Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 7

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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: 978-0-309-12755-4
International Standard Book Number-10: 0-309-12755-6

Additional copies of this report are available from

The National Academies Press
500 Fifth Street, NW
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. 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
EDWARD C. BISHOP, HDR Engineering, Inc., Omaha, NE
RAKESH DIXIT, MedImmune, Inc., Gaithersburg, MD
JEFFREY W. FISHER, University of Georgia, Athens
DAVID P. KELLY, Dupont Company, Newark, DE
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 SNYDER, Rutgers University, Piscataway, NJ
JOHN A. THOMAS, Indiana University School of Medicine, Indianapolis
FREDERIK A. DE WOLFF, Leiden University Medical Center, Leiden, The Netherlands

Staff

RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
KULBIR S. BAKSHI, Senior Program Officer
RUTH E. CROSSGROVE, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH A. ROSE, Editorial Projects Manager
PATRICK BAUR, Research Assistant
KORIN THOMPSON, Project Assistant

Sponsor

U.S. DEPARTMENT OF DEFENSE

COMMITTEE ON TOXICOLOGY

Members

GARY P. CARLSON (*Chair*), Purdue University, West Lafayette, IN
LAWRENCE S. BETTS, Eastern Virginia Medical School, Norfolk
EDWARD C. BISHOP, HDR Engineering, Inc., Omaha, NE
JAMES V. BRUCKNER, University of Georgia, Athens
MARION F. EHRICH, Virginia Polytechnic Institute and State University, Blacksburg
SIDNEY GREEN, Howard University, Washington, DC
WILLIAM E. HALPERIN, UMDNJ–New Jersey Medical School, Newark
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

SUSAN N. J. MARTEL, Senior Program Officer for Toxicology
EILEEN N. ABT, Senior Program Officer for Risk Analysis
ELLEN K. MANTUS, Senior Program Officer
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
TAMARA DAWSON, Program Associate
RADIAH A. ROSE, Editorial Projects Manager

[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

Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research (2009)
Science and Decisions: Advancing Risk Assessment (2009)
Phthalates and Cumulative Risk Assessment: The Tasks Ahead (2008)
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

Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Final Report (2008)
Managing Health Effects of Beryllium Exposure (2008)
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), Volume 3 (2008)
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 (2008)
Review of the U.S. 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), Volume 5 (2008)

Preface

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

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

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

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

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

Acute Exposure Guideline Levels for Selected Airborne Chemicals. It reviews the AEGLs for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol for scientific accuracy, completeness, and consistency with the NRC guideline reports.

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

Two interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of two of the committtee's interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for monochloroacetic acid and phenol (*Thirteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2005) and acetone cyanohydrin and carbon disulfide (*Fourteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2006): Deepak K. Bhalla (Wayne State University), David W. Gaylor (Gaylor and Associates, LLC), and Sam 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 this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowl-

edges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, senior program officer for toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (editorial projects manager), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 7

National Research Council Committee Review of Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

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

REVIEW OF AEGL REPORTS

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

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

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the NRC committee 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 six reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b). This report is the seventh volume in that series. AEGL documents for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol are each published as an appendix in this report. The NRC committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Committee Members

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Government of Canada

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

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

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

Edward Bernas
AFL-CIO
Homewood, IL

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

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

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

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

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

Martha Steele
Massachusetts Department of Public Health
Boston, MA

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

Appendixes

3

Monochloroacetic Acid[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). AEGL-1, AEGL-2, and AEGL-3, as appropriate, will be developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population, including infants and children and other individuals who may be sensitive or susceptible. The three AEGLs have been 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

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

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/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Monochloroacetic acid (MCAA) is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents. Its vapor pressure at room temperature is moderate with reported values between 0.2 hectopascals (hPa) (crystalline substance) and 10 hPa (solution in water). MCAA has a pungent odor.

MCAA is produced by chlorination of acetic acid or hydrolysis of trichloroethylene (also known as trichloroethene) using sulfuric acid. The world production capacity was estimated at 362,500 metric tons/year in 1987. MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethyl-cellulose, herbicides, and thioglycolic acid as well as in the production of plastics, pharmaceuticals, flavors, cosmetics, and other organic chemicals.

MCAA is an acid (pK_a, 2.85) and, therefore, can cause eye and skin irritation upon contact with a diluted MCAA solution and can cause skin corrosion and conjunctival burns upon contact with more concentrated solutions. The systemic toxicity of MCAA is caused by inhibition of enzymes of the glycolytic pathway and the tricarboxylic acid cycle. This metabolic blockage damages organs with a high-energy demand, such as heart, central nervous system (CNS), and muscles, and leads to metabolic acidosis due to the accumulation of lactic acid and citric acid in the body.

No studies are available reporting severe toxic effects in humans after inhalation exposure to MCAA. Mortality was reported in a child after oral uptake of 5-6 milliliters (mL) of an 80% MCAA solution (Rogers 1995). Several lethal accidents have been reported, in which workers were dermally exposed to hot liquid MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and Dubinina 1974); no respiratory tract irritation, effects on lung function parameters, or irritation of skin and mucous membranes were reported for more than 33 workers potentially exposed to MCAA concentrations between <0.13 ppm for 3 h and 0.31 ppm for 7 h (Clariant GmbH, unpublished material, 2000).

The only animal study reporting lethal effects after inhalation exposure was an inadequately described study in which an LC_{50} (concentration with 50% lethality) of 46.8 ppm for 4 h was reported for rats (Maksimov and Dubinina 1974). Several studies report lethal effects after oral exposure with LD_{50} values mostly between 50 and 200 mg/kg for rats, mice and guinea pigs. In a single inhalation experiment on rats, eye squint and slight lethargy were observed during exposure to an analytic concentration of 66 ppm for 1 h (Dow Chemical Co. 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a no-observed-effect level (NOEL) for histologic changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina 1974).

No relevant studies of adequate quality were available for the derivation of the AEGL-1. Therefore, AEGL-1 values were not recommended because of insufficient data. Due to the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

The AEGL-2 was based on a single inhalation study of MCAA in rats (Dow Chemical Co. 1987) in which eye squint and lethargy were observed in rats exposure to 66 ppm for 1 h. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability (1) because the effect level was considered below that of an AEGL-2, (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects, and (3) because of the limited toxicodynamic variability, as the enzymes inhibited by MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and because of the limited toxicodynamic variability with respect to systemic effects, as the enzymes inhibited by MCAA do not vary considerably within and between species. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data and the uncertainties of a

route-to-route extrapolation, AEGL-3 values were not recommended. The AEGLs are summarized in Table 3-1.

1. INTRODUCTION

MCAA is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents.

MCAA is produced by chlorination of acetic acid or hydrolysis of trichloroethylene using sulfuric acid (BUA 1994). (1) The chlorination of acetic acid is carried out in liquid phase at temperatures between 85° and 120°C. Acetic anhydride and acetylchloride may be used as catalysts. The chlorination product contains considerable amounts of acetic acid and dichloroacetic acid. Purification takes place either by selective dechlorination of dichloroacetic acid and subsequent distillation, or by recrystallization from suitable solvents (ECB 2005). (2) Trichloroethylene and sulfuric acid are heated to 130-140°C in the reactor. A mixture of trichloroethylene and sulfuric acid is continuously fed to the bottom of the reactor. The chloroacetic acid and sulfuric acid are permitted to overflow into a cascade, where the chloroacetic acid is distilled at 20 mm Hg, and the sulfuric acid is recycled. The hydrolysis of trichloroethylene yields high-purity MCAA, but has the disadvantage of utilizing a relatively more expensive starting material (ECB 2005).

