# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 8**

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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# Preface

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

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

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

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

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

reviews the AEGLs for acrolein, carbon monoxide, 1,2-dichloroethene, ethylenimine, fluorine, hydrazine, peracetic acid, propylenimine, and sulfur dioxide for scientific accuracy, completeness, and consistency with the NRC guideline reports.

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

The 10 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 ten committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrolein (fourteenth interim report, 2006), carbon monoxide (ninth, eleventh, thirteenth, and sixteenth interim reports, 2003, 2004, 2005, and 2009, respectively), dichloroethene (third, eleventh, thirteenth, fourteenth, and sixteenth interim reports, 2000, 2004, 2005, 2006, and 2009 respectively), ethylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2004, 2005, and 2006 respectively), fluorine (second, eleventh, and thirteenth interim reports, 2000, 2004, and 2006 respectively), hydrazine (second, tenth, twelfth, and fourteenth interim reports, 2000, 2004, 2005, and 2006 respectively), peracetic acid (fourteenth interim report, 2006), propylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2005, and 2006 respectively), and sulfur dioxide (thirteenth and fourteenth interim reports, 2005 and 2006 respectively): Deepak Bhalla (Wayne State University), Joseph Borzelleca (Virginia Commonwealth University), Charles Feigley (University of South Carolina), David Gaylor (Gaylor & Associates), Sidney Green (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene F. Henderson (Lovelace Respiratory Research Institute), Sam Kacew (University of Ottawa), Nancy Kerkvliet (Oregon State University), Charles R. Reinhardt (DuPont Haskell Laboratory [retired]), Andrew G. Salmon (California Environmental Protection Agency), and Bernard M. Wagner (New York University Medical Center).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Iris A. Camacho, Ernest Falke, Marquea D. King, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, Senior Program Officer for Toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Keegan Sawyer (associate program officer), Ruth Crossgrove (senior editor), Radiah Rose (manager, Editorial Projects), Mirsada Karalic-Loncarevic (manager, Technical Information Center), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

# Contents

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

This report is the eighth 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 in experimental animals. 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 (y) of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

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

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

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

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

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

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 ($1 \times 10^{-4}$), 1 in 100,000 ($1 \times 10^{-5}$), and 1 in 1,000,000 ($1 \times 10^{-6}$) exposed persons are estimated.

## REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared seven reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009). This report is the eighth volume in that series. AEGL documents for acrolein, carbon monoxide, cis-1,2-dichloroethene, trans-1,2-dichloroethene, ethylenimine, fluorine, hydrazine, peracetic acid, propyleneimine, and sulfur dioxide 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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# Roster of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

## Committee Members

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Government of Canada

Lynn Beasley
U.S. Environmental Protection Agency
Washington, DC

Alan Becker
College of Health and Human Services
Missouri State University
Springfield, MO

Robert Benson
U.S. Environmental Protection Agency
Region VIII
Denver, CO

Edward Bernas
AFL-CIO
Homewood, IL

Iris Camacho
U.S. Environmental Protection Agency
Washington, DC

George Cushmac
Office of Hazardous Materials Safety
U.S. Department of Transportation
Washington, DC

Richard Erickson
U.S. Navy
Groton, CT

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Texas Commission on Environmental Quality
Austin, TX

David Freshwater
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Washington, DC

Ralph Gingell
Shell Health Services
Houston, TX

John P. Hinz
U.S. Air Force
Brooks Air Force Base, TX

James Holler
Agency for Toxic Substances and Disease Registry
Atlanta, GA

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Exxon Mobil Corporation
Fairfax, VA

Glenn Leach
U.S. Army Center for Health Promotion and Preventive Medicine Toxicity Evaluation
Aberdeen Proving Grounds, MD

Richard W. Niemeier
National Institute for Occupational Safety and Health
Cincinnati, OH

Mattias Oberg
Swedish Institute of Environmental Medicine (Karolinska Institutet)
Stockholm, Sweden

Susan Ripple
The Dow Chemical Company
Midland, Michigan

George Rusch
Chair, NAC/AEGL Committee
Department of Toxicology and Risk Assessment
Honeywell, Inc.
Morristown, NJ

Daniel Sudakin
Oregon State University
Corvallis, OR

Marcel T. M. van Raaij
National Institute of Public Health and Environment (RIVM)
Bilthoven, The Netherlands

George Woodall
U.S. Environmental Protection Agency
Research Triangle Park, NC

Alan Woolf
Children's Hospiral
Boston, MA

## Oak Ridge National Laboratory Staff

Cheryl Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Talmage
Oak Ridge National Laboratory
Oak Ridge, TN

Robert Young
Oak Ridge National Laboratory
Oak Ridge, TN

## National Advisory Committee Staff

Paul S. Tobin
Designated Federal Officer, AEGL Program
U.S. Environmental Protection Agency
Washington, DC

Ernest Falke
U.S. Environmental Protection Agency
Washington, DC

Iris A. Camacho
U.S. Environmental Protection Agency
Washington, DC

Sharon Frazier
U.S. Environmental Protection Agency
Washington, DC

# Appendixes

# 8

# Propylenimine[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 and AEGL-2, and AEGL-3—will be developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be susceptible. The three AEGLs have been 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 Kowetha Davidson (Oak Ridge National Laboratory) and Chemical Managers Mark McClanahan and Ernest V. Falke (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 guideline reports (NRC 1993, 2001).

experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

## SUMMARY

Propylenimine is an aziridine compound used to modify latex surface coating resins to improve adhesion and to modify bonding properties of textiles, paper, and dyes. It is also used in photography, in the pharmaceutical industry, in gelatins, and organic syntheses. Propylenimine is a colorless oily liquid that has an odor similar to that of ammonia. It is flammable and is an explosion hazard. Propylenimine is similar in structure and toxicity to ethylenimine.

No data were found concerning toxicity or the odor detection threshold for propylenimine in humans. A time-response study conducted in rats and guinea pigs showed that one of six guinea pigs died after exposure to 500 ppm for 60 min and none of the six died after exposure to the same concentration for 30 min. Five of six rats died after exposure to 500 ppm for 240 min and none of the six died after exposure to the same concentration for 120 min. No concentration-response data were available for deriving AEGL values from animal studies. Therefore, a relative potency approach was used to derive AEGL-2 values based on lethality data for propylenimine and ethylenimine. Propylenimine was 4 to 8 times less toxic than ethylenimine depending on the species: 4 or 5 times less toxic to the guinea pig and 8 times less toxic to the rat. Tumors developed at multiple sites in rats treated orally with propylenimine for 28 or 60 weeks; therefore, IARC classified propylenimine as Group 2B (possibly carcinogenic to humans). Propylenimine is mutagenic in *Salmonella* and *Drosophila*.

