyl Mercaptan

10 min	30 min	1 h	4 h	8 h
150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)

AEGL-3 value for ethyl mercaptan would be 37 ppm, which is slightly higher than the 8-h AEGL-3 value for hydrogen sulfide of 31 ppm (NRC 2010). Because a robust database exists for hydrogen sulfide and because data suggest that ethyl mercaptan is less toxic than hydrogen sulfide (see Table 1-6), it would be inconsistent with the total data set to have AEGL-3 values for ethyl mercaptan that are in the range of the AEGL-3 values for hydrogen sulfide. Furthermore, use of a total uncertainty factor of 30 would yield a 30-min AEGL-3 value of 150 ppm, which is inconsistent with the finding that a single human exposed to ethyl mercaptan at 112 ppm for 20 min exhibited only a slightly irregular and decreased breathing rate (Shibata 1966b). The conservative AEGL-3 values for short exposure periods are supported by the Zieve et al. (1974) study, wherein ethyl mercaptan at 30,000 ppm for 15 min produced no loss of righting reflex in rats and 33,000 ppm produced loss of righting reflex in 100% of rats. Thus, the total uncertainty factor is 10.

The concentration-time relationship for many irritant and systemically-acting vapors and gases is described in Section 4.6. The 30-min AEGL-3 value is adopted as the 10-min value because of the uncertainties associated with extrapolating a 4-h exposure to a 10-min value. AEGL-3 values for ethyl mercaptan are presented in Table 1-9, and calculations are presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Table 1-10 summarizes the AEGL values for ethyl mercaptan. AEGL-1 values were based on a no-effect level for respiratory changes associated with odor avoidance in rabbits exposed for 20 min. In the absence of relevant data and because of the steep concentration-response curve, AEGL-2 values were calculated as one-third of the AEGL-3 values. These calculations are estimated thresholds for the inability to escape. AEGL-3 values are based on the LC_{01} of 2,250 ppm in mice exposed to ethyl mercaptan for 4 h (Fairchild and Stokinger 1958).

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to ethyl mercaptan are presented in Table 1-11.

TABLE 1-9 AEGL-3 Values for Ethyl Mercaptan

10 min	30 min	1 h	4 h	8 h
450 ppm (1,100 mg/m^3)	450 ppm (1,100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)

TABLE 1-10 AEGL Values for Ethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)
AEGL-2 (disabling)	150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)
AEGL-3 (lethal)	450 ppm (1,100 mg/m^3)	450 ppm (1,100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)

TABLE 1-11 Standards and Guidelines for Ethyl Mercaptan

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)
AEGL-2	150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)
AEGL-3	450 ppm (1,100 mg/m^3)	450 ppm (1,100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)
IDLH (NIOSH)[a]		500 ppm (1300 mg/m^3)			
TLV-TWA (ACGIH®)[b]					0.5 ppm (1.3 mg/m^3)
REL-C (NIOSH)[c]	0.5 ppm (1.3 mg/m^3)	0.5 ppm (1.3 mg/m^3)	0.5 ppm (1.3 mg/m^3)	0.5 ppm (1.3 mg/m^3)	0.5 ppm (1.3 mg/m^3)
PEL-C (OSHA)[d]	10 ppm (25 mg/m^3)	10 ppm (25 mg/m^3)	10 ppm (25 mg/m^3)	10 ppm (25 mg/m^3)	10 ppm (25 mg/m^3)
MAK (Germany)[e]					0.5 ppm (1.3 mg/m^3)
MAC (The Netherlands)[f]					0.4 ppm (1 mg/m^3)

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health [NIOSH 1994]) represents a maximum concentration from which, in the event of respirator failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health effects.

[b]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2004, 2012]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c] REL-C (recommended exposure limit - ceiling, National Institute for Occupational Safety and Health [NIOSH 2011]) is a ceiling value that should not be exceeded at any time during a workday.
[d]PEL-C (permissible exposure limit - ceiling, Occupational Safety and Health Administration (29 CFR 1910.1000 [2006]) is the concentration that should not be exceeded at any time.
[e]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association] DFG 2012) is defined analogous to the ACGIH TLV-TWA.
[f]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

The AEGL-1 values exceed the recommended exposure limit (REL) of the National Institute for Occupational Safety and Health (NIOSH), the threshold limit value (TLV) of the American Conference of Governmental Industrial Hygienists, the Dutch maximal accepted concentration (MAC), and the German maximum workplace concentration (MAK) by a factor of two. The basis of the MAC and MAK values are not available, but the ACGIH (2004) documentation states that the TLV value is based on the very limited human data indicating that irritation of the mucous membranes, lacrimation, and the central nervous system effects were seen at 4 ppm, but is "more experience-based than experimentally derived". Similarly, the NIOSH REL (1978) value was derived:

> based on the effects in humans—headache, nausea, and irritation—of exposure to the chemical at 4 ppm for 4 h/day (Blinova 1965). . . . The minimal effects of olfactory fatigue and mucosal irritation (Gobbatto and Terribile 1968) observed when individuals were exposed to 4 ppm ethanethiol ceased when the inhalation exposure was stopped, and no effects were observed at 0.4 ppm exposure. Because there is no evidence that adherence to the TLV of 0.5 ppm has resulted in any cases of toxicity, NIOSH recommends that the concentration of C1-C12, C16, C18 alkane thiols, or cyclohexanethiol, or any combination of these thiols, in the workplace air should not exceed 0.5 ppm as a ceiling concentration for any 15-min period (pp. 83-84).

The 30-min AEGL-3 value of 450 ppm is very similar to the NIOSH immediately dangerous to life or health value of 500 ppm (NIOSH 1994). That value is based on acute inhalation toxicity in animals as reported by Fairchild and Stokinger (1958), the same study used to derive AEGL-3 values.

8.3. Data Adequacy and Research Needs

The database on acute inhalation studies in animals is sparse, and the few available studies are dated and poorly described. Human studies of short-term

exposure to ethyl mercaptan lack data on exposure concentrations. There were insufficient data to establish a chemical-specific time-scaling relationship for ethyl mercaptan.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR ETHYL MERCAPTAN

Derivation of AEGL-1 Values

Key study:	Shibata, Y. 1966a. Studies on the influence of ethylmercaptan upon the living body: II. On the respiratory function and clinical findings in rabbits which inhaled ethyl mercaptan gas. Shikoku Acta Med. 22(6): 834-843.
Toxicity end point:	No-effect level for respiratory changes associated with odor avoidance in rabbits, 10 ppm for 20 min
Scaling:	Values held constant across time
Uncertainty factor:	3 for interspecies differences 3 for intraspecies variability
All AEGL-1 durations:	10 ppm ÷ 10 = 1.0 ppm

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values and because ethyl mercaptan has a steep concentration-response curve, AEGL-3 values were divided by 3 to estimate a threshold for inability to escape.

10-min AEGL-2:	450 ppm ÷ 3 = 150 ppm
30-min AEGL-2:	450 ppm ÷ 3 = 150 ppm
1-h AEGL-2:	360 ppm ÷ 3 = 120 ppm
4-h AEGL-2:	230 ppm ÷ 3 = 77 ppm
8-h AEGL-2:	110 ppm ÷ 3 = 37 ppm

Derivation of AEGL-3 Values

Key study:	Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Toxicity end point:	4-h LC_{01} of 2,250 ppm was used as an estimated lethality threshold in mice.
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations); time scaling not performed for the 10-min AEGL-3 value because of the uncertainty in extrapolating a 4 h point of departure to a 10-min value. $(2{,}250 \text{ ppm})^3 \times 4 \text{ h} = 4.56 \times 10^{10}$ ppm-h $(2{,}250 \text{ ppm})^1 \times 4 \text{ h} = 9{,}000$ ppm-h
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10-min AEGL-3:	450 ppm (30-min AEGL-3 value adopted)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 4.56 \times 10^{10}$ ppm-h $C^3 = 9.12 \times 10^{10}$ ppm C = 4,501 ppm 4,501 ppm ÷ 10 = 450 ppm
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 4.56 \times 10^{10}$ ppm-h $C^3 = 4.56 \times 10^{10}$ ppm C = 3,572 ppm 3,572 ppm ÷ 10 = 360 ppm
4-h AEGL-3:	$C^3 \times 4 \text{ h} = 4.56 \times 10^{10}$ ppm-h $C^3 = 1.14 \times 10^{10}$ ppm C = 2,251 ppm 2,251 ppm ÷ 10 = 230 ppm
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 9{,}000$ ppm-h $C^1 = 1{,}125$ ppm C = 1,125 ppm 1,125 ppm ÷ 10 = 110 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYL MERCAPTAN

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)

Key reference: Shibata, Y. 1966a. Studies on the influence of ethyl mercaptan upon the living body: II. On the respiratory function and clinical findings in rabbits which inhaled ethyl mercaptan gas. Shikoku Acta. Med. 22(6):834-843.

Test species/Strain/Sex/Number: Rabbits, males, 2/group

Exposure route/Concentrations/Durations: Inhalation; 10, 100, 1,000 ppm for 20 min

Effects:
10 ppm: Unstable fluctuation in respiratory rate.
100 ppm: Decreased respiratory rate (10%) and expiratory volume (10%); increased tidal volume (20%).
1,000 ppm: Decreased respiratory rate (40%) and expiratory volume (20%); increased tidal volume (40%).

End point/Concentration/Rationale: No-effect level for respiratory changes associated with odor avoidance, 10 ppm

Uncertainty factors/Rationale: Use of the full factor of 10 for either interspecies differences or intraspecies variability would yield AEGL-1 values of 0.3 ppm or lower, concentrations that are inconsistent with human data.
Interspecies: 3
Intraspecies: 3

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Values held constant across time because effects are not expected to vary greatly over time.

Data adequacy: The study was considered adequate for derivation of AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)

Data adequacy: Data inadequate to derive AEGL-2 values. AEGL-3 values were divided by 3 to estimate thresholds for the inability to escape. This calculation is supported by the steep concentration-response curve for ethyl mercaptan (lethality in mice exposed for 4 h was 40% at 2,600 ppm, 50% at 2,770 ppm, and 100% at 3,573 ppm; in rats, the LC_{01} value was 3,808 and the LC_{50} value was 4,420 ppm).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
450 ppm (1,100 mg/m^3)	450 ppm (1,100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)

Reference: Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Test species/Strain/Sex/Number: Mice, Swiss-derived, male, 10/group

Exposure route/Concentrations/Durations: Inhalation; 0, 2,600, 3,150, 3,573, 4,438, or 4,832 ppm for 4 h

Effects:

Concentration (ppm)	Mortality
0	0/10
2,600	4/10
3,150	7/10
3,573	10/10
4,438	10/10
4,832	10/10

LC_{50} = 2,770 ppm
LC_{01} = 2,250 ppm

End point/Concentration/Rationale: Estimated lethality threshold in mice, 4-h LC_{01} of 2,250 ppm

Uncertainty factors/Rationale:
Intraspecies: 3, considered sufficient because of steep concentration-response curve (lethality in mice exposed for 4 h was 40% at 2,600 ppm, 50% at 2,770 ppm, and 100% at 3,573 ppm; in rats, the LC_{01} value was 3,808 and the LC_{50} value was 4,420 ppm), which implies limited individual variability.
Interspecies: 3, because the mouse is the most sensitive species. Also, although an interspecies uncertainty factor of 10 might normally be applied because of limited data, AEGL-3 values calculated with a total uncertainty factor of 30 would lead to values approaching or equivalent to the AEGL-3 values for hydrogen sulfide. For example, if a total uncertainty factor of 30 is applied, an 8-h AEGL-3 value for ethyl mercaptan would be 37 ppm, which is slightly higher than the 8-h AEGL-3 value for hydrogen sulfide of 31 ppm (NRC 2010). Because a robust database exists for hydrogen sulfide and because data suggest that ethyl mercaptan is less toxic than hydrogen sulfide (4-h LC_{50} is 4,420 ppm for ethyl mercaptan and 444 ppm for hydrogen sulfide), it would be inconsistent with the total data set to have AEGL-3 values for ethyl mercaptan that are in the range of the AEGL-3 values for hydrogen sulfide. Furthermore, use of a total uncertainty factor of 30 would yield a 30-min AEGL-3 value of 150 ppm, which is inconsistent with the finding that a single human exposed to ethyl mercaptan at 112 ppm for 20 min exhibited only a slightly irregular and decreased breathing rate (Shibata 1966b).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

(Continued)

AEGL-3 VALUES Continued

Time scaling: $C^n \times t = k$; default value of n = 3 was used for extrapolation to the shorter durations (30 min, 1 h, and 4 h) and n = 1 for extrapolation to the longer duration (8 h). The 30-min value was adopted as the 10-min AEGL-3 value because of the uncertainty associated with extrapolating a 4-h exposure to a 10-min value.
Data adequacy: The study was well conducted and used a sufficient number of animals.

APPENDIX C

DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS FOR ETHYL MERCAPTAN

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure on the basis of odor perception. The LOA derivation follows the guidance of Ruijten et al. (2009).

The odor detection threshold (OT_{50}) for ethyl mercaptan was reported to be 0.0000087 ppm (Nagata 2003).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = k_w \times \log (C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ was used due to the lack of chemical-specific data.

$$3 = 2.33 \times \log (C \div 0.0000087) + 0.5$$
$$\log (C \div 0.0000087) = ([3 - 0.5] \div 2.33)$$
$$\log (C \div 0.0000087) = 1.07$$
$$C = (10^{1.07}) \times 0.0000087$$
$$C = 0.000102 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that, in everyday life, factors such as sex, age, sleep, smoking, upper airway infections, and allergy, as well as distractions, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of $4 \div 3 = 1.33$.

$$LOA = C \times 1.33$$
$$LOA = 0.000102 \text{ ppm} \times 1.33$$
$$LOA = 0.00014 \text{ ppm}$$

APPENDIX D

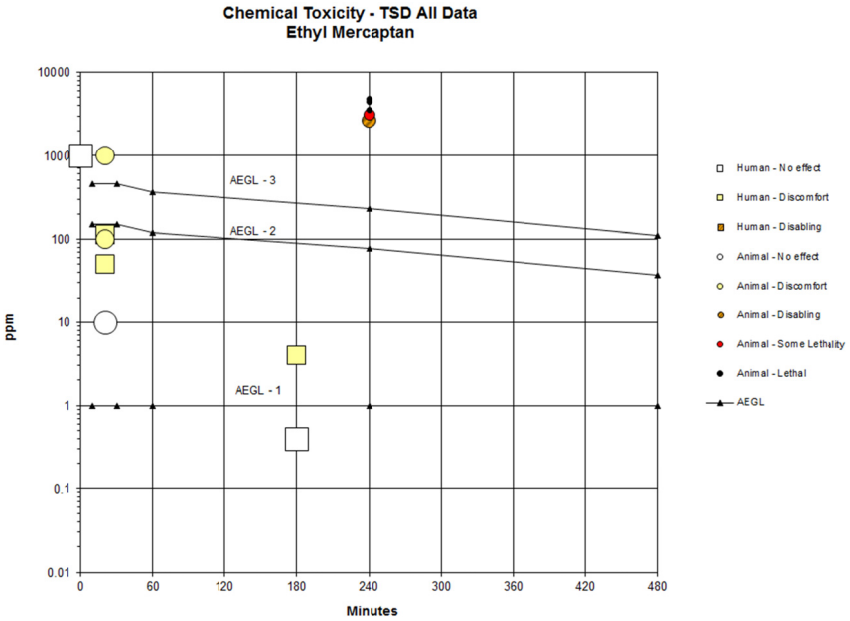

FIGURE D-1 Category plot of toxicity data and AEGL values for ethyl mercaptan.

TABLE D-1 Data Used in Category Plot of AEGL Values for Ethyl Mercaptan

Source	Species	Sex	No. of Exposures	ppm	Min	Category
AEGL-1				1	10	AEGL
AEGL-1				1	30	AEGL
AEGL-1				1	60	AEGL
AEGL-1				1	240	AEGL
AEGL-1				1	480	AEGL
AEGL-2				150	10	AEGL
AEGL-2				150	30	AEGL
AEGL-2				120	60	AEGL
AEGL-2				77	240	AEGL
AEGL-2				37	480	AEGL
AEGL-3				450	10	AEGL
AEGL-3				450	30	AEGL

AEGL-3				360	60	AEGL
AEGL-3				230	240	AEGL
AEGL-3				110	480	AEGL
Shibata 1966a	Rabbit	Male	1	10	20	0
	Rabbit	Male	1	100	20	1
	Rabbit	Male	1	1,000	20	1
Fairchild and Stokinger 1958	Mouse	Male	1	2,600	240	2
	Mouse	Male	1	3,150	240	SL
	Mouse	Male	1	3,573	240	3
	Mouse	Male	1	4,438	240	3
	Mouse	Male	1	4,832	240	3
Katz and Talbert 1930	Human	Male	1	0.00002		0
	Human	Male	1	920		1
Wilby 1969	Human	Male	1	0.0004		0
Blinova 1965	Human	Male	1	4	180	1
Pichler 1918	Human	Male				
Shibata 1966b	Human	Male	1	50	20	1
	Human	Male	1	112	20	1
Amoore and Hautala 1983	Human		1	0.0008		1
Nagata 2003	Human		1	0.00001		1
Zieve et al. 1974	Rats					
	Rats					
Blinova 1965	Human		1	0.4	180	0
NIOSH 1978	Human		5	4.0	180	1
	Human		5	0.4	180	0
Katz and Talbert 1930	Human		1	1,000.0	0.17	0

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

2

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

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

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

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

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

SUMMARY

Methyl mercaptan is a colorless gas with a strong odor. It is used in methionine synthesis and as an intermediate in the manufacture of pesticides, jet fuels, and plastics. It is found in a wide variety of vegetables (such as garlic and onions), in "sour" gas in oil fields, and in coal tar and petroleum distillates. Methyl mercaptan occurs in the human body as a metabolite of the degradation of methionine and other compounds.

Methyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis. Clinical signs of exposure are ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, and vomiting. Paralysis of the locomotor muscles and pulmonary edema have also been observed. Its primary mechanism of action appears to be interference with cytochrome oxidase.

Data on methyl mercaptan were not sufficient to derive AEGL-1 values, so no values are recommended. The level of distinct odor awareness (LOA) for methyl mercaptan is 0.0019 ppm (see Appendix C for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong smell. The LOA should help chemical emergency responders in assessing the public awareness of the exposure on the basis of odor perception.

No robust data on methyl mercaptan consistent with the definition of AEGL-2 were available. Therefore, AEGL-2 values were based on a 3-fold reduction in the AEGL-3 values. These calculations are considered estimated

thresholds for inability to escape and are appropriate because of the steep concentration-response relationship for lethality.

AEGL-3 values for methyl mercaptan were based on the calculated 4-h LC_{01} (lethal concentration, 1% lethality) of 430 ppm for rats (Tansy et al. 1981). An intraspecies uncertainty factor of 3 was applied, and is considered sufficient because of the steepness of the lethality concentration-response relationship, which implies limited individual variability. An interspecies uncertainty factor of 3 was also applied. Although an interspecies uncertainty factor of 10 might normally be applied because of limited data, AEGL-3 values calculated with that larger factor would be inconsistent with the total database. AEGL-3 values would range from 7.3 to 40 ppm if a total uncertainty factor of 30 was used; however, no effects were noted in rats repeatedly exposed to methyl mercaptan at 17 ppm for 3 months. It is unlikely that people exposed to methyl mercaptan in this range for 10 min to 8 h would experience lethal effects. Furthermore, use of a total uncertainty factor of 30 would yield AEGL-3 values 2- to 4-fold lower than the AEGL-3 values for hydrogen sulfide. Because hydrogen sulfide has a robust database and because data suggest that methyl mercaptan is less toxic than hydrogen sulfide, it would be inconsistent with the total data set to derive AEGL-3 values for methyl mercaptan that are below the AEGL-3 values for hydrogen sulfide. Thus, a total uncertainty factor of 10 was used.

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of a chemical-specific exponent, temporal scaling was performed using default values of n = 3 for extrapolating from longer to shorter durations (10 min, 30 min, and 1 h) and n = 1 when extrapolating from shorter to longer durations (8 h).

AEGL values for methyl mercaptan are presented in Table 2-1.

1. INTRODUCTION

Methyl mercaptan is used in methionine synthesis, as an intermediate in the manufacture of pesticides, jet fuels, and plastics, and as a gas odorant to serve as a warning property for odorless but hazardous gases (Farr and Kirwin 1994; Pohanish 2002). Methyl mercaptan is also released from pulp manufacturing plants and in kraft and sulfite mills (Kangas et al. 1984). Concentrations of methyl mercaptan in kraft and sulfite mills may be as high as 15 ppm (Kangas et al. 1984).

Methyl mercaptan is an odorous, colorless gas. The disagreeable odor has been described as garlic-like (Pohanish 2002) or as similar to rotten cabbage (HSDB 2013). It is found in a wide variety of vegetables (such as garlic and onions), in "sour" gas in West Texas oil fields, and in coal tar and petroleum distillates (Farr and Kirwin 1994). Methyl mercaptan occurs in the human body

as a metabolite of the degradation of methionine and other compounds (Binkley 1950; Canellakis 1952). Methyl mercaptan is a major contributor to bad breath in human (NIOSH 1978).

Methyl mercaptan is produced commercially by the reaction of hydrogen sulfide with methanol; production volumes were not found (ATSDR 1992).

The physical and chemical properties of methyl mercaptan are presented in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Methyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis (Farr and Kirwin 1994). Clinical signs of exposure are ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, and vomiting (Deichmann and Gerarde 1973). Paralysis of the locomotor muscles and pulmonary edema have also been observed (NIOSH 1978; Matheson 1982).

Acute hemolytic anemia and methemoglobinemia were found in one male laborer (53-years old) who developed a coma after handling tanks of methyl mercaptan. Transfusions alleviated these hematologic findings. When he arrived at the hospital, his blood pressure ranged from 188/90 to 230/130 mm Hg and his pulse was 120 beats/min. Later, the man was found to have a deficiency of glucose-6-phosphate dehydrogenase. Seizure activity consisted of random myoclonic tremors. On the 28th day in the hospital the man died as the result of emboli in both pulmonary arteries (Shults et al. 1970).

TABLE 2-1 AEGL Values for Methyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)	One-third reduction of AEGL-3 values
AEGL-3 (lethal)	120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm (43 mg/m^3)	LC_{01} in rats (Tansy et al. 1981)

Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.
[a]The absence of AEGL-1 values does not imply that concentrations below AEGL-2 will be without effect.

TABLE 2-2 Physical and Chemical Data on Methyl Mercaptan

Parameter	Value	Reference
Synonyms	Methanethiol; mercaptomethane; methyl sulfhydrate; thiomethyl alcohol	HSDB 2013
CAS registry no.	74-93-1	HSDB 2013
Chemical formula	CH_3SH	HSDB 2013
Molecular weight	48.11	HSDB 2013
Physical state	Water-white liquid or colorless gas	HSDB 2013
Odor	Like garlic or rotten cabbage	Pohanish 2002; HSDB 2013
Melting point	-123°C	HSDB 2013
Boiling point	5.95°C	HSDB 2013
Flash point	< - 17.78°C (open cup)	HSDB 2013
Density/Specific gravity	0.9600 at 25°C	HSDB 2013
Solubility	Soluble in water (23.3 g/L at 20°C); very soluble in alcohol and ether	HSDB 2013
Saturated vapor concentration (neat)	5.0×10^5 ppm 9.9×10^5 mg/m^3 at 25°C	Calculated
Vapor pressure	1,510 mm Hg at 25°C	HSDB 2013
Incompatibility	Strong oxidizers, bleaches, copper, aluminum, nickel-copper alloys	NIOSH 2011
Conversion factors in air	1 mg/m^3 = 0.51 ppm 1 ppm = 1.97 mg/m^3	NIOSH 2011

A 24-year-old male working in a sodium methyl sulfhydrate factory was found dead. Large quantities of methyl mercaptan were detected in his liver, kidneys, lungs, blood, urine, and in the washout solution of his trachea (Shertzer 2001).

In another incident, a 19-year-old was exposed to methyl mercaptan at concentrations greater than 10,000 ppm for a few minutes. Death ensued after 45 min as a result of respiratory arrest and "heart failure". The blood concentration of methyl mercaptan was greater than 2.5 nmol/mL (Syntex Corporation 1979).

2.2. Nonlethal Toxicity

Kangas et al. (1984) collected air samples from kraft and sulfite mills (pulp industry) and reported methyl mercaptan concentrations ranging from 0 to 15 ppm. Thirteen to 15 mill workers reported headache and trouble concentrating; however, they were also simultaneously exposed to hydrogen sulfide, dimethyl sulfide, and dimethyl disulfide. Therefore, symptoms cannot be attributed to any one chemical at any concentration.

2.3. Odor

Katz and Talbert (1930) exposed six human subjects to methyl mercaptan at a range of concentrations via a nosepiece. The subjects rated the odor intensity (see Table 2-3).

Wilby (1969) exposed 34 individuals to methyl mercaptan at 12 concentrations representing a 100-fold range. For each subject an odor recognition threshold was determined on the basis of three trials. The mean odor threshold concentration was 9.9×10^{-4} ppm with a standard deviation of 7.2×10^{-4} ppm and a coefficient of variation of 0.72. No other effects were noted.

Selyuzhitskii (1972) derived an MPC (maximum permissible concentration) of 5×10^{-4} mg/m^3 (2.5×10^{-4} ppm) for methyl mercaptan. MPC was defined as being above the odor threshold concentration but below the "irritating concentration" in man.

Williams et al. (1977) used a dynamic triangle olfactometer, an instrument that measures odor thresholds by dilution and steady state flow, to determine the odor threshold at which 50% of subjects can detect the odor. Using an unspecified number of subjects, the odor threshold for methyl mercaptan was determined to be 1.5×10^{-5} ppm. No other health effects were noted.

Nishida et al. (1979) exposed 8-11 subjects (18-40 years old) to a series of chemicals, including methyl mercaptan. Subjects rated odors on a scale of 0 to 8, where 0 indicated no smell and 8 an extremely strong smell. A PPT_{50} (perceptive threshold to 50% of population) was determined for methyl mercaptan and used to obtain an odor detection level of 0.019 ppm (range 0.010-0.430 ppm). No other health effects were noted.

2.4. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding human exposure to methyl mercaptan were not available.

2.5. Genotoxicity

Genotoxicity studies regarding human exposure to methyl mercaptan were not available.

TABLE 2-3 Odor Intensity of Methyl Mercaptan

Intensity	Description	Concentration (ppm)
0	No odor	0.0030
1	Threshold	0.041
2	Faint	0.57
3	Median, easily noticeable	7.9
4	Strong	110
5	Most intense	1,500

Source: Adapted from Katz and Talbert 1930.

2.6. Carcinogenicity

Carcinogenicity studies regarding human exposure to methyl mercaptan were not available.

2.7. Summary

Data concerning human exposure to methyl mercaptan are limited. Case reports of deaths from accidental exposure to methyl mercaptan were available; however, definitive exposure durations and concentrations were not reported. Nonlethal toxicity data are limited to odor detection or identification studies that had no accompanying health effects information. Data on developmental and reproductive toxicity, genotoxicity, and carcinogenicity in humans were not available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

A 4-h LC_{50} (lethal concentration, 50% lethality) value of 1,664 ppm was reported for an unspecified strain and sex of mice (Horiguchi 1960). Experimental concentrations of 1,300, 1,500, 1,600, 1,800, 1,900, 2,000, and 2,200 ppm appeared to be determined by the nominal concentration of methyl mercaptan used during the exposure period. Animals were observed for 24-h postexposure. No other experimental details were reported. A 6-h nose-only exposure of Swiss-Webster mice to methyl mercaptan at 512 ppm resulted in 17% lethality (5/30). Three female and two male mice were found dead on day 2 (SRI International1996; see Section 3.2.1 for a more detailed description of the study).

3.1.2. Rats

Groups of five male and five female Charles River Sprague-Dawley rats were exposed methyl mercaptan for 4 h at 0, 400, 600, 650, 680, 690, 700(two groups), or 800 ppm, followed by a 14-day observation period (Tansy et al. 1981). Animals were exposed in a 75-L glass chamber that allowed for continuous observation during exposure. Methyl mercaptan was fed through a two-stage corrosion-resistant regulator which was maintained at delivery pressure of 15 psi to a metering flowmeter. The gas was then mixed with air and drawn through the exposure chamber by a vacuum pump. For this 4-h exposure, the LC_{50} value

was 675 ppm and the LC_{01} was 430 ppm. Any animal alive 24 h after the exposure survived until the end of the 14-day observation period. Mortality data from this study are summarized in Table 2-4, where the strength of the concentration-response relationship can be readily seen.

Groups of two male albino rats were exposed to methyl mercaptan at 250, 500, 750, 1,000, or 2,000 ppm for up to 4 h (DuPont 1992). Methyl mercaptan was mixed with air in a carboy and the mixture passed into a bell jar containing the rats; the "nominal" concentrations were calculated from the respective flow rates of the methyl mercaptan and air. Data from this study are summarized in Table 2-5.

Groups of six male WBS/W rats were exposed to methyl mercaptan at 1,000, 1,400, 2,000, or 2,800 ppm for up to 1 h and were observed for up to 7 days (Latven 1977). Two rats were placed in 20-L static exposure chambers. A small volume of air was withdrawn from each chamber and replaced with the required volume of sample (20 mL for 1,000 ppm, 28 mL for 1,400 ppm, 40 mL for 2,000 ppm, or 56 mL for 2,800 ppm). Clinical signs included dyspnea, ataxia, loss of righting reflex, progressive respiratory depression, and cyanosis. Surviving rats showed only dyspnea. Mortality was 0/6 at 1,000 ppm, 1/6 at 1,400 ppm, 5/6 at 2,000 ppm, and 6/6 at 2,800 ppm. A 1-h LC_{50} value of 1,680 ppm (95% CI: 1,428, 1,980 ppm) was calculated. No other experimental details were available.

White female rats were exposed one at a time to methyl mercaptan at concentrations of approximately 500, 700, 1,500, or 10,000 ppm for 30 min (Ljunggren and Norberg 1943). The report implied that only one rat was used for each exposure. At 500 ppm, no effects were observed. Fatigue was noted at 700, with instantaneous recovery after removal from exposure. After 15 min at 1,500 ppm, the rat had difficulty maintaining an upright posture, and by the end of the exposure period exhibited whole-body tremors and was only able to acquire an upright position for a very brief period. Recovery occurred after 5 min. This animal had thickened alveolar walls and exudate containing blood cells in the alveoli. The 10,000-ppm exposure produced convulsions after 1 min and fast superficial respiration after 2 min. The animal was on its side after 6 min, respiration was irregular after 8 min, and death occurred after 14 min. Necropsy findings included "small bleedings in the lungs", alveoli filled with erythrocytes, and moderate amounts of serous fluid in the alveoli.

Male Holtzman or Sprague-Dawley rats (weighing 285 to 325 g) were individually exposed in a 27-L glass chamber to methyl mercaptan at concentrations ranging from 0.08 to 0.2% until they became comatose or for 15 min (Zieve et al. 1974). The mercaptan concentration in the chamber atmosphere was not analyzed, rather concentrations were calculated from the dose injected. A CD_{50} (coma induction in 50% of subjects) value of 0.16% (1,600 ppm) was determined from these exposure concentrations. Blood concentrations of methyl mercaptan found in comatose animals were greater than 0.5 nmoles/mL.

TABLE 2-4 Mortality in Rats Exposed to Methyl Mercaptan for 4 Hours

Concentration (ppm)	Mortality
0	0/10
400	0/10
600	2/10
650	5/10
680	4/10
690	4/10
700[a]	10/10, 10/10
800	10/10

[a]There were two 700 ppm exposure groups. Source: Adapted from Tansy et al. 1981.

TABLE 2-5 Acute Inhalation Toxicity in Rats Exposed to Methyl Mercaptan

Concentration (ppm)	Duration (hours)	Mortality	Clinical Signs	Necropsy Findings
250	4	0/2	Ocular and nasal irritation.	Pneumonitis in half of the rats; considered coincidental.
500	4	0/2	Ocular and nasal irritation, shallow respiration.	Focal atelectasis (9 days after treatment in half of the rats).
750	3-3.5	2/2	Comatose a few minutes before death	None
1,000	3.17	2/2	Shallow respiration, cyanosis, comatose in 3 h	None
2,000	0.33	2/2	Comatose in 15 min	None

Source: DuPont 1992.

3.2. Nonlethal Toxicity

3.2.1. Mice

As part of a bone marrow erythrocyte micronucleus assay, 15 Swiss-Webster mice/sex were exposed nose-only to methyl mercaptan at 0, 114, 258, or 512 ppm for 6 h, and animals were killed 24, 48, or 72 h after exposure (SRI International1996). Methyl mercaptan concentrations were analyzed by gas chromatography hourly during the exposure period, and temperature, relative humidity, and pressure differential were measured at 10-min intervals. Shallow breathing and hypoactivity were observed in all mice in the 258-ppm group during the fourth and fifth hour of exposure and appeared normal by day 2. Shallow breathing at the third and fourth hour of exposure and hypoactivity during the fifth hour were observed in all mice exposed at 512 ppm. Three female and two male mice from the 512-ppm exposure group were found dead on day 2; all surviving mice from the 512-ppm group appeared normal by day 2. No clinical signs were noted in control animals or mice exposed to methyl mercaptan at 114 ppm.

3.3. Subchronic Exposure

Groups of two or four male albino rats were exposed to methyl mercaptan at 100 or 200 ppm for 6 h/day for 6 or 10 days (DuPont 1992). Methyl mercaptan was mixed with air in a carboy and the mixture passed into a bell jar containing the rats; the "nominal" concentrations were calculated from the respective flow rates of the methyl mercaptan and air. Data from this study are summarized in Table 2-6.

Groups of 31 male Charles River Sprague-Dawley rats were exposed methyl mercaptan at 0, 2, 17, or 57 ppm for 7 h/day, 5 days/week for 3 months (Tansy et al. 1981). Animals were exposed in 11.4-ft^3 stainless steel chambers that allowed for continuous observation during exposure. Flow rates were calculated to yield the desired gas concentrations, and were verified by spectrophotometric analysis of gas samples. No animals died during the study, and no treatment-related effects were noted in animals exposed at 0, 2, or 17 ppm. Body weights were decreased by 15% in the 57-ppm group compared with controls. Blood chemistry analysis showed increased total protein and decreased serum albumin at 57 ppm. The observed increased protein might have been due to dehydration, and the decreased albumin may be indicative of liver involvement, although no treatment-related liver histopathology was observed.

3.4. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding animal exposure to methyl mercaptan were not available.

TABLE 2-6 Subchronic Inhalation Toxicity in Rats Exposed to Methyl Mercaptan

Concentration (ppm)	Duration	Mortality	Clinical Signs	Necropsy Findings
100	6 h/d for 10 d	0/2	Occasional restlessness.	Bronchopneumonia (2 rats)
200	6 h/d for 6 d	1/4	Occasional restlessness, red ears.	No effects (2 rats); pneumonia (2 rats, including decedent).
200	6 h/d for 10 d	1/4	Slight dyspnea and chromodacryorrhea after 6th exposure, slight cyanosis, moist rales (decedent).	Decedent: bronchopneumonia; Rat No. 2: coincidental atelectasis; Rat No. 3: slight pulmonary congestion and emphysema; Rat No. 4: slight bronchitis and emphysema, coincidental atelectasis.

Source: DuPont 1992.

3.5. Genotoxicity

In a bone marrow erythrocyte micronucleus assay in mice (SRI International 1996), a statistically significant increase in micronucleated polychromatic erythrocytes was observed in male mice only at the 24-h sacrifice after exposure to methyl mercaptan at 512 ppm for 6 h. (The protocol and clinical signs observed in this study are described in Section 3.2.1.) However, the increase is of questionable biologic significance because the control group had a micronucleus frequency lower than the historical control mean for the laboratory (0.05% vs. 0.21% historical frequency). In another study, Garrett and Fuerst (1974) report that methyl mercaptan was mutagenic in a sex-linked recessive lethal test in *Drosophila melanogaster*; however, no data were presented.

3.6. Carcinogenicity

Carcinogenicity studies in animals exposed to methyl mercaptan were not available.

3.7. Summary

Animal toxicity data for methyl mercaptan are limited. Lethality studies are available for rats and mice, and suggest a steep concentration-response relationship for methyl mercaptan. In studies of rats, 4-h exposures to methyl mercaptan at 600 and 700 ppm caused 20 and 100% lethality, respectively; the 4-h LC_{50} value was 675 ppm; and the 4-h LC_{01} value was 430 ppm (Tansy et al. 1981). In another rat study, a 4-h exposure at 500 ppm caused no lethality (0/2), and a 3.5-h exposure at 750 ppm caused death in both rats (DuPont 1992). Nonlethal effects included dyspnea, cyanosis, and breathing difficulties. Genotoxicity data are limited and equivocal, and no reproductive and developmental toxicity data or carcinogenicity studies on methyl mercaptan were located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Rats injected intraperitoneally with methyl mercaptan excreted CO_2 and volatile sulfur-containing compounds in the expired breath (Canellakis and Tarver 1953). After rats were injected with ^{35}S-methyl mercaptan, approximately 94% of the sulfur was found in the urine as $^{35}SO_4^{2-}$ (Derr and Draves 1983, 1984). Methyl mercaptan and dimethyl sulfide were found in the expired breath of one mouse injected with methyl mercaptan (Susman et al. 1978). Erythrocytes were found to oxidize methyl mercaptan, producing formic acid, sulfite ion, and sulfate ion (Blom and Tangerman 1988).

4.2. Mechanism of Toxicity

The sulfide metabolite allows methyl mercaptan to act similarly to hydrogen sulfide and cyanide by interrupting electron transport through inhibition of cytochrome oxidase (Waller 1977). As a result of the electron transfer blockage, oxidative phosphorylation and aerobic metabolism are compromised, peripheral tissue P_{O2} increases, and the unloading gradient for oxyhemoglobin decreases. High concentrations of oxyhemoglobin are thus found in the venous return, resulting in flushed skin and mucous membranes. Lactic acidemia occurs as a result of the increased demand placed on glycolysis. Although signs of hydrogen sulfide poisoning are essentially identical to those of cyanide poisoning, hydrogen sulfide has a greater tendency to produce conjunctivitis and pulmonary edema (Smith 1991).

The hydrosulfide ion complexes with methemoglobin to form sulfmethemoglobin, which is analogous to cyanmethemoglobin. The dissociation constant for cyanmethemoglobin is 2×10^{-8} mol/L, while the dissociation constant for sulfmeth-emoglobin is approximately 6×10^{-6} mol/L. In both cases, nitrite-induced methemoglobinemia provides protection and had antidotal effects against hydrogen sulfide poisoning (Smith 1991).

4.3. Structure-Activity Relationships

Rat lethality data suggest that the acute toxicity of methyl mercaptan is slightly less than that of hydrogen sulfide and more toxic than other mercaptans tested (with the exception of phenyl mercaptan, benzyl mercaptan, and tert-octyl mercaptan (see Table 2-7).

4.4. Concurrent Exposure Issues

Methyl mercaptan may also have a role in facilitating the toxic effects of ammonia and fatty acids in patients with chronic severe liver disease (Zieve et al. 1974, 1984).

4.5. Species Differences

Because of the limited data on methyl mercaptan, a definitive assessment of species differences is not possible. However, the mechanism of toxicity (interruption of electron transport through inhibition of cytochrome oxidase) is unlikely to vary greatly between species. Also, the overall toxicity database for methyl mercaptan suggests a steep concentration-response relationship; thus, a wide range of effects across a relatively small dose range suggests limited variability.

TABLE 2-7 Comparative Toxicity of Mercaptans

Compound	Rat Intraperitoneal LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	4-h Inhalation LC_{50} (ppm) Rats	Mice	Reference
Hydrogen sulfide	–	–	444	–	Tansy et al. 1981
Methyl mercaptan	–	–	*675*	*1,664*	Horiguchi 1960 (mice); Tansy et al. 1981(rats)
Ethyl mercaptan	226	682	4,420	2,770	Fairchild and Stokinger 1958
Propyl mercaptan	515	1,790	7,200	4,010	Fairchild and Stokinger 1958
Isobutyl mercaptan	917	7,168	>25,000	>25,000	Fairchild and Stokinger 1958
tert-Butyl mercaptan	590	4,729	22,200	16,500	Fairchild and Stokinger 1958
n-Butyl mercaptan	399	1,500	4,020	2,500	Fairchild and Stokinger 1958
n-Hexyl mercaptan	396	1,254	1,080	528	Fairchild and Stokinger 1958
Phenyl mercaptan	9.8	46.2	33	28	Fairchild and Stokinger 1958
Benzyl mercaptan	373	493	>235	178	Fairchild and Stokinger 1958
tert-Octyl mercaptan	12.9	83.5	51 (males)	47 (males)	Fairchild and Stokinger 1958

4.6. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate for derive an empirical value of n for methyl mercaptan. To obtain conservative and protective AEGL values in the absence of a chemical-specific scaling exponent, temporal scaling was performed using a default value of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data on methyl mercaptan consistent with the definition of AEGL-1 were not available. However, headache and trouble concentrating were reported after occupational exposure to methyl mercaptan at concentrations up to 15 ppm (Kangas et al. 1984). In that study, workers were also simultaneously exposed to hydrogen sulfide (≤20 ppm), dimethyl sulfide (≤15 ppm), and dimethyl disulfide (≤1.5 ppm).

5.2. Animal Data Relevant to AEGL-1

Animal data on methyl mercaptan consistent with the definition of AEGL-1 were not available. The study by SRI International(1996) had a no-effect level of 114 ppm in mice exposed for 6 h; however, that concentration is not suitable as a point of departure because the animals exhibited shallow breathing and hypoactivity (an end point relevant to impairment of escape) at the next highest concentration of 258 ppm, and 17% lethality occurred at 512 ppm. Therefore, 258 ppm appears to be near the threshold for lethality (see AEGL-3 derivation). Although the lowest concentration of 250 ppm (nominal) in the DuPont (1992) study produced only ocular and nasal irritation in rats exposed for 4 h, that concentration is also close to the lethality threshold for rats. The 4-h LC_{01} in the Tansy et al. (1981) study was 430 ppm.

5.3. Derivation of AEGL-1

Data on methyl mercaptan were insufficient to derive AEGL-1 values. The only data on humans involve occupational observations in which workers were also simultaneously exposed to hydrogen sulfide, dimethyl sulfide, and dimethyl disulfide. Animal studies do not identify a suitable point of departure for calculating AEGL-1 values. Therefore, no AEGL-1 values are recommended. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values are without effect.

Even though methyl mercaptan has an extremely unpleasant odor, olfactory desensitization or fatigue occurs at high concentrations. Therefore, odor and symptoms of irritation may not adequately provide warning of high concentrations of methyl mercaptan (Shertzer 2001). The level of distinct odor awareness (LOA) for methyl mercaptan is 0.0019 ppm (see Appendix C for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong smell. The LOA should help chemical emergency responders in assessing the public awareness of the exposure on the basis of odor perception.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data on methyl mercaptan relevant to deriving AEGL-2 values were not available.

6.2. Animal Data Relevant to AEGL-2

Shallow breathing and hypoactivity were noted in mice exposed to methyl mercaptan at 258 ppm for 6 h (SRI International1996). However, this concentration cannot be used as a point of departure for calculating AEGL-2 values. At the next higher test concentration of 512 ppm (a less than 2-fold increase), lethality in mice was 17% (5/30). Therefore, 258 ppm is close to the lethality threshold for mice, and also appears to be close to the predicted 6-h lethality threshold for rats. The 4-h LC_{01} in rats is 430 ppm (Tansy et al. 1981) and, when this value scaled to 6 h (n = 1), the 6-h LC_{01} is 287 ppm.

6.3. Derivation of AEGL-2

The only observations consistent with the definition of AEGL-2 are from the study of SRI International(1996), in which shallow breathing and hypoactivity (an end point relevant to impairment of escape) were noted in mice exposed to methyl mercaptan at 258 ppm for 6 h. However, as noted above, this concentration is close to the lethality thresholds for mice and rats and, therefore, cannot be used as a basis for AEGL-2 values. The lethality data also demonstrate a steep concentration-response relationship for methyl mercaptan. Lethality in rats after a 4-h exposure to methyl mercaptan was 20% (2/10) at 600 ppm and 100% (10/10) at 700 ppm, and the 4-h LC_{50} and LC_{01} values were 675 ppm and 430 ppm, respectively (Tansy et al. 1981). In the absence of relevant data on methyl mercaptan and because of its steep concentration-response relationship for lethality, AEGL-2 values were calculated by taking one-third of the AEGL-3 values. Those values are estimated thresholds for the inability to escape. AEGL-2 values for methyl mercaptan are presented in Table 2-8.

AEGL-2 values are considered protective because rats exposed to methyl mercaptan at 57 ppm for 7 h/day, 5 days/week for 3 months experienced only decreased body weight and decreased serum albumin (Tansy et al. 1981). Also, workers exposed to methyl mercaptan at concentrations up to 15 ppm experienced only headache and trouble concentrating (Kangas et al. 1984). However, the workers were also simultaneously exposed to hydrogen sulfide, dimethyl sulfide, and dimethyl disulfide.

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were available for calculating AEGL-3 values. Human fatalities from acute exposure to methyl mercaptan have been reported, but the exposure concentrations were unknown.

TABLE 2-8 AEGL-2 Values for Methyl Mercaptan

10 min	30 min	1 h	4 h	8 h
40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)

7.2. Animal Data Relevant to AEGL-3

A 4-h LC_{50} value of 1,664 ppm was reported for mice exposed to methyl mercaptan (Horiguchi 1960). In rats, the 1-h LC_{50} value was1,680 ppm, and the highest concentration causing no mortality after a 1-h exposure was 1,000 ppm (Latven 1977). A 4-h LC_{50} value of 675 ppm and a 4-h LC_{01} value of 430 ppm were reported for rats exposed to methyl mercaptan (Tansy et al. 1981).

7.3. Derivation of AEGL-3

The LC_{01} of 430 ppm in rats exposed to methyl mercaptan for 4 h (Tansy et al. 1981) was considered an estimate of the lethality threshold in rats, and was used as the point of departure for calculating AEGL-3 values. The 4-h LC_{01} is consistent with observations in mice which suggest that the 6-h lethality threshold is at or above 258 ppm and below 612 ppm (SRI International1996). When the 4-h LC_{01} in rats is scaled to 6 h (n = 1), the 6-h LC_{01} is 287 ppm. An intraspecies uncertainty factor of 3 was applied because of the steepness of the concentration-response relationship in this study (lethality in rats was 20% at 600 ppm and 100% at 700 ppm; 4-h LC_{50} and LC_{01} values were 675 and 430 ppm, respectively), which implies limited individual variability. An interspecies uncertainty factor of 3 was applied. Although a factor of 10 might normally be applied because of limited data on species differences, AEGL-3 values calculated using that larger factor would be inconsistent with the total database. AEGL-3 values would range from 7.3 to 40 ppm if a total uncertainty factor of 30 was used; however, occupational exposures at concentrations up to 15 ppm (with simultaneous exposure to hydrogen sulfide, ≤20 ppm; dimethyl sulfide, ≤15 ppm; and dimethyl disulfide, ≤1.5 ppm) resulted in headache and trouble concentrating (Kangas et al. 1984). Furthermore, no effects were noted in rats repeatedly exposed to methyl mercaptan at 17 ppm for 3 months. Therefore, it is unlikely that people exposed to methyl mercaptan in the range of 7.3 to 40 ppm for 10 min to 8 h would experience lethal effects. Furthermore, those values are 2- to 4-fold below the AEGL-3 values for hydrogen sulfide. Because hydrogen sulfide has a robust database and because data suggest that methyl mercaptan is less toxic than hydrogen sulfide, it would be inconsistent with the total data set to derive AEGL-3 values for methyl mercaptan that are below the AEGL-3 values for hydrogen sulfide. Thus, the total uncertainty factor is 10.

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the

exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific exponent, temporal scaling was performed using default values of n = 3 when extrapolating from longer to shorter durations (10 min, 30 min, and 1 h) and n = 1 when extrapolating from shorter to longer durations (8 h). AEGL-3 values for methyl mercaptan are presented in Table 2-9 and the calculations are presented in Appendix A.

The AEGL-3 values are considered protective because rats exposed to methyl mercaptan at 57 ppm for 7 h/day, 5 days/week for 3 months experienced only decreased body weight and decreased serum albumin (Tansy et al. 1981), and rats exposed at 100 ppm for 6 h/day for 10 days exhibited occasional restlessness and bronchopneumonia at necropsy (DuPont 1992). Furthermore, extrapolation from 4 h to 10 min is supported by the finding that no rats exposed to methyl mercaptan at 1,000 ppm for 1 h died (Latven 1977). Using this end point, an exponent of n = 3, and a total uncertainty factor of 10, would yield a 10-min AEGL-3 value of 182 ppm. This suggests that the 10-min AEGL-3 value of 120 ppm is protective and that time scaling is appropriate. The 8-h AEGL-3 value is supported by a study that shows workers exposed to methyl mercaptan at concentrations up to 15 ppm experienced only headache and trouble concentrating (Kangas et al. 1984). These workers were also simultaneously exposed to hydrogen sulfide, dimethyl sulfide, and dimethyl disulfide.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for methyl mercaptan are presented in Table 2-10. Data on methyl mercaptan were inadequate for deriving AEGL-1 or AEGL-2 values. No values are recommended for AEGL-1 values. However, because of the steep concentration-response relationship for lethality, AEGL-2 values for methyl mercaptan were calculated as one-third of AEGL-3 values. The values are considered thresholds for the inability to escape. AEGL-3 values were based on an LC_{01} of 430 ppm in rats exposed to methyl mercaptan for 4 h (Tansy et al. 1981).

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to methyl mercaptan are presented in Table 2-11.

TABLE 2-9 AEGL-3 Values for Methyl Mercaptan

10 min	30 min	1 h	4 h	8 h
120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm (43 mg/m^3)

TABLE 2-10 AEGL Values for Methyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)
AEGL-3 (lethal)	120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm (43 mg/m^3)

[a]The absence of AEGL-1 values does not imply that concentrations below the AEGL-2 will be without effect.

