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

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 8

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

REVIEW OF AEGL REPORTS

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

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

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

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

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared 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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Appendixes

1

Acrolein[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 [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Cheryl B. Bast (Oak Ridge National Laboratory) and Chemical Managers Robert Snyder and Paul Tobin (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).

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/m³) 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/m³) 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, 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 AEGLs 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

Acrolein is a colorless or yellowish liquid at ambient temperature and pressure. It has an acrid, pungent odor and is highly irritating to mucous membranes, especially the upper respiratory tract and eyes. The odor threshold is <0.1 ppm (Beauchamp et al. 1985). It is manufactured by air oxidation of propylene and is used as an intermediate in the production of acrylic acid. It is also used as a herbicide, algicide, and slimicide, in the cross-linking of protein collagen in leather tanning, as a fixative of histologic samples, and in the production of perfumes. Acrolein has also been used in military poison gas mixtures. The largest sources of human exposure to acrolein are from incomplete combustion of organic materials (such as in urban fires and forest fires), tobacco smoke, and the burning of fat-containing foods (Beauchamp et al. 1985).

The AEGL-1 values were based on very slight eye irritation and "annoyance" or discomfort observed in human subjects exposed to acrolein at 0.09 ppm (Weber-Tschopp et al. 1977). An intraspecies uncertainty factor of 3 was applied and is considered sufficient because minor ocular contact irritation is unlikely to vary greatly among humans. The values were held constant across time for the 10-min, 30-min, 1-h, 4-h, and 8-h time points because minor irritancy is generally a threshold effect, and prolonged exposure is not likely to result in a greatly enhanced effect.

The AEGL-2 was based on a 10-15% decrease in respiratory rate in healthy human subjects exposed to acrolein at 0.3 ppm for 1 h (Weber-Tschopp

et al. 1977). According to ASTM (1991), decreases in respiratory rate in the range of 12% to 20% correspond to slight irritation, and decreases in respiratory rate in the range of 20% to 50% correspond to moderate irritation. Thus, the point-of-departure is considered a no-observed-adverse-effect level (NOAEL) for moderate irritation. An intraspecies uncertainty factor of 3 was applied and is considered sufficient because irritation is unlikely to vary greatly among humans. This uncertainty factor is further justified because of the sensitivity of the methods used, the fact that the point-of-departure effect was only a very small detectable decrease in respiration, the lack of evidence of marked variability across the study group, including women; and the fact that at twice the concentration, respiration was still only slightly decreased. Also, application of the default uncertainty factor of 10 would yield AEGL-2 values in the concentration range where only minor irritation was noted in controlled human studies. This value was back-extrapolated to the 10- and 30-min time points using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 1.2 (derived from lethality data in rats exposed to acrolein from 1 to 4 h). The 1-h exposure of 0.3 ppm was held constant for the 4- and 8-h AEGL-2 values since irritation is generally a threshold effect, and prolonged exposure is not likely to result in a greatly enhanced effect.

The 10-min, 30-min, and 1-h AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 1-h exposure (14 ppm), and the 4-h and 8-h AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 4-h exposure (4.8 ppm) (Ballantyne et al. 1989). Intraspecies and interspecies uncertainty factors (UFs) of 3 each were applied (total UF = 10) and are considered sufficient because irritation is not expected to vary greatly within or among species. Furthermore, application of either an intra- or interspecies uncertainty factor of 10 (total UF = 30) would yield values that are inconsistent with the total database. (For example, AEGL-3 values for acrolein would range from 2.1 to 0.09 ppm and only ocular, nasal, or throat irritation and decreased respiratory rates were observed in humans exposed to acrolein at concentrations of 0.09 to 0.6 ppm for up to 40 min (Weber-Tschopp, et al. 1977). People exposed to this range of acrolein for 10 min to 8 h probably would experience effects defined by AEGL-3. Values were extrapolated using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 1.2 (derived from lethality data in rats exposed to acrolein from 1 to 4 h).

The calculated values are listed in Table 1-1.

1. INTRODUCTION

Acrolein is a colorless or yellowish liquid at ambient temperature and pressure. It has an acrid, pungent odor and is highly irritating to mucous membranes, especially the upper respiratory tract and eyes. The odor threshold is <0.1 ppm (Beauchamp et al. 1985).

TABLE 1-1 Summary of AEGL Values for Acrolein

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	Very slight eye irritation, "annoyance" and discomfort in humans (Weber-Tschopp et al. 1977)
AEGL-2 (Disabling)	0.44 ppm (0.92 mg/m^3)	0.18 ppm (0.41 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)	10-15% decrease in respiratory rate in humans (Weber-Tschopp et al. 1977)
AEGL-3 (Lethal)	6.2 ppm (14 mg/m^3)	2.5 ppm (5.7 mg/m^3)	1.4 ppm (3.2 mg/m^3)	0.48 ppm (1.1 mg/m^3)	0.27 ppm (0.62 mg/m^3)	1 h (10-min, 30-min and 1-h values) or 4 h (4-h and 8-h values) no-effect level for death in rats (Ballantyne et al. 1989)

Acrolein is manufactured by air oxidation of propylene and is used as an intermediate in the production of acrylic acid. It is also used as a herbicide, algicide, and slimicide, in the cross-linking of protein collagen in leather tanning, as a fixative of histologic samples, and in the production of perfumes. Acrolein has also been used in military poison-gas mixtures (ATSDR 2007). The production volume of acrolein in the United States was more than 100-500 million pounds in 1998 (ATSDR 2007).

The largest sources of human exposure to acrolein are from incomplete combustion of organic materials (such as in urban fires and forest fires), tobacco smoke, and the burning of fat-containing foods (Beauchamp et al. 1985).

The chemical structure is depicted below, and the physical and chemical properties of acrolein are presented in Table 1-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Information concerning death in humans following inhalation exposure to acrolein is limited and anecdotal. Henderson and Haggard (1943) reported that exposure to acrolein at 150 ppm is fatal after 10 min. Gosselin et al. (1979) described the case of a 4-year-old boy exposed to smoke containing acrolein from an overheated fryer. Death occurred by "asphyxia" 24 h after the 2-h exposure to smoke. Autopsy indicated massive cellular desquamation of the bronchial lining, miscellaneous debris in the bronchial lumen, and multiple pulmonary infarcts. The boy's 2-year-old brother also died, but no details were presented concerning his case. No acrolein concentration was reported, and smoke components in addition to the acrolein probably were partially responsible for the observed pathology.

$CH_2 = CH\text{-}CHO$

TABLE 1-2 Chemical and Physical Data for Acrolein

Parameter	Data	Reference
Common Name	Acrolein	ATSDR 2007
Synonyms	Acraldehyde, acrylaldehyde, allyl aldehyde, 2-propenal, propylene aldehyde	ATSDR 2007
CAS registry no.	107-02-8	ATSDR 2007
Chemical formula	C_3H_4O	ATSDR 2007
Molecular weight	56.06	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Odor threshold	<0.1 ppm 0.03-0.034 ppm: acrolein-sensitive persons 0.16 ppm	Beauchamp et al. 1985 Beauchamp et al. 1985 ATSDR 2007
Melting, boiling, and flash points	−88°C/52.5°C/−18°C (open cup)	O'Neil et al. 2001
Density	0.8389 g/m^3 at 20°C	O'Neil et al. 2001
Solubility	212,000 mg/L in water at 25°C; miscible with lower alcohols, ethers, hydrocarbons, acetone, benzene	ATSDR 2007
Vapor pressure	210 mm Hg at 20°C	O'Neil et al. 2001
Conversion factors in air	1 ppm = 2.328 mg/m^3 1 mg/m^3 = 0.43 ppm	ATSDR 2007

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Champeix et al. (1966) described high fever, dyspnea, cough, foamy expectoration, cyanosis, and pulmonary edema in a 36-year-old man exposed to an undetermined concentration of acrolein in the course of one work day. Eighteen months after exposure, pneumonopathy, bronchitis, and emphysema were still present. Bauer et al. (1977) described similar respiratory effects in a 21-year-old man exposed to smoke from an overheated pan for 6 h. No other details were available, and components of the smoke in addition to acrolein may have contributed to the observed effects.

2.2.2. Experimental Studies

Lachrymation and marked eye, nose and throat irritation were observed within 20 seconds (s) in individuals exposed to acrolein at 0.81 ppm and within 5 s in those exposed at 1.22 ppm (Sim and Pattle 1957).

The effects of inhalation exposure to acrolein were evaluated in human volunteers in a series of three experiments as follows: (1) a "continuous" exposure at steadily increasing concentrations; (2) several exposures of short duration at continuously increasing concentrations; and (3) a longer exposure period (1 h) at a constant acrolein concentration (Weber-Tschopp et al. 1977). Subjectively perceived irritation and "annoyances" (the closest translation; another term might be "discomfort") by means of a scaled questionnaire; eye-blinking rate; and respiratory rate via an elastic measurement tape that registered breath movements in the lower rib area were recorded during the exposures.

For the "continuous" exposure, 53 healthy students (31 men and 22 women) were divided into groups of three. Each volunteer was subjected to two experiments, one involving exposure to acrolein and the other without acrolein under identical conditions (control experiment). The duration of the experiments was 40 min, during which the acrolein concentration rose from 0 to 0.60 ppm in the first 35 min and remained constant during the last 5 min of the experiment. Each volunteer had to fill out the questionnaire every 5 min. Immediately after that, the blinking rate was measured for two subjects (of the groups of three). For the third subject, the respiratory rate was monitored continuously during the entire experimental period.

In the second of the series of experiments, 42 healthy students (17 men and 25 women) participated in an interrupted exposure experiment. Groups of four subjects were exposed to acrolein at 0, 0.15, 0.30, 0.45, and 0.60 ppm. Each individual was exposed to each concentration for 1.5 min five times with 8-min recovery periods in between. One minute into each exposure, they received the questionnaire.

Finally in the third of the series of experiments, 46 healthy students (21 men and 25 women) were exposed (in groups of three) to acrolein at 0.3 ppm for 60 min. Eye-blinking rate, respiratory rate, and subjective irritation determined immediately before exposure served as the control. The remainder of the protocol was identical to that for "continuous" exposure.

The acrolein was introduced with a microliter syringe, evaporated, and blown into a 30-m^3 climate chamber by means of a carrier gas stream. The acrolein concentrations were measured continually during the experiment with a Technicon air monitor IV system by reaction of acrolein with 4-hexylresorcin in an ethyl alcohol-trichloroacetic acid solution in the presence of mercury chloride. Measured concentrations were within 3.8% of target concentrations.

Annoyance increased with increasing acrolein concentration (from 0 to 0.6 ppm) for both continuous and interrupted exposure regimens. A significant dif-

ference between continuous and interrupted exposure was seen only at 0.15 ppm. Annoyance was significantly higher with the interrupted exposure to acrolein compared with the continuous exposure ($p < 0.01$ for opinion on air quality; $p < 0.05$ for wish to leave the room). During the 1-h exposure at 0.3 ppm, annoyance increased during the first 20-30 min and then remained constant. The authors assumed that during the first phase of exposure, an adaptation to the irritant took place, which disappeared at the higher concentrations and/or longer exposure durations.

In the continuous and the interrupted exposure experiments, ocular and nasal irritation increased significantly with increasing acrolein concentration; apparently, the eyes were more sensitive than the nose. Very slight ocular irritation was reported at 0.09 ppm, whereas nasal irritation was reported at 0.15 ppm. Throat irritation in both experiments was found to be a less sensitive criterion. In the continuous experiment, throat irritation increased significantly only at 0.43 ppm; in the interrupted experiment, there was no change. Ocular, nasal, and throat irritation also increased with increasing exposure duration during the 1-h exposure to acrolein at 0.3 ppm. The subjective irritation reached an intensity that remained constant after about 40 min.

When compared with the control experiment without acrolein where no effects on annoyance or irritation were observed, the differences between control and acrolein experiments were significant ($p < 0.05$).

In the continuous exposure regimen, the eye-blinking rate increased at concentrations from 0.17 ppm and greater in a concentration-dependent manner; the increase became significant ($p < 0.01$) once the acrolein concentration reached 0.26 ppm. The mean initial value of blinking rate was doubled at about 0.3 ppm. In the 1-h exposure (0.3 ppm), the blinking rate reached this point after only 10 min.

The respiratory rate decreased slightly with increasing acrolein concentration in the continuous exposure experiment. Compared with controls, the decrease was statistically significant at 0.6 ppm, with an average decrease of 25%. There was also a decrease in mean respiratory rate over the course of the 1-h exposure to acrolein at 0.3 ppm. An average decrease of 10-15% was observed after both 10 and 20 min of exposure, and the decrease was significant ($p < 0.01$) from 40 min on and fluctuated between 2.9 and 3.4 breaths/min (average 20% decrease).

Summarizing data from all the experiments conducted, thresholds for significant changes of the measured parameters are presented in Table 1-3, while effects at constant exposure of 0.3 ppm are presented in Table 1-4.

In another study, 36 students (26 male and 10 female) were exposed to acrolein at 0, 0.06, 1.3-1.6, or 2.0-2.3 ppm through an eye mask for 5 min (Darley et al. 1960). A 16-cubic-foot glass and aluminum fumigation chamber was constructed and operated as a stirred flow reactor. The chamber was set up in a greenhouse to study damage to plants from acrolein exposure. Three eye irrita-

TABLE 1-3 Effect Thresholds in Human Volunteers Exposed to Acrolein

Effect	Measurement
"Annoyance"	0.09 ppm
Very slight eye irritation	0.09 ppm
Nose irritation	0.15 ppm
Doubling of blinking rate	0.26 ppm
10% decrease in respiratory rate	0.3 ppm
Throat irritation	0.43 ppm
25% Decrease in respiratory rate	0.6 ppm

[a]Values combined from 1-h exposure and "continuous" exposure regimens.

TABLE 1-4 Effects Human in Subjects Exposed to Acrolein at 0.3 ppm

Effect	% of Subjects after 10 min	% of Subjects after 20 min
Wish to leave room	50	72
Moderate eye irritation	18	35
Severe eye irritation	3	18
Moderate Nose Irritation	7	19
Severe nose irritation	1	4
Moderate throat irritation	1	2
Severe throat irritation	0	1
Doubling of blinking rate	66	70
10-15% decrease in respiratory rate	47	60

tion booths were constructed adjacent to the plant exposure chamber. The exhaust air from the chamber was run in an all glass system to a manifold and then through three airflow lines, one to each eye exposure booth. The end of each line was connected to a loose-fitting plastic face mask. Acrolein was diluted in water and the mixture dispensed from a syringe into a stream of oxygen. Concentrations were determined by absorbing the vapors in a buffered semi-carbazide-hydrochloride solution and reading the absorbance on a spectrophotometer. During exposure, the subjects wore activated carbon respirators to breath clean air, and only the eyes were exposed to the acrolein. Each student recorded the degree of irritation every 30 s during the 5-min exposure. Irritation was rated as none (score 0), medium (score 1), or severe (score 2). The maximum value recorded by a subject during a test was used as the response for that experimental session. Average maximum irritation scores are as follows: 0 ppm = 0.361, 0.06 ppm = 0.471, 1.3-1.6 ppm = 1.182, and 2.0-2.3 ppm = 1.476. The filtered-air irritation score (0.361) and the 0.06-ppm acrolein score (0.471) are both <0.5, where 0 is defined as "no irritation" and 1 is defined as "medium irritation."

The conditions of this study did not allow distinguishing between slight irritation caused by other constituents of the greenhouse air, or even air movement in the eye mask, and that caused by acrolein at 0.06 ppm.

2.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding acute human exposure to acrolein were not available.

2.4. Genotoxicity

Genotoxic studies regarding acute human exposure to acrolein were not available.

2.5. Carcinogenicity

Carcinogenicity studies regarding human exposure to acrolein were not available.

2.6. Summary

Information concerning human mortality from acrolein exposure is limited and anecdotal. Nonlethal case reports and experimental studies with healthy human volunteers suggest that low concentrations of acrolein are irritating to the eyes, nose, and throat and cause a decrease in respiratory rate. At higher concentrations, coughing, pulmonary edema (may be delayed in onset), bronchitis, or tracheobronchitis may occur. No information concerning effects in young, elderly, or asthmatic individuals was available. No information concerning reproductive and developmental toxicity, genotoxicity, or carcinogenicity was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Nonhuman Primates

As the result of exposure to acrolein during an escape-performance test, one male baboon died 1.5 h after exposure to 2,780 ppm acrolein and another died 24 h after exposure to 1,025 ppm (Kaplan 1987). Both animals developed severe respiratory effects and died from pulmonary edema. This study is described in detail in section 3.2.1.

3.1.2. Rats

Ballantyne et al. (1989) exposed groups of five male and five female Sprague-Dawley rats to acrolein at 14, 22, 24, 31, or 81 ppm for 1 h or at 4.8, 7.0, 9.1, or 12.1 ppm for 4 h, followed by a 14-day observation period. Acrolein vapor was dynamically generated by metering pure liquid acrolein from a syringe pump into a heated glass evaporator. Glass beads were added to the evaporator to increase the surface area for vaporization. The vapor was then carried to the exposure chamber by a stream of air passing through the evaporator. The different concentrations of acrolein were obtained by varying the generation temperature, airflow rate through the generator, or airflow rate through the chamber. Chamber atmospheres were sampled four to six times during the 1-h exposures and 10 times during the 4-h exposures and were analyzed by gas chromatography. Lachrymation, perinasal, and periocular wetness, and mouth breathing were observed at all acrolein concentrations during exposure. After exposure, perinasal and perioral wetness and encrustation, mouth and audible breathing, decreased breathing rate, and hypoactivity were observed in all groups. Concentration-dependent signs of respiratory distress and hypoactivity were observed during post-exposure days 1 through 6. Body weights of surviving animals decreased during week 1 and recovered thereafter. Combined maleand female LC_{50} values (concentration with 50% lethality) of 26 ppm and 8.3 ppm were calculated for 1 h and 4 h, respectively. Necropsy of decedents revealed perinasal and perioral encrustation, mottled discoloration of the lungs and liver, clear fluid in the trachea and thoracic cavity, gas-filled stomach and intestine, and opaque or cloudy corneas. Histologically, pulmonary congestion and intraalveolar hemorrhage, fibrin deposition in the small airways, and necrosis and exfoliation of bronchiolar epithelia were observed in decedents. Mortality data are summarized in Table 1-5.

TABLE 1-5 Mortality of Rats Exposed to Acrolein for 1 or 4 Hours

Exposure Time	Concentration (ppm) Mean ± Standard Deviation	Mortality		Time to Death After Exposure
		Males	Females	
1-h	81 ± 1	5/5	5/5	3 h- 3 days
	31 ± 2	5/5	5/5	3 h- 6 days
	24 ± 1	2/5	1/5	1-3 days
	22 ± 5	0/5	1/5	2 days
	14 ± 7	0/5	0/5	—
4-h	12.1± 0.4	5/5	3/5	1-3 days
	9.1 ± 1.4	3/5	4/5	1-13 days
	7.0 ± 0.2	3/5	0/5	1-5 days
	4.8 ± 0.2	0/5	0/5	—

Source: Ballantyne et al. 1989. Reprinted with permission; copyright 1989, *Human & Experimental Toxicology*.

3.1.3. Guinea Pigs

Male Dunkin-Hartley guinea pigs were exposed to acrolein at 0 or 1.6 ppm for 7.5 h on each of two consecutive days (Turner et al. 1993). There were no deaths in the control group, and 14% of the acrolein-exposed animals died. In another study, guinea pigs died 6 min into an exposure at 1,600 ppm (Davis et al. 1967). These studies and their nonlethal effects are described in section 3.2.4.

3.1.4. Other Data

Acute lethality data were available for mice, rats, dogs, cats, hamsters, rabbits, and guinea pigs; however experimental details such as animal strains, exposure systems, and concentration-response data were unavailable. These data are summarized in Table 1-6.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

Kaplan (1987) exposed juvenile male baboons (one per concentration) to acrolein at 12, 25, 95, 100, 250, 505 (two animals) 1,025, or 2,780 ppm for 5 min. The animals had been trained to perform an avoidance and escape test. After 5 min of exposure, the escape test was presented to the animal. If the animal did not exit within 10 s, shock was applied to the bars of the cage and maintained for 20 s. If the animal exited within 10 s, the response was designated "avoidance." If the animal exited after 10 s but within 30 s, the response was designated "escape." Avoidance and escape responses were both considered successful escape performance. Exposure to acrolein did not prevent the escape task: all acrolein-exposed animals made the avoidance response. Although not statistically significant, test escape times were slightly less during exposure when compared with pre-exposure times. Baboons exposed at 1,025 and 2,780 ppm developed severe respiratory complications and died from severe pulmonary edema 24 h and 1.5 h after exposure, respectively.

3.2.2. Mice

Kane et al. (1979) exposed groups of four male Swiss-Webster mice to concentrations of aerosolized acrolein ranging from 0.1 to 100 ppm for 10 min to determine a reference dose (RD_{50}). The mice were placed in a glass exposure chamber with the body of each animal in an airtight plethysmograph, and only the head extending into the exposure chamber. Each of the four plethysmographs of the mouse exposure chamber was connected to a pressure transducer to sense pressure changes created during inspiration and expiration. Each

TABLE 1-6 Acute Lethality of Acrolein in Various Animal Species

Species	Concentration (ppm)	Exposure Duration	End Point	Reference
Mouse	875	1 min	Approximate LC_{50}	Albin 1962
Mouse	175	10 min	Approximate LC_{50}	Albin 1962
Mouse	10.5 (only concentration studied)	6 h	Approximately 50% died	Pattle and Cullumbine 1956
Mouse	66	6 h	LC_{50} 24-h observation	Phillippin et al. 1970
Rat	375	10 min	LC_{50}	Catalina et al. 1966
Rat	131	30 min	LC_{50} 21 day observation	Skog 1950
Rat	8	4 h	Approximate LC_{50}	Carpenter et al. 1949
Guinea pig	10.5 (only concentration studied)	6 h	Approximately 50% died	Pattle and Cullumbine 1956
Hamster	25.4	4 h	LC_{50}	Kruysse, 1971
Rabbit	10.5 (only concentration studied)	6 h	Approximately 50% died	Pattle and Cullumbine 1956
Cat	870	2.5 h	Died during exposure	Iwanoff 1910
Cat	650	2.25 h	Died within 18 h	Iwanoff 1910
Cat	600	8 h	Approximate LC_{50}	ITII 1975
Dog	150	30 min	Approximate LC_{50}	Albin 1962

Source: Adapted from Beauchamp et al. 1985.

animal served as its own control, with baseline values established by animals breathing room air. An RD_{50} of 1.68 ppm (95% confidence interval [CI], 1.26-2.24) was determined for acrolein.

To determine if respiratory lesions are produced in mice exposed to acrolein at the RD_{50} concentration, Buckley et al. (1984) exposed groups of 16-24 male Swiss-Webster mice to 1.7 ppm acrolein 6 h/day (d) for 5 days. Acrolein test atmospheres were generated by delivering a prepared mixture in nitrogen from a Teflon bag via a pump into the chamber air supply where it was diluted to achieve the target concentration. Chamber concentrations were measured at least once per hour by infrared spectrometry. A group of 8-10 mice served as unexposed controls. Half of the control and exposed mice were necropsied immediately after the last exposure, and the remaining mice were necropsied 72 h after the last exposure. Acrolein-exposed mice exhibited moderate inflammation, exfoliation, erosion, ulceration, and necrosis; and severe squamous metaplasia of the respiratory epithelium. Moderate ulceration and necrosis and minimal squamous metaplasia of the olfactory epithelium, and minimal serous exudate were also observed in treated animals. There was minimal to moderate recovery after 72 h. No effects were observed in control animals.

In another report, Steinhagen and Barrow (1984) determined acrolein RD_{50} values in two strains of mice: $B6C3F_1$ and Swiss-Webster. Groups of three or four male mice were exposed to acrolein in a 2.7-L head-only exposure chamber. The acrolein atmospheres were generated by peristaltic metering of an acrolein-nitrogen mixture from a Teflon bag to the inhalation chamber supply inlet. The Teflon bag was prepared by vaporizing acrolein into the nitrogen stream during filling. Acrolein bag and chamber concentrations were determined calorimetrically. RD_{50} values of 1.41 ppm (CI, 1.16-1.73) and 1.03 ppm (CI, 0.70-1.52) were determined for $B6C3F_1$ and Swiss-Webster male mice, respectively.

Astry and Jakab (1983) infected female Swiss mice with influenza A/PR8/34 for 45 min by aerosol inhalation. Seven days after virus infection, groups of uninfected and virus-infected mice were challenged by aerosol inhalation of ^{32}P radio-labeled *Staphylococcus aureus* for 45 min. Immediately after bacterial challenge, groups of the virus-infected and uninfected mice were exposed to acrolein vapors at 3 or 6 ppm for 8 h. Acrolein vapor was generated from a temperature-controlled glass diffusion tube device designed to reach rapid steady state and maintain a constant evolution with time. An air supply delivered the vapor to a premixing chamber for final dilution with room air before entering the stainless steel, horizontal-flow exposure chambers. To assess pulmonary bactericidal activity, mice were killed at time zero (immediately after bacterial challenge) and at 8 h after bacterial challenge. Measurements were made from lung homogenates by both the standard pour plate technique and by liquid scintillation counting. Exposure to acrolein suppressed pulmonary antibacterial defenses in a concentration-dependent manner. In animals exposed to acrolein at 3 ppm, 12.3% of the *S. aureus* remained viable in the lungs at 8 h, while 33.9% remained viable at 8 h after exposure to acrolein at 6 ppm. Concen-

trations of acrolein greater than 6 ppm (not specified) did not add to the impairment of bacteriocidal activity but greatly increased sensory irritation (details not provided).

Aranyi et al. (1986) also examined the effect of acrolein inhalation on the female mouse host defense system. In this study, five groups of 18-24 female CD-1 mice per group were exposed to acrolein at 0 or 0.1 ppm (the Threshold Limit Value [TLV] concentration) for a single 3-h exposure and for 3 h/d, for 5 days. The mice were simultaneously challenged by exposure to aerosols of either *Streptococcus zooepidemicus* or ^{35}S *Klebsiella pneumonia.* Animals challenged with *Streptococcus zooepidemicus* were observed for mortality for 14 days, and animals challenged with ^{35}S *Klebsiella pneumonia* were utilized to determine bactericidal activity. No treatment-related effects were observed on mortality or bactericidal activity in mice receiving a single 3-h acrolein exposure or on mortality in the mice receiving the 5-day acrolein exposure. However, a significant ($p \leq 0.01$) decrease in bactericidal activity was observed in animals exposed to acrolein for 5 days, with 84.3% of bacteria killed in 3 h in animals receiving 0 ppm and only 76.7% of bacteria killed in animals receiving 0.1 ppm. Results from Astry and Jakab (1983) and Aranyi et al. (1986) suggest that acrolein exposure may depress the immune system, making exposed individuals less able to fight infection.

3.2.3. Rats

Groups of 20 male Sprague-Dawley rats were exposed to acrolein at concentrations of 0 or 12 ppm for 4 h (Murphy et al. 1964). Concentrated acrolein vapors were produced by passing a stream of air over liquid acrolein held in a diffusion cell in an ice bath. The experimental atmosphere was then produced by metering the concentrated vapors into a dilution stream of clean air. Animals were exposed in 4-cubic-foot, rectangular stainless-steel whole-body exposure chambers. Lung and serum alkaline phosphatase levels were determined in subgroups of five animals at 0, 5, 24, or 48 h after exposure. During and following exposure, animals exhibited eye and respiratory tract irritation, gasping, dyspnea, anorexia, and generalized weakness. Maximum effects on alkaline phosphatase activity were observed at the 24-h time point; average activities were 36% and 72% of control for serum and lung, respectively.

In another experiment reported in the same paper, groups of 20 male Sprague-Dawley rats were exposed similarly to acrolein at 0 or 6.4 ppm for 4 h. Alkaline phosphatase activity was measured in subgroups of five rats at 4, 24, 48, or 96 h after exposure. Maximal effects on alkaline phosphatase were observed 24 h after exposure, with liver alkaline phosphatase activity being approximately 325% of control. Average serum enzyme levels did not vary significantly from controls. Mean adrenal weights of acrolein-exposed rats were 102%, 132%, 123%, and 121% of air controls at the 4-, 24-, 48-, and 96-h time points, respectively. In yet another experiment in the same report, groups of 15

rats were exposed to acrolein at 0 or 4.4 ppm and removed from the exposure chamber in groups of five after 2, 4, or 8 h. All were sacrificed 24 h after the start of the exposure. Lung and kidney alkaline phosphatase activities did not differ from control values. Mean liver activitiy was 35% below control at 2 h, but was twice the control levels at 8 h.

Springall et al. (1990) exposed groups of three Porton Wistar rats to acrolein at 0, 22.2, 81.1, or 248.6 ppm for 10 min. Acrolein vapor was generated by injecting liquid acrolein into the 50-L aluminum and glass exposure chambers at a constant rate from a syringe drive into the chamber inlet through a 27-gauge needle surrounded by a concentric air jet. Vapor concentrations were set by adjusting the syringe drive delivery rate. Chamber concentrations were determined by UV spectrophotometry. Fifteen minutes after exposure, animals were killed and the respiratory tract dissected out. Frozen sections were prepared from upper and lower trachea and lung. Sections were stained with hematoxylin and eosin for morphology and with antisera to the general neuronal marker PGP 9.5, and the neuropeptides calcitonin gene-related peptide (CGRP), substance P (tachykinin), and vasoactive intestinal polypeptide (VIP). Slight edema and occasional small areas of bleeding into the lungs were observed in mid- and high-dose animals, the effect being more marked in the high-dose animals. There was no difference between treated and control animals in PGP 9.5 or VIP immunoreactivity. The acrolein -exposed animals showed a progressive concentration-dependent decrease in the number of nerve fibers immunoreactive for both CGRP and substance P, the most marked effect being with substance P. These results suggest that acute acrolein exposure is affecting only the sensory nerves and not autonomic fibers because substance P and CGRP are the two primary neuropeptides in the sensory innervation of the rodent respiratory tract. Also, these data suggest that the apparent adaptation to acrolein exposure observed in human volunteers (Weber-Tschopp et al. 1977) may in part be due to nerve damage.

3.2.4. Guinea Pigs

Male Dunkin-Hartley guinea pigs (number per group not specified) were exposed to acrolein at 0 or 1.6 ppm for 7.5 h on each of two consecutive days (Turner et al. 1993). Acrolein was aerosolized by passing 100% N_2 (5 mL/min) over a solution of 0.25 mL of acrolein dissolved in 9.75 mL of sterile water. The aerosol solution was mixed with air (28.5 L/min) and was directed into a 72-L polyurethane exposure chamber. The concentration of acrolein in the chamber was determined immediately before the animals were placed in the chamber and each time the acrolein solution was replaced (every 4 h) by absorption spectrophotometry. There was no difference in the percentage of lavage fluid recovered between exposed animals (54.6 ± 1.45) and controls (55.8 ± 1.87). The ratio of wet-to-dry lung weight was significantly ($p < 0.05$) increased after acrolein exposure (6.43 ± 0.21) compared with controls (5.71 ± 0.08). BAL protein was

significantly ($p < 0.05$) increased in acrolein-exposed animals (144 ± 30.4 μg/mL) compared with controls (69.3 ± 20.0 μg/mL). Acrolein-exposed animals had significantly ($p < 0.05$) increased BAL red blood cells, BAL white blood cells, BAL neutrophil, and BAL monocyte counts and significantly ($p < 0.05$) decreased alveolar macrophage counts compared with controls. Epithelial denudation was observed in 17 of 21 of the large airways of acrolein-exposed guinea pigs examined histologically. This effect was not observed in control animals.

Davis et al. (1967) exposed groups of intact or tracheotomized guinea pigs (strain, sex, and number not specified) to acrolein at17 or 1,600 ppm for up to 60 min. Each animal acted as its own control. The test atmosphere was achieved by positive displacement of an equilibrated atmosphere. The displacement was achieved by inflation of a collapsed double-walled plastic bag into a 20-L bottle containing an "appropriate concentration of acrolein." The desired concentrations were achieved by a diluting flow introduced into the system between the reservoir and the exposure chamber. In intact animals exposed at 17 ppm for 60 min, increased resistance ($p < 0.01$), decreased respiration rate ($p < 0.01$), increased tidal volume ($p < 0.05$), decreased minute volume ($p < 0.05$), and no change in compliance were observed. In tracheotomized animals, none of these changes were observed at 17 ppm for 60 min. Tracheotomized animals exposed at 1,600 ppm died approximately 6 min into exposure without any increase in resistance. No other details were provided.

Random-bred male guinea pigs were exposed to acrolein at 0 ppm (14 animals) or 0.6 ppm (10 animals) acrolein for 2 h (Murphy et al. 1963). The animals were exposed through face masks attached to an exposure manifold that was continuously flushed with clean or acrolein-contaminated air. The experimental atmosphere was produced by passing a stream of air over liquid acrolein. The concentrated vapors were metered into a stream of filtered air to obtain the desired concentration in an animal-exposure manifold. Acrolein concentration was measured by colorimetry. Acrolein-exposed animals exhibited increased respiratory flow resistance and tidal volume and decreased respiratory rate. The response peaked in 30 to 60 min and remained constant for the remainder of the exposure period. When the animals were returned to clean air, respiratory function rapidly returned to pre-exposure baseline. Air-exposed animals showed no effects.

3.2.5. Dogs

Anesthetized mongrel dogs were exposed to synthetic smoke consisting of carbon particles (mean diameter 4.3μm) and acrolein at <200 ppm (low concentration, n = 5), 200-300 ppm (mid-concentration, n = 6), or >300 ppm (highconcentration, n = 8) for 10 min (Hales et al. 1988). Physiologic responses were measured for 4-18 h after exposure, depending on early response. Animals were then killed while deeply anesthetized. No significant changes were observed in pulmonary vascular or airway pressures during exposure. Immediately after ex-

posure, blood gases were not different from baseline values. Concentration-related pulmonary edema was observed. Two of five low-concentration dogs developed mild edema at 2 and 4 h, respectively, after smoke exposure. Histologically, edematous animals showed airway mucosal damage, low-level perivascular and intraseptal edema, and low-level patchy intraalveolar edema. Airway damage was limited to the trachea, carina, and large bronchi. Partial pressure of oxygen in arterial blood (PaO_2) fell in low-concentration animals that did not develop pulmonary edema. Edema was consistently produced in mid- and high-concentration dogs, with extravascular lung water ranging from 1.5 to 3.5 and 2.2 to 2.6 times baseline, respectively. In the mid-concentration group, the edema was patchy and developed at an average of 147 ± 57 min after smoke exposure with one animal taking 6 h. Edema onset in the high-dose group was 65 ± 16 min. After edema onset, the pulmonary arterial pressure rose, CO fell and Pa_{02} fell in the mid- and high-concentration groups.

3.3. Developmental and Reproductive Toxicity

SPF OFA rats were exposed to acrolein at 0 or 0.55 ppm continuously for 4 days (Bouley et al. 1976). Three exposed males were then mated with 21 exposed females and the exposures continued for an additional 22 days, at which time the females were killed. No treatment-related effects were observed on the number of pregnant rats or on the number and mean weight of the fetuses.

In another study, Fischer 344 male rats were exposed to acrolein at 0, 0.14, 1.4, or 4.0 ppm for 6 h/d, 5 d/wk for 62 weeks (Kutzman et al. 1981). The males were then mated with untreated females. No effects on number of viable embryos, resorptions, late deaths, corpora lutea, or sperm morphology were observed.

3.4. Genotoxicity

Although genotoxic studies regarding animal exposure to acrolein were not available, in vitro mutagenicity data were located. Acrolein was positive in an *Escherichia. coli* pol A^+/pol A^- assay in the absence of metabolic activation. It was also mutagenic in *Salmonella typhimurium* TA104 without activation, and both positive and negative results have been obtained in strains TA 98 and TA 100 under a variety of experimental conditions. Negative results were obtained with strains TA 1535, TA 1537, and TA 1538. A weak positive response was obtained with *E. coli* WP2 *uvr*A. Glycidaldehyde, an acrolein metabolite, induced mutations in *Klebsiella pneumoniae*, *Salmonella typhimurium* TA 1535 and TA 100, and *Saccharomyces cerevisiae* and was positive in the mouse lymphoma L5178Y/TK assay. Acrolein did not induce DNA cross-linking or strand breaks in *Saccharomyces cerevisiae* (Beauchamp et al. 1985). However, Costa et al. (1997) reported significant DNA-protein cross-linking in cultured human lymphoma cells at lethal concentrations (≥0.15 mM).

3.5. Carcinogenicity

Feron and Kruysse (1977) exposed groups of 18 male and 18 female Syrian golden hamsters to acrolein at 0 or 4.0 ppm for 7 h/d, 5 d/wk for 52 weeks. Abnormal behavior, growth retardation, increased hemoglobin and packed cell volume, increased relative lung weight, decreased relative liver weight, and rhinitis accompanied by hyperplasia and metaplasia of the nasal epithelium were observed in treated hamsters. No increase in tumor incidence was observed; however, the duration of this study may be too short to fully assess carcinogenicity. In another study, Le Bouffant et al. (1980) exposed 20 female Sprague-Dawley rats to acrolein at 8 ppm for 1 h/d, 7 d/wk for 10-18 months. No evidence of carcinogenicity was observed.

3.6. Summary

Acute lethality data for animal species were abundant; however, experimental details were often not available. Nonlethal animal studies indicate that the respiratory system is the target for acrolein toxicity and that acrolein is a potent irritant at relatively low concentrations and short exposure durations. Irritancy was demonstrated by respiratory rate decreases in rodents, signs of irritation such as gasping and dyspnea, and decreased immunoreactivity of sensory nerve fibers in rodents. At higher concentrations and/or longer exposure times, respiratory system histopathology and pulmonary edema were evident. Data also suggest that exposure to acrolein may suppress pulmonary antibacterial defenses. Genotoxicity data are equivocal. There is no evidence that inhaled acrolein is a reproductiveand developmental toxicant or a carcinogen.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Data regarding the metabolism of acrolein following inhalation exposure were not available; however, Patel et al. (1980) investigated the in vitro metabolism of acrolein in rat liver and lung preparations. Oxidation of acrolein to acrylic acid in liver 9,000 g of supernatant and cytosol required either NAD^+ or $NADP^+$ and was inhibited by disulfiram, suggesting the involvement of aldehyde dehydrogenase. Acrolein was also metabolized to acrylic acid when incubated with liver microsomes. In the presence of NADPH and liver or lung microsomes, acrolein was metabolized to glycidaldehyde, a potent mutagen and carcinogen. Hydration of glycidaldehyde to glyceraldehyde was catalyzed by liver and lung epoxide hydrolase. The glycidaldehyde was also a substrate for liver and lung GSH-S transferases. Although glycidaldehyde is formed in vitro, there is no experimental evidence for its formation in vivo. Acrylic acid and glyceraldehyde can be oxidized to carbon dioxide (CO_2). The glyceraldehyde is

metabolized to CO_2 by glycolytic enzymes, and although the pathway of acrylic acid conversion has not been determined, it is possible that it is metabolized as a short-chain fatty acid.

Egle (1972) exposed anesthetized, male and female mongrel dogs to acrolein concentrations ranging from 172 to 262 ppm for 1 to 3 min. Acrolein retention by the entire respiratory tract averaged 80-85% of the inhaled dose and was independent of respiratory rate. Approximately 20% of the inhaled dose reached the lower respiratory tract. Exposure of only the lower respiratory tract resulted in retention of 65-70% concentration-independent retention; in this case, uptake varied inversely with ventilatory rate.

4.2. Mechanism of Toxicity

Many of the effects of acrolein are caused by reaction with sulfhydryl groups. Acrolein is the most toxic of the 2-alkenals (including crotonaldehyde, pentenal, and hexenal) and is also the most reactive toward sulfhydryl groups. Deactivation of the cellular protein sulfhydryl groups could result in disruption of intermediary metabolism, inhibition of cell growth or division, and cell death. The respiratory irritancy of acrolein may be due to reactivity toward sulfhydryl groups in receptor proteins in the nasal mucosa (Beauchamp et al. 1985).

Li et al. (1997) investigated the effects of acrolein on isolated human alveolar macrophage function and response in vitro. Acrolein induced dose-dependent cytotoxicity as evidenced by the induction of apoptosis and necrosis. At lower doses, the heme oxygenase 1 protein was induced; however, stress protein 72 was not induced. These data suggest that acrolein caused a dose-dependent selective induction of a stress response, apoptosis, and necrosis. Macrophage function was examined by cytokine release in response to acrolein exposure. Acrolein caused a dose-dependent inhibition of IL-1β, TNF-α, and IL-12 release. The cytotoxicity and inhibited cytokine release may be responsible for the acrolein-induced immunosuppression described by Astry and Jakab (1983) and Aranyi et al. (1986) in section 3.2.2 of this document.

4.3. Concurrent Exposure Issues

Acrolein forms adducts with glutathione, cysteine, *N*-acetylcystiene, and other thiols. This reaction may ameliorate the toxicity of acrolein at low concentrations. However, these same adducts may substantially contribute to the toxicity of acrolein (by depletion of important cellular molecules) at high concentrations (ATSDR 2007).

In vitro, acrolein enhances the inhibitory effect of styrene and 1,2-dichloroethane on α1-proteinase inhibitors. Decreased α1-proteinase inhibitor activity may result in an increase in lung neutrophil elastase activity, which in turn may cause emphysema to develop. Acrolein also increases the pentobarbital- and hexobarbital-induced sleeping time in rats, possibly through a covalent

reaction between acrolein and cytochrome P-450. This may lead to an inactivation of the P-450, thereby resulting in lengthened barbiturate action (ATSDR 2007).

Exposure of mice to mixtures of acrolein and sulfur dioxide suggested that either chemical could block the irritancy of the other and that recovery was delayed compared with exposure to individual chemicals. It is postulated that a bisulfite-acrolein adduct is formed, and that when exposure ceases, acrolein is released and slows recovery (ATSDR 2007).

4.4. Structure Activity Relationships

Steinhagen and Barrow (1984) compared the sensory irritation potential of a series of saturated and unsaturated aliphatic and cyclic aldehydes by determining the 10-min RD_{50} values in both male B6C3F_1 and male Swiss-Webster mice. α,β-unsaturated aliphatic aldehydes (including acrolein) yielded RD_{50} values between 1 and 5 ppm. Saturated aliphatic aldehydes with two or more carbons yielded RD_{50} values between 750 and 4,200 ppm, and cyclic aldehydes yielded values between 60 and 400 ppm. No differences were observed between mouse strains.

In another study, Nielsen et al. (1984) determined RD_{50} values of propene derivatives in trachea cannulated, male Ssc:CF-1 mice. Values were 2.9, 3.9, 5.0, and 2.9 ppm for allyl acetate, allyl alcohol, allyl ether, and acrolein, respecttively. The potency of these chemicals varied little for the concentration in air necessary to produce a 50% decrease in respiration. However, when potency was expressed in terms of thermodynamic activity, acrolein was found to be 10 times more potent than the other chemicals tested. The authors attributed that finding either to a higher reactivity of the carbon-carbon double bond or the involvement of the aldehyde group in a secondary chemical binding with the sensory receptor.

5. RATIONALE AND AEGL-1

5.1. Human Data Relevant to AEGL-1

Very slight ocular irritation was reported in healthy human volunteers exposed to acrolein at 0.09 ppm for 5 min (Weber-Tschopp et al. 1977).

5.2. Animal Data Relevant to AEGL-1

Effects observed from inhalation exposure of experimental animals to acrolein are generally more severe than those defined by AEGL-1. A modification of the mouse RD_{50} (Kane et al. 1979) could potentially be used to derive AEGL-1 values.

5.3. Derivation of AEGL-1

Because human data are available, they will be used to derive AEGL-1 values. Very slight eye irritation and annoyance or discomfort were observed in human subjects. The effects were observed at 0.09 ppm, the lowest investigated concentration. An intraspecies uncertainty factor of 3 will be applied and is considered sufficient because minor ocular contact irritation is unlikely to vary greatly among humans (NRC 2001, section 2.5.3.4.4). The values will be held constant across time for the 10-min, 30-min, 1-h, 4-h, and 8-h time points because minor irritancy is generally a threshold effect, and prolonged exposure is not likely to result in a greatly enhanced effect (NRC 2001). The AEGL-1 values for acrolein are presented in Table 1-7, and the calculations for these AEGL-1 values are presented in Appendix A.

These AEGL-1 values are considered protective because the data of Darley et al. (1960) suggested no irritation in humans exposed to acrolein at 0.06 ppm for 5 min.

6. RATIONALE AND AEGL-2

6.1. Human Data Relevant to AEGL-2

Moderate to severe ocular and nasal irritation accompanied by a 10-15% decrease in respiratory rate were reported in human volunteers exposed to acrolein at a concentration of 0.3 ppm for 1 h, (Weber-Tschopp et al. 1977).

6.2. Animal Data Relevant to AEGL-2

Slight edema and bleeding into the lungs were observed in dogs exposed to acrolein at 81.1 ppm for 10 min (Springall et al. 1990). However, extrapolating from 10 min to 8 h is of questionable validity. Severe irritation, increased alkaline phosphatase activity, and increased adrenal weight were observed in rats exposed to acrolein at 6.4 ppm for 4 h (Murphy et al. 1964), and Murphy et al. (1963) observed increased respiratory flow resistance and tidal volume and decreased respiratory rate in guinea pigs exposed for 2 h at 0.6 ppm. Although effects observed in the rat and guinea pig studies are consistent with those defined by AEGL-2, the experimental methods and results are incompletely described. A modification of the mouse RD_{50} (Kane et al. 1979) could also potentially be used to derive AEGL-2 values.

TABLE 1-7 AEGL-1 Values for Acrolein

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)

6.3. Derivation of AEGL-2

Because human data are available, they will be used to derive AEGL-2 values. A 10-15% decrease in respiratory rate was noted in humans exposed to acrolein at 0.3 ppm for one h; whereas a 25% decrease in respiratory rate was noted in humans exposed at 0.6 ppm (Weber-Tschopp, et al. 1977). According to ASTM (1991), decreases in respiratory rate in the range of 12-20% correspond to slight irritation, and decreases in respiratory rate in the range of 20-50% correspond to moderate irritation. Decreases in respiratory rates after contact of nasal mucosa with irritants (including acrolein) are due to stimulation of nerve endings of the afferent trigeminal nerve in the nasal mucosa. This mechanism has been described for all species tested, including humans (Alarie et al. 1981). The AEGL-2 will be based on the 10-15% decrease in respiratory rate in healthy human subjects exposed to acrolein at 0.3 ppm for 1 h. This is considered a NOAEL for moderate irritation. An intraspecies uncertainty factor of 3 will be applied and is considered sufficient because irritation is not expected to vary greatly between individuals (NRC 2001, section 2.5.3.4.4). This uncertainty factor is further justified because of the sensitivity of the methods used, the fact that the point-of-departure effect was only a very small detectable decrease in respiration, the lack of evidence of marked variability across the study group, including women; and the fact that at twice the concentration, respiration was still only slightly decreased. Also, application of the default uncertainty factor of 10 would yield AEGL-2 values in the concentration range where only minor irritation was noted in controlled human studies. This value will be back-extrapolated to the 10- and 30-min time points using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 1.2, (derived from lethality data in rats exposed to acrolein from 1 to 4 h; Ballantyne et al. 1989, Appendix D). Time scaling using the exponent, n, derived from rat lethality data is considered appropriate because the mechanism of lethality (pulmonary congestion resulting from severe irritation) is similar to the critical effect (irritation) used for AEGL-2 derivation. The 1-h exposure of 0.3 ppm will be held constant for the 4- and 8-h AEGL-2 values because irritation is generally a threshold effect, and prolonged exposure is not likely to result in a greatly enhanced effect (NRC 2001). The AEGL-2 values for acrolein are presented in Table 1-8, and the calculations for these AEGL-2 values are presented in Appendix A.

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

Human lethality data were sparse and anecdotal and were lacking reliable concentration and time parameters and are thus not appropriate for establishing the AEGL-3 values.

TABLE 1-8 AEGL-2 Values for Acrolein

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.44 ppm (0.92 mg/m^3)	0.18 ppm (0.41 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)

7.2. Animal Data Relevant to AEGL-3

Many lethality data exist in a variety of species (mouse, rat, guinea pig, rabbit, and dog). However, in most cases, experimental parameters are poorly described, and the quality of the data is questionable for AEGL derivation. The rat LC_{50} study of Ballantyne et al. (1989) is an exception and is appropriate for AEGL-3 derivation.

7.3. Derivation of AEGL-3

The 10-min, 30-min, and 1-h AEGL-3 values will be based on the highest concentration causing no mortality in the rat after a 1-h exposure (14 ppm), and the 4-h and 8-h AEGL-3 values will be based on the highest concentration causing no mortality in the rat after a 4-h exposure (4.8 ppm) (Ballantyne et al. 1989). Intraspecies and interspecies uncertainty factors of 3 each will be applied (total UF = 10), and are considered sufficient because irritation is not expected to vary greatly within or among species. Furthermore, application of either an intra- or interspecies uncertainty factor of 10 (total UF = 30) would yield values that are inconsistent with the total database. (For example, AEGL-3 values for acrolein would range from 2.1 to 0.09 ppm, and only ocular, nasal, or throat irritation and decreased respiratory rates were observed in humans exposed to acrolein at 0.09 to 0.6 ppm for up to 40 min (Weber-Tschopp, et al. 1977). It is unlikely that people exposed to this range of acrolein for 10 min to 8 h would experience effects defined by AEGL-3. Values were extrapolated using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 1.2 (derived from lethality data in rats exposed to acrolein from 1 to 4 h). The AEGL-3 values for acrolein are presented in Table 1-9, and the calculations for these AEGL-3 values are presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGL values for various levels of effect and duration of exposure are summarized in Table 1-10. Decreased respiratory rates and sensory irritation in humans were used as the basis for AEGL-1 and AEGL-2. Concentrations causing no deaths in rats were used for the AEGL-3.

8.2. Other Exposure Criteria

The exposure criteria for acrolein exposure have been established and are shown in Table 1-11.

TABLE 1-9 AEGL-3 Values for Acrolein

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	6.2 ppm (14 mg/m^3)	2.5 ppm (5.7 mg/m^3)	1.4 ppm (3.2 mg/m^3)	0.48 ppm (1.1 mg/m^3)	0.27 ppm (0.62 mg/m^3)

TABLE 1-10 Summary of AEGL Values for Acrolein

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)	0.030 ppm (0.070 mg/m^3)
AEGL-2 (Disabling)	0.44 ppm (0.92 mg/m^3)	0.18 ppm (0.41 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)	0.10 ppm (0.23 mg/m^3)
AEGL-3 (Lethal)	6.2 ppm (14 mg/m^3)	2.5 ppm (5.7 mg/m^3)	1.4 ppm (3.2 mg/m^3)	0.48 ppm (1.1 mg/m^3)	0.27 ppm (0.62 mg/m^3)

TABLE 1-11 Extant Standards and Guidelines for Acrolein

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.030 ppm	0.030 ppm	0.030 ppm	0.030 ppm	0.030 ppm
AEGL-2	0.44 ppm	0.18 ppm	0.10 ppm	0.10 ppm	0.10 ppm
AEGL-3	6.2 ppm	2.5 ppm	1.4 ppm	0.48 ppm	0.27 ppm
ERPG-1 (AIHA)[a]			0.1 ppm		
ERPG-2 (AIHA)[a]			0.5 ppm		
ERPG-3.(AIHA)[a]			3 ppm		
IDLH(NIOSH)[b]		2 ppm			
REL-TWA (NIOSH)[c]					0.1 ppm
PEL-TWA (OSHA)[d]					0.1 ppm
TLV-TWA (ACGIH)[e]					Withdrawn
REL-STEL (NIOSH)[f]	0.3 ppm (15 min)				
PEL-STEL (OSHA)[g]	Withdrawn				
TLV-STEL (ACGIH)[h]	0.1 ppm ceiling (15 min)				
MAC (The Netherlands)[i]					0.1 ppm

(Continued)

TABLE 1-11 Continued

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
OELV-LLV (Sweden)[j]					0.1 ppm
OELV-STV (Sweden)[j]	0.3 ppm (15 min)				

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2004). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for acrolein is based on human odor and irritation thresholds. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for acrolein is based on eye and respiratory irritation. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for acrolein is based on animal lethality data and human experience.

[b]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.

[c]REL-TWA (recommended exposure limit–time-weighted average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA.

[d]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Safety and Health Administration) (23 CFR 1910.1000[1999]) is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/d, 40 h/wk.

[e]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) 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 without adverse effect.

[f]REL-STEL (recommended exposure limit–short-term exposure limit, National Institute of Occupational Safety and Health) (NIOSH 2005)is defined analogous to the ACGIH TLV-TWA.

[g]PEL-STEL (permissible exposure limit–short-term exposure limit, Occupational Safety and Health Administration) (23 CFR 1910.1000[1999]) is defined analogous to the ACGIH TLV-STEL.

[h]TLV-STEL (Threshold Limit Value–short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is for a 15-min. exposure

[i]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

[j]OEL-LLV (occupational exposure limit–level-limit value).

OEL-STV (occupational exposure limit–short-term value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level-limit value (1 working day) or a ceiling-limit value (15 min or some other reference time period), and short-time value. (A recommended value consisting of a time-weighted average for exposure during a reference period of 15 min.)

NIOSH immediately dangerous to life and health (IDLH) is defined by the NIOSH/OSHA Standard Completions Program only for the purpose of respirator selection and represents a maximum concentration from which, in the event of respiratory failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health effects.

OSHA permissible exposure level (PEL) is a time-weighted average (8 h/d, 40 h/wk).

8.3. Data Quality and Research Needs

Human data appropriate for derivation of AEGL-1 and AEGL-2 were available in a well-conducted study. However, no information was available concerning acrolein effects in young, elderly or asthmatic individuals. Animal data were available for derivation of AEGL-3 values. Although there are a plethora of acrolein studies, many are not appropriate for derivation of AEGL values. Well-conducted acute toxicity studies in animal species other than the rat might help support the derived AEGL values.

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APPENDIX A

Derivation of AEGL Values for Acrolein

Derivation of AEGL-1

Key study:	Weber-Tschopp et al. 1977
Toxicity end point:	Very slight eye irritation and "annoyance" or discomfort in healthy humans.
Scaling:	None
Uncertainty factor:	3 for intraspecies variability.
AEGL-1: (all time periods)	0.09 ppm ÷ 3 = 0.030 ppm

Derivation of AEGL-2

Key study:	Weber-Tschopp et al. 1977.
Toxicity end point:	10-15% decrease in respiratory rate in healthy humans
Scaling:	$C^{1.2} \times t = k$ for extrapolation to 10 and 30 min (0.3 ppm) $C^{1.2} \times 1$ h = 0.236 ppm-h The 1-h exposure of 0.3 ppm was held constant for the 1-h, 4-h, and 8-h. AEGL-2 values since irritation is generally a threshold effect and a prolonged exposure is not likely to result in a greatly enhanced effect.
Uncertainty factor:	3 for intraspecies variability.
Calculations:	
10-min AEGL-2	$C^{1.2} \times 0.167$ h = 0.236 ppm-h $C^{1.2}$ = 1.41 ppm C = 1.33 ppm 10-min AEGL-2 = 1.33 ÷ 3 = 0.44 ppm
30-min AEGL-2	$C^{1.2} \times 0.5$ h = 0.236 ppm-h $C^{1.2}$ = 0.472 ppm C = 0.535 ppm 30-min AEGL-2 = 0.535 ÷ 3 = 0.18 ppm
1-, 4-, and 8-h AEGL-2	0.3 ppm ÷ 3 = 0.10 ppm

Derivation of AEGL-3

Key study:	Ballantyne et al. 1989
Toxicity end points:	Concentration causing no death in rats for a 1-h exposure (10 min, 30 min, 1 h). Concentration causing no death in rats for a 4-h exposure (4 h, 8 h).
Scaling:	$\frac{\text{10 min, 30 min, 1 h}}{C^{1.2} \times t = k}$ $(14 \text{ ppm})^{1.2} \times 1 \text{ h} = 23.7 \text{ ppm-h}$ $\frac{\text{4 min, 8 h}}{C^{1.2} \times t = k}$ $(4.8 \text{ ppm})^{1.2} \times 4 \text{ h} = 26.27 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies variability. 3 for intraspecies variability.
Calculations:	
10-min AEGL-3	$C^{1.2} \times 0.167 \text{ h} = 23.7 \text{ ppm-h}$ $C^{1.2} = 141.9 \text{ ppm}$ $C = 62.1 \text{ ppm}$ 10-min AEGL-3 = $62.1 \div 10 = 6.2 \text{ ppm}$
30-min AEGL-3	$C^{1.2} \times 0.5 \text{ h} = 23.7 \text{ ppm·h}$ $C^{1.2} = 47.4 \text{ ppm}$ $C = 24.9 \text{ ppm}$ 30-min AEGL-3 = $24.9 \div 10 = 2.5 \text{ ppm}$
1-h AEGL-3	$14 \text{ ppm} \div 10 = 1.4 \text{ ppm}$
4-h AEGL-3	$C^{1.2} \times 4 \text{ h} = 26.27 \text{ ppm-h}$ $C^{1.2} = 6.57 \text{ ppm}$ $C = 4.79 \text{ ppm}$ 1-h AEGL-3 = $4.79 \div 10 = 0.48 \text{ ppm}$
8-h AEGL-3	$C^{1.2} \times 8 \text{ h} = 26.27 \text{ ppm-h}$ $C^{1.2} = 3.28 \text{ ppm}$ $C = 2.69 \text{ ppm}$ 1-h AEGL-3 = $2.69 \div 10 = 0.27 \text{ ppm}$

APPENDIX B

Derivation Summary of AEGL Values for Acrolein

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.030 ppm	0.030 ppm	0.030 ppm	0.030 ppm	0.030 ppm

Key Reference: Weber-Tschopp, A., T. Fischer, R. Gierer, et al. 1977. Experimentally induced irritating effects of acrolein on men. Int. Arch. Occup. Environ. Health 40: 117-130.

Test Species/Strain/Number: Human/31 males and 25 females/young adults.

Exposure Route/Concentrations/Durations:
Inhalation/0 to 0.6 ppm with concentration increasing for 35 min, then constant at 0.6 ppm for 5 min; 0, 0.15, 0.30, 0.45, and 0.60 ppm for several 1.5-min exposures with a recovery period of 8 min between exposures; or 0.3 ppm for 60 min.

Effects: At 0.09 ppm, "annoyance"/discomfort and very slight eye irritation; at 0.15 ppm, nose irritation; at 0.26 ppm, doubling of blinking rate; at 0.3 ppm, 10% decrease in respiratory rate; at 0.43 ppm, throat irritation; and at 0.6 ppm, 25% decrease in respiratory rate. Effects are reported as threshold effects. (0.09 ppm determinant for AEGL-1).

End Point/Concentration/Rationale: eye irritation, annoyance/discomfort in humans at 0.09-ppm threshold.

Uncertainty Factors/Rationale:
Interspecies: 1, subjects were humans.
Intraspecies: 3, considered sufficient because minor ocular contact irritation is not likely to vary greatly between individuals; also, derived values are 2-fold below a no-observed-effect level (NOEL) for irritation in another human study (0.06 ppm, 5 min) (Darley et al. 1960).

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Values were held constant because minor irritation is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect.

Data Adequacy: Well-conducted human study.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.44 ppm	0.18 ppm	0.10 ppm	0.10 ppm	0.10 ppm

Key Reference: Weber-Tschopp, A., Fischer, T., Gierer, R. et al. 1977. Experimentally induced irritating effects of acrolein on men. Int. Arch. Occup. Environ. Health 40:117-130.

Test Species/Strain/Number: Human/31 males and 25 females/young adults.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.44 ppm	0.18 ppm	0.10 ppm	0.10 ppm	0.10 ppm

Exposure Route/Concentrations/Durations:
Inhalation/0 to 0.6 ppm with concentration increasing for 35 min, then constant at 0.6 ppm for 5 min; 0, 0.15, 0.30, 0.45, and 0.60 ppm for several 1.5-min exposures with a recovery period of 8 min between exposures; or 0.3 ppm for 60 min.

Effects: At 0.09 ppm, annoyance/discomfort and very slight eye irritation; at 0.15 ppm, nose irritation; at 0.26 ppm, doubling of blinking rate; at 0.3 ppm, 10-15% decrease in respiratory rate; at 0.43 ppm, throat irritation; at 0.6 ppm, 25% decrease in respiratory rate. Effects are threshold effects (0.3 ppm determinant for AEGL-2).

End Point/Concentration/Rationale: 10-15% decrease in respiratory rate in humans/0.3 ppm/NOAEL for moderate irritation; decreases in respiratory rate in the range of 12% to 20% correspond to slight irritation, and decreases in respiratory rate in the range of 20% to 50% correspond to moderate irritation (ASTM 1991).
Uncertainty Factors/Rationale:
Interspecies: 1, subjects were human.
Intraspecies: 3, considered sufficient because irritation is unlikely to vary greatly among individuals. This uncertainty factor is further justified because of the sensitivity of the methods used, the fact that the point-of-departure effect was only a very small detectable decrease in respiration, the lack of evidence of marked variability across the study group, including women, and the fact that at twice the concentration, respiration was still only slightly decreased. Also, application of the default uncertainty factor of 10 yields AEGL-2 values in the range of concentrations where only minor irritation was noted in controlled human studies.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: The 1-h exposure of 0.3 ppm was adjusted by temporal scaling to obtain the 10- and 30-min AEGL-2 values using the relationship $C^n \times t = k$, where $n = 1.2$ (derived from lethality data in rats exposed to acrolein from 1 to 4 h). The 1-h exposure of 0.3 ppm was held constant for the 4- and 8-h AEGL-2 values because irritation is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect.

Data Adequacy: A well-conducted study in healthy humans was available. Irritative effects remained constant after approximately 40 min.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
6.2 ppm	2.5 ppm	1.4 ppm	0.48 ppm	0.27 ppm

Key Reference: Ballantyne, B., Dodd, D.E., Pritts, D.J., et al. 1989. Acute vapor inhalation toxicity of acrolein and its influence as a trace contaminant in 2-methoxy-3,4-dihydro-2H-pyran. Human Toxicol. 8:229-235.

Test Species/Strain/Sex/Number: Sprague-Dawley rats/ 5 males and 5 females per concentration.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
6.2 ppm	2.5 ppm	1.4 ppm	0.48 ppm	0.27 ppm

Exposure Route/Concentrations/Durations:
Rats/Inhalation: 14, 22, 24, 31, or 81 ppm for 1 h or 4.8, 7.0, 9.1, or 12.1 ppm for 4 h

End Point/Concentration/Rationale: No deaths in rats/14 ppm/threshold for death for 1-h exposure (determinant for 10-min, 30-min, and 1-h AEGL-3 values); no deaths in rats/ 4.8 ppm/threshold for death for 4-h exposure in rats (determinant for 4-h and 8-h AEGL-3 values).

Uncertainty Factors/Rationale: Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Intraspecies and interspecies uncertainty factors of 3 each are considered sufficient because irritation is not expected to vary greatly within or among species. Furthermore, application of either an intra- or interspecies uncertainty factor of 10 (total UF = 30) would yield values that are inconsistent with the total database. (For example, AEGL-3 values for acrolein would range from 2.1 to 0.09 ppm, and only ocular, nasal, or throat irritation and decreased respiratory rates were observed in humans exposed to acrolein at 0.09 to 0.6 ppm for up to 40 min (Weber-Tschopp, et al. 1977)). It is unlikely that people exposed to this range of acrolein for 10-min to 8-h would experience effects defined by AEGL-3.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: $C^n \times t = k$, where n = 1.2, derived from lethality data in rats exposed to acrolein from 1 to 4 h. Data point used for 10-min, 30-min and 1-h AEGL-3 derivation was 1 h. Data point used for 4-h and 8-h AEGL-3 derivation was 4 h (Appendix D).

Data Adequacy: Well-conducted study with appropriate end point for AEGL-3.

APPENDIX C

Category Plot for Acrolein

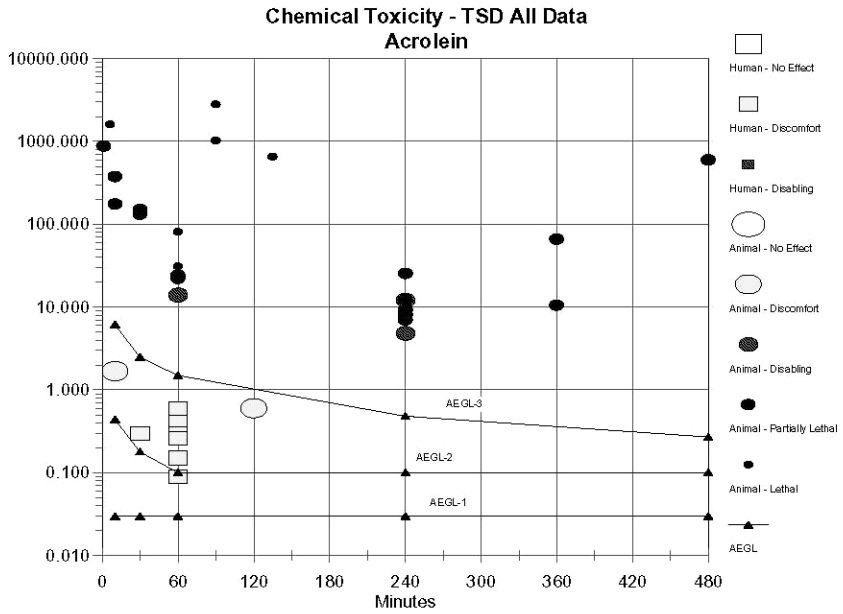

FIGURE C-1 Category plot for acrolein.

APPENDIX D

Temporal Extrapolation for Acrolein

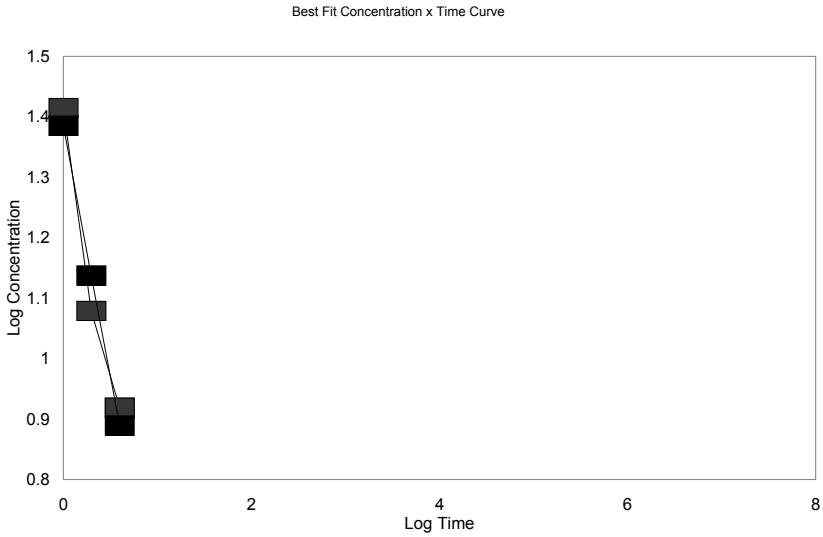

FIGURE D-1 Best fit concentration × time curve.

Time	Conc.	Log Time	Log Conc.	Regression Output:	
1	26	0.0000	1.4150	Intercept	1.3857
2	12	0.3010	1.0792	Slope	-0.8237
4	8.3	0.6021	0.9191	R Squared	0.9598
				Correlation	-0.9797
				Degrees of Freedom	1
				Observations	3

n = 1.21
k = 48.12

Minutes	Conc.	Hours	Conc.
30	1.48	0.5	43.02
60	0.83	1.0	24.30
240	0.27	4.0	7.76
480	0.15	8.0	4.38

2

Carbon Monoxide[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 recommended exposure levels are applicable to the general population, including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [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 Peter Griem (Clariant, Sulzbach, Germany) and Chemical Managers George Rodgers and Iris Camacho (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, 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/m³) 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/m³) 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 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 AEGLs represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Carbon monoxide (CO) is a tasteless, nonirritating, odorless, and colorless gaseous substance. The main source of CO production is the combustion of fuels. Exposure at the workplace occurs in blast-furnace operations in the steel industry and when gasoline- or propane-powered forklifts, chain-saws, or other machines are used in confined spaces, such as companies, tunnels and mines. Environmental exposure to CO can occur while traveling in motor vehicles (9-25 ppm and up to 35 ppm); visiting urban locations with heavily traveled roads (up to 50 ppm); or cooking and heating with domestic gas, kerosene, coal, or wood (up to 30 ppm); as well as in fires and by environmental tobacco smoke. Endogenous CO formation during normal metabolism leads to a background carboxyhemoglobin (COHb) concentration of about 0.5-0.8%. Smokers are exposed to considerable CO concentrations leading to a COHb of about 3-8%.

CO binds to hemoglobin, forming COHb, and thereby renders the hemoglobin molecule less able to bind oxygen. Because of this mechanism, the oxygen transport by the blood and the release of bound oxygen in the tissues are decreased. Tissue damage results from local hypoxia. Organs with a high oxygen requirement, such as the heart and the brain, are especially sensitive for this effect.

AEGL-1 values were not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.

Patients with coronary artery disease show health effects at lower COHb concentrations than children, pregnant women, or healthy adults and thus constitute the most susceptible subpopulation. For the derivation of AEGL-2 values, a level of 4% COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al. 1989a, 1991). In the available studies, the CO exposure alone (that is, with subjects at rest) did not cause angina, but exercise alone did so. However, because all studies used patients with stable exertional angina, who did not experience angina while at rest, the possibility cannot be ruled out that CO exposure alone could cause or increase angina symptoms in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group). The changes in the electrocardiogram (ST-segment depression of 1 mm [corresponding to 0.1 mV] or greater) associated with angina symptoms were considered reversible, but they are indicative of clinically relevant myocardial ischemia requiring medical treatment. An exposure level of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. Ventricular arrhythmias have been observed at a COHb of 5.3% but not at 3.7% (Sheps et al. 1990, 1991); in another study, no effect of CO exposure on ventricular arrhythmia was found at 3% or 5% COHb (Dahms et al. 1993). This exposure level, which corresponds to COHb values of 5.0-5.6% in newborns and children, was considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness, and dyspnea (Crocker and Walker 1985, Klasner et al. 1998), and long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children (Klees et al. 1985). A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations in air, resulting in a COHb of 4% in adults at the end of exposure periods of 10 and 30 min and 1, 4, and 8 h. A total uncertainty factor of 1 was used. A level of 4% COHb was the no-observed-effect level (NOEL) for AEGL-2 effects in patients with coronary artery disease, and the lowest-observed-effect level (LOEL) was estimated at 6-9%. In comparison, the LOEL was about 10-15% in children and 22-25% in pregnant women. Because AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective for other subpopulations, and a total uncertainty factor of 1 was used.

It is acknowledged that apart from emergency situations, certain scenarios could result in CO concentrations that might cause serious effects in persons with cardiovascular diseases. These scenarios include extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defective car exhaust systems), charcoal or wood fire furnaces, and indoor air pollution from tobacco smoke.

The derivation of AEGL-3 values was based on a weight of evidence analysis of human lethal and nonlethal observations. Analysis of lethal cases reported by Nelson (2006a) indicated that most lethal poisoning cases occurred at COHb concentrations higher than 40% and that survival of CO-exposed hu-

mans was likely to be seen at concentrations below 40%. Thus, a 40% COHb concentration seems to be a reasonable threshold for lethality.

This level is supported by experimental studies performed in healthy human subjects. Studies by Haldane (1895), Henderson et al. (1921), and Chiodi et al. (1941) suggest that a COHb of about 34-56% does not cause lethal effects in healthy individuals. Further support come from the studies by Stewart et al. (1970), Nielsen (1971) and Kizakevich et al. (2000), who reported headache as the only symptom when subjects were exposed to 20-33% COHb. A level of 40% COHb was used as the basis for AEGL-3 derivation. This point of departure is supported by studies reporting minimum lethal COHb concentrations in rats and mice of about 50-70% (Rose et al. 1970, E.I. du Pont de Nemours and Co. 1981). A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations in air resulting in a COHb of 40% at the end of exposure periods of 10 and 30 min and 1, 4, and 8 h. A total uncertainty factor of 3 was used. A total uncertainty factor of 3 for intraspecies variability was considered adequate based on supporting evidence for susceptible subpopulations: (1) Exposure to the derived AEGL-3 concentrations will result in COHb values of about 14-17% in adults, which, based on case reports, were considered protective of heart patients against CO-induced myocardial infarction. It should be noted, however, that a clear threshold for this end point cannot be defined because myocardial infarction might be triggered at lower COHb in hypersusceptible individuals. (2) COHb concentrations of 14-17% were considered protective of the unborn against lethal effects because, in the case studies available, stillbirths were found only after measured maternal COHb concentrations were about 22-25% or higher (Caravati et al. 1988; Koren et al. 1991). Animal studies support that result. The AEGL values are listed in Table 2-1.

1. INTRODUCTION

CO is a tasteless, odorless, and colorless gaseous substance (WHO 1999a). CO is produced by both natural and anthropogenic processes. The main source of CO production is the combustion of fuels. The burning of any carbonaceous fuel produces CO and carbon dioxide (CO_2) as the primary products. The production of CO_2 predominates when the air or oxygen supply is in excess of the stoichiometric needs for complete combustion. If burning occurs under fuel-rich conditions, with less air or oxygen than is needed, CO will be produced in abundance (WHO 1999a). Emission sources include gasoline- and diesel-powered motor vehicles, stationary combustion equipment, such as heating and power-generating plants; industrial processes, such as blast-furnace operation in the steel industry; indoor sources, such as gas ovens, unvented kerosene, and gas space heaters; and coal and wood stoves, as well as wildfires and tobacco smoking. Exposure at the workplace occurs in blast-furnace operations in the steel

TABLE 2-1 Summary of AEGL Values for Carbon Monoxide

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	N.R.[a]	N.R.	N.R.	N.R.	N.R.	—
AEGL-2[b] (Disabling)	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)	Cardiac effects in humans with coronary artery disease (Allred et al. 1989a, 1991)
AEGL-3[c] (Lethal)	1700 ppm (1900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)	Lethal poisoning was associated with a COHb ≥40% in most lethal poisoning cases reported by Nelson (2006a); no severe or life-threatening effects in healthy humans at a COHb of 34-56% (Haldane 1895; Henderson et al. 1921; Chiodi et al. 1941)

[a]N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.
[b]It was estimated that exposure to the AEGL-2 concentration–time combinations result in COHb concentrations of 5.3-5.6% in newborns, 4.9-5.2% in 5-year-old children, 4.0% in adults, and 6.2-11.5% in adult smokers.
[c]Exposure to the AEGL-3 concentration–time combinations were estimated to result in COHb concentrations of 19.5-20.1% in newborns, 18.1-187% in 5-year-old children, 13.8-17.2% in adults, and 16.1-23.0% in adult smokers.

industry and when gasoline- or propane-powered forklifts, chain-saws, or other machines are used in confined spaces, such as companies, tunnels, and mines. Low concentrations are produced in the atmosphere by the reactions of hydroxyl radicals with methane and other hydrocarbons as well as by the reactions of alkenes with ozone.

In addition to exogenous sources, humans are also exposed to small amounts of CO produced endogenously. In the process of natural degradation of hemoglobin to bile pigments, oxidation of the tetrapyrrol ring of heme leads to opening of the ring and formation of biliverdin and CO (WHO 1999a). The endogenous CO formation leads to a background COHb concentration in blood of about 0.5-0.8% (NIOSH 1972).

Increased destruction of red blood cells—for example, caused by hematomas, blood transfusion, or intravascular hemolysis—and accelerated breakdown of other heme proteins will lead to increased production of CO. In patients with hemolytic anemia, the CO production rate was 2-8 times higher and blood COHb was 2-3 times higher than in healthy individuals (Coburn et al. 1966).

Smokers are exposed to considerable CO concentrations leading to an average COHb of 4%, with a usual range of 3-8% (Radford and Drizd 1982).

Exposure to CO can also be caused indirectly by exposure to certain halomethanes, particularly dichloromethane (synonym, methylene chloride) because these solvents are at least partly metabolized oxidatively to CO by cytochrome P-450 (Gargas et al. 1986; see ATSDR 2000 for review).

Environmental exposure to CO can occur while traveling in motor vehicles, working, visiting urban locations associated with combustion sources, or cooking and heating with domestic gas, charcoal or wood fires, as well as by environmental tobacco smoke. WHO (1999a) summarized environmental concentrations as follows: CO concentrations in ambient air monitored from fixed-site stations are generally below 9 ppm (8 h average). However, short-term peak concentrations up to 50 ppm are reported on heavily traveled roads. The CO levels in homes are usually lower than 9 ppm; however, the peak value in homes could be up to 18 ppm with gas stoves, 30 ppm with wood combustion, and 7 ppm with kerosene heaters. The CO concentrations inside motor vehicles are generally 9-25 ppm and occasionally over 35 ppm. Similar exposure levels were reported by EPA (2000). The chemical and physical properties of CO are presented in Table 2-2.

2. HUMAN TOXICITY DATA

On the basis of older literature, the COHb in the blood has been correlated with symptoms in healthy adults, shown in the left half of Table 2-3 (WHO 1999a). Very similar tables or descriptions are found in different publications (e.g., Stewart 1975; Winter and Miller 1976; Holmes 1985; Roos 1994; AIHA 1999). However, with respect to both lethal and nonlethal effects of CO, suscep-

TABLE 2-2 Chemical and Physical Data for Carbon Monoxide

Parameter	Data	Reference
Synonyms	None	
Chemical Name	Carbon monoxide	WHO 1999a
CAS Reg. No.	630-08-0	WHO 1999a
Chemical formula	CO	WHO 1999a
Molecular weight	28.01	WHO 1999a
Physical state	Gaseous	WHO 1999a
Color	Colorless	WHO 1999a
Odor	Odorless	WHO 1999a
Melting point	−199°C	WHO 1999a
Boiling point	−191.5°C	WHO 1999a
Density	1.250 g/L at 0°C 1.145 g/L at 25°C	WHO 1999a
Solubility	35.4 mL/L at 0°C 21.4 mL/L at 25°C	WHO 1999a
Explosive limits in air	12.5% (LEL) to 74.2% (UEL)	WHO 1999a
Conversion factors	1 ppm = 1.145 mg/m^3 1 mg/m^3 = 0.873 ppm	WHO 1999a

tible subpopulations have been identified, and effects on these are depicted in the right half of Table 2-3 for comparison (see subsequent sections for references). The unborn fetus and adults with coronary artery disease are considerably more susceptible for lethal effects of CO than healthy adults. For nonlethal effects of CO, subjects with coronary artery disease (increased frequency of arrhythmias and reduced time to onset of angina and to changes in the electrocardiogram) and children (syncopes and long-lasting neurotoxic effects) constitute susceptible subpopulations.

2.1. Acute Lethality

Mortality from CO poisoning is high in England and Wales; 1,365 deaths due to CO exposure were reported in 1985. In the United States, more than 3,800 people annually die from accidental or intentional CO exposure (WHO 1999a).

Immediate death from CO is most likely caused by effects on the heart because the myocardial tissue is most sensitive to hypoxic effects of CO. Severe poisoning results in marked hypotension and lethal arrhythmias, which have been considered responsible for a large number of prehospital deaths. Rhythm disturbances include sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, ventricular tachycardia, and fibrillation (WHO 1999a).

TABLE 2-3 Symptoms Associated with COHb in Healthy Adult Humans and Susceptible Subpopulations

Healthy Adults		Susceptible Subpopulations	
COHb (%)	Symptoms	COHb (%)	Symptoms
≈1	Physiologic background concentration	2	During physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischemia in subjects with coronary artery disease
3-8	Background concentration in smokers	5-6	Increase in cardiac arrhythmias in subjects with coronary artery disease
		7	Headache, nausea in children
10	No appreciable effect, except shortness of breath on vigorous exertion, possible tightness across the forehead, dilation of cutaneous blood vessels	13	Cognitive development deficits in children
		15	Myocardial infarction in subjects with coronary artery disease
20	Shortness of breath on moderate exertion, occasional headache with throbbing in temples	25	Syncopes in children
		25	Stillbirths
30	Decided headache, irritable, easily fatigued, judgment disturbed, possible dizziness, dimness of vision		
40-50	Headache, confusion, collapse, fainting on exertion		
60-70	Unconsciousness, intermittent convulsion, respiratory failure, death if exposure is long continued		
80	Rapidly fatal		

Source: Adapted from WHO 1999a.

The susceptible subpopulations for lethal effects are subjects with coronary artery disease and the unborn fetus (see Section 2.3). The review on death causes by Balraj (1984) shows an association between coronary artery disease and relatively low COHb concentrations. A number of case studies are presented in which CO exposure contributed to myocardial infarction (all cases of infarction are presented in this section irrespective of whether the patients were rescued from death by intensive medical care).

The British Standards Institution (BSI 1989) published the following concentration–time combinations as lethal exposures to CO (used for hazard estimation in fires): 40,000 ppm × 2 min, 16,000 ppm × 5 min, 8,000 ppm × 10 min, 3,000 ppm × 30 min and 1,500 ppm × 60 min. The International Standard Organization (ISO) published lethal exposure concentrations of 12,000-16,000

ppm for 5 min and 2,500-4,000 ppm for 30 min (for an adult engaged in light activity) (ISO 1989). From the documents, it was concluded that the published values are for normal, healthy adults and that the values were based on animal data (especially monkeys; Purser and Berrill 1983); the documents did not discuss the issue of subpopulations at higher risk for lethal effects.

2.1.1. Case Studies

Nelson (2006a) reported data on unvented space heaters related to human lethality and CO poisoning. Sixteen of 22 lethal cases had COHb concentrations more than 40%. Six of 22 cases had COHb concentrations of ≤40%, and two of six cases had pre-existing conditions, such as arteriosclerotic disease and cardiorespiratory failure. A 1942 fatality study reported by Nelson (2006a) summarized COHb data for 68 victims that were found dead in a gas-filled room or in a garage containing exhaust gases at high concentrations. CO concentrations were not provided. Sixty-seven percent of the 68 lethal cases had COHb concentrations of 40-88%. Three-percent of those cases had concentrations of 30-40%. A summary of another fatality study from Poland showed a similar trend of COHb concentrations (Nelson 2006a). Individual data were not provided, and the CO source was not discussed. However, the Polish study considered 321 lethal CO poisonings from 1975 to 1976 and provided COHb concentrations for 220 survivors and 101 fatal cases. The survivors had a mean COHb level of 28.1% (standard deviation [SD] = 14.1), whereas the lethal cases showed an average COHb level of 62.3% (SD = 10.1). Over 80% of the survivors had COHb levels below 40%. In contrast, about 90% of the deceased had COHb levels above 50%. Similar percentages of survivors and deceased were observed at COHb levels of 40-50%, with a slight increase in the number of survivors when compared with that of the deceased. These three studies showed a trend that most lethal cases occurred at COHb concentrations higher than 40% and that survivorship was likely to be seen at concentrations below 40%.

Another study from the Center of Forensic Sciences in Canada evaluated 304 fatal cases from 1965 to 1968 (Nelson 2006a). The mean lethal COHb level was 51 ± 12% with a majority range between 40% and 59% and the highest single frequency range at 45-59%. A report on CO exposure from exhaust fumes in the state of Maryland during 1966-1971 showed COHb levels in the 40-79% range for 98% of lethal cases (Nelson 2006a). The Institute of Forensic Medicine in Oslo reported a study of COHb levels in 54 automobile-exhaust victims. The mean fatal COHb level was 70%, and 40% was the minimum COHb level exhibited by less than 2% of the cases (Nelson 2006a). Another forensic study (Nelson et al. 2006) examining 2,241 fatalities from 1976 to 1985 found that the mean COHb level of all the cases was 64.20% with a SD of 17.47. The data showed that 34% of victims had COHb levels of less than 60%. Of those who died in fires, 41% had COHb levels of less than 60% compared with 22% of the nonfire deaths.

Pach et al. (1978; 1979) reviewed cases of CO poisoning in the Toxicological Clinic, Cracow, Poland, in the years 1975-1976. Excluded from this study were mixed intoxications (e.g., by CO and medicaments). Group A comprised 101 persons (60 men and 41 women, mean age 48 ±15 years) who had died from CO poisoning before arrival at the clinic. Measurement of COHb and autopsy was done on these subjects. Group B comprised 220 subjects (95 men and 125 women, mean age 38 ±18 years) who were treated for CO poisoning. COHb was determined upon arrival at the clinic. Patients were excluded from further analysis if more than 120 min elapsed between the end of exposure and the blood drawing at the clinic (n = 62). For the patients, the COHb level was recalculated at the end of exposure. Mean COHb values for Groups A and B were 62% ± 10% and 28% ± 14%, respectively. In Group A, the percentages of subjects with COHb levels of 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, and 80-90% were 2%, 6%, 26%, 44%, 21%, and 2%, respectively, and 3%, 25%, 32%, 24%, 12%, 3%, 0.6%, and 0.6% of the patients in the corrected Group B had COHb values of 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, and 70-80%, respectively. Within each group, no correlation between COHb and either sex, blood alcohol above 0.1%, or poisoning circumstances (accidental or suicidal) were found. Group A showed a higher percentage (34%) of subjects who were 60 years or older than Group B (13%); Group B had a higher percentage of subjects younger than 30.

Grace and Platt (1981) reported two cases of myocardial infarction due to CO poisoning. In the first case, a 67-year-old man was exposed to increased CO concentrations for about a few weeks in his home due to a rusted-out flue of a gas furnace. The man presented to the emergency room after 3 days of persistent light-headedness with vertigo, brief stabbing anterior chest pain that worsened with deep inspiration, a dry cough, chills, and a mild headache. His wife experienced similar malaise and dizziness that had been resolving over the past week. At the hospital, his symptoms were explained with a diagnosis of viral syndrome, hypokalemia of unclear origin, and diabetes mellitus with diabetic peripheral and autonomic neuropathy. Ten days after discharge he was seen in the emergency room with true vertigo, palpitations, and nausea but was sent home to be followed up as an outpatient. Four days later he returned to the emergency room after development of rectal urgency and an explosive incontinent diarrheal stool, followed by a severe crushing anterior chest pain. With the pain he collapsed on the floor. The electrocardiogram showed an acute myocardial infarction. His COHb (measured on arterial blood gases) was 15.6%; the level of the patient's wife was 18.1%. The patient survived and recovered completely.

In the second case, a 69-year-old man came to the emergency room after awakening 2 days earlier with confusion, nausea, and vomiting. He then passed out and awoke the next day in the bathroom. He crawled to the living room, where he again passed out for an undetermined amount of time, awoke to open his door for fresh air, and then went to bed. He later experienced auditory and visual hallucinations and phoned his neighbor for help. An acute inferior myocardial infarction with secondary mild congestive heart failure and chronic ob-

structive pulmonary disease was diagnosed. During his hospitalization, his sister and daughter-in-law spent a night in his mobile home. They arrived at the emergency room early the next morning with throbbing headaches, vomiting, and vertigo. Their COHb values were 28% and 32%. A faulty gas water heater had caused CO exposure. The patient survived and recovered completely.

Atkins and Baker (1985) described two fatal cases of workers with severe atherosclerotic coronary artery disease. The first worker (age not stated) was a shipping employee in a plant that reconditioned steel dyes. A gas-fired furnace was used for tempering the dyes but also for heating the plant. One day the worker was found unconscious, and resuscitation efforts at a nearby hospital were unsuccessful. Autopsy showed a severe two-vessel coronary artery disease and old scarring and a COHb of 30%. Four other workers of the plant complaining of nausea were seen in the emergency room, but COHb was not obtained. The second worker (age not stated) was operating a bale press in a used-clothing company. As well as gas- and oil-fired heaters, there were a number of propane-fueled forklifts used to transport bales of clothing, and ventilation was poor. Resuscitation was unsuccessful after his collapse. Autopsy revealed three-vessel coronary artery disease and global subendocardial ischemia. Two blood samples showed COHb of 24.1% and 21.5%. Five other workers from the same company were also seen, complaining of light nausea, lightheadedness, and headache. One was hospitalized with a COHb of 35%; the others had levels from 4.1% to 12.8%. CO measurement was performed in the company the next day and revealed concentrations of 135-310 ppm. Concentrations were highest near forklifts (250-310 ppm) and near the bale press (120-230 ppm), which was where the patient had been working at the time of his death.

Ebisuno et al. (1986) reported a case of myocardial infarction after acute CO poisoning in a healthy young man. A 28-year-old male ironworker was admitted to the emergency room complaining of precordial pain. Two hours before admission the patient had been exposed accidentally to CO for about 1 h while working at a blast furnace. After the exposure he experienced a sense of fullness of the head and precordial pain following transient unconsciousness. Blood samples 2 h after the exposure contained COHb of 21%. The electrocardiogram was interpreted as an acute anterior myocardial infarction. The coronary arteriogram 1 month after onset of infarction showed no significant narrowing on both left and right coronary arteries. The left ventriculogram showed a giant aneurysm in the apical portion. During ventricular aneurysmectomy, a massive transmural myocardial necrosis was observed. After surgical treatment, the patient was free of symptoms.

Marius-Nunez (1990) reported the case of a 46-year-old man who suffered an acute myocardial infarction after CO exposure. He was found unconscious in a doorway of a burning apartment. Artificial respiration was initiated until arrival at the emergency room. The electrocardiogram showed sings of myocardial infarction, which was confirmed by high levels of cardiac enzymes in the patient's serum. Blood gas analysis revealed a COHb concentration of 52.2%.

After 3 h of treatment with 100% oxygen, the patient became alert and oriented; COHb was 23%. After 7 h, he was extubated, and a COHb of 13.4% was measured. The patient's medical profile was negative for coronary heart disease risk factors, such as smoking, hypertension, diabetes mellitus, and coronary artery disease. A coronary angiogram performed 1 week later failed to reveal evidence of coronary obstructive lesions.

Balraj (1984) reviewed all deaths that were certified by the Cuyahoga County Coroner's Office for the years 1958-1980 wherein asphyxia by CO was the primary cause of death and a natural disease was the "other" cause of death or vice versa. During the 23-year period, 38 certified deaths were divided into two groups: Group 1 consisted of 28 cases for which the diagnosis including the abnormal COHb was documented by complete postmortem examination. Group 2 consisted of 10 cases for which the diagnosis "other" condition was based on review of medical records, including results of coronary angiogram, serum enzymes, and clinical history; autopsy was not performed on these 10 cases. Group 3 served for comparison, and comprised all deaths of individuals 35 to 86 years of age in whom the COHb was 60% and more (n = 100). A complete autopsy had been performed in each of these cases.

Of the 28 cases in group 1, the primary cause of death was asphyxia by CO in 21 cases. The other condition in 19 of the cases was atherosclerotic coronary artery disease. Of these, eight had hypertensive cardiovascular disease and two had pulmonary emphysema in addition. In the remaining seven cases of group 1, the primary cause of death was atherosclerotic coronary artery disease and the other condition was asphyxia by CO. In group 2, atherosclerotic coronary artery disease was the primary cause of death and asphyxia by CO was the other condition in three cases. In the remaining seven cases, asphyxia by CO was the primary cause of death and in all but one of these cases, the other condition was atherosclerotic coronary artery disease; two of the individuals also had hypertensive cardiovascular disease. The results are presented in Table 2-4.

2.2. Nonlethal Toxicity

Nonlethal effects of CO on humans have been reported in experimental studies in both healthy individuals and in patients with coronary artery disease (see Section 2.2.1). Case studies (see Section 2.2.2) are presented for children and adults and identify children as another susceptible subgroup for nonlethal CO effects.

2.2.1. Experimental Studies

2.2.1.1. Subjects with Coronary Disease

A large number of studies investigated the effects of low CO exposure (COHb < 10%) on healthy individuals and high-risk groups. These experiments

have been reviewed extensively by WHO (1999a) and EPA (2000). In healthy individuals, symptoms, such as decreases in work capacity and decrements of neurobehavioral function, start at a COHb of 5% (WHO 1999a; EPA 2000; Hazucha 2000). With respect to high-risk groups, studies evaluating ST-segment changes in the electrocardiogram and cardiac arrhythmogenic effects in patients with coronary artery disease will be presented here, because these studies gave the most consistent results and also were considered most relevant for AEGL derivation (for review, see WHO 1999a; EPA 2000).

TABLE 2-4 Incidence of Atherosclerotic Coronary Artery Disease and COHb in Fatalities That Involved CO Exposure

		Number of Cases		
		Group 1	Group 2	Group 3
Total		28	10	100
Age (years)	30-40	1	0	22
	41-50	1	0	31
	51-60	7	2	28
	61-70	10	4	10
	71-80	5	2	6
	81-90	4	2	3
COHb (%)	10-30	14	5	0
	40-50	4	3	0
	60 and more	0	0	100
Delayed deaths		10	2	0
Coronary atherosclerosis	Mild	2	Unknown	89
	Moderate	2	Unknown	5
	Severe	24	5	6
Myocardial infarct	Recent	1	0	0
	Old	4	1	2
Heart weight (g)	415 and more	20	Unknown	13

Source: Adapted from Balraj 1984.

Characteristic points of an electrocardiogram are the P wave, reflecting atrial depolarization; the QRS-complex, representing the ventricular muscle depolarization; and the T-wave, reflecting ventricular muscle repolarization. In the normal electrocardiogram, the ST segment is isoelectric, resting at the same potential as the interval between the T wave and the next P wave. Horizontal depression or a downsloping ST segment merging into the T wave occurs as a result of ischemia, ventricular strain, changes in the pattern of ventricular depolarization or drug effects. In chronic ischemic heart disease, there may be moderate degrees of horizontal ST-segment depression or a downward sloping ST segment, flattening or inversion of T waves and prominent U waves. It is difficult to define an abnormal ST-segment depression in precise quantitative terms. However, a myocardial ischemia has to be considered if the beginning of the ST segment is more than 0.5 mm (corresponding to 0.05 mV) below the isoelectric line, and there is an associated T-wave abnormality (Wilson et al. 1991).

Allred et al. (1989a,b; 1991) conducted a multicenter study of effects of low COHb on 63 individuals with coronary artery disease. Male subjects aged 41-75 (mean = 62.1 years) with stable exertional angina pectoris (diagnosis established for more than 3 months; no at-rest symptoms) and a positive stress test (measured by a greater than 1-mm change in the ST segment of the electrocardiogram and occurrence of angina symptoms) were studied in three test centers using standardized test protocols. Only patients showing reproducible effects before and after a test stay in the exposure chamber on the qualifying visit were included. On the subsequent exposure days, the stress test was repeated before the exposure and, if the result was not reproducible compared with the qualifying visit, the visit was repeated on another date; at the second failure in the pretest, the subject was dropped from the study. Further evidence that these subjects had coronary artery disease was provided by the presence of at least one of the following criteria: angiographic evidence of narrowing (~70%) of at least one coronary artery, documented prior myocardial infarction, or a positive stress thallium test demonstrating an unequivocal perfusion defect.

All patients were tested three times on separate days in a double-blind fashion. On each of the 3 exposure days, the subject performed a symptom-limited exercise test on a treadmill (pretest) and was exposed for 50-70 min randomly to air and to CO. (Subjects were exposed to CO concentrations that were experimentally determined to produce an end-exposure COHb of 2.2% or 4.4%; these COHb values were 10% higher than the targeted concentrations to compensate for the CO loss during exercise). Afterward, the subject performed a second symptom-limited exercise test. The mean exposure levels and ranges for the test environment were clean air (0 ppm), 117 ppm (range 42-202 ppm) for a COHb of 2%, and 253 ppm (range 143-357 ppm) for a COHb of 4%. Gas chromatographic measurements of COHb were performed 1 min after the pretest, after 30 and 40 min into exposure, at the end of exposure, and 1 min after the

second stress test. The measurements revealed a post-exercise COHb of 2.0% ± 0.1% and 3.9% ± 0.1%, respectively. The time to onset of angina and the time to 1-mm ST-segment change were determined for each test. The percent changes following exposure at both 2% and 4% COHb were then compared with the same subject's response to the randomized exposure to room air.