Data are not available for deriving AEGL-1 values for propylenimine; therefore, no AEGL-1 values were recommended. The absence of AEGL-1 values does not imply that exposures below AEGL-2 are without adverse health effects. In addition, data are not available for estimating the level of distinct odor awareness (LOA) for propylenimine.

Data consistent with AEGL-2 end points were not available for propylenimine; therefore, the AEGL-2 values were derived based on a relative toxicity approach in which the inhalation toxicity of propylenimine was compared with that of ethylenimine. A relative potency factor of 5, which is the geometric mean of the three relative toxicity values calculated from the inhalation studies in rats and guinea pigs exposed to the same concentrations and/or durations, was applied to the AEGL-2 values for ethylenimine. Use of the geometric mean is common practice in toxicology when calculating means of values associated with risk assessments or other expressions of comparative toxicity. It is typically used because it does not give excessive weight to extreme values ("outliers"). It draws outliers toward the center of the distribution, decreasing the sensitivity of the parameter to undue influence of the outlier (Gad 2005). The geometric mean was used for the propylenimine AEGL-2 assessment because of the variability in relative potency values between ethyleneimine and propylenimine (relative potencies were 8-fold in a rat study and 4- and 5-fold in two guinea pig studies). The AEGL-2 values for ethylenimine based on a no-observed effect level (NOEL) for extreme respiratory difficulty in guinea pigs were 33, 9.8, 4.6, 1.0, and 0.47 ppm for 10 min, 30 min, 1 h, 4 h, and 8 h, respectively. In addition, a modifying factor of 2 was applied to account for the deficient database for propylenimine. The resulting AEGL values for propylenimine are 83, 25, 12, 2.5, and 1.2 ppm for exposure durations of 10 min, 30 min, 1 h, 4 h, and 8 h, respectively.

A single exposure of guinea pigs to 500 ppm of propylenimine for 30 min was a no-observed effect level (NOEL) for lethality and this concentration was used as the point of departure for deriving AEGL-3 values. An uncertainty factor of 10 (3 for interspecies sensitivity and 3 for intraspecies variability) was applied to the NOEL for lethality. An interspecies uncertainty factor of 3 was selected because propylenimine is a reactive direct-acting alkylating agent, and the effects of acute toxicity are expected to be confined to the respiratory tract. Propylenimine-induced respiratory tract damage appears to be due to a direct effect of the alkylating agent on the respiratory epithelium; this mechanism is expected to be similar among species. An uncertainty factor of 3 was applied for intraspecies variability because the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent and these effects are not expected to differ considerably among members of the population. Studies have shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage after exposure to alkylating agents, and DNA damage persists in respiratory and systemic organs following inhalation exposure to these agents. This mechanism is not expected to be different among individuals in the population or among various species. Time scaling was based

on the equation, $C^n \times t = k$, where n = 0.91 was derived by probit analysis of $LC_{50}$ data for guinea pigs exposed to ethylenimine. The AEGL values are summarized in Table 8-1.

## 1. INTRODUCTION

Propylenimine is an aziridine compound similar to that of ethylenimine (Ham 1981). Propylenimine is the second most important aziridine, the first being ethylenimine (Ham 1981). Propylenimine is a colorless oily liquid. One source stated that the odor of propylenimine is similar to that of aliphatic amines (fishy) (Trochimowicz et al. 1994), whereas other sources stated that propylenimine has an odor similar to that of ammonia (Ham 1981; RTECS 2008). Propylenimine is flammable, and it is an explosion hazard (Trochimowicz et al. 1994; HSDB 2006). Propylenimine is used to modify latex surface coating resins to improve adhesion, and propylenimine and its derivatives are used to modify bonding properties of textiles, paper, and dyes. It is also used in photography, in pharmaceutical industries, as an oil additive, in gelatins, and in organic syntheses (IARC 1975; Lewis 1993, Trochimowicz et al. 1994).

The data concerning the toxicity of propylenimine are very limited, necessitating a relative toxicity approach for deriving AEGL-values. Therefore, the AEGL values derived for ethylenimine served as the basis for deriving AEGLs for propylenimine. The physical and chemical properties of propylenimine are presented in Table 8-2.

## 2. HUMAN TOXICITY DATA

### 2.1. Acute Lethality

No reports were found on the acute lethality due to exposure to propylenimine.

### 2.2. Nonlethal Toxicity

No epidemiologic or experimental studies, case reports, or anecdotal data concerning potential nonlethal toxicity, developmental/reproductive toxicity, cancer, or genotoxicity were located in the literature searched. However, the acute toxicity of propylenimine is likely to be similar to that of ethylenimine because of their similar chemical and physical properties. Humans exposed to ethylenimine in air experience skin, eye, and respiratory tract irritation, nausea, vomiting, headache, dizziness, and shortness of breath (Trochimowicz et al. 1994). However, concentrations, exposure durations, and specific routes of exposure were not presented in this report.

**TABLE 8-1** AEGL Values for Propylenimine[a,b] [ppm (mg/m$^3$)]

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h | End Point (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1[c] (Nondisabling) | Not recommended[d] | | | | | |
| AEGL-2[c] (Disabling) | 83 (200) | 25 (58) | 12 (28) | 2.5 (5.8) | 1.2 (2.8) | NOEL for extreme respiratory difficulty (Carpenter et al. 1948) |
| AEGL-3[c] (Lethal) | 170 (398) | 50 (120 ) | 23 (54 ) | 5.1 (12) | 2.4 (5.6 ) | Lethality threshold, Carpenter et al. 1948 |

[a]AEGL-2 and -3 values do not account for the potential cancer risk due to inhalation exposure to propylenimine.
[b]Effects including death, irritation to eyes, and irritation to the respiratory tract may be delayed until after cessation of exposure.
[c]AEGL values for propylenimine = AEGL for ethylenimine × 5 (relative potency factor) ÷ 2 (modifying factor).
[d]The absence of AEGL-1 values does not imply that exposures below the AEGL-2 levels are without adverse health effects.