TABLE 2-11 Standards and Guidelines for Methyl Mercaptan

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)
AEGL-3	120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm 43 mg/m^3)
ERPG-1[a]	–	–	0.005 ppm (0.0098 mg/m^3)	–	–
ERPG-2	–	–	25 ppm (49 mg/m^3)	–	–
ERPG-3	–	–	100 ppm (200 mg/m^3)	–	–
IDLH (NIOSH)[b]		150 ppm (290 mg/m^3)			
TLV-TWA (ACGIH)[c]					0.5 ppm (1 mg/m^3)
REL-C (NIOSH)[d]	0.5 ppm (1 mg/m^3)	0.5 ppm (1 mg/m^3)	0.5 ppm (1 mg/m^3)	0.5 ppm (1 mg/m^3)	0.5 ppm (1 mg/m^3)
PEL-C (OSHA)[e]	10 ppm (20 mg/m^3)	10 ppm (20 mg/m^3)	10 ppm (20 mg/m^3)	10 ppm (20 mg/m^3)	10 ppm (20 mg/m^3)
MAK (Germany)[f]					0.5 ppm (1 mg/m^3)
MAC (The Netherlands)[g]					0.5 ppm (1 mg/m^3)

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 1999].
ERPG-1 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. ERPG-1 for methyl mercaptan is based on the threshold limit value.

ERPG-2 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action. ERPG-2 for methyl mercaptan is based on repeated-dose animal experiments.
ERPG-3 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. ERPG-3 for methyl mercaptan is based on a 4-h acute inhalation study of rats exposed at 400 ppm (Tansy et al. 1981).
[b]ILDH (immediately dangerous to life or health, National Institute for Occupational Safety and Health [NIOSH 1994]) is defined by the NIOSH/OSHA Standard Completions Program only for the purpose of respirator selection, and represents a maximum concentration from which, in the event of respirator failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health effects. IDLH value for methyl mercaptan is based on an acute inhalation toxicity study in rats (Tansy et al. 1981) and by analogy to hydrogen sulfide.
[c]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2004, 2012]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect
[d]REL-C (recommended exposure limit - ceiling, National Institute for Occupational Safety and Health [NIOSH 2011]) is a ceiling value that should not be exceeded at any time during a workday.
[e]PEL-C (permissible exposure limit - ceiling, Occupational Safety and Health Administration (29 CFR 1910.1000 [2006]) is the concentration that should not be exceeded at any time.
[f]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2012) is defined analogous to the ACGIH TLV-TWA. A peak excursion factor (ratio of permitted short-term peak value to the MAK value) for methyl mercaptan is 2.
[g]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

The data requirements for establishing other standards differ from those of AEGLs. The ACGIH (2004, 2012) TLV-TWA was, in part, based on historical occupational experience, as discussed in the 2004 documentation:

> A TLV-TWA of 0.5 ppm (1 mg/m^3) is recommended for occupational exposure to methyl mercaptan to minimize the potential for systemic effects. Animal data have shown that 17 ppm was a no-observed-effect level (NOEL) and 57 ppm produced body weight reductions and minimal hepatic effects. Although the animal NOEL might suggest a somewhat higher exposure limit, the existing TLV-TWA of 0.5 ppm (since 1970) appears to be protective of worker health. Thus, the 0.5 ppm TLV-TWA will be retained.

Supporting documentation for the other guidelines do not provide sufficient detail to understand the quantitative basis for the NIOSH (2011) REL, the OSHA (29 CFR 1910.1000 [2006]) PEL-ceiling, or other guideline values (MAC and MAK). The PEL is a ceiling value of 10 ppm, which is close to the 8-h AEGL-2 value of 7.3 ppm. The ERPG-2 value of 25 ppm value is almost equivalent to the 1-h AEGL-2 value of 23 ppm.

8.3. Data Adequacy and Research Needs

Data on acute inhalation exposure to methyl mercaptan in humans and animals are sparse, and the few studies available are old and poorly reported. There were insufficient data to establish a chemical-specific time-scaling exponent for methyl mercaptan. Acute inhalation toxicity studies in males and females of multiple animal species (rat, mouse, guinea pig, and hamster) exposed for several durations (10 min, 30 min, 1 h, and 4 h) would allow for examination of both interspecies differences and intraspecies variability and for definition of a chemical-specific time-scaling relationship for this chemical. Well-controlled, IRB (institutional review board)-approved, acute human inhalation studies at low concentrations might also allow for derivation of AEGL-1 and AEGL-2 values for methyl mercaptan.

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APPENDIX A

DERIVATION OF AEGL VALUES METHYL MERCAPTAN

Derivation of AEGL-1 Values

Data on methyl mercaptan were inadequate to derive AEGL-1 values. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effect.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values and because methyl mercaptan has a steep concentration-response curve, AEGL-3 values were divided by 3 to estimate thresholds for inability to escape.

10-min AEGL-2:	120 ppm ÷ 3 = 40 ppm
30-min AEGL-2:	86 ppm ÷ 3 = 29 ppm
1-h AEGL-2:	68 ppm ÷ 3 = 23 ppm
4-h AEGL-2:	43 ppm ÷ 3 = 14 ppm
8-h AEGL-2:	22 ppm ÷ 3 = 7.3 ppm

Derivation of AEGL-3 Values

Key study:	Tansy, M.F., F.M. Kendall, J. Fantasia, W.E. Landin, and R. Oberly. 1981. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health 8(1-2):71-88.
Toxicity end point:	Estimated lethality threshold in rats, 4-h LC_{01} of 430 ppm
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations) $(430\ ppm)^3 \times 4\ h = 318{,}028{,}000\ ppm\text{-}h$ $(430\ ppm)^1 \times 4\ h = 1{,}720\ ppm\text{-}h$

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10-min AEGL-3:	$C^3 \times 0.167$ h = 318,028,000 ppm^3-h C^3 = 1,904,359,281 ppm C = 1,240 ppm 1,240 ppm ÷ 10 = 120 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 318,028,000 ppm-h C^3 = 636,056,000 ppm C = 860 ppm 860 ppm ÷ 10 = 86 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 318,028,000 ppm-h C^3 = 318,028,000 ppm C = 682.7 ppm 682.7 ppm ÷ 10 = 68 ppm
4-h AEGL-3:	430.0 ppm ÷ 10 = 43 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 1,720 ppm-h C^1 = 215 ppm C = 215 ppm 215 ppm ÷ 10 = 22 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL MERCAPTAN

Derivation Summary

AEGL-1 VALUES

Data on methyl mercaptan were insufficient to derive AEGL-1 values. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)

Data adequacy: Data inadequate to derive AEGL-2 values. AEGL-3 values were divided by 3 to estimate thresholds for the inability to escape. This calculation is supported by the steep concentration-response relationship for methyl mercaptan (lethality in rats exposed for 4 h was 20% at 600 ppm and 100% at 700 ppm; the 4-h LC_{50} value was 675 ppm and the 4-h LC_{01} value was 430 ppm in rats [Tansy et al. 1981]).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm (43 mg/m^3)

Reference: Tansy, M.F., F.M. Kendall, J. Fantasia, W.E. Landin, and R. Oberly. 1981. Acute and subchronic toxicity of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health 8(1-2):71-88.

Test species/Strain/Sex/Number: Rats, Sprague-Dawley, 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 0, 400, 600, 650, 680, 690, 700 (two groups), or 800 ppm for 4 h

Effects:

Concentration (ppm)	Mortality
0	0/10
400	0/10
600	2/10
650	5/10
680	4/10
690	4/10

(Continued)

AEGL-3 VALUES Continued

700	10/10
700	10/10
800	10/10
LC_{50}	675 ppm
LC_{01}	430 ppm

End point/Concentration/Rationale: Estimated lethality threshold in rats, 4-h LC_{01} of 430 ppm

Uncertainty factors/Rationale:
Intraspecies: 3, considered sufficient because of steep lethality concentration-response relationship (20% mortality at 600 ppm, 100% mortality at 700 ppm), which implies limited individual variability.
Interspecies: 3, although an interspecies uncertainty factor of 10 might normally be applied because of limited data, AEGL-3 values calculated using a total uncertainty factor of 30 would be inconsistent with the total database. AEGL-3 values would range from 7.3 to 40 ppm if the larger factor is used; however, occupational exposures of up to 15 ppm (along with hydrogen sulfide, ≤20 ppm; dimethyl sulfide, ≤15 ppm; and dimethyl disulfide, ≤1.5 ppm) resulted in headache and trouble concentrating (Kangas et al. 1984). Furthermore, no effects were found in rats exposed at 17 ppm for 7 h/d, 5 d/wk for 3 mos. It is unreasonable to expect that people exposed to methyl mercaptan in the range of 7.3 to 40 ppm for 10 min to 8 h would experience lethal effects. Furthermore, those values are 2- to 4-fold below the AEGL-3 values for hydrogen sulfide. Because a robust database exists for hydrogen sulfide and because data suggest that methyl mercaptan is less toxic than hydrogen sulfide (4-h LC_{50} is 675 ppm for methyl mercaptan and 444 ppm for hydrogen sulfide [Tansy et al. 1981]), it would be inconsistent with the total data set to have AEGL-3 values for methyl mercaptan that are in the range of the AEGL-3 values for hydrogen sulfide.
Total uncertainty factor: 10

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; default value of n = 3 was used for extrapolation to the shorter durations (10 min, 30 min, and 1 h) and n = 1 for extrapolation to the longer duration (8 h). Extrapolation from 4 h to 10 min is supported by the fact that no deaths were observed in rats exposed to methyl mercaptan at 1,000 ppm for 1 h (Latven 1977). Using this end point, an exponent n = 3, and total uncertainty factor of 10, would yield a 10-min AEGL-3 value of 182 ppm. This suggests that the 10-min AEGL-3 value of 120 ppm is protective and that time scaling is appropriate.

Data adequacy: The study was well conducted and used a sufficient number of animals of both sexes. The point of departure is an estimated threshold for lethality; the 4-h LC_{01} in rats is consistent with observations in mice, which suggest that the 6-h lethality threshold is at or above 258 ppm and below 612 ppm (SRI International 1996). When the 4-h LC_{01} in rats is scaled to 6 h (n = 1), the 6-h LC_{01} is estimated to be 287 ppm. AEGL-3 values are considered protective because rats exposed to methyl mercaptan at 57 ppm for 7 h/d, 5 d/wk for 3 mos experienced only decreased body weight and decreased serum albumin (Tansy et al. 1981), and rats exposed at 100 ppm for 6 h/d for 10 d experienced occasional restlessness and had bronchopneumonia at necropsy (DuPont 1992).

APPENDIX C

DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS FOR METHYL MERCAPTAN

Even though methyl mercaptan has an extremely unpleasant odor, olfactory desensitization or fatigue occurs at high concentrations. Therefore, odor and symptoms of irritation may not adequately provide warning of high concentrations of methyl mercaptan (Shertzer 2001).

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure on the basis of odor perception. The LOA derivation follows the guidance of van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for methyl mercaptan was calculated to be 0.00012 ppm (van Doorn et al. 2002).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = k_w \times \log (C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ was used due to the lack of chemical-specific data:

$$3 = 2.33 \times \log (C \div 0.00012) + 0.5$$
$$\log (C \div 0.00012) = (3 - 0.5) \div 2.33$$
$$\log (C \div 0.00012) = 1.07$$
$$C = (10^{1.07}) \times 0.00012$$
$$C = 0.00141 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that factors in everyday life, such as sex, age, sleep, smoking, upper airway infections, and allergy, as well as distractions, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of $4 \div 3 = 1.33$.

$$LOA = C \times 1.33$$
$$LOA = 0.00141 \text{ ppm} \times 1.33$$
$$LOA = 0.001875 \text{ ppm}$$

APPENDIX D

CATEGORY PLOT FOR METHYL MERCAPTAN

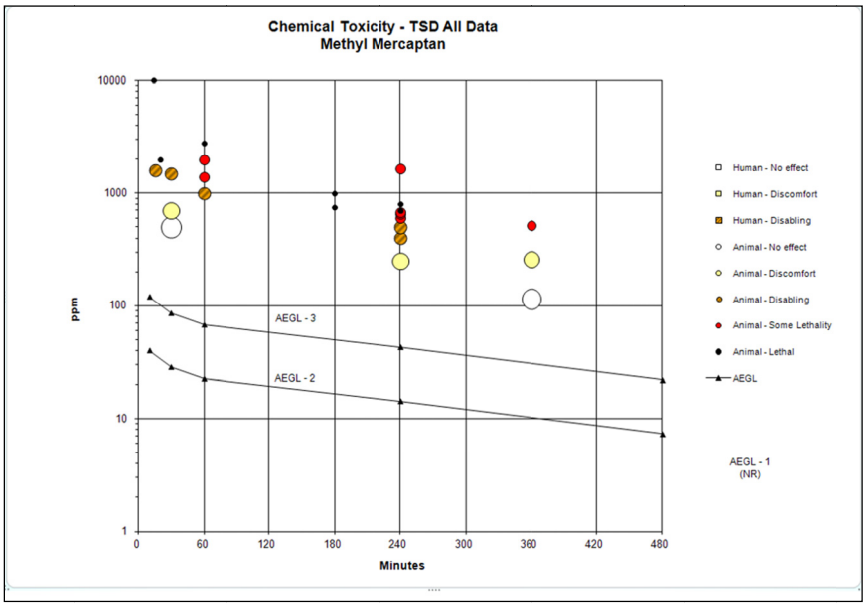

FIGURE D-1 Category plot of toxicity data and AEGL values for methyl mercaptan. The decimal point is lost on this log-scale plot.

TABLE D-1 Data Used in the Category Plot for Methyl Mercaptan

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				40	10	AEGL	
AEGL-2				29	30	AEGL	
AEGL-2				23	60	AEGL	
AEGL-2				14	240	AEGL	
AEGL-2				7.3	480	AEGL	
AEGL-3				120	10	AEGL	
AEGL-3				86	30	AEGL	
AEGL-3				68	60	AEGL	
AEGL-3				43	240	AEGL	
AEGL-3				22	480	AEGL	
Horiguchi 1960	Mouse		1	1,664	240	LC_{50}	
SRI International 1996	Mouse	Both	1	114	360	0	
	Mouse	Both	1	258	360	1	Shallow breathing, hypoactivity
	Mouse	Both	1	512	360	SL	Mortality (5/15); shallow breathing; hypoactivity
Tansy et al. 1981	Rat	Both	1	400	240	2	

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
	Rat	Both	1	600	240	SL	Mortality (2/10)
	Rat	Both	1	650	240	SL	Mortality (5/10)
	Rat	Both	1	680	240	SL	Mortality (4/10)
	Rat	Both	1	700	240	3	Mortality (10/10)
	Rat	Both	1	700	240	3	Mortality (10/10)
	Rat	Both	1	800	240	3	Mortality (10/10)
DuPont 1992	Rat	Male	1	250	240	1	Pneumonitis in 2 rats, considered coincidental
	Rat	Male	1	500	240	2	Focal atelectasis
	Rat	Male	1	750	180	3	Mortality (2/2), coma
	Rat	Male	1	1,000	180	3	Mortality (2/2), shallow respiration, cyanosis, coma
	Rat	Male	1	2,000	20	3	Mortality (2/2), coma
Latven 1977	Rat	Male	1	1,000	60	2	Clinical signs
	Rat	Male	1	1,400	60	SL	Mortality (1/6)
	Rat	Male	1	2,000	60	SL	Mortality (5/6)
	Rat	Male	1	2,800	60	3	Mortality (6/6)
Zieve et al. 1974	Rat	Male	1	1,600	15	2	CD_{50} (coma induction)
Ljunggren and Norberg 1943	Rat	Female	1	500	30	0	
	Rat	Female	1	700	30	1	
	Rat	Female	1	1,500	30	2	
	Rat	Female	1	10,000	14	3	Mortality (1/1)

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

3

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

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Chemical Manager Steve Barbee (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

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

SUMMARY

Phenyl mercaptan is used as an intermediate in the manufacture of pesticides, pharmaceuticals, and amber dyes, and is also used as a mosquito larvicide. It is an odorous, colorless liquid. The disagreeable odor has been described as penetrating, repulsive, and garlic-like (Shertzer 2012).

Phenyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis. Clinical signs of exposure are ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, and vomiting. Paralysis of the locomotor muscles has also been observed. Its primary mechanism of action appears to be interference with cytochrome oxidase.

AEGL-1 values are not recommended for phenyl mercaptan because of insufficient data.

No robust data on phenyl mercaptan consistent with the definition of AEGL-2 were available. Therefore, AEGL-2 values were based on a 3-fold reduction in the AEGL-3 values. These calculations are considered estimated thresholds for inability to escape and are appropriate because of the steep concentration-response relationship for phenyl mercaptan toxicity.

AEGL-3 values were based on a calculated LC_{01} (lethal concentration, 1% lethality) of 10.3 ppm in rats exposed to phenyl mercaptan for 4 h (Fairchild and Stokinger 1958). A total uncertainty factor of 10 was applied: a factor of 3 for interspecies differences and a factor of 3 for intraspecies variability. Those factors are considered sufficient because the mechanism of action (cytochrome oxidase inhibition) is not expected to vary greatly between or within species. Alt-

hough an interspecies or intraspecies uncertainty factor of 10 might normally be applied because of limited data, a total uncertainty factor of 30 would yield AEGL values that are inconsistent with those derived for the structural and mechanistic analogs ethyl mercaptan, methyl mercaptan, and hydrogen sulfide, all of which have a more robust data set than phenyl mercaptan. Values were scaled across time using the equation $C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used to derive values protective of human health (NRC 2001). AEGL values for phenyl mercaptan are presented in Table 3-1.

1. INTRODUCTION

Phenyl mercaptan is used as an intermediate in the manufacture of pesticides, pharmaceuticals, and amber dyes, and is also used as a mosquito larvicide. It is an odorous, colorless liquid. The disagreeable odor has been described as penetrating, repulsive, and garlic-like (Shertzer 2012).

Phenyl mercaptan is produced commercially by reducing benzenesulfonyl chloride with zinc dust in sulfuric acid or by reacting hydrogen sulfide with chlorobenzene (Shertzer 2012). In 1981, the total U.S. production of phenyl mercaptan was probably greater than 2.27×10^6 grams and the total U.S. imports were probably greater than 3.78×10^7 grams (HSDB 2009). The 1983 National Occupational Exposure Survey reported that 879 U.S. workers (692 males, 187 females) were exposed to phenyl mercaptan (RTECS 2009).

The physical and chemical properties of phenyl mercaptan are presented in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information concerning human lethality from acute exposure to phenyl mercaptan was available.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Awareness

Katz and Talbert (1930) exposed six human subjects to phenyl mercaptan at a range of concentrations via a nosepiece. In tests evaluating odor intensity or throat and nasal irritation, the subjects were exposed to a single inhalation of phenyl mercaptan. For ocular irritation tests, the eye was exposed to phenyl mercaptan for 10 seconds. Vapor concentrations were determined by weighing vaporizers containing the phenyl mercaptan before and after a series of odor measurements, and dividing the loss in weight by the volume of air passed through the vaporizer. The subjects described the odor as very disagreeable, repulsive, and persistent.

The odor intensity of phenyl mercaptan is presented in Table 3-3. Faint nasal irritation was observed at 85 ppm and faint ocular irritation was observed at 45 ppm; moderate, strong, and intolerable ocular irritation were reported at 110, 250, 580 ppm, respectively. Nasal and ocular irritation were not reported at 0.4 or 18 ppm, respectively. Throat irritation and headache were noted, but the concentrations at which these effects occurred were not reported.

TABLE 3-1 AEGL Values for Phenyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	1.0 ppm (4.5 mg/m^3)	0.70 ppm (3.2 mg/m^3)	0.53 ppm (2.4 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.17 ppm (0.77 mg/m^3)	One-third reduction of AEGL-3 values
AEGL-3 (lethal)	3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)	LC_{01} in rats (Fairchild and Stokinger 1958)

Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.
[a]The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values will be without effect.

TABLE 3-2 Physical and Chemical Data on Phenyl Mercaptan

Common Name	Phenyl Mercaptan	Reference
Synonyms	Benzenethiol; thiophenol; mercaptobenzene	HSDB 2009
CAS registry no.	108-98-5	HSDB 2009
Chemical formula	C_6H_5SH	HSDB 2009
Molecular weight	110.18	HSDB 2009
Physical state	Water-white liquid	HSDB 2009
Odor	Garlic-like, penetrating, repulsive	Shertzer 2012
Melting point	-14.9°C	
Boiling point	168.3°C	
Density/Specific gravity	1.0728 at 25°C	HSDB 2009
Solubility	835 mg/L at 25°C in water; very soluble in alcohol; miscible with ether, benzene, and carbon disulfide	HSDB 2009
Saturated vapor concentration	2,539 ppm (11,428 mg/m^3) at 25°C	Calculated
Vapor pressure	1.93 mm Hg at 25°C	HSDB 2009
Conversion factors in air	1 mg/m^3 = 0.22 ppm 1 ppm = 4.5 mg/m^3	NIOSH 2011

TABLE 3-3 Odor Intensity of Phenyl Mercaptan

Intensity	Description	Concentration (ppm)
0	No odor	0.000005
1	Detectable	0.00025
2	Faint	0.014
3	Median, easily noticeable	0.72
4	Strong	38
5	Most intense	2,000

Source: Adapted from Katz and Talbert 1930.

Amoore and Hautala (1983) reported an odor threshold for phenyl mercaptan of 0.00094 ppm. This value is the geometric mean of published odor threshold values. AIHA (1989) reported odor thresholds of 0.00003-0.0003 ppm for phenyl mercaptan.

2.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies of human exposure to phenyl mercaptan were not available.

2.4. Genotoxicity

Genotoxicity studies of human exposure to phenyl mercaptan were not available.

2.5. Carcinogenicity

Carcinogenicity studies of human exposure to phenyl mercaptan were not available.

2.6. Summary

Data concerning human exposure to phenyl mercaptan are limited to odor threshold data. Data on acute lethality, developmental and reproductive toxicity, genotoxicity, and carcinogenicity in humans were not available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

Fairchild and Stokinger (1958) exposed groups of 5-10 Swiss-derived male mice (body weight 25-28 g) to phenyl mercaptan at 20, 31, 41, 52, or 79

ppm for 4-h, followed by a 15-day observation period. Vapor generation was achieved by either bubbling a stream of nitrogen gas through a midget fritted-glass bubbler, which contained liquid phenyl mercaptan, or by passage of nitrogen into a borosilicate glass nebulizer containing the phenyl mercaptan. Target concentrations were maintained in an 18-L glass chamber by varying the ratio of volume flow of air and phenyl mercaptan containing compressed nitrogen. Phenyl mercaptan concentrations were measured during exposure periods by absorption of vapors in either isopropyl alcohol or acetone containing an excess of silver nitrate and titrating the uncombined silver amperometrically. Chamber concentrations during tests were uniform after the first 30 min; mean variation for all exposures was approximately 4%. Clinical signs included increased respiration and restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of a prone position, and mild to heavy sedation; however, concentration-response data were not provided. Animals exposed to "maximal lethal concentrations" typically died from respiratory arrest during exposure or shortly after removal from the chamber. Animals exposed to "minimal lethal concentrations" typically died while in a semi-conscious condition of "long duration". Surviving animals often remained in a semi-conscious state of sedation and lethargy 4- to 6-h post-exposure before showing signs of recovery. An LC_{50} (lethal concentration, 50% lethality) value of 28 ppm was calculated by the investigators. A BMC_{01} (benchmark concentration with 1% response) of 26.5 ppm and $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 18.5 ppm were also calculated. LC_{05} and LC_{01} values could not be calculated by the method of Litchfield and Wilcoxon (1949) because there were no data on at least two concentrations the resulted in mortality between 0% and 100%. Mortality data for phenyl mercaptan are presented in Table 3-4.

An oral LD_{50} (lethal dose, 50% lethality) of 267 mg/kg was reported for male albino mice (Hazleton Laboratories 1951).

3.1.2. Rats

Fairchild and Stokinger (1958) exposed groups of 5-10 Wistar-derived male rats (body weight 180-220 g) to phenyl mercaptan at 20, 31, 41, 52, 79, or 132 ppm for 4 h, followed by a 15-day observation period. Vapor generation and test chamber analysis was similar to that described for experiments in mice (see Section 3.1.1). Clinical signs included increased respiration and restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of a prone position, and mild to heavy sedation; however, no concentration-response data were provided for clinical signs. Animals exposed to "maximal lethal concentrations" typically died from respiratory arrest during exposure or shortly after removal from the chamber. Animals exposed to "minimal lethal concentrations" typically died while in a semi-conscious condition of

"long duration". Surviving animals often remained in a semi-conscious state of sedation and lethargy 4- to 6-h post-exposure before showing signs of recovery. An LC_{50} value of 33 ppm was calculated by the investigators. A BMC_{01} of 17.7 ppm and a $BMCL_{05}$ of 13.4 ppm were also calculated. An LC_{05} value of 15.5 ppm and LC_{01} value of 10.3 ppm were calculated by the method of Litchfield and Wilcoxon (1949). Mortality data on phenyl mercaptan are presented in Table 3-4.

Groups of five male and five female albino rats were exposed to phenyl mercaptan at 244, 346, or 595 ppm for 1 h, followed by a 14-day observation period (Stauffer Chemical Company 1969). Clinical signs included ocular edema and erythema, and slight nasal discharge; investigators did not report whether these effects were observed in all test groups. "Acute depression" (no additional information provided) was reported in the 244-ppm group, and dyspnea, gagging, fasciculation, and cyanosis were reported in the 346- and 595-ppm groups while the animals were in the exposure chamber. There were no treatment-related deaths in the 244-ppm group, and animals appeared normal during gross pathologic examination. Treatment-related death was occurred in 3/10 animals at 346 ppm and 10/10 animals at 595 ppm. Decedents exhibited areas of hemorrhage in the lungs, while survivors in the 346-ppm group appeared normal during gross examination. The authors calculated an LC_{50} of 422 ppm. No further experimental details were available.

Fairchild and Stokinger (1958) also administered phenyl mercaptan by oral gavage, intraperitoneal injection, or dermal application to Wistar-derived male rats, followed by a 15-day observation period. An oral LD_{50} of 46.2 mg/kg, an intraperitoneal LD_{50} of 9.8 mg/kg, and a dermal LD_{50} of 300 mg/kg were reported.

3.1.3. Rabbits

Fairchild and Stokinger (1958) administered single dermal applications of phenyl mercaptan at 67, 134, or 213 mg/kg to groups of three New Zealand white rabbits, followed by a 72-h observation period. None of the rabbits in the 67-mg/kg group died, 2/3 rabbits died within 72 h in the 134-mg/kg group, and 3/3 rabbits in the 213-mg/kg group died within 4 h of administration.

3.2. Nonlethal Toxicity

No nonlethal animal toxicity data on phenyl mercaptan were available.

3.3. Repeated-Exposure Studies

Seven adult male albino rats and 12 adult male albino mice were exposed in chambers in which 3.2% of the atmosphere was saturated with phenyl mercaptan for 6 h on the first exposure day and for 8 h/day on the next 3 days (Haz-

leton Laboratories 1951). There were no overnight exposures. Exposures were conducted in a stainless steel chamber with a 30 L/min flow rate.

Mice exhibited excitement, preening, and slight salivation during the first 6 h exposure period. Seven mice were dead the following morning, but the surviving five mice appeared normal (Group A). A second group of 13 adult male albino mice was added to the experiment (Group B). All mice were then exposed 8 h/day for three consecutive days. Of the five remaining mice from group A, two died on day 2 of exposure, two died on day 4, and the fifth died 3 days after the final exposure. Hemorrhagic lungs, irritation of the intestines, and spotted livers and kidneys were found at necropsy. Group B mice also exhibited preening, lacrimation, and salivation immediately after exposure started, and subsequently were lethargic and appeared unkempt. Eleven of the 13 Group-B mice died; deaths occurred between day 1 of exposure and 3 days after the final exposure. Hemorrhagic lungs, irritated intestines, and spotty livers and kidneys were noted in both decedents and animals killed three days after the final exposure.

Rats exhibited preening, lacrimation, and marked salivation during exposure to phenyl mercaptan, followed by unkempt appearance and lethargy. One rat died overnight after the final exposure, and another died 3 days after the final exposure. Hemorrhagic lungs, intestinal irritation, and mottled livers and kidneys were found in the decedents. Surviving rats sacrificed 3 days after the final exposure showed gas-filled and irritated stomachs and intestines, pale brown kidneys, small spleens, mottled livers, and irritated eyes. An odor of phenyl mercaptan was noted when the abdominal cavity was opened.

TABLE 3-4 Mortality in Mice and Rats Exposed to Phenyl Mercaptan for 4 Hours

Concentration (ppm)	Mice	Rats
20	0/10	0/5
31	7/10	5/10
41	10/10	4/6
52	10/10	5/5
79	5/5	10/10
132	–	10/10
BMC_{01}	26.5 ppm	17.7 ppm
$BMCL_{05}$	18.5 ppm	13.4 ppm
LC_{01}	Not applicable	10.3 ppm
LC_{05}	Not applicable	15.5 ppm
LC_{50}	28 ppm	33 ppm

Source: Adapted from Fairchild and Stokinger 1958.

3.4. Developmental and Reproductive Toxicity

Groups of 25 pregnant CD rats were administered phenyl mercaptan by gavage in corn oil at doses of 0, 20, 35, or 50 mg/kg/day on gestation days 6-15 (NTP 1994a). Four high-dose dams died. There was no treatment-related effect on pregnancy rates; dose-related clinical signs in dams were limited to rooting behavior after gavage administration. Maternal body weight, body weight gain, and food consumption were decreased in high-dose dams. High-dose animals showed decreased gravid uterine weight, increased post-implantation loss, decreased live litter size, decreased fetal body weight per litter, and increased incidence of external fetal malformations.

Groups of 15-26 pregnant New Zealand white rabbits were administered phenyl mercaptan in corn oil at doses of 0, 10, 30, or 40 mg/kg/day on gestation days 6-19 (NTP 1994b). On gestation day 30, fetuses were removed from the does and examined. Two does died during the study, one each in the 10- and 30-mg/kg/day groups. No consistent maternal clinical signs were found, and only transient decreases in body weight were noted at 30 and 40 mg/kg/day. There were no treatment-related effects on gravid uterine weight, number of implantation sites/litter, preimplantation loss, live litter size, sex ratio, fetal body weight, or fetal malformations.

In a multigenerational study, male and female Sprague-Dawley rats (F_0) were administered phenyl mercaptan by gavage in corn oil at doses of 9, 18, or 35 mg/kg/day for a 16-week cohabitation period (NTP 1996). During that time, any litters born to F_0 animals were killed on postnatal day 1. Litters born after 17 weeks (F_1) were raised until postnatal day 21, and then selected weanlings were administered phenyl mercaptan at the same doses as their parents. On postnatal day 81, F_1 animals were allowed to cohabitate for 1 week and were killed after their litters (F_2) were delivered. There were dose-related increases in hepatic weight (20-50% in males, 11-36% in females) and renal weight (30-104% in males, 8-20% in females) in all treatment groups of both parental generations. Decreased body weight (7-15%) was observed only in parental males at 35 mg/kg/day. Decreases in sperm motility (5-6%) were noted at 18 and 35 mg/kg/day. Decreases in pup body weight were sporadic, but were generally more pronounced at the higher doses.

3.5. Genotoxicity

Phenyl mercaptan was negative in an Ames *Salmonella typhimurium* assay with strains TA98 and TA100 (LaVoie et al. 1979).

3.6. Carcinogenicity

Carcinogenicity studies of phenyl mercaptan in animals were not available.

3.7. Summary

Animal toxicity data on phenyl mercaptan were limited. Inhalation lethality studies in rats and mice were available that suggest a steep concentration-response curve. In mice exposed to phenyl mercaptan for 4 h, mortality was 0% at 20 ppm, 70% a 31 ppm, and 100% at 41 ppm. The 4-h mouse LC_{50} value was 28 ppm (Fairchild and Stokinger 1958). In the rat, the 4-h LC_{50} value was 33 ppm, whereas the 4-h LC_{01} value was 10.3 ppm (Fairchild and Stokinger 1958). Clinical signs were indicative of central nervous system depression and respiratory arrest and included changes in respiration, restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, skeletal muscle paralysis, light to severe cyanosis, and coma. Repeated inhalation exposure studies in rats and mice reported signs of irritation during exposure and at necropsy. Mottling of the liver and kidneys were also noted at necropsy (Hazleton Laboratories 1951). Data on reproductive and developmental effects of phenyl mercaptan were only available from oral exposure studies. Maternal and fetal effects were found in rats (NTP 1994a), whereas no treatment-related effects were noted in rabbit does or fetuses (NTP 1994b). Phenyl mercaptan was not a reproductive toxicant in a multigenerational study of rats (NTP 1996). Phenyl mercaptan was not mutagenic in an Ames bacterial reverse mutation assay, and no carcinogenicity studies were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Adult rats were orally administered ^{35}S-labeled phenyl mercaptan at a dose of 6 mg/kg (McBain and Menn 1969). One hour after administration, excreted urine was extracted with benzene and the aqueous layer was acidified with sulfuric acid and extracted with ether. The benzene-soluble and water-soluble products were analyzed by thin-layer chromatography and gas-liquid chromatography. The only benzene-soluble metabolite identified was ^{35}S-methylphenyl sulfone. Trace amounts of methylphenyl sulfoxide were also identified. The authors concluded that phenyl mercaptan readily undergoes S-methylation, followed by oxidation of phenylsulfide to methylphenyl sulfone.

4.2. Mechanism of Toxicity

Mercaptans act similarly to hydrogen sulfide and cyanide by interrupting electron transport through inhibition of cytochrome oxidase (NIOSH 1978). As a result of the electron transfer blockage, oxidative phosphorylation and aerobic metabolism may be compromised, peripheral tissue P_{O2} increases, and the unloading gradient for oxyhemoglobin decreases. High concentrations of oxyhemoglobin are thus found in the venous return, resulting in flushed skin and mu-

cous membranes. Lactic acidemia occurs as a result of the increased demand placed on glycolysis. Additionally, repeated-exposure studies of phenyl mercaptan suggest that certain effects, such as renal effects, might be due to the phenol moiety.

4.3. Structure-Activity Relationships

Rat lethality data suggest that the acute inhalation toxicity of phenyl mercaptan is much greater than other mercaptans or hydrogen sulfide (see Table 3-5).

4.4. Concurrent Exposure Issues

Because cyanide, hydrogen sulfide, methyl mercaptan, ethyl mercaptan, and phenyl mercaptan are all cytochrome oxidase inhibitors, an interaction might be possible if individuals were simultaneously exposed to two or more of these compounds (Smith 1991). These interactions could result in lower lethal exposure concentrations for phenyl mercaptan.

TABLE 3-5 Comparative Toxicity of Mercaptans

Compound	Rat Intraperitoneal LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	4-h Inhalation LC_{50} (ppm)		Reference
			Rats	Mice	
Hydrogen sulfide	–	–	444	–	Tansy et al. 1981
Methyl mercaptan	–	–	675	1,664	Horiguchi 1960 (mice); Tansy et al. 1981(rats)
Ethyl mercaptan	226	682	4,420	2,770	Fairchild and Stokinger 1958
Propyl mercaptan	515	1,790	7,200	4,010	Fairchild and Stokinger 1958
Isobutyl mercaptan	917	7,168	>25,000	>25,000	Fairchild and Stokinger 1958
tert-Butyl mercaptan	590	4,729	22,200	16,500	Fairchild and Stokinger 1958
n-Butyl mercaptan	399	1,500	4,020	2,500	Fairchild and Stokinger 1958
n-Hexyl mercaptan	396	1,254	1,080	528	Fairchild and Stokinger 1958
Phenyl mercaptan	*9.8*	*46.2*	*33*	*28*	Fairchild and Stokinger 1958
Benzyl mercaptan	373	493	>235	178	Fairchild and Stokinger 1958
tert-Octyl mercaptan	12.9	83.5	51 (males)	47 (males)	Fairchild and Stokinger 1958

4.5. Species Differences

Because of the limited data available on phenyl mercaptan, a definitive assessment of species variability is not possible. Fairchild and Stokinger (1958) reported similar 4-h LC_{50} values in rats (33 ppm) and mice (28 ppm). However, the latency period for death was shorter in mice than rats. Exposure of rats to phenyl mercaptan at 41 ppm resulted in no deaths during exposure or 24 h post-exposure; in contrast, 4/10 mice died during exposure at 41 ppm and 7/10 died within the first 24 h post-exposure.

4.6. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate to derive an empirical value of n for phenyl mercaptan. To obtain conservative and protective AEGL values in the absence of a chemical-specific scaling exponent, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data on phenyl mercaptan were not available for deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Animal data on phenyl mercaptan were not available for deriving AEGL-1 values.

5.3. Derivation of AEGL-1

AEGL-1 values for phenyl mercaptan are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values are without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data on phenyl mercaptan were not available for deriving AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Fairchild and Stokinger (1958) reported clinical signs of uncoordinated movement, partial muscle paralysis, and mild to heavy sedation in rats exposed to phenyl mercaptan for 4 h; however, no concentration-response data were provided which could be used to identify an AEGL-2 effect level. Stauffer Chemical Company (1969) reported "acute depression" in rats exposed to phenyl mercaptan at 244 ppm for 1 h. This study was considered unsuitable for deriving AEGL-2 values because 244 ppm is seven times higher than the 4-h LC_{50} of 33 ppm estimated by Fairchild and Stokinger (1958).

6.3. Derivation of AEGL-2 Values

No inhalation studies of phenyl mercaptan with concentration and duration information consistent with the definition of AEGL-2 were available. Therefore, AEGL-2 values were based on a 3-fold reduction in the AEGL-3 values. These calculations were considered estimated thresholds for serious or irreversible effects or inability to escape. The calculations are appropriate because of the steep concentration-response curve for lethality. AEGL-2 values for phenyl mercaptan are presented in Table 3-6, and calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human data on phenyl mercaptan were not available for calculating AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

A 4-h LC_{50} value of 28 ppm, $BMCL_{05}$ value of 18.5 ppm, and BMC_{01} value of 26.5 ppm were calculated for mice exposed to phenyl mercaptan (Fairchild and Stokinger 1958). A 4-h LC_{50} value of 33 ppm, $BMCL_{05}$ value of 13.4 ppm, BMC_{01} value of 17.7 ppm, LC_{05} value of 15.5 ppm, and LC_{01} value of 10.3 ppm were calculated for rats (Fairchild and Stokinger 1958). A 1-h LC_{50} value of 422 ppm in rats was also calculated (Stauffer Chemical Company 1969).

TABLE 3-6 AEGL-2 Values for Phenyl Mercaptan

10 min	30 min	1 h	4 h	8 h
1.0 ppm ($4.5 mg/m^3$)	0.70 ppm ($3.2 mg/m^3$)	0.53 ppm ($2.4 mg/m^3$)	0.33 ppm ($1.5 mg/m^3$)	0.17 ppm ($0.77 mg/m^3$)

7.3. Derivation of AEGL-3 Values

The 4-h LC_{01} of 10.3 ppm for rats (Fairchild and Stokinger 1958) is the lowest of the predicted lethality thresholds for phenyl mercaptan (see Table 3-4), and was used to derive AEGL-3 values. The rat data were selected because the BMC_{01} and $BMCL_{05}$ values were lower than the corresponding values in mice, and LC_{01} and LC_{05} values could not be calculated from the mouse data (see Section 3.1.1).

A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. Those factors were considered sufficient because the mechanism of action (cytochrome oxidase inhibition) is not expected to vary greatly between or within species. Although an interspecies or intraspecies uncertainty factor of 10 might normally be applied because of limited data, a total uncertainty of 30 would yield AEGL values that are inconsistent with the AEGL values for the structural and mechanistic analogs ethyl mercaptan, methyl mercaptan, and hydrogen sulfide, all of which have a more robust data set than phenyl mercaptan. Rat lethality data (see Section 4.3) suggest that the acute inhalation toxicity of phenyl mercaptan is approximately 140-fold greater than ethyl mercaptan, 20-fold greater than methyl mercaptan, and 13-fold greater than hydrogen sulfide. A total uncertainty factor of 30 would yield AEGL-3 values that suggest phenyl mercaptan is 450- to 650-fold more toxic than ethyl mercaptan, 120-fold more toxic than methyl mercaptan, and 77- to 180-fold more toxic than hydrogen sulfide. However, using a lower total uncertainty factor of 10 yields AEGL-3 values that suggest phenyl mercaptan is 150- to 230-fold more toxic than ethyl mercaptan, 29- to 42-fold more toxic than methyl mercaptan, and 25- to 58-fold more toxic than hydrogen sulfide. Also, the AEGL-3 point of departure (10.3 ppm) is approximately one-third the 4-h LC_{50} in rats (33 ppm). Thus, a total uncertainty factor of 10 yields values that are protective and are more consistent with relative toxicity data.

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific exponent, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations (10 min, 30 min, and 1 h) and n = 1 when extrapolating to longer durations (8 h). AEGL-3 values for phenyl mercaptan are presented in Table 3-7, and calculations are presented in Appendix A.

Time scaling from the 4-h point of departure to the 10-min AEGL-3 value is supported by the 1-h rat lethality data (Stauffer Chemical Company 1969). The estimated 1-h lethality threshold for rats is 141 ppm (one-third of the LC_{50} value [422 ppm ÷ 3 = 141 ppm]). Time scaling to the 10-min duration, using n = 3, and applying a total uncertainty factor of 10 would yield a 10-min value of 26 ppm, suggesting that the 10-min AEGL value of 3.0 ppm is protective.

TABLE 3-7 AEGL-3 Values for Phenyl Mercaptan

10 min	30 min	1 h	4 h	8 h
3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Table 3-8 presents AEGL values for phenyl mercaptan. AEGL-1 values are not recommended because of insufficient data. Data on phenyl mercaptan were also inadequate for deriving AEGL-2 values, so AEGL-2 values were estimated by taking one-third of the AEGL-3 values. These calculations are considered thresholds for the inability to escape, and are appropriate because of the steep concentration-response curve for phenyl mercaptan. AEGL-3 values were based on the LC_{01} of 10.3 ppm in rats exposed to phenyl mercaptan for 4 h (Fairchild and Stokinger 1958).

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to phenyl mercaptan are presented in Table 3-9.

The data requirements for establishing other standards and guidelines differ from those of AEGLs. The documentation for those values does not provide sufficient detail to understand the quantitative basis of the TLV®-TWA established in 2004 by of the American Conference of Governmental Industrial Hygienists or the earlier TLV-TWA (which was the basis for the Dutch MAC). The NIOSH REL ceiling value was derived in 1978 (NIOSH 1978) as follows:

> Because benzenethiol [phenyl mercaptan] is not only more toxic than the other thiols (Fairchild and Stokinger, 1958) but also has a comparatively marked potential for causing eye and organ damage, e.g., at 0.72 ppm, at one-third the concentration of ethanethiol (2.1 ppm), as indicated by Katz and Talbert (1930), NIOSH recommends that the concentration of benzenethiol in the workplace air should not exceed 0.1 ppm (0.45 mg/cu m) as a ceiling concentration for any 15-min period.

8.3. Data Adequacy and Research Needs

Data on acute inhalation exposure to phenyl mercaptan in humans and animals are sparse, and the few studies available are old and poorly reported. There were insufficient data to establish a chemical-specific time-scaling exponent for phenyl mercaptan.

TABLE 3-8 AEGL Values for Phenyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	1.0 ppm (4.5 mg/m^3)	0.70 ppm (3.2 mg/m^3)	0.53 ppm (2.4 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.17 ppm (0.77 mg/m^3)
AEGL-3 (lethal)	3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)

[a]The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values are without effect.

TABLE 3-9 Standards and Guidelines for Phenyl Mercaptan

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 ppm (4.5 mg/m^3)	0.70 ppm (3.2 mg/m^3)	0.53 ppm (2.4 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.17 ppm (0.77 mg/m^3)
AEGL-3	3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)
TLV-TWA (ACGIH)[a]					0.1 ppm (0.45 mg/m^3)
REL-C (NIOSH)[b]	0.1 ppm (0.5 mg/m^3)	0.1 ppm (0.5 mg/m^3)	0.1 ppm (0.5 mg/m^3)	0.1 ppm (0.5 mg/m^3)	0.1 ppm (0.5 mg/m^3)
MAC (The Netherlands)[c]					0.5 ppm (2 mg/m^3)

[a]TLV-TWA (threshold limit value-time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[b]REL-C (recommended exposure limit-ceiling, National Institute for Occupational Safety and Health [NIOSH 2011]) is a ceiling value that should not be exceeded at any time during a workday.
[c]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands [MSZW 2004]), is defined analogous to the ACGIH TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PHENYL MERCAPTAN

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for phenyl mercaptan because of insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values will be without effect.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values and because phenyl mercaptan has a steep concentration-response curve, AEGL-3 values were divided by 3 to estimate a threshold for inability to escape.

10-min AEGL-2: 3.0 ppm ÷ 3 = 1.0 ppm

30-min AEGL-2: 2.1 ppm ÷ 3 = 0.70 ppm

1-h AEGL-2: 1.6 ppm ÷ 3 = 0.53 ppm

4-h AEGL-2: 1.0 ppm ÷ 3 = 0.33 ppm

8-h AEGL-2: 0.52 ppm ÷ 3 = 0.17 ppm

Derivation of AEGL-3 Values

Key study: Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Toxicity end point: Estimated lethality threshold for rats, 4-h LC_{01} of 10.3 ppm

Time scaling: $C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations)
$(10.3\ ppm)^3 \times 4\ h = 4{,}371\ ppm\text{-}h$
$(10.3\ ppm)^1 \times 4\ h = 41.2\ ppm\text{-}h$

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10-min AEGL-3:	$C^3 \times 0.167$ h = 4,371 ppm- h C^3 = 26,174 ppm C = 29.7 ppm 29.7 ppm ÷ 10 = 3.0 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 4,371 ppm- h C^3 = 8,742 ppm C = 20.6 ppm 20.6 ppm ÷ 10 = 2.1 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 4,371 ppm- h C^3 = 4,371 ppm C = 16.4 ppm 16.4 ppm ÷ 10 = 1.6 ppm
4-h AEGL-3:	10.3 ppm ÷ 10 = 1.0 ppm
8-h AEGL-3:	$C^1 \div 8$ h = 41.2 ppm -h C^1 = 5.15 ppm C = 5.15 ppm 5.15 ppm ÷ 10 = 0.52 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHENYL MERCAPTAN

Derivation Summary

AEGL-1 VALUES

AEGL-1 values for phenyl mercaptan are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values are without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.0 ppm (4.5 mg/m^3)	0.70 ppm (3.2 mg/m^3)	0.53 ppm (2.4 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.17 ppm (0.77mg/m^3)

Data adequacy: Data inadequate to derive AEGL-2 values. AEGL-3 values were divided by 3 to estimate thresholds for the inability to escape.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)

Reference: Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Test Species/Strain/Sex/Number: Rats, Wistar, 5-10 males per group

Exposure route/Concentrations/Durations: Inhalation; 0, 20, 31, 41, 52, 79, or 132 ppm for 4 h

Effects:

Concentration (ppm)	Mortality in Rats
20	0/5
31	5/10
41	4/6
52	5/5
79	10/10
132	10/10

LC_{50} = 33 ppm
LC_{01} = 10.3 ppm

(Continued)

AEGL-3 VALUES

End point/Concentration/Rationale: Estimated lethality threshold in rats, 4-h LC_{01} of 10.3 ppm

Uncertainty factors/Rationale:
Intraspecies: 3
Interspecies: 3
Interspecies and intraspecies uncertainty factors of 3 (total uncertainty factor of 10) are considered sufficient because the mechanism of action for phenyl mercaptan toxicity (cytochrome oxidase inhibition) is not expected to vary greatly between or within species. Although an interspecies or intraspecies uncertainty factor of 10 might normally be applied because of limited data, a total uncertainty factor of 30 would yield AEGL values that are inconsistent with the AEGL values derived for the structural and mechanistic analogs ethyl mercaptan, methyl mercaptan, and hydrogen sulfide, all of which have a more robust data set than phenyl mercaptan. For example, rat lethality data suggest that the acute inhalation toxicity of phenyl mercaptan is approximately 140-fold greater than that of ethyl mercaptan, 20-fold greater than methyl mercaptan, and 13- fold greater than hydrogen sulfide. The 4-h rat LC_{50} value for phenyl mercaptan was 33 ppm (Fairchild and Stokinger 1958), whereas the 4-h rat LC_{50} value for ethyl mercaptan was 4,740 ppm (Fairchild and Stokinger 1958), the 4-h LC_{50} value for methyl mercaptan was 675 ppm (Tansy et al. 1981), and the 4-h LC_{50} value for hydrogen sulfide was 444 ppm (Tansy et al. 1981). Using a total uncertainty factor of 30 would yield values that suggest phenyl mercaptan is 450- to 650-fold more toxic than ethyl mercaptan, 120-fold more toxic than methyl mercaptan, and 77- to 180-fold more toxic than hydrogen sulfide. However, a lower total uncertainty of 10 yields AEGL-3 values that suggest phenyl mercaptan is 150- to 230-fold more toxic than ethyl mercaptan, 29- to 42-fold more toxic than methyl mercaptan, and 25- to 58-fold more toxic than hydrogen sulfide. Also, the AEGL-3 point of departure (10.3 ppm) is approximately one-third the 4-h LC_{50} in rats (33 ppm). Thus, factors of 3 for interspecies difference and intraspecies variability are protective and are more consistent with relative toxicity data.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; default values of n = 1 for extrapolation from shorter to longer durations (8 h) and n = 3 for extrapolation from longer to shorter durations (10 min, 30 min, and 1 h) were used. Time scaling from the 4-h point of departure to the 10-min AEGL-3 value is supported by the 1-h rat lethality data (Stauffer Chemical Company 1969). The estimated 1-h rat lethality threshold is 141 ppm (one-third of the LC_{50} value [422 ppm ÷ 3 = 141 ppm]). Time scaling to 10-min using an exponent of n = 3 and applying a total uncertainty factor of 10 would yield a 10-min value of 26 ppm, suggesting that the 10-min AEGL-3 value of 3.0 ppm is protective.

Data adequacy: The study was well conducted and used a sufficient number of animals. The selected end point represents an estimate threshold for lethality.

