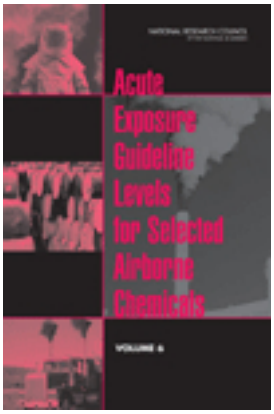

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6

Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

ISBN: 0-309-11214-1, 318 pages, 6 x 9, (2007)

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 6

Committee 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, NW Washington, DC 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 No. W81K04-06-D-0023 between the National Academy of Sciences and the U.S. Department of Defense. 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-13: 978-0-309-11213-0
International Standard Book Number-10: 0-309-11213-3

Additional copies of this report are available from:

National Academy Press
500 Fifth Street., NW
Box 285
Washington, DC 20001

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. Ralph J. Cicerone 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. Charles M. Vest 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. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

Members

DONALD E. GARDNER *(Chair),* Inhalation Toxicology Associates, Raleigh, NC
DANIEL KREWSKI *(past Chair),* University of Ottawa, Ontario, Canada
EDWARD C. BISHOP, HDR Engineering, Inc., Omaha, NE
JAMES V. BRUCKNER, *(past member)* University of Georgia, Athens
RAKESH DIXIT, MedImmune, Inc., Gaithersburg, MD
JOHN DOULL (*past member),* University of Kansas Medical Center, Kansas City
JEFFREY W. FISHER, University of Georgia, Athens
DAVID W. GAYLOR *(past member)*, Gaylor and Associates, LLC, Eureka Springs, AR
KANNAN KRISHNAN *(past member)* University of Montreal, Quebec, Canada
DAVID P. KELLY, Dupont Company, Newark, DE
STEPHEN U. LESTER, *(past member),* Center for Health, Environment, and Justice, Falls Church, VA
JUDITH MACGREGOR, *(past member),* Toxicology Consulting Services, Arnold, MD
PATRICIA M. MCGINNIS (*past member)* Syracuse Research Corporation, Ft. Washington, PA
DAVID A. MACYS, Island County Health Department, Coupeville, WA
FRANZ OESCH, University of Mainz, Mainz, Germany
RICHARD B. SCHLESINGER, Pace University, New York, NY
ROBERT SYNDER, Rutgers University, Piscataway, NJ
JOHN A. THOMAS, Indiana University School of Medicine, Bloomington, IN
CALVIN C. WILLHITE *(past member),* California Department of Toxic Substances Control, Berkeley
FREDERIK A. DE WOLFF, Leiden University Medical Center, Leiden, Netherlands

Staff

KULBIR S. BAKSHI, Senior Program Officer
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
RADIAH A. ROSE, Senior Editorial Assistant
AIDA C. NEEL, Program Associate

Sponsor

U.S. Department of Defense

COMMITTEE ON TOXICOLOGY

Members

WILLIAM E. HALPERIN *(Chair)*, UMDNJ–New Jersey Medical School**,** Newark
LAWRENCE S. BETTS, Eastern Virginia Medical School, Norfolk
EDWARD C. BISHOP, HDR Engineering, Inc., Omaha, NE
JAMES V. BRUCKNER, University of Georgia, Athens
GARY P. CARLSON, Purdue University, West Lafayette, IN
MARION F. EHRICH, Virginia Polytechnic Institute and State University, Blacksburg
SIDNEY GREEN, Howard University, Washington, DC
MERYL H. KAROL, University of Pittsburgh, Pittsburgh, PA
JAMES N. MCDOUGAL, Wright State University School of Medicine, Dayton, OH
ROGER G. MCINTOSH, Science Applications International Corporation, Abingdon, MD
GERALD N. WOGAN, Massachusetts Institute of Technology, Cambridge

Staff

EILEEN N. ABT, Senior Program Officer for Risk Analysis
KULBIR S. BAKSHI, Senior Program Officer
ELLEN K. MANTUS, Senior Program Officer
SUSAN N. J. MARTEL, Senior Program Officer for Toxicology
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
TAMARA DAWSON, Program Associate
RADIAH A. ROSE, Senior Editorial Assistant

BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY[1]