**TABLE 8-2** Physical and Chemical Data for Propylenimine

| Parameter | Data | Reference |
|---|---|---|
| Chemical Name | Propylenimine | HSDB 2006 |
| Synonyms | 2-Methylaziridine; propylene imine; methlyethylenimine | RTECS 2008 |
| CAS Registry No. | 75-55-8 | RTECS 2008 |
| Chemical Formula | $C_3 H_7N$ | RTECS 2008 |
| Molecular Weight | 57.11 | RTECS 2008 |
| Physical State | Colorless oily liquid; colorless mobile liquid; water-white liquid | Trochimowicz et al. 1994; Ham 1981; Lewis 1993 |
| Odor | | |
| Boiling/Freezing Point | 66-67 ºC/-65 ºC | Ham 1981; Lewis 1993 |
| Density | 0.812 at 16/4 ºC<br>0.8039- 0.8070 at 25/25ºC<br>0.802 at 25/4 ºC | Lewis, 1993, HSDB 2006; IARC 1975 |
| Solubility | Miscible or soluble in water; soluble in most organic solvents | Lewis 1993; Trochimowicz et al. 1994 |
| Vapor Pressure | 112 mm Hg at 20.0 ºC<br>179 mm Hg at 30.0 ºC<br>269 mm Hg at 39.0 ºC<br>436 mm Hg at 51.0 ºC<br>760 mm Hg at 66.0 ºC | Ham 1981 |
| Vapor Density | 2.0 (air = 1) | Trochimowicz et al. 1994 |
| Conversion | 1 ppm = 2.34 mg/m$^3$ | NIOSH 2005 |

[a]Density of the liquid and the density of water at the temperature indicated.

### 2.3. Summary

No human toxicity data were available for propylenimine. However, because of its structural and physical and chemical similarity to ethylenimine, propylenimine is expected to cause damage to the eye, respiratory tract, and skin, with onset of effects being delayed depending on the exposure concentration and duration.

## 3. ANIMAL TOXICITY DATA

### 3.1. Acute Lethality

#### 3.1.1. Rats

Carpenter et al. (1948) exposed groups of six rats (weight range 90-120 g) to 500 ppm of propylenimine for 5, 10, 15, 30, 60, 120, or 240 min; only five rats were exposed for 30 min. Although the report did not state it specifically, the animals were probably observed for 14 days, as was reported for studies with ethylenimine. No mortality occurred in groups exposed ≤120 min. Five of six rats exposed to 500 ppm for 240 min died. Other manifestations of toxicity were not specifically described; nevertheless, the authors stated that toxicity of propylenimine was similar to but only one-eighth as severe as that of ethylenimine. Toxicity of ethylenimine was manifested by extreme respiratory difficulty at all concentrations ≥25 ppm, but only after exposure for at least 3 h at 25 ppm. Prostration was observed at 250 ppm (3 h) or 500 ppm (2 h). Death was delayed in all cases with some animals dying more than 10 days after exposure. Gross examination revealed lung congestion and hemorrhage and congestion of all internal organs in animals that died. Microscopic examination of tissues and organs revealed necrosis of the renal tubular epithelium, congested lungs with leakage of fluid and blood into the bronchioles of animals that died. Cloudy swelling was observed in the kidneys of survivors.

#### 3.1.2. Mouse

The lethal concentration for propylenimine reported for mice exposed by inhalation was >2 $g/m^3$ (856 ppm) for a 10-min exposure (RTECS 2008). No other details are known.

#### 3.1.3. Guinea pig

Groups of six guinea pigs (weight range 250-300 g) were exposed to 500 ppm of propylenimine for 5, 10, 30, 60, 120, or 240 min; only five guinea pigs were exposed for 120 min (Carpenter et al. (1948). Although the investigators did not state specifically, the animals were probably observed for 14 days, the

same as reported for studies with ethylenimine. No mortality occurred in groups exposed for 30 min. One of six, three of five, and six of six guinea pigs died after exposure for 60, 120, or 240 min, respectively. Other manifestations of toxicity were not specifically described; nevertheless, the report stated that toxicity of propylenimine was similar to but only one-fourth as potent as that of ethylenimine. Exposure to ethylenimine caused by extreme respiratory difficulty at all concentrations ≥25 ppm, but only after exposure for at least 3 h at 25 ppm. Prostration was observed after exposure to 250 ppm for 3 h or 500 ppm for 2 h. Deaths of guinea pigs exposed to ethylenimine were delayed in all cases with some animals dying more than 10 days after exposure. Gross examination revealed pulmonary congestion and hemorrhage and congestion of all internal organs in animals that died. Microscopic examination of tissues and organs revealed necrosis of the renal tubular epithelium, pulmonary congestion with leakage of fluid and blood into the bronchioles of guinea pigs that died, and cloudy swelling in the kidneys of survivors.

### 3.2. Nonlethal Toxicity

No additional data were available on nonlethal effects of exposure to propylenimine other than discussed above.

### 3.3. Developmental and Reproductive Toxicity

No data were available on potential developmental and reproductive toxicity after inhalation exposure to propylenimine in experimental animals.

### 3.4. Carcinogenicity

The overall incidence of malignant tumors was markedly increased in groups of 26 male and 26 female Charles River CD rats (6 weeks of age) administered propylenimine by gavage (Ulland et al. 1971). The animals were administered doses of 20 or 10 mg/kg body weight twice weekly for 28 or 60 weeks, respectively; all animals were killed at week 60. At 20 mg/kg, 28 tumors were found in 22/52 (males and females combined) rats killed after 60 weeks: gliomas, ear-duct squamous cell carcinomas, intestinal adenocarcinomas, and leukemia in males and mammary tumors (primarily adenocarcinomas), gliomas, and miscellaneous tumors in females. At 10 mg/kg, 45 tumors were found in 37/52 rats killed at the end of the treatment period: gliomas, ear-duct squamous cell carcinomas, intestinal adenocarcinomas, leukemia, and miscellaneous tumors in males and mammary tumors, gliomas, ear-duct squamous cell carcinomas, and miscellaneous tumors in females. Six male and six females serving as controls were killed at 61 weeks; one pituitary adenoma was found. IARC (1975, 1999) evaluated the carcinogenicity data for propylenimine and concluded that the evidence for carcinogenicity was sufficient in experimental ani-

mals and classified the chemical propylenimine as possibly carcinogenic to humans (Group 2B).