APPENDIX C

CATEGORY PLOT FOR PHENYL MERCAPTAN

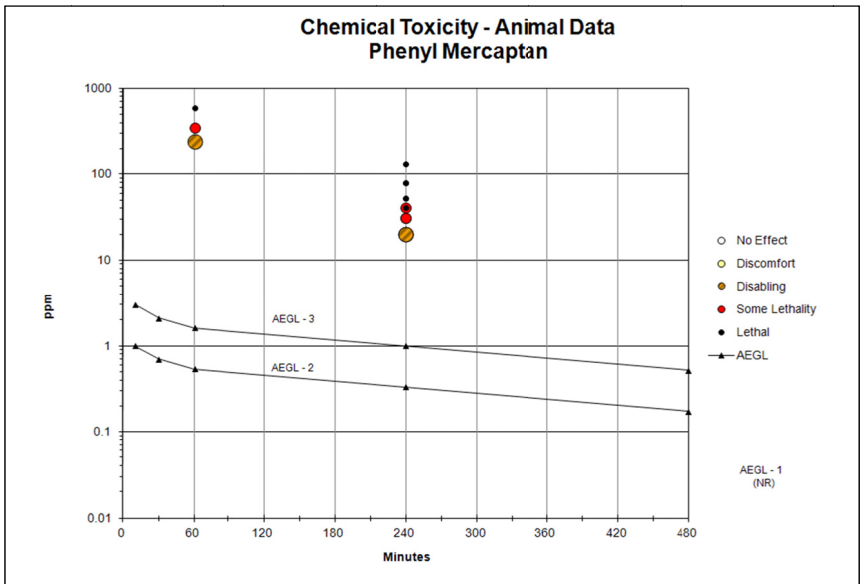

FIGURE C-1 Category plot of toxicity data and AEGL values for phenyl mercaptan. The decimal point is lost on this log-scale plot.

TABLE C-1 Data Used in Category Plot for Phenyl Mercaptan

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				1.00	10	AEGL	
AEGL-2				0.70	30	AEGL	
AEGL-2				0.53	60	AEGL	
AEGL-2				0.33	240	AEGL	
AEGL-2				0.17	480	AEGL	
AEGL-3				3.00	10	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-3				2.10	30	AEGL	
AEGL-3				1.60	60	AEGL	
AEGL-3				1.00	240	AEGL	
AEGL-3				0.52	480	AEGL	
Fairchild and Stokinger 1958	Mouse	Male	1	20	240	2	
	Mouse	Male	1	31	240	SL	Mortality (7/10)
	Mouse	Male	1	41	240	3	Mortality (10/10)
	Mouse	Male	1	52	240	3	Mortality (10/10)
	Mouse	Male	1	79	240	3	Mortality (5/5)
	Rat	Male	1	20	240	2	
	Rat	Male	1	31	240	SL	Mortality (5/10)
	Rat	Male	1	41	240	SL	Mortality (4/6)
	Rat	Male	1	52	240	3	Mortality (5/5)
	Rat	Male	1	79	240	3	Mortality (10/10)
	Rat	Male	1	132	240	3	Mortality (10/10)
Stauffer Chemical Company 1969	Rat	Both	1	244	60	2	
	Rat	Both	1	346	60	SL	Mortality (3/10)
	Rat	Both	1	595	60	3	Mortality (10/10)

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

4

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

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Chemical Manager Glenn Leach (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

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

SUMMARY

tert-Octyl mercaptan is a colorless liquid with a disagreeable odor. It is used in polymer modification and as a lubricant additive. It is generally prepared via acid-catalyzed synthesis. It is moderately irritating to the eyes, and may cause headache, nausea, vomiting, and central nervous system (CNS) effects, resulting in dizziness, convulsions, unconsciousness, and respiratory depression (HSDB 2006).

Data were insufficient to derive AEGL-1 values for tert-octyl mercaptan. Therefore, AEGL-1 values are not recommended.

Data on tert-octyl mercaptan were also insufficient to derive AEGL-2 values. In the absence of appropriate chemical-specific data, AEGL-3 values were divided by 3 to derive AEGL-2 values for tert-octyl mercaptan. This approach is justified by the chemical's steep concentration-response curve for lethality in rats.

AEGL-3 values were based on a 4-h $BMCL_{05}$ (benchmark concentration, 95% confidence limit with 5% response) value for tert-octyl mercaptan of 11.5 ppm, calculated from combined data on female rats (Temple University 1982). This concentration is considered a threshold for lethality and is based on the most sensitive test animals (females). An intraspecies uncertainty factor of 3 was applied and is considered sufficient because the point of departure is based on data from the more sensitive female animals and the steep concentration-response curve for lethality suggests limited intraindividual variability. An interspecies uncertainty factor of 3 was also applied because the limited data suggest

no difference in species sensitivity between rats and mice. Therefore, the total uncertainty factor was 10. Values were scaled across time using the equation $C^n \times t = k$, where default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used to derive values protective of human health (NRC 2001). The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty in extrapolating a 4-h point of departure to a 10-min value.

AEGL values for tert-octyl mercaptan are presented in Table 4-1.

1. INTRODUCTION

tert-Octyl mercaptan is a colorless liquid with a disagreeable odor. It is used in polymer modification and as a lubricant additive. It is generally prepared via acid-catalyzed synthesis. It is moderately irritating to the eyes, and may cause headache, nausea, vomiting, and CNS effects, resulting in dizziness, convulsions, unconsciousness, and respiratory depression (HSDB 2006).

The chemical and physical properties of tert-octyl mercaptan are presented in Table 4-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data on tert-octyl mercaptan were not found.

2.2. Nonlethal Toxicity

Human nonlethal toxicity data on tert-octyl mercaptan were not found. No odor threshold data were available either.

2.3. Case Reports

No case reports on tert-octyl mercaptan were found.

2.4. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of tert-octyl mercaptan in humans were not available.

2.5. Genotoxicity

No information regarding the genotoxicity of tert-octyl mercaptan in humans was available.

TABLE 4-1 AEGL Values for tert-Octyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	0.77 ppm (4.6 mg/m^3)	0.77 ppm (4.6 mg/m^3)	0.60 ppm (3.6 mg/m^3)	0.40 ppm (2.4 mg/m^3)	0.19 ppm (1.1 mg/m^3)	One-third the AEGL-3 values.
AEGL-3 (lethal)	2.3 ppm (14 mg/m^3)	2.3 ppm (14 mg/m^3)	1.8 ppm (11 mg/m^3)	1.2 ppm (7.2 mg/m^3)	0.58 ppm (3.5 mg/m^3)	Threshold for lethality ($BMCL_{05}$) in female rats (Temple University 1982)

[a]The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values will be without effect.
Abbreviations: $BMCL_{05}$, benchmark concentration, 95% confidence limit with 5% response; NR, not recommended.

TABLE 4-2 Chemical and Physical Data on tert-Octyl Mercaptan

Parameter	Value	Reference
Synonyms	tert-octanethiol; 2-methyl-2-heptanethiol; 2-pentanethiol, 2,4,4-trimethyl-	HSDB 2006
CAS registry no.	141-59-3	HSDB 2006
Chemical formula	$C_8H_{18}S$	HSDB 2006
Molecular weight	146.30	HSDB 2006
Physical state	Colorless liquid	HSDB 2006
Boiling point	154 -166°C	HSDB2006
Flash point	43°C	Shertzer 2001
Density/specific gravity	0.848 at 15.5°C	HSDB 2006
Relative vapor density	5.0 (air = 1)	HSDB 2006
Solubility in water	31 mg/L at 25°C	HSDB 2006
Saturated vapor concentration (neat)	6,842 ppm (41,052 mg/m^3)	Calculated
Vapor pressure	5.20 mm Hg at 25°C	HSDB 2006
Conversion factors in air	1 ppm = 6.0 mg/m^3 1 mg/m^3 = 0.17 ppm	

2.6. Carcinogenicity

No information was available regarding the carcinogenicity of tert-octyl mercaptan in humans.

2.7. Summary

No human data on tert-octyl mercaptan were found.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Fairchild and Stokinger (1958) exposed groups of five Wistar-derived male rats (body weight 180 -220g) to tert-octyl mercaptan at 38, 40, 44, 55, 64, 78, or 110 ppm (analytic concentrations) for up to 4 h, followed by a 15-day observation period. Vapor was generated by either bubbling a stream of nitrogen gas through a midget fritted-glass bubbler, which contained liquid tert-octyl mercaptan, or by passage of nitrogen into a borosilicate glass nebulizer containing the tert-octyl mercaptan. Target concentrations were maintained in an 18-L glass chamber by varying the ratio of air flow volume and tert-octyl mercaptan containing compressed nitrogen. Tert-octyl mercaptan concentrations during exposure periods were measured by absorption of vapors in either isopropyl alcohol or acetone containing an excess of silver nitrate and titrating the uncombined silver amperometrically. Chamber concentrations during tests were uniform after the first 30 min; mean variation was approximately 4%. Clinical signs included respiratory stimulation, followed by CNS stimulation initially characterized by a "threshold effect" consisting of localized minimal convulsive movements in the form of repeated facial and ear twitches. Seizures were observed at all concentrations; the severity, frequency, and latency period for the onset of seizures were concentration related. Propulsive and retropulsive thrusts of the trunk were also observed, followed by circumscribed clonic convulsions of the forebody and forelimbs, resulting in a sitting position while pawing in the air. These effects were followed by generalized clonic seizures of the forelimbs and hindlimbs that caused a loss of upright position. Exophthalmus with conjunctival congestion and salivation accompanied the seizures. Muscle relaxation, irregular labored breathing, and coma preceded death. An LC_{50} (lethal concentration, 50% lethality) value of 51 ppm was calculated by the investigators. A BMC_{01} of 34.4 ppm and $BMCL_{05}$ of 31.8 ppm were also calculated. Mortality data from this study are presented in Table 4-3.

Groups of five male and five female Sprague-Dawley rats were exposed to tert-octyl mercaptan at 0, 7, 15, 19, 29, 59, 71, or 110 ppm for 4 h, followed by a 14-day observation period (Temple University 1982). Exposures were conducted in an 11.4-ft^3 stainless-steel chamber. Vapor was generated by heating liquid tert-octyl mercaptan and passing air through at a constant rate. Chamber delivery system parameters were set at values calculated to produce target chamber concentrations. Analyses of tert-octyl mercaptan concentrations in the test atmospheres were performed by colorimetric titration four to 20 times during each 4-h exposure.

Clinical signs were noted in females at concentrations of 19 ppm and higher. The animals seized the wire mesh bottom of the exposure chamber with their teeth and claws, their backs were arched and tails extended, and they remained rigidly in this position until death or until the survivors were pried loose by the investigator. Salivation and a final convulsive leap were sometimes observed. Clinical signs included tremors and prostration in two of five males exposed at 71 ppm and all males exposed at 110 ppm. Animals that survived the first 24 h after exposure also survived until the end of the 14-day observation period. All surviving rats gained weight by the end of the observation period, and gross necropsy revealed no abnormalities. LC_{50} values of 33 ppm (males and females combined), 59 ppm (males), and 17 ppm (females) were calculated by the investigators. BMC_{01} values of 59.7 ppm (males) and 13.8 ppm (females) ppm and $BMCL_{05}$ values of 52 ppm (males) and 11.3 ppm (females) were also calculated. Mortality data from this study are presented in Table 4-4.

TABLE 4-3 Mortality in Wistar Rats Exposed to tert-Octyl Mercaptan for 4 Hours

Concentration (ppm)	Mortality	Comments
38	0/5	Seizures within 45 min to 1.5 h; average of 2 mild seizures
40	1/6	Seizures within 45 min to 1.5 h
44	1/5	Seizures within 45 min to 1.5 h
55	3/5	Seizures within 45 min to 1.5 h
64	5/5	Seizures within 20-30 min, at intervals of several minutes; all dead within 3 h, 10 min
78	6/6	Seizures within 20-30 min, at intervals of several minutes; all dead within 2 h, 50 min
110	6/6	Seizures within 10-15 min, at close intervals (2-3 min apart); all dead within 2 h, 45 min
LC_{50}		51 ppm (46.5-54.5 ppm)
$BMCL_{05}$		31.8 ppm
BMC_{01}		34.4 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Adapted from Fairchild and Stokinger 1958.

TABLE 4-4 Mortality in Sprague-Dawley Rats Exposed to tert-Octyl Mercaptan for 4 Hours

	Mortality		
Concentration (ppm)	Male	Female	Combined
0	0/5	0/5	0/10
7 ± 0.7	0/5	0/5	0/10
15 ± 3.0	0/5	1/5	1/10
19 ± 3.0	0/5	5/5	5/10
29 ± 2.0	0/5	5/5	5/10
59 ± 3.0	0/5	5/5	5/10
71 ± 1.0	4/5	5/5	9/10
110 ± 3.0	5/5	5/5	10/10
LC_{50}	59 ppm	17 ppm	33 ppm (16-66 ppm)
$BMCL_{05}$	52 ppm	11.3 ppm	4.8 ppm
BMC_{01}	59.7 ppm	13.8 ppm	4.6 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Temple University 1982.

Because of the results of the study above indicated that females are much more sensitive than male rats to acute lethality from tert-octyl mercaptan, another study was conducted in female rats. Groups of 10 female Sprague-Dawley rats were exposed to tert-octyl mercaptan at 12, 14, 17, 18, or 19 ppm for 4 h, followed by a 14-day observation period (Temple University 1982). The experimental methods were similar to those described for the previous study. Tremors and clonic convulsions were observed in all test groups. All animals that survived the first 24 h after exposure also survived until the end of the observation period. No signs of hemorrhage or other signs of visible pathology were found in rats that died. At the end of the 14-day observation period, 19 of 21 surviving rats gained weight, and gross necropsy revealed no abnormalities. An LC_{50} value of 17 ppm (15-19 ppm) was calculated by the investigators. A BMC_{01} value of 10.7 ppm and $BMCL_{05}$ value of 10.1 ppm was also calculated. Mortality data from this study are presented in Table 4-5.

When the data on female rats presented in Tables 4-4 and 4-5 are combined to calculate benchmark levels, a 4-h $BMCL_{05}$ of 11.5 ppm and BMC_{01} of 14.7 ppm result (see Appendix C). Combining the data is acceptable because the data sets are from the same laboratory and used similar experimental methods.

Groups of five male and five female Charles River CD rats were exposed to tert-octyl mercaptan at 23, 24, 25, 73, 77, or 79 ppm (nominal concentrations) for 4 h, followed by a 14-day observation period (Amoco 1979). Exposures were conducted in a 160-L cubical, stainless steel and glass chamber. Test vapors

were generated by passing air at a rate of 10 L/min through a round-bottom flask containing tert-octyl mercaptan in a heating jacket. Chamber concentrations were calculated from the ratio of the rate of vapor dissemination to the rate of total chamber airflow. Clinical signs included convulsions, with females affected more frequently and with greater severity than males; clinical signs were observed at 73 ppm or higher in males and at 24 ppm or higher in females. All surviving rats lost weight on day 1 post-exposure compared with pre-exposure values. Male survivors gained weight by the end of the observation period; however, female survivors only maintained their body weight. Rats dying during exposure had red- or pink-colored lungs or lungs with red patches or scattered red pin points at necropsy. No gross pathologic effects were noted in animals killed at the end of the observation period. LC_{50} values of 50 ppm (males and females combined), 79 ppm (males), and 24 ppm (females) were calculated by the investigators. BMC_{01} values of 65.9 ppm (males) and 21.5 ppm (females) ppm and $BMCL_{05}$ values of 63.9 ppm (males) and 21.0 ppm (females) were also calculated. Data from this study are presented in Table 4-6.

A group of 10 male Wistar rats was exposed to tert-octyl mercaptan at 330 ppm (nominal concentration) and observed until death (Pharmacology Research Inc. 1970). All of the rats died; deaths occurred within 19, 22, 26, 27, 30, 32, 40, and 49 min of exposure. Clinical signs included muscular spasms, violent clonic convulsions, prostration, and terminal dyspnea.

Fairchild and Stokinger (1958) administered tert-octyl mercaptan by oral gavage in ethanol, intraperitoneal injection, or dermal application to Wistar-derived male rats, followed by 15-day observation periods. An oral LD_{50} (lethal dose, 50% lethality) of 85.3 mg/kg, an intraperitoneal LD_{50} of 12.9 mg/kg, and a dermal LD_{50} of 1,954 mg/kg were reported.

TABLE 4-5 Mortality in Female Sprague-Dawley Rats Exposed to tert-Octyl Mercaptan for 4 Hours

Concentration (ppm)	Mortality
12 ± 0.6	1/10
14 ± 0.5	3/10
17 ± 1.4	5/10
18 ± 0.7	10/10
19 ± 1.7	10/10
LC_{50}	17 ppm (15-19 ppm)
$BMCL_{05}$	10.1 ppm
BMC_{01}	10.7 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Temple University 1982.

TABLE 4-6 Mortality in Charles-River Rats Exposed to tert-Octyl Mercaptan for 4 Hours

	Mortality		
Concentration (ppm)	Male	Female	Combined
23	0/5	0/5	0/10
24	0/5	1/5	1/10
25	0/5	5/5	5/10
73	0/5	5/5	5/10
77	4/5	5/5	9/10
79	5/5	5/5	10/10
LC_{50}	79 ppm	24 ppm	50 ppm
$BMCL_{05}$	63.9 ppm	21.0 ppm	*
BMC_{01}	65.9 ppm	21.5 ppm	*

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
*P-value <0.1; therefore, not reported.
Source: Amoco 1979.

Nine of 10 rats administered tert-octyl mercaptan at 50 mg/kg in sesame oil by stomach tube died within 30-143 min after intubation (Pharmacology Research Inc. 1970). The surviving rat was observed for 5 days. Clinical signs included muscular spasms, violent clonic convulsions, prostration, and terminal dyspnea.

3.1.2. Mice

Fairchild and Stokinger (1958) exposed groups of 10 Swiss-derived male mice (body weight 25 -28 g) to tert-octyl mercaptan at 38, 40, 44, 55, 64, or 78 ppm (analytic concentrations) for up to 4 h, followed by a 15-day observation period. Vapor was generated and the test chamber analyzed in the same manner as the study in rats. Clinical signs in the mice were similar to those described for the rat in Section 3.1.1. An LC_{50} value of 47 ppm was calculated by the investigators. A BMC_{01} of 34.4 ppm and $BMCL_{05}$ of 33.6 ppm were also calculated. Mortality data from this study are presented in Table 4-7.

Groups of five male MF1 mice were exposed to tert-octyl mercaptan at 42, 58, 84, 117, or 167 ppm (nominal concentrations) for 1 h, followed by a 6-day observation period (Pharmacology Research Inc. 1969). Clinical signs were noted at all test concentrations and included hypertonicity, hypersensitivity, and multiple clonic-tonic convulsions. Mortality was 0/5, 2/5, 4/5, 5/5, and 5/5 at concentrations of 42, 58, 84, 117, and 167 ppm, respectively. All deaths occurred during exposure. An LC_{50} value of 69 ppm was calculated by the investigators. A BMC_{01} of 37.6 ppm and $BMCL_{05}$ of 28.4 ppm were also calculated. No further details were available.

TABLE 4-7 Mortality in Male Swiss Mice Exposed to tert-Octyl Mercaptan for 4 Hours

Concentration (ppm)	Mortality	Comments
38	0/10	–
40	2/10	–
44	4/10	–
55	9/10	–
64	10/10	All dead within 3 h
78	10/10	All dead within 1 h, 35 min
LC_{50}		47 ppm (45.3-48.7 ppm)
$BMCL_{05}$		33.6 ppm
BMC_{01}		34.4 ppm

Abbreviations: BMC_{01}, benchmark concentration with 1% response; $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; LC_{50}, lethal concentration, 50% lethality.
Source: Adapted from Fairchild and Stokinger 1958.

3.1.3. Rabbits

Fairchild and Stokinger (1958) administered single dermal applications of tert-octyl mercaptan at 213, 427, or 854 mg/kg to groups of two New Zealand white rabbits, followed by a 72-h observation period. Both rabbits in the 854-mg/kg group died within 8 h, and none of the rabbits in the 213- or 427-mg/kg groups died.

Ten albino rabbits were administered a single dermal application of tert-octyl mercaptan at 200 mg/kg for 4 h, followed by a 5-day observation period (Pharmacology Research Inc. 1970). No mortality or signs of toxicity were observed, and animals had normal body weight gain.

3.1.4. Summary of Animal Lethality Data

Inhalation lethality studies of tert-octyl mercaptan in rats and mice are available. Lethality data suggest a steep concentration-response curve for tert-octyl mercaptan. In studies of male rats exposed to tert-octyl mercaptan for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958), 0% at 59 ppm and 80% at 71 ppm (Temple University 1982), and 0% at 73 ppm and 100% at 79 ppm (Amoco 1979). In a study of female rats exposed to tert-octyl mercaptan for 4 h, mortality was10% at 12 ppm and 100% at 18 ppm. In mice exposed for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958). Rat data suggest that females are much more sensitive to tert-octyl mercaptan than males; calculated 4-h LC_{50} values were 59 ppm for male rats and 17 ppm for female rats in one study (Temple University 1982) and 79 ppm for males and 24 ppm for females in another (Amoco 1979).

Clinical signs were indicative of CNS stimulation followed by central depression and finally death from respiratory failure.

3.2. Nonlethal Toxicity

No animal data on the nonlethal toxicity of tert-octyl mercaptan were found.

3.3. Developmental and Reproductive Effects

No animal developmental and reproductive data on tert-octyl mercaptan were found.

3.4. Genotoxicity

No genotoxicity data on were found.

3.5. Carcinogenicity

No carcinogenicity data on tert-octyl mercaptan were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Metabolism and disposition data for tert-octyl mercaptan were not available.

4.2. Mechanism of Toxicity

Most mercaptans act similarly to hydrogen sulfide and cyanide by interrupting electron transport through inhibition of cytochrome oxidase, and general signs of acute mercaptan poisoning are indicative of central depression and respiratory paralysis, followed by death from respiratory failure (NIOSH 1978). However, data suggest that tert-octyl mercaptan acts differently because an initial effect of CNS stimulation is observed. Fairchild and Stokinger (1958) reported that the stimulatory effects of tert-octyl mercaptan were typical of other CNS stimulants such as picrotoxin and metrazol, and that the compound appeared to act at various levels of the cerebrospinal axis. Convulsive seizures were spontaneous in origin (not triggered by external stimuli), and tert-octyl mercaptan had an analeptic action on the higher CNS centers, as evidenced by the fact that subconvulsant doses stimulated the respiratory and vasomotor centers (Fairchild and Stokinger 1958). The analeptic action was demonstrated by the ability of tert-octyl mercaptan to counteract depression produced by barbiturates. Even though the CNS stimulation is unique to tert-octyl mercaptan, the

final result of acute toxicity is similar to other mercaptans: the CNS stimulation was followed by central depression and then death from respiratory failure.

4.3. Structure-Activity Relationships

Acute intraperitoneal, oral, and inhalation data in rats and inhalation data in mice suggest that tert-octyl mercaptan is more toxic than other mercaptans tested (with the exception of phenyl mercaptan) and more toxic than hydrogen sulfide (see Table 4-8).

4.4. Species Variability

Although data are limited, acute lethality studies suggest that rats and mice have similar sensitivity to the lethal effects of tert-octyl mercaptan. The 4-h LC_{50} is 51 ppm in male rats and 47 ppm in male mice (Fairchild and Stokinger 1958).

4.5. Gender Variability

Experimental data in rats (see Tables 4-4 and 4-5) suggest that females are more sensitive than males to the toxic effects of tert-octyl mercaptan (Amoco 1979; Temple University 1982).

4.6. Temporal Extrapolation

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of data to calculate an empirical value of n, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data on tert-octyl mercaptan relevant deriving AEGL-1 values were available.

5.2. Animal Data Relevant to AEGL-1

No animal data on tert-octyl mercaptan relevant to deriving of AEGL-1 values were available.

TABLE 4-8 Comparative Toxicity of Mercaptans

Compound	Rat Intraperitoneal LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	4-h Inhalation LC_{50} (ppm)		Reference
			Rats	Mice	
Hydrogen sulfide	–	–	444	–	Tansy et al. 1981
Methyl mercaptan	–	–	675	1,664	Horiguchi 1960 (mice); Tansy et al. 1981(rats)
Ethyl mercaptan	226	682	4,420	2,770	Fairchild and Stokinger 1958
Propyl mercaptan	515	1,790	7,200	4,010	Fairchild and Stokinger 1958
Isobutyl mercaptan	917	7,168	>25,000	>25,000	Fairchild and Stokinger 1958
tert-Butyl mercaptan	590	4,729	22,200	16,500	Fairchild and Stokinger 1958
n-Butyl mercaptan	399	1,500	4,020	2,500	Fairchild and Stokinger 1958
n-Hexyl mercaptan	396	1,254	1,080	528	Fairchild and Stokinger 1958
Phenyl mercaptan	9.8	46.2	33	28	Fairchild and Stokinger 1958
Benzyl mercaptan	373	493	>235	178	Fairchild and Stokinger 1958
tert-Octyl mercaptan	*12.9*	*83.5*	*51 (males)*	*47 (males)*	Fairchild and Stokinger 1958

5.3. Derivation of AEGL-1 Values

AEGL-1 values for tert-octyl mercaptan are not recommended because of insufficient data.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on tert-octyl mercaptan relevant to deriving of AEGL-2 values were found.

6.2. Animal Data Relevant to AEGL-2

No animal data on tert-octyl mercaptan relevant to deriving AEGL-2 values were found.

6.3. Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data, AEGL-3 values were divided by 3 to derive AEGL-2 values for tert-octyl mercaptan. This approach is justified because of the steep concentration-response curve for lethality. (See Section 7.3 for description of lethality data that demonstrates the steepness.) AEGL-2 values were presented in Table 4-9, and calculations are presented in Appendix A.

The AEGL-2 values are considered protective for the following reasons. No effects (clinical signs or mortality) were noted in male or female rats exposed to tert-octyl mercaptan at 7 ppm for 4 h (Temple University 1982), and a slightly higher concentration of 12 ppm caused clinical signs (tremors and clonic convulsions) in 90% and mortality in 10% of the female rats (Temple University 1982). If 7 ppm was used as a point of departure and the same time-scaling procedure and uncertainty factors were applied as described earlier, the resulting values (1.4 for the 10- and 30-min, 1.1 ppm for the 1-h, 0.70 ppm for the 4-h, and 0.35 for the 8-h values) would be slightly higher than the AEGL-2 values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on tert-octyl mercaptan relevant to deriving AEGL-3 values were available.

7.2. Animal Data Relevant to AEGL-3

A 4-h LC_{50} value of 51 ppm was calculated by Fairchild and Stokinger (1958) for Sprague-Dawley rats; a BMC_{01} of 34.4 ppm and $BMCL_{05}$ of 31.8 ppm were also calculated from this study.

In another study of Sprague-Dawley rat (Temple University 1982), 4-h LC_{50} values of 33 ppm (males and females combined), 59 ppm (males), and 17 ppm (females) were calculated by the investigators; BMC_{01} values of 59.7 ppm (males) and 13.8 ppm (females) and $BMCL_{05}$ values of 52 ppm (males) and 11.3 ppm (females) were also calculated. In a follow-up study with female Sprague-Dawley rats (Temple University1982), a 4-h LC_{50} value of 17 ppm (15-19 ppm) was calculated by the investigators; a BMC_{01} value of 10.7 ppm and $BMCL_{05}$ value of 10.1 ppm were also calculated. Combining the female rat data from the original and follow-up studies yields a 4-h $BMCL_{05}$ of 11.5 ppm and BMC_{01} of 14.7 ppm.

In a study with Charles River rats (Amoco 1979), 4-h LC_{50} values of 50 ppm (males and females combined), 79 ppm (males), and 24 ppm (females) were calculated by the investigators; BMC_{01} values of 65.9 ppm (males) and 21.5 ppm (females) ppm and $BMCL_{05}$ values of 63.9 ppm (males) and 21.0 ppm (females) were also calculated.

TABLE 4-9 AEGL-2 Values for tert-Octyl Mercaptan

10 min	30 min	1 h	4 h	8 h
0.77 ppm (4.6 mg/m^3)	0.77 ppm (4.6 mg/m^3)	0.60 ppm (3.6 mg/m^3)	0.40 ppm (2.4 mg/m^3)	0.19 ppm (1.1 mg/m^3)

In a mouse study (Fairchild and Stokinger 1958), a 4-h LC_{50} value of 47 ppm was calculated by the investigators; a BMC_{01} of 34.4 ppm and $BMCL_{05}$ of 33.6 ppm were also calculated. In another mouse study (Pharmacology Research Inc. 1970), a 1-h LC_{50} value of 69 ppm was calculated by the investigators; a BMC_{01} of 37.6 ppm and $BMCL_{05}$ of 28.4 ppm were also calculated.

7.3. Derivation of AEGL-3 Values

The 4-h $BMCL_{05}$ value of 11.5 ppm calculated from the combined female rat data (Atochem 1982) was used as the point of departure for AEGL-3 values. That concentration is considered a threshold for lethality based on the most sensitive test animals (females). This point of departure was chosen over the most conservative benchmark value calculated from a single study (10.1 ppm) because the statistical goodness-of-fit was much greater for the combined data set ($p = 0.86$) than for a single data set ($p = 0.15$). An intraspecies uncertainty factor of 3 was applied and was considered sufficient because the point of departure is based on data from the more sensitive female rats. Calculated 4-h LC_{50} values were 59 ppm for male rats and 17 ppm for female rats in one study (Temple University 1982) and 79 ppm for males and 24 ppm for females in another (Amoco 1979). Also, the steep concentration-response curve implies limited intraindividual variability. In studies of male rats exposed to tert-octyl mercaptan for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958), 0% at 59 ppm and 80% at 71 ppm (Temple University 1982), and 0% at 73 ppm and 100% at 79 ppm (Amoco 1979). In a study of female rats exposed to tert-octyl mercaptan for 4 h, mortality was10% at 12 ppm and 100% at 18 ppm. In mice exposed for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958). An interspecies uncertainty factor of 3 was applied because the limited data suggest no difference in species sensitivity between rats and mice (the 4-h LC_{50} is 51 ppm for male rats and 47 ppm for male mice [Fairchild and Stokinger 1958]). Therefore, the total uncertainty factor was 10. Values were scaled across time using the equation $C^n \times t = k$, where default values of $n = 3$ when extrapolating to shorter durations and $n = 1$ when extrapolating to longer durations were used to derive values protective of human health (NRC 2001). The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty in extrapolating a 4-h point of departure to a 10-min value.

AEGL-3 values for tert-octyl mercaptan are presented in Table 4-10, and calculations are provide in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values are not recommended for tert-octyl mercaptan because of insufficient data. AEGL-2 values were derived by dividing the AEGL-3 values by 3, and the AEGL-3 values were based on a threshold for lethality in female rats ($BMCL_{05}$). AEGL values for tert-octyl mercaptan are presented in Table 4-11.

8.2. Comparisons with Other Standards and Guidelines

There are no other exposure standards or guidelines for tert-octyl mercaptan.

8.3. Data Adequacy and Research Needs

Human data on tert-octyl mercaptan are limited. Additional data on toxicity in females in species other than rats would be helpful.

TABLE 4-10 AEGL-3 Values for tert-Octyl Mercaptan

10 min	30 min	1 h	4 h	8 h
2.3 ppm (14 mg/m^3)	2.3 ppm (14 mg/m^3)	1.8 ppm (11 mg/m^3)	1.2 ppm (7.2 mg/m^3)	0.58 ppm (3.5 mg/m^3)

TABLE 4-11 AEGL Values for tert-Octyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.77 ppm (4.6 mg/m^3)	0.77 ppm (4.6 mg/m^3)	0.60 ppm (3.6 mg/m^3)	0.40 ppm (2.4 mg/m^3)	0.19 ppm (1.1 mg/m^3)
AEGL-3 (lethal)	2.3 ppm (14 mg/m^3)	2.3 ppm (14 mg/m^3)	1.8 ppm (11 mg/m^3)	1.2 ppm (7.2 mg/m^3)	0.58 ppm (3.5 mg/m^3)

Abbreviation: NR, not recommended.
[a]The absence of AEGL-1 values does not imply that concentrations below AEGL-2 values will be without effect.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR TERT-OCTYL MERCAPTAN

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for tert-octyl mercaptan because of insufficient data.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values and because tert-octyl mercaptan has a steep concentration-response curve, AEGL-3 values were divided by 3 to estimate a threshold for inability to escape.

10-min AEGL-2:	2.3 ppm ÷ 3 = 0.77 ppm
30-min AEGL-2:	2.3 ppm ÷ 3 = 0.77 ppm
1-h AEGL-2:	1.8 ppm ÷ 3 = 0.60 ppm
4-h AEGL-2:	1.2 ppm ÷ 3 = 0.40 ppm
8-h AEGL-2:	0.58 ppm ÷ 3 = 0.19 ppm

Derivation of AEGL-3 Values

Key study:	Temple University. 1982. Initial Submission: Final Report on a Study to Establish an LC_{50} Concentration of t-Octyl Mercaptan in Adult Sprague-Dawley Rats of Both Sexes (Final), September 17, 1982. Submitted to EPA by Atochem North America, Inc., King of Prussia, PA with Cover Letter Dated 12/23/91. EPA Document No, 88920000497. Microfiche No. OTS0534950.
Toxicity end point:	4-h threshold for lethality in female rats, $BMCL_{05}$ of 11.5 ppm
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations); time scaling not performed for the 10-min AEGL-3 because of the uncertainty in extrapolating a 4-h point of departure to a 10-min value. $(11.5 \text{ ppm})^1 \times 4 \text{ h} = 46 \text{ ppm-h}$ $(11.5 \text{ ppm})^3 \times 4 \text{ h} = 6{,}084 \text{ ppm-h}$

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-3:	2.3 ppm (30-min AEGL-3 value adopted)
30-min AEGL-3:	$C^3 \times 0.5$ h = 6,084 ppm-h C = 23 ppm C = 23 ppm ÷ 10 = 2.3 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 6,084 ppm-h C = 18 ppm C = 18 ppm ÷ 10 = 1.8 ppm
4-h AEGL-3:	11.5 ppm ÷ 10 = 1.2 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 46 ppm-h C = 5.8 ppm C = 5.8 ppm ÷ 10 = 0.58 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR tert-OCTYL MERCAPTAN

AEGL-1 VALUES

Data are insufficient to derive AEGL-1 values for tert-octyl mercaptan; therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.77 ppm (4.6 mg/m^3)	0.77 ppm (4.6 mg/m^3)	0.60 ppm (3.6 mg/m^3)	0.40 ppm (2.4 mg/m^3)	0.19 ppm (1.1 mg/m^3)

Data adequacy: Data inadequate to derive AEGL-2 values. AEGL-3 values were divided by 3 to estimate thresholds for the inability to escape.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.3 ppm (14 mg/m^3)	2.3 ppm (14 mg/m^3)	1.8 ppm (11 mg/m^3)	1.2 ppm (7.2 mg/m^3)	0.58 ppm (3.5 mg/m^3)

Reference: Temple University. 1982. Initial Submission: Final Report on a Study to Establish an LC_{50} Concentration of t-Octyl Mercaptan in Adult Sprague-Dawley Rats of Both Sexes (Final), September 17, 1982. Submitted to EPA by Atochem North America, Inc., King of Prussia, PA with Cover Letter Dated 12/23/91. EPA Document No. 88920000497. Microfiche No. OTS0534950.

Test species/Strain/Sex/Number: Rat, Sprague-Dawley, females, 10/group

Exposure route/Concentrations/Durations: Inhalation; 7, 15, 19, 29, 59, 71, 110 ppm and 12, 14, 17, 18, 19 ppm for 4 h

Effects:

Concentration (ppm)	Mortality
7	0/5
15	1/5
19	5/5
29	5/5
59	5/5
71	5/5
110	5/5
12	1/10
14	3/10

(Continued)

AEGL-3 VALUES Continued

17	5/10
18	10/10
19	10/10

BMCL05 = 11.5 ppm

BMC01 = 14.7 ppm

End point/Concentration/Rationale: Threshold for lethality, $BMCL_{05}$ of 11.5 ppm

Uncertainty factors/Rationale:
Interspecies: 3, data suggest no difference in species sensitivity between rats and mice (4-h LC_{50} is 51 ppm for male rats and 47 ppm male mice [Fairchild and Stokinger 1958]).
Intraspecies: 3, considered sufficient because the point of departure is from the more sensitive female rats. Calculated 4-h LC_{50} values were 59 ppm for male rats and 17 ppm for female rats in one study (Temple University 1982) and 79 ppm for males and 24 ppm for females in another (Amoco 1979). Also, the steep concentration-response curve implies limited intraindividual variability. In studies of male rats exposed to tert-octyl mercaptan for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958), 0% at 59 ppm and 80% at 71 ppm (Temple University 1982), and 0% at 73 ppm and 100% at 79 ppm (Amoco 1979). In a study of female rats exposed to tert-octyl mercaptan for 4 h, mortality was10% at 12 ppm and 100% at 18 ppm. In mice exposed for 4 h, mortality was 0% at 38 ppm and 100% at 64 ppm (Fairchild and Stokinger 1958).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty in extrapolating a 4-h point of departure to 10-min value.

Data adequacy: Well-conducted studies in rats and mice. Additional studies of females in species other than rats species would be useful.

APPENDIX C

BENCHMARK CALCULATION FOR TERT-OCTYL MERCAPTAN

Temple University (1982): Combined female data for two studies

Probit Model (Version: 2.9; Date: 09/23/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Fri Jun 13 10:37:19 2008

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 = COLUMN2
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1

Total number of observations = 13
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 = -2.865
Slope = 1.09606

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Intercept
Background	1	-0.19
Intercept	-0.19	1

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

Parameter Estimates

Variable	Estimate	Standard Error	95.0% Wald Confidence Interval	
			Lower Confidence Limit	Upper Confidence Limit
Background	0.13443	0.0579167	0.0209153	0.247945
Intercept	-50.7551	0.346663	-51.4345	-50.0756
Slope	18	NA		

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)	No. Parameters	Deviance Test	DF	P-value
Full model	-18.793	13			
Fitted model	-22.802	2	8.01802	11	0.7117
Reduced model	-60.1424	1	82.6988	12	<0.0001

AIC: 49.6039

Goodness of Fit

		Scaled			
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.0000	0.1344	0.672	0	5	-0.881
7.0000	0.1344	0.672	0	5	-0.881
15.0000	0.1537	0.768	1	5	0.287
19.0000	0.9893	4.946	5	5	0.233
29.0000	1.0000	5.000	5	5	0.000
59.0000	1.0000	5.000	5	5	0.000
71.0000	1.0000	5.000	5	5	0.000
110.0000	1.0000	5.000	5	5	0.000
12.0000	0.1344	1.344	1	10	-0.319
14.0000	0.1349	1.349	3	10	1.528
17.0000	0.6502	6.502	5	10	-0.996
18.0000	0.9119	9.119	10	10	0.983
19.0000	0.9893	9.893	10	10	0.329

Chi-square = 6.19; DF = 11; P-value = 0.8602

Benchmark Dose Computation

Specified effect = 0.05
Risk type = Extra risk
Confidence level = 0.95
BMD = 15.3075
BMDL = 11.5133

Probit Model (Version: 2.9; Date: 09/23/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Fri Jun 13 10:40:03 2008

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 = COLUMN2
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1

Total number of observations = 13
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 = -2.865
Slope = 1.09606

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Intercept
Background	1	-0.19
Intercept	-0.19	1

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

Parameter Estimates

		Standard	95.0% Wald Confidence Interval	
Variable	Estimate	error	Lower confidence limit	Upper confidence limit
Background	0.13443	0.0579167	0.0209153	0.247945
Intercept	-50.7551	0.346663	-51.4345	-50.0756
Slope	18	NA		

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

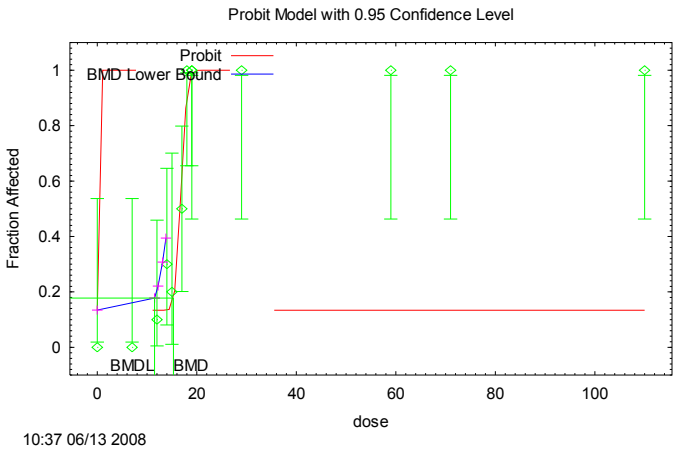

FIGURE C-1 Probit model with 0.95 confidence level.

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance Test	DF	P-value
Full model	-18.793	13			
Fitted model	-22.802	2	8.01802	11	0.7117
Reduced model	-60.1424	1	82.6988	12	<0.0001

AIC: 49.6039

Goodness of Fit

	Scaled				
Dose	Estimated prob-ability	Expected	Observed	Size	Residual
0.0000	0.1344	0.672	0	5	-0.881
7.0000	0.1344	0.672	0	5	-0.881
15.0000	0.1537	0.768	1	5	0.287
19.0000	0.9893	4.946	5	5	0.233
29.0000	1.0000	5.000	5	5	0.000
59.0000	1.0000	5.000	5	5	0.000
71.0000	1.0000	5.000	5	5	0.000
110.0000	1.0000	5.000	5	5	0.000
12.0000	0.1344	1.344	1	10	-0.319
14.0000	0.1349	1.349	3	10	1.528
17.0000	0.6502	6.502	5	10	-0.996
18.0000	0.9119	9.119	10	10	0.983
19.0000	0.9893	9.893	10	10	0.329

Chi-square = 6.19; DF = 11; P-value = 0.8602

Benchmark Dose Computation

Specified effect = 0.01
Risk type = Extra risk
Confidence level = 0.95
BMD = 14.7388
BMDL = 10.2853

APPENDIX D

CATEGORY PLOT FOR tert-OCTYL MERCAPTAN

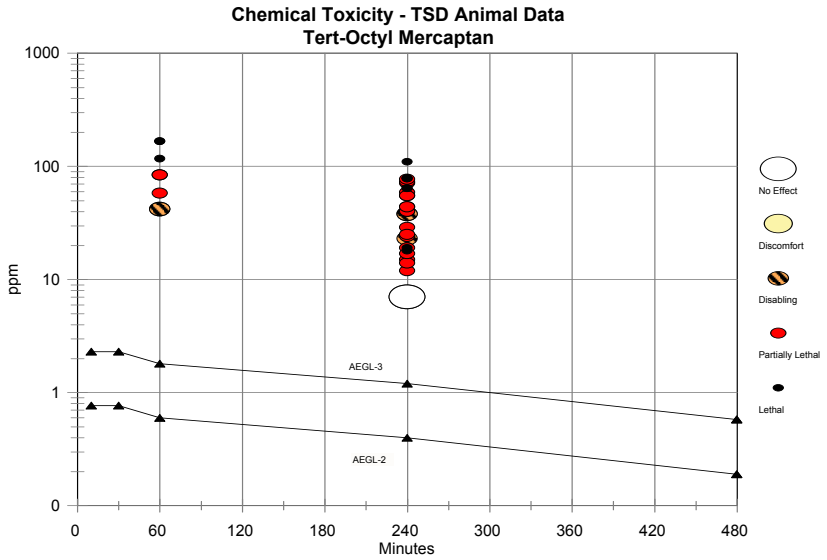

FIGURE D-1 Category plot of toxicity data and AEGL values for tert-octyl mercaptan. The decimal point is lost on this log-scale plot.

TABLE D-1 Data Used in Category Plot for tert-Octyl Mercaptan

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.77	10	AEGL	
AEGL-2				0.77	30	AEGL	
AEGL-2				0.60	60	AEGL	
AEGL-2				0.40	240	AEGL	
AEGL-2				0.19	480	AEGL	
AEGL-3				2.3	10	AEGL	
AEGL-3				2.3	30	AEGL	
AEGL-3				1.8	60	AEGL	
AEGL-3				1.2	240	AEGL	
AEGL-3				0.58	480	AEGL	
	Rat	Male	1	38	240	2	Seizures
	Rat	Male	1	40	240	PL	Mortality 1/6; seizures
	Rat	Male	1	44	240	PL	Mortality 1/5; seizures
	Rat	Male	1	55	240	PL	Mortality 3/5; seizures
	Rat	Male	1	64	240	3	Mortality 5/5; seizures
	Rat	Male	1	78	240	3	Mortality 6/6; seizures

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
	Rat	Male	1	110	240	3	Mortality 6/6; seizures
	Rat	Male/Female	1	7	240	0	No effects
	Rat	Male/Female	1	15	240	PL	Mortality: male 0/5; female 1/5
	Rat	Male/Female	1	19	240	PL	Mortality: male 0/5; female 5/5
	Rat	Male/Female	1	29	240	PL	Mortality: male 0/5; female 5/5
	Rat	Male/Female	1	59	240	PL	Mortality: male 0/5; female 5/5
	Rat	Male/Female	1	71	240	PL	Mortality: male 4/5; female 5/5
	Rat	Female	1	12	240	PL	Mortality 1/10
	Rat	Female	1	14	240	PL	Mortality 3/10
	Rat	Female	1	17	240	PL	Mortality 5/10
	Rat	Female	1	18	240	3	Mortality 10/10
	Rat	Female	1	19	240	3	Mortality 10/10
	Rat	Male/Female	1	23	240	2	Convulsions
	Rat	Male/Female	1	24	240	PL	Mortality: male 0/5; female 1/5
	Rat	Male/Female	1	25	240	PL	Mortality: male 0/5; female 5/5
	Rat	Male/Female	1	73	240	PL	Mortality: male 0/5; female 5/5
	Rat	Male/Female	1	77	240	PL	Mortality: male 4/5; female 5/5
	Rat	Male/Female	1	79	240	3	Mortality: male 5/5; female 5/5
	Mouse	Male	1	38	240	2	Seizures
	Mouse	Male	1	40	240	PL	Mortality 2/10
	Mouse	Male	1	44	240	PL	Mortality 4/10

Mouse	Male	1	55	240	PL	Mortality 9/10
Mouse	Male	1	64	240	3	Mortality 10/10
Mouse	Male	1	78	240	3	Mortality 10/10
Mouse	Male	1	42	60	2	Convulsions
Mouse	Male	1	58	60	PL	Mortality 2/5
Mouse	Male	1	84	60	PL	Mortality 4/5
Mouse	Male	1	117	60	3	Mortality 5/5
Mouse	Male	1	167	60	3	Mortality 5/5

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

5

Lewisite[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 Cheryl Bast (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Manager Warren Jederberg (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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 concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Because lewisite compounds were developed as chemical warfare agents, military literature is a major source of relevant toxicity data. Consequently, many of the study reports have “limited distribution", which is a separate issue from “classification”. For various reasons, sources may have a restricted distribution because of treaty restrictions on data access with allies, concerns regarding distribution of engineering information characterizing agent dissemination or generation in other sections of the same document, and related issues. To ensure public access to pertinent toxicity data originating from limited-distribution materials, pertinent data from those sources have been incorporated into this chapter.[2]

Lewisite-1 (L-1) is an organic arsenical with vesicant properties. It can exist as a *trans*-isomer or a *cis*-isomer; in aqueous solutions, the *cis*-isomer undergoes photoconversion to the *trans*-isomer. Lewisite causes local corrosive damage and may cause systemic poisoning after absorption through skin or mucous membranes. Exposure to lewisite causes almost immediate irritation and burning sensation in the eyes, skin, upper respiratory tract, and lungs. Death may result from direct pulmonary damage or from circulatory failure due to fluid loss and

[2]The NRC committee that reviewed this document was not provided with the limited-distribution materials, so it relied on the information as presented in the text.

arrhythmia. Death that occurs within 24 h of exposure is likely due to pulmonary damage (Lindberg et al. 1997). Lewisite-2 (L-2) and lewisite-3 (L-3) are co-products concurrently formed with L-1(Trammel 1992). L-1 yield is greater than 65%, and approximate yields of L-2 and L-3 are 7-10% and 4-12%, respectively (Lindberg et al. 1997). L-2 and L-3 are present in smaller quantities and have comparatively low volatility, so those compounds will be less toxicologically significant than L-1. Furthermore, the toxicity of L-2 and L-3 is comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL values were derived for "lewisite", rather than for the individual lewisite compounds, and are considered protective for L-1, L-2, and L-3 compounds.

Appropriate data were not available for deriving AEGL-1 values for lewisite. Odor cannot be used as a warning for potential exposure. For L-1, the odor threshold is reported to be between 14-23 mg/m^3 (1.7-2.7 ppm), concentrations greater than those that are highly irritating and higher than the AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended.

No inhalation studies with both concentration and duration parameters and with effects consistent with the definition of AEGL-2 end points were available. Therefore, the AEGL-2 values for lewisite, were determined by taking a three-fold reduction in the AEGL-3 values; the resulting values are considered to be estimated thresholds for irreversible effects (NRC 2001). The reduction approach is considered appropriate because of the steep concentration-response curve for mortality from lewisite. In studies with mice, the 10-min LC_{50} (lethal concentration, 50% lethality) was 200 mg/m^3 [24 ppm], and the 10-min LC_{100} (lethal concentration, 100% lethality) was 240 mg/m^3 [28 ppm]. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3 [15 ppm], and the LC_{50} was 176 mg/m^3 [21 ppm]).

AEGL-3 values for lewisite were based on lethality data for L-1 in dogs (Armstrong 1923). Points of departure were the calculated LC_{01} values: 38.7 mg/m^3 (4.6 ppm) for the 10-min value, 14.0 mg/m^3 (1.7 ppm) for the 30-min value, 7.4 mg/m^3 (0.87 ppm) for the 1-h value, 2.1 mg/m^3 (0.25 ppm) for the 4-h value, and 1.1 mg/m^3 (0.13 ppm) for the 8-h value. The LC_{01} values are considered estimated lethality thresholds. Interspecies and intraspecies uncertainty factors of 3 each were applied. The interspecies uncertainty factor of 3 is supported by data suggesting little species variability with regard to lethality from inhalation exposure to lewisite; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the two- to three-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats. The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation. Thus, the total uncertainty factor was 10.