Members

JONATHAN M. SAMET (*Chair*), Johns Hopkins University, Baltimore, MD
RAMÓN ALVAREZ, Environmental Defense Fund, Austin, TX
JOHN M. BALBUS, Environmental Defense Fund, Washington, DC
DALLAS BURTRAW, Resources for the Future, Washington, DC
JAMES S. BUS, Dow Chemical Company, Midland, MI
RUTH DEFRIES, University of Maryland, College Park
COSTEL D. DENSON, University of Delaware, Newark
E. DONALD ELLIOTT, Willkie, Farr & Gallagher LLP, Washington, DC
MARY R. ENGLISH, University of Tennessee, Knoxville
J. PAUL GILMAN, Covanta Energy Corporation, Fairfield, NJ
JUDITH A. GRAHAM (Retired), Pittsboro, NC
WILLIAM M. LEWIS, JR., University of Colorado, Boulder
JUDITH L. MEYER, University of Georgia, Athens
DENNIS D. MURPHY, University of Nevada, Reno
DANNY D. REIBLE, University of Texas, Austin
JOSEPH V. RODRICKS, ENVIRON International Corporation, Arlington, VA
ARMISTEAD G. RUSSELL, Georgia Institute of Technology, Atlanta
ROBERT F. SAWYER, University of California, Berkeley
KIMBERLY M. THOMPSON, Harvard School of Public Health, Boston, MA
MARK J. UTELL, University of Rochester Medical Center, Rochester, NY

Senior Staff

JAMES J. REISA, Director
DAVID J. POLICANSKY, Scholar
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
EILEEN N. ABT, Senior Program Officer for Risk Analysis
SUSAN N.J. MARTEL, Senior Program Officer for Toxicology
KULBIR BAKSHI, Senior Program Officer
ELLEN K. MANTUS, Senior Program Officer
RUTH E. CROSSGROVE, Senior Editor

[1]This study was planned, overseen, and supported by the Board on Environmental Studies and Toxicology.

OTHER REPORTS OF THE
BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Estimating Mortality Risk Reduction and Economic Benefits from Controlling Ozone Air Pollution (2008)
Respiratory Diseases Research at NIOSH (2008)
Evaluating Research Efficiency in the U.S. Environmental Protection Agency (2008)
Hydrology, Ecology, and Fishes of the Klamath River Basin (2008)
Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment (2007)
Models in Environmental Regulatory Decision Making (2007)
Toxicity Testing in the Twenty-first Century: A Vision and a Strategy (2007)
Sediment Dredging at Superfund Megasites: Assessing the Effectiveness (2007)
Environmental Impacts of Wind-Energy Projects (2007)
Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget (2007)
Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues (2006)
New Source Review for Stationary Sources of Air Pollution (2006)
Human Biomonitoring for Environmental Chemicals (2006)
Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment (2006)
Fluoride in Drinking Water: A Scientific Review of EPA's Standards (2006)
State and Federal Standards for Mobile-Source Emissions (2006)
Superfund and Mining Megasites—Lessons from the Coeur d'Alene River Basin (2005)
Health Implications of Perchlorate Ingestion (2005)
Air Quality Management in the United States (2004)
Endangered and Threatened Species of the Platte River (2004)
Atlantic Salmon in Maine (2004)
Endangered and Threatened Fishes in the Klamath River Basin (2004)
Cumulative Environmental Effects of Alaska North Slope Oil and Gas Development (2003)
Estimating the Public Health Benefits of Proposed Air Pollution Regulations (2002)
Biosolids Applied to Land: Advancing Standards and Practices (2002)
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)
Acute Exposure Guideline Levels for Selected Airborne Chemicals (six volumes, 2000-2008)
Toxicological Effects of Methylmercury (2000)
Strengthening Science at the U.S. Environmental Protection Agency (2000)
Scientific Frontiers in Developmental Toxicology and Risk Assessment (2000)
Ecological Indicators for the Nation (2000)
Waste Incineration and Public Health (2000)
Hormonally Active Agents in the Environment (1999)
Research Priorities for Airborne Particulate Matter (four volumes, 1998-2004)
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 (five volumes, 1989-1995)
Science and Judgment in Risk Assessment (1994)
Pesticides in the Diets of Infants and Children (1993)
Dolphins and the Tuna Industry (1992)
Science and the National Parks (1992)
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 Academies Press:
(800) 624-6242 or (202) 334-3313
www.nap.edu