The world production capacity was estimated at 362,500 metric tons/year in 1987 (KEMI 1994). Europe produced about 145,000 metric tons in 1999 (ECB 2005), and the United States produced about 39,000 metric tons in 1989 (OECD 1996). Imports into the United States comprised about 17,000 metric tons of chloroacetic acids in 2003 (USITA 2004). The TRI database (DHHS 2008) lists 17 sites in the United States where production and use of MCAA causes emissions to the air.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	N.R.[b]	N.R.	N.R.	N.R.	N.R.	Insufficient data
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)	Eye squint and lethargy in rats (Dow Chemical Co. 1987)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.	Insufficient data

[a]Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid, and fatal intoxications have been observed when 10% or more of the body surface was involved.
[b]Not recommended because of insufficient data.

MCAA is pumped in molten form (about 80°C) or as 80% aqueous solution through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites (ECETOC 1999; ECB 2005). Therefore, an inhalation exposure during accidental releases cannot be ruled out (ECETOC 1999), although no case of severe intoxication by inhalation has been published in the literature.

MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethylcellulose, herbicides, thioglycolic acid as well as in the production of plastics, pharmaceuticals, flavors, cosmetics, and other organic chemicals (KEMI 1994; ECB 2005).

Haloacetic acids, including MCAA, are a group of chemicals that are formed along with other drinking-water disinfection byproducts (e.g., trihalomethanes) when chlorine or other disinfectants used to control microbial contaminants in the water react with naturally occurring organic and inorganic matter in water. Depending on the amount of bromide in the source water, varying amounts of chlorinated, brominated, and mixed bromochlorohaloacetic acids are produced. EPA (63 Fed. Reg. 69390 [1998]) published the stage 1 Disinfectants/Disinfection Byproducts Rule to regulate a group of five haloacetic acids at a maximum contaminant level of 0.06 mg/L (60 ppb) annual average. A very small inhalation exposure might result from this water contamination. Xu and Weisel (2003) measured an aerosol-bound concentration of haloacetic acids at 6.3 nanograms (ng)/m³ during showering with water containing haloacetic acids at 250 µg/L. Chemical and physical properties of MCAA are listed in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Deaths after inhalation of MCAA have not been reported in the literature (ECETOC 1999). Lethal effects have occurred after oral intoxication and after dermal exposure to hot, liquid MCAA (BUA 1994; IUCLID 1996; ECETOC 1999). Some of these incidences are described in the following paragraphs.

Feldhaus et al. (1993) and Rogers (1995) reported a case study of a fatal acute oral exposure. A 5-year old girl was accidentally given 5-6 mL of an 80% MCAA-containing wart remover. One and one- half hours after exposure, she developed refractory ventricular tachycardia, pulmonary edema, and acidemia. The patient died 8 h after ingestion despite medical intervention. An autopsy revealed diffuse gastric erosions, fatty infiltration of the liver, and pulmonary and cerebral edema. The postmortem MCAA concentration in serum was 100 mg/L as determined by gas chromatography and mass spectroscopy. The exposure corresponds to an oral dose of about 200-240 mg/kg (see section 7.1).

Fatal cases and life-threatening poisonings in workers have been described after skin contact (BUA 1994; IUCLID 1996): Christofano et al. (1970) reported

TABLE 3-2 Chemical and Physical Data for MCAA

Parameter	Data	Reference
Molecular formula	$ClCH_2$-COOH ($C_2H_3ClO_2$)	NTP 1992
Molecular weight	94.5 g/mol	NTP 1992
CAS Registry Number	79-11-8	NTP 1992
Physical state	Solid	NTP 1992
Color	Colorless	NTP 1992
Synonyms	Chloroacetic acid; monochloroethanoic acid; chloroethanoic acid; Monochloressigsäure; Chlorethansäure	OECD 1996; Greim 1998
Vapor pressure	0.1 mm Hg (at 20°C) ca. 0.2 hPa (crystalline substance at 20°C) 1 hPa (at 20°C) 10 hPa (solution in water at 20°C) 1 mm Hg (at 43°C) 4.4 hPa (liquid at 65°C) 8.23 mm Hg (at 80°C) 10 mm Hg (at 81°C) 40 mm Hg (at 109.2°C) 100 mm Hg (at 130.7°C) 400 hPa (at 169°C)	Dow Chemical Co. 1987 Greim 1998 IUCLID 1996 IUCLID 1996 Weast 1984 IUCLID 1996 Dow Chemical Co. 1987 Weast 1984 Weast 1984 Weast 1984 Weast 1984
Density	1.58 g/cm³ (solid) 13,707 g/cm³ (liquid)	OECD 1996
Melting point	63°C (-crystalline form, common form) 56.2°C (-crystalline form) 52.5°C (-crystalline form)	Weast 1984
Boiling point	187.8°C (-crystalline form) 187.9°C (-crystalline form) 187.8°C (-crystalline form)	Weast 1984
Solubility	Very soluble in water (4,210 g/L at 20°C); soluble in methanol, ethanol, acetone, ether, dioxane, DMF, DMSO	IUCLID 1996; BG Chemie 1993; Weast 1984
Acidity, pK_a	2.85	Weast 1984
Odor	Pungent odor	ICPS & CEC 1994
Explosive limits in air	No data	
Conversion factors	1 ppm = 3.92 mg/m^3 (at 1,013 hPa, 25°C) 1 mg/m^3 = 0.26 ppm (at 1,013 hPa, 25°C)	BG Chemie 1993

a case, in which about 10% of the body surface was contaminated with warm MCAA solution. Although the contaminated skin was immediately rinsed with water for more than 1 h, first-grade burns, anxiety, restlessness, and shock developed, followed by death about 10 h after the accident. Ruty et al. (1988) re-

ported on the case of a 47-year-old worker, who had pressurized, molten (about 90°C) MCAA squirted on both legs. Although the legs were immediately rinsed with water, 6% of the body area showed first-grade burns. Four hours after the accident, nausea, vomiting, cardiovascular shock, unconsciousness, and coma developed. Arrhythmia, hypotension, and severe metabolic acidosis were found. The patient was treated with ethanol, an effective antidote for fluoroacetic acid intoxications. His symptoms ameliorated after 24 h, and the patient returned to work 3 months later. Kulling et al. (1992) reported the case of a 38-year-old man who was splashed with an 80% MCAA solution on 25-30% of his body surface. On admission to hospital 1 h after the accident, he had epidermal and dermal superficial burns and showed slight disorientation. One hour later, he developed agitation, cardiac failure and coma. He later developed severe metabolic acidosis, rhabdomyolysis, renal insufficiency, and cerebral edema and died on day 8 after the accident because of severe CNS damage.