The AEGL values for lewisite are presented in Table 5-1.

TABLE 5-1 AEGL Values for Lewisite

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)	One-third of AEGL-3 values
AEGL-3 (lethal)	3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)	Dog LC_{01} values (Armstrong 1923).

Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.
[a]Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values is without adverse effects.

1. INTRODUCTION

Lewisite is an organic arsenical with vesicant properties. It can exist as a *trans*- or *cis*-isomer; in aqueous solutions, the *cis*-isomer undergoes photoconversion to the *trans*-isomer. Pure lewisite is a colorless, odorless oily liquid; however, synthesized agent is an amber to dark brown liquid with a geranium-like odor (Munro et al. 1999). Lewisite causes local corrosive damage and may cause systemic poisoning after absorption through skin or mucous membranes. Exposure to lewisite causes almost immediate irritation and burning sensation of the eyes, skin, upper respiratory tract, and lungs. Death may result from direct pulmonary damage or circulatory failure from fluid loss and arrhythmia. Death that occurs within 24 h of exposure is likely due to pulmonary damage (Lindberg et al. 1997).

Lewisite was developed as a chemical warfare blister agent during the latter part of World War I and was named after its inventor Captain W. Lee Lewis. When the first ship loaded with lewisite reached Europe in 1918, the war ended, and the cargo was dumped into the sea. During the period between World War I and World War II, few studies on lewisite were conducted; however, when World War II began, the research efforts intensified. Results of those studies suggested that lewisite had limited utility as a war gas because of hydrolysis to a nonvolatile and water insoluble oxide, poor penetration of protective clothing, and difficulty in attaining lethal concentrations on the battle field (Lindberg et al. 1997). Also, lewisite is so immediately irritating at low concentrations (about 6-8 mg/m^3) that troops would be warned of its presence, even before detecting the geranium-like odor at 14-23 mg/m^3, and take protective action by deploying gas masks or retreating from the toxic atmosphere (Gates et al. 1946).

Lewisite-1 (L-1) is formed by the reaction of acetylene with arsenic trichloride using aluminum trichloride as a catalyst. Arsenic trichloride, lewisite-2 (L-2),

and lewisite-3 (L-3) are co-products concurrently formed with L-1 (Trammel 1992). L-1 yield is greater than 65%, and approximate yields of arsenic trichloride, L-2, and L-3 are 16-21%, 7-10%, and 4-12%, respectively (Lindberg et al. 1997). Therefore, an accidental release from storage tanks of L-1 will likely be the release of a mixture of L-1, L-2, L-3, and arsenic trichloride. Exposure will be to these compounds and to potential hydrolysis products, sodium arsenite ($NaAsO_2$) and arsenic acid (H_3AsO_4). Toxicologic data on arsenic trichloride are limited; however, effects are similar to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). With regard to lethality, arsenic trichloride appears to be approximately 2-3 times less toxic than L-1; the LCt_{50} (lethal concentration [product of concentration and time] that will cause death in 50% of the exposed population) for arsenic trichloride is 4,000-5,000 mg-min/m^3 whereas the LCt_{50} for L-1 is 1,200-1,500 mg-min/m^3 (Flury 1921). L-2 and L-3 will be less significant toxicologically because of their smaller quantities and comparatively low volatility. However, the toxicity of L-2 and L-3 is reportedly comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL values were derived for "lewisite" rather than for the individual lewisite compounds, and are considered protective for L-1, L-2, and L-3. In addition, in the review of literature, L-1, L-2, and L-3 are discussed only if the primary literature makes a distinction.

A summary of the nomenclature for the lewisite compounds is presented in Table 5-2, and chemical and physical data are summarized in Table 5-3.

2.1. Acute Lethality

Gates et al. (1946) estimated (based on animal data presented later in this chapter) that the inhalation LC_{50} for lewisite vapor in humans was 120 mg/m^3 for 10 min and 50 mg/m^3 for 30 min. An LC_{50} of 3,300 mg/m^3 for 30 min for lewisite vapor absorption through the bare skin was also estimated. This estimate is based on animal data and assumes that absorption of lewisite through skin is a function of the ratio of surface exposed to body volume. A dermal LD_{50} of more than 40 mg/kg was also estimated by Gates et al. (1946) based on animal data presented later in this chapter.

TABLE 5-2 Nomenclature for Lewisite Agents

Common Name	Military Designator	Chemical Names and Synonyms	CAS Registry No.
Lewisite-1	L or L-1	2-Chlorovinyldichloroarsine; (2-chlorovinyl)arsenous dichloride; beta-chlorovinyldichloroarsine; dichloro(2-chlorovinyl) arsine; chlorovinylarsine dichloride; EA 1034	541-25-3
Lewisite-2	L-2	*bis*-(2-chlorovinyl)chloroarsine	40334-69-8
Lewisite-3	L-3	*tris*-(2-chlorovinyl)arsine	40334-70-1

Sources: Gates et al. 1946; Cookson and Nottingham 1969; USACHPPM 1996.

TABLE 5-3 Chemical and Physical Data for Lewisite Compounds

Parameter	Value	Reference
Chemical formula		
Lewisite-1 (L or L-1)	$ClCH=CHAsCl_2$	Gates et al. 1946
Lewisite-2 (L-2)	$(ClCH=CH)_2$ AsCl	Gates et al. 1946
Lewisite-3 (L-3)	$(ClCH=CH)_3As$	Gates et al. 1946
Molecular weight		
Lewisite-1 (L or L-1)	207.32	HSDB 2008;
Lewisite-2 (L-2)	233.32	Lindberg et al. 1997
Lewisite-3 (L-3)	259.35	
Physical state		
Lewisite-1 (L or L-1)	Oily liquid for all forms	Lindberg et al. 1997
Lewisite-2 (L-2)		
Lewisite-3 (L-3)		
Color		
Lewisite-1 (L or L-1)	Mixture: amber to brown	Munro et al. 1999
Lewisite-2 (L-2)	Colorless (pure)	Munro et al. 1999
Lewisite-3 (L-3)	–	
Melting point		
Lewisite-1 (L or L-1)	0.1°C	HSDB 2008
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Boiling point		
Lewisite-1 (L or L-1)	190°C	Trammel 1992
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Specific gravity (water = 1)		
Lewisite-1 (L or L-1)	1.888 at 20°C	HSDB 2008
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Density (air = 1)		
Lewisite-1 (L or L-1)	7.1	Trammel 1992
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Solubility		
Lewisite-1 (L or L-1)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Lewisite-2 (L-2)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Lewisite-3 (L-3)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Vapor pressure		
Lewisite-1 (L or L-1)	0.34 mm Hg at 25°C; 0.22 mm Hg at 20°C	USACHHPM 1996
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Conversion factors		
Lewisite-1 (L or L-1)	1 mg/m^3 = 0.118 ppm	
Lewisite-2 (L-2)	1 ppm = 8.48 mg/m^3	
Lewisite-3 (L-3)		

2. HUMAN TOXICITY DATA

2.2. Nonlethal Toxicity

2.2.1. Individual Studies

Lewisite is immediately and highly irritating at concentrations of about 6-8 mg/m^3. The geranium-like odor is reportedly detectable at 14-23 mg/m^3 (Gates et al. 1946).

Inhalation of lewisite at10 mg/m^3 for 30 min reportedly resulted in severe intoxication and incapacitation that lasted for several weeks, and exposure at 10 mg/m^3 for 15 min caused inflammation of the eyes and swelling of the eyelids (Franke 1968, as cited in Ottinger et al. 1973). Ottinger et al. (1973) is a review article, and did not provide experimental details or information regarding the severity of effects. No further details were available.

A dermal vapor study was conducted by Eldridge (1923). To select "men of average resistance" for the study, pin-point drops of 0.1 or 2% solutions of liquid lewisite in alcohol were applied to the forearms of 52 male volunteers at Edgewood Arsenal. If a subject showed no reaction to the 2% solution, he was classified as "resistant" and not used in the dermal vapor study. If a subject showed a marked reaction to the 0.1% solution, he was classified as "sensitive" and not used in the dermal vapor study. Of the 52 men, 14 were resistant and 3 were sensitive. Further dermal tests with liquid lewisite were done on the sensitive and resistant subjects; the tests showed that the sensitive subjects had no effects when treated with a 0.01% lewisite solution, and the resistant subjects developed blistering with a 5% solution. Dermal effects included blanching or graying of the skin, followed by severe erythema within 15-30 min. Vesication, accompanied by some edema, occurred within 12 h. Within less than 24 h, a raised area of redness measuring 2 × 2.5 inches in diameter appeared, accompanied by a 1.5-inch diameter blister surrounded by hundreds of minute vesicles. Forty-eight hours later, the raised area of redness had increased to 6 × 3.5 inches in diameter, and fluid seeped from the blister. The smaller vesicles also ruptured as the severity of the burns continued to increase up to the fourth day. No change was noted from days 4 to 7, and from day 7 onward improvement was observed until the burns were completely healed by the end of week 4. The men described a stinging sensation that lasted for 2 min and occurred within 2.5 min of exposure. No further sensation was noted until approximately 20 min later, when the stinging sensation was again reported and lasted for approximately 2 h. Five hours later, a "continuous feeling of discomfort" was described; burning lasted until the blister ruptured 22.5 h after lewisite was administered. Intermittent stinging and burning followed and the area became sore to the touch. By the end of day 6, the pain was more severe and occurred at shorter time intervals. By day 9, all pain had resolved.

Groups of 1-7 men (from the 35 male volunteers of average sensitivity described above) were exposed on their arms to varying concentrations of lewisite vapor for periods ranging from 10 min to 3 h to determine the concentration nec-

essary to produce blistering (Eldridge 1923). The exposure apparatus allowed for a constant stream of air-lewisite mixture to pass over a square centimeter area of the subject's forearm under atmospheric pressure. Lewisite concentrations were determined by dividing the loss in weight of the gas container by the total volume of air passing through the apparatus during the test. Skin burns ranged in severity from reddish discoloration to a clear watery blister over the entire burned area, accompanied by reddening, swelling, and hardening of the surrounding skin. The burns reached maximum severity in 36-48 h, and healing was complete in 6 days to 2 weeks. The men reported that the healed skin remained sensitive for several weeks after the healing was complete. Data from this study are summarized in Table 5-4.

Lewisite liquid at doses of 3.5, 7, and 14 μg produced erythema and vesication of human skin, and doses of 22, 32, and 40 μg produced vesication (NDRC 1944).

Davis (1943) analyzed fluid from human lewisite blisters and found arsenic at 0.8-1.3 mg/mL, equivalent to 2.5-4.0 mg of lewisite.

2.2.2. Case Report

A male worker at Pine Bluff Arsenal experienced lewisite burns over 20% of his body surface, with the majority of burns on his legs. He hadan anemia 10-15 days after the burn, but had no signs of systemic arsenic poisoning (Gates et al. 1946). No further information was available on this incident.

2.3. Developmental and Reproductive Effects

Human developmental and reproductive toxicity data concerning lewisite were not found.

2.4. Genotoxicity

Human genotoxicity toxicity data concerning lewisite were not found.

TABLE 5-4 Average Lewisite Concentration Causing Blistering on Human Forearm Skin

Duration of Exposure (min)	Average Blistering Concentration (mg/m^3)
5	2,090
10	1,040
30	340
60	150
120	62
180	26.2

Source: Eldridge 1923.

2.5. Carcinogenicity

In 1940, a World War II German soldier was accidentally exposed to lewisite on his lower right leg. The blistered lesion never healed, and was diagnosed as malignant in 1948. Bowen's disease (intraepidermal squamous cell carcinoma) was diagnosed 38 years later (Krause and Grussendorf 1978).

Wada et al. (1962) reported increased incidences of cancer mortality (14% respiratory tract; 9.6% digestive tract) in workers from the Okuno-Jima poison gas factory. When cancer rates were correlated with job classification, the frequency of respiratory and gastrointestinal tract neoplasms were highest in workers involved in the production of mustard gas or lewisite, followed by those who worked indirectly with mustard gas or lewisite, and the lowest frequency was found in those that had no direct contact with mustard or lewisite (Yamakido et al. 1985). However, this information is confounded by the fact that workers were also exposed to mustard gas in addition to lewisite, and the factory also produced hydrocyanic acid, diphenylcyanarsine, chloroacetophenone, and phosgene.

2.6. Summary

Exposure to lewisite in air and by contact to liquid causes immediate irritation, burning, and corrosive damage to the eyes and exposed skin; inhalation exposure may also affect the upper airway and lungs. Human exposure data are dated and studies are, in many cases, not well described. No information concerning developmental or reproductive toxicity or genotoxicity with regard to lewisite exposure in humans was identified. Information suggesting an increased cancer incidence in workers from a Japanese poison gas factory is confounded because workers were exposed to several chemicals. Selected data on humans exposed to lewisite by inhalation are summarized in Table 5-5, and selected data on human exposed to liquid lewisite are presented in Table 5-6.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several inhalation LC_{50} values were identified in the literature. In some cases no detailed methods were presented; however, only data from studies where concentrations were reported to be analytically determined are presented in this chapter. Oral, dermal, subcutaneous, and intravenous LD_{50} values were also identified in a variety of species.

A 9-min LC_{50} of 166 mg/m^3 was reported for rats (Gates et al. 1946). An oral LD_{50} of 50 mg/kg (U.S. Army 1974), dermal LD_{50} of 24 mg/kg (Cameron et al. 1946), and subcutaneous LD_{50} of 1 mg/kg (Cameron et al. 1946) were reported for rats.

TABLE 5-5 Data on Humans Exposed to Lewisite in Air

Effect	Exposure Duration (min)	Concentration (mg/m^3)	C × T ($mg\text{-}min/m^3$)	Reference
Odor perception	Threshold	14-23	–	Gates et al. 1946
Nasal irritation, mild	Threshold	0.8	–	Prentis 1937
Irritation, pronounced	Threshold	2.0	–	Cherkes et al. 1965
Irritation, highly irritating	Threshold	6-8	–	Gates et al. 1946
Irritation, severe	Threshold	10-30	–	Cherkes et al. 1965
Ocular inflammation/ swelling	15	10	150	Ottinger et al. 1973
Incapacitation	30	10	300	Ottinger et al. 1973
Skin lesions (skin exposure)	5	2,090	10,450	Eldridge 1923
	10	1,040	10,400	
	30	340	10,200	
	60	150	9,000	
	120	62	7,440	
	180	26.2	4,716	
Estimated inhalation LC_{50}	10	120	1,200	Gates et al. 1946
Estimated inhalation LC_{50}	30	50	1,500	Gates et al. 1946
Estimated percutaneous LC_{50}	30	3,300	100,000	Gates et al. 1946

TABLE 5-6 Skin Effects in Humans Exposed to Liquid Lewisite

Dose (μg)	Effect	Incidence	Reference
3.5	Erythema	24/29	NRDC 1944
	Vesication	21/29	
7	Erythema	30/30	NRDC 1944
	Vesication	30/30	
14	Erythema	26/26	NRDC 1944
	Vesication	26/26	
22	Vesication	10/10	CWS 1944
32	Vesication	7/9	CWS 1944
40	Vesication	100%	CWS 1944

3.1.1. Rats

Olajos et al. (1998) exposed groups of six male and six female Sprague-Dawley rats (head-only) to product solution (waste stream) from the chemical neutralization of Chemical Agent Identification Sets (CAIS). The CAIS waste stream contained chloroform (vehicle), *t*-butanol (vehicle), and lewisite. Exposures to the CAIS waste stream were at 6,000, 12,000, 18,000, or 24,000 ppm and to the chloroform-butanol solvent were at 24,000 ppm for 1 h. The concen-

tration of lewisite in the test atmospheres was 0, 0.17, 0.67, 0.96, and 0.31 mg/m^3 for the vehicle controls and the 6,000, 12,000, 18,000, and 24,000 ppm groups, respectively. Toxic signs were consistent with those of chloroform and butanol, and were noted in the control (vehicle) and waste-stream exposed animals. Ocular effects (corneal opacity and erosion) and pulmonary function effects (decreased minute volume) were similar in control and waste-stream exposed groups. The authors concluded that effects were due to chloroform and butanol, not lewisite.

3.1.2. Mice

Silver and McGrath (1943) exposed groups of 20 male CF-1 mice to varying concentrations of *cis*- or *trans*-lewisite for 10 min. Animals were exposed in a 386-L continuous flow chamber. Lewisite was vaporized by passing 20-30 L of air per minute (L/min) through lewisite in a bubbler at room temperature. Chamber airflow was maintained at 250 L/min. Lewisite concentrations in the chamber were measured analytically using a wet test meter. No animals were placed in the chamber until the chamber atmosphere reached equilibrium (approximately 10 min). Ten-min mouse LC_{50} values of 190 and 200 mg/m^3 were determined for the *cis*- and *trans*-isomers, respectively. All mice exposed to lewisite for 10 min at 240 mg/m^3 died.

3.1.3. Dogs

In an acute inhalation toxicity study, Armstrong (1923) exposed groups of dogs (sex not reported) to varying concentrations of L-1(purity 99%) for 7.5, 15, 30, 60, 120, or 240 min. The number of dogs per group varied from 1 to 17 (see Table 5-7); no explanation for the variation was provided. The dogs were exposed in an air-tight glass chamber (74.9 × 69.6 × 71.2 cm) with a sliding front and entrance and exit ports for the air-lewisite mixture. Affluent air was supplied by an air pump and was passed through a series of drying bottles. Dried air was then passed through a flowmeter to regulate the amount entering the exposure chamber. This metered stream then entered a bubbler containing the lewisite; the bubbler was immersed in a water bath so that it could be heated or cooled. The temperature of the bath and flow rate was then adjusted to predetermined points (from blank runs) to obtain the desired chamber concentrations. Lewisite concentrations in the exposure chamber were determined analytically from samples aspirated from the chamber during exposures.

Clinical signs in dogs exposed for 7.5 or 15 min included detection of lewisite within 30 seconds, as evidenced by continual eye blinking, followed by excessive nasal secretion, lacrimation, and sneezing (Armstrong 1923). Vomiting occurred and ocular irritation was observed in some dogs before exposure ended. In dogs exposed for 30-min or longer, frequent retching, vomiting, extreme salivation, and labored breathing were observed, in addition to signs noted

for shorter exposure durations. Necropsy of dying animals revealed a thick membrane in the nostrils, larynx, and trachea, accompanied by purulent bronchitis, hemorrhage, pneumonia, inflammation of the entire respiratory tract, edema, and congestion of the lungs. Congestion of the liver and kidneys were also noted. Generally, all clinical signs and pathology increased in severity with increasing exposure duration and concentration. LC_{01} values for the five AEGL durations were calculated to be 38.7 mg/m^3 for 10 min, 14.0 mg/m^3 for 30 min, 7.4 mg/m^3 for 1 h, 2.1 mg/m^3 for 4 h, and 1.1 mg/m^3 for 8 h (ten Berge et al. 1986). Lethality data on lewisite are summarized in Table 5-7.

TABLE 5-7 Lethality Data from a Study of Dogs Exposed to Lewisite-1

Exposure Duration	Concentration (mg/m^3)	Mortality	LC_{50} (mg/m^3)	When Death Occurred
7.5 min	126	0/2	176	–
	176	7/12		15-69 h post-exposure
	231	10/17		13-57 h post-exposure
	274	4/4		12-37 h post-exposure
	330	1/1		14 h post-exposure
15 min	68.7	1/4	100	12 h post-exposure
	87.7	2/5		28 and 40 h post-exposure
	96	3/5		24-60 h post-exposure
	102	2/3		36 and 84 h post-exposure
	125	6/12		12-96 h post-exposure
	233	3/3		10-24 h post-exposure
30 min	11.5	0/1	48	–
	24.5	0/4		–
	30.6	0/2		–
	41.5	0/2		–
	48	2/3		14 and 44 h post-exposure
	58.6	4/4		24-84 h post-exposure
60 min	5.8	0/2	25.7	–
	8	0/5		–
	25	5/9		18-56 h post-exposure
	35	5/9		4-36 h post-exposure
	43	5/7		17-20 h post-exposure
	53	1/1		12 h post-exposure
120 min	4.8	0/4	11.8	–
	12.5	2/3		47 and 72 h post-exposure
	17.9	4/6		12-24 h post-exposure
	24.5	4/5		24-84 h post-exposure
	34.5	3/3		12-29 h post-exposure
240 min	2.1	0/3	6.6	–
	6.2	5/9		16-76 h post-exposure
	10	10/17		2-78 h post-exposure
	16.9	2/2		48 and 37 h post-exposure

Source: Armstrong 1923.

Harrison et al. (1946) exposed dogs to lewisite at 50 mg/m^3 for 30 min (8 dogs), 61 mg/m^3 for 30 min (9 dogs), or 121 mg/m^3 for 10 min (5 dogs). Clinical signs included vomiting, urination, defecation, salivation, and respiratory distress; 80% of the dogs died 3-48 h after exposure. No other information was available.

A dermal LD_{50} of 15 mg/kg (Cameron et al. 1946) and subcutaneous LD_{50} of 2 mg/kg (Cameron et al. 1946) were reported for dogs.

3.1.4. Rabbits

A 7.5-min LC_{50} of 160 mg/m^3 and a 60-min LC_{50} of 25 mg/m^3 was reported for rabbits (Gates et al. 1946). A dermal LD_{50} of 6 mg/kg (Cameron et al. 1946) and intravenous LD_{50} of 0.5 mg/kg (Cameron et al. 1946) were also reported.

3.1.5. Guinea Pigs

A 9-min LC_{50} of 111 mg/m^3 and a 60-min LC_{50} of 8 mg/m^3 were reported for guinea pigs (Gates et al. 1946). A dermal LD_{50} of 12 mg/kg (Cameron et al. 1946) and subcutaneous LD_{50} of 1 mg/kg (Cameron et al. 1946) were also reported.

3.1.6. Goats

A 100-min LC_{50} of 12.5 mg/m^3 (Gates et al. 1946) and a dermal LD_{50} of 15 mg/kg (Cameron et al. 1946) were reported for goats.

3.2. Nonlethal Toxicity

3.2.1. Rats

No treatment-related deaths occurred in rats exposed a CAIS waste stream (containing chloroform [vehicle], *t*-butanol [vehicle], and lewisite) at 6,000 or 12,000 ppm. The concentration of lewisite in these test atmospheres was 0.17 mg/m^3 for the 6,000 ppm group and 0.96 mg/m^3 for the 12,000 ppm group. This study is discussed in more detail in Section 3.1.1.

3.2.2. Dogs

Ocular lesions, but no deaths, were reported in dogs exposed to lewisite at 20 mg/m^3 for 30 min (Gates et al. 1946). No additional experimental details, including severity of effects, were reported.

3.2.3. Rabbits

Ocular lesions, but no deaths, were reported in rabbits exposed to lewisite at 1 mg/m^3 for 30 min (Gates et al. 1946). No additional experimental details, including severity of effects, were reported.

3.2.4. Pigs

Lindsay et al. (2004) dermally exposed three large white pigs to lewisite at 0.3 mg/cm^2. While under anesthesia, an area of dorsal skin (35 cm × 25 cm) was shaved. Exposures were then conducted using inverted glass chambers; lewisite (in hexane) was pipetted onto 10-cm^2 glass-fiber discs fitted tightly in the roof of each circular, glass chamber. The heat from the animals vaporized the lewisite so that the skin was exposed to vapor, but not lewisite liquid. Pigs were monitored in their pens for 24 h and were then killed. Full skin thickness samples from control (non-exposed) and lewisite-treated skin were excised to examine the degradative processes in connective tissue components of skin, especially glycoproteins, using immunostaining and gel electrophoresis. There was no evidence of cross linking of laminin or of type III or IV collagen in lewisite-treated pigs. There was evidence of degradation of laminin and type IV collagen only.

3.3. Developmental and Reproductive Effects

Hackett et al. (1987) administered lewisite to CD rats and New Zealand white rabbits by gastric intubation. Rats were dosed daily on days 6 through 15 of gestation with lewisite at 0, 0.5, 1.0, 2.0, or 2.5 mg/kg in a range-finding study and with 0, 0.5, 1.0, or 1.5 mg/kg in a teratology study. Rabbits were dosed on gestation days 6 through 19 with lewisite at 0, 0.5, 1.0, 1.5, and 2.0 mg/kg in a range-finding study and at 0, 0.07, 0.2, and 0.6 mg/kg in a teratology study. In rats, no maternal of fetal effects were noted at 1.5 mg/kg. At 2.0 mg/kg, maternal mortality (10%), decreased maternal and fetal body weight, and decreased numbers of viable fetuses were found. In rabbits, maternal mortality ranged from 13% in the 0.07-mg/kg group to 100% in the 2.0-mg/kg group. This mortality rate limited the sample size and made identification of other potential fetal or maternal effects difficult. However, at 0.07 mg/kg, only maternal mortality was noted. At 0.6 mg/kg (highest dose in the teratology study), effects included 86% maternal mortality, decreased maternal body weight gain, an increased incidence of fetal stunting, and a tendency toward decreased fetal body weight (Hackett et al. 1987).

In a 42-week, two-generation reproductive study in rats, parental males and females were administered lewisite in sesame oil by gastric intubation at 0, 0.10, 0.25, or 0.60 mg/kg/day for 5 days/week prior to mating, during mating, and after mating until the birth of offspring. Dams continued to be exposed to lewisite during lactation. After weaning, male and female offspring selected to

continue on the study were exposed similarly to lewisite. There were no treatment-related effects on reproductive performance, fertility, or reproductive organ weights of male or female rats through two consecutive generations. There were no treatment-related effects in offspring (Sasser et al. 1989).

3.4. Genotoxicity

Lewisite did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA102 with or without metabolic activation up to concentrations limited by toxicity (1.0 μg/plate) (Stewart et al. 1989). Lewisite was negative for mutation at the HGPRT locus in Chinese hamster ovary (CHO) cells at concentrations ranging from 0.12 to 2.0 μM (Jostes et al. 1989). However, lewisite induced chromosomal aberrations in CHO cells at concentrations of 0.50, 0.75, and 1.0 μM (Jostes et al. 1989). Lewisite was negative in the *Drosophilla melanogaster* sex-linked recessive lethal assay (Auerbach and Robson 1946, 1947) and negative in a dominant lethal assay in CD rats at concentrations of 0.375, 0.75, or 1.5 mg/kg (Bucci et al. 1993).

3.5. Carcinogenicity

No data were located regarding the carcinogenicity of lewisite in animals.

3.6. Summary

A summary of the acute inhalation data on lewisite is presented in Table 5-8, and Table 5-9 summarizes acute toxicity data by other routes of exposure. Animal data are limited but suggest that lewisite is highly irritating and corrosive, causing dermal and ocular lesions by contact with liquid or vapor. Inhalation LC_{50} values were identified in several species, and the weight of evidence suggests limited interspecies variability ($C \times T$ is relatively constant across species). There is no evidence that lewisite is a reproductive or developmental toxicant in rats or rabbits in the absence of maternal toxicity. Genotoxicity assay results were generally negative; the only positive result was in chromosome aberrations in CHO cells. No information concerning carcinogenicity in animals was found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

According to a secondary source, lewisite is readily absorbed through the mucous membranes, and is also readily absorbed through the skin because of its lipophilicity (HSDB 2008).

TABLE 5-8 Summary of Acute Inhalation Data from Animals Exposed to Lewisite

Species	Exposure Duration (min)	Concentration (mg/m^3)	C × T ($mg\text{-}min/m^3$)	Effect	Reference
Lethal Effects					
Rat	9	166	1,494	LC_{50}	Gates et al. 1946
Mouse	10	190	1,900	LC_{50}	Silver and McGrath 1943
Mouse	10	200	2,000	LC_{50}	Silver and McGrath 1943
Mouse	10	240	2,400	LC_{100}	Silver and McGrath 1943
Guinea pig	9	111	999	LC_{50}	Gates et al. 1946
Guinea pig	60	8	480	LC_{50}	Gates et al. 1946
Rabbit	7.5	160	1,200	LC_{50}	Gates et al. 1946
Rabbit	60	25	1,500	LC_{50}	Gates et al. 1946
Dog	7.5	176	1,320	LC_{50}	Armstrong 1923
Dog	15	100	1,500	LC_{50}	Armstrong 1923
Dog	30	48	1,440	LC_{50}	Armstrong 1923
Dog	60	25.4	1,542	LC_{50}	Armstrong 1923
Dog	120	11.8	1,416	LC_{50}	Armstrong 1923
Dog	240	6.24	1,584	LC_{50}	Armstrong 1923
Goat	100	12.5	1,250	LC_{50}	Gates et al. 1946
Nonlethal Effects					
Rabbit	30	1	30	Ocular lesions, no death	Gates et al. 1946
Dog	30	20	600	Ocular lesions, no death	Gates et al. 1946

4.2. Mechanism of Toxicity

Dermal or intravenous exposure to lewisite leads to local skin edema and pulmonary edema due to increased capillary permeability. There is no evidence of edema or capillary permeability in any other part of the body. The increased capillary permeability results in blood plasma loss and leads to a sequence of physiological events termed "lewisite shock" which is similar to shock observed in severe burn cases. Functional changes in the lungs, kidneys, respiratory tract, cardiovascular system, and lymphatic system may be the result of a disturbance of osmotic equilibrium (Goldman and Dacre 1989).

TABLE 5-9 Summary of Acute Oral, Dermal, Subcutaneous, and Intravenous Data from Animals Exposed to Lewisite

Route of Administration	Species	LD_{50} (mg/kg)	Reference
Oral	Rat	50	U.S. Army 1974
Dermal	Rat	24	Cameron et al. 1946
	Guinea pig	12	Cameron et al. 1946
	Rabbit	6	Cameron et al. 1946
	Dog	15	Cameron et al. 1946
	Goat	15	Cameron et al. 1946
Subcutaneous	Rat	1	Cameron et al. 1946
	Guinea pig	1	Cameron et al. 1946
	Rabbit	2	Cameron et al. 1946
	Dog	2	Cameron et al. 1946
Intravenous	Rabbit	0.5	Cameron et al. 1946

As reviewed in Goldman and Dacre (1989) and Young (1999), the mechanism of toxicity of lewisite is the formation of stable complexes between the arsenite moiety of lewisite and sulfhydryls groups that are critical to the function of proteins and thiol cofactors (e.g., dihydrolipoic acid, keratin, alcohol dehydrogenase, pyruvate dehydrogenase, succinic dehydrogenase, succinic oxidase, hexokinase). The formation of stable complexes with protein thiols is also the primary mechanism of toxicity of arsenite. Although lewisite can hydrolyze to yield arsenite, the reaction occurs at alkaline conditions and/or high temperature and is unlikely to be important in lewisite toxicology (Goldman and Dacre 1989).

4.3. Structure-Activity Relationships

Lewisite and arsenite share a common mechanism of action in disruption of protein function by formation to complexes with protein sulfhydryls. Toxicologic data on arsenic trichloride, L-2 and L-3, co-products concurrently formed with L-1, are limited. However, effects are similar qualitatively to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). With regard to lethality, arsenic trichloride appears to be approximately 2-3 times less toxic than L-1; the LCt_{50} for arsenic trichloride is 4,000-5,000 mg-min/m^3 whereas the LCt_{50} for L-1 is 1,200-1,500 mg-min/m^3 (Flury 1921). The toxicity of L-2 and L-3 is reportedly comparable to L-1 (Lindberg et al. 1997). Silver and McGrath (1943) found no substantial difference in 10-min LC_{50} values (190 and 200 mg/m^3) for the *cis*- and *trans*-isomers of lewisite.

Inhalation data for sodium arsenite, a hydrolysis product of L-1, are not available. However, Inns et al. (1988) compared the acute intravenous toxicity of lewisite and sodium arsenite in New Zealand white rabbits. The LD_{50} of lewisite was 1.8 mg/kg. Rapid panting was noted 5 min after injection, and was followed by prostration and death within 4 h. By 24 h after injection, surviving rabbits appeared normal. The LD_{50} for sodium arsenite was 7.6 mg/kg, with hypoactivity noted 20 min after injection. On the basis of trivalent arsenic content, lewisite was 6.5 times more toxic than the inorganic sodium arsenite, and clinical signs and times of death and recovery differed between the compounds. Severe pulmonary damage (gross and histopathologic) was found in rabbits treated with lewisite, but not in animals treated with sodium arsenite. Also, arsenic levels in the liver, kidneys, brain, stomach, duodenum, spleen, and bladder were much greater in sodium arsenite-treated rabbits than in lewisite-treated rabbits. However, arsenic content in the lungs was similar. These data suggest different mechanisms of toxicity for lewisite and inorganic trivalent arsenic, and that arsenite is not an appropriate surrogate for lewisite.

4.4. Other Relevant Information

4.4.1. Species Variability

The selected animal mortality data presented in Table 5-8 show that the concentration-time products from LC_{50} data sets are relatively constant across species, except for the two guinea pig data points. This suggests that there is relatively little species variability with respect to lethal response to lewisite inhalation exposure. Findings are consistent with the expectation that little species variability will be observed for highly corrosive substances.

4.4.2. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Using LC_{50} data from the dog (the species with the most robust data set, see Table 5-7), which included exposures ranging from 7.5 min to 4-h, an n value of 1.03 is derived (see Figure 5-1).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data were relevant for establishing AEGL-1 values for lewisite.

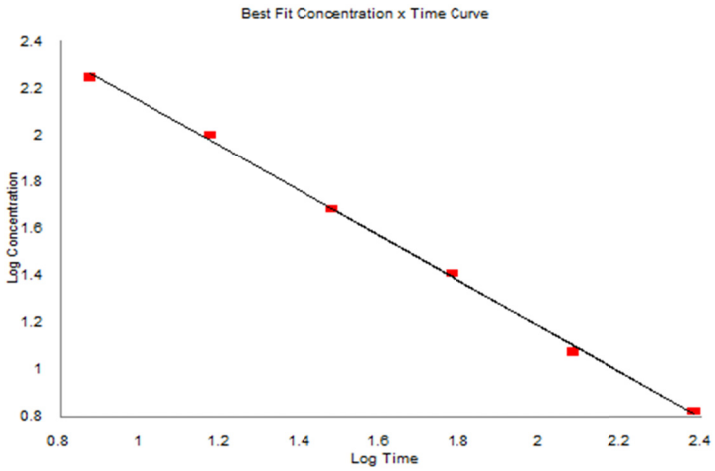

FIGURE 5-1 LC_{50} Data for Lewisite in Dogs. Source: Armstrong 1923.

5.2. Animal Data Relevant to AEGL-1

No animal data were relevant for establishing AEGL-1 values for lewisite.

5.3. Derivation of AEGL-1

Appropriate data were not available to derive AEGL-1 values for lewisite. Odor cannot be used as a warning for potential exposure, because the odor threshold (14-23 mg/m^3 for L-1) is higher than concentrations that are highly irritating and higher than the AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended. Lack of AEGL-1 values does not imply that exposure at concentrations below the AEGL-2 values is without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were available for establishing AEGL-2 values for lewisite.

6.2. Animal Data Relevant to AEGL-2

No animal data were available for establishing AEGL-2 values for lewisite. Ocular inflammation and lesions reported by Gates et al. (1946) and Ottinger et al. (1973) were considered an inappropriate basis for AEGL-2 values. The Ottinger et al. (1973) report is a review paper, which noted that "a lower concentration of 0.01 mg/L causes inflammation to the eyes and swelling of the lid after 15 minutes" (as

cited in Franke 1968); however, no experimental details were provided and attempts to obtain the Franke (1968) report were not successful. Because the primary data could not be obtained for review, the information was considered unsuitable for deriving AEGL-2 values. Gates et al. (1946) reported approximate concentrations necessary to produce ocular lesions in 30 min (0.001 mg/L in rabbits and 0.20 mg/L in dogs); however, no experimental details or descriptions of the lesions were reported. For both the Ottinger et al. (1973) and Gates et al. (1946) reports, sufficient detail is not available to determine the severity of effects and do not provide no-effect levels.

6.3. Derivation of AEGL-2

No inhalation data with both concentration and duration parameters and with effects consistent with the definition of AEGL-2 end points were available. Therefore, the AEGL-2 values for lewisite were determined by taking a three-fold reduction in the AEGL-3 values; the resulting values are considered to be estimated thresholds for irreversible effects (NRC 2001). The reduction approach is considered appropriate because of the steep concentration-response curve for mortality from lewisite. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL-2 values for lewisite are presented in Table 5-10, and the calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data with concentration and duration parameters consistent with the definition of AEGL-3 were available.

7.2. Animal Data Relevant to AEGL-3

Gates et al. (1946) reported LC_{50} values for several test species: a 9-min LC_{50} of 166 mg/m^3 for rats; a 9-min LC_{50} of 111 mg/m^3 and a 60-min LC_{50} of 8 mg/m^3 for guinea pigs; a 7.5-min LC_{50} of 160 mg/m^3 and a 60-min LC_{50} of 25 mg/m^3 for rabbits; and a 100-min LC_{50} of 12.5 mg/m^3 in goats. Silver and McGrath (1943) reported 10-min LC_{50} values for mice of 190 and 200 mg/m^3 for *cis*- and *trans*-isomers of lewisite, respectively. Armstrong (1923) reported the following LC_{50} values for dogs: 176 mg/m^3 for 7.5 min, 100 mg/m^3 for 15 min, 48 mg/m^3 for 30 min, 25.4 mg/m^3 for 60 min, 11.8 mg/m^3 for 120 min, and 6.24 mg/m^3 for 240 min. The mouse study (Silver and McGrath 1943) and dog study (Armstrong 1923) were well-conducted and well-described, but the studies by Gates et al. (1946) were not well described.

TABLE 5-10 AEGL-2 Values for Lewisite

10 min	30 min	1 h	4 h	8 h
1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)

7.3. Derivation of AEGL-3

The dog lethality study (Armstrong, 1923) was used as the basis of AEGL-3 values. Points of departure were the calculated LC_{01} values: 38.7 mg/m^3 for the 10-min value, 14.0 mg/m^3 for the 30-min value, 7.4 mg/m^3 for the 1-h value, 2.1 mg/m^3 for the 4-h value, and 1.1 mg/m^3 for the 8-h value. The LC_{01} values are considered estimates of lethality thresholds. Interspecies and intraspecies uncertainty factors of 3 each were applied. The interspecies uncertainty factor of 3 is supported by data that suggest little species variability with regard to lethality from inhalation exposure to lewisite; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the two- to three-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats (see Table 5-8 for summary of supporting data). The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL values were derived for lewisite as a mixture of L-1, L-2, and L-3, rather than for the individual lewisite compounds. L-2 and L-3 are co-products concurrently formed with L-1 (Trammel 1992). L-1 yield is greater than 65%, and approximate yields of L-2 and L-3 are 7-10% and 4-12%, respectively (Lindberg et al. 1997). L-2 and L-3, because of their smaller quantities and comparatively low volatility, will be less toxicologically significant than L-1. Furthermore, the toxicity of L-2 and L-3 is comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL-values derived for lewisite are considered protective for L-1, L-2, and L-3 compounds. AEGL-3 values for lewisite are presented in Table 5-11, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for lewisite is presented in Table 5-12. Data were insufficient to derive AEGL-1 values. AEGL-2 values are based on a three-fold reduction in AEGL-3 values, and AEGL-3 values are based on lethality data in dogs.

TABLE 5-11 AEGL-3 Values for Lewisite

10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

TABLE 5-12 AEGL Values for Lewisite

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)
AEGL-3 (lethal)	3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

[a]NR, not recommended; absence of an AEGL-1 does not imply that exposure below the AEGL-2 values is without adverse effect.

8.2. Comparisons with Other Standards and Guidelines

No exposure standards or guidelines were for L-1, L-2, or L-3 were found.

8.3. Data Adequacy and Research Needs

Human data were insufficient for deriving AEGL values for lewisite. Mouse and dog lethality studies were well conducted and were not inconsistent with the limited lethality data in other species. No data on concentration-response relationships for AEGL-2 effects were suitable for deriving AEGL-2 values. Data were available only for L-1; however, given the low volatility and small volume of L-2 and L-3 in total lewisite and the similar toxicity of L-2 and L-3 with L-1 (Lindberg et al. 1997), AEGL-values derived for lewisite should be protective for L-1, L-2, and L-3 compounds.

9. REFERENCES

Because lewisite compounds were developed as chemical warfare agents, military literature is a major source of relevant toxicity data. Consequently, many of the study reports have “limited distribution", which is a separate issue from “classification”. For various reasons, sources may have a restricted distribution because of treaty restrictions on data access with allies, concerns regarding distribution of engineering information characterizing agent dissemination or generation in other sections of the same document, and related issues. To ensure

public access to pertinent toxicity data originating from limited-distribution materials, pertinent data from those sources have been incorporated into this chapter.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR LEWISITE

Derivation of AEGL-1 Values

The available data were insufficient to derive AEGL-1 values for lewisite.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values, a one-third reduction of the AEGL-3 values was used to derive AEGL-2 values (NRC 2001).

10-min AEGL-2: $3.9\ mg/m^3 \div 3 = 1.3\ mg/m^3$

30-min AEGL-2: $1.4\ mg/m^3 \div 3 = 0.47\ mg/m^3$

1-h AEGL-2: $0.74\ mg/m^3 \div 3 = 0.25\ mg/m^3$

4-h AEGL-2: $0.21\ mg/m^3 \div 3 = 0.070\ mg/m^3$

8-h AEGL-2: $0.11\ mg/m^3 \div 3 = 0.037\ mg/m^3$

Derivation of AEGL-3 Values

Key study: Armstrong, G.C. 1923. The toxicity of M-1 by inhalation for dogs. Chapter II in The Toxicity, Pathology, Chemistry, Mode of Action, Penetration, and Treatment for M-1 and its Mixtures with Arsenic Trichloride, Part 1. ADB954935. Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. (unclassified report/limited distribution).

Toxicity end point: Calculated LC_{01} values (estimated 1% lethality thresholds)

10-min	$38.7\ mg/m^3$
30-min	$14.0\ mg/m^3$
1-h	$7.4\ mg/m^3$
4-h	$2.1\ mg/m^3$
8-h	$1.1\ mg/m^3$

Uncertainty factors: 3 for interspecies differences
3 for intraspecies variability

	Appropriate chemical-specific data were not available to derive AEGL-3 values for L-2 or L-3. However, L-2 and L-3 exist as a small fraction of total lewisite (7-10% for L-2 and 4-12% for L-3) and have comparatively low volatilities. Because of these chemical characteristics, AEGL-3 values for L-1 were adopted as AEGL-3 values for the mixture of L-1, L-2, and L-3.

Calculations:

10-min AEGL-3:	$38.7\ mg/m^3 \div 10 = 3.9\ mg/m^3$
30-min AEGL-3:	$14.0\ mg/m^3 \div 10 = 1.4\ mg/m^3$
1-h AEGL-3:	$7.4\ mg/m^3 \div 10 = 0.74\ mg/m^3$
4-h AEGL-3:	$2.1\ mg/m^3 \div 10 = 0.21\ mg/m^3$
8-h AEGL-3:	$1.1\ mg/m^3 \div 10 = 0.11\ mg/m^3$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR LEWISITE

Derivation Summary

AEGL-1 VALUES

The available data on lewisite were inadequate to derive AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)

Data adequacy: The available data on lewisite were inadequate to derive AEGL-2 values. When data are lacking and the concentration-response curve is steep, AEGL-2 values may be derived by dividing the AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for lewisite. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

Key reference: Armstrong, G.C. 1923. The toxicity of M-1 by inhalation for dogs. Chapter II in The Toxicity, Pathology, Chemistry, Mode of Action, Penetration, and Treatment for M-1 and its Mixtures with Arsenic Trichloride. Part 1. ADB954935. Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. (unclassified report/limited distribution).

Test species/Strain/Number: Dog; breed not specified; 1-17 per group.

Exposure route/Concentrations/Durations:
Inhalation; 126, 176, 231, 274, and 330 mg/m^3 for 7.5 min
Inhalation; 68.7, 87.7, 96, 102, 125, and 233 mg/m^3 for 15 min
Inhalation; 11.5, 24.5, 30.6, 41.5, 48, and 58.6 mg/m^3 for 30 min
Inhalation; 5.8, 8, 25, 35, 43, and 53 mg/m^3 for 1 h
Inhalation; 4.8, 12.5, 17.9, 24.5, and 34.5 mg/m^3 for 2 h
Inhalation; 2.1, 6.2, 10, and 16.9 mg/m^3 for 4 h

Effects:

Concentration (mg/m^3)	
176	7.5-min LC_{50}
100	15-min LC_{50}

48	30-min LC_{50}
25.7	1-h LC_{50}
11.8	2-h LC_{50}
6.6	4-h LC_{50}
38.7	10-min LC_{01}
14.0	30-min LC_{01}
7.4	1-h LC_{01}
2.1	4-h LC_{01}
1.1	8-h LC_{01}

End point/Concentration/Rationale: Calculated LC_{01} values, considered thresholds for lethality.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, data suggest little species variability with regard to lethality from inhalation exposure to L-1; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the 2- to 3-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats.
Intraspecies: 3, steep concentration-response curve with regard to lethality implies limited intraspecies variation. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Points of departure were time-specific LC_{01} values.

Data adequacy: Data are adequate to derive AEGL-3 values for lewisite.

APPENDIX C

CALCULATION OF LC_{01} VALUE FOR DOGS

Data source: Armstrong (1923)
Filename: ten Berge Spreadsheet Data for Log Probit Model
Date: 15 October 2010 Time: 09:03:51

Sequence No.	Concentration (mg/m^3)	Minutes	Exposed	Responded
1	126	7.5	2	0
2	176	7.5	12	7
3	231	7.5	17	10
4	274	7.5	4	4
5	330	7.5	1	1
6	68.7	15	4	1
7	87.7	15	5	2
8	96	15	5	3
9	102	15	3	2
10	125	15	12	6
11	233	15	3	3
12	11.5	30	1	0
13	24.5	30	4	0
14	30.6	30	2	0
15	41.5	30	2	0
16	48	30	3	2
17	58.6	30	4	4
18	5.8	60	2	0
19	8	60	5	0
20	25	60	9	5
21	35	60	9	5
22	43	60	7	5
23	53	60	1	1
24	4.8	120	4	0
25	12.5	120	3	2
26	17.9	120	6	4
27	24.5	120	5	4
28	34.5	120	3	3
29	2.1	240	3	0
30	6.2	240	9	5
31	10	240	17	10
32	16.9	240	2	2

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

Chi-Square = 15.93
Degrees of freedom = 29
Probability Model = 9.76E-01

Ln(Likelihood) = -29.24

B 0 = -7.7323E+00 Student t = -3.1898
B 1 = 1.7999E+00 Student t = 5.3334
B 2 = 1.6615E+00 Student t = 5.2230

Variance B 0 0 = 5.8761E+00
Covariance B 0 1 = -8.1104E-01
Covariance B 0 2 = -7.6250E-01
Variance B 1 1 = 1.1390E-01
Covariance B 1 2 = 1.0355E-01
Variance B 2 2 = 1.0120E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 1.083
Lower limit (95% CL) = 0.976
Upper limit (95% CL) = 1.191

Estimation of concentration mg/m^3 at response of 1%
Minutes = 10
Point estimate concentration mg/m^3 = 3.869E+01 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 1.699E+01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 5.741E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 30
Point estimate concentration mg/m^3 = 1.403E+01 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 6.185E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 2.064E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 60
Point estimate concentration mg/m^3 = 7.400E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 3.237E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 1.094E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 120
Point estimate concentration mg/m^3 = 3.903E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 1.682E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 5.838E+00 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 240
Point estimate concentration mg/m^3 = 2.058E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 8.675E-01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 3.138E+00 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 480
Point estimate concentration mg/m^3 = 1.085E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 4.447E-01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 1.697E+00 for response of 1%

APPENDIX D

CATEGORY PLOT FOR LEWISITE

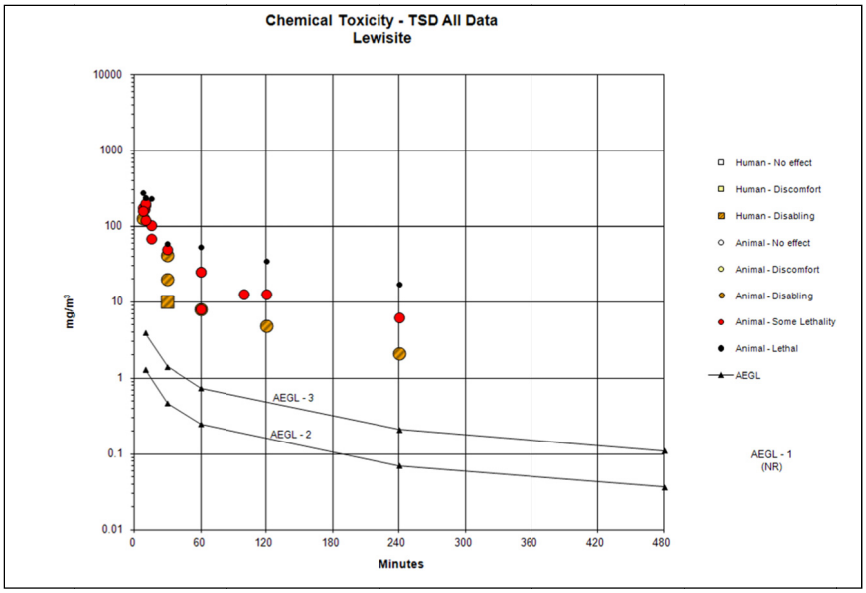

FIGURE D-1 Category plot of animal and human toxicity data and AEGL values for lewisite.