When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST-segment change, exposure to CO levels producing COHb of 2% resulted in an overall statistically significant 5.1% decrease in the time to attain this level of ischemia. For individual centers, results were significant in one, borderline significant in one and nonsignificant in one. At 4% COHb, the decrease in time to the ST criterion was 12.1% (statistically significant for all patients; the effect was found in 49 of 62 subjects) relative to the air-day results. Significant effects were found in all three test centers. The maximal amplitude of the ST-segment change was also significantly affected by the CO exposures: at 2% COHb, the maximal increase was 11%, and at 4% COHb, the increase was 17% relative to the air day.

At 2% COHb, the time to angina was reduced by 4.2% in all patients (effects were significant in two test centers and nonsignificant in one center). At 4% COHb, the time was reduced by 7.1% in all patients (effects were significant in one, borderline significant in one, and nonsignificant in one center). The two end-points (time to angina and time to ST change) were also significantly correlated.

Only at 4% COHb, a significant reduction was found in the total exercise time and in the heart-rate blood-pressure product. (This double product provides a clinical index of the work of the heart and myocardial oxygen consumption.)

A number of other studies also evaluated the same end points. A reduced time to onset of exercise-induced chest pain was reported at a COHb of 2.5-3.0% (Aronow et al. 1972), 3% (Kleinman et al. 1989), 2.9%, 4.5% (Anderson et al. 1973), and 3.9% (Kleinman et al. 1998). No significant depression of the ST segment was found at a COHb of 3.8% (Sheps et al. 1987) and 3.9% (Kleinman et al. 1998). The differences in these studies has been explained (WHO 1999a) as differences in experimental methodology and analysis of data and as differences in subject populations and sample size.

Sheps et al. (1990; 1991) assessed the effect of CO exposure on ventricular arrhythmias. Forty-one subjects with established coronary artery disease (36 men and 5 women) with a mean age of 62.8 ± 1.1 years were analyzed. Patients were categorized based on arrhythmia frequency on the training day before, during, and 6 h after exercise: 10 had no arrhythmias (0-2 ventricular premature depolarizations (VPD)/h), 11 had low-level arrhythmias (3-50 VPD/h), 11 had intermediate-level arrhythmias (51-200 VPD/h), and 9 had high-level arrhythmias (>200 VPD/h). The protocol was performed over 4 consecutive days. Day 1 was the familiarization session and instructions were given on using the 24 h ambulatory electrocardiogram recorder. A symptom-limited maximal bicycle exercise test was also done. Days 2 to 4 were exposure days with either pure

room air or CO (100 or 200 ppm) administered in a randomized double-blind fashion. COHb measurements were performed before exposure, 30 and 60 min into exposure, at the end of exposure, and before and after exercise using an IL-282 CO oximeter. Exposures were stopped when the target level of 4% or 6% COHb was reached. Exposure durations were 94.2 ± 4.2 (SE) min (range 40 to 170 min) for the 4% level and 82.3 ± 2.9 (SE) min (range 39 to 135 min) for the 6% level. On all three test days, the mean pre-exposure COHb was 1.8%. The post-exposure and post-exercise COHb measured were 1.46% and 1.36% for air exposure, 4.01% and 3.93% for the 4% group, and 5.91% and 5.02% for the 6% group. Comparisons of arrhythmia data were done at 1.41%, 3.71%, and 5.33% COHb, respectively.

During the exposure period, the mean number of single VPD/h on the room-air day was significantly higher than that on the 4% COHb day, but no significant difference in the mean number of VPD/h was noted between room-air and 6% COHb exposure. When the baseline level of VPD frequency was controlled for by calculating the difference between the VPD frequency during exposure and the VPD frequency before exposure, there was no significant difference between the room-air and the 4% COHb exposure.

During the exercise period, the frequency of single VPD/h was greater on the 6% exposure day than on the room-air day (167 ± 38 vs. 127 ± 28 VPD/h; $p = 0.03$). This effect was still significant when the baseline VPD level was controlled for (117 ± 34 vs. 74 ± 26, $p = 0.04$). For this analysis, data from subjects in the low, medium, and high VPD frequency groups were pooled. The difference remained significant when all subjects, including those categorized in the "no arrhythmia" group were included in the analysis. The VPD frequency was not significantly increased at 4% COHb.

The initial findings (essentially negative) of this study in 10 patients with ischemic heart disease and no ectopy during baseline monitoring were published separately (Hinderliter et al. 1989).

Dahms et al. (1993) studied 28 men and 5 women with documented coronary artery disease and a minimum of 30 ventricular ectopic beats per hour over a 20 h period. On three testing days, the subjects were exposed in a randomized double-blind fashion to either room air or sufficient CO to increase their COHb concentrations to 3% or 5% in 1 h. The mean exposure concentrations during this hour were 159 ± 25 ppm and 292 ± 31 ppm, respectively. This was followed by a maintenance exposure to mean concentrations of 19.3 and 31 ppm, respectively, for an additional 90 min, which included the exercise test (after 60 min of equilibrium exposure) and the immediate post-exercise phase. The subjects then left the laboratory and resumed their normal daily activity to determine changes in ventricular ectopic beats after CO exposure. To this end, continuous 20 h ambulatory electrocardiograms were obtained with the recorder placed on the patients 2 h before CO exposure. There was no significant change in the frequency of single ventricular ectopic beats at rest from 115 ± 28 (in room air) to 121 ± 31 at 3% COHb and 94 ± 23 at 5% COHb. Exercise increased the frequency of ven-

tricular ectopic beats (from a baseline of 116 to 206 during exercise and 375 during exercise recovery for the room-air exposure), but there was no additional effect from CO exposure. Analysis of the data based on grouping of the subjects by the severity of disease (ventricular ectopic beat frequency, ejection fraction, and presence of exercise-induced ischemia) indicated no proarrhythmic effect of CO.

2.2.1.2. Healthy Adults

Chiodi et al. (1941) exposed each of 4 male subjects (aged 21-33 years) repeatedly to CO concentrations of 0.15-0.35% (1,500-3,500 ppm) for 70 min or longer. During 1 h before exposure, basal oxygen consumption, ventilation, pulse rate and blood pressure were recorded, and arterial blood for pH determination was obtained. The subject, remaining in rest during exposure, then breathed CO-containing air from a 600-liter gasometer. The measurement of the above mentioned parameters was continued during exposure. In one set of experiments, the test subjects reached 3.4% to 10.4% COHb (eight experiments in total with the following COHb at the end of exposure: 4.6%, 6.3%, 7.2%, 9.2%, and 9.8% in one subject and 3.4%, 9.5%, and 10.4% in the other). In another set of experiments, three subjects reached 27% to 52% COHb at the end of exposure (in 11 of a total of 22 experiments a COHb of 40% to 52% was measured). The following COHb values were measured at the end of exposure: 0, 31, 32, 32, 33, 39, 41, 42, 43, 45 and 52% in subject H.C., 0, 27, 35, 41, 43 and 48% in subject F.C. and 0, 0, 41, 42 and 44% in subject S.H. No statement was made on whether any symptoms were observed. The cardiac output increased 20-50% at COHb >40%, while the changes were negligible at COHb of <30%. No effects on the other parameters measured were found.

Henderson et al. (1921) exposed volunteers in a 6.4-m^3 gas-tight, steel-walled exposure chamber. CO was generated by dripping formic acid into strong sulfuric acid. A defined volume of CO was led into the chamber and mixed with an electric fan. Analysis of the exposure concentration in the chamber was done using the iodine pentoxide method. Subjects (9 men and 1 woman; number of subjects at each concentration given in brackets) were exposed for 1 h at 200 ppm (2), 300 ppm (3), 400 ppm (11), 500 ppm (1), 600 ppm (9), 800 ppm (4), 900 ppm (1) or 1000 ppm (1) CO. Blood samples were taken before exposure, at 30 min into the exposure, at the end of the exposure (60 min) and once or twice during the next 3 h after exposure. The COHb was determined using the carmine method. Directly after leaving the exposure chamber, subjects breathed several times into a bladder bag and CO was determined in the exhaled air using the iodine pentoxide method. CO concentrations in alveolar air after 60 min were 130-136 ppm at an exposure concentration of 400 ppm, 120-230 ppm at 600 ppm and 140-230 ppm at 800 ppm. The COHb percentage ranged from 11-12% at 200 ppm, 10-14% at 300 ppm, 14-22% at 400 ppm, 16-26% at 600 ppm, 26-

34% at 800 ppm, 34% at 900 ppm and 38% at 1000 ppm. After exposure to up to 500 ppm for 60 min, no symptoms were observed. At 600 ppm, 2/9 subjects reported slight frontal headache. At 800 ppm all subjects reported decided frontal headache during 4-8 h. At 900 ppm insomnia and irritability occurred in addition to headache. At 1,000 ppm, irritability, throbbing frontal headache, and at times Cheyne-Stokes breathing were observed. The Romberg test (ability to stand erect with eyes closed) showed a marked loss of equilibrium after a 60-min exposure to 800 ppm or higher.

Haldane (1895) reported on a series of 11 studies in which the author exposed himself to different CO concentrations for different exposure times. The exposure conditions and effects are summarized in the following Table 2-5. The subject breathed the CO atmosphere from a mouthpiece. No mentioning of an analytic measurement of the exposure concentrations used was made. At the end or one or more times during the exposure, the exposure was interrupted and the subject walked in the room or ran up a flight of stairs (once or a few times) to investigate the effect of physical exertion at different COHb levels. The COHb was determined colorimetrically by measuring the amounts of carmine solution that had to be added to the diluted blood sample or to an equal dilution of normal, oxygenated blood to adopt the color of a CO-saturated blood dilution. For COHb <70%, the author found his COHb determinations accurate within a 5% error. Although the exposure measurement of this study does not meet today's standards, the reported COHb values are in fairly well agreement with the values calculated from the given exposure concentration and exposure time using the mathematical model of Coburn, Forster and Kane (see Section 4.4.4) when assuming a resting ventilation rate (see Table B-4 in Appendix B).

Stewart et al. (1970) performed 25 CO inhalation exposure experiments on a total of 18 healthy men (age 24-42). They were exposed and sedentary in a chamber at <1, 25, 50, 100, 200, 500, or 1,000 ppm for periods of 30 min to 24 h. The chamber atmosphere was monitored continuously by infrared spectroscopy and periodically by gas chromatography. The subjects performed the following psychoneurologic tests: hand and foot reaction time in a driving simulator, Crawford collar and pin test, Crawford screw test, hand-steadiness test, Flanagan coordination test, othorator visual test, complete audiogram, resting 12-lead electrocardiogram, standard electroencephalogram, visual-evoked response and time-estimation–hand-reaction-time test. No subjective symptoms or objective signs of illness were noted during or in the 24 h following exposure to CO at 25 ppm for 8 h, 50 ppm for 1, 3, or 8 h, or 100 ppm for 1, 3, or 8 h. There was no detectable change from control values in the clinical tests. A significant relationship between the Crawford collar and pin test and CO concentration was considered a chance finding by the authors. Of 11 subjects exposed to CO at 200 ppm for 4 h, three subjects reported they had developed a "mild sinus" headache in the final hour. In the clinical tests, no detectable statistical change from control values was observed. In the first exposure at 500 ppm for 1.8 h, one of the

TABLE 2-5 Effects of Acute Carbon Monoxide Exposure in a Human Subject

Number	Exposure Concentration, Volume % (ppm)	Total Exposure Time (min)	Observations	At Time (min)/ COHb (%)
1	0.50 (5,000)	11.5	No symptoms; hyperpnea after running upstairs	
2	0.39 (3,900)	30.5	No symptoms	15 min/23%
			Slight feeling of palpitation, pulse 102	22 min
			Palpitation, respiration 18, pulse 120, feeling abnormal	29 min
			After running upstairs, became giddy, much out of breath, palpitations, slightly impaired vision	30.5 min/39%
3	0.40 (4,000)	24	No symptoms except unusual hyperpnea and giddiness after running upstairs	24 min/27%
4	0.36 (3,600)	29	—	18 min/26%
			On walking, throbbing in the head and palpitations, on running, giddy, short of breath	29 min/37%
5	0.41 (4,100)	29	—	15 min/13%
			Very slight hyperpnea and palpitations	28 min
			After running, marked giddiness and impairment of vision and hearing (for 1-2 min)	29 min/35%
6	0.12 (1,200)	120	—	15 min/8%
			Slight tendency to palpitations, pulse 96	33 min
			No symptoms	46 min/18%
			Slight palpitations, sleepy	67 min
			After running (no exposure), distinct dimness of vision and hearing, slight tendency to stagger, abnormal hyperpnea	90 min/27%
			Slight hyperpnea while sitting	104 min
			Distinct hyperpnea, feeling uneasy, dull, and abnormal; after running, weak in the legs, markedly impaired vision, and hearing, confusion	120 min/37%

(Continued)

TABLE 2-5 Continued

Number	Exposure Concentration, Volume % (ppm)	Total Exposure Time (min)	Observations	At Time (min)/ COHb (%)
7	0.21 (2,100)	71.5	—	20 min/17%
			Very slight feeling of fullness, throbbing in the head	34 min
			—	40 min/39%
			Feeling decidedly abnormal, slight hyperpnea, marked throbbing	43 min
			Breathing decidedly deeper, pulse 104	45 min
			Feeling decidedly abnormal, impaired vision, slight feeling of giddiness	54 min
			Hyperpnea more distinct, beginning to look pale/yellowish	59 min
			—	61 min/44.5%
			Feeling worse shortly after any movement in the chair	63 min
			Hyperpnea marked, slight confusion of mind	65 min
			Vision dim, limbs weak, difficulty in getting up and walking without assistance; at 6 min after exposure, very unsteady walking, nearly falling, very indistinct vision	71 min/49%
8	Irregular due to disconnected tubing, 0.43% for last 10 min	35	Hardly able to stand, no walking alone without falling down	35 min, 56%
9	0.027 (270)	210	—	60 min/7%
			—	120 min/11%
			—	180 min/15%
			No symptoms; after running, very slight unusual shortness of breath and palpitations	210 min/14%

Source: Adapted from Haldane 1895.

two subjects reported light-headedness after 20 min of exposure, which was believed to be due to hyperventilation. After 1 h of exposure, both subjects were aware of a 10% increase in heart rate with the minimal exertion of walking to the blood port. After 90 min of exposure, the second subject noted the onset of mild frontal headache. During the second exposure to CO at 500 ppm for 2.3 h, the same subjects developed mild frontal headaches after 1 h of exposure. Minimal exertion caused a transient intensification of the pain. Both headaches remained mild during the first post-exposure hour; then they intensified into excruciatingly severe occipitofrontal headaches, reaching a pain peak 3.5 h after exposure, and persisted for 7 h. During the third exposure at 500 ppm, the occurrence of mild frontal headaches was noted after 1 h of exposure. Immediately after exposure, both subjects were placed in a hyperbaric chamber and administered oxygen and the mild headaches were gone within minutes. The mean COHb reached after 2.3 h of exposure at 500 ppm was about 25.5%; after 4 h of exposure at 200 ppm, about 16.0%; and after 8 h of exposure at 100 ppm, about 12.5%.

In another experiment (Kizakevich et al. 2000) evaluating cardiovascular responses of exercising individuals, 16 healthy young men performed a sequence of brief (5 min) multilevel treadmill and hand-crank exercises at <2% COHb and again after attaining 5%, 10%, 15%, or 20% COHb on different days. Noninvasive impedance cardiography was used to estimate cardiac output, stroke volume, heart rate, cardiac contractility, and time-to-peak ejection time. The electrocardiogram was used to assess myocardial irritability and ischemia and changes in cardiac rhythm. The results showed that compensatory cardiovascular responses to submaximal upper- and lower-body exercise (e.g., increased heart rate, cardiac contractility, cardiac output) occur after CO exposures. These changes were highly significant for exposures attaining 20% COHb. The authors concluded that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20% COHb.

Nielsen (1971) investigated the effect of CO exposure on thermoregulation. Experiments were performed repeatedly on two subjects. Subject JHB reached COHb concentrations of 25% (mean of eight experiments) and 33% (four experiments), and subject PJC reached 30% (four experiments). After reaching the desired COHb concentration, the subjects exercised on a chair-ergometer for 1 h at a medium-to-high workload (mean heart rate 120-170 beats per minute). The subjects were not exposed continuously to CO during exercise, but the COHb level was maintained by breathing a calculated volume of CO from an anesthesia bag for 1-1.5 min every 15 min during exercise. CO exposure led to an increase in the plateau level of the deep-body temperature during exercise of 0.3-0.5°C. The lactic acid concentration was not increased after exercise at air exposure (120 mg/L in JHB and 79 mg/L in PJC) but increased during CO exposures (309-660 mg/L in both subjects). The authors stated neither the absence nor the presence of any symptoms of CO exposure.

2.2.2. Case Studies

2.2.2.1. Children

Klasner et al. (1998) published a retrospective chart review on a mass poisoning at an elementary school. The CO leak was discovered at noon, about 4 h after school started. Of the 564 people at school, 504 were children. Any child who showed evidence or complained of symptoms was sent to a hospital by ambulance or school bus. One of three hospitals received 177 children (mean age of 8.7 ± 1.8 years; age range of 4-12 years). All children were given 100% oxygen by face mask in the hospital (the authors stated that only few of them received simple face-mask oxygen en route to the hospital). The level of poisoning was assessed according to standardized poison-center data sheets (TESS, toxic exposure surveillance sheets) and was recorded as unknown (6 cases), no effect (16 cases), minor effect (124 cases), or moderate effect (30 cases). One child, for whom the data-sheet classification listed a major effect, was considered miscoded by the authors because the medical record showed that this child was sent home from the hospital without further treatment. Symptoms were present in 155 children, and a mean COHb of 7.0% (95%-C.I. 6.6-7.5%) was measured in 147 children (blood was drawn at the same time that oxygen therapy began). The authors estimated that the children were exposed at least 60 min (in some cases, 90 to 120 min) to fresh air prior to obtaining their initial COHb concentration. In the 177 children, the following symptoms (number of mentionings) were observed (some children reported more than one symptom): headache (139), nausea (69), dizziness (30), dyspnea (19), vomiting (13), abdominal pain (11), drowsiness (9), and other symptoms (0). The authors found a correlation between the total number of symptoms reported and the COHb concentration; thus, children with higher COHb concentrations were slightly more likely to report more symptoms. The authors did not mention how many of the 60 adults experienced symptoms, but stated that symptomatic adults were taken to adult hospital facilities.

Crocker and Walker (1985) analyzed 28 patients with CO poisoning that were 14 years old or younger; 25 of the 28 CO exposures were secondary to faulty venting or faulty combustion of gas furnaces, 2 of 28 were secondary to faulty combustion of a gas stove, and 1 of 28 was secondary to motor-vehicle exhaust. Twelve patients had COHb concentrations of less than 15% and were completely asymptomatic. These patients were considered to have nontoxic exposures, and they were not studied further. Of the 16 patients (mean age 7.0 ± 3.8 years, three were younger than 5 years) with a COHb of 15% or higher, 16 of 16 experienced nausea, 12 of 16 experienced associated vomiting, 13 of 14 (no information on two) complained of headache, and 11 of 16 patients were reported to be lethargic. Three of 14 patients reported visual problems, such as blurred or double vision. Nine of 16 reported at least one syncopal episode with an average COHb concentration of 31.6% and a threshold level of 24.3%. Every

patient with a COHb of 24.5% or higher experienced syncope. Lethargy was reported in 11of 16 patients at a mean COHb of 25.9% and a threshold of 18.6%. Symptoms and COHb concentrations are presented in Table 2-6. All patients were successfully treated with hyperbaric oxygen. The authors provided the COHb measured after hospital admission but did not give any information on the delay between the end of exposure and measurement and on (probable) oxygen administration before hospital admission (e.g., oxygen by face mask during ambulance transport).

Patient followup using parental telephone interview and medical-record review 3-12 months after the poisoning was used to screen for neurologic sequelae. Three patients had developed problems: a 12-year-old boy with 36.1% COHb had developed chronic headaches, a 6-year-old girl with 36.9% COHb had developed memory difficulties after suffering a major motor seizure during the poisoning episode, and an 8-year-old girl with 24.5% COHb developed poor school performance, which were attributed to her long-standing poor reading ability; psychological evaluation revealed no cognitive deficits. The former two children reported complete resolution of their symptoms 9 months after exposure.

Klees et al. (1985) investigated the neurotoxic sequelae of CO poisoning in children who had been brought to the emergency department of St. Pierre Hospital, Brussels, following CO poisoning (irrespective of whether they were subsequently hospitalized). Cases were only studied when followup was possible: in a short-term followup of 20 children who were submitted psychological tests at the time of the intoxication and who were re-examined about 3 months later, and in a long-term followup of 14 children who were re-examined 2-11 years after the intoxication. The authors listed the COHb measured after hospital admission, but did not give any information on the delay between the end of exposure and measurement, nor did they indicate a (probable) oxygen administration before hospital admission (e.g., oxygen by face mask during ambulance transport).

In the long-term followup, 6 of the 14 children (age 2.8-12.1 years at the time of intoxication; mean age of 7.8 years) exhibited serious disorders (spatial organization problems; constructive apraxia; or deterioration of lexical activity, as well as spelling and arithmetic); two of them had a previous history of psychological difficulties but displayed additional difficulties after the poisoning. COHb concentrations of 13% to 32% (mean 21%) have been reported for four of six children (no data on the other two children were available). Seven of the 14 children (ages of over 6 years, except for one 3.5-year-old child; mean age 9.8 years) exhibited slight impairment of visual memory and concentration; these children had COHb concentrations of 16% to 26% (mean 22%). One child of this group did not display any sequelae.

In the short-term followup, the authors grouped the 20 children according to age. In children below 3 years of age (six aged 2.0-2.9 years), medium intoxications (a COHb of 16-27% reported in five whose symptoms included loss of

TABLE 2-6 Symptom Threshold Values for Pediatric Carbon Monoxide Toxicity

Symptom	Threshold COHb (%)	Average COHb (%)	Percentage of Patients[a] (%)
None	<15	<15	100
Nausea	16.7	27.1	100
Vomiting	19.8	29.4	78.6
Headache	16.7	28.3	91.6
Lethargy	18.6	25.9	78.6
Visual symptoms	24.5	32.5	25.0
Syncope	24.5	31.6	64.3
Seizures	36.9	36.9	6.3

[a]The percentage of patients showing the respective symptom refers to the 16 patients with a COHb of more than 15% except for asymptomatic patients ("None"), which refers to the 12 patients with a COHb of less than 15%.
Source: Adapted from Crocker and Walker 1985.

consciousness, but no coma) did not produce manifest sequelae except for a momentary standstill in the child's progress of about 2 months, but their negative behavior was found to be amplified (more nervous, more irritable, and more anxious). However, it was not possible to determine whether these behavioral disturbances were a direct effect of the CO intoxication or whether they were due to neurophysiologic causes or to the stressful psychological conditions surrounding the intoxication. In one case of severe intoxication (symptoms included coma; a COHb of 37%), developmental level regression (motricity and language), violent anger, and nervosity were observed.

In eight children 4 to 9 years old, the intoxication did not alter the intellectual capacities, but in six cases (reported COHb concentrations of 4%, 6%, 25%, and 27%; missing data for two children) the mnestic and instrumental aspects of the cognitive development were modified (the other two were difficult to evaluate due to intellectual retardation and language retardation). Visual-spatial perceptions and topographical memory were particularly perturbed, as was auditory memory.

In 10 children over 10 years of age, difficulty in perceiving and organizing the material to be memorized either auditorily or visually was found in the three children less than 12 years of age (COHb of 26%, 27%, and 36%). With the three children over 14 years of age, one case (30% COHb) of serious balance impairment was observed and two cases showed some slowness and instability (COHb of 26% and 30%).

Meert et al. (1998) evaluated clinical characteristics and neurologic outcome of all children with CO poisoning admitted to the Children's Hospital of Michigan, Detroit, between January 1987 and December 1996. Exposures were categorized as (1) severely toxic when COHb was >25%, (2) toxic when COHb was between 10.1% and 25%, (3) suspected toxic when COHb was ≤10% with

acute neurologic manifestations, or (4) nontoxic when COHb was ≤10% without acute neurologic manifestations. Of 106 cases (median age of 3.5 years; range of 0.1 to 14.9 years) investigated, 37 had exposures that were severely toxic, 37 were toxic, 13 were suspected toxic, and 19 were nontoxic. The most common presenting symptoms included altered level of consciousness (lethargy, unresponsiveness), metabolic acidosis, tachycardia and hypertension. All exposures were accidental, occurring as a result of smoke inhalation during house fires in 95 cases, motor vehicle exhaust in six cases, and defective heating system in five cases. Forty-three children had an associated cutaneous burn injury. All patients received normobaric oxygen for a median period of 5.5 h (range 0.6 to 44 h). Fifteen patients died, eight from hypoxic-ischemic encephalopathy after cardiopulmonary arrest at presentation, three from massive burn injury, and four from late complications of burn injury. Nine survivors suffered neurologic sequelae: (1) six had persistent deficits, such as cognitive and motor deficits or developmental delay (of these, four had presented with respiratory or cardiorespiratory arrest with COHb concentrations of 31.5% to 45%, and the other two had COHb concentrations of 14.8% and 5.9% and had severe burns with 40% and 75%, respectively, of the body-surface area affected), and (2) three patients developed delayed neurologic syndromes (two children had COHb concentrations of 33.3% and 34.8% with transient tremors, cognitive deficits, and hallucinations starting after 4 and 14 days that resolved spontaneously after about 2 months; and one child had a COHb of 3.1% and developed deficits in cognitive and interpersonal skills after 51 days and in whom brain imaging revealed bilateral occipital lobe infarcts).

Further information on pediatric CO poisoning can be found in the review of White (2000).

2.2.2.2. Adults

Burney et al. (1982) reported an epidemiologic and clinical investigation of 184 persons exposed to CO in a public school. CO release was from a furnace and was caused because of a door to the exhaust chamber had been inadvertently left ajar. The CO was distributed throughout the school building by a forced air heating system. Exposure began at 7.30 a.m. and ended at 10.00 a.m. Of the 184 exposed persons (146 students and 38 teachers, mean age for all exposed was 20 years), 160 became ill and 96 were transported to four hospitals for treatment. COHb levels were measured on 66 persons and showed a mean of 18.2 ± 6.4%, with almost half falling between 21% and 25%. Persons in whom COHb levels were drawn had a mean exposure time of 107 ± 33 min. Of the 160 persons who became ill, the following symptoms were reported for 159 persons: headache (90%), dizziness (82%), weakness (53%), nausea (46%), trouble thinking (46%), shortness of breath (40%), trouble with vision (26%), and loss of consciousness (6%). For headache, dizziness, muscle weakness, trouble with vision and trouble with thinking, a strong correlation between symptom and duration of exposure

was found, while nausea, shortness of breath, and loss of consciousness did not show this correlation. The authors corrected the measured COHb level for the delay between exposure and the drawing of blood samples and reported a corrected mean COHb of 20.7±7.0%.

Ely et al. (1995) reported a poisoning incident in a warehouse of a small sewing company. A propane-fueled forklift was in use in the warehouse in which a total of 30 people worked. The forklift was parked in a position where its exhaust focused directly into an air intake duct that communicated with a vent opening above a table in the inspection and packing area, where five people worked. On the day of the incident, one man reported pronounced nausea, vomiting, dizziness, and had a tonic-clonic seizure. Simultaneously, other coworkers developed chest pain and dyspnea. The warehouse was evacuated immediately. Air CO measurements were 386 ppm in the sewing area and 370 ppm in an unrelated work area. Thirty persons treated for CO exposure had complaints of severe headaches (93%), dizziness (63%), weakness (63%), nausea (60%), chest pain or tightness (57%), shortness of breath (50%), vomiting (37%), abdominal pains (33%), muscle cramping (30%), difficulty concentrating (23%), visual changes (20%), and confusion (17%). Twenty-six patients had expiratory CO analyses after being treated with 100% oxygen for over 2 h. Expiratory CO was higher in those from the inspection and packing area (21.1±0.7% versus 8.4±4.8%). These persons were among the most severely ill. The authors extrapolated the mean expiratory CO concentration of 21.1% back to a COHb of about 35% at the end of exposure. Two years after the incident, followup was obtained for 25 (83%) of the patients: 11 (44% of those reached) reported seeing physicians for persisting symptoms (numbness in arms or legs, 36%; restlessness, 36%; persistent headaches, 32%; irritable or violent behavior, 16%; confusion, 16%; incontinence, 16%; difficulty walking or moving arms/legs, 16%; memory loss, 16%; difficulty speaking, 4%).

Sokal and Kralkowska (1985) analyzed 39 patients (18 men, 21 women) that were hospitalized for acute CO poisoning. 25 patients were intoxicated by household gas and 14 patients by coal-stove gas. The patients' ages ranged from 13 to 78 years. The duration of the poisoning varied between 1 and 14 h and was established on the basis of an epidemiologic review of the circumstances of poisoning. The severity of poisoning evaluated on admission to hospital according to the clinical criteria presented in Table 2-7. On basis of the clinical criteria, 16 cases were classified as degree I, 12 as degree II, 8 as degree III, and 4 as degree IV. For statistical analysis the mild and moderate cases (I and II) were pooled into one group and the severe and very severe cases (III and IV) into another. Results presented in Table 2-8 show that mean COHb in severe and very severe poisonings were only slightly higher (not statistically significant) than those in the mild and moderate group. On the other hand, the average duration of exposure that induced severe or very severe poisonings was about twice as long as that associated with mild and moderate poisonings. In the severe and very severe

TABLE 2-7 Severity of Carbon Monoxide Poisoning

Grade I (mild)	Headache, vomiting, tachycardia, no disturbances of consciousness
Grade II (moderate)	Disturbances or loss of consciousness without other neurologic symptoms, tachycardia, pain-induced reflexes still intact
Grade III (severe)	Loss of consciousness, intense muscular tonus, neurologic symptoms, tachycardia and tachypnea, circulatory and respiratory disturbances not observed
Grade IV (very severe)	Loss of consciousness, clinical signs of central nervous system damage, circulatory and respiratory disturbances

Source: Sokal and Kralkowska 1985. Reprinted with permission; copyright 1985, *Archives of Toxicology*.

TABLE 2-8 COHb, Exposure Duration, and Lactate Concentrations in Relation to Severity of Carbon Monoxide Poisoning

Parameter	Mild and Moderate Poisonings (no.)	Severe and Very Severe Poisonings (no.)	Very Severe Poisonings (no.)
COHb (%)	27 ± 12 (27)	34 ± 13 (11)	31 ± 14 (3)
Exposure duration (h)	4.6 ± 3.3 (27)	9.1 ± 3.5 (12)	10.3 ±1.3 (4)
Blood lactate concentration (μmol/mL)[a]	4.1 ± 3.6 (27)	8.8 ± 3.1 (11)	11.0 ± 2.2 (3)

[a]Blood lactate concentrations in 12 control individuals was 1.4 ± 0.3 μmol/mL.
Source: Sokal and Kralkowska 1985. Reprinted with permission; copyright 1985, *Archives of Toxicology*.

poisonings, the lactic acid concentration in blood, as an indicator of metabolic acidosis, was significantly higher. For pyruvate and glucose concentrations, no significant differences were found (not shown).

Deschamps et al. (2003), in a prospective study, measured effects on memory 1 month after an acute CO intoxication. Of all patients examined in the hospital for suspicion of acute CO intoxication over 4 years (n 944), 230 patients fulfilled the inclusion criterion of a COHb level of 11% or higher in the first blood sample measured at the hospital. After applying further inclusion criteria, that is, ages between 18 and 60, fluent in the French language, no disease or risk factor that might impair memory (e.g., excessive alcohol consumption, treatment with psychotropic drugs, drug abuse, neurologic or psychiatric diseases, and exposure to solvents or heavy metals), 38 patients were suitable for inclusion, of which 32 were examined. The median COHb in the first blood sample was 23%. Median blood CO at the end of exposure was calculated as 30%. The median number of days between intoxication and psychometric testing was 31. Each patient was paired with a control with respect to gender, age, and educational

level. Tests were selected to study several types of memory, that is, long-term and working memory (verbal Buschke's test) and short-term memory (digit span [verbal] and Corsi's test [visual]). Other tests addressed disturbances of attention (simple reaction-time test, verbal fluence test) and divided attention (reaction time test with double task and color and word decoding test). The only tests indicating a lower performance of patients were for number recall and fatigability (mean reaction time was higher for the second part of the trial than for the first part). The results did not correlate with the end-of-exposure to COHb. In several other tests, patients showed a better performance than controls, some of these tests showed a positive correlation between result and the end of exposure to COHb. The authors concluded that 1 month after the incident, the memory of the patients was not lower than in paired controls and was even higher for learning and word recall.

2.3. Developmental and Reproductive Toxicity

Koren et al. (1991) described a prospective, multicenter study of acute CO poisoning during pregnancy. Between December 1985 and March 1989, a total of 40 cases of CO poisoning during pregnancy were collected. All pregnant women were in good health prior to the CO poisoning and had not suffered from a known chronic illness. The 40 pregnancies included three twin births, one termination of pregnancy at 16 weeks of gestation, and four births that were pending. The CO poisoning was caused by malfunctioning furnaces (n = 23), malfunctioning water heaters (n = 7), car fumes (n = 6), methylene chloride exposure (n = 3), and yacht engine fumes (n = 1). The exposure occurred during the first trimester (n = 12), second trimester (n = 14), or third trimester (n = 14). The clinical grade of poisoning was based on clinical signs and symptoms as shown in Table 2-9. Cases in which COHb values were available or could be estimated from the known ambient CO concentrations are presented in Table 2-10. Adverse fetal outcome occurred only after grade 4 or 5 poisoning.

Caravati et al. (1988) reported on six cases of acute CO poisoning during pregnancy (all cases of patients with CO poisoning during pregnancy admitted to two teaching hospitals in Salt Lake City during a 2-year period). Results of COHb measurements and outcomes are given in Table 2-11. Cases 5 and 6 were treated with 100% oxygen for 5 h before the COHb measurement, which is between 3 and 4 half-life times of CO under this condition, using a half-life time of 80 min for treatment with 100% oxygen (Peterson and Stewart 1970). It can be concluded that at the end-of-exposure, COHb values were about 8-16-fold higher and thus were about 40-80% in case 5 and 22-44% in case 6. In conclusion, the three cases of stillbirths were associated with maternal COHb concentrations of 22% or higher.

TABLE 2-9 Severity of Carbon Monoxide Poisoning

Grade 1	Alert, oriented, headache, dizziness, nausea
Grade 1+	As Grade 1, but another person exposed in the same incidence was unconscious
Grade 2	Alert, alterations of mental state, more pronounced headache, dizziness, nausea
Grade 3	Not alert, disorientation, loss of recent memory, muscle weakness, incoordination
Grade 4	Disoriented, depressed sensorium, limited and inappropriate response to simple commands
Grade 5	Comatose, responding only to pain or not responding to any stimulus

Source: Adapted from Koren et al. 1991.

TABLE 2-10 Overview of Clinical Scoring, COHb and Fetal Outcome

Grade	COHb (%)	Time of Exam After Exposure (h)	Treatment[a]	Outcome
5	40-50	2	HfO, 2 h	Elective termination (in the text the authors state: fetal death at term followed by maternal demise)
5	26	1	HfO, 3 h	Stillborn
4	39	2	HybO, 2 h	Normal
4	25	2	HfO, 2 h	Cerebral palsy compatible with postanoxic encephalopathy
4	21	2	HybO, 2 h	Normal
2	13.8	1	HfO, 7 h and HybO, 2 h	Normal
1	18	Unknown	HfO, 12 h	Normal
1	14	Unknown	None	Normal
1	6.2	1.5	None	Normal
1	2.4	Unknown	None	Normal
1	0.8	1	None	Normal
1	2	Unknown	None	Normal
Cases with indirect measures of exposure				
1+	32, measured in affected son	2	HfO, 12 h	Normal
1+	32	—	None	Fetal bradycardia
1	32	—	None	Normal
1	14	—	None	Normal
1	14	—	None	36-week gestation
1	5	—	None	Normal

[a]HfO, high-flow oxygen; HybO, hyperbaric oxygen.
Source: Adapted from Koren et al. 1991.

TABLE 2-11 Overview of Maternal Clinical Effects, CoHb and Fetal Outcome

Case	COHb (%)	Time Between End of Exposure and Blood Sampling (h)	Treatment	Maternal Effects and Fetal Outcome
1 28-year-old, pregnancy week 20	9.6	8	100% oxygen by face mask for 10 h; then COHb had reduced to 1.7%	Poisoning was caused by a gas-leak in the restaurant where the woman worked; during a 6 h working period, she developed severe headache, nausea and dizziness; she visited hospital 6 h later with persisting headache, lethargy and dizziness; she was discharged in good health and delivered a normal female infant weighing 2900 g four months later.
2 32-year-old, pregnancy week 16	23	Not stated	100% oxygen by face mask for 10 h; after 2.5 and 9.5 h COHb was 8.9 and 1.8%, respectively.	Poisoning was caused by clogged furnace; she complained of headache, nausea and dizziness of 48 h duration; she was discharged 36 h later in good health and delivered a term healthy male infant weighing 2920 g.
3 19-year-old, pregnancy week 30	39	not stated	100% oxygen by face mask for 8 h; after 5 h COHb had reduced to 4%	Poisoning was caused by a malfunctioning heater; after 18 h exposure she complained of severe headache and nausea; she was discharged after 8 h of oxygen therapy and delivered a healthy 3940-g male infant.
4 18-year-old, pregnancy week 41	32	not stated	Oxygen treatment using iron lung	The woman was found unconscious and was combative on arrival in the emergency department; her mental status rapidly improved and she recalled having nausea, vomiting and headache earlier that day; fetal heart tones were absent and the woman delivered a stillborn female infant the next day.
5 20-year-old, pregnancy week 38	5	5 h with oxygen treatment	100% oxygen by face mask during ambulance and helicopter transport to the hospital	The woman was found awake outside her home together with case 6; they had occluded the furnace the evening before to improve heating; she delivered a stillborn 3380-g male fetus 36 h later.

6 18-year-old, pregnancy week 13	2.8	5 h with oxygen treatment	100% oxygen by face mask during ambulance and helicopter transport to the hospital	The woman was found unconscious together with case 5; fetal heart rate was 136 per min at the scene and 190-200 per min 5 h after the exposure; after 5 h, she was somnolent but oriented and regained full mental alertness during the next 2 h; fetal heart rate decreased to 150-160 per min the next day and the woman was discharged; she delivered a nonviable 1210-g fetus at 33 weeks of gestation; autopsy revealed brachycephaly, craniosynostosis, multiple organ cavity anomalies, multiple contractures of extremities, hypoplastic lungs and a small brain with hydrocephalus.

Source: Adapted from Caravati et al. 1988.

Farrow et al. (1990) reported a case of fetal death in a 20-year-old woman, who was exposed to CO due to use of a portable propane heater in her unventilated mobile home. She arrived by ambulance at the hospital approximately 60 min after being found unconscious at her mobile home. En route to hospital she had been intubated and had received 100% supplemental oxygen. Her measured COHb at the time of admission was 7%. On the second day in hospital, the patient delivered a 1,050-g stillborn female fetus. On gross autopsy, bright red discoloration of the skin and visceral organs was noted. A fetal COHb of 61% was measured. The authors assumed that the mother had reached a minimal COHb of 40 to 50% because she was found unconscious.

2.4. Genotoxicity

No studies documenting genotoxic effects of CO in humans were located in the available literature.

2.5. Carcinogenicity

No studies documenting carcinogenic effects of CO in humans were located in the available literature.

2.6. Summary

In healthy adults, death from CO poisoning occurs at COHb larger than 50% (Steward et al. 1970; Steward 1975; Pach et al. 1978, 1979; AIHA 1999; WHO 1999a). At a COHb of about 16%, headaches can develop (Steward et al. 1970). Subtle (nonadverse) effects, such as decrements in neurobehavioral function start at about 5% COHb (WHO 1999a; EPA 2000).

Analysis of lethal cases reported by Nelson (2006a) indicated that most lethal poisoning cases occurred at COHb levels higher than 40% and that survival of CO-exposed humans were likely to be seen at levels below 40%. Persons with coronary artery disease constitute a subpopulation that is much more susceptible to the effects of CO. Case reports indicate that death through myocardial infarction can occur at COHb around 20-30% and as low as about 15% in this group (Grace and Platt 1981; Balraj 1984; Atkins and Baker 1985; Ebisuno et al. 1986;). In individuals with coronary artery disease, a COHb of 2.0 or 4.0% can significantly reduce the time to onset of angina and the time to 1-mm ST-segment change in the electrocardiogram during physical exercise (Allred et al. 1989a,b, 1991). At 5.3%, but not at 3.7% COHb an increased arrhythmia frequency was observed in subjects with coronary artery disease (Sheps et al. 1990, 1991).

Children and the unborn also constitute susceptible subpopulations: Measured COHb of higher than 22-25% in the mothers' blood may lead to stillbirths

(Caravati et al. 1988; Koren et al. 1991). After CO poisonings associated with mean COHb of 21% (range 13-32%) irreversible neurotoxic effects resulting in defects in the cognitive development and in behavioral alterations were observed in a long-term followup study, especially in young children (mean COHb 21%) (Klees et al. 1985). Acute symptoms of CO poisoning in children include effects, such as nausea, vomiting, headache and lethargy. These symptoms were reported to occur already at a COHb of 7% in one study (Klasner et al. 1998), while in another study a threshold of 16.7-19.8% COHb was found (Crocker and Walker 1985). Visual symptoms and syncopes occurred at a threshold of 24.5% COHb, at higher COHb every child experienced at least one syncope (Crocker and Walker 1985).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data for acute inhalation exposure have been reported for rats, mice, and guinea pigs. The lethality data are summarized in Table 2-12 and graphically presented in Figure 2-1.

3.1.1. Rats

E.I. du Pont de Nemours and Co. (1981) determined LC_{50} values for male Crl:CD rats (weight 250 ± 25 g) at exposure times of 5, 15, 30, and 60 min. The experiment was performed in duplicate with one set of animals exposed head only to the test gas, while the other set was unrestrained inside a 175-liter rectangular exposure chamber. In restrained rats, respiration rate was monitored by recording pressure fluctuations due to breathing in a body plethysmograph. During CO exposures, the chamber atmosphere was monitored continuously for oxygen (BioMarine Industries model 225 oxygen meter), CO_2 and CO (InfraRed Industries model 702-D nondispersive analyzer) using infrared analyzers. Blood from CO-exposed rats that died during or within 30 min of exposure was collected by cardiac puncture. The blood was measured for hemoglobin, COHb and oxyhemoglobin by an Instrumentation Laboratories model 282 CO-Oximeter. The post-exposure observation period was 14 days during which time body weights were monitored.

Nearly all the deaths occurred during the exposure period; of all animals that died, only 2 of 216 restrained and 3 of 148 unrestrained rats died after the exposure period. The authors reported LC_{50} values for the 5-, 15-, 30-, and 60-min exposure periods for the unrestrained rats at 10,151 ppm (95% C.I., 9,580-10,953 ppm), 5,664 ppm (95% C.I., 5,218-6,078 ppm), 4,710 ppm (95% C.I., 4,278-5,254 ppm), and 3,954 ppm (95% C.I., 3,736-4,233 ppm), respectively.

TABLE 2-12 Summary of LC_{50} Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time (min)	Remark	Reference
Rat	14200	5		Darmer et al. 1972
Rat	10151	5	Crl:Cd strain, male	E.I. du Pont de Nemours and Co. 1981
Rat	8636	15		Hartzell et al. 1985
Rat	5664	15	Crl:Cd strain, male	E.I. du Pont de Nemours and Co. 1981
Rat	5607	30		Herpol et al. 1976
Rat	5500	30		Kimmerle 1974
Rat	5207	30		Hartzell et al. 1985
Rat	4710	30	Crl:Cd strain, male	E.I. du Pont de Nemours and Co. 1981
Rat	4070	30		Haskell Laboratories 1978 (in E.I. du Pont de Nemours and Co. 1981)
Rat	4670	60		Kimmerle 1974
Rat	3954	60	Crl:Cd strain, male	E.I. du Pont de Nemours and Co. 1981
Rat	1807	240	Sprague-Dawley strain, male	Rose et al. 1970
Mouse	10127	15		Kishitani and Nakamura 1979
Mouse	3570	30	Swiss-Webster strain	Hilado et al. 1978
Mouse	8000	30	ICR strain	Hilado et al. 1978
Mouse	2444	240	Swiss albino strain, male	Rose et al. 1970
Guinea pig	5718	240	Hartley strain, male	Rose et al. 1970

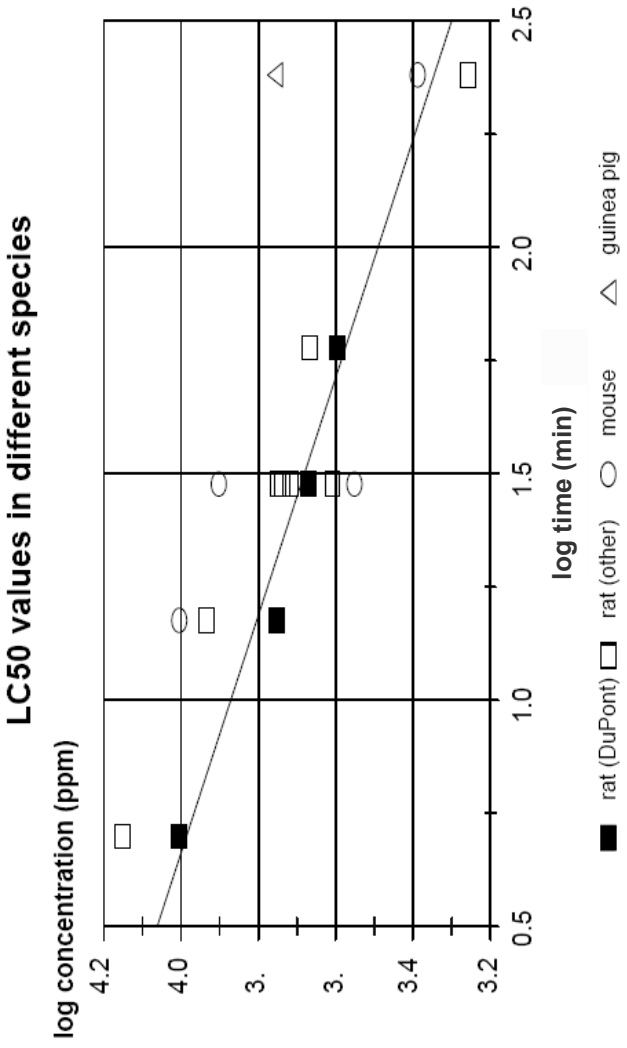

FIGURE 2-1 LC_{50} values for CO in different species.

The LC_{50} values were lower (higher toxicity) for restrained rats. For the respective exposure-duration values of 10,754, 4,318, 2,890 and 1,888 ppm were obtained. The RD50 for rats exposed to CO was 15,000 ppm. The COHb values were 60% or higher in rats that had died after unrestrained exposure and 50% or higher in rats that had died after restrained exposure.

Darmer et al. (1972) reported an LC_{50} of 14,200 ppm for 5 min of exposure. Haskell Laboratory (1978) [in E.I. du Point de Nemours (1981)] obtained an LC_{50} of 4,070 ppm for a 30-min exposure. Hartzell et al. (1985) reported an LC_{50} of 8,636 ppm for a15-min exposure and 5,207 ppm for a 30-min exposure. Kimmerle (1974) reported an LC_{50} of 5,500 ppm for a 30-min and 4,670 ppm for a 60-min exposure.

Rose et al. (1970) reported an LC_{50} of 2,070 mg/m^3 (95% C.I. 1,831-2,241 mg/m^3, 1,807, 1,598-1,956 ppm) for a 4 h exposure in male Sprague-Dawley rats. The COHb in animals that had died was between 50% and 80%.

3.1.2. Mice

Pesce et al. (1987) exposed groups of about 100 OF_1-strain mice/age group/sex to 5.5 Torr (about 7,200 ppm; final analytic concentration) for 76 min or to 4.4 Torr (about 5,800 ppm) for 146 min. For the 76-min exposure, survival rates were 36% for 31-day-old males and 22% for 184-day-old males. Of the exposed females, 57% of 31-day-old females and 63% of 184-day-old females survived. After exposure for 146 min, survival rates were 40% for 34-day-old males, 27% for 85-day-old males, 24% for 230-day-old males, and 27% for 387-day-old males 48% for 34-day-old females, 67% for 85-day-old females, and 56% for 387-day-old females. Except for the about 1-month-old mice, male mice showed a significantly lower survival than females. Survival was not significantly influenced by age.

Winston and Roberts (1978) investigated the influence of age on lethal effects of CO on mice (strain not stated; male mice were used in all groups, except for the two youngest groups that comprised both males and females). Animals of different age were exposed to CO at 2,000 ppm for up to 6 h in stainless steel exposure chambers. The analytic concentration was determined by an automated gas chromatograph. Mortality occurred in 3 of 37 2-day-old mice, 21 of 32 17-day-old mice, 16 of 20 30-day-old mice, 11 of 17 54-day-old mice, 10 of 20 108-day-old mice, and 6 of 18 150-day-old mice. The animals of the youngest and that of the oldest age group were found to be more resistant to CO. These two groups were also found less susceptible to lethal effects from hypoxic hypoxia when mice were exposed to a reduced oxygen concentration of 7.5%.

Hilado et al. (1978) reported 30-min LC_{50} values of 3,570 ppm for Swiss-Webster mice and 8,000 ppm for ICR mice. Respiratory distress was the only sign observed during the exposures.

Rose et al. (1970) reported an LC_{50} of 2,800 mg/m^3 (95% C.I., 2,679-2,926 mg/m^3, 2,444, 2,339-2,554 ppm) for a 4 h exposure in male Swiss albino mice. COHb was not determined.

3.1.3. Guinea Pigs

Rose et al. (1970) reported a LC_{50} of 6550 mg/m^3 (95% C.I., 5509-7788 mg/m^3, 5,718, 4809-6799 ppm) for 4 h of exposure in Hartley guinea pigs. The COHb in animals that had died was between 57% and 90%.

The solid line was calculated by Probit analysis from the data in E.I. du Pont de Nemours and Co. (1981). The slope of this line indicates a time scaling exponent of n = 2.6. Analysis of all data yielded a value of n = 2.8. The LC_{50} values are taken from Table 2-12.

3.2. Nonlethal Toxicity

A large number of studies investigated nonlethal effects of single and repeated CO exposures in animals (see WHO [1999a] for review). Reported here are only studies that support or add information to the effects seen in humans because these studies were considered most relevant. These effects include syncope-like observations and behavioral effects in monkeys, effects on heart function in dogs, as well as developmental and reproductive toxic effects in different species.

3.2.1. Monkeys

Purser and Berrill (1983) studied the behavioral effects of CO exposure on cynomolgus monkeys (three male animals 4-5 years old). The basic behavioral model consisted of an individual monkey placed in a chamber with a lever press at one end a reward (chocolate candy) dispenser at the other. At 5-min intervals throughout the test session a buzzer was sounded and a light flashed over the lever. If the monkey pressed the lever within a 1-min period, a candy was presented in the dispenser. The monkey then moved the length of the chamber to pick up the candy. The major performance parameter measured was the time from the animal releasing the lever to its first touch of the dispenser, that is, the time taken to traverse the chamber. Each session consisted of the following stages: (1) a 25-min pre-exposure period during which baseline CO_2 production and behavioral task performance times were established, (2) 2.5% CO was introduced into the chamber at a sufficiently high flow rate to increase the concentration to 900 ppm within 1 min, (3) CO at 900 ppm was maintained for 30 min, during which the effects on clinical condition, CO_2 production and behavioral task performance were examined, (4) the chamber was flushed of CO, decreasing the concentration to less than 100 ppm within 4 min, (5) animals were main-

tained for anther 45 min in the chamber while their clinical condition, CO_2 production and behavioral task performance were monitored. CO_2 and CO concentrations were monitored continuously using infrared analyzers. Five preliminary experiments were conducted on CO at 1,000 ppm, followed by the main experimental series that consisted of 10 exposures at 900 ppm, three for each animal, and one preliminary run. For three exposures (one for each animal), the animals were removed from the chamber 5 min after the exposure period so that venous blood samples could be taken for COHb analysis.

During the four preliminary exposures to CO at 1,000 ppm, there was generally no visible effect on the animals until 18-20 min of exposure had elapsed, at which time they generally became less active, occasionally sitting down for short periods. At approximately 25 min, a dramatic change occurred over a period of 1-2 min, and the animals went from an apparently normal state to one of severe intoxication. This change was preceded by one or more warning signs at approximately 23 min, which consisted of momentary closure of eyes, yawning and shaking of the head. Immediately prior to collapse the animals sometimes paced around in a mechanical fashion, often swaying as they walked. As few as 20 seconds (s) later, the animals were lying or rolling on the floor, sometimes attempting to rise before sitting on the floor or lying down again. During recovery, the animals remained in a state of severe intoxication for approximately 30 min, lying down with their eyes closed. On three occasions animals vomited during this period. After 25-30 min the animals were usually sufficiently recovered to get up and move around the chamber, in response to the buzzer they would sometimes move toward or even press the lever, although they made no attempt to fetch the candy. The performance of the behavioral task was unaffected during the first 15 min of exposure, but before the first minor clinical signs there was generally a slowing of response.

During exposures to 900 ppm, the first signs generally occurred after 20-25 min when the animals became less active, followed by the minor warning signs at approximately 26 min. Although in most cases the animals were lying down at the end of the exposure period, they did not appear to be severely intoxicated and in six of nine exposures the signs were mild, and the animals did not reach a state of collapse. During the recovery period the animals remained in a state of intoxication for approximately 16 min. Recovery was more rapid than that following exposure to 1,000 ppm, as all animals performed the behavioral task within 25 min of the exposure. The first effects upon the chamber traverse time occurred at 15 min into the exposure as a slight, statistically significant decrement in performance. The decrement at 20 min was not statistically significant while at 25 min it was highly significant, as the mean response time was twice the preexposure response time (1.10 s vs. 0.62 s). The first time that the test was conducted successfully on all occasions was after 25 min of recovery when the mean chamber traverse time was three times as long as the mean pre-exposure time. From 30 to 45 min, the animals were more active and response times gradually improved but did not reach the pre-exposure level.

The mean COHb measured at the end of the exposure was 32.9% (range 31.7-34.8%). CO_2 production, indicating the metabolism in the animals, decreased gradually throughout the exposure (statistically significant at 25 and 30 min of exposure) and then increased gradually toward pre-exposure levels during the recovery period (significantly lower until 15 min into the recovery period).

From earlier experiments, the authors estimated COHb of 16-21% for the period of 15-20 min when deficits in behavioral task performance were started during the exposure period. In the state of severe intoxication, the animals were capable of performing some coordinated behavioral actions when they were sufficiently stimulated (e.g., by loud noise or removing them from the chamber). The authors report that in unpublished experiments using higher CO concentrations, the animals passed rapidly from this stage to one of deep coma.

DeBias et al. (1976) reported that CO exposure (100 ppm for 6 h; resulting in a COHb of 9.3%) reduced the threshold for ventricular fibrillation induced by an electrical shock applied to the myocardium of monkeys during the final stage of ventricular repolarization. The voltage required to induce fibrillation was highest in normal animals breathing air and lowest in infarcted animals breathing CO. Additivity was found for the effects of infarction alone and CO exposure alone, each of which required significantly less voltage for fibrillation.

3.2.2. Dogs

Aronow et al. (1979) reported that CO exposure increased the vulnerability of the heart to induced ventricular fibrillation in normal dogs breathing 100 ppm CO for 2 h (resulting COHb was 6.3-6.5%). The ventricular fibrillation was induced by an electrical stimulus applied to the myocardium.

Sekiya et al. (1983) reported that exposure to CO concentrations of 3,000 ppm for 15 min followed by 130 ppm for 1 h (resulting COHb was 13-15%) increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation, which was induced in anaesthetized dogs more by coronary artery ligation than by ligation alone.

3.3. Developmental and Reproductive Toxicity

3.3.1. Pigs

Dominick and Carson (1983) exposed pregnant sows to CO concentrations between 150 and 400 ppm for 48-96 h between gestational days 108-110 (average gestation was 114 days). They showed a significant linear increase in the number of stillbirths as a function of increasing CO concentration. Stillbirths were significantly elevated above control levels when the maternal COHb exceeded 23% saturation. These saturation levels were obtained at approximately 250 ppm.

Morris et al. (1985) exposed 16 pigs to 0, 200, or 250 ppm from gestational day 109 until birth (maternal COHb at 24 h into the exposure was 0, 13.6%, and 17.1%, respectively). Stillbirth rates for the three groups (total of 123 piglets) were2.3%, 2.4%, and 4.8%, respectively. The study authors stated that the stillbirth rate was not affected because the observed rates were lower than the industrial norm of 5-10%. The COHb in neonatal piglets at birth were 0, 19.8%, and 22.4%, respectively. The authors found impairment of negative geotaxis behavior and open field activity 24 h after birth in the 250-ppm group. Activity in open field was significantly reduced at 48 h after birth in piglets from both exposure groups.

3.3.2. Rabbits

Astrup et al. (1972) reported an increase in fetal mortality and malformations in rabbits exposed to CO at 180 ppm continuously throughout gestation. Maternal COHb was 16-18%.

Rosenkrantz et al. (1986) exposed rabbits to high concentrations of CO-containing cigarette smoke (12 puffs of CO at 2,700-5,400 ppm; exposure to puffs of cigarette smoke by face mask; each puff sequence consisted of 30 s of cigarette smoke and 30 s fresh air) for 12 min daily from gestational days 6-18. The COHb level reached at the end of each exposure was 16%. A large number of fetal deaths, but no malformations were observed in exposed animals.

3.3.3. Rats

Choi and Oh (1975) exposed rats to CO at 750 ppm for 3 h/d on gestational days 7, 8, or 9. An excess of fetal absorptions and stillbirths as well as a decrease in body length and an increase in skeletal anomalies were observed. COHb was not determined.

Penney et al. (1980) exposed pregnant COBS rats for the last 18 days of gestation to CO at 200 ppm. The mean maternal COHb was about 27.8%, and the mean fetal level was 27.0%. The body weight of the pups was significantly lower than that of controls. The heart weight of both exposed females and pups was significantly increased.

Mactutus and Fechter (1985) exposed Long-Evans rats continuously throughout gestation to CO at 0 or 150 ppm. Mean COHb was 15.6% vs. 1% in control subjects. At 120 days of age, CO-exposed rats acquired a conditioned avoidance response equally well as control animals. However, following a 24 h interval, the CO-exposed rats failed to demonstrate significant retention. In a second experiment in which animals received 50 training trials per day until a criterion of 10 consecutive avoidance responses was met, the prenatal CO-exposed rats again acquired the task as well as control animals. When the rats were tested for retention 28 days later, a significant memory impairment was again observed in terms of trials required to retain the avoidance criterion as

well as in total percent avoidance. At 1 year of age, the CO-exposed rats showed impairment relative to air-exposed controls in both the original learning and retention of the two-way avoidance response.

3.3.4. Mice

Singh and Scott (1984) exposed groups of 17 pregnant CD-1 mice to CO concentrations of 0, 65, 125, 250, or 500 ppm for 24 h/d on gestational days 6 to 17. Mice were killed and examined on day 18. No signs of maternal toxicity were observed at any dose. The mean percent fetal mortality per litter was 4.52%, 5.89%, 12.50%, 15.50%, and 55.30%, respectively. Besides a dose-dependent increase in embryo lethality, fetus weights were significantly reduced at exposure levels of 125 ppm or higher. No fetal malformations were detected. COHb was not determined.

Singh (1986) exposed CD-1 mice to CO at 0, 65, or 125 ppm continuously during gestational days 7 to 18 (COHb not determined). No signs of maternal toxicity were observed. Exposure did not affect the number of live pups born per litter or their birth weight. Prenatal exposure to 125 ppm significantly increased the time required by pups for righting reflex on day 1 of birth and negative geotaxis on day 10. Prenatal exposure at both concentrations significantly decreased the mean aerial righting score of pups on day 14.

3.4. Genotoxicity

No information regarding the carcinogenicity of CO in animals was located in the available literature.

3.5. Carcinogenicity

No information regarding the carcinogenicity of CO in animals was located in the available literature.

3.6. Summary

Several CO-exposure studies reported LC_{50} values in rats, mice, and guinea pigs. In the study of E.I. du Pont de Nemours and Co. (1981), the following LC_{50} values were calculated by Probit analysis: 1,0151 ppm for 5 min, 5,664 ppm for 15 min, 4,710 ppm for 30 min, and 3,954 ppm for 60 min.

In a study in cynomolgus monkeys exposed to CO at 900 ppm, no signs of intoxication occurred during the first 20-25 min (corresponding to COHb of about 16-21%). At 25 min, the animals' performance in a behavioral test significantly decreased, and at the end of the exposure period (30 min), animals became less active and were lying down. After about 25 min of exposure at 1,000

ppm, the animals went into a state of severe intoxication within 1-2 min and were virtually unable to perform coordinated movements (Purser and Berrill 1983).

In developmental toxicity tests, CO caused an increase in the rate of stillbirths or fetal mortality in pigs after 2-3 days of exposure to COHb at over 23% (Dominick and Carson 1983); in rabbits after continuous exposure to 16-18% COHb throughout gestation (Astrup et al. 1972) as well as after daily exposure to high CO concentrations in cigarette smoke (exposure for 12 min/d on gestational days 6-18, resulting in a COHb of 16%) (Rosenkrantz et al. 1986); in rats after three exposures at 750 ppm for 3 h/d (Choi and Oh 1975); and in mice after exposure at 125 ppm for 11 days (Singh and Scott 1984). Significant memory impairment in behavioral tests were found in young rats after continuous CO exposure throughout gestation (mean maternal COHb was 15.6%) (Mactutus and Fechter 1985).

In monkeys, a COHb of 9.3% resulted in reduced threshold for electric-shock-induced ventricular fibrillation (DeBias et al. 1976). A similar effect was found in dogs at 6.3-6.5% COHb (Aronow et al. 1979). A COHb of 13-15% increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in a myocardial infarction model in dogs (Sekiya et al. 1983).

SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism, and Disposition

CO is produced endogenously in normal metabolism. When an α-methylene bridge in the heme group of hemoglobin is broken during the catabolic process, one molecule of CO is released. It has been estimated that this production amounts to approximately 0.3 to 1.0 mL/h with an additional 0.1 mL/h resulting from a similar catabolic process involving other heme-containing compounds (e.g., myoglobin as well as cytochrome and catalase enzymes). This endogenous production of CO gives rise to a baseline or back ground level of approximately 0.5-0.8% COHb (NIOSH 1972).

Almost all the CO that has been inhaled is eliminated through the lungs when the previously exposed person enters an atmosphere free of CO. CO not only binds to hemoglobin forming COHb, but 10-50% of the total body store of CO is also distributed to extravascular sites, such as skeletal muscle, where it can bind to myoglobin. Extravascular CO can be slowly metabolized to CO_2 (Fenn 1970). Inside the cells, CO can bind to all heme proteins capable of binding oxygen, such as myoglobin, cytochrome c oxidase, cytochrome P-450 enzymes, and tryptophan oxygenase (WHO 1999a). However, the exact extent of this binding in vivo as well as the physiologic consequences in terms of inhibition of protein and enzyme function and the existence and relevance of possible toxic effects has not been clearly shown until now (cf. extensive discussion in WHO 1999a).

The time required to eliminate half of the gas is 3-5 h (Landaw 1973), depending on the amount of respiration, which acts to wash it out of the body. Peterson and Stewart (1970) reported a range of 128-409 min for the elimination half-time in 39 experiments, with an average of 320 min in human subjects who breathed normal air after CO exposure. Increased oxygen pressure helps to dislodge it from the hemoglobin. One hundred percent oxygen given at atmospheric pressure reduces the elimination half-life rate to about 80 min (Peterson and Stewart 1970). Weaver et al. (2000) reported a half-life of 74 ± 25 min for COHb in CO-poisoned patients receiving 100% oxygen. Klasner et al. (1998) reported a half-life of 44 min for 26 children (4-12 years old) when given 100% oxygen via face mask. Hyperbaric oxygen at 3 bar pressure reduces the half-life to about 20-25 min (Landaw 1973; Beard 1982).

4.2. Mechanism of Toxicity

If not stated otherwise, the information on the mechanism of toxicity is taken from the extensive recent reviews of WHO (1999a) and EPA (2000). The best understood biologic effect of CO is its combination with hemoglobin (Hb) to form COHb, thereby rendering the hemoglobin molecule less able to bind with oxygen. Although the rate of CO binding with hemoglobin is about one-fifth slower and the rate of dissociation from hemoglobin is an order of magnitude slower than the respective rates for oxygen, the CO chemical affinity for hemoglobin (represented by the Haldane coefficient M) is about 245 times greater than that for oxygen. One part of CO and 245 parts of oxygen would form equal parts of oxyhemoglobin and COHb (50% each), which would be achieved by breathing air containing 21% oxygen and 570 ppm CO. The steady-state ratio of COHb to oxyhemoglobin is proportional to the ratio of their respective partial pressures:

$$COHb:O_2Hb = M\ (P_{CO}:P_{O2}).$$

Under dynamic conditions, competitive binding of oxygen and CO to hemoglobin is complex: the greater the number of heme groups bound to CO, the greater the affinity of free heme groups for oxygen. CO not only occupies oxygen-binding sites, molecule for molecule, thus reducing the amount of available oxygen, but also alters the characteristic relationship between oxyhemoglobin and the partial pressure of oxygen, which in normal blood is S shaped. The difference in the partial pressure of oxygen between freshly oxygenated arterial blood ($P(O_2)$ = 100 mm Hg) and mixed venous blood ($P(O_2)$ = 40 mm Hg) represents a release to the tissues of approximately 5 mL of O_2/100 mL of blood (NIOSH 1972). With increasing COHb in blood, the dissociation curve is shifted gradually to the left, and its shape is transformed into that of a rectangular hy-

perbola. This changes the release of oxygen to the tissues appreciably: the oxygen content of the blood is not only lowered during exposure to CO, but the shift of the oxyhemoglobin dissociation curve to the left decreases the amount of remaining oxygen that is made available to the tissues. Both mechanisms serve to effectively lower the tissue partial pressure of oxygen and hence can create a generalized tissue hypoxia. Because the shift occurs over a critical saturation range for release of oxygen to tissues, a reduction in oxyhemoglobin by CO poisoning will have more severe effects on the release of oxygen than the equivalent reduction of hemoglobin due to anemia.

Although the brain has a higher requirement for oxygen than the heart, the coronary circulation, in contrast to the cerebral circulation, must supply an even increased amount of oxygen during periods of generalized tissue hypoxia because under these circumstances, the heart is forced to increase both its rate and its output to meet the normal oxygen demands of the body. This increase in myocardial activity demands an increased oxygen supply to the myocardium, which must be met by the coronary circulation. Under hypoxic conditions, increased oxygen supply to the peripheral tissues can be accommodated by increased blood flow (via vascular dilatation) and increased oxygen extraction by the tissues. The myocardium under these circumstances appears only to increase the flow of blood rather than to extract an additional amount of oxygen from the coronary circulation. The peripheral tissues normally extract only 25% of the oxygen content of the perfusing arterial blood during resting conditions, and the myocardium extracts 75%, thus leaving the mixed venous blood only 25% saturated. This mechanism has the overall effect of maintaining the myocardial oxygen tension at a higher level than would be present in other muscle tissue and thus ensures a continual aerobic metabolism, even under hypoxic duress. In terms of oxygen partial pressure, the mixed venous blood of the peripheral tissues is approximately 40 mm Hg, and the mixed venous blood of the coronary circulation is only 20 mm Hg. In the presence of COHb (and the shift to the left of the oxyhemoglobin dissociation curve), however, the arterio-venous difference can only be maintained by an increased flow in the coronary circulation. In an individual with diminished coronary circulation because of coronary heart disease, however, this situation may result in a decrease in the venous oxygen partial pressure of the myocardium precipitated by an inability to maintain the normal arterio-venous gradient. Studies in dogs suggest that exercise plus an increased COHb, in addition to the global myocardial hypoxia, leads especially to areas of relative hypoxia in the left ventricle secondary to redistributive changes in subendocardial blood flow (Einzig et al. 1980). This hypoxic effect is further enhanced, as mentioned above, by an increase in cardiac rate and output as a general response to peripheral tissue hypoxemia. A person with diminished coronary circulation caused by coronary heart disease may consequently be constantly near the point of myocardial tissue hypoxia, which can ultimately lead to myocardial infarction.

4.3. Issues Related to Postmortem CO Determination in Humans

4.3.1. Potential Factors Influencing COHb Levels

Data on the postmortem decay of COHb are sparse. Rodat et al. (1987) reported on the stability of CO after death. A CO poisoning due to a running truck engine in a nonventilated area was discussed. The autopsy was performed 10 months after the death due to insurance claims. The body was decomposed, but some muscle tissue was recovered and tested for COHb levels, which were 26%. Muscle tissue as well as other human tissues, such as brain, lung, and kidney, may be used for diagnosing death due to lethal exposure to CO (Vreman et al. 2006). The report did not discuss measurements from blood samples, presumably due to the decomposition of blood. Following death, the report indicated that COHb levels disintegrate over time, releasing reduced hemoglobin. In addition, the report indicated that the formation of sulfur compounds in a putrefied cadaver makes it difficult to interpret the absorption spectra of the COHb measurements, a phenomenon that has been acknowledged by others (Winek and Prex 1981; Kojima et al. 1986). Rodat et al. (1987) and Kojima et al. (1986) also suggested that the endogenous formation of CO after death is very low,

People who die of CO poisoning often show sublethal COHb levels in their blood (R. Coburn, personal commun., April 8, 20008). The lungs rapidly absorb CO, which avidly combines with hemoglobin at 230 to 270 times greater than with oxygen (Ellenhorn 1997; Larsen 2006). Oxygen therapy increases oxygen delivery and pulmonary excretion of CO by displacing CO from the hemoglobin and decreasing the half-life of COHb (Roos 1994; Ellenhorn 1997), in turn explaining the sublethal COHb levels in blood samples from deceased people exposed to CO.

CO shifts from the blood into the muscle tissue have been reported in the literature (Luomanmaki and Coburn 1969; Bruce and Bruce 2006). In order for shifts to occur, blood must be flowing in capillaries. Presumably during the moving of corpses after death, blood could be pushed through capillaries to a small extent (R. Coburn, personal commun., April 8, 2008), leading to CO shifts, but no studies were found reporting this phenomenon in human cadavers.

Oxidation of CO to CO_2 has been reported in living animals and humans. The rate of oxidation in skeletal and cardiac muscle was found to be small but still measurable (Fenn and Cobb 1932; Clark 1950; Luomanmaki and Coburn 1969). It is unknown whether this oxidation occurs in cadavers and what its effects are on the CO decay rates after death.

Once blood is collected from a cadaver, the postmortem samples may be measured more than once, and results would depend on storage and treatment of samples. Levine et al. (1990) found a 19% decrease in measured COHb levels when blood was refrigerated for 3 months and then frozen for 3 months. The refrigerated blood samples were first tested by microdiffusion techniques (sensitivity of approximately 5%) within 1 month of being obtained from victims of a

hotel fire on December 31, 1986. The samples remained refrigerated until being mailed frozen to a second laboratory for testing (received March 26, 1987). The samples were frozen upon arrival and were thawed and refrozen several times during the next 3 months for experimental purposes. After sonication and filtration, the samples were analyzed on a CO-oximeter IL-282 (sensitivity not given). The authors concluded that aging of blood samples and methods of storage could affect accuracy of analytic results. This result was supported by another study, which determined that the contact of the sample with air could decrease the percent of COHb saturation (Chace et al. 1986). That result is in contrast to reports that CO would be stable for months to years in stored samples (vacutainer tubes, especially heparin-anticoagulated tubes) (Kunsman et al. 2000; Hampson 2008). Proper storage of samples would prevent loss of CO (Nelson 2006b).

4.3.2. Influence on Collection Site on Measured COHb Concentrations

Reductions in the percent of COHb saturation are also associated with differences between COHb measurements derived from heart blood and from peripheral blood specimens. Levine et al. (2002) studied data from 42 CO poisoning cases. The Office of the Chief Medical Examiner in the state of Maryland provided the data. Blood samples from the heart and the subclavian veins were analyzed in a CO oximeter. The specific heart site for blood collection was not reported. Also, the report did not indicate whether the deceased individuals with decreased COHb were given oxygen therapy. Blood samples with COHb saturation levels greater than 12% were confirmed and quantitated by gas chromatography. The latter analysis measured both CO content and CO capacity and did not measure hemoglobin concentration, which tends to vary in postmortem specimens (Levine et al. 2002). Samples were normalized for hemoglobin, ensuring that differences between the heart blood and peripheral blood were not caused by significant differences in hemoglobin between the two blood samples. The average heart blood COHb level was 42% (range = 11-79; SD = 19.95; median = 38), and the average peripheral blood COHb level was 39% (range = 4.2-71; SD = 17.07; median = 37). The average heart blood to peripheral blood (H:P) ratio was 1.09. Sixty-two percent of the cases (26 of 42) had an H:P ratio of 0.9 to 1.1, whereas 74% of the cases (31 of 42) had an H:P ratio of 0.8 to 1.2. Statistical analysis showed no statistically significant differences in COHb levels between heart and peripheral blood samples (Levine et al. 2002). The report acknowledged that there might be instances (e.g., cardiopulmonary resuscitation) where differences between heart blood and peripheral blood COHb levels might occur in isolated cases, but in general, there were no significant differences between the two blood sources.

Dalpe-Scott et al. (1995) calculated the H:P ratio of drug concentrations in postmortem blood samples for 113 drugs representing 320 cases. Thirty-five CO

poisoning cases were examined. The average H:P ratio was 1.0 (range 0.9- 1.5). The specific COHb levels were not provided. Data from Dalpe-Scott et al. (1995) confirmed those findings in Levine et al. (2002).

Differences among COHb levels in the heart blood when compared with those found in the periphery (e.g., femoral vein) have been reported in cases that received cardiopulmonary resuscitation. Rice (1976) found wide variation in COHb levels in 300 consecutive fatal cases of CO poisoning. Source of CO poisoning, such as fire and gas heaters, was not identified in most of the 300 cases; four case studies identified the source in the paper. The author hypothesized that levels below 50% COHb were probably low due to the dissociation of COHb after death when oxygen therapy was given in an attempt to resuscitate the person. A summary of the case findings is given below.

Case 1: A child (14 months) was found apparently dead in a smoldering room fire. Artificial respiration was given on the way to the hospital and continued for about an hour before death was pronounced. Subclavian blood showed COHb levels of 15%. The report did not indicate if it was collected from the subclavian artery or vein. Blood from the femoral vein reported a 31% COHb, or a 2-fold difference between sites. The ratio of subclavian blood to femoral blood was 0.48.

Case 2: A man of 57 yrs died of CO poisoning. The CO source was a disconnected coal gas supply pipe. The emergency personnel found him cold but gave him artificial respiration on the way to the hospital where he was pronounced dead. Subclavian blood showed COHb levels of 32%. The report did not indicate if it was collected from the subclavian artery or vein. Blood from the femoral vein reported a COHb of 52%, or a 1.6-fold difference between sites. The ratio of subclavian blood to femoral blood was 0.62.

Case 3: A woman of 43 yearrs was exposed to CO during a fire. Fire personnel recovered her and attempted resuscitation using artificial respiration and pure oxygen. Subclavian blood showed a COHb of 42%. The report did not indicate if it was collected from the subclavian artery or vein. The common iliac vein showed a COHb of 45%. Blood from the femoral vein reported a COHb of 59%, or a 1.2-fold difference when compared with the subclavian vein. The ratio of subclavian blood to femoral blood was 0.71, and the ratio of subclavian blood to iliac blood was 0.93.

Case 4: An infant of 5 months died in a room fire. Artificial respiration was performed on the infant. Femoral samples were not provided. Blood draining the blood cavity was taken and a COHb of 48% was reported, whereas the subclavian blood was reported to have a COHb of 34%. The report did not indicate if it was collected from the subclavian artery or vein. The ratio of subclavian blood to peripheral blood was 0.71.

Rice (1976) explained the results by pointing out that blood with high concentrations of COHb does not coagulate, and artificial respiration would

have pushed blood to move into and out of the lungs. Thus, oxygen therapy would have increased the dissociation of COHb in the blood, and the amount of the dissociation would have depended on the vigor and the duration of the artificial respiration. The disassociation would be higher in the blood from the lungs, the heart, and the blood vessels in close proximity to the lungs and heart.

Currently, the standard forensic practice is to collect blood from suitably isolated peripheral sites (e.g., femoral vein), which are less likely to be subject to postmortem chemical redistribution (Flanagan et al. 2005; Drummer 2007). The common practice of procuring blood samples from live persons has been venipuncture of the antecubital area of the arm (Ernst 2005).

Gas chromatography is considered the most precise and accurate technique to measure COHb concentrations, but other techniques, such as spectrophotometric analyses, worked well (Lee et al. 1975; Mahonoey et al. 1993; R. Coburn, personal commun., April 8, 2008).

4.4. Other Relevant Information

4.4.1. Species Variability

With regard to lethal effects, COHb concentrations of 50-80% have been reported as lethal in rats and guinea pigs (Rose et al. 1970; E.I. du Pont de Nemours and Co. 1981). In apparently healthy people who died from CO poisoning, usually COHb concentrations of 60% or higher are found (Stewart 1975; Winter and Miller 1976; Balraj 1984; Holmes 1985; AIHA 1999).

Syncopes have been reported to occur in children at a threshold of 24.5% COHb (Crocker and Walker 1985). In monkeys with COHb concentrations little higher than 16-21%, syncopelike effects occurred (Purser and Berrill 1983). The lowest COHb that resulted in cognitive-development defects in children in a long-term followup study was 13% (Klees et al. 1985). In mice, memory impairment was found in the offspring of rats exposed continuously at 15.6% COHb during gestation (Mactutus and Fechter 1985).

Taken together, these studies imply a limited variability among species for different effects with regard to the COHb at which these effects occur. However, the exposure conditions necessary to reach a certain COHb differ among species because of different affinities for CO in their hemoglobin.

The equilibrium COHb of different species is determined by the species-specific Haldane (affinity) constant M. Reported values are 228 for dogs and 195 for monkeys (Sendroy and O'Neal 1955), 170 for rats and 117 for guinea pigs (F.L. Rodkey, and J.D. O'Neal, Naval Medical Research Institute, Bethesda, MD, 1970, as cited in Jones et al. 1971). Jones et al. (1971) reported equilibrium COHb in different species after 48 h continuous exposure as shown in Table 2-13. Using the mathematical model described in Appendix B, corresponding COHb values for a 70-kg man can be calculated as 7.9%, 13.8%, and 25.0% for 51, 96, and 200 ppm, respectively.

TABLE 2-13 COHb after 48 Hours Continuous Exposure to Carbon Monoxide

CO Concentration (ppm)	Species	COHb in Blood, % (n)
51	dog	5.7 (2)
51	monkey	5.3 (3)
51	rat	5.1 (15)
51	guinea pig	3.2 (15)
96	dog	12.5 (2)
96	monkey	10.3 (3)
96	rat	7.5 (15)
96	guinea pig	4.9 (15)
200	dog	20.8 (2)
200	monkey	20.0 (3)
200	rat	16.4 (15)
200	guinea pig	9.4 (15)

Source: Adapted from Jones et al. 1971.

4.2.2. Intraspecies Variability

Experiments in mice did not indicate that very young or very old animals were more susceptible to lethal effects of CO exposure (Winston and Roberts 1978; Pesce et al. 1987). However, there is considerable variability within human subpopulations: a COHb of about 15% only leads to very slight symptoms, such as headache, in healthy adults (Stewart et al. 1970; WHO 1999a). In contrast, the same COHb was reported to cause long-lasting defects in the cognitive development and behavioral alterations in children (Klees et al. 1985) or even to contribute to death from myocardial infarction in individuals with coronary artery disease (Grace and Platt 1981; Balraj 1984). In case reports of myocardial infarction, other subjects exposed under the same conditions (and sometimes had higher COHb) did not experience effects above the AEGL-2 (Grace and Platt 1981; Atkins and Baker 1985).

Subpopulations at higher risk for toxic effects of CO include the following groups:

1. Fetuses are at higher risk because of higher CO affinity and slower CO elimination (see Sections 2.3 and 4.4.4). The severity of exposure and maternal clinical signs appear to be associated with fetal mortality (Koren et al. 1991). A review by Greingor et al. (2001) noted that CO crosses the placenta through passive diffusion or is facilitated by a carrier. As the fetus increases in age and weight, placental CO diffusion increases. When the mother is exposed to CO, the amount of oxygen in her blood decreases, and oxygen transported across the placenta decreases and puts the fetus in a hypoxic state. CO crosses the placenta

as it dissociates from maternal hemoglobin and binds to fetal hemoglobin. The only source of fetal oxygen is the mother, and maternal treatment for CO poisoning reduces fetal COHb levels (Greingor et al. 2001). Clearance of CO in the fetus would be dependent on the mother's oxygen intake. Children have the same type of hemoglobin as adults but are more susceptible than adults because they breathe a greater amount of air per body weight than adults.

The binding affinities of embryonic hemoglobin suggest that fetuses are more susceptible to CO intoxication when compared with adult hemoglobin. Embryonic hemoglobins (Gower I, Gower II, and Portland) are present until about 8-12 weeks of gestation. Fetal hemoglobin is expressed from about 5 weeks of gestation until 9 months after birth. Adult hemoglobin starts being produced between 3-6 months after birth (Orville 2008). Under physiologic conditions, the binding constants of fetal and adult hemoglobin to CO are 0.09 μM and 0.13 μM, respectively, meaning that the binding affinity for CO is higher for fetal hemoglobin than for adult hemoglobin (Di Cera et al. 1989). The rate constants for the binding of CO to the three embryonic hemoglobins are $3.0 \times 10^{-}6$ M/s (Gower I), $2.0 \times 10^{-}6$ M/s (Gower II), and $3.5 \times 10^{-}6$ M/s (Portland) compared with $4.0 \times 10^{-}6$ M/s for adult hemoglobin at pH 6.5 (Hofmann and Brittain 1996). No data were located that reported on whether embryos are more susceptible than fetuses. Data on the susceptibility of embryos to CO are mostly qualitative.

2. Children are at higher risk because they develop acute neurotoxic effects (e.g., headaches and nausea), long-lasting neurotoxic effects (e.g., memory deficits) and impaired ability to escape (e.g., syncopes) at lower COHb concentrations than adults (see Section 2.2.2.1). Children also have developing organs (brain and lungs), which may be affected differently than the developed organs of adults (ATSDR 2002). Children tend to be more susceptible than adults because they breathe a greater amount of air per body weight than adults.

3. People are at higher risk who have pre-existing diseases, either known or unknown, that already decrease the availability of oxygen to critical tissues; this group includes those who have coronary artery disease (see Sections 2.2.1 and 2.2.1.1), chronic obstructive lung disease, chronic anemia, and hemoglobinopathies, such as sickle cell anemia. For example, in sickle-cell disease, the average lifespan of red blood cells with abnormal hemoglobin is 12 days compared with an average of 120 days in healthy individuals with normal hemoglobin. "As a result, baseline COHb levels can be as high as 4%. Presumably, exogenous exposure to CO, in conjunction with higher endogenous CO levels, could result in critical levels of COHb. However, it is not known how ambient or near-ambient air levels of CO would affect individuals with these disorders" (EPA 2000; see also WHO 1999a). Due to physiologic adaptation in these subpopulations, they are not considered more susceptible than patients with coronary artery disease.

4. People at high altitude are at higher risk, especially those not living there long enough for physiologic adaptation. "It is important to distinguish between the long-term resident of high altitude and the newly arrived visitor from

low altitude. Specifically, the visitor will be more hypoxemic than the fully adapted resident. One would postulate that the combination of high altitude with carbon monoxide would pose the greatest risk to persons newly arrived at high altitude who have underlying cardiopulmonary disease, particularly because they are usually older individuals. Surprisingly, this hypothesis has never been tested adequately" (WHO 1999a). Due to physiologic adaptation, people living at high altitude are not considered generally more susceptible than patients with coronary artery disease. Because it is generally not advisable for patients with severe coronary artery disease to travel to places at high altitude, it is not considered necessary to especially take that part of the identified susceptible subpopulation (that is, patients with coronary artery disease; see below) into account when deriving AEGL values.

An estimated 62 million people in the United States (about 20% of the population) have one or more types of cardiovascular disease (American Heart Association 2002). For the major diseases within the category of total cardiovascular disease, about 50 million Americans have high blood pressure, 13 million have coronary heart disease, 4.9 million have heart failure, 4.7 million have cerebrovascular disease (stroke), and 1 million have congenital cardiovascular defects.

The prevalence of cardiovascular diseases increases with age. It is 10% for males and 4% for females at age 25-34, 51% for males and 48% for females at age 55-64, and 71% for males and 79% for females at age 75 or older (American Heart Association 2002).

Coronary heart disease caused more than one of every five deaths in the United States in 2000. Cause of death was listed as coronary heart disease in 681,000 cases and myocardial infarction in 239,000 deaths. Fifty percent of men and 63% of women who died suddenly of coronary heart disease had no previous symptoms of this disease (American Heart Association 2002).

Within the group of people with coronary heart disease, 7.6 million had myocardial infarction (heart attack) and 6.6 million had angina pectoris (chest pain) (American Heart Association 2002). The prevalence of angina pectoris in the British adult population is about 4% (Williams and Stevens 2002).

Angina pectoris is a symptom of coronary heart disease. Common features of an attack are central chest pain, pain radiating to the lower jaw or arms, and shortness of breath. The pain occurs when there is insufficient oxygen delivery to the heart, leading to ischemia. This is usually, although not exclusively, a result of an atheromatous narrowing (stenosis) in one or more of the coronary arteries. Angina can classified broadly as stable or unstable, depending on its severity and pattern of occurrence. Stable angina is typically provoked by exercise (e.g., hurrying across a street or climbing a long flight of stairs), stress, or extremes of temperature and is relieved by either rest or sublingual nitrates or both. Unstable angina is understood as anginal pain that occurs with lesser degrees of exertion, with increasing frequency, or at rest (that is, without exertion). The pain may be more severe and last longer and requires more intensive inter-

vention (usually hospitalization for initiation of medication under cardiac monitoring). If left untreated, unstable angina may result in a heart attack and irreversible damage to the heart. The diagnosis of angina is generally based on clinical history, electrocardiograph stress testing (where patients are exercised on a treadmill to look at the effect on their electrocardiogram), and coronary angiography (to look for narrowings in the coronary arteries) (Williams and Stevens 2002).

4.4.3. Time Scaling

The LC_{50} values for different exposure periods are shown in Figure 2-1. Overall the distribution does not seem to argue against a linear relationship between log(concentration) and log(time), and from the data from E.I. du Pont de Nemours and Co. (1981), a value of 2.6 can be calculated for the exponent n from the slope. Regression analysis of all data yielded a value of n = 2.8. However, taking a closer look at the data from this study suggests that the data might be distributed nonlinearly and that the slope decreases with increasing exposure time.

The AEGL-2 and AEGL-3 exposure concentrations were derived from a mathematical model based on the same COHb at the end of the respective exposure periods. These values are also distributed nonlinearly in a log-log plot: the slope between the two shortest exposure periods (10 and 30 min) is equivalent to n = 1.0-1.1, and the slope between the two longest exposure periods (4 and 8 h) is equivalent to n = 2.9-3.4. This nonlinearity is probably caused by the fact that the COHb depends strongly on the ventilation rate and lung blood flow for short exposure rates; for long exposure rates the COHb becomes independent of these parameters and exclusively depends on the affinity of hemoglobin for CO (represented by the Haldane constant M). Because rats have a higher ventilation rate per kilogram of body weight than humans, their COHb concentrations reach the steady state faster, and, therefore, for the same exposure time, the slope for rats is smaller than the corresponding slope for humans, that is, the COHb concentration depends strongly on the ventilation rate in humans compared with rats.

4.4.4. Mathematical Models of COHb Formation

In 1965, Coburn et al. developed a differential equation (CFK model) to describe the major physiologic variables that determine the COHb in blood using data from patients with increased endogenous production of CO due to anemia (Coburn et al. 1965). The CFK model is represented by the following equation:

$$\frac{d(COHb)_t}{dt} = \frac{V_{CO}}{Vb} - \frac{COHb_t * P_{O2}}{M * B * Vb * OHb} + \frac{P_{CO}}{B * Vb}$$

where

$B = 1/D_L + P_L/V_A$
M = Ratio of affinity of blood for CO to that for O_2; M = 218
OHb = mL of O_2 per mL blood; OHb = 0.2
$COHb_t$ = mL of CO per mL blood at time
P_{O2} = average partial pressure of oxygen in the lung capillaries; P_{O2} = 100 mm Hg
V_{CO} = rate of endogenous CO production; V_{CO} = 0.007 mL/min
D_L = diffusivity of the lung for CO; D_L = 30 mL/min mm Hg
P_L = barometric pressure minus the vapor pressure of water at body temperature
P_L = 713 mm Hg
Vb = blood volume; Vb = 5,500 mL
P_{CO} = partial pressure of CO in the air inhaled (mm Hg)
V_A = alveolar ventilation rate; V_A = 6,000 mL/min (awake), 4,000 mL (sleeping)
t = exposure duration (min)

Peterson and Stewart (1970) reported that the CFK model well predicted COHb measured in 18 healthy male students, aged between 24 and 42 years, who were exposed to the following combinations of CO concentrations and exposure times: about 50 ppm for 30 min to 24 h, about 100 ppm for 15-480 min, about 200 ppm for 15-120 min, and about 500 ppm for 15-114 min. They used the following integrated form of the CFK equation and parameters:

$$\frac{A * COHb_t - B * V_{CO} - P_{CO}}{A * COHb_0 - B * V_{CO} - P_{CO}} = \exp(-t\,A / B * Vb)$$

where

$A = P_{O2}/M$ OHb
$B = 1/D_L + P_L/V_A$
M = Ratio of affinity of blood for CO to that for O_2; M = 218
OHb = mL of O_2 per mL blood; OHb = 0.2
$COHb_t$ = mL of CO per mL blood at time
$COHb_0$ = mL of CO per mL blood at beginning of the exposure
P_{O2} = average partial pressure of oxygen in the lung capillaries; P_{O2} = 100 mm Hg
V_{CO} = rate of endogenous CO production; V_{CO} = 0.007 mL/min
D_L = diffusivity of the lung for CO; D_L = 30 mL/min mm Hg
P_L = the vapor pressure of water at body temperature, P_L = 713 mm Hg
Vb = blood volume; Vb = 5,500 mL
P_{CO} = partial pressure of CO in the air inhaled (mm Hg)
V_A = alveolar ventilation rate; V_A = 6,000 mL/min (awake), 4,000 mL (sleeping)
t = exposure duration (min)

In another study by Peterson and Stewart (1975), data from a series of human exposures to CO were analyzed to determine the fit to the theoretical CFK equation. A group of 19 men and 3 women were exposed to concentrations of 50, 100, or 200 ppm for 0.33-5.25 h. Three exercise levels from sedentary to 0, 150, or 300 kpm/min on an ergometer were used (15 subjects in total). These levels resulted in mean ventilation rates of 10.1 (9.1 for women), 14.0, 24.0 (19.7 for women), and 29.7 L/min, respectively. The CFK model predicted COHb for both men and women as well as for resting and exercising subjects within a standard error of about 2%. In contrast to the original model, which assumes all variables to be constant except t, P_L, $COHb_t$, and P_{CO}, the following parameter alterations were introduced:

P_{O2}: When the partial pressure of oxygen in inspired air (Pi_{O2}) is less than the 149-mm Hg found under normal conditions, the partial pressure of oxygen in the lung capillaries will be less than the value of 100 mm Hg assumed by Coburn and coworkers. From measurements of oxygen partial pressure in arterial blood, which is assumed to be the same as the oxygen partial pressure in lung capillaries, the following equation was derived:

$P_{O2} = 1/(0.072\text{-}0.00079\ Pi_{O2} + 0.000002515\ (Pi_{O2})^2)$ and $Pi_{O2} = Fi_{O2}$ $(P_B - 47 - Pi_{CO})$ with
Fi_{O2} = fraction of oxygen in inspired air,
P_B = barometric pressure (mm Hg), and
Pi_{CO} = partial pressure of CO in inspired air.

D_L: Body-size effects on diffusivity at rest were calculated from published data as

$D_L = 1/(-0.0287 + 0.1188/A)$ with A = body surface in m^2.

Vb: The published blood volume relationship of 74 mg/kg of body weight for men and 73 mL/kg for women was used.

V_A: The alveolar ventilation rate was expressed as

$V_A = V_E - f\ V_D$; with V_E = total rate of ventilation (mL/min),
f = respiration rate (min^{-1}), and
V_D = dead space (mL).

OHb_t: At standard concentrations, 1 g of hemoglobin will hold 1.38 mL of oxygen and thus $OHb_{max} = 1.38\ [Hb]/100$, with [Hb] being the hemoglobin concentration in blood (g/100 mL). During and after CO exposure, the value of OHb_t that must be used is actually $OHb_t = OHb_{max} - COHb_t$. In this case, the CFK equation can only be solved by iterative procedures.

COHb: This value can be converted to the more conventional percentage saturation by % COHb = COHb 100/$OHb_{max.}$

Tikuisis et al. (1992) studied the rate of formation of COHb in healthy young males at a low (45 W) and moderate (90 W) exercise load. Ten nonsmoking subjects were exposed to CO on two separate occasions distinguished by the activity level. Each experiment began with an exposure to 3,000 ppm for 3 min during a rest period followed by three intermittent exposures ranging from 3,000 ppm for 1 min at low exercise to 667 ppm for 3 min at moderate exercise. The net increase in COHb after all exposures (about 10%) deviated by <1% between the values measured and the values predicted from the CFK model. Within this deviation, there was a general tendency of the CFK equation to underpredict the increase in COHb for the exposures at rest and the first exercise exposure and to overpredict levels for the latter two exposures at exercise.

Benignus et al. (1994) exposed 15 men to 7,652 mg/m³ (6683 ppm) CO for 3.1-6.7 min at rest. Except for the Haldane constant M, which was assumed to be 245, all other physiologic parameters of the CFK equation were measured for each individual from the very beginning of exposure. Arterial COHb was considerably higher than the venous COHb. The rate of increase in blood COHb and the arterial-venous COHb differences varied widely among individuals. The peak arterial COHb at the end of exposure ranged from 13.9% to 20.9%. The peak venous levels reached during the recovery period ranged from 12.4% to 18.1%. The arterial-venous difference ranged from 2.3% to 12.1% COHb. The CFK equation overestimated venous blood COHb, whereas arterial blood levels were significantly and consistently underestimated.

Hill et al. (1977) developed a mathematical model to predict values of blood COHb in mother and fetus for prolonged exposures to CO at 30-300 ppm. During CO exposure, fetal COHb lag behind maternal COHb by several hours. During prolonged uptake, fetal levels eventually overtake maternal levels and approach equilibrium values as much as 10% higher than the mother's due to the higher affinity of CO for fetal hemoglobin than for adult hemoglobin. During CO washout, the fetal levels again lag behind the mothers.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

CO has no odor and does not cause irritative effects. A large number of studies investigated the effects of low CO exposure (COHb at <10%) on healthy individuals and high-risk groups. In these studies, effects on healthy persons, such as decreases in work capacity and decrements of neurobehavioral function, start at a COHb of 5% (WHO 1999a; EPA 2000).

In patients with coronary artery disease, which constitute the most susceptible subpopulation, the time to onset of angina and the time to 1-mm ST-segment change in the electrocardiogram during physical exercise were significantly reduced at a COHb of 2.0% or 4.0% (Allred et al. 1989a,b; 1991).

5.2. Animal Data Relevant to AEGL-1

No studies in experimental animals were located that were considered relevant for the derivation of AEGL-1 values. The studies describing effects of CO on cardiac function, such as Sekiya et al. (1983), DeBias et al. (1976), and Aronow et al. (1979), normally use models in which the heart was damaged additionally by an electric stimulus or by coronary artery ligation. Effects of CO exposure found in these systems can hardly be extrapolated quantitatively to humans.

5.3. Derivation of AEGL-1

CO is an imperceptible toxic gas. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms were noted in healthy humans and monkeys (Haldane 1895; Purser and Berrill 1983).