2.2. Nonlethal Toxicity

Clariant GmbH (unpublished material, 2000) reported that routine medical examinations of workers of two plants, producing MCAA and sodium monochloroacetate, respectively, revealed no respiratory tract irritation, effects on lung-function parameters, or irritation of skin and mucous membranes. The number of potentially exposed workers was 33 in one plant and not stated for the other. Concentrations of MCAA and sodium monochloroacetate, respectively, were measured at individual workplaces about every 1 to 2 years between 1991 and 2000. Measurements were carried out either as area or personal sampling by drawing a defined volume of air through a 0.01-mol/L sodium hydroxide solution during a time period between 275 and 430 min followed by ion chromatography analysis. Results are given in Table 3-3.

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm) (for this study, an exposure time of 1 min was stated in Izmerov et al. [1982]). The experimental details were not described by the authors.

An odor threshold of 0.01 ppm cited from an unpublished correspondence from Dow Chemical Co. was reported by AIHA (1993). Oelert and Florian (1972) cited an odor threshold of 0.045 ppm; however, the authors did not state whether this value was taken from the literature or whether and how they measured the odor threshold.

Knapp (1923) reported a case in which occupational exposure to MCAA had resulted in severe damage of the cornea (keratitis traumatica), but did not provide details of the exposure.

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. The exposure corresponds to an oral dose of about 2.1 mg/kg/day (d) (see section 6.1).

TABLE 3-3 Results of Monochloroacetic Acid Measurements at Workplace

Plant	Workplace Situation	Individual MCAA Concentrations Measured Between 1991 and 2000	Number of Workers and Exposure Time Per Workshift
SMCA production	Area of rollers for production of MCAA flakes	Area sampling; 1, <1, <1, 1, 1, 1, 1 mg/m³ (MCAA measured) (0.26, <0.26, <0.26, 0.26, 0.26, 0.26, 0.26 ppm)	1 person for 1 h
SMCA production	Filling of MCAA flakes	Personal sampling; <1, 1.2, 1, <1, 1 mg/m³ (MCAA measured) (<0.26, 0.31, 0.26, <0.26, 0.26 ppm)	Max. 4 persons for 7 h
SMCA production	SMCA mixer	Area sampling; 0.81, 0.89 mg/m³ (SMCA measured) (0.21, 0.23 ppm)	1 person for 1 h
SMCA production	Filling of bags with SMCA	Personal sampling; 0.49, 0.45, <0.40 mg/m³ (SMCA measured) (0.13, 0.12, <0.10 ppm)	1 person for 6 h
MCAA production	Round and sampling men work area in five buildings	Personal sampling; <1, <1, <1,<1,<1, <1, <1, <1,<1,<1, 0.8, <0.5, <0.5, <0.5, <0.5, <0.5, <0.5 mg/m³ (MCAA measured) (<0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, 0.21, <0.13, <0.13, <0.13, <0.13, <0.13, <0.13 ppm)	8 persons for 3 h

Abbreviations: SMCA; sodium monochloroacetate; MCAA, monochloroacetic acid.
Source: Adapted from Clariant GmbH, upublished material, 2000.

2.3. Reproductive and Developmental Toxicity

No studies documenting developmental or reproductive effects of MCAA in humans were identified (IUCLID 1996; MEDLINE and TOXLINE search, November 2003).

2.4. Genotoxicity

No studies documenting genotoxic effects of MCAA in humans were identified (IUCLID 1996; Greim 1998; MEDLINE and TOXLINE search, November 2003).

2.5. Carcinogenicity

No studies documenting carcinogenic effects of MCAA in humans were identified (IUCLID 1996; Greim 1998; MEDLINE and TOXLINE search, November 2003).

2.6. Summary

No studies are available on severe toxic effects in humans after inhalation exposure to MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and Dubinina 1974; Rodionova and Ivanov 1979); no respiratory tract irritation, effects on lung-function parameters or irritation of skin and mucous membranes were reported for more than 33 workers potentially exposed to MCAA concentrations at less than 0.13 ppm for 3 h and at 0.31 ppm for 7 h (Clariant GmbH, unpublished material, 2000). Mortality of a child was reported after oral uptake of 5-6 mL of an 80% MCAA solution (Feldhaus et al. 1993; Rogers 1995). Several lethal accidents were reported in which workers were dermally exposed to hot liquid MCAA or aqueous MCAA solutions (BUA 1994; IUCLID 1996; ECETOC 1999).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several studies are available that report oral lethal doses of MCAA in different animal species. The oral lethality data are summarized in Table 3-4. Only one study was found that reported lethal effects after inhalation exposure.

3.1.1. Nonhuman Primates

In a metabolic study, Dow Chemical Co. (1976) administered MCAA intravenously to one male rhesus monkey. The animal was given 75 mg/kg on day 1 and 200 mg/kg on day 2. It died 2 h after the second dose. No signs of toxicity other than vomiting were reported; the cause of death remained undetermined. (Note: The study would be ethically unacceptable today.)

3.1.2. Rats

Maksimov and Dubinina (1974) observed no deaths in albino rats exposed to MCAA vapor at 5 mg/m³ (1.3 ppm). (The authors stated that this was the maximum achievable vapor concentration at 20°C.) When MCAA was heated to 95°C and rats were exposed to the condensed aerosol, the authors reported an LC_{50} of 180 (146-221) mg/m³ (46.8 ppm) for 4 h (exposure duration taken from Izmerov et al. 1982). The experimental details were not described by the authors.

Hoechst AG (1979a) administered 1% (weight/volume[w/v]) solutions of MCAA in water to groups of 10 female Wistar rats that were deprived of food for 16 h before and 2 h after gavage. The post-exposure observation period was

TABLE 3-4 Summary of Acute Oral Lethal Doses in Laboratory Animals

Species	Dose (mg/kg)	Study Type/Size	Type of MCAA solution	Signs and Symptoms	Reference
Cattle	100	1 animal	No details reported	Anorexia, ruminal atony, diarrhea, fibrillar muscle twitchings, survived	Dalgaard-Mikkelsen and Rasmussen 1961
	150	1 animal		Colic, diarrhea, generalized muscle twitching, dyspnea, death after 9 h	
Rabbit	90	LD_{50} (no details reported)	Neutralized solution	Apathy	Woodard et al. 1941
Guinea pig	79.8	LD_{50} (10 animals/group)	Neutralized solution	Apathy	Woodard et al. 1941
Rat	102	LD_{50} (4 rats/group)	Non-neutralized solution in water	Central nervous system effects, death after 1-4 h	Berardi 1986
Rat	90.4	LD_{50} (10 rats/group)	1% solution in water	Restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes and dyspnea	Hoechst AG 1979a
Rat	76.2	LD_{50} (5-20 rats/group)	Neutralized solution	Apathy	Woodard et al. 1941
Rat	55	LD_{50} (no details reported)	10% non-neutralized solution in water	Not reported	Maksimov and Dubinina 1974
	580	LD_{50} (no details reported)	10% neutralized solution		
Mouse	260	LD_{50} (8-10 mice/group)	Non-neutralized solution	Immobility, ataxia, slight tremors, labored respiration, death after 3-6 h	Berardi and Snyder1983
Mouse	255	LD_{50} (10 mice/group)	Neutralized solution	Apathy	Woodard et al. 1941