TABLE D-1 Data Used in the Category Plot for Lewisite

Source	Species	Sex	No. of Exposures	mg/m^3	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				1.3	10	AEGL	
AEGL-2				0.47	30	AEGL	
AEGL-2				0.25	60	AEGL	
AEGL-2				0.070	240	AEGL	
AEGL-2				0.037	480	AEGL	
AEGL-3				3.9	10	AEGL	
AEGL-3				1.4	30	AEGL	
AEGL-3				0.74	60	AEGL	
AEGL-3				0.21	240	AEGL	
AEGL-3				0.11	480	AEGL	
Franke 1968	Human		1	10	30	2	Severe intoxication, incapacitation
Silver and McGrath 1943	Mouse	Male	1	240	10	3	Mortality (10/10)
Armstrong 1923	Dog		1	126	7.5	2	Mortality (0/2)
	Dog		1	176	7.5	SL	Mortality (7/12)
	Dog		1	274	7.5	3	Mortality (4/4)
	Dog		1	68.7	15	SL	Mortality (1/4)
	Dog		1	102	15	SL	Mortality (2/3)
	Dog		1	233	15	3	Mortality (3/3)

	Dog	1	41.5	30	2	Mortality (0/2)
	Dog	1	58.6	30	3	Mortality (4/4)
	Dog	1	8	60	2	Mortality (0/5)
	Dog	1	25	60	SL	Mortality (5/7)
	Dog	1	53	60	3	Mortality (1/1)
	Dog	1	4.8	120	2	Mortality (0/4)
	Dog	1	12.5	120	SL	Mortality (2/3)
	Dog	1	34.5	120	3	Mortality (3/3)
	Dog	1	2.1	240	2	Mortality (0/3)
	Dog	1	6.2	240	SL	Mortality (5/9)
	Dog	1	16.9	240	3	Mortality (2/2)
Harrison et al. 1946	Dog	1	50	30	SL	
	Dog	1	121	10	SL	
Gates et al. 1946	Dog	1	20	30	2	Ocular lesions
Silver and McGrath 1943	Mouse	1	240	10	3	100% mortality (10/10)
Gates et al. 1946	Rat	1	166	9	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	190	10	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	200	10	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	240	10	3	100% mortality (10/10)
Gates et al. 1946	Guinea pig	1	8	60	SL	LC_{50}
Gates et al. 1946	Rabbit	1	160	7.5	SL	LC_{50}
Gates et al. 1946	Rabbit	1	25	60	SL	LC_{50}
Gates et al. 1946	Goat	1	12.5	100	SL	LC_{50}

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

6

Methyl Isothiocyanate[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

[1]This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Susan Ripple (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

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

SUMMARY

Methyl isothiocyanate (MITC) is a colorless crystalline solid that occurs primarily as a decomposition product of pesticides applied as soil fumigants. MITC injected into soil rapidly vaporizes. A level of distinct odor awareness (LOA) of 27 ppm for MITC was calculated.

The database for MITC includes a controlled human clinical study that evaluated odor threshold and ocular irritation, acute and repeated-exposure inhalation studies in rats, and oral studies of reproductive and developmental toxicity in rats and rabbits. MITC is a potent, direct-acting irritant to the eyes and respiratory tract. Death results from acute pulmonary congestion and hemorrhage. Developmental studies indicate that MITC was not teratogenic but caused delayed growth at maternally toxic concentrations. Although MITC is an alkylating agent, most genotoxicity studies reported negative results. Carcinogenicity studies of MITC administered orally to rats and mice did not find a significant neoplastic response.

AEGL-1 values are based on a study of human volunteers (Russell and Rush 1996). This study met the criteria for using data on human subjects outlined in the Standing Operating Procedures for AEGLs (NRC 2001, Section 2.3.2). Slight and transient ocular irritation was reported by subjects exposed to MITC at a concentration of 0.8 ppm. Blinking rate was slightly increased, but there was no tearing or redness of the eye. Thus, 0.8 ppm was considered the highest concentration without notable discomfort and was used as the point of departure for deriving AEGL-1 values. An intraspecies uncertainty factor of 3 was applied, because MITC appears to have a direct-acting irritant mechanism

of toxicity and metabolic and physiologic differences are unlikely to play a major role (NRC 2001). Also, the range of human sensitivity to ocular irritants is approximately two-fold (Kjaergaard et al. 1992). Because 0.8 ppm was tested for up to 4 h, that concentration was used for all the AEGL-1 exposure durations. Furthermore, there is adaptation to the slight irritation that defines the AEGL-1. The AEGL-1 values are supported by no-effect concentrations in repeated-exposure studies with rodents (Rosskamp et al. 1978; Klimisch 1987).

No acute clinical studies or acute toxicology studies in laboratory animals were identified that were relevant deriving AEGL-2 values. The degree of ocular irritation observed in the study by Russell and Rush (1996) was not of sufficient severity to impair escape. In the absence of data that address AEGL-2 end points, the AEGL-3 for MITC values were divided by 3 to derive the respective AEGL-2 values. This approach is appropriate for chemicals with evidence of a steep concentration-response curve (NRC 2001).

The point of departure for AEGL-3 values was the highest nonlethal concentration of 94 ppm in a study of rats exposed for 4 h (Jackson et al. 1981). Interspecies and intraspecies uncertainty factors of 3 each are generally applied to chemicals that are direct-acting irritants (NRC 2001). However, such an approach in this instance would result in values inconsistent with the human volunteer study by Russell and Rush (1996). Therefore, interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were applied. Time-scaling was performed using the equation $C^n \times t = k$, with default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolating to longer durations (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of uncertainties associated with extrapolating a 4-h point of departure to a 10-min value.

AEGL values for MITC are presented in Table 6-1.

1. INTRODUCTION

MITC is a colorless crystalline solid that is used as a soil fumigant (Lam et al. 1993; HSDB 2012). It is produced by the action of carbon disulfide on methylamine or by reacting sodium methyldithiocarbamate with ethyl chlorocarbonate (HSDB 2012). Metam sodium (sodium *N*-methyldithiocarbamate), which decomposes to MITC, is the third most commonly used agricultural pesticide in the United States (Pruett et al. 2001); however, production data were not located. MITC injected into soil immediately vaporizes (Nihon Schering 1990).

Metam sodium and dazomet are propesticides (compounds that are converted to pesticides) which hydrolyze in soil to MITC as the ultimate toxicant (Lam et al. 1993). Upon dilution with water, metam sodium decomposes to MITC which evolves as a gas of hydrogen sulfide and lesser amounts of methylamine and carbon disulfide. Ditrapex® and Trapex® contain 20% MITC (Nihon Schering 1990). Ditrapex® contains 40% 1,2-dichloropropene, a nematicide. MITC is phytotoxic and planting is delayed until the soil fumigant has decomposed completely.

TABLE 6-1 AEGL Values for Methyl Isothiocyanate[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	No evidence of notable discomfort (ocular irritation) at several time points in humans (Russell and Rush 1996)
AEGL-2 (disabling)	21 ppm (63 mg/m^3)	21 ppm (63 mg/m^3)	17 ppm (51 mg/m^3)	10 ppm (30 mg/m^3)	5.3 ppm (16 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	63 ppm (190 mg/m^3)	63 ppm (190 mg/m^3)	50 ppm (150 mg/m^3)	31 ppm (94 mg/m^3)	16 ppm (47 mg/m^3)	Nonlethal concentration in rats (Jackson et al. 1981)

[a]A level of distinct odor awareness (LOA) of 27 ppm was calculated for MITC (see Appendix A). The LOA is defined as the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience strong odor intensity. Calculation of the LOA does not imply that exposure below the LOA is without effects.

MITC belongs to the chemical class mustard oils. It has been considered as a possible military poison (Verschueren 2001). The toxicity of MITC was reviewed by Nihon Schering (1990), NRA (1997), and Rubin et al. (2003). MITC has a pungent, horseradish-like odor at room temperature; its vapors irritate mucous membranes and it is a potent lacrimator (Nihon Schering 1990).

The chemical and physical properties of MITC are presented in Table 6-2.

2. HUMAN TOXICITY DATA

2.1. Odor Threshold and Odor Awareness

MITC has a pungent horseradish-like odor at room temperature (Nihon Schering 1990). Odor thresholds reportedly range from approximately 0.1 ppm (Nesterova 1969) to 5 ppm (Verschueren 2001). The odor threshold determined in a controlled clinical study was 1.7 ppm (Russell and Rush 1996; EPA 2006a). Using the data of Russell and Rush (1996), a level of distinct odor awareness (LOA) of 27 ppm was calculated for MITC (see Appendix A). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity.

The propesticide metam sodium hydrolyzes into MITC and hydrogen sulfide, and the odor of hydrogen sulfide might be present at metam sodium application sites.

TABLE 6-2 Chemical and Physical Properties of Methyl Isothiocyanate

Parameter	Value
Synonyms	Isothiocyanatomethane; methyl mustard oil; Trapex
CAS registry no.	556-61-6
Chemical formula	C_2H_3NS
Molecular weight	73.12
Physical state	Colorless crystals
Melting point	36°C
Boiling point	119°C
Density/specific gravity (water =1)	1.0691 at 37°C
Solubility in water	7.6 g/L at 25°C
Vapor density (air =1)	2.53
Vapor pressure	3.54 mm Hg at 25°C
Saturated vapor concentration (calculated from vapor pressure)	~27,000 ppm (~82,000 mg/m^3)
Flammability limits	Lower 2.5%; Upper 30%/MITC-Fume
Conversion factors (calculated)	1 ppm = 2.99 mg/m^3 1 mg/m^3 = 0.33 ppm

Source: HSDB 2012.

2.2. Accidents and Community Exposures

In 1991, a railroad tank car in California derailed and spilled 19,000 gallons of metam sodium into the Sacramento River (Alexeeff et al. 1994). The hydrolysis product MITC was released to the air. Many individuals downriver of the incident reported odors. Over 240 individuals complained of ocular and throat irritation, dizziness, and shortness of breath. Ambient air concentrations, measured on the fourth day after the accident (12-h integrated samples) ranged from 0.2 to 37 ppb. Average concentrations reported on the fifth through tenth day ranged from below the limit of detection (<1 ppb) to 2.6 ppb. Estimates of peak concentrations during the first two days were 140-1,600 ppb for exposures of a few minutes to 1 h; these estimates were for areas within 500 meters of the river.

Cone et al. (1994) assessed the occurrence of persistent respiratory disorders among adults exposed as a result of the metam sodium spill. Exposures were most likely to a mixture of metam sodium hydrolysis products which include MITC, hydrogen sulfide gas, methylamine, and carbon disulfide. Among a group of 197 persons referred for health evaluation, 20 were identified as having persistent irritant-induced asthma and 10 were identified as having persistent exacerbation of pre-existing asthma. Cases of irritant-induced asthma met the

following criteria: onset of upper respiratory symptoms within 24 h of exposure; onset of lower respiratory symptoms within 1 week and persisting for more than 3 months; no prior history of respiratory illness (confirmed by medical records); location and activity consistent with exposure during and for 1 week after the spill; and nonspecific airway hyper-responsiveness demonstrated by methacholine challenge. Most (17/20) of the irritant-induced asthma cases met the criteria for reactive airway distress syndrome (RADS).

O'Malley et al. (2004) documented illnesses among residents of a community near a potato field where metam sodium was applied with a sprinkler. Air concentrations of MITC were estimated with air models using application information and meteorological data. Concentrations were estimated to range from 0.5 ppm to just over 1 ppm (1-h time-weighted averages). Peak concentrations at 1 and 3 min were estimated to be 4 and 7 ppm, respectively. No data were reported regarding concentrations of other hydrolysis products of metam sodium, which includes a mixture of known irritants. Residents were interviewed to obtain information on symptoms and proximity to the potato field during pesticide application. Among those closest to the application site (≤0.5 miles), symptoms consisted of irritation of the eyes or upper respiratory tract (burning of eyes, nose, or throat) in 51/135, non-specific systemic symptoms such as headache, nausea, diarrhea, abdominal pain, or malaise in 22/135, "systemic irritant" response (not otherwise specified) in 45/135, and respiratory irritation (but not asthma or lower respiratory irritation) in 6/135. Frequency of complaints decreased with distance from the application site.

O'Malley et al. (2005) reported illnesses related to soil incorporation (shank application) of metam sodium near a rural community in California. Several hours after application of 25,000 pounds of metam sodium to a 100-acre field, 250 nearby residents experienced ocular and upper-respiratory irritation, non-specific systemic symptoms, and lower-respiratory-tract complaints. Some residents sought medical treatment. After the incident, residents were interviewed directly or via medical records in order to correlate symptoms with area and activity. The most serious illnesses were associated with individuals who had pre-existing lung diseases, such as asthma and emphysema. MITC concentrations were estimated based on field treatment, projected emissions, and weather conditions. Modeling results indicted 1-h MITC concentrations in the affected areas of 0.8-1.0 ppm, with peak concentrations between 2.4 and 3.2 ppm.

Bretaudeau Deguigne et al. (2011) described a series of 106 case reports of exposure to metam sodium at a poison control center in France. Most (96) cases were accidentally exposed via inhalation, and the most commonly reported symptoms attributed to MITC exposure were irritation of the eyes (76/96 inhalation exposures) and throat and nose (65/96). Exposure concentrations were not reported. Of the 96 exposed, only four had cough or dyspnea; the investigator reported that there were no cases of persistent irritant-induced asthma or exacerbation of asthma.

2.3. Clinical Studies

In order to determine the thresholds for odor detection and ocular irritation, healthy adult volunteers were exposed to measured concentrations of MITC in a laboratory setting (Russell and Rush 1996[2]; reviewed in EPA 2006a). This study met the criteria for use of data from human subjects discussed in the Standing Operating Procedures for AEGLs (NRC 2001, Section 2.3.2). In the olfactory threshold study, 33 individuals (16 males, 17 females; age range of 18-34 years) were exposed to three reference control odorants: pyridine, acetic acid, and *n*-butyl alcohol, as well as MITC. The odorants were dispensed in a controlled double-blind fashion through one of three presentation ports. A technician chose the odorant and the subject was responsible for determining from which port the odorant was dispersed. There was a 30-sec rest period between odorant presentations. Each volunteer was tested over a range of concentrations for each odorant until a threshold, determined under a standard procedure, was satisfactorily ascertained. The observed odor threshold for MITC ranged from 0.2 to 8 ppm, with a geometric mean of 1.7 ppm.

The ocular irritation study was conducted with 70 adult volunteers (38 males, 32 females; age range of 18-67 years). Four exposure durations of 1 min, 14 min, 4 h, and 8 h were used. In the 1-min trial, subjects were exposed to MITC at concentrations up to 3.3 ppm. In the 14-min trial, 9-10 subjects were exposed at 0 (air only), 0.6, 1.9, or 3.3 ppm. In the 4-h trial, there was both an air and acetic acid control; concentration of MITC tested were 0.23 ppm (12 subjects) or 0.8 ppm (9 subjects). In the 8-h study, 12 subjects were exposed to air only, seven were exposed to acetic acid, and 16 subjects were exposed to MITC at 0.22 ppm. Subjects were permitted two 15-min rest periods and a lunch break during the 8-h study. An olfactometer was used to dispense the test materials through a manifold system. A total hydrocarbon analyzer was used to monitor the flow of test material through the tubing; samples were collected on carbon tube samplers, desorbed, and measured with gas chromatography. The subjects were exposed via goggles. No additional details of the methods were available.

Subjective irritation was measured on a Likert scale in which irritation was rated from no irritation to a feeling the subject would like to end the exposure; the mid-point was described as similar to that of cutting a single mild onion. Subjective irritation, blink rates, and tearing were assessed at several time points. Baseline responses were determined pre-exposure and from exposure to the air control. Visual acuity and ocular morphology were assessed at the beginning and end of each exposure (methods not provided). The results of this study are summarized in Table 6-3. The no-observed-effect levels (NOELs) for the 1-

[2]Russell and Rush (1996) is an unpublished report prepared by the University of California and Western Research Center and submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention. The report is not publicly available. A U.S. EPA AEGL staff member with FIFRA clearance reviewed the original report and confirmed the details provided in the U.S. EPA (2006a) Data Evaluation Record for the study.

and 14-min exposures were 3.3 and 0.6, respectively. The NOEL range for the two longer duration exposures was 0.22-0.23 ppm. The lowest-observed-effect level (LOELs) for the 14-min and 1- through 8-h intervals were 1.9 and 0.8 ppm, respectively. During the first hour of the 4-h trial at 0.8 ppm, subjective irritation was rated at 25 ± 14% on a scale of 1 to 100. During the second hour of the 4-h trial at 0.8 ppm, blink rates increased from 3 ± 9/min in the control group to 16 ± 11/min in the 0.8-ppm group. Thereafter, blink rate did not increase with exposure duration. No statistically significant positive tearing responses were observed; photographs of the participant's eyes failed to show notable, exposure-related changes. Comments from the subjects indicated that recovery began immediately after removal of the goggles and was complete within 20 min at the highest concentration.

2.4. Community Exposures

Lee et al. (2002) reported ambient concentrations of MITC (and other pesticides or pesticide breakdown products) in California during months associated with pesticide application. With 2 weeks of air monitoring data, generally collected from samplers placed atop the roofs of community building, mean concentrations of MITC were 2.1 μg/m^3 (0.7 ppb) in urban communities (range not reported) and 4.9 μg/m^3 (1.6 ppb) in rural communities (range up to 18 μg/m^3 [6 ppb]). The 15-day maximum concentration was 8.4 μg/m^3 (2.8 ppb). The publication reported little information on the areas sampled.

TABLE 6-3 Ocular Irritation in Human Subjects

Exposure Duration	NOEL[a] (ppm)	LOEL (ppm)	Description
1 min	3.3	–	
4 min	0.60	1.9	Subjective ocular irritation[b]
14 min	0.60	1.9	Subjective ocular irritation
1 h	0.23	0.8	Subjective ocular irritation
1.5 h	0.22	–	
2 h	0.23	0.8	Subjective ocular irritation, increased blink rate.
3 h	0.23	0.8	Subjective ocular irritation, increased blink rate.
3.5 h	0.22	–	
4 h	0.23	0.8	Subjective ocular irritation
6 h	0.22	–	
8 h	0.22	–	

[a]The 0.22- and 0.23-ppm concentrations were tested on different days.
[b]Ocular irritation did not include redness or tearing.
Source: Rubin et al. 2003.

Merriman and Hebert (2007) reported the results of an air monitoring study measuring MITC concentrations in the air of an agricultural region of Washington State during the fall season when metam sodium fumigation is typically done. Five residential sites and one commercial site were selected for monitoring. Twenty-four-hour samples comprised of two 12-h day and night subsamples were collected over the course of 1 month (September 26 to October 25, 2005); a total of 201 samples were collected. The frequency of measurements above the detection limit (0.01 ppb) was 199/201. The maximum 12-h time-weighted average concentration of MITC was 67 $\mu g/m^3$ (22 ppb); the average over the 30-day sampling period was 10 $\mu g/m^3$ (3.3 ppb).

2.5. Developmental and Reproductive Toxicity

No studies of developmental or reproductive toxicity of MITC in humans were found.

2.6. Genotoxicity

Negative results were obtained with MITC at concentrations of 3.0 or 5.0 µg/mL in an in vitro cytogenetic chromosome aberration test using cultured human lymphocytes (Rubin et al. 2003). MITC induced micronuclei and DNA strand breaks in cultured human hepatoma cells at concentrations that were cytotoxic (Kassie et al. 2001).

2.7. Chronic Toxicity and Carcinogenicity

No studies of the chronic toxicity or potential carcinogenicity of MITC in humans were found.

2.8. Summary

In studies with human volunteers, the odor threshold for MITC ranged from 0.2 to 8 ppm, with a geometric mean of 1.7 ppm (Russell and Rush 1996). Volunteers were exposed to referent odorants including *n*-butyl alcohol. In a study with 70 volunteers, ocular irritation was examined at discrete time intervals (Russell and Rush 1996). No ocular irritation was observed in association with MITC at 3.3 ppm (the highest concentration tested) for 1 min, 0.6 ppm for 14 min, or 0.22-0.23 ppm for 1-8 h. When exposed at 1.9 ppm for 14 min or at 0.8 ppm for 1-8 h, subjects reported ocular irritation slightly less than that associated with cutting a single mild onion. MITC failed to induce signs of genotoxicity in an in vitro test for chromosome damage in cultured human lymphocytes (Rubin et al. 2003), and induced strand breaks in human hepatoma cells at cytotoxic concentrations (Kassie et al. 2001).

No human studies addressing the potential for reproductive and developmental toxicity or chronic toxicity and carcinogenicity were found.

3. ANIMAL TOXICITY DATA

Data on MITC were reviewed by Nihon Schering (1990), Alexeeff et al. (1994), NRA (1997), HSDB (2012), and Rubin et al. (2003). MITC is a primary ocular irritant when instilled into the eye of rabbits (100 mg), causing severe inflammation with corneal opacity, iritis, and conjunctival swelling (Nihon Schering 1990). In studies with several species, cats were the most sensitive species, exhibiting irritation of the ocular mucosa (Nesterova 1969). No details of those studies were available.

3.1. Acute Lethality

Clark and Jackson (1977) exposed groups of five male and five female Sprague-Dawley CFY rats whole-body to five concentrations of MITC ranging from 600 to 3,100 mg/m^3 (200 to 1,037 ppm) for 1 h. The test material administered in the study was a pesticide formulation that contains MITC as an active ingredient. The conversion used to estimate the MITC concentration in the chamber (the concentration reported by secondary sources) was not clearly explained in the original report. Hyperactivity that began within 5 min of exposure was observed in all MITC-treated groups. Ocular irritation, dyspnea, and hypoactivity were observed during the remainder of the exposure period. Most rats exposed at 3,100 mg/m^3 (1,037 ppm) died; death was preceded by convulsions. No deaths occurred at 630 mg/m^3 (210 ppm). The 1-h LC_{50} was 1,900 mg/m^3 (635 ppm). Necropsy of animals that died revealed pulmonary congestion and hemorrhage of the lungs.

Jackson et al. (1981; reviewed in EPA 2006b)[3] exposed groups of five male and five female Sprague-Dawley rats to six different concentrations of MITC for 4 h (concentrations not specified). The test material was MITC. Clinical signs noted during exposure included closure of the eyes, lacrimation, and peripheral vasodilation in all rats and a hunched posture in the majority of the animals. Peripheral vasodilation persisted for several hours after exposure. Opacity of the eyes was observed in rats exposed at ≥500 mg/m^3 (≥167 ppm). No mortality or gross pathologic changes were observed at 282 mg/m^3 (94 ppm), but lung weight was increased and lung rales were observed on day 1 and reoccurred on day 6 post-exposure. The calculated 4-h LC_{50} was 180 ppm for

[3] Jackson et al. (1981) is an unpublished report prepared by Huntingdon Research Center and submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention. The report is not publicly available. A U.S. EPA AEGL staff member with FIFRA clearance reviewed the original report and confirmed the details provided in the U.S. EPA (2006b) Weight-of-Evidence Discussion for the study.

both sexes. Necropsy and histopathologic examination of the animals that died revealed congestion, edema, bronchiolitis, interstitial pneumonitis, and intra-alveolar hemorrhage of the lungs, accompanied by increased lung weight and focal hepatic necrosis. Distention of the stomach and intestines was attributed to swallowing air (gasping) prior to death.

Ullman (1985) reported 100% mortality in Wistar rats within 30 min of exposure to MITC at 10 ppm. These results conflict with those of the other acute toxicity studies, as well as with the repeated-exposure studies with the same strain of rats (see Section 3.3). Nesterova (1969) reported no deaths in rats (strain unidentified) exposed to MITC at 26 ppm for 4 h, whereas 80-100% of mice died at 25-26 ppm. No details of the methods of the Nesterova (1969) were reported. With the exception of these two studies, the acute lethality data for MITC are presented in Table 6-4.

3.2. Nonlethal Acute Toxicity

No acute toxicity studies other than those summarized in Section 3.1 were found.

3.3. Repeated Exposure Studies

Groups of five male and five female SPF Wistar/Chubb:THOM rats were exposed whole-body to MITC for 6 h/day, 5 days/week for 28 days (Klimisch 1987; EPA 2006b). Measured concentrations of MITC were 0, 1.7, 6.8, and 34 ppm. Beginning on the third exposure day and continuing throughout the study, rats exposed at 6.8 or 34 ppm exhibited eyelid closure, somnolence, and ruffled fur during each daily exposure. No clinical signs were observed in the 1.7-ppm group. Additional clinical signs observed in the 34-ppm group included reddish nasal discharge, salivation, ocular discharge, and dyspnea. Except for ruffled fur and respiratory distress in the 34-ppm group, clinical signs resolved between exposures. Body weight and several clinical-chemistry parameters were reduced in the high-exposure group at sacrifice. Histopathologic examination revealed rhinitis in the nasal cavity, atrophy of the olfactory epithelium, metaplasia of the nasal respiratory epithelium, tracheal epithelial proliferation, bronchial pneumonia and bronchial and bronchiolar epithelial proliferation, and emphysema. The no-observed-adverse-effect level was 1.7 ppm.

TABLE 6-4 Acute Lethality Data on Methyl Isothiocyanate

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	210	1 h	No mortality	Clark and Jackson, 1977
	635	1 h	LC_{50}	
Rat	94	4 h	No mortality	Jackson et al. 1981
	180	4 h	LC_{50}	

Groups of 10 male and 10 female Wistar were exposed nose-only to MITC (95.69% pure) at concentrations of 0, 1, 10, or 45 ppm for 4 h/day, 5 days/week for 12-13 weeks (Rosskamp et al. 1978; EPA 2006b). No clinical signs were observed in the 1- or 10-ppm groups. Reduced physical activity accompanied by salivation and nasal discharge was recorded throughout the study in the 45-ppm group. Body weight was reduced only in the 45-ppm group, and body weight gain was reduced by 11-15% in the 10-ppm group and by 47-63% in the 45-ppm group. Histologic examination of the nasal passages was not performed. The results of repeated exposure studies of MITC are summarized in Table 6-5.

MITC was immunotoxic in repeated exposure, oral studies. Daily administration of MITC at 15-55 mg/kg by gavage for 5 days to $B6C3F_1$ mice resulted in a decrease in thymus weight and cellularity and changed peripheral white blood cell populations (Keil et al. 1996). MITC was administered in Hanks balanced salt solution. Oral administration (gavage, water vehicle) of metam sodium to female $B6C3F_1$ mice at 300 mg/kg for 10 or 14 days decreased thymus weight, increased spleen weight, increased bone marrow cellularity, reduced mature lymphocyte subpopulations in the thymus, depleted major subpopulations of thymocytes, and reduced body weight (Pruett et al. 1992).

3.4. Developmental and Reproductive Toxicity

No inhalation studies that evaluated the potential for MITC to induce reproductive or developmental toxicity were found.

The results of two- and three-generation oral reproductive studies with the rat and oral development toxicity studies with the rat and rabbit are summarized in Table 6-6. Parameters of reproductive performance were not altered by treatment in any generation. In the three-generation study, the irritant effects of MITC resulted in lesions of the stomach in all treatment groups. In the developmental toxicity studies, doses that affected fetal parameters also produced maternal toxicity. No teratogenic effects were evident.

TABLE 6-5 Results of Repeated Exposure Studies of Methyl Isothiocyanate in Rats

Concentration (ppm)	Exposure Duration	Effect	Reference
1.7	6 h/d, 5 d/wk for 28 d	No clinical signs.	Klimisch 1987
6.8		Eyelid closure, somnolence, ruffled fur.	
34		Eyelid closure, somnolence, ruffled fur, nasal discharge, salivation, ocular discharge, dyspnea, nasal and lung lesions.	
1	4 h/d, 5 d/wk for 12-13 wk	No clinical signs.	Rosskamp et al. 1978
10		No clinical signs.	
45		Apathetic appearance, salivation, nasal discharge, reduced body weight.	

TABLE 6-6 Developmental and Reproductive Studies of Oral Exposure to Methyl Isothiocyanate

Species	Exposure	Effect	Reference
Developmental Toxicity			
Rat	2, 10, or 50 ppm in drinking water, 70-77 days prior to mating, two generations	No effect on fertility, reproductive performance, or development or growth of offspring; reduced water consumption (10 and 50 mg/kg).	Barker 1987
Rat	1, 3, 10, or 30[a] mg/kg by gavage, starting at 28 days of age until litters delivered, three-generations	No mortality at 1, 3, or 10 mg/kg; no reproductive or developmental effects; stomach lesions in dams.	Pflaum et al. 1978
Reproductive Toxicity			
Rat	1, 5, or 25 mg/kg by gavage, GDs 6-15	Fetal growth retardation at 25 mg/kg, secondary to decreases in maternal food intake and body weight.	Irvine 1983
Rat	3, 10, or 30 mg/kg by gavage, GDs 6-15	No effect on reproductive indices; some fetal growth retardation at 30 mg/kg.	Hellwig and Hildebrand 1987
Rabbit	1, 3, or 5 mg/kg by gavage, GDs 7-19	Reduced fetal weight and shorter crown to rump length at 5 mg/kg, secondary to maternal toxicity evidenced by reduced food consumption and lower weight gain.	Irvine 1984
Rabbit	1, 3, or 10 mg/kg by gelatin capsules, GDs 6-18	Maternal deaths, fetal toxicity, reduced fetal body weight and survival at 10 mg/kg/day; possible maternal toxicity at 3 mg/kg/day (2 deaths vs. 1 in controls).	Ladd and Smith 1976
Rabbit	1, 3, or 10 mg/kg by gavage, GDs 6-28	No clinical signs; no maternal or fetal toxicity observed.	Becker et al. 1986

[a]30-mg/kg group was terminated at week 5.
Abbreviations: GD, gestation day.

A three-generation oral study was conducted with Charles River CD rats (Pflaum et al. 1978). Beginning at 28 days of age in all generations, groups of 10 male and 20 female rats were administered MITC at 0, 3, 10, or 30 mg/kg by gavage. At week 5, the 30-mg/kg group was terminated and a 1 mg/kg group added. Dosing was 5 days/week until the animals were killed. Each generation was allowed to reach maturity, mate, and produce two litters. The first litter was killed at weaning, and the second litter became the parental animals for the next generation. Each parental generation was killed after littering twice. There were no mortalities or changes in body weight or body weight gain in any generation.

Reproductive indices, gross fetal abnormalities, and organ weights were comparable among all groups. Histopathologic examination of each parental generation revealed lesions of the forestomach, which were dose-related in incidence and severity.

Groups of 24-28 mated CD rats were given MITC by gavage in corn oil at doses of 0, 1, 5, or 25 mg/kg/day on gestation days (GD) days 6-15 (Irvine 1983). There were no differences in pregnancy incidence among the groups and there were no clinical signs except for staining of fur in the high-dose group. For dams, there was a dose-related reduction in food intake, but it was statistically significant only in the high-dose group; this group also had a non-significant reduction in body weight gain. Gross necropsy revealed thickening of the stomach wall, occasionally accompanied by adhesions of viscera to the stomach (24/27 in the 25-mg/kg group, 1/28 in the 5-mg/kg group). Fetuses of dams exposed at 25-mg/kg/day were smaller in body weight and had reduced crown-rump length with delayed skeletal ossification compared with other groups. Fetal growth retardation in the 25-mg/kg group was associated with decreased maternal food intake and reduced weight gain.

Similar to the above study, mated Wistar rats were administered MITC (in corn oil) by gavage at 0, 3, 10, and 30 mg/kg on days 6-15 of gestation (Hellwig and Hildebrand 1987). Dams were killed on GD 20. There were no deaths or clinical signs other than reddish coloration of the snout in some high-dose dams. There were no significant differences in reproductive or developmental parameters (numbers of corpora lutea, implantations, live fetuses, and sex distribution). The number of fetuses weighing less than 75% of the mean fetal weight per litter was increased in the high-dose group. There was no evidence of teratogenicity.

New Zealand white rabbits were administered MITC (in corn oil) by gavage at 0, 1, 3, or 5 mg/kg on GDs 7-19 (Irvine, 1984). At 5 mg/kg, maternal food consumption was reduced and accompanied by a decrease in body weight gain. Fetal body weight was reduced at 5 mg/kg, but litter sizes were larger.

Maternal deaths of rabbits (7/17 does) were observed following administration of MITC (in gelatin capsules) at 10 mg/kg on GDs 6-18 (Ladd and Smith 1976). All does that died had enlarged gall bladders and multiple red foci on their liver surfaces. Maternal toxicity was also observed at 3 mg/kg, as evidenced by two deaths and reduced body weight gain in survivors. Survivors gained weight comparable to that of the control rabbits over GDs 18-29. Delayed ossification of the sternum was observed in fetuses of all the dose groups.

Becker et al. (1986) administered MITC (in corn oil) by gavage at 0, 1, 3, or 10 mg/kg to groups of 16 mated chinchilla rabbits on GDs 6-18. Mean maternal body weight was reduced over the dosing period, but body weights of the low-dose group were higher than those of the control group because of increased food consumption. There was no effect of treatment on the mean number of implantations, number of live fetuses, embryonic or fetal death, or pre-implantation and post-implantation losses. Fetal weight and sex distribution were comparable among groups. There was no evidence of teratogenicity.

3.5. Genotoxicity

Mutagenicity and genotoxicity studies of MITC were reviewed and summarized by NRA (1997) and Rubin et al. (2003). Although some of the studies did not report details, there was no clear evidence of mutagenicity or genotoxicity attributable to MITC treatment. MITC was tested for mutagenicity, with and without metabolic activation, in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in several laboratories. MITC was also studied for mutagenicity in *Escherichia coli* strain wP2 hcr and at the HGPRT locus in cultured Chinese hamster V79 cells. There was no consistent evidence of mutagenicity in any of these studies.

MITC failed to induce sister chromatid exchanges in cultured Chinese hamster V79 cells, but gave positive results at some time points in an in vitro chromosome aberration test in the same system. MITC was negative in two rec assays using *Bacillus subtilis*, and it failed to induce unscheduled DNA synthesis in an assay with cultured primary rat hepatocytes. In an in vivo micronucleus test with CD-1 mice, MITC (110 mg/kg) did not show evidence of clastogenesis.

MITC (100 µg/mL) caused a marginal increase in mutations in *S. typhimurium* TA100 and TA98 (Kassie et al. 2001). Treatment with MITC induced repairable DNA damage in *E. coli*, and addition of a metabolic activation system reduced these effects. An in vivo micronucleus test with mice treated by gavage with MITC at 90 mg/kg produced only a marginal response.

3.6. Chronic Toxicity and Carcinogenicity

No chronic toxicity or carcinogenicity studies of inhalation exposure to MITC were found. Two-year bioassays with the rat and mouse in which MITC was administered via the drinking water were available.

MITC was administered to groups of 60 male and 60 female Sprague-Dawley rats in the drinking water at concentrations of 2, 10, or 50 ppm for 104 weeks (Brown 1981). Vapor loss from the water bottles was minimized with a redesign of the water bottles. Average doses over the 2 years were 0, 0.08, 0.37, or 1.60 mg/kg/day for males and 0, 0.12, 0.56, or 2.65 mg/kg/day for females. Additional groups of 10 rats of each sex were similarly treated and killed after 52 weeks. No histopathologic lesions were present in any organ at 52 weeks. Survival was similar among the groups. Water intake and body weight were decreased in males in the 50-ppm group, an effect the investigators attributed to MITC making the water unpalatable. Food intake was comparable to controls. No oncogenic response was found at any dose.

In a 106-week study, MITC was administered in drinking water at concentrations of 0, 5, 20, 80, or 200 ppm to groups of 70 male and 70 female ICR-JCR mice (Sato 1980). Calculated doses, based on drinking water analysis and water consumption were 0, 0.68, 2.74, 9.82, or 21.34 mg/kg/day for males and 0, 0.76, 3.04, 10.81, or 24.06 mg/kg/day for females. Mortality was comparable for all

groups (35-56%). No specific clinical signs were observed, but ruffled hair and dull coat were noted at 80 and 100 ppm. Body weight gain in males and females at 200 ppm and in males at 80 ppm was decreased. There were no differences in food consumption. Observed changes in hematology and clinical chemistry parameters were either transient or not dose related. There was no abnormal tissue histopathology. No differences in tumor types or time to appearance of tumors were found between the treatment groups.

3.7. Summary

Two acute inhalation toxicity studies with rats were available. The 1- and 4-h LC_{50} values were 635 and 180 ppm, respectively (Clark and Jackson 1977; Jackson et al. 1981). Respective highest nonlethal concentrations were 210 and 94 ppm. The study by Clark and Jackson (1977) administered a pesticide formulation containing MITC to the animals, and estimated MITC exposure concentrations; however, the means of estimating the MITC exposures was not clearly explained in the report. In repeated exposure studies, no clinical signs were observed in rats exposed to MITC at 1 or 1.7 ppm (Rosskamp et al. 1978; Klimisch 1987). Signs of ocular irritation were observed at 6.8 ppm in one study (6 h/day) but not at 10 ppm (4 h/day) in another study. No deaths were observed in rats after a 28-day exposure to MITC at 34 ppm (6 h/day, 5 days/week) or after 12-13 weeks at 45 ppm (4 h/day, 5 days/week).

Only oral studies were available that evaluated the reproductive and developmental toxicity of MITC. Two reproductive studies were conducted in rats, and the developmental toxicity studies were conducted in rats and rabbits. Parameters of reproductive performance were not altered by MITC treatment in any generation. In a three-generation reproduction study, the irritant effect of MITC resulted in gastric lesions in all treatment groups. In the developmental toxicity studies, doses that affected fetal parameters also produced maternal toxicity. No evidence that MITC was teratogenic was found.

No clear or consistent evidence of mutagenicity or genotoxicity was found when MITC was tested in a variety of standard short-term bacterial and mammalian cell systems. No evidence of carcinogenicity was found in rats or mice after chronic oral exposure to MITC.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

In rats, MITC is conjugated with glutathione and excreted in the urine as the corresponding mercapturic acid. Metabolism of MITC was studied in rats and mice after intraperitoneal injection (Lam et al. 1993). MITC was labeled with $^{13}CH_3$, $^{14}CH_3$, or ^{13}CS; metabolites were identified with ^{13}C-nuclear magnetic resonance and quantified by high-performance liquid chromatography and radiocar-

bon counting. Mice excreted 80% of the ^{14}C-radiocarbon label in the urine; feces were a minor route of elimination. Recovery of $^{14}CO_2$ was 3.8%. The carcass contained 6% of the radiolabel after 48 h. The liver and kidneys generally had highest ^{14}C tissue values. For the rat, identification of *S*-(*N*-methylthiocarbamoyl) glutathione in the bile and *S*-(*N*-methylthiocarbamoyl)mercapturic acid in the urine indicates that direct conjugation with glutathione is the primary detoxification mechanism. The mercapturate was a minor metabolite in the urine of mice. Mennicke et al. (1983) also identified the dithiocarbamidic acid esters in rat urine after oral administration of MITC.

Pharmacokinetic parameters were similar following oral administration of MITC (Hawkins et al. 1987). Rats were given ^{14}C-radiolabeled MITC at 4.4 or 33 mg/kg by gavage. By 24 h, 88-96% of the dose was absorbed. The thyroid, liver, kidneys, whole blood, and adrenals were relatively high sites of accumulation. Tissue concentrations at 168 h did not exceed 2.3% of the administered dose. The metabolites *N*-acetyl-*S*-(*N*-methylthiocarbamoyl)-L-cysteine and the corresponding cysteine conjugate were identified in the urine.

4.2. Mechanism of Toxicity

Clinical signs and respiratory tract pathology consistent with the actions of a primary irritant have been observed in laboratory studies with rodents. Humans exposed to MITC complained of burning eyes and skin, nausea, sore throat, salivation, coughing, and shortness of breath. Dourson et al. (2010) proposed that trigeminal nerve stimulation occurs first, followed by ocular irritation, and finally respiratory effects. The available data, while limited, do not provide clear evidence that MITC exposure is associated with systemic toxicity.

4.3. Structure-Activity Relationships

The isothiocyanates (R-N=C=S) are less toxic than the isocyanate congeners (R-N=C=O). Sulfur is less electronegative than oxygen and hydrogen bonding of sulfur takes place less readily than with oxygen (Finar 1986). In general, the thiols are less water soluble than the corresponding alcohols, likely due to their inability to form hydrogen bonds with water.

4.4. Other Relevant Information

4.4.1. Species Variability

Acute and repeat inhalation studies with MITC were all conducted with the rat. In oral reproductive and developmental studies with the rat and rabbit, no clear differences in species sensitivity were evident.

4.4.2. Susceptible Populations

No data on subpopulations that may be particularly sensitive to MITC exposure were found. MITC is a direct-acting respiratory irritant. As such, individuals with respiratory diseases such as asthma or emphysema might be more sensitive.

4.4.3. Concentration-Exposure Duration Relationship

No information on a concentration-exposure duration relationship was located. Acute rodent studies were conducted for two durations (1 or 4 h). Although an n value of approximately 1 can be calculated from these two studies, there is much uncertainty in extrapolating from two data points. The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases has been described by the equation $C^n \times t = k$, where the exponent n values range from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirical exponent, default values of n = 3 and n = 1 when extrapolating to shorter and longer durations, respectively, is used (NRC 2001). This method will yield the most conservative AEGL estimates.

4.4.4. Concurrent Exposure Issues

MITC is a decomposition product of metam sodium, which can also yield other breakdown products including hydrogen sulfide, methyl isocyante, carbon disulfide, and methyl amine, depending on the soil pH and environmental conditions (O'Malley et al. 2004). Thus, exposure to MITC may occur concurrently with exposure to these other compounds, resulting in symptoms that may not be solely related to MITC toxicity.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A study conducted with human volunteers measured ocular irritation, considered the most sensitive irritant response to MITC (Russell and Rush 1996). Ocular irritation was determined in 70 volunteers, tested in groups of 9-16 individuals, at discrete time intervals of 1 and 14 min and 4 and 8 h. No ocular irritation was reported in association with exposure at 3.3 ppm for 1 min, 0.6 ppm for 14 min, or 0.22-0.23 ppm for 1-8 h. When exposed to MITC at 1.9 ppm for 14 min or 0.8 ppm for 1-8 h, subjects reported ocular irritation slightly less than that associated with cutting a single mild onion. The study was well-designed and well-conducted.

5.2. Summary of Animal Data Relevant to AEGL-1

Acute animal studies were generally conducted at much higher concentrations than the clinical study, and subjective responses cannot be ascertained in animals. In repeated-exposure studies, no clinical signs were observed in rats exposed to MITC at 1.7 ppm for 6 h/day, 5 days/week for 28 days (Klimisch 1987) or in rats exposed at 1 ppm for 4 h/day, 5 days/week for 12-13 weeks (Rosskamp et al. 1978).

5.3. Derivation of AEGL-1

The study with human volunteers (Russell and Rush 1996) was the most appropriate for derivation of AEGL-1 values. Although the study examined only ocular irritation (through the use of goggle exposures), that effect is believed to be a more sensitive indicator of MITC exposure (occurring more quickly and at lower concentrations) than nasal or respiratory irritation (Dourson et al. 2010). No ocular irritation was reported in association with exposure to MITC at 3.3 ppm for 1 min, 0.6 ppm for 14 min, or 0.22-0.23 ppm for 1-8 h. When exposed at 1.9 ppm for 14 min or 0.8 ppm for 1-8 h, subjects reported ocular irritation slightly less than that associated with cutting a single mild onion. The effect at 0.8 ppm was a slight, transient, and subjective effect. Blinking rate was slightly increased, but there was no tearing or redness of the eye. A concentration of 0.8 ppm was considered the highest concentration that was not associated with notable discomfort and was selected as the point of departure. An intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. According to NRC (2001), "in those cases in which the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulations is unlikely to differ, an intraspecies uncertainty factor of 3-fold is generally used. Typically, this response involves a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role." Additional support for an uncertainty factor of 3 is provided by the inclusion of young adults (subjects ranged in age from 18-67 years, mean of 32 years) in the group of subjects in the study by Russell and Rush (1996). Kjaergaard et al. (1992) evaluated the range of human sensitivity to ocular irritation by carbon dioxide among 158 volunteers, and observed no differences based on gender or smoking status, but observed that young adults (<40 years of age) were more sensitive than the elderly. The threshold for ocular irritation among sensitive individuals was within a factor of 2 of the average response of young adults (Kjaergaard et al. 1992).

Because 0.8 ppm was tested for up to 4 h, this concentration was used for all AEGL-1 exposure durations (see Table 6-7). Furthermore, there is adaptation to the slight irritation that defines the AEGL-1 effects. The 0.8-ppm value is supported by no-effect concentrations in repeated-exposure studies with rodents. No signs of ocular irritation or other clinical signs were observed in rats exposed

at 1.7 ppm for 6 h/day, 5 days/week for 28 days (Klimisch 1987) or in rats exposed at 1 ppm for 4 h/day, 5 days/week for 12-13 weeks (Rosskamp et al. 1978). Application of total uncertainty factors of 3 or 10 to the animal data would bring the values (0.33-0.56 ppm or 0.10-0.17 ppm, respectively) close to or below the no-effect level of 0.22-0.23 ppm observed in the clinical study. The AEGL-1 calculations are presented in Appendix B, a derivation summary is presented in Appendix C, and a category plot of the relationship between AEGL values and toxicity data is presented in Appendix D.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Ocular irritation may be sufficient to impair escape, so is a relevant AEGL-2 end point. Russell and Rush (1996) observed several measures of ocular irritation in human volunteers exposed to MITC at 0.8 ppm for up to 4 h. With 3 and 4 h of exposure, all nine subjects appeared to respond positively on the Likert scale (indicating irritation), with mean Likert scale responses of 39 ± 19% and 39 ± 26%, respectively (compared with 5 ± 6% and 4 ± 6% in controls). If 50% on the Likert scale was considered equivalent to the irritation from the cutting of a single mild onion, and the mean response at 0.8 ppm was below this level, this degree of ocular irritation would not be expected to impair escape. No other human studies were available for development of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

No acute exposure studies with laboratory animals relevant to deriving AEGL-2 values were identified. In repeated exposure studies, rats exposed to MITC at 6.8 ppm for 6 h/day, 5 days/week for 28 days showed signs of ocular irritation and general discomfort during daily exposure periods, beginning on the third exposure day and continuing throughout the study (Klimisch 1987). These signs were reversible between exposures. Rats exposed at 10 ppm for 4 h/day, 5 days/week for 12-13 weeks did not have clinical signs (Rosskamp et al. 1978). These concentrations are close to the derived 4- and 8-h AEGL-2 values (10 and 5.3 ppm, respectively [see below]). No clinical signs were seen at 1 or 1.7 ppm.

TABLE 6-7 AEGL-1Values for Methyl Isothiocyanate

10 min	30 min	1 h	4 h	8 h
0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)

6.3. Derivation of AEGL-2

In lethality studies with rats, the concentration-response curve for MITC was steep. In a 1-h study with rats (Clark and Jackson 1977), the highest nonlethal concentration of 210 ppm is about one-third the LC_{50} of 635 ppm. In a 4-h study with rats (Jackson et al. 1981), the highest nonlethal concentration of 94 ppm is about one-half the LC_{50} of 180 ppm. In the absence of data that address AEGL-2 end points and with evidence of a steep concentration-response curve, the AEGL-3 values were divided by 3 to derive AEGL-2 values (NRC 2001). AEGL-2 values are presented Table 6-8; the calculations are presented in Appendix B, and a category graph of the relationship between AEGL values and toxicity data are presented in Appendix D.

Although acute studies that address AEGL-2 end points are not available, repeat-exposure studies (Rosskamp et al. 1978; Klimisch, 1987) support the AEGL-2 values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human studies were available to derive AEGL-3 values for MITC.

7.2. Summary of Animal Data Relevant to AEGL-3

One- and 4-h inhalation studies were conducted in rats. The 1- and 4-h LC_{50} values were 635 ppm (Clark and Jackson 1977) and 180 ppm (Jackson et al. 1981), respectively. No deaths occurred at 210 ppm for 1 h or at 94 ppm for 4 h.

7.3. Derivation of AEGL-3

The study by Clark and Jackson (1977) used a pesticide formulation containing MITC as the test material, and the calculation used to estimate the MITC concentration in the chamber was not specified. In light of the uncertainties associated with this study, it was not used to derive AEGL-3 values. The POD for the AEGL-3 values is the highest 4-h nonlethal concentrations of 94 ppm in the study of rats (Jackson et al. 1981). Interspecies and intraspecies uncertainty factors of 3 each are usually applied to chemicals that are direct-acting irritants

TABLE 6-8 AEGL-2 Values for Methyl Isothiocyanate

10 min	30 min	1 h	4 h	8 h
21 ppm (63 mg/m^3)	21 ppm (63 mg/m^3)	17 ppm (51 mg/m^3)	10 ppm (30 mg/m^3)	5.3 ppm (16 mg/m^3)

(NRC 2001). However, application of a total uncertainty factor of 10 would result in AEGL-3 values that are inconsistent with the human exposure study (Russell and Rush 1996). Therefore, interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were applied. Reduction of an uncertainty factor is appropriate when the weight of the evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Time scaling was performed using the equation $C^n \times t = k$. Because the available data were insufficient for establishing an empirical value of n, default values of n = 3 and n = 1 when extrapolating to shorter and longer durations, respectively, were used (NRC 2001). Because of the uncertainty associated with extrapolating a 4-h POD to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value.

The longer-term AEGL-3 values are supported by repeated-exposure studies. Rats tolerated MITC at 45 ppm (a concentration higher than the 4- and 8-h AEGL-3 values of 27 and 13 ppm, respectively) for 4 h/day, 5 days/week for 12-13 weeks (60-65 exposures) without any deaths (Rosskamp et al. 1978). AEGL-3 values for MITC are presented in Table 6-9, the calculations are presented in Appendix B, and a category graph of the relationship between AEGL-3 values and toxicity data are presented in Appendix D.

If the 1-h nonlethal concentration of 210 ppm from the Clark and Jackson (1977) study were used to derive 10-min, 30-min, and 1-h AEGL-3 values, estimates of 130, 88, and 70 ppm, respectively, would result. The estimates are comparable (slightly higher) than those estimated from the 4-h POD (63, 63, and 50 ppm, respectively).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for MITC are presented in Table 6-10.

8.2. Comparison with Other Standards and Guidelines

No exposure standards or guidelines for MITC were identified.

