Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 2

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

NATIONAL RESEARCH COUNCIL

OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street., N.W. Washington, D.C. 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This project was supported by Contract Nos. DAMD17-89-C-9086 and DAMD17-99-C-9049 between the National Academy of Sciences and the U.S. Army. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-08511-X

Additional copies of this report are available from:

The National Academies Press
500 Fifth Street, N.W.
Box 285
Washington, DC 20055

800-624-6242
202-334-3313 (in the Washington metropolitan area)
http://www.nap.edu

Printed in the United States of America

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M. Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M. Alberts and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council

www.national-academies.org

SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

Members

DANIEL KREWSKI, *(Chair*), University of Ottawa, Ottawa, Ontario, Canada
EDWARD C. BISHOP, Parsons Corporation, Fairfax, Virginia
JAMES V. BRUCKNER, University of Georgia, Athens
JOHN DOULL, University of Kansas Medical Center, Kansas City
DONALD E. GARDNER, Inhalation Toxicology Associates, Inc., Raleigh, North Carolina
DAVID W. GAYLOR, Gaylor and Associates, Little Rock, Arkansas
FLORENCE K. KINOSHITA, Hercules Incorporated, Wilmington, Delaware
KANNAN KRISHNAN, University of Montreal, Canada
STEPHEN U. LESTER, Center for Health, Environment and Justice, Falls Church, Virginia
HARIHARA MEHENDALE, University of Louisiana, Monroe
FRANZ OESCH, University of Mainz, Mainz, Germany
RICHARD B. SCHLESINGER, New York University School of Medicine, Tuxedo
CALVIN C. WILLHITE, State of California, Berkeley
FREDERIK DE WOLFF, Leiden University, Leiden, Netherlands

Staff

KULBIR S. BAKSHI, Program Director
KELLY A. CLARK, Editor
AIDA NEEL, Administrative Assistant

COMMITTEE ON TOXICOLOGY

Members

BAILUS WALKER, JR. *(Chair*), Howard University Medical Center and American Public Health Association, Washington, D.C.
MELVIN E. ANDERSEN, Colorado State University, Denver
EDWARD C. BISHOP, Parsons Corporation, Fairfax, Virginia
GARY P. CARLSON, Purdue University, West Lafayette, Indiana
JANICE E. CHAMBERS, Mississippi State University, Mississippi State
LEONARD CHIAZZE, JR., Georgetown University, Washington, D.C.
JUDITH A. GRAHAM, American Chemistry Council, Arlington, Virginia
SIDNEY GREEN, Howard University, Washington, D.C.
SAM KACEW, Department of Pharmacology Faculty of Medicine and University of Ottawa, Ontario,Canada
NANCY KERKVLIET, Oregon State University, Agricultural and Life Sciences, Corvallis
MERYL KAROL, University of Pittsburgh, Pittsburgh, Pennsylvania
STEPHEN U. LESTER, Center for Health Environment and Justice, Falls Church, Virginia
HARIHARA MEHENDALE, The University of Louisiana at Monroe, Monroe
DAVID H. MOORE, Battelle Memorial Institute, Bel Air, Maryland
CALVIN C. WILLHITE, State of California, Berkeley
LAUREN ZEISE, California Environmental Protection Agency, Oakland

Staff

KULBIR S. BAKSHI, Program Director
SUSAN N.J. MARTEL, Senior Program Officer
ABIGAIL E. STACK, Program Officer
RUTH CROSSGROVE, Managing Editor
KELLY CLARK, Editorial Assistant
AIDA NEEL, Administrative Assistant
JESSICA BROCK, Senior Project Assistant

BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Members

GORDON ORIANS *(Chair)*, University of Washington, Seattle
JOHN DOULL *(Vice Chair)*, University of Kansas Medical Center, Kansas City
DAVID ALLEN, University of Texas, Austin
INGRID C. BURKE, Colorado State University, Fort Collins
THOMAS BURKE, Johns Hopkins University, Baltimore, Maryland
WILLIAM L. CHAMEIDES, Georgia Institute of Technology, Atlanta
CHRISTOPHER B. FIELD, Carnegie Institute of Washington, Stanford, California
DANIEL S. GREENBAUM, Health Effects Institute, Cambridge, Massachusetts
BRUCE D. HAMMOCK, University of California, Davis
ROGENE HENDERSON, Lovelace Respiratory Research Institute, Albuquerque, New Mexico
CAROL HENRY, American Chemistry Council, Arlington, Virginia
ROBERT HUGGETT, Michigan State University, East Lansing
JAMES H. JOHNSON, Howard University, Washington, D.C.
JAMES F. KITCHELL, University of Wisconsin, Madison
DANIEL KREWSKI, University of Ottawa, Ottawa, Ontario
JAMES A. MACMAHON, Utah State University, Logan
WILLEM F. PASSCHIER, Health Council of the Netherlands, The Hague
ANN POWERS, Pace University School of Law, White Plains, New York
LOUISE M. RYAN, Harvard University, Boston, Massachusetts
KIRK SMITH, University of California, Berkeley
LISA SPEER, Natural Resources Defense Council, New York, New York

Senior Staff

JAMES J. REISA, Director
DAVID J. POLICANSKY, Associate Director and Senior Program Director for Applied Ecology
RAYMOND A. WASSEL, Senior Program Director for Environmental Sciences and Engineering
KULBIR BAKSHI, Program Director for the Committee on Toxicology
ROBERTA M. WEDGE, Program Director for Risk Analysis
K. JOHN HOLMES, Senior Staff Officer
SUSAN N.J. MARTEL, Senior Staff Officer
SUZANNE VAN DRUNICK, Senior Staff Officer
RUTH E. CROSSGROVE, Managing Editor

OTHER REPORTS OF THE
BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

The Airliner Cabin Environment and Health of Passengers and Crew (2002)
Arsenic in Drinking Water: 2001 Update (2001)
Evaluating Vehicle Emissions Inspection and Maintenance Programs (2001)
Compensating for Wetland Losses Under the Clean Water Act (2001)
A Risk-Management Strategy for PCB-Contaminated Sediments (2001)
Toxicological Effects of Methylmercury (2000)
Strengthening Science at the U.S. Environmental Protection Agency: Research-Management and Peer-Review Practices (2000)
Scientific Frontiers in Developmental Toxicology and Risk Assessment (2000)
Copper in Drinking Water (2000)
Ecological Indicators for the Nation (2000)
Waste Incineration and Public Health (1999)
Hormonally Active Agents in the Environment (1999)
Research Priorities for Airborne Particulate Matter (3 reports, 1998-2001)
Ozone-Forming Potential of Reformulated Gasoline (1999)
Arsenic in Drinking Water (1999)
Brucellosis in the Greater Yellowstone Area (1998)
The National Research Council's Committee on Toxicology: The First 50 Years (1997)
Carcinogens and Anticarcinogens in the Human Diet (1996)
Upstream: Salmon and Society in the Pacific Northwest (1996)
Science and the Endangered Species Act (1995)
Wetlands: Characteristics and Boundaries (1995)
Biologic Markers (5 reports, 1989-1995)
Review of EPA's Environmental Monitoring and Assessment Program (3 reports, 1994-1995)
Science and Judgment in Risk Assessment (1994)
Pesticides in the Diets of Infants and Children (1993)
Protecting Visibility in National Parks and Wilderness Areas (1993)
Dolphins and the Tuna Industry (1992)
Science and the National Parks (1992)
Assessment of the U.S. Outer Continental Shelf Environmental Studies Program, Volumes I-IV (1991-1993)
Human Exposure Assessment for Airborne Pollutants (1991)
Rethinking the Ozone Problem in Urban and Regional Air Pollution (1991)
Decline of the Sea Turtles (1990)

Copies of these reports may be ordered from the National Academy Press
(800) 624-6242 or (202) 334-3313
www.nap.edu

Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. The people 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. 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, along with 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.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances —consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal

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

and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 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 the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the second volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the appropriateness of the AEGLs for five chemicals for their scientific validity, completeness, and consistency with the NRC guideline reports.

This report has been reviewed in draft form by individuals chosen 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 this report: Leonard Chiazze, Jr., of Georgetown University; Sidney Green of Howard University; Sam Kacew of the University of Ottawa; and Ralph Kodell of the National Center for Toxicological Research.

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 the report before its release. The review of this report was overseen by Robert A. Goyer, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was 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 subcommittee gratefully acknowledges the valuable assistance provided by the following persons: Roger Garrett, Paul Tobin, Ernest Falke, and Letty Tahan (all from EPA); George Rusch (Honeywell, Inc.); William Bress (Vermont Department of Health); George Rogers (University of Louisville); Po Yung Lu, Cheryl Bast, and Sylvia Talmage (all from Oak Ridge National Laboratory). Aida Neel was the project assistant. Kelly Clark edited the report. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. The sub-

committee particularly acknowledges Kulbir Bakshi, project director for the subcommittee, for bringing the report to completion. Finally, we would like to thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

Daniel Krewski, *Chair*
Subcommittee on Acute Exposure
Guideline Levels

Bailus Walker, *Chair*
Committee on Toxicology

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 2

Introduction

This report is the second 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, and what steps to take in case of 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 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" (IDLH) values developed by the National Institute for Occupational Safety and

Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), 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 h, and only once in a lifetime for the general population, which includes infants, children, the elderly, and persons with diseases, such as asthma, heart disease, or lung 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 Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). 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 November1995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] 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.

---

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The roster of NAC is shown on page 8.

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 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 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 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NAC guidelines report *Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances*(NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on a chemical. 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 from 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, the data from the most sensitive animal species are used to set AEGLs. Uncertainty factors are commonly used when animal data are used to estimate minimal 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 sexes), developmental, neurotoxic, respiratory, and other organ-related effects—are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, theoretical 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; NRC in press). The NRC assigned this project to the COT Subcommittee on Acute Exposure Guideline Levels. The subcommittee has expertise in toxicology, epidemiology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

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 Subcommittee on Acute Exposure Guideline Levels for final evaluation.

The NRC subcommittee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the subcommittee by the authors of the reports. The NRC subcommittee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001). 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 the AEGL reports, the NRC subcommittee cannot verify all the data used by NAC. The NRC subcommittee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

This report is the second volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. AEGL reports for aniline, arsine, monomethylhydrazine, and dimethylhydrazine were reviewed in the first volume. AEGL documents for five chemicals—phosgene, propylene glycol dinitrate, 1,1,1,2-tetrafluoroethane, 1,1-dichloro-1-fluoroethane, and hydrogen cyanide—are published as an appendix to this report. The subcommittee

concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Committee Members

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

Steven Barbee
Arch Chemicals, Inc.
Norwalk, CT

Ernest Falke
Chair, SOP Workgroup
U.S. Environmental Protection Agency
Washington, DC

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

George Alexeeff
Office of Environmental Health Hazard Assessment
California EPA
Oakland, CA

David Belluck
Office of Environmental Services
Minnesota Department of Transportation
Oakdale, MN

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

Jonathan Borak
Yale University
New Haven, CT

William Bress
Vermont Department of Health
Burlington, VT

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

Albert G. Dietz
U.S. Department of Energy
Germantown, MD

Larry Gephart
Exxon Mobil Biomedical Sciences
Annandale, NJ

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

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

Thomas C. Hornshaw
Office of Chemical Safety
Illinois Environmental Protection Agency
Springfield, IL

Nancy K. Kim
Division of Environmental Health Assessment
New York State Department of Health
Troy, NY

Loren Koller
Loren Koller & Associates
Corvallis, OR

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

Mark A. McClanahan
Centers for Disease Control and Prevention National Center for Environmental Health
Doraville, GA

John Morawetz
International Chemical Workers Union
Cincinnati, OH

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

Marinelle Payton
Department of Public Health
Jackson State University
Jackson, MS

Zarena Post
Texas Natural Resource Conservation Commission
Austin, TX

George Rodgers
Department of Pediatrics
Division of Critical Care
University of Louisville
Louisville, KY

Robert Snyder
Environmental and Occupational Health Sciences Institute
Piscataway, NJ

Thomas J. Sobotka
U.S. Food and Drug Administration
Laurel, MD

Kenneth Still
Naval Health Research Center
Wright-Patterson AFB, OH

Richard Thomas
International Center for Environmental Technology
McLean, VA

Oak Ridge National Laboratory Staff

Po-Yung Lu
Oak Ridge National Laboratory
Oak Ridge, TN

Cheryl B. Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Carol S. Forsyth
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Milanez
Oak Ridge National Laboratory
Oak Ridge, TN

Robert H. Ross
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

Annetta Watson
Oak Ridge National Laboratory
Oak Ridge, TN

National Advisory Committee Staff

Roger Garrett
Director, AEGL Program
U.S. Environmental Protection Agency
Washington, DC

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

Letty Tahan
Senior Scientist
U.S. Environmental Protection Agency
Washington, DC

Appendix

1

Phosgene[1]

Acute Exposure Guideline Levels

SUMMARY

Phosgene is a colorless gas at ambient temperature and pressure. Its odor has been described as similar to new-mown hay. Phosgene is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal. The production of dyestuffs, isocyanates, carbonic acid esters (polycarbonates), acid chlorides, insecticides, and pharmaceutical chemicals requires phosgene. Manufacture of phosgene is approximately 1 million tons per year (y) in the United States, and more than 10,000 workers are involved in its manufacture and use. Manufacture of phosgene in the United States is

[1]This document was prepared by AEGL Development Team member Cheryl Bast of Oak Ridge National Laboratory and Bill Bress (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

almost entirely captive—it is used in the manufacture of other chemicals within a plant boundary. Only one company sells phosgene on the U.S. merchant market.

Inhalation is the most important route of exposure for phosgene. Because of phosgene's mild upper respiratory, eye, and skin irritancy and mildly pleasant odor, an exposed victim may not actively seek an avenue of escape before lower respiratory damage has occurred (Currie et al. 1987a; Lipsett et al. 1994). Pulmonary edema is the cause of death after a clinical latency period of ≤24 hours (h) (Franch and Hatch 1986).

Appropriate data were not available for deriving AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 parts per million (ppm), a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤24 h.