OTHER REPORTS OF THE COMMITTEE ON TOXICOLOGY

Review of Toxicologic and Radiologic Risks to Military Personnel from Exposures to Depleted Uranium (2008)
Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Volume 1 (2007), Volume 2 (2008)
Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents (2005)
Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel (2004)
Spacecraft Water Exposure Guidelines for Selected Contaminants, Volume 1 (2004), Volume 2 (2007)
Toxicologic Assessment of Jet-Propulsion Fuel 8 (2003)
Review of Submarine Escape Action Levels for Selected Chemicals (2002)
Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (2001)
Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity (2001)
Acute Exposure Guideline Levels for Selected Airborne Contaminants, Volume 1 (2000), Volume 2 (2002), Volume 3 (2003), Volume 4 (2004), Volume 5 (2007), Volume 6 (2007)
Review of the US Navy's Human Health Risk Assessment of the Naval Air Facility at Atsugi, Japan (2000)
Methods for Developing Spacecraft Water Exposure Guidelines (2000)
Review of the U.S. Navy Environmental Health Center's Health-Hazard Assessment Process (2000)
Review of the U.S. Navy's Exposure Standard for Manufactured Vitreous Fibers (2000)
Re-Evaluation of Drinking-Water Guidelines for Diisopropyl Methylphosphonate (2000)
Submarine Exposure Guidance Levels for Selected Hydrofluorocarbons: HFC-236fa, HFC-23, and HFC-404a (2000)
Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents (1999)
Toxicity of Military Smokes and Obscurants, Volume 1(1997), Volume 2 (1999), Volume 3 (1999)
Assessment of Exposure-Response Functions for Rocket-Emission Toxicants (1998)
Toxicity of Alternatives to Chlorofluorocarbons: HFC-134a and HCFC-123 (1996)
Permissible Exposure Levels for Selected Military Fuel Vapors (1996)
Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Volume 1 (1994), Volume 2 (1996), Volume 3 (1996), Volume 4 (2000)

Preface

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

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

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, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the sixth volume in the

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

series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for allylamine, ammonia, aniline, arsine, crotonaldehyde, *trans* and *cis* + *trans*, 1, 1-dimethylhydrazine, 1, 2-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Deepak K. Bhalla, Wayne State University; David W. Gaylor, Gaylor and Associates, LLC; and Samuel Kacew, University of Ottawa.

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 Goyer, University of Western Ontario (Emeritus). Appointed by the National Research Council, he 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.

After the review of the draft was completed, the committee evaluated AEGLs that were developed for 8 metal phosphides. Because the acute toxicity of metal phosphides results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based upon phosphine AEGLs. Therefore Chapter 10 of this report was expanded to present AEGL values for phosphine and the metal phosphides. We wish to thank Ian Greaves, University of Minnesota, and Wallace Hayes, Harvard School of Public Health, for their review of this revised chapter. The review was overseen by Samuel Kacew.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. Other staff members who contributed to this effort are Raymond Wassel (senior program officer), Aida Neel (program associate), Ruth Crossgrove (senior editor), Radiah Rose (senior editorial assistant), and Mirsada Karalic-Loncarevic (manager, Technical Information Center). The committee particularly acknowledges

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

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

William E. Halperin, *Chair*
Committee on Toxicology

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 6

Introduction

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hour (h), and

only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (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 (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

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

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

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

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

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

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to 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 *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from in vivo and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports.

Thus far, the committee has prepared five reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2001b, 2002, 2003, 2004, 2007). This report is the sixth volume in that series. AEGL documents for allylamine, ammonia, aniline, arsine, crotonaldehyde, cis/trans-, crotonaldehyde, trans-iso, 1, 1-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides are each published as an appendix to this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

NRC (National Research Council) 2007. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. 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

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

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Government of Canada

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

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

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

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

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

Ralph Gingell
Shell Health Services
Houston, TX

Roberta Grant
Texas Commission on Environmental Quality
Austin, TX

Dieter Heinz
National Fire Protection Association
Atascadero, CA

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

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

Martha Steele
Massachusetts Department of Public Health
Boston, MA

Edward Bernas
AFL-CIO
Homewood, IL

Gail Chapman
U. S. Navy
Wright Patterson AFB, OH

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

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

Susan Ripple
The Dow Chemical Company
Midland, Michigan

Daniel Sudakin
Oregon State University
Corvallis, OR

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

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

Alan Woolf
Children's Hospiral
Boston, MA

Oak Ridge National Laboratory Staff

Cheryl Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Milanez
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Talmage
Oak Ridge National Laboratory
Oak Ridge, TN