TABLE 6-9 AEGL-3 Values for Methyl Isothiocyanate

10 min	30 min	1 h	4 h	8 h
63 ppm (190 mg/m^3)	63 ppm (190 mg/m^3)	50 ppm (150 mg/m^3)	31 ppm (94 mg/m^3)	16 ppm (47 mg/m^3)

TABLE 6-10 AEGL Values for Methyl Isothiocyanate

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)
AEGL-2 (disabling)	21 ppm (63 mg/m^3)	21 ppm (63 mg/m^3)	17 ppm (51 mg/m^3)	10 ppm (30 mg/m^3)	5.3 ppm (16 mg/m^3)
AEGL-3 (lethal)	63 ppm (190 mg/m^3)	63 ppm (190 mg/m^3)	50 ppm (150 mg/m^3)	31 ppm (94 mg/m^3)	16 ppm (47 mg/m^3)

8.3. Data Adequacy and Research Needs

Data from clinical studies and studies with laboratory animals were adequate to develop AEGL values for MITC. However, the available acute animal data are limited to two studies in rats (Clark and Jackson 1977; Jackson et al. 1981) and included one study that administered a pesticide formulation containing MITC as the test material (Clark and Jackson 1977). Additional information on acute toxicity of MITC in other species would be helpful. Similarly, although available animal data and human exposure incidents suggest that ocular irritation is a more sensitive indicator of exposure than upper-respiratory-tract irritation, more rigorous investigation is needed to support this finding.

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APPENDIX A

DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS FOR METHYL ISOTHIOCYANATE

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure from odor perception. The LOA derivation follows the guidance of van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for MITC was reported to be 1.7 ppm (Russell and Rush 1996). This value is the geometric mean of detection thresholds that ranged from 0.2 to 8 ppm among a panel of 33 individuals.

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = kw \times \log (C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default of kw = 2.33 was used due to the lack of chemical-specific data:

$$3 = 2.33 \times \log (C \div 1.7) + 0.5, \text{ which can be rearranged to}$$
$$\log (C \div 1.7) = (3 - 0.5) \div 2.33 = 1.07, \text{ and results in}$$
$$C = (10^{1.07}) \times 1.7 = 20 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. The factor takes into account that in everyday life, factors such as sex, age, sleep, smoking, upper airway infections, allergy, and distraction, may increase the odor detection threshold by up to a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. A factor of one-third is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of $4 \div 3 = 1.33$.

$$LOA = C \times 1.33 = 20 \text{ ppm} \times 1.33 = 27 \text{ ppm}$$

The LOA for MITC is 27 ppm.

APPENDIX B

DERIVATION OF AEGL VALUES FOR METHYL ISOTHIOCYANATE

Derivation of AEGL-1 Values

Key study:	Russell, M.J., and T.I. Rush. 1996. Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation. Report No. RR 96-049B, Sensory Testing Laboratory, University of California, Davis, CA. Unpublished report submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention.
Toxicity end point:	Lowest-observed-effect level (0.8 ppm) for ocular irritation in the clinical study was a NOAEL for ocular irritation according to the definition of the AEGL-1 value; exposure durations of 1-480 min.
Time scaling:	None, because NOAELs for each exposure duration were used.
Uncertainty factors:	3 for intraspecies variability; based on direct-acting irritant mechanism of toxicity in which metabolic and physiologic differences are unlikely to play a major role (NRC 2001), and based on data showing approximately 2-fold range of human sensitivity to ocular irritants (Kjaergaard et al. 1992).
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-1:	C = 0.8 ÷ 3 ppm = 0.27 ppm
30-min AEGL-1:	C = 0.8 ÷ 3 ppm = 0.27 ppm
1-h AEGL-1:	C = 0.8 ÷ 3 ppm = 0.27 ppm
4-h AEGL-1:	C = 0.8 ÷ 3 ppm = 0.27 ppm
8-h AEGL-1:	C = 0.8 ÷ 3 ppm = 0.27 ppm

Derivation of AEGL-2 Values

In the absence of data for deriving AEGL-2 values for MITC and because MITC has a steep exposure-response curve in lethality studies (Clark and Jackson 1977; Jackson et al. 1981), AEGL-2 values were calculated by dividing the AEGL-3 values by 3 (NRC 2001).

10-min AEGL-2:	63 ppm ÷ 3 = 21 ppm
30-min AEGL-2:	63 ppm ÷ 3 = 21 ppm
1-h AEGL-2:	50 ppm ÷ 3 = 17 ppm
4-h AEGL-2:	31 ppm ÷ 3 = 10 ppm
8-h AEGL-2:	16 ppm ÷ 3 = 5.3 ppm

Derivation of AEGL-3 Values

Key study:	Jackson, G.C., G.C. Clark, D.E. Prentice, R.M. Read, C. Gopinath, and C. Cherry. 1981. Methyl Isothiocyanate: Acute Inhalation Toxicity in Rats. 4 Hour Exposure. RZ No. 81/082, Huntingdon Research Centre, Huntingdon, England. Unpublished report submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention.
Toxicity end points:	NOAEL of 94 ppm for lethality in rats during 4-h exposure
Time scaling:	$C^n \times t = k$; default values of n = 3 and n = 1 for scaling to shorter and longer exposure durations, respectively (NRC 2001). 30-min and 1-h values: $(94 \text{ ppm} \div 3)^3 \times 240 \text{ min} = 7.383 \times 10^6$ ppm-min 8-h value: $(94 \text{ ppm} \div 3)^1 \times 240 \text{ min} = 7{,}520$ ppm-min
Uncertainty factors:	3 for intraspecies variability; humans are not expected to vary greatly in their response to a direct-acting irritant (NRC 2001). Application of a higher uncertainty factor would result in concentrations inconsistent with human clinical studies.

Modifying factor: None

Calculations:

10-min AEGL-3: Set equal to 30-min AEGL-3 = 63 ppm

30-min AEGL-3: $C^3 \times 30$ min = 7.383×10^6 ppm-min
C = 63 ppm

1-h AEGL-3: $C^3 \times 60$ min = 7.383×10^6 ppm-min
C = 50 ppm

4-h AEGL-3: C = 94 ppm ÷ 3
C = 31 ppm

8-h AEGL-3: $C^1 \times 480$ min = 7,520 ppm-min
C = 16 ppm

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL ISOTHIOCYANATE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)

Key Reference: Russell, M.J., and T.I. Rush. 1996. Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation. Report No. RR 96-049B, Sensory Testing Laboratory, University of California, Davis, CA. Unpublished report submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention.

Test species/Gender/Number): Human volunteers, male and female, 9-16 per group

Exposure route/Concentration/Duration: Inhalation; 0, 0.60, 1.9, or 3.3 ppm for 1 or 14 min; 0, 0.23, or 0.8 ppm for 4 h; 0 or 0.22 ppm for 8 h

Effects:

	No ocular irritation	Mild ocular irritation
1 min	3.3 ppm	—
14 min	0.60 ppm	1.9 ppm
1 h	0.23 ppm	0.8 ppm
4 h	0.23 ppm	0.8 ppm
8 h	0.22 ppm	—

End point/Concentration/Rationale: Ocular irritation was mild (less than that associated with cutting one mild onion) and, thus, did not represent the notable discomfort that constitutes an AEGL-1 effect (NRC 2001).

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because human data were used
Intraspecies: 3, based on direct-acting irritant mechanism of toxicity in which metabolic and physiologic differences are unlikely to play a major role (NRC 2001), and based on data showing an approximately 2-fold range of human sensitivity to ocular irritants (Kjaergaard et al. 1992).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: None; the POD was tested for durations of 1-4 h with no increase in severity of effect; therefore, the irritant effects of MITC are not expected to become more severe with increasing duration at this concentration.

Data adequacy: The study was well conducted and used an adequate numbers of healthy individuals. Ocular irritation is considered the most sensitive end point in studies with MITC.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
21 ppm (63 mg/m^3)	21 ppm (63 mg/m^3)	17 ppm (51 mg/m^3)	10 ppm (30mg/m^3)	5.3 ppm (16 mg/m^3)

Data adequacy: Data on MITC were inadequate for deriving AEGL-2 values. When data are lacking and the concentration-response curve is steep, AEGL-2 values may be derived by dividing the AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for MITC. In a 1-h study with rats (Clark and Jackson 1977), the highest nonlethal concentration of 210 ppm is about one-third the LC_{50} of 635 ppm. In a 4-h study with rats (Jackson et al. 1981), the highest nonlethal concentration of 94 ppm is about one-half the LC_{50} of 180 ppm.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
63ppm (190 mg/m^3)	63 ppm (190 mg/m^3)	50 ppm (150 mg/m^3)	31 ppm (94 mg/m^3)	16 ppm (47 mg/m^3)

Key reference: Jackson, G.C., G.C. Clark, D.E. Prentice, R.M. Read, C. Gopinath, and C. Cherry. 1981. Methyl Isothiocyanate: Acute Inhalation Toxicity in Rats. 4 Hour Exposure. RZ No. 81/082, Huntingdon Research Centre, Huntingdon, England. Unpublished report submitted to U.S. EPA's Office of Chemical Safety and Pollution Prevention.

Test species/Strain/Number: Rat; Sprague-Dawley; groups of 5 per sex

Exposure route/Concentration/Duration: Inhalation ; six concentrations for 4 h

Effects: No mortality at 94 ppm; LC_{50} = 180 ppm

End point/Concentration/Rationale: 94 ppm, highest 4-h nonlethal concentration

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1
Intraspecies: 3, considered sufficient to protect the sensitive population with respiratory diseases; application of larger uncertainty factors would conflict with results of clinical studies.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; default values of n = 3 and n = 1 for scaling to shorter and longer exposure durations, respectively (NRC 2001). Due to uncertainty in extrapolating a 4-h point of departure to a 10-min value, the 10-min AEGL-3 was set equal to the 30-min AEGL-3 value.

Data adequacy: The 4-h study used multiple concentrations and an adequate numbers of animals. The values are supported by repeated-exposure studies performed in different laboratories.

APPENDIX D

CATEGORY PLOT FOR METHYL ISOTHIOCYANATE

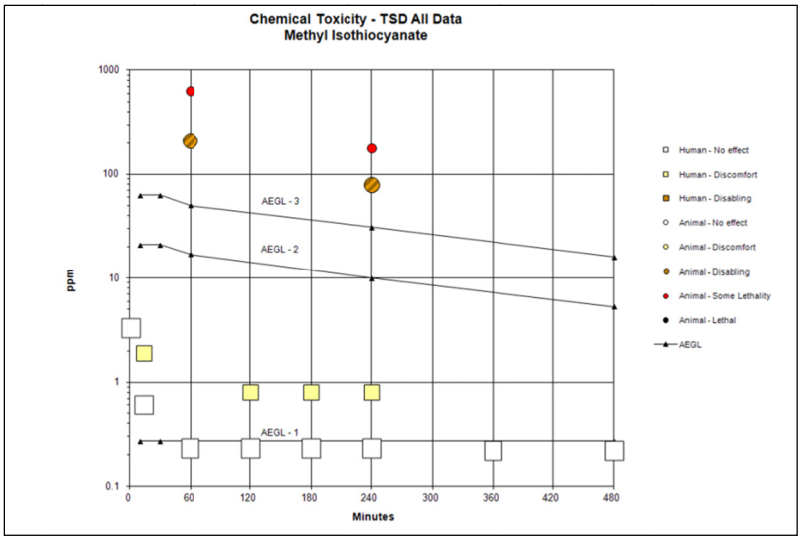

FIGURE D-1 Category plot of animal and human data and AEGL values for methyl isothiocyanate.

TABLE D-1 Data Used in the Category Plot for Methyl Isothiocyanate

Source	Species	ppm	Minutes	Category	Comments
AEGL-1		0.27	10	AEGL	
AEGL-1		0.27	30	AEGL	
AEGL-1		0.27	60	AEGL	
AEGL-1		0.27	240	AEGL	
AEGL-1		0.27	480	AEGL	
AEGL-2		21	10	AEGL	
AEGL-2		21	30	AEGL	
AEGL-2		17	60	AEGL	
AEGL-2		10	240	AEGL	
AEGL-2		5.3	480	AEGL	
AEGL-3		63	10	AEGL	
AEGL-3		63	30	AEGL	
AEGL-3		50	60	AEGL	

(Continued)

TABLE D-1 Continued

Source	Species	ppm	Minutes	Category	Comments
AEGL-3		31	240	AEGL	
AEGL-3		16	480	AEGL	
Russell and Rush 1996	Human	3.3	1	0	No ocular irritation
	Human	0.60	14	0	No ocular irritation
	Human	0.23	60	0	No ocular irritation
	Human	0.23	120	0	No ocular irritation
	Human	0.23	180	0	No ocular irritation
	Human	0.23	240	0	No ocular irritation
	Human	0.22	360	0	No ocular irritation
	Human	0.22	480	0	No ocular irritation
	Human	1.9	14	1	Subjective ocular irritation
	Human	0.8[a]	120	1	Subjective ocular irritation; increased blink rate
	Human	0.8[a]	180	1	Subjective ocular irritation; increased blink rate
	Human	0.8[a]	240	1	Subjective ocular irritation
Clark and Jackson 1977	Rat	210	60	2	1-h highest nonlethal value
	Rat	635	60	SL	1-h LC_{50}
Jackson et al. 1981	Rat	94	240	2	4-h highest nonlethal value
	Rat	180	240	SL	4-h LC_{50}

Categories: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal.
[a]Note: the discomfort associated with human exposure at 0.8 ppm (Russell and Rush 1996) was below the threshold for notable discomfort that constitutes an AEGL-1 effect.

7

Selected Monoisocyanates[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

[1]This document was prepared by the AEGL Development Team composed of Robert Young and Carol Wood (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Managers Susan Ripple and Marc Ruijten (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Four monoisocyanates are considered in this chapter: ethyl isocyanate, *n*-butyl isocyanate, cyclohexyl isocyanate, and phenyl isocyanate. These monoisocyanates appear to exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate. AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived.

Data on ethyl isocyanate and cyclohexyl isocyanate were limited to rat lethality studies that used few animals, lacked analytic measurement of concentrations, and had 100% mortality at nearly all test concentrations. Because of the data limitations, AEGL-2 and AEGL-3 values were based on the AEGL values for methyl isocyanate. A comparison of the available lethality data on the three chemicals suggests that use of methyl isocyanate as a surrogate and applying a modifying factor of 2, to account for the possibility that ethyl isocyanate and cyclohexyl isocyanate might be more toxic, results in sufficiently protective AEGL values. For example, when groups of three rats were exposed to ethyl isocyanate for 6 h, all rats survived at 27 ppm and no rats survived at 82 ppm. When three rats were exposed for 6 h to cyclohexyl isocyanate at 18 ppm, one

died on day 7 post-exposure and the others were killed on day 8, presumably due to moribund condition. For comparison, the 6-h LC_{50} (lethal concentration, 50% lethality) for methyl isocyanate in rats was 6.1 ppm (NRC 2003).

Rat lethality data were adequate to derive AEGL-3 values for *n*-butyl isocyanate and phenyl isocyanate, and AEGL-2 values were estimated as one-third of the corresponding AEGL-3 values. To derive AEGL-3 values for these compounds, an interspecies uncertainty factor of 3 was applied because of the limited species variability exhibited by methyl isocyanate. A factor of 10 was applied to account for intraspecies variability, as was done for methyl isocyanate (NRC 2003). A modifying factor 3 was also applied because data on the potential developmental toxicity of *n*-butyl isocyanate and phenyl isocyanate were lacking; methyl isocyanate is a known developmental toxicant.

AEGL values for the selected monoisocyanates are presented in Table 7-1. AEGL values for methyl isocyanate and toluene diisocyanate are presented in Table 7-2 for comparison.

1. INTRODUCTION

The monoisocyanates generally occur as colorless to yellow liquids, and typically have a high vapor pressure and pungent odor. When heated, monoisocyanates decompose and form toxic fumes of hydrogen cyanide and nitrogen oxides (IPCS 1997, 2002). Cyclohexyl isocyanate decomposes in water, and unlike some isocyanates, it does not self-polymerize (Eastman Kodak 1990). The chemical and physical properties of ethyl, *n*-butyl, cyclohexyl, and phenyl isocyanate are presented in Table 7-3.

Ethyl isocyanate is used as an intermediate in the manufacture of pharmaceuticals and pesticides. It may be produced by the reaction of phosgene with amines or amine salts. The thermal cleavage of urethanes, performed using the appropriate amine, urea, and alcohol, is a common commercial production method (HSDB 2007a).

n-Butyl isocyanate is used in closed systems for the manufacture of chemicals, dyes, and pesticides (ANPON 2008). Global production of *n*-butyl isocyanate is estimated at 1,000 to 5,000 metric tons per year (OECD 2005). Phenyl isocyanate is used in the production of polymers and as an intermediate in organic syntheses (Richter 1986; Karol and Kramarik 1996).

Current use and production information for cyclohexyl isocyanate were not found.

In the sections below, general factors to consider in developing AEGL values for the selected monoisocyanates are presented first, and are followed by chemical-specific data.

TABLE 7-1 AEGL Values for Selected Monoisocyanates[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
Ethyl isocyanate						
AEGL-1 (non-disabling)	NR	NR	NR	NR	NR	Insufficient warning properties; possible systemic effects at concentrations lower than those that produce irritation.
AEGL-2 (disabling)	0.20 ppm (0.58 mg/m^3)	0.065 ppm (0.19 mg/m^3)	0.034 ppm (0.099 mg/m^3)	0.0085 ppm (0.025 mg/m^3)	0.0040 ppm (0.012 mg/m^3)	Based on AEGL-2 values for methyl isocyanate
AEGL-3 (lethal)	0.60 ppm (1.7 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.10 ppm (0.29 mg/m^3)	0.025 ppm (0.073 mg/m^3)	0.013 ppm (0.038 mg/m^3)	Based on AEGL-3 values for methyl isocyanate
Cyclohexyl isocyanate						
AEGL-1 (non-disabling)	NR	NR	NR	NR	NR	Insufficient warning properties; possible systemic effects at concentrations lower than those that produce irritation.
AEGL-2 (disabling)	0.20 ppm (1.0 mg/m^3)	0.065 ppm (0.33 mg/m^3)	0.034 ppm (0.17 mg/m^3)	0.0085 ppm (0.043 mg/m^3)	0.0040 ppm (0.020 mg/m^3)	Based on AEGL-2 values for methyl isocyanate
AEGL-3 (lethal)	0.60 ppm (3.1 mg/m^3)	0.20 ppm (1.0 mg/m^3)	0.10 ppm (0.51 mg/m^3)	0.025 ppm (0.13 mg/m^3)	0.013 ppm (0.066 mg/m^3)	Based on AEGL-3 values for methyl isocyanate AEGL-3
n-*Butyl isocyanate*						
AEGL-1 (non-disabling)	NR	NR	NR	NR	NR	Insufficient warning properties; possible systemic effects at concentrations lower than those that produce irritation.
AEGL-2 (disabling)	0.10 ppm (0.41 mg/m^3)	0.10 ppm (0.41 mg/m^3)	0.083 ppm (0.34 mg/m^3)	0.053 ppm (0.21 mg/m^3)	0.026 ppm (0.11 mg/m^3)	One third of AEGL-3 values.
AEGL-3 (lethal)	0.31 ppm (1.3 mg/m^3)	0.31 ppm (1.3 mg/m^3)	0.25 ppm (1.0 mg/m^3)	0.16 ppm (0.65 mg/m^3)	0.078 ppm (0.32 mg/m^3)	No morality in rats exposed at 14 ppm for 4 h (Pauluhn et al. 1990).

(Continued)

TABLE 7-1 Continued

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
Phenyl isocyanate[b]						
AEGL-1 (non-disabling)	NR	NR	NR	NR	NR	Insufficient warning properties; possible systemic effects at concentrations lower than those that produce irritation.
AEGL-2 (disabling)	0.012 ppm (0.058 mg/m^3)	0.012 ppm (0.058 mg/m^3)	0.0096 ppm (0.047 mg/m^3)	0.0061 ppm (0.030 mg/m^3)	0.0030 ppm (0.015 mg/m^3)	One-third of AEGL-3 values.
AEGL-3 (lethal)	0.036 ppm (0.18 mg/m^3)	0.036 ppm (0.18 mg/m^3)	0.029 ppm (0.14 mg/m^3)	0.018 ppm (0.088 mg/m^3)	0.0091 ppm (0.044 mg/m^3)	4-h $BMCL_{05}$ of 1.64 ppm in rats (Bayer AG 1991a)

[a]When more than one of the monoisocyanates is detected at a scene, the lowest AEGL should be applied to the sum total concentration of all detected monoisocyanates because of a presumed common mode of action. On the basis of toxicity data on methyl isocyanate, it is plausible that exposure to these monoisocyanates might be associated with systemic toxicity at concentrations below those associated with irritation. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 values are without effect.

[b]Phenyl isocyanate has shown dermal sensitizing effects. Its respiratory sensitizing potential is unknown. Individuals who have a strong reaction might not be protected within the definition of effects for each AEGL level.

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% confidence limit with a 5% response; MF, modifying factor; NR, not recommended; and UF, uncertainty factor.

TABLE 7-2 AEGL Values for Methyl Isocyanate and Toluene Diisocyanate

Classification	10 min	30 min	1 h	4 h	8 h
Methyl isocyanate					
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.40 ppm (0.94 mg/m^3)	0.13 ppm (0.32 mg/m^3)	0.067 ppm (0.16 mg/m^3)	0.017 ppm (0.034 mg/m^3)	0.0080 ppm (0.020 mg/m^3)
AEGL-3 (lethal)	1.2 ppm (2.8 mg/m^3)	0.40 ppm (0.95 mg/m^3)	0.20 ppm (0.47 mg/m^3)	0.050 ppm (0.12 mg/m^3)	0.025 ppm (0.060 mg/m^3)
Toluene 2,4- and 2,6-diisocyanate					
AEGL-1 (nondisabling)	0.02 ppm (0.14 mg/m^3)	0.02 ppm (0.14 mg/m^3)	0.02 ppm (0.14 mg/m^3)	0.01 ppm (0.07 mg/m^3)	0.01 ppm (0.07 mg/m^3)
AEGL-2 (disabling)	0.24 ppm (1.71 mg/m^3)	0.17 ppm (1.21 mg/m^3)	0.083 ppm (0.59 mg/m^3)	0.021 ppm (0.15 mg/m^3)	0.021 ppm (0.15 mg/m^3)
AEGL-3 (lethal)	0.65 ppm (4.63 mg/m^3)	0.65 ppm (4.63 mg/m^3)	0.51 ppm (3.63 mg/m^3)	0.32 ppm (2.28 mg/m^3)	0.16 ppm (1.14 mg/m^3)

[a]Insufficient warning properties; possible systemic effects at concentrations lower than those that produce irritation. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

2. CONSIDERATIONS RELEVANT TO THE SELECTED MONOISOCYANATES

2.1. Absorption, Distribution, Metabolism, and Excretion

Metabolism and disposition data are not available for ethyl isocyanate, *n*-butyl isocyanate, cyclohexyl isocyanate, or phenyl isocyanate. Data on the distribution of the related compound methyl isocyanate are available. Tissue radioactivity levels in guinea pigs exposed to ^{14}C-methyl isocyanate at 0.38-15.2 ppm for 1-6 h were proportional to the concentration-time product (Kennedy et al. 1993). Radioactivity was highest in the proximal airways but was detected throughout the entire nasal respiratory epithelial layer. In the tracheobronchial region and in the lung, the radioactivity accumulated in the subepithelial level extending to the terminal bronchiole, but was not detected in the alveolar region.

Isocyanates are known to form labile glutathione conjugates from which they may subsequently be released at a distal location (Zoltán and Klaassen 2001).

2.2. Mechanism of Toxicity

No studies that address the mechanism(s) of toxicity for ethyl isocyanate, *n*-butyl isocyanate, cyclohexyl isocyanate, or phenyl isocyanate are available. Because the toxicity of these monoisocyanates are clinically similar to that described for the structurally similar compound methyl isocyanate (respiratory tract irritation with delayed lethality), these compounds might share a similar mode of action.

TABLE 7-3 Chemical and Physical Data on Selected Monoisocyanates

Parameter	Ethyl Isocyanate	*n*-Butyl Isocyanate	Cyclohexyl Isocyanate	Phenyl Isocyanate
Synonyms	Isocyanatoethene; isocyanic acid, ethyl ester	1-Isocyanatobutane; isocyanic acid, butyil ester	Isocyanatocyclohexane isocyanic acid cyclohexyl ester	Isocyanatobenzene; carbamil; phenyl carbamide
CAS registry no.	109-90-0	111-36-4	3173-53-3	103-71-9
Chemical formula	C_3H_5NO	C_5H_9NO	$C_7H_{11}NO$	C_7H_5NO
Molecular weight	71.1	99.1	125.17	119.12
Physical state	Liquid	Liquid	Colorless liquid[a]	Liquid
Melting point	–	-75°C	–	-30°C
Boiling point	60°C	115°C	166°C[a]	158-168°C
Flash point	–	19°C (closed cup)	48°C (closed cup)[b]	55.5°C (open cup)
Density/specific gravity	0.9031 g/cm³	0.88 g/cm³ at 20°C	0.98 g/cm³ at 25°C	1.0956 g/cm³ at 20°C
Relative vapor density (air = 1)	2.45	3.0	4.3[b]	–
Solubility in water	Insoluble	Slightly soluble	Decomposes[a]	Reacts violently[c]
Vapor pressure	200 mm Hg at 25°C	17.6 mm Hg at 25°C	94.6 mmHg at 20°C[d]	1.15 mm Hg at 20°C[c]
Conversion factors in air	1 ppm = 2.9 mg/m^3 1 mg/m^3 = 0.34 ppm	1 ppm = 4.05 mg/m^3 1 mg/m^3 = 0.25 ppm	1 ppm = 5.11 mg/m^3 1 mg/m^3 = 0.196 ppm	1 ppm = 4.87 mg/m^3 1 mg/m^3 = 0.21 ppm

Source: HSDB 2007a,b, 2012, 2013 except where noted; [a]Eastman Kodak 1990; [b]IPCS 1997; [c]ICI 1977; [d]Sigma Aldrich 2012.

Results from human and animal studies indicate that methyl isocyanate is a severe irritant to mucous membranes. Ocular irritation was the most pronounced symptom reported in human experimental studies (Mellon Institute 1963, 1970; Kimmerle and Eben 1964). The most frequently reported symptoms in a population exposed to methyl isocyanate in Bhopal, India, were burning of the eyes, coughing, respiratory distress from pulmonary congestion, watering of the eyes, nausea, vomiting, muscle weakness, and central nervous system involvement secondary to hypoxia (Kamat et al. 1985; Lorin and Kulling 1986; Misra et al. 1987; Weill 1987; Andersson et al. 1988; Kamat et al. 1992). Human (Varma and Guest 1993) and animal (Fowler and Dodd 1986) fatalities are attributed to pulmonary edema.

Cyanide does not contribute significantly to the toxicity of methyl isocyanate. Cyanomethemoglobin was not found in the population exposed to methyl isocyanate in Bhopal (Misra et al. 1987), pulmonary lesions are not characteristic of cyanide intoxication (Weill 1987; Varma 1989), and standard thiosulfate/nitrite cyanide antidotes have not been successful in preventing deaths in animal studies (Nemery et al. 1985; Bucher et al. 1987; Varma et al. 1988). Finally, the time-to-death in humans and animals was not consistent with that associated with high dose cyanide intoxication (Varma and Guest 1993).

Developmental toxicity was observed in rodents after controlled exposure to methyl isocyanate. The mechanism of the systemic toxicity is unknown.

2.3. Structure-Activity Relationships

Data on the selected monoisocyanates are limited, so information on related compounds was also consulted. Toluene diisocyanate and methyl isocyanate have robust databases that include animal and human studies. The monoisocyanates reviewed in this chapter appear more similar to methyl isocyanate than 2,4- or 2,6-toluene diisocyanate with respect to lethality and respiratory irritation. Lethality benchmarks for the monoisocyanates are similar to those for methyl isocyanate; 4-h LC_{50} values in rats were 4.6 ppm for phenyl isocyanate (Bayer AG 1991a), 18 ppm for *n*-butyl isocyanate (Bayer AG 1978), and 5-18 ppm for methyl isocyanate (NRC 2003). For toluene diisocyanate, 4-h LC_{50} estimates for rats were 14-51 ppm (NRC 2004). In addition, deaths from toluene diisocyanate occur soon after exposure (within 36 h after a 1-h exposure in a rat study [Horspool and Doe 1977]), whereas deaths from the monoisocyanates, including methyl isocyanate, can occur as late as 30 days after exposure. Little respiratory-irritation data were available for comparison of the monoisocyanates. RD_{50}s (concentrations that reduce the respiratory rate by 50%) were estimated to be 1.3 ppm for mice exposed to methyl isocyanate for 90 min (Ferguson et al. 1986) and 2.7 ppm for rats exposed to phenyl isocyanate for 45 min

(Pauluhn et al. 1995). RD_{50}s for toluene diisocyanate were estimated to be 1.37-2.12 ppm in rats exposed for 3 h, 0.39 ppm in mice exposed for 1 h, and 0.8 ppm in mice exposed for 10 min (NRC 2004).

Differences exist in the sensitization potential, developmental effects, and systemic toxicity of methyl isocyanate and 2,4- or 2,6-toluene diisocyanate; however, no data are available to determine which of these structurally-related compounds is more representative of the selected monoisocyanates with respect to these end points. Karol and Kramarik (1996) noted that respiratory sensitization is a result of exposure to diisocyanates not monoisocyanates in the workplace. Toluene diisocyanate is a proven respiratory sensitizer in both human and laboratory animals (NRC 2004). Methyl isocyanate is not a respiratory sensitizer in animals (Mellon Institute 1970). No data on the sensitizing potential of ethyl isocyanate, *n*-butyl isocyanate, or cyclohexyl isocyanate were available. However, a mouse ear-swelling test indicated that phenyl isocyanate is a potent contact sensitizer in mice, stimulating both cellular and humoral immune responses (Karol and Kramarik 1996). Phenyl isocyanate was more potent than toluene diisocyanate in the ear-swelling test (Karol and Kramarik 1996). The potential for respiratory sensitization by phenyl isocyanate is not known.

Systemic effects have been well-documented after exposure to methyl isocyanate but not toluene diisocyanate. Methyl isocyanate produced fetal and neonatal deaths after inhalation exposure, but toluene diisocyanate did not. No inhalation data on the developmental toxicity of ethyl, *n*-butyl, cyclohexyl, or phenyl isocyanate in animals were available. In an oral exposure study, no evidence of developmental toxicity was observed in mice administered a single dose of phenyl isocyanate at 9.8 mg/kg (one-twentieth of the LD_{50} [lethal dose, 50% lethality]) on gestation days 4, 7, 11, or 15 (Nehez et al. 1989). Cardiac arrhythmias have been reported in studies of methyl isocyanate but not in studies of toluene diisocyanate. For methyl isocyanate, systemic effects may occur at concentrations equal to or below those that cause irritation (NRC 2003).

In summary, the selected monoisocyanates exhibit toxic effects (respiratory irritation and delayed lethality) that are more similar to those associated with methyl isocyanate than with toluene diisocyanate. Differences exist in the sensitization potential, developmental effects, and systemic toxicity of methyl isocyanate and 2,4- or 2,6-toluene diisocyanate; however, the data are insufficient to determine which of these structurally-related compounds is more representative of the selected monoisocyanates with respect to these effects.

2.4. Species Differences

Toxicity data on ethyl isocyanate, *n*-butyl isocyanate, cyclohexyl isocyanate, and phenyl isocyanate in species other than the rat are lacking. Lethality data for the related compounds methyl isocyanate and toluene diisocyanate exhibit little species variability, as shown in Table 7-4.

TABLE 7-4 Lethality (LD_{50}s) of Methyl Isocyanate and Toluene Diisocyanate in Different Species

	1 h	2 h	3 h	4 h	6 h
Methyl isocyanate (ppm)					
Rat	41-45	21-27	–	5-18	6.1
Mouse	–	–	27	–	12
Guinea pig	–	–	27	11	5.4
Toluene diisocyanate (ppm)					
Rat	66	–	–	14-51	–
Mouse	–	–	–	9.7	–
Guinea pig	–	–	–	13	–
Rabbit	–	–	–	11	–

Sources: NRC 2003, 2004.

2.5. Concurrent Exposure Issues

Limited data comparing the toxicity of the four selected monoisocyanates with the well-studied compound methyl isocyanate suggest similarities in toxicity among the monoisocyanates that may reflect a common mode(s) of action. Thus, the lowest AEGL value for any of the detected monoisocyanates at an emergency scene should be applied to the sum total concentration of all monoisocyanates when multiple monoisocyanates are present.

2.6. Concentration-Exposure Duration Relationship

The relationship between concentration and duration of exposure with respect to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. The investigators analyzed individual animal data sets by probit analysis, with exposure duration and exposure concentration as independent variables. An exponential function of $C^n \times t = k$, 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. For methyl isocyanate, rat LC_{50} data were used to estimate an empirical value for n of 1.0. However, data were inadequate to calculate an empirical value of n for the selected monoisocyanates in this chapter. Thus, default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used.

2.7. Special Considerations

Some of the toxicity data on the four monoisocyanates in this chapter may have uncertainty with respect to exposure concentrations. One analysis (DuPont, unpublished material, 2008) showed that impinger/gas chromatography (GC) methods used to analyze *n*-butyl isocyanate underestimated concentrations when

compared with XAD-7 tube/high performance liquid chromatography (HPLC) analysis. In 1994, 20 air samples were collected side-by-side in various areas of a production facility using the impinger and XAD-7 tube sampling methods and subsequently analyzed using GC and HPLC methods, respectively. Comparison of the data showed that the XAD-7/HPLC method generally measured higher concentrations (two-fold higher on average) than the impinger/GC method; however, the magnitude of the difference was not consistent across the samples and the measurements were not always higher (see Table 7-5). A second analysis (Mobay 1978) reported that the Marcali colorimetric method underestimated concentrations of phenyl isocyanate (in a rat lethality study) when compared with HPLC analysis, and that the HPLC results were more consistent with the calculated concentrations. Information in the Mobay Corp. (1978) report was insufficient to allow an independent evaluation of the differences. Whether the analytic uncertainties also apply to ethyl isocyanate and cyclohexyl isocyanates is not known; however, studies of the latter two compounds were conducted in the 1960s and concentrations were calculated rather than measured. In light of the potential analytic uncertainties, information on the method used to analyze exposure concentrations is included in the descriptions of the toxicity data for the individual monoisocyanates presented later in this chapter.

TABLE 7-5 Comparison of *n*-Butyl Isocyanate Concentrations Obtained Using Impinger/GC and XAD-7 Tube/HPLC Methods

Impinger/GC (ppb)	XAD-7 Tube/HPLC (ppb)	Difference
1.3	9.4	623%
1.9	11.8	521%
2.5	10.5	320%
3.8	5	32%
4.4	9.4	114%
4.5	5.7	27%
5.2	7.1	37%
5.3	4.6	-13%
5.7	5.6	-2%
6.5	10	54%
6.6	9.6	45%
6.6	11	67%
8	11.6	45%
8.1	10.1	25%
8.3	9.1	10%
8.4	12.9	54%
10.7	21.3	99%
13.6	10.4	-24%
27	40.9	51%
32.4	24.5	-24%
	Average percent difference	103%

Source: DuPont, unpublished material, 2008.

2.8. Data Adequacy and Research Needs

Some of the toxicity data on the four monoisocyanates in this chapter may have uncertainty with respect to exposure concentrations, as discussed in detail in Section 2.7. As will be discussed in subsequent sections, no data relevant to AEGL-1 or AEGL-2 end points in humans or animals exposed to ethyl isocyanate or cyclohexyl isocyanate were available. Toxicity data on ethyl isocyanate and cyclohexyl isocyanate are primarily from poorly-documented unpublished lethality studies that used small groups of rats. Thus, data on the well-studied, related compound—methyl isocyanate—were used to derive AEGL values for these two isocyanates. Additional research on the inhalation toxicity of ethyl isocyanate and cyclohexyl isocyanate might provide data suitable for the deriving chemical-specific AEGL values. Animal data were adequate to derive AEGL-3 values for *n*-butyl isocyanate and phenyl isocyanate; AEGL-2 values were derived from corresponding AEGL-3 values.

Methyl isocyanate is a developmental toxicant, and developmental effects were the basis for AEGL-2 and AEGL-3 values for this compound (NRC 2003). No inhalation data on the developmental toxicity of the four monoisocyanates in humans or animals were available. An oral study found no developmental toxicity in mice treated once with phenyl isocyanate at 9.8 mg/kg on gestation days 4, 7, 11, or 15 (Nehez et al. 1989). To account for the potential developmental toxicity of *n*-butyl isocyanate and phenyl isocyanate, a modifying factor was applied in the derivation of AEGL-2 and AEGL-3 values. Additional research on the developmental toxicity of these selected monoisocyanates might provide opportunities to refine the AEGL values for these compounds.

Of the two well-studied isocyanates, toluene diisocyanate is a known and potent respiratory sensitizer, whereas methyl isocyanate is not. The potential for respiratory sensitization induced by the four monoisocyanates is not known. However, phenyl isocyanate has been found to be a potent dermal sensitizer (Karol and Kramarik 1996). A cautionary note has been included in the AEGL tables for phenyl isocyanate to indicate that individuals who have a strong reaction might not be protected within the definition of effects for each AEGL level; this note is the same as used for the AEGL values for toluene diisocyanate (NRC 2004). Additional research on the potential respiratory sensitization of phenyl isocyanate would be beneficial.

3. ETHYL ISOCYANATE

3.1. Human Toxicity Data

No information regarding lethality, nonlethal toxicity, developmental toxicity, genotoxicity, or carcinogenicity in humans after acute inhalation exposure to ethyl isocyanate was available.

3.2. Animal Toxicity Data

3.2.1. Acute Lethality

Groups of three rats (strain and sex not specified) were exposed to ethyl isocyanate at 27 ppm for 6 h, 82 ppm for 6 h, or 506 ppm for 2 h and 50 min (Eastman Kodak 1964). Documentation of this study was limited to a summary table with few details. A known amount of liquid ethyl isocyanate was placed in a 6-cc test tube in a exposure chamber (24-24.5°C), and air was pumped into the chamber. Exposure concentrations were calculated from the amount of compound placed in the chamber and the chamber volume. Clinical signs in all the test groups were consistent with irritation. No deaths occurred in the 27-ppm group and all rats in the 82- and 506-ppm groups died within 24 h. Animals in the 27-ppm group were killed 14 days post-exposure; at necropsy, the lungs were reportedly hemorrhagic. Mortality and clinical data are summarized in Table 7-6.

3.2.2. Nonlethal Toxicity

No information on the nonlethal toxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity of ethyl isocyanate in animals was available.

TABLE 7-6 Lethality and Clinical Findings in Rats Exposed to Ethyl Isocyanate

Calculated Concentration (ppm)	Duration	Mortality	Time of Death	Clinical Signs (time observed)
27	6 h	0/3	–	Blepharism, piloerection (1 min); lacrimation (15 min); dark eyes (1 h); nasal discharge (1 hr, 20 min).
82	6 h	3/3	Within 24 h (none during exposure)	Blepharism, piloerection, lacrimation (1 min). Gasping, dyspnea, dark eyes (20 min); ptyalism (55 min).
506	2 h, 50 min	3/3	2 h, 15 min; 2 h, 20 min; 2 h, 50 min	Blepharism, piloerection, lacrimation (immediately); ptyalism (1 min); gasping, dyspnea, dark eyes (5 min); nasal discharge (15 min); prostration (1 h, 35 min); convulsions (2 h, 15 min).

Source: Eastman Kodak 1964.

3.3. Data Analysis for AEGL-1 Values

3.3.1. Human Data Relevant to AEGL-1

No human data relevant to deriving AEGL-1 values for ethyl isocyanate were available.

3.3.2. Animal Data Relevant to AEGL-1

No animal data relevant to deriving AEGL-1 values for ethyl isocyanate were available.

3.3.3. Derivation of AEGL-1 Values

AEGL-1 values were not derived for ethyl isocyanate. The available data suggest that ethyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for ethyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

3.4. Data Analysis for AEGL-2 Values

3.4.1. Human Data Relevant to AEGL-2

No human data relevant to deriving AEGL-2 values for ethyl isocyanate were available.

3.4.2. Animal Data Relevant to AEGL-2

No animal data relevant to deriving AEGL-2 values for ethyl isocyanate were available. In the only available study, blepharism and lacrimation were observed in three rats exposed at 27 ppm for 6 h; that concentration was the only nonlethal exposure level examined (Eastman Kodak 1964).

3.4.3 Derivation of AEGL-2 Values

The toxicologic database on ethyl isocyanate was inadequate to derive AEGL-2 values. Therefore, AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that ethyl

isocyanate might be more toxic than methyl isocyanate. AEGL-2 values for ethyl isocyanate are presented in Table 7-7, and the calculations are presented in Appendix A.

3.5. Data Analysis for AEGL-3 Values

3.5.1. Human Data Relevant to AEGL-3

No human data relevant to deriving AEGL-3 values for ethyl isocyanate were available.

3.5.2. Animal Data Relevant to AEGL-3

Only one study on the acute lethality of ethyl isocyanate was available. Groups of three rats were exposed by inhalation to ethyl isocyanate at three concentrations for up to 6 h. All rats survived exposure at 27 ppm, whereas all animals died at 82 ppm and 506 ppm (Eastman Kodak 1964). Documentation of the study provided few details and concentrations were calculated rather than analytically confirmed.

3.5.3. Derivation of AEGL-3 Values

The toxicologic database on ethyl isocyanate was inadequate to derive AEGL-3 values. As discussed in Section 2.3 (Structure-Activity Relationships), ethyl isocyanate and the other three monoisocyanates considered in this chapter are structurally similar to and exert toxic effects comparable to methyl isocyanate. Therefore, AEGL-3 values were determined by using the AEGL-3 values established for the methyl isocyanate and dividing them by a modifying factor of 2 to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate. A comparison of the available lethality data on the two chemicals suggests that use of methyl isocyanate as a surrogate with a modifying factor of 2 to account for potentially higher toxicity results in sufficiently protective AEGL values. When groups of three rats were exposed to ethyl isocyanate for 6 h, all rats survived at 27 ppm and no rats survived at 82 ppm. For comparison, the 6-h LC_{50} for methyl isocyanate in rats (6/sex) was 6.1 ppm (NRC 2003). AEGL-3 values for ethyl isocyanate are presented in Table 7-8, and the calculations are presented in Appendix A.

TABLE 7-7 AEGL-2 Values for Ethyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.58 mg/m^3)	0.065 ppm (0.19 mg/m^3)	0.034 ppm (0.099 mg/m^3)	0.0085 ppm (0.025 mg/m^3)	0.0040 ppm (0.012 mg/m^3)

TABLE 7-8 AEGL-3 Values for Ethyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.60 ppm (1.7 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.10 ppm (0.29 mg/m^3)	0.025 ppm (0.073 mg/m^3)	0.013 ppm (0.038 mg/m^3)

Consideration was also given to basing AEGL-3 values on the study of ethyl isocynate conducted by Eastman Kodak (1964), in which 27 ppm caused no deaths in a group of three rats exposed for 6 h. If this approach is used, an interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 10 would be applied, as well as a modifying factor of 10 to account for the sparse database on ethyl isocyanate. Time scaling would be performed using the equation $C^n \times t = k$, with default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations. These calculations would result in AEGL-3 values of 0.30 ppm for 10 min, 0.21 ppm for 30 min, 0.16 ppm for 1 h, 0.10 ppm for 4 h, and 0.068 ppm for 8 h. However, this approach has greater uncertainty, particularly with respect to poor documentation of the study, small numbers of animals tested, and lack of analytic confirmation of the exposure concentrations (Eastman Kodak 1964).

3.6. Summary of AEGLs

3.6.1. AEGL Values and Toxicity End Points

AEGL-1 values are not recommended for ethyl isocyanate because of insufficient data and the potential for systemic effects to occur at concentrations below those associated with irritation. AEGL-2 and AEGL-3 values for ethyl isocyanate were estimated using the AEGL values established for methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate. AEGL values for ethyl isocyanate are presented in Table 7-9.

3.6.2. Other Standards and Guidelines

There are no other standards or guidelines for ethyl isocyanate.

4. CYCLOHEXYL ISOCYANATE

4.1. Human Toxicity Data

No information regarding the lethality, nonlethal toxicity, developmental toxicity, genotoxicity, or carcinogenicity in humans following acute inhalation exposure to cyclohexyl isocyanate was available.

TABLE 7-9 AEGL Values for Ethyl Isocyanate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[b] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.20 ppm (0.58 mg/m^3)	0.065 ppm (0.19 mg/m^3)	0.034 ppm (0.099 mg/m^3)	0.0085 ppm (0.025 mg/m^3)	0.0040 ppm (0.012 mg/m^3)
AEGL-3 (lethal)	0.60 ppm (1.7 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.10 ppm (0.29 mg/m^3)	0.025 ppm (0.073 mg/m^3)	0.013 ppm (0.038 mg/m^3)

[a]When more than one of the monoisocyanates is detected at a scene, the lowest AEGL value should be applied to the sum total concentration of all detected monoisocyanates because of a presumed common mode of action for these chemicals.
[b]NR, not recommended. On the basis of toxicity data on methyl isocyanate, it is plausible that exposure to ethyl isocyanate might be associated with systemic toxicity at concentrations below those associated with irritation. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

4.2. Animal Toxicity Data

4.2.1. Lethality

Groups of three rats (strain and sex not specified) were exposed to cyclohexyl isocyanate at 17.79, 53.2, or 1,017 ppm for up to 6 h (Eastman Kodak 1990, 1992). Documentation of the study, which was conducted in 1964 and submitted to the U.S. Environmental Protection Agency under the Toxic Substances Control Act Test Submission (Section 8D), consists of a tabular report. Chamber atmospheres were generated by passing air through a gas washing bottle or through a short open-end bubbler and diluting with clean air. The method for determining chamber concentrations was not specified, so whether the concentrations were calculated or measured is unknown. During exposure at 17.79 ppm, clinical signs of toxicity included blinking within 5 min, rough hair coat by 10 min, vasodilatation after 1 h and 25 min, lacrimation and accelerated respiration at 1 h and 55 min, and dyspnea in 4 h and 25 min. One rat died on day 7 post-exposure and the remaining animals were killed on day 8, presumably due to moribund condition. All of the treated animals had enlarged and spongy lungs that exhibited collapse and were consolidated by acute inflammatory exude; congestion of the kidneys and liver was also seen. At 53.2 ppm, clinical signs were similar, but appeared slightly earlier, and also included salivation at 3 h and 50 min and gasping in 4 h and 50 min. Two animals died in 6 h and the third rat died 12 days later. At 1,017 ppm, all rats died within 4 h and 10 min after exhibiting pronounced clinical signs.

Six male rats (strain not specified) were exposed whole-body to cyclohexyl isocyanate at an average chamber concentration of 1,401 ppm (Younger Laboratories 1974). Saturated vapors (generated by passing air through a 500-mL

flask containing 42.4 g of cyclohexyl isocyanate) were introduced into the chamber and the concentration was calculated from the amount of material vaporized. All animals died within 2.5 h after the start of exposure. Clinical signs of irritation were observed before death, and pulmonary hemorrhage was found at necropsy. In a similar experiment, four male and four female rats died within 2 h after the start of exposure to saturated vapor of cyclohexyl isocyanate generated in the same manner (Crawford and Anderson 1974); vapor concentrations were not estimated in this study.

Groups of five male and five female Wistar rats were exposed whole-body to saturated vapors of cyclohexyl isocyanate for 3 min, 10 min, or 1 h, followed by a 14-day observation period (Bayer AG 1980a). All rats exposed for 3 min survived until the end of the observation period; clinical signs of irritation were observed during exposure and persisted until 2 days post-exposure. Necropsy revealed speckled or dark red spots on the lungs in about 50% of the rats. Animals exposed for 10 min died within 11 days post-exposure; clinical signs of irritation and respiratory problems were observed. All rats died during the 1-h exposure. Necropsy of the animals that died in the 10-min and 1-h groups revealed enlarged lungs with dark red spots, fluid in the thoracic cavity, lobulated pattern of the liver, and bloated stomach. A summary of the acute lethality data from studies of rats exposed to cyclohexyl isocyanate are presented in Table 7-10.

TABLE 7-10 Acute Lethality in Rats Exposed to Cyclohexyl Isocyanate

Concentration (ppm)	Duration	Lethality	Clinical and Necropsy Findings	Reference
17.79	6 h	1/3 on day 7 2/3 killed on day 8	Irritation, lacrimation, dypsnea, inflammation in lungs, congestion of kidney and liver.	Eastman Kodak 1990, 1992
53.2	6 h	2/3 during exposure 1/3 on day 12	Same effects as the 17.79-ppm group, plus salivation, and gasping.	
1,017	4 h	3/3 after 4 h	Same effects as the 53.2-ppm group, but more severe.	
1,401	1-2.5 h	6/6	Irritation, hemorrhage in lungs.	Younger Laboratories 1974
Saturated	2 h	8/8	None reported.	Crawford and Anderson 1974
	3 min	0/10	Irritation, dark spots on lungs.	Bayer AG 1980a
	10 min	10/10 within 11 days	Respiratory problems, enlarged lungs with red spots, fluid, lobulated liver.	
	1 h	10/10 during exposure	Same effects as the 10-min group.	

4.2.2. Nonlethal Toxicity

No information on the nonlethal toxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity of cyclohexyl isocyanate in animals was found.

4.3. Data Analysis for AEGL-1 Values

4.3.1. Human Data Relevant to AEGL-1

No human data relevant to calculating AEGL-1 values for cyclohexyl isocyanate were available.

4.3.2. Animal Data Relevant to AEGL-1

No animal data relevant to calculating AEGL-1 values for cyclohexyl isocyanate were available.

4.3.3. Derivation of AEGL-1 Values

AEGL-1 values were not derived for cyclohexyl isocyanate. The available data suggest that cyclohexyl isocyanate and the three other selected monoisocyanates considered in this chapter exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for cyclohexyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

4.4. Data Analysis for AEGL-2 Values

4.4.1. Human Data Relevant to AEGL-2

No human data relevant to calculating AEGL-2 values for cyclohexyl isocyanate were available.

4.4.2. Animal Data Relevant to AEGL-2

No animal data relevant to calculating AEGL-2 values for cyclohexyl isocyanate were available. All of the concentrations of cyclohexyl isocyanate tested were associated with 100% mortality (Crawford and Anderson 1974; Younger Laboratories 1974; Bayer AG 1980a; Eastman Kodak 1990, 1992).