AEGL-2 values were based on chemical pneumonia in rats (exposure at 2 ppm for 90 min) (Gross et al. 1965). An uncertainty factor (UF) of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly among individuals. Therefore, the total UF is 10. The 1.5-h value was then scaled to the 30-min and 1-, 4-, and 8-h AEGL exposure periods using $C^n \times t = k$, where $n = 1$ (Haber's law), because Haber's law has been shown to be valid for phosgene within certain limits. Haber's law was originally derived from phosgene data (Haber 1924). The 30-min value is also adopted as the 10-min value, because extrapolation would yield a 10-min AEGL-2 value approaching concentrations that produce alveolar edema in rats; Diller et al. (1985) observed alveolar pulmonary edema in rats exposed to phosgene at 5 ppm for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min AEGL-2 value of 0.5 ppm.

The 30-min and 1-, 4-, and 8-h AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 30-min exposure (15 ppm) (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and

because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals. Therefore, the total UF is 10. The value was then scaled to the 1-, 4-, and 8-h AEGL periods using $C^n \times t = k$, where n = 1 (Haber's Law), because Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber 1924). The 10-min AEGL-3 value was based on the highest concentration causing no mortality in the rat or mouse (36 ppm) after a 10-min exposure (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals (total UF, 10).

The calculated values are listed in Table 1-1.

1. INTRODUCTION

Phosgene is a colorless gas at ambient temperature and pressure. Its odor has been described as similar to new-mown hay (Leonardos et al. 1968). This mild odor and the weak acute irritant properties, however, provide little warning of its presence (Lipsett et al. 1994). The odor threshold has been established between 0.5 and 1.5 ppm (2.06 and 6.18 mg/m^3) (Lipsett et al. 1994).

Phosgene is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal. Manufacture of phosgene is approximately 1 million tons per year (y) in the United States, and more than 10,000 workers are involved in its manufacture and use (Currie et al. 1987a). Manufacture of phosgene in the United States is almost entirely captive (more than 99% is used in the manufacture of other chemicals within a plant boundary). Only one company sells phosgene on the U.S. merchant market. Over 80% of the phosgene used in the United States is involved in the manufacture of polyisocyanates in the polyurethane industry. The polycarbonate industry accounts for approximately 10% of phosgene used, and the remaining 10% is used in the production of aliphatic diisocyanates, monoisocyanates, chloroformates, agrochemicals, and intermediates for dyestuffs and pharmaceuticals. Phosgene can also be used in metal recovery operations (platinum, uranium, plutonium, and niobium) and has been used for manufacturing aluminum chloride, beryllium chloride, and boron trichloride. It has been pat-

TABLE 1-1 Summary of Proposed AEGL Values for Phosgene (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)	Chemical pneumonia rats (Gross et al. 1965)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)	Highest concentration causing no mortality in the rat after a 30-min or 10-min exposure (Zwart et al. 1990)

ented as a stabilizer for liquid SO_2. In addition, many pesticides have been produced by reaction of a thiol or dithiol with phosgene to produce thiol chloroformates (Kirk-Othmer 1991).

Inhalation is the most important route of exposure for phosgene. Because of phosgene's mild upper respiratory, eye, and skin irritancy and mildly pleasant odor, an exposed victim may not actively seek an avenue of escape before lower respiratory damage has occurred (Currie et al. 1987a; Lipsett et al. 1994). Pulmonary edema is the cause of death after a clinical latency period of $\leq$24 h (Franch and Hatch 1986).

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Diller and Zante (1982) performed an extensive literature review concerning human phosgene exposure, and found that a great majority of data were

TABLE 1-2 Physical and Chemical Data

Parameter	Data	Reference
Synonyms	Carbonyl chloride, carbon oxychloride, carbonic dichloride, chloroformyl chloride	Lipsett et al. 1994; EPA 1986
Chemical formula	$COCL_2$	Lipsett et al. 1994
Molecular weight	98.92	Lipsett et al. 1994
CAS registry no.	75-44-5	Lipsett et al. 1994
Physical state	Gas	Lipsett et al. 1994
Vapor pressure	1215 mm Hg at 20°C	EPA 1986
Vapor density	3.4 (air = 1)	Lipsett et al. 1994
Specific gravity	1.381 g/l at 20°C	ACGIH 2000
Melting/boiling/ flash point	-128°C/8.2°C/not applicable	Lipsett et al. 1994; NIOSH 1994
Solubility	Decomposes in water and alcohol; soluble in organic solvents	EPA 1986
Conversion factors in air	1 ppm = 4.11 mg/m^3 1 mg/m^3 = 0.24 ppm	Lipsett et al. 1994
Incompatibility	Alkalis, ammonia, alcohols, copper	NIOSH 1997

anecdotal or rough estimates and, thus, did not contain reliable exposure concentrations and/or durations. Information synthesized from this review is presented in Table 1-3. Based on observations during World War I, the 2 min LC_{50} value for humans was estimated to be 790 ppm (Chasis 1944).

Many case reports describe symptomology and postmortem results from human phosgene poisonings; however, exposure concentrations were not reported. Six men were occupationally exposed to phosgene when a pipe ruptured (Stavrakis 1971). A 24-y-old who had received the heaviest exposure arrived at the emergency room minutes after the accident. Upon admission, the patient was symptom-free; however, he was treated with methenamine intravenously and admitted for a 24-h observation. During this time, he remained symptom free and was discharged with no evidence of phosgene injury. The other five patients arrived at the emergency room between 6 and

TABLE 1-3 Effect of Phosgene Exposure in Healthy Humans

Effect[a]	Cumulative Phosgene Exposure
LCT_1	~300 ppm·min
LCT_{50}	~500 ppm·min
LCT_{100}	~1,300 ppm·min

[a]Lethal concentration × time product.

Source: Diller and Zante 1982.

12 h after the accident, presenting with various degrees of phosgene intoxication. One 31-y-old who had been exposed "in almost the same degree as the previous patient" rapidly developed pulmonary edema. He also exhibited extreme hemoconcentration and leukocytosis. He did not respond to methenamine treatment and died 3.5 h after admission. The other four exposed workers were hospitalized for various periods of time and recovered satisfactorily.

A 23-y-old man (healthy nonsmoker) was exposed to phosgene at an estimated concentration of at least 5-10 ppm for 5 to 10 seconds (s) (Bradley and Unger 1982). He began coughing upon exposure to phosgene and experienced dyspnea and chest tightness within 30 min. Four hours after exposure, he was hospitalized with hypotension, tachycardia, tachypnea, cyanosis, and pulmonary edema. The patient was intubated and administered dopamine and methylprednisolone. From the second to the sixth day of hospitalization, he developed mediastinal and subcutaneous emphysema, bilateral pneumohydrothoraces, elevated white blood cell counts, fever, and hemiparesis on the right side. Death occurred after the patient developed ventricular fibrillation.

Misra et al. (1985) described another accidental occupational phosgene poisoning case. A 30-y-old male was exposed to phosgene at an undetermined concentration and immediately began coughing and experienced a sense of suffocation and burning eyes. After removal to fresh air and administration of oxygen, he felt better. However, approximately 7.5 h after the exposure, he was rushed to the emergency room with difficulty breathing. Despite oxygen administration and antibiotic therapy, his condition deteriorated. He died approximately 18 h after exposure. An autopsy showed pulmonary edema and bronchiolar necrosis, both of which were more severe in the lower lobes of the lungs than in the upper lobes.

Hegler (1928) reported the effects of a phosgene accident that occurred in Hamburg, Germany, on May 20, 1928. Eleven metric tons of "pure phosgene" were released from a storage tank on a warm, dry, slightly windy day. Within

a few hours, people as far as six miles from the release site began reporting to hospitals. Three hundred people reported to hospitals within a few days of the accident. Effects ranged from mild or moderate illness to death; ten people were reported to have died. In general, exposed persons exhibited symptoms consistent with other reported phosgene poisonings (headache, dizziness, nausea and vomiting, irritant cough, and sickening-sweet taste, followed by a latency period and then pulmonary symptoms). Autopsies on six of the fatalities showed pulmonary effects in all cases. Fatty degeneration of the kidneys, liver, and heart were observed in a few cases and were thought to be secondary to the pulmonary damage. In an atypical case, damage in the gray matter of the brain and spinal cord, hyperemia, and signs of bleeding in the white matter were observed at autopsy. That patient died 11.5 days (d) postexposure from a blood clot lodged in the lung. It was uncertain if the extrapulmonary effects were due to phosgene exposure.

2.2. Nonlethal Toxicity

NIOSH (1976) performed two studies to determine the odor threshold of phosgene. In the first, 56 military personnel were exposed to phosgene at increasing concentrations until all subjects could detect odor. The lowest detectable concentration was 0.4 ppm. Thirty-nine percent of subjects could detect odor at 1.2 ppm, and 50% of subjects detected odor at 1.5 ppm. In the other study, four subjects identified 1.0 ppm as the lowest concentration at which the distinctive "new-mown hay" odor of phosgene could be detected.

In their literature review, Diller and Zante (1982) also identified nonlethal effects from phosgene exposure (lethal effects are described in Section 2.1). Nonlethal information synthesized from this review is presented in Table 1-4. From the above data and from animal data for "initial lung damage," Diller and Zante (1982) synthesized information for nonlethal effects of phosgene in humans (Table 1-5).

2.2.1. Case Reports

A 30-y-old male was occupationally exposed to phosgene at an unknown concentration(Stavrakis 1971). After a short episode of coughing, he returned to work and completed the final 3 h of his shift. Approximately 4 h post-

TABLE 1-4 Acute Irritative Effects of Phosgene Exposure in Humans

Effect	Phosgene Concentration
Throat irritation	3.1 ppm
Ocular irritation	4.0 ppm
Cough	4.8 ppm
Severe eye and airway irritation	10 ppm

Source: Diller and Zante 1982

exposure, he presented at the emergency room with severe dyspnea, restlessness, chest pain, and persistent, productive cough. Chest x-rays confirmed acute pulmonary edema. He was treated and discharged free of symptoms 5 d after the phosgene exposure.

An investigator was exposed to phosgene at an undetermined concentration during an experiment (Delephine 1922). He entered the phosgene chamber "at frequent intervals" over a period of 45 min to take instrument readings. At first, he experienced only laryngeal and conjunctival irritation, but as the phosgene concentration increased, he was forced to hold his breath and not stay in the room for more than 1 min. Toward the end of the experiment, some phosgene escaped from the chamber. At this time, the investigator and a colleague experienced a violent cough and began to run away. During their escape, both men had to stop frequently due to the violent nature of their coughs. After exiting the contaminated area, both individuals continued to cough for approximately 20 min. They then improved for 3 or 4 h, after which they experienced a choking sensation that lasted approximately 24 h. Marked lassitude lasted for an additional few days, after which recovery appeared to be complete.

Everett and Overholt (1968) discussed a 40-y-old male who received a "massive" phosgene exposure. His initial symptoms included coughing and burning of the eyes, which subsided within 5 min. He was asymptomatic for the next 2 h, after which a hacking cough began. Three hours after exposure, mild dyspnea was present, and 6 h postexposure, severe dyspnea and moist rales were observed. He was admitted to an intensive care unit 8 h postexposure and presented with anxiety, agitation, cyanosis, thirst, constant cough, and severe pulmonary edema. By the fifth day in the hospital, he was asymptomatic, and by the seventh day, pulmonary function and chest x-ray were normal. A 2-y follow-up was unremarkable.

TABLE 1-5 Effect of Phosgene Exposure in Humans

Effect	Phosgene Exposure
Odor perception	>0.4 ppm
Odor recognition	>1.5 ppm
Ocular, nasal, throat, and bronchiolar irritation	>3 ppm
Initial lung damage	>30 ppm·min
Clinical pulmonary edema	>150 ppm·min

Source: Diller and Zante 1982.

Regan (1985) described a phosgene release from a toluene diisocyanate plant. Fifteen employees were exposed to phosgene at an undetermined concentration, resulting in the hospitalization of four workers. Two of the four were released after an overnight observation. The other two were in more serious condition. One of them, a 31-y-old male, had pulmonary edema, rales in both lungs, and left chest pain 8 h postexposure. He was treated with oxygen, bronchodilators, steroids, and antibiotics and returned to work 6 d after the accident. His follow-up was unremarkable. The second man, a 47-y-old smoker, presented with dyspnea, bilateral rales, and pulmonary edema 11 h postexposure. He was also treated with oxygen, bronchodialators, steroids, and antibiotics but continued to deteriorate. He remained critical for 3 d with low right-side heart pressure, low arterial pressure, hemoconcentration, and leukocytosis. He was asymptomatic by 12 d postexposure. He had mild pulmonary obstruction four weeks after the accident; however, it is unclear if that was a result of phosgene exposure or of his smoking.

Longer-term effects from acute phosgene exposure have also been described. Galdston et al. (1947a) described the late effects of phosgene poisoning in six workers (two male, four female; ages 31-50). After an acute, accidental, occupational exposure to phosgene all of these workers experienced the typical effects of acute phosgene exposure. Chronic clinical findings present from 1 to 24 months (mo) postexposure included rapid, shallow breathing and changes in pulmonary function. However, no correlation was observed between the magnitude of phosgene exposure or the severity of acute effects and the severity of chronic symptoms. Galdston et al. (1947a) attributed the severity of chronic symptoms to the subjects' psychological state. Smoking habits were not reported, and long-term follow-up was not performed.

Galdston et al. (1947b) also examined five males (ages 24-50) who had repeated occupational exposure to phosgene in "small amounts" during the course of 1.5 to 3.5 y. The subjects were examined with regard to pulmonary function and cardiac status. The subjects exhibited transitory effects such as cough, shortness of breath on exertion, and pain or tightness of the chest. These symptoms abated upon removal from phosgene exposure for several weeks. Results suggested that although symptoms of chronic exposure to low concentrations of phosgene are generally not as disabling as those from acute exposure, emphysema may develop after chronic exposure. Also, pulmonary function effects are more severe after chronic low-level exposure than after recovery from a serious acute exposure.

