Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 8

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

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Preface

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

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

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

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

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

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

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

The 10 interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the ten committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrolein (fourteenth interim report, 2006), carbon monoxide (ninth, eleventh, thirteenth, and sixteenth interim reports, 2003, 2004, 2005, and 2009, respectively), dichloroethene (third, eleventh, thirteenth, fourteenth, and sixteenth interim reports, 2000, 2004, 2005, 2006, and 2009 respectively), ethylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2004, 2005, and 2006 respectively), fluorine (second, eleventh, and thirteenth interim reports, 2000, 2004, and 2006 respectively), hydrazine (second, tenth, twelfth, and fourteenth interim reports, 2000, 2004, 2005, and 2006 respectively), peracetic acid (fourteenth interim report, 2006), propylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2005, and 2006 respectively), and sulfur dioxide (thirteenth and fourteenth interim reports, 2005 and 2006 respectively): Deepak Bhalla (Wayne State University), Joseph Borzelleca (Virginia Commonwealth University), Charles Feigley (University of South Carolina), David Gaylor (Gaylor & Associates), Sidney Green (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene F. Henderson (Lovelace Respiratory Research Institute), Sam Kacew (University of Ottawa), Nancy Kerkvliet (Oregon State University), Charles R. Reinhardt (DuPont Haskell Laboratory [retired]), Andrew G. Salmon (California Environmental Protection Agency), and Bernard M. Wagner (New York University Medical Center).

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

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

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

Contents

NATIONAL RESEARCH COUNCIL COMMITTEE REVIEW OF ACUTE EXPOSURE GUIDELINE LEVELS OF SELECTED AIRBORNE CHEMICALS **3**

ROSTER OF THE NATIONAL ADVISORY COMMITTEE FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR HAZARDOUS SUBSTANCES **9**

APPENDIXES

1 **ACROLEIN** **13**
Acute Exposure Guideline Levels

2 **CARBON MONOXIDE** **49**
Acute Exposure Guideline Levels

3 **1,2-DICHLOROETHENE** **144**
Acute Exposure Guideline Levels

4 **ETHYLENIMINE** **186**
Acute Exposure Guideline Levels

5 **FLUORINE** **230**
Acute Exposure Guideline Levels

6 **HYDRAZINE** **274**
Acute Exposure Guideline Levels

7 **PERACETIC ACID** **327**
Acute Exposure Guideline Levels

8 **PROPYLENIMINE** **368**
Acute Exposure Guideline Levels

9 **SULFUR DIOXIDE** **393**
Acute Exposure Guideline Levels

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.

REFERENCES

NRC (National Research Council). 1968. Atmospheric Contaminants in Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1972. Atmospheric Contaminants in Manned Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984a. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1984b. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1984c. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 1984d. Toxicity Testing: Strategies to Determine Needs and Priorities. Washington, DC: National Academy Press.

NRC (National Research Council). 1985a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1985b. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1986a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council). 1986b. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 7. Washington, DC: National Academy Press.

NRC (National Research Council). 1988. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1996a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1996b. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 2000a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 2000b. Methods for Developing Spacecraft Water Exposure Guidelines. Washington, DC: National Academy Press.

NRC (National Research Council). 2001a. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council) 2001b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council) 2002a. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council) 2002b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol 2. Washington, DC: National Academy Press.

NRC (National Research Council) 2003. Acute Exposure Guideline Levels for Selected Airborne Chemical, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council) 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council) 2007a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council) 2007b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council) 2008a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council) 2008b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council) 2009. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 7. Washington, DC: National Academy Press.

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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.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 2004. Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. Fairfax ,VA: AIHA Press.

Alarie, Y., L. Kane, and C. Barrow. 1981. Sensory irritation: The use of an animal model to establish acceptable exposure to airborne chemical irritants. Pp. 48-92 in Toxicology: Principles and Practice, Vol. 1, A.L. Reeves, ed. New York: John Wiley and Sons.

Albin, T.B. 1962. Acrolein handling and toxicity. Pp. 234-239 in Acrolein, C.W. Smith, ed. New York: John Wiley and Sons.

Aranyi, C., W.J. O'Shea, J.A. Graham, and F.J. Miller. 1986. The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundam. Appl. Toxicol. 6(4):713-720.