In patients with coronary artery disease, which constitute the most susceptible subpopulation, effects, such as significant electrocardiogram changes, reduced time to the onset of angina, and increased cardiac arrhythmia, start occurring at exposure concentrations little higher than current ambient air quality guidelines (e.g., the U.S. national air quality guideline of 9 ppm for 8 h) (National Air Pollution Control Administration 1970; 65 Fed. Regist.50201[2000]; EPA 2000; Raub 2000), the WHO air quality guideline of 10 mg/m^3 (9 ppm) for 8 h (based on 2.5% COHb) (WHO 1999a), and the designated European Union limit value of 10 mg/m^3 (9 ppm) for 8 h (EC 1999). These cardiac effects were considered above the AEGL-1 and thus would not constitute a suitable basis for the derivation of AEGL-1 values.

AEGL-1 values are not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.

In addition, CO exposure concentrations encountered frequently in everyday life are at or above the concentration range in which an AEGL-1 would have to be set: smokers have COHb concentrations in the range of 3-8% (Radford and Drizd 1982), and CO concentrations between about 10 and 50 ppm, which can be found on heavily traveled roads; inside motor vehicles; and in homes with gas-, coal-, wood- or kerosene-fired heaters, and stoves, correspond to an equilibrium COHb range of 1.8-7.5% (see Figure 2-2 and Table 2-14).

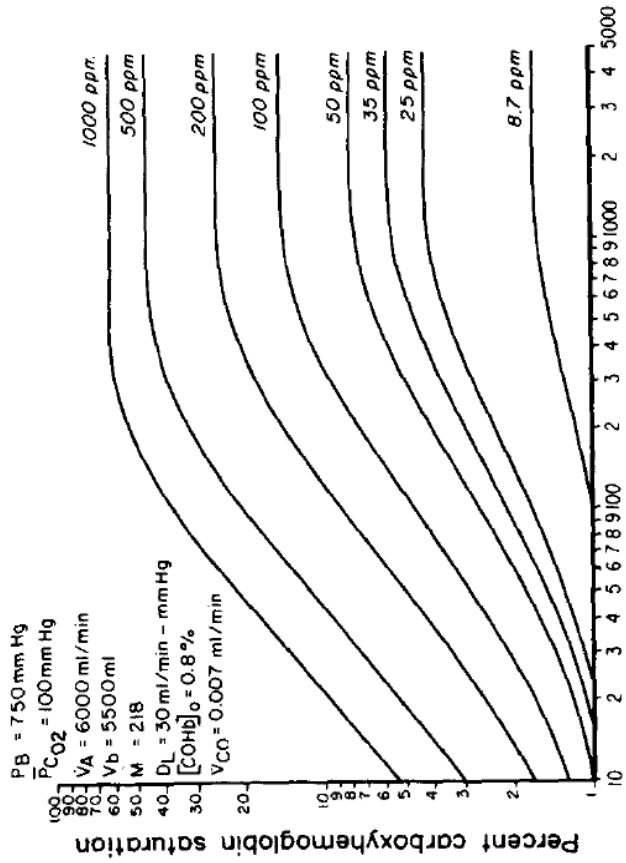

FIGURE 2-2 COHb for different exposure concentration–time combinations. Source: Peterson and Stewart 1975.

TABLE 2-14 AEGL-1 Values for Carbon Monoxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a]N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In patients with coronary artery disease, COHb of 2 or 4% significantly reduced the time to angina and the time to 1-mm change in the ST segment of the electrocardiogram during physical exercise; at 4% the total exercise time and the heart-rate-blood-pressure product were also significantly reduced (Allred et al. 1989a,b, 1991). A reduced time to onset of exercise-induced chest pain at a COHb between 2.5% and 4.5% was also reported by several other studies (Aronow et al. 1972; Anderson et al. 1973; Sheps et al. 1987; Kleinman et al. 1989, 1998).

Sheps et al. (1990, 1991) reported that, in patients with coronary artery disease, the frequency of ventricular premature depolarizations was significantly increased at a COHb of 5.3%, but not at 3.7%, compared with room air exposure. Dahms et al. (1993) found no increased frequency of ventricular ectopic beats at a COHb of 3% or 5%.

Klasner et al. (1998) analyzed a mass poisoning of 504 school children. In 147 of 155 children who showed symptoms, the mean COHb measured about 1 h (up to 2 h) after removal from the CO atmosphere was 7.0%COHb. Of all children that were examined in the hospital (177) (mean age 8.7 years), the following symptoms were observed: headache (139), nausea (69), dizziness (30), dyspnea (19), vomiting (13), abdominal pain (11), and drowsiness (9).

In an analysis of CO poisonings in 16 children (up to 14 years of age) with a COHb of 15% or higher, Crocker and Walker (1985) reported thresholds for effects, such as nausea, vomiting, headache, and lethargy of 16.7% to 19.8% COHb (average concentrations in children displaying these symptoms were 25.9-29.4%). Visual symptoms and syncopes occurred at a threshold of 24.5% COHb (average 31.6-32.5%). All nine children with a COHb of 24.5% or higher experienced at least one syncope.

In an investigation on the long-term effects of CO poisoning in children, who were evaluated 2-11 years after the poisoning, Klees et al. (1985) reported that 6 of the 14 children exhibited serious disorders (spatial organization problems, constructive apraxia, and deterioration of lexical activity, as well as spelling and arithmetic). Compared with the other seven children who exhibited only slight impairment of visual memory and concentration, the first group of more severely affected children were younger (mean age 7.8 years; range 2.8-12.1 years) than the latter group (mean age 9.8 years; range 3.5-14.5). There was no

difference in measured COHb (mean 21% [range 13-32%] in the younger group vs. 22% [16-26%] in the latter group). A short-term followup (3 months after the poisoning) suggested that medium intoxications (reported COHb of 16-27%) did not produce manifest sequelae except for a momentary standstill in the child's progress of about 2 months.

Kizakevich et al. (2000) reported that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20% COHb. Stewart et al. (1970) found that a CO exposure of healthy subjects resulting in 12.5% to 25.5% COHb did not affect the results of several neurophysiologic tests. Nielsen (1971) did not report on severe effects in three subjects that were repeatedly exposed to CO resulting in concentrations of 25-33% COHb. In a poisoning incident at the workplace, severe headaches, dizziness, weakness, nausea, chest pain, shortness of breath, and other symptoms were reported for a COHb of about 35% (Ely et al. 1995).

6.2. Animal Data Relevant to AEGL-2

In a study in cynomolgus monkeys, Purser and Berrill (1983) reported that during exposure to CO at 900 ppm for a total of 30 min, no signs of intoxication occurred until 20-25 min (corresponding to COHb of about 16-21%). At 25 min into the exposure, the animals' performance in a behavioral test significantly decreased. At the end of the exposure period, the animals became less active, most of them were lying down, but did not collapse. At 1,000 ppm, no effects were observed during the first 16-20 min. At this time, the animals became less active and sat down for short periods. At about 25 min, the animals went into a state of severe intoxication within 1-2 min, in which animals were lying down with eyes closed, they sometimes vomited and were virtually unable to perform coordinated movements.

Significant memory impairment in behavioral tests were found in young rats after continuous CO exposure throughout gestation (mean maternal COHb was 15.6%) (Mactutus and Fechter 1985).

In monkeys, a COHb of 9.3% resulted in reduced threshold for electric-shock-induced ventricular fibrillation (DeBias et al. 1976). Aronow et al. (1979) reported that CO exposure increased the vulnerability of the heart to induced ventricular fibrillation in normal dogs breathing 100-ppm CO for 2 h (resulting COHb was 6.3-6.5%). The ventricular fibrillation was induced by an electrical stimulus applied to the myocardium. A COHb of 13-15% increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in a myocardial infarction model in dogs (Sekiya et al. 1983).

6.3. Derivation of AEGL-2

The derivation of AEGL-2 values was based on effects in patients with coronary artery disease. An estimated 62 million people in the United States

(about 20% of the population) have one or more types of cardiovascular disease (American Heart Association 2002). For the major diseases within the category of total cardiovascular disease, about 50 million Americans have high blood pressure, 13 million have ischemic (coronary) heart disease, 5 million have heart failure, 4 million have cerebrovascular disease (stroke), and 2 million have rheumatic fever or heart disease.

For the derivation of AEGL-2 values a level of 4% COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al. 1989a,b, 1991).

Characteristic points of an electrocardiogram are the P wave, reflecting atrial depolarization, the QRS complex, representing the ventricular muscle depolarization, and the T wave, reflecting ventricular muscle repolarization. In the normal electrocardiogram, the ST segment is isoelectric, resting at the same potential as the interval between the T wave and the next P wave. Horizontal depression or a downsloping ST segment merging into the T wave occurs as a result of ischemia, ventricular strain, changes in the pattern of ventricular depolarization or drug effects. In chronic ischemic heart disease, there may be moderate degrees of horizontal ST-segment depression or a downward sloping ST segment, flattening or inversion of T waves and prominent U waves. It is difficult to define an abnormal ST-segment depression in precise quantitative terms. However, a myocardial ischemia has to be considered if the beginning of the ST segment is more than 0.5 mm (corresponding to 0.05 mV) below the isoelectric line, and there is an associated T-wave abnormality (Wilson et al. 1991).

According to the practice guidelines for chronic stable angina (Gibbons et al. 1999), an ST-segment depression at rest is a marker for adverse cardiac events in patients with and without known coronary artery disease. Additional exercise-induced ST-segment depression in the patient with ≥1 mm of rest ST-segment depression is a reasonably sensitive indicator of coronary artery disease. The ST-segment depression is indicative of clinically relevant myocardial ischemia requiring medical treatment. From the ST-segment depression, the Duke treadmill score can be calculated. It equals the exercise time in minutes minus (5 × the ST-segment deviation, during or after exercise, in millimeters) minus (4 × the angina index, which has a value of 0 if there is no angina, 1 if angina occurs, and 2 if angina is the reason for stopping the test). Among outpatients with suspected coronary artery disease, the two-thirds of patients with scores indicating low risk (score ≥5) had a 4-year survival rate of 99% (average annual mortality rate 0.25%), and the 4% who had scores indicating high risk (score ≤10) had a 4-year survival rate of 79% (average annual mortality of 5%) (Gibbons et al. 1999).

In the available experimental studies, the CO exposure alone (that is, with subjects at rest) did not cause angina, while exercise alone did so. Moreover, the changes in the electrocardiogram (ST-segment depression of 1 mm or greater) as well as the angina symptoms can be considered fully reversible after a single

incident. This effect level was considered to be below that defined for AEGL-2. All experimental studies used patients who had stable exertional angina and did not experience angina while at rest. Thus, it is considered likely that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. In hypersusceptible patients, more severe effects, even including myocardial infarction, cannot be ruled out.

In contrast to the anecdotal case reports on myocardial infarction discussed in the derivation of AEGL-3, the studies investigating electrocardiogram changes and angina symptoms in patients with coronary artery disease, used here for the derivation of AEGL-2 values, are high-quality, well-conducted experimental studies with well-characterized exposure conditions and information on interindividual variability.

An exposure concentration of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. This effect has been observed at a COHb of 5.3% but not of 3.7% (Sheps et al. 1990, 1991). In another study, no effect of CO exposure on ventricular arrhythmia was found at 3% or 5% COHb (Dahms et al., 1993). No experimental studies in heart patients are available that used significantly higher levels of COHb.

Use of a concentration of 4% COHb as a point of departure for the derivation of AEGL-2 values is supported by the studies in animals: a COHb of 9.3% resulted in a reduced threshold for electric-shock-induced ventricular fibrillation in monkeys (DeBias et al. 1976) and a COHb of 6.3-6.5% increased the vulnerability of the heart to electrically induced ventricular fibrillation in healthy dogs (Aronow et al. 1979). These animal studies suggest that a level below 6-9% COHb should be selected for AEGL-2 derivation to protect individuals with compromised cardiac function.

A total uncertainty factor of 1 for intraspecies variability was considered adequate based on supporting evidence in other susceptible subpopulations (children, pregnant women, older people and smokers):

1. The derived AEGL-2 values would result in a COHb of 4.9-5.2% in 5-year-old children (see Table B-2 in Appendix B). This level is considered protective of neurotoxic effects in children: (1) In the study by Klasner et al. (1998), acute neurotoxic effects, such as headache, nausea, dizziness, dyspnea, and vomiting, were found at a mean COHb of 7.0% (measured after a mean time of 1 h [up to 2 h] after removal of the children from the CO atmosphere). That result suggests that at the end of exposure, COHb had been from 10% to 14%. These values were estimated using the mathematical model of Coburn et al. (1965) and Peterson and Stewart (1975). (2) In the study by Crocker and Walker (1985), a threshold of 24.5% COHb for syncopes in children, an effect that was considered to impair the ability to escape, was reported. (3) In the study by Klees et al. (1985) that investigated long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children, the lowest concentration resulting in cognitive development defects was 13% COHb in the

long-term followup study. The COHb concentrations reported in the Crocker and Walker (1985) as well as in the Klees et al. (1985) studies were measured after hospital admission and may have been considerably lower than concentrations at the end of the CO exposure, as was also described in the Klasner et al. (1998) study. The percentage of children that received oxygen before hospital admission was probably considerably higher in Crocker and Walker (1985) and Klees et al. (1985) because, after acute exposure to high CO concentrations (e.g., by fires in homes), severe poisoning symptoms occurred. Oxygen administration reduces the elimination half-life in children to about 44 min (Klasner et al. 1998).

The observations in children are supported by observations in experimental animals. In the study by Purser and Berrill (1983) at a COHb little higher than 16-21%, syncopelike effects occurred in monkeys and mice; memory impairment was found in the offspring of rats exposed continuously at a COHb of 15.6% during gestation (Mactutus and Fechter 1985).

2. Caravati et al. (1988) and Koren et al. (1991) described cases of stillbirth after CO exposure of pregnant women. In these cases, the COHb concentrations measured in the maternal blood were higher than 22-25%. There are no studies reporting effects on the unborn after a single acute exposure resulting in lower COHb levels (EPA 2000). Cigarette smoking of pregnant women is associated with a lower birth weight; however, these effects cannot be clearly attributed to CO only because cigarette smoke is a complex mixture of chemicals (EPA 2000). There is no evidence that a single elevation of COHb has any negative effects on pregnancy.

3. There is no evidence that elderly people without cardiovascular disease are more susceptible to an acute CO exposure than younger adults (WHO 1999a; EPA 2000). Therefore, AEGL-2 values derived on effects in coronary artery disease patients are likely to protect other elderly people.

4. In smokers with a background COHb of 3-8% from smoking, exposure to the AEGL-3 concentration–time combinations will result in 6.2-11.5% COHb (see Table B-2 in Appendix B). Smokers may show an adaptive response to their chronically elevated COHb levels, as evidenced by increased red-blood-cell volumes or reduced plasma volumes (EPA 2000). This adaptive response is likely to reduce the effect level in smokers compared with nonsmokers exposed to the same total COHb level. The estimated COHb exposure level in smokers who are healthy adults is unlikely to lead to significant health effects (Stewart et al. 1970; Nielsen 1971; Kizakevich et al. 2000). For pregnant women, cigarette smoking alone may cause effects on the unborn (EPA 2000). A single additional exposure to COHb levels of 6.2-11.5% over a "smoking background" of 3-8% COHb is considered unlikely to contribute significantly to the effects of smoking during pregnancy. No study is available that compared the effects on the cardiovascular system of a 4% elevation of the background COHb level in nonsmoking and smoking patients with coronary artery disease. However, a single exposure to COHb levels of 6.2-11.5% over a smoking background of 3-8%

COHb is considered unlikely to contribute significantly to the effects of smoking on the cardiovascular system.

In conclusion, patients with coronary artery disease must be considered more susceptible to the effects of CO than other subpopulations, such as children, elderly people, and pregnant women who may be more susceptible than healthy adults. A level of 4% COHb was the NOEL for AEGL-2 effects in patients with coronary artery disease; the LOEL was estimated at 6-9%. In comparison, the LOEL was about 10-15% in children and 22-25% in pregnant women. Since AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective also for other subpopulations, and a total uncertainty factor of 1 was used.

Using the CFK model (Coburn et al. 1965; Peterson and Stewart 1975), exposure concentrations were calculated for 10 min, 30 min, 1 h, 4 h, and 8 h to result in an end-of-exposure COHb of 4% in adults (see Appendix B). Calculations were performed for a 70-kg man with a starting COHb of 0.75% due to endogenous CO production and using a ventilation rate of 23 m^3/day. Somewhat higher end-of-exposure COHb would result for children. For a 5-kg child with an alveolar ventilation rate of 3,580 mg/min, COHb values from 4.9% to 5.2% were calculated for the different AEGL time points. For a 3.5-kg newborn with an alveolar ventilation rate of 1,250 mL/min, COHb values from 5.3% to 5.6% were calculated. Higher COHb values will also be obtained in people having a higher starting COHb concentration as a result of other exposures. For smokers having typical starting COHb concentrations of 3% to 8%, COHb values of 6.2% to 11.5% will result from exposure to AEGL-2 concentration–time combinations.

A total uncertainty factor of 1 was used. An intraspecies uncertainty factor of 1 was considered adequate because the values are based on observations in the most susceptible human subpopulation (patients with coronary artery disease).

It is acknowledged that apart from emergency situations, certain scenarios could lead to CO concentrations that may cause serious effects in persons with cardiovascular diseases. These scenarios include extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defective car exhaust systems), charcoal or wood-fire furnaces, and indoor air pollution by tobacco smoking.

The values are listed in Table 2-15.

TABLE 2-15 AEGL-2 Values for Carbon Monoxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

A large number of deaths occur annually due to acute poisonings in fires and in closed locations (e.g., in private homes and workplaces). In the latter instance, poisoning usually occurs because gas-, oil- or coal-fired furnaces or stoves are operated without sufficient ventilation. In apparently healthy people who died from CO poisoning, usually COHb concentrations of 60% or higher are found (Stewart 1975; Winter and Miller 1976; Balraj 1984; Holmes 1985; AIHA 1999). In early experimental studies, healthy subjects were exposed to sufficient concentration–time combinations to reach levels of about 40% to 55% COHb (Haldane 1895; Chiodi et al. 1941). Effects described at this level of CO exposure included hyperpnea, confusion of mind, dim vision, and unsteadiness or inability to walk (Haldane 1895). Henderson et al. (1921) exposed subjects for 1 h to 34-38% COHb. Subjects showed a marked loss of equilibrium in the Romberg test, irritability, and throbbing frontal headache, and at times Cheyne-Stokes breathing was observed.

Nelson (2006a) reported on human deaths related to CO poisoning from unvented space heaters. Sixteen of 22 lethal cases had COHb levels at more than 40%. Six of 22 victims had COHb levels at ≤40% and two of six had pre-existing conditions, such as arteriosclerotic disease and cardiorespiratory failure. A 1942 fatality study reported by Nelson (2006a) summarized COHb data for 68 victims that were found dead in a gas-filled room or in a garage containing exhaust gases at high concentrations. CO concentrations were not provided. Sixty-seven percent of the 68 cases died with 40-88% COHb levels. Three-percent of the cases died with 30-40% COHb levels. Summary of another fatality study from Poland showed a similar trend of COHb levels (Nelson 2006a). Individual data were not provided, and the CO source was not discussed. However, the Polish study considered 321 lethal CO poisonings from 1975 to 1976 and provided COHb levels for 220 survivors and 101 fatal cases. The survivors had a mean COHb level of 28.1% (SD = 14.1), whereas the lethal cases showed an average COHb level of 62.3% (SD = 10.1). Over 80% of the survivors had COHb levels below 40%. In contrast, about 90% of the deceased had COHb levels above 50%. Similar percentages of survivors and deceased were observed at COHb levels of 40-50% with a slight increase in the number of survivors when compared with that of the lethal cases. These three studies showed a trend that most lethal cases occurred at COHb levels higher than 40% and that survivorship was likely to be seen at levels below 40%.

Another study from the Center of Forensic Sciences in Canada evaluated 304 fatal cases from 1965 to 1968 (Nelson 2006a). The mean lethal COHb level was 51% ± 12% with a majority range of 40-59% and the highest single frequency range of 45-59%. A report on CO exposure from exhaust fumes in the

state of Maryland during 1966-1971 showed COHb levels in the 40-79% range for 98% of lethal cases (Nelson 2006a). The Institute of Forensic Medicine in Oslo reported a study of COHb levels in 54 automobile exhaust victims. The mean fatal COHb level was 70%, and 40% was the minimum COHb level exhibited by less than 2% of the cases (Nelson 2006a). Another forensic study (Nelson et al. 2006) examining 2,241 fatalities between the years of 1976-1985 found that the mean COHb level of all the cases was 64.20% with an SD of 17.47. The data showed that 34% of victims had COHb levels of less than 60%. Of those who died in fires, 41% had COHb levels of less than 60% compared with 22% of the nonfire deaths.

Kizakevich et al. (2000) reported that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20% COHb. Stewart et al. (1970) found that a CO exposure of healthy subjects resulting in 12.5% to 25.5% COHb did not affect the results of several neurophysiologic tests. Nielsen (1971) did not report on severe effects in three subjects who were repeatedly exposed to CO resulting in concentrations of 25-33% COHb.

In susceptible groups of the population, deaths may be caused by considerable lower exposure to CO: Caravati et al. (1988) and Koren et al. (1991) described cases of stillbirth after CO exposure of pregnant women. In these cases, the COHb measured in the maternal blood were higher than 22-25%.

Persons with coronary artery disease constitute another susceptible subpopulation (Balraj 1984). Several case reports indicate that death through myocardial infarction can occur after repeated or prolonged exposure. The corresponding COHb levels measured after transport to the hospital (and thus not representing the end-of-exposure concentrations) were about 20-30% and as low as about 15% (Grace and Platt 1981; Atkins and Baker 1985; Ebisuno et al. 1986).

7.2. Animal Data Relevant to AEGL-3

Several studies reported LC_{50} values for rats, mice, and guinea pigs for exposure durations of 5 min to 4 h. The values are given in Table 2-12 and are shown in Figure 2-1. Similar to humans, the minimum lethal COHb concentrations in rats and mice were about 50-70% (Rose et al. 1970; E.I. du Pont de Nemours and Co. 1981).

An increase in the rate of stillbirths was reported in pigs after a 2-3 day-exposure to CO resulting in maternal COHb above 23% (Dominick and Carson 1983). Increased rates in fetal mortality were also observed in rabbits after continuous exposure maternal COHb of 16-18% throughout gestation (Astrup et al. 1972) as well as after daily exposure to high CO concentrations in cigarette smoke (exposure for 12 min/day on gestational days 6-18, resulting in COHb of 16%) (Rosenkrantz et al. 1986).

7.3. Derivation of AEGL-3

Most of the human reports did not document how long the victims were acutely exposed to CO. Despite this uncertainty in the exposure duration, it was possible to set AEGL-3 values by using the CFK model, which calculated the exposure concentrations at the various AEGL time durations (10 min, 30 min, 1 h, 4 h, and 8 h) that would produce a certain COHb concentration in the blood associated with a lethality threshold. Although victims of CO poisoning exhibit a wide range of COHb levels, a weight-of-evidence analysis of numerous lethal human cases and their COHb levels at their time of death helped to set the lethality threshold at a 40% COHb level. Note that the database included reports of COHb levels in individual cases or summaries where COHb data were averaged or reported by COHb ranges. The approach of using all available data was preferred over the selection of an individual key study for AEGL-3 derivations because it was the only way the evaluation could have a broad picture of COHb levels reported in humans with different demographics (e.g., in sex, age, and disease status), type of CO exposure source, possible variation in sample collection, and absence or presence of oxygen therapy to humans prior to death. Also, the weight-of-evidence approach would average out the studies' uncertainties.

Nelson (2006a) reported on human deaths related to CO poisoning from unvented space heaters. Sixteen of 22 lethal cases had COHb levels at more than 40%. Six of 22 victims had COHb levels at ≤40% and two of six had preexisting conditions, such as arteriosclerotic disease and cardiorespiratory failure. A 1942 fatality study reported by Nelson (2006a) summarized COHb data for 68 victims that were found dead in a gas-filled room or in a garage containing exhaust gases at high concentrations. CO concentrations were not provided. Sixty-seven percent of the 68 cases died with 40-88% COHb levels. Three-percent of the cases died with 30-40% COHb levels. Summary of another fatality study from Poland showed a similar trend of COHb levels (Nelson 2006a). Individual data were not provided, and the CO source was not discussed. However, the Polish study considered 321 lethal CO poisonings from 1975 to 1976 and provided COHb levels for 220 survivors and 101 fatal cases. The survivors had a mean COHb level of 28.1% (SD = 14.1), whereas the lethal cases showed an average COHb level of 62.3% (SD = 10.1). Over 80% of the survivors had COHb levels below 40%. In contrast, about 90% of the deceased had COHb levels above 50%. Similar percentages of survivors and deceased were observed at COHb levels of 40-50% with a slight increase in the number of survivors when compared with that of the lethal cases. These three studies showed a trend that most lethal cases occurred at COHb levels higher than 40% and that survivorship was likely to be seen at levels below 40%.

Another study from the Center of Forensic Sciences in Canada evaluated 304 fatal cases from 1965 to 1968 (Nelson 2006a). The mean lethal COHb level was 51% ± 12% with a majority range of 40-59% and the highest single frequency range of 45-59%. A report on CO exposure from exhaust fumes in the

state of Maryland during 1966-1971 showed COHb levels in the 40-79% range for 98% of lethal cases (Nelson 2006a). The Institute of Forensic Medicine in Oslo reported a study of COHb levels in 54 automobile exhaust victims. The mean fatal COHb level was 70%, and 40% was the minimum COHb level exhibited by less than 2% of the cases (Nelson 2006a). Another forensic study (Nelson et al. 2006) examining 2,241 fatalities between the years of 1976-1985 found that the mean COHb level of all the cases was 64.20% with an SD of 17.47. The data showed that 34% of victims had COHb levels of less than 60%. Of those who died in fires, 41% had COHb levels of less than 60% compared with 22% of the nonfire deaths.

The 40% COHb level is also supported by experimental studies performed in healthy human subjects. Studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895) suggest that a COHb of about 34-56% does not cause lethal effects in healthy individuals. Further support comes from the studies by Kizakevich et al. (2000), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when subjects were exposed to 20-33% COHb. Several case reports indicate that in patients with coronary artery disease, CO exposure can contribute to myocardial infarction. In the published cases of myocardial infarction, the following COHb values were measured after transport to the hospital: 52.2% (Marius-Nunez 1990), 30%, 22.8% (Atkins and Baker 1985), 21% (Ebisuno et al. 1986), and 15.6% (Grace and Platt 1981). A level of 40% COHb was used as the basis for AEGL-3 derivation. This point of departure is further supported by studies in animals reporting minimum lethal COHb levels in rats and mice of about 50-70% (Rose et al. 1970; E.I. du Pont de Nemours and Co. 1981).

Another uncertainty of the human reports used to support a lethality threshold level of 40% COHb was that they did not address whether the COHb measurement was derived from a peripheral site (e.g., femoral vein) or from central blood. This type of information is missing in many of the CO poisoning reports. Although it remains uncertain where the blood samples were taken, data from Levine et al. (2002) and Dalpe-Scott et al. (1995) ruled out significant postmortem changes in COHb levels that were demonstrated by similar heart blood to peripheral blood (H:P) ratios between central and peripheral blood.

Using the CFK model (Coburn et al. 1965; Peterson and Stewart 1975), exposure concentrations were calculated that would result in a COHb of 40% at the end of exposure periods for 10 and 30 min as well as for 1, 4 and 8 h (see Appendix B).

AEGL-3 values calculated with an intraspecies uncertainty factor of 10 would lead to an approximate 4% COHb level in exposed healthy adults. The values would be conservative and more protective of susceptible populations, including the developing fetus, children, and those with compromised circulatory systems, especially at longer exposure durations. However, 4% COHb is the approximate background level in smokers (WHO 1999a). At that level, healthy individuals have decreases in work capacity and decrements of neurobehavioral functions (WHO 1999a; EPA 2000; Hazucha 2000). Furthermore, workers com-

plained of light nausea, lightheadedness, and headache at COHb levels of 4.1-12.8% (Atkins and Baker 1985). These effects are below the lethality threshold. At slightly higher COHb levels (5-6%), there may be an increase in cardiac activity in subjects with coronary artery disease (WHO 1999a). Therefore, a total uncertainty factor of 3 for intraspecies variability was considered adequate based on the following supporting evidence in susceptible subpopulations:

1. Exposure to the derived AEGL-3 concentrations will result in COHb values of about 14-17% in adults (see Table B-4 in Appendix B). In the reported cases of myocardial infarction, the measured COHb was normally above 20%, except in one case in which the measured COHb was about 15%. In this case (Grace and Platt 1981), the man was exposed during several weeks to (presumably) the same high CO concentration in his home and presented two times to the emergency room with signs of CO intoxication (which were misdiagnosed) until the infarction occurred. Therefore, the derived AEGL-3 values are considered to protect heart patients against CO-induced myocardial infarction. It should be noted, however, that a clear threshold for this end point cannot be defined because myocardial infarction might be triggered at lower COHb in hypersusceptible individuals, and myocardial infarction can also occur spontaneously or by trigger effects (e.g., psychological stress and physical exertion), which have no relevant effects on the health of normal subjects.

2. With regard to stillbirths, a COHb of 14-17% was considered protective of lethal effects on the unborn because, in the case studies available, stillbirths were found only after measured maternal COHb of about 22-25% or higher (Caravati et al. 1988; Koren et al. 1991). In the clinic, a measured COHb of about 15-20% in pregnant women (implicating a higher end-of-exposure level) is considered a severe CO intoxication that could require hyperbaric oxygen treatment (Ellenhorn 1997; Tomaszewski 1998). Available animal studies reported increased rates of stillbirths after a 2-3-day exposure at a maternal COHb above 23% (Dominick and Carson 1983), after continuous exposure at a maternal COHb of 16-18% (Astrup et al. 1972), and after repeated short-term exposures at a maternal COHb of 16% (Rosenkrantz et al. 1986). Taken together, the animal data support the conclusion that pregnant women should not be exposed to COHb levels higher than about 14-17% to prevent lethal effects on the unborn.

3. In smokers with a background COHb of 3-8% from smoking, exposure to the AEGL-3 concentration–time combinations will result in COHb levels between 16.1 and 23.0% (see Table B-4 in Appendix B). Smokers may show an adaptive response to their chronically elevated COHb levels, as evidenced by increased red-blood-cell volumes or reduced plasma volumes (EPA 2000). This adaptive response is likely to reduce the effect level in smokers compared with nonsmokers exposed to the same total COHb level. The estimated COHb exposure level in smokers is considered protective of lethal effects if they are healthy adults. Also, from the discussion above, it is considered unlikely that smoking pregnant women will have an increase risk of stillbirths at the AEGL-3 exposure

level. As discussed above, a threshold for the induction of myocardial infarction by CO exposure cannot be defined. Therefore, heavy smokers with coronary artery disease, which have a higher risk for myocardial infarction already from smoking (American Heart Association 2002), may be at somewhat higher risk compared with nonsmoking patients.

The values are listed in Table 2-16.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 2-17. They were derived using the following key studies and methods.

AEGL-1 values are not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.

The AEGL-2 was based on cardiovascular effects in patients with coronary artery disease, who constitute the most susceptible subpopulation. For the derivation of AEGL-2 values, a level of 4% COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion. The changes in the electrocardiogram (ST-segment depression of 1 mm or greater) associated with angina symptoms were fully reversible. An exposure level of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations resulting in a COHb of 4% at the end of exposure periods of 10 and 30 min and 1, 4, and 8 h. An intraspecies uncertainty factor of 1 was used. A total uncertainty factor of 1 was used. An intraspecies uncertainty factor of 1 was considered adequate because the values are based on observations in the most susceptible human subpopulation (patients with coronary artery disease).

The AEGL-3 values were based on COHb levels of 40% in human blood derived from a weight-of-evidence analysis of lethal and nonlethal poisoning cases (Nelson 2006a). A threshold for lethality of

40% is also supported by experimental studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895), in which exposures resulting in COHb of 34-56% did not cause lethal effects in healthy individuals. Further support comes from the studies of Kizakevich et al. (2000), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when health adults were exposed to 20-33% COHb. A level of 40% COHb was used as the basis for AEGL-3 derivation. A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations resulting in a COHb of 40% at the end of exposure periods of 10 and 30 min and

1, 4, and 8 h. An intraspecies uncertainty factor of 3 was used. The derived values (corresponding to a COHb value of about 15%) are supported by information on effects, such as myocardial infarction and stillbirths, reported in more susceptible subpopulations.

All inhalation data are summarized in Figure 2-3. The data were classified into severity categories chosen to fit into definitions of the AEGL health effects. The category severity definitions are no effect, discomfort, disabling, some lethality, lethal, and AEGL. In the figure depicting the COHb levels, the AEGL lines are drawn at the COHb levels for adults. The gray boxes above the lines indicate the range of COHb levels in neonates, children, and smokers (with 8% COHb from smoking).

The single exposure animal data point in the AEGL-2 COHb box represents the study by Aronow et al. (1979) using dogs with electrically damaged hearts. The two single exposure human data points in the box represent the study by Sheps et al. (1990; 1991) reporting increase arrhythmia in heart patients and the study by Klasner et al. (1998) reporting moderate neurotoxic effects in children.

8.2. Comparison with Other Standards and Criteria

Other standards and guidance levels for workplace and community exposures are listed in Table 2-18. The German BAT (Biologischer Arbeitsstoff-Toleranz-Wert; biologic exposure index) is 5% COHb, equivalent to a concentration of 30 ppm CO (Henschler and Lehnert 1994). The ACGIH Biological Exposure Index (BEI) is 3.5% COHb at the end of shift, equivalent to a CO concentration in end exhaled air of 20 ppm (ACGIH 2001).

TABLE 2-16 AEGL-3 Values for Carbon Monoxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	1,700 ppm (1,900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)

TABLE 2-17 Summary of AEGL Values for Carbon Monoxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	N.R.[a]	N.R.	N.R.	N.R.	N.R.
AEGL-2 (Disabling)	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)
AEGL-3 (Lethal)	1,700 ppm (1,900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)

[a]N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations, which do not yet cause AEGL-1 effects in the general population.

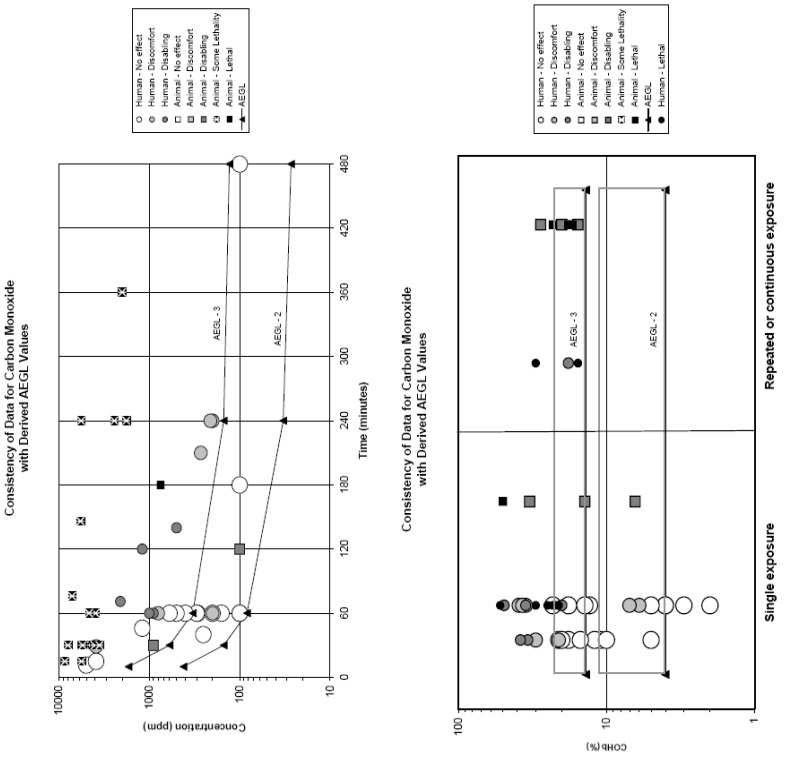

FIGURE 2-3 Categorical representation of all CO inhalation data.

TABLE 2-18 Extant Standards and Guidelines for Carbon Monoxide

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	N.R.[a]	N.R.	N.R.	N.R.	N.R.
AEGL-2	420 ppm	150 ppm	83 ppm	33 ppm	27 ppm
AEGL-3	1700 ppm	600 ppm	330 ppm	150 ppm	130 ppm
ERPG-1 (AIHA)[b]			200 ppm		
ERPG-2 (AIHA)			350 ppm		
ERPG-3 (AIHA)			500 ppm		
EEGL (NRC)[c]	1500 ppm	800 ppm	400 ppm		50 ppm (24 h)
IDLH (NIOSH)[d]		1,200 ppm			
REL-TWA (NIOSH)[e]					35ppm (200 ppm ceiling)
PEL-TWA (OSHA)[f]					50ppm
TLV-TWA (ACGIH)[g]					25ppm
MAK (Germany)[h]					30 ppm
MAK Spitzenbegrenzung (Germany)[i]		60 ppm			
Einsatztoleranzwert (Germany)[j]				100 ppm	
MAC (The Netherlands)[k]					25 ppm
Air Quality Guideline (WHO)[l]	87 ppm for 15 min	52 ppm	26 ppm		9 ppm
National Ambient Air Quality Standard (U.S.)[m]			35 ppm		9 ppm
Ambient Air Limit Value (EU)[n]					9 ppm

[a]N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations, which do not yet cause AEGL-1 effects in the general population.

[b]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 1999). The ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 value is based on a COHb of 5-6%, which, based on the original CFK model using a ventilation rate at rest, is considered to be produced by 1 h CO exposure to 200 ppm. This exposure level is not expected to produce any effects during a 1 h exposure period. While delayed transient effects, such as headache, are possible, no permanent effects in more susceptible individuals are expected. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 value is based on a COHb of 10-12%, which, based on the original CFK model using a ventilation rate at rest, is considered to be produced by 1 h CO exposure to 350 to 500 ppm. This exposure level is expected to cause slight neurologic symptoms (increased threshold of visual light) in healthy individuals and chest pain at less exertion in heart patients. (Comment: The ERPG derivation does not discuss the CO effects on children. Moreover, model calculation for deriving ERPG values assumed a resting

ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed). The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 is based on the belief that humans can generally tolerate COHb of 20% for brief periods without substantial toxicity. Based on the original CFK model using a ventilation rate at rest, it was considered that exposure to 500 ppm for 1 h will lead to a COHb of about 15%. (Comment: The ERPG derivation does not discuss the CO effects on children. Moreover, model calculation for deriving ERPG values assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[c]EEGL (emergency exposure guidance levels, National Research Council) (NRC 1985) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury. The NRC document states that 400 ppm (460 mg/m^3) was determined as the concentration of CO to which a 1 h exposure would result in a COHb level of less than 10% in resting individuals. The committee cautions that sensitive individuals, such as persons with angina or heart disease, should not be exposed to concentrations approaching the EEGL as they may incur serious adverse health effects (Comment: The EEGL derivation excludes patients with coronary artery disease. Moreover, model calculation for deriving EEGL values assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[d]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. The IDLH value is based on the observation by Henderson et al. 1921, that exposure of a healthy man at 1,000 ppm for 1 h caused unpleasant but no dangerous symptoms, and that more severe symptoms develop at 40% COHb (Steward 1975). According to the CFK model, a 30-min exposure at 1,200 ppm will produce a COHb of 10-13%. (Comment: The IDLH derivation does not discuss patients with coronary artery disease. In the Henderson et al. (1921) study, the subject was sitting still during exposure and developed Cheyne-Stokes breathing at the end of exposure, which is considered a serious effect. Moreover, model calculation in the IDLH derivation assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[e]REL-TWA (Recommended Exposure Limits - Time Weighted Average National Institute of Occupational Safety and Health,) (NIOSH 1996) is defined analogous to the ACGIH-TLV-TWA.

[f]PEL-TWA (Permissible Exposure Limits - Time Weighted Average Occupational Health and Safety Administration (29CFR Part 1910.1000 [2000]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[g]TLV-TWA (, Threshold Limit Value - Time Weighted Average American Conference of Governmental Industrial Hygienists) (ACGIH 2001)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. "This value is intended to maintain blood COHb levels below 3.5%, to minimize the potential for adverse neurobehavioral changes, and to maintain cardiovascular work and exercise capacities."

[h]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (Henschler 1981; DFG 1999) is defined analogous to the ACGIH-TLV-TWA.

[i]MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,1] (DFG 1999) constitutes the maximum average concentration to which workers can be exposed for a period up to 30

min, with no more than four exposure periods per workshift; total exposure may not exceed 8 h TWA MAK.

[j]Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) (Buff and Greim 1995) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 h without any health risks.

[k]MAC ([maximum workplace concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004)is defined analogous to the ACGIH-TLV-TWA.

[l]Air quality guideline (WHO 1999a)is based on a COHb of 2.5%, which should not be exceeded even when a normal subject engages in light or moderate exercise.

[m]U.S. National Ambient Air Quality Standard (National Air Pollution Control Administration 1970; 65 Fed. Regist.50201[2000]; EPA 2000).

[n]EU limit value for ambient air (EC 1999).

Most studies relating COHb on health effects do not investigate whether the frequency or severity of the effects increase with exposure time (at a constant COHb). There is thus an uncertainty concerning the increase of effects with time at a constant COHb. This is true for all AEGLs. Studies elucidating this exposure-effect-time relationship could support the derived AEGL-2 and AEGL-3 values.

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APPENDIX A

Time-Scaling Calculations for AEGL Values

Derivation of AEGL-2

Key study:	Allred et al. (1989a,b, 1991); Sheps et al. (1990, 1991)
Toxicity end point:	In an experimental study in 63 subjects with coronary artery disease, a significantly reduced time to ST-segment depression in the electrocardiogram and a significantly reduced time to onset of angina pectoris during physical exercise were found at 2 or 4% COHb (Allred et al. 1989a,b; 1991). At higher COHb of 5.3, but not at 3.7%, a significantly increased frequency of exercise-induced arrhythmias was found (Sheps et al. 1990, 1991). AEGL-2 values were derived on a COHb of 4%.
Mathematical model:	The CFK model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations resulting in a COHb of 4% at the end of the exposure periods. Concentrations were calculated for 10 and 30 min, 1, 4 and 8 h (see Appendix B).
Scaling:	Instead of a time scaling according to $C^n \times T = const.$, a mathematical model was used to calculated exposure concentrations for the relevant time periods (see Appendix B).
Uncertainty factors:	Uncertainty factor of 1 1 for intraspecies variability
Calculations:	
10-min AEGL-2	10-min AEGL-2 = 424 ppm/1 = 420 ppm (480 mg/m^3)
30-min AEGL-2	30-min AEGL-2 = 150 ppm/1 = 150 ppm (170 mg/m^3)
1 h AEGL-2	1 h AEGL-2 = 83 ppm/1 = 83 ppm (95 mg/m^3)
4 h AEGL-2	4 h AEGL-2 = 33 ppm/1 = 33 ppm (38 mg/m^3)
8 h AEGL-2	8 h AEGL-2 = 27 ppm/1 = 27 ppm (31 mg/m^3)

Derivation of AEGL-3

Key study:	Haldane (1895); Henderson et al. (1921); Chiodi et al. (1941); Nelson (2006a)
Toxicity end point:	Exposure of healthy subjects to sufficient concentration-time combinations to reach levels of about 34% to 56% COHb did not result in severe or life-threatening effects. At this level of CO exposure, Haldane described symptoms that included hyperpnea, confusion of mind, dim vision, and unsteadiness and inability to walk. Also, analysis of lethal cases reported by Nelson (2006a) indicated that most lethal poisoning cases occurred at COHb

	levels higher than 40% and that survival of CO-exposed humans were likely to be seen at levels below 40%. Thus, a 40% COHb level seems a reasonable threshold for lethality.
Mathematical model:	The CFK model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations resulting in a COHb of 40% at the end of the exposure periods. Concentrations were calculated for 10 and 30 min and 1, 4 and 8 h (see Appendix B).
Scaling:	Instead of a time scaling according to $C^n \times T = const.$, a mathematical model was used to calculated exposure concentrations for the relevant time periods (see Appendix B).
Uncertainty factors:	Total uncertainty factor of 3 3 for intraspecies variability
Calculations:	
10-min AEGL-3	10-min AEGL-3 = 5,120 ppm/3 = 1,700 ppm (1,900 mg/m^3)
30-min AEGL-3	30-min AEGL-3 = 1810 ppm/3 = 600 ppm (690 mg/m^3)
1 h AEGL-3	1 h AEGL-3 = 998 ppm/3 = 330 ppm (380 mg/m^3)
4 h AEGL-3	4 h AEGL-3 = 439 ppm/3 = 150 ppm (170 mg/m^3)
8 hAEGL-3	8 h AEGL-3 = 403 ppm/3 = 130 ppm (150 mg/m^3)
	The COHb levels corresponding to the AEGL-3 values are given in Table B-4 in Appendix B.

APPENDIX B

Mathematical Model for Calculating COHb and Exposure Concentrations

Studies describing model: Coburn et al. (1965); Peterson and Stewart (1975)

Model: For the calculation of concentration-time combinations that result in a certain COHb, the model of Coburn, Forster, and Kane (CFK model) (see Section 4.4.4) was used.

Since this model in the formulation of Peterson and Stewart (1975) calculates COHb larger than 100% at high-exposure concentrations, the following correction proposed by Peterson and Stewart (1975) was used: the amount of bound oxygen is actually not constant but is dependent on the COHb; therefore,

$$Ohb_t = Ohb_{max} - COHb_t.$$

Because, in this case, the CFK equation can only be solved iteratively, calculations were done using time steps (Δt) of 1 min for the period of 0-10 min, steps of 5 min between 10 and 60 min, steps of 15 min between 60 and 240 min, and steps of 20 min between 240 and 480 min. In each step, the COHb of the step before was used to calculate Ohb_t. For the first step, a background COHb of 0.75% was assumed.

The alveolar ventilation rate was calculated as

$V_A = V_E - fV_D$ (Peterson and Stewart 1975) with
V_E = total rate of ventilation (mL/min),
f = respiration rate (min^{-1}), and
V_D = dead space (mL).

Derivations were done for a 70-kg man, assuming a blood volume of 5,500 mL (Coburn et al. 1965) and a daily inhalation volume (V_E) of 23 m^3 (8 h resting and 16 h light/nonoccupational activity; WHO 1999b), a respiration rate (f) of 18 min^{-1} and a dead space (V_D) of 2.2 mL/kg (Numa and Newth 1996). Calculations using the following equation were carried out in a spreadsheet computer program:

$$\Delta(COHb)_t = \left(\frac{V_{CO}}{Vb} - \frac{COHb_{t-1} * P_{O2}}{M * B * Vb\ (OHb_{\max} - COHb_{t-1})} + \frac{P_{CO}}{B * Vb} \right) \Delta t$$

where

$COHb_t$ = mL of CO per mL blood at time t (min)
Conversion: % COHb = COHb 100/Ohb_{max}
V_{CO} = rate of endogenous CO production, V_{CO} = 0.007 mL/min
Vb = blood volume, Vb (70-kg man) = 5,500 mL, Vb (5-yr child, 20 kg) = 1,500 mL
Vb (newborn, 3.5 kg) = 400 mL
M = ratio of affinity of blood for CO to that for O_2, M = 218 (newborn: M = 240)
$B = 1/D_L + P_L/V_A$ with D_L = diffusivity of the lung for CO, D_L = 30 mL/min mm Hg

P_L = barometric pressure minus the vapor pressure of water at body temperature
P_L = 713 mm Hg
V_A = alveolar ventilation rate, V_A (70-kg man) = 23 m^3/d * 1 • 10^6 mL/m^3 * 1/1,440 min/d – 18/min * 2.2 mL/kg * 70 kg, V_A (70-kg man) = 13,200 mL/min
V_A (5-y child) = 3,580 mL/min, V_A (newborn) = 1,250 mL/min
Ohb_{max} = mL of O_2 per mL blood under normal conditions, Ohb = 0.2
P_{O2} = average partial pressure of oxygen in the lung capillaries, P_{O2} = 100 mm Hg
P_{CO} = partial pressure of CO in the air inhaled (mm Hg)
Conversion: P_{CO} (mm Hg) = P_{CO} (ppm)/1,316
t = exposure duration (min)

Calculations: For the derivation of AEGL-2 values, exposure concentrations were calculated that would result in a COHb of 4%. A representation of the spreadsheet for the 60-min AEGL-2 is shown in Figure B-1. Results are shown in Table B-1.

For children, newborns, and adult smokers, the end-of-exposure COHb values for exposure to the concentrations calculated in Table B-1 were computed using the CFK model in Table B-2.

TABLE B-1 Concentration–Time Combinations Resulting in 4% COHb

	For a 70-kg Adult Man	
Exposure Time (min)	Exposure Concentration (ppm)	Exposure Concentration (ppm), Rounded
10	424	420
30	150	150
60	83	83
240	33	33
480	27	27

TABLE B-2 COHb Values for AEGL-2 Concentration–Time Combinations in Different Subpopulations

Exposure Time (min)	Exposure Concentration (ppm)	5-y-old Child	Newborn	Healthy Adult	Adult Smoker (3% COHb)	Adult Smoker (8% COHb)
10	420	5.2	5.5	4.0	6.2	11.2
30	150	5.2	5.6	4.0	6.3	11.3
60	83	5.2	5.6	4.0	6.4	11.4
240	33	5.0	5.4	4.0	6.6	11.5
480	27	4.9	5.3	4.0	6.7	11.5

For the derivation of AEGL-3 values, exposure concentrations were calculated that would result in a COHb of 40%. A representation of the spreadsheet for the 60-min value is shown in Figure B-2. Results are shown in Table B-3.

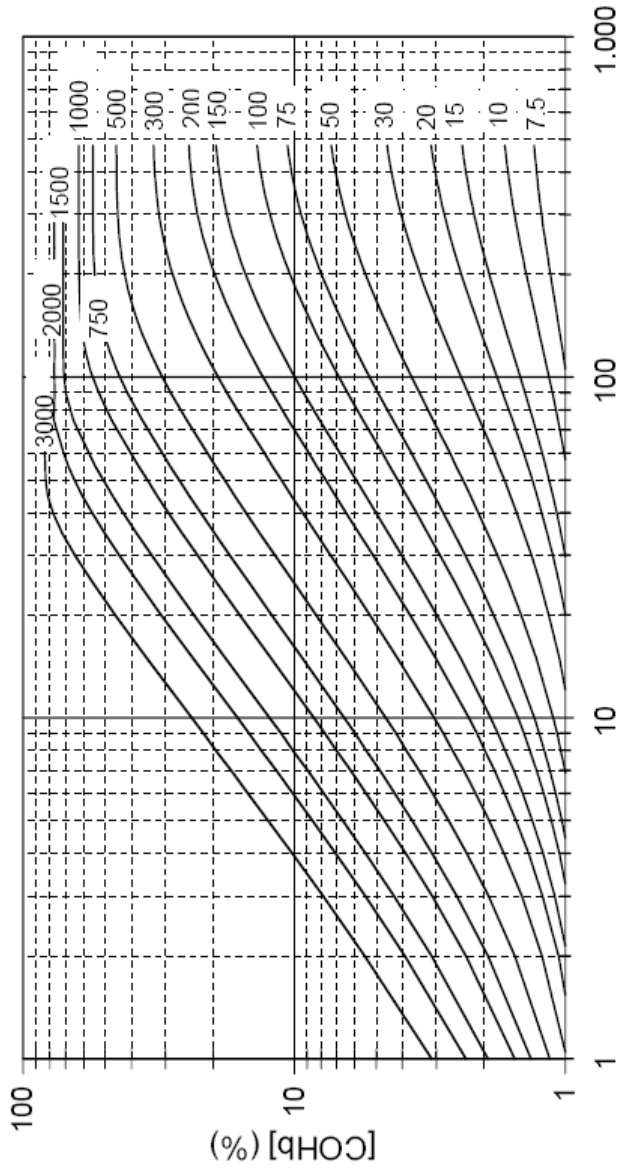

FIGURE B-1 COHb vs. exposure time plots. Data are shown for CO exposure concentrations indicated (70-kg man).

CFK Modell for Calculation of COHb

Dr. Peter Griem

Model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975)

Model parameters (see TSD):

PL	713	mm Hg		
M	218			
OHb	0.2	ml/ml blood		
PO2	100	mm Hg		
Vb	5500	ml		
Vco	0.007	ml/min		
D	0.0015	ml CO/ml blood	in %:	0.75
Va	13200	ml/min		
DL	30	ml/min mm Hg		
COHbt	0.02	ml CO/ml blood	in %:	10
COHbo	0.0015	ml CO/ml blood	in %:	0.75
Exp. Time	60	min		
Exp. Conc.				
CO	998	ppm		

Physiologic parameters:

	70-kg adult	20-kg child	3.5-kg newborn
			200
			0.27
	5500	1500	400
	13200	3580	1250

Auxiliary expressions:

A	2.293578
B	0.0873485
COHbt	0.02
COHbo	0.0015
a	0.7509257

Results for exposure to 998 ppm:

time (min)	COHb (%)
10	8.4349598
30	22.664894
60	40.019622
240	62.314719
480	62.3289

Calculated COHb (according to original CFK model) after exposure to 998 ppm for 60 min:

COHb:	0.0835478	ml/ml blood	41.773906	%

Calculated COHb according to model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975):

time (min)	dt	dHbCO	HbCO	%
			0.0015	0.75
1	1	0.0015726	0.0030726	1.536301
2	1	0.0015649	0.0046375	2.31876
3	1	0.0015572	0.0061947	3.097335
4	1	0.0015493	0.007744	3.871983
5	1	0.0015414	0.0092853	4.642662
6	1	0.0015333	0.0108187	5.409326
7	1	0.0015252	0.0123439	6.171932
8	1	0.001517	0.0138609	6.930437
9	1	0.0015087	0.0153696	7.684794
10	1	0.0015003	0.0168699	8.43496
15	5	0.0074593	0.0243292	12.1646
20	5	0.0072379	0.0315671	15.78355
25	5	0.0070043	0.0385714	19.28572
30	5	0.0067584	0.0453298	22.66489
35	5	0.0064999	0.0518297	25.91485
40	5	0.0062291	0.0580588	29.02939
45	5	0.0059463	0.0640051	32.00254
50	5	0.0056522	0.0696572	34.82862
55	5	0.0053477	0.075005	37.50248
60	5	0.0050343	0.0800392	40.01962

FIGURE B-2 Calculation of 60-min exposure concentration that would result in 40% COHb in a healthy adult.

TABLE B-3 Concentration–Time Combinations Resulting in 40% COHb

	Concentration for a 70-kg Adult Man	
Exposure Time (min)	Exposure Concentration (ppm)	Exposure Concentration (ppm), Rounded
10	5,120	5,100
30	1,810	1,800
60	998	1,000
240	439	440
480	403	400

For children, newborns, healthy nonsmoking adults, and smokers, the end-of-exposure COHb values for exposure to the AEGL-3 exposure concentration–time combinations were computed using the CFK model. For all subpopulations, the endogenous CO production rate was adjusted so that the starting level of 0.75% for children and newborn and 3% and 8% for smokers were constant without additional CO exposure (Table B-4).

The following end-of-exposure COHb values were calculated for the series of experiments reported by Haldane (1895) (Table B-5). Since exposure occurred while the subject was sitting on a chair, a ventilation rate of 7.5 L/min was used for the calculation (WHO 1999b). The alveolar ventilation rate was calculated as

VA (70-kg man) = 3,600 L/8 h * 1 • 103 mL/L* 1/480 min/8 h − 18/min *
2.2 mL/kg * 70 kg
VA (70-kg man) = 4,700 mL/min

TABLE B-4 COHb Values for AEGL-3 Concentration–Time Combinations in Different Subpopulations

Exposure Time (min)	Exposure Concentration (ppm)	5-yr Child	Newborn	Healthy Adult	Smoker (3% COHb)	Smoker (8% COHb)
10	1,700	18.7	19.9	13.8	16.1	21.1
30	600	18.5	19.8	14.0	16.2	21.1
60	330	18.3	19.6	14.1	16.4	21.2
240	150	18.6	20.1	16.4	18.6	22.7
480	130	18.1	19.5	17.2	19.2	23.0

TABLE B-5 Comparison of Reported and Calculated COHb Values for the Data by Haldane (1895)

Experiment Number	Concentration (ppm)	Time (min)	COHb Measured (%)	COHb Calculated (%)
1	5,000	11.5	Not done	22
2	3,900	30.5	39	43
3	4,000	24	27	35
4	3,600	29	37	38

(Continued)

TABLE B-5 Continued

Experiment Number	Concentration (ppm)	Time (min)	COHb Measured (%)	COHb Calculated (%)
5	4,100	29	35	43
6	1,200	120	37	46
7	2,100	71	49	50
8	Irregular	35	56	—
9	270	210	14	17
10	210	240	13	15
11	460	240	23	30

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR CARBON MONOXIDE

Derivation Summary for Carbon Monoxide

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a]N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations that do not yet cause AEGL-1 effects in the general population.

Reference: Not applicable.

Test Species/Strain/Number: Not applicable/not applicable/not applicable.

Exposure Route/Concentrations/Durations: Not applicable/not applicable/not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: CO is the classical example of a tasteless, nonirritating, odorless and colorless toxic gas. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms were noted in monkeys and healthy humans (Haldane 1895; Purser and Berrill 1983). In patients with coronary artery disease, which constitutes the most susceptible subpopulation, effects, such as significant electrocardiogram changes, reduced time to the onset and increased cardiac arrhythmia, start occurring at exposure concentrations little higher than current ambient air quality guidelines, e.g., the U.S. national air quality guideline of 9 ppm for 8 h (National Air Pollution Control Administration 1970; 65 Fed. Regist. 50201[2000]; EPA 2000), the WHO air quality guideline of 10 mg/m^3 (9 ppm) for 8 h (based on 2.5% COHb) (WHO 1999a) and the designated European Union limit value of 10 mg/m^3 (9 ppm) for 8 h (EC 1999). These effects were considered above the AEGL-1 effect level and thus would not constitute a suitable basis for the derivation of AEGL-1 values. AEGL-1 values were not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2) at concentrations, which do not yet cause AEGL-1 effects in the general population. In addition, CO exposures encountered frequently in everyday life are at or above the concentration range, in which AEGL-1 would have to be set: smokers have COHb in the range of 3-8% (Radford and Drizd 1982) and CO concentrations between about 10 and 50 ppm, which can be found on heavily traveled roads, inside motor vehicles and in homes with gas-, coal-, wood- or kerosene-fired heaters and stoves, correspond to an equilibrium COHb of 1.8-7.5% (see Figures 2-2 and B-1).

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Not applicable.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
420 ppm	150 ppm	83 ppm	33 ppm	27 ppm

References: Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, M. Pagano, R.H. Selvester, S.M. Walden, and J. Warren. 1989a. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N. Engl. J. Med. 321(21):1426-1432; Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, D. Hayes, M. Pagano, R.H. Selvester S.M. Walden, and J. Warren. 1989b. Acute Effects of Carbon Monoxide Exposure on Individuals with Coronary Artery Disease. Research Report No. 25. Health Effects Institute, Cambridge, MA.; Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, M. Pagano, R.H. Selvester, S.M. Walden, and J. Warren. 1991. Effects of carbon monoxide on myocardial ischemia. Environ. Health Perspect. 91:89-132.

Test Species/Strain/Sex/Number: Humans with coronary artery disease/not applicable/male/63.

Exposure Route/Concentrations/Durations: Inhalation/mean concentrations of 0, 117 or 253 ppm for 50-70 min were used, adjusted individually to reach COHb concentrations of 2.2% or 4.4% at the end of exposure (about 2 or 4% COHb in the subsequent exercise tests).

Effects:
When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST-segment change in the electrocardiogram, exposure to CO levels producing COHb of 2% resulted in a overall statistically significant 5.1% decrease in the time to attain this level of ischemia. For individual centers (patients were tested in one of three centers), results were significant in one, borderline significant in one and nonsignificant in one center. At 4% COHb, the decrease in time to the ST criterion was 12.1% (statistically significant for all patients, the effect was found in 49/62 subjects) relative to the air-day results. Significant effects were found in all three test centers. The maximal amplitude of the ST-segment change was also significantly affected by the CO exposures: at 2% COHb the maximal increase was 11% and at 4% COHb the increase was 17% relative to the air day.

At 2% COHb, the time to exercise-induced angina was reduced by 4.2% in all patients (effects were significant in two test centers and nonsignificant in one center). At 4% COHb, the time was reduced by 7.1% in all patients (effects were significant in one, borderline significant in one and nonsignificant in one center). The two end-points (time to angina and time to ST change) were also significantly correlated. Only at 4% COHb a significant reduction in the total exercise time and in the heart rate-blood pressure product was found (this double product provides a clinical index of the work of the heart and myocardial oxygen consumption).

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
420 ppm	150 ppm	83 ppm	33 ppm	27 ppm

End Point/Concentration/Rationale:
Patients with coronary artery disease show health effects at lower COHb levels than children, pregnant women or healthy adults and, thus, constitute the most susceptible subpopulation. For the derivation of AEGL-2 values a level of 4% COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al. 1989a,b; 1991). In the available studies, the CO exposure alone (that is, with subjects at rest) did not cause angina, while exercise alone did so. However, it should be noted that all studies used patients with stable exertional angina, who did not experience angina while at rest. Thus, it cannot be ruled out that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. The changes in the electrocardiogram (ST-segment depression of 1 mm or greater) associated with angina symptoms were considered reversible, but is indicative of clinically relevant myocardial ischemia requiring medical treatment. An exposure level of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. Ventricular arrhythmias have been observed at COHb of 5.3%, but not at 3.7% (Sheps et al. 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3 or 5% COHb (Dahms et al. 1993). An exposure level of 4% COHb was considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness and dyspnea (Crocker and Walker 1985; Klasner et al. 1998), and long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children (Klees et al. 1985).

It is acknowledged that apart from emergency situations, certain scenarios could lead to CO concentrations which may cause serious effects in persons with cardiovascular diseases. These scenarios include extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defect car exhaust systems), charcoal or wood-fire furnaces, and indoor air pollution by tobacco smoking.

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applicable.
Intraspecies: 1
A level of 4% COHb was the NOEL for AEGL-2 effects in patients with coronary artery disease, while the LOEL was estimated at 6-9%. In comparison, the LOEL was about 10-15% in children and 22-25% in pregnant women. Since AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective also for other subpopulations and a total uncertainty factor of 1 was used.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
420 ppm	150 ppm	83 ppm	33 ppm	27 ppm

Time Scaling: A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations in air resulting in a COHb of 4% at the end of exposure periods of 10 and 30 min and 1, 4 and 8 h.

Data Adequacy: AEGL-2 values were based on cardiac effects in subjects with coronary artery disease, which constitute the most susceptible subpopulation. Several high quality studies are available addressing end points such as time to the onset of exercise-induced angina, time to the onset of exercise-induced 1-mm ST-segment changes in the electrocardiogram and frequency of exercise-induced arrhythmias. However, no experimental studies in heart patients are available that used significantly higher levels of COHb than about 5% COHb.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1,700 ppm	600 ppm	330 ppm	150 ppm	130 ppm

Key Reference: Haldane, J. 1895. The action of carbonic acid on man. J. Physiol. 18:430-462; Henderson, Y., H.W. Haggard, M.C. Teague, A.L. Prince, and R.M. Wunderlich. 1921. Physiological effects of automobile exhaust gas and standards of ventilation for brief exposures. J. Ind. Hyg. 3(3):79-92; Chiodi, H., D.B. Dill, F. Consolazio, and S.M. Horvath. 1941. Respiratory and circulatory responses to acute carbon monoxide poisoning. Am. J. Physiol. 134:683-693; Nelson, G. 2006a. Effects of carbon monoxide in man. Pp. 3-62 in Carbon Monoxide and Human Lethality: Fire and Non-fire Studies, M.M. Hirschler, ed. New York: Taylor and Francis.

Test Species/Strain/Sex/Number: Nelson (2006a): Humans/not applicable/both sexes/~3,010 subjects (Haldane 1895; Henderson et al. 1921; Chiodi et al. 1941: Humans (healthy young males)/not applicable/males/4 (total)

Exposure Route/Concentrations/Durations: Inhalation/Nelson (2006a) reported COHb levels in deceased subjects poisoned by inhalaling CO; Chiodi et al. (1941): repeated test on three subjects that reached COHb of 27-52% at the end of exposure; individual COHb values were 31, 32, 32, 33, 39, 41, 42, 43, 45 and 52% in subject H.C., 27, 35, 41, 43 and 48% in subject F.C. and 41, 42 and 44% in subject S.H.; Haldane (1895): repeated exposure of one subject reaching the following COHb at the end of exposure (time in min): 13% (240 min), 14% (210 min), 23% (240 min), 27% (24 min), 35% (29 min), 37% (29 min), 37% (120 min), 39% (30.5 min), 49% (71 min), 56% (35 min).

Effects: At a COHb of about 40-56%, Haldane (1895) described symptoms included hyperpnea, confusion of mind, dim vision and unsteady/inability to walk. Chiodi et al. (1941) found no effect on oxygen consumption, ventilation, pulse rate, blood pressure and blood pH; the cardiac output increased 20-50% at COHb >40%, while the changes were negligible at COHb of <30%. Nelson (2006a) reported COHb measurements in lethal poisoning human cases and the data indicated that most lethal poisoning cases occurred at COHb levels higher than 40% and that survival of CO-exposed humans were likely to be seen at levels below 40%.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1,700 ppm	600 ppm	330 ppm	150 ppm	130 ppm

End Point/Concentration/Rationale: The derivation of AEGL-3 values was based on observations in humans. Analysis of lethal cases reported by Nelson (2006a) indicated that most lethal poisoning cases occurred at COHb levels higher than 40% and that survival of CO-exposed humans were likely to be seen at levels below 40%. Thus, 40%COHb level seems a reasonable threshold for lethality. This level is supported by experimental studies suggest that a COHb of about 34-56% does not cause lethal effects in healthy individuals. Further support come from the studies by Kizakevich et al. (2000), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when subjects were exposed to 20-33% COHb. The point of departure of 40% COHb is also supported by studies in animals reporting minimum lethal COHb levels in rats and mice of about 50-70% (E.I. du Pont de Nemours and Co., 1981; Rose et al., 1970). Further support comes from published cases of myocardial infarction that measured COHb levels after transport to the hospital: 52.2% (Marius-Nunez 1990), 30%, 22.8% (Atkins and Baker 1985), 21% (Ebisuno et al., 1986), 15.6% (Grace and Platt 1981).

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable.
Intraspecies: 3
An intraspecies uncertainty factor of 3 was supported by information on effects, such as myocardial infarction and stillbirths, reported in more susceptible subpopulations.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: A mathematical model (Coburn et al. 1965; Peterson and Stewart 1975) was used to calculate exposure concentrations in air resulting in a COHb of 40% at the end of exposure periods of 10 and 30 min and 1, 4 and 8 h.

Data Adequacy: AEGL-3 values were based on 40% COHb levels derived from the analysis of clinical cases of lethal and nonlethal poisoning. The AEGL-3 values derived using an intraspecies uncertainty factor of 3 (corresponding to an COHb of about 15%) are supported by the available case reports of lethal effects (myocardial infarction, stillbirths) in more susceptible subpopulations. Lethal effects from myocardial infarction in hypersusceptible patients with coronary artery disease at even lower CO concentrations, which could be at the upper end of the range of CO concentrations found inside buildings and in ambient air outside, cannot be excluded.

3

1,2-Dichloroethene[1]
cis-1,2-Dichloroethene
trans-1,2-Dichloroethene

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, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Cheryl B. Bast (Oak Ridge National Laboratory) and Chemical Manager 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

1,2-Dichloroethene is a flammable, colorless liquid existing in both cis- and trans- forms and as a mixture of these two isomers. It is one of a number of two carbon chlorocarbons produced in a reaction mixture resulting from processes involved in the chlorination of ethylene to produce chlorinated monomers and solvents. The trans-isomer is commercially isolated by distillation and sold as a highly purified product that is used in precision cleaning of electronic equipment. The compound is a narcotic. Data on narcosis in humans, cats, rats, and mice, and systemic effects in cats, rats, and mice were available for development of AEGLs. The data were considered adequate for derivation of the three AEGL classifications.

The AEGL-1 was based on human exposure to 825 ppm *trans*-1,2-dichloroethene for 5 min (Lehmann and Schmidt-Kehl 1936). This concentration is a no-effect-level for eye irritation. This value was divided by an uncertainty factor of 3 to protect sensitive individuals and is considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Using the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm). This uncertainty factor of 3 was applied for AEGL-1 values for both the cis- and trans-isomers. Since data suggest that the cis- isomer is approximately twice as toxic as the trans-isomer with regard to narcosis and

lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. Although the AEGL-1 point-of-departure is a NOEL for eye irritation, the use of the modifying factor is justified for the cis- isomer because slight dizziness, a possible mild narcotic effect, was noted at the concentration used as starting point for the derivation of the AEGL-1. The same value was applied across the 10- and 30-min, 1-, 4-, and 8-h exposure time points since mild irritation is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect.

The AEGL-2 for the 4- and 8-h time points was based on narcosis observed in pregnant rats exposed to 6,000 ppm of the trans- isomer for 6 h (Hurtt et al. 1993). Uncertainty factors of 3 each (total UF = 10) were applied for both inter- and intraspecies differences. The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; de Jong and Eger 1975; Stevens et al. 1975). This total uncertainty factor of 10 was applied for AEGL-2 values for both the cis- and trans- isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The AEGL-2 for the 10- and 30- min and 1-h time points was set as a maximum exposure level for anesthetic effects in humans (Lehmann and Schmidt-Kehl 1936). Since data suggest that the cis- isomer is approximately twice as toxic as the trans- isomer with regard to narcosis and lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The AEGL-3 for the 4- and 8-h time points was based on a concentration (12,300 ppm) causing no mortality in rats exposed to *trans*-1,2-dichloroethene for 4-h (Kelly 1999). An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). An intraspecies UF of 3 was also applied and is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; de Jong and Eger 1975; Stevens et al. 1975). The total uncertainty factor of 10 was applied for AEGL-3 values for both the cis- and trans- isomers. The concentration-exposure time relationship for many irri-

tant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The AEGL-3 for the 10- and 30- min and 1-h time points was set as a maximum exposure level for intracranial pressure, nausea, and severe dizziness in humans (Lehmann and Schmidt-Kehl 1936). Since data suggest that the cis- isomer is approximately twice as toxic as the trans-isomer with regard to narcosis and lethality in experimental animals, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The calculated values are listed in Tables 3-1 and 3-2.

1. INTRODUCTION

1,2-Dichloroethene is an extremely flammable, colorless liquid with a harsh odor, existing as both cis- and trans- forms and as a mixture (ATSDR 1996). It is one of a number of two carbon chlorocarbons produced in a reaction mixture resulting from processes involved in the chlorination of ethylene to produce chlorinated monomers and solvents. The trans- isomer is commercially isolated by distillation and sold as a highly purified product that is used in precision cleaning of electronic equipment. The compound reacts with alkalis to form chloroacetylene gas, reacts violently with potassium hydroxide and sodium hydroxide, and can be combined with dinitrogen tetraoxide to form shock-sensitive explosives. Because of volatility, inhalation is the primary route of exposure of 1,2-dichloroethene to humans. Exposure may occur as the result of releases from production or use facilities, from contaminated wastewater and waste disposal sites, and from burning of polyvinyl and vinyl polymers (ATSDR 1996). In 1977, production of the cis-/trans- mixture was reported by one company as 10 to 50 million pounds and by another company as 1 to 10 million pounds (NTP 2002). The only manufacturer of the cis- isomer reported production of 0.1 to 10 million pounds; no production estimates for the trans-isomer were reported (NTP 2002). The physicochemical data for 1,2-dichloroethene are shown in Table 3-3.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

An accidental fatality from occupational exposure to 1,2-dichloroethene occurred when a male rubber factory worker entered a vat containing rubber

TABLE 3-1 Summary of AEGL Values for *trans*-1,2-Dichloroethene [ppm(mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	Ocular irritation in humans (Lehmann and Schmidt-Kehl 1936)
AEGL-2 (Disabling)	1,000 (3,960)	1,000 (3,960)	1,000 (3,960)	690 (2,724)	450 (1,782)	Narcosis in rats: 4- and 8-h (Hurtt et al. 1993); Anesthetic effects in humans (Lehmann and Schmidt-Kehl 1936)
AEGL-3 (Lethality)	1,700 (6,732)	1,700 (6,732)	1,700 (6,732)	1,200 (4,752)	620 (2,455)	No death in rats: 4- and 8-h (Kelly 1999); Nausea, intracranial pressure, and dizziness in humans: 10-, 30-min, and 1-h (Lehmann and Schmidt-Kehl 1936)

TABLE 3-2 Summary of AEGL Values for *cis*-1,2-Dichloroethene [ppm(mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)	Ocular irritation in humans (Lehmann and Schmidt-Kehl 1936)
AEGL-2 (Disabling)	500 (1,980)	500 (1,980)	500 (1,980)	340 (1,346)	230 (911)	Narcosis in rats: 4- and 8-h (Hurtt et al. 1993); Anesthetic effects in humans (Lehmann and Schmidt-Kehl 1936)
AEGL-3 (Lethality)	850 (3,366)	850 (3,366)	850 (3,366)	620 (2,455)	310 (1,228)	No death in rats: 4- and 8-h (Kelly 1999); Nausea, intracranial pressure, and dizziness in humans:10-, 30-min, and 1-h (Lehmann and Schmidt-Kehl 1936)

TABLE 3-3 Chemical and Physical Data for 1,2-Dichloroethene

Parameter	Data	Reference
Chemical Name	1,2-Dichloroethene	ATSDR 1996
Synonyms	1,2-Dichloroethylene, acetylene dichloride,sym-dichloroethylene, Dioform (trade name)	O'Neil et al. 2001
CAS Registry No.	540-59-0 (mixture), 156-59-2 (cis), 156-60-5 (trans)	ATSDR 1996
Chemical formula	$C_2H_2Cl_2$	O'Neil et al. 2001
Molecular weight	96.9	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Odor threshold	17 ppm; ethereal, slightly acrid odor	O'Neil et al. 2001
Melting/boiling/flash point	-80.5°C /60.3°C /6°C (cis); -50.0°C /48.0°C /4°C (trans)	ATSDR 1996
Density	1.2837 (cis) or 1.2565 (trans) g/cm^3	ATSDR 1996
Solubility in water	3.5 (cis) or 6.3 (trans) g/L at 25°C	ATSDR 1996
Vapor pressure	180 (cis) or 265 (trans) mm Hg at 20 °C	ATSDR 1996
LogK_{ow}	1.86 (cis), 2.06 (trans)	ATSDR 1996
Bioconcentration factor (BCF)	ND	
Henrys' Law constant	3.37×10^{-3} (cis) or 6.72×10^{-3} (trans) atm-m^3/mol	ATSDR 1996
Conversion factors in air	1 mg/m^3 = 0.25 ppm 1 ppm = 3.96 mg/m^3 at 25 °C	ATSDR 1996

dissolved in 1,2-dichloroethene (Hamilton 1934). Symptoms of toxicity, exposure concentration and duration, and isomeric composition of the vapor were not reported. No other data concerning human lethality from 1,2-dichloroethene exposure were located in the available literature.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Short-term inhalation experiments were conducted with "relatively" low concentrations of trans-dichloroethene (Lehmann and Schmidt-Kehl 1936). Two doctoral candidates self-administered the chemical (as a vapor) in a well insulated 10 m^3 room. Using a manual sprayer and later a vaporizer (with attached oxygen tank), the chemical was uniformly distributed through the exposure chamber by means of fan and a ventilator. The concentration of trans-dichloroethene in the exposure chamber was determined analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Both individuals were exposed simultaneously

in the same room. They appeared to react very similarly. Experiments lasted for 5 to 30 min. Based on concentrations of trans-dichloroethene in inspired and expired air, the authors estimated that approximately 73% of the chemical was absorbed. Exposure parameters and effects are presented in Table 3-4.

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding human exposure to 1,2-dichloroethene were not available.

2.3. Developmental and Reproductive Toxicity

No developmental and reproductive toxicity data concerning 1,2-dichloroethene were identified in the available literature.

2.4. Genotoxicity

No data concerning the genotoxicity of 1,2-dichloroethene in humans were identified in the available literature.

2.5. Carcinogenicity

No data concerning the carcinogenicity of 1,2-dichloroethene in humans were identified in the available literature.

TABLE 3-4 Effects of Inhalation Exposure to *trans*-1,2-Dichloroethene[a]

Time	Concentration (ppm)	Effect
5 min	275	No effect
	950	Slight burning of eyes
	1700[b]	Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea
	2200[b]	Severe dizziness after 5 min; intracranial pressure; nausea
10 min	825	Slight dizziness after 5 min
	1200	Dizziness after 5 min; initially, slight burning of the eyes; drowsiness
30 min	1000	Dizziness after 10 min; slight burning of eyes

[a]Two human subjects were exposed.
[b]Symptoms persisted for 2 hours post-exposure.
Source: Adapted from: Lehmann and Schmidt-Kehl 1936.

2.6. Summary

Only anecdotal data regarding human lethality from exposure to 1,2-dichloroethene were available, and exposure concentration, time and isomeric composition were not reported. Nonlethal exposure-response data suggest that 1,2-dichloroethene induces reversible neurological symptoms in humans. Exposures involved two human subjects exposed to concentrations of 275 to 2,200 ppm *trans*-1,2-dichloroethene/m^3 for 5 to 30 min.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

Gradiski et al. (1978) reported a 6-h LC_{50} of 21,723 ppm *trans*-1,2-dichloroethene for female OF1SPF mice; the cause of death was not reported.

Lehmann and Schmidt-Kehl (1936) exposed groups of three mice (sex and strain not specified) to *cis*-1,2-dichloroethene as follows: 65,000 mg/m^3 (16,250 ppm) for 140 min, 70,000 mg/m^3 (17,500 ppm) for 77 min, or 90,000 mg/m^3 (22,500 ppm) for 66 min. All of these mice died. In the same study, groups of three mice were also exposed to the trans- isomer as follows: 75,000 mg/m^3 (18,750 ppm) for 102 min, 80,000 mg/m^3 (20,000 ppm) for 95 min, 105,000 mg/m^3 (26,250 ppm) for 32 min, or 129,000 (32,250 ppm) mg/m^3 for 30 min (see Table 3-10). All of these mice also died.

3.1.2. Rats

Groups of 5 male and 5 female Crl:CD (SD)BR rats were exposed to 12,300, 22,500, 28,100, or 34,100 ppm *trans*-1,2-dichloroethene or 12,100, 13,500, 15,700, or 23,200 ppm *cis*-1,2-dichloroethene for 4 h in a 300-L stainless steel and glass chamber (Kelly 1999). The test atmospheres were generated by metering liquid dichloroethene into a heated glass Instatherm flask with either a Fluid Metering pump or a Hamilton Syringe Drive. Nitrogen introduced into the flask swept the dichloroethene vapor into the air supply duct to the exposure chamber. The chamber concentration of dichloroethene was controlled by varying the amount of the metered liquid delivered to the evaporation flask. The chamber concentration of test substance was determined by gas chromatography at 15-min intervals during each exposure. Chamber airflow, temperature, and relative humidity were monitored continually. Liver, kidney, lung, and heart were examined histologically. The 4-h LC_{50} value was 24,100 ppm for *trans*-1,2 dichloroethene and 13,700 ppm for *cis*-1,2-dichloroethene. Data are summarized in Table 3-5.

TABLE 3-5 Four-Hour Exposure of Rats to *cis*- and *trans*-1,2-Dichloroethene

Concentration (ppm)	Mortality	Observations	
trans-1,2-Dichloroethene			
		During Exposure[a]	After Exposure
12,300	0/10	Prostrate, decreased response followed by no response to alerting stimulus, normal response 30 min after exposure	Normal weight gain
22,500	4/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Lethargy, irregular respiration, slight weight loss one day followed by normal weight gain
28,100	7/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Weakness, slight to severe weight loss one day followed by normal weight gain
34,100	10/10	Prostrate, no response to alerting stimulus	—
cis-1,2-Dichloroethene			
12,100	0/10	Prostrate, no response to alerting stimulus (recovery in 1 h post-exposure)	Normal weight gain rate
13,500	6/10	Prostrate, no response to alerting stimulus (recovery time not noted)	Weakness, irregular respiration, immediately after exposure, slight to severe weight loss one day followed by normal weight gain; centrilobular fatty liver changes (2/10)
15,700	10/10	Prostrate, no response to alerting stimulus	Centrilobular fatty liver changes (4/10)
23,200	10/10	Prostrate, no response to alerting stimulus	—

[a]Deaths occurred during exposure.

Source: Kelly 1999. Reprinted with permission; copyright 1999, Dupont.

3.1.3. Cats

Cats (2/concentration) were exposed to *cis*-1,2-dichloroethene at concentrations ranging from 20,000 to 114,000 mg/m^3 (5,000 to 28,500 ppm) for 9 to 360 min (Lehmann and Schmidt-Kehl 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 360-L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: (1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or (2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: (1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or (2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations, suggesting reliability and accuracy in the exposure concentrations. The mean experimental ventilation rate was 1050 L/h. The exposures resulted in death at various times, ranging from 3 min to 7 days, after exposure (see Table 3-9 for details).

3.2. Nonlethal Toxicity

3.2.1. Cats

Fasted cats (2/experiment) were exposed to *cis*- or *trans*-1,2-dichloroethene vapors in a series of experiments (Lehmann and Schmidt-Kehl 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 360 L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: 1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or 2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: 1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or 2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations. The

mean experimental ventilation rate was 1050 L/h. Due to the variability in researchers, there were some inconsistencies in observations. End points measured included equilibrium effects, lethargy, light narcosis, and deep narcosis. Effects on equilibrium were defined as swaying and difficulty in getting up and moving around. Lethargy was defined as the complete inability to move and was tested by gently lifting the head with a wooden rod. If the head fell back following removal of the rod, the cat was considered lethargic. Light narcosis was defined as the absence of extremity reflexes, and deep narcosis was defined as the absence of corneal and extremity reflexes. Also observed were irritating effects on mucous membranes (eyes, nose, mouth, salivary glands) and respiratory rate. The animals were observed for at least 8 days after exposure. Respiratory rates corresponding to lethargy, light narcosis, and deep narcosis were 61, 75, and 72 breaths/min, respectively, for the trans isomer; and 85, 99, and 92 reaths/min, respectively, for the cis- isomer. Study design and observations are presented in Tables 3-6 through 3-9.

3.2.2. Rats

Groups of six female SPF Wistar rats (180-200 g) were given single 8-h exposures to *trans*-1,2-dichloroethene vapors at 0, 200, 1,000, or 3,000 ppm (Freundt et al. 1977). Experimental concentrations were monitored by gas chromatography, and were within 3% of the nominal concentrations. Animals were sacrificed immediately after the exposure period. The incidence of slight to severe fatty degeneration of hepatic lobules and Kupffer cells and pulmonary capillary hyperaemia and alveolar septum distention was increased in all treatment groups when compared to controls. Pneumonic infiltration and fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation were observed in animals in the 3,000 ppm group. Decreased serum albumin, urea nitrogen, and alkaline phosphatase activity were observed in the 1,000 ppm group after 8 h of exposure; however, these effects are of questionable biological significance because none were outside the normal range for rats. Leukocyte counts were decreased after exposure to 200 ppm 1,2-dichloroethene for 8 h, and a decreased erythrocyte count was observed in the 1,000 ppm group after 8 h. It should be noted that the results of this study are inconsistent with the total database for 1,2-dichloroethylene and results, especially the reported pathological changes, are of questionable toxicological significance.

In another study, Freundt and Macholz (1978) exposed groups of 10 female Wistar rats to *cis*- or *trans*-1,2-dichloroethene at 0, 200, 600, 1,000, or 3,000 ppm for 8 h. A statistically significant ($p < 0.05$), dose-dependent increase in hexobarbital sleeping time and zoxazolamine paralysis time was observed in all treated groups, indicating decreased activity of the P-450 enzymes that normally metabolize these compounds. The effect was observed in animals exposed to both isomers; however, the effect was more severe in rats exposed to the cis-isomer.

TABLE 3-6 Sublethal Effects in Cats Exposed to *trans*-1,2-Dichloroethene for 22-248 Minutes[a]

Concentration [mg/m^3 (ppm)]	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
72,000 (18,000)	348	7-8	37-43	320-340	330-345
86,400 (21,600)	213	4	22-23	152-157	206-210
110,000 (27,500)	75	3-5	8-9	20-21	69-70
147,000 (36,750)	23	1-3	5	7-9	14-18
189,200 (47,300)	22	1	3	5	12-13

[a]Lehmann and Schmidt-Kehl 1936. Two animals/exposure (1 male and 1 female; or 2 males); body weight 2.05-4.05 kg. Symptoms of irritation (salivation, licking, sneezing, and eye blinking) occurred immediately and after several minutes. Following deep narcosis, corneal reflexes returned after a few minutes to ½ h. One animal died (exposure not given).
[b]Time in minutes after initiation of exposure when effect was observed.

TABLE 3-7 Sublethal Effects in Cats Exposed to *trans*-1,2-Dichloroethene for 10-390 Minutes[a]

Concentration (mg/m^3 (ppm)	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
43,000 (10,750)	390	57-60	325-390	Absent	Absent
52,000 (13,000)	360	18-21	100-115(spasms)	Absent	Absent
97,000 (24,250)	163	19	18-19 (spasms)	Absent	No data
101,500 (26,250)	268	2-3	16-18 (spasms)	172-192 (spasms in 1 male)	238-268
117,000 (29,250)	188	Instantly-2 min	3-10 (cough spasms)	27-83	178-188
129,000 (32,250)	129	3-4 (spasms)	6-14 (spasms)	40-100	87-158

(Continued)

TABLE 3-7 Continued

Concentration (mg/m^3 (ppm)	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
136,000 (34,000)	136	No data	4-5	21-42	127-132
138,000 (34,500)	50	Immediately (1 male)	6-9	19-21 (spasms in 1 female)	49-50
158,500 (39,500)	15	No data	4-6	11-12	14-15 (spasms)
191,000 (47,750)	10	5	3-9 (spasms in 1 male)	7-10	9-12

[a]Lehmann and Schmidt-Kehl 1936. Two cats/exposure (1 male and 1 female, or 2 males); body weight 2.1-4.5 kg.
Symptoms of irritation (salivation, licking, coughing, biting) occurred immediately and after several minutes. Vomiting occurred in 2 animals. Following deep narcosis, corneal and leg reflexes returned after a few minutes. Three animals died (exposure not given). Spasms (convulsions) affected extremities, chewing muscles, and diaphragm, but were not severe.
[b]Time after initiation of exposure when effect was observed.

TABLE 3-8 Sublethal Effects in Cats Exposed to *cis*-1,2-Dichloroethene for 17-288 Minutes

Concentration (mg/m^3 (ppm))	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
38,200 (9550)	288	60	121-165	238-265	246-285
39,600 (9900)	225	18-61	40-27	140-142	155-224
42,200 (10,500)	162	1 (1 male)	22-46	56-57	153-161
42,500 (10,625)	210	absent	43-65	55-65	141-210
50,600 (12,650)	117	2-6	13-22	32-35	72-114
56,300 (14,075)	66	5	14-17	25-26	64-66
61,400 (15,350)	26	3-5	12-15	16-19	24-25

76,000 (19,000)	24	5	10-11	13	16-19
100,000 (25,000)	17	2.5-5	7-8	9-10	12-13

[a]Lehmann and Schmidt-Kehl 1936. Two cats/exposure (1 male and 1 female, or 2 males); body weight 2-3.2 kg.
Symptoms of irritation (salivation, licking, sneezing) occurred immediately and after several minutes. Vomiting occurred in 2 animals. Following deep narcosis, corneal and leg reflexes returned after a few minutes, and ability to walk after a few minutes to ½ h. Three animals died (exposure not given).
[b]Time after initiation of exposure when effect was observed.

TABLE 3-9 Cats Exposed to *cis*-1,2-Dichloroethene for 9-360 Minutes[a]

Concentration [mg/m^3 (ppm)]	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
20,000 (5000)	360	120-180, head and leg spasms	Absent after 360 min	Absent after 360 min	Absent after 360 min, 1 died after 2 d
35,000 (8750)	234	120, leg spasms	122-126	125-171, scratching	230-232,1 died
42,000 (10,500)	48	7	17	20	48, 1 died after 3 min
48,000 (12,000)	105	No data	12-44	15-68	27-104, 1 died after 1 d
49,000 (12,500)	122	7	37-69	72-88	90-121, 1 died after 5 d
53,000 (13,250)	118	8	17-30, spasms	21-60, restless, nystagmus	118-124,1 died after 2 d
62,000 (15,500)	49	6	10-17	4-20	12-48, both died on first d
64,000 (16,000)	37	No data	17-21	26	36-31
68,000 (17,000)	25	5, restless, scratching and biting	7-12, Leg spasms	17-22	21-23

(Continued)

TABLE 3-9 Continued

Concentration [mg/m^3 (ppm)]	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Light Narcosis (min)[b]	Deep Narcosis (min)[b]
77,000 (19,250)	25	Restless	6, spasms	8-9	13-24, 1 died after 7 d
98,000 (24,500)	20	3-5	8-10	11-18	12-20
114,000 (28,500)	9	No data	3-4	5	7-9, 1 died

[a]Lehmann and Schmidt-Kehl 1936. Two cats/exposure (1 male and 1 female, or 2 males); only one male cat was exposed to 42 mg/L for 48 min; body weight 2.2-4.6 kg.
[b]Time after initiation of exposure when effect was observed.

Hurtt et al. (1993) exposed groups of 24 pregnant Crl:CD BR rats to *trans*-1,2-dichloroethene at 0, 2,000, 6,000, or 12,000 ppm in 150-L square, pyramidal, stainless steel and glass exposure chambers 6 h/d on days 7-16 of gestation. The test atmosphere was generated by vaporization of the dichloroethene from glass, gas-washing bottles placed in temperature-regulated water baths and the vaporized test material was swept into 3-neck glass mixing flasks. Filtered, conditioned dilution air was added to the mixing flasks at 30 L/min to sweep vapors into the exposure chamber. The chamber concentration of test substance was determined by gas chromatography at 30-min intervals during each exposure. Chamber airflow, temperature, and relative humidity were monitored continually. Decreased body weight gain was observed in dams exposed at 12,000 ppm, and decreased maternal food consumption was observed in dams exposed at 6,000 and 12,000 ppm. Narcotizing effects were observed in dams exposed at 6,000 and 12,000 ppm. Signs of eye irritation were observed immediately following exposure(s). At 2,000 ppm, 13/24 animals exhibited a clear ocular discharge and 3/24 exhibited periocular wetness. At 6,000 ppm, 22/24 had ocular discharge and 17/24 had periocular wetness, and at 12,000 ppm all 24 dams showed both ocular discharge and periocular wetness. Alopecia, lethargy and salivation were observed in dams exposed to 12,000 ppm. An increase in the mean number of resorptions per litter was observed at 6,000 and 12,000 ppm; however, the values were within historical control ranges. A decrease in mean combined female fetal weight was observed at 12,000 ppm. No other fetal effects were observed.

In a subchronic exposure study, groups of 15 male and 15 female Crl:CD (SD)BR rats were exposed to *trans*-1,2-dichloroethene (99.9% pure) at 0, 200, 1,000, or 4,000 ppm for 6 h/d, 5 d/wk for 90 days in a 1,400-L stainless steel and glass chamber (Kelly 1998). The test atmospheres were generated by metering liquid dichloroethene into a heated glass Instatherm flask with either a Fluid Metering pump or a Hamilton Syringe Drive. Nitrogen introduced into the flask swept the dichloroethene vapor into the air supply duct to the exposure chamber. The chamber concentration of dichloroethene was controlled by varying the amount of the metered liquid delivered to the evaporation flask. The chamber concentration of test substance was determined by gas chromatography at 15-min intervals during each exposure. Chamber airflow, temperature, and relative humidity were monitored continually. No treatment-related effects on body weight, body weight gain, food consumption, clinical signs, clinical chemistry, hematology, gross or microscopic pathology or liver cell proliferation were observed.

In a 14-week feeding study, groups of 10 male and 10 female F344/N rats were fed diets with microcapsules containing *trans*-1,2-dichloroethene (NTP 2002). Dietary concentrations of microencapsulated *trans*-1,2-dichloroethene at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm resulted in average daily doses of 190, 380, 770, 1,540, and 3,210 mg/kg for male rats and 190, 395, 780, 1,580, and 3,245 for female rats. Groups of 10 rats/sex served as untreated and vehicle controls. There was no treatment-related mortality. Mean body weights of males

in the 50,000 ppm group were decreased approximately 6% ($p \leq 0.01$) compared to vehicle controls. On day 21 and at week 14, there were slight decreases ($p \leq 0.05$ or 0.01) in hematocrit values, hemoglobin concentrations, and erythrocyte counts in males and females in the 25,000 and 50,000 ppm groups. At week 14, these effects were also noted in males in the 6250 and 12,500 ppm groups. Liver weights were increased up to 10% ($p \leq 0.05$ or 0.01) in females in the 6250 ppm group and higher compared to vehicle controls, and kidney weights were decreased approximately 22% ($p \leq 0.05$) in males in the 25,000 and 50,000 ppm groups. No treatment-related gross or microscopic lesions were noted.

In another oral study, McCauley et al. (1995) administered *cis*-1,2-dichloroethene by gavage in corn oil to groups of 10 male and 10 female Sprague-Dawley rats. Doses were 1.0, 3.0, 10.0, and 22.0 mmol/kg/day for 14-days or 0.33, 1.00, 3.00, or 9.00 mmol/kg/day for 90 days. There were no treatment-related deaths or histopathlogical lesions noted. Increased relative liver weights ($p \leq 0.05$) were noted in both sexes and all doses tested in the 14-day study (up to 19% increase) and at 1.0 mmol/kg and above in the 90-day study (up to 26% increase).

3.2.3. Mice

Three mice (sex not given)/experiment were exposed to either cis- or trans 1,2-dichloroethene vapors (Lehmann and Schmidt-Kehl 1936). "Pure" chemical was obtained from I.G. Farben and was further purified by multiple fractionated distillations followed by boiling point measurements. Ambient air was suctioned from a 136 L exposure chamber utilizing a large gas valve which was rotated by means of a bucket wheel located in a water container on the same level as the valve. The experimental aerosol was produced by one of two methods: (1) either by passing a small stream of air through a Woulfsche flask containing a measured amount of chemical for a given time period and adding chemical by opening a burette or (2) by forcing a side air stream through a bulb tube containing the liquid dichloroethene and mixing with the main air stream. The concentration of dichloroethene in the exposure chambers was determined in one of two ways: (1) by dividing the evaporated portion of the chemical by the air volume over a specific time period or (2) analytically by determining the chlorine content in the gas mixture employing the "lime method" from which the dichloroethene content was then calculated. Actual concentrations achieved ranged from 98.2% to 100.7% of the nominal concentrations. The mean experimental ventilation rate was 1050 L/h. Observations included effects on equilibrium (described as swaying), lethargy (described as the inability to move), and loss of foot reflexes. Also observed were irritating effects on mucous membranes (eyes, nose, mouth, salivary glands) and respiratory rate. Data are summarized in Tables 3-10 and 3-11.

TABLE 3-10 Effects in Mice Exposed to *cis*-1,2-Dichloroethene for 66-150 Minutes[a]

Concentration [mg/m^3(ppm)]	Time (min)	Effects on Equilibrium (min)[b]	Lethargy (min)[b]	Loss of Reflex (min)[b]	Death/Recovery
27,000 (6750)	150	13	91	86 (2 mice)	Recovery in 3-19 min
40,000 (10,000)	150	7	11	24	Recovery in 10 min
50,000 (12,500)	149	5	9	19	Recovery in 10 min
65,000 (16,250)	140	3	6	9	All died in 75-140 min
70,000 (17,500)	77	1	3	5	All died in 55-77 min
90,000 (22,500)	66	1	3	4	All died in 24-66 min

[a]Lehmann and Schmidt-Kehl 1936. 3 animals/exposure; sex not given; body weight 17-25 g; time at which effect occurred is average for 3 mice. At the beginning of exposure, the animals became restless and excited. After a few min, they assumed a side position which occurred almost simultaneously with a loss of reflexes at the higher concentrations. The respiratory rate was usually in the range of 150-180 breaths/minute, but occasionally reached as high as 300. Fewer spasms were seen in animals exposed to the cis- isomer compared to the trans- isomer. None of the animals that survived the exposure period, died later. Recovery occurred rapidly.
[b]Time after initiation of exposure when effect was observed.