Diller et al. (1979) examined 12 originally healthy workers 3 to 9 y after intoxication with phosgene (ten workers), nitric oxide (one worker), or treflon smoke (one worker). Six of the 12 individuals complained of pulmonary symptoms for 3 y postexposure, and three of the 12 showed slight to severe lung function effects. The severity of lung function decrement correlated more closely with smoking habits than with the severity of chemical intoxication. Diller et al. (1979) concluded that originally healthy survivors of phosgene intoxication recover fairly well over a period of years. However, individuals with preexisting chronic bronchitis may suffer significant chronic deterioration of lung function after acute phosgene intoxication, as an additional observation over 25 y showed. The individual, a light smoker who had mild chronic bronchitis since childhood, was exposed to phosgene and smoke at age 35. He developed severe pulmonary edema and was hospitalized for 7 weeks (wk) following the exposure. During the months following the exposure, his general condition worsened and the bronchitis became more severe. After 2 y, pulmonary function (forced expiratory volume [FEV] and vital capacity [VC]) was decreased to 70% of normal. Ten years postexposure, he developed pulmonary emphysema, and VC and FEV were decreased to 50% of normal.

Herzog and Pletscher (1955) observed squamous metaplasia of the ciliated bronchial epithelium in two patients exposed to undetermined concentrations of phosgene. The metaplasia was observed 3 mo or 3 y postexposure, respectively.

In a phosgene processing factory, phosgene concentrations were measured over an 8-mo period with a device capable of detecting phosgene at 0-0.5 ppm (Henschler 1971). Positive values, of relatively short duration, were recorded on only 32 of 240 d: 22 d, 0.05 ppm; 6 d, between 0.06 and 0.1 ppm; 3 d, between 0.1 and 0.5 ppm; 1 d, 0.5 ppm (of short duration). For longer time

periods, elevated concentrations were measured on three occasions: twice for 3 h, between 0.015 and 0.035 ppm, and once for 1.5 h, 0.35 ppm. The above described conditions produced no intoxication or adverse effects on lung function.

In another factory, use of a phosgene indicator badge revealed an average of 34 phosgene exposures per year during the period from 1978 to 1988 (Kaerkes 1992). The workforce contained approximately 200 individuals ranging in age from <20 to 60 y. Exposure concentrations ranged from <50 to 300 ppm·min. Below 50 ppm·min, no signs or symptoms of phosgene toxicity were observed in 75 of 88 individuals; however, three cases of temporary pulmonary edema were observed.

In another report, Sandall (1922) examined 83 British soldiers 3 y after phosgene exposure. Shortness of breath upon exertion (70%), cough with expectoration (54%), tight feeling in chest (25%), sporadic giddiness (14%), and nausea (12%) were the most frequently reported complaints. No physical lung abnormalities were noted in 53% of the men.

2.2.2. Epidemiologic Studies

Polednak (1980) studied a uranium processing plant where phosgene was produced as a by-product of a chemical process in which UO_3 was combined with CCl_4 to produce UCl_4. Leaks and system failures resulted in the accidental release of phosgene into work areas. Although extensive monitoring data were not available, it was determined that the average exposure was below the detection limit of monitoring instruments used at that time. However, there were three to five episodes daily when concentrations exceeded the 1 ppm exposure limit recognized as the occupational standard of the time.

Approximately 30 y after exposure, there were no significant increases in mortality from overall cancer or cancers at specific anatomical sites, in diseases of the respiratory system, or in overall mortality noted in this cohort. However, the exposure period covered by the study was short, the exposed groups were small, and the exposure levels were not well documented. Consequently, evidence presented in this study is inadequate to assess the carcinogenicity of phosgene.

Polednak and Hollis (1985) reported a follow-up of the study discussed above. The study update reported the mortality experience of individuals through the end of 1978 and included 694 routinely exposed white male chemical workers, 97 acutely exposed chemical workers, and 9,280 controls.

Vital status ascertainment for the routinely exposed group and the controls was approximately 90% complete using Social Security Administration (SSA) records. For the acutely exposed group, SSA records as well as state death indexes were used to ascertain vital status, which was approximately 92% complete. Five individuals in the routinely exposed group, nine in the acutely exposed group, and 72 controls were lost to follow-up.

Approximately 35 y after exposure to phosgene, no increase in overall mortality or mortality from cancer or respiratory disease was noted in this cohort.

NIOSH (1976) compared the medical records of 326 workers exposed to phosgene with those of 6,288 unexposed workers from the same plant. Personal air sample measurements at this plant (20-min samples) showed phosgene concentrations ranging from undetectable to 0.02 ppm, and there was a 15 sample average of 0.003 ppm. Fixed-position air samples (20-min or 2-h collection) ranged from undectable to 0.13 ppm in 51 of 56 samples, and >0.14 ppm in 5 of 56 samples. There were no differences in pulmonary function or deaths attributable to respiratory disease between the exposed and control populations.

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

Polednak (1980) and Polednak and Hollis (1985) examined a cohort of chemical workers exposed to phosgene at chronic low levels as well as daily exposures above 1 ppm. Approximately 35 y after exposure to phosgene, no increase in overall mortality or mortality from cancer or respiratory disease

was noted. These studies are described in detail in Section 2.2.2 (Epidemiologic Studies).

2.6. Summary

Although there is a paucity of acute human data containing known exposure concentrations and times, reports of human phosgene poisonings present a relatively consistent set of clinical effects and sequelae. After acute phosgene exposure, brief (≤20 min) ocular and throat irritation, cough, nausea and vomiting, and dizziness are experienced, followed by a period (≤24 h) of apparent well-being. After this clinical latency phase, cough accompanied by expectoration, a sensation of pain or tightness of the chest, shortness of breath, and a choking sensation are experienced. Clinical findings may include hemoconcentration, leukocytosis, rales, and pulmonary edema. After recovery, rapid shallow breathing, shortness of breath on exertion, and a sense of decreased physical fitness may persist for months. Pulmonary emphysema may occur with repeated exposure to phosgene. Epidemiology studies have shown no increase in cancer in workers exposed to phosgene compared with controls. No information concerning reproductive and developmental toxicity or genotoxicity was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mouse

Zwart et al. (1990) exposed groups of five male and five female Swiss mice to phosgene at varying concentrations for 5, 10, 30, or 60 min. The test atmosphere was monitored at both the inlet and outlet of the glass exposure chambers by gas chromatography and infrared analysis. Ten-minute LC_{50} values were 77 and 61 ppm for males and females, respectively. Thirty-minute LC_{50} values were 18 and 11 ppm for males and females, respectively, and 60-min LC_{50} values were determined to be 9 and 5 ppm for males and females, respectively.

Cameron et al. (1942) exposed 20 mice to phosgene at an average concentration of 0.86 ppm for 5 h. Twelve mice were dead the next morning. Sev-

eral other acute lethality studies of phosgene in mice have been reported. However, these studies do not contain experimental details such as strain or gender of mouse, number of animals exposed, or analytical methodology. These values, in addition to those of Zwart et al. (1990), are presented in Table 1-6.

3.1.2. Rats

Zwart et al. (1990) exposed groups of five male and five female Wistar rats to phosgene at varying concentrations for 5, 10, 30, or 60 min. The test atmosphere was monitored at both the inlet and outlet of the glass exposure chambers by gas chromatography and infrared analysis. The 10-min LC_{50} value was 80 ppm, and the 30- and 60-min LC_{50} values were 20 and 12 ppm, respectively.

A total of 118 male Wistar rats were exposed to phosgene at 0.5 to 4.0 ppm for 5 min to 8 h (Rinehart 1962; Rinehart and Hatch 1964). The exposures were varied to give CT products between 12 and 360 ppm·min and were carried out in 1,700-L wooden exposure chambers operating at a constant ventilation rate of 1,000 L/min. The chamber surfaces were lacquered, and thus, potential loss of phosgene by reaction with the wooden surface was minimized. This system provided for air "turnover" every 2 min and a 99% equilibrium time of 8 min. Air samples were taken frequently during exposures, and adjustments were made when necessary to maintain constant phosgene concentrations. An $L(CT)_0$ of 180 ppm·min, a 75-min LC_{50} of 4 ppm, and a 125-min LC_{100} of 4 ppm were determined. The authors concluded that different combinations of concentration and time exposure giving equal products of C × T constitute equally effective doses.

Several other acute lethality studies of phosgene in rats have been reported. However, as is the case with the mice, these studies do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These studies are summarized in Table 1-7.

Box and Cullumbine (1947b) investigated phosgene-induced lethality in rats after the rats had experienced an exposure to phosgene at a nonlethal concentration. Rats were divided into two groups (12 per group). Half of each group was exposed to 19.2 ppm phosgene for 10 min and the other half served as a control group. Five days later, the preexposed and control rats were exposed to phosgene at 55.2 , 60, 75.6, and 105.6 ppm for 10 min. The rats were then observed for the next 48 h for deaths. The pretreated rats had a reduced percentage of mortality (33%) compared with the control animals

TABLE 1-6 Acute Lethality of Phosgene in Mice

Time (min)	LC_{50} (ppm)	Reference
1	850	Chasis 1944
1	3,300	Moor and Gates 1946
5	33	Kawai 1973
10	77 (male); 61 (female)	Zwart et al. 1990
15	15	Cameron and Foss 1941
30	18 (male); 11 (female)	Zwart et al. 1990
30	5.1	Kawai 1973
60	9 (male); 5 (female)	Zwart et al. 1990

(74%). Thus, partial protection from phosgene-induced lethality was obtained by the phosgene pretreatment.

3.1.3. Guinea Pigs

The few acute lethality studies of phosgene in guinea pigs do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These less-than-adequate studies are summarized in Table 1-8.

3.1.4. Rabbits

As was the case with guinea pigs, the few acute lethality studies of phosgene in rabbits do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These less than adequate studies are summarized in Table 1-9.

3.1.5. Cats

Wirth (1936) reported no deaths in cats exposed to phosgene at 1.8 ppm for 470 min. A 1-min LC_{50} of 1,482 ppm was reported by Moor and Gates (1946), and a 15-min LC_{50} of 80 ppm was reported by Underhill (1920). No

TABLE 1-7 Acute Lethality of Phosgene in Rats

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	NR	10	35	LC_{20}	Shils 1943
NR	NR	10	60	LC_{40}	Shils 1943
NR	NR	1	1,625	LC_{50}	Chasis 1944
NR	44/NR	10	38-75	LC_{50}	Box and Cullumbine 1947a
NR	NR	12	30	LC_{50}	Chasis 1944
NR	NR	15	35	LC_{50}	Cameron and Foss 1941
NR	NR	20	15	LC_{50}	Kimmerle and Diller 1977
Wistar	40/NR	30	10-15	LC_{75}	Henschler and Laux 1960
NR	NR	20	25	LC_{50}	Rothlin 1941
NR	NR	12	85	LC_{60}	Shils 1943
NR	NR	10	40	LC_{70}	Kimmerle and Diller 1977
NR	32/NR	10	39-103	LC_{75}	Box and Cullumbine 1947a
Wistar	40/NR	20	25	LC_{50}	Henschler and Laux 1960
NR	NR	3	220	LC_{100}	Winternitz et al. 1920
NR	12/NR	10	147	LC_{100}	Box and Cullumbine 1947a
NR	10/NR	13	73	LC_{100}	Schultz 1945

(Continued)

TABLE 1-7 *Continued*

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	NR	20	37	LC_{100}	Rothlin 1941
NR	NR	30	22	LC_{100}	Winternitz et al. 1920

NR, not reported.

details, such as number, gender, strain of cat, or methodology, were provided in any of these studies.

3.1.6. Dogs

Meek and Eyster (1920) exposed eight mongrel dogs (gender not specified) to phosgene at 80-100 ppm for 30 min. All eight died within 24 h postexposure. Pulmonary edema with some evidence of cardiac effects was observed at necropsy.

Additional dog lethality information is presented in Table 1-10.

3.1.7. Goats

Karel and Weston (1947) reported a 10-min LC_{50} of 250 ppm for a group of 30 female and 1 male goat, and Underhill (1920) reported a 15-min LC_{50} of 180 ppm for a group of 61 goats. All goats died when exposed to phosgene at 8,750 ppm for 1 min (Tobias 1945), 500 ppm for 3 min, or 110 ppm for 30 min (Winternitz et al. 1920). No further experimental details were available.

3.1.8. Sheep

A 10-min LC_{50} value of 333 ppm was determined from exposing groups of two Dorset crossbred wethers to phosgene at concentrations of 135, 240, 427, or 758 ppm for 10 min, followed by a 24-h observation period (Keeler et al. 1990b). Animals that died displayed a mixture of stringy mucous and frothy white material from the proximal trachea to the smaller bronchioles that

TABLE 1-8 Acute Lethality of Phosgene in Guinea Pigs

Exposure Time (min)	Concentration (ppm)	End Point	Reference
1	672	LC_{50}	Chasis, 1944
15	32	LC_{50}	Underhill, 1920
30	18	LC_{50}	Chasis, 1944
30	141	LC_{50}	Moor and Gates, 1946
9	85	LC_{99}	Coman et al., 1947
3	220	LC_{100}	Winternitz et al., 1920
30	20	LC_{100}	Winternitz et al., 1920
20	77	LC_{100}	Ong, 1972

filled the alveoli, perivascular spaces, and interlobular septa. Sheep that survived the 24-h postexposure period were noted to have airways with scant amounts of mucus and frothy white material and mild to moderate alveolar edema.

3.1.9. Nonhuman Primates

Chasis (1944) reported a 1-min LC_{50} of 240 ppm for a group of monkeys. The strain, gender, and number of animals were not reported. A 1-min LC_{50} of 500 ppm was reported for 19 male and 18 female Rhesus monkeys (Weston and Karel 1947). Moor and Gates (1946) found that all monkeys died when exposed to phosgene at a concentration of 1,087 ppm for 1 min. No other experimental details were available for either study.