4.4.3. Derivation of AEGL-2 Values

The toxicologic database for cyclohexyl isocyanate was inadequate to derive AEGL-2 values. AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate and dividing them by a modifying factor of 2 to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate. AEGL-2 values for cyclohexyl isocyanate are presented in Table 7-11, and the calculations are provided in Appendix A.

4.5. Data Analysis for AEGL-3 Values

4.5.1. Human Data Relevant to AEGL-3

No human data relevant to calculating AEGL-3 values for cyclohexyl isocyanate were available.

4.5.2. Animal Data Relevant to AEGL-3

All of the studies on cyclohexyl isocyanate were conducted in rats, and all of the test concentrations resulted in 100% mortality (Crawford and Anderson 1974; Younger Laboratories 1974; Bayer AG 1980a; Eastman Kodak 1990, 1992). The lowest concentrations of cyclohexyl isocyanate tested in these studies were 17.79 ppm for 6 h, 1,017 ppm for 4 h, and 1,401 ppm for 2.5 h or less.

4.5.3. Derivation of AEGL-3 Values

The toxicologic database for cyclohexyl isocyanate was inadequate to derive AEGL-3 values. AEGL-3 values were determined by using the AEGL-3 values established for the related compound methyl isocyanate and dividing them by a modifying factor of 2 to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate. A comparison of the available lethality data on the two chemicals suggests that this approach results in sufficiently protective AEGL values. When three rats were exposed to cyclohexyl isocyanate at 18 ppm for 6 h, one died on day 7 post-exposure and the other two were killed on day 8, presumably because of moribund condition. For comparison, the 6-h LC_{50} for methyl isocyanate in rats is 6.1 ppm (NRC 2003). AEGL-3 values for cyclohexyl isocyanate are presented in Table 7-12, and the calculations are provided in Appendix A.

TABLE 7-11 AEGL-2 Values for Cyclohexyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.20 ppm (1.0 mg/m^3)	0.065 ppm (0.33 mg/m^3)	0.034 ppm (0.17 mg/m^3)	0.0085 ppm (0.043 mg/m^3)	0.0040 ppm (0.020 mg/m^3)

TABLE 7-12 AEGL-3 Values for Cyclohexyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.60 ppm (3.1 mg/m^3)	0.20 ppm (1.0 mg/m^3)	0.10 ppm (0.51 mg/m^3)	0.025 ppm (0.13 mg/m^3)	0.013 ppm (0.066 mg/m^3)

4.6. Summary of AEGLs

4.6.1. AEGL Values and Toxicity End Points

AEGL-1 values are not recommended for cyclohexyl isocyanate because of insufficient data and because of the potential for systemic effects to occur at concentrations below those associated with irritation. AEGL-2 and AEGL-3 values for cyclohexyl isocyanate were estimated from those established for methyl isocyanate and dividing them by a modifying factor of 2 to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate. AEGL values for cyclohexyl isocyanate are presented in Table 7-13.

4.6.2. Other Standards and Guidelines

There are no other standards or guidelines for cyclohexyl isocyanate.

5. *n*-BUTYL ISOCYANATE

5.1. Human Toxicity Data

5.1.1. Acute Lethality

No information regarding lethality in humans after acute inhalation exposure to *n*-butyl isocyanate was available.

5.1.2. Nonlethal Toxicity

An industrial hygiene survey conducted at a facility using *n*-butyl isocyanate as a chemical intermediate reported that exposure to *n*-butyl isocyanate at a concentration of 5-10 ppb (0.005-0.01 ppm) resulted in "noticeable" ocular irritation, and that normal work operations were not possible at 50 ppb (0.05 ppm) (Haskell Laboratory 1989). The report included an opinion that exposure to *n*-butyl isocyanate at 50 ppb (0.05 ppm) was not expected to impair ability to escape, but did not provide any supporting details. Concentrations of *n*-butyl isocyanate were measured using an impinger/gas chromatograph (GC) method. A later report compared measurements using this method with those obtained from XAD-7 tube/HPLC (DuPont, unpublished material, 2008), and found that the

impinger/GC method underestimated *n*-butyl isocyanate concentrations by 40-400%. Analysis of those data indicates that, when averaged across all of the samples, the XAD-7 tube/HPLC method gave results that were two-fold higher than the impinger/GC method (see Table 7-5).

DuPont (unpublished material, 2008) also reported the findings of two industrial hygiene surveys. In one assessment, subjective responses regarding ocular irritation and lacrimation were obtained from five workers who were not required to wear respirators. Data collected from the workers' personal air samplers indicated that "personnel did not experience eye irritation/lacrimation up to 52.8 ppb over a 7- to 8-h sample" (measured concentrations were 12.9-52.8 ppb [0.013-0.053 ppm]). In the second assessment, air monitoring data were assessed in conjunction with daily logs recording reports of ocular irritation or lacrimation by persons not wearing respirators. This assessment concluded that "personnel without respiratory protection were not experiencing eye irritation when air sample results indicated airborne butyl isocyanate levels ranging from 8 to 40 ppb" (DuPont, unpublished material, 2008). Neither survey was sufficiently rigorous to be used as a basis for deriving AEGL values.

5.1.3. Developmental and Reproductive Effects, Genotoxicity, and Carcinogenicity

No information regarding the developmental or reproductive toxicity, genotoxicity, or carcinogenicity of *n*-butyl isocyanate in humans was available.

TABLE 7-13 AEGL Values for Cyclohexyl Isocyanate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[b] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.20 ppm (1.0 mg/m^3)	0.065 ppm (0.33 mg/m^3)	0.034 ppm (0.17 mg/m^3)	0.0085 ppm (0.043 mg/m^3)	0.0040 ppm (0.020 mg/m^3)
AEGL-3 (lethal)	0.60 ppm (3.1 mg/m^3)	0.20 ppm (1.0 mg/m^3)	0.10 ppm (0.51 mg/m^3)	0.025 ppm (0.13 mg/m^3)	0.013 ppm (0.066 mg/m^3)

[a]When more than one of the monoisocyanates is detected at a scene, the lowest AEGL value should be applied to the sum total concentration of all detected monoisocyanates due to presumed common mode of action for these chemicals.
[b]NR, not recommended. On the basis of toxicity data on methyl isocyanate, it is plausible that exposure to cylcohexyl isocyanate might be associated with systemic toxicity at concentrations below those associated with irritation. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

5.2. Animal Toxicity Data

5.2.1. Acute Lethality

In experiments conducted by Younger Laboratories for Monsanto Chemical Company (Younger Laboratories 1956), groups of three male rats died 10-15 min after being exposed to an unspecified concentration of *n*-butyl isocyanate (described only as "considerably less than saturated"). Another group of three rats exposed to "relatively low" concentrations died after 45, 60, and 75 min. All rats exhibited signs of irritation and respiratory distress immediately after exposure began. Necropsy revealed severe edema in the nasal passages and pulmonary congestion.

Mobay Chemical Company (1961) conducted experiments in which groups of six rats were exposed to a saturated vapor of *n*-butyl isocyanate (about 22,000 ppm). Although the experimental protocol specified a 6-h exposure, results showed that all six rats died within 10-15 min. No further details of the experiments were provided.

The acute inhalation toxicity of *n*-butyl isocyanate in groups of six male Spartan Sprague-Dawley rats (200-300 g) was reported by IRDC (1965). Rats were exposed to *n*-butyl isocyanate at 5.5, 7.9, 10.9, 12.0, 18.9, 21.7, 27.9, 28.2, or 34.6 mg/m^3 (1.4, 1.9, 2.7, 3.0, 4.7, 5.4, 7.0, 7.1, and 8.7 ppm) for 1 h in a 9-L, airtight chamber, and were subsequently observed for 14 days. *n*-Butyl isocyanate vapor was generated by heating the compound in a U-tube submersed in a water bath, and the resulting vapor was passed through glass wool filters and calcium chloride drying tubes. Concentrations were adjusted by varying the infusion rate into the U-tube. Samples of the chamber atmosphere were analyzed spectrophotometrically and compared to a pre-established standard curve. Clinical signs of toxicity in rats exposed to *n*-butyl isocyanate increased with concentration and included hypoactivity, increased grooming and escape behavior during exposure, salivation, lacrimation, dyspnea, and death. Group-specific mortality incidences and necropsy findings are presented in Table 7-14. Although no deaths occurred at 12.0 mg/m^3 (3.0 ppm), deaths in the groups exposed at 7.9 and 10.9 mg/m^3 (1.9 and 2.7 ppm, respectively) suggest that the absence of mortality in the 12-mg/m^3 group was probably a function of the small group size. The investigators calculated a 1-h LC_{50} of 15.2 mg/m^3 (95% CI: 12.1-19.0 mg/m^3), equivalent to 3.8 ppm, using the method of Litchfield and Wilcoxon (1949). As shown in Table 7-14, lethality was often delayed.

A lethality assay using groups of six male ChR-CD rats exposed to *n*-butyl isocyanate (purity not specified) for 4 h was conducted by DuPont (Haskell Laboratory 1968). Concentrations of 12.5, 17.5, 22, 31.5, and 33.5 ppm were measured by impinger/GC analysis. Vapor was generated by metering *n*-butyl isocyanate into a heated (125-150°C) stainless steel T-tube. Vapor was then carried via measured air flow to a 16-L bell jar containing the rats. Rats exhibited irregular breathing, hyperemia, gasping, pale ears, and lacrimation during exposure. Post-exposure observations included 10-20% loss of body weight during

the first day; respiratory distress characterized by gasping, labored breathing, congestion, and rales; red discharge from the eyes; and priapism. Lethality findings are presented in Table 7-15. Some deaths occurred during the 30-day observation period at all test concentrations. Body weight loss and signs of respiratory distress were observed throughout the post-exposure period. Death occurred during exposure only at the two highest concentrations. Pathology findings included dark red-colored, edematous lungs, necrosis and desquamation of respiratory epithelium, and signs of increased capillary permeability. Surviving rats exhibited regeneration of the bronchial epithelium and proliferation of connective tissue resulting in fibrotic changes and atelectasis. Bronchopneumonia was evident in many rats by post-exposure day 14. A 4-h LC_{50} of 15.6 ppm (95% CI: 13.3-18.2 ppm) was reported.

TABLE 7-14 Lethality in Rats After Exposure to n-Butyl Isocyanate Vapor for 1 Hour

Concentration[a] (mg/m^3) [ppm]	Lethality	Comments and Necropy Findings
5.5 mg/m^3 (1.4 ppm)	0/6	No gross lesions in four rats; two had 8-mm areas of congestion or hemorrhage in lungs.
7.9 mg/m^3 (1.9 ppm)	1/6	Death on post-exposure day 1; rat had hemorrhagic lungs. All survivors had inflated lungs and involuted thymus; four had mucus in trachea and bronchi; two had lungs with dark areas or areas of consolidation; one had gastric edema and hemorrhage.
10.9 mg/m^3 (2.7 ppm)	2/6	Deaths on post-exposure days 9 and 13. Survivors had inflated lungs, and three had involuted thymus and fluid in small intestine.
12.0 mg/m^3 (3.0 ppm)	0/6	All rats had inflated lungs; two had pulmonary consolidation; one had pulmonary congestion; one had lungs with dark areas; one had pulmonary hyperemia; one had mucus in the trachea.
18.9 mg/m^3 (4.7 ppm)	6/6	Five deaths on post-exposure day 2, one death on post-exposure day 13. No necropsy findings reported.
21.7 mg/m^3 (5.4 ppm)	4/6	Two deaths on post-exposure day 2, one death each on days 9 and 11. Survivors had lungs with dark foci/consolidation, fluid in gastrointestinal tract.
27.9 mg/m^3 (7.0 ppm)	6/6	Two deaths on day of exposure, four deaths on
28.2 mg/m^3 (7.1 ppm)	6/6	post-exposure day 1.
34.6 mg/m^3 (8.7 ppm)	6/6	One death on day of exposure, five deaths on post-exposure day 1. All deaths on day of exposure.

[a]Measured spectrophotometrically.
Source: IRDC 1965.

TABLE 7-15 Lethality in Male Rats Exposed to *n*-Butyl Isocyanate for 4 Hours

	Mortality		
Concentration[a] (ppm)	During Exposure	14-Days Post-Exposure	30-Days Post-Exposure
12.5	0/6	0/6	2/6
17.5	0/6	2/6	3/6
22	0/6	2/6	5/6
31.5	2/6	6/6	6/6
53.5	2/6	6/6	6/6

[a]Measured by impinger/GC.
Source: Haskell Laboratory 1968.

A series of studies on *n*-butyl isocyanate were conducted by Bayer AG Institute for Toxicology for Miles, Inc. (Bayer AG 1978), which submitted the reports (in German) to EPA's toxic substances control act test submissions (TSCATS Section 8E) database. The studies included: 1- and 4-h lethality experiments in rats; another 1-h lethality study in rats; a study of cholinesterase activity in rats exposed to a lethal concentration; and a study of nonlethal effects in rats exposed for 4 h. The study of nonlethal effects was published by Pauluhn et al. (1990), and is described in Section 5.2.2.1. Salient portions of the acute lethality studies were translated to describe the other studies. In a 1-h inhalation study, groups of five male and five female Wistar rats were exposed to *n*-butyl isocyanate at 156, 520, or 978 mg/m^3. Vapors were generated at room temperature and distributed through the chamber with a fan, and were analyzed by flame ionization detection (FID). Mortality incidences were recorded 14 days post-exposure (see Table 7-16). A 1-h LC_{50} of 425 mg/m^3 (95% CI: 280-646 mg/m^3) or its equivalent of 105 ppm (95% CI: 70-162 ppm) was reported for males and females. Labored breathing was apparent as soon as exposure was initiated at all concentrations. During the post-exposure period, animals exhibited dull and unkempt coat, stiff gait, tearing, and labored breathing. Areas of the ocular and nasal mucosa were reddened and swollen. In the 4-h lethality study, groups of five male rats were exposed to *n*-butyl isocyanate at 90 or 285 mg/m^3 (22 or 70 ppm) and groups of five female rats were exposed at 90, 285, or 469 mg/m^3 (22, 70, and 116 ppm) (Bayer AG 1978). Mortality data from this study are presented in Table 7-16. A 4-h LC_{50} of 80 mg/m^3 (18 ppm) was reported for female rats; the 4-h LC_{50} for males was less than 90 mg/m^3 (22.5 ppm). Clinical observations were observed in all groups and were consistent with those reported in the 1-h study.

In a second 1-h inhalation study, groups of five male and five female Wistar rats were exposed to *n*-butyl isocyanate at 375, 887, or 932 mg/m^3 (94, 222, and 233 ppm), and followed for 28 days (Bayer AG 1978). The experimental design prevented dermal contact with the vapor, although details of the apparatus were not provided. Concentrations were analyzed by FID. Mortality incidences were

recorded at 28 days post-exposure (see Table 7-16). The 1-h LC_{50} values estimated for male and female rats were 500 mg/m^3 (125 ppm) and 600 mg/m^3 (150 ppm), respectively. Animals in all the exposure groups exhibited labored breathing, and sedation was observed in some. Mucosal irritation was observed. Necropsy findings included pulmonary edema, emphysema, and "spotty changes"; pale liver and spleen; lobular appearance of the liver; and distended stomach and intestines.

Lethality benchmarks for *n*-butyl isocyanate are presented in Table 7-17.

5.2.2. Nonlethal Toxicity

5.2.2.1. Rats

IRDC (1965) exposed groups of six rats to *n*-butyl isocyanate at concentrations of 5.5, 7.9, 10.9, 12.0, 18.9, 21.7, 27.9, 28.2, or 34.6 mg/m^3 for 1 h. Clinical signs included hypoactivity, increased grooming (during exposure), escape behavior (during exposure), salivation, lacrimation, and dyspnea. Although these responses were reportedly related to concentration, it was unclear which (if any) were associated with the nonlethal exposures. Deaths occurred in all but the 5.5 mg/m^3-ppm and 12.0 mg/m^3-groups (see Section 5.2.1).

TABLE 7-16 Lethality in Rats Exposed to *n*-Butyl Isocyanate for 1 or 4 Hours

Concentration	Lethality	Time of Death
1-h, 14-day follow-up		
156 mg/m^3 (39 ppm)	0/5 (males) 0/5 (females)	
520 mg/m^3 (130 ppm)	3/5 (males) 4/5 (females)	8-14 days post-exposure 9-13 days post-exposure
978 mg/m^3 (245 ppm)	5/5 (males) 5/5 (females)	1-3 days post-exposure 1 h to 12 days post-exposure
1-h, 28-day follow-up		
375 mg/m^3 (94 ppm)	1/10 (males) 2/10 (females)	10 days post-exposure 12 and 21 days post-exposure
887 mg/m^3 (222 ppm)	10/10 (males) 9/10 (females)	8 h to 24 days post-exposure 4-16 days post-exposure
932 mg/m^3 (233 ppm)	10/10 (males) 10/10 (females)	6 h to 12 days post-exposure 2-22 days post-exposure
4-h, 14-day follow-up		
90 mg/m^3 (22 ppm)	4/5 (males) 3/5 (females)	7-10 days post-exposure 11-12 days post-exposure
285 mg/m^3 (70 ppm)	5/5 (males) 4/5 (females)	1 h to 8 days post-exposure 9-14 days post-exposure
469 mg/m^3 (116 ppm)	5/5 (females)	2 h to 4 days post-exposure

[a]Measured by flame ionization detection.
Source: Bayer AG 1978.

TABLE 7-17 Lethality Benchmarks for *n*-Butyl Isocyanate

Study (analytic method)	Lethality Benchmark	Comments
IRDC 1965 (spectrophotometry)	1-h LC_{50}: 3.8 ppm	Deaths delayed 1-13 days
Haskell Laboratory 1968 (impinger/GC)	4-h LC_{50}: 15.6 ppm	Post-exposure deaths; time to death was a function of concentration.
Bayer AG 1978 (FID)	1-h LC_{50}: 105 ppm (males and females)	Followed for 14 days
	1-h LC_{50}: ~125 ppm (males)	Followed for 28 days
	1-h LC_{50}: ~150 ppm (females)	Followed for 28 days
	4-h LC_{50}: <22.5 ppm (males)	Followed for 14 days
	4-h LC_{50}: ≈18 ppm (females)	Followed for 14 days

Pulmonary function, arterial blood gases, acid-base status, and bronchioalveolar lavage fluid (BALF) composition were analyzed in groups of 20 male Wistar rats (WISW SPF-Cpb; 9-12 weeks old) exposed to *n*-butyl isocyanate (technical grade, 99.5%) at target concentrations of 0, 8, 25, or 50 mg/m^3 for 4 h (Pauluhn et al. 1990). Analytic concentrations of 7.6, 23.5, and 55.2 mg/m^3 (equivalent to 1.9, 5.9, and 14 ppm) were determined by HPLC analysis of three samples (sampling rate of 0.5 L/min). The animals were exposed using a head-nose only dynamic method that prevented mixing of the test atmosphere with exhaled air and also prevented hydrolytic degradation and aerosol formation. Rats exposed to *n*-butyl isocyanate at 7.6 mg/m^3 exhibited only transient clinical signs (hypothermia, bradypnea, and mucous membrane irritation) during the first day. In the 23.5- and 55.2-mg/m^3 groups, signs of severe respiratory distress were observed that resolved within 1week in the 23.5-mg/m^3 group but persisted through the 4-week observation period in the 55.2-mg/m^3 group. At the highest concentration, decreased body temperature (data not provided in report) was detected 10-min post-exposure. Observations at 4 weeks post-exposure included minor (but statistically insignificant relative to controls) changes in some pulmonary function parameters, significantly decreased arterial oxygen, increased arterioalveolar oxygen difference, and significantly increased blood proteins, lactate dehydrogenase (LDH) activity levels, and relative lung weight. Histopathologic examinations of the lungs revealed the greatest effect in rats exposed at the highest concentration, which included gross findings of consolidation, distention, hemorrhagic areas, edema, and pleural effusions. Microscopic changes included increased numbers of alveolar macrophages, perivascular round-cell infiltration, focal fibroproliferative reactions, emphysema, thickening of the septa, and pneumonia in rats exposed at 23.5 mg/m^3 or higher; the effects were described as occurring "marginally" in the 23.5-mg/m^3 group. In summary, a 4-h exposure of male rats to *n*-butyl isocyanate at 7.6 mg/m^3 produced minor transi-

ent clinical effects that fully resolved within 24 h. More notable effects were observed at 23.5 mg/m^3, which resolved within 1 week, and persistent clinical effects and notable histopathologic findings consistent with significant pulmonary injury were found at 55.2 mg/m^3.

5.2.2.2. Guinea Pigs

Tests of *n*-butyl isocyanate-bovine serum albumin conjugate in groups of four male Hartley guinea pigs induced only a weak, transient response (Haskell Laboratory 1982). The experiments involved multiple head-only exposures for 10-min/day, 5 days/week until a positive respiratory response occurred. During exposure, guinea pigs were placed in Lucite® body plethysmographs which were connected to an air pressure transducer to assess changes in respiratory rate. Three guinea pigs developed a positive response to *n*-butyl isocyanate after 2 weeks but the response was transient and of insufficient duration to allow for assessing the response to a challenge with other isocyanates. The concentration of *n*-butyl isocyanate-bovine serum albumin conjugate that generated the transient response was not specified.

5.2.3. Repeated Exposure

In a lung function study, groups of 20 male Wistar rats were exposed (head-nose only) to *n*-butyl isocyanate vapors at target concentrations of 0 (conditioned air), 1, 5, 15, or 25 mg/m^3 (0, 0.25, 1.25, 3.75, 6.25 ppm) for 6 h/day for 5 days, and were observed for 5 weeks (Pauluhn and Eben 1991). Analytic concentrations of 0, 1.09, 6.22, 14.67, and 25.97 mg/m^3 (0, 0.27, 1.55, 3.67, and 6.49 ppm) were determined by HPLC analysis of nitro-reagent reaction product. Twelve rats in the 25 mg/m^3-group died 2 weeks after exposure; no deaths occurred in the other groups. No clinical signs of toxicity were observed in rats of the 1- or 5 mg/m^3-groups. At 15 and 26 mg/m^3, rats exhibited unkempt appearance, labored breathing, reduced motility, hypothermia, and serous nasal discharge. Overall evaluation of lung function revealed no significant differences in the 1-mg/m^3 group compared with the control group. Rats in the 15-mg/m^3 group exhibited some effects (BALF composition) that were marginally different from controls. On the basis of clinical signs, pulmonary function test results, and BALF analysis, the investigators concluded that delayed lethality was the result of obstructive and progressive lung damage with associated severe disturbance of ventilatory perfusion.

5.2.4. Developmental and Reproductive Effects

No information on the developmental or reproductive toxicity of *n*-butyl isocyanate vapor in animals was available.

5.2.5. Genotoxicity

n-Butyl isocyanate was not mutagenic in *Salmonella typhimurium* strains TA 1535,TA 1537, TA 98, or TA 100 with or without metabolic activation (OECD 2005). In the mouse lymphoma assay, *n*-butyl isocyanate was genotoxic only in the absence of metabolic activation, but it was not determined if this was the result of gene mutation or chromosomal aberrations (OECD 2005). No in vivo genotoxicity data were available.

5.2.6. Carcinogenicity

No information on the carcinogenicity of *n*-butyl isocyanate vapor in animals was available.

5.3. Data Analysis for AEGL-1

5.3.1. Human Data Relevant to AEGL-1

Data relevant to AEGL-1 effects in humans are limited to industrial hygiene reports noting that exposure to *n*-butyl isocyanate at concentrations as high as 40-50 ppb (0.040-0.050 ppm) did not cause ocular irritation in workers (Haskell Laboratory 1989; DuPont, unpublished material, 2008). However, the reports were not sufficiently rigorous or well documented to form the basis of AEGL-1 values for *n*-butyl isocyanate.

5.3.2. Animal Data Relevant to AEGL-1

Reliable exposure-response data for AEGL-1 severity effects in animals were not available for *n*-butyl isocyanate. Signs of irritation and respiratory distress were observed in surviving rats in lethality studies, but the severity of the nonlethal effects was not specified.

5.3.3. Derivation of AEGL-1 Values

AEGL-1 values were not derived for *n*-butyl isocyanate or any of the other three selected monoisocyanates. The available data suggest that *n*-butyl isocyanate and the other monisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for *n*-butyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

5.4. Data Analysis for AEGL-2

5.4.1. Human Data Relevant to AEGL-2

The industrial hygiene report of DuPont (Haskell Laboratory 1989) provided the only information on *n*-butyl isocyanate relevant to AEGL-2 effects in humans. The report stated that exposure to *n*-butyl isocyanate at 50 ppb (0.05 ppm) for an unspecified duration was considered incompatible with normal work operations, but would not impair escape. However, no details of exposure estimates or health evaluations were provided; thus, the data were considered unsuitable for deriving AEGL-2 values.

5.4.2. Animal Data Relevant to AEGL-2

A single 4-h exposure of rats to *n*-butyl isocyanate at a concentration 23.5 mg/m^3 (5.9 ppm) resulted in signs of severe respiratory distress which resolved within 1 week, whereas exposure at 55.2 mg/m^3 (14 ppm) resulted in persistent clinical effects (Pauluhn et al. 1990). Histopathologic findings at 55.2 mg/m^3 were consistent with significant pulmonary injury; "marginal" pulmonary histopathologic findings were reported at 23.5 mg/m^3, but details of the incidence and severity of effects were not provided (Pauluhn et al. 1990); thus, it is difficult to evaluate whether the findings were consistent with AEGL-2 effects.

In a repeated exposure study, rats exposed to *n*-butyl isocyanate at 15 mg/m^3 (3.8 ppm) for 6 h/day for 5 consecutive days had minor changes in BALF composition but no significant histopathologic findings; in rats similarly exposed at 25 mg/m^3 (6.3 ppm), 60% mortality (12/20) occurred during post-exposure week 2 (Pauluhn and Eben 1991).

5.4.3. Derivation of AEGL-2 Values

The available human data and single-exposure animal toxicity data were inadequate for deriving AEGL-2 values for *n*-butyl isocyanate. Therefore, AEGL-2 values were determined by adjusting the AEGL-3 values for *n*-butyl isocyanate; each of the corresponding AEGL values was divided by 3. This approach is justified by the steep concentration-response curve observed in a mortality study; no rats died after a 1-h exposure at 39 ppm, and 70% (7/10) died at 130 ppm (Bayer AG 1978). AEGL-2 values for *n*-butyl isocyanate are presented in Table 7-18, and their derivation is presented Appendix A.

TABLE 7-18 AEGL-2 Values for *n*-Butyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.10 ppm (0.41 mg/m^3)	0.10 ppm (0.41 mg/m^3)	0.083 ppm (0.34 mg/m^3)	0.053 ppm (0.21 mg/m^3)	0.026 ppm (0.11 mg/m^3)

For comparison, consideration was given to possible AEGL-2 values based on the repeated-exposure study of Pauluhn and Eben (1991). The no-effect level relevant to AEGL-2 values in that study was 3.8 ppm; only minor changes in BALF composition were observed. If 3.8 ppm is used as the point of departure (assuming a 6 h duration), AEGL-2 values could be calculated by applying a total uncertainty factor of 30 (3 for interspecies differences and 10 for intraspecies variability), applying a modifying factor of 3 (to account for potential developmental toxicity of *n*-butyl isocyanate based on data for the related compound methyl isocyanate), and performing time scaling with the equation $C^n \times t = k$ (using default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations). The resulting AEGL-2 values would be 0.097, 0.097, 0.077, 0.048, and 0.032 ppm for 10-min, 30-min, 1-h, 4-h, and 8-h durations, respectively. These values are consistent with those obtained by adjusting the AEGL-3 values.

5.5. Data Analysis for AEGL-3

5.5.1. Human Data Relevant to AEGL-3

No data on lethality in humans exposed to *n*-butyl isocyanate vapor were available.

5.5.2. Animal Data Relevant to AEGL-3

Lethality data on inhalation exposure to *n*-butyl isocyanate are only available for rats exposed for 1 or 4 h (IRDC 1965; Haskell Laboratory 1968; Bayer AG 1978); lethality benchmarks from these studies are presented in Table 7-17. In addition to lethality studies, a pulmonary function study (Pauluhn et al. 1990) identified a nonlethal concentration of 14 ppm for a 4-h exposure. Table 7-19 compares these studies. The 1-h studies identified divergent LC_{50} and nonlethal concentrations, despite using similar group sizes. Likewise, the 4-h studies also had inconsistent results; 14 ppm was not lethal to male rats in the study by Pauluhn et al. (1990), whereas LC_{50} values of 15.6 and about 20 ppm were identified in the studies by DuPont (Haskell Laboratory 1968) and Miles, Inc. (Bayer AG 1978).

The Pauluhn et al. (1990) study was selected as the basis for deriving AEGL-3 values. The study was the only one to use HPLC analysis, a method that appears to be more reliable than either spectrophotometric methods or GC analysis. Furthermore, the study was published, and used large group sizes (20 per exposure).

5.5.3. Derivation of AEGL-3 Values

The highest nonlethal concentration of 14 ppm in the 4-h rat study by Pauluhn et al. (1990) was selected as the point of departure for deriving AEGL-3 values. That study tested a larger number of rats and used a more reliable analytic

technique (HPLC analysis) for measuring exposure concentrations than other studies. An interspecies uncertainty factor of 3 was applied on the basis of LC_{50} data on the related compound methyl isocyanate, which showed relatively little interspecies differences (about a 2-fold difference in 6-h LC_{50}s among rats, mice, and guinea pigs; see Section 2.4). An intraspecies uncertainty factor was 10 was also applied. Both uncertainty factors are consistent with those applied in the derivation of AEGL-3 values for methyl isocyanate (NRC 2003). Finally, a modifying factor of 3 was applied to account for potential developmental toxicity of *n*-butyl isocyanate on the basis of data on methyl isocyanate.

Time scaling was performed using the equation $C^n \times t = k$. Default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations were used. Because of uncertainties associated with extrapolating a 4-h point of departure to a 10-min value, the 30-min AEGL-3 values was adopted as the 10-min value. AEGL-3 values for *n*-butyl isocyanate are presented in Table 7-20, and the calculations are presented in Appendix A.

5.6. SUMMARY OF AEGLS

5.6.1. AEGL Values and Toxicity End Points

AEGL-1 values are not recommended for *n*-butyl isocyanate or any of the other selected monoisocyanates because of insufficient data and the potential for systemic effects to occur at concentrations below those associated with irritation. AEGL-2 values for *n*-butyl isocyanate were derived by dividing the AEGL-3 values by 3, because of the lack of reliable data on AEGL-2 end points. A concentration causing no mortality in rats exposed for 4 h (Pauluhn et al. 1990) was used as the basis of AEGL-3 values for *n*-butyl isocyanate. AEGL values are summarized in Table 7-21.

TABLE 7-19 Comparison of Lethality Data on *n*-Butyl Isocyanate

Study	Sampling and Analysis Method	Follow-up (days)	No. of Animals	Highest Nonlethal Concentration (or Lowest Lethal Concentration) (ppm)	LC_{50} (ppm)
1 hour					
IRDC 1965	Spectrophotometry	14	6 males	1.4	3.8
Bayer AG 1978	FID	14	5 males, 5 females	39	105
Bayer AG 1978	FID	28	10 males 10 females	None (94) None (94)	~125 ~150
4 hours					
Haskell Laboratory 1968	Impinger/GC	30	6 males	None (12.5)	15.6
Bayer AG 1978	FID	14	5 males 5 females	None (22) None (22)	<22.5 18
Pauluhn et al. 1990	HPLC	28	20 males	14	Not applicable

TABLE 7-20 AEGL-3 Values for *n*-Butyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.31 ppm (1.3 mg/m^3)	0.31 ppm (1.3 mg/m^3)	0.25 ppm (1.0 mg/m^3)	0.16 ppm (0.65 mg/m^3)	0.078 ppm (0.32 mg/m^3)

TABLE 7-21 AEGL Values for *n*-Butyl Isocyanate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[b] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.10 ppm (0.41 mg/m^3)	0.10 ppm (0.41 mg/m^3)	0.083 ppm (0.34 mg/m^3)	0.053 ppm (0.21 mg/m^3)	0.026 ppm (0.11 mg/m^3)
AEGL-3 (lethal)	0.31 ppm (1.3 mg/m^3)	0.31 ppm (1.3 mg/m^3)	0.25 ppm (1.0 mg/m^3)	0.16 ppm (0.65 mg/m^3)	0.078 ppm (0.32 mg/m^3)

[a]When more than one of the monoisocyanates is detected at a scene, the lowest AEGL value should be applied to the sum total concentration of all detected monoisocyanates because of a presumed common mode of action.

[b]NR, not recommended. On the basis of toxicity data on methyl isocyanate, it is plausible that exposure to *n*-butyl isocyanate may be associated with systemic toxicity at concentrations below those associated with irritation. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 value are without effect.

5.6.2. Other Exposure Criteria

Standards and guidelines for exposure to *n*-butyl isocyanate are presented in Table 7-22. Emergency response planning guidelines (ERPGs) for *n*-butyl isocyanate were derived in 1994 (AIHA 2011). The 1-h ERPG-1 value was based on an industrial hygiene survey (Haskell Laboratory 1989); this study was not used to derive AEGL values because it lacked adequate documentation. The ERPG-2 was also based on the survey study, which concluded that 0.05 ppm was not expected to impede escape. Finally, the ERPG-3 of 1 ppm is based on a calculated LC_{01} of 6.8 ppm for rats exposed to *n*-butyl isocyanate for 4 h (Haskell Laboratory 1968). As noted earlier in this chapter, these data were not used to derive AEGL values because of the uncertainty associated with the analytic method (gas chromatograph) used to measured *n*-butyl isocyanate.

6. PHENYL ISOCYANATE

6.1. Human Toxicity Data

No information regarding lethality, nonlethal toxicity, developmental toxicity, genotoxicity, or carcinogenicity in humans after acute inhalation exposure to phenyl isocyanate was available.

TABLE 7-22 Standards and Guidelines for *n*-Butyl Isocyanate

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.10 ppm	0.10 ppm	0.083 ppm	0.053 ppm	0.026 ppm
AEGL-3	0.31 ppm	0.31 ppm	0.25 ppm	0.16 ppm	0.078 ppm
ERPG-1 (AIHA)[a]			0.01 ppm		
ERPG-2 (AIHA)			0.05 ppm		
ERPG-3 (AIHA)			1.0 ppm		

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2011)
ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

6.2. Animal Toxicity Data

6.2.1. Acute Lethality

Four albino rats exposed to phenyl isocyanate at a concentration of 0.33 mg/L (about 67 ppm) died after 1 h (2 rats), 2 h, and 2.5 h of exposure (SA 1954). In a second experiment, all rats survived exposure to phenyl isocyanate at 0.14 mg/L (about 29 ppm) for 4 h. Concentrations were determined by spectrophotometric analysis and comparison with a standard curve. No other information was provided in the report.

Groups of four male and four female Alderley Park rats were exposed for 1 h to phenyl isocyanate (purity not specified) in a 17-L chamber at concentrations of 0.358, 1.325, 1.45, 2.167, 4.368, 6.08, 7.942, or 9.187 ppm, and were observed for 14 days (see Table 7-23) (ICI 1977; Mobay 1978). Concentrations of phenyl isocyanate was determined by a colorimetric technique (Marcali method; phenyl isocyanate content in absorption media determined by spectrophotometric analysis and comparison with a standard curve). The 1-h LC_{50} was estimated to be 3.9 ppm (95% CI: 2.9-5.3 ppm). Most deaths occurred 8-12 days after exposure. In a preliminary summary of this study, Mobay Corp. (1978) reported that the chamber concentrations had been analyzed by both the Marcali method and by HPLC analysis, and that the two methods gave divergent results. According to Mobay (1978), the HPLC values were closer to the calculated concentrations. The original report (ICI 1977) did not discuss analysis of the chamber concentrations by HPLC, and

Mobay (1978) did not provide individual exposure concentrations measured by HPLC. On the basis of the HPLC results, Mobay (1978) estimated a 1-h LC_{50} of 12.6 ppm (95% CI: 8.4-19.0 ppm). Uncertainty with respect to the reliability of the Marcali method for analyzing exposure concentrations, coupled with lack of documentation on the exposure concentrations estimated by HPLC analysis, limits the use of this study for calculating AEGL values.

TABLE 7-23 Lethality in Rats Exposed to Phenyl Isocyanate for 1 Hour

Concentration[a] (ppm)	Lethality	Comments
0.358	0/8	No clinical signs; small hemorrhagic sites on lungs of one male and one female found at necropsy.
1.325	0/8	No clinical signs in females; slight body weight loss and signs of toxicity (piloerection, wheezing, hunched posture) in males; four males with evidence of lung damage at necropsy; all animals had increased lung weight.
1.45	0/8	Slight wheezing after exposure; reversible body weight loss in males; no clinical signs in females; no significant findings at necropsy.
2.167	2/4 males 2/4 females	Males: deaths on days 5 and 12; increased lung weight and focal hemorrhage. Females: deaths on days 7 and 12; increased lung weight and focal hemorrhage,
4.368	1/4 males 3/4 females	Males: death on day 8; respiratory distress; pulmonary hemorrhage; air in intestines; increased lung weight. Females: deaths on days 4, 5, 8; respiratory distress; pulmonary hemorrhage; air in intestines; increased lung weight.
6.08	2/4 males 2/4 females	Males: deaths on days 10 and 12; labored respiration; hunched posture; focal pulmonary hemorrhage; air in intestines; increased lung weight. Females: deaths on days 8 and 13; labored respiration; hunched posture; focal pulmonary hemorrhage; air in intestines; increased lung weight.
7.942	4/4 males 4/4 females	Males: deaths on days 7, 9, and 8 (two rats); signs of severe respiratory distress; all animals moribund; focal pulmonary hemorrhage; air in intestines; increased lung weight. Females: deaths on days 8 (two rats) and 12 (two rats); signs of severe respiratory distress; all animals moribund; focal pulmonary hemorrhage; air in intestines; increased lung weight.
9.187	4/4 males 3/4 females	Males: deaths on days 1, 9, 11, and 14; severe respiratory distress; moribund; necropsy findings indicative of severe pulmonary damage. Females: deaths on days 6, 9, and 14; severe respiratory distress; moribund; necropsy findings indicative of severe pulmonary damage.

[a]Analyzed by Marcali method.
Sources: Adapted from ICI 1977 and Mobay 1978.

In an experiment in which groups of five male and five female Wistar rats were exposed to a saturated atmosphere of phenyl isocyanate (about 1,600 ppm at 20°C) for 3, 10, or 30 min, all rats died (Bayer AG 1981). Time to death was inversely related to exposure duration: 8-11 days for the 3-min exposure, 3-24 h for the 10-min exposure, and 32-59 min for the 30-min exposure. The observation period was 14 days. The only gender-related differences in findings occurred in the group exposed for 10 min; male rats died as early as 3 h after exposure whereas all female rats died at 24 h. Signs of toxicity (ocular and nasal irritation and respiratory distress) appeared very quickly, and rats that survived the first week experienced body weight loss. Necropsy findings confirmed pulmonary damage.

In an acute inhalation toxicity study in rats, groups of five male and five female young adult Wistar rats were exposed to phenyl isocyanate (99.9% pure) for 4 h at measured concentrations of 0.7, 5.4, 15.2, 11.7, 27.9, 47.1, and 87.8 mg/m^3 (equivalent to 0.14, 1.1, 3.1, 2.4, 5.7, 9.7, and 18 ppm) (Bayer AG 1991a). Controls were exposed to clean air only. On the basis of clinical signs and gross pathology findings, the primary target of toxicity appeared to be the respiratory tract. Most rats died within 9 days. The investigators reported a 4-h LC_{50} of 22 mg/m^3 (95% CI: 19-27 mg/m^3) for males and females combined; mortality data are presented in Table 7-24. No mortality occurred at concentrations of 0.7 and 5.4 mg/m^3 (0.14 and 1.1 ppm, respectively).

In summary, lethality data for phenyl isocyanate vapor are only available for rats. Lethality benchmarks for phenyl isocyanate are summarized in Table 7-25.

6.2.2. Nonlethal Toxicity

In the 4-h study of phenyl isocyanate in rats (Bayer AG 1991a) described in Section 6.2.1, no clinical signs of toxicity were observed at 0.7 mg/m^3 (0.14 ppm). Exposure at 5.4 mg/m^3 (1.1 ppm) resulted in slightly slowed and labored breathing in some rats. At 11 and 15.2 mg/m^3 (2.4 and 3.1 ppm), these symptoms were accompanied by unkempt ruffled fur, coughing sounds, serous nasal secretions, and decreased locomotor activity, tachypnea, cyanosis, high-stepping gait, and emaciated appearance; one death occurred among the 20 rats exposed at these two concentrations. Rats in the highest exposure groups (27.9 mg/m^3 [5.7 ppm] and higher), which experienced significant mortality, also exhibited rattling sounds, lethargy, and prostration. Reflex testing on the day of exposure or shortly thereafter revealed no signs of neurological effects. Marginal hypothermia was noted in rats exposed to phenyl isocyanate at 15.2 mg/m^3; higher concentrations were associated with marked hypothermia as well as depressed body weight. At necropsy, inflated lungs were found in rats exposed at 15.2 mg/m^3 and higher that survived the observation period. Rats that died before the observation period ended had inflated, edematous, mucous-filled lungs; hydrothorax; reddened nasal areas; bloody mucous-filled gastrointestinal tracts; reddened mucosa of the small intestines; pale liver, spleen, and kidneys; and lobular appearance of the liver.

TABLE 7-24 Lethality in Rats Exposed to Phenyl Isocyanate for 4 Hours

Exposure Concentration (ppm)	Mortality		
	Females	Males	Total
0.14	0/5	0/5	0/10
1.1	0/5	0/5	0/10
2.4	0/5	1/5	1/10
3.1	0/5	0/5	0/10
5.7	3/5	4/5	7/10
9.7	5/5	5/5	10/10
18	5/5	5/5	10/10

[a]Analyzed by high performance liquid chromatography.
Source: Bayer AG 1991a.

TABLE 7-25 Summary of Rat Lethality Benchmarks for Phenyl Isocyanate

Study (analytic method)	Lethality Benchmark	Comments
SA1954 (not specified)	1-2.5 h at 67 ppm	100% lethality
	4 h at 29 ppm	No deaths.
ICI 1977; Mobay 1978 (Marcali method and HPLC)	1-h LC_{50}: 12.6 ppm (by HPLC) or 3.9 ppm (by Marcali method)	Deaths at 8-12 d post-exposure
Bayer AG 1991a (HPLC)	4-h LC_{50}: 4.6 ppm	Most deaths at 9 d post-exposure
Bayer AG 1981 (saturated vapor; not measured)	3 min at 1,600 ppm	10/10 died at 8-11 d
	10 min at 1,600 ppm	10/10 died at 3-24 h
	30 min at 1,600 ppm	10/10 died at 32-59 min

In a pilot study by Pauluhn et al. (1995), groups of four male Wistar rats exposed (nose-only) to analytically determined phenyl isocyanate concentrations of 0, 1.9, 5.14, or 12.92 mg/m^3 (0, 0.4, 1.1, and 2.7 ppm) for 45 min exhibited a concentration-related decrease in respiratory rate (approximately 20-50% decrease relative to controls). On the basis of data presented graphically, the highest exposure (12.92 mg/m^3) resulted in a decrease in respiratory rate of about 50%, suggesting that the RD_{50} for phenyl isocyanate in rats is about 13 mg/m^3 (2.7 ppm). The investigators reported an estimated threshold exposure for upper respiratory tract sensory irritation of 1.1 mg/m^3 (0.2 ppm). A bradypnoic response was observed, but no evidence of changes in minute volume or tidal volume were found.

6.2.3. Repeated Exposure

Groups of 10 male and 10 female young-adult Wistar rats were exposed to phenyl isocyanate at 0, 0.12, 0.57, or 3.14 mg/m^3 (0, 0.03, 0.1, or 0.7 ppm) for 6

h/day for 5 days, and were observed for 3 weeks (Bayer AG 1991b). Concentrations of phenyl isocyanate were determined by HPLC analysis. No rats died at any concentration. No significant clinical signs were observed in the rats exposed at 0.03 or 0.1 ppm, and no effects on body weight or rectal temperature were found. Rats exposed at 0.7 ppm exhibited serous nasal discharge but had no cumulative effects. Lung lavage fluid and LDH analysis on days 7-8 of the experiment revealed no significant treatment-related effects in the 0.7-ppm group. Although there were no observations reported after just one exposure, results of this study indicated that multiple 6-h exposures to phenyl isocyanate at 0.1 ppm were without serious effect and multiple exposures at concentrations as high as 0.7 ppm did not result in significant toxicologic consequences.

In a study by ICI (1980), groups of eight male and eight female Alderley Park, Wistar-derived rats were exposed to phenyl isocyanate at concentrations of 0.05 ppm or 0.5 ppm for 6 h/day for 11 days. The original protocol specified a 3-week study duration, but severe respiratory distress in the rats necessitated a shorter duration. Control groups included rats exposed to clean air or petroleum ether (the diluent used with the test article). Test atmospheres were generated by heating a known amount of phenyl isocyanate and diluting the vapor with petroleum ether. Exposures were conducted in 60-L Perspex chambers that allowed for individual housing of the rats. Airflow was 15-45 L/min depending on the exposure group. Phenyl isocyanate concentrations were determined by the Marcali method, and were found to vary from the target concentrations by 25% or more. Rats in the control groups and the 0.05-ppm group exhibited no clinical signs and results of post-mortem exams were unremarkable. Two rats in the 0.5-ppm group died (on days 9 and 11), and most exhibited signs of respiratory distress and overall poor condition as early as the first exposure day. The investigators concluded that, under the conditions of this experiment, 0.05 ppm was close to a no-effect level. However, uncertainty with respect to the reliability of the Marcali analytic method limits the utility of this study for deriving AEGL values.

In a 2-week study, groups of 20 male Wistar rats were exposed (nose-only) for 6 h/day, 5 days/week to phenyl isocyanate at concentrations of 0, 1.04, 4.1, 7.18, or 10.39 mg/m^3 (0, 0.2, 0.8, 1.5, or 2.1 ppm) (Pauluhn et al. 1995). With the exception of Goblet cell hyperplasia in the nasal and paranasal regions and main bronchi of rats in the 4-mg/m^3 group, the incidences of histopathologic lesions in rats of the 1- or 4-mg/m^3 groups was not significantly different than controls. Rats in these groups were free of clinical signs. Findings in the two highest exposure groups were indicative of significant airway injury and decrements in pulmonary function consistent with the clinical signs of respiratory-tract irritation. Most of the signs observed in the 7- and 10-mg/m^3 groups regressed during the first post-exposure week, although sporadic recurrence of irregular breathing patterns and wheezing was observed. Necropsy findings in these groups included macroscopic lung lesions (hepatoid foci and red areas or complete redness of the lung surface) and pleural adhesions.

6.2.4. Developmental and Reproductive Effects

No information regarding the developmental and reproductive toxicity of phenyl isocyanate vapor in animals was available.

6.2.5. Genotoxicity

Phenyl isocyanate was not toxic in *Salmonella* at concentrations of 2,500-12,500 µg/plate. There was no significant evidence of mutagenic effects in *Salmonella*/microsome tests (Bayer AG 1980b). Results of a mouse micronucleus test revealed no evidence of a clastogenic effect from phenyl isocyanate at 30 mg/kg (Bayer AG 1990).

6.2.6. Carcinogenicity

No information regarding the carcinogenicity of phenyl isocyanate vapor in animals was available.

6.3. Data Analysis for AEGL-1

6.3.1. Human Data Relevant to AEGL-1

No data regarding AEGL-1 severity effects in humans exposed to phenyl isocyanate are available.

6.3.2. Animal Data Relevant to AEGL-1

Pauluhn et al. (1995) estimated a threshold for upper respiratory tract sensory irritation of 1.1 mg/m^3 (0.2 ppm) in a study of Wistar rats exposed to phenyl isocyanate for 45 min. A bradypnoic response was observed, but no evidence of changes in minute volume or tidal volume was found. In a follow-up multiple exposure study (6 h/day, 5 days/week for 2 weeks), rats exposed to phenyl isocyanate at concentrations up to 0.2 ppm had no discernible effects (Pauluhn et al. 1995). The incidence of histopathologic lesions in the 1- or 4-mg/m^3 (0.2 or 0.8 ppm) groups was not significantly different from those of controls. Rats in these exposure groups were also free of clinical signs.

6.3.3. Derivation of AEGL-1 Values

AEGL-1 values were not derived for phenyl isocyanate. The available data suggest that phenyl isocyanate and the other three selected monisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic

toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for phenyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

6.4. Data Analysis for AEGL-2

6.4.1. Human Data Relevant to AEGL-2

No information regarding AEGL-2 severity effects in humans following inhalation exposure to phenyl isocyanate was available.

6.4.2. Animal Data Relevant to AEGL-2

Studies with rats indicate that respiratory-tract irritation and subsequent tissue damage are the critical effects from exposure to phenyl isocyanate vapor. No rats died after exposure to phenyl isocyanate at 0.03, 0.1, or 0.7 ppm for 6 h/day for 5 days, and observed for 3 weeks (Bayer AG 1991b). No significant clinical signs were observed in rats exposed at 0.03 or 0.1 ppm, and no effects on body weight or rectal temperature were found. Rats exposed at 0.7 ppm exhibited serous nasal discharge but no cumulative effects. Lung lavage fluid and LDH analysis on days 7-8 revealed no significant treatment-related effects in the 0.7-ppm group. Although no observations were reported after just one exposure, results of this study indicated that multiple 6-h exposures to phenyl isocyanate at 0.1 ppm were without serious effect and multiple exposures to concentrations as high as 0.7 ppm did not result in significant toxicologic consequences. Pauluhn et al. (1995) reported that rats exposed to phenyl isocyanate up to 4 mg/m^3 (0.8 ppm) for 6 h/day, 5 days/week for 2 weeks exhibited no clinical signs of toxicity, no gross lesions in the respiratory tract, no significant findings regarding BAL analysis, and no effects on organ and body weights. The only histopathologic finding was Goblet cell hyperplasia in the nasal and paranasal regions and main bronchi. In another study, hypothermia and respiratory-tract irritation were observed in rats exposed at 5 mg/m^3 (1.1 ppm) for 4 h (Bayer AG 1991a).