Robert Young
Oak Ridge National Laboratory
Oak Ridge, TN

National Advisory Committee Staff

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

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

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

3

Aniline[1]

Acute Exposure Guideline Levels

UPDATE OF ANILINE AEGLS

In Volume 1 of the series Acute *Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), acute exposure guideline level (AEGL) values were developed for 30 minutes (min) and 1, 4, and 8 hours (h). Since that time, AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The Summary below is from Volume 1 and contains additional discussion to address the development of 10-min values.

SUMMARY

Aniline is an aromatic amine used chiefly by the chemical industry in the manufacture of dyes, dye intermediates, rubber accelerators, antioxidants, drugs, photographic chemicals, isocyanates, herbicides, and fungicides. Production of aniline oil in 1993 was approximately 1 billion pounds. The primary effect of an acute exposure to aniline is the oxidation of hemoglobin in red blood cells, resulting in the formation of methemoglobin. The effect occurs following inhalation, ingestion, or dermal absorption. In conjunction with methemoglobinemia, chronic exposures or exposures to high concentrations may produce signs and symptoms of headache, paresthesia, tremor, pain, narcosis/coma, cardiac arrhythmia, and possibly death.

[1]This document was prepared by AEGL Development Team members Robert Snyder and George Rodgers of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Sylvia Talmage of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

No reliable data on human exposures via the inhalation route were located. All AEGL values are based on a study in which rats were exposed to concentrations of 0, 10, 30, 50, 100, or 150 parts per million (ppm) for 8 or 12 h (Kim and Carlson 1986). The only reported effect was methemoglobin formation. The relationship between aniline concentration and methemoglobin formation appeared to be linear. Furthermore, the relationship between methemoglobin formation and time, between 3 and 8 h, was also linear when the aniline concentration was held constant at 100 ppm. Methemoglobin reached an asymptote at 8 h. Based on the linear relationships between aniline concentration and methemoglobin formation and between methemoglobin formation and time at a constant aniline concentration, a linear relationship between concentration and exposure duration ($C^1 \times t = k$) was chosen for time-scaling aniline concentrations to the appropriate AEGL exposure durations. Although the key study (Kim and Carlson 1986) used an 8-h exposure, methemoglobin measurements were taken at several time points during the study, and other studies with 4-h (E.I. du Pont de Nemours 1982; Pauluhn 2002) and 10-min exposures (Kakkar et al. 1992) support the derived AEGL values. Thus, the 8-h AEGL values from the Kim and Carlson study were extrapolated back to 10 min. Following a 10-min exposure, the concentration of methemoglobin in blood is unlikely to reach steady state, as typically seen 6-8 h after the initiation of exposure.

The AEGL-1 was based on an exposure of rats to a concentration of 100 ppm for 8 h, which resulted in elevation of methemoglobin from a control value of 1.1% (range, 0.4-2.1%) to 22%. A review of the published data indicates that methemoglobin levels of 15-20% in humans result in clinical cyanosis but no hypoxic symptoms. Although inhalation data for comparison purposes are not available, oral ingestion data suggest that humans may be considerably more sensitive to methemoglobin-forming chemicals than rats. Therefore, a default uncertainty factor of 10-fold was used for interspecies extrapolation (NRC 1993). Several sources also indicate that newborns may be more sensitive to methemoglobin-forming chemicals than adults. Because of the lack of specific quantitative data on sensitive human subpopulations and the fact that there are data suggesting greater susceptibility of infants, a default uncertainty factor of 10-fold was also used for intraspecies extrapolation. It is believed that an intraspecies uncertainty factor of 10 is protective of the general population, including susceptible individuals. A default uncertainty factor of 10 for each of the interspecies and intraspecies variabilities is also supported by the small database of information and the lack of reliable human inhalation studies. The data were scaled across time using $C^1 \times t = k$ because of data indicating a linear relationship between concentration and exposure duration as related to methemoglobin formation. The AEGL-1 values are supported by the data of Pauluhn (2002) in which dogs exposed to 46 ppm for 4 h had the same methemoglobin concentration (4.7%) as rats exposed to 50 ppm for 8 h (Kim and Carlson 1986; at 50 ppm, methemoglobin steady state in the blood is attained after several hours but prior to the full 8-h exposure).