### 3.5. Genotoxicity

Speck and Rosenkranz (1976) demonstrated that propylenimine (1.5 μg/plate) was mutagenic in *Salmonella typhimurium* strain TA100 incubated under aerobic or anaerobic conditions. Vogel and Nivard (1997) determined that propylenimine was mutagenic in the sex-linked recessive lethal assay using repair-deficient *Drosophila melanogaster*.

### 3.6. Summary

Propylenimine was lethal in rats after exposure to 500 ppm for 240 min, whereas it was lethal in guinea pigs after exposure to 500 ppm for 60, 120, or 240 min. The effects of propylenimine were similar to but less severe than those of ethylenimine. The data were not adequate for calculating $LC_{50}$ values for either rats or guinea pigs. Propylenimine administered orally induces malignant tumors at multiple sites in rats exposed for 28 or 60 weeks. IARC (1975) classified propylenimine as Group 2B (possibly carcinogenic to humans) based on *sufficient evidence* in animals. Propylenimine is genotoxic in a variety of in vitro assay systems, including *Salmonella typhimurium* and *Drosophila*. No studies were available on nonlethal, developmental toxicity, or reproductive toxicity in animals.

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism, Disposition, and Kinetics

No data were available on absorption, tissue distribution, metabolism, or elimination of propylenimine in humans or experimental animals. However, ethylenimine is excreted primarily in urine after intraperitoneal injection of radiolabeled compound, with a small percentage eliminated in expired air (Wright and Rowe 1967). Ethylenimine showed a two-compartment elimination pattern; one compartment had a half-time of 16 h and the other had a half-time of 56 days. Tissue distribution showed uptake by all tissues with the greatest uptake (specific activity) in liver followed by cecum, spleen, kidneys, intestines, and bone marrow. Ethylenimine was metabolized to unknown substances primarily by a route that did not involve oxidation. In addition, either the parent compound or a metabolite that retained the aziridine ring reacted with tissue components (Wright and Rowe 1967). Absorption, distribution, and excretion of propylenimine are expected to be qualitatively similar to that of ethylenimine because the two compounds have similar structures, physical/chemical properties, and biological effects.

### 4.2. Mechanism of Toxicity

No data were available on the mechanism of toxicity of propylenimine; however, because of its structural similarity to ethylenimine, propylenimine is likely a reactive alkylating agent, with signs of toxicity being delayed until after exposure is terminated (insidious) depending on the exposure concentration. The mechanism of toxicity of propylenimine is expected to be similar to that of ethylenimine and mustard compounds.

### 4.3. Structure–Activity Relationship

Propylenimine is structurally similar to ethylenimine, and data for ethylenimine have been summarized (see Chapter 4). Briefly these data showed that exposure of an individual to a high, but unknown concentration of ethylenimine for no more than 5 min caused eye irritation, respiratory tract irritation, salivation, vomiting, breathlessness, pulmonary edema, and death (Gresham and West 1975). Exposure of humans to a nonlethal concentration for 1.5 to 2 h caused clinical signs that were delayed in onset: photophobia, very severe vomiting, and coughing. Clinical observations associated with acute exposure to ethylenimine included fever, conjunctival irritation, evidence of liver inflammation, transitory hemoconcentration, eosinophilia, mild albuminuria, extensive respiratory irritation manifested by decreased respiratory function, and ulceration of the posterior nasal cavity (Weightman and Hoyle 1964).

The effects in animals exposed to propylenimine by inhalation are similar to those described for ethylenimine. Morality results and $LC_{50}$ values for rats and guinea pigs exposed to ethylenimine are presented in Table 8-3. Mice died after exposure to 1170 ppm ethylenimine for 10 min; the $LC_{50}$ was 2236 ppm for a 10-min exposure (Silver and McGrath 1948).

### 4.4. Other Relevant Information

#### 4.4.1. Species variability

Data were not available to assess the sensitivity of different species exposed to propylenimine. However, data for ethylenimine showed very little difference in response between rats and guinea pigs exposed to ethylenimine at similar concentrations and durations of exposure. Mice, rats, and guinea pigs showed the characteristic delayed mortality response after inhalation exposure to ethylenimine, and the clinical signs of toxicity in the three species were similar. Because of the chemical similar structure and physical properties of propylenimine and ethylenimine, the toxicity of propylenimine is also expected to be similar across species.

**TABLE 8-3** Effects of Acute Exposure of Wistar Rats and Guinea Pigs to Ethylenimine

| Exposure Duration (min) | Species | Exposure Concentration (ppm) | Mortality Response | $LC_{50}$[a](ppm) |
|---|---|---|---|---|
| 5 | Rat | 100 | 0/6 | 2558 |
| | | 250 | 0/6 | |
| | | 500 | 1/6 | |
| | | 1000 | 1/5 | |
| | | 4000 | 4/6 | |
| | Guinea pig | 250 | 0/6 | 2906 |
| | | 500 | 0/6 | |
| | | 1000 | 0/6 | |
| | | 4000 | 4/6 | |
| 10 | Rat | 500 | 2/6 | 1407 |
| | | 1000 | 4/6 | |
| | | 2000 | 1/6 | |
| | | 4000 | 5/6 | |
| | Guinea pig | 2000 | 1/12 | 2824 |
| | | 4000 | 6/6 | |
| 15 | Rat | 100 | 0/6 | 545 |
| | | 250 | 1/6 | |
| | | 500 | 3/6 | |
| | | 1000 | 5/6 | |
| | | 2000 | 5/6 | |
| | | 4000 | 6/6 | |
| | Guinea pig | 250 | 0/6 | 1283 |
| | | 500 | 0/6 | |
| | | 1000 | 0/6 | |
| | | 2000 | 6/6 | |
| 30 | Rat | 500 | 5/6 | Not determined |
| | | 1000 | 6/6 | |
| | | 2000 | 5/5 | |
| | Guinea pig | 100 | 0/6 | 364 |
| | | 250 | 0/6 | |
| | | 500 | 5/6 | |
| | | 1000 | 6/6 | |
| 60 | Rat | 100 | 0/6 | 268 |
| | | 250 | 2/6 | |
| | | 500 | 6/6 | |
| | Guinea pig | 25 | 0/12 | 235 |
| | | 100 | 1/6 | |
| | | 250 | 2/6 | |
| | | 500 | 6/6 | |
| 120 | Rat | 50 | 0/6 | 259 |
| | | 100 | 1/6 | |
| | | 250 | 3/6 | |