Mouse	165	LD_{50} (no details reported)	No details reported	Respiratory paralysis	Morrison and Leake 1941
Goose	50	2 animals	No details reported	No symptoms	Christiansen and Dalgaard-Mikkelsen 1961
	75	Same animals, 2 wk later		Incoordination, seizures, death after 4-6 h	

14 days. Mortality was 0 of 10 animals at a dose of 40 g/kg, 2 of 10 at 63 mg/kg, 5 of 10 at 100 mg/kg and 10 of 10 at 160 mg/kg. Death occurred between 128 min and 24 h after gavage. Symptoms before death included restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes, and dyspnea. Gross pathologic examination revealed brownish-red livers with prominent lobular structuring and light-red to pink spotted lungs. In surviving animals, the same symptoms occurred to a lesser extent but were not observed longer than 48 h after exposure. Using Probit analysis, an oral LD_{50} of 90.4 mg/kg (95% CI [95% confidence interval] 73.6-112 mg/kg) was calculated by the study authors.

Using subcutaneous injection of a 50% solution of MCAA in saline, an LD_{50} of 97.4 (89.9-105.5) mg/kg was reported for Wistar rats (10 animals/group) (Hoechst AG 1979d). Dermal LD_{50}s were 305 (242-384) mg/kg for a 40% non-neutralized MCAA solution in water (Hoechst AG 1979d) and more than 2,000 mg/kg for sodium monochloroacetate in saline (Hoechst AG 1988c).

Berardi (1986) reported an oral LD_{50} of 102 mg/kg (95% CI 51-204 mg/kg) using groups of four Sprague-Dawley rats and gavage of a non-neutralized MCAA solution in water.

Woodard et al. (1941) reported an oral LD_{50} of 76.2 mg/kg (95% CI 70.7-82.2 mg/kg) using a neutralized MCAA solution and groups of 5 to 20 rats (strain not specified).

Maksimov and Dubinina (1974) investigated oral LD_{50} values in albino rats administered a 10% of MCAA solution. A value of 55 mg/kg was found when the acid solution was used, and a value of 580 mg/kg was determined for the neutralized solution. No experimental details were provided.

Using subcutaneous injection, Hayes et al. (1973) determined an LD_{50} in groups of 5-10 male Sprague-Dawley rats of 108 mg/kg (95% CI 88-133 mg/kg).

Using intravenous injection of a 20% MCAA solution in phosphate buffer, pH 7, Elf Atochem (1995) reported an LD_{50} of 75 (53-117) mg/kg in Sprague-Dawley rats. Clinical signs were hypokinesia, sedation, dyspnea, lateral decubitus, suffocation, coma, and death (after 1-3 h).

Mitroka (1989) reported the following 24-h mortality of Sprague-Dawley rats injected neutralized MCAA solution intravenously with 20, 40, 80 and 100 mg/kg in zero of six, one of six, four of 5, and six of six animals, respectively. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli and a dark ruddy eye color. Death usually occurred 1-4 h after exposure. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath, and unconsciousness. No consistent differences were observed in the gross appearance of organs of unexposed and exposed animals upon necropsy.

Using MCAA administration via implanted minipumps, Rozman (2000) found that the relationship between dose and time to MCAA-induced coma in male Sprague-Dawley rats followed the $C \times t = k$ relationship. The time-dose combinations were between about 125 mg/kg for about 60 min to about 50

mg/kg for about 120 min. The details of these experiments are not provided in the publication and have not been published until now.

3.1.3. Mice

Berardi (1986) reported an oral LD_{50} of 260 mg/kg (95% CI 214-316 mg/kg) using groups of 8-10 Swiss-Webster mice and gavage of a non-neutralized MCAA solution in water. Reported symptoms included immobility, head bobbing, ataxia, hyperreactivity to stimuli, slight tremors, clasping of front paws, and labored respiration. Death occurred 3-6 h after MCAA administration. Using dermal application of molten (65°C) MCAA for 2 min followed by rinsing with water, an LD_{50} of 490 (428-562) mg/kg was found. After subcutaneous injection of MCAA into Swiss-Webster mice (eight animals/group), reported LD_{50} values were 150 (129-175) mg/kg for non-neutralized MCAA solution in water and 130 (105-160) mg/kg for neutralized MCAA solution.

Woodard et al (1941) found an oral LD_{50} of 255 mg/kg (95% CI 196-334 mg/kg) using a neutralized MCAA solution and groups of 10 mice (strain not specified). Morrison and Leake (1941) published an oral LD_{50} of 165 mg/kg for MCAA in mice.

Mitroka (1989) reported the following 24-h mortality of Swiss-Webster mice injected neutralized MCAA solution intravenously with 100, 125, 160, and 200 mg/kg in zero of seven, one of four, five of seven, and four of four animals, respectively. Signs of intoxication appeared within 2 h of expsoure. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli, and a dark ruddy eye color. Death usually occurred 3-12 h after exposure. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath, and unconsciousness. No consistent differences were observed in the gross appearance of organs of unexposed and exposed animals upon necropsy.

3.1.4. Other Species

Woodard et al (1941) reported an oral LD_{50} of 79.8 mg/kg (95% CI 71.8-88.6 mg/kg) for guinea pigs (10 animals/group) and about 90 mg/kg for rabbits (1-10 animals/group) using a neutralized MCAA solution (respective strains not specified).

Dalgaard-Mikkelsen and Rasmussen (1961) evaluated oral toxicity in cattle. Doses of 0, 50, 100, and 150 mg/kg were given to one animal each by stomach tube. A dose of 50 mg/kg resulted in inappetence of 24 h duration. A dose of 100 mg/kg produced severe symptoms of intoxication with anorexia, ruminal atony, diarrhea, and fibrillar muscle twitchings. The animal recovered within 2 weeks. Administration of 150 mg/kg caused colic, diarrhea, generalized fibrillar muscle twitching, and dyspnea. The animal died 9 h after dosing.

Christiansen and Dalgaard-Mikkelsen (1961) gave doses of 50 mg/kg by oral gavage to two geese. No symptoms were observed. The same animals were

given 75 mg/kg 2 weeks later. After 3 h, incoordination and seizures were observed; the animals died after 4 to 6 h.

3.2. Nonlethal Toxicity

A small number of studies describe nonlethal effects after inhalation exposure. Signs of irritation were observed after inhalation and after oral exposure of animals to MCAA.

3.2.1. Rats

Dow Chemical Co. (1987) exposed a group of six female and six male Fischer 344 rats to MCAA vapor by inhalation for 1 h. The test material was vaporized into a stainless steel and glass 112-L Rochester-type inhalation chamber. The targeted concentration of MCAA was 1,000 ppm. The nominal chamber concentration was calculated based on the amount of test material used and the total air passed through the chamber during each exposure period. The nominal concentration was 964 ppm. The analytic concentration in the chamber was determined by taking an air sample from the chamber by pulling air through a glass tube containing silica gel during exposure and subjecting this sample to ion chromatography. The actual analytic concentration of MCAA vapor during exposure was calculated to be 66 ppm. It was stated that an analytic concentration of 1,000 ppm was not feasible due to "substantial recrystallization of MCAA in the presence of room temperature (23°C) air."