TABLE 3-11 Mice Exposed to *trans*-1,2-Dichloroethene for 30-155 Minutes[a]

Concentration (mg/m^3[ppm])	Time (min)	Effects on Equilibrium (min)[b]	Decreased Activity, Lethargy (min)[b]	Loss of Reflex (min)[b]	Death/Recovery
45,000 (11,250)	155	19	115	155	Recovery in 5-10 min
50,000 (12,500)	135	15	110	119	Recovery in 5 min
58,000 (14,500)	110	14	48	94	Recovery in 10 min
67,000 (16,750)	132	10	20	57	Recovery in 25 min
75,000 (18,750)	102	10	18	44	All died in 121-142 min
80,000 (20,000)	95	5	9	19	All died in 66-92 min
105,000 (26,250)	32	4	8	16	All died in 21-32 min
129,000 (32,250)	30	3	6	11	All died in 11-28 min

[a]Lehmann and Schmidt-Kehl 1936. 3 Animals/exposure; sex not given; body weight 17-25 g; times at which effect occurred is average for 3 mice. There was no remarkable irritation of mucous membranes; initially the animals were quiet. Shortly before lethargy set in, spasmodic jumping and rapid respiration were observed. Cyanosis occurred during narcosis.
[b]Time after initiation of exposure when effect was observed.

In another study, DeCeaurriz et al. (1983) exposed groups of 10 male Swiss OF1 mice weighing 20 to 25 g to 0, 1582, 1720, 2194, or 2485 ppm 1,2-dichloroethene (99%) vapors for 4 h.. Differences in mean total duration of immobility between control and experimental groups were measured over a 3 min period after exposure in a behavioral despair swimming test. Immobility was defined as cessation of struggling to get out of the water (suggesting prolongation of escape-directed behavior). A dose-related decrease, ranging from 23 to 71%, in mean duration of immobility was observed in exposed animals when compared to controls. Data are summarized in Table 3-12.

In a 14-week feeding study, groups of 10 male and 10 female B6C3F1 mice were fed diets with microcapsules containing *trans*-1,2-dichloroethene (NTP 2002). Dietary concentrations of microencapsulated *trans*-1,2-dichloroethene at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm resulted in average daily doses of 480, 920, 1,900, 3,850, and 8,065 mg/kg for male mice and 450, 915, 1,830, 3,760, and 7,925 mg/kg for female mice. Groups of 10 mice/sex served as untreated and vehicle controls. There was no treatment-related mortality. Mean body weight gain of females in the 12,500, 25,000, and 50,000 ppm groups was decreased approximately 4-7% ($p \leq 0.01$) compared to vehicle controls. There were no effects on hematology parameters or organ weights, and no treatment-related gross or microscopic lesions were noted.

3.3. Developmental and Reproductive Toxicity

Hurtt et al. (1993) exposed groups of 24 pregnant Crl:CD BR rats to *trans*-1,2-dichloroethene at 0, 2,000, 6,000, or 12,000 ppm for 6 h/day on days 7-16 of gestation. This study was previously described in section 3.2.2. No other developmental and reproductive data concerning 1,2-dichloroethene were identified.

TABLE 3-12 Immobility in Mice Exposed to 1,2-Dichloroethene Vapors for 4 Hours[a]

Concentration [mg/m^3(ppm)]	Time (h)	Duration of Immobility (s ± SE)		Percent Change from Control
		Control	Exposed	
6,265 (1,582)	4	79.2±10.0	60.6±7.4	-23
6,811 (1,720)	4	94.5±6.5	51.7±8.3[b]	-45
8,776 (2,194)	4	79.2±10.0	33.9±6.6[b]	-57
9,840 (2,485)	4	94.0±9.0	26.9±6.2[b]	-71

[a]DeCeaurriz et al. 1983.
[b]Significantly different from control, $p < 0.05$.
Source: DeCeaurriz et al. 1983. Reprinted with permission; copyright 1983, *Toxicology and Applied Pharmacology*.

3.4. Genotoxicity

Neither *trans*-, *cis*-, or *cis*- and *trans*-1,2-dichloroethene were mutagenic in *Salmonella typhimurium* strains TA97 (cis- isomer only), TA98, TA100, TA1535, or TA1537, with or without metabolic activation (Mortelmans et al. 1986; Zeiger et al. 1988; NTP 2002). In CHO cells in vitro, *cis*-1,2-dichloroethene induced sister chromatid exchanges (SCEs) in the absence of metabolic activation; results were equivocal with S9. The cis- and trans- mixture induced increases in SCE frequency in cultured CHO cells with and without metabolic activation; however, the trans-isomer was negative in this assay (NTP 2002). Neither isomer nor the isomeric mixture included chromosomal aberrations in CHO cells with or without metabolic activation (NTP 2002). In vivo genotoxicity studies, *trans*-1,2-dichloroethene was negative in a mouse bone marrow chromosomal aberration assay (Cerna and Kypenova 1977; NTP 2002), in host-mediated gene mutation assays in *S. typhimurium* and in gene mutation and gene conversion assays in *Saccharomyces cerevisiae* (Cerna and Kypenova 1977; Cantelli-Forti and Bronzetti 1988). *cis*-1,2-Dichloroethene was positive in a mouse bone marrow chromosomal aberration assay (Cerna and Kypenova 1977), and in host-mediated gene mutation assays in *S. typhimurium* and *S. cerevisiae* (Cerna and Kypenova 1977; Cantelli-Forti and Bronzetti 1988). Results were equivocal for the cis- isomer in a gene conversion assay in *S. cerevisiae* (Cerna and Kypenova 1977; Cantelli-Forti and Bronzetti 1988).

3.5. Carcinogenicity

No data concerning the carcinogenicity of 1,2-dichloroethene were identified in the available literature.

3.6. Summary

Lethal toxicity data are limited. Four-hour LC_{50} values of *trans*-1,2-dichloroethene at 24,100 ppm and *cis*-1,2-dichloroethene at 13,700 ppm have been reported in rats. No-effect-levels for death for 4-h of exposures were 12,300 ppm for *trans*-1,2-dichloroethene and 12,100 ppm for *cis*-1,2-dichloroethene (Kelly 1999). A 6-h LC_{50} of *trans*-1,2-dichloroethene at 21,723 ppm has been reported in OF1SPF mice (Gradiski et al. 1978). Also, deaths were observed, following a progression of narcotic effects, in both cats and mice exposed to various regimens of 1,2-dichloroethene (Lehmann and Schmidt-Kehl 1936). Nonlethal toxicity data indicate that 1,2-dichloroethene has a narcotic effect and that the cis- isomer is more potent than the trans- isomer with respect to narcosis (Lehmann and Schmidt-Kehl 1936). Narcotic observations indicated a progression from equilibrium effects, followed by lethargy, light narcosis (loss

of limb reflex, maintenance of corneal reflex), finally deep narcosis (loss of corneal reflex), and in some cases, as indicated above, death. Narcotic effects were also observed in pregnant rats exposed to *trans*-1,2-dichloroethene at 6,000 and 12,000 ppm, and dose-related ocular irritation was observed in pregnant rats exposed at 2,000, 6,000, and 12,000 ppm. Decreased fetal weight was observed in offspring of these rats exposed to *trans*-1,2-dichloroethene at 12,000 ppm (Hurtt et al. 1993). No treatment-related effects were noted in a 90-day study in rats repeatedly exposed to *trans*-1,2-dichloroethene at 4,000 ppm (Kelly 1998).

4. SPECIAL CONSIDERATIONS

4.1. Absorption, Distribution, Metabolism and Disposition

Blood:air partition coefficients, as well as liquid:air and tissue: air partition coefficients for both *cis*- and *trans*-1,2-dichloroethene have been reported. The *cis*-1,2-dichloroethene blood:air partition coefficient was reported as 9.58 and the *trans*-1,2-dichloroethene blood:air partition coefficient as 6.04. Gargas et al. (1988, 1989) also determined liquid:air and tissue:air partition coefficients for both isomers using 0.9% saline, olive oil, rat blood, rat liver, rat muscle and rat fat tissue. The reported partition coefficients for *cis*-1,2-dichloroethene are: rat blood:air = 21.6; saline:air = 3.25; olive oil:air = 278; fat:air = 227, liver:air = 15.3, and muscle:air = 6.09. Partition coefficients for *trans*-1,2-dichloroethene were reported as follows: rat blood:air = 9.58; saline:air = 1.41; olive oil:air = 178; fat:air = 148, liver:air = 8.96, and muscle:air = 3.52. The higher blood:air partition coefficient of the cis- isomer compared with the trans- isomer is likely a major factor in the more rapid and more extensive uptake of the cis- isomer into the systemic circulation and in the greater narcotic potency of the cis- isomer.

No data were located concerning the distribution of *cis*- or *trans*-1,2-dichloroethene by any route in any species.

1,2-Dichloroethene is metabolized by the hepatic mixed function oxidase system; it binds to the active site of the cytochrome P450 isoform, CYP2E1, resulting in inhibition of its own metabolism (Costa and Ivanetich 1982; Barton et al. 1995; Hanioka et al. 1998; Lilly et al. 1998). Both the cis- and trans- isomer are metabolized by CYP2E1 to an epoxide intermediate that covalently binds to proteins, forming *S*-methylcysteine amino acid adducts (NTP 2002). The epoxide intermediate is then transformed to 2,2-dichloroacetaldehyde by spontaneous rearrangement, which is then converted to 2,2-dichloroethanol and 2,2-dichloroacetate by cytolsolic and/or mitochondrial aldehyde and alcohol dehydrogenases (Costa and Ivanetich 1982; ATSDR 1996). The aldehyde formed from the cis- isomer yields primarily dichloroethanol with small concentrations of dichloroacetate, while the trans- isomer yields primarily dichloroacetate with only small amounts of dichloroethanol.

cis-1,2-Dichloroethene has a 4-fold greater rate of turnover in hepatic microsomes when compared to the trans- isomer. The elimination of 1,2 dichloroethene follows zero-order kinetics above the metabolic saturation point and first-order kinetics below the saturation point. The cis- isomer has been shown to have a higher rate of first-order clearance than the trans- isomer (ATSDR 1996).

Inhalation pharmacokinetics were studied in male Wistar rats exposed to *cis*- or *trans*-1,2-dichloroethene using a closed inhalation chamber and analyzed with a nonphysiologically constrained, two-compartment model (Filser and Bolt 1979). The zero-order V_{max} elimination rate for the cis- isomer was 0.67 mg/h·kg, and the value for the trans- isomer was 2.4 mg/h·kg. The authors suggested that the low maximal velocities were due to inactivation of CYP450 by reactive epoxy intermediates. Gargas et al. (1990) conducted a study to compensate for enzyme inhibition-resynthesis, and determined V_{max} values of 3 mg/h·kg for the cis- isomer and 2.49 mg/h·kg for the trans- isomer.

4.2. Mechanism of Toxicity

1,2-Dichloroethene metabolites modify the heme moiety of cytochrome P-450, resulting in loss of both cytochrome P-450 and heme. The modification may account for the in vivo and in vitro inhibition of metabolism of other cytochrome P-450 substrates by 1,2-dichloroethene. A suicide enzyme inhibition-resynthesis model has been used to describe the metabolism of 1,2-dichloroethene, meaning that the cytochrome P-450 may inactivate itself and enhance the toxicity of other xenobiotics detoxified by the mixed function oxidase system (Gargas et al. 1990). The CYP2E1-catalyzed oxidation of 1,2-dichloroethene to an epoxide, 2,2-dichloroacetaldehyde, and 2,2-dichloroethanol represents metabolic activation. Each of these metabolites is cytotoxic, and collectively, they may be responsible for the hepatic centrilobular fatty degeneration observed in animal studies after 1,2-dichloroethene administration (Lehmann and Schmidt-Kehl 1936; Kelly 1999). The more rapid and extensive metabolism of the cis- isomer and the more extensive production of dichloroethanol and its unstable predecessors from the cis- isomer are consistent with this isomer's greater ability to affect the liver (Kelly 1999).

At high concentrations, 1,2-dichloroethene possesses anesthetic properties similar to other chlorinated ethenes. Eger et al. (2001) identified a MAC (minimum alveolar concentration) of 0.0183% ± 0.0031% for *trans*-1,2-dichloroethene and a MAC of 0.0071% ± 0.0006% for *cis*-1,2-dichloroethene for induction of anesthesia in rats. These data suggest that the cis- isomer is approximately 2.5-times more potent than the trans- isomer with regard to anesthesia induction. Data presented in this document suggest that the cis- isomer is approximately twice as effective as the trans- isomer in producing narcosis and with regard to lethality. Kelly (1999) reported 4-h LC_{50} rat values of 24,100 ppm and 13,700 ppm for *trans*- and *cis*-1,2-dichloroethene, respectively. Rats exposed to *trans*-1,2-dichloroethene at 12,300 ppm recovered from a lack of

stimulus response in approximately 30 min, whereas, rats exposed to the cis-isomer at 12,100 ppm took approximately 1 h to recover from similar effects (Kelly 1999). In general, it took animals exposed to the trans- isomer 2 to 3 times longer to lose equilibrium than when exposed to the same concentration of the cis- isomer. For example, data in Tables 3-10 and 3-11 indicate that mice exposed to 50,000 mg/m^3 of the cis- isomer lost equilibrium in 5 min, whereas it took 15 min for mice exposed to the trans- isomer to lose equilibrium. Similarly, cats exposed to of the cis- isomer at 53,000 mg/m^3 lost equilibrium in 8 min, whereas it took 18-21 min for cats exposed to the trans- isomer at 52,000 mg/m^3 to lose equilibrium (data from Tables 3-7 through 3-9).

4.3. Other Relevant Information

4.3.1. Species Variability

Interspecies Variability

trans-1,2-Dichloroethene inhalation lethality data suggest little species variability between rats and mice. Gradiski et al. (1978) reported a 6-h LC_{50} of 21,723 ppm for mice. (However, no experimental details were available for this study.). (Kelly 1999) reported a 4-h LC_{50} of 24,100 ppm for rats.

McCarty et al. (1991) have shown that for acute exposures the critical brain concentration of halocarbons required to produce a given level of narcosis is relatively constant across species.

Intraspecies Variability

de Jong and Eger (1975) compared the MAC (minimum alveolar concentration) of nine anesthetics required to induce adequate anesthesia in 50% (AD_{50}) or 95% (AD_{95}) of patients. The ratios of AD_{95}:AD_{50} ranged from 1.1 to 1.4, suggesting a steep concentration-response curve in the vapor concentration required to produce anesthesia.

Gregory et al.(1969) examined the MAC (minimum alveolar concentration) of halothane required to induce anesthesia in 8 age groups (0-0.5 years, 0.5-2.5 years, 2.5-6 years, 7-11 years, 12-18 years, 19-30 years, 31-55 years, and 70-96 years). The number of patients per age group ranged from 8 to 24. The MAC was found to be the highest in newborns (1.08%) and lowest in the elderly (0.64%). These data suggested relatively little intraspecies variability with regard to age.

Stevens et al. (1975) also found little variability with regard to age when comparing MAC of isoflurane required for anesthesia. The MAC were 1.28% ± 0.01 for age range 19-30 years, 1.15% ± 0.06 for age range 32-55 years, and 1.05%±0.05 for age over 55 years.

4.3.2. Physical and Chemical Properties

1,2-Dichloroethene is highly flammable and will produce toxic fumes of hydrogen chloride when burning. It also forms explosive hazards when combined with metals and alloys and will detonate by heat, impact, or friction when mixed with nitric acid (ATSDR 1996).

4.3.3. Concurrent Exposure Issues

No information was located concerning exposure to 1,2-dichloroethene in conjunction with other chemicals that might be found concurrently in the workplace or environment. However, as previously described, 1,2-dichloroethene is metabolized by and may inhibit cytochrome P-450. Thus, 1,2-dichloroethene may potentiate the toxicity of compounds that are normally detoxified through cytochrome P-450 dependent metabolism and may antagonize the toxicity of compounds that are activated by cytochrome P-450. Ethanol in alcoholic beverages induces CYP2E1, and isozyme involved in the metabolic activation of 1,2-dichloroethene and other halocarbons, and thus may enhance the metabolic activation and increase liver toxicity of chlorinated hydrocarbons, including 1,2-dichloroethene. Also, as previously described in section 3.2.2, Freundt and Macholz (1978) observed prolonged hexobarbital sleeping time and zoxazolamine paralysis time in rats treated with 1,2-dichloroethene, suggesting that 1,2-dichloroethene may inhibit P-450 catalyzed detoxification of other chemicals.

4.4. Temporal Extrapolation

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$. In the absence of chemical specific data, an n of 3 will be applied to extrapolate to shorter time periods, and an n of 1 will be applied to extrapolate to longer time periods, to provide AEGL values that would be protective of human health (NRC 2001).

Although use of an exponent ‘n’ of 1 for extrapolating from shorter-term to longer-term time points may often overestimate risks for volatile organic compounds (VOCs) (Bruckner et al. 2004), this approach is considered appropriate for 1,2-dichloroethylene. For most well-metabolized VOCs, such as trichloroethylene, blood concentrations rapidly attain near steady-state during inhalation exposures. As a consequence, adverse effects typically increase only modestly with time for the longer exposure periods (once steady-state is reached). However, *cis*- and *trans*-1,2-dichloroethylene are distinctive in that they are suicide inhibitors (the trans- isomer is a more potent suicide inhibitor

than the cis- isomer) (Lilly et al. 1998). As a result, blood and brain concentrations of 1,2-dichloroethylene should continue to increase during prolonged exposures, rather than reaching near steady-state. The parent compounds are responsible for producing the CNS depression.

Furthermore, although Barton et al. (1995) published a model that was used to predict interactions between *trans*-1,2-dichloroethylene and other halocarbons, it has not been validated for humans; and thus was not used for time scaling of this chemical.

5. RATIONALE AND AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data indicate that *trans*-1,2-dichloroethene at a concentration of 275 ppm for 5 min had no effect, a concentration of 825 ppm caused slight dizziness after 5 min, and slight eye irritation was observed at a concentration of 950 ppm for 5 min (Lehmann and Schmidt-Kehl 1936). The odor threshold is 17 ppm (ATSDR 1996).

5.2. Animal Data Relevant to AEGL-1

Signs of dose-related ocular irritation were observed in pregnant rats exposed to *trans*-1,2-dichloroethene at 2,000, 6,000, and 12,000 ppm for 6 h/day during days 7-16 of gestation (Hurtt et al. 1993). The irritation was observed immediately following exposures. At 2,000 ppm the ocular irritation was considered minor and thus consistent with the definition of AEGL-1, because 13 of 24 animals exhibited clear-eye discharge, but only 3 of 24 animals exhibited periocular wetness. If significant discharge were occurring, a greater number of animals would be expected to exhibit periocular wetness.

5.3. Derivation of AEGL-1

Since human data are available, they will be used to derive AEGL-1 values. The NOEL for eye irritation of 825 ppm was used as the point of departure (Lehmann and Schmidt-Kehl 1936). This value was divided by an uncertainty factor of 3 to protect sensitive individuals and is considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Using the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm). The values were held constant across the 10- and 30-min, 1-, 4-, and 8-h exposure time points since mild irritantancy is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect. The animal data previously described

in this report (Section 4.2) suggest that the cis- isomer is approximately twice as toxic as the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. Although the AEGL-1 point-of-departure is a NOEL for eye irritation, the use of the modifying factor is justified for the cis- isomer because slight dizziness, a possible mild narcotic effect, was noted at the concentration used as starting point for the derivation of the AEGL-1.

The values for AEGL-1 are given in Table 3-13 (trans- isomer) and Table 3-14 (cis- isomer).

6. RATIONALE AND AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data indicate that a concentration of 1,000 ppm *trans*-1,2-dichloroethene caused dizziness in two subjects after 10 min (Lehmann and Schmidt-Kehl 1936). Higher concentrations caused greater dizziness, drowsiness, burning of the eyes, intracranial pressure, and nausea.

6.2. Animal Data Relevant to AEGL-2

Narcosis was observed in pregnant rats exposed to *trans*-1,2-dichloroethene at 6,000 and 12,000 ppm for 6 h/day during days 7-16 of gestation (Hurtt et al. 1993). Cats exposed to *trans*-1,2-dichloroethene at 43,000 mg/m^3 (10,750 ppm) exhibited effects on equilibrium after 57 min and lethargy after 325 min of exposure, while cats exposed to *cis*-1,2-dichloroethene at 20,000 mg/m^3 (5,000 ppm) exhibited head and leg spasms after 120 min (Lehmann and Schmidt-Kehl 1936). Mice exposed to *trans*-1,2-dichloroethene at 45,000 mg/m^3 (11,250 ppm) exhibited effects on equilibrium after 19 min, lethargy after 115 min, and loss of reflex after 155 min of exposure, while mice exposed to *cis*-1,2-dichloroethene at 27,000 mg/m^3 (6,750 ppm) exhibited effects on equilibrium after 13 min, lethargy after 91 min, and loss of reflex after 82 min of exposure (Lehmann and Schmidt-Kehl 1936). The total exposure times of mice for the trans- and cis- isomers were 155 and 150 min, respectively. The trans-exposed mice recovered 5-10 min after the end of the exposure period, and the cis-exposed mice recovered within 3-19 min after exposure.

TABLE 3-13 AEGL-1 for *trans*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)

TABLE 3-14 AEGL-1 for *cis*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)

6.3. Derivation of AEGL-2

The narcosis observed in the well-conducted study of pregnant rats exposed to the trans- isomer at 6,000 ppm was used to derive AEGL-2 values for the 4- and 8-h time points. Uncertainty factors of 3 each (total UF = 10) were applied for both inter- and intraspecies differences. The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; de Jong and Eger 1975; Stevens et al. 1975). This total uncertainty factor of 10 was applied to AEGL-2 values for both the cis- and trans- isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The 10-, 30-, and 60-min values extrapolated with n=3 would be 1,400 ppm for 10- and 30-min and 1,100 ppm for 1-h. However, these values are within the range of exposure times and concentrations in which healthy adult humans responded with symptoms reaching a level of severe dizziness (Lehmann and Schmidt-Kehl 1936). Dizziness was seen in humans after exposure at 1,000 ppm for 10 min, and the exposure lasted for 30 min. Therefore, the 10-min, 30-min, and 1-h values were set as maximum exposure values of 1,000 ppm for anesthetic effects in humans.

The animal data previously described in this report (section 4.2) suggest that the cis- isomer is approximately twice as toxic than the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only.

The values for AEGL-2 are given in Table 3-15 (trans- isomer) and Table 3-16 (cis- isomer).

TABLE 3-15 AEGL-2 for *trans*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	1,000 (3,960)	1,000 (3,960)	1,000 (3,960)	690 (2,724)	450 (1,782)

TABLE 3-16 AEGL-2 for *cis*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	500 (1980)	500 (1,980)	500 (1,980)	340 (1,346)	230 (911)

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

Although there has been a report of a human fatality associated with accidental exposure to 1,2-dichloroethene, the exposure concentration and duration are not known (Hamilton 1934). Dizziness, intracranial pressure, and nausea were observed in two human subjects exposed to 1,700 ppm *trans*-1,2-dichloroethene for 5 min (Lehmann and Schmidt-Kehl 1936).

7.2. Animal Data Relevant to AEGL-3

Four-hour rat LC_{50} values of 24,100 ppm and 13,700 ppm were reported for *trans*- and *cis*-1,2-dichloroethene, respectively (Kelly 1999). In the same study, no deaths were reported for 4-h exposures at 12,300 ppm for the trans-isomer and at 12,100 ppm for the cis- isomer (Kelly 1999). No histopathologic changes were noted in the liver, heart, kidney, or lungs in any of the rats in the Kelly (1999) study. Exposure of cats to *cis*-1,2-dichloroethene at concentrations ranging from 5,000 to 28,500 ppm for 9 to 360 min resulted in death at various times after exposure (Lehmann and Schmidt-Kehl 1936). Varying degrees of equilibrium effects, lethargy, light narcosis, and/or deep narcosis were observed in cats prior to death. Decreases in combined and mean female fetal weight were observed in pregnant rats exposed to *trans*-1,2-dichloroethene at 12,000 ppm for 6 h/day on days 7-16 of gestation. In another study, female Wistar rats exhibited severe fatty degeneration of hepatic lobules and kupffer cells, pulmonary capillary hyperemia, alveolar septum distention, pneumonic infiltration, and fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation after exposure to *trans*-1,2-dichloroethene at 3,000 ppm for 8 h (Freundt et al. 1977). However, these pathology data are contradicted by a recent study showing no treatment-related effects in rats exposed to *trans*-1,2-dichloroethene at up to 4,000 ppm for 6 h/day, 5 days/week for 90 days (Kelly 1998).

7.3. Derivation of AEGL-3

The concentration (12,300 ppm) causing no death in rats exposed to *trans*-1,2-dichloroethene for 4 h was used as the basis of AEGL-3 for the 4- and 8-h time points. An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard

to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). An intraspecies UF of 3 was also applied and is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; de Jong and Eger 1975; Stevens et al. 1975). The total uncertainty factor of 10 was applied for AEGL-3 values for both the cis- and trans- isomers. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The 10-, 30-, and 60-min values extrapolated with n = 3 are 3,500, 2,500, and 2,000 ppm respectively. However, these values are within the range of exposure times and concentrations in which healthy humans responded with severe dizziness. Dizziness, intracranial pressure, and nausea were observed at 1,700 ppm. Therefore, the 10-, 30-, and 60-min values were set at 1,700 ppm because healthy adult humans exposed for 5 min to 1,700 ppm experienced dizziness, intracranial pressure (unspecified) and nausea which persisted for ½ hour after exposure (Lehmann and Schmidt-Kehl 1936). Similar effects were seen with exposures of humans to 2,200 ppm for 5 min which resulted in severe dizziness, intracranial pressure (unspecified) and nausea which persisted for ½ hour after exposure. The animal data previously described in this report (Section 4.2) suggest that the cis- isomer is approximately twice as toxic than the trans- isomer with regard to narcosis and lethality in experimental animals. Therefore, a modifying factor of 2 was applied in the derivation of the cis- isomer values only. (Although the concentration causing no death observed in the cis- isomer rat experiment could be used to derive AEGL-3 values for this isomer, the approach of dividing the trans- values by 2 was chosen to be consistent with the AEGL-1 and AEGL-2 derivations.).

The values for AEGL-3 are given in Table 3-17 (trans- isomer) and Table 3-18 (cis- isomer).

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 3-19 (trans- isomer) and Table 3-20 (cis- isomer). AEGL-1 values were based on a NOEL for ocular irritation in humans. AEGL-2 values were based on narcosis in rats (4- and 8-h) or anesthetic effects

in humans (10-, 30-, and 60-min). AEGL-3 values were based on a no-effect-level for death in rats (4- and 8-h) or dizziness, intracranial pressure, and nausea in humans (10-, 30-, and 60-min).

8.2. Other Exposure Criteria

Other standard and guidance levels are listed in Table 3-21.

TABLE 3-17 AEGL-3 for *trans*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	1,700 (6,732)	1,700 (6,732)	1,700 (6,732)	1,200 (4,752)	620 (2,455)

TABLE 3-18 AEGL-3 for *cis*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	850 (3,366)	850 (3,366)	850 (3,366)	620 (2,455)	310 (1,228)

TABLE 3-19 Relational Comparison of AEGL Values for *trans*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)
AEGL-2 (Disabling)	1,000 (3,960)	1,000 (3,960)	1,000 (3,960)	690 (2,724)	450 (1,782)
AEGL-3 (Lethality)	1,700 (6,732)	1,700 (6,732)	1,700 (6,732)	1,200 (4,752)	620 (2,455)

TABLE 3-20 Relational Comparison of AEGL Values for *cis*-1,2-Dichloroethene [ppm (mg/m^3)]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)
AEGL-2 (Disabling)	500 (1,980)	500 (1,980)	500 (1,980)	340 (1,346)	230 (911)
AEGL-3 (Lethality)	850 (3,366)	850 (3,366)	850 (3,366)	620 (2,455)	310 (1,228)

TABLE 3-21 Extant Standards and Guidelines for 1,2-Dichloroethene

Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
	Trans- isomer				
AEGL-1	280 ppm	2,80 ppm	280 ppm	280 ppm	280 ppm
AEGL-2	1,000 ppm	1,000 ppm	1,000 ppm	690 ppm	450 ppm
AEGL-3	1,700 ppm	1,700 ppm	1,700 ppm	1,200 ppm	620 ppm
	cis- isomer				
AEGL-1	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm
AEGL-2	500 ppm	500 ppm	500 ppm	340 ppm	230 ppm
AEGL-3	850 ppm	850 ppm	850 ppm	620 ppm	310 ppm
IDLH (NIOSH)[a]	1,000 ppm				
REL-TWA (NIOSH)[b]					2,00 ppm
PEL-TWA (OSHA)[c]					2,00 ppm
TLV-TWA(ACGIH)[d]					2,00 ppm
MAK (Germany)[e]					2,00 ppm
MAC (The Netherlands)[f]					2,00 ppm

[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. The IDLH for 1,2-dichloroethene is based on acute inhalation toxicity data in humans.

[b]REL-TWA (recommended exposure limits–time weighted average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA.

[c]PEL-TWA (permissible exposure limits–time-weighted average, Occupational Health and Safety Administration) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/wk.

[d]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists,) (ACGIH 2003) 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.

[e]MAK (maximale rbeitsplatzkonzentration [maximum workplace concentration], German Research Association) (DFG 2002) 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

Data from human studies are sparse. Exposure times are short-term, ranging from only 5 to 30 min. Furthermore, the only quantitative human data are from 1936, and although the study appears to be thorough and well described, it

is likely that analytical measurements were not as precise as those used today. Data from animal studies are more abundant and encompass a wider range of exposure periods. More recent animal studies include greater numbers of experimental animals and almost certainly improved methodology.

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APPENDIX A

Time-Scaling Calculations for 1,2-Dichloroethene

Derivation of AEGL-1

Key study:	Lehmann and Schmidt-Kehl 1936
Toxicity end point:	825 ppm, 5 min: NOEL for ocular irritation in humans
Scaling:	None: values were held constant across time points
Uncertainty factors:	3 for intraspecies variability (*trans*- and *cis*-1,2-dichloroethene)
Modifying factor:	2 for differential isomer toxicity (*cis*-1,2-dichloroethene only)

10-, and 30-min and 1-, 4-, and 8-h AEGL-1

825 ppm ÷ 3 = 275 ppm
trans-1,2-dichloroethene AEGL-1 = 280 ppm
cis-1,2-dichloroethene AEGL-1 = 280 ppm ÷ 2 = 140 ppm

Derivation of AEGL-2

Key Studies:	Lehmann and Schmidt-Kehl 1936 (10-, 30-, and 60-min) Hurtt et al. 1993 (4- and 8-h)
Toxicity end points:	Anesthetic effects in humans (10-, 30-, and 60-min) Narcosis in rats (4- and 8-h)
Scaling	Maximum exposure level at 10-, 30-, and 60-min $(6{,}000\ \text{ppm})^3 \times 6\ \text{h} = 1.3 \times 10^{12}\ \text{ppm}^3\cdot\text{h}$ (4-h) $(6{,}000\ \text{ppm})^1 \times 6\ \text{h} = 36{,}000\ \text{ppm}\cdot\text{h}$ (8-h)
Uncertainty factors:	3 for intraspecies variability (*trans*- and *cis*- 1,2 dichloroethene; 4- and 8-h) 3 for interspecies variability (*trans*- and *cis*- 1,2-dichloroethene; 4- and 8-h)
Modifying factor:	2 for differential isomer toxicity (*cis*-1,2-dichloroethene only)

10- and 30-min and 1-h AEGL-2

trans-1,2-dichloroethene AEGL-2 = 1,000 ppm
cis-1,2-dichloroethene AEGL-1 = 1,000 ppm ÷ 2 = 500 ppm

4-h AEGL-2	$C^3 \times 4\ \text{h} = 1.3 \times 10^{12}\ \text{ppm}^3\cdot\text{h}$ $C^3 = 3.25 \times 10^{11}\ \text{ppm}$ C = 6,875 ppm 4 h *trans*-1,2-dichloroethene AEGL-2= 6,868 ppm/10 = 690 ppm 4 h *cis*-1,2-dichloroethene AEGL-2 = 6,868 ppm/20 = 340 ppm
8-h AEGL-2	$C^1 \times 8\ \text{h} = 36{,}000\ \text{ppm}\cdot\text{h}$ $C^1 = 4{,}500\ \text{ppm}$

C = 4,500 ppm
8 h *trans*-1,2-dichloroethene AEGL-2 = 4,500 ppm/10 = 450 ppm
8 h *cis*-1,2- dichloroethene AEGL-2 = 4,500 ppm/20 = 230 ppm

Derivation of AEGL-3

Key Studies:	Lehmann and Schmidt-Kehl 1936 (10-, 30-, and 60-min) Kelly 1999 (4- and 8-h)
Toxicity end point:	Nausea, intracranial pressure, dizziness in humans (10-, 30-, and 60-min) No-effect-level for death in rats (4- and 8-h)
Scaling	Maximum exposure level at 10-, 30-, and 60-min $(12{,}300\ ppm)^3 \times 4\ h = 7.44 \times 10^{12}\ ppm^n h$ (4-h) $(12{,}300\ ppm)^1 \times 4\ h = 49{,}200\ ppm^n h$ (8-h)
Uncertainty factors:	3 for intraspecies variability (*trans*- and *cis*- 1,2- dichloroethene; 4- and 8-h) 3 for interspecies variability (*trans*- and *cis*- 1,2-dichloroethene; 4- and 8-h)
Modifying factor:	2- for differential isomer toxicity (*cis*-1,2-dichloroethene only)

10, and 30-min and 1-h AEGL-3

trans-1,2-dichloroethene AEGL-3 = 1,700 ppm
cis-1,2-dichloroethene AEGL-3 = 1,700 ÷ 2 = 850 ppm

4 h AEGL-3

$C^3 \times 4\ h = 7.44 \times 10^{12}$ ppm-h
$C^3 = 1.86 \times 10^{12}$ ppm
C = 12,298 ppm
4 h *trans*-1,2-dichloroethene AEGL-3= 12,298 ppm/10 = 1,200 ppm
4 h *cis*-1,2-dichloroethene AEGL-3 = 12,298 ppm/20 = 620 ppm

8 h AEGL-3

$C^1 \times 8\ h = 49{,}200$ ppm-h
$C^1 = 6{,}150$ ppm
C = 6,150 ppm
8 h *trans*-1,2-dichloroethene AEGL-3 = 6,150 ppm/10 = 620 ppm
8 h *cis*-1,2-dichloroethene AEGL-3 = 6,150 ppm/20 = 310 ppm

APPENDIX B

Derivation Summary of AEGL Values for 1,2-Dichloroethene (trans- and cis- isomers)

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
280 ppm	280 ppm	280 ppm	280 ppm	280 ppm

Key Reference: Lehmann, K.B., and L. Schmidt-Kehl. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene [in German]. Arch. Hyg. 116:131-268.

Test Species/Strain/Number: Human subjects/2

Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min

Effects: 275 ppm: No effects (5 min Total exposure)
825 ppm: Slight dizziness after 5 min (10 min exposure); determinant for AEGL-1
950 ppm: Slight burning of eyes (5 min)
1,000 ppm: Dizziness after 10 min; slight burning of eyes (30 min exposure)
1,200 ppm: Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
1,700 ppm: Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea (5 min exposure)
2,200 ppm: Severe dizziness; intracranial pressure; nausea (5 min exposure)

End Point/Concentration/Rationale: 825 ppm for 5 min; no effect level for eye irritation; odor present.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable, human data used.
Intraspecies: 3 - Considered sufficient because using the default value of 10 for intraspecies variability would generate AEGL-1 values which are not supported by the total data set. (Utilizing the full uncertainty factor of 10, yields an AEGL-1 value of 83 ppm; no effects were noted in humans exposed to 275 ppm).

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable; human data used

Time Scaling: Values were held constant across time since minor irritation is a threshold effect and is not likely to increase over time.

Data Quality and Research Needs: Although the values developed are considered to be protective, data are sparse due to the exposure of only two subjects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1,000 ppm	1,000 ppm	1,000 ppm	690 ppm	450 ppm

Key Reference: Lehmann, K.B., and L. Schmidt-Kehl. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene [in German]. Arch. Hyg. 116:131-268. (10-, and 30-min and 1-h)	Key Reference: Hurtt, M.E., R. Valentine, and L. Alvarez. 1993. Developmental toxicity of inhaled *trans*-1,2-dichloroethylene in the rat. Fundam. Appl. Toxicol. 20(2):225-230. (4- and 8-h)
Test Species/Strain/Number: Human subjects/2	Test Species/Strain/Number: rat/Crl:CD BR pregnant females/24/group
Exposure Route/Concentrations/ Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 min	Exposure Route/Concentrations/ Durations: 0, 2000, 6000, or 12,000 ppm, 6 h/d, d 7-16 of gestation
Effects: 275 ppm No effects (5 min) 825 ppm Slight dizziness after 5 min 950 ppm Slight burning of eyes (5 min) 1,000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure) 1,200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure) 1,700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea 2,200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)	Effects: 2,000 ppm Clear ocular discharge (after single 6-h exposure) 6,000 ppm Narcosis, ocular irritation (after single 6-h exposure) 1,200 ppm Ocular irritation, narcosis, lethargy, decreased body weight gain
End Point/Concentration/Rationale: 1,000 ppm for 10 min; threshold for anesthetic effects	End point/Concentration/Rationale: 6,000 ppm, 6 h/narcosis
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable - human data used. Intraspecies:1 -threshold for anesthetic effect	Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 Intraspecies: 3 The interspecies UF of 3 is considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). The intraspecies UF of 3 is considered

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1,000 ppm	1,000 ppm	1,000 ppm	690 ppm	450 ppm
			sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; Stevens et al. 1975; de Jong and Eger 1975)	
Time Scaling: Held constant at threshold for anesthetic effects			Time Scaling: $C^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-h) or 3 (4-h)	
Data Quality and Research Needs: Although recent studies are well conducted, human and animal data are in apparent conflict.				

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1,700 ppm	1,700 ppm	1,700 ppm	1,200 ppm	620 ppm
Key Reference: Lehmann, K.B., and L. Schmidt-Kehl. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene [in German]. Arch. Hyg. 116:131-268. (10-, and 30- min and 1-h)			Key Reference: Kelly, D.P. 1999. *trans*-1,2-dichloroethylene and *cis*-1,2-dichloroethylene: Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Laboratory Project ID: DuPont-2806. (4- and 8-h)	
Test Species/Strain/Number: Human subjects/2			Test Species/Strain/Number: Rat/Crl:CD (SD)/5/sex/group	
Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1,000, 1,200, 1,700, or 2,200 ppm for 5-30 min			Exposure Route/Concentrations/Durations: Inhalation/ 0, 12,300, 22,500, 28,100, or 34,100 ppm/4 h	
Effects: 275 ppm No effects (5 min) 825 ppm Slight dizziness after 5 min 950 ppm Slight burning of eyes (5 min) 1,000 ppm Dizziness after 10 min; slight burning of eyes (30 min exposure) 1,200 ppm Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)			Mortality: 12,300 ppm 0/10 22,500 ppm 4/10 28,100 ppm 7/10 34,100 ppm 10/10	

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1,700 ppm	1,700 ppm	1,700 ppm	1,200 ppm	620 ppm
1,700 ppm Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea 2,200 ppm Severe dizziness; intracranial pressure; nausea (5 min exposure)				
End Point/Concentration/Rationale: 1,700 ppm for 3 min; dizziness, intracranial pressure, nausea			End Point/Concentration/Rationale: 12,300 ppm, 4 h/NOEL for death	
Uncertainty Factors/Rationale: Total Uncertainty Factor: 1 Interspecies: Not applicable - human data used. Intraspecies 1 - conservative AEGL-3 end point			Uncertainty Factors/Rationale: Total Uncertainty Factor: 10 Interspecies: 3 Intraspecies: 3 An uncertainty factor of 3 was applied for interspecies differences because rat and mouse lethality data indicate little species variability with regard to death. The interspecies UF of 3 is also considered sufficient because data suggest that the critical brain concentration of a halocarbon required to produce a given level of narcosis is relatively constant across species (McCarty et al. 1991). The intraspecies UF of 3 is considered sufficient because data suggest that there is little variability between vapor concentrations of anesthetic required to produce anesthesia and age or sex of the patient (Gregory et al. 1969; Stevens et al. 1975; de Jong and Eger 1975).	
Time Scaling: Held constant across time points; conservative AEGL-3 end point			Time Scaling: $C^n \times t = k$, where the exponent n is the conservative default of 1 (8-h) or 3 (4-h)	
Data Quality and Research Needs: Although recent studies are well conducted, human and animal data are in apparent conflict.				

APPENDIX C

Category Plots for *trans*-1,2-Dichloroethene and *cis*-1,2-Dichloroethene

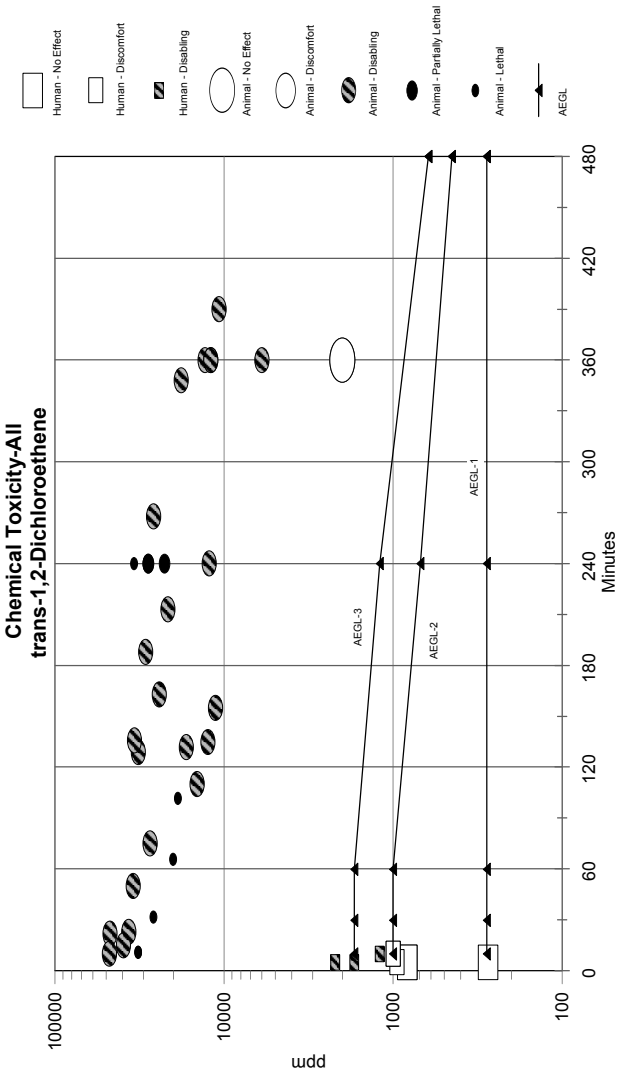

FIGURE C-1 Category plots for *trans*-1,2-dichloroethene.

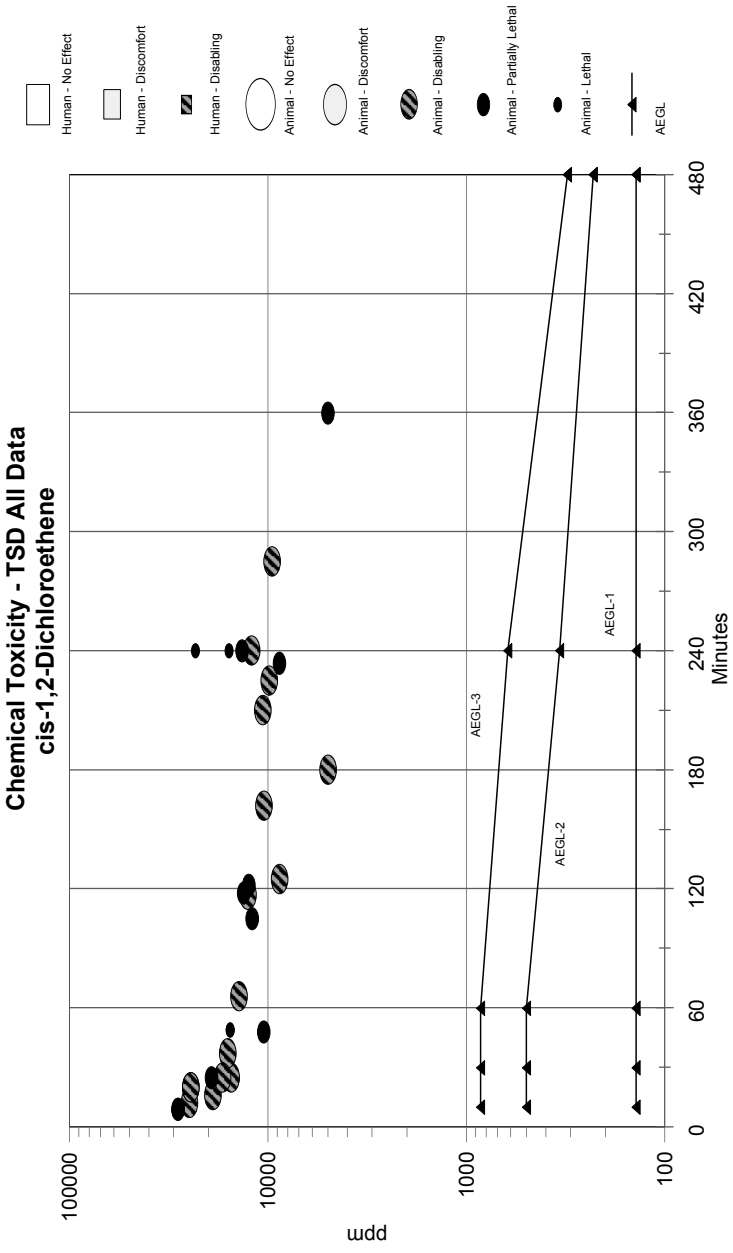

FIGURE C-2 Category plots for *cis*-1,2-dichloroethene.

4

Ethylenimine[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 min (min) to 8 h (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 Manager 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

Ethylenimine is a volatile, clear, colorless, flammable explosive liquid that has an odor similar to that of ammonia and an odor threshold reported as 2 ppm in air; however an odor detection (OD_{50}) was reported as 0.698. It is a very reactive direct-acting alkylating agent, the activity of which is similar to that of nitrogen and sulfur mustards. It is also very caustic, attacking numerous substances including plastics, metals, and glass that does not contain carbonate or borax. Estimates of annual U.S. production of ethylenimine range between 1.65 and 4.85 million pounds prior to 1994. Ethylenimine is used in the manufacture of products such as triethylenemelamine, paper, textile chemicals, adhesive binders, and petroleum refining chemicals. Ethylenimine is stored in 320-pound cylinders, but shipping quantities are unknown.

Relevant data on ethylenimine consisted of only a few case reports in humans and acute inhalation lethality studies in laboratory animals. Toxicity due to exposure to ethylenimine is generally delayed and includes irritation to contact organs (skin, eyes, oral cavity, and upper and lower respiratory tract), systemic toxicity, and death depending upon the concentration. At extremely high concentrations, however, irritation to contact organs may occur during or soon after exposure. The time course of irritation caused by ethylenimine is different from that caused by primary irritants such as ammonia, which causes an immediate response upon exposure regardless of concentration.

One person died after a brief exposure to a high, but unknown concentration of ethylenimine. Soon after exposure he experienced eye irritation, salivation, vomiting, and breathlessness. Pulmonary edema was diagnosed but was not considered the cause of death. Several people exposed to ethylenimine and *N*-ethylethylenimine for 1½ to 2 h suffered severe eye and respiratory tract irritation and vomiting that were delayed 3 to 7½ h after exposure, followed by hemoconcentration (increased in hemoglobin concentration), eosinophilia, and albuminuria. Occupational exposure to ethylenimine has produced skin sensitization, slow-healing dermatitis, rapidly reversible irritation to the eyes and respiratory tract, and blistering, reddening, and edema of the scrotum. Direct contact of liquid ethylenimine with the tongue caused delayed inflammation and edematous swelling in the mouth and inflammation of the eyes, and direct contact of liquid ethylenimine with the skin caused necrotizing painless burns. Ethylenimine is genotoxic in all test systems investigated including bacteria, fungi, plants, insects, and cultured mammalian cells. It is clastogenic in cultured human cells. Repeated subcutaneous injections of rats with ethylenimine produced sarcomas at the injection site, chronic oral administration produced pulmonary and liver tumors in mice, and a single subcutaneous injection of 7-day old mice produced pulmonary tumors.

Acute inhalation LC_{50} values were 2558, 1407, 545, 268, 259, 58, and 35 ppm for rats exposed to ethylenimine for 5, 10, 15, 60, 120, 240, or 480 min, respectively; LC_{50} values were 2906, 2824, 1283, 364, 235, 158, 45, and 27 ppm for guinea pigs exposed for 5, 10, 15, 30, 60, 120, 240, or 480 min, respectively (Carpenter et al. 1948); and the LC_{50} value was 2236 ppm for mice exposed for 10 min. In all studies, the time to death and other signs of toxicity were delayed depending on exposure concentration. Signs of toxicity in these animals included eye irritation, respiratory tract irritation, respiratory difficulty, prostration, complete loss of muscular coordination (mouse only), and convulsions (mouse only). Systemic effects included lung damage, congestion in lungs and all internal organs, damage to the kidney tubules, and albuminuria in rats and guinea pigs.

Data were not available for deriving AEGL-1 values for ethylenimine. The absence of AEGL-1 values does not imply that exposure below the AEGL-2 is without adverse health effects. The level of distinct odor awareness (LOA) for ethylenimine is 10.9 ppm. The LOA represents the concentration above which it is predicted that more than one-half the exposed population will experience at least a distinct odor intensity and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. Ethylenimine may not have distinct AEGL-1 warning properties.

No animal studies designed specifically to examine nonlethal toxicity due to acute inhalation exposure to ethylenimine were located in the search, and the human case report involved exposure to other substances that could have contributed to the observed toxic effects. Although the logical point of departure

(POD) for deriving AEGL-2 values is the no-observed-effect level (NOEL) for extreme respiratory difficulty in guinea pigs exposed to 10 ppm ethylenimine for 480 min (Carpenter et al. 1948), this derivation would lead to AEGL-2 values close to or exceeding the life-threatening AEGL-3 concentrations. Therefore, AEGL-2 values were derived using the next shorter duration of 240 min, which also is a clear NOEL for respiratory difficulty in guinea pigs exposed to 10 ppm. The total uncertainty factor was 10. An uncertainty factor of 3 was applied for interspecies differences, because ethylenimine is a very reactive direct-acting alkylating agent, and the AEGL-2 effects would most likely be confined to the respiratory tract. Respiratory tract damage appears to be due to 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 were the most sensitive targets in rat, guinea pigs, and humans. 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 the alkylating activity is not expected to vary appreciably among individuals in the population. Five male students responded similarly to an exposure to ethylenimine with respect to the time of onset of symptoms and the intensity of effects. Studies have shown that DNA damage is likely the initiating step in a cascade of events leading to cell damage and DNA damage can persist in lungs and systemic organs following inhalation exposure to alkylating agents. This mechanism is unlikely to be different among individuals in the human population or among species. Scaling across the pertinent time frames was based on the equation $C^{0.91} \times t = k$, where n = 0.91 was derived from the LC_{50} data for guinea pigs. The AEGL-2 values do not account for the potential carcinogenicity of ethylenimine, because quantitative data were not available for deriving a unit risk value.

AEGL-3 values were based on an acute inhalation study in rats (Carpenter et al. 1948). The LC_{01} (lethality threshold) of 15 ppm for the 8-h exposure duration was estimated by probit analysis. The 8-h LC_{01} was selected because it had the smallest standard error. A total uncertainty factor of 10 was applied to the LC_{01}. An uncertainty factor of 3 was applied for interspecies differences based on the same rationale as described for AEGL-2 derivation. In addition, the LC_{50} values for three test animal species were within a factor of 2 of each other, and like other effects of ethylenimine, death was delayed in all three species. Similarly, humans experienced a delay in the onset of life-threatening and/or very serious effects after exposure to ethylenimine. An uncertainty factor of 3, instead of the default of 10, was applied for intraspecies variability based on the same rationale described for the AEGL-2 derivation. Scaling across the pertinent time frames was based on the equation $C^{1.1} \times t = k$, where n = 1.1 was derived from LC_{50} data for rats.

AEGL values derived for ethylenimine are presented in Table 4-1.

TABLE 4-1 Summary of AEGL Values for Ethylenimine[a,b] [ppm (mg/m^3)]

Classification	10- min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	Not recommended[c]					
AEGL-2 (Disabling)	33 (59)	9.8 (18)	4.6 (8.2)	1.0 (1.8)	0.47 (0.84)	NOEL for extreme respiratory difficulty (Carpenter et al. 1948)
AEGL-3 (Lethal)	51 (91)	19 (34)	9.9 (18)	2.8 (5.0)	1.5 (2.7)	Threshold for lethality (Carpenter et al. 1948)

[a]AEGL-2 and -3 values do not account for the potential cancer risk associated with exposure to ethylenimine, because quantitative data were not available for deriving a unit risk value.
[b]Effects at these concentrations may be delayed following exposure.
[c]The absence of AEGL-1 values does not imply that exposure below the AEGL-2 is without adverse health effects.

1. INTRODUCTION

Ethylenimine is a volatile, clear, colorless, flammable, and explosive liquid. It readily polymerizes, and it behaves like a secondary amine (Trochimowicz et al. 1994). Ethylenimine is highly caustic, attacking materials such as cork, rubber, many plastics, metals, and glass except those without carbonate or borax (Gresham and West 1975), and it polymerizes explosively on contact with silver, aluminum, or acid (IARC 1999). Ethylenimine has a high vapor pressure; therefore, it readily vaporizes at room temperature. It has a strong ammonia-like odor detectable by humans at 1.5 to 2 ppm (Carpenter et al. 1948, Santodonato 1985). Van Doorn et al. (2002) reported an odor detection (OD_{50}) of 0.698 ppm. Physical and chemical properties of ethylenimine are presented in Table 4-2.

Ethylenimine is a direct-acting monofunctional alkylating agent. The alkylating property is dependent on formation of an ethylenimonium ion, and the free base can be transported across the cell membrane (Ramel 1981). About 91% of ethylenimine is present as the imonium ion at pH 7. The activity of ethylenimine is similar to that of nitrogen and sulfur mustards.

Ethylenimine is used as an intermediate in the production of triethylenemelamine; polymerized ethylenimine is used in paper, textile chemicals, adhesive binders, petroleum refining chemicals, fuels, lubricants, coating resins, varnishes, lacquers, agricultural chemicals, cosmetics, ion-exchange resins, photographic chemicals, colloid flocculants, and surfactants (Trochimowicz et al. 1994). In 1964, 750 metric tons (1.65 million pounds) of ethylenimine were being produced annually in the United States and twice that rate was produced by 1978 (Ham 1981). Santodonato (1985) reported production in the United States as greater than 3.3 million pounds in 1978. World production in 1981 was about 12,500 tons (Ham 1981). In 1994, Trochimowicz et al. noted that there was only one domestic producer of ethylenimine, which had a production capac-

ity of 2.2 million kilograms (4.85 million pounds). Cordova Chemical Co. Muskegon, MI produced ethylenimine in the early 1980s, and announced that they would no longer permit shipping of the material off site as of January 1983 (Santodonato 1985), and are no longer producing the chemical (personal communication, March 25, 1997). Current producer(s) of ethylenimine are unknown, and no current information on shipping quantities was found in the literature. According to a NIOSH report, ethylenimine is stored in 320-pound cylinders (Ruhe 1982).

The database on inhalation exposure to ethylenimine is limited to only a few human case reports and acute inhalation studies in animals.

TABLE 4-2 Physical and Chemical Data for Ethylenimine

Parameter	Data	Reference
Chemical Name	Ethylenimine	
Synonyms	Ethyleneimine, aziridine, dimethylenimine, azacyclopropane, azirane, ENT-50324	RTECS 2008
CAS Reg. No.	151-56-4	RTECS 2008
Chemical Formula	C_2H_5N	RTECS 2008
Molecular Weight	43.08	RTECS 2008
Physical State	Clear, colorless liquid mobile, colorless, very volatile fluid	Lewis 1993 Trochimowicz et al. 1994
Odor	Ammonia-like	Carpenter et al. 1948
Melting Point	-73.96°C -71°C	O'Neil et al. 2001 Verschueren 1996
Boiling Point	56 to 57°C at 760 mm Hg 55 to 56°C	O'Neil et al. 2001 Verschueren 1996
Freezing Point	-78°C	Lewis 1993
Flash Point	-11.1°C	Lewis 1993
Density	0.8321 (24°C /4°C)	O'Neil et al. 2001
Solubility	Completely miscible in water Soluble in alcohol	Verschueren 1996 O'Neil et al. 2001
Vapor Pressure	13.3 kPa (100 mm Hg) at 9.7°C 160 mm Hg at 20 °C 250 mm Hg at 30°C	Ham 1981 O'Neil et al. 2001 Verschueren 1996
Vapor density	1.5	Verschueren 1996
Autoignition Temperature	322°C	Lewis 1993
Flammability Limits in air	3.6 to 46%	Lewis 1993
Explosive limit	3.6% (lower) to 4.6% (upper)	Trochimowicz et al. 1994
Saturated conc. in air	375 g/m^3 at 2°C 567 g/m^3 at 30°C	Verschueren 1996
Alkalinity	Strongly alkaline	O'Neil et al. 2001
Conversion	1 mg/m^3 = 0.56 ppm; 1 ppm = 1.79 mg/m^3	Verschueren 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Gresham and West (1975) described an accident in which a 57-year-old man was exposed to ethylenimine vapor for "probably not more than five minutes" while dispensing the chemical into small containers. He showed signs of eye, nasal, and laryngeal irritation along with salivation, vomiting, and acute breathlessness. Clinical examination revealed that he had pulmonary edema. He required assisted respiration for several weeks and was dismissed from the hospital 5 weeks after admission. Three weeks later, he was readmitted to the hospital as his condition suddenly deteriorated as he developed shortness of breath, a wheezy cough, bronchospasm, tracheal ulcerations, and stenosis. He died 2 weeks later (10 weeks after exposure). The autopsy showed collapsed and flabby trachea and bronchi and pulmonary edema. Histopathologic examination showed destruction of the cartilaginous structure of the tracheobronchial tree, i.e. the mucosa was replaced by granulation or occasionally fibrous tissue. Granulomatous polyps were found in the smaller bronchi along with emphysema and bronchopneumonia. There was some debate whether tracheal destruction was a direct effect of inhaling ethylenimine or if it was caused by the extensive delay in granulation resulting from the aggressive steroid therapy in the early stages of treatment. The authors concluded that the tracheal damage was likely due to delayed granulation of the trachea caused by steroid therapy; consequently, there was doubt that his death resulted from inhaling ethylenimine. The concentration of ethylenimine to which this worker was exposed was not known, but the severity of the initial symptoms suggested that exposure was intense.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

Carpenter et al. (1948) reported that 2 ppm was the lowest concentration at which eight subjects detected the odor of ethylenimine upon entering a room. The odor of ethylenimine is described as being similar to that of ammonia; therefore, the odor does not serve as a specific warning for the presence of ethylenimine in the air (Carpenter et al. 1948).

The level of distinct odor awareness (LOA) for ethylenimine calculated based on an odor threshold (OT_{50}) of 0.698 ppm and using the guidance provided by van Doorn et al. (2002) is 10.9 ppm. The LOA calculation is presented in Appendix C.

2.2.2. Experimental Studies, Case Reports, and Anecdotal Data

Carpenter et al. (1948) reported that eye and nose irritation does not occur in humans exposed to concentrations of ethylenimine vapor less than 100 ppm,

and that the onset of irritation is not "prompt" at this concentration. [This type of irritation appears to be different from that caused by a primary sensory irritant, which usually occurs immediately upon exposure.] No additional information was provided in this report to support the authors'conclusion. These are the only data reported by Carpenter et al. (1948), and no additional inferences or conclusions can be drawn from these data.

Exposure to ethylenimine was associated with skin sensitization in two laboratory workers. Severe slow-healing dermatitis of the hand in one worker engaged in production of ethylenimine and conjunctivitis, nasal irritation, and throat irritation that persisted for about 1 day in two or three workers was reported by Carpenter et al. (1948). No additional information was provided in this report.

In an attempt to force five male college students from a room, they were exposed successively to ammonia, isopentane, ethylenimine, and *N*-ethylethylenimine during a 2- to 3-h period (Weightman and Hoyle 1964). The men were exposed in a 10 × 14-foot ventilated room at a temperature of about 7 to 16°C.

They were first exposed to 500 mL of household ammonia and 100 mL of isopentane; the odors were removed with a ventilation fan in about 5 to 10 min. One hour later, they were exposed to 20 g of ethylenimine and 100 g of *N*-ethylethylenimine. When the men left the room about 1½ to 2 h later, they were aware of lacrimation and smarting of the eyes. However, it was not until 3 to 7 h later that symptoms of lacrimation, eye inflammation, photophobia, nausea, vomiting, and inflammation of the respiratory tract caused the men to seek medical attention. Profound hacking cough with normal chest findings developed in the first 12 h. Clinical observations included fever, conjunctival irritation, evidence of liver inflammation, transitory increase in hemoglobin concentrations up to 20 g, eosinophilia (7 to 13%), mild albuminuria, and extensive respiratory irritation manifested by decreased respiratory (pulmonary) function. Ulceration of the posterior nasal cavity was reported for one student and an abnormal electrocardiogram was noted in another. The students were released from the hospital within 11 to 25 days. Three students recovered completely in about 3 months, whereas two continued to show residual conjunctival inflammation and reduced respiratory function. The effects experienced by the students cannot be attributed entirely to ethylenimine, because these exposures involved both ethylenimine and *N*-ethylethylenimine. However, some symptoms (lacrimation, eye inflammation, photophobia, nausea, vomiting and extreme respiratory tract irritation) are similar to those described after exposure to sulfur mustard, another alkylating agent (ATSDR 2003, NRC 2003).

Ammonia causes irritation immediately upon exposure; the delayed onset of irritation to the eyes and respiratory tract of the students suggests that the eye and respiratory tract inflammation was not caused by exposure to ammonia. Isopentane is unlikely to cause damage to the respiratory tract. Concentrations up to 500 ppm are without effect in humans, and the LC_{50} for isopentane is extremely high for the mouse (1,000,000 mg/m^3 = 339,000 ppm) (Cavender 1994). Toxicity information on *N*-ethylethylenimine could not be found; it is possible

that *N*-ethylethylenimine could be a weak alkylating agent similar to ethylenimine, and it may have contributed to the effects observed in the students.

Five maintenance workers in an ethylenimine plant experienced irritation and swelling of the scrotum after exposure to ethylenimine fumes (vapor) or in one case liquid ethylenimine (Thiess et al. 1971). Symptoms did not become noticeable until several hours after exposure or until the day after exposure. A burning sensation in the scrotal area, reddening and blistering of the scrotal skin, and painful swelling of the scrotum occurred in one worker after liquid ethylenimine was spilled on his trousers. He recovered within 8 days. The other workers who wore protective clothing and respirators experienced no signs or symptoms suggestive of exposure to the eyes or respiratory tract. Exposure to the scrotal area was believed to have occurred via the bottom opening of the pant legs of the rubber suits, which conducted the vapors like a chimney. One worker experienced superficial erosion and intense reddening of the scrotal area, another experienced severe swelling and blister formation on the scrotum, and two experienced "considerable" scrotal swelling. The skin lesions healed within a few days except for one worker who had edema that extended to the penis and preputium and aggravated a preexisting condition. He required surgery (circumcision) and 4 weeks to recover. The swelling of the scrotum was caused by edema of the scrotal area. The authors noted that spermiogenesis was not affected suggesting that the effects were local involving only the skin.

Danehy and Pflaum (1938) described a worker who inadvertently spilled one drop (about 50 μL) of ethylenimine on his tongue; he immediately rinsed his mouth with water. Two hours after the incident, vomiting occurred several times at about 30-min intervals followed by inflammation and edema of the epithelium in the mouth and throat, swelling of the uvula, and inflammation of the eyes. The symptoms resolved within 2 days after the incident. Inhalation exposure from this incident was possible, but would have been negligible. Danehy and Pflaum (1938) also reported that vapors (no concentration reported) inhaled for a short period of time (23 min) were "definitely toxic" to humans.

2.2.3. Epidemiologic Studies

No epidemiologic studies on the toxicity of ethylenimine were located in the literature searched.

2.3. Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies were located in the available literature.

2.4. Carcinogenicity

An unconfirmed report noted that no evidence of carcinogenicity was found among 144 ethylenimine workers after 40 years of experience (D.J. Kilian, Dow Chemical, personal communication, Oct. 17, 1973). No other information on the potential carcinogenicity of ethylenimine in humans was located in the available literature.

2.5. Genotoxicity

There was no significant increase in chromosome aberrations in leukocytes of chemical workers exposed to <0.5 ppm of ethylenimine for a mean of 8 years (Gaeth and Thiess 1972). No other in vivo human genotoxicity data were located in the available literature.

Significantly increased frequencies of chromatid breaks/gaps and exchanges were induced in cultured human embryonic lung fibroblast cells (WI-38) and in human leukocytes incubated with 10^{-4} M ethylenimine. Increased frequencies in chromatid breaks/gaps were observed in human fibroblast cells incubated with 10^{-5} M ethylenimine (Chang and Elequin 1967).

2.6. Occupational Exposure

Occupational exposure to ethylenimine can occur during its production or use. Because ethylenimine is a suspect carcinogen, OSHA (29 CFR 1910.1003 [1999]) require that workers be protected against contact with and exposure to ethylenimine; therefore, occupational exposure is expected to be very low. Ruhe (1982) reported air concentrations ranging from 0.01 to 0.03 mg/m^3 in an area where workers connect and disconnect ethylenimine cylinders. The air samples were collected by six lapel samplers worn by workers who wore full protective equipment including airline respirators (a type of supply air respirator) while carrying out these operations. The four workers handling the ethylenimine cylinders reported no health problems. The exposure to the workers were probably lower than the measured air concentrations. No other data on occupational exposure were located in the available literature.

2.7. Summary

Although the odor threshold for ethylenimine is reported to be about 2 ppm, there is no specific warning of the presence of ethylenimine in air because the odor is similar to that of ammonia. Because individuals would not be able to distinguish the odor of ammonia and ethylenimine, they would not take steps to

avoid or lessen exposure if they thought they were exposed to ammonia. In contrast to ammonia, eye and respiratory tract inflammation or irritation may not be noticed during the actual exposure to ethylenimine.

One human fatality occurred after a brief exposure to a high, but unknown concentration of ethylenimine. Irritation was noticed soon after exposure, probably because of the high exposure concentration. However, it is possible that the cause of death was due to the secondary effects of treatment (steroid therapy) rather than exposure to ethylenimine.

Nonlethal effects due to inhalation exposure to ethylenimine are characterized by irritation or damage to contact organs; the effects are delayed in onset depending on exposure concentration. Severe eye and respiratory tract inflammation, photophobia, nausea, vomiting, and coughing may develop several hours after exposure to ammonia, isopentane, ethylenimine, and *N*-ethylethylenimine in succession. Hemoconcentration (markedly increased hemoglobin concentration), eosinophilia, albuminuria, and evidence of liver inflammation were noted during clinical examination. Symptoms following exposure to ammonia or isopentane are different from those described in this report suggesting that these compounds did not cause the observed effects. Skin sensitization, severe slow-healing dermatitis, and rapidly reversible eye and respiratory tract irritation have been associated with occupational exposure to ethylenimine. Direct contact of liquid ethylenimine on the tongue resulted in delayed serious effects on the oral cavity and eyes, and direct contact of liquid on the skin caused necrotizing painless burns. No data were found on the developmental/reproductive toxicity of ethylenimine in humans. Ethylenimine is clastogenic in cultured human cells. An unconfirmed report noted that no evidence of carcinogenicity was found among 144 ethylenimine workers after 40 years of experience (D.J. Kilian, Dow Chemical, personal communication, 1973).

Table 4-3 summarizes the lethal and nonlethal effects of ethylenimine in humans.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Carpenter et al. (1948) conducted acute toxicity studies in Wistar rats exposed to ethylenimine by inhalation at concentrations ranging from 25 to 4000 ppm and exposure durations ranging from 5 to 480 min (8 h) (see Table 4-3). Each group consisted of five or six male rats. The concentration of ethylenimine in the exposure chamber was not determined analytically, but was verified by delivery rate, total volume of test material delivered, and consistent mortality response with increasing concentration. The age of the rats was not reported, but they weighed between 60 and 180 g at the time of exposure. The animals were

TABLE 4-3 Summary of Lethal and Nonlethal Effects on Ethylenimine in Humans

Concentration (ppm)	Exposure Time	Effects	Comments	Reference
2 ppm	NA	Odor detection		Carpenter et al. 1948
Unknown	<5 min	Vomiting, eye irritation, severe respiratory effects including pulmonary edema and destruction of tracheobronchial tree, death 10 weeks after exposure	Death may have been caused by aggressive steroid therapy	Gresham and West 1975
Unknown	1½ to 2 h	Severe vomiting, eye inflammation, photophobia, hemoconcentration, eosinophilia, coughing, extensive respiratory irritation	Lacrimation and smarting of the eyes were noted at the end of exposure; other effects were delayed for several hours, the individuals were hospitalized 11 to 25 days; residual eye and respiratory effects remained 3 months after exposure; exposure to ammonia and isopentane ruled out as causative agents; *N*-ethylethylenimine could not be ruled out	Weightman and Hoyle 1964
Unknown	Not reported	Damage to scrotal skin (reddening, blistering, swelling); no evidence of testicular effects	Protective equipment prevented exposure to the eyes and respiratory tract; delayed onset (~12-24 h)	Thiess et al. 1971
Unknown	Unknown	Skin sensitization	Occurred in a laboratory worker	Carpenter et al. 1948
Unknown	Unknown	Severe dermatitis, conjunctivitis, nose and throat irritation	Effects on eyes, nose, and throat were transient	Carpenter et al. 1948
NA (one drop on tongue, ca. 50 µL)	Not reported, but probably only seconds	Inflammation and edema of the epithelium of the oral cavity, inflammation of the eyes	Inhalation exposure was possible, but negligible; study showed insidious nature of ethylenimine	Danehy and Pflaum 1938
Spill of liquid on skin	Not reported	Necrotizing painless burns to hand; no other effects	This study involved skin contact with liquid ethylenimine	Weightman and Hoyle 1964

(Continued)

TABLE 4-3 Continued

Concentration (ppm)	Exposure Time	Effects	Comments	Reference
<0.5 ppm	8 yr	No chromosome aberrations detected	This is an occupational exposure study	Gaeth and Thiess 1972
10^{-5} to 10^{-4} M	8 h	Chromosome aberrations in human leukocytes and embryonic lung fibroblast cells	*In vitro* study	Chang and Elequin 1967

observed for 14 days after exposure. Clinical signs of toxicity consisted primarily of eye and respiratory tract irritation. Eye and nasal irritation occurred at concentrations of 100 ppm or higher, after 60 min at 100 ppm and immediately at concentrations greater than 100 ppm. No eye irritation was evident at concentrations of 10 to 50 ppm. Extreme respiratory difficulty was evident at all concentrations ≥25 ppm, but was not observed in less than 3 h at 25 ppm. No other details were presented concerning respiratory difficulty. Prostration was observed after exposure to 250 ppm for 3 h and after exposure to 500 ppm for 2 h. Prostration was not observed at other concentrations; at the higher concentration, death occurred without prostration. The individual exposure concentration, duration of exposure, mortality response at each concentration, and LC_{50} values are presented in Table 4-4. Deaths were generally delayed; one-half the deaths occurred before the end of day 3 and 9% occurred after day 10. Gross examination showed congestion and hemorrhage in the lungs and congestion in all internal organs. Microscopic examination showed pulmonary congestion and leakage of fluid and red blood cells into the bronchioles. Tubular epithelial necrosis and various degrees of cloudy swelling were seen in the kidneys. Clinical pathology showed albuminuria and transient leukopenia in rats the second day after exposure to 100 ppm for 120 min.

3.1.2. Mice

Silver and McGrath (1948) exposed groups of 20 mice (strain and sex not specified) to nine concentrations of ethylenimine ranging from 2.1 to 6.1 mg/L (1176 to 3416 ppm) for 10 min and observed the surviving animals for 10 days. Exposures were based on measured concentrations of ethylenimine in the chamber atmosphere. The mortality response for each group is presented in Table 4-5. The mouse LC_{50} values may be slightly underestimated, because the mice were observed for only 10 days instead of 14 days after exposure. In the rat and guinea pig studies, 9% of the animals died more than 10 days after exposure (Carpenter et al. 1948). During exposure, the animals showed signs of eye and nose irritation within 2 min of initiating exposure and became hyperactive. Normal behavior resumed upon termination of exposure. Deaths occurred between 24 h postexposure to the end of the observation period. Prior to death, extreme prostration, complete loss of muscular coordination, and occasional violent convulsions were noted. The LC_{50} for a 10-min exposure was 2236 ppm.

Groups of mice were exposed to ethylenimine vapor at six concentrations ranging from 0.2 to 6.0 mg/L (114 to 3414 ppm) for 10 min and observed for 10 days (Todd and Taugher 1918). All mice died after exposure to concentrations of ≥3.5 mg/L (1960 ppm), whereas all mice survived after exposure to ≤1.0 mg/L (560 ppm). The deaths were delayed, but occurred within 48 h after exposure. No other details were available.

TABLE 4-4 Effects of Acute Exposure to Ethylenimine in Wistar Rats

Exposure Duration (min)	Exposure Concentration (ppm)	Mortality Response	LC_{50}[a] (ppm)
5	100, 250, 500, 1000, 4000	0/6, 0/6, 1/6, 1/5, 4/6	2558
10	500, 1000, 2000, 4000	2/6, 4/6, 1/6, 5/6	1407
15	100, 250, 500, 1000, 2000, 4000	0/6, 1/6, 3/6, 5/6, 5/6, 6/6	545
30	500, 1000, 2000	5/6, 6/6, 5/5	Could not be determined
60	100, 250, 500	0/6, 2/6, 6/6	268
120	50, 100, 250	0/6, 1/6, 3/6	259
240	25, 50, 100, 250	0/6, 2/5, 6/6, 6/6	58
480	25, 50	1/6, 5/6	35

[a]LC_{50} values calculated by probit analysis.
Source: Carpenter et al. 1948.

TABLE 4-5 Mortality in Mice Exposed to Ethylenimine Vapor for 10 Minutes

Concentration		
mg/L	ppm	Mortality (%)
2.1	1176	3/20 (15)
2.3	1288	3/20 (15)
2.9	1624	7/20 (35)
3.3	1848	3/20 (15)
3.4	1904	10/20 (50)
3.5	1960	4/20 (20)
3.7	2072	9/20 (45)
4.2	2352	13/20 (65)
6.1	3416	18/20 (90)

LC_{50} value = 2236 ppm

Source: Silver and McGrath 1948. Reprinted with permission; copyright 1948, *Journal of Industrial Hygiene and Toxicology*.

3.1.3. Guinea Pig

Carpenter et al. (1948) conducted acute toxicity studies in guinea pigs exposed to ethylenimine at concentrations ranging from 10 to 4000 ppm for durations ranging from 5 to 480 min (8 h). Each group consisted of 5, 6, or 12 guinea

pigs of both sexes. The concentration of ethylenimine in the exposure chamber was not determined by analytical measurement, but was verified by delivery rate, total volume of test material delivered, and consistent mortality response with increasing concentration. The age of the guinea pigs was not reported, but most weighed between 250 and 300 g when exposed to ethylenimine. The animals were observed for 14 days after exposure. The individual exposure concentrations, durations of exposure, mortality responses at individual concentrations, and LC_{50} values are presented in Table 4-6. Deaths were generally delayed with 50% dying by the end of day 3 and another 9% dying after day 10. Clinical signs of toxicity consisted primarily of eye and respiratory tract irritation. Eye irritation occurred 60 min after exposure to 100 ppm and immediately after exposure to concentrations greater than 100 ppm. No signs of eye irritation were observed at 10 to 50 ppm. Extreme respiratory difficulty was evident at all concentrations ≥25 ppm; it was not observed in less than 3 h at 25 ppm. Respiratory difficulty was not observed in guinea pigs exposed to 10 ppm for any duration. Prostration was observed 3 h after exposure to 250 ppm and 2 h after exposure to 500 ppm. Prostration was not evident at other concentrations; at the higher concentrations, death occurred without a preceding period of prostration. Gross pathologic examination showed congestion and hemorrhage in the lungs and congestion in all internal organs. Microscopic examination showed evidence of pulmonary congestion and leakage of fluid and red blood cells into the bronchioles. Tubular epithelial necrosis and various degrees of cloudy swelling were seen in the kidneys. Clinical pathology studies showed transient leukopenia, neutrophilia, and lymphopenia in guinea pigs exposed to 100 ppm of ethylenimine for 120 min.

3.2. Nonlethal Toxicity

Six guinea pigs were shaved and exposed (except for the head) to ethylenimine vapor at a concentration of 4000 ppm for 4 h (Carpenter et al. 1948). No signs of toxicity were observed during the 14-day observation period, and no toxic effects on the skin were reported. There also was no effect on body weight gain. In contrast to inhalation exposure, no microscopic abnormalities were seen in the kidneys in guinea pigs that did not inhale ethylenimine. This study suggests that ethylenimine vapor was not absorbed into the systemic circulation through the skin or it is not absorbed at levels sufficient to cause systemic effects in the guinea pig. Studies on subcutaneous administration of ethylenimine showed that single or repeated injections of doses ≥1.25 mg/kg produced a characteristic lesion in the renal medulla, renal papillary necrosis (Axelsen 1978).

3.3. Developmental and Reproductive Toxicity

No data were available on potential developmental or reproductive toxicity in laboratory animals exposed to ethylenimine by any route.

TABLE 4-6 Effects of Acute Exposure to Ethylenimine in Guinea Pigs

Exposure Duration (min)	Exposure Concentration (ppm)	Mortality Response	LC_{50}[a] (ppm)
5	250, 500, 1000, 4000	0/6, 0/6, 0/6, 4/6	2906
10	2000, 4000	1/12, 6/6	2824
15	250, 500, 1000, 2000	0/6, 0/6, 0/6, 6/6	1283
30	100, 250, 500, 1000	0/6, 0/6, 5/6, 6/6	364
60	25, 100, 250, 500	0/12, 1/6, 2/6, 6/6	235
120	50, 100, 250, 500	0/6, 1/6, 5/6, 6/6	158
240	10, 25, 50, 100, 250	0/6, 2/5, 2/6, 6/6, 6/6	45
480	10, 25, 50	0/6, 2/6, 6/6	27

[a]LC_{50} values calculated using probit analysis.
Source: Carpenter et al. 1948. Reprinted with permission; copyright 1948, *Journal of Industrial Hygiene and Toxicology*.

3.4. Carcinogenicity

No data were available on the potential carcinogenicity of ethylenimine in laboratory animals exposed by inhalation. Oral and subcutaneous injection studies were available.

Walpole et al. (1954) studied the carcinogenicity of ethylenimine in rats injected subcutaneously with ethylenimine. Six male and six female albino rats per group were injected twice weekly with ethylenimine in arachis oil such that a total dose of 2.0 mg was administered in a total volume of 2.0 mL. Another six males and six females were treated similarly with a total dose of 1.0 to 1.2 mg in 1.0 to 1.2 mL of water. Controls were injected with similar volumes of arachis oil or water alone. Sarcomas developed at the injection site in 6/12 rats receiving ethylenimine in arachis oil compared with 0/24 receiving a comparable volume of arachis oil alone and in 2/12 rats injected with ethylenimine in water. A control for the latter groups injected with water was not described. The investigators did not explain the different responses after injecting ethylenimine in arachis oil and water.

BRL (1968) reported the results of carcinogenicity studies in which ethylenimine was given to mice by subcutaneous injection or by gavage/dietary administration. A single dose of 4.64 mg/kg was injected subcutaneously (distilled water vehicle) into 18 male and 18 female $B6C3F_1$ or $B6AKF_1$ mice. The same number of animals were given 4.64 mg/kg by gavage (gelatin vehicle) from 7 to 28 days of age inclusive; the compound was then administered at a dietary concentration delivering approximately the same dosage level until sacrificed 18 months after initiating the study. The dietary concentration was not adjusted to maintain the same dosage with changing body weight. There was no statistically significant increase in the incidence of tumors at any site in animals

injected with ethylenimine. Oral administration resulted in significant increases in incidences of pulmonary adenomas and hepatomas in male and female $B6C3F_1$ mice and male $B6AKF_1$ males; the incidence of pulmonary adenomas was significantly increased in $B6AKF_1$ females.

Groups of 18 male and 18 female 7-day old $(C57BL/6 \times C3H/Anf)F_1$ and the same number of 7-day old $(C57Bl/6 \times AKR)F_1$ mice were injected subcutaneously with a 4.64-mg/kg body weight dose of ethylenimine and observed for 80 weeks (BRL 1968). The male mice of both strains developed lung tumors (5 or 6 of 18 mice), and two mice of the $(C57BL/6 \times C3H/Anf)F_1$ developed hepatomas and lymphomas. The total tumor incidence for both male strains was significantly greater than that of the controls. Only one female of each strain developed a lung tumor.

IARC (1999) recently evaluated the potential carcinogenicity of ethylenimine and concluded that ethylenimine is *possibly carcinogenic to humans* (Group 2B). This conclusion took into consideration that ethylenimine is a direct-acting alkylating agent that is mutagenic in a large number of test systems, including bacteria, insects, mammalian cells in culture, and mice (assessed in vivo by the dominant lethality test). IARC (1999) also noted that ethylenimine forms DNA adducts that are promutagenic.

3.5. Genotoxicity

Ethylenimine is a very reactive monofunctional alkylating agent; the formation of an ethylenimonium ion accounts for its alkylating activity (Verschaeve and Kirsch-Volders 1990). Ethylenimine is a direct-acting genotoxic agent requiring no metabolic activation for its genotoxic activity. Ramel (1981) reported that ethylenimine had been tested for genetic toxicity in about 150 species and concluded that it is a very potent direct-acting mutagen, producing point mutations and chromosome aberrations. This chemical "is very mutagenic in all test systems investigated;" only a few negative results have been published and these were attributed to the use of low doses (Verschaeve and Kirsch-Volders 1990).

Ethylenimine is mutagenic in the Ames test in *Salmonella typhimurium* strains TA100 and TA1535 (Haroun and Ames 1981; Ramel 1981; Verschaeve and Kirsch-Volders 1990). It induces mitotic recombinations, gene conversions, and forward mutations in yeast and other fungi (Brockman et al. 1981; Loprieno 1981; Zimmermann 1981; Verschaeve and Kirsch-Volders 1990). Ethylenimine has been tested extensively in a variety of plant species and has been shown to be mutagenic and/or clastogenic in barley, wheat, *Crepis capillaris*, cotton, lettuce, cucumber, tobacco, rice, maize, and other plants. Ethylenimine induces high frequencies of dominant lethal mutations, sex-linked and autosomal recessive lethal mutations, and translocations in *Drosophila melanogaster* (Vogel et al. 1981). Ethylenimine is genotoxic in *Bracon hebetor* (parasitic wasp) and silkworm caterpillars and pupae (Verschaeve and Kirsch-Volders 1990). Chi-

nese hamster ovary cells had chromosome breaks after in vitro incubation with ethylenimine (Velazquez et al. 1973).

No studies were found on potential genotoxicity in laboratory animals exposed to ethylenimine by the inhalation route. Dominant lethality was evidenced by postimplantation loss in female mice mated with male C57BL/6 mice that received intraperitoneal injections of 5-6 mg/kg ethylenimine. The dominant lethality studies showed that postmeiotic spermatozoa were the target of ethylenimine (Malashenko 1968, Malashenko and Egorov 1968).

3.6. Summary

The LC_{50} values for mice, rats, and guinea pigs are summarized in Table 4-7. All deaths occurred after exposure was terminated. In rats and guinea pigs, eye irritation was delayed at 100 ppm but occurred immediately upon initiating exposure to higher concentrations. Respiratory difficulty occurred at concentrations of 25 ppm and above, but at 25 ppm, respiratory difficulty was not observed in animals exposed for less than 3 h. No deaths or signs of toxicity occurred in guinea pigs exposed to 10 ppm of ethylenimine for 4 or 8 h; rats were not exposed to 10 ppm (Carpenter et al. 1948). All groups of mice were exposed to high concentrations (>1100 ppm), and the signs of toxicity (eye and respiratory irritation) occurred during the 10-min exposure. Death, however, was delayed and was preceded by prostration (seen at two concentrations in rats and guinea pigs), loss of muscular coordination, and convulsions (not observed in rats and guinea pigs) (Silver and McGrath 1948). Gross and histopathologic examination showed damage to the lungs, congestion in all internal organs, and damage to the kidney manifested by tubular necrosis and albuminuria in rats. The response to inhaled ethylenimine in rats and guinea pigs were similar, suggesting a similar mode of action, and mice responded similarly to rats and guinea pigs, with some minor differences. A quantitative difference may exist for the three species as evidenced by a twofold difference in the LC_{50} values for 10-min exposures to ethylenimine.

No inhalation studies specifically designed to examine effects of inhaling nonlethal concentrations of ethylenimine were located in the available literature. One study showed that dermal only exposure to ethylenimine vapor at a concentration of 4000 ppm for 4 h failed to elicit any signs of toxicity in guinea pigs (Carpenter et al. 1948).

Ethylenimine is a very reactive direct-acting alkylating agent that is genotoxic in all test systems investigated including bacteria, yeast and other fungi, various plant species, insects, and mammalian cells in vitro. An in vivo oral study showed dominant lethality in mice after intraperitoneal injection of ethylenimine (Malashenko and Egorov 1968). Ethylenimine has not been tested for carcinogenicity by the inhalation route, but it is carcinogenic in mice at a

TABLE 4-7 Summary of Lethality Data for Experimental Animals[a]

Species/Sex	LC_{50}[a] ppm	LC_{50}[a] mg/m^3	Exposure Time (min)	Comments
Rat	2558	4579	5	1/6 Died at lowest lethal concentration, 500 ppm
Guinea pig	2906	5202	5	None died at second highest concentration tested, 1000 ppm
Rat	1407	2519	10	2/6 Died at lowest concentration tested, 500 ppm
Mouse	2236	4002	10	3/20 died at lowest concentration tested, 1176 ppm
Guinea pig	2824	5055	10	1/12 Died at lowest concentration tested, 2000 ppm
Rat	545	976	15	Lowest lethal concentration, 250 ppm (1/6 died)
Guinea pig	1283	2279	15	No deaths at second highest concentration, 1000 ppm
Rat	Could not be determined	—	30	5/6 Died at lowest concentration tested, 500 ppm
Guinea pig	364	652	30	5/6 Deaths at 500 ppm; no deaths at 250 ppm
Rat	268	480	60	Lowest lethal concentration, 250 ppm (2/6 died)
Guinea pig	235	421	60	Lowest lethal concentration, 100 ppm (1/6 died)
Rat	259	464	120	Lowest lethal concentration, 100 ppm, (1/6 died)
Guinea pig	158	283	120	Lowest lethal concentration, 100 ppm (1/6 died)
Rat	58	104	240	Lowest lethal concentration, 50 ppm (2/5 died)
Guinea pig	45	81	240	Lowest lethal concentration, 25 ppm (2/5 died)
Rat	35	63	480	1/6 Died at lowest concentration tested, 25 ppm
Guinea pig	27	48	480	Lowest lethal concentration, 25 ppm (2/6 died)

[a]LC_{50} values of lowest tested concentration causing death.
Sources: Carpenter et al. 1948 (rat and guinea pig data); Silver and McGrath 1948 (mouse data).

distant site (lung tumors) after a single subcutaneous injection, in rats at the injection site (sarcomas) in rats after multiple subcutaneous injections (Walpole et al. 1954; BRL 1968), and after oral administration (hepatomas and pulmonary tumors) (BRL 1968).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

Data on absorption, distribution, and metabolism after inhalation exposure to ethylenimine were not located in the available literature. Wright and Rowe (1967) studied the distribution, metabolism, and excretion of ethylenimine in male Dow-Wistar rats after intraperitoneal injection of 80 µg of ethylenimine-[^{14}C] (0.30 to 0.42 mg/kg) and found that 3.37 to 4.85% of the dose was expired as $^{14}CO_2$ during the first 24 or 96 h after dosing. In addition, a volatile basic radioactive substance tentatively identified as unmetabolized ethylenimine was also eliminated in expired air. These levels ranged from 0.95 to 2.75% of the dose within 24 to 96 h. The major route of excretion was urine, which contained between 45.8 and 58.6% of the dose between 24 and 96 h. A small amount of unmetabolized ethylenimine was excreted in urine, but the largest fraction was converted to unidentified metabolites. By comparison, Jackson and James (1965) reported that rats injected with 1.0 to 2.9 mg/kg of ethylenimine excreted 10 to 38% of the dose in urine within 6 h and mice injected with 1.0 to 5.0 mg/kg excreted 7 to 28% in urine. Wright and Rowe (1967) also noted that ethylenimine was not eliminated in feces. They reported a 6-h half time of excretion as CO_2 and a 2-h half time of elimination as ethylenimine in expired air. Overall elimination of ethylenimine showed two compartments; one with an elimination half time of 16 h and one with a half time of 56 days. The authors noted that the long half time of elimination was due to the binding of the radioactive material to tissue components and that the material incorporated into tissues was the parent compound and not a metabolite.

Tissue distribution studies showed that all tissues accumulated radioactive material to some degree within the first 24 h, but it was markedly reduced by 96 h (Wright and Rowe 1967). The highest specific activity was found in the liver followed in decreasing order by cecum, spleen, kidneys, intestines, and bone marrow. The long half-life suggests that the material accumulating in tissues turned over very slowly and was not available for further metabolism.

The metabolites of ethylenimine were not identified. Wright and Rowe (1967) concluded that a portion of the ethylenimine is converted to a substance that can be converted to CO_2, but the major portion proceeded by a route that did not involve oxidation. They further noted that ethylenimine or a metabolite retaining the aziridine ring reacted with tissues components.

4.2. Mechanism of Toxicity

Ethylenimine causes extreme inflammation and blistering upon contact with skin, eyes, and respiratory tract. The effects are delayed relative to the time of exposure. Ethylenimine is a very reactive alkylating agent and its toxicity may be related to its alkylating properties. Ethylenimine forms ethylenimonium ions (Ramel 1981) that readily alkylate macromolecules via amino, sulfhydro, and carboxyl groups on proteins and phosphate and amino groups on nucleic acids (Hemminki 1994; Trochimowicz et al. 1994).

Death and other effects occurring after inhalation exposure to ethylenimine are delayed, i.e. depending on the concentration, effects may not become apparent until long after exposure started or was terminated (insidious nature of ethylenimine). The delayed effects suggest that biologic accumulation may be a factor in initiating overt toxic responses.

Although ethylenimine is a potent irritant that causes inflammation and blistering upon direct contact with tissue, there is no evidence indicating that it is a sensory irritant via stimulation of the trigeminal nerve. Silver and McGrath (1948) compared acute toxicity in groups of mice exposed to ethylenimine with mice exposed to ammonia for 10 min. The concentrations of both compounds were in the lethal range. Mice exposed to ammonia (primary irritant) exhibited immediate signs (within 1 min) of initiating exposure, closing of eyes, gasping, and pawing and scratching of the nose. Then the mice became quiet and death, which was preceded by convulsions, occurred about 5 min after exposure started; almost all mice that died did so during exposure. The surviving animals recovered rapidly after cessation of exposure. The effect of ethylenimine on mice was described in Section 3.1.2. Mice exposed to ethylenimine also showed evidence of eye and nose irritation; however, no deaths occurred during the first 24 h after exposure. Silver and McGrath (1948) stated that the physiological actions of ammonia and ethylenimine are quite different. They also acknowledged the insidious nature of ethylenimine and stated that the secondary peak of deaths 4-5 days after exposure resembles that of nitrogen mustards.

Ethylenimine is toxicologically similar to the mustard compounds. Papirmeister et al. (1985) proposed a mechanism by which mustard compounds induce vesicant activity in the skin. The initial step in the proposed mechanism is the rapid alkylation of DNA followed by depurination of DNA, DNA strand breaks, activation of poly(ADP-ribose polymerase), depletion of NAD^+, inhibition of glycolysis, activation of the hexose monophosphate shunt, release of protease, and cell damage leading to blistering. Ethylenimine reacts with guanosine and deoxyguanosine to form 7-aminoethylguanine derivatives in vitro, which readily undergo depurination (Hemminki 1994). Rao et al. (1999) showed that sulfur mustard damages DNA in lungs, liver, spleen, and thymus of mice after exposure by inhalation or dermal contact, and that the damage persists for at least 7 days depending on the tissue and concentration of sulfur mustard.

Ethylenimine is a blistering agent and is likely to produce damage in the eyes, skin, and respiratory tract in a manner similar to that of the mustards. A more detailed discussion of the mechanism of toxicity of sulfur mustard was presented by Watson and Griffin (1992) and NRC (2003).

4.3. Structure–Activity Relationship

Carpenter et al. (1948) conducted acute inhalation studies with three compounds structurally similar to ethylenimine: ethylenediamine, propylenimine, and triethylamine. No deaths occurred in groups of rats or guinea pigs exposed to 1000 ppm of ethylene diamine for up to 8 h and observed for 14 days. Exposure to 500 ppm of propylenimine for 240 min caused the death of 5/6 rats; exposure for 1, 2, or 4 h caused the death of 1/6, 3/5, and 6/6 guinea pigs, respectively. No deaths occurred among six guinea pigs per group exposed to triethylamine at concentrations of 250 or 500 ppm for 4 h; 2/6 deaths occurred at 1000 ppm for 4 h, and 4/6 deaths occurred at 2000 ppm for 2 h. Based on the lethality data, ethylenimine is more acutely toxic than either of the latter substances.

4.4. Other Relevant Information

4.4.1. Species Variability

The LC_{50} values showed only small differences in sensitivity to ethylenimine between the rat and guinea pig at specific exposure concentrations and durations. The differences in exposure concentrations selected for the experiments made it difficult to compare the mouse with the rat and guinea pig. The LC_{50} for a 10-min exposure is similar for the mouse (2236 ppm) and guinea pig (2824 ppm). At individual exposure concentrations, however, rats were more sensitive than mice followed by guinea pigs for a 10-min exposure. Rats were more sensitive than guinea pigs for a 15-min exposure and equally sensitive to guinea pigs for a 60-min exposure, but guinea pigs were slightly more sensitive than rats for exposure times greater than 60 min. Since only five or six animals per group were exposed at most concentrations and times, the detection level of the experiment was very low. The selection of exposure concentrations for each exposure duration could account for some of the difference between species, and variations in exposure concentrations, which were not measured, also could have contributed to the species differences.

All species showed the characteristic delayed mortality after inhalation exposure to ethylenimine and showed similar clinical signs of toxicity. Eye and respiratory tract irritation and characteristic delayed response also have been observed in humans exposed to ethylenimine.

4.4.2. Susceptible Subpopulations

No data are available on susceptible subpopulations exposed to ethylenimine. Ethylenimine is a potent respiratory irritant, but there is no evidence that it is a primary irritant that could trigger a response in asthmatics at concentrations lower than those causing effects in the general population.

4.4.3. Concentration-Exposure Duration Relationship

The LC_{50} data for rats and guinea pigs can be used to determine the relationship between the concentration of ethylenimine and the exposure duration. A linear relationship was observed for LC_{50} concentration and exposure durations ranging from 5 to 480 min (8 h) when plotted as a log-log relationship. These data for the rat (Figure 4-1) and guinea pig (Figure 4-2) are presented below. The calculated values of n are 1.1 for the rat data and 0.91 for the guinea pig data.

5. DATA ANALYSIS AND AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Ethylenimine has an ammonia-like odor and an odor detection threshold of 2 ppm (Carpenter et al. 1948). Odor will not serve as a specific warning to the presence of ethylenimine, because its odor is similar to that of ammonia. No other data pertinent to deriving AEGL-1 values for ethylenimine were available.