*(Continued)*

**TABLE 8-3** Continued

| Exposure Duration (min) | Species | Exposure Concentration (ppm) | Mortality Response | $LC_{50}$[a] (ppm) |
|---|---|---|---|---|
| | Guinea pig | 50 | 0/6 | 158 |
| | | 100 | 1/6 | |
| | | 250 | 5/6 | |
| | | 500 | 6/6 | |
| 240 | Rat | 25 | 0/6 | 58 |
| | | 50 | 2/5 | |
| | | 100 | 6/6 | |
| | | 250 | 6/6 | |
| | Guinea pig | 10 | 0/6 | 45 |
| | | 25 | 2/5 | |
| | | 50 | 2/6 | |
| | | 100 | 6/6 | |
| | | 250 | 6/6 | |
| 480 | Rat | 25 | 1/6 | 35 |
| | | 50 | 5/6 | |
| | Guinea pig | 10 | 0/6 | 27 |
| | | 25 | 2/6 | |
| | | 50 | 6/6 | |

[a] $LC_{50}$ values calculated by probit analysis.
Source: Carpenter et al. 1948. Reprinted with permission; copyright 1948, American Medical Association.

### 4.4.2. Susceptible Subpopulations

No data are available to assess the toxicity of propylenimine in potentially susceptible subpopulations.

### 4.4.3. Concentration-Exposure Duration Relationship

Data were not available for evaluating the concentration-exposure duration relationship for propylenimine. For ethylenimine, a linear relationship was obtained for the log-log plot of $LC_{50}$ concentration versus exposure duration for rats and guinea pigs. Because propylenimine and ethylenimine have similar chemical structures and activity; the concentration-exposure duration relationship is expected to be similar.

### 4.4.4. Other Data

The oral $LD_{50}$ for propylenimine is 19 mg/kg body weight (12-30 mg/kg) for rats dosed by gavage (Carpenter et al. 1948). The approximate $LD_{50}$ is 0.043 mL/kg body weight when applied to the skin of guinea pigs and 0.005 mL when instilled in the eye of rabbits (Trochimowicz et al. 1994).

## 5. DATA ANALYSIS AND AEGL-1

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

No human data were available for deriving AEGL-1 values.

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

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

### 5.3. Derivation of AEGL-1

Data are not available for deriving AEGL-1 values for propylenimine; therefore, no values are recommended (Table 8-4).

## 6. DATA ANALYSIS AND AEGL-2

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

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

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

No animal data were available for deriving AEGL-2 values.

### 6.3. Derivation of AEGL-2

The relative toxicity approach is utilized for deriving AEGL-2 values for propylenimine, because no data on propylenimine are available. Propylenimine is structurally similar to ethylenimine. The toxicity of propylenimine is qualitatively similar to that of ethylenimine; however, propylenimine is four to eight times less toxic than ethylenimine by the inhalation route (Carpenter et al. 1948). The data for relative toxicity are summarized in Table 8-5. In acute inhalation studies reported by Carpenter et al. (1948), propylenimine is four or five times less toxic than ethylenimine to the guinea pig and eight times less toxic to the rat. The relative potency factor of 5 is the geometric mean of the three relative toxicity values calculated from the inhalation studies with rats and guinea

**TABLE 8-4** AEGL-1 Values for Propylenimine

| Chemical | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| Propylenimine | NR | NR | NR | NR | NR |

NR: Not Recommended. The absence of AEGL-1 values does not imply that exposures below the AEGL-2 are without adverse health effects.

pigs. Therefore, a relative potency factor value of 5 was used to derive AEGL-2 values for propylenimine. Use of the geometric mean is common practice in toxicology when calculating means of values associated with risk assessments or other expressions of comparative toxicity. It is typically used because it does not give excessive weight to extreme values ("outliers"). It draws outliers toward the center of the distribution, decreasing the sensitivity of the parameter to undue influence of the outlier (Gad 2005). The geometric mean was used for the propylenimine AEGL-2 assessment because of the variability in relative potency values between ethyleneimine and propylenimine (relative potencies were 8-fold in a rat study and 4- and 5-fold in two guinea pig studies). The AEGL-2 values for ethylenimine (see Chapter 4) are presented below along with the currently derived values for propylenimine (Table 8-6). The AEGL-2 values for ethylenimine were derived from the no-observed-effect level for extreme respiratory difficulty in guinea pigs (10 ppm for 240 min); no deaths occurred at this concentration (Carpenter et al. 1948). Uncertainty factors of 3 for both interspecies sensitivity and intraspecies variability (total = 10) were applied to the exposure concentration (see Chapter 4). Scaling across time frames was accomplished using the equation, $C^n \times t = k$, where the value n = 0.91 was calculated from $LC_{50}$ data for guinea pigs exposed to ethylenimine for durations ranging from 5 to 480 min. A modifying factor of 2 was applied to account for additional uncertainty due to the deficient database for propylenimine; a larger value was not selected because the AEGL-2 values for propylenimine would approximate those of ethylenimine. Propylenimine is carcinogenic to animals exposed by the oral route; IARC (1975) classified propylenimine as Group 2B (possibly carcinogenic to humans). The AEGL-2 values do not take into consideration the potential carcinogenicity of propylenimine to humans.

**TABLE 8-5** Relative Potency of Propylenimine and Ethylenimine in Laboratory Animals

| Route | Species | Propylenimine | Ethylenimine | Relative Toxicity |
|---|---|---|---|---|
| Inhalation | Rat[a] | 500 ppm for 240 min; mortality: 5/6 deaths | 500 ppm for 30 min; mortality: 5/6 deaths | Ethylenimine 8 times more toxic |
| | Guinea pig[a] | 500 ppm for 240 min; mortality: 6/6 deaths | 500 ppm for 60 min; mortality: 6/6 deaths | Ethylenimine 4 times more toxic |
| | Guinea pig[a] | 500 ppm for 60 min; mortality: 1/6 | 100 ppm for 60 min; mortality: 1/6 | Ethylenimine 5 times more toxic |
| | Mouse[b] | Lethal concentration >856 ppm for 10 min. | 899 ppm for 10 min; mortality: 3/20 | Relative potency undetermined |
| Skin | Guinea pig[a,c] | 0.043 mL/kg bw | 0.014 mL/kg bw | Ethylenimine 3 times more toxic |

[a]Carpenter et al. 1948.
[b]RTECS 2008; Silver and McGrath 1948.
[c]Trochimowicz et al. 1994.