During all exposures, all rats (12/12) showed eye squint and slight lethargy. Although the expression "slight lethargy" is used in the text, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

Hercules (1969a) exposed groups of three rats, mice and guinea pigs by inhalation to MCAA-saturated vapor generated at 75°C (nominal concentration 27,000 mg/m^3; 7,020 ppm). No deaths occurred after exposure for 3, 5, or 10 min, although nasal discharge and lung hyperemia were observed. In a similar study involving exposure of groups of two rats, mice and guinea pigs to saturated MCAA vapor (nominal concentration 31,000 mg/m^3; 8,060 ppm) mild lacrimation, nasal discharge, and dyspnea, but no mortality, was found (Hercules 1969b). No experimental details were reported. The relevance of these studies is compromised by the fact that no information about the analytic concentrations was provided.

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate. The exposure duration and other experimental details were not stated by the authors.

Maksimov and Dubinina (1974) exposed 75 rats and 18 guinea pigs to MCAA at 5.8 ± 3.0 and 20.8 ± 1.0 mg/m³ (1.5 ± 0.8 and 5.4 ± 0.3 ppm) over a period of 4 months (probably continuous exposure; exact exposure conditions were not stated by the authors). In the high-dose group, the following observations were made: a reduction in body weights of guinea pigs and rats during weeks 2 and 10; a reduction in oxygen uptake on days 3 and 15; a lowering of the rectal body temperature on days 2 and 15; and a reduction in the chloride concentration in urine at the end of month 2 and hemoglobinemia during month 4. The pathomorphologic investigation revealed inflammatory changes in the respiratory organs and tracheal catarrh, bronchitis, and bronchopneumonia. In the low-dose group, only very slight effects were found: a lower oxygen uptake on day 3; a lower rectal temperature on days 7 and 14, and a reduction in the chloride concentration of the urine in month 4. Morphologic examinations revealed only slight effects on the respiratory organs—effects that were not considered significant compared with the control group by the authors. The experimental details were not described by the authors.

NTP (1992) exposed groups of five male and five female Fischer 344 rats to MCAA in water by gavage at 0, 7.5, 15, 30, 60, and 120 mg/kg once daily for a total of 12-dose days over a 16-day period. One male rat of the high-dose group died on the third day of dosing (symptoms observed within 4 h after dosing were lacrimation, prostration, bradypnea, decreased limb tone, ataxia, and an impaired gasping reflex); no other deaths occurred. Lacrimation was also observed in males receiving 60 or 120 mg/kg and females receiving 15 mg/kg or higher. No gross or histologic lesions were observed.

Bryant et al. (1992), also described in NTP (1992), exposed groups of 20 male and 20 female Fischer 344 rats to oral doses of MCAA at 0, 30, 60, 90, 120, or 150 mg/kg in water by gavage once daily, 5 d/wk for up to 13 weeks. All rats receiving 120 or 150 mg/kg and all but one receiving 90 mg/kg died before the end of the exposure period. Other deaths included two male rats and one female rat receiving 60 mg/kg and one female rat receiving 30 mg/kg. A complete pathologic and histopathologic examination on all early deaths and all surviving animals at the end of the exposure period was done. The final mean body weights of rats surviving to the end of the study were similar to those of the controls. Relative heart weights of male and female rats in the 60-mg/kg groups as well as those of female rats in the 30-mg/kg group were significantly lower than controls. Relative weights of liver and kidney of male and female rats at 60 mg/kg were significantly greater than those of the controls. Blood urea nitrogen was increased in a dose-related trend in males at 90-150 mg/kg and in females at 60-150 mg/kg. Male rats at 150 mg/kg and females at 60, 120, and 150 mg/kg had a significant increase in serum alanine aminotransferase activity compared with controls. Chemical-related degenerative and inflammatory changes (including cardiomyopathy) were observed in the hearts of male and female rats receiv-

ing 60, 90, 120, or 150 mg/kg. In these dose groups, acute or subacute cardiomyopathy was observed in the rats that died before the end of the study and was considered to be the cause of death in these animals. No cardiomyopathy or other histologic effects were observed at a dose of 30 mg/kg.

Bhat et al. (1991) gave a neutralized solution of MCAA at 1.9 mmol/L of drinking water to male Sprague-Dawley rats (number not stated) for 90 days. On day 90, body weights were not significantly reduced compared with controls (426.8 ± 22.1 g vs. 448.2 ± 22.8 g); liver weights were reduced (13.25 ± 0.64 g vs. 14.68 ± 0.78 g). Minimal to mild morphologic liver alterations were observed (enlarged portal veins, increased numbers of bile ducts, areas of edema, and inflammatory cells surrounding the portal veins). Increased perivascular inflammation compared with controls was observed in the lungs. The dose tested was equivalent to about 20 mg/kg/d (BIBRA 1997).

Daniel et al. (1991) administered the sodium salt of MCAA by oral gavage for a period of 90 consecutive days to Sprague-Dawley rats. Groups of 10 male and 10 female rats received daily doses of 0, 15, 30, 60 or 120 mg/kg. At 120 mg/kg, 30% of females and 80% of the males died, 7 of the 11 deaths occurred within the first 3 days of treatment, while the other 4 deaths occurred between days 14 and 90. In the early deaths, hemorrhagic and congested lungs were observed but considered a postmortem change. In the later deaths, liver lesions were found. One male in each of the 60- and 15-mg/kg groups died. No apparent dose-response-related differences between treated and control groups in body or organ weights were found with the exception of significant increased liver and kidney weights in females at 120 mg/kg. Relative liver weights were increased in both females and males at 60 and 120 mg/kg. Histopathologic examination revealed a significant increase in chronic renal nephropathy and increased splenic pigmentation at 60 mg/kg/d (120-mg/kg/d group excluded due to mortality). In female but not in male rats, significantly increased numbers of white blood cells were found at 30, 60, and 90 mg/kg, and sporadic but not dose-related changes were found in subpopulations (lymphocytes and monocytes) at doses of 15 mg/kg or higher. Increased blood urea nitrogen levels in females at 120 mg/kg and in males at 15 and 30 mg/kg, but not 60 and 120 mg/kg, as well as increased creatinine levels in females at 15 and 30 mg/kg, but not at 60 and 120 mg/kg, and in males at all dose levels were found.

3.2.2. Mice

NTP (1992) exposed groups of five male and five female $B6C3F_1$ mice by gavage to MCAA in water once daily using doses of 0, 15, 30, 60, 120 and 240 mg/kg for males and 0, 30, 60, 120, 240, and 480 mg/kg for females for a total of 12-dose days over a 16-day period. All mice receiving 240 mg/kg or higher died within 2 days; no other deaths occurred except for one male in the 15-mg/kg group. Clinical findings in animals that died included lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection,

decreased limb tone, and impaired gasping. Lacrimation was also observed in females receiving 120 mg/kg. No changes in organ weights and gross or histologic lesions were observed.