5.2. Summary of Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1

Data were not available for deriving AEGL-1 values for ethylenimine; therefore, no values are recommended (Table 4-8). The absence of AEGL-1 values does not imply that exposures below the AEGL-2 are without adverse health effects.

6. DATA ANALYSIS AND AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data relevant to AEGL-2 were discussed in Section 2.2. Ethylenimine exposure causes skin sensitization, severe slow-healing dermatitis, blister-

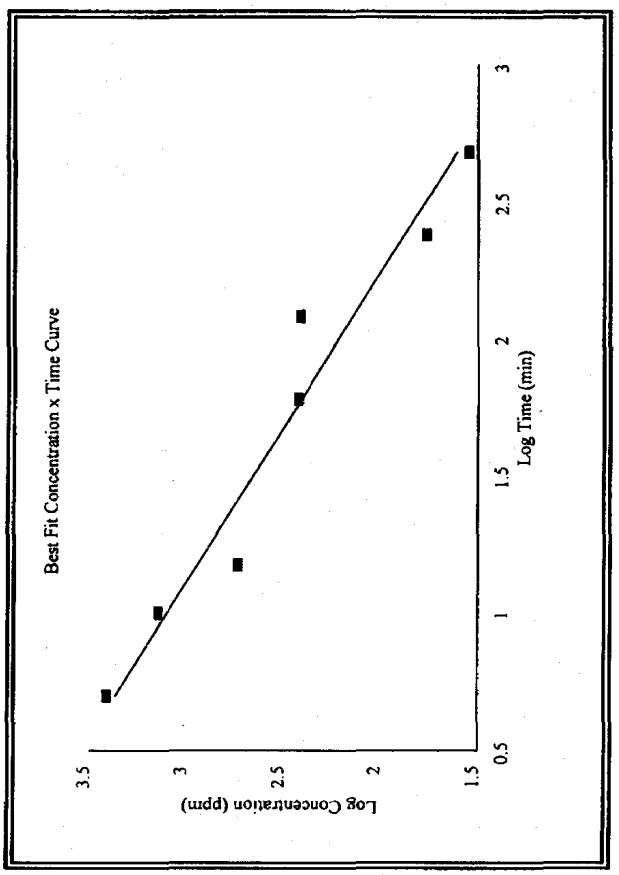

FIGURE 4-1 Rat data: Concentration–time curve for LC_{50} values for ethylenimine.

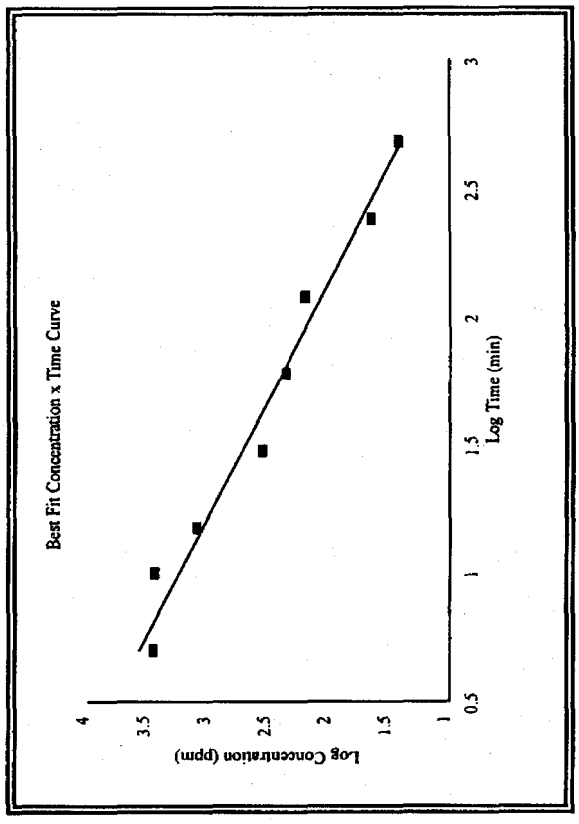

FIGURE 4-2 Guinea pig data: Concentration–time curve LC values for ethylenimine.

TABLE 4-8 AEGL-1 Values for Ethylenimine [ppm (mg/m^3)]

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

NR: Not recommended. The absence of AEGL-1 values does not imply that exposure below the AEGL-2 is without adverse health effects.

ing, reddening, and edema of the scrotum, nasal irritation, and throat irritation. Carpenter et al. (1948) reported that irritation does not occur in humans exposed to less than 100 ppm; these investigators did not describe the subjects or exposure protocol.

Five male students exposed successively to ammonia, isopentane, ethylenimine, and *N*-ethylethylenimine over a period of 2- to 3-h, experienced lacrimation, eye inflammation, coughing, respiratory tract inflammation, nausea, and vomiting; clinical findings included hemoconcentration, eosinophilia, albuminuria, and liver inflammation (Weightman and Hoyle 1964). Most of the effects were delayed in onset or the attainment of maximum severity. Ammonia and isopentane can be ruled out as causative agents; however, no data were found on the toxicity of *N*-ethylethylenimine and it cannot be ruled out as a contributing factor to the observed effects (see section 2.2.1). Exposure concentrations were not reported for ammonia, isopentane, ethylenimine, or *N*-ethylethylenimine. Another case report described scrotal skin irritation with no testicular involvement in several men exposed to ethylenimine vapor; no exposure concentrations or durations were reported (Thiess et al. 1971).

6.2. Summary of Animal Data Relevant to AEGL-2

No animal studies specifically designed to examine the nonlethal effects of exposure to ethylenimine were available for deriving AEGL-2 values. An acute lethality study showed that exposure to 10 ppm for 240 or 480 min was not lethal and did not affect the eyes or respiratory tract of guinea pigs. A concentration of 25 ppm did not cause death or respiratory difficulty in guinea pigs exposed for 60 min, but caused death after exposure for 240 min. No deaths occurred among rats exposed to 25 ppm for 240 min, but this concentration caused extreme respiratory difficulty after 3 h of exposure to both species. Although no deaths occurred in either rats or guinea pigs exposed to 50 ppm for 120 min, extreme respiratory difficulty was observed at this concentration.

6.3. Derivation of AEGL-2

Data are sparse for deriving AEGL-2 values. The acute inhalation studies used to derive LC_{50} values for rats and guinea pigs were considered for deriving AEGL-2 values. Exposure concentrations of 25 ppm for durations greater than 3 h caused extreme respiratory and may impair escape. Therefore, the next lowest concentration of 10 ppm (240 min), which caused no respiratory difficulty in

guinea pigs, was used for deriving AEGL-2 values. Although the logical point of departure (POD) for deriving AEGL-2 values is the no-observed-effect level (NOEL) for extreme respiratory difficulty in guinea pigs exposed to 10 ppm ethylenimine for 480 min (Carpenter et al. 1948), this derivation would lead to AEGL-2 values close to or exceeding the life-threatening AEGL-3 concentrations. Therefore, AEGL-2 values were derived using the next shorter duration of 240 min, which also is a clear NOEL for respiratory difficulty in guinea pigs exposed to 10 ppm. The total uncertainty factor is 10. An uncertainty factor of 3 was applied for interspecies differences, because ethylenimine is a very reactive direct-acting alkylating agent, and the AEGL-2 effects would most likely 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, and this mechanism is not expected to be different among species (NRC 2003). 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 rat, guinea pigs, and humans. 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 the alkylating activity is not expected to vary considerably among individuals in the population. Five male students responded similarly to an exposure to ethylenimine with respect to the time of onset of symptoms and the intensity of effects. Studies have shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage (Papirmeister et al. 1985) and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to alkylating agents (Rao et al. 1999), such as ethylenimine. Extrapolation across the pertinent time frames was based on ten Berge's equation $C^n \times t = k$, where n = 0.91 (Figure 4-2). The value of n was derived by regression analysis of the LC_{50} data for guinea pigs exposed 5 to 480 min to ethylenimine. The resulting AEGL-2 values are presented in Table 4-9.

The AEGL-2 values are below the irritation threshold of 100 ppm reported by Carpenter et al. (1948). Quantitative data are not adequate for deriving cancer risk estimates (unit risk value) for inhaled ethylenimine (see Appendix B).

7. DATA ANALYSIS AND AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Only one death due to exposure to ethylenimine was found in the literature. A worker died after an intense exposure to an unknown concentration of ethylenimine for 5 min or less (Gresham and West 1975). Detailed exposure conditions were not reported. Signs and symptoms of exposure included eye irritation, vomiting, severe respiratory irritation, and pulmonary edema. Because the patient was treated aggressively with steroids, death may have been due to secondary effects of treatment and not to exposure to ethylenimine.

TABLE 4-9 AEGL-2 Values for Ethylenimine [ppm (mg/m^3)]

10 min	30 min	1 h	4 h	8 h
33 (59)	9.8 (18)	4.6 (8.2)	1.0 (1.8)	0.47 (0.84)

7.2. Summary of Animal Data Relevant to AEGL-3

Acute lethality studies were conducted in rats and guinea pigs exposed to ethylenimine at concentrations ranging from 10 to 4000 ppm for 5 to 480 min (Carpenter et al. 1948) and in mice exposed to 1176 to 3416 ppm for 10 min (Silver and McGrath 1948). All deaths in all species and at all concentrations were delayed, occurring 24 h to more than 10 days after exposure. All species showed signs of eye and respiratory tract irritation; in addition, the mouse showed signs of muscular incoordination and developed convulsions. Prostration was observed before death of rats and guinea pigs. The quality of the studies was similar, except for calculated instead of analytically-determined exposure concentrations for rats and guinea pigs Carpenter et al. (1948). LC_{50} values for the rat and guinea pig were not reported by Carpenter et al. (1948), but were calculated by probit analysis. At the shorter exposure durations (5 to 15 min), LC_{50} values were slightly higher for the guinea pig than the rat. However, at the longer durations (360 min), the values for the guinea pig were slightly lower, but still comparable to those for the rat. The postexposure observation period was only 10 days for mice and the studies on rats and guinea pigs showed that 9% of the deaths occurred after day 10 of the observation period showing that an extended observation period is important in evaluating mortality after exposure to ethylenimine.

7.3. Derivation of AEGL-3

The acute lethality studies in rats and guinea pigs were adequate for deriving AEGL-3 values for ethylenimine, and both studies were used to estimate lethality thresholds (LC_{01}). These values are presented in Table 4-10. A 30-min LC_{01} could not be determined from the rat data; the data were unsuitable for probit analysis because a dose-response relationship was not observed at the concentrations tested. The LC_{01} values show considerable variation for both species, but the standard error for the LC_{01} for the 480-min exposure to the rat is small compared with the standard errors for the other LC_{01} values. Therefore, the LC_{01} for the 480-min exposure to the rat (15 ppm) served as the basis for deriving AEGL-3 values.

A total uncertainty factor of 10 was applied to the LC_{01}. An uncertainty factor of 3 was applied for interspecies differences, because ethylenimine is a very reactive direct-acting alkylating agent, and the AEGL-2 effects would most likely be confined to the respiratory tract. Respiratory tract damage appears to

TABLE 4-10 Estimates of the Threshold for Lethality (LC_{01}) to Ethylenimine

Species	Exposure Duration (min)	LC_{50}[a] (ppm)	LC_{01}[a] (ppm)
Rat	5	2558 ± 1792	37 ± 53
	10	1407 ± 977	3 ± 16
	15	545 ± 162	35 ± 30
	30	Not determined	Not determined
	60	268 ± 57	70 ± 38
	120	259 ± 259	20 ± 24
	240	58 ± 14	11 ± 7
	480	35 ± 5	15 ± 6
Guinea pig	5	2906 ± 1583	139 ± 146
	10	2824 ± 319	1580 ± 292
	15	1283 ± 326	231 ± 144
	30	364 ± 79	77 ± 45
	60	235 ± 77	19 ± 16
	120	158 ± 37	30 ± 17
	240	45 ± 13	4 ± 3
	480	27 ± 6	7 ± 4

[a] LC_{50} and LC_{01} values (derived using probit analysis) ± standard error.

be due to a direct effect of an alkylating agent on the respiratory epithelium, and this mechanism is not expected to be different among species (NRC 2003). 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 rat, guinea pigs, and humans. In addition, the LC_{50} values for three test animal species were within a factor of 2 of each other, and like other effects of ethylenimine, death and serious effects were delayed in all three species. Similarly, humans experienced a delay in the onset of life-threatening and/or very serious effects after exposure to ethylenimine. 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 the alkylating activity is not expected to vary considerably among individuals in the population. Five male students responded similarly to an exposure to ethylenimine with respect to the time of onset of symptoms and the intensity of effects. Studies have shown that DNA damage is probably the initiating step in a cascade of events leading to cell damage (Papirmeister et al. 1985) and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to alkylating agents (Rao et al. 1999), such as ethylenimine. An uncertainty factor of 3, instead of the default of 10, was applied for intraspecies variability

based on the same rationale described for AEGL-2 derivation. Time frame scaling was determined by linear regression of the LC_{50} values for the rat exposed for durations ranging from 10 to 480 min; the value of *n* is 1.1 (Figure 4-1). The ten Berge equation for time frame scaling is as follows: $C^n \times t = k$, where C = concentration, n = 1.1, t = duration of exposure, and k = constant. The AEGL-3 values are presented in Table 4-11.

The AEGL-values presented in Table 4-11 are all below the 100 ppm that Carpenter et al. (1948) reported as the threshold for irritation in humans. The LC_{01} (15 ppm) for the 8-h exposure is less than the lowest concentration causing death in rats and guinea pigs. The AEGL-3 for a 60-min exposure is threefold lower than the concentration causing no deaths in rats and only one death in guinea pigs.

Ethylenimine has carcinogenic activity in rodents by oral and parenteral routes and is placed in a class of suspect human carcinogen by OSHA (29 CFR 1910.1003 [1999]) and is classified as *possibly carcinogenic to humans* by IARC (1999). Because quantitative data are not available for deriving a unit risk value, AEGL-3 values for ethylenimine do not take potential cancer risk into consideration.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Acute Toxicity End Points

Data were not available for deriving AEGL-1 values; therefore, no values are recommended. The absence of AEGL-1 values does not imply that exposures below the AEGL-2 are without adverse health effects. AEGL-2 values were based on a NOEL for extreme respiratory difficulty in guinea pigs exposed to ethylenimine for 240 min. Uncertainty factors of 3 for intraspecies variability and 3 for interspecies differences (total uncertainty factor was 10) were applied to the NOEL. Time scaling was based on the equation $C^n \times t = k$, where $n = 0.91$ was derived from guinea pig data.

The human data were not adequate for deriving AEGL-3 values. AEGL-3 values were based on the estimated lethality threshold (LC_{01}) for rats exposed to ethylenimine for 480 min. Uncertainty factors of 3 for intraspecies variability and 3 for interspecies differences (total uncertainty factor was 10) were applied to the LC_{01}. Time scaling was based on the equation $C^n \times t = k$, where $n = 1.1$ was derived from rat data. The AEGL values are summarized in Table 4-12.

8.2. Comparison with Other Standards and Criteria

The ACGIH TLV-TWA is 0.5 ppm (0.88 mg/m^3) (ACGIH 2001) and the IDLH is 100 ppm (NIOSH 1996). The ACGIH TLV has assigned a skin notation (ACGIH 2001); it causes dermatitis and sensitization. OSHA (29 CFR 1910.1003 [1999]) considers ethylenimine to be an occupational suspect car-

TABLE 4-11 AEGL-3 Values for Ethylenimine [ppm (mg/m3)]

10 min	30 min	1 h	4 h	8 h
51 (91)	19 (34)	9.9 (18)	2.8 (5.0)	1.5 (2.7)

TABLE 4-12 Summary of AEGL Values for Ethylenimine[a,b] [ppm (mg/m^3)]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	Not recommended[c]					
AEGL-2 (Disabling)	33 (59)	9.8 (18)	4.6 (8.2)	1.0 (1.8)	0.47 (0.84)	NOEL for extreme respiratory difficulty (Carpenter et al. 1948)
AEGL-3 (Lethal)	51 (91)	19 (34)	9.9 (18)	2.8 (5.0)	1.5 (2.7)	Threshold for lethality (Carpenter et al. 1948)

[a]AEGL-2 and -3 values do not take into consideration the potential cancer risk due to exposure to ethylenimine, because quantitative data were not available for deriving a unit risk value.
[b]Effects at these concentrations may be delayed until after exposure.
[c]The absence of AEGL-1 values does not imply that exposure below the AEGL-2 level is without adverse health effects.

cinogen; a permissible exposure level (PEL) was not established. OSHA (29 CFR 1910.1003 [1999]) requires that employees engaged in handling ethylenimine be protected against contact with and exposure to ethylenimine. When working with ethylenimine under certain conditions, OSHA regulations require that workers be supplied with full body protective clothing, half-face filter-type respirator with a filter for dusts, mists, and fumes, or air-purifying cartridges or canisters (29 CFR 1910.1003 [1999]). Table 4-13 compares existing standards and guidelines with the derived AEGL values. No other standards or guidelines are available for ethylenimine.

8.3. Data Quality and Research Needs

There are significant data gaps concerning human and animal studies on ethylenimine exposure. Human studies are precluded because ethylenimine is a suspect carcinogen. Acute lethality studies were available in three laboratory species, two of which were exposed to varying concentration of ethylenimine for durations ranging from 5 to 480 min. The log concentration vs log time plot showed a linear relationship of the LC_{50} values for the entire range of exposure durations. Therefore, the data for deriving AEGL-3 values were robust and could be scaled over the full range of relevant time periods (10 to 480 min). The only studies available for deriving AEGL-2 values were the acute lethality studies in rats and guinea pigs. The AEGL-2 values were, therefore, derived from a no-effect-level for extreme respiratory difficulty determined from the guinea pig

TABLE 4-13 Extant Standards and Guidelines for Ethyleneimine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended				
AEGL-2	33 ppm	9.8 ppm	4.6 ppm	1.0 ppm	0.47 ppm
AEGL-3	51 ppm	19 ppm	9.9 ppm	2.8 ppm	1.5 ppm
IDLH (NIOSH)[a]	NA	100 ppm	NA	NA	NA
PEL-TWA (OSHA)[b]	No values established; considered to be an occupational suspect carcinogen				
TLV-TWA (ACGIH)[c]	0.5 ppm (8-h), skin; Confirmed Animal Carcinogen with Unknown Relevance to Humans				
MAK (Germany)[d]	No value (carcinogenicity category 2: shown to cause cancer in animals; skin absorption; germ mutagen category 3A)				

[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]PEL-TWA (Permissible Exposure Limits - Time Weighted Average, Occupational Health and Safety Administration) (29 CFR 1910.1003 [1999]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[c]TLV-STEL (Threshold Limit Value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2001) 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.

[d]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration] [German Research Association) (DFG 2000) is defined analogous to the ACGIH-TLV-TWA.

no-effect-level for extreme respiratory difficulty determined from the guinea pig study. Guinea pigs but not rats were exposed to the lowest concentration not associated with a very serious effect. Therefore, AEGL-2 values were derived from one data point in one species. In addition, data are not available for deriving cancer risk values for ethylenimine; therefore, the AEGL values do not take into account potential carcinogenicity. Because it is a very reactive direct-acting alkylating agent, there is concern about potential carcinogenicity of ethylenimine after a single exposure as demonstrated in mice receiving a single subcutaneous injection (BRL 1968). A single-exposure inhalation carcinogenicity study would provide data for conducting a cancer risk assessment.

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APPENDIX A

Derivation of AEGL Values for Ethylenimine

Derivation of AEGL-2

Key study:	Carpenter et al. 1948
Toxicity End Point:	NOEL for extreme respiratory difficulty; 10 ppm for a 240-min exposure to guinea pigs
Time Scaling:	$C^n \times t = k$; n = 0.91 based on regression analysis of the guinea pig data C = 10 ppm/10 (uncertainty factor) = 1.0 ppm $C^n \times t = k$; C = 1.0 ppm, t = 240 min, n = 0.91 k = 240 ppm min
Uncertainty Factors:	Total = 10: 3 for interspecies differences, because 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 direct effect of an alkylating agent on the respiratory epithelium, and this mechanism is not expected to be different among species (NRC 2003). 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. 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 and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to alkylating agents. Alkylating activity of ethylenimine is not expected to vary appreciably among individuals in the population.
Calculations:	
10-min AEGL-2	$C = (k/t)^{1/0.91} = (240 \text{ ppm min}/10 \text{ min})^{1/0.91} = 33$ ppm
30-min AEGL-2	$C = (k/t)^{1/0.91} = (240 \text{ ppm min}/30 \text{ min})^{1/0.91} = 9.8$ ppm
1-h AEGL-2	$C = (k/t)^{1/0.91} = (240 \text{ ppm min}/60 \text{ min})^{1/0.91} = 4.6$ ppm
4-h AEGL-2	$C = (k/t)^{1/0.91} = (240 \text{ ppm min}/240 \text{ min})^{1/0.91} = 1.0$ ppm
8-h AEGL-2	$C = (k/t)^{1/0.91} = (240 \text{ ppm min}/480 \text{ min})^{1/0.91} = 0.47$ ppm

Derivation of AEGL-3

Key Study:	Carpenter et al. 1948
Toxicity End Point:	Threshold for lethality: the LC_{50} for a 480 min exposure was 35 ppm, the data was extrapolated to a LC_{01} (15 ppm)
Time Scaling:	$C^n \times t = k$; n = 1.1 based on regression analysis of the rat data C = 15 ppm/10 (total uncertainty factor) = 1.5 ppm $C^n \times t = k$; C = 1.5 ppm, t = 480 min, n = 1.1 k = 749.7934 ppm min
Uncertainty Factors:	Total = 10: 3 for interspecies differences, because 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 direct effect of an alkylating agent on the respiratory epithelium, and this mechanism is not expected to be different among species (NRC 2003). 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. In addition, the LC_{50} values for three species are within a factor of 2 and signs of very serious or life-threatening toxicity appear to be similar between animals and humans. 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 and DNA damage is persistent in respiratory and systemic organs following inhalation exposure to alkylating agents. Alkylating activity of ethylenimine is not expected to vary appreciably among individuals in the population
Calculations:	
10-min AEGL-3	$C = (k/t)^{1/1.1} = (749.7934 \text{ ppm min}/10 \text{ min})^{1/1.1} = 51$ ppm
30-min AEGL-3	$C = (k/t)^{1/1.1} = (749.7934 \text{ ppm min}/30 \text{ min})^{1/1.1} = 19$ ppm
1-h AEGL-3	$C = (k/t)^{1/1.1} = (749.7934 \text{ ppm min}/60 \text{ min})^{1/1.1} = 9.9$ ppm
4-h AEGL-3	$C = (k/t)^{1/1.1} = (749.7934 \text{ ppm min}/240 \text{ min})^{1/1.1} = 2.8$ ppm
8-h AEGL-3	$C = (k/t)^{1/1.1} = (749.7934 \text{ ppm min}/480 \text{ min})^{1/1.1} = 1.5$ ppm

APPENDIX B

Quantitative Cancer Assessment for Ethylenimine

Two reports were available for assessing the potential carcinogenicity of ethylenimine. In one study, 50% of rats injected subcutaneously with ethylenimine in arachis oil developed sarcomas at the injection site, whereas no rats injected with arachis oil alone and only 17% injected with ethylenimine in water developed sarcomas (Walpole et al. 1954). The route or exposure for this study precludes deriving a risk value for comparison with AEGL values.

Seven-day old male and female mice of two strains given a subcutaneous injection of ethylenimine (4.64 mg/kg body weight) and observed for 80 weeks caused an increase in the incidence of lung tumors in male mice of both strain and in the total incidence of tumors in male mice (BRL 1968). Although this is a single exposure study, it cannot be used to derive risk values for inhalation exposure, because the test material was administered subcutaneously. This study shows that ethylenimine can induce a carcinogenic response distant from the application site after only a single dose.

In another study, two strains of male and female mice were administered ethylenimine by gavage for 3 weeks followed by ethylenimine in feed for up to 18 months (BRL 1968). All groups exposed to ethylenimine developed neoplasms (pulmonary adenomas and/or hepatomas) by the end of the study. This study cannot be used to derive risk values because of the lack of an adequate dose term for the mouse. Ethylenimine was administered by gavage at a specific dose (4.64 mg/kg/day) from 7- to 28-days of age followed by administration in feed for up to 18 months at a concentration that delivered the gavage dose. The investigators stated that the concentration of ethylenimine in feed corresponded to the gavage dose, but the actual concentration of ethylenimine in the feed was not reported. The concentration was likely based on body weight and feed consumption of a 28-day old mouse, and this concentration was not adjusted during the course of the study to maintain a constant dose. Therefore, because body weight and food consumption change markedly with growth of the mouse, the dose received between day 28 of age until termination of the study also changes markedly and cannot be estimated. Consequently, without an estimate of the dose term, a quantitative assessment cannot be conducted for comparison with AEGL values. Further, only one experimental dose was used in this study, precluding an adequate dose-response assessment.

APPENDIX C

Derivation of the Level of Distinct Odor Awareness (LOA) for Ethylenimine

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

The odor detection threshold (OT_{50}) for ethylenimine is 0.6980 ppm (van Doorn et al. 2002). The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

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

For the Fechner coefficient, the default $k_w = 2.33$ will be used because of the lack of chemical specific data:

$$3 = 2.33 \times \log (C/0.6980) + 0.5, \text{ which can be rearranged to}$$
$$\log (C/0.6980) = (3 - 0.5)/2.33 = 1.07, \text{ and results in}$$
$$C = (10^{1.07}) \times 0.6980 = 8.2008 \text{ ppm.}$$

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

$$LOA = C \times 1.33 = 8.20078 \text{ ppm} \times 1.33 = 10.907 \text{ (van Doorn et al. 2002)}$$

Therefore, the LOA for ethylenimine is 10.907 ppm.

APPENDIX D

Derivation Summary for Ethylenimine AEGL Values

AEGL -1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended				
Key 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. Total uncertainty factor: Interspecies: Not applicable. Intraspecies: Not applicable.				
Modifying Factor: Not applicable.				
Animal to Human Dosimetric Adjustment: Not applicable.				
Time Scaling: Not applicable.				
Data Adequacy: Data were not available for deriving AEGL-1 values.				

AEGL -2 VALUES

10 min	30 min	1 h	4 h	8 h
33 ppm	9.8 ppm	4.6 ppm	1.0 ppm	0.47 ppm
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: male guinea pigs, 6 per group				
Exposure Route/Concentration/Durations: Inhalation; 10, 25, 50, 100, or 250 ppm for 240 min				
Effects: Guinea pigs were exposed for 240 min. Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm 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 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
33 ppm	9.8 ppm	4.6 ppm	1.0 ppm	0.47 ppm

End Point/Concentration/Rationale: No-effect-level for lethality in the guinea pig: 10 ppm exposure for 4 h; effects at 25 ppm and higher were more severe than those defined for AEGL 2. The logical point of departure (POD) is 10 ppm for 480 min, but this POD would lead to AEGL-2 values close to or exceeding the life-threatening AEGL-3 concentrations.

Uncertainty Factors/Rationale:
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 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, and the alkylating activity of ethylenimine is not expected to vary appreciably among individuals in the population. Studies have shown that DNA damage is probably 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: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times k = t$, where $n = 0.91$ derived empirically from guinea pig LC_{50} data with exposure times ranging from 5 min to 480 min.

Data Adequacy: The only studies available for deriving AEGL-2 values were the acute lethality studies in rats and guinea pigs. The AEGL-2 values were, therefore, derived from a no-effect-level for extreme respiratory difficulty determined from the guinea pig study. Ethylenimine has carcinogenic activity; but these values do not take into consideration the potential excess lifetime cancer risk due to a single exposure.

AEGL -3 VALUES

10 min	30 min	1 h	4 h	8 h
51 ppm	19 ppm	9.9 ppm	2.8 ppm	1.5 ppm

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:
Male Wistar rats, 6 per group.

Exposure Route/Concentration/Durations:
Inhalation, 25 or 50 ppm for 480 min.

(Continued)

AEGL -3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
51 ppm	19 ppm	9.9 ppm	2.8 ppm	1.5 ppm

Effects: Exposure was for 480 min.
Effects occurred at both concentrations.
Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty
Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs.
Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys.
Mortality: 25 ppm (1/6) and 50 ppm (5/6)

End Point/Concentration/Rationale:
The threshold for lethality in rats exposed for 480 min exposure was 15 ppm (LC_{01}), derived by probit analysis of the data.

Uncertainty Factors/Rationale:
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 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. In addition, LC_{50} values for three species did not vary by more than twofold and signs of very serious or life-threatening toxicity appear to be similar between animals and humans.

Intraspecies: 3 - the effects appear to involve direct contact of the eyes or respiratory epithelium with a very reactive alkylating agent, and the alkylating activity of ethylenimine is not expected to vary appreciably among individuals in the population. Studies have shown that DNA damage is probably 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: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times k = t$, where n = 1.1 derived empirically from rat LC_{50} data for exposures from 5 min to 480 min. The 480 min value gave the LC_{01} with the smallest standard error. All other values were calculated from 480 min.

Data Adequacy: Acute lethality studies were available for three laboratory species, two of which were exposed to varying concentration of ethylenimine for duration ranging from 5 to 480 min. The log concentration versus log time plot showed a linear relationship of the LC_{50} values for the entire range of exposure durations. Therefore, the data set available for deriving AEGL-3 values was robust and it could be extrapolated over the full range of relevant time periods (10 to 480 min). Ethylenimine has potential carcinogenic activity; however, data were not available for deriving cancer risk values. The AEGL values do not take into consideration the potential excess lifetime cancer risk due to a single exposure.

APPENDIX E

Category Plot for Ethylenimine

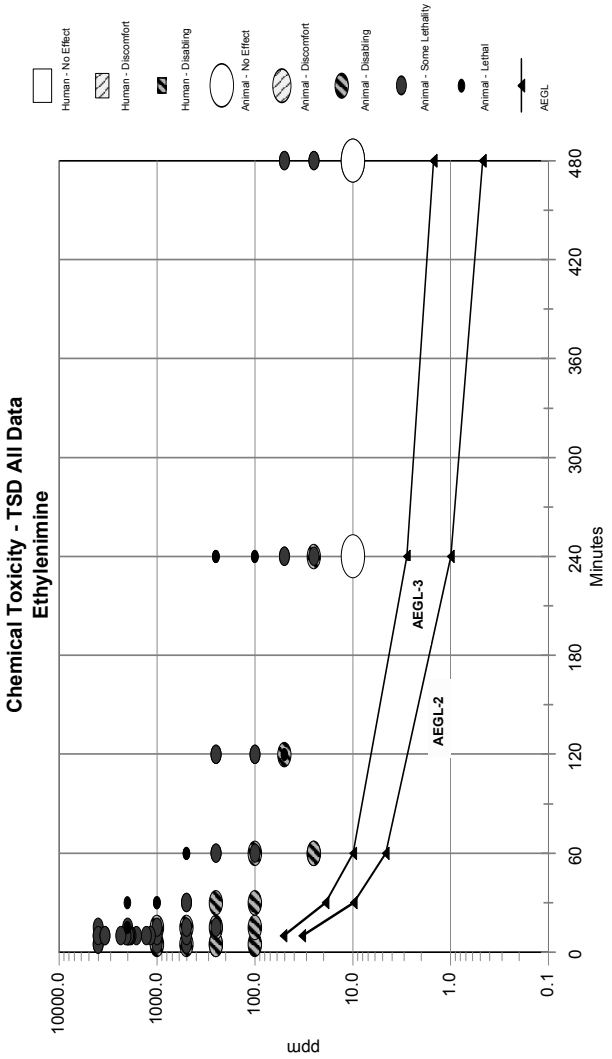

FIGURE E-1 Category plot for ethylenimine.

5

Fluorine[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 mins (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, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory) and Chemical Manager 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

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

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

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

Airborne concentrations below the AEGL-1 represent exposure 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

Fluorine is a reactive, highly irritating and corrosive gas used in the nuclear energy industry, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons. Fluorine is a severe irritant to the eyes, mucous membranes, lungs, and skin; the eyes and the respiratory tract are the target organ and tissues of an acute inhalation exposure. Death is due to pulmonary edema. Data on irritant effects in humans and lethal and sublethal effects in five species of mammals (dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGL values.

Regression analyses of the concentration-exposure durations (for the fixed end point of mortality) for all of the animal species reported in the key study (Keplinger and Suissa 1968) determined that the relationship between concentration and time is $C^n \times t = k$, where n = approximately 2 (actual value of n for the most sensitive species in irritation and lethality studies, the mouse, is 1.77). This concentration exposure duration relationship was applied to both the AEGL-2 and AEGL-3 levels because the irritant and corrosive action of fluorine on the respiratory tissues differs by only a matter of degree for these AEGL levels: (1) respiratory irritation with edema resulting in mild, reversible lung congestion, and (2) severe respiratory irritation resulting in severe lung congestion. Death results from acute pulmonary edema and consequent respiratory failure. Although the data base for fluorine is small, the data from the key study, aug-

mented with data from several other studies, were considered adequate for derivation of the three AEGL classifications for five time periods.

The AEGL-1 was based on the observation that adult volunteers could tolerate exposure to 10 ppm for 15 min without irritant effects (Keplinger and Suissa 1968). Although this value is below the definition of an AEGL-1 (slight irritation), it provides the longest controlled exposure duration for which no irritation in humans was reported. An intraspecies uncertainty factor of 3 was applied because fluorine is highly corrosive to the tissues of the respiratory tract and effects are not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 was considered adequate to protect this sensitive subpopulation because the value was a NOAEL and because shorter-term, repeated exposures produced no substantially greater effects in healthy individuals. The value is supported by a second study in which volunteers "tolerated" exposure to 10 ppm for an undefined period of time (Belles 1965). A modifying factor of 2 was applied based on a limited data base and short exposure durations. The resulting value of 1.7 ppm was used across all AEGL-1 exposure durations because, at mildly irritating concentrations, adaptation to slight sensory irritation occurs. As noted, this value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Mild lung congestion was selected as the threshold for irreversible, long-lasting effects as defined by the AEGL-2. The AEGL-2 was based on an animal study in which mild lung congestion was observed in mice at 67 ppm for 30 min and 30 ppm for 60 min (Keplinger and Suissa 1968). Effects were slightly less serious in three other species. Although concentrations causing irritant effects or lethality in three other species for the same time periods suggested similar species sensitivity, the mouse data, because of slightly lower values, were chosen as the basis for developing the AEGL-2 and AEGL-3. Similar sensitivity was observed among all species in the key study; therefore, an interspecies uncertainty factor of 1 was applied to address interspecies variability. Fluorine is a highly corrosive gas that reacts directly with the tissues of the respiratory tract, with no pharmacokinetic component involved in the toxicity; therefore, there is likely to be little difference among individuals in response to fluorine at concentrations that define the AEGL-2. The 30- and 60-min values for the mouse were divided by an intraspecies uncertainty factor of 3 to protect sensitive individuals, since effects are not likely to differ greatly among individuals, and by a modifying factor of 2, based on a limited data base. The 30-min value was time scaled to the 10-min AEGL-2, and the 60-min value was time scaled to the 4-h AEGL-2 value. Time scaling was based on the $C^{1.77} \times t = k$ relationship. The value of n was derived from regression analysis of the mouse lethality data in the key

study. The 8-h-AEGL-2 value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs. The 10- and 30-min AEGL-2 values are supported by studies in which human volunteers found short-term exposures to 15-25 ppm irritating to the eyes, nose, and throat (Rickey 1959; Keplinger and Suissa 1968).

The AEGL-3 values were derived from the highest exposures that resulted in no deaths in five species over 4 exposure durations (13 tests) for up to 45 days post exposure, but did produce severe lung congestion in the mouse (Keplinger and Suissa 1968). Severe lung congestion in the sensitive mouse was considered the threshold for lethality as defined by the AEGL-3. For the mouse, the 60-min highest non-lethal value was 75 ppm. This value is one-half of the 60-min LC_{50} value for the mouse. Because of the similar species sensitivity in the key study, based on both irritant effects and lethality, an interspecies uncertainty factor of 1 was considered sufficient to account for interspecies variability. The values were divided by an uncertainty factor of 3 to protect sensitive individuals (fluorine is a highly reactive, corrosive gas whose effect on respiratory tract tissues is not expected to differ greatly among individuals) and by a modifying factor of 2, based on a limited data base. Using the 60-min value of 75 ppm, AEGL-3 values for the other exposure times were calculated based on the $C^{1.77} \times t = k$ relationship. The value of n was derived from regression analysis of the mouse lethality data in the key study. The 8-h value was set equal to the 4-h value because fluorine would react with or be scrubbed by the nasal passages at these fairly low time-scaled concentrations. The safety of setting the 8-h value equal to the 4-h value is supported by another study in which a 7-h experimental exposure concentration of 100 ppm that resulted in an overall 60% mortality for four species (Eriksen 1945; Stokinger 1949) is higher than the extrapolated 7-h LC_{50} values for the mouse (50 ppm) and rat (65 ppm) based on the Keplinger and Suissa (1968) study. The calculated values are listed in Table 5-1.

1. INTRODUCTION

Fluorine belongs to the halogen group of elements; these elements do not occur in the elemental state in nature. When formed experimentally, fluorine is a pale yellow, diatomic gas (F_2) with a choking, irritating odor. Fluorine is used in the nuclear energy industry to produce gaseous uranium hexafluoride, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons (Teitelbaum 2001).

Chemically, fluorine is the most electronegative of the halogens and is the most powerful oxidizing agent known (Teitelbaum 2001). It reacts vigorously with most oxidizable substances at room temperature, frequently with ignition. It also combines with most other elements to form fluorides. Reaction with water results in decomposition of the water and formation of hydrofluoric acid, oxygen

(di)fluoride, hydrogen peroxide, oxygen, and ozone (O'Neil et al. 2001). Other relevant chemical and physical properties are listed in Table 5-2.

Fluorine is produced in an enclosed system of fluorine-generating cells. Anhydrous hydrogen fluoride, the basic starting material is mixed with potassium fluoride-hydrogen fluoride to form potassium bifluoride (KHF_2) which contains various concentrations of free hydrogen fluoride. Fluorine is produced by the electrolysis of anhydrous potassium bifluoride. Commercial fluorine plants operate in the United States, Canada, France, Germany, Italy, Japan, the United Kingdom, and South Africa. In 2003, the total commercial production capacity of fluorine in these countries was estimated at approximately 20,000 tons/year. Production data were unavailable for Russia and China. At most sites, elemental fluorine is used captively for the production of inorganic fluorides. The primary use of elemental fluorine is in the manufacture of uranium hexafluoride (Shia 2003).

In the U.S., fluorine is packaged and shipped under pressure (415 psi) in steel cylinders conforming to Department of Transportation specifications. The size of cylinders containing pure fluorine is limited to 2.7 kg; cylinders containing mixtures of 10-20% fluorine in nitrogen can contain up to 500 kg fluorine (Shia 2003).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of lethal effects from acute inhalation exposure to fluorine were identified. At low concentrations, fluorine is extremely irritating to the nose and eyes.

TABLE 5-1 Summary of AEGL Values for Fluorine

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1[a,b] (Nondisabling)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	No irritant effects - humans (Keplinger and Suissa 1968)
AEGL-2[c] (Disabling)	20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)	Mild lung congestion - mice (Keplinger and Suissa 1968)
AEGL-3 (Lethal)	36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)	Severe lung congestion - mice (Keplinger and Suissa 1968)

[a]The characteristic, pungent odor of fluorine will be noticeable at this concentration.
[b]The same value was used across all time periods because, at mildly irritating concentrations, adaptation to sensory irritation occurs.
[c]30-min and 1-h values are based on separate data points.

TABLE 5-2 Chemical and Physical Data for Fluorine

Parameter	Data	Reference
Chemical Name	Fluorine	ATSDR 2003
Synonyms	Bifluoriden, fluor, fluorine-19, fluoro	HSDB 2005
CAS Registry No.	7782-41-4	HSDB 2005
Chemical formula	F_2	O'Neil et al. 2001
Molecular weight	37.99	O'Neil et al. 2001
Physical state	Pale, yellowish green gas	O'Neil et al. 2001
Melting/boiling point	-219.61°C /-188.13°C	O'Neil et al. 2001
Density	1.695 g/cm^3 (air = 1.29)	Lewis 1993
Solubility	No data; reacts with water	O'Neil et al. 2001
Vapor pressure	1 mm Hg at -223°C >10 atm at 20°C	HSDB 2005 Teitelbaum 2001
Flammability	Nonflammable; powerful oxidizing agent	AAR 1987
Conversion factors	1 ppm = 0.64 mg/m^3 1 mg/m^3 = 1.554 ppm	ATSDR 2003

2.2. Nonlethal Toxicity

No human studies documenting specific fluorine exposure levels and time of exposure were found for acute, irreversible effects. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the exposure times, were not given. Fluorine has a characteristic, pungent odor (O'Neil et al. 2001). The odor threshold for fluorine is 0.10-0.20 ppm (Rickey 1959; Amoore and Hautala 1983). Available human data are summarized in Table 5-3 and discussed below.

Rickey (1959) reported on an outdoor spill test conducted by the U.S. Air Force. Two volunteers walked into the dispersed cloud downwind of a test spill. The measured concentration was 25 ppm which the men were able to tolerate; a specific exposure time was not stated. Following the exposure, both men developed sore throats and chest pains that lasted 6 h. The author stated that 20-50 ppm cannot be tolerated by humans but did not give additional data to support the statement.

TABLE 5-3 Summary of Irritant Effects in Humans

Concentration (ppm)	Exposure Time	Effects	Reference
10	Not stated	"Tolerated"	Belles 1965
10	15 min	No irritation of eyes, nose, or respiratory tract	Keplinger and Suissa 1968
10	3-5 min every 15 min for 2-3 h	slight irritation to the eyes and skin; no respiratory difficulty	Keplinger and Suissa 1968
15-25	Three breaths	Eye and nasal irritation	Belles 1965
25	Not stated	Tolerated; sore throats and chest pains of 6 h duration	Rickey 1959
25	5 min	Slight irritation to eyes, inhaled intermittently without difficulty	Keplinger and Suissa 1968
50	3 min	Irritating to eyes and slightly irritating to nose	Keplinger and Suissa 1968
67	1 min	Irritating to eyes and nose but not unbearable	Keplinger and Suissa 1968
78	1 min	Irritating to eyes and nose; caused coughing when inhaled	Keplinger and Suissa 1968
100	0.5 min	Very irritating to eyes and nose; no "after effects"	Keplinger and Suissa 1968
100	1 min	Very irritating to eyes and nose (subjects did not inhale); slightly irritating to the skin	Keplinger and Suissa 1968
100-200	Not stated	Reaction with skin and body hair	Belles 1965

Belles (1965) reported a series of tests involving nine male volunteers. All tolerated repeated short-term exposure to 10 ppm without "intolerable" discomfort. Concentrations of 15 to 25 ppm caused some eye and nasal irritation to the majority of subjects after just three breaths. Skin exposure tests indicated that reaction with body hair and dermal irritation may be expected between 100 and 200 ppm.

Keplinger and Suissa (1968) exposed five adult volunteers (19-50 years of age) to concentrations up to 100 ppm via a face mask. These tests were designed to test for irritation only. A concentration of 10 ppm for up to 15 min was reported to be nonirritating to the eyes and nose. A concentration of 25 ppm for 5 min caused slight irritation to the eyes but could be inhaled without respiratory difficulty. A concentration of 50 ppm for 3 min was irritating to the eyes and slightly irritating to the nose. Concentrations of 67 to 100 ppm for 1 min were irritating to the eyes and nose and became uncomfortable after a few seconds. The subjects reported the 67 ppm concentration as being less irritating than cigarette smoke in the eye. The subjects did not inhale at the 100 ppm concentration; inhalation exposure to 78 ppm caused coughing. The 100 ppm concentration caused slight irritation of the skin and a "sticky" feeling. According to the authors, the eyes were the most sensitive indicator of irritation in humans. Keplinger and Suissa (1968) also reported that a few repeated exposures at a concentration of 10 ppm for 3 to 5 min every 15 min over a 2- to 3-h time period caused only slight irritation to the eyes and skin. No respiratory difficulty was reported.

Lyon (1962) reported a lack of significant medical findings in 61 workers exposed to fluorine concentrations in excess of 0.1 ppm. Over a nine-year period, yearly average air concentrations ranged from 0.3 to 1.4 ppm (range <0.1 to 24.7 ppm). Workers were exposed either for 50-60% of their work time for periods of 7-9 months or 10% of their work time at the highest concentrations. Average daily urine fluorine excretion was 1.1 mg/L. Medical records of workers exposed to average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) were evaluated for the last four years of exposure. These workers reported fewer incidences of respiratory complaints or diseases than a similar group of 2000-3000 nonexposed workers. Usefulness of the study is limited by the lack of fluorine determination in urine of unexposed workers and the inability of the measurement technique to differentiate between fluorine and hydrogen fluoride. However, the author noted that samples were taken only when the characteristic odor of fluorine was present and the characteristic odor of hydrogen fluoride was absent. In contrast, Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency over that in the non-exposed population.

There is potential for individuals to become sensitized to halogens following acute exposure. A review of studies on drinking water fluoridation and a study with rabbits treated with sodium fluoride did not indicate that immune reactions occurred (ATSDR 2003).

2.3. Developmental/Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to fluorine. Fluoride is rapidly absorbed following oral ingestion, crosses the placenta in limited amounts, and is found in placental and fetal tissue (ATSDR 2003). Studies on the incidence of reproductive or developmental effects in areas using fluoridated water have found no correlation between fluoridation levels and birth defects (ATSDR 2003).

2.4. Genotoxicity

No data concerning the genotoxicity of fluorine in humans were identified in the available literature.

2.5. Carcinogenicity

Although several studies indicated an increase in respiratory cancers among workers engaged in several industries where they could be exposed to hydrogen fluoride or fluoride dusts, the concomitant exposure to other chemicals and smoking status of the workers, along with the lack of clear exposure concentration make the studies of questionable relevance (ATSDR 2003). There is no carcinogenicity data for fluoride gas.

2.6. Summary

No human data involving acute lethal exposures were located. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the duration of exposure, were not given. In a fairly well reported study with human volunteers, 10 ppm for 15 min caused no irritation of the eyes, nose, or respiratory tract and 10 ppm for 3 to 5 min every 15 min for 2 to 3 h caused slight irritation to the eyes and skin but no respiratory difficulty.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Data on acute lethal concentrations of fluorine for exposure durations of 5 min to 7 h are available for the rat, mouse, guinea pig, and rabbit. A study with the dog involved repeated exposure. Data on single acute exposures are summarized in Table 5-4.

TABLE 5-4 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	10,000	5 min	100% mortality	Eriksen 1945;
	1000	30 min	100% mortality	Stokinger 1949
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	54% mortality	
Rat	700	5 min	LC_{50}	Keplinger and
	390	15 min	LC_{50}	Suissa 1968
	270	30 min	LC_{50}	
	185	1 h	LC_{50}	
Mouse	10,000	5 min	100% mortality	Eriksen 1945;
	1000	30 min	100% mortality	Stokinger 1949
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	96% mortality	
Mouse	600	5 min	LC_{50}	Keplinger and
	375	15 min	LC_{50}	Suissa 1968
	225	30 min	LC_{50}	
	150	1 h	LC_{50}	
Guinea pig	10,000	5 min	100% mortality	Eriksen 1945;
	1000	30 min	100% mortality	Stokinger 1949
	500	1 h	100% mortality	
	200	3 h	90% mortality	
	100	7 h	no mortality	
Guinea pig	395	15 min	LC_{50}	Keplinger and
	170	1 h	LC_{50}	Suissa 1968
Rabbit	10,000	5 min	100% mortality	Eriksen 1945;
	1000	30 min	100% mortality	Stokinger 1949
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	88% mortality	
Rabbit	820	5 min	LC_{50}	Keplinger and
	270	30 min	LC_{50}	Suissa 1968

[a] LC_{50} and 100% mortality values were obtained at 14 days post exposure.

3.1.1. Dogs

No studies on single exposures were located. In short-term, repeated exposures, groups of five dogs (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 h/day, 5 days/week for a total exposure of 170 h. Concentrations were estimated by metering; no analyses were made. At the two higher concentrations, dogs exhibited seizures followed by death. At the 16 ppm exposure, mortality was 100% by the 60^{th} h of exposure. No toxic symptoms and no deaths were observed at the two lower

concentrations. Histological changes included moderate to moderately severe hemorrhage and liver congestion in 4 of 4 animals at 16 ppm, red discoloration of the lungs, mild bronchitis, and bronchiectasis in 4 of 5 dogs at 5 ppm, pulmonary hemorrhage and edema in 2 of 5 dogs at 2 ppm, and no consistent significant damage at 0.5 ppm.

3.1.2. Rats

Eriksen (1945) and Stokinger (1949) reported the same study in which a fluorine concentration of 10,000 ppm for an exposure time of 5 min was fatal to rats (sex and strain unspecified) within 24 h, with the majority of deaths occurring by the end of the exposure period. Thirty minutes of exposure to 1000 ppm caused 87% mortality and mortality reached 100% by 14 days post exposure. A concentration of 500 ppm for 1 h caused 90% mortality by the end of the exposure period. Percent mortality increased at 24 h post exposure, and at 14 days, all animals were dead. By 4 days post exposure, mortality was 100% for rats exposed to 200 ppm for 3 h. At 14 days after exposure to 100 ppm for 7 h, 54% of the animals were dead.

Autopsy results indicated that fluorine gas was severely corrosive to the respiratory tract as shown by bronchial and alveolar necrosis. Death was attributed to respiratory failure resulting from acute pulmonary damage involving edema, emphysema, and hemorrhage. Gross observations of animals surviving the 100 and 200 ppm concentrations and sacrificed 14 days post exposure revealed that lung damage was either slight or had undergone substantial repair. Kidney abnormalities including general engorgement, slight edema, slight swelling of the cortex and inflammation of the medulla were observed (frequency not stated) at 14 days post exposure but not at the end of the exposure period. Technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable in this study; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Osborne-Mendel rats (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 min. The LC_{50} values were 700, 390, 270, and 185 ppm, respectively. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 h after exposure. A few deaths were recorded after 24 h. Animals that lived for 48 h post exposure generally survived the 14-day observation period. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs. No deaths were reported in rats tested at 50% of the LC_{50} for each of the time periods.

Repeated daily exposures of rats (sex and strain unspecified) to concentrations of 0.5, 2, 5, and 16 ppm were conducted over a period of 21-35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 h/day, 5 days/week. Rats exposed at the two highest concentrations had symptoms of

coarsening and stiffening of the fur and irritation of the eyes and nose; these symptoms were mild at the two lower concentrations. Mortalities at the end of the exposure period were 0, 8, 27, and 50% at 0.5, 2, 5, and 16 ppm, respectively. A 10% weight loss occurred at the 16 ppm exposure concentration, but weight gains occurred at the lower exposure concentrations. Blood and hematology parameters were unchanged at all concentrations. Severe pulmonary irritation, oral lesions, and testicular degeneration occurred at 16 ppm; no grossly observable lung changes occurred at the two lower concentrations.

3.1.3. Mice

Eriksen (1945) and Stokinger (1949) exposed mice (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, 500 ppm for 1 h, and 200 ppm for 3 h were 100% fatal by the end of a 14-day post-exposure period. A concentration of 100 ppm for 7 h resulted in 96% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Swiss-Webster mice (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 min. The LC_{50} values for the mice for the four respective time intervals were 600, 375, 225, and 150 ppm. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 h after exposure. A few deaths were recorded after 24 h. Animals that lived for 48 h post exposure generally survived the 14-day observation period. No deaths were reported in mice tested at 50% of the LC_{50} for each of the time periods. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs.

3.1.4. Guinea Pigs

Eriksen (1945) and Stokinger (1949) exposed guinea pigs (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for exposure times of 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, and 500 ppm for 1 h were 100% fatal by the end of a 14-day post exposure period. A concentration of 200 ppm for 3 h resulted in 90% mortality, and a concentration of 100 ppm for 7 h resulted in no mortality. The majority of animals that died did so by the end of the exposure period. Au-

topsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. Sublethal concentrations produced gross changes in the liver and kidneys (not further described). As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of five New England guinea pigs (sex unspecified) to measured concentrations of fluorine for periods of 15 or 60 min. LC_{50} values were 395 ppm at 15 min and 170 ppm at 60 min. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Cause of death and organ pathology were the same as discussed for the rat and mouse above.

3.1.5. Rabbits

Eriksen (1945) and Stokinger (1949) exposed rabbits (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, 500 ppm for 1 h, and 200 ppm for 3 h were 100% fatal by the end of a 14-day post exposure period. A concentration of 100 ppm for 7 h resulted in 88% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. In rabbits, pulmonary hemorrhage was a more important component of lung damage than in other species. Death was attributed to respiratory failure resulting from acute pulmonary damage. “Infectious processes” were present in the lungs of some survivors. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 5 New England rabbits (sex unspecified) to measured concentrations of fluorine for two time periods. LC_{50} values for exposures of 5 and 30 min were 820 and 270 ppm, respectively. Clinical signs and organ pathology were the same as for the rat and mouse discussed above.

In short-term, repeated exposures, rabbits (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime was not stated, but was presumably 5 h/day for a total exposure of 170 h. At the two higher concentrations, mortality was 100%; at 2 ppm, 2 of 10 rabbits died; and at 0.5 ppm, 1 of 18 rabbits died. Histological changes included liver congestion and moderate to moderately severe lung hemorrhage in 4 of 4 animals at 16 ppm and moderate pulmonary irritation and slight liver damage in 4 of 5 animals at 5 ppm. At 2 ppm

there was mild bronchial inflammation in 3 of 4 animals, and at 0.5 ppm there was little or no pulmonary damage.

3.2. Nonlethal Toxicity

Studies conducted at concentrations that were less than lethal are summarized in Table 5-5. Data are presented for the dog, rat, mouse, guinea pig, and rabbit. The latter four species were exposed to concentrations approximating 50, 25, and 12.5% of their respective LC_{50} values for exposure durations of 5, 15, 30, and 60 min.

3.2.1. Dogs

Dogs (sex and strain unspecified) exposed to 93 ppm for 60 min had symptoms of irritation, cough, slight labored breathing, and vomiting (Keplinger and Suissa 1968). Examinations at 7 to 14 days post exposure revealed small areas of hemorrhage in the lungs. Dogs exhibited only eye irritation at an exposure of 68 ppm for 1 h. No irritation or gross pathologic changes in the lung were evident following exposure to 38 ppm for 1 h. In short-term, repeated exposures, dogs treated with fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 h/day) showed no significant lung damage (Stokinger 1949).

3.2.2. Rats

Sublethal effects of inhalation exposure to fluorine were assessed in Osborne-Mendel rats (sex unspecified) exposed to concentrations of 500 ppm and 350 ppm (71% and 50% of the 5-min LC_{50} values) for 5 min, 195 ppm (50% of the 15-min LC_{50}) for 15 min, and 140 ppm (50% of the 30-min LC_{50}) for 30 min (Keplinger and Suissa 1968). Very few signs of intoxication were observed immediately after exposure. Rats exposed to these concentrations experienced marked irritation of the eyes and respiratory tract immediately after exposure, and labored breathing and lethargy were observed several hours later. At sacrifice (up to 45 days post exposure), there was moderate to severe diffuse congestion of the lungs.

Sublethal exposures produced kidney and liver damage (Keplinger and Suissa 1968). Kidney damage was characterized by focal areas of coagulation necrosis in the cortex and focal areas of lymphocytic infiltration throughout the cortex and medulla. Liver damage included coagulation necrosis, periportal hemorrhages, and diffuse cloudy swelling. Kidney damage occurred at the same concentrations as lung involvement. Liver involvement occurred only at the highest sublethal concentrations. No-effect concentrations for organ pathology were 79 ppm for 5 min, 65 ppm for 15 min, 51 ppm for 30 min, and 30 ppm for 60 min.

TABLE 5-5 Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Dog	93	1 h	irritation, cough, slight labored breathing, vomiting, small areas of hemorrhage in lungs	Keplinger and Suissa 1968
	93	15 min	slight lung congestion	
	68	1 h	eye irritation	
	38	1 h	no effect	
Rat	500	5 min	marked signs of intoxication, severe changes in lungs	Keplinger and Suissa 1968; Keplinger 1969
	350	5 min	moderate lung congestion	
	325	5 min	moderate lung congestion	
	175	5 min	labored breathing; mild lung congestion	
	150	5 min	very mild lung congestion	
	88	5 min	no effect	
Rat	195	15 min	irritation, labored breathing, moderate diffuse congestion	Keplinger and Suissa 1968
	98	15 min	very mild lung congestion	
	49	15 min	no effect	
Rat	140	30 min	irritation of eyes and nose, slight labored breathing, moderate diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	68, 70	30 min	very mild lung congestion	
	35	30 min	no effect	
Rat	140	1 h	severe diffuse lung congestion, kidney and liver changes	Keplinger and Suissa 1968; Keplinger 1969
Rat	93	1 h	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	75	1 h	mild diffuse lung congestion	
	47	1 h	very mild diffuse lung congestion	
	28	1 h	no effect	

Mouse	467	5 min	marked irritation of eyes and respiratory tract, labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	321	5 min	moderate diffuse lung congestion	
	300	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	
	174	5 min	slightly labored breathing; very mild diffuse lung congestion	
	130	5 min	very mild lung congestion	
	79	5 min	no effect	
Mouse	350, 359	15 min	severe diffuse lung congestion to congestion with hemorrhages	Keplinger and Suissa 1968; Keplinger 1969
	265, 285	15 min	moderate diffuse lung congestion	
	188	15 min	eye irritation and labored breathing; moderate diffuse lung congestion	
	87	15 min	very mild diffuse lung congestion	
	65	15 min	no effect	
Mouse	113	30 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	64, 67	30 min	very mild lung congestion	
	32	30 min	no effect	
Mouse	75	1 h	eye irritation and labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	55	1 h	very mild lung congestion	
	50	1 h	labored breathing; mild diffuse lung congestion	
	30	1 h	very mild diffuse lung congestion	
	15	1 h	no effect	
Guinea pig	198	15 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	70	15 min	no effect	

(Continued)

TABLE 5-5 Continued

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Guinea pig	135	1 h	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	73	1 h	no effect	
Guinea pig	100	7 h	severe damage to the respiratory system	Eriksen 1945; Stokinger 1949
Rabbit	410	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	Keplinger and Suissa 1968
	134	5 min	slightly labored breathing	
	51	5 min	no effect	
Rabbit	135	30 min	eye irritation, very mild diffuse congestion	Keplinger and Suissa 1968
	71	30 min	no irritation, very mild diffuse congestion	
	32	30 min	no effect	

[a]Measured up to 45 days post exposure; serial sacrifice revealed that effects did not become worse with time and, in some cases, lung changes showed some regression starting 7 days post-exposure.

Mild effects of inhalation exposure to fluorine were assessed in rats exposed to concentrations equal to 25% of the LC_{50} values for exposure times of 5, 15, 30, and 60 min (175, 98, 70, and 47 ppm, respectively) (Keplinger and Suissa 1968). Rats exposed to these concentrations experienced eye irritation, slightly labored breathing and very mild to mild diffuse congestion of the lungs. No-effect levels and exposure times were 88 ppm for 5 min, 49 ppm for 15 min, 35 ppm for 30-min, and 28 ppm for 60 min.

Groups of 10 Osborne-Mendel rats were treated with single and repeated exposures of fluorine (Keplinger 1969). Single exposures occurred for 5 min at concentrations of 85-150 ppm and 256-450 ppm, for 30 min at 46-68 ppm, and for 60 min at 45-75 ppm and 88-170 ppm. The animals were sacrificed immediately after exposure or at 7, 14, 21, or 45 days after the last exposure; however, the day of sacrifice for each test was not reported. Gross pathology results were not well described, and results of each individual test were not reported; those results that were reported are summarized in Table 5-5. Single exposures for 5 min at 85-150 ppm induced very mild lung congestion and some kidney changes, but no liver lesions. At the higher concentrations, 256-450 ppm, moderate diffuse congestion of the lungs and gross damage (primarily discoloration) of the liver and kidneys occurred. Following exposure to 46-68 ppm for 30 min, the livers were grossly normal while the lungs and kidneys showed slight gross pathologic changes. Exposure for 60 min at the lower concentration range resulted in lung and kidney changes but no effect on the liver. At the higher concentration range, severe diffuse congestion and hemorrhages of the lungs were observed. Both the kidneys and livers showed gross changes.

Keplinger (1969) also reported on repeated exposure. Lung, kidney and liver effects in rats exposed four times at daily to weekly intervals to various concentrations were compared with effects following a single treatment at the same concentration. Effects on the lungs (congestion, hemorrhage), kidneys, and liver were greater following the single exposure than following the repeated weekly exposures. For example, four repeated exposures to 30 ppm for 60 min every other day produced lesser effects than a single exposure to 30 ppm for 60 min; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

3.2.3. Mice

Sublethal effects of inhalation exposure to fluorine were assessed in Swiss-Webster mice exposed to concentrations equal to 78% of the 5-min LC_{50} (467 ppm) and 50% of the 5-min, 15-min, 30-min, and 1-h LC_{50} values (300, 188, 113, and 75 ppm, respectively) (Keplinger and Suissa 1968). A few additional tests were carried out at concentrations between the LC_{50} and 50% of the LC_{50} (Keplinger 1969). Very few signs of intoxication were observed immediately after exposure. Mice exposed to 467 ppm for 5 min experienced marked irritation of the eyes and respiratory tract immediately after exposure and la-

bored breathing and lethargy were observed several hours later. At sacrifice there was severe diffuse congestion of the lungs. At concentrations equal to 50% of the 5-min, 15-min, and 60-min LC_{50} values, mice showed moderate to severe diffuse congestion of the lungs.

In mice exposed to sublethal concentrations (specific concentrations not stated) there was some evidence of gross damage to the lungs, liver, and kidneys (Keplinger and Suissa 1968). Histological examination of the lungs revealed massive hemorrhages into the alveolar spaces and coagulation necrosis of alveoli with peribronchial lymphocytic proliferation. After 7 days there was proliferation of septal cells, macrophages and lymphocytes. Beginning at 7 days post exposure, livers showed coagulation necrosis, periportal hemorrhages and diffuse cloudy swelling. Focal areas of coagulation necrosis appeared in the cortex of the kidney and focal areas of lymphocytic infiltration appeared throughout the cortex and medulla. Concentrations that caused no effects in the lungs did not cause effects in the liver or kidneys. Damage occurred in both the lung and kidney at the same concentration; liver changes occurred at higher concentrations. Although not specifically stated for each species, some or all of these same effects occurred in other species to the same or a lesser degree.

Mild effects were observed in mice at 174 ppm (5 min), 87 ppm (15 min), 67 ppm (30 min), and 50 ppm (60 min) (Keplinger and Suissa 1968). No-effect concentrations for organ pathology were 79 ppm for 5 min, 65 ppm for 15 min, 51 ppm for 30 min, and 30 ppm for 60 min. Four repeated exposures such as 30 ppm for 60 min every other day produced lesser effects than a single exposure of the same magnitude; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

3.2.4. Guinea pigs

Disabling, irreversible effects were not observed in New England guinea pigs exposed to concentrations lower than the LC_{50} values (Keplinger and Suissa 1968). In guinea pigs exposed to 50% of the 15-min LC_{50} (198 ppm), signs of eye and respiratory irritation and labored breathing and gross lung changes of mild diffuse congestion were present. At exposures to concentrations of 100 and 70 ppm for 5 min, mild effects were occasionally observed. For the 60-min exposures, eye and respiratory irritation and mild diffuse congestion of the lung were observed at 135 ppm (79% of the 60-min LC_{50}) and no effects were observed at 73 ppm (43% of the 60-min LC_{50}).

3.2.5. Rabbits

Eye and respiratory irritation and moderate diffuse congestion of the lungs were observed in New Zealand rabbits exposed to 410 ppm for 5 min (50% of the 5-min LC_{50}) (Keplinger and Suissa 1968). Effects in rabbits at 16% of the

5-min LC_{50} (134 ppm) and 50% of the 30-min LC_{50} (135 ppm) were slight to mild (Keplinger and Suissa 1968). In short-term, repeated exposures, rabbits administered fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 h/day) showed little or no lung damage (Stokinger 1949).

3.3. Developmental and Reproductive Toxicity

No studies addressing developmental or reproductive effects following acute inhalation exposure to fluorine were located.

3.4. Genotoxicity

No data on inhalation exposures were located in the available literature. Genotoxicity studies were conducted with sodium fluoride or potassium fluoride. Negative results were found for *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 with or without metabolic activation, and positive results were found in the mouse lymphoma (with and without activation), sister chromatid exchange (with and without activation), and chromosome aberration tests (without activation) (NTP 1990), but generally at doses that produced cellular toxicity (ATSDR 2003).

3.5. Chronic Toxicity and Carcinogenicity

No carcinogenicity studies using acute or longer-term inhalation exposure were located. Because inhaled fluorine would exert its systemic effects as fluoride ion, oral studies of fluoride administration may be relevant. A chronic oral carcinogenicity study in which sodium fluoride was administered to male and female rats and mice in the drinking water resulted in equivocal evidence of bone cancer in male rats, but not in female rats or mice of either gender (NTP 1990). The cancer was a rare bone osteosarcoma. Another chronic oral study, with sodium fluoride administered in the feed found no evidence of cancer in male or female rats (Maurer et al. 1990).

3.6. Summary

LC_{50} concentrations for the mouse, rat, guinea pig, and rabbit from the study of Keplinger and Suissa (1968) are summarized in Table 5-6 and graphed in Figure 5-1. With the exception of the 5-min LC_{50} for the rabbit, the LC_{50} values for all four species at the different exposure times were not statistically significantly different. Additionally, a 7-h LC_{54} value of 100 ppm for the rat was available (Eriksen 1945; Stokinger 1949).

TABLE 5-6 Summary of LC_{50} Data in Animals (ppm)

Exposure Time	Rat	Mouse	Guinea Pig	Rabbit
5 min	700	600	—	820
15 min	390	375	395	—
30 min	270	225	—	270
60 min	185	150	170	—

Abbreviation: A dash (—) indicates no data.
Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

No data on acute inhalation and developmental toxicity were located. Genotoxicity was observed only at concentrations that were toxic to cells (ATSDR 2003). Chronic and carcinogenicity studies with oral. administration of sodium fluoride resulted in equivocal evidence of cancer in one study (NTP 1990) and no evidence of cancer in a second study (Maurer et al. 1990).

The only experimental data available for longer-term exposures was the 7-h exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). At this exposure concentration and duration, the mouse and rabbit were the most sensitive species as indicated by high mortality, the rat was intermediate in sensitivity, and the guinea pig was the least sensitive species with no mortality.

Lowest values for disabling, irreversible effects; nondisabling, reversible effects; and no-effect concentrations for various exposure periods for each species are summarized in Table 5-7. In many cases, the listed concentration is the only tested concentration.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Pharmacokinetic data from acute exposures were not available. Metabolic/kinetic considerations are not relevant regarding the determination of AEGL values as animals die of acute respiratory failure. Fluorine is hygroscopic and will react with the moist mucus membranes of the respiratory passages.

Following inhalation, fluorine may be absorbed by the lungs, particularly following the formation of hydrofluoric acid by reaction with moisture in the lungs. Fluoride from the circulating blood is deposited in the bone where it substitutes for the hydroxyl group of hydroxyapatite, the principal mineral component of bone. Renal excretion of fluoride is rapid; accumulation in the kidney occurs as fluoride is concentrated in the urine for elimination (Teitelbaum 2001).

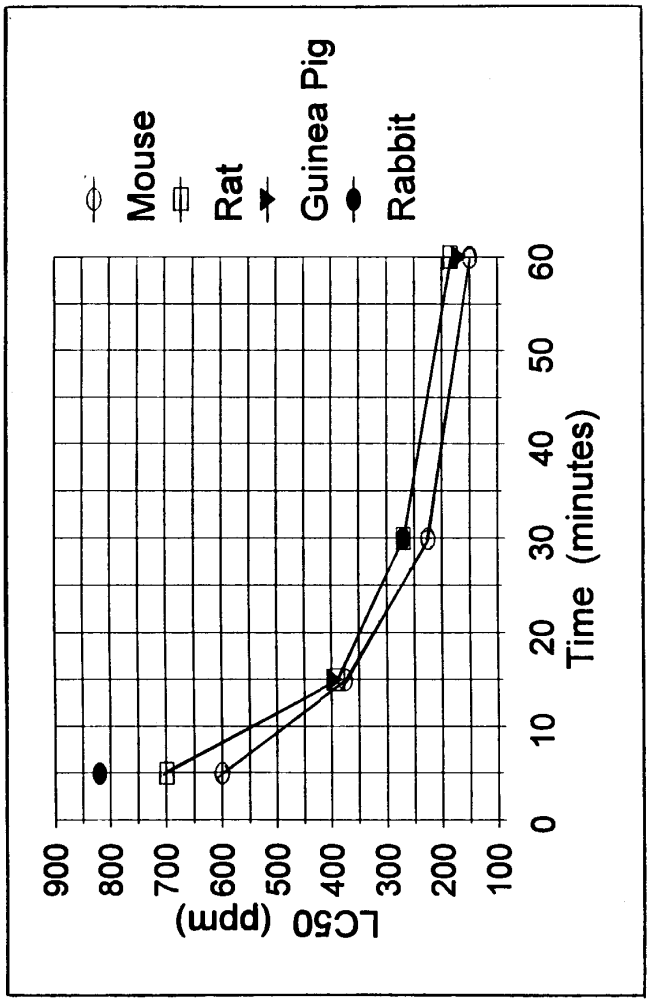

FIGURE 5-1 LC_{50} values for four species of animals. The continuous lines represent values for the mouse and rat. Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

TABLE 5-7 Summary of Nonlethal Effects in Animals[a]

Species	Exposure Time	Disabling Effects (ppm)	Nondisabling Effects (ppm)	No Effect (ppm)
Dog	5 min	—	—	—
	15 min	—	93	—
	30 min	—	—	—
	60 min	93	68	38
Rat	5 min	325	150	88
	15 min	195	98	49
	30 min	140	70	35
	60 min	140	47	28
Mouse	5 min	300	130	79
	15 min	188	87	65
	30 min	—	64, 67	32
	60 min	75	30	15
Guinea pig	5 min	—	—	—
	15 min	—	198	70
	30 min	—	—	—
	60 min	—	135	73
Rabbit	5 min	410	134	51
	15 min	—	—	—
	30 min	—	135	32
	60 min	—	—	—

[a]Effects include both irritation and organ lesions.
A dash (—) indicates no data.
Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

4.2. Mechanism of Toxicity

Although fluorine reacts with water vapor in the moist respiratory passages, some fluorine persists in saturated water vapor for periods up to 1 h (Slabbey and Fletcher 1958). Therefore, it is likely that some of the inhaled fluorine will persist in the elemental form in the saturated air of the respiratory tract and will be carried into the lungs. The available studies show that damage to the respiratory tract, particularly the lung (edema, emphysema, and hemorrhage), is the major pathology associated with acute exposure to fluorine (Eriksen 1945; Stokinger 1949; Keplinger and Suissa 1968; Keplinger 1969). Fluorine is characterized as a severe irritant to the eyes, mucous membranes, skin, and lungs (NRC 1984; ACGIH 2004). Serious systemic effects are unlikely to occur from an acute exposure. In the studies summarized in Table 5-5, the eye and tissues of the respiratory tract sustain the impact of an acute exposure. Therefore, the concentration of fluorine in the inhaled air and not the absorbed dose is the primary determinant of effects.

4.3. Structure-Activity Relationships

The combined human and animal data on fluorine are sufficient for derivation of inhalation exposure guidelines and the use of structure-activity comparisons is not necessary. Like hydrogen chloride (HCl) and chlorine (Cl_2), fluorine is an irritant to the eyes, skin, and respiratory tract. When compared with mortality data for HCl and chlorine (Cl_2), fluorine is more toxic than HCl and slightly more toxic than Cl_2 to laboratory rodents. Mortality data indicate that HF is more toxic than HCl but less toxic than F_2 to laboratory rodents (Wohlslagel et al. 1976; Teitelbaum 2001; ATSDR 2003; NRC 2004). Kusewitt et al. (1989) exposed Fischer 344 rats to hydrogen halides at concentrations of 100 to 1000 ppm for 30 min. Tissue injury was confined to the nasal region with relative toxicities of HF>HCl≥HBr.

Penetration of any chemical to the lungs depends on water solubility. The more water soluble halides are scrubbed in the upper respiratory passages, and there is less penetration to the bronchioles and lungs. Fluorine decomposes water, forming HF, OF_2, hydrogen peroxide, oxygen, and ozone (O'Neil et al. 2001). The same reaction is predicted to occur in the moist respiratory passages. However, some unreacted fluorine will penetrate to the lungs. The water solubility of chlorine is 0.092 mol/L (25ºC), and the water solubility of bromine is 0.214 mol/L (20ºC). For the end point of lethality, the order of water solubility is also the order of toxicity, i.e., fluorine is poorly scrubbed and therefore more easily penetrates to the lungs, resulting in lower LC_{50} values than for the other halogens. For example, the 1-h LC_{50} values for chlorine in the rat range from 293-455 ppm (NRC 2004), whereas, the value for fluorine in the Keplinger and Suissa 1968 study is 185 ppm. Both chlorine and bromine are more readily scrubbed in the upper respiratory tract than is fluorine.

4.4. Concentration-Exposure Duration Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure duration (ten Berge et al. 1986). The only available data for scaling across time are LC_{50} data for the rat, mouse, and guinea pig for 5, 15, 30, and 60-min exposure durations. These data show that the association between concentration and exposure duration is a logarithmic one and the equations derived from the empirical data by regression analysis are expressed as $C^n \times t = k$ (where C = concentration, t = time in minutes, and k is a constant). For the three species the equations derived from the LC_{50} data are

$$C^{1.87} \times t = 1.05 \times 10^6 \text{ ppm-min (rat)}$$
$$C^{1.77} \times t = 4.45 \times 10^5 \text{ ppm-min (mouse)}$$
$$C^{1.64} \times t = 2.79 \times 10^5 \text{ ppm-min (guinea pig)}$$

Therefore, the relationship between concentration and time in approximately $C^2 \times t = k$. Appendix A contains a graph of this relationship for the mouse data.

4.5. Other Relevant Information

4.5.1. Susceptible Populations

No data on susceptible populations were located. Fluorine is highly irritating and corrosive to the tissues of the respiratory tract. The direct action of fluorine on the respiratory tract is not expected to vary greatly among most individuals. Although no data on fluorine exposures and asthmatics were located, studies with chlorine indicate that, compared with the general population, the respiratory tract of some asthmatics may be very reactive to the presence of irritant gases (NRC 2004). Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency compared to that in the non-exposed population.

4.5.2. Species Variability

A comparison of the animal and human data indicates that humans may be more sensitive to the irritant effects of fluorine than animals in that experimental animals suffered no gross effects at concentrations that humans found intolerable. For example, a concentration of 73 ppm for 1 h was a no-effect concentration for the guinea pig, but humans could not inhale 78 ppm for a short time without coughing.

Rats and rabbits exposed to 10,000 ppm of fluorine exhibited similar pulmonary damage; however, pulmonary hemorrhage was extensive in the rabbit whereas it was absent or extremely slight in the rat (Eriksen 1945; Stokinger 1949). At concentrations of 200 ppm and above, mortality rates were similar for rats, mice, rabbits, and guinea pigs for the different time periods. Guinea pigs succumbed more rapidly than the other three species at the three highest exposure levels (10,000, 1000, and 500 ppm), but showed less mortality at the 200 ppm level and no mortality at the 100 ppm level. These data, although slightly conflicting at times, do not indicate great species variability in response to fluorine exposures.

In another study, the 5-, 15-, 30-, and 60-min LC_{50} values for the rat, mouse, rabbit, and guinea pig were remarkably similar with only slightly lower values for the mouse compared to the other species (Keplinger and Suissa 1968). In all cases, death resulted from acute pulmonary edema and consequent respiratory failure. The similarity in LC_{50} values for each time period suggests similar species sensitivity.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A number of authors report 10 ppm as a concentration that caused either no discomfort or sensory irritation (Belles 1965; Keplinger and Suissa 1968). A higher level of 25 ppm caused eye irritation during a 5-min exposure (Keplinger and Suissa 1968), sore throat and chest pains that lasted for 6 h (duration of exposure not specified but presumed short) (Rickey 1959), and eye and nasal irritation after three breaths (Belles 1965). Humans were also exposed to 10 ppm for 3 to 5 min every 15 min over a 2- to 3-h period with only slight irritation to the eyes and skin (Keplinger and Suissa 1968).

5.2. Summary of Animal Data Relevant to AEGL-1

The animal data indicated that at 25% of the LC_{50}, there were mild signs of intoxication characterized by slight labored breathing and closed eyes (Keplinger and Suissa 1968). Below 25% of the LC_{50} there were no gross signs of lung pathology. Using the data of Keplinger and Suissa (1968) and Keplinger (1969), Ricca (1970) estimated the no-effect concentration with respect to lung, liver, and kidney pathology (based on $C \times t$ values) at 15% of the rat LC_{50} concentration. For the 1-h exposure, this concentration would be 28 ppm.

However, absence of apparent effects and gross signs of intoxication does not ensure that slight irritation or discomfort did not take place. No-effect concentrations are listed in Table 5-7. No-effect concentrations for the rat are 35 ppm for 30 min and 28 ppm for 60 min. For the mouse, the 30- and 60-min no-effect concentrations are 32 ppm and 15 ppm, respectively; the 60-min no-effect concentrations for the dog and guinea pig are 39 and 73 ppm, respectively. For all species, the 30-min no-effect concentrations range from 32 to 35 ppm and the 60-min no-effect concentrations range from 15 to 73 ppm. These values do not necessarily indicate the relative sensitivity of the species but, rather, reflect the experimental concentrations selected by the researchers.

5.3. Derivation of AEGL-1

Because human data for irritant effects are available, they should be used to derive the AEGL-1. The data of Keplinger and Suissa (1968) are the most comprehensive for humans exposed to 10 ppm. The 10 ppm concentration for 15 min was reported as a no-effect level for eye and nasal irritation but can be considered the threshold for notable discomfort as the next highest concentration tested, 25 ppm, produced slight to moderate discomfort. The 15-min time was the longest exposure duration for which no irritation was reported. An intraspecies uncertainty factor of 3 was applied to this NOAEL value because the con-

tact irritation from the highly corrosive fluorine is not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 is considered adequate to protect this sensitive subpopulation because the value is a NOAEL and because shorter-term, repeated exposures produced only slight irritation in healthy individuals. The value is supported by a second study in which volunteers "tolerated" exposure to 10 ppm for an undefined period of time (Belles 1965).

The clinical and experimental data base for human and animal exposures is limited to a single study (Keplinger and Suissa 1968). Other than the review of fluorine industrial exposures by Machle and Evans (1940) in which asthma attacks occurred more frequently in the industry than in non-exposed populations, no data on sensitive populations were found. A modifying factor of 2 was applied based on this limited database. The resulting value of 1.7 ppm (10 ppm/6) was used across all AEGL-1 exposure durations (Table 5-8 and Appendix B) because at mildly irritating concentrations there is accommodation to irritating gases. This value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

A category plot of the animal and human data in relation to the AEGL values can be found in Appendix C.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Irritant effects were noted in human volunteers at concentrations of 25 ppm for 5 min and 50 ppm for 3 min. Irritant effects at these concentrations were described as slight and are below the discomfort described by the AEGL-2 definition. The concentration of 67 ppm for 1 min was described as irritating to the eyes and nose but not unbearable. This description is similar to that of the AEGL-2, but the exposure period is extremely short.

6.2. Summary of Animal Data Relevant to AEGL-2

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to approximately 25% of the LC_{50} as mild with slightly labored breathing, closed eyes, and mild to very mild lung congestion. For the respective species, 30-min concentrations corresponding to 20-25%

of the LC_{50} were 70 ppm (rat), 67 ppm (mouse), and 71 ppm (rabbit). One-hour concentrations corresponding to 20-43% of the LC_{50} were 47 ppm (rat), 30 ppm (mouse), and 73 ppm (no-effect concentration for guinea pig); these data are summarized in Table 5-7.

6.3. Derivation of AEGL-2

Mild lung congestion was chosen as the threshold for irreversible or other serious, long-lasting effects as defined by the AEGL-2. The mouse was chosen as the most sensitive species although the experimental results for respective exposure periods for the tested species are very similar. The single data set (Keplinger and Suissa 1968) was extensive, being based on five species and four exposure durations. The mildest effects noted in the Keplinger and Suissa (1968) study were very mild or mild diffuse congestion which were observed at approximately 25% (20-43%) of the LC_{50} values. The rapid change in effects as the LC_{50} is successively halved indicates the steepness of the dose-response curve for fluorine.

The mouse 30-min and 1-h values which caused very mild lung congestion were chosen for calculation of the AEGL-2 values. These concentrations are 67 ppm (30% of the 30-min LC_{50}) and 30 ppm (20% of the 60-min LC_{50}), respectively. An interspecies uncertainty factor of 1, an intraspecies uncertainty factor of 3, and a modifying factor of 2 were then applied to these numbers to derive the AEGL-2 (see discussion of uncertainty factors for AEGL-3). Extrapolation across time was based on the equation for the mouse, $C^{1.77} \times t = k$. The 4- and 8- h values were scaled from the 1-h value (see Appendix B for calculations). The values are listed in Table 5-9. The 8-h-AEGL-2 value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs.

Although human exposure for durations longer than 1 min were to concentrations below the definition of the AEGL-2, a comparison of the human data with the derived values can be made. Extrapolating the 3-min exposure to 50 ppm from the data of Keplinger and Suissa (1968) to a 30-min time period results in a value of 13.6 ppm. The effects during this exposure, eye irritation (not otherwise specified) and slight nose irritation, are below the definition of the AEGL-2.

TABLE 5-8 AEGL-1 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
1.7 ppm ($2.6\ mg/m^3$)	1.7 ppm ($2.6\ mg/m^3$)	1.7 ppm ($2.6\ mg/m^3$)	1.7 ppm ($2.6\ mg/m^3$)	1.7 ppm ($2.6\ mg/m^3$)

TABLE 5-9 AEGL-2 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No information on irreversible or life-threatening effects caused by fluorine in humans was located. A concentration of 50 ppm was characterized as irritating and concentrations of 67-100 ppm were "very irritating and became uncomfortable after a few seconds."

7.2. Summary of Animal Data Relevant to AEGL-3

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to 50% of the LC_{50} values as "dyspnea, lethargy, red nose, and swollen eyes." No deaths occurred in any species (dog, rat, mouse, guinea pig, rabbit) at approximately 50% of the respective LC_{50} values. All species tested at 50% of the LC_{50} survived for up to 45 days post exposure. Effects ranged from disabling, characterized by respiratory irritation and labored breathing with severe diffuse lung congestion (mouse, 50% of the 1-h LC_{50}), to practically non-disabling, characterized by no eye or nose irritation and very mild diffuse lung congestion (guinea pig, 43% of the 1-h LC_{50}). At 50% of the 15-min LC_{50}, guinea pigs showed signs of respiratory irritation and labored breathing and gross changes in the lungs of mild diffuse congestion. Mice were tested at 50, 34, 20, and 10% of the LC_{50} for a 60-min exposure period. At a concentration equal to 50% of the 60-min LC_{50}, the mouse showed signs of irritation and labored breathing and severe diffuse congestion of the lungs. At concentrations equal to 34 and 20% of the 60-min LC_{50}, effects in the mouse were mild and very mild diffuse congestion, respectively, whereas the guinea pig, tested at 43% of its 60-min LC_{50} suffered no effects. The dog was tested at a concentration closer to one-third (93 ppm) rather than one-half of the 1-h LC_{50} concentration for the other species; at this concentration effects on the lungs were slight and would be more likely defined as an AEGL-2 level of effect. From the data involving effects at concentrations lower than the LC_{50} values for the various time periods, the guinea pig appears to be the least sensitive species and the mouse is the most sensitive species. The only experimental data available for longer term exposures was the 7-h exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). The extrapolated data of Keplinger and Suissa (1968), 7-h LC_{50} values of 65 and 50 ppm for the rat and mouse, respectively, yield more conservative concentrations.

7.3. Derivation of AEGL-3

The LC_{50} values for the rat and mouse are very close for the 15, 30, and 60 min time periods (Keplinger and Suissa 1968). At 15 and 60 min, the mouse, rat, and guinea pig LC_{50} values are almost identical (Table 5-6). At 30 min the mouse, rat, and rabbit LC_{50} values are very close. The strong concordance of the LC_{50} values between four animal species at three time points presents a strong case for the conclusion that lethality is a function of the concentration of fluorine in the air. Therefore, the exposure concentration equals the dose for fluorine and there is no need for scaling factors among species. Keplinger and Suissa (1968) demonstrated that at 50% of the LC_{50} there were no deaths in five tested species in a total of 13 tests conducted over a 5- to 60-min exposure duration. Therefore, 50% of the LC_{50} concentration was chosen as the NOEL for "life threatening effects." The mouse was chosen as the most sensitive species although all of the LC_{50} values were very similar. The 60-min value of 75 ppm was used as the basis for the AEGL-3.

Fluorine is a contact-site, direct-acting toxicant; there is no metabolic or pharmacokinetic component to fluorine-induced effects and there is likely to be little difference between species or among individuals in the response of biological tissues to fluorine exposure. The fact that the LC_{50} values for four species were essentially identical, and the mechanism of action is direct chemical (corrosive) destruction of lung tissue would argue for the use of an uncertainty factor of 1 when extrapolating from animals to man. However, the data used to develop the AEGL-3 were obtained primarily from one laboratory and not confirmed elsewhere. Therefore, a modifying factor of 2 is used for this uncertainty. A factor of 3 is added to account for variability in human susceptibility (fluorine is a highly reactive, corrosive gas whose effect on the respiratory tissues is not expected to differ greatly among individuals). The combined uncertainty/modifying factor is 6. Concentrations were scaled across time using the $C^{1.77} \times t = k$ relationship. Scaling from the 1-h experimental value to the 8-h exposure duration was considered realistic based on the similarity of extrapolated LC_{50} values from the Keplinger and Suissa (1968) study and the 7-h experimental values from the Eriksen (1945) and Stokinger (1949) study. The 8-h value was set equal to the 4-h value as was done for the AEGL-2. Values are summarized in Table 5-10 and calculations are in Appendix B.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

In summary, the AEGL values for various levels of effects and various time periods were derived using the following methods. The AEGL-1 was based on a study with human volunteers in which a concentration of 10 ppm administered for 15 min produced no irritation of the eyes, nose, or respiratory tract.

TABLE 5-10 AEGL-3 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)

This value was divided by 3 to account for differences in human sensitivity. Although no data on asthmatics, potentially susceptible populations were found, the fact that healthy humans have "tolerated" short-term exposures to 17 ppm indicates that the uncertainty factor of 3 is sufficient. A modifying factor of 2 was applied based on a limited data base. Because accommodation to the irritant effects of irritant gases occurs at mildly irritating concentrations, the derived value of 1.7 ppm was applied across all AEGL-1 time intervals.

In the absence of relevant human data, animal data were used to derive the AEGL-2 and AEGL-3 values. AEGL-2 values were derived based on concentrations equal to 25% of the LC_{50} values from a study with the most sensitive species, the mouse. These concentrations, 67 and 30 ppm for 30- and 60 min exposures, respectively, produced only very mild lung congestion. An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the use of a single data set were then applied to these numbers. Extrapolation across time was based on the regression equation for LC_{50} values and exposure times in the mouse, $C^{1.77} \times t = k$.

The AEGL-3 values were based on data using the laboratory mouse in which severe effects but no deaths were noted at 50% of the 30- and 60-min LC_{50} values (113 and 75 ppm, respectively). A concentration equal to 50% of the 60-min LC_{50} was selected from the mouse studies and scaled to other exposure times using the equation $C^{1.77} \times t = k$. An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the fact that the data set came from one laboratory and was not confirmed elsewhere were applied.

The AEGLs are summarized in Table 5-11. A summary of the derivations is contained in Appendix D.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 5-12. The AEGL values are very close to other guidelines for emergency exposures. The NIOSH IDLH 30-min value refers to respirator use, but is slightly higher (25 ppm) than the 30-min AEGL-3 of 19 ppm. The NIOSH IDLH is based on the observation of Rickey (1959) that two men were able to tolerate 25 ppm very briefly but both developed sore throats and chest pains that lasted 6 h; 50 ppm could not be tolerated. The definitions of the preliminary ERPGs correspond to the three AEGLs. The ERPG 1-h values were recently changed from 2, 7.5, and 10 ppm to 0.5, 5, and 20 ppm, reasonably close to the AEGL values. Documentation for the values was not given in this source. The

NRC Emergency Exposure Guidance Levels (EEGLs) are for occupational exposures and not the general public. The 30- and 60-min EEGLs are 10 and 7.5 ppm whereas the 30- and 60-min AEGL-2 values are 11 and 5 ppm. The EEGL guidelines are based on the human and animal data of Keplinger and Suissa (1968).

Although the populations are not comparable, the ACGIH TLV-TWA and STEL of 1 and 2 ppm, respectively, are similar to the AEGL-1 value of 1.7 ppm. The ACGIH TLV-TWA guideline is based on the lack of significant medical findings in workers exposed to fluorine for 7 years (Lyon 1962) coupled with evidence of tolerance development in animals (Keplinger 1969). The ACGIH TLV-STEL is based on the human study in which exposures to 10 ppm, repeated for 3 to 5 min every 15 min for 2-3 h, produced only slight irritation to the eyes and skin (Keplinger and Suissa 1968). The OSHA PEL-TWA is also based on the Lyon (1962) study; however, OSHA and NIOSH believed that the Lyon study did not involve 61 workers continually exposed but instead was a compilation of data on workers who may have had some short-term exposure to fluorine. Thus, their TWA is 10 times lower than that of ACGIH. Neither NIOSH nor OSHA have promulgated short-term exposure limits (STELs). The German MAK and Dutch MAC peak limits are both 0.2 ppm.

8.3. Data Adequacy and Research Needs

Data from human studies are sparse and used healthy human subjects; exposures were usually short-term, with some exposure durations not stated. The study by Keplinger and Suissa (1968) used several short exposure durations and concentrations were measured. Data from animal studies used five species and encompassed a wide range of exposure concentrations and exposure durations, but none of the durations was for longer than 1 h for less than lethal effects. The animal studies were undertaken 27-47 years ago and analytical techniques have improved since then. The data base for human studies is inadequate (except for the AEGL-1) and the data base for animal studies is adequate, at least for 30- and 60-min exposures.

TABLE 5-11 Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1[a] (Nondisabling)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm 2.6 mg/m^3)
AEGL-2[b] (Disabling)	20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)
AEGL-3 (Lethal)	36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)

[a]AEGL-1 values held constant across time because of accommodation to mildly irritating concentrations of irritant gases.
[b]30-min and 1-h AEGL-2 values are based on separate data points.

TABLE 5-12 Extant Standards and Guidelines for Fluorine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
AEGL-2	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
AEGL-3	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
ERPG-1 (AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			20 ppm		
EEGL (NRC)[b]	15 ppm	10 ppm	7.5 ppm		
IDLH (NIOSH)[c]		25 ppm			
REL-TWA (NIOSH)[d]					0.1 ppm
PEL-TWA (OSHA)[e]					0.1 ppm
TLV-TWA (ACGIH)[f]					1 ppm
TLV-STEL (ACGIH)[g]					2 ppm
MAK (Germany)[h]					0.1 ppm
MAK Peak Limit (Germany)[i]					0.2 ppm
MAC Peak Limit (The Netherlands)[j]					0.2 ppm? (0.5mg/m3)
OELV-LLV (Sweden)					0.1 ppm
OELV-STV (Sweden)	0.3 ppm (15 min.)				

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2004).

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[b]EEGL (Emergency Exposure Guidance Levels, National Research Council (NRC 1984).

The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c]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.

[d]REL-TWA (Recommended Exposure Limits - Time Weighted Average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[e]PEL-TWA (Permissible Exposure Limits - Time Weighted Average, Occupational Health and Safety Administration) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[f]TLV-TWA (Threshold Limit Value - Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2004) 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.

[g]TLV-STEL (Threshold Limit Value - Short Term Exposure Limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2004) 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.

[h]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration-German Research Association] (DFG 2002) is defined analogous to the ACGIH-TLV-TWA.

[i]MAK Spitzenbegrenzung (Peak Limit [give category]) (German Research Association 2002) (DFG 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than 2 exposure periods per work shift; total exposure may not exceed 8-h MAK.

[j]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.

[k]OELV -LLV(Occupational Exposure Limit Value-Level Limit Value).

[j]OELV -CLV(Occupational Exposure Limit Value-Ceiling Limit Value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level limit value (one working day) or a ceiling limit value (15 min or some other reference time period), and short time value (A recommended value consisting of a time-weighted average for exposure during a reference period of 15 min).

Although data from one study could be used to estimate the concentration-exposure duration relationships for several animal species ($C^n \times t = k$), the longest exposure duration was only 1 h. The study of Eriksen (1945) and Stokinger (1949), although flawed due to difficulty in monitoring the test concentrations, tend to support the extrapolation to longer exposure times. Their single data

point for the rat, 54% mortality at a concentration of 100 ppm for 7 h, when extrapolated to a 1-h exposure gives an approximate LC_{50} of 300 ppm (the actual concentration is probably lower due to chamber losses [Ricca 1970]). This value is within a factor of 2 of the 1-h LC_{50} for the rat of 187 ppm in the Keplinger and Suissa study.

The total body of data on the sublethal and lethal effects of fluorine is reasonably consistent. The mechanism of action is understood. Although most of the experimental exposures were of short duration, at least one additional experimental value is consistent with the derived time-scaling relationship. Application of an intraspecies uncertainty factor of 3 to the human data, an interspecies uncertainty factor of 1 to the animal data, and a modifying factor of 2 to reasonably consistent but limited human and animal data is appropriate to insure the safety of the values.