**TABLE 8-6** AEGL-2 Values for Ethylenimine and Derived Values for Propylenimine[a] [ppm ($mg/m^3$)]

| Chemical | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| Ethylenimine | 33 (59) | 9.8 (18) | 4.6 (8.2) | 1.0 (1.8) | 0.47 (0.84) |
| Propylenimine | 83 (200) | 25 (58) | 12 (28) | 2.5 (5.8) | 1.2 (5.6) |

[a]AEGL values for propylenimine = AEGL for ethylenimine × 5 (relative potency factor) ÷ 2 (modifying factor).

## 7. DATA ANALYSIS AND AEGL-3

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

No human data were available for deriving AEGL-3 values.

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

Two acute inhalation studies were available for evaluating the toxicity of propylenimine. One study showed that exposure to propylenimine at a concentration of 500 ppm resulted in 5/6 deaths in rats exposed for 240 min and no deaths after exposure for 120 min (Carpenter et al. 1948). The other study showed that exposure to 500 ppm for 60 min resulted in 1/6 deaths in guinea pigs and 500 ppm for 30 min resulted in no deaths (Carpenter et al. 1948).

### 7.3. Derivation of AEGL-3

A 30-min exposure to 500 ppm propylenimine was not lethal to guinea pigs; this concentration was used to derive AEGL-3 values. An uncertainty factor of 3 for interspecies differences and 3 for intraspecies variability (total uncertainty factor = 10) was applied to the no-effect levels for lethality. Effects experienced after exposure to propylenimine are expected to be qualitatively similar but less severe compared with the same concentration of ethylenimine. Therefore, the rationale for selecting uncertainty factors is the same as that used for ethylenimine (see Chapter 4). An interspecies uncertainty factor of 3 was selected because propylenimine is a very reactive direct-acting alkylating agent, and the AEGL-2 effects are expected to be confined to the respiratory tract. Respiratory tract damage appears to be due to a direct effect of an alkylating agent on the respiratory epithelium; this mechanism is expected to be similar among species (NRC 2003). The time of onset of signs and symptoms of exposure on the eyes and respiratory tract is expected to be delayed in both humans and animals. An uncertainty factor of 3 was applied for intraspecies variability because the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent and these effects are not expected to differ considerably among members of the population. Studies have

shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage (Papirmeister et al. 1985) after exposure to alkylating agents, and DNA damage can persist in respiratory and systemic organs following inhalation exposure to these agents (Rao et al. 1999). The resulting value was scaled across the relevant exposure durations using the equation: $C^n \times t = k$, where n = 0.91 derived by regression analysis of $LC_{50}$ data for guinea pigs exposed to ethylenimine. AEGL-3 values are presented in Table 8-7. Propylenimine is carcinogenic to animals exposed by the oral route; IARC (1975, 1999) classified propylenimine as Group 2B (possibly carcinogenic to humans). The AEGL-3 values do not take into consideration the potential carcinogenicity to humans.

## 8. SUMMARY OF AEGLs

### 8.1. AEGL Values and Toxicity End Points

AEGL values for propylenimine are summarized in Table 8-8. Human data were not available for deriving AEGL values and animal data were available only for AEGL-3 derivation.

Data were not available for deriving AEGL-1 values for propylenimine; therefore, no values are recommended. The absence of AEGL-1 values does not imply that exposure below AEGL-2 is without adverse health effects. Data were not available for deriving AEGL-2 values. Propylenimine is structurally and toxicologically similar to ethylenimine, AEGL-2 values were derived based on the relative potency compared with the AEGL values for ethylenimine. The relative potency factor was 5 was applied to the AEGL-2 values for ethylenimine, and then a modifying factor of 2 was applied to account for a limited database on propylenimine.

The AEGL-3 values were derived from the concentration (500 ppm) of propylenimine and the longest exposure duration that resulted in no deaths to guinea pigs. Uncertainty factors of 3 each for interspecies differences and 3 for interspecies variability (total = 10) were applied to the no-effect level for mortality.

### 8.2. Comparison of AEGLs with Other Standards and Criteria

The recommended threshold limit value – time-weighted-average (TLV-TWA) for propylenimine is 2 ppm (ACGIH 2000). This value was based on the comparison of toxicity to ethylenimine (TLV-TWA = 0.5 ppm). A skin notation was also recommended because of its similarity to ethylenimine (ACGIH 2000). The IDLH recommended by the National Institute for Occupational Safety and Health (NIOSH 1996) is 100 ppm based on the data of Carpenter et al. (1948,

1949). The Occupational Safety and Health (29 CFR 1910.1000 [1997]) permissible exposure level (PEL) for propylenimine is 2 ppm (5 mg/m$^3$) with a skin designation. Table 8-9 compares existing standards and guidelines with the derived AEGL values. No other standards or guidelines have been published for propylenimine.

**TABLE 8-7** AEGL-3 Values for Propylenimine [ppm (mg/m$^3$)]

| Chemical | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| Propylenimine | 170 (398) | 50 (120) | 23 (54) | 5.1 (12) | 2.4 (5.6) |

**TABLE 8-8** AEGL Values for Propylenimine[a,b] [ppm (mg/m$^3$)]

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h | End Point (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1[c] | No data available for deriving AEGL-1 values | | | | | |
| AEGL-2[c] | 83 (200) | 25 (58 ) | 12 (28 ) | 2.5 (5.8 ) | 1.2 (2.8) | NOEL for extreme respiratory difficulty (Carpenter et al. 1948) |
| AEGL-3[c] | 170 (398) | 50 (120 ) | 23 (58) | 5.1 (12 ) | 2.4 (5.6 ) | Lethality threshold (Carpenter et al. 1948) |

[a]AEGL-2 and -3 values do not account for the potential cancer risk due to inhalation of propylenimine.
[b]Effects including death, irritation to eyes, and irritation to the respiratory tract may be delayed until after exposure is terminated.
[c]AEGL values for propylenimine = AEGL for ethylenimine × 5 (relative potency factor) ÷ 2 (modifying factor).