Bryant et al. (1992) (also described in NTP 1992) exposed groups of 20 male and 20 female B6C3F_1 mice to oral doses of MCAA in water at 0, 25, 50, 100, 150, or 200 mg/kg by gavage once daily, 5 d/wk for up to 13 weeks. All mice receiving 200 mg/kg died or were killed when moribund before the end of the exposure period (all but two died within the first week). Two males given 200 mg/kg and one female given 100 mg/kg died from gavage trauma; two male controls died from unknown causes. With the exception of females receiving 200 mg/kg, the mean body weights of dosed mice were similar to those of controls. Cholinesterase levels were significantly decreased in female mice receiving 150 or 200 mg/kg at weeks 8 and 13. No chemical related lesions were observed in mice of either sex. Hepatocellular vacuolization was seen in mice in the 200-mg/kg group that died during the study. No effects were observed at a dose of 100 mg/kg.

3.3. Reproductive and Developmental Toxicity

No studies evaluating developmental or reproductive toxic effects after inhalation exposure were located in the literature (MEDLINE and TOXLINE search, November 2003).

Smith et al. (1990) exposed pregnant Long-Evans rats to 0, 17, 35, 70, and 140 mg/kg (daily gavage) during gestational days 6 to 15. The body-weight increase was significantly reduced in the highest exposure group. No effects on the number of resorptions and birth weight were found. The rate of visceral malformations (especially of the heart and cardiovascular system) was between 1.2% in controls and 6.4% in the highest dose group, but no dose-dependency was observed. No skeletal malformations were found. This study has only been published as an abstract, and no details were reported.

Johnson et al. (1998) exposed pregnant Sprague-Dawley rats during gestational days 1-22 to MCAA at 1,570 ppm in drinking water as well as to other halogenated hydrocarbons. The authors calculated the dose for exposure to MCAA as 33 mg/kg/d. No signs of maternal toxicity were observed. No effects on the number of mean implantation sites and resorption sites were found. MCAA produced no cardiac abnormalities. Of the substances tested, only trichloroacetic acid caused a significant increase in the number of cardiac abnormalities.

Bhunya and Das (1987) injected single doses of MCAA intraperitoneally at 12.5, 25, and 50 mg/kg into groups of three male Swiss mice. After 35 days, an increased number of malformed sperm was found in the two highest dose groups.

3.4. Genotoxicity

In genetic toxicity testing in the NTP (1992) study, MCAA was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 (with and without metabolic activation using rat liver S9 mix). It induced trifluorothymidine resistance in L5178Y mouse lymphoma cells in the absence of S9 mix and induced sister chromatid exchanges in Chinese hamster ovary cells in the absence but not in the presence of S9 mix. MCAA did not induce chromosomal aberrations in Chinese hamster ovary cells (with and without activation). MCAA administered in feed was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*; results were equivocal when MCAA was administered by injection.

Several other reports have been published on negative results in assays for mutations in bacteria and positive as well as negative results in tests for mutations and sister chromatid exchanges in eucaryotic cells in vitro (see BG Chemie 1993; IUCLID 1996; ECETOC 1999).

Bhunya and Das (1987) injected MCAA intraperitoneally at 12.5, 25, and 50 mg/kg one time or at 10 mg/kg five times into male and female Swiss mice. A significantly increased rate of chromosomal aberrations was observed for all doses after 6-120 h in the bone marrow. No effect was seen 24 h after oral gavage or subcutaneous injection of 50 mg/kg.

3.5. Carcinogenicity

In a NTP carcinogenicity study (NTP 1992) male and female Fischer 344 rats were given 0, 15, or 30 mg/kg and male and female $B6C3F_1$ mice were given 0, 50, and 100 mg/kg by gavage of a MCAA solution in water for 5 d/wk for 2 years. In both species there was no evidence of carcinogenic activity of MCAA. In mice, but not in rats, a dose-dependent increase in inflammation of the nasal mucosa and metaplasia of the olfactory epithelium was found, as well as squamous metaplasia of the forestomach.

DeAngelo et al. (1997) performed a 2-year carcinogenicity study in Fischer 344 rats. Animals were given MCAA at 50, 500, and 2,000 mg/L in drinking water. Due to severe inhibition of body-weight gain, the high dose was reduced to 1,500 mg/L at 8 weeks and further to 1,000 mg/L at 24 weeks. The authors calculated time-weighted mean daily doses of MCAA at 3.5, 26.1, and 59.9 mg/kg/d. They found no significant differences in animal survival between the control and exposed groups. No increased incidence of neoplastic lesions was found.

3.6. Summary

The only animal study reporting lethal effects after inhalation of MCAA

was an inadequately described study in which an LC_{50} of 46.8 ppm for 4 h was reported for rats (Maksimov and Dubinina 1974). Several studies report lethal effects after oral exposure. LD_{50} data presented in Table 3-4 are mostly from 50 to 200 mg/kg for rats, mice, and guinea pigs. In addition, lethal doses in other species were 200 mg/kg in a rhesus monkey (Dow Chemical Co. 1976), 150 mg/kg for a cow (Dalgaard-Mikkelsen and Rasmussen 1961), and 75 mg/kg for geese (Christiansen and Dalgaard-Mikkelsen 1961).

In a single inhalation experiment on rats, eye squint and slight lethargy were observed during MCAA exposure at 66 ppm for 1 h (Dow Chemical Co. 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a NOEL for histologic changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina 1974).

After repeated oral gavage for 2 weeks, lacrimation was observed in male rats receiving MCAA at 60 or 120 mg/kg and in female rats receiving 15 mg/kg or higher (NTP 1992). In experiments performed in parallel, lacrimation was also observed in female mice receiving 120 mg/kg (NTP 1992). In subchronic studies using oral exposure by gavage or drinking water, a dose of 30 mg/kg in rats and 100 mg/kg in mice had no or only minor effects (Bhat et al. 1991; Daniel et al. 1991; Bryant et al. 1992; NTP 1992).

The study by Smith et al. (1990) suggests that high doses of MCAA (close to the LD_{50} in other rat strains) can cause maternal toxicity and malformations in the offspring. The effect on fertility upon intraperitoneal injection (Bhunya and Das 1987) requires further study using other exposure routes. There is no evidence of genotoxic potential in bacterial mutagenicity studies, in vitro chromosomal aberration tests, and in vitro and in vivo primary DNA damage assays. Gene mutation tests in mammalian cells gave contradictory results, and in one study, increased chromosomal aberrations were found after intraperitoneal injection in mice. No carcinogenic activity of MCAA was found in mice and rats after oral administration of MCAA by gavage or drinking water.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No quantitative absorption rate data are available for inhalation exposure. An oral absorption rate of 82% (^{14}C recovery in urine was 70%) was found in a rat that was given 1-^{14}C-labeled MCAA (Dow Chemical Co. 1976). A rate of 90% in 24 h for the cumulative excretion of MCAA in urine was reported in Sprague-Dawley rats after an oral dose of 1-^{14}C-labeled MCAA at 9.4 mg/kg (Kaphalia et al. 1992). Berardi (1986) reported values for cumulative excretion in urine of 51% in 24 h and 52.5% in 72 h in Sprague-Dawley rats and 32.0-59.3% in 24 h and 33.7-60.8% in 72 h in Swiss-Webster mice. Lethal effects in

humans after dermal contact with liquid MCAA indicate a considerable dermal absorption.