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APPENDIX A

Time-Scaling Graph for Fluorine

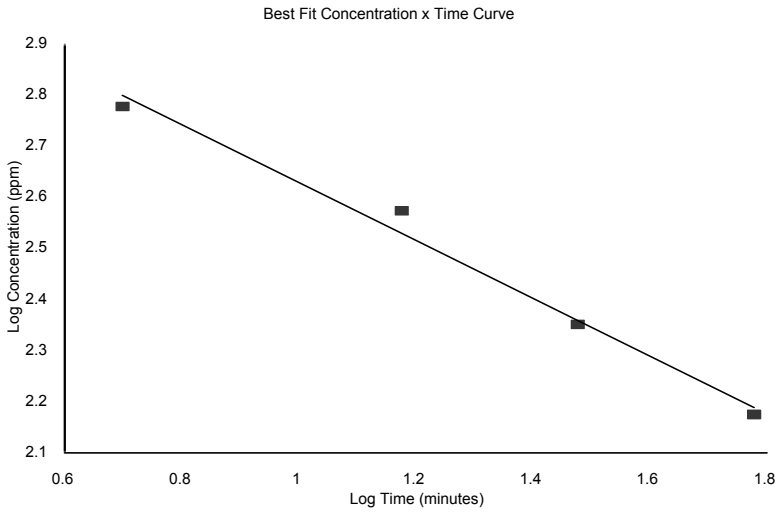

FIGURE A-1 LC_{50} values for the mouse. Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

Time (minutes)	Concentration (ppm)	Log time	Log concentration
5	600	0.6990	2.7782
15	375	1.1761	2.5740
30	225	1.4771	1.3522
60	150	1.7782	2.1761

Regression Output:	
Intercept	3.1958
Slope	-0.5658
R Squared	0.9872
Correlation	-0.9936
Degrees of Freedom	2
Observations	4

n = 1.77
k = 444989

APPENDIX B

Derivation of AEGL Values for Fluorine

Derivation of AEGL-1

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	No irritant effects in humans exposed to 10 ppm for 15 min
Scaling:	Not used; because accommodation to low concentrations of fluorine, the values were not time-scaled
Uncertainty factor:	3 for differences in human sensitivity (an uncertainty factor of 3 rather than 10 was used because 10 ppm for 15 min is a no-effect level; in addition, fluorine reacts chemically with the tissues of the respiratory tract and effects are unlikely to differ among individuals).
Modifying factor:	2 to account for a single data set.
Calculation:	10 ppm/6 = 1.7 ppm

Derivation of AEGL-2

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	Very mild diffuse lung congestion in mice exposed to 67 ppm for 30 min and 30 ppm for 1 h.
Scaling:	$C^{1.77} \times t = k$ (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar LC_{50} values) 3 to account for differences in human sensitivity (the toxicity end point is a mild effect level and the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals).
Modifying factor:	2 to account for a single data set.
Calculations:	$(67 \text{ ppm}/6)^{1.77} \times 30 \text{ min} = 2091 \text{ ppm}^{1.77} \cdot \text{min}$ $(30 \text{ ppm}/6)^{1.77} \times 60 \text{ min} = 1035.92 \text{ ppm}^{1.77} \cdot \text{min}$
10-min AEGL-2	$C^{1.77} \times 10 \text{ min} = 2091 \text{ ppm}^{1.77} \cdot \text{min}$ C = 20 ppm
30-min AEGL-2	67 ppm/6 = 11 ppm
1-h AEGL-2	30 ppm/6 = 5 ppm
4-h AEGL-2	$C^{1.77} \times 240 \text{ min} = 1035.92 \text{ ppm}^{1.77} \cdot \text{min}$ C = 2.3 ppm
8-h AEGL-2	Because of accommodation to low concentrations of irritant gases, the 8-h value was set equal to the 4-h value. C = 2.3 ppm

Derivation of AEGL-3

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	Severe diffuse lung congestion in mice exposed to 75 ppm for 1 h.
Scaling:	$C^{1.77} \times t = k$ (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar LC_{50} values) 3 to account for differences in human sensitivity (the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals).
Modifying factor:	2 to account for a single data set.
Calculations:	$(75 \text{ ppm}/6)^{1.77} \times 60 \text{ min} = 5244.23 \text{ ppm}^{1.77}\cdot\text{min}$
10-min AEGL-3	$C^{1.77} \times 10 \text{ min} = 5244.23 \text{ ppm}^{1.77}\cdot\text{min}$ C = 36 ppm
30-min AEGL-3	$C^{1.77} \times 30 \text{ min} = 5244.23 \text{ ppm}^{1.77}\cdot\text{min}$ C = 19 ppm
60-min AEGL-3	75 ppm/6 = 13 ppm
4-h AEGL-3	$C^{1.77} \times 240 \text{ min} = 5244.23 \text{ ppm}^{1.77}\cdot\text{min}$ C = 5.7 ppm
8-h AEGL-3	Because of accommodation to low concentrations of irritant gases, the 8-h value was set equal to the 4-h value. C = 5.7 ppm

APPENDIX C

Category Graph of Toxicity Data and AEGL Values for Fluorine

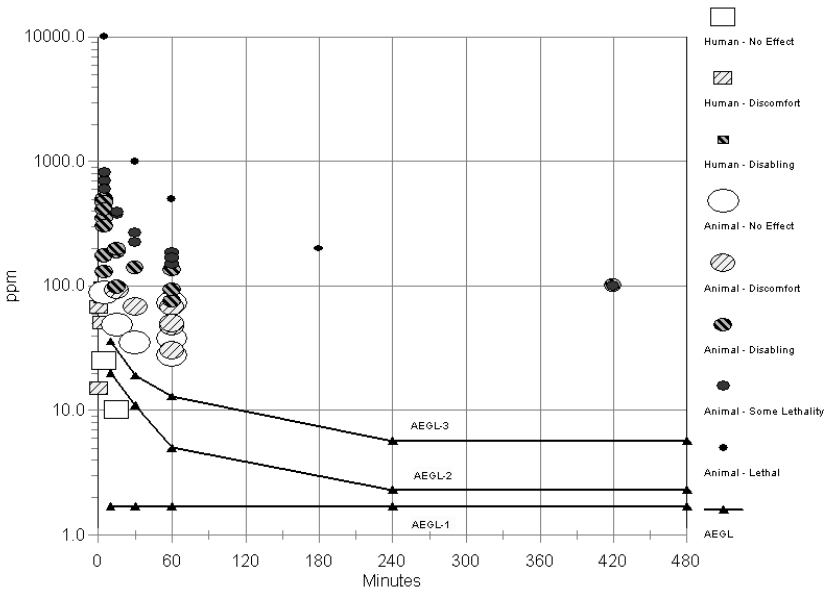

FIGURE C-1 Category graph of toxicity data and AEGL values for fluorine.

APPENDIX D

Derivation Summary for Fluorine AEGLs

AEGL-1 VALUES

10-min	30-min	1-h	4-h	8-h
1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm

Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29(1):10-18.

Test Species/Strain/Number: 5 human subjects

Exposure Route/Concentrations/Durations: Inhalation: 10-100 ppm for various exposure durations.

Effects:
10 ppm for 15 min: no eye, nose or respiratory irritation (basis for AEGL-1)
25 ppm for 5 min: eye irritation
50 ppm for 3 min: irritating to eyes, slightly irritating to nose
67 ppm for 1 min: irritating to eyes and nose
100 ppm for 1 min: very irritating to eyes and nose; subjects did not inhale

End Point/Concentration/Rationale: 10 ppm for 15 min resulted in no sensory irritation in healthy human subjects. Although this value is below the definition of an AEGL-1, it provides the longest exposure duration for which no irritation is reported. All studies indicated that fluorine is highly irritating and corrosive.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable, human subjects were tested
Intraspecies: 3- The effect was a NOAEL for sensory irritation. Limited workplace monitoring data showed that workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Modifying Factor: 2 - to account for a limited data base.

Animal to Human Dosimetric Adjustment: Not applicable; human data used.

Time Scaling: Not applied; at mildly irritating concentrations, adaptation to sensory irritation occurs.

Data Adequacy: The key study was well conducted and documented; data in supporting studies were limited.

AEGL-2 VALUES

10-min	30-min	1-h	4-h	8-h
20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm

Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29(1):10-18.

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:
Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 min
32, 65, 87, 188, 375 ppm for 15 min
16, 32, 67, 113, 225 ppm for 30 min
15, 30, 50, 75, 150 ppm for 1 h

Effects (the 30-min and 1-h exposures were considered):
30-min exposures:
16 ppm: no toxic signs, no gross lung pathology
32 ppm: no toxic signs, no gross lung pathology
67 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
13 ppm: irritation and labored breathing, mild diffuse lung congestion
225 ppm: LC_{50}
1-h exposures:
15 ppm: no toxic signs, no gross lung pathology
30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
50 ppm: labored breathing, mild diffuse lung congestion
75 ppm: irritation and labored breathing, severe diffuse lung congestion
150 ppm: LC_{50}

End Point/Concentration/Rationale: 67 ppm for 30 min and 30 ppm for 1 h resulted in very mild diffuse lung congestion. Very mild lung congestion was considered the threshold for serious long-lasting effects such as severe lung congestion, seen at the next highest level tested.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - The effect (lung congestion) as well as LC_{50} values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-min LC_{50} value for the rabbit, the LC_{50} values for all four species at 15, 30, and 60 min were very similar.
Intraspecies: 3 - At the AEGL-2 concentrations, the effect of irritant gases is expected to be directly damaging to the tissues. The corrosive effect is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where n = 1.77; based on regression analysis of the mouse (the most sensitive species) LC_{50} data from the study conducted at 5, 15, 30, and 60 min (Keplinger and Suissa 1968). The 10-min value was time scaled from the 30-min value and the 4-h value was time scaled from the 1-h value. The 8-h value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with or be scrubbed by the nasal passages.

Data Adequacy: The key study was well conducted and documented; there were limited confirming data from other laboratories.

AEGL-3 VALUES

10-min	30-min	1-h	4-h	8-h
36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm

Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29(1):10-18.

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:
Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 min
32, 65, 87, 188, 375 ppm for 15 min
16, 32, 67, 113, 225 ppm for 30 min
5, 30, 50, 75, 150 ppm for 1 h

Effects: The 1-h substudy using the mouse was considered
15 ppm: no toxic signs, no gross lung pathology
30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
50 ppm: labored breathing, mild diffuse lung congestion
75 ppm: irritation and labored breathing, severe diffuse lung congestion
150 ppm: LC_{50}

End Point/Concentration/Rationale: 75 ppm for 1 h resulted in irritation and labored breathing and severe diffuse lung congestion in the mouse. No deaths occurred. Severe diffuse lung congestion was considered the threshold for lethality.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - The effects (lung congestion) as well as LC_{50} values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-min LC_{50} for the rabbit, the LC_{50} values for all four species a t 15, 30, and 60 min were very similar. Thus, the concentration:end point did not differ greatly among species.
Intraspecies: 3 - Lung congestion at a specific concentration is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where n = 1.77; based on regression analysis of the mouse (the most sensitive species) LC_{50} data from the study conducted at 5, 15, 30, and 60 min (Keplinger and Suissa 1968). The values were time scaled from the 1-h data. The 8-h value was set equal to the 4-h value as was done for the AEGL-2. The safety of setting the 8-h value equal to the 4-h value is supported by another study in which a 7-h exposure to 100 ppm resulted in an overall 60% mortality in four species (Eriksen 1945; Stockinger 1949). The time-scaled 7-h LC_{50} values from the key study for the mouse (50 ppm) and rat (65 ppm) are lower.

Data Adequacy: The key study was well conducted and documented, but there were limited confirming data from other laboratories.

6

Hydrazine[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 levels, 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 sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 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 notable discomfort, irritation, or certain

[1]This document was prepared by the AEGL Development Team composed of Robert A. Young (Oak Ridge National Laboratory) and Chemical Manager Richard Thomas (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).

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

SUMMARY

Hydrazine (m.w. 32.05) is a liquid at room temperature with a vapor pressure of 14.4 mm Hg at 25°C. This simple diamine (H_2NNH_2) is a powerful reducing agent. The chemical acts as an oxygen scavenger and is highly reactive with many other chemicals. Hydrazine is used in various chemical manufacturing processes (production of flexible and rigid foams, pesticides) and by the military as a missile and rocket propellant, and in power sources. U.S. production is estimated at 20 million pounds and world-wide production at 80 million pounds. Hydrazine has an ammonia-like odor with an odor threshold of 3.0 to 4.0 ppm.

Human data on the toxicity of hydrazine following acute inhalation exposure are limited to anecdotal accounts that lack definitive exposure data. The utility of this information is compromised by non-quantitative exposures, concurrent exposure with other chemicals, and involvement of simultaneous multiple exposure routes.

Data from animal studies indicate that hydrazine may be metabolized to acetylhydrazine, diacetylhydrazine, ammonia, and urea, and may form hydrazones with pyruvate and 2-oxoglutarate. The biotransformation of hydrazine is mediated, at least in part, by hepatic monooxygenases. The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate portal-of-

entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine *per se* is a plausible determinant of acute port-of-entry toxic effects.

AEGLs were based upon data sets defining toxicity end points that were specific for the AEGL level. No data were available with which to empirically determine a concentration-exposure duration relationship for hydrazine. This relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Because there were no data to empirically derive the chemical-specific exponent, the default values of n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points were used in the $C^n \times t = k$ equation in accordance with the SOP manual.

AEGL-1 values were based upon a study by House (1964) in which male monkeys exhibited skin flushing and eye irritation after an initial 24-h continuous exposure to 0.4 ppm hydrazine. Although the monkeys in this study were subjected to the 24-h continuous exposure for an additional 89 days, only effects occurring during the first 24 h were considered in the development of the AEGL-1 values. In the absence of chemical specific data, an n of 3 was applied to extrapolate the 24-h (0.4 ppm) exposure from the House (1964) study to the AEGL -1 time frames ($k = 0.4\ ppm^3 \times 24\ h = 1.54\ ppm^3\ h$). An uncertainty factor of 3 was applied for interspecies variability because the surface contact irritation by the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals. Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, 0.1 ppm (the 30-min, 1-h, 4-h, and 8-h values were all approximately 0.1 ppm) was considered appropriate for all AEGL-1 durations.

The level of distinct odor awareness (LOA) for hydrazine is 63 ppm (see Appendix E). The odor LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA may assist chemical emergency planners and responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-2 was derived based upon data from a study by Latendresse et al. (1995) in which rats exposed to hydrazine (750 ppm) for 1 h exhibited nasal lesions. The 1-h exposure to 750 ppm values was scaled to AEGL-specific durations using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the toxic response to inhaled hydrazine. Because the toxic response to acute low-level exposures results from direct contact of the highly reactive hydrazine, the reduction from a default value of 10 is justified. Similarly, an uncertainty factor of 3 was applied for intraspecies variability because the portal-of-entry effect of the reactive hydrazine is likely attributed to direct interaction with res-

piratory tract tissues. This contact irritation is not likely to vary considerably among individuals. A modifying factor of 2 was applied to account for data inadequacies regarding identification of toxic responses consistent with AEGL-2 level effects (i.e., serious or irreversible, but nonlethal, effects of acute inhalation exposure to hydrazine). Although the more recent studies such as those by Latendresse et al. (1995) and HRC (1993) appear to have reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties in the accuracy of exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 has been applied to account for the impact of these deficiencies. This resulted in a total adjustment of 60-fold for derivation of AEGL-2 values. The critical effect (nasal lesions) is consistent with the continuum of hydrazine toxicity (i.e., respiratory tract irritation, pulmonary tissue damage, and potential tumorigenicity) and, therefore, was considered appropriate for AEGL-2 development.

The AEGL-3 values were derived based upon a rat inhalation study (HRC 1993). The lethality threshold was estimated by a three-fold reduction of the 1-h LC_{50} (3192 ppm/3 = 1064 ppm). This was considered a tenable estimate considering that rats survived multiple 1 h exposures to 750 ppm of hydrazine (Latendresse et al. 1995). This approach was also justified by the steep exposure-response curve for hydrazine. Temporal scaling was again applied using the exponential expression $C^n \times t = k$ where n = 3 for extrapolation to shorter times and n = 1 when extrapolating to longer times. A total uncertainty factor of 10 was applied for derivation of the AEGL-3 values as described for AEGL-2. Although the more recent study by HRC (1993) had reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties in the accuracy of exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 was applied to account for the impact of these deficiencies. This resulted in a total adjustment of 30-fold for derivation of AEGL-3 values.

Cancer inhalation slope factors for hydrazine were derived and compared to AEGL values based upon 10^{-4}, 10^{-5}, and 10^{-6} cancer risk levels. The assessment revealed that AEGL-2 values derived from noncarcinogenic toxicity end points were greater than the exposure concentrations calculated for the 10^{-4} excess cancer risk level. However, the available animal data suggest that the tumorigenic response to inhaled hydrazine is a function of prolonged tissue irritation resulting from repeated exposures and not the result of a single low exposure. For this reason and because the AEGL values are applicable to rare events or single, once-in-a-lifetime exposures to limited geographic areas and small populations, the AEGL values based on noncarcinogenic end points were considered to be more appropriate.

The AEGL values, their respective toxicity end points, and references are summarized below in Table 6-1.

TABLE 6-1 Summary of AEGL Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	Eye and facial irritation in monkeys (House 1964)[a]
AEGL-2 (Disabling)	23 ppm 30 mg/m^3	16 ppm (21 mg/m^3)	13 ppm (17 mg/m^3)	3.1 ppm (4.0 mg/m^3)	1.6 ppm (2.1 mg/m^3)	Nasal lesions in rats (Latendresse et al. 1995)
AEGL-3 (Lethal)	64 ppm (83 mg/m^3)	45 ppm (59 mg/m^3)	35 ppm (46 mg/m^3)	8.9 ppm (12 mg/m^3)	4.4 ppm (5.7 mg/m^3)	Lethality in rats (HRC 1993)

[a]Because the contact irritation response to the extremely reactive hydrazine is concentration dependent rather than time-dependent, the AEGL-1 is the same for all time periods.

1. INTRODUCTION

Hydrazine, a simple diamine, is a powerful reducing agent. It acts primarily as an oxygen scavenger and is highly reactive with many other chemicals (WHO 1987). Contact with strong oxidizers (e.g., hydrogen peroxide, nitrogen tetroxide, chlorine, fluorine) will result in immediate ignition or explosions, and contact with catalytic metals may result in flaming decomposition. Hydrazine is used as a chemical intermediate in various manufacturing procedures including the manufacture of pharmaceuticals, plastic blowing agents, dyes, and agricultural chemicals. It is used extensive in military applications as a missile and rocket propellant, and in chemical power sources. (USAF 1989). Hydrazine also occurs naturally as a nitrogen fixation product of *Azobacter agile* (Raphaelian 1963). U.S. production is estimated at 20 million pounds and world-wide production at 80 million pounds.

The National Research Council Committee on Toxicology (NRC 1985) summarized the toxicologic data for hydrazine for development of Emergency and Continuous Exposure Guidance Levels. Garcia and James (1996) also summarized data regarding the toxicology of hydrazine for the development of Spacecraft Maximum Allowable Concentrations (SMACS).

For derivation of AEGL values, acute exposure studies are preferentially examined. Subchronic and chronic studies generally have not been included in the data analysis for AEGL derivation because of the great uncertainty in extrapolating such data to acute exposure scenarios. Such studies may be addressed when the data provide meaningful insight into understanding toxicity mechanisms or for other special considerations.

The primary physicochemical data for hydrazine are presented in Table 6-2. Hydrazine may also occur as the methylated derivatives, monomethylhydrazine and dimethylhydrazine (symmetrical and unsymmetrical isomers). The reactivity of hydrazine is especially important regarding accurate assessment of

exposure concentrations under experimental conditions. Early reports (Comstock et al. 1954) noted such concerns when reporting concentrations of hydrazine in exposure chambers. Because of the extreme reactivity of the compound (up to 99% of the hydrazine would be lost to absorption onto the chamber walls or body surface of the test animals), nominal concentration estimates were found to be a gross overestimation of actual exposure concentrations.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Definitive information was not available regarding the acute lethality of humans following inhalation exposure to hydrazine. However, Sotaniemi et al. (1971) reported a fatality in a worker exposed to hydrazine once per week for six months. A post-exposure simulation provided an estimated hydrazine concentration of 0.05 ppm (0.071 mg/m^3). Possible renal involvement (tubular necrosis, inflammation, hemorrhage, and enlarged kidneys were noted and considered to be a contributing factor to the fatality), neurological effects (tremors), and pulmonary involvement were also noted.

TABLE 6-2 Chemical and Physical Data for Hydrazine

Parameter	Data	Reference
Chemical Name	Hydrazine	
Synonyms	Diamide; diamine; hydrazine base; hydrazine anhydrous; levoxine	O'Neil et al. 2001 USAF 1989
CAS Registry No.	302-01-2	O'Neil et al. 2001
Chemical formula	H2NNH2	O'Neil et al. 2001
Molecular weight	32.05	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Odor	ammoniacal and pungent	WHO 1987
Melting/boiling/flash point	2.0°C /113.5°C /37.8°C	Weiss 1980
Specific gravity[a]	1.011 at 15°C/4°C	O'Neil et al. 2001
Solubility in water	Miscible	O'Neil et al. 2001
Vapor pressure	14.4 mm Hg at 25°C	Schiessl 1985
Relative vapor density	1.1	WHO 1987
Conversion factors in air	1 mg/m^3 = 0.76 ppm 1 ppm = 1.3 mg/m^3	USAF 1989

[a]Density of liquid at 15°C relative to the density of water at 4°C.

2.2. Nonlethal Toxicity

Hydrazine has an irritating, ammonia-like odor. An odor threshold of 3.0 to 4.0 ppm has been reported (Jacobson et al. 1955). Because of its irritating nature, a level of distinct odor awareness (LOA) was determined for hydrazine. The level of distinct odor awareness (LOA) for hydrazine is 63 ppm (see Appendix E). The odor LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA may assist chemical emergency planners and responders in assessing the public awareness of the exposure due to odor perception.

2.2.1. Case Reports

A single exposure of a 35-year old man to 35% liquid hydrazine (exposure duration was approximately 5 min) was reported by Brooks et al. (1985). The incident involved dermal and oral exposure to liquid hydrazine of unknown dose level and resulted in a pins-and-needles sensation, rash, and disorientation within 2 h. Within 5 h the signs and symptoms included, muscle pain, diarrhea, nausea, abdominal cramping, and respiratory problems (chest tightness, coughing, wheezing). The exposure resulted in a prolonged asthma-like illness (reactive airways dysfunction syndrome) that persisted for 5-6 months.

Cognitive disorders were reported for a worker exposed to hydrazine (concentration unknown). Following removal from the exposure, some improvement in the condition of the individual was observed (Richter et al. 1992).

In an investigation of the role of acetylation phenotype on hydrazine metabolism and excretion by workers involved in the production of hydrazine hydrate, Koizumi et al. (1998) noted that the study population was routinely exposed to hydrazine concentrations of 0.07- 0.12 ppm (8-h TWA). There was no indication that this exposure resulted in signs of toxicity.

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding nonlethal effects in humans involving exposure to hydrazine were limited to a study of workers in hydrazine manufacturing by Roe (1978), a follow-up study by Wald et al. (1984), a study by Contassot et al. (1987), and study by Morgenstern and Ritz (2001). Generally, the available epidemiological studies on worker populations from different facilities are inconclusive due to small cohort sizes in some studies, compromised record keeping, various confounding factors, and inadequate exposure characterizations.

In both the Roe (1978) study and the follow-up study by Wald et al. (1984), observed worker mortality (facility in the United Kingdom) did not differ significantly from the expected mortality, and no deaths were reported that

could be attributed to nasopharyngeal cancers. Because specific exposure concentrations were not available for this study, the exposure groups were categorized as little or no exposure, <1.0 ppm, and 1.0 to 10 ppm.

In the study by Contassot et al. (1987), a cohort of 130 male workers exposed to hydrazine for at least six months were divided into three exposure groups: low level (0.1 ppm), medium level (0.1 to 1.0 ppm) and high level (>1.0 ppm). Although initial conclusions indicated no excess risk of cancer, subsequent analysis suggested that the standard incidence ratio achieved significance for cancers in the high exposure group. A qualifying statement, however, noted that there were problems with record keeping and that the significance was greatly reduced when skin cancers were excluded.

Results of an occupational study of 6107 males (Rocketdyne Corp.) exposed (prior to 1980) to hydrazine and methylated hydrazines (1-methylhydrazine and 1,1-dimethylhydrazine) for at least two years during work associated with rocket propellants was reported by Morgenstern and Ritz (2001). Possible concurrent exposures to pulmonary toxicants such as asbestos, chlorine, fluorine, beryllium, hydrogen peroxide, rocket engine exhaust, and various solvents were noted. Hydrazine exposure was categorized as medium, high or no exposure based upon type of work. Relative to the group with no hydrazine exposure, the low-exposure group was not associated with excess lung cancer mortality but a relative risk of 1.68 (95% confidence interval of 1.12-2.52) was determined for the high exposure group. The investigators concluded that occupational exposure to hydrazine and other chemicals associated with the rocket engine testing increased lung cancer risk and possible risk to other cancers. Cancer risks for lymphopoietic and lung cancer were increased (rel. risk of 2.01 and 2.45, respectively) for earlier time periods (i.e., 1960s vs 1980s). Definitive exposure data were not provided in the study report.

2.3. Developmental and Reproductive Toxicity

Reports providing information regarding the reproductive and developmental effects of hydrazine exposure in humans were not available.

2.4. Genotoxicity

Human genotoxicity data relevant to AEGL derivation were not available.

2.5. Carcinogenicity

Wald et al. (1984) reported no significant increase in mortality (47 deaths reported) due to cancer in 427 workers exposed to an undetermined concentration of hydrazine. The follow-up period used in this study was relatively short and may have compromised the ability to detect a weak carcinogenic response.

Epidemiologic studies have also been conducted (see Section 2.2.2.).

2.6. Summary

Data regarding the effects of acute exposure of humans to hydrazine are lacking. Although anecdotal information (Brooks et al. 1985) is available, the reported situation involved exposure via multiple routes (dermal, oral, and probably inhalation) and no exposure concentration data were reported. Reports by Sotanieme et al. (1971) and Richter et al. (1992) regarding inhalation exposure also lacked definitive exposure data. Therefore, there are no human data available that are acceptable for derivation of AEGL values.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Discussions in this section are limited to those studies providing information on acute exposures or to longer-term studies that indicated lethality during the first few days of exposure. For example, MacEwen et al. (1981) conducted a 12-month inhalation exposure study using male and female F344 rats, Syrian golden hamsters, and C57BL/6 mice. Although slight (but statistically insignificant) increases in mortality were noted early during the exposure regimen, these observations could not be attributed to acute exposure but noted only at monthly intervals. Therefore, such data are not considered primary for derivation of AEGL values.

3.1.1. Nonhuman Primates

House (1964) exposed groups of 10 male Rhesus monkeys to hydrazine at an average concentration of 0.78 ppm (1 mg/m^3) (range: 0.25-1.38 ppm [0.33-1.8 mg/m^3]) continuously for 90 days. Hydrazine was introduced into the exposure chambers via saturation of a carrier gas (nitrogen) with hydrazine. The exposure of the monkeys was uninterrupted for the duration of the experiment. The hydrazine concentration was measured colorimetrically from samples extracted from the chamber at various times (10-18 samples/day for the first 10 days; 3 times/day thereafter). A 20% mortality was reported following completion of the 90-day exposure. The two deaths occurred during days 21-30 and 81-90.

3.1.2. Dogs

Acute inhalation exposure data for dogs are limited. In an inhalation study by Comstock et al. (1954), a mongrel dog was exposed to hydrazine at 18 mg/m^3 (14 ppm), 6 h/day, 5 days/week. The dog exhibited anorexia and fatigue by the

second day of exposure and vomiting ensued after day 2 with the dog becoming progressively weaker until week 13 when it died. Weatherby and Yard (1955) exposed two mongrel dogs to hydrazine (3-6 mg/m^3) for 6 h/day, 5 days/week. After 5 days of exposure both dogs exhibited muscular incoordination and weakness. On the seventh day, one dog died and the other was terminated. Pathological examination indicated primarily renal (proximal cortical congestion, capillary damage) and hepatic (central zone fatty changes, hyalinization of hepatocytes, distended bile canaliculi) involvement, with minor pulmonary effects.

An i.v.LD_{50} of 25 mg/kg was reported for dogs (Witkin 1956). The value is, however, based upon only two dose groups (20 and 30 mg/kg) with only two dogs per group. During a 10-day observation period, both dogs of the low dose group survived while both of the high dose group died within 2 h.

3.1.3. Rats

Several studies have examined the effect of acute exposure to hydrazine and methylated hydrazine derivatives. The testing protocols and quality of the studies varied considerably, and species variability was evident.

In a study reported by Comstock et al. (1954), groups of six male Wistar rats (150- 250 g) each were exposed to hydrazine vapors at a concentration of ≈20,000 mg/m^3 (≈15,280 ppm) for 0.5, 1, 2, or 4 h. Saturated hydrazine vapor was introduced into the chamber (20L, 25ºC) at a rate of 0.002 m^3/min. The rats were placed into the chamber after equilibrium was attained. Immediately after introduction into the chamber the rats began scratching and grooming themselves. After 1-2 min, their eyes were partially to completely closed. During the first 2 h of exposure, the rats exhibited alternating periods of restlessness and inactivity. The aforementioned signs are considered normal responses to exposure to a saturated vapor atmosphere. However, shortly thereafter, the rats exhibited pronounced salivation and a red-colored material (porphyrin secreted by the Harderian glands) was observed accumulating around the nares. Such porphyrin secretion is known to be a sensitive indicator of local irritation. The results of this study are shown in Table 6-3. Mortality rates of 33-67% were noted for the 4-h exposure period (latency period not specified). Hyperactivity and/or convulsions were observed in rats that died. No immediate deaths occurred during the 0.5-h exposure period but three of 18 rats had died within the 14-day postexposure period. Necropsy findings included pulmonary edema with localized damage to the bronchial mucosa. Incidence data for these findings were not provided. The results of this study are compromised by the difficulty in assessing chamber concentrations and the resulting extreme variability in the actual concentrations.

Comstock et al. (1954) also conducted an additional test in which the hydrazine concentration was more accurately determined by using a quantitative

TABLE 6-3 Acute Inhalation Toxicity of Hydrazine Vapor in Male Rats

Concentration (mg/m^3)[a]	Exposure Period (h)	C × t ($mg\text{-}h/m^3$)	Immediate Lethality	14-Day Lethality
20,000	4	80,000	4/6	5/6
20,000	4	80,000	3/6	4/6
20,000	2	40,000	2/6	3/6
20,000	2	40,000	0/6	4/6
21,000	1	21,000	0/6	0/6
20,000	1	20,000	0/6	2/6
20,000	1	20,000	0/6	0/6
21,000	0.5	10,500	0/6	0/6
20,000	0.5	10,500	0/6	2/6
20,000	0.5	10,500	0/6	1/6

[a]Nominal concentration, analytical determination would be considerably lower.
Source: Comstock et al. 1954. Reprinted with permission; copyright 1954, American Medical Association.

analytical method based upon hydrazine's reactivity with sulfuric acid. The test protocol was the same as for the preceding test. With the exception of one rat each in the 4-h and 1-h groups, exposure to hydrazine vapors did not result in immediate lethality. However, deaths were observed for all exposure durations during the 14-day postexposure period and occurred throughout the 14-day period. The results of this phase of the study are shown in Table 6-4.

Upon analyzing the immediate lethality of hydrazine when exposure is expressed as a concentration × time product (C × t), there does not appear to be any meaningful correlation. For example, deaths were observed at C × t values of 436 and 831 $mg\text{-}h/m^3$ while exposure as high as 1,600 $mg\text{-}h/m^3$ did not result in immediate death. When considering the lethality rate over a 14-day postexposure period, the highest C × t product (1,600 $mg\text{-}h/m^3$) resulted in a substantially higher lethality rate (83%) than lower c × t values (Table 6-5). However, an accurate and meaningful assessment of lethality relative to exposure expressed as a c × t product is compromised by the fact that determination of actual hydrazine concentration in the exposure chambers was highly variable and possibly of questionable accuracy, and that lethality was assessed as both immediate and up to 14 days postexposure. Additionally, these findings are compromised by the low number of animals in each of the exposure groups.

These same investigators also conducted multiple short-term exposure experiments in which rats were exposed to hydrazine at a average daily concentration of 295 mg/m^3 (actual concentration during the Day 1 exposure period was 288 mg/m^3) for 6 h/day, 5 days/week for 1 week. None of the 20 rats died following the initial 6-h exposure on day 1 although 16 of 20 rats died following completion of the 5-day exposure regimen. Body weight loss of 10-20 g and

signs of pulmonary toxicity (pulmonary edema with localized damage to the bronchial mucosa) were noted for surviving rats. Additional multiple, intermittent exposure experiments using hydrazine concentrations ranging from 26-140 mg/m^3 were also conducted and showed that initial exposures did not result in lethality but that signs of toxicity and death did occur following multiple exposures. There were no definitive relationships observed between exposure frequency and lethality.

TABLE 6-4 Acute Inhalation Toxicity in Rats Exposed to Hydrazine Vapor

Concentration (mg/m^3)[a]	Exposure Duration (h)	C × t ($mg\text{-}h/m^3$)	Immediate Lethality	14-Day Lethality
352	4	1,408	0/6	2/6
344	4	1,376	0/6	3/6
400	4	1,600	0/6	5/6
109	4	436	1/6	3/6
227	4	908	0/6	1/6
756	2	1,512	0/6	1/6
405	2	810	0/6	1/6
129	2	258	0/6	2/6
128	2	256	0/6	1/6
285	2	570	0/6	2/6
831	1	831	1/6	3/6
151	1	151	0/6	1/6
106	1	106	0/6	1/6
185	1	185	0/6	0/6

[a]Analytical determination based upon quantitative relationship of hydrazine/sulfuric acid reaction.
ND: Not determined; exposure time too short for chemical analysis.
Source: Comstock et al. 1954. Reprinted with permission; copyright 1954, American Medical Association.

TABLE 6-5 Lethality in Rats Following 1-Hour Nose-Only Exposure to 64% Hydrazine Aerosol[a]

Exposure Group (mg/L)	Males	Females	Total
Control	0/5	0/5	0/10
0.65	0/5	0/5	0/10
2.04	0/5	0/5	0/10
3.24	1/5	3/5	4/10
4.98	2/5	4/5	6/10

[a]With the exception of one female in the 3.24 mg/L exposure group that died 3 days post exposure, all deathsoccurred overnight following the exposure; there was a 14-day post-exposure observation period.

Jacobson et al. (1955) assessed the toxicity of hydrazine and the methylated derivatives of hydrazine using several species including male white rats (groups of 10; strain not specified) exposed to hydrazine and observed for up to 14 days. A 4-h LC_{50} of 750 mg/m^3 (570 ppm) was estimated. Based upon a ventilation rate of 0.223 m^3/day for rats (0.35 kg) (EPA 1986), this is equivalent to 112 mg/kg/day. Hydrazine appeared to be less toxic than the methylated hydrazine derivatives. These lethality data are summarized in Section 4.3. (see Table 6-9).

Witkin (1956) reported on the acute lethality of hydrazine in several animal species, including rats, following various routes of administration other than inhalation. LD_{50} values were determined by regression analysis using log-dose probit units from four dose groups of 10 male Wistar rats (100-200 g) administered hydrazine i.v., i.p., or orally. Deaths occurred in the groups given 40 and 70 mg/kg; specific doses for the lower dose groups were not provided. The LD_{50} determinations were based upon deaths occurring in a 10-day observation period. In rats, the i.v., i.p. and oral LD_{50} values were estimated at 55 ± 2.7, 59 ± 3.9, and 60 ± 3.8 mg/kg, respectively. Deaths occurred at days 1, 3, and 4 in the 40 mg/kg group (1 death on each day) and on days 1 (5 deaths), 3, 4, and 6 (1 death each day). These data are summarized in Section 7.2. (see Table 6-12).

House (1964) conducted 90-day continuous exposure of male Sprague-Dawley rats to an average concentration of 0.78 ppm (0.25-1.38 ppm) hydrazine. The treatment resulted in 98% mortality with deaths occurring after 41 days of treatment. Although it was noted that the exposed rats were "weak and sick early in the test," neither specific times nor characterization of the effects were provided.

An acute inhalation study to assess lethality of hydrazine in rats was conducted by Huntingdon Research Centre (HRC 1993). In this study, male and female Sprague-Dawley rats (5/sex/group) were exposed (nose only) for 1 h to an aerosol of hydrazine (64% aqueous solution, mass median aerodynamic diameter ± geometric standard deviation of 5.0 ± 2.56, 1.1 ± 3.56, 1.8 ± 3.04, and 2.4 ± 2.40 for the 0.65, 2.04, 4.98, and 3.24 mg/L exposure atmospheres, respectively). The rats were observed throughout the exposure period (clinical signs recorded at the end of chamber equilibration period and at 0.25, 0.5, 0.75, and 1 h during exposure) and daily (or more frequently as necessary) for an additional 14 days. During the exposure, the rats exhibited exaggerated respiratory movements. During the post-exposure observation period, clinical signs included death (two highest exposures only), exaggerated respiratory movements, noisy respiration, lethargy, secretions from the eyes, brown staining around the snout and jaws, and poorly groomed appearance. The lethality data are summarized in Table 6-5.

Using a log probit method, LC_{50} values for the 64% hydrazine atmosphere were estimated as: 9.0, 5.3, and 6.5 mg/L, respectively, for males, females, and sexes combined (equivalent to 9,000, 5,300, and 6,500 mg/m^3). Based upon hydrazine alone, these respective estimates were 5.8, 3.4, and 4.2 mg/L (equivalent to 5,800, 3,400, and 4,200 mg/m^3). Recovery from signs of exposure was ob-

served on day 2 for the 0.65 mg/L groups, and on days 3-4 for the 2.04 mg/L groups. For some rats in the higher exposure groups, exaggerated respiratory movements were observed throughout the post-exposure observation period.

3.1.4. Mice

Comstock et al. (1954) exposed groups of 10 female mice (strain not specified) to hydrazine vapor in various exposure protocols. Exposures (6 h/day for 5 days) to concentrations ranging from 160-611/mg/m^3 (average daily exposure of 295 mg/m^3) did not result in lethality until day 3. There did not appear to be a definitive concentration-effect relationship; three mice died on Day 3, 5 mice died on Day 4, but no deaths occurred on Day 5. Pathological examination revealed pulmonary edema and localized, unspecified damage to the bronchial mucosa.

Acute toxicity assays using groups of 10 female white mice (strain not specified) and other species were conducted by Jacobson et al. (1955). Based upon 4-h exposures, an LC_{50} of 330 mg/m^3 (252 ppm) was estimated. Based upon a ventilation rate of 0.039 m^3/day for a 30 g mouse (EPA 1986), this is equivalent to 17.9 mg/kg/day.

The acute lethality of hydrazine in mice following i.v., i.p., and oral administration was reported by Witkin (1956). LD_{50} values were determined by regression analysis using log-dose probit units from four dose groups of 10 male Webster-Swiss mice (20-30 g) although the actual doses of each group were not provided in the report. In mice, the i.v., i.p. and oral LD_{50} values were estimated at 57 ± 7.5, 62 ± 4.0, and 59 ± 7.2 mg/kg, respectively. These data are summarized along with data for other species in Section 7.2. The LD_{50} determinations were based upon deaths occurring in 10-day observation period. House (1964) conducted 90-day continuous exposure of male ICR Swiss albino mice to hydrazine at concentrations of 0.78 ppm (0.25-1.38 ppm). The treatment resulted in 99% mortality with deaths occurring after 41 days of treatment. Although it was noted that the exposed rats were "weak and sick early in the test", neither specific times nor characterization of the effects were provided.

3.1.5. Hamsters

MacEwen and Vernot (1981) exposed groups of 10 male Syrian golden hamsters (whole-body exposure) to hydrazine at concentrations of 2770, 2450, 2140, 1920, 1600, or 1280 ppm for 1 h. The hamsters were observed during the exposure and for 14 days following exposure. Deaths occurring during the exposure and during the 14-day postexposure period were used for estimating the LC_{50}. The lethality data for this experiment are shown in Table 6-6. Probit analysis was used to estimate an LC_{50} of 2,585 ppm.

TABLE 6-6 Lethality in Hamsters Following 1-Hour Inhalation (Whole Body) Exposure to Hydrazine[a]

Exposure (ppm)	Mortality	Comments
2270	9/10	3 Deaths within 1 h; 4 deaths within 15 h, 1 death at 3 days, and 1 death at 4 days
2450	3/10	1 Death at 12 h, 1 death at 1 day, and 1 death at 3 days
2140	3/10	1 Death at 5 min, 1 death at 1 day, and 1 death at 2 days
1920	3/10	1 Death at 1 day, a death at 3 days, and 1 death at 11 days
1600	2/10	1 Death at 1 h, 1 death at 11 days
1280	2/10	1 Death at 8 days and 1 death at 12 days

[a]14-Day postexposure observation period.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

No data were located that specifically identified irreversible, nonlethal effects in nonhuman primates following acute exposure to hydrazine. House (1964) exposed groups of 10 male rhesus monkeys to hydrazine continuously at an average concentration of 0.78 ppm (1 mg/m^3) (range: 0.25-1.38 ppm [0.33-1.8 mg/m^3]) for 90 days. Hydrazine was introduced into the exposure chambers via saturation of a carrier gas (nitrogen) with hydrazine. The exposure of the monkeys was uninterrupted for the duration of the experiment. The hydrazine concentration was measured colorimetrically from samples extracted from the chamber at various times (10-18 samples/day for the first 10 days; 3 times/day thereafter). Although effects of exposure were observed within 24-48 h, the effects (skin flushing and signs of ocular irritation) would be considered reversible. It is important to note that during days 1 through 10, the exposure period of concern for the aforementioned effects, the exposure concentration averaged 0.4 ppm (0.52 mg/m^3). The incidences of these effects were not reported but their occurrence provides limited data associating the induction of a non-disabling and assumably reversible effect with exposure to a specific concentration of hydrazine. Pathological examinations at termination of the 90-day treatment period indicated involvement of the kidneys, heart and liver but these were not the result of acute exposure. Because the monkeys were sacrificed upon exposure termination, the reversibility of the pathological findings could not be determined.

3.2.2. Dogs

Data regarding serious and/or persistent effects in dogs following acute exposure to hydrazine were limited to studies by Comstock et al. (1954) and Weatherby and Yard (1955).

In the first study, two mongrel dogs were exposed to hydrazine at a concentration of 6 mg/m^3 (4 to 6 ppm), 6 h/day, 5 days/week for up to 28 weeks. During the first week, both dogs were slightly affected (lassitude) and during the middle of the second week refused food and lost weight. After 11 weeks of exposure muscular tremors were observed and additional effects (fatigue, anorexia, vomiting) occurred sporadically through week 27. At the end of week 28 both dogs appeared normal.

In the report by Weatherby and Yard (1955), two male mongrel dogs were exposed to hydrazine at concentrations of 3 to 6 mg/m^3 (2 to 5 ppm), 6 h per day, 5 days per week. After 5 days of exposure, the dogs were extremely weak and exhibited muscular incoordination. On the seventh day one dog was moribund and the other dog was terminated. In another experiment one male and one female dog were exposed similarly but to hydrazine concentrations of 4 to 8 mg/m^3 (3 to 6 ppm). Within 24 h, the male exhibited muscular incoordination and weakness but improved and remained asymptomatic until terminated. Necropsy of the first pair of dogs indicated extensive hepatic lesions while the second pair of dogs exhibited only minimal hepatic involvement.

3.2.3. Rats

House (1964) also exposed male Sprague-Dawley rats to hydrazine at an average concentration of 0.78 ppm for 90 days. The exposure resulted in 98% mortality and, although the authors noted that the rats appeared to be weak and sick early in the treatment, no assessment of reversibility of this condition was possible. Clinical chemistry parameters were measured prior to treatment, and at days 30 and 60. Treatment-related alterations were minimal (minor decrease in hematocrit and changes in polymorphonuclear leukocytes and urine specific gravity) but because of the 30-day and 60-day evaluations, could not be attributed to acute exposure. Assessment of reversibility was not possible because of the high mortality rate during the exposure period.

Becker et al. (1981) noted a 6.6% reduction in body weight and histopathologic changes (palor, fatty liver) in the livers of rats given hydrazine intragastrically at dose of 3 mg/kg/day for four days. Methylation of hepatic DNA was also detected.

MacEwen and Vernot (1981) exposed 10 male and 10 female F344 rats and 20 male hamsters to hydrazine at concentrations of 750 ppm for 1 h twice per week for five weeks. Although notable decrease in body weight were observed for the exposed animals, no deaths occurred indicating that a 1-h exposure at 750 ppm is not lethal in this species and strain.

In the study by Comstock et al. (1954), rats exposed to hydrazine at nominal concentrations of 81-630 ppm (106-831 mg/m^3) exhibited signs of irritation (restlessness, scratching, lacrimation, eye closure) within 1-2 min. Within 2 h, the rats exhibited alternating periods of hyperactivity and inactivity, and porphyrin secretion from the Harderian gland. Although delayed lethality (17-33% at

14 days) was associated with exposures as short as 0.5 h, it is possible that the irritation effects at 1-2 min (probably a response to vapor condensation) would be reversible upon removal from the test atmosphere.

Kulagina (1962) reported alteration of conditioned reflex responses in rats exposed for 2 h to 19 ppm hydrazine (24.7 mg/m^3). Adverse effects on motor coordination were observed in rats exposed to 0.74-4 ppm hydrazine (0.9-5.2 mg/m^3), 4 h/day, 6 days/week for 7 months. There were no deaths among these rats and the altered responses returned to normal 3-4 weeks after cessation of exposure. Although the exposure duration is subchronic, the report verifies that notable alterations in neurological responses in rats are reversible even after prolonged exposure. Although these data suggest that a C × t product of 3,494 mg-h/m^3 is not lethal for intermittent exposures.

More recently, Latendresse et al. (1995) conducted experiments in which groups of five male and five female F-344 rats and 10 male Syrian golden hamsters were exposed to 750 ppm hydrazine for 1 h. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. The 1-h exposure to hydrazine resulted in lesions of the nasal transitional epithelium. These lesions were characterized as minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis. Another phase of this study exposed rats and hamsters for 10 weeks at 1 h per week to hydrazine at concentrations of 75 or 750 ppm. Male and female rats exposed to 750 ppm and female rats exposed to 75 ppm exhibited significant reductions in body weight ($p < 0.05$). Hamsters in the 750-ppm group also exhibited significant reductions ($p < 0.05$) in body weight gain compared to controls. Exposure-induced lesions including desquamation, necrosis, apoptosis, and squamous metaplasia were observed in the nasal transitional epithelium during the exposure period. Although apoptosis and squamous metaplasia were observed after the exposure, the alterations appeared to revert back to normal-appearing transitional epithelium with incidences of lesions at 24 months being low: epithelial hyperplasia (4/99 males, 1/95 females); polyploid adenomas (4/99 males, 6/95 females) and; squamous cell carcinoma (1/99 males) were also observed in rats held up to 28 months postexposure. Hamsters exposed to 750 ppm hydrazine (1 h/week for 10 weeks) exhibited similar incidences of hyperplasia (2/94) and neoplasia (5/94). However, none of the lesions observed in the exposed animals were seen in the control animals.

3.2.4. Mice

House (1964) also conducted inhalation exposure studies in male ICR Swiss mice. The protocol was identical as for rats (see Section 3.2.3.). A high mortality early in the exposure period (98% within 4 weeks) precluded the evaluation of reversibility of effects. There were no findings in mice relevant to non-disabling, reversible effects following acute exposure to hydrazine.

Kulagina (1962) noted alteration of conditioned reflex responses in mice exposed for 2 h to 19 ppm hydrazine (24.7 mg/m^3).

3.2.5. Hamsters

MacEwen and Vernot (1981) exposed 20 male Syrian golden hamsters to hydrazine at concentrations of 750 ppm for 1 h twice per week for five weeks. Although no deaths occurred, notable decreases (no statistical analysis performed) in body weight were observed for the exposed animals.

Latendresse et al. (1995) conducted experiments in which groups of 10 male Syrian golden hamsters were exposed to 750 ppm hydrazine for 1 h. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. The 1-h exposure to hydrazine resulted in lesions of the nasal transitional epithelium. These lesions were characterized as minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis.

3.3. Developmental and Reproductive Toxicity

3.3.1. Rats

Developmental toxicity of parenterally administered hydrazine has been reported. Lee and Aleyassine (1970) reported fetal toxicity (reduced size, pallor, edema and petachiae) and lethality in rats following subcutaneous administration of hydrazine (8 mg/kg) during days 11-21 of gestation. The administered dose also resulted in marked maternal toxicity characterized by body weight loss.

In a study by Keller et al. (1982), pregnant Fischer 344 rats were administered hydrazine in physiologic saline i.p. at doses of 2.5 (n = 17), 5.0 (n = 19), or 10.0 (n = 6) mg/kg, on days 6 through 15 of gestation. Controls (n = 27) were given equivalent volumes of saline, i.p. A dose-response in no. of resorptions/litter was observed. This response was statistically significant ($p \leq 0.05$) at doses of 5.0 or 10 mg/kg. Maternal toxicity (body weight loss) was also observed in these groups during the treatment period. Pregnant rats were also exposed to hydrazine percutaneously (30-min, covered exposure of 2.5 cm square area) at doses of 5.0 or 50.0 g/kg on day 9 of gestation. The higher dose also resulted in a high incidence of embryolethality. Results of the i.p. injection experiment are shown in Table 6-7.

In a second experiment reported by Keller et al. (1982), pregnant F344 rats were given hydrazine (10 mg/kg, i.p.) on gestation days 7-9, 10-12, or 13-15. This protocol was used because the former dosing protocol resulted in excessive embryolethality that precluded meaningful assessment of possible developmental effects during later developmental periods. Based upon resorptions/litter,

fetal weight, and incidence of anomalies, exposure during gestation days 7-9 appeared to be the most critical. However, similar to the preceding experiment, dams exhibited body weight loss during the treatment period. The results of this experiment are shown in Table 6-8.

TABLE 6-7 Developmental Effects of Hydrazine in Rats Following i.p. Administration on Gestation Days 6-15

Parameter	Dose (mg/kg)			
	0	2.5	5.0	10
Number of litters	27	17	19	6
Implants/litter[a]	8.2 ± 0.6	8.1 ± 0.7	6.5 ± 0.7	7.0 ± 1.9
Resorptions/litter[a]	1.5 ± 0.4	1.8 ± 0.4	3.3 ± 0.7[b]	6.0 ± 2.3[b]
No. litters with >50% resorption	4	1	10	5
Fetal wt[a]	3.1 ± 0.04	3.1 ± 0.04	2.9 ± 0.1[b]	3.1 ± 0.3
No. fetuses examined	27(181)	17(107)	15(60)	1(6)
Litters (fetuses) affected	8(11)	4(5)	7(8)	1(3)
Anomalies[c]	6	3	4	3
Major malformations	7[d,e]	3[d]	4[f]	3

[a]Values are means ± S.E.
[b]Significantly different from control, $p \leq 0.05$.
[c]Supernumerary ribs, fused ribs, delayed ossification, moderate hydronephrosis, moderate dilation of brain ventricles, other similar but less frequently occurring abnormalities.
[d]Major malformation was anophthalmia.
[e]Three fetuses with anophthalmia in one litter.
[f]Major malformations were anophthalmia (2), right side aorta (1), and monorchid (1).
Source: Keller et al. 1982.

TABLE 6-8 Developmental Effects in Rats Following i.p. Administration of Hydrazine (10 mg/kg) at Various Times During Gestation

Parameter	Gestational Exposure Period			
	Control (6-15)	7-9	10-12	13-15
Number of litters	27	11	1	10
Implants/litter[a]	8.2 ± 0.6	7.5 ± 1.1	8.9 ± 1.0	7.7 ± 1.4
Resorptions/litter[a]	1.5 ± 0.4	6.1 ± 1.10[b]	0.8 ± 0.4	1.0 ± 0.3
Litters with >50% resorption	4	8	0	0
Fetal wt[a]	3.1 ± 0.04	2.7 ± 0.1[b]	3.1 ± 0.1	2.9 ± 0.5[b]
No. fetuses examined	27(181)	8(16)	10(81)	10(57)
Litters (fetuses) affected	8(11)	6[b](8)	4(4)	4(4)
Anomalies	6	8[c]	2	4
Major malformations	7	0	2[d]	4

[a]Values are means ± S.E.
[b]Significantly different from control, $p \leq 0.05$.
[c]Major malformations were anophthalmia and adrenal agenesis.
[d]Anomalies detected were supernumerary ribs (2), moderate hydronephrosis (2), and moderate hydrocephalus (4).
Source: Keller et al. 1982.

An inhalation exposure (nose-only) study, Keller (1988) exposed pregnant rats (strain not specified) on gestation day 9 to 500 or 50 ppm of hydrazine for 1 h. Although no teratogenic effects were observed, exposure to 500 ppm hydrazine resulted in 48% embryolethality that was concurrent with maternal toxicity. Embryolethality at 50 ppm hydrazine was similar to that observed for unexposed controls; 3% and 4%, respectively. However, data were lacking regarding exposure atmosphere analysis, characterization of the maternal toxicity, and protocol details.

3.4. Genotoxicity

There were no inhalation genotoxicity data available for hydrazine. Hydrazine has been shown to be mutagenic in various microbial tests and evidence of genotoxic potential in mammals has been shown following oral and parenteral administration (reviewed by NRC 1985; Garcia and James 1996). This review concluded that hydrazine has the potential for inducing somatic mutations. Intraperitoneal injection of hydrazine (10 to 120 mg/kg) in mice during the early stages of spermatogenesis did not induce unscheduled DNA synthesis (Sotomayor et al. 1982), and Epstein and Shafner (1968) reported negative results in mouse dominant-lethal test. However, positive results in sister chromatid exchange in various murine tissues have been reported (Couch et al. 1986; Neft and Conner 1989). *In vitro* studies (summarized in ATSDR 1997) have indicated the genotoxic potential of hydrazine with and without metabolic activation and include methyl DNA adducts in human but not hamster V79 cells, gene mutations in human teratoma cells, and unscheduled DNA synthesis. Hydrazine was positive in the Ames test using TA1535, TA100, TA1537, and TA98 strains of *Salmonella typhimurium* (Parodi et al. 1981) and mutagenicity was demonstrated in strain WP2 of *Escherichia coli* (Noda et al. 1986).

Leakakos and Shank (1994) reported that DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic (25 or 50 mg/kg). This conclusion was based upon findings of methylguanine adducts (7-methylguanine and O^6-methylguanine) in hepatic DNA of neonatal rats given subcutaneous injections of hydrazine. Inhibition of restriction at specific sites following necrogenic doses was provided as evidence of a hydrazine-specific genotoxic response.

3.5. Carcinogenicity

3.5.1. Dogs

There were no treatment related effects observed in male or female beagle dogs (four per group) exposed to hydrazine at concentrations of 0.25-5.0 ppm

(0.35-6.55 mg/m^3) 6 h per day, 5 days per week for one year (MacEwen et al. 1981).

Vernot et al. (1985) conducted 1-year inhalation exposure of dogs to hydrazine at concentrations of 0.25 or 1.0 ppm for 6 h/day, 5 days/week. The dogs were maintained an additional 38 months postexposure. No tumors attributed to hydrazine were observed in any of the dogs.

3.5.2. Rats

MacEwen et al. (1981) exposed groups of 100 rats of both sexes to 0.05-5.0 ppm (0.07-6.55 mg/m^3) hydrazine for one year (6 h/day, 5 days/week). Evidence of inflammatory changes in the respiratory tract were observed at the lowest exposure but were more prevalent and more severe at the highest exposure. The histopathologic changes included squamous cell metaplasia of the nasal cavity, larynx, and trachea. Hyperplastic changes were observed in the nasal and pulmonary epithelia, and inflammatory changes were observed in the larynx and trachea. At the highest exposure tested, male rats exhibited a significant increase in squamous metaplastic changes in the nasal region (47/99; $p \leq 0.001$), nasal epithelial hyperplasia (21/99; $p \leq 0.001$), squamous metaplasia of the larynx (18/29; $p \leq 0.001$) and trachea (10/97; $p \leq 0.001$), inflammatory changes in the larynx (72/92; $p \leq 0.001$) and trachea (52/97; $p \leq 0.001$), and pulmonary epithelia hyperplasia (6/99; $p \leq 0.001$). What appears to be a published report of this study is described below.

Vernot et al. (1985) reported on a 1-year inhalation exposure of rats to hydrazine at concentrations of 0.05, 0.25, 1.0, or 5.0 ppm for 6 h/day, 5 days/week. The rats were maintained an additional 18 months postexposure. A dose-dependent increased incidence was noted for benign nasal adenomatous polyps (58/98 treated vs 1/146 control in males, and 28/95 treated vs 0/145 control in females; $p \leq 0.01$) and villous polyps (12/98 vs 0/146 in males only; $p \leq 0.01$), and thyroid carcinomas (13/98 vs 1/146 males only; $p \leq 0.05$). The nasal tumors were often associated with chronic irritation. The increased incidence of thyroid carcinoma was significant (13/98 vs 7/146; $p \leq 0.5$) in the 5.0 ppm males at the end of the 18-month observation period. Squamous cell carcinomas and bronchial carcinomas were also increased in males but significantly so.

Latendresse et al. (1995) conducted experiments in which groups of five male and five female F-344 rats were exposed to 75 or 750 ppm hydrazine for 1 h/week for 10 weeks. Control animals were exposed to air without hydrazine. Male and female rats exposed to 750 ppm and female rats exposed to 75 ppm exhibited significant reductions in body weight ($p < 0.05$). Hamsters in the 750-ppm group also exhibited significant reductions ($p < 0.05$) in body weight gain compared to controls. Exposure-induced lesions including desquamation, necrosis, apoptosis, and squamous metaplasia were observed in the nasal transitional

epithelium during the exposure period. Although apoptosis and squamous metaplasia were observed after the exposure, the alterations appeared to revert back to normal-appearing transitional epithelium with incidences of lesions at 24 months being low: epithelial hyperplasia [4/99 males, 1/95 females]; polyploid adenomas [4/99 males, 6/95 females] and; squamous cell carcinoma [1/99 males]) were also observed in rats held up to 28 months postexposure. However, none of the lesions observed in the exposed animals were seen in the control animals.

3.5.3. Mice

Groups of 400 female C57BL/6 mice were exposed to hydrazine (0.05, 0.25, or 1.0. ppm) 6 h/day, 5 days/week for up to one year (MacEwen et al. 1981). A group of 800 female mice exposed to clean air served as controls. The mice appeared to be resistant to the oncogenic effects of hydrazine. The only significant response was 3% incidence (12/379; $p \leq 0.05$) in pulmonary adenomas in the highest exposure tested. A published report of this study appeared as Vernot et al. (1985).

The 1-year inhalation study by Vernot et al. (1985) also examined mice (400 females per group) exposed to hydrazine at concentrations of 0.05, 0.25, or 1.0 ppm for 6 h/day, 5 days/week. The mice were maintained an additional 15 months postexposure. As described above, pulmonary adenomas were slightly increased in mice of the 1.0 ppm group.

3.5.4. Hamsters

Latendresse et al. (1995) conducted experiments in which groups of 10 male Syrian golden hamsters were exposed to 75 or 750 ppm hydrazine for 1 h/week for 10 weeks. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. Hamsters exposed to 750 ppm hydrazine (1 h/week for 10 weeks) exhibited hyperplasia (2/94) and neoplasia (5/94). None of the lesions observed in the exposed animals were seen in the control animals.

Vernot et al. (1985) and MacEwen et al. (1981) also utilized hamsters in their 1-year inhalation exposure studies of hydrazine. Groups of 200 males hamsters were exposed to hydrazine at concentrations of 0.25, 1.0, or 5.0 ppm for 6 h/day, 5 days/week. The hamsters were maintained an additional year. Evidence of degenerative changes, including amyloidosis, was observed in hamsters exposed to 0.25 ppm hydrazine and higher. The incidence of nasal adenomatous polyps was significantly increased (16/160 vs 1/181; $p \leq 0.05$) in the 5.0-ppm group relative to unexposed controls.

3.6. Summary

Acute lethality data for inhalation exposure to hydrazine were available for dogs, rats, mice and hamsters, although the data for dogs are compromised by the small numbers of animals and the use of mongrels rather than a fixed breed. Some data from earlier studies are also compromised by inadequacies in accuracy of exposure concentration measurements, highly variable concentrations during the testing period, and variabilities in observation periods for assessing lethality. Acute lethality data following parenteral routes (i.e., iv, i.p.) and oral administration are available for dogs, rats, and mice. These data were discussed with reference to route-dependent variability in lethality. The route of administration does not appear to significantly affect the qualitative nature of hydrazine toxicity (Krop 1954; Witkin 1956; NRC 1985), although dose-response alterations are observed and nasal lesions appear to be more prominent in inhalation exposures. Some studies have also shown that hydrazine may induce embryolethality at maternally toxic doses.

There is evidence that long-term exposure of rats to hydrazine may cause an increased incidence in nasal tumors or histopathologic changes indicative of a possible tumorigenic response (Vernot et al. 1985; Latendresse et al. 1995). Based upon the animal data, however, it appears that repeated exposures resulting in long-term tissue irritation is instrumental in the observed tumorigenic responses.

Definitive exposure-response data regarding non-disabling, reversible health effects in animals following acute inhalation exposure to hydrazine were limited. Muscular incoordination and weakness was observed in dogs (Weatherby and Yard 1955), alteration of conditioned response behaviors was noted for rats (Kulagina 1962), and nasal lesions observed in rats following a single exposure (Latendresse et al. 1995).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Studies with animals have shown that hydrazine may be metabolized to acetylhydrazine, diacetylhydrazine, ammonia, and urea, and may form hydrazones with pyruvate and 2-oxoglutarate (Wright and Timbrell 1978; Timbrell et al. 1982; Preece et al. 1991; Timbrell 1992). These studies also indicated that urinary excretion to be a major route of elimination following various administration routes. The biotransformation of hydrazine is mediated, at least in part, by hepatic monooxygenases and acetyltransferases (Timbrell 1992; Koizumi et al. 1998).

Differential rates of hydrazine metabolism by humans and the role of acetylation phenotype was investigated by Koizumi et al. (1998). Acetylation phenotype was determined for 297 workers involved in the production of hydrazine

hydrate. Based on analysis of 12 individuals from this study population, the mean biological half-life of hydrazine among individual workers of various acetylation phenotype varied about 2-fold ($p < 0.05$); 3.94 ± 1.70 h, 2.25 ± 0.37 h, and 1.86 ± 0.67 h, respectively, for slow, intermediate and rapid acetylators. Exposure to hydrazine was reportedly 0.07-0.12 ppm (8-h TWA).

Timbrell (1992) reported that hepatic uptake of hydrazine by rats following intraperitoneal administration appeared to be a saturable process. In experiments with rats exposed via inhalation to hydrazine at concentrations of 10-500 ppm for 1 h, Llewellyn et al.(1986) found that 1.7-4% and 4.5-11.4% of the absorbed dose was excreted as urinary acetyl hydrazine and diacetylhydrazine, respectively.

The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate port-of-entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine may be instrumental in the manifestation of acute port-of-entry toxic effects. However, the systemic effects (e.g., convulsions, cardiovascular collapse) and delayed lethality attributed to hepatic and renal effects, may be affected by absorption, distribution and excretion kinetics, as well as metabolism processes. This is consistent with early reports of lipid accumulation in the liver and kidneys of experimental animals following single and repeated doses of hydrazine (Comstock et al. 1954).

4.2. Mechanism of Toxicity

Although the acute lethality of hydrazine has been demonstrated in several species following multiple routes of administration, time to lethality following inhalation exposure appears to be extremely variable. As exemplified in the studies by Comstock et al. (1954) and Witkin (1956), inhalation exposure to hydrazine for exposure periods (0.5 to 4 h) may result in lethality as long as 14 days following cessation of exposure. Such latency complicates the estimation of acute exposure values and their possible resultant effects. Additionally, some consideration must also be given to the steep slope of the concentration effect curve for lethal effects of hydrazine. Jacobson et al. (1955) noted the slope of the exposure concentration/lethality curve to be 7.32 ± 1.8 and 3.79 ± 1.6 (±SE) for rats and mice, respectively. The steep slope generated by the rat lethality data implies a relatively smaller ratio between the dose causing low mortality and that causing a high mortality. This is a relevant point of concern regarding establishing an effect level based upon hydrazine lethality. The available data suggest that there may be little margin between lethal effects and nonlethal effects following inhalation exposure to hydrazine.

4.3. Structure-Activity Relationships

The toxicity of methylated derivatives of hydrazine (monomethylhydrazine and the symmetrical and unsymmetrical isomers of dimethylhydrazine [1,1-

dimethylhydrazine and 1,2-dimethylhydrazine, respectively]) have also been studied. Jacobson et al. (1955) reported excessive salivation, vomiting, respiratory distress and convulsions in dogs exposed to monomethylhydrazine and unsymmetrical dimethylhydrazine. Fourteen day mortality in three groups of dogs (three dogs/group) exposed for 4 h to monomethylhydrazine at concentrations of 29, 21, and 15 ppm were 2/3, 2/3, and 0/3, respectively. Fourteen day mortality in three groups of dogs (three dogs/group) exposed for 4 h to unsymmetrical dimethylhydrazine at concentrations of 111, 52, and 24 ppm were 3/3, 1/3, and 0/3, respectively. In studies reported by Rinehart et al. (1960), 29/30 mice exposed continuously to symmetrical dimethylhydrazine (140 ppm) died within two weeks and 8/30 mice exposed to 75 ppm died within five weeks. Rinehart et al. (1960) also reported that 1/3 dogs exposed intermittently to symmetrical hydrazine (25 ppm) died within three days. For rodents, estimated LC_{50} values for monomethylhydrazine, unsymmetrical dimethylhydrazine and symmetrical dimethylhydrazine are shown in Table 6-9.

Jacobson et al. (1955) noted that the toxic actions of hydrazine and its methylated derivatives were similar; all are respiratory irritants and convulsants. However, it was observed that monomethylhydrazine also induced severe intravascular hemolysis in dogs.

Witkin (1956) reported i.v., i.p., and oral LD_{50} values for mice and rats, and i.v. LD_{50} values for dogs. Similar to hydrazine, the route of administration had minimal effect on the LD_{50} within species. Generally, monomethylhydrazine and symmetrical dimethylhydrazine appeared to be somewhat more toxic in mice than was hydrazine. Results of this study showed that the unsymmetrical isomer of dimethylhydrazine was less acutely toxic than hydrazine or the other hydrazine derivatives.

TABLE 6-9 LC_{50} Values for Rodents Exposed to Monomethylhydrazine and Dimethylhydrazine Isomers

Species	LC_{50} (ppm)	LC_{50} (mg/m^3)
Monomethylhydrazine		
Rat	74	139
Mouse	56	105
Hamster	143	270
Unsymmetrical dimethylhydrazine		
Rat	252	618
Mouse	172	423
Hamster	392	962
Symmetrical dimethylhydrazine		
Rat	280-400	364-520

Source: Jacobson et al. 1955. Reprinted with permission; copyright 1955, American Medical Association.

House (1964) reported unsymmetrical dimethylhydrazine to be less toxic to monkeys, rats, and mice. Mortality rates over a 90-day inhalation exposure to 0.56 ppm (0.73 mg/m^3) were 20, 98, and 99% for monkeys, rats, and mice, respectively.

The database on hydrazine derivatives provides no additional information that would be applicable to deriving AEGL values for hydrazine.

4.4. Other Relevant Information

4.4.1. Species Variability

The limited available data suggest that the lethal concentration of hydrazine varies somewhat among the species tested. Some of this variability, however, may be attributed to the difficulties in accurately measuring and maintaining the experimental hydrazine concentrations, especially in earlier studies. As shown in Tables 6-12 and 6-13 in Section 7.2, both the LC_{50} and the LD_{50} values are very similar for rats and mice. The estimated LD_{50} for the dog suggests greater sensitivity but this value is based upon only two doses and two test animals per dose. Overall, there still appears to be uncertainty regarding species variability in the toxic response to hydrazine and, more importantly from the standpoint of AEGL development, uncertainty regarding the sensitivity of humans relative to laboratory species. Furthermore, definitive data were not available regarding species variability in irreversible, nonlethal effects of acute exposure to hydrazine.

4.4.2. Physical and Chemical Properties

The extreme reactivity of hydrazine also deserves special attention with regard to accurate assessment of experimental exposure concentrations. As shown in the studies of Jacobson et al. (1955) and Comstock et al. (1954), accurate and consistent measurement of hydrazine concentrations even under experimental conditions is difficult and subject to many variabilities (size of chamber, number and size of animals, chamber construction material, etc.). The highly reactive nature of hydrazine *per se* is a plausible determinant of acute port-of-entry toxic effects.

4.4.3. Concurrent Exposure Issues

Although data analyzing the adverse effects of concurrent exposure to hydrazine and other chemicals are not available, this may be an important issue, especially for those chemicals with irritant properties. Furthermore, hydrazine is a highly reactive reducing agent that may react with many other chemicals (especially oxidizers), thereby altering their effects on physiologic systems.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data were not available for deriving an AEGL-1. The odor threshold for hydrazine is 3 to 4 ppm.

5.2. Animal Data Relevant to AEGL-1

Data regarding the nonlethal, reversible effects of hydrazine on animals following acute exposures were limited. Data from some of the earlier studies were compromised by difficulties in determining the actual hydrazine concentrations in the exposure chambers. Acute exposures (<24 h) of animals to hydrazine resulted in irritation at various exposures. A cumulative exposure as low as 106 mg/m^3 for 1-2 min was reported to cause irritation in rats while exposure to 975 mg/m^3 for 1 h produced nasal lesions in rats. Eye and facial irritation in monkeys was noted following an exposure of 0.52 mg/m^3 for ≈24 h, and neurological effects (alteration of conditioned responses) were observed in mice following exposure to 24.7 mg/m^3 for 2 h. Repeated 8 h/day occupational exposure of rocket plant workers was without signs of acute toxicity (Koizumi et al. 1998).

5.3. Derivation of AEGL-1

The data from the study by House (1964) in which male monkeys were continuously exposed to hydrazine at 0.52 mg/m^3 (equivalent to 0.4 ppm average concentration for the first 10 days of the 90-day exposure period) resulting in skin flushing and swollen eyes after 24 h of exposure was used as the basis for the AEGL-1. Based upon the available data, this exposure represents the lowest exposure resulting in a definitive effect that could be considered consistent with the definition of an AEGL-1. Exponential scaling with the equation, $C^n \times t = k$ (ten Berge et al. 1986), was used to derive exposure duration-specific values. Data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical specific data, an n of 3 was applied to extrapolate the 24-h 0.4 ppm exposure from the House (1964) study to the 8-h AEGL -1 time frame ($k = 0.4\ ppm^3 \times 24\ h = 1.54\ ppm^3$-h). Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, 0.1 ppm (the 30-min, 1-h, 4-h, and 8-h values were all approximately 0.1 ppm) was considered appropriate for all AEGL-1 durations. (Table 6-10 and Appendix A).

TABLE 6-10 AEGL-1 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)

A total uncertainty factor of 10 was applied to derive the AEGL-1 values (each uncertainty factor of 3 is actually the geometric mean of 1 and 10 [i.e., 3.16], hence; 3.16 × 3.16 = 10). An uncertainty factor of 3 was applied for interspecies variability because the surface contact irritation by the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data were not available for deriving an AEGL based upon nonlethal, irreversible effects of hydrazine exposure.

6.2. Summary of Animal Data Relevant to AEGL-2

Data were limited regarding irreversible, nonlethal effects of acute exposure to hydrazine. AEGL-2 values were first derived based upon several studies. Using the data from Weatherby and Yard (1955) showing muscular incoordination and weakness in one of two dogs exposed for 6 h, results in the most conservative AEGL-2 estimates. These data, however, are greatly compromised by the use of only two animals (only one of which responded) and the use of mongrel dogs. The developmental toxicity data of Keller (1988) provides a reasonable data set for AEGL-2 derivation but results in AEGL-2 values that are somewhat higher than those derived using the other data sets. The data of Kulagina (1962) is of questionable use for AEGL derivation because of the subjective nature of assessing alterations in behavioral responses.

Results of a study in rats by Becker et al. (1981) identified long-term deleterious effects but not immediately disabling effects. The toxicity end points reported included body weight reduction, fatty liver and methylation of hepatic DNA following intragastric administration of hydrazine at a dose of 3 mg/kg/day for up to 4 days. These effects are considered severe enough to result in serious and irreversible impairment of health over time, especially if one considers the methylation of hepatic DNA to represent a possible precursor to a carcinogenic response. However, the use of route-to-route extrapolation may be

tenuous due to the uncertainties in toxicokinetics between inhalation and oral routes.

The study by Latendresse et al. (1995) appeared to provide the best data for AEGL-2 derivation. Results of this study showed the induction of nasal lesions in rats following a single 1-h exposure to 750 ppm hydrazine. The nasal lesions were characterized by histopathologic analysis and were shown to be reversible upon removal from exposure. This toxicologic response is indicative of an initial response that is part of a continuum of tissue damage resulting from hydrazine exposure. It is the highest tested exposure that did not lead to lethality and, due to its reversibility and a severity that is less than that consistent with AEGL-2 tier definition, is considered as the critical effect for AEGL-2 development. The experiments also utilized the inhalation exposure route, and measurement of hydrazine concentrations did not appear to be a confounding factor regarding the validity of the experimental results.

6.3. Derivation of AEGL-2

The data from the Latendresse et al. (1995) study showing nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) in rats following a 1-h exposure to 750 ppm was considered to be appropriate for setting AEGL-2 values. The study protocol and analytical techniques were superior to earlier studies and histopathologic data were available. The toxicity end point involved a specific region of the respiratory tract (nasopharyngeal region) and, although toxicologically and physiologically serious, was reversible upon removal from exposure.

Due to the extreme reactivity of hydrazine, exposure concentration measurements in earlier studies on multiple species were imprecise. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the toxic response to inhaled hydrazine. Because much of the toxic response to acute low-level exposures is likely a function of the extreme reactivity of hydrazine, the reduction from a default value of 10 is justified. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is likely attributed to direct interaction with respiratory tract tissues. This contact irritation is not likely to vary considerably among individuals. Additionally, variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism has been shown to vary approximately 2-fold. A modifying factor of 2 was applied to account for data inadequacies regarding the identification of toxic responses consistent with AEGL-2 level effects (i.e., serious or irreversible, but nonlethal, effects of acute inhalation exposure to hydrazine). Although the more recent studies such as those by Latendresse et al.(1995) and HRC (1993) appear to have more reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties regarding the variability in response among species. At least some

of this variability may be the results of inaccurate exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 has been applied to account for the impact of these data deficiencies. This resulted in a total adjustment of 60-fold for derivation of AEGL-2 values (Table 6-11).

Because data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (Appendix A).

As previously noted, the data on nonlethal, irreversible effects resulting from acute exposure to hydrazine are limited. The key study (Latendresse et al. 1995) used to derive the AEGL-2 values appears to provide the highest confidence among the data available for AEGL-2 type effects or an estimation of a threshold for such effects.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Although there is a report on one human fatality resulting from hydrazine exposure, the case involved repeated exposure to approximately 0.05 ppm(estimated from a post-exposure simulation) over a 6-month period (Sotaniemi et al. 1971). The confounding effects of a repeated exposure scenario (e.g., compromised tissue repair in the presence of repeated insults, excretion and detoxication kinetic considerations, etc.), and uncertainties regarding the estimate derived from a simulated exposure prevent the use of this report in deriving a defensible AEGL Level 3 value.

7.2. Animal Data Relevant to AEGL-3

Developmental toxicity of hydrazine by i.p. and percutaneous routes has been demonstrated in rats (Lee and Aleyassine 1970; Keller et al. 1982, Keller 1988). Because the significant findings (increased resorptions/litter, decreased fetal weight, embryolethality, increased incidences of anomalies) were concurrent with maternal toxicity (decreased body weight during gestational treatment period), it is difficult to attribute the developmental effects directly to hydrazine exposure *per se* and to consider hydrazine a selective developmental toxicant. Because of the route of administration and the inherent uncertainties of route-to-route extrapolation, the data from Lee and Aleyassine (1970) and Keller et al. (1982) were not used for deriving the AEGL-3 levels. Several studies utilizing inhalation exposures were considered for derivation of an AEGL-3 values.

The acute lethality of inhaled hydrazine has been reported by several investigators (Comstock et al. 1954; Jacobson et al. 1955; Keller 1988; HRC 1993). Keller (1988) reported embryolethality following 1-h exposure to 500

ppm hydrazine but experimental protocol details and analytical data are lacking. Although Keller (1988) reported maternal toxicity and embryolethality resulting from a 1-h exposure to 500 ppm hydrazine, Latendresse et al. (1995) reported only nasal lesions (necrosis, exfoliation, and acute inflammation) in rats and hamsters exposed to 750 ppm for 1 h but did not note any overt clinical signs of toxicity in exposed animals (body weight was decreased in those animals receiving multiple exposures but did not appear to be significant in those subjected to 1-h exposure). LC_{50} values of considerable variability have also been reported by several investigators (Comstock et al. 1954; Jacobson et al. 1955; MacEwen and Vernot 1981; HRC 1993). For comparison, summaries of LD_{50} and LC_{50} values are shown in Table 6-12 and 6-13, respectively.

7.3. Derivation of AEGL-3

Although several inhalation studies are available that provide data showing lethality or life-threatening effects acute exposure to hydrazine, the quality of the studies varies considerably. Earlier studies tended to be compromised to varying degrees by analytical deficiencies in determining the hydrazine concentration of the experimental exposures. Several studies were identified for derivation of AEGL-3 values (Appendix A). These included the acute exposure studies by Jacobson et al. (1955), Keller (1988), HRC (1993).

A notable range of values were obtained depending upon the study used. Although AEGL-3 values derived from the embryolethality data reported by Keller (1988) provide the most conservative AEGL-3 values, this study was compromised by the absence of details for experimental protocol and results (see Section 3.4.1). The AEGL-3 values derived from the Jacobson et al. (1955) data were similar although slightly lower.

The AEGL-3 values were derived based upon the data from the HRC study that provided a 1-h LC_{50} of 4.2 mg/L (3,192 ppm) in rats (both sexes). Although a 1-h LC_{01} of 334 ppm was estimated from the HRC data using the method of Litchfield and Wilcoxon (1949), it was considered to be inappropriate for derivation of AEGL-3 values because it was not consistent with the recent data from Latendresse et al. (1995) that showed 1-h exposure of rats to 750 ppm did not result in any lethalities. It is believed that a 3-fold reduction of the 1-h LC_{50} (3,192 ppm/3 = 1,064 ppm) provides an estimate of the lethality threshold that is consistent with the available data. For example, the Latendresse et al. (1995) study demonstrated that rats exposed to 750 ppm for 1 h per week for 10 consecutive weeks did not experience mortality.

TABLE 6-11 AEGL-2 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	23 ppm (30 mg/m^3)	16 ppm (21 mg/m^3)	13 ppm (17 mg/m^3)	3.1 ppm (4.0 mg/m^3)	1.6 ppm (2.1 mg/m^3)

TABLE 6-12 Summary of LD_{50} Values for Hydrazine in Studies by Witkin (1956) and Jacobson et al. (1955)

Species	LD_{50} (mg/kg)	Route of Administration	Time of Death	Reference
Rat	55	I.V.	10 d[a]	Witkin 1956
	59	I.P.	10 d	Witkin 1956
	60	Oral	10 d[a]	Witkin 1956
	112	Inhalation	4 h[b]	Jacobson et al. 1955
Mouse	57	I.V.	10 d[a]	Witkin 1956
	62	I.P.	10 d[a]	Witkin 1956
	59	Oral	10 d[a]	Witkin 1956
	18	Inhalation	4 h[b]	Jacobson et al. 1955
Dog	25	I.V.	10 d[a]	Witkin 1956

[a]Observation period.
[b]Duration of exposure; conversion to internal dose (mg/kg) based upon default values for body weight and ventilation rate for rats (EPA 1986).

TABLE 6-13 Summary of LC_{50} Values for Hydrazine in Studies by Jacobson et al. (1955), Comstock et al. (1954), HRC (1993), and MacEwen and Vernot (1981)

Species	LC_{50} (mg/m^3 [ppm])	Exposure Duration (h)	C × t ($mg\text{-}h/m^3$)	Reference
Rat	750 [570]	4	3,000	Jacobson et al. 1955
Rat	344 [260][a]	4	1,376	Comstock et al. 1954
Rat	831 [630][b]	4	3,324	Comstock et al. 1954
Rat	4,200 [3,192][c]	1	4,200	HRC 1993
Hamster	3,360 [2,585][d]	1	3,360	MacEwen and Vernot 1981
Mouse	330 [252]	4	1,320	Jacobson et al. 1955

[a]50% lethality at 8 days postexposure.
[b]50% lethality at 13 days postexposure.
[c]Value is for males and female combined (males 1-h LC_{50}: 5,800 mg/m^3; females 1-h LC_{50} 3,400 mg/m^3.
[d]14-day postexposure observation.

Additionally, the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5. To obtain AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points (10 min and 30 min) and n = 1 when extrapolating to longer time points (4 and 8 h) using the $C^n \times t = k$ equation (Appendix A).

Uncertainty factors were applied as described for AEGL-2. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the lethal response to inhaled hydrazine. Because

much of the toxic response to acute low-level exposures is likely a function of the extreme reactivity of hydrazine and resulting direct-contact damage to tissues, the reduction from a default value of 10 is justified. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is likely attributed to direct interaction with respiratory tract tissues. This contact irritation is not likely to vary considerably among individuals. A modifying factor of 3 for interspecies variability was applied to account for the high degree of variability in the data. As previously described in Section 6.3, the more recent studies by Latendresse et al. (1995) and HRC (1993) utilized more sophisticated exposure chambers assuring more reliable hydrazine exposures. However, the overall data set for hydrazine is still somewhat deficient in reliably determining species variability in the toxic response to inhaled hydrazine. The AEGL-3 values are shown in Table 6-14.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

A summary of the AEGLs for hydrazine and their relationship to one another are shown in Table 6-15. For AEGL development, an effort was made to identify exposures and toxicity end points specific for the three AEGL levels thereby avoiding the uncertainty involved in extrapolating severity of effects from one effect level (e.g. extrapolation of reversible, nondisabling effects from effects that are clearly lethal). For hydrazine three different data sets and toxic end points were used for derivation of the three AEGL tiers.

The values for the three AEGL tiers appear to be relationally valid, both among the exposure periods for a given AEGL tier as well as across the exposure durations of three AEGL tiers. Furthermore, exposure to AEGL-1 or AEGL-2 values for any of the specified durations, would not result in doses known to induce developmental toxicity in laboratory animals (5 mg/kg, Keller et al. 1982, see Section 3.4.1). It must be noted that the AEGL-1 values are very close to current detection limits (0.05-0.6 ppm) for hydrazine (OSHA 2003).

TABLE 6-14 AEGL-3 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	64 ppm (83 mg/m^3)	45 ppm (59 mg/m^3)	35 ppm (46 mg/m^3)	8.9 ppm (12 mg/m^3)	4.4 ppm (5.7 mg/m^3)

TABLE 6-15 Relational Comparison of AEGL Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm
AEGL-2 (Disabling)	23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm
AEGL-3 (Lethality)	64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm

The AEGL-1 was developed based upon skin flushing and swollen eyes in rhesus monkeys after 24 h continuous exposure to 0.5 mg hydrazine/m^3 (0.4 ppm) (House 1964). The exposure continued for 90 days and resulted in a 20% mortality although the first death did not occur until days 21-30. Pathological findings in the hydrazine-exposed monkeys were most notable in the heart, kidneys, and liver. It is assumed that the effects of concern regarding the AEGL-1 would have been reversible and not life-threatening. The data based upon effects in a nonhuman primate were considered to be more relevant than data from rodent species (Comstock et al. 1954; Kulagina 1962; Latendresse et al. 1995) described in Section 3.2.3. The AEGL-1 was further adjusted (to 0.1 ppm for all time periods) due to the extreme reactivity and potential for irritation below the odor threshold. Furthermore, an analysis of occupational exposure to hydrazine by Koizumi et al. (1998) indicated that repeated 8 h/day exposure to hydrazine at 0.1 ppm did not result in signs of toxicity.

The AEGL-2 was based upon data showing the induction of nasal lesions following a single 1-h exposure of rats to 750 ppm hydrazine (Latendresse et al. 1995). The lesions were reversible upon removal from the exposure. Although this end point is not consistent with the severity of effect routinely identified for AEGL-2 development, it represents the only definitive nonlethal end point associated with definitive exposure. The end point, albeit a conservative estimate for AEGL-2 type effects, does represent an important effect consistent with the continuum of hydrazine toxicity (i.e., respiratory tract irritation, tissue damage, and potential tumorigenicity). Therefore, it is considered an appropriate basis for AEGL-2 development.

The AEGL-3 is based upon lethality data in rats exposed by nose-only inhalation to hydrazine at concentrations of 0.65, 2.04, 3.24, and 4.98 mg/L (HRC 1993). The HRC report identified a 1-h LC_{50} of 3,192 ppm. This reported 1-h LC_{50} was reduced three-fold as an estimate of the lethality threshold and used in the development of the AEGL-3 values.

The divergence from order-of-magnitude uncertainty factor application in AEGL derivations was adopted for several reasons. For the AEGL-1 type effects that are of rapid onset (e.g., skin flushing eye irritation) and that may more be appropriately considered surface contact effects, interspecies variability may be small and, therefore, an uncertainty factor of 3 appeared to be justified. For such effects in acute exposure scenarios, the relevance of order-of-magnitude dose/exposure adjustments is questionable because the exposure duration may be insufficient for expression of interspecies and intraspecies variability in toxicodynamics and toxicokinetics. By definition, the AEGLs address "susceptible but not hyper-susceptible individuals". Therefore, a 3-fold adjustment was considered appropriate to account for some level of individual variability without being unrealistically conservative in the AEGL derivation. The order-of-magnitude adjustments are more likely to be relevant and appropriate in long-term exposures.

Because long-term inhalation exposure to hydrazine has been shown to be tumorigenic in several species, a cancer assessment was also performed (Ap-

pendix B). Following the methods of NRC (1986), AEGL-2 values were derived based on two available data sets. Both data sets identified nasal tumors in rats following 1-year inhalation exposure to hydrazine. Although data from the animal studies affirm the carcinogenic potential of hydrazine following inhalation exposure, the observed tumorigenic responses appear to be a function of prolonged tissue irritation resulting from long-term repeated exposures and are unlikely to occur following a single low exposure. This was especially evident in the study by Latendresse et al. (1995) that showed repeated exposures were necessary for reversible histopathologic changes in rat nasal epithelium. Additionally, the work reported by Leakakos and Shank (1994) showed that showed DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic. Therefore, it would appear that hydrazine AEGL values that address rare, or single once-in-a-lifetime exposures should not be based upon cancer risk.

A graphic representation of the AEGL values and their relationship to one another and to available data are shown in the category plot in Appendix D.

8.2. Comparison with Other Standards and Criteria

Exposure standards and guidelines for hydrazine have been established by several organizations. All currently available values are shown in Table 6-16. Because most of these standards are derived to be protective against any adverse health effects and in certain cases intended for repeated or prolonged exposure durations, they are comparable only to the AEGL-1 values. Hydrazine is a suspected human carcinogen (A2) based upon the formation of nasal tumors in rats exposed to hydrazine for one year (MacEwen et al. 1981), and the NRC SPEGLs were derived with respect to this carcinogenic potential. Although the AEGLs were not derived based upon carcinogenic potential, the AEGL-1 values vary by less than an order of magnitude relative to the NRC SPEGLs and the ACGIH TLV.

8.3. Data Adequacy and Research Needs

Definitive exposure-response data for hydrazine toxicity in humans are not available. However, qualitative information on the human experience affirms that hydrazine vapor is highly irritating. Animal data from earlier studies were often compromised by uncertain quantitation of exposure atmospheres, use of exposure durations that were not consistent with those of interest for AEGL development, poor exposure-response relationships for acute exposures, and imprecise characterization of toxicologic end points relative to acute exposures.

More recent studies in laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations and provided more focus on specific toxicologic end points (e.g., contact irritation, nasal lesions,

and lethality) resulting from acute exposures. Data from these studies enabled the development of AEGL values consistent with the methodologies described in the Standing Operating Procedures of the National Advisory Committee for AEGLs (NRC 2001).

Because the AEGL values are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic end points were considered to be more appropriate than those based upon a potential carcinogenic response. Furthermore, the available animal data suggest that the tumorigenic response to inhaled hydrazine is a function of prolonged tissue irritation resulting from repeated exposures and not the result of a single low exposure.

TABLE 6-16 Extant Standards and Guidelines for Hydrazine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm
AEGL-2 (Disabling)	23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm
AEGL-3 (Lethal)	64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm
ERPG-1(AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			30 ppm		
SPEGL (NRC)[b]			0.12 ppm	0.03 ppm	0.015 ppm
SMAC (NRC)[c]			4 ppm		
STPL(NRC)[d]	15 ppm	10 ppm	5 ppm		
IDLH (NIOSH)[e]		50 ppm	0.03 ppm		
REL-TWA (NIOSH)[f]			(2-h ceiling)		
PEL-TWA (NIOSH)[g]					1 ppm
TLV-TWA(ACGIH)[h]					0.01 ppm
MAK (Germany)[i]					-
MAC (The Netherlands)[j]					0.1ppm

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2002).

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[b]SPEGL (Short-term Public Emergency Guidance Level, National Research Council). (NRC 1985)

[c]SMAC (Spacecraft Maximum Allowable Concentration, National Research Council) (Garcia and James 1996)

[d]STPL (Short-Term Public Exposure Limit, National Research Council). (Shaffer and Wands 1973)

[e]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.

[f]REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits-Time Weighted Average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the-TLV-TWA, with cancer notation.

[g]PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits Time Weighted Average, Occupational Health and Safety Administration) (OSHA 2003, 29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[h]TLV-TWA (Threshold Limit Value-Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2002) 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.

[i]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2002) is defined analogous to the ACGIH-TLV-TWA.

[j]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration] Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2000) is defined analogous to the ACGIH-TLV-TWA.

In lieu of definitive exposure-response data for humans, quantitative data in multiple animal species would serve to reduce the uncertainty in interspecies variability and also allow for more precise predictions regarding the toxicologic responses of humans following acute exposure to hydrazine. The use of an adequate numbers of animals in these studies would also assist in reducing the uncertainty regarding individual variability in the toxic response to hydrazine. Studies addressing toxic end points consistent with those of AEGL-1 and AEGL-2 type effects would allow for more precisely defining the thresholds for these levels.

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APPENDIX A

Derivation of AEGL Values

Derivation of AEGL-1

Key Study:	House (1964). Monkeys exposed continuously by inhalation to 0.4 ppm (0.52 mg/m^3) exhibited flushing of the face and eye irritation.
Uncertainty factors:	3 for interspecies variability (the highly reactive hydrazine appears to be equally irritating to all species); 3 represents the geometric mean of 10 (3.16) 3 for intraspecies variability (the contact irritation due to the extreme reactivity of hydrazine is not likely to vary among individuals); 3 represents the geometric mean of 10
Total uncertainty factor adjustment:	$3.16 \times 3.16 = 10$
Time scaling:	$C^3 \times t = k$ (ten Berge et al. 1986)
Calculations:	0.4 ppm/10 = 0.04 ppm $C^3 \times t = k$ $(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$
10-min AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 10 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.21 ppm
30-min AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 30 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.15 ppm
1-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 60 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.12 ppm
4-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 240 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.07 ppm
8-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 480 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.06 ppm

Note: The above represents the basis for the initial AEGL-1 derivations. Because of the extreme reactivity of hydrazine and its great capacity as a direct-contact irritant, 0.1 ppm was adopted as the AEGL-1 for all time periods (the calculated values for 30 min, 1 h, 4 h, and 8 h are all approximately 0.1 ppm).

Derivation of AEGL-2

Key Study:	Latendresse et al. (1995). Rats exposed for 1 h to 750 ppm hydrazine exhibited nasal lesions. The lesions were reversible following cessation of exposure. Compared to unexposed controls, there was no significant increase in lethality in males exposed to a single 1-h exposure to 750 ppm or following 10 weekly 1-h exposures. Although a significant increased mortality ($p > 0.05$) was observed in female rats at 30 months, there was no increased lethality at 14.5 months following the single 1-h exposure. Furthermore, there were no deaths in rats following 10 consecutive weekly 1-h exposures. There was no significant difference in mortality of similarly exposed male and female hamsters at any time point. Therefore, the 750 ppm exposure represents an exposure that will result in notable irritation and histopathological changes.
Uncertainty factors:	3 for interspecies variability; available data disallow a definitive assessment of species variability although the direct-contact reactivity of hydrazine would limit dosimetric variability. 3 for intraspecies variability; available data (clinical signs and histopathologic correlates) indicate that hydrazine toxicity is a port-of-entry toxicant and acts by direct-contact mechanisms due to the extreme reactivity of hydrazine. The irritation and resulting tissue damage are not likely to vary among individuals. Additionally, variability in acetylation phenotypes among humans reportedly varies by approximately 2-fold thereby implying minimal variability in this aspect of hydrazine metabolism.
Modifying factor:	2 for data inadequacies; definitive exposure-response data specific to AEGL-2 level effects are unavailable for inhalation exposure. An additional modifying factor of 3 has been applied to account for the uncertainties in the measurement of exposure concentrations in earlier studies. While not an issue for recent studies such as Latendresse et al. (1995) and HRC (1993), this deficiency compromises the incorporation of older data into assessing species variability.
Time scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

Calculations:	750 ppm/60 = 12.5 ppm $C^3 \times t = k$ $(12.5 \text{ ppm})^3 \times 60 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ $C^1 \times t = k$ $(12.5 \text{ ppm})^1 \times 60 \text{ min} = 750 \text{ ppm-min}$
10-min AEGL-2	$C^3 \times 10 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ C = 23 ppm
30-min AEGL-2	$C^3 \times 30 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ C = 16 ppm
1-h AEGL-2	C = 12.5 ppm (rounded to 13 ppm)
4-h AEGL-2	$C^1 \times 240 \text{ min} = 750 \text{ ppm}^1\text{-min}$ C = 3.1 ppm
8-h AEGL-2	$C^1 \times 480 \text{ min} = 750 \text{ ppm}^1\text{-min}$ C = 1.6 ppm

Derivation of AEGL-3

Key Study:	HRC 1993. Lethality in rats following 1-h nose-only inhalation exposure. A 3-fold reduction in the reported LC_{50} of 4.2 mg/L (3,192 ppm) is used as an estimate of the lethality threshold (3,192 ppm/3 = 1,064 ppm). The rat data from the recent Latendresse et al. (1995) study indicated that this exposure would not be lethal to rats exposed for 1 h. The steep exposure-response curve for hydrazine also suggests derivation of an $LC_{0\,1}$(3,192 ppm) derived by a Litchfield and Wilcoxon analysis may represent an exposure below the lethality threshold. Data from recent studies such as the HRC (1993) report and Latendresse et al. (1995) are also more reliable than older studies due to improved analytical techniques (older studies likely underestimated hydrazine concentrations due to its extreme reactivity).
Uncertainty factors:	3 for interspecies variability; the extreme reactivity of hydrazine resulted in compromised and variable exposure concentration data; the order-of-magnitude adjustment is considered adequate for to account for dosimetry differences among species. 3 for intraspecies variability; available data (clinical signs and histopathologic correlates) indicate that hydrazine toxicity is a port-of-entry toxicant and acts by direct-contact mechanisms that are not likely to vary by an order of magnitude across species.
Modifying factor:	3 for inadequacies regarding measurement of exposure concentrations in earlier studies which compromise a definitive assessment of species variability.

Time scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.
Calculations:	1064 ppm/30 = 35.5 ppm $C^3 \times t = k$ $(35.5 \text{ ppm})^3 \times 60 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ $C^1 \times t = k$ $(35.5 \text{ ppm})^1 \times 60 \text{ min} = 2130 \text{ ppm-min}$
10-min AEGL-3	$C^3 \times 10 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ C = 64 ppm
30-min AEGL-3	$C^3 \times 30 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ C = 45 ppm
1-h AEGL-3	C = 35 ppm
4-h AEGL-3	$C^1 \times 240 \text{ min} = 2130 \text{ ppm-min}$ C = 8.9 ppm
8-h AEGL-3	$C^1 \times 480 \text{ min} = 2130 \text{ ppm-min}$ C = 4.4 ppm

APPENDIX B

Carcinogenicity Assessment for Hydrazine AEGLs

Key Study: Vernot et al. 1985

Administered Dose (ppm)	Human Equivalent Dose[a] (mg/kg/day)	Tumor Incidence[b]
0	0	0/146
0.05	0.0009	2/96
0.25	0.004	1/94
1.0	0.017	9/97
5.0	0.084	58/98

[a]Transformed animal dose (TAD) converted to human equivalent dose (HED): TAD × 20 m^3/day × 1/70 kg.HED entered into GLOBAL86; unit risk converted back to mg/m^3.
[b]Nasal adenomatous polyps, male rats (female rats and hamsters exhibited lower but statistically significant incidences [$p \leq 0.01$] as well).

The cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC 1986). The value derived from the animal data and GLOBAL86 was divided by 2.4 to adjust for dose and study duration ($[24 \text{ mos}/18 \text{ mos}]^3 = 2.4$). This adjustment accounts for the proportional effect of age on the tumorigenic response and provides the following VSD:

$$\text{Virtually safe dose (VSD) } d = 3.2 \times 10^{-7} \text{ mg/m}^3$$

Calculate 24-h exposure:

$$\text{24-h exposure} = d \times 25{,}600$$
$$= (3.2 \times 10^{-7} \text{ mg/m}^3) \times 25{,}600$$
$$= 0.008 \text{ mg/m}^3$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short term exposures under the multistage model [Crump and Howe 1984]):

$$\frac{\text{24 - h exposure}}{6} = \frac{0.008 \text{ mg/m}^3}{6} = 0.0013 \text{ mg/m}^3$$

$$0.0013 \text{ mg/m}^3 = \frac{1 \times 10^4}{1 \times 10^6 \text{ (risk at d)}} = 0.13 \text{ mg/m}^3$$

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes $1/f \times 24$ h (NRC 1985). For a 1×10^{-4} risk:

24-h exposure = 0.13 mg/m^3 (0.1 ppm)
8-h = 0.39 mg/m^3 (0.3 ppm)
4-h = 0.78 mg/m^3 (0.6 ppm)

1-h = 3.12 mg/m^3 (2.4 ppm)
0.5-h = 6.24 mg/m^3 (4.7 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

Because long-term inhalation exposure to hydrazine has been shown to be tumorigenic in several species, a cancer assessment was also performed (Appendix B). Following the methods of NRC (1986), AEGL-2 values were derived based on two available data sets. Both data sets identified nasal tumors in rats following 1-year inhalation exposure to hydrazine. Although data from the animal studies affirm the carcinogenic potential of hydrazine following inhalation exposure, the observed tumorigenic responses appear to be a function of prolonged tissue irritation resulting from long-term repeated exposures and are unlikely to occur following a single low exposure. This was especially evident in the study by Latendresse et al.(1995) that showed repeated exposures were necessary for reversible histopathologic changes in rat nasal epithelium. This contention is also supported by the work of Leakakos and Shank (1994) that showed DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic. Therefore, it would appear that hydrazine AEGL values that address rare, or single once-in-a-lifetime exposures should not be based upon cancer risk.