3.2. Nonlethal Toxicity

3.2.1. Mice

Hatch et al. (1986) exposed Swiss albino mice (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h in an 11.3 ft^3 Rochester-type

TABLE 1-9 Acute Lethality of Phosgene in Rabbits

Exposure Time (min)	Concentration (ppm)	End Point	Reference
30	17	LC_{40}	Frosolono 1977
1	3,200	LC_{50}	Moor and Gates 1946
15	187	LC_{50}	Underhill 1920
20	110	LC_{50}	Cameron and Courtice 1946
20	20	LC_{50}	Laquer and Magnus 1921
30	100-135	LC_{70}	Halpern et al. 1950
30	93	LC_{75}	Frosolono 1976
30	82	LC_{90}	Shils 1943
35	151	LC_{99}	Coman et al. 1947
15	220	LC_{100}	Winternitz et al. 1920
30	110	LC_{100}	Winternitz et al. 1920

chamber. The phosgene was mixed with filtered room air before the metering orifice of the chamber and introduced into the chamber airstream. The chamber airstream had a flow rate of 1 chamber volume per minute, and the chamber air was sampled every 10 min. Phosgene concentrations were first determined by gas chromatography, and an infrared analyzer was used for a second check. Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar aveolar lavage fluid protein (LFP), an indicator of pulmonary edema. The LFP findings were 292 ± 18, 302 ± 21, 941 ± 105, 1,302 ± 149, or 2,168 ± 167 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a statistically significantly ($p < 0.05$) altered protein concentration was 0.2 ppm.

In another study, Illing et al. (1988) exposed groups of 37-39 female CD-1 mice to phosgene at 0.1 to 0.5 ppm for 4 h. Animals were exposed in stainless steel exposure chambers. Phosgene concentrations were monitored primarily by gas chromatography and double checked by infrared analysis. There was a significant ($p < 0.05$) increase in pentobarbital-induced sleeping time in mice exposed at 0.15 to 0.5 ppm compared with air controls. No significant differences were observed in cytochrome P450 levels, body weights, or liver weights between phosgene-exposed mice and air controls.

TABLE 1-10 Acute Lethality of Phosgene in Dogs

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	12/NR	10	110	LC_{25}	Cameron and Courtice 1946
NR	NR	1	2,100	LC_{50}	Chasis 1944
NR	NR	10	45	LC_{50}	Kimmerle and Diller 1977
NR	24/NR	15	60-70	LC_{50}	Underhill 1920
NR	NR	20	502	LC_{50}	Chasis 1944
NR	6/NR	30	100-175	LC_{50}	Patt et al. 1946
NR	NR	30	78	LC_{55}	Postel and Swift 1945
Mongrel	18/NR	3	745-880	LC_{70}	Coman et al. 1947
NR	94/NR	20	135	LC_{70}	Freeman et al. 1945
NR	42/NR	30	98	LC_{70}	Postel and Swift 1945
Mongrel	15/M,F	30	124	LC_{90}	Schultz 1945
Mongrel	32/NR	10	39-103	LC_{75}	Box and Collumbine 1947
Mongrel	NR	3	734	LC_{99}	Coman et al. 1947
Mongrel	NR	30	90	LC_{99}	Coman et al. 1947

NR, not reported.

Box and Cullumbine (1947b) exposed a group of 37 mice to phosgene at 144 ppm for an unspecified period of time. Subgroups of four or five of these

mice were sacrificed on postexposure days 1, 2, 3, 4, 5, 7, 10, or 14. A histopathological examination was performed on the lungs of these animals. Varying degrees of edema, patches of leucocytic infiltration, and bronchial and bronchiolitic epithelia being lifted by edema were observed on postexposure day 1. More severe edema and collapsed lungs with leukocytic infiltration were observed on postexposure days 2-5. The lungs of the remaining mice were essentially normal by postexposure days 10 through 14.

3.2.2. Rats

A total of 118 male Wistar rats were exposed to phosgene at 0.5 to 4.0 ppm for 5 min to 8 h (Rinehart 1962; Rinehart and Hatch 1964). The exposures were varied to give CT products between 12 and 360 ppm·min and were carried out in 1,700-L wooden exposure chambers operating at a constant ventilation rate of 1,000 L/min. The chamber surfaces were lacquered, and thus, potential loss of phosgene by reaction with the wooden surface was minimized. This system provided for air "turnover" every 2 min and a 99% equilibrium time of 8 min. Air samples were taken frequently during exposures, and adjustments were made when necessary to maintain constant phosgene concentrations. In addition to the lethality data presented in Section 3.1.2, several conclusions were also drawn concerning nonlethal end points. First, the CT product appears to be a valid way to express pulmonary irritation due to phosgene exposure. This is based on the finding of equal degrees of respiratory response, as measured by reduction in pulmonary gas exchange capacity, from exposures to various combinations of C and T that yield the same CT product. Second, there is no decrease in pulmonary performance from exposures less than CT = 30 ppm·min, but above this level, gas exchange capacity decreases directly with a *log* increase in CT. Finally, for low level exposures (below CT = 100), the major site of action is the respiratory bronchioles, although above this level, the alveoli are involved.

In a later publication of the above experiment (Gross et al. 1965), pulmonary pathology from the phosgene-exposed rats was described. Exposure to phosgene at high concentrations (2 ppm for 90 min) produced chemical pneumonia, and exposure at lower concentrations produced "chronic pneumonitis." The degree of pneumonitis produced by phosgene was rated as slight, moderate, or severe. Slight pneumonitis was defined as mural thickening of respiratory bronchioles with involvement of adjacent alveoli. Moderate pneumonitis was defined as alveolar involvement in a peribronchiolar zone that extends no

more than one-third of the distance to the next bronchiole. Severe pneumonitis was defined as mural thickening of the respiratory bronchioles accompanied by obliteration of adjoining alveoli and air spaces containing desquamated alveolar cells. The lowest 1-h phosgene concentration producing moderate pneumonitis was 0.8 ppm. The same effect occurred with 1-h exposures to phosgene at 0.9, 2.5, or 3 ppm. This occurred in two of three rats, the third rat displaying slight pneumonitis.

Hatch et al. (1986) exposed Sprague-Dawley rats (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar aveolar lavage fluid protein (LFP). The LFP findings were 340 ± 38, 258 ± 18, 506 ± 54, 1,642 ± 116, or 2,471 ± 125 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p < 0.05$) increased protein concentration was 0.2 ppm.

Male Sprague-Dawley rats were exposed to phosgene at 0, 0.125, 0.25, 0.5, or 1 ppm for 4 h and sacrificed on day 0, 1, 2, or 3 postexposure (Currie et al. 1987a). Animals were exposed in 0.32 m^3 Rochester-type inhalation chambers. The air flow was 0.32 m^3/min, and the gas mixture passed downward through stainless steel wire cages holding the animals and was exhausted at the bottom through a water scrubber. Temperature in the chambers was 23.0 ± 3.4°C, and humidity was 60 ± 10% during exposures. The chambers were monitored by both infrared analysis and gas chromatography continuously during exposure, and even phosgene distribution was assured by sampling from various areas of the exposure chamber. Measured phosgene concentrations were within 2% to 6% of target concentrations. Exposure-related changes were observed in body weights, wet lung weights, LFP concentrations, and total cell count and differential cell count in lavage fluid. Body weights were decreased immediately after exposure through day 2 for the 0.5- and 1-ppm exposure groups. Wet lung weights were increased in the 0.5 ppm exposure group on postexposure days 1, 2, and 3 and in the 1-ppm exposure group immediately after exposure and on postexposure days 1, 2, and 3. The relative wet-lung-to-body-weight ratios were increased immediately after exposure and on days 1, 2, and 3 in the 0.5- and 1-ppm exposure groups. LFP concentrations were increased in the 0.25-ppm exposure group on day 1 and in the 0.5- and 1-ppm exposure groups immediately after exposure and on days 1, 2, and 3. Total cell counts in lavage fluid were elevated in the 1-ppm exposure group on days 2 and 3. Percentage of polymorphonuclear leukocytes

were increased in the 0.25-ppm exposure group on days 1 and 2 and in the 0.5- and 1-ppm exposure groups on days 1, 2, and 3. The LFP and cellular parameters had their peak effect on day 1 postexposure and had begun a return to control values by day 3 postexposure, suggesting that the pulmonary damage was reversible or rapidly repairable.

In another study, Currie et al. (1987b) exposed male Sprague-Dawley rats to phosgene at 0, 0.05, 0.125, 0.25, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Currie et al. (1987a). Animals were sacrificed immediately after exposure and at days 1, 2, and 3 postexposure. The ATP concentrations in lungs were significantly ($p < 0.05$) decreased immediately after exposure at all exposure concentrations. The 1-ppm exposure group also had decreased ATP concentrations on day 1 and increased ATP concentrations on days 2 and 3. All other exposure groups had ATP concentrations similar to control values on days 1, 2, and 3. LFP concentrations were only measured immediately after exposure and were linearly increased at 0.25, 0.5, and 1 ppm.

Frosolono and Pawlowski (1977) exposed anesthetized male CFE Carworth rats to phosgene at 0, 100, 200, or 430 ppm for approximately 10 min. Animals were exposed in a 364-L glass and stainless-steel chamber, and phosgene concentrations were estimated with a phosgene detector tube. The authors stated that "the analytical method for the determination of phosgene concentrations is not highly precise … and concentrations given should be considered putative or nominal." Groups of six to eight rats per concentration were sacrificed 0, 30, 60, or 90 min after exposure. No percentage change of lung water (used as a measure of pulmonary edema) was observed in rats exposed to phosgene at 100 or 200 ppm and sacrificed 0 and 30 min after exposure. However, 60 min postexposure, the 100-ppm exposure group had a 6.7% increase in lung water and the 200-ppm exposure group had an 8.7% increase in lung water. Cytochrome C oxidase activities (specific and total) from the lungs were decreased, ranging from 30.1% to 79.8% after rats were exposed at 100 ppm and sacrificed 0, 30, and 60 min after exposure. After exposure at 200 ppm, relative serum lactic dehydrogenase (LDH) activities were increased from 1- to 3-fold over the postexposure time of 0 to 90 min. An exposure at 430 ppm resulted in decreased lung LDH activities (specific and total) ranging from 3.3% to 70.8% in the organelle fractions (homogenate and soluble). The authors suggested that the decreased LDH activities were indicative of cellular damage resulting in increased serum LDH activities.

In a different report, Pawlowski and Frosolono (1977) describe pulmonary ultrastructural alterations in male CFE Carworth rats exposed to phosgene in

a manner essentially identical to that described in Frosolono and Pawlowski (1977). Immediately after exposure, animals exposed to phosgene at 100 ppm exhibited vesiculation of ciliated and Clara cell cytoplasm in the bronchiolar epithelium, and interstitial edema was observed 30 min postexposure. In animals exposed to phosgene at 200 ppm, interstitial edema was observed immediately after exposure, and focal Type I cell discontinuities and interstitial and intracellular edema were present 30 min postexposure. At 48 min postexposure to phosgene at 200 ppm, interstitial cellular edema with general septal thickening and involvement of Type II cells was observed. At 430 ppm, cytoplasmic sequestration figures were observed in Type II cells 60 min postexposure.

In another study, lavage protein concentrations and histopathological assessments of the lungs were determined in male Wistar rats (10-15 per group) exposed to phosgene at 0, 0.1, 0.15, 1, 2.5, or 5 ppm for 10, 20, 50, 60, 250, 330, or 500 min (Diller et al. 1985). The exposure concentrations and durations were paired to provide different exposure scenarios corresponding to ≤ 50 ppm·min. A special 7-L plexiglass chamber was constructed to achieve reliable exposures at low concentrations of phosgene. Air exchange was 8-fold per minute, and consistency of phosgene concentration throughout the chamber was confirmed by a movable suction probe. Long-term mean phosgene concentrations were measured by collection of the gas samples in a glass bubbler and subsequent titration. Consistency throughout exposure was determined by a galvanometric analyzer, and concentration was checked using detector paper. Animals were sacrificed either 24 or 48 h after the phosgene exposure. A phosgene concentration at 50 ppm·min (5 ppm for 10 min) was required to produce alveolar edema. A concentration of 50 ppm·min was also required to produce an increase in LFP, and widening of pulmonary interstices was observed at 25 ppm·min. No phosgene threshold was observed for the latter two parameters down to 0.1 ppm, indicating that the CT = k relationship is valid for these two parameters. However, under the conditions of this study, Haber's rule appears to be valid for pulmonary edema only down to 5 ppm.

Franch and Hatch (1986) exposed male Sprague-Dawley rats to phosgene at either 1 ppm for 4 h with the sacrifices occurring immediately after exposure and on recovery period days 1, 2, 7, or 14 or 1 ppm for 7 h with the sacrifices occurring hourly during the exposure period. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were 0.98 ± 0.03 ppm for the 4-h exposure regimen and 1.03 ± 0.02 ppm for the 7-h exposure regimen. Body weights of rats exposed at 1 ppm for 4 h were significantly ($p \leq 0.01$) decreased to 13% below controls on day 1 postexposure. Body weights in-

creased toward control values, achieving 3% below controls on day 14. Food consumption was also decreased compared with controls but was less than 10% below normal by day 4. Lung weights of exposed animals were 60% greater than controls immediately after exposure and remained elevated through day 7 postexposure. Lung nonprotein sulfhydryl (NPSH) content was similar in control and exposed rats on day 1, had increased to 80% above controls on day 2, and decreased back to control levels by day 7. Glucose-6-phosphate dehydrogenase (G6PD) activity was increased 40% in exposed animals compared with controls from days 1 through 14. Sequential examination every hour during a 7-h exposure revealed lung weights increasing 4 h into the exposure, reaching a maximum elevation of 60% above controls at 6 h. Both the NPSH levels and G6PD activities were decreased in this exposure regimen.

Frosolono and Currie (1985) investigated the effect of phosgene on the pulmonary surfactant system (PSS) in groups of six to14 rats exposed to phosgene at 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). The actual chamber concentration was 1.0 ± 0.06 ppm. Animals were sacrificed immediately after exposure, or on postexposure days 1, 2, or 3. Pulmonary edema was present immediately after exposure and persisted through day 3. Phosphatidylinositol levels were significantly ($p < 0.05$) decreased compared with controls immediately after exposure only. Phosphatidylserine and phosphatidylethanolamine levels were significantly increased compared with controls on days 1,2, and 3 postexposure. Phosphatidylcholine levels were increased at all time points compared with controls.