**TABLE 8-9** Extant Standards and Guidelines for Propyleneimine

| | Exposure Duration | | | | |
|---|---|---|---|---|---|
| Guideline | 10 min | 30 min | 1 h | 4 h | 8 h |
| AEGL-1 | No values were derived | | | | |
| AEGL-2 | 83 ppm | 25 ppm | 12 ppm | 2.5 ppm | 1.2 ppm |
| AEGL-3 | 170 ppm | 50 ppm | 23 ppm | 5.1 ppm | 2.4 ppm |
| IDLH (NIOSH)[a] | NA | 500 ppm | NA | NA | NA |
| REL-TWA (NIOSH)[b] | 2 ppm (8-h TWA), skin designation | | | | |
| PEL-TWA (NIOSH)[b] | 2 ppm (8-h TWA); skin designation | | | | |
| TLV-TWA (ACGIH)[c] | 2 ppm (8-h), skin notation | | | | |
| MAK (Germany)[d] | No value (carcinogenicity category 2: shown to cause cancer in animals; skin absorption) | | | | |
| MAC (the Netherlands)[e] | 0.63 mg/m3 (8-h) | | | | |

[a]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[b]REL-TWA (Recommended Exposure Limits, National Institute of Occupational Safety and Health) (NIOSH 1996) is defined analogous to the ACGIH TLV-TWA.
[c]PEL-TWA (Permissible Exposure Limits - Time Weighted Average, Occupational Health and Safety Administration) (29 CFR 1910.1000 [1997]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[d]TLV-STEL (Threshold Limit Value - Short Term Exposure Limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2000) is defined as a 15 min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than 4 times per day. There should be at least 60 min between successive exposures in this range.
[e]MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2000) 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.

### 8.3. Data Quality and Research Needs

Numerous data gaps exist concerning toxicity of propylenimine to humans and animals. Human studies are precluded because propylenimine is carcinogenic in animals and is, therefore, a suspect carcinogen in humans. Because the data set for deriving AEGL values for propylenimine was deficient, a relative toxicity approach was used to derive AEGL-2 values for propylenimine. The available data indicate that propylenimine is structurally and toxicologically similar to ethylenimine. Therefore, the relative potency approach was a reasonable approach for deriving the AEGL-2 values for propylenimine. Concentration-response data were not available for propylenimine; therefore, a no-effect level for lethality from a time-response study (rats and guinea pigs were exposed to the same concentration for different time periods) was used to derive the AEGL-3 values. Standard acute inhalation studies for propylenimine would provide definitive data for deriving AEGL-1, -2 and -3 values. A single-exposure carcinogenicity study would provide data for carcinogen risk assessment.

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## APPENDIX A

## Derivation of AEGL Values for Propylenimine

### DERIVATION OF AEGL-3

| | |
|---|---|
| Key Study: | Carpenter et al. 1948 |
| Toxicity End Point: | Lethality: NOEL for lethality: 500 ppm for 30 min |
| Time Scaling: | $C^n \times t = k$; n = 0.91 based on regression analysis of the guinea pig data.<br><br>C = 500 ppm/10 (uncertainty factor) = 50 ppm<br>$C^n \times t = k$; C = 50 ppm, t = 30 min, n = 0.91<br>k = 1054.8336 ppm minutes |
| Uncertainty Factors: | Total = 10:<br>3 for interspecies sensitivity, because propylenimine a reactive direct-acting alkylating agent, and the AEGL-2 effects are expected to be confined to the respiratory tract. Respiratory tract damage appears to be due to direct effect of an alkylating agent on the respiratory epithelium; this mechanism is expected to be similar among species. The time of onset of signs and symptoms of exposure on the eyes and respiratory tract is expected to be delayed in both humans and animals.<br><br>3 for intraspecies variability, because the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent. Studies have shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage after exposure to alkylating agents, and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to these agents. The alkylating activity of propylenimine is not expected to vary appreciably among individuals in the population |
| Calculations: | |
| 10-min AEGL-3 | $C = (k/t)^{1/0.91} = (1054.8 \text{ ppm minutes}/10 \text{ min})^{1/0.91} = 170$ ppm |
| 30-min AEGL-3 | $C = (k/t)^{1/0.91} = (1054.8 \text{ ppm minutes}/30 \text{ min})^{1/0.91} = 50$ ppm |
| 1-h AEGL-3 | $C = (k/t)^{1/0.91} = (1054.8 \text{ ppm minutes}/60 \text{ min})^{1/0.91} = 23$ ppm |
| 4-h AEGL-3 | $C = (k/t)^{1/0.91} = (1054.8 \text{ ppm minutes}/240 \text{ min})^{1/0.91} = 5.1$ ppm |
| 8-h AEGL-3 | $C = (k/t)^{1/0.91} = (1054.8 \text{ ppm minutes}/480\text{min})^{1/0.91} = 2.4$ ppm |

# APPENDIX B

## Carcinogenicity Assessment

## QUANTITATIVE CANCER ASSESSMENT FOR PROPYLENIMINE

Only one carcinogenicity study (Ulland et al. 1971) was available for propylenimine. In this study rats were administered propylenimine by gavage at two different doses for different time periods. The study author combined incidences of tumors at different anatomical sites but provided no data indicating that the incidence of each tumor type was related to administration of propylenimine. Therefore, these data are not suitable for a dose-response assessment of propylenimine.

## APPENDIX C

## Derivation Summary of AEGL Values for Propylenimine

### AEGL-1 VALUES

| 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|
| Not recommended. | | | |
| Reference: Not applicable. | | | |
| Test Species/Strain/Number: Not applicable. | | | |
| Exposure Route/Concentration/Durations: Not applicable. | | | |
| Effects: Not applicable. | | | |
| End Point/Concentration/Rationale: Not applicable. | | | |
| Uncertainty Factors/Rationale: Not applicable.<br>Total uncertainty factor: Not applicable.<br>Interspecies: Not applicable.<br>Intraspecies: Not applicable. | | | |
| Modifying Factor: Not applicable. | | | |
| Animal to Human Dosimetric Adjustment: Not applicable. | | | |
| Time Scaling: Not applicable. | | | |
| Data Quality and Support for AEGL Values: No data are available. | | | |

### AEGL-2 VALUES

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 83 (200) | 25 (58) | 12 (28) | 2.5 (5.8) | 1.2 (2.8) |
| Reference: Carpenter, C.P., H.F. Smyth, Jr., and C.B. Shaffer. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30(1):2-6 (see Chapter 4). | | | | |
| Test Species/Strain/Number: Ethylenimine: male guinea pigs, 6 per group. | | | | |
| Exposure Route/Concentration/Durations: Ethylenimine: inhalation; 10, 25, 50, 100, or 250 ppm for 240 min. | | | | |
| Effects: Ethylenimine: Guinea pigs were exposed for 240 min.<br>Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm.<br>Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm.<br>Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys at 25-250 ppm; no effects at 10 ppm.<br>Mortality: 10 ppm, (0/6), 25 ppm (2/6), 50 ppm (2/6), 100 ppm (6/6), and 250 ppm (6/6). | | | | |

*(Continued)*

**AEGL-2 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 83 (200) | 25 (58) | 12 (28) | 2.5 (5.8) | 1.2 (2.8) |

End Point/Concentration/Rationale:
Ethylenimine: No-effect-level for lethality in the guinea pig, 10 ppm exposure for 4 h; effects at 25 ppm and higher were above the definition for AEGL 2. The AEGL-2 values for propylenimine were derived based on the relative potency approach. Ethylenimine is five times more toxic than propylenimine.