ASTM (American Society for Testing and Materials). 1991. Standard test method for estimating sensory irritancy of airborne chemicals, E981-84 Vol. 11.04. Pp. 610-618 in Annual Book of ASTM Standards, Vol. 11. Philadelphia: American Society for Testing and Materials.

Astry, C.L., and G.J. Jakab. 1983. The effects of acrolein exposure on pulmonary antibacterial defenses. Toxicol. Appl. Pharmacol. 67(1):49-54.

ATSDR (Agency for Toxic Substances and Disease Registry). 2007. Toxicological Profile for Acrolein. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. August

2007[online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp124.pdf [accessed Oct. 21, 2008].

Ballantyne, B., D.E. Dodd, I.M. Pritts, D.J. Nachreiner, and E.H. Fowler. 1989. Acute vapour inhalation toxicity of acrolein and its influence as a trace contaminant in 2-methoxy-3,4-dihydro-2H-pyran. Hum. Toxicol. 8(3):229-235.

Bauer, K., K. Czech, and A. Porter. 1977. Severe accidental acrolein intoxication in the home [in German]. Wien Klin. Wochhenschr. 89(7):243-244.

Beauchamp, R.O., D.A. Andjelkovich, A.D. Klingerman, K.T. Morgan, and H.D. Heck. 1985. A critical review of the literature on acrolein toxicity. Crit. Rev. Toxicol. 14(4):309-380.

Bouley, G., A. Dubreuil, J. Godin, M. Boisset, and C. Boudène. 1976. Phenomena of adaptation in rats continuously exposed to low concentrations of acrolein. Ann. Occup. Hyg. 19(1):27-32.

Buckley, L.A., X.Z. Jiang, R.A. James, K.T. Morgan, and C.S. Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. Toxicol. Appl. Pharmacol. 74(3):417-429.

Carpenter, C.P., H.F. Smyth, and U.C. Pozzani. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31(6):343-346.

Catalina, P., L. Thieblot, and J. Champeix. 1966. Experimental respiratory lesions by inhalation of acrolein in the rat [in French]. Arch. Mal. Prof. 27(12):857-867.

Champeix, J., L. Courtial, E. Perche, and P. Catalina. 1966. Acute broncho-pneumopathy from acrolein vapors [in French]. Arch. Mal. Prof. 27(10):794-796.

Costa, M., A. Zhitkovich, M. Harris, D. Pastenbach, and M. Gargas. 1997. DNA-protein cross-links produced by various chemicals in cultured human lymphoma cells. J. Toxicol. Environ. Health 50(5):433-449.

Darley, E.F., J.T. Middleton, and M.J. Garber. 1960. Plant damage and eye irritation from ozone-hydrocarbon interactions. J. Agr. Food. Chem. 8(6):483-485.

Davis, T.R., S.P. Battista, and C.J. Kensler. 1967. Mechanism of respiratory effects during exposure of guinea pigs to irritants. Arch. Environ. Health 15(4):412-419.

Egle, J.L. 1972. Retention of inhaled formaldehyde, propionaldehyde, and acrolein in the dog. Arch. Environ. Health 25(2):119-124.

Feron, V.J., and A. Kruysse. 1977. Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. J. Toxicol. Environ. Health 3(3):379-394.

Gosselin, B., F. Wattel, C. Chopin, P. Degand, J.C. Fruchart, D. van der Loo, and O. Crasquin. 1979. A case of acute acrolein poisoning [in French]. Nouv. Presse. Med. 8(30):2469-2472.

Hales, C.A., P.W. Barkin, W. Jung, E. Trautman, D. Lamorghini, N. Herrig, and J. Burke. 1988. Synthetic smoke with acrolein but not HCl produces pulmonary edema. J. Appl. Physiol. 64(3):1121-1133.

Henderson, Y., and H.W. Haggard. 1943. Noxious Gases. New York: Reinhold Publishing Co.

ITII (International Technical Information Institute). 1975. Acrolein. Pp. 13-14 in Toxic and Hazardous Industrial Chemical Safety Manual for Handling and Disposal with Toxicity and Hazard Data. International Technical Information Institute, Tokyo, Japan (as cited in Beauchamp et al. 1985).