Jaskot et al. (1989) exposed groups of male Sprague-Dawley rats (16 per group) to phosgene at 0 or 0.5 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). The actual chamber concentration was 0.54 ± 0.05 ppm. The rats were sacrificed immediately or 24 h postexposure. Phosgene-exposed rats showed no changes in angiotensin-converting enzyme (ACE) activity in lavage fluid or serum compared with controls. Whole-lung ACE activity was significantly increased immediately after exposure and 24 h postexposure, with increases of 55% and 44% above controls, respectively. Phosgene-exposed rats also had increased ACE activity in lavage cell pellets, with increases of 50% and 54% above controls at 0 and 24 h, respectively.

Assessment of pulmonary immunocompetence was determined by exposing male Fischer 344 rats to phosgene at 0.1, 0.5, or 1 ppm for 4 h and measuring pulmonary natural killer cell activity on day 1, 2, 4, or 7 postexposure (Burleson and Keyes 1989). The animals were exposed in a Rochester cham-

ber; temperature and humidity were maintained at 23.3 ± 1.7°C and 60 ± 10%, respectively. The chamber atmosphere was continuously monitored during exposures by both gas chromatography and infrared analysis. The actual chamber concentrations were 0.97, 0.49, and 0.10 ppm for the 1-, 0.5-, or 0.1-ppm groups, respectively. The pulmonary natural killer activities in the rats exposed at 1 ppm were significantly ($p < 0.05$) decreased on days 1, 2, and 4. A decrease ($p < 0.05$) in natural killer cell activity was also observed in the 0.5-ppm group. No effect was noted in the 0.1-ppm group.

Another immunological assessment, pulmonary cytotoxic T-lymphocyte (CTL) activity, was examined in male Fischer 344 rats exposed to phosgene at 0 or 1 ppm for 4 h. Animals were exposed in a Rochester exposure chamber, and the exposure atmosphere was monitored by gas chromatography and infrared analysis. The actual exposure concentration was 1.0 ± 0.04 ppm. Twenty-four hours after phosgene exposure, subsets of both the control and phosgene-treated rats were infected with influenza virus. The remaining control and phosgene-exposed rats were sham infected with uninfected lung homogenate. Animals were sacrificed on day 2, 5, 7, 10, 15, or 20 postinfection (Ehrlich et al. 1989).

A significant suppression of CTL activity was noted in phosgene-exposed, influenza-infected rats compared with air-controls, air-infected, and phosgene-treated sham-infected animals. This effect was observed only on day 10 postinfection; however, this is a time when peak activity is normally detected in control rats. Body weights were significantly decreased ($p < 0.05$) in phosgene-exposed, infected and uninfected rats on day 2 postinfection and in phosgene-exposed, infected animals at day 5. Lung weights were significantly increased ($p < 0.05$) in phosgene-exposed, infected and uninfected rats on days 2 and 5 postinfection compared with air-infected and air-uninfected controls.

3.2.3. Guinea Pigs

Cameron et al. (1942) exposed ten guinea pigs to phosgene at an average concentration of 0.86 ppm for 5 h. All survived an apparent 24-h postexposure period.

Hatch et al. (1986) exposed Hartley guinea pigs (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters are similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchi-

olar alveolar lavage fluid protein (LFP). The LFP findings were 305 ± 19, 228 ± 47, 407 ± 75, 524 ± 47, or 1,212 ± 149 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p < 0.05$) altered protein concentration was 0.5 ppm.

In another study, Hartley guinea pigs (five per group) were exposed to phosgene at 0, 0.25, or 0.5 ppm for 4 h (Slade et al. 1989). The exposure chamber and atmosphere generation and measurement systems were similar to those used by Hatch et al. (1986). The LFP concentrations were measured 16 to 18 h after exposure. These investigators found that the LFP concentrations were elevated by 90% in animals exposed to phosgene at 0.25 ppm and 250% in animals exposed at 0.5 ppm, when compared with controls.

3.2.4. Hamsters

Hatch et al. (1986) exposed Syrian Golden hamsters (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar alveolar lavage fluid protein (LFP). The LFP findings were 319 ± 6, 347 ± 14, 520 ± 63, 1,289 ± 92, or 3,035 ± 111 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p < 0.05$) altered protein concentration was 0.2 ppm.

3.2.5. Rabbits

Cameron et al. (1942) exposed ten rabbits to phosgene at an average concentration of 0.86 ppm for 5 h. All survived an apparent 24-h postexposure period.

Hatch et al. (1986) exposed New Zealand white rabbits (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar alveolar lavage fluid protein (LFP). The LFP findings were 292 ± 11, 309 ± 20, 346 ± 26, 517 ± 68, and 855 ± 71 (units not pro-

vided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p < 0.05$) altered protein concentration was 0.5 ppm.

3.2.6. Dogs

Coman et al. (1947) exposed adult mongrel dogs to phosgene at 108-197 ppm for 30 min and sacrificed the animals 0.63 to 8.58 h after exposure or exposed the dogs to phosgene at 71-80 ppm for 3 min and sacrificed the animals 0.13 to 5.32 h after exposure. Mild to severe emphysema was observed in all dogs, severity generally correlating to exposure concentration and time. Swelling and sloughing of the bronchiolar mucosa were then observed and were usually confined to bronchioles proximal to the respiratory bronchioles. Transient bronchiolar constriction, followed by dilatation of the bronchioles, was also observed. Congestion of the lung and alveolar edema usually followed in the lower exposure concentrations at the 30-min exposure time with the lung congestion preceding alveolar edema in the higher exposure concentrations at the 3-min exposure time. Lung–to–body weight ratios increased as both exposure concentration and/or sacrifice time after exposure increased.

In another study, adult mongrel dogs were exposed to phosgene for 30 min at concentrations that fluctuated between 24 and 40 ppm (Clay and Rossing 1964). The experimental design was as follows: (1) two dogs served as controls, (2) seven dogs were exposed one or two times and sacrificed 1 or 2 d after the last exposure, (3) seven dogs were exposed four to 10 times and sacrificed from 1 to 7 d after the last exposure, (4) five dogs were exposed 15 to 25 times and sacrificed immediately or from 1 to 14 d after the last exposure, and (5) four dogs were exposed 30 to 40 times and sacrificed immediately or from 1 to 12 wk after the last exposure. For all animals exposed one or two times, acute bronchiolitis or peribronchiolitis developed. Pulmonary emphysema was produced in dogs receiving more than two exposures.

3.2.7. Sheep

Groups of ten unanesthetized, adult sheep were exposed to phosgene at 0 or 767 ppm for 10 min (Assaad et al. 1990). Blood samples were collected

immediately before the exposure and 15, 30, 60, 120, 180, or 240 min after the exposure; also, plasma prostacyclin and thromboxane metabolites (6-keto-$PGFl_a$ and TXB_2) concentrations were measured. Levels of both metabolites were significantly ($p < 0.05$) increased in the exposed animals compared with pre-exposure baseline values and air-control values. The 6-keto-$PGFl_a$ returned to control values by 180 min, whereas the TXB_2 did not. The authors concluded that (1) acute lung injury occurred immediately following exposure even though pulmonary edema and symptoms of pulmonary toxicity developed 4 to 8 h after exposure, (2) phosgene may induce pulmonary edema by injuring cell membranes, and (3) arachidonic acid metabolites may be useful as early, nonspecific markers for phosgene-induced lung injury.

In a subsequent study (Assaad et al. 1991), ten unanesthetized, adult sheep were exposed to phosgene at 0 or 767 ppm for 10 min and were sacrificed 4 h after exposure. Gross examination of the lungs revealed congestion and edema, and the light microscopic evaluation demonstrated alveolar and interstitial edema, fibrin and neutrophil exudation in the air spaces, and increased alveolar macrophages. The electron microscopic examination revealed that Type I pneumocytes had intracellular swelling, necrosis, and denuding of basement membrane with the preservation of the tight junctions. Type II pneumocytes showed loss of lamellar bodies, cytoplasmic swelling, and damage to the endoplasmic reticulum. Endothelial cells showed increased density and vesicular activity, cytoplasmic swelling, and displacement of the basement membrane.

Five Dorset-crossbred wether sheep underwent surgery in order to provide simultaneous information concerning phosgene exposure and pulmonary vascular and interstitial fluid dynamics (Keeler et al. 1990a). The efferent duct of the caudal mediastinal lymph node was cannulated to monitor pulmonary lymph flow. Additionally, a carotid atrial catheter, a pulmonary artery catheter, and a left atrial catheter were implanted to monitor systemic and pulmonary hemodynamics. After a 5- to 7-d recovery period, the sheep were exposed to phosgene at 480-600 ppm for 10 min. The control pulmonary lymph flow rate was 10.3 ± 2.2 g/h, and the exposed sheep values were 19.5 ± 6.0, 21.5 ± 6.0, 22.5 ± 6.0, 24.0 ± 5.9, 26.5 ± 5.3, 26.9 ± 6.0, or 27.3 ± 5.8 g/h for 1, 1.5, 2, 2.5, 3, 3.5, or 4 h postexposure, respectively. There was a small increase in mean pulmonary microvascular pressure but no change in the ratio of lymph-to-plasma protein concentration. Sheep were sacrificed 4 h after exposure. Histopathological evaluations of the lungs revealed diffuse, moderate alveolar and interlobular edema.

3.2.8. Goats

Cameron et al. (1942) exposed two goats to an average phosgene concentration of 0.86 ppm for 5 h. Both survived an apparent 24-h postexposure period.

3.2.9. Cats

Cameron et al. (1942) exposed two cats to an average phosgene concentration of 0.86 ppm for 5 h. One cat became "very ill" with considerable labored breathing, but both survived an apparent 24-h postexposure period.

3.2.10. Monkeys

Cameron et al. (1942) exposed two monkeys to an average phosgene concentration of 0.86 ppm for 5 h. One of the monkeys became "very ill" with considerable labored breathing, but both survived an apparent 24-h postexposure period.

3.3. Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies regarding animal exposure to phosgene were not available.

3.4. Genotoxicity

Genotoxic studies regarding animal exposure to phosgene were not available. However, the two highly reactive chlorines of phosgene suggest that it could act on DNA in a similar manner to that of bifunctional alkylating agents (Shah et al. 1979).

3.5. Carcinogenicity

A study by Selgrade et al. (1989) showed that exposure to phosgene at very low levels enhances the susceptibility of mice to lung tumor formation.

Female C57BL/6 mice were exposed for 4 h to phosgene at 0.01 (N = 13), 0.025 (N = 28), or 0.05 ppm (N = 35) and injected intravenously with syngeneic B16 melanoma cells on the following day. Controls were injected with tumor cells and exposed to air. The lungs were removed 2-3 wk after tumor cell injection and the tumors were counted. Compared with controls, there was a statistically significant ($p < 0.05$) increase in the number of B16 melanoma tumors in the lungs of mice treated with phosgene at 0.025 or 0.05 ppm. The number of tumors per lung were 105, 110, or 185 in mice treated with 0.01, 0.025, or 0.05 ppm, respectively, compared with 90, 75, or 100 in the respective control groups. Exposure to 0.025 ppm was considered the lowest-observed-effect level. Extending the exposure time from 4 to 8 h did not alter the susceptibility to B16 tumors at 0.01 ppm.

In other experiments using a higher concentration, mice were exposed by inhalation to phosgene at 0.5 ppm for 4 h and injected intravenously with melanoma tumor cells on the following day or injected with tumors and then exposed at 0.5 ppm for 4 h/d for 4 consecutive days. There was a significant increase ($p < 0.05$) in the number of lung tumors in the group exposed to phosgene prior to inoculation (96 tumors per lung compared with 38 tumors per lung for controls). Although the number of tumors in mice exposed to phosgene on 4 consecutive days beginning immediately after tumor injection was higher than in controls (65 tumors per lung compared with 48 tumors per lung for controls), the difference was not statistically significant. These experiments showed that exposure following tumor injection had little effect on tumor susceptibility compared with phosgene exposure prior to tumor injection.

3.6. Summary

Animal lethality studies are abundant; however, the studies are of varying quality and many are incompletely reported. Thus, the utility of the lethality studies must be considered on a case by case basis. Even though there are limitations concerning these studies, there appears to be little species variability between rats, mice, and guinea pigs, and the CT = k relationship appears to be generally valid. (Although at very high or very low concentrations or at exposure times so short that the animal can hold its breath, the CT = k relationship may not hold.)

Many nonlethal acute inhalation studies exist and are of generally good quality. These studies also suggest that there are few differences between species after acute exposure to phosgene and that the type and sequence of

effects are similar in humans and experimental animals. Many of the nonlethal toxicity studies describe biochemical changes in lung fluid, whose pathogenesis is likely due to acylation (see Section 4.2). Selected biochemical and other nonlethal effects are summarized in Table 1-11.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Following inhalation exposure, a small portion of phosgene hydrolyzes to hydrochloric acid (HCl) and carbon dioxide (CO_2) in the mucous coating of the upper respiratory tract (Diller 1985), but in the moist atmosphere of the terminal spaces of the lungs, more extensive hydrolysis is thought to occur (Beard 1982). Although phosgene is only slightly soluble in water, once in solution it rapidly hydrolyzes to HCl and CO_2. However, phosgene reacts even faster with other functional groups, such as amino, hydrazino, and sulfhydryl groups (Jaskot et al. 1991; Diller 1985).

4.2. Mechanism of Toxicity

The toxicity of phosgene is due to both acylation and hydrolysis. The acylation is most important and results from the reaction of phosgene with nucleophiles such as amino, hydroxyl, and sulfhydryl groups of macromolecules. The acylation causes lipid and protein denaturation, irreversible membrane changes, and disruption of enzymatic function. Phosgene depletes lung glutathione, and glutathione reductase and superoxide dismutase increase as a result of the lung's response to injury. Cellular glycolysis and oxygen uptake are decreased following exposure to phosgene, and there is a decrease of intracellular ATP and cyclic AMP associated with increased permeability of pulmonary vessels and pulmonary edema. Phosgene exposure also causes increased lipid peroxidation and increased leukotriene synthesis but no change in cyclooxygenase metabolism (TEMIS 1997).