6.4.3. Derivation of AEGL-2 Values

Animal data relevant to AEGL-2 values were available for phenyl isocyanate. However, those data would lead to 4- and 8-h AEGL-2 values that are very similar to AEGL-3 values (see below). Therefore, to provide adequate protection, AEGL-3 values were divided by 3 to derive AEGL-2 values for phenyl isocyanate. This approach is recommended by NRC (2001) for compounds with a steep concentration-response relationship. Mortality data from a study of rats exposed to phenyl isocyanate for 4 h indicates a steep relationship; no rats died at 3.1 ppm and 70% died at 5.7 ppm (Bayer AG 1991a). AEGL-2 values for

phenyl isocyanate presented in Table 7-26, and the calculations are presented in Appendix A.

If AEGL-2 values were calculated on the basis of the available animal data for phenyl isocyanate, the most relevant point of departure would be the estimated threshold for respiratory-tract injury. In the Pauluhn et al. (1995) study, 0.8 ppm would be a no-effect level for AEGL-2 severity effects. AEGL-2 values could be calculated by applying a total uncertainty factor of 30 (3 for interspecies differences and 10 for intraspecies variability), applying a modifying factor of 3 (to account for potential developmental toxicity of *n*-butyl isocyanate on the basis of data for the related compound methyl isocyanate), and performing time scaling with the equation $C^n \times t = k$ (using default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations). This approach would results in 4- and 8-h AEGL-2 values of 0.01 and 0.007 ppm, respectively. Because these values are very close to the 4- and 8-h AEGL-3 values of 0.018 and 0.009 ppm for this compound, this approach was not used to derive AEGL-2 values for phenyl isocyanate.

6.5. Data Analysis for AEGL-3

6.5.1. Human Data Relevant to AEGL-3

No information regarding AEGL-3 severity effects in humans following vapor exposure to phenyl isocyanate was available.

6.5.2. Animal Data Relevant to AEGL-3

Only rat lethality data are available for phenyl isocyanate. The candidate studies include a 1-h study using groups of four male and four female rats (ICI 1977; Mobay 1978) and a 4-h study using five male and five female rat (Bayer AG 1991a). ICI (1977) and Mobay (1978) reported different LC_{50} values, depending on the analytic technique used to measure phenyl isocyanate; an LC_{50} of 3.9 ppm measured by Marcali colorimetric analysis or 12.6 ppm measured by HPLC analysis. The highest nonlethal concentration was 1.45 ppm, as measured by the Marcali method. Uncertainty with respect to the reliability of the Marcali method for analyzing exposure concentrations, coupled with lack of documentation on the exposure concentrations estimated by HPLC analysis, limited the use of this study for deriving AEGL-3 values.

TABLE 7-26 AEGL-2 Values for Phenyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.012 ppm (0.058 mg/m^3)	0.012 ppm (0.058 mg/m^3)	0.0096 ppm (0.047 mg/m^3)	0.0061 ppm (0.030 mg/m^3)	0.0030 ppm (0.015 mg/m^3)

In the Bayer AG (1991a) study, groups of five male and five female young-adult Wistar rats were exposed to phenyl isocyanate for 4 h at concentrations of 0.7, 5.4, 15.2, 11.7, 27.9, 47.1, and 87.8 mg/m^3 (0.14, 1.1, 3.1, 2.4, 5.7, 9.7, and 18 ppm). Concentrations were determined by HPLC analysis. The investigators reported a 4-h LC_{50} of 22 mg/m^3 (95% CI: 19-27 mg/m^3); the highest nonlethal concentration was 5.4 mg/m^3. Benchmark dose modeling of the data resulted in $BMCL_{05}$ (benchmark concentration, 95% confidence limit with a 5% response) and BMC_{01} (benchmark concentration with 1% response) estimates of 1.64 and 1.73 ppm, respectively. This study was selected for use in deriving AEGL-3 values for phenyl isocyanate.

Monsanto (SA 1954) reported a nonlethal concentration of 29 ppm for phenyl isocyanate in a 4-h study of four rats; however, this study was not considered as a basis for deriving AEGL values because the number of animals tested was small, the sex and strain of rat were not specified, and no additional details were provided in the report. In addition, the nonlethal concentration in this study was much higher than concentrations associated with lethality (3.1 ppm and higher) in a later study with better documentation (Bayer AG 1991a).

6.5.3. Derivation of AEGL-3 Values

The 4-h $BMCL_{05}$ value of 1.64 ppm calculated from the rat lethality data reported by Bayer AG (1991a) was used as the basis for deriving AEGL-3 values for phenyl isocyanate. This point of departure is supported by data from a study of repeated 6-h exposures to phenyl isocyanate, in which 2.1 ppm was not lethal to 20 male rats exposed for 2 weeks (Pauluhn et al. 1995). Interspecies and intraspecies uncertainty factors of 3 and 10, respectively, were applied. An interspecies uncertainty factor of 3 was considered appropriate on the basis of mortality data on the related compound methyl isocyanate that indicated limited species differences; about a two-fold difference in 6-h LC_{50}s for rats, mice, and guinea pigs was found (see Section 2.4). A factor of 3 is also consistent with that used for deriving AEGL values for methyl isocyanate. A factor of 10 was applied to account for intraspecies variability, and was also consistent with the factor applied in the derivation of AEGL-3 values for methyl isocyanate (NRC 2003). Finally, a modifying factor of 3 was applied to account for potential developmental toxicity of phenyl isocyanate on the basis of data on methyl isocyanate.

Time scaling was performed using the equation $C^n \times t = k$, with default values of n =1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations. Because of the uncertainties associated with extrapolating a 4-h point of departure to a 10-min value, the 30-min AEGL-3 was adopted as the 10-min value. AEGL-3 values for phenyl isocyanate are presented in Table 7-27, and the calculations are presented in Appendix A.

6.6. Summary of AEGLs

6.6.1. AEGL Values and Toxicity End Points

AEGL-1 values are not recommended for phenyl isocyanate because of insufficient data, and because of the potential for systemic effects to occur at concentrations below those associated with irritation.

Although data on AEGL-2 end points for phenyl isocyanate were available, calculations using those data would result in AEGL-2 values very close to AEGL-3 values. Therefore, AEGL-2 values were derived from the AEGL-3 values for phenyl isocyanate by dividing them by 3 to provide adequate protection. The $BMCL_{05}$ calculated using data from a 4-h lethality study (Bayer AG 1991a) was used as the point of departure for AEGL-3 values for phenyl isocyanate.

AEGL values for phenyl isocyanate are presented in Table 7-28.

6.6.2. Other Exposure Criteria

Only two exposure guidelines for phenyl isocyanate were found. The Swedish Work Environment Authority (SWEA 2005) has a level limit value (occupational limit for one working day) of 0.005 ppm and a 5-min ceiling value (occupational limit for a 5-min period) of 0.01 ppm.

TABLE 7-27 AEGL-3 Values for Phenyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.036 ppm (0.18g	0.036 ppm (0.18 mg/m^3)	0.029 ppm (0.14 mg/m^3)	0.018 ppm (0.088 mg/m^3)	0.0091 ppm (0.044 mg/m^3)

TABLE 7-28 AEGL Values for Phenyl Isocyanate[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[b] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.012 ppm (0.058 mg/m^3)	0.012 ppm (0.058 mg/m^3)	0.0096 ppm (0.047 mg/m^3)	0.0061 ppm (0.030 mg/m^3)	0.0030 ppm (0.015 mg/m^3)
AEGL-3 (lethal)	0.036 ppm (0.18 mg/m^3)	0.036 ppm (0.18 mg/m^3)	0.029 ppm (0.14 mg/m^3)	0.018 ppm (0.088 mg/m^3)	0.0091 ppm (0.044 mg/m^3)

[a]When more than one of the monoisocyanates is detected at a scene, the lowest AEGL should be applied to the sum total concentration of all detected monoisocyanates because of a presumed common mode of action. Phenyl isocyanate has shown dermal sensitizing effects. Its respiratory sensitizing potential is unknown. Individuals who have a strong reaction might not be protected within the definition of effects for each level.

[b]NR, not recommended. On the basis of toxicity data on methyl isocyanate, it is plausible that exposure to phenyl isocyanate may be associated with systemic toxicity at concentrations below those associated with irritation. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR SELECTED MONOISOCYANATES

Ethyl Isocyanate

Derivation of AEGL-1 Values

AEGL-1 values were not derived for ethyl isocyanate because of insufficient data. The available data suggest that ethyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for ethyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

The toxicologic database on ethyl isocyanate was inadequate to derive AEGL-2 values. AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate.

Calculations:

10-min AEGL-2:	0.40 ppm ÷ 2 = 0.20 ppm
30-min AEGL-2:	0.13 ppm ÷ 2 = 0.065 ppm
1-h AEGL-2:	0.067 ppm ÷ 2 = 0.034 ppm
4-h AEGL-2:	0.017ppm ÷ 2 = 0.0085 ppm
8-h AEGL-2:	0.008 ppm ÷ 2 = 0.0040 ppm

Derivation of AEGL-3 Values

The toxicologic database on ethyl isocyanate was inadequate to derive AEGL-3 values. As discussed in Section 2.3 (Structure-Activity Relationships), ethyl isocyanate and the three other monoisocyanates considered in this chapter

are structurally similar to and exert toxic effects comparable to methyl isocyanate. AEGL-3 values were determined by using the AEGL-3 values established for methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate. A comparison of the available lethality data on the two chemicals suggests that this approach results in sufficiently protective AEGL values. When groups of three rats were exposed to ethyl isocyanate for 6 h, all rats survived at 27 ppm and no rats survived at 82 ppm. For comparison, the 6-h LC_{50} for methyl isocyanate in rats (6/sex) was 6.1 ppm (NRC 2003).

Calculations:

10-min AEGL-3: 1.2 ppm ÷ 2 = 0.60 ppm

30-min AEGL-3: 0.40 ppm ÷ 2 = 0.20 ppm

1-h AEGL-3: 0.20 ppm ÷ 2 = 0.10 ppm

4-h AEGL-3: 0.050 ppm ÷ 2 = 0.025 ppm

8-h AEGL-3: 0.025 ppm ÷ 2 = 0.013 ppm

Cyclohexyl Isocyanate

Derivation of AEGL-1 Values

AEGL-1 values were not derived for cyclohexyl isocyanate because of insufficient data. The available data suggest that cyclohexyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for cyclohexyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

The toxicologic database on cyclohexyl isocyanate was inadequate to derive AEGL-2 values. AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate.

Calculations:

10-min AEGL-2: 0.40 ppm ÷ 2 = 0.20 ppm

30-min AEGL-2: 0.13 ppm ÷ 2 = 0.065 ppm

1-h AEGL-2: 0.067 ppm ÷ 2 = 0.034 ppm

4-h AEGL-2: 0.017ppm ÷ 2 = 0.0085 ppm

8-h AEGL-2: 0.008 ppm ÷ 2 = 0.0040 ppm

Derivation of AEGL-3 Values

The toxicologic database on cyclohexyl isocyanate was inadequate to derive AEGL-3 values. AEGL-3 values were determined by using the AEGL-3 values established for methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2 to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate. A comparison of the available lethality data on the two chemicals suggests that this approach results in sufficiently protective AEGL values. When three rats were exposed to cyclohexyl isocyanate at 18 ppm for 6 h, one died on day 7 post-exposure and the other two were killed on day 8, presumably because of moribund condition. For comparison, the 6-h LC_{50} for methyl isocyanate in rats is 6.1 ppm (NRC 2003).

Calculations:

10-min AEGL-3: 1.2 ppm ÷ 2 = 0.60 ppm

30-min AEGL-3: 0.40 ppm ÷ 2 = 0.20 ppm

1-h AEGL-3: 0.20 ppm ÷ 2 = 0.10 ppm

4-h AEGL-3: 0.050 ppm ÷ 2 = 0.025 ppm

8-h AEGL-3: 0.025 ppm ÷ 2 = 0.013 ppm

_n_-Butyl Isocyanate

Derivation of AEGL-1 Values

AEGL-1 values were not derived for *n*-butyl isocyanate because of insufficient data. The available data suggest that *n*-butyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1

values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for *n*-butyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

The toxicologic database on *n*-butyl isocyanate was inadequate to derive AEGL-2 values. In particular, the 4-h study by Pauluhn et al. (1990) lacked data on the incidence and severity of histopathologic findings. AEGL-2 values were determined by dividing the AEGL-3 values for *n*-butyl isocyanate by 3 (NRC 2001). This approach is justified by the steep concentration-response curve observed in mortality studies; no rats died after a 1-h exposure at 39 ppm, and 70% (7/10) died at 130 ppm (Bayer AG 1978).

Calculations:

10-min AEGL-2:	0.31 ppm ÷ 3 = 0.10 ppm
30-min AEGL-2:	0.31 ppm ÷ 3 = 0.10 ppm
1-h AEGL-2:	0.25 ppm ÷ 3 = 0.083 ppm
4-h AEGL-2:	0.16 ppm ÷ 3 = 0.053 ppm
8-h AEGL-2:	0.078 ppm ÷ 3 = 0.026 ppm

Derivation of AEGL-3 Values

Key study:	Pauluhn, J., A. Eben, and G. Kimmerle. 1990. Functional, biochemical, and histological evidence of airway obstruction in rats following a four-hour acute inhalation exposure to *n*-butyl isocyanate. Exp. Pathol. 40:197-203.
Critical effect:	Highest nonlethal concentration (14 ppm) in a 4-h rat study. Study tested more animals and used a more reliable analytic method (HPLC analysis) to measure concentrations of *n*-butyl isocyanate than other studies.

Time scaling:	The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence data to determine an empirical value of n, default values of n = 1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations were used. The 10-min AEGL-3 value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 4-h point of departure to a 10-min value (NRC 2001). $(14 \text{ ppm})^1 \times 4 \text{ h} = 56 \text{ ppm-h}$ $(14 \text{ ppm})^3 \times 4 \text{ h} = 10{,}976 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; 6-h LC_{50}s for the related compound methyl isocyanate differed about two-fold between rats, mice, and guinea pigs (see Section 2.4). A factor of 3 is also consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003). 10 for intraspecies variability; this factor is consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).
Modifying factor:	3 to account for potential developmental toxicity of *n*-butyl isocyanate, on the basis of data on methyl isocyanate.
Calculations:	
10-min AEGL-3:	0.31 ppm (set equal to the 30-min AEGL-3)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 10{,}976 \text{ ppm-h}$ $C = 28 \text{ ppm}$ $28 \text{ ppm} \div 90 = 0.31 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 10{,}976 \text{ ppm-h}$ $C = 22 \text{ ppm}$ $22 \text{ ppm} \div 90 = 0.25 \text{ ppm}$

4-h AEGL-3: 14 ppm ÷ 90 = 0.16 ppm

8-h AEGL-3: $C^1 \times 8$ h = 56 ppm-h
C = 7 ppm
7 ppm ÷ 90 = 0.078 ppm

Phenyl Isocyanate

Derivation of AEGL-1 Values

AEGL-1 values were not derived for phenyl isocyanate because of insufficient data. The available data suggest that phenyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for phenyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

Data on phenyl isocyanate were not used to derive AEGL-2 value because they would lead to 4- and 8-h AEGL-2 values that are very similar to AEGL-3 values (see below). Therefore, AEGL-3 values for phenyl isocyanate were divided by 3 to derive AEGL-2 values. This approach is justified by the steep concentration-response curve observed in mortality studies; in a 4-h study, no rats (0/10) died after exposure at 3.1 ppm and 70% (7/10) died after exposure at 5.7 ppm (Bayer AG 1991a).

If AEGL-2 values were to be calculated from animal data for phenyl isocyanate, the point of departure would be a no-effect level of 0.8 ppm identified in a repeated exposure study (Pauluhn et al. 1995). An uncertainty factor of 3 for interspecies differences and a factor of 10 intraspecies variability would be applied. Time scaling would be performed using the equation $C^n \times t = k$, with default values of n = 3 for extrapolating to shorter durations and n =1 for extrapolating to longer durations. This approach would lead to 4- and 8-h AEGL-2 values of 0.01 and 0.007 ppm, respectively. These values are very close to the AEGL-3 values of 0.018 and 0.009 ppm for this compound, so this approach was not used to derive AEGL values.

Calculations:

10-min AEGL-2: 0.036 ppm ÷ 3 = 0.012 ppm

30-min AEGL-2:	0.036 ppm ÷ 3 = 0.012 ppm
1-h AEGL-2:	0.029 ppm ÷ 3 = 0.0096 ppm
4-h AEGL-2:	0.018 ppm ÷ 3 = 0.0061 ppm
8-h AEGL-2:	0.0091 ppm ÷ 3 = 0.0030 ppm

Derivation of AEGL-3 Values

Key study:	Bayer, AG. 1991a. Phenyl isocyanate; Untersuchungen zur akuten inhalationstoxizität an der Ratte. Report No.. 20354. Study No. T7037386, Bayer AG Institut für Toxikologie, Wuppertal-Elberfeld, Germany.
Critical effect:	Estimated lethality threshold in rats (4-h $BMCL_{05}$ of 1.64 ppm)
Time scaling:	The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence data to determine an empirical value of n, default values of n = 1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations were used. The 10-min AEGL-3 value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 4-h point of departure to a 10-min value (NRC 2001). $(1.64 \text{ ppm})^1 \times 4 \text{ h} = 6.56 \text{ ppm-h}$ $(1.64 \text{ ppm})^3 \times 4 \text{ h} = 17.644 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; 6-h LC_{50}s for the related compound methyl isocyanate differed about two-fold between rats, mice, and guinea pigs; see Section 2.4). A factor of 3 is also consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).

	10 for intraspecies variability; this factor is consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).
Modifying factor:	3 to account for potential developmental toxicity of phenyl isocyanate, on the basis of data on methyl isocyanate.
Calculations:	
10-min AEGL-3:	Set equal to the 30-min AEGL-3 of 0.036 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 17.644 ppm-h C = 3.2 ppm 3.2 ppm ÷ 90 = 0.036 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 17.644 ppm-h C = 2.6 ppm 2.6 ppm ÷ 90 = 0.029 ppm
4-h AEGL-3:	C × 4 h = 6.56 ppm-h C = 1.64 ppm 1.64 ppm ÷ 90 = 0.018 ppm
8-h AEGL-3:	C × 8 h = 6.56 ppm-h C = 0.82 ppm 0.82 ppm ÷ 90 = 0.0091 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR SELECTED MONOISOCYANATES

Derivation Summary for Ethyl Isocyanate

AEGL-1 Values for Ethyl Isocyanate

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

Data adequacy: AEGL-1 values were not derived for ethyl isocyanate because of inadequate data. The available data suggest that ethyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for ethyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

AEGL-2 Values for Ethyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.58 mg/m^3)	0.065 ppm (0.19 mg/m^3)	0.034 ppm (0.099 mg/m^3)	0.0085 ppm (0.025 mg/m^3)	0.0040 ppm (0.012 mg/m^3)

Modifying factor: 2, to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate.

Data adequacy: The toxicologic database on ethyl isocyanate was inadequate to derive AEGL-2 values. AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2.

AEGL-3 Values for Ethyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.60 ppm (1.7 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.10 ppm (0.29 mg/m^3)	0.025 ppm (0.073 mg/m^3)	0.013 ppm (0.038 mg/m^3)

Modifying factor: 2, to account for the possibility that ethyl isocyanate might be more toxic than methyl isocyanate.

Data adequacy: The toxicologic database for ethyl isocyanate was inadequate to derive AEGL-3 values. As discussed in Section 2.3 (Structure-Activity Relationships), ethyl isocyanate and the other three monoisocyanates considered in this chapter are structurally similar to and exert toxic effects comparable to methyl isocyanate.

A comparison of the available lethality data on the chemicals suggests that use of methyl isocyanate as a surrogate for ethyl isocyanate and applying a modifying factor of 2 to account for potentially higher toxicity results in sufficiently protective AEGL values. When groups of three rats were exposed to ethyl isocyanate for 6 h, all rats survived at 27 ppm and no rats survived at 82 ppm. For comparison, the 6-h LC_{50} for methyl isocyanate in rats (6/sex) was 6.1 ppm (NRC 2003).

Derivation Summary for Cyclohexyl Isocyanate

AEGL-1 Values for Cyclohexyl Isocyanate

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

Data adequacy: AEGL-1 values were not derived for cyclohexyl isocyanate because of inadequate data. The available data suggest that cyclohexyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for cyclohexyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

AEGL-2 Values for Cyclohexyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.20 ppm (1.0 mg/m^3)	0.065 ppm (0.33 mg/m^3)	0.034 ppm (0.17 mg/m^3)	0.0085 ppm (0.043 mg/m^3)	0.0040 ppm (0.020 mg/m^3)

Modifying factor: 2, to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate.

Data adequacy: The toxicologic database for cyclohexyl isocyanate was inadequate to derive AEGL-2 values. AEGL-2 values were determined by using the AEGL-2 values established for the related compound methyl isocyanate (NRC 2003) and dividing them by a modifying factor of 2.

AEGL-3 Values for Cyclohexyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.60 ppm (3.1 mg/m^3)	0.20 ppm (1.0 mg/m^3)	0.10 ppm (0.51 mg/m^3)	0.025 ppm (0.13 mg/m^3)	0.013 ppm (0.066 mg/m^3)

Modifying factor: 2, to account for the possibility that cyclohexyl isocyanate might be more toxic than methyl isocyanate.

(Continued)

AEGL-3 Values for Cyclohexyl Isocyanate Continued

Data adequacy: The toxicologic database for cyclohexyl isocyanate was inadequate to derive AEGL-3 values. AEGL-3 values were determined by using the AEGL-3 values established for the related compound methyl isocyanate and dividing them by a modifying factor of 2. A comparison of the available lethality data on the two chemicals suggests that this approach results in sufficiently protective AEGL values. When three rats were exposed to cyclohexyl isocyanate at 18 ppm for 6 h, one died on day 7 post-exposure and the other two were killed on day 8, presumably because of moribund condition. For comparison, the 6-h LC_{50} for methyl isocyanate in rats is 6.1 ppm (NRC 2003).

Derivation Summary for *n*-Butyl Isocyanate

AEGL-1 Values for *n*-Butyl Isocyanate

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

Data adequacy: AEGL-1 values were not derived for *n*-butyl isocyanate because of inadequate data. The available data suggest that *n*-butyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for *n*-butyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

AEGL-2 Values for *n*-Butyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.10 ppm (0.41 mg/m^3)	0.10 ppm (0.41 mg/m^3)	0.083 ppm (0.34 mg/m^3)	0.053 ppm (0.21 mg/m^3)	0.026 ppm (0.11 mg/m^3)

Data adequacy: The toxicologic database on *n*-butyl isocyanate was inadequate to derive AEGL-2 values. In particular, the 4-h study by Pauluhn et al. (1990) lacked data on the incidence and severity of histopathologic findings. In the absence of adequate data, the AEGL-3 values for *n*-butyl isocyanate were divided by 3 to derive AEGL-2 values (NRC 2001). This approach is justified by the steep concentration-response curve observed in mortality studies; no rats died after a 1-h exposure at 39 ppm, and 70% (7/10) died at 130 ppm (Bayer AG 1978).

AEGL-3 Values for *n*-Butyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.31 ppm (1.3 mg/m^3)	0.31 ppm (1.3 mg/m^3)	0.25 ppm (1.0 mg/m^3)	0.16 ppm (0.6 mg/m^3)	0.078 ppm (0.32 mg/m^3)

Reference: Pauluhn, J., A. Eben, and G. Kimmerle. 1990. Functional, biochemical, and histological evidence of airway obstruction in rats following a four-hour acute inhalation exposure to *n*-butyl isocyanate. Exp. Pathol. 40:197-203.

Test species/Strain/Sex/Number: Rat, Wistar, males, 20/group

Exposure route/Concentrations/Durations: Inhalation; 0, 8, 25, 50 mg/m^3 (0, 1.9, 5.9, 14 ppm) for 4 h

Effects: No deaths (assessed up to 28 days post-exposure)

End point/Concentration/Rationale: Estimated lethality threshold of 14 ppm (4-h nonlethal concentration). Study tested more animals, had a 28-day follow-up period, and used a more reliable analytic method (HPLC analysis) to measure concentrations of *n*-butyl isocyanate than other studies.

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3, because 6-h LC_{50}s for the related compound methyl isocyanate differed about two-fold between rats, mice, and guinea pigs (see Section 2.4). A factor of 3 is also consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).
Intraspecies: 10, is consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).

Modifying factor: 3, to account for potential developmental toxicity of *n*-butyl isocyanate on the basis of data on methyl isocyanate.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; default values of n = 1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations. The 10-min AEGL-3 value was set equivalent to the 30-min value because of uncertainties associated with extrapolating a 4-h point of departure to a 10-min value (NRC 2001).

Data adequacy: Although lethal and nonlethal toxicity data are available for only one species, data on the related compound methyl isocyanate provide support for the AEGL derivations.

Derivation Summary for Phenyl Isocyanate

AEGL-1 Values for Phenyl Isocyanate

10 min	30 min	1 h	4 h	8 hr
NR	NR	NR	NR	NR

Data adequacy: AEGL-1 values were not derived for phenyl isocyanate because of inadequate data. The available data suggest that phenyl isocyanate and the three other selected monoisocyanates exert toxic effects, including delayed lethality, that are similar to those induced by methyl isocyanate (see Section 2.3). AEGL-1 values were

(Continued)

AEGL-1 Values for Phenyl Isocyanate Continued

not derived for methyl isocyanate because it has poor warning properties, and because systemic toxicity is possible at concentrations lower than those associated with AEGL-1 effects (NRC 2003). On the basis of similarities between the selected monoisocyanates and methyl isocyanate, AEGL-1 values were not derived for phenyl isocyanate. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 values are without effect.

AEGL-2 Values for Phenyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.012 ppm (0.058 mg/m^3)	0.012 ppm (0.058 mg/m^3)	0.0096 ppm (0.047 mg/m^3)	0.0061 ppm (0.030 mg/m^3)	0.0030 ppm (0.015 mg/m^3)

Data adequacy: AEGL-3 values for phenyl isocyanate were divided by 3 to derive AEGL-2 values (NRC 2001). This approach is justified by the steep concentration-response relationship; in a 4-h lethality study in rats, there was no mortality (0/10) at 3.1 ppm and 70% (7/10) mortality at 5.7 ppm (Bayer AG 1991a). If AEGL-2 values were to be calculated from animal data on phenyl isocyanate, the point of departure would be a no-effect level of 0.8 ppm identified in a repeated exposure study (Pauluhn et al. 1995). An uncertainty factor of 3 for interspecies differences and a factor of 10 intraspecies variability would be applied. Time scaling would be performed using the equation $C^n \times t = k$, with default values of n = 3 for extrapolating to shorter durations and n =1 for extrapolating to longer durations. This approach would lead to 4- and 8-h AEGL-2 values of 0.01 and 0.007 ppm, respectively. These values are very close to the AEGL-3 values of 0.018 and 0.009 ppm for this compound, so this approach was not used to derive AEGL values.

AEGL-3 Values for Phenyl Isocyanate

10 min	30 min	1 h	4 h	8 h
0.036 ppm (0.18 mg/m^3)	0.036 ppm (0.18 mg/m^3)	0.029 ppm (0.14 mg/m^3)	0.018 ppm (0.088 mg/m^3)	0.0091 ppm (0.044 mg/m^3)

Reference: Bayer, AG. 1991a. Phenyl isocyanate; Untersuchungen zur akuten Inahlationstoxizität an der Ratte. Bercht- Nr. 20354. Studien-Nr. T7037386, Bayer AG Institut für Toxikologie.

Test species/Strain/Sex/Number: Rat, Wistar, 4 males and 4 females per group

Exposure route/Concentrations/Durations: Inhalation; 0, 2.1, 10.4, 20.8, 31.3, 64.6, 82.9, or 150.2 mg/m^3 (0, 0.4, 2.2, 4.4, 6.6, 7.7, 17.4, and 31.3 ppm) for 4 h

Effects: Lethality

End point/Concentration/Rationale: Estimated lethality threshold (4-h $BMCL_{05}$ 1.64 ppm)

Uncertainty factors/Rationale:
Total uncertainty factor adjustment: 30

Interspecies: 3, because 6-h LC_{50}s for the related compound methyl isocyanate differed about two-fold between rats, mice, and guinea pigs (see Section 2.4). A factor of 3 is also consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003). Intraspecies: 10, is consistent with the one used for deriving AEGL-3 values for methyl isocyanate (NRC 2003).
Modifying factor: 3, to account for potential developmental toxicity of phenyl isocyanate on the basis of data on methyl isocyanate.
Animal-to-human dosimetric adjustment: Not applicable
Time scaling: $C^n \times t = k$; default values of n = 1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations. The 10-min AEGL-3 value was set equivalent to the 30-min value because of uncertainties associated with extrapolating a 4-h point of departure to a 10-min value (NRC 2001).
Data adequacy: Although lethal and nonlethal toxicity data are available for only one species, data on the related compound methyl isocyanate provide support for the AEGL values.

APPENDIX C

CATEGORY PLOTS FOR SELECTED MONOISOCYANATES

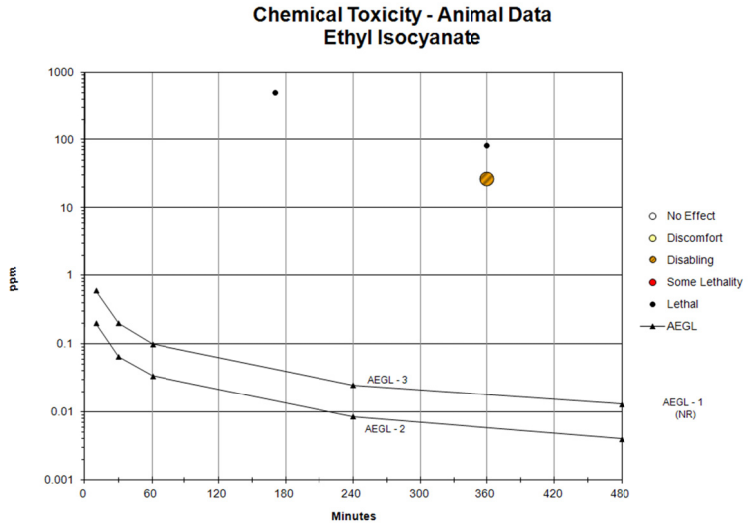

FIGURE C-1 Category plot of toxicity data and AEGL values for ethyl isocyanate.

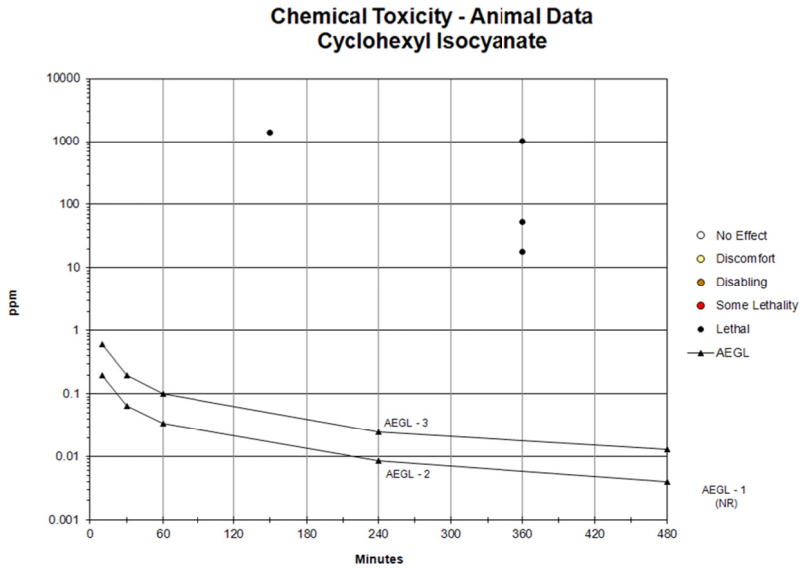

FIGURE C-2 Category plot of toxicity data and AEGL values for cyclohexyl isocyanate.

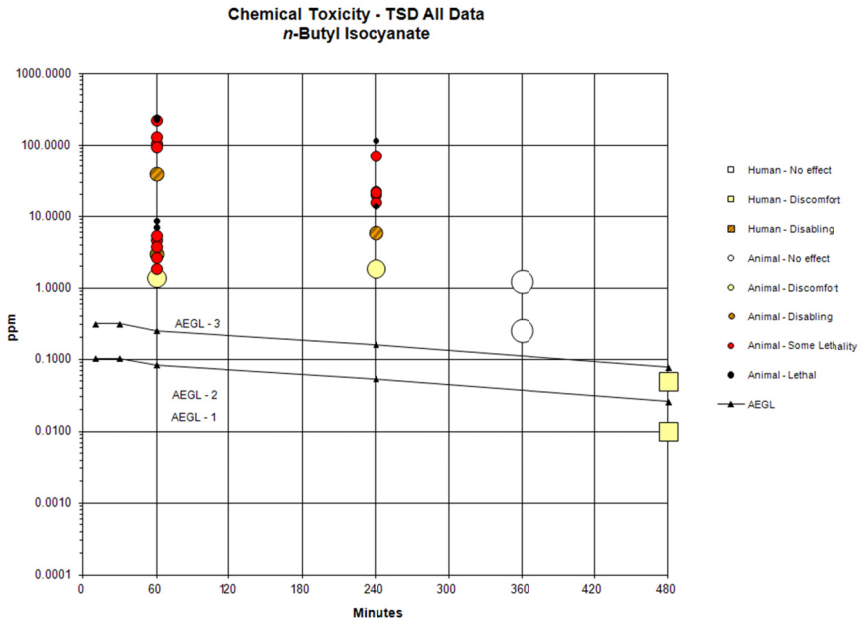

FIGURE C-3 Category plot of toxicity data and AEGL values for *n*-butyl isocyanate.

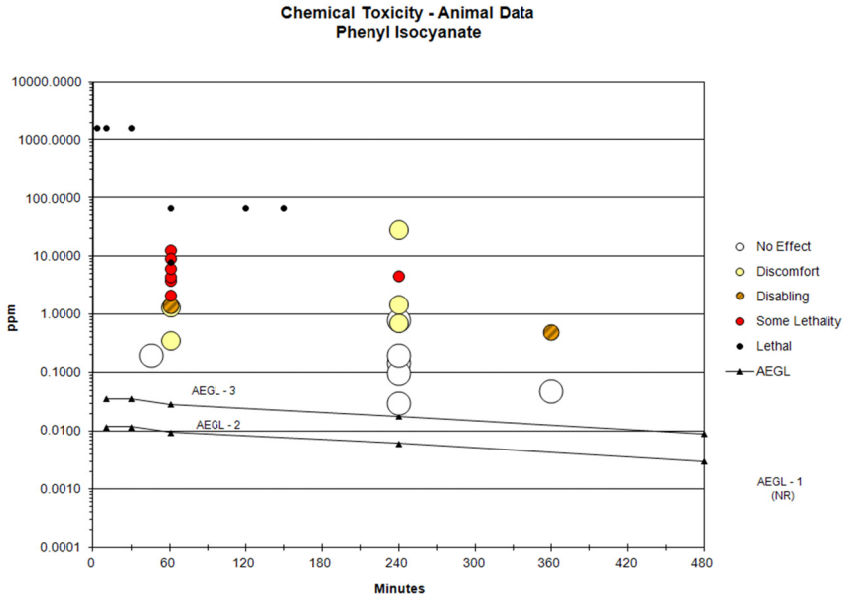

FIGURE C-4 Category plot of toxicity data and AEGL values for phenyl isocyanate.

TABLE C-1 Data Used in Category Plot for Ethyl Isocyanate

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.20	10	AEGL	
AEGL-2				0.065	30	AEGL	
AEGL-2				0.034	60	AEGL	
AEGL-2				0.0085	240	AEGL	
AEGL-2				0.0040	480	AEGL	
AEGL-3				0.60	10	AEGL	
AEGL-3				0.20	30	AEGL	
AEGL-3				0.10	60	AEGL	
AEGL-3				0.025	240	AEGL	
AEGL-3				0.013	480	AEGL	
Eastman Kodak 1964	Rat		1	27	360	2	
	Rat		1	82	360	3	Mortality (3/3)
	Rat		1	506	170	3	Mortality (3/3)

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

TABLE C-2 Data Used in Category Plot for Cyclohexyl Isocyanate

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.20	10	AEGL	
AEGL-2				0.065	30	AEGL	
AEGL-2				0.034	60	AEGL	
AEGL-2				0.0085	240	AEGL	
AEGL-2				0.0040	480	AEGL	
AEGL-3				0.60	10	AEGL	
AEGL-3				0.20	30	AEGL	
AEGL-3				0.10	60	AEGL	
AEGL-3				0.025	240	AEGL	
AEGL-3				0.013	480	AEGL	
Eastman Kodak 1990, 1992	Rat		1	17.79	360	3	Mortality (3/3), irritation, lacrimation, dypsnea, inflammation in lungs, congestion of kidney and liver.

(Continued)

TABLE C-2 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
	Rat		1	53.2	360	3	Mortality (3/3, two during exposure, one on day 12), irritation, lacrimation, dypsnea, inflammation in lungs, congestion of kidney and liver.
	Rat		1	1,017	360	3	Mortality (3/3, after 4 h), irritation, lacrimation, dypsnea, inflammation in lungs, congestion of kidney and liver, salivation, gasping.
Younger Laboratories 1974	Rat		1	1,401	150	3	Mortality (6/6), no other details
Crawford and Anderson 1974	Rat		1	Saturated	120	3	Mortality (8/8), no other details
Bayer AG 1980a	Rat		1	Saturated	3	2	No deaths, respiratory problems, enlarged lungs with red spots, fluid, lobulated liver.
	Rat		1	Saturated	10	3	Mortality (10/10, within 11 days), respiratory problems, enlarged lungs with red spots, fluid, lobulated liver.
	Rat		1	Saturated	60	3	Mortality (10/10, during exposure), respiratory problems, enlarged lungs with red spots, fluid, lobulated liver.

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

TABLE C-3 Data Used in Category Plot for *n*-Butyl Isocyanate

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.10	10	AEGL	
AEGL-2				0.10	30	AEGL	
AEGL-2				0.083	60	AEGL	
AEGL-2				0.053	240	AEGL	
AEGL-2				0.026	480	AEGL	
AEGL-3				0.31	10	AEGL	
AEGL-3				0.31	30	AEGL	
AEGL-3				0.25	60	AEGL	
AEGL-3				0.16	240	AEGL	
AEGL-3				0.078	480	AEGL	
Haskell 1989 (industrial hygiene report)	Human		1	0.01	480	1	
Haskell 1989 (industrial hygiene report)	Human		1	0.05	480	1	

(Continued)

TABLE C-3 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
IRDC 1965	Rat	Male	1	1.4	60	1	
IRDC 1965	Rat	Male	1	1.9	60	SL	
IRDC 1965	Rat	Male	1	2.7	60	SL	
IRDC 1965	Rat	Male	1	3.0	60	2	
IRDC 1965	Rat	Male	1	4.7	60	SL	
IRDC 1965	Rat	Male	1	5.4	60	SL	
IRDC 1965	Rat	Male	1	7.0	60	3	
IRDC 1965	Rat	Male	1	7.1	60	3	
IRDC 1965	Rat	Male	1	8.7	60	3	
Bayer AG 1978	Rat	Both	1	106	60	SL	LC_{50}
Bayer AG 1978	Rat	Male	1	22.5	240	SL	LC_{50}
Bayer AG 1978	Rat	Male	1	20.0	240	SL	LC_{50}
Pauluhn and Eben 1991	Rat	Male	5	0.25	360	0	Multiple exposures; no clinical signs after 6 h/d for 5 d.
Pauluhn and Eben, 1991	Rat	Male	5	1.3	360	0	Multiple exposure study; no clinical signs after 6 h/d for 5 d.
Haskell 1968	Rat	Male	1	15.6	240	SL	LC_{50}
IRDC 1965	Rat	Male	1	3.8	60	SL	LC_{50}
Pauluhn et al. 1990	Rat	Male	1	1.9	240	1	Transient clinical signs (hypothermia, bradypnea, mucous membrane irritation).

Pauluhn et al. 1990	Rat	Male	1	14.0	240	3	Pulmonary function changes even at 4 wk post-exposure, pathologic findings in lungs.
Pauluhn et al. 1990	Rat	Male	1	5.9	240	2	Notable pulmonary effects that resolved within 1 wk.
Bayer AG 1978	Rat	Both	1	39	60	2	No mortality
Bayer AG 1978	Rat	Both	1	130	60	SL	Mortality (7/10)
Bayer AG 1978	Rat	Both	1	245	60	3	Mortality (10/10)
Bayer AG 1978	Rat	Both	1	94	60	SL	Mortality (3/20)
Bayer AG 1978	Rat	Both	1	222	60	SL	Mortality (19/20)
Bayer AG 1978	Rat	Both	1	233	60	3	Mortality (20/20)
Bayer AG 1978	Rat	Both	1	22	240	SL	Mortality (7/10)
Bayer AG 1978	Rat	Both	1	70	240	SL	Mortality (9/10)
Bayer AG 1978	Rat	Female	1	116	240	3	Mortality (5/5)

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

TABLE C-4 Data Used in Category Plot for Phenyl Isocyanate

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.012	10	AEGL	
AEGL-2				0.012	30	AEGL	
AEGL-2				0.0096	60	AEGL	
AEGL-2				0.0061	240	AEGL	
AEGL-2				0.0030	480	AEGL	
AEGL-3				0.036	10	AEGL	
AEGL-3				0.036	30	AEGL	
AEGL-3				0.029	60	AEGL	
AEGL-3				0.018	240	AEGL	
AEGL-3				0.0091	480	AEGL	
SA 1954	Rat		1	67	60	3	
SA 1954	Rat		1	67	120	3	
SA 1954	Rat		1	67	150	3	
Mobay 1978	Rat	Both	1	12.6	60	SL	LC_{50}
ICI 1980	Rat	Both	1	3.9	60	SL	LC_{50}

ICI 1977, Mobay 1978	Rat	Both	1	0.358	60	1	No clinical signs, minor histopathologic findings.
ICI 1977, Mobay 1978	Rat	Both	1	1.325	60	1	Minor clinical signs, pulmonary damage at necropsy.
ICI 1977; Mobay 1978	Rat	Both	1	1.45	60	2	Minor clinical signs, notable histopathologic effects.
ICI 1977, Mobay 1978	Rat	Both	1	2.167	60	SL	2/4 males, 2/4 females dead 5-12 d post-exposure.
ICI 1977, Mobay 1978	Rat	Both	1	4.368	60	SL	1/4 males, 3/4 females dead at 4-8 d post-exposure.
ICI 1977, Mobay 1978	Rat	Both	1	6.08	60	SL	2/4 males, 2/4 females dead at 8-13 d post-exposure.
ICI 1977, Mobay 1978	Rat	Both	1	7.942	60	3	100% lethality at 7-12 d post-exposure.
ICI 1977, Mobay 1978	Rat	Both	1	9.187	60	SL	4/4 males, 3/4 females dead at 1-14 d post-exposure.
ICI 1980	Rat	Both	11	0.05	360	0	No clinical signs, no histopathologic findings.
ICI 1980	Rat	Both	11	0.5	360	2	Respiratory distress on first day of exposure.
Bayer AG 1981	Rat	Both	1	1,600	3	3	Dead at 3-11 d.
Bayer AG 1981	Rat	Both	1	1,600	10	3	Dead at 3-24 h post-exposure.
Bayer AG 1981	Rat	Both	1	1,600	30	3	Dead at 32-59 min post-exposure.
SA 1954	Rat		1	29	240	1	No deaths but effects uncertain.

(Continued)

TABLE C-4 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
Bayer AG 1991b	Rat		5	0.03	240	0	No clinical signs after multiple exposures.
Bayer AG 1991b	Rat		5	0.10	240	0	No clinical signs after multiple exposures.
Bayer AG 1991b	Rat		5	0.70	240	1	Serous nasal discharge after 5 d, no findings for BAL and LDH analysis.
Pauluhn et al. 1995	Rat	Male	1	0.20	45	0	Threshold for respiratory tract irritation.
Pauluhn et al. 1995	Rat	Male	10	0.20	240	0	No clinical signs, no histopathologic findings.
Pauluhn et al. 1995	Rat	Male	10	0.80	240	0	No clinical signs, no histopathologic findings.
Pauluhn et al. 1995	Rat	Male	10	1.50	240	1	Signs of irritation, histopathologic findings after full exposure duration.
Bayer AG 1991a	Rat	Both	1	0.14	240	0	
Bayer AG 1991a	Rat	Both	1	1.1	240	0	
Bayer AG 1991a	Rat	Both	1	2.4	240	SL	Mortality (1/10)
Bayer AG 1991a	Rat	Both	1	3.1	240	0	
Bayer AG 1991a	Rat	Both	1	5.7	240	SL	Mortality (7/10)
Bayer AG 1991a	Rat	Both	1	9.7	240	3	Mortality (10/10)
Bayer AG 1991a	Rat	Both	1	18	240	3	Mortality (10/10)

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

APPENDIX D

BENCHMARK DOSE MODELING FOR PHENYL ISOCYANATE

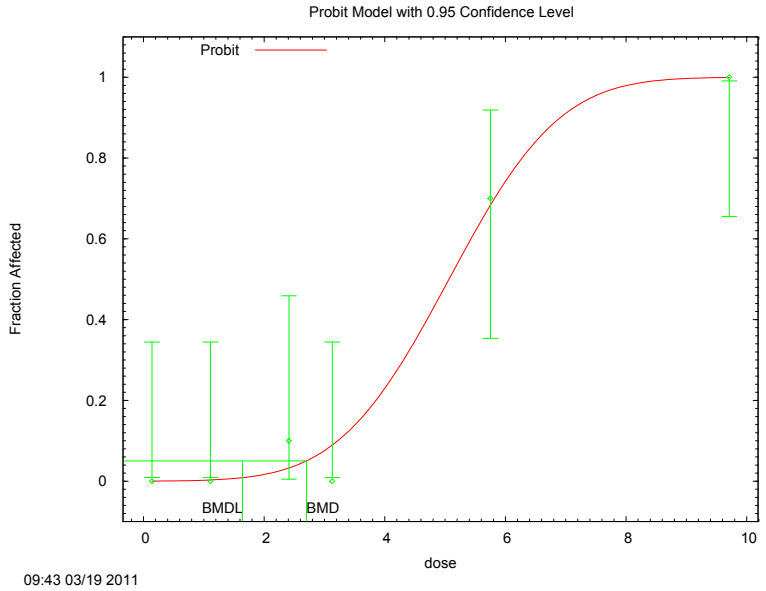

FIGURE D-1 Probit model (with 0.95 confidence level) of phenyl isocyanate data from 4-h lethality study (Bayer AG 1991a).

Probit Model. (Version: 3.2; Date: 10/28/2009)
Input Data File: C:\Documents and Settings\BayerAG1991.dax.(d)
Gnuplot Plotting File: C:\Documents and Settings\ BayerAG1991.plt
Sat Mar 19 10:43:49 2011

BMDS_Model_Run

The form of the probability function is:

P[response] = CumNorm(Intercept+Slope*Dose),

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = Col2
Independent variable = Col1
Slope parameter is not restricted

Total number of observations = 6
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

Default Initial (and Specified) Parameter Values
Background = 0 Specified
Intercept = -2.56468
Slope = 0.462909

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.94
Slope	-0.94	1

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

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Confidence Limit	Upper Confidence Limit
Intercept	-3.51993	0.86272	-5.21083	-1.82903
Slope	0.69465	0.185701	0.330683	1.05862

Analysis of Deviance Table

Model	Log (likelihood)	No. of Parameters	Deviance Test	DF	P-value
Full model	-9.35947	6			
Fitted model	-10.8144	2	2.90976	4	0.573
Reduced model	-36.6519	1	54.5848	5	<0.0001

AIC: 25.6287

Goodness of Fit

				Scaled	
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.1400	0.0003	0.003	0.000	10	-0.056
1.1100	0.0030	0.030	0.000	10	-0.173
2.4100	0.0325	0.325	1.000	10	1.205
3.1300	0.0892	0.892	0.000	10	-0.990
5.7500	0.6824	6.824	7.000	10	0.120
9.7100	0.9994	9.994	10.000	10	0.079

Chi-square = 2.49; DF = 4; P-value = 0.6472

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 2.70217
$BMCL_{05}$ = 1.64064
BMC_{01}

Probit Model. (Version: 3.2; Date: 10/28/2009)
Input Data File: C:\Documents and Settings\BayerAG1991a.dax(d)
Gnuplot Plotting File: C:\Documents and Settings\ BayerAG1991a.plt
Sat Mar 19 10:44:31 2011

BMDS_Model_Run

The form of the probability function is:

P[response] = CumNorm(Intercept+Slope*Dose),

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = Col2
Independent variable = Col1
Slope parameter is not restricted

Total number of observations = 6
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

Default Initial (and Specified) Parameter Values
Background = 0 Specified
Intercept = -2.56468
Slope = 0.462909

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.94
Slope	-0.94	1

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

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Standard Error	Lower Confidence Limit	Upper Confidence Limit
Intercept	-3.51993	0.86272	-5.21083	-1.82903
Slope	0.69465	0.185701	0.330683	1.05862

Analysis of Deviance Table

Model	Log (likelihood)	No. of Parameters	Deviance Test	DF	P-value
Full model	-9.35947	6			
Fitted model	-10.8144	2	2.90976	4	0.573
Reduced model	-36.6519	1	54.5848	5	<0.0001

AIC: 25.6287

Goodness of Fit

		Scaled			
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.1400	0.0003	0.003	0.000	10	-0.056
1.1100	0.0030	0.030	0.000	10	-0.173
2.4100	0.0325	0.325	1.000	10	1.205
3.1300	0.0892	0.892	0.000	10	-0.990
5.7500	0.6824	6.824	7.000	10	0.120
9.7100	0.9994	9.994	10.000	10	0.079

Chi-square = 2.49; DF = 4; P-value = 0.6472

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC_{01} = 1.72968
BMCL = 0.591986