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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 15

Committee on Acute Exposure Guideline Levels

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

Contents

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

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

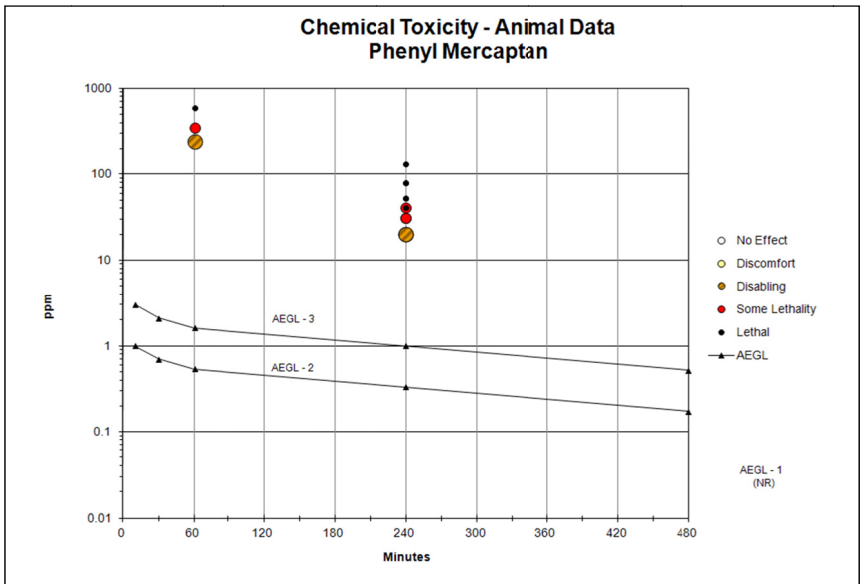

FIGURE C-1 Category plot of toxicity data and AEGL values for phenyl mercaptan. The decimal point is lost on this log-scale plot.

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.