The hydrogen chloride formed by the hydrolysis of phosgene causes initial irritation to the eyes, nasopharynx, and respiratory tract. However, because of phosgene's poor water solubility, a minimal amount of hydrogen chloride is formed (TEMIS 1997).

TABLE 1-11 Summary of Selected Nonlethal Effects of Phosgene

Phosgene Concentration (ppm)	Exposure Time (h)	Species	Effect	Reference
0.05	4	Rat	Decreased ATP	Currie et al. 1987b
0.1	1	Rat	No edema; no histopathology	Diller et al. 1985
0.1	4	Rat	Lung histopathology	Diller et al. 1985
0.1	4	Rat	No decrease in PNKC activity	Burleson and Keyes 1989
0.1	4	Rat	No increase in LFP levels	Hatch et al. 1986
0.1	4	Rat	Decreased ATP; no changes in LFP level	Currie et al. 1987b
0.1	4	Mouse	No changes in LFP levels	Hatch et al. 1986
0.1	4	Hamster	No changes in LFP levels	Hatch et al. 1986
0.125	4	Rat	No changes in LFP levels; no lung weight change	Currie et al. 1987a
0.2	4	Rat	Increased levels of LFP	Currie et al. 1987b
0.2	4	Mouse	Increased levels of LFP	Hatch et al. 1986
0.2	4	Guinea Pig	No changes in LFP levels	Hatch et al. 1986
0.2	4	Rabbit	No changes in LFP levels	Hatch et al. 1986
0.2	4	Hamster	Increased levels of LFP	Hatch et al. 1986
0.25	4	Rat	Increased levels of LFP and PMN;	Currie et al. 1987a

FIGURE 1-11 *Continued*

Phosgene Concentration (ppm)	Exposure Time (h)	Species	Effect	Reference
0.25	4	Guinea Pig	Increased levels of LFP	Slade et al., 1989
0.5	4	Rat	Decreased body weight; increased lung weight; increased levels of LFP	Currie et al. 1987a
0.5	4	Guinea Pig	Increased levels of LFP	Hatch et al. 1986
0.5	4	Rabbit	Increased levels of LFP	Hatch et al. 1986
0.5	4	Rat	Decreased PNKC activity	Burleson and Keyes 1989
0.5	4	Rat	Increased ACE activity	Jaskot et al., 1989
1	4	Rat	Increased lung weight (14 d); decreased body weight; increased G6PD activity and NPSH content	Franch and Hatch 1986
1	4	Rat	Decreased PNKC activity	Burleson and Keyes 1989
1	4	Rat	Increased lung weight; decreased body weight; suppressed cytotoxic T-lymphocytes	Ehrlich et al. 1989

4.3. Structure-Activity Relationships

Phosgene is a reactive intermediate of both chloroform and carbon tetrachloride metabolism. Chloroform is metabolized by oxidative dehydrochlorination of its carbon-hydrogen bond to form the highly unstable trichloro-methanol (Cl_3COH), which is then spontaneously converted to phosgene. This reaction is catalyzed by cytochrome P-450 and occurs in both the liver and kidneys. The evidence for phosgene formation from chloroform was the isolation of 2-oxothioazolidine-4-carboxylic acid from the microsomal incubation of chloroform in the presence of cysteine. This compound is the expected product of the reaction of phosgene with cysteine (Pohl et al. 1977; Mansuy et al. 1977). The electrophilic phosgene further reacts with water to yield CO_2 and Cl^- (major end products of chloroform metabolism), but significant amounts of phosgene bind covalently with proteins and lipids or conjugate with cysteine or glutathione (GSH) (EPA 1985).

Covalent binding of phosgene with cellular macromolecules has been proposed as a mechanism of chloroform-induced hepatic and renal toxicity (Pohl et al. 1980a,b), and it is generally accepted that the carcinogenic activity of chloroform resides in its highly reactive intermediate metabolites such as phosgene. Irreversible binding of reactive chloroform metabolites to cellular macromolecules support several theoretical concepts as a mechanism for its carcinogenicity (EPA 1985).

Covalent macromolecular binding of phosgene may be prevented to some extent by endogenous GSH (Sipes et al. 1977). Phosgene reacts with two molecules of GSH to form diglutathionyl dithiocarbonate (GSCOSG), a compound identified as a metabolite of chloroform in rat liver microsomes and mouse kidney homogenates incubated with chloroform in the presence of GSH (Pohl et al. 1981; Branchflower et al. 1984). In mouse kidney homogenates, GSCOSG was shown to be further metabolized by kidney α-glutamyl transpeptidase to *N*-(2-oxothiazolidine-4-carbonyl)-glycine, which in turn is hydrolyzed, possibly in the presence of cysteinyl glycinase, to 2-oxothiazolidine-4-carboxylic acid (Branchflower et al. 1984).

The metabolism of carbon tetrachloride proceeds via cytochrome P-450-dependent dehalogenation (Sipes et al. 1977). The first step involves cleavage of one carbon-chlorine bond to yield Cl^- and a trichloromethyl free radical, which is then oxidized to the unstable intermediate trichloromethanol, the precursor of phosgene. Hydrolytic dechlorination of phosgene yields CO_2 and HCl (Shah et al. 1979). Although there are similarities in the metabolism of chloroform and carbon tetrachloride, metabolic activation of chloroform produces primarily phosgene, whereas the level of phosgene production from

carbon tetrachloride appears to be small. Pohl et al. (1981) compared the amount of phosgene (as diglutathionyl dithiocarbamate) produced by the aerobic metabolism of carbon tetrachloride and the amount produced from chloroform by liver microsomes from phenobarbital-treated rats. The results indicate that phosgene production from carbon tetrachloride is only 4% of that produced from chloroform. The reactive metabolites of both chloroform and carbon tetrachloride covalently bind to proteins and lipids but bind only minimally to DNA and nucleic acids. The failure of the reactive species (e.g. phosgene, trichloromethyl free radical, and other metabolites) to significantly bind to DNA has been ascribed to their short half-lives and to their lack of nuclear penetration (EPA 1985).

Given to intact rats, ^{14}C-phosgene labeled liver proteins and to a smaller extent lipids (Reynolds 1967). The pattern of labeling was different from that of ^{14}C-carbon tetrachloride and was similar to that of ^{14}C-chloroform. It was also shown that ^{36}Cl-carbon tetrachloride radioactivity was stably incorporated into liver lipid and protein, pointing to the trichloromethyl radical rather than phosgene as the reactive form of carbon tetrachloride. Cessi et al. (1966) reported that phosgene labeled the terminal amino groups of polypeptides in a manner similar to in vivo protein labeling produced by carbon tetrachloride. However, after inhalation, phosgene reacts completely with lavage fluid, lung tissue, and lung capillary blood so that it is unlikely that phosgene will reach tissue beyond the lung (Diller 1974).

4.4. Other Relevant Information

4.4.1. Haber's Law and Time Scaling

The concept of a "death product" was introduced by Haber to explain the relationship between the extent of exposure to phosgene and death (Haber 1924). According to "Haber's law," the biological effect of phosgene is directly proportional to the exposure, expressed as the product of the atmospheric concentration (C) and the time of exposure (T), or CT = k, where k can be death, pulmonary edema, or other biological effects of phosgene exposure (EPA 1986). Haber's law has subsequently been shown by other investigators to be valid for both nonlethal and lethal effects within certain limits.

For example , Rinehart (1962) and Rinehart and Hatch (1964) showed that the CT product appears to be a valid way to express pulmonary irritation due to phosgene exposure in rats. This is based on the finding of equal degrees of respiratory response, as measured by reduction in pulmonary gas exchange

capacity, from exposures to various combinations of C and T that yield the same CT product.

Rat and mouse lethality data from the well-conducted study of Zwart et al. (1990) also suggest that Haber's law is valid for phosgene. The study by ten Berge et al. (1986) has shown that the concentration–exposure-time relationship for many irritant and systemically acting vapors and gasses can be described by the relationship $C^n \times t = k$. When the 10- to 60-min rat LC_{50} data are utilized in a linear regression analysis a value of the exponent, n, of 0.93 is obtained. The mouse 10- to 60-min lethality data yield a value of 1.3 for n.

Thus, the fact that these empirically derived values for the exponent n approximate 1 is further support that Haber's law is valid for phosgene.

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data were relevant for establishing AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

No animal data were relevant for establishing AEGL-1 values.

5.3. Derivation of AEGL-1

Appropriate data were not available for derivation of AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of $\leq$24 h.

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were relevant to establishing the AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Chemical pneumonia was observed in rats exposed to phosgene at 2.0 ppm for 90 min (Gross et al. 1965). Biochemical markers of phosgene exposure, such as increased LFP, were observed in mice, rats, guinea pigs, hamsters, and rabbits exposed at up to 1 ppm for 4 h (Hatch et al. 1986; Diller et al. 1985). Other effects defined by AEGL-2 included "very ill" monkeys with labored breathing (Cameron et al. 1942) and acute bronchiolitis or peribronchiolitis in dogs (Clay and Rossing 1964). However, a lack of experimental details in the monkey and dog studies renders them inappropriate for AEGL derivation.

6.3. Derivation of AEGL-2

The chemical pneumonia observed in rats exposed to phosgene at 2 ppm for 90 min (Gross et al. 1965) will be used as the basis for deriving AEGL-2 values. This end point was chosen because at a $C \times t$ product of 180 ppm·min, approximately 60% of rats exhibited chemical pneumonia. Whereas, at $C \times t$ products $\leq$180 ppm·min, only 15% of exposed rats showed pneumonia or chemical pneumonitis. An uncertainty factor (UF) of 3 will be applied for interspecies extrapolation because little species variability is observed in lethal and nonlethal end points after exposure to phosgene. A UF of 3 will also be applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. Thus, the total UF is 10. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Haber's law ($C \times t = k$; $n = 1$) has been shown to be valid for phosgene within certain limits and will be used for scaling of the AEGL values for phosgene for the 30-min and 1-, 4-, and 8-h time points. The 30-min value is also adopted as the 10-min value, because extrapolation would yield a 10-min AEGL-2 value close to concentrations producing alveolar edema in rats. The AEGL-2 values for phosgene are presented in Table 1-12, and the calculations for these AEGL-2 values are presented in Appendix A.

These AEGL-2 values are supported by the nonlethal toxicity studies of Franch and Hatch (1986) and Ehrlich et al. (1989). In both of these studies, rats exposed to phosgene at 1 ppm for 4 h developed severe pulmonary edema and body-weight loss. If this exposure regimen and a total UF of 10 are uti-

TABLE 1-12 Proposed AEGL-2 Values for Phosgene (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)

lized to calculate AEGL-2 values, similar supporting values of 0.8, 0.4, 0.1, and 0.05 ppm are obtained for the 30-min and 1-, 4-, and 8-h time points, respectively. The 10-min value is supported by the fact that Diller et al. (1985) observed alveolar pulmonary edema in rats exposed at 5 ppm for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min value of 0.5 ppm.

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were relevant to establishing the AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Many lethality data exist for a variety of species (mouse, rat, guinea pig, rabbit, cat, dog, goat, sheep, and monkeys). However, in most cases, experimental parameters are poorly described, and the quality of the data is questionable for AEGL derivation. The mouse and rat LC_{50} studies of Zwart et al. (1990) are the exception and are appropriate for AEGL-3 derivation.

7.3. Derivation of AEGL-3

The highest concentration causing no mortality in the rat after a 30-min exposure is 15 ppm (Zwart et al. 1990). This value will be used as the basis for deriving 30-min and 1-, 4-, and 8-h AEGL-3 values. The highest concentration causing no mortality in the rat and mouse after a 10-min exposure is 36 ppm (Zwart et al. 1990); this value will be used as the basis for the 10-min AEGL-3 value. A UF of 3 will be applied for interspecies extrapolation

TABLE 1-13 Proposed AEGL-3 Values for Phosgene (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)

because little species variability is observed both in lethal and nonlethal end points after exposure to phosgene. A UF of 3 will also be applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. Thus, the total UF is 10. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Haber's law ($C \times t = k$; $n = 1$) has been shown to be valid for phosgene within certain limits and will be used for scaling of the AEGL values for phosgene across time for the 1-, 4-, and 8-h values. The AEGL-3 values for phosgene are presented in Table 1-13 (above), and the calculations for these AEGL-3 values are presented in Appendix A.

8. SUMMARY OF PROPOSED 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 1-14. Data were insufficient for deriving

TABLE 1-14 Summary of Proposed AEGL Values for Phosgene (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)

AEGL-1 values. Chemical pneumonia in rats was used as the basis for AEGL-2, and the highest concentration causing no mortality in the rat after a 10- or 30-min exposure (and mice, 10-min value only) was used for AEGL-3.

8.2. Comparison with Other Standards and Guidelines

Table 1-15 provides existing standards and guidelines for phosgene.

TABLE 1-15 Extant Standards and Guidelines for Phosgene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm
AEGL-3	3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm
ERPG-1[a]			NA		
ERPG-2[a]			0.2 ppm		
ERPG-3[a]			1 ppm		
EEGL (NRC)[b]			0.2 ppm		0.02 ppm (24-h)
NIOSH IDLH[c]	2 ppm				
NIOSH STEL[d]	0.2 ppm (15-min ceiling)				
NIOSH REL[d]					0.1 ppm (10-h)
OSHA PEL-TWA[e]					0.1 ppm
ACGIH TLV[f]					0.1 ppm
MAK (Germany)[g]					0.02 ppm
MAC (Netherlands)[h]					0.02 ppm

[a]ERPG (emergency response planning guidelines) (AIHA 2000) The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The

ERPG-1 for phosgene is not derived. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for phosgene is based on pulmonary pathology and function studies suggestion that concentrations exceeding 0.2 ppm may produce serious pulmonary effects in some individuals. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for phosgene is based on acute animal inhalation data indicating that concentrations exceeding 1 ppm for 1 h may by expected to produce pulmonary edema and possible mortality in a heterogeneous human population. As of 2000, the ERPG values for phosgene are under ballot consideration and review.