Key Study: MacEwen et al. (1981) significant increased tumor incidence in mice (pulmonary adenomas), rats (nasal adenomas, adenocarcinomas), and hamsters (nasal cavity polyps) exposed to highest concentration. Exposure protocol: male and female rats exposed to hydrazine at 0, 0.05, 0.25, 1.0, or 5.0 ppm, 6 h/day, 5 days/week for one year; 12- to 38-month postexposure observation.

The cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC 1986).

Virtually safe dose (VSD) exposure level (d) of 2×10^{-4} ug /m^3 (2×10^{-7} mg/m^3) for a 1×10^{-6} risk level for hydrazine was selected (EPA 2002). This risk level was based upon an inhalation unit risk of 4.9×10^{-3} per ug /m^3 derived from the MacEwen et al. (1981) data using the linearized multistage procedure.

$$d = 2 \times 10^{-4} \text{ ug /m}^3$$

Assuming the carcinogenic effect to be a linear function of cumulative dose, a single-day exposure is equivalent to d × 25,600 days (average lifetime).

$$\text{24-h exposure} = d \times 25{,}600$$
$$= (2 \times 10^{-7} \text{ mg/m}^3) \times 25{,}600$$
$$= 0.005 \text{ mg/m}^3$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short term exposures under the multistage model [Crump and Howe 1984]).

$$\frac{\text{24 - h exposure}}{6} = \frac{0.005\ \text{mg/m}^3}{6} = 0.0008\ \text{mg/m}^3$$

For a 1×10^{-4} risk, the extent of risk based on the 24-h exposure concentration becomes:

$$0.008\ \text{mg/m}^3 = \frac{1 \times 10^4}{1 \times 10^{-6}\ \text{(risk at d)}} = 0.08\ \text{mg/m}^3$$

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f × 24 h (NRC 1985). For a 1×10^{-4} risk:

24-h exposure = 0.08 mg/m^3 (0.06 ppm)
8-h = 0.24 mg/m^3 (0.2 ppm)
4-h = 0.48 mg/m^3 (0.4 ppm)
1-h = 1.9 mg/m^3 (1.5 ppm)
0.5 h = 3.8 mg/m^3 (2.9 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

APPENDIX C

Derivation Summary for Hydrazine AEGLs

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm

Key Reference: House, W.B. 1964. Tolerance Criteria for Continuous Inhalation Exposure to Toxic Materials. III. Effects on Animals of 90-day Exposure to Hydrazine, Unsymmetrical Dimethylhydrazine (UMDH), Decaborane, and Nitrogen Dioxide. ASD-TR-61-519 (III). Wright-Patterson Air Force Base, OH.

Test Species/Strain/Number: 10 male rhesus monkeys.

Exposure Route/Concentrations/Durations:
Inhalation: average of 0.78 ppm (range: 0.25-1.38 ppm) continuous (24 h/day, 7 days/week) exposure for 90 days; 0.4 ppm for first 10 days (determinant for AEGL-1)

Effects: Eye and facial irritation within 24 h.

End Point/Concentration/Rationale:
0.4 ppm for the first 24 h resulted in mild irritation which is a defined AEGL-1 end point.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3: Contact irritation is not likely to vary greatly among species because hydrazine is a highly reactive and direct acting irritant. Also, a nonhuman primate was the test species.
Intraspecies: 3: Hydrazine will be extremely reactive with all biological tissues resulting in irritation and reversible tissue damage upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applied; insufficient data.

Time Scaling: $C^n \times t = k$ where $n = 3$ to scale from 24-h exposure to 4-h and 8-h exposure periods. Due to the extreme reactivity of hydrazine, however, the contact irritant effects were considered to be concentration dependent and, therefore, the 0.1 ppm concentration derived for the 4-h and 8-h periods was applied for all time periods.

Data Adequacy:
Quantitative data pertaining to AEGL-1 type effects are limited. The data provided by House (1964) for nonhuman primates, however, are consistent with the human experience regarding the irritant effects of low level hydrazine exposure.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm

Reference: Latendresse, J.R., G.B. Marit, E.H. Vernot, C.C. Haun, and C.D. Flemming. 1995. Oncogenic potential of hydrazine in the nose of rats and hamsters after 1 or 10 1-h exposures. Fundam. Appl. Toxicol. 27(1): 33-48.

Test Species/Strain/Sex/Number:
5 male and 5 female Fischer-344 rats and 10 Syrian golden hamsters, 10/exposure group.

Exposure Route/Concentrations/Durations: Inhalation: 750 ppm for 1 h.

Effects:
Exposure Effect:
750 ppm for 1 h Nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis; determinant for AEGL-2).

End Point/Concentration/Rationale:
750 ppm for 1 h resulted in nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) that were considered to be an estimate of a threshold for an AEGL-2 effect.
Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies:
3: An uncertainty factor of 3 for interspecies variability was applied to account for possible species-dependent uncertainties in the toxic response to inhaled hydrazine.
Intraspecies:
3: Hydrazine is extremely reactive with all biological tissues resulting in irritation and tissue damage upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals. Additionally, variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism has been shown to vary approximately 2-fold.

Modifying Factor: 2 for inadequacies in the database pertaining to AEGL-2 effects
3 for the uncertainties in the measurement of exposure concentrations in earlier studies. While not an issue for recent studies such as Latendresse et al. (1995) and HRC (1993), this deficiency compromises the use of older data for assessing species variability.

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling:
$C^n \times t = k$ where n = 1 or 3 (k = 117188 ppm^3-min when n = 3 and k = 750 ppm-min when n = 1); The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using n = 3 when extrapolating to shorter exposure durations points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

Data Adequacy:
Although the toxicity end points selected for AEGL-2 derivation are not consistent with an effect severity consistent with the AEGL-2 definition, they are consistent with the continuum of effects known to occur as a result of hydrazine exposures that could result in more serious responses. Because of the know toxicity of hydrazine and its carcinogenic potential, the somewhat conservative approach was justified. Species variability is poorly defined due primarily to data deficiencies.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm

Key Reference: Huntingdon Research Centre 1993. Hydrazine 64% Aqueous Solution: Acute Inhalation Toxicity in Rats 1-h Exposure. Huntingdon Research Centre, Cambridge, England. CMA 8/930523. Chemical Manufacturers' Association, Washington, DC.

Test Species/Strain/Sex/Number: Male and female Sprague-Dawley rats, 5/sex/group.

Exposure Route/Concentrations/Durations:
Inhalation: 0, 0.65, 2.04, 3.24, 4.9 mg/L for 1 h (nose-only exposure to 64% aerosol)

Effects

Concentration	Mortality
2.04 mg/L (1556 ppm)	0/10
3.24 mg/L (2472 ppm)	4/10
4.98 mg/L (6596 ppm	6/1

Reported LC_{50}: 4959 ppm (64% aerosol); 3192 ppm (hydrazine alone)

End Point/Concentration/Rationale:
When compared to the data from Latendresse et al. (1995), where rats survived multiple 1-h exposures to 750 ppm, the calculated 1-h LC_{01} of 334 ppm appeared to be unrealistically low and not scientifically defensible as an estimated lethality threshold. Therefore, a three-fold reduction in the 1-h LC_{50} (3192 ppm/3 = 1064 ppm) was determined to be an estimate of the lethality threshold for a 1-h exposure duration that is consistent with the currently available data.
Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies:
3-An uncertainty factor of 3 for interspecies variability was applied to account for possible species-dependent uncertainties in the toxic response to inhaled hydrazine.
Intraspecies:
3-Hydrazine will be extremely reactive with all biological tissues resulting in irritation and severe tissue damage at high concentrations upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals.

Modifying Factor: 3 for inadequacies regarding measurement of exposure concentrations in earlier studies which compromise a definitive assessment of species variability

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 1 or 3 (k=2684333 ppm^3-min when n = 3 and k = 2130 ppm-min when n = 1); The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

Data Adequacy:
Lethality data are available for several animal species. Lethality values quantitatively derived from a recent study were considered appropriate as the basis for AEGL-3 derivation. Species variability is poorly defined.

APPENDIX D

Category Plot for Hydrazine AEGLs

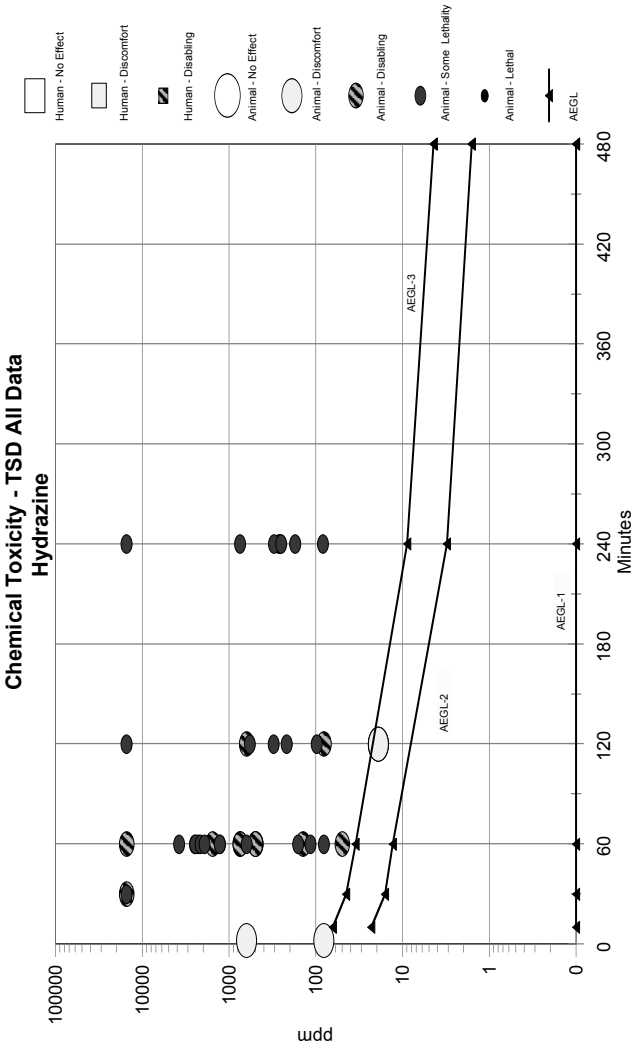


FIGURE D 1 Category plot for hydrazine.

APPENDIX E

Level of Distinct Odor Awareness (LOA) for Hydrazine

DERIVATION OF THE LOA: HYDRAZINE

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

The odor detection threshold (OT_{50}) for hydrazine was calculated to be 4 ppm (van Doorn et al. 2002).

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

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

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

$$3 = 2.33 \times \log (C/4) + 0.5 \text{ which can be rearranged to}$$
$$\log (C/4) = (3\text{-}0.5)/2.33 = 1.07 \text{ and results in}$$
$$C = (10^{1.07}) \times 4 = 47 \text{ ppm}$$

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

The LOA for hydrazine is 63 ppm.

$$LOA = C \times 1.33 = 47 \text{ ppm} \times 1.33 = 63 \text{ ppm}$$

7

Peracetic Acid[1]

Acute Exposure Guideline Levels

PREFACE

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

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

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

[1]This document was prepared by the AEGL Development Team composed of Kowetha Davidson (Oak Ridge National Laboratory) and Chemical Manager William Bress (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).

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

Peracetic acid is produced by the catalytic action of sulfuric acid on acetic acid and hydrogen peroxide. Technical or commercial peracetic acid products contain different concentrations of peracetic acid, acetic acid, and hydrogen peroxide, but the concentration of peracetic acid does not exceed 40%. Peracetic acid is unstable; it decomposes to its original constituents under conditions that vary with concentration, temperature, and pH. Peracetic acid is used as a disinfectant against bacteria, fungi, and viruses in the food and medical industry, as a bleaching agent, as a polymerization catalyst or co-catalyst, in the epoxidation of fatty acid esters, as an epoxy resin precursor, and in the synthesis of other chemicals.

Peracetic acid is corrosive/irritating to the eyes, mucous membranes of the respiratory tract, and skin. It causes lacrimation, extreme discomfort, and irritation to the upper respiratory tract in humans after exposure to concentrations as low as 15.6 mg peracetic acid/m^3 (5 ppm) for only 3 min. Eye irritation, clinical signs, and pathologic lesions indicative of respiratory tract irritation have been observed in laboratory animals exposed by inhalation to various concentrations of peracetic acid aerosols. Exposure to lethal concentrations of peracetic acid causes hemorrhage, edema, and consolidation of the lungs, whereas nonlethal concentrations cause transient weight loss or reduced weight gain in addition to slight to moderate signs of respiratory tract irritation. Human data were available

for deriving AEGL-1 and -2 values and animal data were available for deriving AEGL-3 values.

The AEGL-1 value is 0.52 mg/m^3 (0.17 ppm) for all exposure durations from 10 min to 8 h. This value was derived from an exposure concentration of 1.56 mg/m^3 (0.5 ppm), which, according to Fraser and Thorbinson (1986), is expected to cause no discomfort and according to McDonagh (1997) is not immediately irritating but would be unpleasant for an extended period of time. Therefore, 1.56 mg/m^3 is considered to be the threshold for irritation to mucous membranes and eyes. An intraspecies uncertainty factor of 3 was applied to 1.56 peracetic acid mg/m^3, because peracetic acid is a corrosive/irritant substance and the effects, which are confined to the upper respiratory tract, are expected to be similar for individuals within the population. The rationale for proposing the same value for all time points, is as follows: (1) effects of peracetic acid exposure correlate with concentration more than time, and (2) and peracetic acid is freely soluble in water; therefore, it should be effectively scrubbed in the nasal passages, particularly at the very low AEGL-1 concentration.

The AEGL-2 value is 1.56 mg/m^3 (0.5 ppm) for all exposure durations from 10 min to 8 h based on an exposure concentration of 4.7 mg/m^3, which, according to Fraser and Thorbinson (1986), is expected to be associated with slight to tolerable discomfort to nasal membranes and eyes for exposure durations up to 20 min. There was no increase in irritation with exposure duration. An intraspecies uncertainty factor of 3 was applied because peracetic acid is a corrosive/irritating substance and the effects, which are confined to the upper respiratory tract, are expected to be similar among individuals in the population. The rationale for proposing the same value for all exposure durations is discussed above for AEGL-1 values.

The AEGL-3 values are derived from the study of Janssen (1989). This study showed that rats exposed to Proxitane 1507 (15% peracetic acid, ~28% acetic acid, 14% hydrogen peroxide, ~1% "stabilizer," and ~43% water) aerosols at concentrations of 130, 300, or 320 mg/m^3 for 30 min had mortality responses of 0/5, 0/5, and 3/5 rats, respectively. Exposures to aerosol concentrations of 150, 390, or 1450 mg/m^3 for 60 min resulted in the death of 0/5, 2/5, and 5/5 rats, respectively. Clinical signs indicative of respiratory tract irritation were observed at all concentrations and increased in severity with increased exposure concentration for each exposure duration. Clinical signs suggestive of nervous system effects were also observed, but could have been due to extreme respiratory tract discomfort. The AEGL values were derived from the highest concentration at which no mortality was observed: 300 mg/m^3 for a 30-min exposure and 150 mg/m^3 for a 60-min exposure. The total uncertainty factor is 10. Interspecies and intraspecies uncertainty factors of 3 were applied because mucous membranes of the respiratory tract are not expected to show significant variation in response to corrosive/irritating substances concentrations that cause physical damage and that approach the threshold for lethality regardless of species or the individuals in the population. The data, however, suggest that humans may be slightly more sensitive than animals to peracetic acid. The rationale for

the intraspecies uncertainty factor of 3 was the same as described for AEGL-1. The intraspecies uncertainty factor of 3 and the interspecies uncertainty factor of 3 were applied to 300 and 150 mg/m^3 for the 30- and 60-min exposures, respectively. The equation, $C^n \times t = k$, where n = 1.6 (estimated from 1- and 4-h LC_{50} data for rat), was used to scale the 60-min exposure to 4- and 8-h values and the 30-min exposure to 10 min.

The AEGL values are summarized in Table 7-1.

1. INTRODUCTION

Peracetic acid is produced by the catalytic action of sulfuric acid on acetic acid and hydrogen peroxide (Lewis 1993). These constituents are found in the most concentrated commercial grades of peracetic acid at the following approximate concentrations (weight %): 40% peracetic acid, 40%, acetic acid, 5% hydrogen peroxide, 1% sulfuric acid, and 13% water, along with 500 ppm of a "stabilizer" (Bock et al. 1975). The stabilizer was not identified. Peracetic acid decomposes as it is diluted with water, particularly when diluted to 10 or 20% peracetic acid. Sulfuric acid catalyzes the decomposition of peracetic acid and is present in sufficient amounts in 10 to 20% peracetic acid products to catalyze the decomposition of peracetic acid to the individual constituents: acetic acid and hydrogen peroxide. At more dilute concentrations of peracetic acid, decomposition occurs more slowly, because sulfuric acid is no longer present in sufficient quantities to catalyze its decomposition. However, very dilute solutions (0.2%) will decompose more rapidly at elevated temperatures (4 weeks at 4ºC vs 1 week at 40 ºC). In addition, increasing the pH to 7.0 results in greater than 50% decomposition of peracetic acid after 1 day compared with almost no decomposition after 7 days at pH 2.7 (the natural pH of 0.2% peracetic acid) (Mucke 1977). Peracetic acid is known as a powerful oxidizing agent. It is unstable upon contact with organic materials and it explodes at 110ºC (Lewis 1993).

Because of its effectiveness against bacteria, fungi, and viruses, peracetic acid is used as a disinfectant in the food and medical industries (Bock et al. 1975; Fishbein 1979; Lewis 1993). It is also used as a beaching agent in the paper and textile industries, as a polymerization catalyst or co-catalyst, in the epoxidation of fatty acid esters, as an epoxy resin precursor, and in the synthesis of other chemicals (Bock et al. 1975; Fishbein 1979).

The database for peracetic acid is limited; however, limited quantitative human and animal data are available for deriving AEGL values. The animal data for inhalation studies were performed primarily on aerosols of trade name products or diluted grades of peracetic acid referred to as Proxitane 1507 (15% peracetic acid, ~28% acetic acid, and 14% hydrogen peroxide) or Proxitane AHC (~5% peracetic acid, 19% (minimum) hydrogen peroxide, and 10% acetic acid). Measurements of atmospheric concentrations in the inhalation chambers showed

TABLE 7-1 Summary of AEGL Values for Peracetic Acid

Classification	10 min	30 min	1 h	4 h	8 h	End Point /Reference
AEGL-1 (Nondisabling)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	Threshold for irritation (Fraser and Thorbinson 1986; McDonagh 1997)
AEGL-2 (Disabling)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	Mild irritation (Fraser and Thorbinson 1986)
AEGL-3[a] (Lethal)	60 mg/m^3	30 mg/m^3	15 mg/m^3	6.3 mg/m^3	4.1 mg/m^3	Highest concentration causing no deaths (Janssen 1989a)

[a]AEGL-3 values are based on exposure to aerosol; therefore, concentrations are not converted to ppm.

that the relative concentrations of peracetic acid, acetic acid, and hydrogen peroxide varied in aerosols generated from the same product, thus demonstrating the instability of peracetic acid in the product or the aerosol. Although a contributing effect of acetic acid and hydrogen peroxide cannot be ruled out in the toxicity studies described in this report, it appears, however, that acetic acid and hydrogen peroxide are considerably less toxic than peracetic acid. Sulfuric acid concentrations were not reported for the products (Proxitane 1507 and Proxitane AHC) used in these studies, but would be expected to account for only a very small fraction since the highest concentration of sulfuric acid in most products was only 1%. The physical and chemical data for peracetic acid are presented in Table 7-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on human lethality due to exposure to peracetic acid were found in the literature searched.

2.2. Nonlethal Toxicity

Bock et al. (1975) reported that peracetic acid was intensely irritating to the human nasal passages. There was no additional information documenting the source of this information. McDonagh (1997) and an associate conducted measurements of airborne peracetic acid concentrations in two caprolactone distillation plants. Peracetic acid, which is used in caprolactone monomer production, was distilled in the distillation houses of the plant. The monitoring took place

over a 3-h period. Peracetic acid vapor was measured at total peroxygen content; hydrogen peroxide was not expected to comprise a large proportion of the measured substance in the vapor. In one area, peracetic acid concentrations ranged from 0.5 to 0.6 ppm (1.56-1.87 mg/m^3); these concentrations were not considered to be immediately irritating, but would have been considered "unpleasant for an extended period" of time. Peracetic acid concentrations of 0.13 to 0.17 ppm (0.40-0.53 mg/m^3) in another area were considered tolerable and not unpleasant. McDonagh and his associate spent most of their time in an area where the average peracetic acid concentration measured for a 10-min sampling time was 0.17 ppm (0.53 mg/m^3). They noted no lacrimation at any time during their 3-h exposure. McDonagh (1997) recommended 0.15 ppm (0.47 mg/m^3) as an acceptable 8-h occupational exposure limit for peracetic acid. This concentration would be perceptible, but not irritating or unpleasant.

TABLE 7-2 Physical and Chemical Data for Peracetic Acid

Parameter	Data	Reference
Chemical Name	Peracetic acid	O'Neil et al. 2001
Synonyms	Peroxyacetic acid, acetic peroxide, ethaneperoxoic acid, acetyl hydroperoxide, Proxitane 4002, Proxitane 1507, Proxitane AHC	O'Neil et al. 2001; RTECS 2003
CAS Registry No.	79-21-0	RTECS 2003
Chemical Formula	CH_3COOOH	O'Neil et al. 2001
Molecular Weight	76.05	O'Neil et al. 2001
Physical State	Colorless liquid	Lewis 1993
Boiling/Freezing/ Flash Point	105 ºC/-30 ºC/40.5 ºC	Lewis 1993
Density	1.15 at 20 ºC	Lewis 1993
Solubility	Freely soluble in H_2O, alcohol, ether, H_2SO_4	O'Neil et al. 2001
Vapor Pressure	14.5 mm Hg at 25ºC	HSDB 1997
Explosion point	110 ºC	Lewis 1993
Henry's Law Constant	2.08×10^{-6} atmm^3/mol at 25 ºC	HSDB 1997
Conversion factors	1 ppm= 3.04 mg/m^3 at 20 ºC and 101kPa 1mg/ m^3= 0.33 ppm	IUCLID 2000

Fraser and Thorbinson (1986) conducted fogging studies in a chicken house using Tenneco Organics' "Peratol" diluted to 1:20 (5% peracetic acid = 1904 mg/L in the liquid formulation) to determine atmospheric levels of peroxygen and establish safe working practices. Measurements of aerosol concentrations were taken at various distances from the fogging unit to establish the spread and distribution of peracetic acid concentrations. The analytical procedure measured total peroxygen concentration, which was calculated as hydrogen peroxide (H_2O_2). The details of the analytical method were not presented in the report. The fogging unit was placed about 1 m off the ground, and measurements were taken at various locations (the shed apex, the floor, and sides of the shed). The first half of Table 7-3 presents the concentrations, time of measurements starting at 3:30 (p.m. assumed), and physiological responses to peracetic acid. The authors did not report the number of subjects exposed to the aerosol. Lacrimation was noted at 5 ppm (15.6 mg/m^3), extreme discomfort was noted at concentrations ≥2.5 ppm (7.79 mg/m^3), and 2.0 ppm (6.23 mg/m^3) was considered unbearable in one instance and tolerable for 2 min in another. After 23 min, the fogging unit was turned off and refilled; during this time, the concentration of peracetic acid dropped to <0.5, 0.5- 1.0, and 1.0-1.5 ppm (1.56, 1.56-3.12, and 3.12-4.7 mg/m^3) at 0.3, 2, and 4 meters, respectively, above ground; a slight discomfort of nasal and eye membranes was noted during this phase. For the next 1 h and 15 min, the concentrations ranged from 2.0 to 3.0 ppm (6.23 to 9.35 mg/m^3); these concentrations were associated with unbearable or extreme discomfort.

At 5:20 p.m., the fogger was turned off and the concentrations of peracetic acid began to decrease. The second half of Table 7-3 describes the concentrations and observed physiological responses after shutoff. After the fogger was turned off, the concentrations on peracetic acid decreased from 2.0 ppm (6.23 mg/m^3) to ≤0.5 ppm within 45 min. During this time the physiological responses decreased from extreme discomfort of mucous membranes to mild discomfort at 0.5-1.0 ppm (1.56-3.12 mg/m^3) to no discomfort at ≤ 0.5 ppm (1.56 mg/m^3). No irritation to the chest occurred at any time during this test.

2.3. Summary

No data on human lethality caused by exposure to peracetic acid were found in the literature, and the data on nonlethal effects are limited. Peracetic acid is extremely irritating to mucous membranes of the eyes and nasal passages at low concentrations. Exposure to aerosols generated from diluted Peratol was associated with lacrimation at 5 ppm (15.6 mg/m^3), extreme discomfort and irritation to mucous membranes at ≥2.0 ppm (6.23 mg/m^3); slight or mild discomfort at 0.5-1.5 ppm (1.56-4.67 mg/m^3), and no discomfort at <0.5 ppm (1.56 mg/m^3) (Fraser and Thorbinson 1986). Exposure to peracetic acid vapor at concentrations of 0.13-0.17 ppm (0.40-0.53 mg/m^3) for up to 3 h were detectable, tolerable, and not unpleasant (McDonagh 1997). Irritation to the chest did not

occur at concentrations ≥5 ppm (15.6 mg/m^3), and no data were available for exposure of humans to concentrations >5 ppm (15.6 mg/m^3). In the study by McDonagh (1997), humans were exposed to peracetic acid vapor, and in the study by Fraser and Thorbinson (1986) humans were exposed to the aerosols. There was agreement between exposure to aerosol and vapors at 0.5 ppm (1.56 mg/m^3), the highest vapor concentrations reported; both studies reported either no discomfort or only mild or slight discomfort at this concentration. There were no comparable levels between the two studies at the higher exposure concentrations.

TABLE 7-3 Physiologic Response to Low Level Exposure to Peracetic Acid Aerosols Generated by a Fogger

Time	ppm (as total H_2O_2)[a]	Observed Effects
3.30	5 (15.6)	Lacrimation, extreme discomfort, irritation of nasal membranes
3.37	5 (15.6)	Lacrimation, extreme discomfort, irritation of nasal membranes
3.53	1 to 1.5 (3.12-4.67)	Slight discomfort of nasal and eye membranes, decreasing with concentration
	0.5 to 1.0 (1.56-3.12)	
	<0.5 (1.56)	
4.05	2.0 (6.23)	Irritation considered unbearable
5.00	2.5 (7.79)	Extreme discomfort of nasal membranes
5.10	2.5 (7.79)	Extreme discomfort
	3.0 (9.35)	Extreme discomfort
5.15	3.0 (9.35)	Extreme discomfort
5.20	2.0 (6.23)	Irritation tolerable for 2 min
Concentrations and response after the fogger was turned off (minutes)		
5 - 10	2.0 (6.23)	Extreme discomfort of mucous membranes
15-20	1to 1.5 (3.12-4.67)	Discomfort of mucous membranes
25	1.0 (3.12)	Discomfort tolerable
30	0.5 to 1.0 (1.56-3.12)	Discomfort mild
35- 45	≤ 0.5 (1.56)	No discomfort

[a]Measurements taken at different locations relative to fogging unit; numbers in parentheses are concentrations in mg/m^3.
Source: Fraser and Thorbinson 1986. Reprinted with permission; copyright 1986, Solvay SA.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Janssen (1989a) conducted a study in which groups of five male CPB-WU Wistar derived rats were exposed to Proxitane 1507 (15% peracetic acid, ~28% acetic acid, 14% hydrogen peroxide, ~1% stabilizer, and ~43% water) aerosol by nose-only inhalation in a 40 L dynamic flow chamber. The chamber was constructed of aluminum, and the inside walls were coated with silver and a thin layer of polytetrafluoroethylene. The test atmospheres were generated with a stainless-steel nebulizer, and test concentrations were analyzed as total peroxygen concentration corrected for the amount of hydrogen peroxide. Chamber concentrations (converted from mg/L to mg/m^3) of the constituents in the test material and exposure durations are listed in Table 7-4. The study author did not comment on the greater than zero concentration of constituents in the control atmosphere, but it may be related to the detection limit of the analytical procedure or natural occurrence of hydrogen peroxide in the atmosphere (ATSDR 1998). Respiratory rates were determined during exposure, clinical signs of toxicity were recorded for 14 days after exposure, and body weight was measured on post-exposure days 2, 7, and 14. Postmortem studies included gross examination, measurement of lung weight, and histopathological examination of the lungs. The results are summarized in Table 7-4.

Deaths occurred only in groups exposed to peracetic concentrations ≥320 mg/m^3 regardless of exposure duration (320 mg/m^3 for 15 or 30 min, 390 mg/m^3 for 60 min, and 1450 mg/m^3 for 60 min). The LC_{50} for the 60-min exposure to peracetic acid was 476 mg/m^3. Clinical signs of toxicity included effects primarily indicative of extreme respiratory irritation (reduced respiratory rate, respiratory difficulties, blood around the nose and mouth, sneezing, and rubbing the nose) and those that may be indicative of nervous system effects (passivity, decreased alertness and startle response, piloerection, salivation, decreased coordination and muscle tone), but were probably related to extreme discomfort of the animals.

The only effect on the eyes was drooping eye lids. The severity of the clinical signs (slight, moderate, severe) as well as the number of signs observed in each group and time of disappearance of clinical signs increased with concentration of test material and exposure duration. Clinical signs disappeared 1.5 h to 5 days after exposure. Respiratory rates measured during exposure showed maximum depressions to 22 to 41% of preexposure rates in all exposure groups. Body weight measurements showed transient decreases on day 2 after exposure to 320 mg/m^3 for 15 or 30 min and 150 mg/m^3 or 1450 mg/m^3 for 60 min.

TABLE 7-4 Effects of Nose-Only Inhalation Exposure to Proxitane 15077 in Male Rats

Group Number	Exposure Time (min)	Concentration (mg/m^3)[a]			Effects		
		Peracetic Acid	Acetic Acid	H_2O_2	Mortality	Clinical Signs and Body Weight[a]	Gross Pathology
10 (control)	60	<70	<70	<50	0/5	+	URT (0/5); LRT (1/5)
8	15	300	767	<50	0/5	+, bw (no effect)	URT (0/5); LRT (2/5)
3	15	320	2000	<70	1/5	+, ++, wt. loss	URT (1/5); LRT (1/5)
6	30	130	210	10	0/5	+, bw (no effect)	URT (0/5); LRT (0/5)
9	30	300	767	<50	0/5	+, ++, bw (no effect)	URT (0/5); LRT (1/5)
4	30	320	2000	<70	3/5	+, ++, +++, bw (no data)	URT (2/5); LRT (5/5)
7	60	150	290	9	0/5	+, ++, ↓ bw	URT (0/5); LRT (1/5)
5	60	390	2800	4	2/5	+, ++, +++, bw (no data)	URT (2/5); LRT (4/5)
2	60	1450	6600	450	5/5	+, ++, +++, bw (no data)	URT (3/5); LRT (2/5)

[a]+, ++, +++ refer to slight, moderate, and severe clinical signs, respectively.
Abbreviations: bw = body weight; ↓ = decrease; URT = upper respiratory tract; LRT = lower respiratory tract.
Source: Janssen 1989a.

Macroscopic examinations showed effects indicative of respiratory irritation (blood around the nose, red nasal and tracheal mucosa, bloody fluid in the trachea, dark red lungs, and red or dark spots on the lungs) particularly in animals that died during the study. The animals surviving to study termination showed only red or dark spots on the lungs. In addition, the stomach and small intestines were distended with gas and the liver was swollen in animals exposed to ≥320 mg/m^3. Absolute and relative lung weights were elevated in rats exposed to 320 or 390 mg/m^3. Only one animal each exposed to 300, 390, or 1450 mg/m^3 showed microscopic effects in the lungs. Although it appeared that the observed effects were caused by exposure to peracetic acid, most effects also showed increased severity with the increased concentrations of measured acetic acid and hydrogen peroxide. Based on lethality data, it is unlikely that acetic caused the effects observed in the rats; however, a contributing effect cannot be ruled out for either constituent. See Section 4.4.4. for a brief discussion of the toxicity of acetic acid and hydrogen peroxide (Janssen 1989a).

Janssen and Van Doorn (1994) conducted a 4-h acute inhalation study in rats with Proxitane AHC. The chemical composition of the test material was as follows: 4.7 to 5.4% (~5%) peracetic acid, 19% (minimum) hydrogen peroxide, 10% acetic acid, water, and 1% surfactant. Groups of five male and five female Wistar derived rats were exposed to aerosols of the test material by nose-only inhalation in an aluminum chamber with the inside walls coated with silver and a thin layer of polytetrafluoroethylene. The test concentrations of peracetic acid in the chamber were analyzed as total peroxygen concentration corrected for the amount of hydrogen peroxide. The concentrations of peracetic acid and other constituents are presented in Table 7-5. Each group was exposed to the test atmospheres for 4 h and surviving animals were observed for 14 days. An unexposed control group was included. The mortality response is summarized in Table 7-5 In Group B exposed to peracetic acid at 267 mg/m^3, four of five male rats died by day 3 and all females had died by day 4 (four died before day 2). In Group D exposed to 185 mg/m^3, two males died on day 1 and two females had died by day 3. The LC_{50} for the combined sexes was 204 mg/m^3. Numerous clinical signs including apathy, respiratory difficulties, reduced respiratory rate, noisy breathing, cyanosis, lacrimation, salivation, ptosis, twitching, hypothermia, abnormal gait and posture, crusts on nose, and blood under cage were observed in rats of all groups except lacrimation, cyanosis, and salivation were not observed at 87 mg/m^3. Fewer clinical signs were observed in the lowest exposure group compared with the highest exposure groups. The clinical signs disappeared after day 1 for males or day 3 for female rats exposed to 87 mg/m^3 and after day 3 or 4 for the remaining groups. The clinical signs were considered to be related to the corrosive/irritant properties of the test material. The body weights of rats exposed to the test atmospheres were much less than those of the controls on day 2 after exposure due to pronounced weight losses of 36 to 52 g for males and 19 to 34 g for females ($p<0.01$ all groups compared with controls). Body weights of all exposed groups showed signs of recovery between day 2

TABLE 7-5 Concentrations of Peracetic Acid, Acetic Acid, and Hydrogen Peroxide During a 4-Hour Exposure and Mortality Effects During the 14-Day Observation Period

Parameter	Concentration (mg/m^3)			
	Group C	Group A	Group D	Group B
Peracetic acid	87	163	185	267
Acetic acid	441	887	1337	1598
Hydrogen peroxide	200	467	595	1075
Mortality				
Males	0/5	0/5	2/5	4/5
Females	0/5	0/5	2/5	5/5
Combined sexes	0/10	0/10	4/10	9/10

LC_{50} = 204 mg/m^3, 95% confidence limits = 186 to 233 mg/m^3.
Source: Janssen and van Doorn 1994.

and 7 after exposure. Absolute and relative lung weights were elevated in all groups. Gross examination showed no abnormalities in male or female rats exposed to 87 mg/m^3. Red or brown staining or blood around the nose and/or mouth was observed in rats exposed to ≥163 mg/m^3. In addition, red spots were observed on the lungs of rats receiving ≥163 mg/m^3, and lung consolidation or edema was observed in animals that died due to exposure. It is unlikely that acetic acid or hydrogen peroxide was the cause of mortality in the rats. The lowest lethal concentration for a 4-h exposure of rats to acetic acid (39, 216 mg/m^3) is about 30 times greater than the LC_{50} (1283 mg/m^3) calculated from the acetic acid concentrations in Table 7-5. Likewise, the LC_{50} for hydrogen peroxide reported for rats (1972 mg/m^3) is almost 3 times greater that the LC_{50} (684 mg/m^3) calculated from the data in Table 7-5 Therefore, the concentrations of acetic acid and hydrogen peroxide appear too low to have caused the deaths among the rats exposed to peracetic acid.

3.1.2. Mice

Merka and Urban (1978) conducted a study in which groups of ten mice were exposed in a dynamic chamber to aerosols of Persteril (commercial product containing 40% peracetic acid) or laboratory peracetic acid produced from equimolar concentrations of acetic acid and hydrogen peroxide and using sulfuric acid as the catalyst. In contrast to Persteril, the laboratory product contained no sulfuric acid. The mice were exposed to peracetic acid concentrations at 150, 300, 450, 600, 800, 1000, 1300, or 1600 mg/m^3 for 60 min. The animals were observed for 20 days. Animals exposed to peracetic acid (specific concentrations not reported) showed signs of eye and respiratory irritation during exposure (restlessness, bristling fur, half closing of eyelids, and nose rubbing along with

respiratory distress, gasping, and increased respiration, which varied with concentration). The eyelids were red and swollen and a secretion was observed around the eyes and snout within the first 24 h; hair loss occurred later. The LC_{50} was 524 mg/m^3 for laboratory peracetic acid and 512 mg/m^3 for Persteril. The similar LC_{50} values showed that the small amount of sulfuric acid in Persteril had no effect on lethality in the mouse. One or two mice died during exposure; other mice died during the observation period. The study authors did not report lethality data for individual groups. Histological examination of the animals that died and those that survived revealed lesions only in the lungs. None occurred in the heart, liver, spleen, or kidneys. Lung lesions in mice that died within 2 days consisted of extensive foci of hemorrhagic exudative inflammation involving the parenchyma of the entire lungs; foci of alveolar inflammation with serous exudate, red blood cells (RBCs), macrophages with phagocytosed aerosol particles; and desquamated epithelial cells. The severity of the lesions increased with exposure concentration. The lungs of animals that died about day 6 after exposure showed evidence of focal bronchopneumonia characterized by hyperemia of the alveolar septa and serohemorrhagic exudate containing desquamated epithelial cells and macrophages with phagocytosed aerosol particles. The lungs of animals surviving to 20 days showed diffuse inflammatory lesions at concentrations >600 mg/m^3 and focal inflammatory lesions at ≤600 mg/m^3.

3.2. Nonlethal Toxicity

3.2.1. Rat

Janssen (1989b) exposed groups of five CPB-WU Wistar derived male rats by nose-only inhalation to aerosols of Proxitane 1507 (15% peracetic acid, ~28% acetic acid, 14% hydrogen peroxide, ~1% stabilizer, and ~43% water) at concentrations and exposure durations listed in Table 7-6. The test concentrations of peracetic acid were analyzed as total peroxygen corrected for the amount of hydrogen peroxide. The concentrations of acetic acid in the chamber atmospheres were not reported by the study author. The study author also did not comment on the greater than zero concentration of hydrogen peroxide in the control atmosphere. The exposure conditions and chamber were the same as described by Janssen (1989a) (Section 3.1.1). The animals were observed for 7 or 14 days after exposure; body weights were measured on days 2, 7, and 14 (where appropriate). Necropsies were performed on all animals, the lungs were weighed, and the lungs and nasal cavities were processed for microscopic examination. The group exposed to peracetic acid at 589 mg/m^3 for 60 min and one control group were necropsied after 14 days; all others were necropsied after 7 days. The results are summarized in Table 7-6. The only clinical signs observed during exposure were "struggling" and irregular or shallow breathing patterns after 5 to 10 min and gasping in the group exposed to 589 mg/m^3 for 60

TABLE 7-6 Effects of Nose-only Inhalation Exposure to Proxitane 15077 on Male Rats

Group Number	Exposure Time (min)	Concentration (mg/m^3)[a]		Effects[b]		
		Peracetic Acid	H_2O_2	Clinical Signs and Body Weight Gain	Pathology	
					Gross	Microscopic
1 (control)	90	<16	<16	bw, slight ↓	0/5	0/5
2 (control)	90	<16	<16	bw, slight ↓	3/5	0/5
3	15	499	172	+, ++; bw, no change	0/5	5/5
6	30	304	111	+, ++; bw, slight ↓	1/5	4/5
4	30	578	193	+, ++, +++; bw, marked ↓	1/5	5/5
7	60	329	115	+, ++; bw, moderate ↓	2/5	5/5
5	60	589	233	+, ++, +++; bw, marked ↓	2/5	4/5
9	90	172	63	+, ++; bw, moderate ↓	0/5	5/5
8	90	355	119	+, ++; bw, moderate ↓	1/5	5/5

[a]Concentration reported as mg/L by the study author converted to mg/m^3.

[b]+, ++, +++ refer to slight, moderate, and severe clinical signs, respectively; body weight gain: slight ↓ = ≤5 g, moderate ↓ = >5 to 15 g, marked ↓ = >15 g.

Abbreviations: bw = body weight; ↓ = decrease.

Source: Janssen 1989b.

min. Clinical signs observed after exposure were indicative of effects on coordination and muscle tone, extreme discomfort, and respiratory irritation as described by Janssen (1989a) (Section 3.1.1). Rats exposed to 578 or 589 mg/m^3 (30 or 60 min) showed slight to severe clinical signs; rats in all other exposure groups showed slight to moderate clinical signs; rats in the control group showed no clinical signs. The study author noted that a twofold increase in exposure time produced a smaller effect on clinical signs than a twofold increase in exposure concentration indicating that effects are due more to exposure concentration than duration. Two rats exposed at 589 mg/m^3 for 60 min were killed moribund about 24 h after exposure, and the remaining animals survived to study termination. Absolute body weights were not significantly different from those of controls except for the group exposed to 578 mg/m^3 for 30 min. Almost all groups including controls lost weight during the first two days of the study; however, the groups exposed to peracetic acid for 30, 60, and 90 min lost significantly more weight than controls (except for Group 6). There were no treatment-related macroscopic or microscopic findings in the lungs, and lung weights were similar in the treated and control groups. Slight to moderate to severe squamous metaplasia of the nasal turbinates and/or lateral walls and epithelial atrophy of the dorsal meatus were observed in all treated groups. The study author noted that the chamber atmospheres for Groups 3 and 6 did not reach equilibrium during sampling.

In a preliminary study, Janssen (1989c) examined the effect of peracetic acid on the respiratory rate in groups of three CPB-WU Wistar derived male rats exposed by nose-only inhalation for 25 min to aerosols of Proxitane 1507 containing peracetic acid and hydrogen peroxide at the concentrations presented in Table 7-7. The chamber and exposure conditions were the same as described by Janssen (1989a) (Section 3.1.1). The test concentrations of peracetic acid were analyzed as total peroxygen concentration corrected for the amount of hydrogen peroxide. A plethysmograph was used to measure respiratory rates before, during, and after exposure to the test material. The rats were killed and necropsied 24 h after exposure. The lungs were weighed and processed for microscopic examination along with the trachea and nasal cavities. The mean percent of the greatest (extreme) depression in respiratory rates ranged from 31.9-67.1% in groups exposed to peracetic acid concentrations ranging from 8.4 to 36.3 mg/m^3 (Table 7-7). The depression in respiratory rates did not show a clear exposure-related trend. The mean RD_{50} for all groups was 22.7 mg/m^3, 21.5 mg/m^3 with Group 1 omitted, and 24.1 mg/mg^3 with Group 3 omitted. According to the investigator, depression in the respiratory rate was considered biologically significant only if it exceeded 20% of the preexposure rate. After exposure, the respiratory rates of all animals returned to approximately normal rates. The only observed clinical sign of toxicity was a slightly hunched appearance after removal of the plethysmograph. No abnormalities were observed during necropsy, lung weight was not affected, and no treatment-related microscopic findings were observed in the nose, trachea, or lungs.

TABLE 7-7 Effects of Nose-Only Inhalation Exposure to Proxitane 15077 Aerosols for 25 Min on Male Rats

	Concentration (mg/m^3)				
	Group 3	Group 1	Group 5	Group 2	Group 4
Peracetic acid	8.4 mg/m^3	12.2 mg/m^3	13.9 mg/m^3	17.4 mg/m^3	36.3 mg/m^3
H_2O_2	3.3	3.3	1.9	5.4	13.1
Extreme depression, mean (%)	46.9	32.6	31.9	44.2	67.1

Source: Janssen 1989c.

In a follow-up study, Janssen (1990) examined the effect of higher concentrations of Proxitane 1507 (15% peracetic acid, ~28% acetic acid, 14% hydrogen peroxide, ~1% stabilizer, and ~43% water) aerosols on the respiratory rate in groups of three CPB-WU Wistar derived male rats. The animals were exposed to the test substance by nose-only inhalation for 25 min as described by Janssen (1989c). The test concentration of peracetic acid were analyzed as total peroxygen concentration corrected for the amount of hydrogen peroxide. Respiratory rates were measured using a plethysmograph before, during, immediately after, and 24 h after exposure to the test atmospheres. The concentrations of peracetic acid and hydrogen peroxide in the exposure chambers and the percent depression of respiratory rates are presented in Table 7-8. The respiratory rates were depressed 76-78% during exposure of each group. The respiratory rates improved after exposure and returned to normal in two Group 3 rats exposed to the lowest concentration of peracetic acid. The respiratory rate had returned to normal in Group 1 and 2 animals by 24 h. Necropsy revealed no gross abnormalities; however, microscopic examination showed moderate to severe necrosis in the nasal turbinates of all animals exposed to the test material. Evidence of very slight to slight pulmonary inflammation was observed in one or two animals of each group, but no control group was included for comparison. Therefore, the pulmonary effects should not be considered treatment related.

Benes et al. (1966) showed that rats exposed to peracetic acid at concentrations ranging from 7.2 to 72 mg/m^3 aerosol for 4 h exhibited signs of restlessness, lacrimation, and nasal discharge, whereas labored breathing and lung edema were seen at 237 mg/m^3. Repeated exposure to 7.2 mg/m^3 for 1 h/day for 28 days was without effects, whereas repeated exposure to 22 mg/m^3 for the same time period resulted in increased lung and liver weights, depression of body weight gain, and inflammation in the lungs. No additional information was available for this study.

Whitman (1991) conducted a study in which a group of 10 Sprague-Dawley rats (5 males and 5 females) were exposed to an aerosol/vapor mixture generated from a 0.15% use dilution of peracetic acid. A 5% peracetic acid solution was diluted with distilled water to prepare the 0.15% dilution. The study

TABLE 7-8 Effects of Nose-only Inhalation Exposure to Proxitane 15077 Aerosols for 25 Min on Male Rats

	Concentration (mg/m^3)[a]		
	Group 3	Group 2	Group 1
Peracetic acid	221.0 mg/m^3	315.3 mg/m^3	461.5 mg/m^3
Hydrogen peroxide	22.4	23.1	59.8
% Respiratory depression, mean[b]	76.3	78.4	76.3
	16.0	29.6	49.2

[a]Average of two measurements of atmospheres taken during exposure: just before and during measurement of respiratory rate.
[b]Top row, % of extreme depression during exposure compared with pre-exposure respiratory rate; bottom row, % of depression after exposure compared with pre-exposure respiratory rate.
Source: Janssen 1990.

author did not describe the content of other constituents in the test material. The animals were exposed for 4 h in a dynamic chamber. The theoretical equilibration time was 23 min. The nominal concentration (calculated based on amount of material lost and total air flow through the chamber) was 66.171 mg/L; the analytical concentration of total test material was 7.669 mg/L; and the analytical concentration of peracetic acid was 0.0117 mg/L (11.7 mg/m^3). The animals were observed for 14 days and were sacrificed and subjected to gross examination after the observation period. A control group for comparison was not included in this study. A dense fog was formed in the chamber during exposure inhibiting the observation of a few animals. During exposure, the animals closed their eyes, had decreased activity, and had material on their fur. The study author considered these responses normal for aqueous aerosol exposure. After exposure, all animals had wet, matted fur, two had clear ocular discharge, and one had fine tremors attributed to mild hypothermia because of wet fur. Almost all animals had recovered by the second day after exposure except for one that had a clear oral and ocular discharge and wet and matted fur on day 8 post-exposure and a dry red nasal discharge on day 9 postexposure. This animal was normal for the remainder of the observation period. Five rats lost a small amount of weight the day after exposure; otherwise, all rats gained weight during the observation period. At necropsy, one animal had mottled, red to dark red lungs and two rats had dark red foci on the mandibular lymph nodes. All animals survived to study termination.

3.2.2. Mice

Merka and Urban (1978) conducted a study in which groups of 10 mice were exposed in a dynamic chamber to laboratory peracetic acid aerosols at concentrations of 70 to 140 mg/m^3 for 60 min, three times/week for 4 weeks and

observed for an additional 2 weeks. The animals exposed to peracetic acid showed retarded weight gain compared with controls not exposed to the test chemical. Isolated small foci of inflammation were seen in the lungs of mice killed at the end of the 14-day observation period.

Heinze et al. (1979) reported that exposure of mice (no descriptive information provided) to 30 mg peracetic acid (1.2 mL volume of a 6.25% solution of Wofasteril) released in a 20-L room for 45 min had no effect on immune function as tested on animals given an erysipelas vaccine and challenged with erysipelas "germ" (bacteria). Atmospheric peracetic acid concentrations were not quantified by an analytical procedure.

3.2.3. Other Species

Heinze et al. (1979) examined the effect of daily releases of 2 mL of a 6.15% Wofasteril solution/m^3 of air (50 mg peracetic acid/m^3) on uninfected and *Chlamydia*-infected (by intratracheal instillation) calves and pigs . The animals were exposed 1 h/day for an unspecified period of time. The droplet size of the aerosol was 0.5 to 0.6 μm. Peracetic acid-treated animals developed a transient severe irritative cough accompanied by nasal secretion, lacrimation, and salivation. Transient vomiting and labored breathing and weight loss were also observed after day 19 in treated pigs. Increased pulse and breathing rates, decreased erythrocyte count and hemoglobin concentration, and lesions in the lungs, kidneys, and liver were observed after exposure to peracetic acid. There was no evidence that effects of *Chlamydia* infection were exacerbated by exposure to peracetic acid.

Calves and young pigs exposed daily to peracetic acid at 50 mg/m^3 exhibited decreased body weight gain, decreased serum aspartate aminotransferase activity, and histologic evidence of lung irritation (Friebig and Reuter 1975). The duration of exposure was not reported.

According to Uhlemann (1971) guinea pigs and a pig were not affected by a single inhalation exposure to peracetic acid aerosols (50 μm droplet size) at concentrations of 250 or 500 mg/m^3, whereas rabbits exhibited labored breathing at the higher concentration but not at the lower concentration.

3.3. Carcinogenicity

There are no studies on the carcinogenicity of peracetic acid administered by inhalation. Bock et al. (1975) conducted a study in which groups of 30 female ICR Swiss mice (55 to 69 days of age) received repeated topical applications of peracetic acid in water or acetone. In one study, groups of mice received a single topical application of 125 μg of 7,12-dimethylbenz[a] anthracene (DMBA) to the shaved dorsal skin followed by topical applications of 0.2 mL of 0, 0.3, 1.0, or 3.0 % peracetic acid in water 5 days/week for 66 weeks. By the end of the treatment period, 0, 7, 27, and 80% of the mice in each group, respec-

tively, had developed skin tumors; 3% of the mice receiving 1.0% peracetic acid alone and 17% of the mice receiving 3.0% peracetic acid alone developed "skin cancer." In another experiment, groups of mice received no topical applications of peracetic acid, topical applications of 1.0% peracetic acid in acetone, or topical applications of 2.0% peracetic acid in water (5 days/week) without prior treatment with DMBA. After 52 weeks, 10% of the group receiving peracetic acid in water developed skin tumors; none were skin cancer. Tumors did not develop in mice receiving no peracetic acid or in mice receiving peracetic acid in acetone. Topical application of 2% decomposed peracetic acid in water or 1% decomposed peracetic acid in acetone to DMBA-initiated mice for 58 weeks resulted in a very low incidence of skin tumors (7%); the low incidence was not considered treatment-related. The study authors concluded that peracetic acid is a strong skin tumor promoter and a weak complete carcinogen. Bock et al. (1975) also reported that 4% peracetic acid was "excessively lethal." They provided no additional information on the number of applications required to cause lethality.

3.4. Genotoxicity

Agnet et al. (1976) tested peracetic acid in *Salmonella typhimurium* spot test to detect point, frame-shift, and deletion mutations. Peracetic acid induced deletion but not point or frame-shift mutations. Lai et al. (1996) reported that peracetic acid induced unscheduled DNA synthesis (no additional information was provided). Peracetic acid was negative in the SOS chromotest (Yin et al. 1989).

Koch et al. (1989) conducted an in vivo test in which Wofasteril (40% peracetic acid, 27% acetic acid, and 14% hydrogen peroxide) was injected intraperitoneally into male ICR mice once per day for 5 consecutive days at a concentration of 0.1% or 0.05% in a volume of 0.2 mL/34 g body weight (2.6 or 1.3 mg/kg/day, respectively). Sperm abnormalities, indicative of mutagenic potential, were evaluated 36 days after the first injection. At 2.6 mg/kg/day, Wofasteril induced a twofold increase in abnormal sperm compared with controls receiving 0.2 mL of distilled water. No increase was observed at 1.3 mg/kg/day. A mouse bone marrow test conducted by Paldy et al. (1984) showed an increase in "mutated" chromosomes (17% vs 3% for controls) in mice injected (intraperitoneal) once a day for 5 days with 1.6 mg peracetic acetic/kg/day.

3.5. Summary

Lethality studies on peracetic acid were conducted with products containing different concentrations (weight %) of peracetic acid, acetic acid, and hydrogen peroxide. Sulfuric acid may have been present at very low concentrations in some products. The LC_{50} values for inhalation exposure to peracetic acid

aerosols were 476 mg/m^3 for rats and 512 to 514 mg/m^3 for mice exposed for 1 h and 204 mg/m^3 for rats exposed for 4 h. The study in mice showed that the small amount of sulfuric acid that may have been present in the exposure chambers had no effect on lethality of mice, because the LC_{50} values were similar with or without possible exposure to small amounts of sulfuric acid. Death was caused by severe damage to the lungs (hemorrhage, consolidation, and edema). Respiratory effects were much less severe in survivors, including those in groups where deaths occurred.

Data concerning effects of peracetic acid at nonlethal concentrations are summarized in Table 7-9. These studies showed effects on the respiratory tract and body weight gain. Concentrations of peracetic acid aerosols ranging from 8.4-36.3 mg/m^3 caused 28 to 65% decreases in respiratory rate during a 25-min exposure, and the RD_{50} was 22.7 mg/m^3 (Janssen 1989c); concentrations ranging from 71 to 156 ppm caused 71-74% decreases during a similar exposure time (Janssen 1990). In rats, respiratory irritation was slight to moderate, weight loss was moderate, and nasal lesions were slight to moderate after inhaling about 304-329 mg/m^3 30 or 60 min, whereas respiratory irritation was slight to severe, weight loss was marked, and nasal lesions were slight to moderate or severe after inhaling about 578-589 mg/m^3 for 30 to 60 min (Janssen 1989b). Rats that inhaled 172 or 355 mg/m^3 for 90 min had slight to moderate respiratory irritation and moderate weight loss, and slight to severe nasal lesions (Janssen 1989b). Inhalation of 7.2-72 mg/m^3 for 240 min caused restlessness, lacrimation, and nasal discharge, and 237 mg/m^3 for 240 min caused labored breathing and lung edema (Benes et al. 1966). Rats showed no effects when exposed to 2.3 ppm for 60 min/day for 28 days; however exposure to 7 ppm under similar conditions caused increased lung and liver weight, depressed weight gain, and lung inflammation (Benes et al. 1966). Similar effects were observed in mice that inhaled 70-140 mg/m^3, 1 h/day, 3 times per week, for 4 weeks (Merka and Urban 1978). Effects of exposure to peracetic acid were more prevalent and more severe after exposure was terminated than during exposure. In addition, effects were more severe after doubling the exposure concentration than doubling the exposure duration.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

No studies on the uptake, distribution, metabolism, or elimination of inhaled peracetic acid were found in the sources searched. Peracetic acid is freely soluble in water (O'Neil et al. 2001) and should be effectively scrubbed in the upper respiratory tract. Effects on the lower respiratory tract would occur only at concentrations that exceed the scrubbing capacity of the nasal passages.

TABLE 7-9 Summary of Nonlethal Effects of Peracetic Acid in Experimental Animals

Species/Stain/Sex	Exposure Time	Exposure Concentration (mg/m^3)	Effect	Reference
Rat/Wistar/M	15 min	499	Slight to moderate signs of respiratory irritation; no change in body weight	Janssen 1989b
	25 min	8.4	47% Depression in respiratory rate	Janssen 1989c
	25 min	12.2-13.9	32-33% Depression in respiratory rate	
	25 min	17.4	44% Depression in respiratory rate	
	25 min	36.3	67% Depression in respiratory rate	
	25 min	221-462	76-78% Depression in respiratory rate; moderate to severe necrosis of nasal turbinates	Janssen 1990
	30 min	304	Slight to moderate signs of respiratory irritation, slight transient weight loss, slight to moderate nasal lesions	Janssen 1989b
	30 min	578	Slight to severe signs of respiratory irritation, marked transient weight loss, slight to severe nasal lesions	Janssen 1989b
	60 min	329	Slight to moderate signs of respiratory irritation, moderate transient weight loss, slight to moderate nasal lesions	Janssen 1989b
	60 min	589	Slight to severe signs of respiratory irritation, marked transient weight loss, slight to moderate nasal lesions	Janssen 1989b

(Continued)

TABLE 7-9 Continued

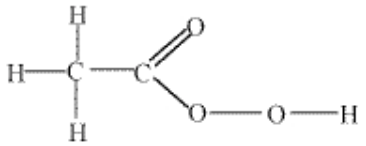
Species/Stain/Sex	Exposure Time	Exposure Concentration (mg/m^3)	Effect	Reference
	60 min × 28 d	7.2	No effects	Benes et al. 1966[a]
	60 min × 28 d	22	Increased lung and liver weight, depressed weight gain, lung inflammation	Benes et al. 1966[a]
	90 min	172	Slight to moderate signs of respiratory irritation, moderate transient weight loss, slight to severe nasal lesions	Janssen 1989b
	90 min	355	Slight to moderate respiratory irritation, moderate transient weight loss, slight to severe nasal lesions	Janssen 1989b
	240 min	7.2-72	Restlessness, lacrimation, and nasal discharge	Benes et al. 1966[a]
	240 min	237	Labored breathing and lung edema	Benes et al. 1966[a]
	240 min	11.7	Clear ocular and oral discharge, transient weight loss, gross findings in the lungs	Whitman 1991
Mouse	1 h, 3×/wk, 4 wks	70-140	Retarded weight gain, small foci of inflammation in lungs 14 days after treatment terminated	Merka and Urban 1978

[a]Cited from secondary source.

4.2. Mechanism of Toxicity

Peracetic acid is a corrosive chemical; therefore, it causes irritation to mucous membranes. Lacrimation and respiratory tract irritation were observed in humans (Fraser and Thorbinson (1986) and rats (Janssen, 1989a,b; Janssen and Van Doorn 1994) and eye and respiratory tract irritation were observed in mice (Merka and Urban 1978) exposed to peracetic acid. The effects in some cases were delayed. For example, deaths caused by exposure to peracetic acid occurred 1 or more days after exposure depending upon the atmospheric concentration. Exposures to extremely high concentrations are expected to cause deaths during exposure.

4.3. Structure–Activity Relationship



Peracetic acid is a peroxy acid that has the following general structure:

Peroxy acids are irritating to skin, eyes, and mucous membranes of the respiratory tract. Peroxy acids are members of a broader group of chemicals called organic peroxides. Many of these chemicals are also considered to be respiratory irritants (Galvin and Farr 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The LC_{50} values for 1-h exposures to the rat (476 mg/m^3) and mouse (512-524 mg/m^3) are similar, indicating a similar species response to inhalation exposure to peracetic acid. Whether the animals died or survived after exposure to peracetic acid, the effects were indicative of respiratory tract irritation in mice and rats. Effects of inhalation exposure on calves and pigs were qualitatively similar to those observed in rodents. Lacrimation occurred in humans exposed to 15.6 mg/m^3 for 3.5 min and respiratory tract irritation occurred at concentrations > 1.56 mg/m^3 with only mild effects occurred at the lower concentrations (Fraser and Thorbinson 1986); Janssen and van Doorn (1994) reported no lacrimation in rats exposed to 87 mg/m^3 for 4 h, but serious respiratory effects were observed. In contrast, Benes et al. (1966) reported lacrimation and upper respira-

tory tract effects in rats exposed to 7.2-72 mg/m^3 for 4 h. These results show that similar effects are observed in humans and animals and that humans may be slightly more sensitive to exposure to peracetic acid than animals.

4.4.2. Susceptible Subpopulations

Peracetic acid is a corrosive and extremely irritating substance that attacks mucous membranes of the respiratory tract and eyes; therefore, very little difference in sensitivity is expected among individuals within the general population. No data were available on the response of asthmatics to inhaled peracetic acid.

4.4.3. Concentration–Exposure Duration Relationships

The n-value of 1.6 was estimated from the rat lethality data by determining the value of n, which, when applied to the 1-h LC_{50} of 476 mg/m^3 (Janssen 1989a), would closely predict the 4-h LC_{50} of 204 mg/m^3 (Janssen and Van Doorn 1994). Although only two LC_{50} values were available for estimating the n-value, the estimated value is considered more appropriate than using default values.

4.4.4. Concurrent Exposure Issues

Two constituents in peracetic acid are acetic acid and hydrogen peroxide, and these may have contributed to the observed toxic effects of peracetic acid. Aerosols or vapors will contain these constituents in addition to peracetic acid. It appears, however, that acetic acid and hydrogen peroxide are considerably less toxic than peracetic acid. The following toxicity information on hydrogen peroxide and acetic acid was cited from secondary sources.

Hydrogen peroxide has a vapor pressure of 5 mm Hg at 30º C, and it is miscible in water (ACGIH 1991). The LC_{50} value for hydrogen peroxide is 1418 ppm (1972 mg/m^3) for a 4-h exposure to rats and the LC_{LO} is 227 ppm (316 mg/m^3) for an unknown exposure time to mice (NIOSH 1996a). The LC_{50} for the rat exposed to hydrogen peroxide is about 10 times greater than the LC_{50} for rats exposed to peracetic acid. Dogs exposed to 7 ppm (10 mg/m^3) vapor concentration of 90% hydrogen peroxide for 6 h/day for 6 months developed skin irritation, sneezing, lacrimation, and bleached hair, and rabbits exposed to 22 ppm (31 mg/m$_3$) (frequency not reported) for 3 months developed bleached hair and skin irritation (Oberst et al. 1954). The carcinogenicity of hydrogen peroxide has been tested by the oral, subcutaneous, intramuscular, and topical routes of exposure, and IARC (1985) considers the evidence for carcinogenicity as limited for experimental animals.

Acetic acid has a vapor pressure of 11.4 mm Hg at 20ºC, and it is freely soluble in water (Katz and Guest 1994). Inhalation of acetic acid vapor is re-

ported to cause marked irritation to the eyes, nose, and throat in humans at concentration of 816-1226 ppm (2000-3005 mg/m^3) for 3 min, and exposure to 50 ppm (123 mg/m^3) is reported to be intolerable because of intense irritation (NIOSH 1996b). Exposure to acetic acid at 10 ppm is reported to be relatively nonirritating (Sterner 1943), 20-30 ppm (49-74 mg/m$_3$) has been reported to be without danger, and occupational exposure to 60 ppm plus 1 h daily exposure to 100-260 ppm (245-637 mg/m^3) for 7-12 years caused only slight irritation (Vigliani and Zurlo 1955). The LC_{50} for acetic acid is 5000-5620 ppm (12,255-13,775 mg/m^3) for a 1-h exposure to mice. (NIOSH 1996b) The lowest lethal concentration for a 4-h exposure of rats to acetic acid is 16,000 ppm (39,216 mg/m^3)(Katz and Guest 1994), which is about 190 times greater than the LC_{50} for a 4-h exposure to peracetic acid. The data show that acetic acid and peracetic acid may produce similar effects on the respiratory tract, but peracetic acid is markedly more toxic than acetic acid. The RD_{50} was reported as 163 ppm (400 mg/m^3) for the mouse (NIOSH 1996b). Exposure to concentrations >1000 ppm (2451 mg/m^3) produces irritation to the conjunctiva and upper respiratory tract of mice (Katz and Guest 1994).

Sulfuric acid also is found in some commercial grades of peracetic acid. Humans exposed to sulfuric acid at concentrations of 1 mg/m^3 for 10-15 min did not detect the substance by odor, taste, or irritation (these data were cited in NRC 1984). The LC_{50} for inhalation exposure to sulfuric acid aerosols ranged from 19 to 59.8 mg/m^3 for guinea pigs (ATSDR 1998). In rats, 2/2 animals died after exposure to 699 mg/m^3 for 7 h or after exposure to 1470 mg/m^3 for 3.5 h. No rats died after exposure to 461 mg/m^3 for 7 h or after exposure to 718 mg/m^3 for 3.5 h. In mice, 2/5 animals died after exposure to 699 mg/m^3 for 7 h or after exposure to 549 mg/m^3 for 3.5 h (secondary citation by ATSDR 1998). LC_{50} values were not reported for the rat or mouse, but the data indicate that they are much less sensitive to sulfuric acid than are guinea pigs.

4.4.5. Other Data

Peracetic acid was used at a concentration of 0.2% to disinfect the hands of personnel in a virus laboratory over a 5 year period and caused no adverse effects; a concentration of 0.5%, however, was irritating to the skin (Mucke 1970).

Peracetic acid caused irritation to the skin of guinea pigs following direct contact (Bulnes et al. 1982). Application of 3% peracetic acid to depilitated guinea pig skin for 2, 3, or 5 h caused microscopic lesions characterized by congestion, hemorrhage, edema of the dermis, capillary vasodilation, perivascular effect (neutrophil granulocytes), and gelatinous edema of the dermis. Application of 3% peracetic acid for 1 h or 1% for up to 5 h was without macroscopic or microscopic effects.

5. DATA ANALYSIS AND AEGL-1

5.1. Human Data Relevant to AEGL-1

McDonagh (1997) reported that exposure to peracetic acid at 1.56-1.87 mg/m^3 was not immediately irritating, but would have been considered "unpleasant for an extended period;" 0.40-0.53 mg/m^3 was tolerable and not unpleasant for up to 3 h. According to Fraser and Thorbinson (1986), exposure to 3.12-4.67 mg/m^3 for 15-20 min is not expected to cause discomfort to mucous membranes, and 1.56-3.12 mg/m^3 for 25-30 min is expected to cause only mild or tolerable discomfort. No discomfort is expected for subjects exposed to ≤1.56 mg/m^3 for 35-45 min.

5.2. Animal Data Relevant to AEGL-1

Rats exposed to peracetic acid at 12.2-13.9 mg/m^3 for 25 min showed a reduction of only 32-33% in respiratory rate, whereas rats that inhaled a slightly lower concentration of 8.4 mg/m^3 showed a greater reduction of 47% (Janssen 1989c). These data show the inconsistency of the results regarding depression of respiratory rates in rats exposed to peracetic acid. Only mild effects were observed in rats exposed to 11.7 mg/m^3 (closed eyes, decreased activity, clear ocular discharge) for 4 h and observed for 14 days (Whitman 1991). The study author did not mention that the rats had redness of the eyes or lacrimation during exposure. In a repeat exposure study using mice exposed to 70-140 mg/m^3 for 60 min/day, 3 times/week, for 4 weeks, only small foci of inflammation were observed when the animals were killed 14 days after the last exposure. If damage to the respiratory tract occurred during the exposure period, it was repaired during the post-exposure period.

5.3. Derivation of AEGL-1

Because decreases in respiratory rate in rats exposed to peracetic showed no clear concentration-response relationship, the human data are considered more appropriate and more relevant for deriving AEGL-1 values. In the study by Fraser and Thorbinson (1986), humans exposed to peracetic acid at ≤1.56 mg/m^3 (concentrations reported as hydrogen peroxide) experienced no discomfort, and McDonagh (1997) reported that 1.56 mg peracetic/m^3 is not immediately irritating. An intraspecies uncertainty factor of 3 was applied because peracetic acid is a corrosive and irritant substance, the effects are confined to the upper respiratory tract, and the effects are expected to be similar for most individuals within the population. The same value is for all exposure durations from 10 min to 8 h. The rationale for having the same value is as follows: (1) effects of peracetic acid exposure appear to correlate more with concentration than with time, and (2) peracetic acid is freely soluble in water, and therefore, should be effectively

scrubbed by the nasal tissues, particularly at the very low concentration for AEGL-1. The AEGL-1 values are summarized in Table 7-10.

6. DATA ANALYSIS AND AEGL-2

6.1. Human Data Relevant to AEGL-2

Fraser and Thorbinson (1986) reported that lacrimation and extreme discomfort occurred after exposure to peracetic acid at 15.6 mg/m^3 for only 7 min; extreme discomfort and unbearable irritation, but no lacrimation, was reported for exposures to concentrations ranging from 6.23-9.35 mg peracetic acid/m^3 for 1 h and 20-25 min (6.23 mg peracetic acid/m^3 for 55 min, 7.79-9.35 mg peracetic acid/m^3 for 15 min, and 6.23 mg/m^3 for 10-15 min). Exposure to 6.23 mg peracetic acid/m^3 was considered tolerable for 2 min. Effects in the lower respiratory tract were not noted even for exposure to 15.6 mg peracetic acid/m^3, which is extremely irritating to the upper respiratory tract. Peracetic acid is freely soluble in water (O'Neil et al. 2001) and is expected to be effectively scrubbed in the upper respiratory tract.

6.2. Animal Data Relevant to AEGL-2

Animal data relevant to deriving AEGL-2 values have been summarized in Table 7-9. Inhalation exposure to peracetic acid causes irritation to the mucous membranes of the respiratory tract and eyes at concentrations below those causing death. Concentrations of peracetic acid aerosols ranging from 8.4-36.3 mg peracetic acid/m^3 caused 32 to 67% decreases in respiratory rates during a 25-min exposure, but not in a dose-related manner (Janssen 1989c). Exposure to peracetic acid concentrations ranging from 221-462 mg/m^3 for 25 min caused decreases of 76-78% in the respiratory rates (Janssen 1990). Generally, respiratory irritation, weight loss, and nasal lesions in rats were slight to moderate at concentrations ranging from 172-355 mg/m^3 for exposure durations ranging from 30 to 90 min (Janssen 1989b). Severe signs of respiratory irritation were observed in rats exposed to 578-589 mg/m^3 for 30 or 60 min (Janssen 1989b). Exposure to 7.2-72 mg/m^3 for 240 min caused restlessness, lacrimation, and nasal discharge, and 237 mg/m^3 for 240 min caused labored breathing and lung edema (Benes et al. 1966). No effects were observed in rats that inhaled 7.2 mg/m^3, 1 h/day repeatedly for 28 days, whereas restlessness, lacrimation, and

TABLE 7-10 AEGL-1 Values for Peracetic Acid

10 min	30 min	1 h	4 h	8 h
0.52 mg/m3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)

nasal discharge were observed in rats exposed one time to 7.2-72 mg/m^3 for 4 h (Benes et al. 1966). Increased lung and liver weights, depressed weight gain, and lung inflammation were reported for rats exposed to 21.8 mg/m^3 under similar conditions (Benes et al. 1966). Similar effects were observed in mice exposed to 70-140 mg/m^3 1 h/day, 3 times per week, for 4 weeks (Merka and Urban 1978). These studies showed that effects were more severe after doubling the exposure concentration than after doubling the exposure duration.

6.3. Derivation of AEGL-2

For the most part, animals exposed to low concentrations of peracetic acid displayed the most severe clinical signs after exposure was terminated, whereas humans exposed to low concentrations reported only mucous membrane irritation during exposure. However, the animals were restrained during exposure in some studies. The evidence further suggests that humans may be slightly more sensitive to inhaled peracetic acid than animals. This conclusion is supported by observations of lacrimation in humans exposed to 15.6 mg/m^3 for 3.5 min (Fraser and Thorbinson 1986), no lacrimation but serious respiratory effects were observed in animals exposed to 87 mg/m^3 for 4 h (Janssen and van Doorn 1994) and lacrimation was observed in animals exposed to 7.2-72 mg/m^3 for 4 h (Benes et al. 1966).

AEGL-2 values are derived from human data reported by Fraser and Thorbinson (1986). They reported that exposure to peracetic acid at 6.23 mg/m^3 for up to 1 h caused extreme discomfort and unbearable irritation, but exposure to 6.23 mg/m^3 for 2 min was also considered tolerable. A slightly lower concentration of 4.67 mg/m^3 caused discomfort or slight discomfort for exposure for durations up to 20 min. The effects at 6.23 peracetic acid mg/m^3 appear to be more serious than those described by the definition of AEGL-2 and could hinder the ability to escape. Although irritation to the upper respiratory tract was extreme, lower respiratory effects did not occur even at concentrations as high as 15.6 mg/m^3. Moreover, peracetic acid is freely soluble in water and should be effectively scrubbed in the nasal passages at the concentrations considered for deriving AEGL-2 values. Although the effects at 4.67 mg/m^3 are slightly less severe than those defined by AEGL-2, this level is more appropriate for deriving the AEGL-2 than the higher level of 6.23 mg/m^3. An intraspecies uncertainty factor of 3 is applied because peracetic acid is a corrosive/irritant substance and the effects, which are confined to the upper respiratory tract, are expected to be similar and not expected to vary by more than a factor of 3 for most individuals in the population. The same value is for all exposure durations from 10 min to 8 h. The rationale for proposing the same AEGL-2 value for all exposure durations is as follows: (1) effects of peracetic acid exposure correlate with concentration more than time, and (2) peracetic acid is freely soluble in water and at low concentrations should be effectively scrubbed in the nasal passages. The AEGL-2 values are summarized in Table 7-11.

TABLE 7-11 AEGL-2 Values for Peracetic Acid [mg/m^3 (ppm)]

10 min	30 min	1 h	4 h	8 h
1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)

7. DATA ANALYSIS AND AEGL-3

7.1. Human Data Relevant to AEGL-3

No data on human lethality caused by exposure to peracetic acid were found in the literature searched.

7.2. Animal Data Relevant to AEGL-3

Three animal lethality studies were available for deriving AEGL-3 values. In one study, rats were exposed to peracetic acid aerosol at concentrations 130 to 320 mg/m^3 for 30 min, 150 to 1450 mg/m^3 for 1 h (Janssen 1989a), and 87 to 267 mg/m^3 ppm for 4 h (Janssen and van Doorn 1994). Proxitane 1505 (15% peracetic acid, ~28% acetic acid, and 14% hydrogen peroxide) was used for the 30-min and 1-h studies and Proxitane AHC (~5% peracetic acid, 10% acetic acid, and 19% hydrogen peroxide) was used for the 4-h study. The mortality responses for the studies are presented in Tables 7-4 and 7-5. The LC_{50} for peracetic acid was 476 mg/m^3 for the 1-h exposure and 204 mg/m^3 for the 4 h study; the LC_{50} was not calculated for the 30-min exposure because there were only two relevant concentrations. Clinical signs were primarily related to respiratory tract irritation and adverse effects on body weight gain. Animals that died showed gross or microscopic evidence of pulmonary hemorrhage, edema, or consolidation. Surviving animals showed less severe effects.

7.3. Derivation of AEGL-3

The AEGL-3 values are derived from the study of Janssen (1989a). This study showed that rats exposed to Proxitane 1507 (15% peracetic acid~28% acetic acid, 14% hydrogen peroxide, ~1% "stabilizer," and ~43% water) aerosols at peracetic acid concentrations of 130, 300, 320 mg/m^3 for 30 min had mortality responses of 0/5, 0/5 and 3/5 rats, respectively. Exposures to aerosol concentrations of 150, 390, and 1450 mg/m^3 for 60 min resulted in mortality responses of 0/5, 2/5, and 5/5, respectively. Clinical signs indicative of respiratory irritation were observed at all concentrations and increased in severity with exposure concentration for each exposure duration. The AEGL values were derived from the highest concentration that did not cause death at either exposure duration: 300 mg/m^3 for a 30-min exposure duration and 150 mg/m^3

for a 60-min exposure duration. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 3 (total uncertainty factor = 10) were applied to 300 mg/m^3 and 150 mg/m^3 for the 30- and 60-min exposures, respectively. Uncertainty factors of 3 were applied because the mucous membranes of the respiratory tract are not expected to show vast differences in response to corrosive/irritant substances at concentrations that cause severe physical damage or at the threshold for lethality regardless of species or the individuals in the population. The equation, $C^n \times t = k$, where n = 1.6 (estimated from the 1- and 4-h rat lethality data), was used to scale the 60-min exposure to 4- and 8-h values and the 30-min exposure to 10 min. The AEGL-3 values are summarized in Table 7-12.

8. SUMMARY OF AEGLs

8.1. AEGL Values

The AEGL-1 value was based on a concentration of peracetic acid that is not expected to be detectable, unpleasant, or cause discomfort (1.56 mg/m^3) or no more than mild discomfort (1.56 - 3.12 mg/m^3). An uncertainty factor of 3 was applied to 1.56 mg/m^3 to account for human variability.

The AEGL-2 value of 1.6 mg/m^3 for all exposure durations was based on human data showing slight to mild irritation or discomfort to mucous membranes due to exposure to peracetic acid at a concentration of 4.7 mg mg/m^3. The same value is for all exposure durations from 10 min to 8 h. An uncertainty factor of 3 was applied to account for human variability.

The AEGL-3 values were based on NOELs for lethality in rats exposed to Proxitane 1507 (containing 15% peracetic acid) for 30 min and 1 h. Uncertainty factors of 3 for intraspecies variability and 3 for interspecies sensitivity were applied to the NOELs. The equation $C^{1.6} \times t = k$ was used to scale the 30-min exposure to 10 min and the 1-h exposure was used to scale to 4 and 8 h. The value of n was estimated from rat data.

The AEGL values are presented in Table 7-13.

8.2. Comparison of AEGLs with Other Standards and Criteria

There are no OSHA (Occupational Safety and Health Administration) standards, NIOSH (National Institute for Occupational Safety and Health) recommendations, or ACGIH TLV, AIHA-ERPG, or MAK values for peracetic acid. SOLVAY (1998) (Belgium manufacturer of peracetic acid) derived emergency exposure indexes (EEI) for accidental releases of peracetic acid based on the methodology of the European Chemical Industry Ecology and Toxicology Centre (ECETOC). These values are derived for general population exposures. The values are as follows:

TABLE 7-12 AEGL-3 Values for Peracetic Acid

10 min	30 min	1 h	4 h	8 h
60 mg/m^3	30 mg/m^3	15 mg/m^3	6.3 mg/m^3	4.1 mg/m^3

TABLE 7-13 Summary of AEGL Values for Peracetic Acid

Classification	10 min	30 min	1 h	4 h	8 h	End Point /Reference
AEGL-1 (Nondisabling)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	Threshold for irritation (Fraser and Thorbinson 1986; McDonagh 1997)
AEGL-2 (Disabling)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	Mild irritation (Fraser and Thorbinson 1986)
AEGL-3 (Lethal)	60 mg/m^3	30 mg/m^3	15 mg/m^3	6.3 mg/m^3	4.1 mg/m^3	Highest concentration causing no deaths (Janssen 1989a)

SLV-EEI-3 (death/permanent incapacity) = 50 ppm (156 mg mg/m^3): the threshold above which mortality and/or irreversible effects could be observed for an exposure of up to 60 min.

SLV-EEI-2 (disability) = 3 ppm (9 mg mg/m^3): the threshold level above which intense lacrimation, extreme nose discomfort and transient incapacitation (inability of self-protection but without residual consequences) could be observed for an exposure of up to 60 min.

SLV-EEI-1(discomfort) = 0.15 ppm (0.45 mg mg/m^3): the threshold level above which discomfort could be observed for an exposure of up to 8 h per day.

8.3. Data Quality and Research Needs

Human data on exposure to peracetic acid were limited. This substance is corrosive to mucous membranes causing extreme discomfort depending on the concentration. Therefore, additional humans studies would not be feasible except for very low concentrations (below irritation levels in normal subjects) using healthy exercising subjects. The animal studies found in the literature were well conducted considering the circumstances. Peracetic acid occurs in mixtures with acetic acid, hydrogen peroxide, a stabilizer, and sometimes sulfuric acid. Commercial preparations vary in the concentrations of the three components. Because of the instability of peracetic acid, the aerosol or vapor may have different compositions of peracetic acid, acetic acid, and hydrogen peroxide. Variations in the composition of the test material could lead to inconsistencies in the

observed effects. Therefore, acute inhalation studies using the same commercial product to study lethal and nonlethal effects after exposure for 30 min, and 1, 4, and 8 h would aid in the evaluation of the toxicity of peracetic acid.

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APPENDIX A

Derivation of AEGL Values for Peracetic Acid

Derivation of AEGL-1

Key Study:	McDonagh 1997; Fraser and Thorbinson 1986
Toxicity End Point:	Threshold for irritation
Time Scaling:	Not applicable.
Uncertainty Factors:	NA for interspecies sensitivity (AEGL-1 derived from human data).
	3 for intraspecies variability; peracetic acid is corrosive and response to upper respiratory tract and eyes is expected to be similar among individuals in the population.
Modifying Factor:	1
Calculations:	1.56 $mg/m^3/3 = 0.52$ mg/m^3
	The same value applied for 10-min to 8-h exposure durations.

Derivation of AEGL-2

Key Study:	Fraser and Thorbinson 1986
Toxicity End Point:	Slight upper respiratory tract irritation.
Uncertainty Factor:	NA for interspecies sensitivity (AEGL-2 derived from human data).
	3 for intraspecies variability; peracetic acid is corrosive and effects in the upper respiratory tract are expected to be similar among individuals in the population.
Modifying Factor:	1
Calculations:	4.67 mg/m^3 /3 = 1.6 mg/m^3
	The same value applied to 10-min to 8-h durations.

Derivation of AEGL-3

Key Study:	Janssen 1989a
Toxicity End Point:	Highest nonlethal concentration of 96 ppm for a 30-min exposure and 48 ppm for a 60-min exposure in the rat.
Time Scaling:	$C^n \times t = k$; n = 1.6 based on analysis of rat lethality data.
Uncertainty Factors:	3, for interspecies sensitivity: mucous membranes of the respiratory tract of humans and animals are not expected to show vast differences in response to corrosive/irritant substances at concentrations that cause severe physical damage or at the threshold for lethality. 3, for intraspecies variability: mucous membranes of individuals are not expected to show a great difference in response to a corrosive/irritant substance such as peracetic acid.
Modifying Factor:	1
Calculations:	
10-min AEGL-3	$C = (k/t)^{1/1.6} = (6927\ mg/m^3\ min/10\ min)^{1/1.6}$ $C = 59.6 = 60\ mg/m^3$
30-min AEGL-3	$300\ mg/m^3/10$ (uncertainty factor) $= 30\ mg/m^3$ $C^n \times t = k$; $C = 30\ mg/m^3$, t = 30 min, n = 1.6 $k = 6927\ mg/m^3 \bullet min$ $C = (k/t)^{1/1.6} = (6927\ mg/m^3\ min/30\ min)^{1/1.6}$ $C = 30\ mg/m^3$
1-h AEGL-3	$150\ mg/m^3/10$ (uncertainty factor) $= 15.0\ mg/m^3$ $C^n \times t = k$; $C = 15\ mg/m^3$, t = 60 min, n = 1.6 $k = 4569.8008\ mg/m^3 \bullet min$ $C = (k/t)^{1/1.6} = (4570\ mg/m^3\ min/60\ min)^{1/1.6}$ $C = 15\ mg/m^3$
4-h AEGL-3	$C = (k/t)^{1/1.6} = (4570\ mg/m^3\ min/240\ min)^{1/1.6}$ $C = 6.3\ mg/m^3$
8-h AEGL-3	$C = (k/t)^{1/1.6} = (4570\ mg/m^3\ min/480\ min)^{1/1.6}$ $C = 4.1\ mg/m^3$

APPENDIX B

Derivation Summary: AEGLs for Peracetic Acid

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)	0.52 mg/m^3 (0.17 ppm)

Key References: (I) McDonagh, J. 1997. Atmospheric Monitoring of Peracetic Acid on the Existing Caprolactone Plant Distillation Houses A and B, Assessment of Results. Document No. EE970192.M01. Memorandum to R.A. Haffenden et al., from J. McDonagh, Solvay Interox, Warrington. April 30, 1997. (II) Fraser, J.A.L., and A. Thorbinson. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm. Solvay Interox, Warrington, UK.

Test Species/Strain/Number:
Humans/two subjects (I); number unknown (II)

Exposure Route/Concentration/Durations:
Inhalation, 0.40-0.53 mg/m^3 (0.13-0.17 ppm) for up to 3 h (I); 1.56-1.87 mg/m^3 (0.5-0.6 ppm) for unknown time (I), <1.56-4.67 mg/m^3 for 12 min; ≤1.56 to ≥6.23 mg/m^3 for 45 min (II).

Effects: 1.56-3.12 mg/m^3: mild discomfort
1.56-1.87 mg/m^3: no immediate irritation; may be unpleasant for extended period.
≤1.56 mg/m^3: no discomfort.
0.40-0.53 mg/m^3: detectable, but tolerable and not unpleasant.

End Point/Concentration/Rationale:
Threshold for irritation of 1.56 mg/m^3; the effects range from detectable but tolerable and not unpleasant to no discomfort.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable.
Intraspecies: 3, individuals in the population are expected to respond similarly and by a factor no greater than 3 when exposed to corrosive/irritant agents that affect the upper respiratory tract.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Human data were limited but were generally supported by animal data. The human data showed that irritation or discomfort at concentrations≤1.56 mg/m^3 is expected to be absent or minimal. Neither study reported the number of subjects exposed to peracetic acid.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)	1.6 mg/m^3 (0.5 ppm)

Key Reference: Fraser, J.A.L., and A. Thorbinson. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm. Solvay Interox, Warrington, UK.

Test Species/Strain/Number:
Humans, number exposed is unknown.

Exposure Route/Concentration/Durations:
Inhalation, range of 15.6 mg/m^3 for 7 min; <1.56-4.67 mg/m^3 for 12 min; 6.23-9.35 mg/m^3 for 1 h and 15 min; ≤1.56-6.23 mg/m^3 for 45 min.

Effects: All effects were associated with the upper respiratory tract or eyes.
6.23-15.6 mg/m^3: lacrimation, extreme upper respiratory discomfort or irritation
6.23 mg/m^3: unbearable irritation or extreme discomfort, but tolerable for 2 min
3.13-4.67 mg/m^3: slight or tolerable discomfort (upper respiratory tract and eyes)
1.36-3.12 mg/m^3: mild discomfort; ≤1.56 mg/m^3: no discomfort.

End Point/Concentration/Rationale:
Slight upper respiratory tract irritation at 4.7 mg/m^3

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable.
Intraspecies: 3, individuals in the population are expected to respond similarly and by a factor no greater than 3 when exposed to corrosive/irritant agents that affect the upper respiratory tract.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy:
The number of subjects exposed to peracetic acid was not reported by the investigators. The AEGL-2 value was based on a concentration that caused discomfort or slight discomfort, which is below the definition for AEGL-2; the next higher concentrations caused unbearable irritation after 2 min. Therefore, the lower concentration was more appropriate for deriving AEGL-2 values. The rationale for selecting the same value for all time points is as follows: (1) effects of peracetic acid exposure correlate with concentration more than time, and (2) peracetic acid is freely soluble in water and should be effectively scrubbed in the nasal passages, particularly at the very low AEGL-2 concentration.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
60 mg/m^3	30 mg/m^3	15 mg/m^3	6.3 mg/m3	4.1 mg/m^3

Key Reference: Janssen, P.J.M. 1989a. Acute Inhalation Toxicity Studies of Proxitane 1507 in Male Rats (I). Report No. S. 8906, Int. Doc. No. 56645/25/89. Duphar B.V., Weesp, The Netherlands, and Solvay, Brussels, Belgium.

Test Species/Strain/Number:
Rat/ CPB-WU Wistar/5 males per group.

Exposure Route/Concentration/Durations:
Inhalation: 130, 300, or 320 mg/m^3 for 30 min and 150, 390, or 1450 mg/m^3 for 60 min.

Effects: Clinical signs: signs of extreme respiratory irritation and discomfort, drooping eyelids, transient weight loss, reduced respiratory rate.
Gross pathologic effects: blood around nose, red nasal and tracheal mucosa, bloody fluid in trachea, dark red lungs, red or dark spots on lungs, elevated lung weight
Mortality: 0/5 rats at 300 mg/m^3 and 3/5 at 320 mg/m^3 for 30 min; 0/5 at 150 mg/m^3, 2/5 at 390 mg/m^3, and 5/5 at 1450 mg/m^3 for 60 min.

End Point/Concentration/Rationale:
Highest non-lethal concentrations for rats exposed for 30 or 60 min; the concentrations were 300 mg/m^3 for 30 min and 150 mg/m^3 for 60 min.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, mucous membranes of the respiratory tract of humans and animals are not expected to show vast differences in response to corrosive/irritant substances at concentrations that cause severe physical damage or at the threshold for lethality.
Intraspecies: 3, mucous membranes of individuals are not expected to show a great difference in response to a corrosive/irritant substance such as peracetic acid.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times t = k$, where n = 1.6 based on analysis of rat LC_{50} data for 1 and 4 h exposures.

Data Adequacy:
The animal studies were well conducted; however, the different compositions of peracetic acid probably contributed to the inconsistencies of the results. The animal studies were conducted with aerosols instead of the vapor.

APPENDIX C

Category Plot for Peracetic Acid

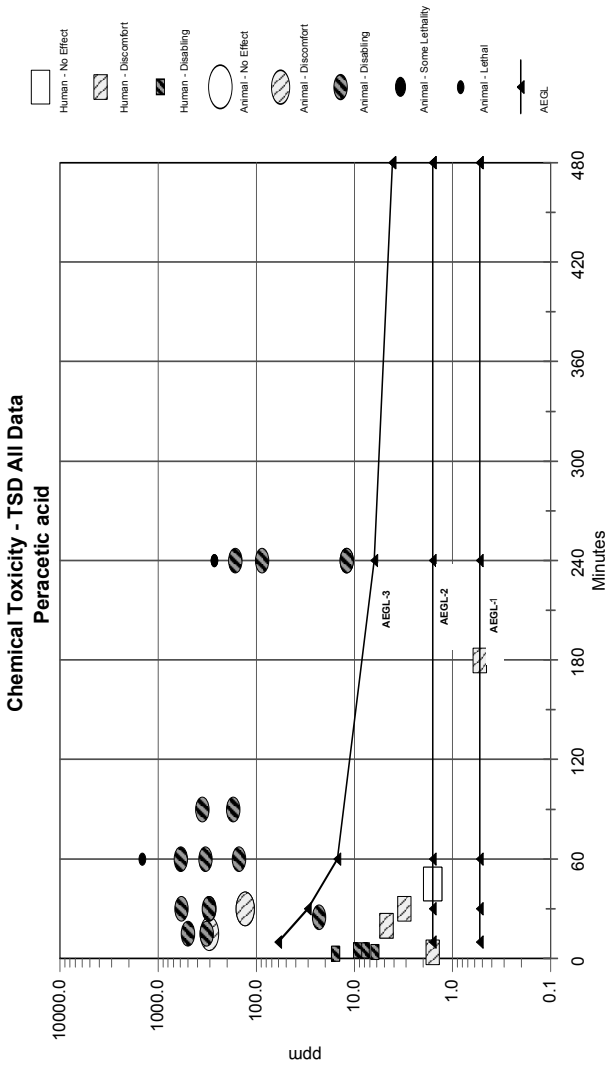

FIGURE C-1 Category plot for peracetic acid.

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 0.8039- 0.8070 at 25/25ºC 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 179 mm Hg at 30.0 ºC 269 mm Hg at 39.0 ºC 436 mm Hg at 51.0 ºC 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. C = 500 ppm/10 (uncertainty factor) = 50 ppm $C^n \times t = k$; C = 50 ppm, t = 30 min, n = 0.91 k = 1054.8336 ppm minutes
Uncertainty Factors:	Total = 10: 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. 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. Total uncertainty factor: Not applicable. Interspecies: Not applicable. 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. Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm. Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm. 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. 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

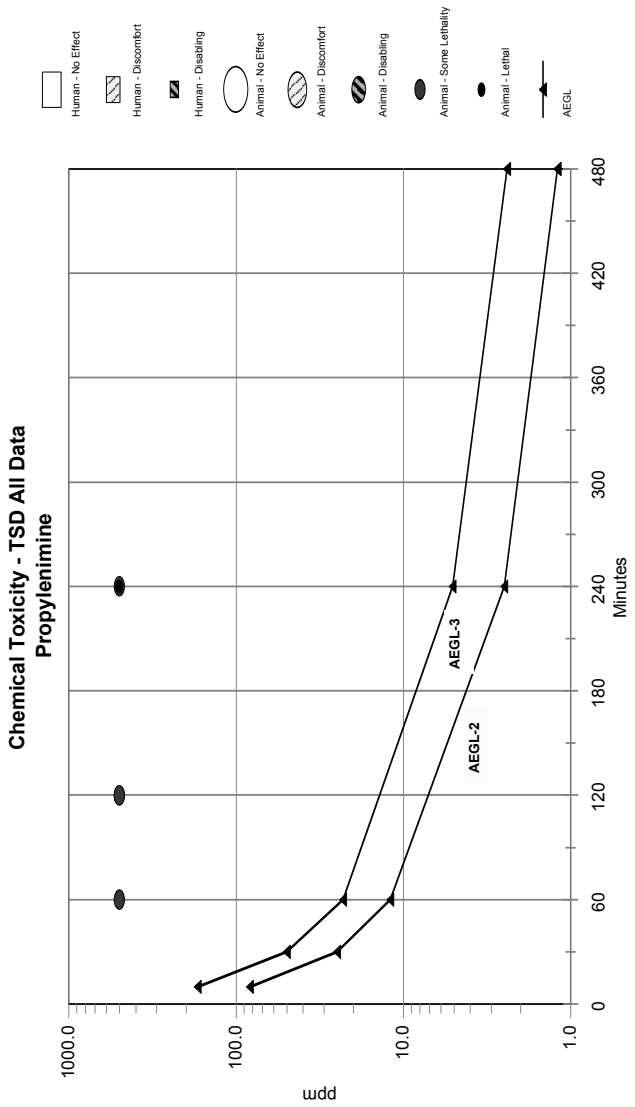

FIGURE D-1 Category plot for propylenimine.

9

Sulfur Dioxide[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, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Cheryl B. Bast (Oak Ridge National Laboratory) and Chemical Managers Loren Koller and George Woodall (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).

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

Sulfur dioxide is a colorless gas at ambient temperature and pressure. It can be detected by taste at concentrations of 0.35-1.05 ppm and has a pungent, irritating odor with an odor threshold of 0.67-4.75 ppm. Sulfur dioxide is used in the production of sodium sulfite, sulfuric acid, sulfuryl chloride, thionyl chloride, organic sulfonates, disinfectants, fumigants, glass, wine, industrial and edible protein, and vapor pressure thermometers. It is also used during the bleaching of beet sugar, flour, fruit, gelatin, glue, grain, oil, straw, textiles, wood pulp, and wood. Sulfur dioxide is also used in leather tanning, brewing and preserving, and in the refrigeration industry. It is a by-product of ore smelting coal, and fuel-oil combustion, paper manufacturing, and petroleum refining (WHO 1984).

Sulfur dioxide is an irritant of the upper respiratory tract and eyes. Conjunctivitis, corneal burns, and corneal opacity may occur from direct contact with high concentrations of sulfur dioxide. Death from respiratory arrest may occur from acute over-exposure, while survivors may develop bronchitis, bronchopneumonia, and fibrosing obliterative bronchiolitis. Bronchoconstriction accompanied by increased pulmonary resistance may be asymptomatic or may occur with high-pitched rales. Moderate exposure may result in a prolonged expiratory phase. Respirable particles, cold air, dry air, exercise, and

mouth-breathing may increase the severity of adverse effects caused by sulfur dioxide (WHO 1984).

