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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans.

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

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

REVIEW OF AEGL REPORTS

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

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

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

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

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared seven reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009). This report is the eighth volume in that series. AEGL documents for acrolein, carbon monoxide, cis-1,2-dichloroethene, trans-1,2-dichloroethene, ethylenimine, fluorine, hydrazine, peracetic acid, propyleneimine, and sulfur dioxide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Roster of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Committee Members

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Government of Canada

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

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

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

Edward Bernas
AFL-CIO
Homewood, IL

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

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

Richard Erickson
U.S. Navy
Groton, CT

Neeraja Erranguntla
Texas Commission on Environmental Quality
Austin, TX

David Freshwater
U. S. Department of Energy
Washington, DC

Ralph Gingell
Shell Health Services
Houston, TX

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

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

Clarion E. Johnson
Exxon Mobil Corporation
Fairfax, VA

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

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

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

Susan Ripple
The Dow Chemical Company
Midland, Michigan

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

Daniel Sudakin
Oregon State University
Corvallis, OR

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

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

Alan Woolf
Children's Hospiral
Boston, MA

Oak Ridge National Laboratory Staff

Cheryl Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Talmage
Oak Ridge National Laboratory
Oak Ridge, TN

Robert Young
Oak Ridge National Laboratory
Oak Ridge, TN

National Advisory Committee Staff

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

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

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

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

Appendixes

3

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

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

1. INTRODUCTION

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

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

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

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

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

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

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

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

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

2.2. Nonlethal Toxicity

2.2.1. Case Reports

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

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

2.2.2. Epidemiologic Studies

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

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

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

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

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

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

2.6. Summary

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

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mice

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

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

3.1.2. Rats

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

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

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

[a]Deaths occurred during exposure.

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

3.1.3. Cats

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

3.2. Nonlethal Toxicity

3.2.1. Cats

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

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

3.2.2. Rats

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

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

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

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

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

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

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

(Continued)

TABLE 3-7 Continued

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

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

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

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

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

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

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

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

(Continued)

TABLE 3-9 Continued

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

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

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

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

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

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

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

3.2.3. Mice

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

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

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

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

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

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

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

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

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

3.3. Developmental and Reproductive Toxicity

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

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

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

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

3.4. Genotoxicity

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

3.5. Carcinogenicity

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

3.6. Summary

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

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

4. SPECIAL CONSIDERATIONS

4.1. Absorption, Distribution, Metabolism and Disposition

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

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

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

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

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

4.2. Mechanism of Toxicity

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

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

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

4.3. Other Relevant Information

4.3.1. Species Variability

Interspecies Variability

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

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

Intraspecies Variability

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

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

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

4.3.2. Physical and Chemical Properties

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

4.3.3. Concurrent Exposure Issues

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

4.4. Temporal Extrapolation

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

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

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

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

5. RATIONALE AND AEGL-1

5.1. Human Data Relevant to AEGL-1

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

5.2. Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1

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

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

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

6. RATIONALE AND AEGL-2

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

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

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

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

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

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

6.3. Derivation of AEGL-2

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

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

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

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

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

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

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

7. RATIONALE AND AEGL-3

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

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

7.3. Derivation of AEGL-3

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

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

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

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

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

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

8.2. Other Exposure Criteria

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

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

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

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

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

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

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

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

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

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

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

[a]IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The IDLH for 1,2-dichloroethene is based on acute inhalation toxicity data in humans.

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

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

[d]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists,) (ACGIH 2003) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]MAK (maximale rbeitsplatzkonzentration [maximum workplace concentration], German Research Association) (DFG 2002) is defined analogous to the ACGIH TLV-TWA.

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

8.3. Data Quality and Research Needs

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

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

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APPENDIX A

Time-Scaling Calculations for 1,2-Dichloroethene

Derivation of AEGL-1

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

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

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

Derivation of AEGL-2

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

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

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

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

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

Derivation of AEGL-3

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

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

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

4 h AEGL-3

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

8 h AEGL-3

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

APPENDIX B

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

AEGL-1 VALUES

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

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

Test Species/Strain/Number: Human subjects/2

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

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

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

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

Modifying Factor: Not applicable.

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

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

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

AEGL-2 VALUES

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

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

(Continued)

AEGL-2 VALUES Continued

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

AEGL-3 VALUES

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

(Continued)