[b]EEGL (emergency exposure guidance levels) (NRC 1985) The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury. The EEGL for phosgene is based on the "most relevant animal exposure studies (Gross et al. 1965; Rinehart and Hatch 1964)" and studies suggesting that animals do not tolerate phosgene at 0.2 ppm administered 5 h/d for 5 d (Cameron and Foss 1941; Cameron et al. 1942).

[c]IDLH (immediately dangerous to life and health) (NIOSH 1997) 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 phosgene is based on acute inhalation toxicity data in humans (Diller 1978).

[d]NIOSH REL-STEL (recommended exposure limit-short-term exposure limit) (NIOSH 1997) is analogous to the ACGIH TLV-TWA.

[e]OSHA PEL-TWA (permissible exposure limit–time-weighted average) (OSHA 1994) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/w.

[f]ACGIH TLV-TWA (Threshold Limit Value–time-weighted average) (ACGIH 2000) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]MAK (Maximale Argeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is analogous to the ACGIH-TLV-TWA.

[h]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

No reliable, quantitative human data exist. Human data are limited to descriptive effects from accidental exposure and are thus inappropriate for derivation of AEGL values. There is, however, a plethora of acute inhalation data in many experimental species. The database is sufficient to have good confidence in AEGL-2 and AEGL-3 values.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists, Inc). 2000. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th Edition.

AIHA (American Industrial Hygiene Association). 2000. Emergency Response Planning Guidelines. AIHA, Akron, Ohio.

Assaad, A., Trotz, M., Moore, D., Nold, J, Corcoran, K., Hurt, H., Keeler, J., Phillips, K., and Said, S.I. 1990. Arachidonic acid metabolites as early markers of phosgene-induced acute lung injury and pulmonary edema. World Conference on Lung Health. Boston, MA. May 20-24. Am. Rev. Respir. Dis. 141: A420.

Assaad, A., Nold, J., Petrali, J., Moore, D., Mitcheltree, L., Corcoran, K., and Phillips, K. 1991. Pulmonary pathological alterations in sheep exposed to lethal dose of phosgene. 75th Annual Meeting of the American Societies for Experimental Biology, Atlanta, Georgia. April 21-25. FASEB J. 5:A484.

Beard, R.R. 1982. Inorganic compounds of oxygen, nitrogen, and carbon. In: Patty's Industrial Hygiene and Toxicology, Vol 2C, Clayton, G.D. and Clayton, F.E., Eds. John Wiley & Sons, New York. Pp. 4126-4128.

Box, G.E.P. and Cullumbine, H. 1947a. The relationship between survival time and dosage with certain toxic agents. Br. J. Pharmacol. 2:27-37.

Box, G.E.P. and Cullumbine, H. 1947b. The effect of exposure to sub-lethal doses of phosgene on the subsequent L(Ct)50 for rats and mice. Brit. J. Pharmacol. 2:38-55.

Bradley, B.L. and Unger, K.M. 1982. Phosgene inhalation: A case report. Texas Med. 78:51-53.

Branchflower, R.V., Nunn, D.S., Highet, R.J., et al. 1984. Nephrotoxicity of chloroform: metabolism to phosgene by the mouse kidney. Toxicol. Appl. Pharmacol. 72:159-168.

Burleson, G.R. and Keyes, L.L. 1989. Natural killer activity in Fischer 344 rat lungs as a method to assess pulmonary immunocompetence: Immunosuppression by phosgene inhalation. Immunopharmacol. Immunotoxicol. 11:421-443.

Cameron, G.R. and Courtice, F.C. 1946. The production and removal of oedema fluid in the lung after exposure to carbonyl chloride (phosgene). J. Physiol. 105:175-185. (Cited in EPA 1986)

Cameron, G.R. and Foss, G.L. 1941. Effect of low concentrations of phosgene for 5 hours on 5 consecutive days in groups of different animals. Washington, DC: British Embassy Defense Staff; Porton report no. 2316, serial no. 63. (Cited in EPA 1986)

Cameron, G.R., Courtice, F.C., and Foss, G.L. 1942. Effects of exposing different animals to a low concentration of phosgene 1:1,000,000 (4 mg/m^3) for 5 hours. (Chapter IX in First Report on Phosgene Poisoning. Portion Report No. 2339.) Washington, D.C. British Defense Staff. British Embassy. (Cited in EPA 1986)

Cessi, C., Columbini, C., and Mameli, L. 1966. The reaction of liver proteins with a metabolite of carbon tetrachloride. Biochem. J. 101:46-47c.

Chasis, H. 1944. Phosgene: Review of Literature on the effect of exposure in man and experimental animals. Contract W-49-036-CWS-1.

Clay, J.R. and Rossing, R.G. 1964. Histopathology of exposure of phosgene: An attempt to produce pulmonary emphysema experimentally. Arch. Pathol. 78:544-551.

Coman, D.R., Bruner, H.D., Horn, R.C., Friedman, M., Boche, R.D., McCarthy, M.D. Gibbon, M.H., and Schultz, J. 1947. Studies on experimental phosgene poisoning: I. The pathologic anatomy of phosgene poisoning with special reference to the early and late phases. Am. J. Pathol. 23:1037-1074.

Currie, W.D., Hatch, G.E., and Frosolono, M.F. 1987a. Pulmonary alterations in rats due to acute phosgene inhalation. Fundam. Appl. Toxicol. 8:107-114.

Currie, W.D., Hatch, G.E., and Frosolono, M.F. 1987b. Changes in lung ATP concentration in the rat after low-level phosgene exposure. J. Biol. Toxicol. 2:105-114.

Delephine, S. 1922. Summary notes on two fatalities due to inhaling phosgene. J. Ind. Hygiene. 4:433-440.

DHEW (U.S. Department of Health, Education, and Welfare). 1968. Eighth revision international classification of diseases, adapted for use in the United States. Public Health Services Publication No. 1693:1.

Diller, W.F. 1974. Klinik und Pathologie der phosgenvergiftung. Pneumonologie. 150:139-148.

Diller, W.F. 1978. Medical phosgene problems and their possible solution. J. Occup. Med. 20:189-193.

Diller, W. F., Bruch, J., and Dehnen, W. 1985. Pulmonary changes in the rats following low phosgene exposure. Arch. Toxicol. 57:184-190.

Diller, W.F. 1985. Pathogenesis of phosgene poisoning. Toxicol. Ind. Health. 1: 7-15.

Diller, W.F., Schnellbaecher, F., and Wuestefeld, E. 1979. Late pulmonary sequelae of phosgene poisoning or inhalation-toxic pulmonary edema. Arbeitsmed. Arbeitsschultz Prophyl. 29: 5-16. (Cited in EPA 1986)

Diller, W.F. and Zante, R. 1982. Dosis-wirkungs-beziehungen bei phosgeneinwirkung auf mensch und tier. Zbl. Arbeitsmed. 32: 360-368

Ehrlich, J.P., Gunnison, A.F., and Burleson, G.R. 1989. Influenza virus-specific cytotoxic T-lymphocyte activity in Fischer 344 rat lungs as a method to assess pulmonary immunocompetence: Effect of phosgene inhalation. Inhalation Toxicol. 1:129-138.

EPA (U.S. Environmental Protection Agency), 1985. Health Assessment Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA 600/8-84-004F.

EPA (U.S. Environmental Protection Agency). 1986. Health Assessment Document for Phosgene. Office of Health and Environmental Assessment. EPA/600/8-86/022A. Everett, E.D. and Overholt, E.L. 1968. Phosgene poisoning. JAMA. 205: 243-245.

Franch, S. and Hatch, G.E. 1986. Pulmonary biochemical effects of inhaled phosgene in rats. J. Toxicol. Environ. Health 19:413-423.

Freeman, S., Grodins, F.S., and Kosman, A.J. 1945. The use of helium in the treatment of phosgene poisoning. In: Fasciculus on chemical warfare medicine: v. II, respiratory tract. Washington, DC: National Research Council, Committee on Treatment of Gas Casualities; pp. 541-550. (Cited in EPA 1986)

Frosolono, M.F. 1976. Basic Mechanism, diagnostic procdures and therapeutic countermeasures for phosgene poisoning in animals. Final report, MCA. (Cited in EPA 1986)

Frosolono, M.F. 1977. Basic Mechanism, diagnostic procdures and therapeutic countermeasures for phosgene poisoning in animals. Final report, MCA. (Cited in EPA 1986)

Frosolono, M.F. and Currie, W.D. 1985. Response of the pulmonary surfactant system to phosgene. Toxicol. Ind. Health. 1: 29-35.

Frosolono, M.F. and Pawlowski, R. 1977. Effect of phosgene on rat lungs after single high-level exposure: I. Biochemical alterations. Arch. Environment Health 32: 271-277.

Frosolono, M.F. and Currie, W.D. 1985. Effect of phosgene on the pulmonary surfactant system (PSS): Dose-response relationships. Biochemistry 24:3386.

Galdston, M., Leutscher, J.A., Longcope, W.T., et. al. 1947a. A study of the residual effects of phosgene poisoning in human subjects: I. After acute exposure. J. Clin. Invest. 26:145-168.

Galdston, M., Leutscher, J.A., Longcope, W.T., and Ballich, N.L. 1947b. A study of the residual effects of phosgene poisoning in human subjects: II. After chronic exposure. J. Clin. Invest. 26:169-181.

Gross, P., Rinehart, W.E., and Hatch, T. 1965. Chronic pneumonitis caused by phosgene. Arch. Environ. Health. 10: 768-775.

Haber, F.R. 1924. Zur geschichte des gaskrieges [On the history of the gas war]. In: Fuenf Vortraege aus den Jahren 1920-23 [Five lectures from the years 1920-

1923]. Berlin, Germany: Verlag von Julius Springer; pp. 76-92. (Cited in EPA 1986)

Halpern, B.N., Cruchaud, S., Vermeil, G., and Roux, J.L. 1950. Experimental study on the pathogenesis and treatment of acute pulmonary edema. Arch. Int. Pharmacodyn. Ther. 82:425-476. (Cited in EPA 1986)

Hatch, G.E., Slade, R., Stead, A.G., and Graham, J.A. 1986. Species comparison of acute inhalation toxicity of ozone and phosgene. J. Toxicol. Environmental Health 19:43-53.

Hedlund, L.W., and Putman, C.E. 1985. Methods for detecting pulmonary edema. Toxicol. Ind. Health. 1:59-67.

Hegler, C. 1928. On the mass poisoning by phosgene in Hamburg. I. Clinical observations. 54:1551-1553.

Henschler, D. 1971. German MAK Criteria. (From Ehrlicher, H. 1971. Personal Communication, Department of Medicine, Bayer AG, Leverkusen).

Henschler, D. and Laux, W. 1960. On the specificity of a tolerance increase by repeated inhalation of pulmonary edema-producing gases. Naunyn-Schmiedbergs Arch. Exp. Pathol. Pharmakol. 239:433-441. (Cited in EPA 1986)

Herzog, H. And Pletscher, A. 1955. Die wirkung von industriellen reizgasen auf die bronchialschleimhaut des menschen. Schweizerische Medizinische Wochenschrift. 85:477-481.

Illing, J.W., Mole, M.L., Graham, J.A, et al. 1988. Influence of phosgene inhalation on extrapulmonary effects in mice. Inhalation Toxicol. 1:13-20.

Jaskot, R.H., Grose, E.C., and Stead, A.G. 1989. Increase in angiotensin-converting enzyme in rat lungs following inhalation of phosgene. Inhalation Toxicol. 1:71-78.

Jaskot, R.H., Grose, E.C., Richards, J.H., and Doerfler, D.L. 1991. Effects of inhaled phosgene on rat lung antioxidant systems. Fund. Appl. Toxicol. 17:666-674.

Kaerkes, B. 1992. Experiences with a phosgene indicator badge during an eleven-year period. M.D. Dissertation, Heinrich-Heine University. Duesseldorf, Germany.

Karel, L. and Weston, R.E. 1947. The biological assay of inhaled substance by the dosimetric method: The retained median lethal dose and the respiratory response in unanesthetized, normal goats exposed to different concentrations of phosgene. J. Ind. Hyg. Toxicol. 29:23-28.

Kawai, M. 1973. [Inhalation toxicity of phosgene and trichloronitromethane (chloropicrin)]. J. Sangyo Igaku 15:406-407.

Keeler, J.R., Hurt, H.H., Nold, J.B., Corcoran, K.D., and Tezak-Reid, T.M. 1990a. Phosgene-induced lung injury in sheep. Inhalation Toxicol. 2:391-406.

Keeler, J.R., Hurt, H.H., Nold, J.B., and Lennox, W.J. 1990b. Estimation of the LCt50 of phosgene in sheep. Drug Chem Toxicol. 13:229-239.

Kimmerle, G. and Diller, W. 1977. Unveroffentilichte Untersuchungen. (Cited in EPA 1986)

Kirk-Othmer.. 1991. Encyclopedia of Chemical Technology. Fourth Edition. Volume 18. John Wiley & Sons. New York. Phosgene. pp. 645-655.

Laquer, E. and Magnus, R. 1921. Combat gas poisoning. III. Experimental pathology of phosgene poisoning. Z. Gesamte Exp. Med. 13:31-107.

Leonardos, G., Kendall, D.A., and Barnard, N.J. 1968. Odor threshold determinations of 53 odorant chemicals. Presented at the 61th Annual Meeting of the Air Pollution Control Association, St. Paul, Minn., June 23-27. [Requested. NIOSH, 1976, page 29]

Lipsett, M.J., Shusterman, D.J., and Beard, R.R. 1994. Phosgene. In: Industrial hygiene and toxicology, 4th ed. Vol. II, part F. Clayton, G.D. and Clayton, F.E. editors, J. Wiley & Sons, Inc. pp. 4557-4563.

MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]). 2000. SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands.

MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration]) 2000. Deutsche Forschungsgemeinschaft (German Research Association).

Mansuy, D., Beaune, P., Crestell, T., Lange, M., and Leroux, M. 1977. Evidence for phosgene formation during liver microsomal oxidation of chloroform. Biochem. Biophys. Res. Comm. 79:513-517.

Meek, W.J. and Eyster, J.A.E. 1920. Experiments on the pathological physiology of acute phosgene poisoning. Am. J. Physiol. 51:303-320.