Yllner (1971) injected doses of 0.07, 0.09, and 0.1 g/kg 1-^{14}C-labeled MCAA subcutaneously into mice and measured radioactivity after 24, 48, and 72 h in urine, feces, and expired air. Within 72 h, 82-88% of the radioactivity was eliminated in urine, 8% was eliminated via the lungs, and 0.2-0.3% was eliminated in feces, and 2-3% remained in the body. The main metabolites found in urine were *S*-carboxymethyl-L-cysteine (33-43% in free form and 1-6% as glutathione conjugate) and thiodiacetic acid (33-42%) as well as MCAA (6-22%), glycolic acid (3-5%), and oxalic acid (0.1-0.2%). The authors suggested two metabolic pathways: (1) conjugation with glutathione resulting in formation of *S*-carboxymethyl glutathione, which can be further metabolized to *S*-carboxymethyl-L-cysteine and further to thiodiacetic acid; and (2) enzymatic hydrolysis of the chlorine-carbon bond and formation of glycolic acid that can be degraded completely to carbon dioxide.

In the urine of rats, thiodiglycolic acid, but not *S*-carboxymethyl-L-cysteine, was found. However, according to the study, *S*-carboxymethyl-L-cysteine might have been present in bile but could not be identified unequivocally (Dow Chemical Co. 1976).

Hayes et al. (1972, 1973) injected rats with 1-^{14}C-labeled MCAA subcutaneously at 162 mg/kg. After 2 h, higher radioactivity was found in kidneys and liver than in plasma, and heart and brain had similar levels to plasma. A similar distribution was found after administration of 53 mg/kg. A biphasic elimination curve was observed with half-life times of 90 min and 17 h.

The fact that rodents can be exposed for long periods of time (90 days or 2 years) (Daniel et al. 1991; Bryant et al. 1992; NTP 1992; DeAngelo et al. 1997) at daily doses close to the oral LD_{50} (see Table 3-4) argues for rapid clearance of MCAA after each exposure.

4.2. Mechanism of Toxicity

The biochemical basis of systemic MCAA toxicity is the inhibition of single enzymes of the glycolytic and tricarboxylic acid metabolic pathways. The blockage of these metabolic processes results in inhibition of energy metabolism (ATP generation) and in accumulation of lactic acid in the glycolytic pathway, causing metabolic acidosis.

Prolonged incubation of isolated rat heart mitochondria with MCAA inhibits both pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (van Hinsbergh and Vermeer 1994) via an indirect inhibition through formation of oxalate from MCAA (Mitroka 1989) or a direct inhibition through slow alkylation or sulfhydryl groups (van Hinsbergh and Vermeer 1994). Since the inhibition of the enzymes of the glycolytic (pyruvate dehydrogenase) and tricarboxylic acid (α-ketoglutarate dehydrogenase) metabolic pathways has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis,

which results in lactate accumulation (van Hinsbergh and Vermeer 1994). In vitro, MCAA inhibited oxidation of radiolabeled acetate to carbon dioxide by rat liver homogenate (Hayes et al. 1973), indicating an inhibitory effect on the tricarboxylic acid cycle. Blockade of aerobic energy metabolism can be expected to especially damage organs and tissue with a high-energy demand, such as heart, CNS, and skeletal muscles (Kulling et al. 1992).

It has been suggested that in analogy to monofluoroacetic acid, MCAA could also inhibit the tricarboxylic-acid-cycle enzyme aconitase (IUCLID 1996). Experimental evidence suggests organ-specific differences with respect to aconitase inhibition by MCAA and by monofluoroacetic acid: about 1.5-2 h after oral administration of MCAA at 24, 48, or 96 mg/kg to Fischer 344 rats, an inhibition of aconitase was detected in the heart (54%, 55%, and 46% inhibition, respectively) but not in the liver (0% inhibition at all doses), while monofluoroacetic acid inhibited aconitase in both organs (4.0%, 10.5%, and 21.0% inhibition, respectively; same inhibition in both organs) (Bryant et al. 1992; NTP 1992). These findings suggest that different isoenzymes with different susceptibility to the inhibitory effect of MCAA are expressed in the two organs. In the experiments, no dose-response relationship was revealed: a 33-55% inhibition was found after doses between 4 and 150 mg/kg.

After intravenous injection of MCAA at 40 or 80 mg/kg (neutralized solution in phosphate buffer) in rats, blood and cerebrospinal fluid lactate concentrations increased progressively with time until death (1-2 h after dosing) (Mitroka 1989). In the blood, a significant increase in lactate concentrations was found for the 80-mg/kg dose starting at 60 min, and a very slight increase was seen for the 40-mg/kg dose. In the cerebrospinal fluid, significant increases were found for the 40-mg/kg dose at 120 min and for the 80-mg/kg dose at 60 min (Mitroka 1989). The accumulation of lactate in the brain can contribute to the lethal effects of MCAA, especially since the removal of lactate from the brain via the blood-brain barrier is slow. The damage of the blood-brain barrier by MCAA has also been shown by Berardi (1986) and Berardi et al. (1987): nearly lethal doses administered orally to mice (257 and 380 mg/kg) led to an increased entry of radiolabeled dopamine and inulin into all brain regions; in addition, red blood cells were found in the brain parenchyma. The associated neurologic dysfunction was characterized by front paw rigidity. At doses that caused no or little mortality (80, 118, and 174 mg/kg) the concentration of radioactive inulin did not differ from controls.

Unlike monofluoroacetate and like monoiodoacetic acid, MCAA can bind to sulfhydryl groups (Yllner 1971; Hayes et al. 1973; van Hinsbergh and Vermeer 1994). After oral administration, MCAA was shown to bind to sulfhydryl groups in the kidney and liver of rats. Direct inhibition of sulfhydryl groups in the kidney may account for the anuria present in animals receiving toxic levels of MCAA, which could contribute to enzyme inhibition and renal dysfunction (Hayes et al. 1973). Renal insufficiency was also found in humans after oral intoxication (Kulling et al. 1992), and renal nephropathy was found after subchronic oral exposure in rats (Daniel et al. 1991).

MCAA causes severe local effects on skin and eyes: after occlusive application of MCAA paste at 100 and 500 mg (solution in 0.05 mL 0.9% sodium chloride) to the skin of rabbits, corrosion (at both doses) and mortality (all animals died at the higher dose) were observed (Hoechst AG 1979e). After occlusive application for 24 h of a 10% solution to the intact rabbit skin, there was marked hyperemia and edema (Rodionova and Ivanov 1979). Sodium monochloroacetate did not produce any signs of irritation when applied for 4 h to the skin of rabbits (Hoechst AG 1988d). MCAA was extremely irritant to the rabbit eye (instillation of 100 mg MCAA as paste into conjunctival sac; Hoechst AG 1979e), and sodium monochloroacetate induced moderate irritation (instillation of 100 mg sodium monochloroacetate into conjunctival sac; Hoechst AG 1988d). From this, it can be expected that inhalation of MCAA vapor or MCAA aerosol can cause local irritation and tissue damage in the respiratory tract either by local decrease of the pH or by local enzyme inhibition.