Uncertainty Factors/Rationale: Ethylenimine
Total uncertainty factor: 10
Interspecies: 3 - ethylenimine is a very reactive direct-acting alkylating agent, and the AEGL-2 effects would be confined to the respiratory tract. Respiratory tract damage appears to be due to the direct effect of an alkylating agent on the respiratory epithelium, and this mechanism is not expected to be different among species. Humans and animals exhibit delays between the time of exposure and the onset of symptoms and the eyes and respiratory tract are the most sensitive targets in both species.
Intraspecies: 3 - the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent. Studies have shown that DNA damage is likely the initiating step in a cascade of events leading to cell damage and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to alkylating agents.

Modifying Factor: 2 because of a deficient database.

Animal to Human Dosimetric Adjustment: 1

Time Scaling: Ethylenimine: $C^n \times k = t$, where n = 0.91 derived empirically from guinea pig LC50 data with exposure times ranging from 5 min to 480 min.

Data Adequacy: No acute toxicity data for propylenimine were available for deriving AEGL-2 values. Therefore, AEGL-2 values for propylenimine were derived by the relative potency method; a relative potency of 5 was selected for propylenimine (based on lethality data, propylenimine was considered to be 5 times less toxic than ethylenimine). The resulting AEGL values were reduced by a factor of 2 because of a deficient database. The AEGL 2 values for ethylenimine were 33, 9.8, 4.6, 1.0, and 0.47 for 30 min, 1 h, 4 h, and 8 h, respectively.

**AEGL-3 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 170 (398) | 50 (120) | 23 (54) | 5.1 (12) | 2.4 (5.6) |

Key Reference: Carpenter, C.P., H.F. Smyth, Jr., and C.B. Shaffer. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30(1):2-6.

Test Species/Strain/Number: guinea pig/6 per group.

Exposure Route/Concentration/Durations: inhalation/500 ppm for 5, 10, 30, 60, 120, or 240 min.

Effects: lethality, 1/6, 3/5, 6/6 at 60, 120, and 240 min, respectively; no deaths after exposures ≤30 min.

*(Continued)*

**AEGL-3 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 170 (398) | 50 (120) | 23 (54) | 5.1 (12) | 2.4 (5.6) |

End Point/Concentration/Rationale: no effect level for lethality

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - propylenimine is a reactive direct-acting alkylating agent, and the AEGL-3 effects are expected to be confined to the respiratory tract. Respiratory tract damage appears to be due to the direct effect of an alkylating agent on the respiratory epithelium; this mechanism is expected to be similar among species. The time of onset of signs and symptoms of exposure on the eyes and respiratory tract is expected to be delayed in both humans and animals.
Intraspecies: 3 - the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent. Studies have shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage after exposure to alkylating agents, and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to these agents.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: None applied.

Time Scaling: $C^n \times k = t$, where n = 0.91 derived empirically from $LC_{50}$ data in which guinea pigs were exposed to ethylenimine for times ranging from 5 min to 480 min.

Data Adequacy: Very few data were available for deriving AEGL-3 values for propylenimine. A standard acute lethality study has not been conducted for propylenimine; therefore, the time-response study in which rats and guinea pigs were exposed to 500 ppm for different time periods was used to derive AEGL-3 values. The data for the guinea pig showed that this species is more sensitive to propylenimine exposure than the rats; lethality occurred after exposure of guinea pigs to 500 ppm for 60 min and after exposure of rats to 500 ppm for 240 min.

**APPENDIX D**

**Category Plot for Propylenimine**

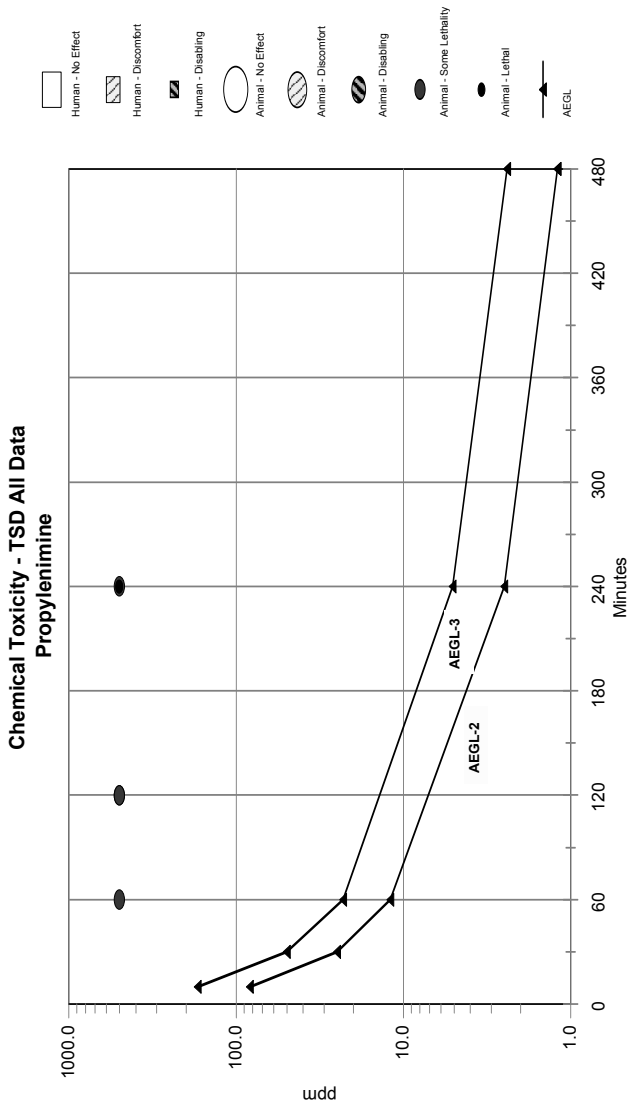


**FIGURE D-1** Category plot for propylenimine.