Misra, N.P., Manoria, P.C., and Saxena, K. 1985. Fatal pulmonary oedema with phosgene poisining. J. Assoc. Physicians India. 33:430-431.

Moor, S. and Gates, M. 1946. Technical report of division G/NDRC. (Cited in EPA 1986)

NIOSH (National Institute of Occupational Safety and Health). 1976. Criteria for a recommended standard: occupational exposure to phosgene. NIOSH-76-137.

NIOSH (National Institute of Occupational Safety and Health). 1997. Phosgene. NIOSH Pocket Guide to Chemical Hazards. pp. 252-253.

NRC (National Research Council). 1985. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants. Phosgene. pp. 69-86. National Academy Press. Washington, D.C.

Ong, S.G. 1972. Treatment of phosgene poisoning with antiserum: anaphylactic shock by phosgene. Arch. Toxicol. 29:267-278. (Cited in EPA 1986)

OSHA (Occupational Safety and Health Administration). 1994. Limits for Air Contaminants. U. S. Department of Labor. 29 CFR 1910.1000.

Patt, H.M., Tobias, J.M., Swift, M.N., Postel, S., and Gerard, R.W. 1946. Hemodynamics in pulmonary irritant poisoning. Am. J. Physiol. 147:329-339.

Pawlowski, R. and Frosolono, M.F. 1977. Effect of phosgene on rat lungs after single high-level exposure. II. Ultrastructural alternations. Arch. Environ. Health 32:278-283.

Pohl, L.R., Bhooshan, B., Whittaker, N.F., and Krishna, G. 1977. Phosgene: a metabolite of chloroform. Biochem. Biophys. Res. Comm. 79:684-691.

Pohl, L.R., Martin, J.L., and George, J.W. 1980a. Mechanism of metabolic activation of chloroform by rat liver microsomes. Biochem. Pharmacol. 29:3271-3276.

Pohl, L.R., Martin, J.L., Taburet, A.M. and George, J.W. 1980b. Oxidative bioactivation of haloforms into hepatotoxins. In: Microsomes, Drug Oxidations, and Chemical Carcinogenesis, Vol. II. Coon, M.J., et al., Eds. Academic Press, New York. Pp. 881-884.

Pohl, L.R., Branchflower, R.V., Highet, R. J., et al. 1981. The formation of diglutathionyl dithiocarbonate as a metabolite of chloroform, bromotrichloromethane, and carbon tetrachloride. Drug. Metab. Dispos. 9:334-338.

Polednak, A.P. and Hollis, D.R. 1985. Mortality and causes of death among workers exposed to phosgene in 1943-1945. Toxicol. Ind. Health. 1:137-148.

Polednak, A.P. 1980. Mortality among men occupationally exposed to phosgene in 1943-1945. Environ. Res. 22:357-367.

Postel, S. and Swift, M. 1945. Evaluation of the bleeding-transfusion treatment of phosgene poisoning. In: Fasciculus on chemical warfare medicine: v. II, respiratory tract. Washington, DC: National Research Council, Committee on Treatment of Gas Casualties; pp. 664-690. (Cited in EPA 1986)

Regan, R.A. 1985. Review of clinical experience in handling phosgene exposure cases. Toxicol. Ind. Health. 1:69-71.

Reynolds, E.S. 1967. Liver parenchymal cell injury. IV. Pattern of incorporation of carbon and chlorine from carbon tetrachloride into chemical constituents of liver in vivo. J. Pharmacol. Exp. Ther. 155:126-127.

Rinehart, W.E. 1962. A study of the concentration x time (CT) relationship in sublethal exposures to phosgene (dissertation). Pittsburgh, PA. University of Pittsburgh. Publication No. 62-6675. University Microfilms, Inc. Ann Arbor, MI.

Rinehart, W.E. and Hatch, T. 1964. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. AIHA Journal. 25:545-553.

Rothlin, E. 1941. Pathogenesis and treatment for phosgene intoxication. Schweiz. Med. Wochenschr. 71:1526-1535. (Cited in EPA 1986)

Sandall, T.E. 1922. The later effects of gas poisoning. Lancet. 203: 857-859. (Cited in EPA 1986)

Schultz, J. 1945. The prophylactic action of hexamethylenetetramine in phosgene poisoning. In: Fasciculus on chemical warfare medicine: v. II, Respiratory tract. Washington, DC: National Research Council, Committee on Treatment of Gas Casualties; pp. 691-712.

Selgrade, M.K., Starnes, D.M., Illing, J.W., Daniels, M.J., and Graham, J.A. 1989. Effects of phosgene exposure on bacterial, viral, and neoplastic lung disease susceptability in mice. Inhalation Toxicol. 1:243-259.

Shah, H., Hartman, S.P., and Weinhouse, S. 1979. Formation of carbonyl chloride in carbon tetrachloride metabolism by rat liver in vitro. Cancer Res. 39:3942-3947.

Shils, S.E. 1943. The therapeutic and prophylactic value of hexamethylenetetramine in phosgene poisoning. MD (EA) Memorandum report Nr. 81 V. 19. (Cited in EPA 1986)

Sipes, I.G., Krishna, G., and Gillette, J.R. 1977. Bioactivation of carbon tetrachloride, chloroform, and bromotrichloromethane: role of cytochrome P-450. Life Sciences. 20: 1541-1548.

Slade, R., Highfill, J.W., and Hatch, G.E. 1989. Effects of depletion of ascorbic acid or nonprotein sulfhydryls on the acute inhalation toxicity of nitrogen dioxide, ozone, and phosgene. Inhalation Toxicol. 1:261-271.

Stavrakis, P. 1971. The use of hexamethylenetetramine (HMT) in treatment of acute phosgene poisoning. Ind. Med. 40:30-31.

TEMIS (Trauma Emergency Medical Information System). 1997. Phosgene.

ten Berge, W.F., Zwart, A. and Appleman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazardous Materials 13:301-309.

Tobias, J.M. 1945. The pathological physiology of the lung after phosgene. In: Fasciculus on chemical warfare medicine: v. II, respiratory tract. Washington, DC: National Research Council, Committee on Treatment of Gas Casualties; pp. 331-391. (Cited in EPA 1986)

Underhill, F.P. 1920. The lethal war gases. Physiology and experimental treatment. New Haven Yale University Press.

Weston, R.E. and Karel, L. 1946. An application of the dosimetric method for biologically assaying inhaled substances: The determination of the retained median lethal dose, percentage retention, and respiratory response in dogs exposed to different concentrations of phosgene. J. Pharmacol. Exptl. Ther. 88:195.

Weston, R.E. and Karel, L. 1947. An adaptation of the dosimeteric method for use in smaller animals. The retained median lethal dose and the respiratory response in normal, unanesthetized, Rhesus monkeys (*Macaca mulatta*) exposed to phosgene. J. Ind. Hyg. Toxicol. 29:29-33.

Winternitz, M.C, Lambert, R.A., and Jackson, L. 1920. The pathology of phosgene poisoning. In: Collected studies on the pathology of was gas poisoning. New Haven, CT: Yale Univ. Press; pp. 35-66.

Wirth, W. 1936. Uber die wirkung kleinster phosgenmengen. Arch. Exp. Pathol. Pharmacol. 181:198-206.

Zwart, A., Arts, J.H.E., Klokman-Houweling, J.M., and Schoen, E.D. 1990. Determination of concentration-time-mortality relationships to replace LC50 values. Inhalation Toxicol. 2:105-117.

Appendixes

APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Data were insufficient for derivation of AEGL-1 values for phosgene.

Derivation of AEGL-2

Key study:	Gross et al. (1965)
Toxicity end point:	Chemical pneumonia in rats
Scaling:	$C \times t = k$ (2 ppm) × 1.5 h = 3 ppm·h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability
10-min AEGL-2:	0.6 ppm (30-min value adopted as the 10-min value)
30-min AEGL-2:	$C \times 0.5$ hr = 3 ppm·h C = 6 ppm 30-min AEGL-2 = 6 ppm/10 = 0.6 ppm
1-h AEGL-2:	$C \times 1$ h = 3 ppm·h C = 3 ppm 1-h AEGL-2 = 3 ppm/10 = 0.3 ppm
4-h AEGL-2:	$C \times 4$ h = 3 ppm·h C = 0.75 ppm 4-h AEGL-2 = 0.75 ppm/10 = 0.075 ppm
8-h AEGL-2:	$C \times 8$ h = 3 ppm·h C = 0.375 ppm

8-h AEGL-2 = 0.375 ppm/10 = 0.038 ppm

Derivation of AEGL-3

Key study:	Zwart et al. (1990)
Toxicity end point:	The highest concentration causing no mortality in the rat or mouse after a 10-min exposure (10-min). The highest concentration causing no mortality in the rat after a 30-min exposure (30-min, 1-, 4-, and 8-h).
Scaling (30-min, 1-, 4-, and 8-h) :	$C \times t = k$ (15 ppm) × 0.5 h = 7.5 ppm·h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability
10-min AEGL-3:	10-min AEGL-3 = 36 ppm/10 = 3.6 ppm
30-min AEGL-3:	C × 0.5 h = 7.5 ppm·h C = 15 ppm 30-min AEGL-3 = 15 ppm/10 = 1.5 ppm
1-h AEGL-3:	C × 1 h = 7.5 ppm·h C = 7.5 ppm 1-h AEGL-3 = 7.5 ppm/10 = 0.75 ppm
4-hr AEGL-3:	C × 4 h = 7.5 ppm·h C = 1.875 ppm 4-h AEGL-3 = 1.875 ppm/10 = 0.19 ppm
8-h AEGL-3:	C × 8 h = 7.5 ppm·h C = 0.94 ppm 8-h AEGL-3 = 0.94 ppm/10 = 0.094 ppm

APPENDIX B

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR PHOSGENE (CAS No. 75-44-5)

AEGL-1				
10 min	30 min	1 h	4 h	8 h
NA	NA	NA	NA	NA
Key reference: NA				
Test species/Strain/Number: NA				
Exposure route/Concentrations/Durations: NA				
Effects: NA				
End point/Concentration/Rationale: NA				
Uncertainty factors/Rationale: NA				
Modifying factor: NA				
Animal to human dosimetric adjustment: NA				
Time scaling: NA				
Confidence and Support for AEGL values: Data were insufficient for derivation of AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤24 h.				

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm
Key reference: Gross, P., Rinehart, W. E., and Hatch, T. 1965. Chronic pneumonitis caused by phosgene. Arch. Environ. Health. 10: 768-775.				
Test species/Strain/Number: Wistar rats/ 118 males				
Exposure route/Concentrations/Durations: Rats/Inhalation: 0.5 to 4.0 ppm for 5 min to 8 h to give C × T products between 12 and 360 ppm·min (2 ppm for 1.5 h was determinant for AEGL-2)				
Effects: 2 ppm for 1.5 h: chemical pneumonia; 0.9 ppm for 1 h: "chronic pneumonitis"				
End point/Concentration/Rationale: Rats/2 ppm for 1.5 h/chemical pneumonia				
Uncertainty factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 - little species variability is observed with both lethal and nonlethal end points in many studies after exposure to phosgene Intraspecies: 3 - due to the steep concentration-response curve and effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals.				
Modifying factor: Not applicable				
Animal to human dosimetric adjustment: Insufficient data				
Time scaling: $C^n \times t = k$ where n = 1. Haber's Law (C × t = k) has been shown to be valid for phosgene within certain limits (EPA 1986). Haber's Law was originally derived from phosgene data (Haber 1924). Reported 1.5 h data point used for AEGL-2 derivation. AEGL values for the 30-min and 1-, 4-, and 8-h exposure periods were based on extrapolation from the 1.5 h value. The 30-min value is also adopted as the 10-min value because Diller et al. (1985) observed alveolar pulmonary edema in rats exposed to 5 ppm phosgene for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min value of 0.5 ppm.				
Data adequacy: The database is rich. The calculated AEGL-2 values are supported by rat studies where exposure of rats to 1 ppm phosgene for 4 h resulted in severe pulmonary edema and body weight loss. (Franch and Hatch 1986; Erlich et al. 1989). Use of these data (and application of a total UF of 10) results in supporting AEGL-2 values of 0.8, 0.4, 0.1, and 0.05 ppm for the 30 min, 1 h, 4 h, and 8 h time points, respectively. The 10-min value is supported by Diller et al. (1985) as described above in the time scaling section.				

AEGL-3				
10 min	30 min	1 h	4 h	8 h
3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm

Reference: Zwart, A. et al. 1990. Determination of concentration-time-mortality relationships to replace LC50 values. Inhalation Toxicol. 2: 105-117.

Test species/Strain/Sex/Number: Wistar rats/ 5 males and 5 females

Exposure route/Concentrations/Durations: Rats/Inhalation: 12, 15, 16, 17, or 24 ppm for 30 min (the highest concentration causing no mortality in the rat after a 30-min exposure of 15 ppm was determinant for AEGL-3)

Effects:

Concentration	*Mortality*
12 ppm	0/10
15 ppm	0/10
16 ppm	1/10
17 ppm	5/10
24 ppm	9/10

End point/Concentration/Rationale: The highest concentration causing no mortality in the rat after a 30-min exposure 30-min experimental no-effect-level for death (15 ppm) was used as a threshold for death in rats for the 30-min, 1-, 4-, and 8-h values. The highest concentration causing no mortality in the rat after a 10-min exposure (36 ppm) was utilized for the 10-min value.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - little species variability is observed with both lethal and nonlethal end points in many studies after exposure to phosgene
Intraspecies: 3 - due to the steep concentration-response curve and effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals .

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$ where n = 1. Haber's Law ($C \times t = k$) has been shown to be valid for phosgene within certain limits (EPA 1986). Haber's Law was originally derived from phosgene data (Haber 1924). Reported 30-min data point used to determine the 30-min AEGL value. AEGL-3 values for 1-, 4-, and 8-h were based on extrapolation from the 30 min value. The 10-min value was based on a reported 10-min data point.

Data adequacy: The AEGL-3 values are based on a well-conducted study in rats and the database is rich.