The AEGL-2 was based on the same study with rats in which a concentration of 150 ppm for 8 h resulted in elevation of methemoglobin from a control value of 1-41%. This level of methemoglobin is associated with fatigue, lethargy, exertional dyspnea, and headache in humans and was considered the threshold for disabling effects. Since the same mode of action applies to AEGL-2 effects, the 150-ppm concentration was divided by a combined uncertainty factor of 100 and scaled across time using the same reasons and relationships as for the AEGL-1.

Data on concentrations of aniline-inducing methemoglobin levels at the threshold for lethality were not available. Based on the fact that the relationship between the concentration of aniline and methemoglobin formation is linear, the dose-response curve from the study on which the AEGL-1 and AEGL-2 values were based was extrapolated to a concentration resulting in a >70% level of methemoglobin, the threshold for lethality according to Kiese (1974) and Seger (1992). The concentration of 250 ppm for 8 h was chosen as the threshold for lethality. Since the same mode of action applies to AEGL-3 effects, the 250-ppm concentration was divided by a combined uncertainty factor of 100 and scaled across time using the same rationale as for the AEGL-1.

Several studies with rats support the AEGL-3 values. A 10-min exposure to aniline at 15,302 ppm resulted in no clinical signs (Kakkar et al. 1992), and a 4-h exposure at 359 ppm (E. I. du Pont de Nemours 1982) resulted in severe toxic effects but no deaths. Dividing each of these values by a total uncertainty factor of 100 and scaling across time using $C^1 \times t = k$ results in values similar to those derived from the Kim and Carlson study. Studies with repeated exposures of rats resulted in additional effects on the blood and spleen, but concentrations up to 87 ppm, 6 h/day, 5 days/week, for 2 weeks were not disabling or life-threatening.

The derived AEGLs are listed in Table 3-1. Because aniline is absorbed through the skin in quantities sufficient to produce systemic toxicity, a skin notation was added to the summary table. The reported odor threshold for aniline ranges from 0.012 to 10 ppm. Therefore, the odor of aniline will be noticeable by most individuals at the AEGL-1 concentrations. The odor is somewhat pungent but not necessarily unpleasant.

TABLE 3-1 Summary of AEGL Values for Aniline[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[b] (nondisabling)	48 ppm (182 mg/m^3)	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)	22% methemoglobin: cyanosis (Kim and Carlson 1986)
AEGL-2 (disabling)	72 ppm (274 mg/m^3)	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)	41% methemoglobin: lethargy (Kim and Carlson 1986)

(Continued)

TABLE 3-1 Continued

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-3 (lethal)	120 ppm (456 mg/m^3)	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)	>70% methemoglobin: lethality (extrapolated from data of Kim and Carlson 1986)

[a]Cutaneous absorption of the neat material may occur, adding to the systemic toxicity.
[b]The aromatic, amine-like odor of aniline will be noticeable by most individuals at these concentrations.

REFERENCES

E.I. du Pont de Nemours. 1982a. Inhalation median lethal concentration (LC_{50}). OTS 84003A, Docket 878220239. E.I. du Pont de Nemours and Co., Inc., Wilmington, DE.

Kakkar, P., S. Awasthi, and P.N. Viswanathan. 1992. Oxidative changes in brain of aniline-exposed rats. Arch. Environ. Contam. Toxicol. 23(3):307-309.

Kiese, M. 1974. Methemoglobinemia: A Comprehensive Treatise. Cleveland, OH: CRC Press.

Kim, Y.C., and G.P. Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fundam. Appl. Toxicol. 7(1):144-152.

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

NRC (National Research Council). 2000. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 1. Washington, DC: National Academy Press.

Pauluhn, J. 2002. Aniline-induced methemoglobinemia in dogs: Pitfalls of route-to-route extrapolations. Inhal. Toxicol. 14(9):959-973.

Seger, D.L. 1992. Methemoglobin-forming chemicals. Pp. 800-806 in Hazardous Materials Toxicology: Clinical Principles of Environmental Health, J.B. Sullivan, and G.R. Krieger, eds. Baltimore, MD: Williams & Wilkins.