AEGL-1 values were based on the weight-of-evidence from human asthmatic data suggesting that 0.20 ppm may be a NOEL for bronchoconstriction in exercising asthmatics. No treatment-related effects were noted in asthmatics exposed to 0.2 ppm for 5 min (Linn et al. 1983b), 0.25 ppm for 10-40 min (Schacter et al. 1984), 0.25 ppm for 75 min (Roger et al. 1985), 0.5 ppm for 10-40 min (Schacter et al. 1984), or 0.5 ppm for 30 min (Jorres and Magnussen 1990). However, an increase in airway resistance (SRaw) of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 min (Bethel et al. 1985); the increase in SRaw in this study, but not in the other studies, may be attributed to the lower relative humidity (36%) in the Bethel et al. (1985) study compared to the other studies (70-85%). No uncertainty factors were applied because the weight of evidence approach utilized studies from a sensitive human population, exercising asthmatics. The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO_2 for 3-h exhibited increases in SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-h into the exposure, and a decrease of 12% at the end of the 3-h exposure period. These data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-1 values for SO_2 were held constant across all time points. Exposure to concentrations at the level of derived AEGL-1 values is expected to have no effect in healthy individuals, but the concentrations are consistent with the definition of AEGL-1 for asthmatic individuals.

AEGL-2 values were based on the weight-of-evidence from human asthmatic data suggesting that 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-min to 3-h (Hackney et al. 1984; Schacter et al. 1984). No uncertainty factors were applied because the weight of evidence approach utilized studies from a sensitive human population, exercising asthmatics. The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO_2 for 3-h exhibited increases in SRaw of 322% 10 min into exposure, 233% 20 min into the exposure, 26% 1-hr into the exposure, 5% 2 h into the exposure, and a decrease of 12% at the end of the 3 h exposure period. These data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-2 values for SO_2 were held constant across all time points. Exposure to concentrations at the level of derived AEGL-2 values is expected to have no effect in healthy individuals, but the concentrations are consistent with the definition of AEGL-2 for asthmatic individuals.

The AEGL-3 values were based on a calculated $BMLC_{05}$ in rats exposed to SO_2 for 4-h (573 ppm) (Cohen et al. 1973). An uncertainty factor of 10 was

applied for intraspecies extrapolation due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability; this factor of 3 was considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 h (Amdur 1959), in dogs exposed to 400 ppm SO_2 for 2 h (Jackson and Eady 1988), or in rats exposed to 593 ppm for 4-h (Cohen et al. 1973). Furthermore, a median lethal exposure time (Lt_{50}) of 200 min was reported for mice exposed to 900 ppm SO_2 (Bitron and Aharonson 1978) and three of eight rats died when exposed to 965 ppm for 240 min (Cohen et al. 1973), suggesting limited interspecies variability. Data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal end point is obtained within 10 min. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 was applied to extrapolate to the 1-h time period, and n of 1 was used for extrapolation to the 8-h time period to provide AEGL values that would be protective of human health (NRC 2001). The 1-h AEGL-3 value was also adopted as 10-min and 30-min values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods.

The calculated values are listed in Table 9-1.

1. INTRODUCTION

Sulfur dioxide is a colorless gas at ambient temperature and pressure. It can be detected by taste at concentrations of 0.35-1.05 ppm and has a pungent, irritating odor with an odor threshold of 0.67-4.75 ppm. It is soluble in water and forms sulfurous acid which is slowly oxidized to sulfuric acid by dissolved oxygen. In the gaseous state, sulfur dioxide may react with oxygen to form sulfur trioxide which then reacts with moisture to form sulfuric acid. Sulfuric acid may also be associated with airborne particles and react with the particles to form other sulfur compounds (WHO 1984).

Sulfur dioxide is produced by burning sulfur or iron pyrites in air and is used in the production of sodium sulfite, sulfuric acid, sulfuryl chloride, thionyl chloride, organic sulfonates, disinfectants, fumigants, glass, wine, industrial and edible protein, and vapor pressure thermo-meters. It is also used during the bleaching of beet sugar, flour, fruit, gelatin, glue, grain, oil, straw, textiles, wood pulp, and wood. Sulfur dioxide is also used in leather tanning, brewing and preserving, and the refrigeration industry. It is a by-product of ore smelting, coal and fuel-oil combustion, paper manufacturing, and petroleum refining (WHO 1984).

TABLE 9-1 Summary of AEGL Values for Sulfur Dioxide

.	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m$^{3)}$	0.20 ppm (0.52 mg/m^3)	NOEL for bronchoconstriction in exercising asthmatics (Linn et al. 1983b; Schacter et al. 1984; Bethel et al. 1985; Roger et al. 1985; Jorres and Magnussen 1990)
AEGL-2 (Disabling)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	Moderate bronchoconstriction in exercising asthmatics (Hackney et al. 1984; Schacter et al. 1984)
AEGL-3 (Lethality)	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	19 ppm (49 mg/m^3)	9.6 ppm (25 mg/m^3)	Calculated BMCLC05 in the rat after a 4-h exposure (Cohen et al. 1973)

Sulfur dioxide is an irritant of the upper respiratory tract and eyes. Conjunctivitis, corneal burns, and corneal opacity may occur from direct contact with high concentrations of sulfur dioxide. Death from respiratory arrest may occur from acute over-exposure, while survivors may develop bronchitis, bronchopneumonia, and fibrosing obliterative bronchiolitis. Bronchoconstriction accompanied by increased pulmonary resistance may be asymptomatic or may occur with high-pitched rales. Moderate exposure may result in a prolonged expiratory phase of the respiratory cycle. Co-exposure to respirable particles may increase the severity of adverse effects caused by sulfur dioxide (WHO 1984).

The chemical structure is depicted below, and the physicochemical properties of sulfur dioxide are presented in Table 9-2.

O = S = O

2. HUMAN TOXICITY DATA

2.1. Case Reports

2.1.1. Acute Lethality

Charan et al. (1979) described an industrial accident in a paper mill resulting in the deaths of two of five exposed workers. Two maintenance workers (ages 56 and 59 years, nonsmokers) were repairing a digester partially filled with wooden chips. The digester was in a large shed where the tempera-

ture was 70 F. The valve of a line containing SO_2 and steam was accidentally opened by another worker and the digester was immediately filled with concentrated SO_2 under pressure. Both workers climbed out using a rope ladder suspended in the digester. Both workers died of respiratory arrest within 5 min of escape from the digester. Post-mortem examination revealed a "coagulated appearance" of the pharynx and larynx, frequent denudation of superficial columnar epithelium accompanied by retention of basal cells, and pink edema fluid in the airways. Histologic examination of the lungs showed extensive sloughing of the mucosa of the large and small airways and hemorrhagic alveolar edema. Three additional workers, presumably exposed to lower concentrations of SO_2, survived the accident; these include a worker who helped the trapped workers escape, an individual wearing a dual-cartridge mask ascending to the top of the digester by an open elevator, and a fireman who responded to the accident. The acute symptoms in the 3 survivors included ocular, nasal, and throat irritation and soreness, chest tightness, and intense dyspnea. The eyes had severe conjunctivitis and superficial corneal burns and the pharyngeal mucosa was hyperemic but free of ulcerations. Pulmonary function tests performed at regular intervals showed that one survivor was asymptomatic, one survivor developed asymptomatic mild obstructive and restrictive disease, and the third survivor developed symptomatic severe airway obstruction unresponsive to bronchodialators. No SO_2 exposure concentrations were provided.

TABLE 9-2 Physical and Chemical Data for Sulfur Dioxide

Parameter	Data	Reference
Chemical Name	Sulfur dioxide	ATSDR 1998
Synonyms	Sulfurous anhydride, sulfur oxide, sulfurous oxide, sulfurous acid anhydride	O'Neil et al. 2001
CAS Registry No.	7446-09-5	ATSDR 1998
Chemical Formula	SO_2	O'Neil et al. 2001
Molecular Weight	64.06	O'Neil et al. 2001
Physical State	Gas (or liquid)	ATSDR 1998
Odor	Pungent, irritating	ATSDR 1998
Melting/Boiling/Flash Point	-72ºC/-10ºC/no data	O'Neil et al. 2001
Density	2.927 g/L (gas)	ATSDR 1998
Solubility	Soluble in water and organic solvents	O'Neil et al. 2001
Vapor Pressure	3000 mm Hg at 20ºC	ATSDR 1998
Conversion factors in air	1 ppm = 2.6 mg/m^3 1 mg/m^3 = 0.38 ppm	NRC 1984

In another report, Galea (1964) describes an accident in a pulp and paper mill where two men were exposed to an undetermined concentration of SO_2 for 15 to 20 min. One worker was a 45-year-old man who was a heavy smoker. He survived the accident but exhibited a delayed chronometric vital capacity, prolonged expiratory phase, and marked respiratory fatigue four months after the accident. The second worker was a 35-year-old man who was a non-smoker. He presented with slight ocular irritation and pain on deep breathing. He was released from the hospital a few days after the accident since his clinical condition had improved. Ten days later, he was readmitted complaining of a dry, irritable cough, dyspnea, and mucous. He had rales at both lung bases and required a tracheotomy on the seventh day of his readmission. He died the following day, seventeen days after the date of the accident. Extensive peribronchiolar fibrosis and bronchiolotis obliterans was assumed to be responsible for the acute emphysematous changes consistent with the immediate cause of death.

Rabinovitch et al. (1989) described an accident in an underground copper mine where three healthy male workers were exposed to high concentrations of SO_2 as the result of a copper iron sulfide dust explosion. One miner died within mins. The other two survived by covering their heads with rubber pants and using compressed air to provide adequate ventilation. They were rescued 3.5 h after the explosion at which time the measured SO_2 concentration was greater than 40 ppm. No other toxic gases were identified and particles of copper and iron were at background levels for the mine. The survivors presented with intense burning of the eyes, nose, and throat, dyspnea, diffuse precordial and retro sternal chest pain, nausea, vomiting, and urinary incontinence. One of the workers had skin irritation resulting in first degree burns. Two weeks after the accident, all of their symptoms except the dyspnea had resolved. Within three weeks of the accident, both workers had severe airway obstruction, hypoxemia, markedly decreased exercise tolerance, ventilation-perfusion mismatch, and evidence of active inflammation (positive gallium scan). Progressive improvement was observed over the next year; however, ventilation-perfusion scans remained abnormal.

In another mining accident, nine workers were descending into a mine in a cage of a hoist at which time a pyrite (FeS_2) explosion occurred (Harkonen et al. 1983). The workers were exposed to gases, primarily an undetermined concentration of SO_2, for 20 to 45 min. At the mining level, the workers tried to rescue themselves by breathing from compressed air vents. One of the workers died and the others were injured. The lung function of the survivors was followed for 4 years. The largest decreases in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximal midexpiratory flow were observed 1 week after the accident. Pyrometer indicated obstructive findings in 6 workers and restrictive findings in 1 worker. After three months, no further lung function decrement occurred; however, four years after the accident, bronchiolar obstruction was still present in three workers.

2.1.2. Nonlethal Toxicity

Wunderlich et al. (1982) described an accident where a 12-year-old boy fell into a pit (4 m deep; 2.45 × 1.45 m area) containing SO_2 on the grounds of a chemical manufacturing plant. He was not able to free himself and remained in the pit for approximately 4 h until he was found and rescued. Several days later, the measured concentration of SO_2 in the pit was 4.8 ppm; thus, it is possible that the concentration was higher at the time of the accident. He presented with acute irritation of the eyes and mucous membranes of the upper airways, rhinopharyngitis, laryngitis, bronchitis, conjunctivitis, and corneal lesions. These effects persisted for five days and were followed by a symptom-free period of three days. Bronchitis, bronchiolitis, alveolitis, emphysema of the lung, and bronchiectasis then developed and persisted for 12 months in spite of aggressive therapy. Thereafter, lung emphysema and continuous partial respiratory insufficiency, accompanied by ventilatory obstruction were observed for 4 years. No follow-up beyond four years was reported.

Charan et al. (1979), Galea (1964), Rabinovitch et al. (1989), and Harkonen et al. (1983) describe cases where both non-lethal and lethal effects were observed. These case-reports are described in Section 2.1.1.

2.2. Epidemiologic Studies

2.2.1. Occupational Exposure

Lung function and sputum cytology were compared between copper smelter workers chronically exposed to 0.3 to 4 ppm SO_2 and a control group of mine repair shop workers (Archer et al. 1979). All subjects were white males and exposed and control subjects were paired by age and smoking habits. Measurements of FVC, FEV_1, FEF_{50}, and closing volume were made both before and after the work shift for both exposed and control workers. Sputum samples for cytological analysis were also collected from both groups of workers. Mean FEV_1 and FVC values were significantly ($p<0.05$) decreased after a work shift in the smelter compared to controls and significantly more smelter workers had decreased FEV_1 and FEF_{50} values during the day when compared to controls. Also, more smelter workers complained of chest tightness compared to the control workers. Smelter workers had a higher percentage of sputum samples with moderate and marked atypical than controls; however, the cytological effects did not reach statistical significance.

Sulfur dioxide is used as a bleaching agent in the production of brooms. In another workplace monitoring study, Savic et al. (1987) compared a group of 190 workers from a broom manufacturing factory with a group of 43 workers not exposed to SO_2 in the workplace (no other information concerning the

control groups was provided). Sulfur dioxide concentrations in the broom factory ranged from 0 to 0.285 ppm during the summer (windows were open) and from 6.5 to 56.8 ppm in the winter. Dust concentrations were similar in both summer (0-21 mg/m^3) and winter (3-27 mg/m^3). The most common subjective symptoms reported by exposed workers included coughing (94.2%), dyspnea (91.0%), burning of the nose, eyes, and throat (74.7%), tearing (64.7%), and substernal pain (75.3%). Sulfate concentration in the urine and methemoglobin concentration in the blood of exposed workers was significantly increased ($p<0.01$) compared to controls. No difference was found in sulfhemoglobin concentrations.

2.2.2. Community Exposure: Ambient Air Pollution

Many studies concerning the relationship between SO_2 exposure in polluted air and human health have been conducted; however, these studies are confounded by the presence of particulate matter and other air pollutants. Perhaps the most notable example of increased mortality from SO_2 and particulate matter exposure occurred in London in the 1950's (IPCS 1979). The London episode lasted 5 days. The number of deaths was approximately 4000 more (a three-fold increase) than would have been expected under normal circumstances. Most deaths occurred in the elderly and in people with preexisting cardiac or respiratory disease. Peak SO_2 concentrations were 1.3 ppm while particulate matter concentrations were too high to be monitored (4.5 mg/m^3 was provided as a conservative estimate). The excess deaths were attributed to bronchitis or to other impairments of the respiratory tract. Increased mortality from cardiac effects was also observed. The effects observed from this incident are attributed to the combination of SO_2 and extremely high concentration of particulate matter. Direct attribution of effects to SO_2 is toxicologically questionable because of the exceptionally high concentrations of particulate matter (see Section 4.4).

More recently, Touloumi et al. (1994) examined the effects of air pollution on mortality in Athens, Greece from 1984-1988. Mean SO_2 levels (averaged over 2 recording stations) for the 5-year period ranged from 0.014 to 0.027 ppm. Total mortality was associated with SO_2, smoke, and CO, with both SO_2 and smoke being independent predictors of daily mortality. The strongest association was found for mortality lagged for 1 day. However, this study is of limited use due to the confounding pollutants and long exposure period (up to 5 years). In another study, Rahlenbeck and Kahl (1996) examined the relationship between mortality and air pollution in East Berlin for the winters of 1981-1989. When controlling for temperature and humidity, both SO_2 and suspended particles were found to be contributors to excess mortality, the strongest association found for mortality lagged for 2 days. The mean SO_2 concentration over the 9-year period was 0.063 ppm.

Rao et al. (1973), Castellsague et al. (1995), and Goldstein and Weinstein (1986) found no relationship between air pollution sulfur dioxide peaks and asthma attack rates in children. In another study, Partti-Pellinen et al. (1996) found increased incidences of cough, respiratory infections, and headache in residents living near a pulp mill compared with a reference community. The average SO_2 concentrations were 0.00038 ppm in the reference community and 0.00076-0.0011 ppm in the exposed community. However, in view of the existing experimental database, it is likely that confounding pollutants, and not solely SO_2, contributed to the observed effects.

Many other reports have shown an association between sulfur dioxide exposure and respiratory symptoms such as decreased lung function, coughing, chest tightness, and increased incidences of respiratory infections (Stebbings and Hayes 1976; Saric et al. 1981; Vedal et al. 1987; Hoek and Brunekreef 1993; Braback et al. 1994; Schwartz et al. 1994; Higgins et al. 1995; Soyseth et al. 1995; Braun-Fahrlander et al. 1997; Peters et al. 1997). However, these epidemiological studies are of limited usefulness to define a precise cause-effect relationship since other air pollutants, especially particulate matter, ozone, and nitrogen oxides, are also present.

2.3. Experimental Studies

Many controlled human studies examining the effects of SO_2 are available and indicate that the respiratory system is the principal target after acute exposure. Data show that asthmatics are particularly sensitive to the effects of SO_2 and that effects are enhanced (in both healthy individuals and asthmatics) by exercise. Since it would not be feasible to include all available human SO_2 data, the studies summarized below are considered sufficient to be quantitatively representative of data describing effects from acute exposure to SO_2. Selected data from controlled exposures to SO_2 in non-asthmatic individuals are presented in Table 9-3 and data from asthmatic individuals are presented in Table 9-4.

2.3.1. Nonasthmatic Subjects

Amdur et al. (1953) exposed 14 healthy males (ages 28-58 years) to varying concentrations of SO_2 through a face mask for 10 min. At 5 ppm most subjects complained of dryness in the throat and upper respiratory passages. Decreased respiratory volume and increased respiratory rate were noted at 1-8 ppm SO_2.

TABLE 9-3 Selected Data from Exposure of Nonasthmatic Humans to SO_2

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
1-8 ppm	10 min	14	Exposure through facemask	1-8 ppm: ↓Respiratory volume ↑ respiratory rate 5 ppm: dry throat	Amdur et al. 1953
0.75 ppm	2 h	16	21 ºC, 60% RH, Treadmill exercise 45 min. after entering chamber	SRaw: ↑ 2-55% (14.6% avg)	Stacy et al. 1981
0.4 ppm 2.0 ppm 4.0 ppm	20 min	8	20 ºC, 50% RH, exercise 75 W, last 15 min of exposure	No effects on respiratory function parameters. Nasal irritation: 4 ppm (5/8) Throat irritation: concentration-dependent at 0.4, 2, and 4 ppm	Sandstrom et al. 1988
4.0 ppm 8.0 ppm	20 min	10 4	20 ºC, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrphage activity	Sandstrom et al. 1989a
8.0 ppm	20 min	22	20 ºC, 50% RH, exercise 75 W	Transient concentration-related ↑ alveolar macrophage activity	Sandstrom et al. 1989b
4.0 ppm 5.0 ppm 8.0 ppm 11.0 ppm	20 min	22	20 ºC, 50% RH, at rest	Transient ↑in alveolar macrophage activity. Concentration-related up to 8 ppm, no further increase at 1 ppm	Sandstrom et al. 1989c
1.0 ppm	4 h	20	22.2 ºC, 60% RH, exercise 100 W	No effects on lung function parameters. Upper respiratory irritation (4/20) Ocular irritation (1/20)	Kulle et al. 1984

(Continued)

TABLE 9-3 Continued

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
1 ppm 5 ppm 13 ppm	10-30 min	11	Resting	No effects 39%↑ Pulmonary flow res. 72%↑ Pulmonary flow res. Peak response 5-10 min	Frank et al. 1962
1-2 ppm 4-6 ppm 14-17 ppm	30 min	6	Resting; exposures to SO_2 alone or in combination with 18 mg/m^3 NaCl	No effects ↑ Pulmonary flow resistance ↑ Pulmonary flow resistance	Frank et al. 1964
15 ppm 29 ppm	10 min	11	Compared nose breathing vs mouth breathing	↑ Pulmonary flow resistance 15 ppm: 3% Nose; 20% mouth 29 ppm: 18% Nose; 65% mouth	Frank et al. 1964
0.55 ppm	10 min	11		No nasal or eye irritation	Dautrebrande and Capps 1950
1 ppm 5 ppm 25 ppm	6 h	15	Resting	No effects Irritation. ↓FEV_1, ↓Nasal mucous flow Irritation. ↓FEV_1, ↓nasal mucous flow	Andersen et al. 1974

TABLE 9-4 Selected Data from Exposure of Asthmatic Humans to Sulfur Dioxide

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 ºC, 85% RH, exercise 48 L/min	None	Linn et al. 1983b
0.25 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984
0.25 ppm	5 min	19	23 ºC, 36% RH, exercise 60 L/min	SRaw ↑134%	Bethel et al. 1985
			23 ºC, 36% RH, exercise 80-90 L/min	SRaw ↑139%	
		9			
0.25 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min intermittent	None	Roger et al. 1985
0.4 ppm	5 min	23	23 ºC, 85% RH, exercise 48 L/min	SRaw ↑69% $V_{max25-75}$ ↓10%	Linn et al. 1983b
0.5 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984
0.5 ppm	5 min	10	23 ºC, 41% RH, exercise 60 L/min	SRaw ↑238%	Bethel et al. 1983a
0.5 ppm	5 min	9	23 ºC, 80% RH, exercise 27 L/min	None	Bethel et al. 1983b
			23 ºC, 80% RH, exercise 41 L/min	None	
			23 ºC, 80% RH, exercise 61 L/min	SRaw ↑219%	
0.5 ppm	1 min	8	22 ºC, 75% RH, exercise 60 L/min	SRaw ↑34%	Balmes et al. 1987
	3 min			SRaw ↑173%	
	5 min			SRaw ↑234%	
0.5 ppm	20 min	46	23 ºC, 92% RH, exercise 30 L/min for 10 min	SRaw ↑131%	Magnussen et al. 1990
0.5 ppm	30 min	14	24 ºC, 50% RH, at rest	None	Jorres and Magnussen 1990

(Continued)

TABLE 9-4 Continued

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.5 ppm	50 min	10	22 ºC, 75% RH, 30 min rest + 20 min exercise 43 L/min face mask	Nasal resistance ↑30% FEV_1 ↓16% V_{max-50} ↓26% V_{max-75} ↓26%	Koenig et al. 1985
0.5 ppm	50 min	10	22 ºC, 75% RH, 30 min rest + 20 min exercise 43 L/min mouthpiece	Nasal resistance ↑32% FEV_1 ↓24% V_{max-50} ↓46% V_{max}-75 ↓56%	Koenig et al. 1985
0.5 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min, intermittent	SRaw ↑100%	Roger et al. 1985
0.5 ppm	3 min x 3	8	23 ºC, 82% RH, exercise (hyperventilating) intermittent	SRaw ↑104% (1st) SRaw ↑35% (2nd) SRaw ↑30% (3rd)	Sheppard et al. 1983
0.6 ppm	5 min	22	21 ºC, 20% RH, exercise 50 L/min 21 ºC, 80% RH, exercise 50 L/min 38 ºC, 20% RH, exercise 50 L/min 38 ºC, 80% RH, exercise 50 L/min	SRaw ↑206% SRaw ↑157% SRaw ↑89% SRaw ↑39%	Linn et al. 1985
0.6 ppm	5 min	23	23 ºC, 85% RH, exercise 48 L/min	SRaw ↑120% $V_{max25-75}$ ↓26% FEV_1 ↓13%	Linn et al. 1983b
0.75 ppm	3 h	17	22 ºC, 85% RH, exercise 45 L/min (first 10-min of exposure)	Sraw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV_1 : ↓20% (at 15-min)	Hackney et al. 1984

0.75 ppm	10 min	23	23 ºC, 90% RH, exercise 40 L/min facemask mouthpiece	SRaw ↑186% SRaw ↑321%	Linn et al. 1983a
0.75 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV_1 ↓8%	Schacter et al. 1984
1.0 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV_1 ↓14%	Schacter et al. 1984
1.0 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al. 1985
1.0 ppm	30 min	10	26 ºC, 70% RH, exercise 41 L/min (3-10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al. 1987
1.0 ppm	30 min	10	26 ºC, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al. 1987
1.0 ppm	1 min 3 min 5 min	8	22 ºC, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al. 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 ºC, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al. 1988

Source: Adapted from EPA 1994.

Stacy et al. (1981) examined the effect of SO_2 exposure on healthy nonsmoking males between the ages of 18 and 40 years. A total of 31 subjects were studied. Sixteen subjects were exposed to 0.75 ± 0.04 ppm SO_2 and 15 were exposed to air for 2 h. All subjects had intradermal skin tests for 16 allergens common to the geographical area where the study was performed. Relative humidity in the exposure chamber was maintained at 60% and temperature at 21ºC. Recirculation and reconditioning of chamber air through HEPA filters kept total particle mass to < 3 μg/m^3 and particle count at 1×10^5 particles/ m^3, thus, creating unfavorable conditions for sulfate formation. Each subject exercised on a treadmill at 6.4 kmph and 10% incline beginning 45 min after entry into the chamber. Only parameters related to air flow resistance were significantly affected by SO_2 exposure, although spirometric parameters exhibited a similar trend. At the end of the first hour of exposure, airway resistance (SRaw) was increased between 2% and 55% in 14 of 16 subjects exposed to SO_2. The average increase was 14.6% compared with a mean decrease of 10.3% in air-exposed subjects. The SO_2-exposed subjects positive for allergen skin-tests appeared to be more reactive to SO_2 than those negative for allergen skin-tests. A component of this study examining nasal mucosa was published later (Carson et al. 1987). Nasal epithelium was obtained from 7 of the subjects and showed increases in the incidence of compound cilia accompanied by abnormal ciliary membrane ultrastructure in 4 of the 7 subjects.

In another study, Sandstrom et al. (1988) exposed eight healthy, nonsmoking subjects (ages 21-29 years, sex not specified) to 0, 0.4, 2, or 4 ppm SO_2 for 20 min. During the first 5min of exposure, the electrodes on the subjects were adjusted by a technician. The subjects then worked on a bicycle ergometer at a work load of 75 W for the remaining 15 min. The exposure chamber was made of anodized aluminum and had a volume of 14.1 m^3. During exposure the chamber temperature was 20ºC, relative humidity was approximately 50%, and there was one air exchange every 2 min. The SO_2 atmosphere in the chamber was produced by addition of a gas stream from a 1% SO_2 gas tube to the chamber air inlet. The chamber air was analyzed continuously by color metric titration. There were no treatment-related effects on heart rate, breathing rate, $FEV_{1.0}$, FEF_{25-75}, FVC, gas distribution, or closing volume. Five of eight subjects reported nasal irritation at 4 ppm only. Unpleasant odor was reported more frequently ($p<0.05$) at the end of the exposure to 4 ppm SO_2 than before exposure at the beginning of this exposure period. Throat irritation was significantly ($p<0.05$) increased during exposure to 2 ppm SO_2. It was also reported more frequently during and at the end of 4 ppm SO_2 exposure than before exposure ($p<0.02$) and was also more common ($p<0.05$) at the end of exposure to 4 ppm compared to the end of the 0.4 ppm exposure period.

Sandstrom et al. (1989a) also examined the effects of SO_2 exposure on broncho-alveo-lar lavage fluid (BAL) parameters. Healthy subjects (ages 22-30 years, sex not specified) were exposed to 4 (10 subjects) or 8 ppm (4 subjects) SO_2 for 20 min while exercising on a bicycle ergometer with a work

load of 75 W. The exposure chamber and test atmosphere gen-eration were the same as that described above in Sandstrom et al. (1988). An increase in alveolar macrophage activity was observed 24 h after exposure to 4 ppm SO_2 as evidenced by an increase in lysozyme positive macrophages. Twenty-four hours after exposure to 8 ppm of SO_2 a further increase (2 to 4 times higher than pre-exposure values) was observed and was accompanied by an increase in total numbers of macrophages and lymphocytes. Seventy-two hours post-exposure, the BAL fluid from subjects exposed to 8 ppm had returned to baseline values.

In another report, Sandstrom et al. (1989b) exposed 22 healthy males (ages 22-27 years) to 8 ppm SO_2 for 20 min. The exposure chamber, atmosphere generation, and exercise regimen were identical to that described above. BAL was analyzed from 8 subjects at each of the following time intervals: 2 weeks before exposure, and 4, 8, 24, and 72 h after exposure. Increased numbers of lysozyme positive macrophages, lymphocytes, and mast cells were observed 4 h after exposure. Lymphocytes, lysozyme-positive macrophages, total alveolar macrophage counts, and total cell number reached a peak at 24 h post-exposure and had returned to pre-exposure values by 72 h. Sandstrom et al. (1989c) also exposed 22 healthy males (ages 22-37 years) to 4, 5, 8, or 11 ppm SO_2 for 20 min. Exposure conditions were the same as those described above; however, no exercise period was included. Mast cells, lymphocytes, lysozyme positive macrophages, and the total number of macrophages were increased in BAL fluid 24 h post-exposure. The effects were concentration dependent at 4, 5, and 8 ppm, but no further increase was detected at 11 ppm.

Kulle et al. (1984) exposed twenty healthy, nonsmoking adults (10 males and 10 females) ages 20 to 35 years-old to filtered air or 1 ppm SO_2 for 4 h. Each subject served as his own control and exercised for 15 min at both 1 and 3 h into the exposure period. The exercise consisted of riding a bicycle ergonometer at a work load of 100 watts at 60 RPM and was designed to ensure a short period of increased ventilation and to simulate the type of activity engaged in by many city dwellers. The exposures were conducted in a 22.2-m^3 exposure room with a ventilation rate of 8.49 m^3/min, allowing for a complete air change every 2.6 min. Temperature was maintained at 22.2°C and relative humidity at 60%. Air entering the room was passed through HEPA filters and activated carbon fibers to remove contaminants. Sulfur dioxide was metered into the room by an air input diffuser and the concentration continuously monitored by a pulsed fluorescent analyzer and a flame photometric analyzer. There were no treatment-related effects on lung function as measured by spirometry, body plethysmography, and methacholine inhalation challenge. Four subjects reported upper respiratory irritation and one reported ocular irritation during SO_2 exposure. Seven subjects perceived the presence of the SO_2 due to odor and/or taste.

Eleven healthy male adults were exposed to 0, 1, 5, or 13 ppm SO_2 for up to 30 min (most exposures were for 10 min) (Frank et al. 1962). Exposures were spaced 1 month apart and subjects were seated in a volume displacement

body plethysmograph, breathing through the mouth while respiratory measurements were made with an esophageal catheter. The SO_2 was administered by occlusion of one port of a wide T-tube that led to room air through which the subjects had been breathing, and by opening the other port leading to the SO_2 source. Subjects were blind to the SO_2 concentration administered, with the exception of one subject who was an author of the study. Pulmonary flow resistance was increased an average of 39% above controls at 5 ppm ($p<0.01$) and an average of 72% above control at 13 ppm ($p<0.001$). Within 1 min of exposure, flow resistance increased ($p<0.001$), with a greater increase observed after 5 min ($p<0.05$). No further increase occurred after 10 min, and the authors concluded that the peak response occurred between 5 and 10 min. Cough, irritation, and increased salivation were also observed at 5 ppm. No treatment-related effects were observed at 1 ppm.

In another study, Frank et al. (1964) administered SO_2 alone or in combination with a physiologically inert NaCl aerosol to 6 healthy non-smoking adult males. The SO_2 concentra-tions were 1-2, 4-6, or 14-17 ppm; NaCl aerosol concentration averaged 18 mg/m^3 (range 10-30 mg/m^3). Techniques of exposure and measurement were similar to those described above in Frank et al. (1962). Changes in pulmonary flow resistance induced by SO_2 and the SO_2 -NaCl aerosol mixture were similar. No significant effect was observed at 1-2 ppm SO_2 with or without NaCl. A concentration-dependent increase in pulmonary flow resistance was observed at 4-6 and 14-17 ppm SO_2 with or without NaCl. Exposures lasted 30 min and as in the previous study, maximum effect was observed after 10 min and receded partially thereafter. In another study, Frank et al. (1964) compared oral and nasal SO_2 administration. Oral exposures were performed similarly to those described above, while nasal exposures were accomplished through a hard plastic mask fitted over the bridge of the nose and lower face. Concentrations of SO_2 were 15 or 29 ppm. Pulmonary flow resistance increased maximally at 10 min and was approximately 20% for 15 ppm mouth breathers, 65% for 28 ppm mouth breathers, 3% for 15 ppm nose breathers, and 18% for 28 ppm nose breathers. Cough or chest irritation was common in mouth breathers and rare in nose breathers.

Dautrebrande and Capps (1950) found no subjective nasal or ocular irritation in 11 healthy adults exposed to 0.55 ppm SO_2 for 10 min. Douglas and Coe (1987) applied various concentrations of SO_2 to the eyes of healthy adult subjects through close fitting goggles. In a separate set of experiments, various concentrations of SO_2 were administered via a mouthpiece. Ocular irritation was measured subjectively, whereas lung response was measured objectively via a plethysmograph. The threshold for ocular irritation was determined to be 5 ppm and the bronchoconstriction threshold was 1 ppm. Andersen et al. (1974) exposed 15 healthy males (ages 20-28 years) to 0, 1, 5, or 25 ppm SO_2 for 6 h. Sulfur dioxide was metered through rotameters to the inlet duct for ventilating air to the climate chamber. Thorough mixing was accomplished by two fans upstream in the chamber. The SO_2 concentration was continuously monitored by a conductivity method. Nasal mucous flow was decreased at 5

and 25 ppm but not at 1 ppm. Decreases were concentration-dependent and ranged from 13 to 80% of controls. The decrease was greatest in the anterior portion of the nose; however, the affected area increased with increasing exposure time. An increase in nasal airflow resistance and a decrease in forced expiratory volume in one second were observed at 5 and 25 ppm, with little or no effect at 1 ppm. Five subjects complained about dryness in the nose and pharynx after exposure to 5 ppm SO_2. After the 25 ppm exposure, only two subjects had no complaints of irritative effects; dryness or a slight pain in the nose and pharynx was reported by 10 subjects, rhinorrhoea was reported by two subjects, and slight conjunctival pain was reported by 3 subjects. No subjective effects were reported at 1 ppm.

Rondinelli et al. (1987) exposed 10 healthy men (ages 55-73 years) to 0.5 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol, 1 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol, or 1 mg/m^3 sodium chloride droplet aerosol alone. Subjects were exposed for 20 min at rest and 10 min during moderate exercise on a treadmill. Significant ($p<0.05$) decreases in FEV_1 were observed 2-3 min post-exercise in all treatment regimens. The decrease observed after sodium chloride aerosol and 1.0 ppm SO_2 was significantly greater than that observed after sodium chloride aerosol alone; however, average decreases were in the range of only 5-8% below baseline values.

2.3.2. Asthmatic Subjects

Schachter et al. (1984) examined the effects of SO_2 on ten asthmatic (4 males, 6 females, age 27.3±5.1 years) and ten healthy (5 males, 5 females, age 26.1 ±6.3 years) humans. Subjects were exposed in a 3 x 3.7 x 2.4 m chamber with laminar airflow from floor to ceiling. The vertical flow system provided uniform gas conditions with no stagnant areas. The desired SO_2 concentrations were achieved by mixing concentrated gas (0.5% SO_2, balance nitrogen) with the chamber air in the circulating flow stream. Levels of SO_2 were continuously monitored from all chamber areas using a fluorescent SO_2 analyzer. Exposures were 0, 0.25, 0.50, 0.75, or 1.0 ppm SO_2 for 40 min. During the first 10 min, subjects exercised on a cycloergometer at 450 kpm/min. On separate days, subjects were exposed to 0 or 1.0 ppm SO_2 for 40 min in the absence of exercise. No significant effects were observed in pulmonary function parameters during the exercise or non-exercise protocols in nonasthmatic subjects at any SO_2 concentration. No effects were observed in non-exercising asthmatics or in exercising asthmatics at 0.50 ppm or below. In exercising asthmatics exposed to 0.75 ppm SO_2, effects were observed in airway resistance (150% increase), forced expiratory volume in one second (mean -8%), and maximal expiratory flow (mean -22%). In exercising asthmatics exposed to 1 ppm SO_2, significant ($p<0.05$) effects were observed in airway resistance (470% increase), forced expiratory volume in one second (mean -14%), and maximal expiratory flow (mean -27%), suggesting a concentration-response relation-

ship. Pulmonary effects had resolved 10 min after the end of exercise even though SO_2 was still present in the chamber atmosphere.

Balmes et al. (1987) exposed two female and six male nonsmoking adult asthmatics to humidified air for 5 min or 0.5 or 1.0 ppm SO_2 for 1, 3, or 5 min during eucapnic hyperpnea (60 L/min). Each exposure occurred at the same time on a separate day. Metered flows of SO_2 from a calibrated tank and air from a compressed air source were mixed in a 3-L glass mixing chamber. The subjects inhaled the SO_2 from a mouthpiece attached and SO_2 concentrations were measured continuously with a pulsed fluorescent SO_2 analyzer just proximal to the mouthpiece. Bronchoconstriction, as indicated by increases in SRaw, increased over baseline with increasing exposure time and concentration. SRaw was increased 46% after exposure to 0 ppm for 5 min, and 34%, 173% and 234%, after exposure to 0.5 ppm for 1-min, 3-min, and 5-min, respectively. SRaw was increased 46% after exposure to 0 ppm for 5 min, and 93%, 395% and 580%, after exposure to 1.0 ppm for 1-min, 3-min, and 5-min, respectively. The effects observed after the 1 min exposures were confined to 2 subjects who also developed chest tightness. After each 3 and 5 min exposure, 7 of 8 subjects developed increases in SRaw accompanied by wheezing, chest tightness, or dyspnea and requested bronchodilator therapy.

Linn et al. (1985) exposed 22 young adult asthmatics (13 males and 9 females, ages 18-33 years) to all combinations of 2 atmospheric conditions (purified air and 0.6 ppm SO_2), 2 temperatures (21 and 38 ºC), and 2 levels of relative humidity (20 and 80%). Exposure involved exercise on a constant-load bicycle ergometer at a work load sufficient to produce a ventilation rate of 50 L/min. The exercise lasted 5 min plus a brief warm-up and cool-down period. Exposure atmospheres were produced from SO_2 in a high-pressure cylinder being metered into a purified air inlet duct in a manner providing uniform stable concentrations inside the chamber. SO_2 levels were continuously monitored with duplicate flame photometric analyzers. Symptom questionnaires and body plethysmographic measurements were completed before and after each exposure. Physiologic changes during clean air exposures were small under all temperature and humidity conditions. At high temperature with high humidity, no change in SRaw or SGaw were noted. At low temperature with high humidity or high temperature with low humidity, SRaw and SGaw were increased approximately 10%. At low temperature with low humidity SRaw and SGaw were increased approximately 20% during clean air exposure. Bronchoconstrictive responses were more severe in SO_2 exposures compared to clean air exposures, but followed a similar pattern with regard to temperature and humidity. In SO_2 exposures, mean SRaw increased 39% at high temperature and high humidity, 89% at high temperature and low humidity, 157% at low temperature and high humidity, and 206% at low temperature and low humidity. Corresponding decreases in SGaw (specific airway conductance) were 22, 44, 62, and 61%, respectively. Subjective reporting of upper and lower respiratory symptoms increased with exposure to SO_2 and appeared to be mitigated by high temperature.

In another study, Linn et al. (1983a) exposed 23 young adult asthmatics (15 males, 8 females, mean age 23 years) to 0 or 0.75 ppm SO_2 for 10-min during bicycle exercise (40 L/min) once while breathing unemcumbered and once via a mouthpiece while wearing nose clips. At 0 ppm, SRaw was increased 54% by either exposure route. At 0.75 ppm, SRaw was increased 186% by oronasal breathing and 321% by mouthpiece.

In another study, Linn et al. (1983b) exposed 23 young adult asthmatics (13 males, 10 females, ages 19-31 years) to 0, 0.2, 0.4, or 0.6 ppm SO_2 for 5-min while exercising (48 L/min). Exposures were random order at 1-week intervals. At 0.2 ppm, there were no effects on SRaw, FEV_1, FVC or $V_{max25-75}$ compared to controls. At 0.4 ppm, SRaw was increased 69%, and $V_{max25-75}$ was decreased 10%, but there was no effect on FEV_1. At 0.6 ppm, SRaw was increased 120%, $V_{max25-75}$ was decreased 26%, and FEV_1 was decreased 13%. Addition-ally, 21 of 23 subjects reported increased symptoms (cough, irritation, wheezing, and chest tightness) at 0.6 ppm, and 3 subjects required medication to relieve symptoms. No apparent effects were noted the next day or week.

Linn et al. (1984) also exposed a group of 14 asthmatics (12 males, 2 females, ages 18-33 years) to 0 or 0.6 ppm SO_2 for 6-h periods on 2 successive days. Subjects exercised (50 L/min) for 5 min near the beginning of exposure and for an additional 5 min after 5 h of exposure. At all other times, they were resting. Increases in SRaw were 136% after the first exercise period on day 1, 120% after the second exercise period on day 1, and 147% after the first exercise period on day 2, 100% after the second exercise period on day 2.

Bethel et al. (1983a) exposed ten asthmatics (8 males, 2 females, ages 22-36 years) to 0 or 0.5 ppm SO_2 for 5 min during moderately heavy bicycle exercise (60 L/min). Subjects were allowed to breathe freely. Mean SRaw was increased 238% after the exposure period. Bethel et al. (1983b) also exposed nine asthmatics (3 males, 5 females, ages 20-37 years) to 0 or 0.5 ppm SO_2 during low (27 L/min), moderate (41 L/min), or high exercise (61 L/min) via a mouthpiece while wearing a nose clip (oral breathing) or via a face mask (oronasal breathing). Each exposure was 5 min in duration. No SRaw effects were noted with low- or moderate exercise rates; however, SRaw was increased 219% compared to baseline at the high exercise rate.

In another study, Bethel et al. (1985) exposed 19 asthmatic adults (16 males, 3 females, ages 22–46 years) to 0 or 0.25 ppm SO_2 for 5 min while performing vigorous exercise (60 L/min). SRaw increased 77% in the 0 ppm group and 134% in the 0.25 ppm group. Nine (7 males, 2 females) of these original 19 subjects then repeated the exposure, with more vigorous exercise (89-90 L/min); SRaw increased 102% in the 0 ppm group and 139% in the 0.25 ppm group.

Fourteen asthmatics (12 male, 2 female, ages 19-50 years) were exposed to 0, 0.5, or 1.0 ppm SO_2 for 10 min during light, medium, or heavy exercise (average ventilation 30, 36, and 43 L/min, respectively) (Gong et al. 1995). The ventilation rates were targeted to bracket a typical adult switching point

from nasal to oronasal breathing. Exposures were con-ducted in a double-walled insulated cubical plexiglass chamber (2.2 m^3). Air was supplied at a rate of 15 air changes/hour with no recirculation. SO_2 was metered into the air supply from a cylinder containing 5% SO_2 in nitrogen; concentration was continuously monitored with a pulsed fluorescent analyzer. At 0.5 ppm SO_2 during light exercise, mild to moderate (subjective ratings on a 1 to 10 scale) respiratory effects were reported by subjects, while at 1.0 ppm and heavy exercise, effects were rated as moderate to severe. Effects included shortness of breath, wheezing, and chest tightness. Both FEV_1 and SRaw showed significant ($p>0.05$) exposure-related effects; however, the exact magnitude is difficult to ascertain from the format of the reported data.

Roger et al. (1985) exposed 28 male asthmatics (ages 19-34) to 0, 0.25, 0.50, or 1.0 ppm SO_2. Each 75-min exposure period included three 10-min periods of moderate treadmill exercise. Exposures were in a random order at approximately the same time of day and day of the week, with at least 1 week between exposures. Exposures were conducted in a 4 x 6 x 3.2 m stainless steel chamber with continuous reconditioning and recirculation of the air. The SO_2 concentrations were continuously monitored with pulsed fluorescent analyzers. There was no significant effect on SRaw after the 0.25 ppm SO_2 exposure. SRaw was increased two- and three-fold after exposures of 0.5 and 1.0 ppm, respectively. Increases were greatest after the first 10 min exercise periods and less after the latter two 10-min periods (with the exception of one subject whose bronchoconstriction increased with increasing exercise and who was unable to complete the protocol). Shortness of breath and chest discomfort were reported ($p<0.001$) after 10 min of 1.0 ppm SO_2 exposure. Wheezing, deep breathing discomfort, and cough were also reported.

Horstman et al. (1986) exposed 27 male asthmatics (ages 18-35 years) to 0, 0.25, 0.50, or 1.0 ppm SO_2 for periods of 10-min, each on separate days. The test chamber and exposure conditions were similar to those described above (Roger et al. 1985). During exposures, subjects breathed normally and performed moderate exercise (42 L/min). Before and 3 min after each exposure SRaw was measured by body plethysmography. Those subjects whose SRaw was not doubled by exposure to 1.0 ppm were exposed to 2.0 ppm SO_2 for 10 min. Concentration-response curves of relative change in SRaw vs. SO_2 concentration were constructed for each subject to determine the concentration of SO_2 producing a 100% increase in SRaw over exercise in clean air. Substantial variation was observed: 25% of subjects experienced a 100% increase in SRaw at <0.5 ppm, 20% of subjects experienced a 100% increase only at concentrations >1.95 ppm. The median concentration for a 100% increase in SRaw was 0.75 ppm.

Horstman et al. (1988) exposed 12 male asthmatics (ages 22-37) to 0 or 1.0 ppm SO_2 for 0, 0.5, 1.0, 2.0, or 5.0 min (in random order on separate days) to determine the shortest duration of exposure sufficient to induce bronchoconstriction significantly greater than that observed by exposure to clean air. The test chamber and exposure conditions were similar to those described

above (Roger et al. 1985). The subjects exercised (40 L/min) on a treadmill during exposure. SRaw and symptom ratings increased with increased exposure duration, with significance ($p<0.025$) being achieved at 2.0 min (121% increase) and 5.0 min (307% increase) exposures. Half of the subjects reported moderate or severe shortness of breath, chest discomfort, and/or wheezing after the 2- or 5-min exposures, and four subjects required bronchodilator therapy.

Sheppard et al. (1983) exposed eight asthmatic adults (4 males, 4 females, ages 22-36 years) to 0.5 ppm SO_2 via mouthpiece for 3 sets of 3-min intervals while hyperventilating. Each exposure period was separated by a 30-min rest period. The exposure protocol was repeated 24-h and 1-week after the initial set of exposures. SRaw was increased 104% after the first 3-min exposure, 35% after the 30-min rest, and 30% after the third exposure. An increase in SRaw of 83% was observed at the 24-hr exposure, and 129% one week later.

Hackney et al. (1984) exposed 17 young adult asthmatics (13 males, 4 females, mean age 25 years) to 0.75 ppm SO_2 for a 3-h period, exercising vigorously (45 L/min) for the first 10-min and resting thereafter. SRaw and symptoms were reported preexposure, immediately post-exercise, and after 1, 2, and 3-h of exposure. On separate occasions, comparable exposures were performed and FEV was measured after 15-min of exposure, in addition to the other tests. The exposure techniques are similar to those of Linn et al. (1985) described above except that relative humidity was 85%. In the exposure without spirometry, SRaw was increased 263% immediately after exercise (10-min into exposure), 200% at 20-min, 34% at 1-hr, 0% at 2-hr and was decreased 12% at 3-hr compared to preexposure values. In the exposure with spirometry, SRaw was increased 322% immediately after exercise (10-min into exposure), 233% at 20-min, 26% at 1-hr, 5% at 2-hr and was decreased 9% at 3-hr compared to preexposure values. FEV_1 was decreased 20% after 15-min of exposure. "Symptom scores" for low- and upper-respiratory irritation and nonrespiratory (headache, fatigue) symptoms were significantly ($p<0.01$) increased after 10-min of exposure, and had returned to pre-exposure values at 1-, 2-, and 3-hr time points. These data suggest that effects peak within 10-min into the exposure and then subside within 1-hr.

Kehrl et al. (1987) exposed ten male asthmatics (ages 25-33 years) to 0 or 1.0 ppm SO_2 while performing 3 sets of 10-min treadmill exercise (41 L/min) separated by 15-min rest periods. The test chamber and exposure conditions were similar to those described above (Roger et al. 1985). SRaw was measured by whole body plethysmography before each exposure and after each exercise. Total mean SRaw was increased 172% after the first exercise, 137% after the second exercise, and 106% after the third exercise. A separate portion of the study involved exposure to SO_2 at 0 or 1.0 ppm for a continuous 30 min period while exercising, with mean SRaw increasing 233% at the end of the 30-min exposure period.

Fourteen asthmatics (10 males, 4 females, ages 20-55 years) were exposed to 0 or 0.5 ppm SO_2 for 30 min while at rest (Jorres and Magnussen 1990). Subjects breathed the test atmosphere through a mouthpiece that was attached to a two-way valve and an air delivery bag. SO_2 concentration was continuously monitored by a fluorescent analyzer. No increase in SRaw was observed and no exposure-related subjective symptoms were noted.

Magnussen et al. (1990) exposed 46 adult asthmatics (21 males, 25 females, ages 16-62 years) to 0 or 0.5 ppm SO_2 for 20 min. During, the first 10-min of the exposure period, the subjects were at rest. The subjects then performed 10-min of isocapnic hyperventilation at a level of 30 L/min. Subjects breathed the test atmosphere through a mouth-piece, and SO_2 concentration was monitored by a fluorescent analyzer. A 45% increase in SRaw was observed after exposure to air, whereas a 163% increase in SRaw was observed after exposure to 0.5 ppm SO_2.

Koenig et al. (1980) exposed nine adolescent asthmatics (7 males, 2 females, ages 14-18 years) to filtered air, 1 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol, or 1 mg/m^3 sodium chloride droplet aerosol alone. Seated subjects breathed the test atmospheres by mouth through a rubber facemask. Exposures lasted 60 min and were divided into 30-min sections with a brief (5 to 7 min) interruption at the end of the first 30 min for functional measurements. Maximal flow at 50 and 75% of expired vital capacity were decreased with exposure to the SO_2-sodium chloride droplet aerosol. The mean change for V_{max75} was -14% after 30 min and -12% after 60 min of exposure. All nine subjects had a decrease after 30 min, and 7 were decreased after 60 min. The mean change for V_{max50} was -8% after 30 min, with effects noted in all 9 subjects. There was no effect after 60 min exposure. No other pulmonary function effects were noted in any exposure group. No subjective symptoms were reported.

Koenig et al. (1983) studied nine adolescent asthmatics (6 males, 3 females, ages 12-16 years). Exposures via mouthpiece were to 0.5 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol, or 1 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol, or 1 mg/m^3 sodium chloride droplet aerosol alone. Exposures were 40-min in duration, which included 30-min at rest followed by 10-min exercising on a treadmill. No effects were noted in the sodium chloride aerosol alone group. FEV_{10} decreased 15% at 0.5 ppm SO_2 and 23% at 1.0 ppm SO_2. Total respiratory resistance increased 47% at 0.5 ppm and 71% at 1.0 ppm and V_{max50} and V_{max75} were decreased 30 and 35%, respectively at 0.5 ppm and 51 and 61%, respectively at 1.0 ppm. Seven of the subjects then similarly inhaled 0.5 ppm SO_2 and 1 mg/m^3 sodium chloride droplet aerosol via a face mask. No pulmonary function effects were noted.

Koenig et al. (1985) studied ten adolescent asthmatics (5 males, 5 females, ages 14-18 years). Exposures were both via mouthpiece or facemask to 0.5 ppm SO_2 and were 50 min in duration, which included 30-min at rest followed by 20-min exercising on a treadmill (43 L/min). After mouthpiece exposures, nasal resistance increased 32%, FEV_1 decreased 24%, and V_{max50} and

V_{max75} were decreased 46 and 56%, respectively. Total respiratory resistance increased 60%. Facemask exposure resulted in an increase in nasal resistance of 30%, a decrease in FEV_1 of 16%, and V_{max50} and V_{max75} were decreased 26%.

2.4. Developmental and Reproductive Toxicitys

Developmental and reproductive data regarding human exposure to SO_2 were not available.

2.5. Genotoxicity

Genotoxicy studies regarding acute human exposure to SO_2 were not available. However, the incidence of chromosomal aberrations and sister chromatid exchanges was increased in lymphocytes from workers at an Indian fertilizer plant who were exposed to an average of 15.9 ppm SO_2 (Yadav and Kaushik 1996) and in workers exposed to 0.13 to 4.57 ppm SO_2 in a Chinese sulfuric acid factory (Meng and Zhang 1990). The significance of these findings is questionable since no confounding exposures were discussed. Exposure of mammalian cells to SO_2 resulted in toxicity, but not mutagenicity (Thompson and Pace 1962).

2.6. Carcinogenicity

No information suggesting an increased cancer incidence from SO_2 exposure in humans was located.

2.7. Summary

Although no specific concentrations were reported, case reports suggest that exposure to apparently high concentrations of SO_2 may cause death via asphyxia secondary to pulmonary edema and irreversible airway obstruction. Epidemiological studies from occupational exposures and ambient air pollution also indicate that the respiratory system is the primary target for SO_2 toxicity. With regard to air pollution, the elderly and chronically ill appear to be more sensitive than healthy young adults; however, attributing the observed toxicity to SO_2 is difficult due to the presence of confounding factors such as smoke, particulates, and other air pollutants. Controlled experimental studies show that mild irritation, bronchoconstriction, and lung function changes are observed after exposure to low concentrations of SO_2. Asthmatics are more sensitive than healthy people to the effects of SO_2 and healthy elderly subjects may be more sensitive than healthy young people, but less sensitive than asthmatics. Exercise exacerbates the respiratory effects of SO_2 in both healthy

and asthmatic subjects. Data also suggest that cold air, dry air, the presence of other parti-culates and oral, rather than nasal, breathing may enhance the toxic effects of SO_2. The body of experimental data suggests that 0.25 ppm may be a threshold for bronchoconstriction in asthmatics, and that a significant proportion of asthmatics will experience bronchoconstriction requiring medication or cessation of activity at 0.4-0.5 ppm. Data also suggest that a maximum response is obtained during the first 10-min of exposure and that continued or repeated exposures do not enhance the bronchoconstrictive response. Occupational exposures suggest that SO_2 may be clastogenic; however, because confounding factors, such as exposure to other chemicals, were not considered, no definitive conclusions can be made regarding genotoxicity. No information concerning reproductive/developmental toxicity or carcinogenicity was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

Hilado and Machado (1977) exposed groups of four Swiss-albino mice to nominal SO_2 concentrations (no analytical data were presented) of 1190 to 14,286 ppm and monitored time to first sign of incapacitation, time to convulsions, and time to death. Animals were exposed in a 4.2 liter, polymethyl methacrylate chamber. The SO_2 was injected with a 60 ml syringe which had been filled from a gas supply cylinder. Time to first sign of incapacitation was under 3 min for 3500 to 14,300 ppm SO_2 and increased to 6 min as SO_2 concentration was decreased to 1100 ppm. Average time to staggering increased from 1 to 6 min and average time to convulsions increased from 2 to 8 min as SO_2 concentration decreased from 14,300 to 3500 ppm. Average time to death increased from 3 to 8 min as SO_2 concentration decreased from 14,300 to 4800 ppm. There were no deaths in animals exposed to 1190 ppm SO_2 for 30 min.

Bitron and Aharonson (1978) exposed groups of 14 male albino mice (21±1 g, 1 month old) to 900 ppm SO_2 for 25-640 min (9 exposure groups), 1400 ppm SO_2 for 15 to 180 min (13 exposure groups), or 1900 ppm SO_2 for 10 to 75 min (9 exposure groups). Median lethal exposure time (Lt_{50}) for each concentration was calculated to be 200 min, 38 min, and 10 min for the 900, 1400, and 1900 ppm SO_2 concentrations, respectively.

3.1.2. Rats

Groups of eight male CD outbred rats (150 g) were exposed to varying concentrations of SO_2 in a portable stainless-steel chamber for 4 h and observed for 14 days (Cohen et al. 1973). The test atmospheres were maintained

by metering SO_2 directly into the incoming air and were monitored at frequent intervals by an iodometric procedure. The actual SO_2 concentrations were maintained within 5% throughout exposures. Data are summarized in Table 9-5. An LC_{50} of 1057 ppm and $BMCL_{05}$ of 573 ppm were calculated (by the author of this document) using the Litchfield and Wilcoxon method.

Male Swiss Albino rats (250-300 g) were exposed to 0 (51 rats) or 0.87 ppm SO_2 (50 rats) for 24 h (Baskurt 1988). The experimental atmosphere was obtained by continuous mixing of filtered ambient air at a flow rate of 30 L/min with SO_2 gas at a constant rate. Air samples were obtained from the exposure chamber with an impinger and the SO_2 concentration was measured by a hydrogen peroxide-acid titration method. Hematocrit values were increased ($p<0.005$) in the SO_2 exposed group compared to controls (43.55±0.41% vs 41.97±0.35%). Sulfhemoglobin values were also increased ($p<0.05$) in the SO_2 exposed group compared to controls (0.6±0.08% vs. 0.08±0.02%).

3.2. Nonlethal Toxicity

3.2.1. Rats

In another study, Langley-Evans et al. (1997) examined the effect of a low protein maternal diet on later susceptibility to pulmonary injury from SO_2 exposure. Rats were fed diets containing 180 g casein/kg diet (control diet), or 120, 90, or 60 g casein/kg diet (experimental diets). After acclimation to the diets for 14 days, the rats were mated and maintained on the same diet until parturition. Within 12 h of parturition, all dams were transferred to standard diets and the same diet was used to wean the pups. At 7 weeks of age, groups of 4 to 16 male rats were exposed to 0 or 0.11 ppm SO_2, 5 h/day for 28 days. The exposure chamber had a volume of 0.5 m^3 and a flow rate of 7 L/min. The test atmosphere was produced by mixing the contents of SO_2 from cylinders with compressed air. The SO_2 concentration was monitored with an "industrial monitor. Rats exposed to 90 or 60 g/casein/kg diet in utero exhibited greater pulmonary injury, as evidenced by broncho-alveolar lavage, than those exposed to control diet in utero. Maternal diet or SO_2 exposure influenced liver GSH concentrations. GSH was lower in livers of rats exposed to the 120 g casein/kg maternal diet than in the 180 g/kg diet controls. Rats exposed to 60 g/kg diets had higher hepatic GSH levels than the 120 g/kg rats. SO_2 exposure had no effect on hepatic GSH in the 180 or 90 g/kg diet group. In the 60 g/kg diet group, hepatic GSH was lowered by SO_2 exposure. Conversely, rats exposed to the 120 g/kg diet had greater hepatic GSH in response to SO_2 exposure.

TABLE 9-5 Mortality in Rats Exposed to Sulfur Dioxide for 4 Hours

SO_2 Concentration (ppm)	Mortality
224	0/8
593	0/8
965	3/8
1168	5/8
1319	8/8

3.2.2. Guinea Pigs

Amdur (1959) exposed groups of 10 to 30 guinea pigs to approximately 2.6, 20, 100, 200, or 750 ppm SO_2 in a dynamic exposure chamber for 1 h. (SO_2 concentrations are approximations from a graph). The SO_2 atmosphere was generated by metering 1% SO_2 in air from a cylinder into the main air stream. The air sample was collected in hydrogen-peroxide sulfuric acid reagent and the increase in conductivity was measured. Increased airway resistance was observed at all exposure concentrations. Data are summarized in Table 9-6.

Amdur (1959) also exposed a group of six guinea pigs to 24 ppm SO_2 for 3 h. Increased airway resistance progressed from 20% at the end of the first hour to 86% at the end of the third hour. Three hours after exposure, the resistance had returned to control levels.

3.2.3. Rabbits

Groups of 21 rabbits were exposed to 0 or 0.57 ppm SO_2 for 10 min (Islam and Oberbarnscheidt 1994). Respiratory flow was slightly decreased and respiratory resistance was slightly increased in SO_2 exposed animals compared to controls. There were no effects on tidal volume or dynamic compliance. The magnitude of the changes was difficult to assess since all results were presented graphically.

TABLE 9-6 Increased Airway Resistance in Guinea Pigs Exposed to Sulfur Dioxide for 1 Hour

SO_2 Concentration	Number of Animals	% Increase in Airway Resistance[a]
2.6 ppm	16	20%
20 ppm	18	25%
100 ppm	10	70%
200 ppm	30	140%
750 ppm	13	300%

[a]Approximate values estimated from graph.

3.2.4. Dogs

Anesthetized, intubated mongrel dogs (20-30 kg) were exposed to 0 (3 dogs) or 500 ppm (7 dogs) SO_2 for 1 h (Hulbert et al. 1989). The SO_2 atmosphere was generated by mixing pure SO_2 with air using a Matheson dyna blender and flow controller. Four SO_2-exposed dogs were sacrificed, in pairs, at 1 and 6 h after exposure, and their tracheas removed and fixed for microscopic examination. Three dogs were sacrificed immediately after the SO_2 exposure, their tracheas removed, epithelium isolated and maintained *in vitro* (in buffer) before being fixed for microscopic examination 1 and 6 h post-exposure. Tracheal epithelial damage was not observed in any controls, but was observed in all dogs exposed to SO_2. Findings were similar whether tissues were obtained fresh or had been maintained *in vitro*. At 1 h, injury was difficult to assess because the tracheal surfaces were covered with exfoliated cells or were in total disarray. After 6 h, the lesions were well defined and large flattened cells covered the basement membranes where mucosal cells had exfoliated.

In another study, Jackson and Eady (1988) exposed 8 anesthetized and intubated beagle dogs of both sexes to 400 ppm SO_2 for 2 h. Each dog was artificially respired with the SO_2-air mixture (12 mL/kg, 20 breaths/min) which was analyzed with a Drager gas sampling system. Exposure to SO_2 caused an immediate increase in lung reactivity to histamine aerosol. The lungs were most reactive immediately after exposure and lung reactivity had returned to control levels 2 h after exposure. The total number of cells obtained from BAL fluid increased after SO_2 exposure; initially, the increase was due to an increase in epithelial cells (0.25 and 1 h) and later by neutrophils (1, 2, 3, and 4 h). No changes were observed in lymphocyte, macrophage, eosinophils, goblet cells, or mast cells in lavage fluid.

3.3. Developmental and Reproductive Toxicity

Murray et al. (1979) exposed groups of 40 and 32 CF-1 mice to 0 and 23.9 ppm SO_2, respectively, during days 6 through 15 of gestation, and groups of 20 New Zealand white rabbits to 0 or 70 ppm SO_2 from days 6 through 18 of gestation. Animals were exposed under dynamic airflow conditions in stainless steel and glass Rochester chambers with a 4.3 m^3 volume. The chamber airflow was 800 L/min and the SO_2 atmosphere was generated by metering SO_2 at known rates through rotometers into the airstream being drawn into the chamber. Concentrations were analyzed by infrared spectrometry. A marginal, although statistically significant ($p<0.05$), decrease in mouse fetal body weight was noted (1.05±0.11 g for controls vs 1.00±0.08 g for test animals). No other treatment-related, biologically significant effects were noted in either mice or rabbits.

Pregnant CD-1 albino mice were exposed to 0, 32, 65, 125, or 250 ppm SO_2 from days 7 to 17 of gestation (Singh 1982). The exposure duration for each day was not reported. Exposures were conducted in plexiglass chambers with a total gas flow rate of 450 mL/min. The SO_2 concentration was monitored at each chamber inlet via infrared spectrometry. The mice were sacrificed on day 18 of gestation. No signs of maternal toxicity were noted during the exposure period and no treatment related developmental effects were noted. In a similar study, Singh (1989) exposed pregnant CD-1 mice to 0, 32, or 65 ppm SO_2 from days 7 to 18 of gestation. Again, the duration of exposure each day was not reported. Dams were allowed to deliver. Increased time for righting reflex was observed for pups exposed to both SO_2 concentrations compared to controls on postnatal day 1. Increased negative geotaxis was noted in exposed offspring on postnatal day 10. Birth weights of 65 ppm pups were 89% of controls. No other effects were noted.

Petruzzi et al. (1996) exposed adult male and female CD-1 mice to 0, 5, 12, or 30 ppm SO_2 for 24 days, from 9 days before the formation of breeding pairs through pregnancy day 12-14. Exposures were near-continuous, covering approximately 80% of the total time and were conducted in stainless steel exposure chambers with a hatch glass in the front door. SO_2 was delivered from aluminum bottles and differing concentrations were obtained by varying the flow and gas pressure from the bottles. SO_2 concentrations were monitored with an ultra-violet SO_2 analyzer. Actual concentrations were within 10% of target concentrations. Within 1 h of the start of exposure, increased rearing and social interactions were observed and were more evident in males than in females. Observations on days 3, 6, and 9 showed dose-dependent decreased grooming and increased digging. Food and water consumption decreased in treated animals and increased in controls after the formation of breeding pairs. No effects were noted for reproductive performance or neurobehavioral development of the offspring. In another report from the same laboratory, the male CD-1 mice prenatally exposed to 0, 5, 12, or 30 ppm SO_2 from the Petruzzi et al. (1996) study were examined for changes in behavior as adults (Fiore et al. 1998). At adulthood, following a 4 week isolation period, they underwent a 20 min aggressive encounter with a CD-1 male opponent. Dose-related increases were noted for body sniffing and nonsocial activities, whereas freezing, tail rattling, and defensive behaviors were decreased.

3.4. Genotoxicity

Genotoxic studies regarding animal exposure to SO_2 were not available. However, high bisulfite concentrations formed from SO_2 at nonphysiological pH were positive in assays with phage T_4 (Summers and Drake 1971), phage T (Hayatsu and Miura 1970), *E. coli* (Mukai et al. 1970), and *S. cerevisiae* (Dorange and Dupuy 1972). The biological significance of this mutagenic response is questionable as the effect may be due to the pH shift.

3.5. Carcinogenicity

Peacock and Spence (1967) exposed mice to 0 (41 males, 39 females) or 500 ppm (35 males, 30 females) SO_2 5 min/day, 5 days/week for 2 years. Data suggested possible treatment-related lung tumors; however, since only one concentration was tested these data are of limited use. In females, the incidence of lung adenomas and carcinomas was 13/30 in treated animals and 5/30 in controls. In males, the incidence of lung adenomas and carcinomas was 15/28 in treated animals and 11/35 in controls.

3.6. Summary

Well-conducted animal lethality studies are limited to a mouse study defining median lethal time to death (Lt_{50}) and a rat study yielding a 4-h LC_{50} of 1057 ppm and a $BMCL_{05}$ of 573 ppm SO_2. Non-lethal toxicity studies are more abundant and show that, as in humans, relatively low concentrations of SO_2 induce bronchoconstriction and associated increase in airway resistance in a number of animal species. Respiratory tract pathology is observed at higher SO_2 concentrations. SO_2 was generally not a developmental or reproductive toxicant. Genotoxic studies regarding exposure to SO_2 are equivocal and the carcinogenicity study, although suggesting a possible increase in pulmonary tumors, is of poor quality and thus of limited use.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Although the main effects of SO_2 are on the respiratory tract, much of an inhaled dose may be transferred into systemic circulation. During inhalation, SO_2 may react with water in the respiratory tract to form sulfurous acid or may be oxidized to form sulfur trioxide. Sulfur trioxide reacts rapidly with water to form sulfuric acid. Sulfurous acid dissociates to sulfite and bisulfate ions, which are in chemical equilibrium. Bisulfite ions react by sulfonation, autooxidation, and by addition to cytosine. Most inhaled SO_2 is detoxified in the liver by the sulfite-oxidase pathway, which forms S-sulfonates that can be found in the plasma and sulfates that are excreted in the urine. The S-sulfonates are long-lived and supply the circulation with bisulfite that may reach many tissues. In rabbits exposed to 10 ppm SO_2, the half-life for clearance of plasma protein S-sulfonates was 4.1 days. Some circulating S-sulfonates may decompose to SO_2 which is exhaled (WHO 1984).

4.2. Mechanism of Toxicity

SO_2 is a water-soluble irritant which causes upper-airway irritation and may induce increased airway resistance via reflex bronchoconstriction. The exact mechanism responsible for SO_2 -induced bronchoconstriction is not known. However, the rapid onset and reversibility of SO_2-induced bronchoconstriction observed in asthmatics is likely due to decreased airway caliber caused by contraction of airway smooth muscle. Constriction of airway smooth muscle in response to environmental stimuli can be induced by intrinsic chemical and/or physical stimuli, acting via neural and/or humoral pathways. SO_2 may act either directly on smooth muscle or may cause the release of chemical mediators from the tissue, especially the release of histamine from mast cells. Other potential pharmacological mediators of SO_2 -induced bronchoconstriction are leukotrienes and prostaglandin F2-alpha, both of which are released in the airways and may cause smooth muscle contraction (Horstman and Folinsbee 1989).

4.3. Temporal Extrapolation

The impact of exposure duration on the magnitude of low-concentration SO_2-induced bronchoconstriction in asthmatics and healthy humans appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO_2 for 3-h exhibited increases in SRaw of 322% 10-min into the exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, and 5% 2-h into the exposure. At the end of the 3-h exposure period, SRaw was decreased 12%. These, and other data presented in Tables 4 and 5, suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Furthermore, there is no evidence that any other effect is relevant at low sulfur dioxide concentrations; the respiratory response is a first-level, sensitive response to SO_2 exposure. This phenomenon is also observed with healthy humans. For example, maximum pulmonary flow resistance was observed within 5 to 10 min when healthy adult males were exposed to 5 or 13 ppm SO_2 for up to 30 min (Frank et al. 1962) or 4-6 or 14-17 ppm SO_2 for up to 30 min (Frank et al. 1964). Therefore, time scaling will not be utilized for AEGL values for SO_2.

Data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal end point is obtained within 10 min. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relation-ship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 may be applied to extrapolate to shorter time periods, and n of 1 may be used for ex-

trapolation to the 8-h time period to provide AEGL values that would be protective of human health (NRC 2001).

4.4. Concurrent Exposure

As previously stated, the relationship between SO_2 exposure in polluted air and human health effects is confounded by the presence of other air pollutants, especially nitrogen oxides, ozone, smoke and particulate matter. Several controlled human studies have examined the health effects resulting from concurrent exposure to SO_2 and other chemicals. As previously described, inert sodium chloride aerosols had no added effect when administered to healthy subjects in conjunction with SO_2 (Frank et al. 1964; Rondinelli et al. 1987). In human asthmatics, Jorres and Magnussen (1990) demonstrated an amplified response to SO_2 after a 30 min exposure to 0.75 ppm NO_2. Data from a study by Rigas et al. (1997) suggests that exposure to SO_2 may enhance absorption of ozone in the lungs of healthy adult males. In asthmatic subjects, exposure to a combination of 400 ppb NO_2 + 200 ppb SO_2 enhanced the airway response to an inhaled allergen (*Dermatophagoides pteronyssinus*) (Rusznak et al. 1996).

Amdur (1959) examined the effect of concurrent exposure of SO_2 and sulfuric acid mist or inert sodium chloride aerosol on guinea pigs and found that particle size was a factor in the magnitude of response. When animals were exposed to 0.8μ sulfuric acid mist particles and SO_2, a synergistic response was observed with regard to bronchoconstriction; however, when 2.5μ sulfuric acid particles were administered with SO_2, no synergism was observed. The response was actually slightly less than the response to SO_2 alone. When sodium chloride aerosols of 0.04μ and 2.5μ were administered in combination with SO_2, a similar response was noted with regard to bronchoconstriction; potentiation was observed with the smaller particles but not by the larger particles.

5. RATIONALE AND AEGL-1

5.1. Human Data Relevant to AEGL-1

Upper respiratory and throat irritation were noted in healthy males (Amdur et al. 1953; Frank et al. 1962) exposed to 5 ppm SO_2 for 10-30 min. Throat and nasal irritation were reported in healthy, exercising subjects exposed to 2 or 4 ppm SO_2 for 20 min (Sandstrom et al. 1988). Upper respiratory and ocular irritation were noted in healthy adults exposed to 1 ppm SO_2 for 4 h with intermittent exercise (Kulle et al. 1984). No treatment-related effects were noted in exercising asthmatics exposed to 0.2 ppm for 5 min (Linn et al. 1983b), 0.25 ppm for 10-40 min (Schacter et al. 1984), 0.25 ppm for 75 min (Roger et al. 1985), or 0.5 ppm for 10-40 min (Schacter et al. 1984). An increase in

SRaw of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 min (Bethel et al. 1985).

5.2. Animal Data Relevant to AEGL-1

Amdur (1959) observed a 20% and 25% increase in airway resistance in guinea pigs exposed to 2.6 and 20 ppm SO_2, respectively, for 1 h.

5.3. Derivation of AEGL-1

A weight of evidence approach utilizing the human asthmatic data will be utilized to derive AEGL-1 values for SO_2. The body of experimental data suggests that 0.20 ppm may be a NOEL for bronchoconstriction in exercising asthmatics, based on the fact that no treatment-related effects were noted in asthmatics exposed to 0.2 ppm for 5 min (Linn et al. 1983b), 0.25 ppm for 10-40 min (Schacter et al. 1984), 0.25 ppm for 75 min (Roger et al. 1985), 0.5 ppm for 10-40 min (Schacter et al. 1984), or 0.5 ppm for 30 min (Jorres and Magnussen 1990). However, an increase in SRaw of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 min (Bethel et al. 1985); the increase in SRaw in this study, but not in the other studies, may be attributed to the lower relative humidity (36%) in the Bethel et al. (1985) compared to the other studies (70-85%). No uncertainty factors will be applied because the weight of evidence approach utilized studies from a sensitive human population, that of exercising asthmatics. The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO_2 for 3-h exhibited increases in SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-h into the exposure, and a decrease of 12% at the end of the 3-h exposure period. These, and other data presented in Tables 3 and 4, suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-1 values for SO_2 will be held constant across all time points. The AEGL-1 values for SO_2 are presented in Table 9-7, and the calculations for these AEGL-1 values are presented in Appendix A.

Exposure to these AEGL-1 values are expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-1 for asthmatic individuals.

TABLE 9-7 AEGL-1 Values for Sulfur Dioxide

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)

6. RATIONALE AND AEGL-2

6.1. Human Data Relevant to AEGL-2

A 72% increase in pulmonary flow resistance accompanied by cough, irritation, and increased salivation was observed in healthy males exposed to 13 ppm SO_2 for 10 min (Frank et al. 1962). A 65% increase in pulmonary flow resistance, cough, and chest irritation were observed in healthy male mouth-breathers exposed to 28 ppm SO_2 for 10 min (Frank et al. 1962). Asthmatics developed increased airway resistance of 5- to 322% after exposure to 0.75 ppm SO_2 for up to 3 h (Hackney et al. 1984). An increase in SRaw of 150%, decrease in FEF of 22%, and decrease in FEV_1 of 8% were observed in exercising asthmatics exposed to 0.75 ppm SO_2 for 10-40 min (Schacter et al. 1984).

6.2. Animal Data Relevant to AEGL-2

Amdur (1959) observed a 70% increase in airway resistance in guinea pigs exposed to 100 ppm SO_2 for 1 h and an increase of 85% in guinea pigs exposed to 24 ppm for 3 h. Tracheal pathology was observed in anesthetized dogs exposed to 500 ppm SO_2 for 1 h.

6.3. Derivation of AEGL-2

A weight of evidence approach utilizing the human asthmatic data will be utilized to derive AEGL-2 values for SO_2. Data suggest that 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-min to 3-h (Hackney et al. 1984; Schacter et al. 1984). No uncertainty factors will be applied because the weight of evidence approach utilized studies from a sensitive human population, that of exercising asthmatics. The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to 0.75 ppm SO_2 for 3-h exhibited increases SRaw of 322% 10-min into exposure, 233% 20-min into the exposure, 26% 1-hr into the exposure, 5% 2-h into the exposure, and a decrease of 12% at the end of the 3-h exposure period. These, and other data presented in Tables 3 and 4, suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-2 values for SO_2 were held constant across all time points. The AEGL-2 values for SO_2 are presented in Table 9-8, and the calculations for these AEGL-2 values are presented in Appendix A.

Exposure to these AEGL-2 values are expected to have no effect in healthy individuals, but are consistent with the definition of AEGL-2 for asthmatic individuals.

TABLE 9-8 AEGL-2 Values for Sulfur Dioxide

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were relevant to establishing the AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

No deaths were observed in mice exposed to 1190 ppm (nominal concentration) SO_2 for 30 min (Hilado and Machado 1977). No deaths occurred in rats exposed to 593 ppm SO_2 for 4 h; an LC_{50} of 1057 ppm; and an $BMCL_{05}$ of 573 ppm were also calculated from the same study (Cohen et al. 1973).

7.3. Derivation of AEGL-3

The AEGL-3 values will be based on a calculated $BMLC_{05}$ in rats exposed to SO_2 for 4-h (573 ppm) (Cohen et al. 1973). An uncertainty factor of 10 will be applied for intraspecies extrapolation due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability; this factor of 3 was considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 h (Amdur 1959), in dogs exposed to 400 ppm SO_2 for 2 h (Jackson and Eady 1988), or in rats exposed to 593 ppm for 4-h (Cohen et al. 1973). Furthermore, a median lethal exposure time (Lt_{50}) of 200 min was reported for mice exposed to 900 ppm SO_2 (Bitron and Aharonson 1978), and three of eight rats died when exposed to 965 ppm for 240 min (Cohen et al. 1973), suggesting limited interspecies variability. Data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal end point is obtained within 10 min. Therefore, time scaling will be utilized in the derivation of AEGL-3 values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of n for sulfur dioxide. Therefore, an n of 3 was applied to extrapolate to the 1-h time period, and n of 1 was used for extrapolation to the 8-h time period to provide AEGL values that would be protective of human health (NRC 2001). The 1-h

AEGL-3 value was also adopted as 10-min and 30-min values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods. The AEGL-3 values for SO_2 are presented in Table 9-9, and the calculations for these AEGL-3 values are presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 9-10. A weight-of-evidence approach from studies in exercising asthmatics was used to derive AEGL-1 (NOEL for bronchoconstriction) and AEGL-2 (moderate respiratory effects) values. A calculated $BMCL_{05}$ in rats was used as the basis for AEGL-3.

8.2. Other Exposure Criteria

Standards and guidance levels for workplace and community exposures for sulfur dioxide are listed in Table 9-11. In addition to the standards listed in Table 9-11, air quality standards have also been developed for SO_2. The National Ambient Air Quality Standard is 0.14 ppm, with a significant harm level of 1.0 ppm for a 1-h average (64 Fed. Reg. 42530[1999]).

8.3. Data Adequacy and Research Needs

The data base for human exposure for effects defined by AEGL-1 and AEGL-2 is relatively good as controlled chamber studies with both asthmatic and otherwise healthy volunteers are available. These studies, when considered together, provide good threshold-response information and are appropriate for derivation of AEGL-1 and AEGL-2 values. Case reports of accidental human exposure to sulfur dioxide leading to effects consistent with the definitions of AEGL-3 did not include concentration or duration parameters adequate for derivation of values. Studies sufficient for derivation of AEGL-3 values were limited to animal data.

TABLE 9-9 AEGL-3 Values for Sulfur Dioxide

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	19 ppm (49 mg/m^3)	9.6 ppm (25 mg/m^3)

TABLE 9-10 Summary of AEGL Values for Sulfur Dioxide

Classification	0-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)	0.20 ppm (0.52 mg/m^3)
AEGL-2 (Disabling)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)	0.75 ppm (1.95 mg/m^3)
AEGL-3 (Lethality)	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	30 ppm (78 mg/m^3)	19 ppm (49 mg/m^3)	9.6 ppm (25 mg/m^3)

TABLE 9-11 Extant Standards and Guidelines for Sulfur Dioxide

Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm
AEGL-2	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm
AEGL-3	30 ppm	30 ppm	30 ppm	19 ppm	9.6 ppm
ERPG-1(AIHA)[a]	0.3 ppm				
ERPG-2 (AIHA)[a]	3 ppm				
ERPG-3 (AIHA)[a]	15 ppm				
EEGL(NRC)[b]	30 ppm (10 min)	20 ppm (30 min)	10 ppm (60 min)		5 ppm (24 hr)
IDLH (NIOSH)[c]	100 ppm				
REL-TWA (NIOSH)[d]					2 ppm
PEL-TWA(OSHA)[e]					5 ppm
TLV-TWA(ACGIH)[f]					2 ppm
REL-STEL (NIOSH)[g]	5 ppm				
TLV-STEL(ACGIH)[h]	5 ppm				
MAK (Germany)[i]					0.5 ppm
MAC(The Netherlands)[j]					2 ppm
OELV- LLV (Sweden)[k]					2 ppm
OELV- CLV (Sweden)[k]	5 ppm				

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2002).

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for SO_2 is based on increased airway resistance in exercising asthmatics.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for SO_2 is based on bronchoconstriction requiring bronchodilation therapy in asthmatics exposed to 5 ppm for 10-min.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for SO_2 is based on potential induction of bronchospasm in asmatic or sensitive individuals that may trigger cardiopulmonary events in individuals with pre-existing heart disease. As of 2000, the ERPG values for SO_2 are under ballot review and consideration.

[b]EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC 1984) The EEGLs for SO_2 are based on concentrations at which people can continue to function in an emergency situation and be unlikely to suffer irreversible respiratory effects. They are intended for specific populations (military and space personnel) and may not be applicable to the general population.

[c]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. The IDLH for SO_2 is based on acute inhalation toxicity data in humans.

[d]REL-TWA (Recommended Exposure Limits, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA.

[e]PEL-TWA (Permissible Exposure Limits - Time Weighted Average, Occupational Health and Safety Administration) (29 CFR 1910.1000[1998]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[f]TLV-TWA (Threshold Limit Value - Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) 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. The value for SO_2 is based on irritation.

[g]REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH TLV-STEL.

[h]TLV-STEL (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Short Term Exposure Limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003). The value for SO_2 is based on irritation.

[i]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration] German Research Association) (DFG 2002) is defined analogous to the ACGIH-TLV-TWA.

[j]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.

[k]OELV -LLV(Occupational Exposure Limit Value-Level Limit Value).

[l]OELV -CLV(Occupational Exposure Limit Value-Ceiling Limit Value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level limit value (one working day) or a ceiling limit value (15 min or some other reference time period), and short time value (A recommended value consisting of a time-weighted average for exposure during a reference period of 15 min).

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APPENDIX A

Time-Scaling Calculations for Sulfur Dioxide

Derivation of AEGL-1

Key Study: Weight-of -evidence approach suggests 0.20 ppm is NOEL for bronchoconstriction in exercising asthmatics (see table below)

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 ºC, 85% RH, exercise 48 L/min	None	Linn et al. 1983b
0.25 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984
0.25 ppm	5 min	19 9	23 ºC, 36% RH, exercise 60 L/min	SRaw ↑134%	Bethel et al. 1985
			23 ºC, 36% RH, exercise 80-90 L/min	SRaw ↑139%	
0.25 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min intermittent	None	Roger et al. 1985
0.4 ppm	5 min	23	23 ºC, 85% RH, exercise 48 L/min	SRaw ↑69% $V_{max25-75}$ ↓10%	Linn et al. 1983b
0.5 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984

Toxicity end point: NOEL for bronchoconstriction in exercising asthmatics

Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-1 values for SO_2 will be held constant across all time points.

Uncertainty factors: None: subjects were exercising asthmatics
10-min, 30-min, 1-h, 4-h, and 8-h AEGL-1 = 0.20 ppm

Derivation of AEGL-2

Key study: Weight-of -evidence approach suggests 0.75 ppm induces moderate respiratory response in exercising asthmatics for exposure durations of 10-min to 3-h ppm (see table below)

Toxicity end point:	Moderate, but reversible, respiratory effects in exercising asthmatics
Scaling:	Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-2 values for SO_2 were held constant across all time points.
Uncertainty factors:	None: subjects were exercising asthmatics 10-min, 30-min, 1-h., 4-h, and 8-h AEGL-2 = 0.75 ppm

0.75 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV_1 ↓8%	Schacter et al. 1984
0.75 ppm	3 h	17	22 ºC, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV_1 : ↓20% (at 15-min)	Hackney et al. 1984
1.0 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV_1 ↓14%	Schacter et al. 1984
1.0 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al. 1985
1.0 ppm	30 min	10	26 ºC, 70% RH, exercise 41 L/min (3-10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al. 1987
1.0 ppm	30 min	10	26 ºC, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al. 1987
1.0 ppm	1 min 3 min 5 min	8	22 ºC, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al. 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 ºC, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al. 1988

Derivation of AEGL-3

Key study:	Cohen et al. 1973
Toxicity end point:	$BMCL_{05}$ in rats exposed for 4 h (573 ppm)
Scaling:	$C^3 \times t = k$ $(573\ ppm)^3 \times 4\ h = 752530068\ ppm \cdot h$ $C^1 \times t = k$ $(573\ ppm)^1 \times 4\ hr = 2292\ ppm \cdot h$
Uncertainty factors:	10 for intraspecies variability 3 for interspecies variability
10-min AEGL-3	1-h AEGL-3 value adopted as 10-min value because asthmatic humans are highly sensitive to sulfur dioxide at short time periods
30-min AEGL-3	1-h AEGL-3 value adopted as 30-min value because asthmatic humans are highly sensitive to sulfur dioxide at short time periods
1-h AEGL-3	$C^3 \times 1\ h = 752530068\ ppm \cdot h$ $C^3 = 752530068\ ppm$ $C = 909$ 1-h AEGL-3 = 909 ppm/30 = 30 ppm
4-h AEGL-3	4-h AEGL-3 = 573 ppm/30 = 19 ppm
8-h AEGL-3	$C^1 \times 8\ hr = 2292\ ppm \cdot hr$ $C^1 = 287\ ppm$ $C = 287$ 8-h AEGL-3 = 287 ppm/30 = 9.6 ppm

APPENDIX B

Derivation Summary of AEGLs for Sulfur Dioxide

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm

Weight-of -evidence approach suggests 0.20 ppm is NOEL for bronchoconstriction in exercising asthmatics

Time Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-1 values for SO_2 will be held constant across all time points.

Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.

Weight of Evidence for AEGL-1

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 ºC, 85% RH, exercise 48 L/min	None	Linn et al. 1983b
0.25 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984
0.25 ppm	5 min	19 9	23 ºC, 36% RH, exercise 60 L/min 23 ºC, 36% RH, exercise 80-90 L/min	SRaw ↑134% SRaw ↑139%	Bethel et al. 1985
0.25 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min intermittent	None	Roger et al. 1985
0.4 ppm	5 min	23	23 ºC, 85% RH, exercise 48 L/min	SRaw ↑69% $V_{max25-75}$ ↓10%	Linn et al. 1983b
0.5 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	None	Schacter et al. 1984

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm

Weight-of -evidence approach suggests 0.75 ppm induced moderate bronchoconstriction in exercising asthmatics.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm

Time Scaling: The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-min and increases minimally or resolves beyond 10-min of exposure. Therefore, AEGL-2 values for SO_2 were held constant across all time points.

Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.

Weight of Evidence for AEGL-2

0.75 ppm	3 h	17	22 ºC, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV_1 : ↓20% (at 15-min)	Hackney et al. 1984
0.75 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV_1 ↓8%	Schacter et al. 1984
1.0 ppm	10-40 min	10	23 ºC, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV_1 ↓14%	Schacter et al. 1984
1.0 ppm	75 min	28	26 ºC, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al. 1985
1.0 ppm	30 min	10	26 ºC, 70% RH, exercise 41 L/min (3- 10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al. 1987
1.0 ppm	30 min	10	26 ºC, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al. 1987
1.0 ppm	1 min 3 min 5 min	8	22 ºC, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al. 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 ºC, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al. 1988

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
30 ppm	30 ppm	30 ppm	19 ppm	9.6 ppm

Reference: Cohen, H.J., R.T. Drew, J.L. Johnson, and K.V. Rajagopalan. 1973. Molecular basis of the biological function of molybdenum: The relationship between sulfite oxidase and the acute toxicity of bisulfite and SO_2. Proc. Natl. Acad. Sci. USA 70(12):3655-3659.

Test Species/Strain/Sex/Number: CD outbred rats/8 males/concentration.

Exposure Route/Concentrations/Durations: Rats/Inhalation: 224, 593, 965, 1168, or 1319 ppm/4 h ($BMCL_{05}$ of 573 ppm, was determinant for AEGL-3).

End Point/Concentration/Rationale: $BMCL_{05}$/ 573 ppm/ threshold for death for 4 h exposure in rats.

Effects: Concentration:	Mortality
224 ppm	0/8
593 ppm	0/8
965 ppm	3/8
1168 ppm	5/8
1319 ppm	8/8

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Intraspecies = 10: due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans.
Interspecies = 3: considered sufficient because no deaths were reported in guinea pigs exposed to 750 ppm SO_2 for 1 h (Amdur 1959), in dogs exposed to 400 ppm SO_2 for 2 h (Jackson and Eady 1988), or in rats exposed to 593 ppm for 4-h (Cohen et al. 1973). Furthermore, a median lethal exposure time (Lt_{50}) of 200 min was reported for mice exposed to 900 ppm SO_2 (Bitron and Aharonson 1978) and three of eight rats died when exposed to 965 ppm for 240 min (Cohen et al. 1973), suggesting limited interspecies variability.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: Data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal end point is obtained within 10 min. Therefore, time scaling was utilized in the derivation of AEGL-3 values. An n of 3 was applied to extrapolate to the 1-h time period, and n of 1 was used for extrapolation to the 8-h time period to provide AEGL values that would be protective of human health (NRC 2001). The 1-h AEGL-3 value was also adopted as 10-min and 30-min values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods.

Data adequacy: Well-conducted study with appropriate end point for AEGL-3.

APPENDIX C

Category Plots for Sulfur Dioxide

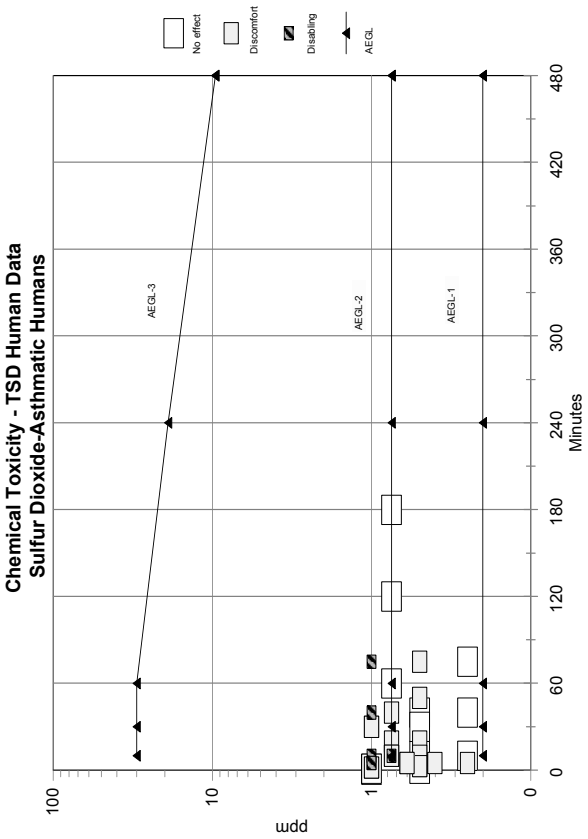

FIGURE C-1 Category plots for sulfur dioxide for asthmatic humans.

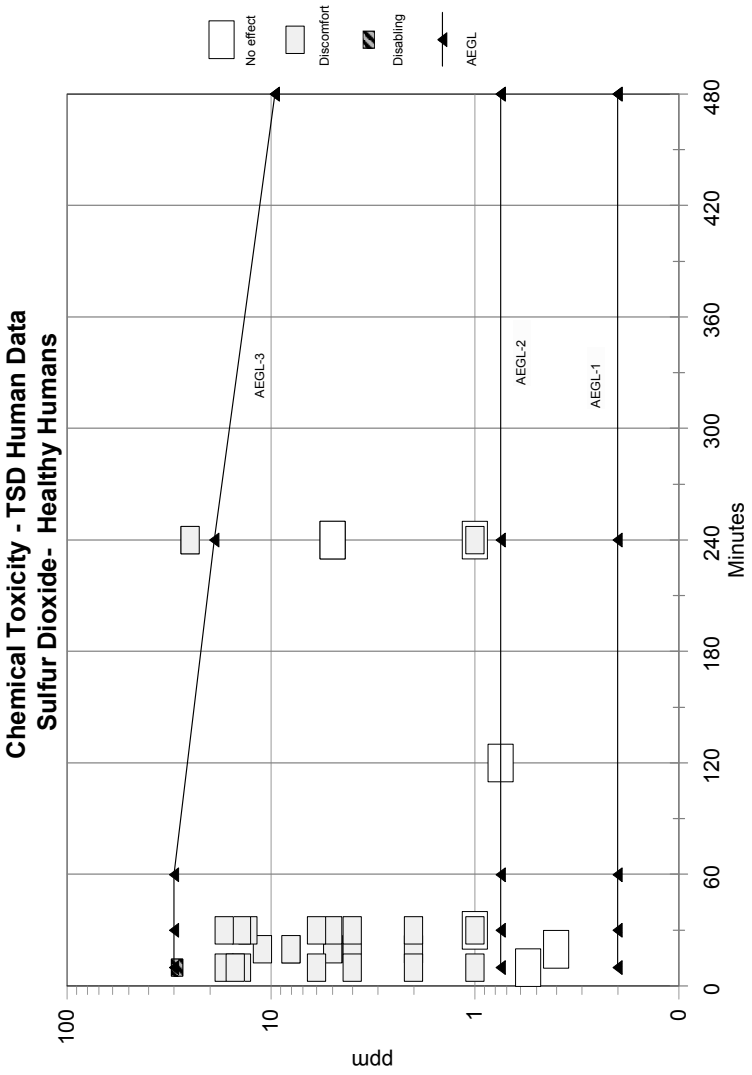

FIGURE C-2 Category plots for sulfur dioxide for healthy humans.

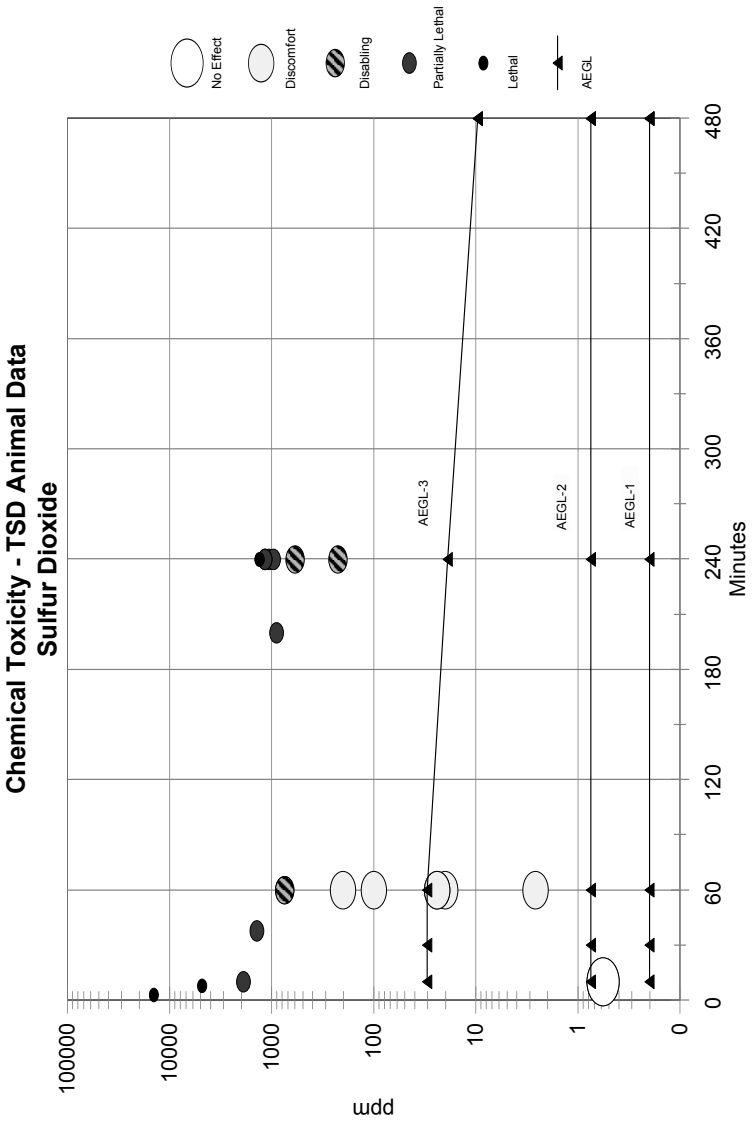

FIGURE C-3 Category plots for sulfur dioxide for animals.