AEGL-3 VALUES Continued

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

APPENDIX C

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

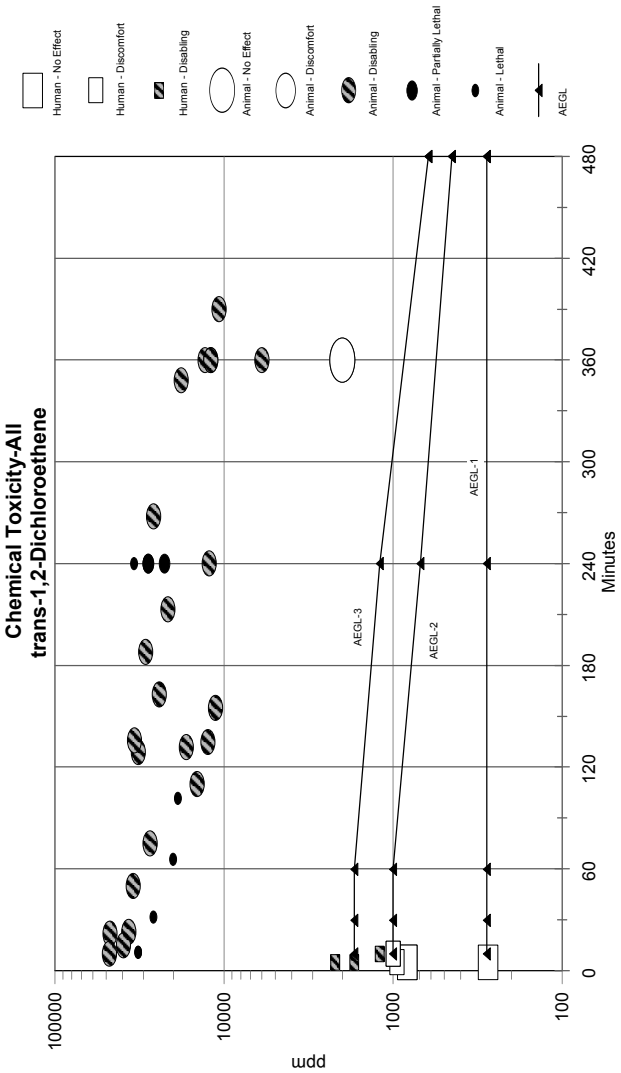

FIGURE C-1 Category plots for *trans*-1,2-dichloroethene.

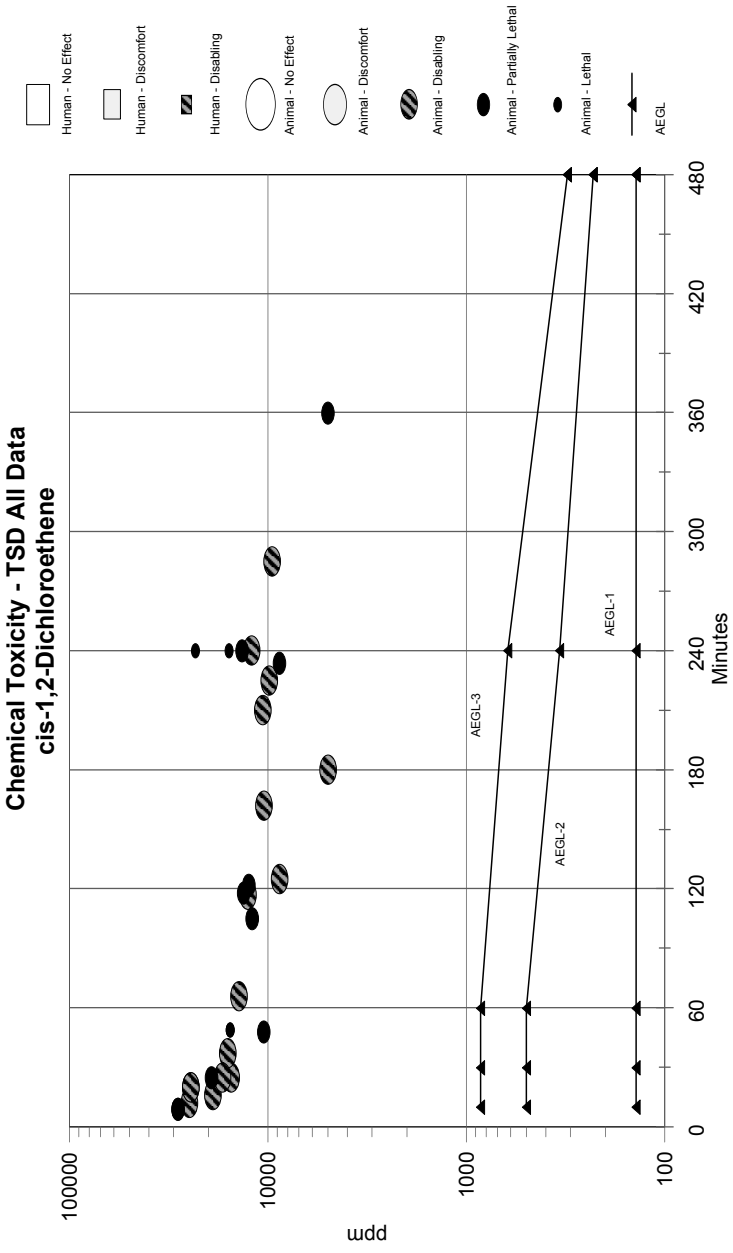

FIGURE C-2 Category plots for *cis*-1,2-dichloroethene.