Iwanoff, N. 1910. Experimentelle Studien uber den Einfluss technisch und hygienisch wichtiger Gase und Dampfe auf den Organismus. XVI, XVII, XVIII. Uber einige

praktisch wichtige Aldehyde (Formaldehyd, Acetaldehyd, Akrolein). Arch. Hyg. 73:307-340 (as cited in Beauchamp et al. 1985).

Kane, L.E., C.S. Barrow, and Y. Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40(3):207-229.

Kaplan, H.L. 1987. Effects of irritant gases on avoidance/escape performance and respiratory response in the baboon. Toxicology 47(1-2):165-179.

Kruysse, A. 1971. Acute Inhalation Toxicity of Acrolein in Hamsters. Report R 3516. Zeist,The Netherlands: Central Institute for Nutrition and Food Research (as cited in Feron and Kruysse 1977).

Kutzman, R.S., E.A. Popenoe, M. Schmaeler, and R.T. Drew. 1981. Changes in rat lung structure and composition as a result of subchronic exposure to acrolein. Toxicology 34(2):139-151.

Le Bouffant, L., J.C. Martin, H. Daniel, J.P. Henin, and C. Normand. 1980. Action of intensive cigarette smoke inhalation on the rat lung. Role of particulate and gaseous cofactors. J. Natl. Cancer Inst. 64(2):273-284.

Li, L., R.F. Hamilton, D.E. Taylor, and A. Holian. 1997. Acrolein-induced cell death in human alveolar macrophages. Toxicol. Appl. Pharmacol. 145(2):331-339.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Acrylaldehyde. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Oct. 24, 2008].

Murphy, S.D., D.A. Klingshirn, and C.E. Ulrich. 1963. Respiratory response of guinea pigs during acrolein inhalation and its modification by drugs. J. Pharmacol. Exp. Therap. 141:79-83.

Murphy, S.D., H.V. Davis, and V.L. Zaratzian. 1964. Biochemical effects in rats from irritating air contaminants. Toxicol. Appl. Pharmacol. 6:520-528.

Nielsen, G.D., J.C. Bakbo, and E. Holst. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. Toxicol. 54(4):292-298.

NIOSH (National Institute of Occupational Safety and Health). 1996. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLH): NIOSH Chemical Listing and Documentation of Revised IDLH Values (as of 3/1/95)-Acrolein. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health. August 1996 [online]. Available: http://www.cdc.gov/niosh/idlh/107028.html [accessed Oct. 16, 2008].

NIOSH (National Institute of Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards: Acrolein. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health, Cincinnati, OH. September 2005 [online]. Available: http://www.cdc.gov/niosh/npg/npgd0011.html [accessed Oct. 16, 2008].

NRC (National Research Council). 1993. Guidance for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

O'Neil, M.J., A. Smith, P.E. Heckelman, J.R. Obenchain, Jr., J. Gallipeau, and M.A. D'Arecca. 2001. Acrolein. Pp. 24 in The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th Ed. Whitehouse Station, NJ: Merck.

Patel, J.M., J.C. Wood, and K.C. Leibman. 1980. The biotransformation of allyl alcohol and acrolein in rat liver and lung preparations. Drug. Metab. Dispos. 8(5):305-308.

Pattle, R.E., and H. Cullumbine. 1956. Toxicity of some atmospheric pollutants. Br. Med. J. 2(4998):913-916.

Phillippin, C., A. Gilgen, and E. Grandjean. 1970. Toxicological and physiological investigation on acrolein inhalation in the mouse. Int. Arch. Arbeitsmed. 26(4):281-305.

Sim, V.M., and R.E. Pattle. 1957. Effect of possible smog irritants on human subjects. JAMA 165(15): 1908-1913.

Skog, E. 1950. A toxicological investigation of lower aliphatic aldehydes. I. Toxicity of formaldehyde, acetaldehyde, propionaldehyde and butyraldehyde, as well as acrolein and crotonaldehyde. Acta Pharmacol. Toxicol. 6(4):299-318.

Springall, D.R., J.A. Edginton, P.N. Price, D.W. Swanston, C. Noel, S.R. Bloom, and J.M. Polak. 1990. Acrolein depletes the neuropeptides CGRP and substance P in sensory nerves in rat respiratory tract. Environ. Health Perspect. 85:151-157.

Steinhagen, W.H., and C.S. Barrow. 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. Toxicol. Appl. Pharmacol. 72(3):495-503.

Swedish Work Environment Authority. 2005. Occupational Exposure Limit Value and Measures against Air Contaminants. AFS 2005:17 [online]. Available: http://www.av.se/dokument/inenglish/legislations/eng0517.pdf [accessed Oct. 21, 2008].

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Turner, C.R., R.B. Stow, S.D. Talerico, E.P. Christian, and J.C. Williams. 1993. Protective role for neuropeptides in acute pulmonary response to acrolein in guinea pigs. J. Appl. Physiol. 75(6): 2456-2465.

Weber-Tschopp, A., T. Fischer, R. Gierer, and E. Grandjean. 1977. Experimentally induced irritating effects of acrolein on men [in German]. Int. Arch. Occup. Environ. Health 40(2):117-130.

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

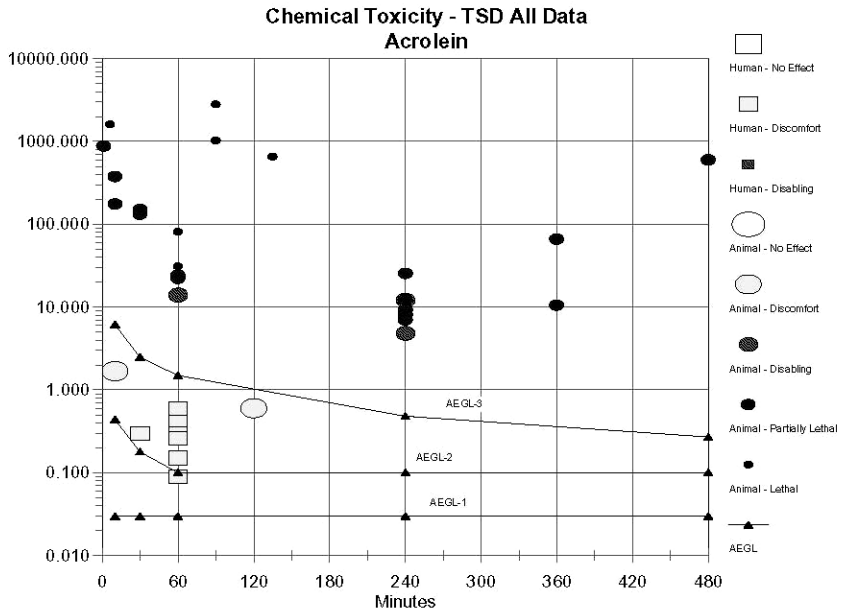

FIGURE C-1 Category plot for acrolein.

APPENDIX D

Temporal Extrapolation for Acrolein

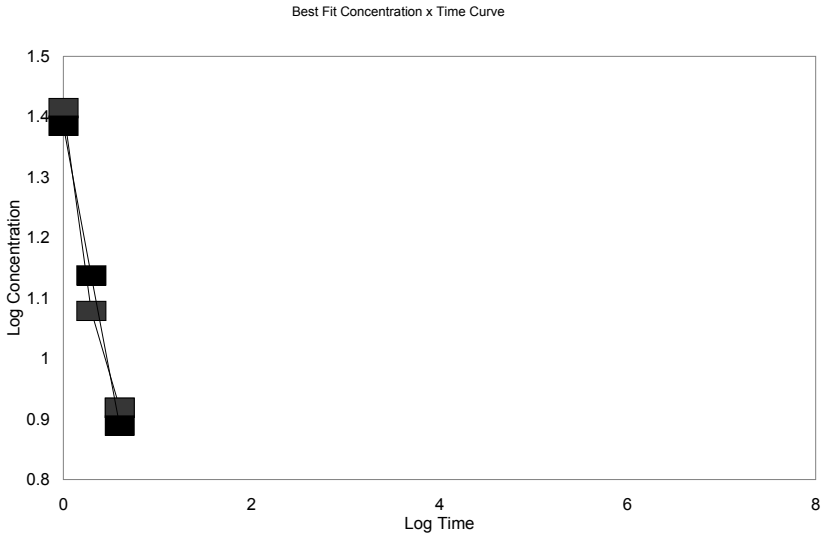

FIGURE D-1 Best fit concentration × time curve.

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