4.3. Structure-Activity Relationships

4.3.1. Studies Using Alkyl Esters of MCAA

Hoechst AG (1988a) determined the acute inhalation toxicity of chloroacetic acid methyl ester. Groups of five female and five female Wistar rats were exposed whole body for 4 h in an exposure chamber at 90, 210, 315, and 385 ppm. The concentration in the exposure chamber was measured by infrared spectroscopy using a Miran analyzer and by gas chromatography. The post-exposure observation period was 14 days. Mortality rates were 0 of 10 animals at 90 and 210 ppm, 7 of 10 at 315 ppm, and 10 of 10 at 385 ppm. Death occurred between 270 min and 6 days after exposure.

Torkelson et al. (1971) exposed groups of four to five female rats in an exposure chamber to different concentrations of chloroacetic acid methyl ester for different exposure times. The following mortality was observed for different exposure periods: two of four animals at 1,000 ppm for 1 h; four of five at 2,000 ppm and zero of four at 500 ppm for 2 h; five of five at 2,000 ppm, five of five at 500 ppm, and zero of four at 250 ppm for 4 h; and zero of four at 100 ppm for 7 h. The authors noted severe irritation at 250-1,000 ppm and slight irritation at 100 ppm. In rabbits, 7- and 4-h exposures at 100 ppm caused delayed conjunctival and corneal irritation; 50 ppm did not cause eye irritation.

Hoechst AG (1988b) exposed groups of 10 female and 10 male Wistar rats repeatedly to chloroacetic acid methyl ester at 0, 10, 33, and 100 ppm (6 h/d, 5 d/w, total of 20 exposures). Mean concentrations measured in the exposure chamber by a Miran infrared analyzer were 10.4, 32.3, and 100.1 ppm, respectively. Gross morphologic and histologic examinations were performed in half of the animals after the last exposure and in the other half after a 14-day recovery period. At 10 ppm, narrowed palpebral fissures were observed only during the first exposure, which was interpreted as a sign of irritation. Additional signs

in the 33-ppm group were sneezing and increased hair grooming, which were observed only during individual exposures. Additional signs in the 100-ppm group were incoordination, retracted flanks, irregular respiration, passiveness, and standing hair, some of which persisted until the next morning and into the recovery period. Food-consumption decrease, body-weight increase, and significantly increased relative lung weights were found in the 100-ppm group. No histopathologic alterations or differences in hematologic and clinical chemistry parameters were observed.

Hoechst AG (1979b) determined the acute oral toxicity of chloroacetic acid ethyl ester administered to groups of 10 female Wistar rats by gavage of a 5% (w/v) solution in sesame oil. The post-exposure observation period was 14 days. Mortality was 0 of 10 animals at a dose of 80 mg/kg, 2 of 10 at 125 mg/kg, 5 of 10 at 200 mg/kg, and 10 of 10 at 315 mg/kg. Death occurred between 136 min and 24 h after gavage. Symptoms before death included crouching, balance disturbance, prone position, and passiveness. No abnormal findings were observed in gross pathologic examinations. Using Probit analysis, an LD_{50} of 180 (151-215) mg/kg was calculated by the authors.

Using the same study design, a 0.5% (w/v) solution of chloroacetic acid methyl ester in sesame oil was used (Hoechst AG, 1979c). Mortality was 0 of 10 animals at doses of 50 and 80 mg/kg, 4 of 10 at 100 mg/kg, 8 of 10 at 125 mg/kg, and 10 of 10 at 200 and 315 mg/kg. Using Probit analysis, an LD_{50} of 107 (95% CI 97.2-121) mg/kg was calculated by the authors.

4.3.2. Studies with Other Monohaloacetic Acids

Hayes et al. (1973) found that the subcutaneous LD_{50} for three haloacetic acids varied considerably in rats and that toxicity is probably caused by differing mechanisms. LD_{50} (95% CI) values were 5 (4-6) mg/kg for monofluoroacetic acid, 60 (54-67) mg/kg for monoiodoacetic acid, and 108 (88-133) mg/kg for MCAA. The mean time to death was 130 (112-151) min for MCAA, 310 (292-360) min for monofluoroacetic acid, and 480 (343-672) min for monoiodoacetic acid. MCAA and monoiodoacetic acid, but not monofluoroacetic acid, significantly reduced the total sulfhydryl concentration in rat liver at an LD_{90} dose after 5% of the time to death. In vitro, MCAA did not alkylate sulfhydryl groups of cysteine.

In mice, Morrison and Leake (1941) found oral LD_{50} values of 63 mg/kg for monoiodoacetate, 100 mg/kg for monobromoacetate, and 165 mg/kg for MCAA.

4.3.3. Conclusions from Structure-Activity Relationships

Several studies evaluated the toxicity of MCAA esters on rats. Although the LD_{50} values for oral administration are comparable to the LD_{50} values for MCAA (see Table 3-4), lethal effects after inhalation exposure to MCAA esters

occurred at considerably higher concentrations. Although Maksimov and Dubinina (1974) reported a 4-h LC_{50} of 46.8 ppm for MCAA, a 4-h exposure at 210 ppm for chloroacetic methyl ester did not result in deaths, and at 315 ppm, 7 of 10 rats died (Hoechst AG 1988a). This difference suggests toxicokinetic and toxicodynamic differences between MCAA and its alkyl esters. Compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value, and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure. In summary, the inhalation studies using MCAA esters cannot be used as supportive evidence for MCAA data.

Oral lethality data for different monohaloacetic acids found a considerable difference in LD_{50} values. These findings and the probable differences in biochemical mechanism presented in section 4.2 argue for different toxicodynamic properties of the different monohaloacetic acids and do not support the use of data on other monohaloacetic acids as supportive evidence for MCAA data.

4.4. Other Relevant Information

4.4.1. Species Variability

Lethal effects have been suggested to be mediated by damage to the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain; that, in turn, results from inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and aconitase). Because these enzymes are evolutionarily highly conserved, a limited interspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values is small: LD_{50} values for different species (mean values of LD_{50} values given in Table 3-4) were 90 mg/kg for rabbits, 79.8 mg/kg for guinea pigs, 80.9 mg/kg for rats (mean of all LD_{50}s except the 580 mg/kg value), and 227 mg/kg for mice; moreover, one of the cattle survived an oral dose of 100 mg/kg, showing only moderate toxic effects (another died at 150 mg/kg) (Dalgaard-Mikkelsen and Rasmussen 1961), and a rhesus monkey survived intravenous injection of 75 mg/kg (and died after another dose of 200 mg/kg the next day) (Dow Chemical Co. 1976). Good data are available for two of these species only, namely, rats and mice, and the difference between these two species is also in line with what can be expected on the basis of standard

scaling using (body weight)$^{0.75}$. No data are available that would suggest a large species difference for local effects in the respiratory tract.

4.4.2. Intraspecies Variability

Lethal effects have been suggested to be mediated by damage of the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain; that, in turn, is secondary to inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and aconitase). Because these enzymes are housekeeping enzymes, which are required for energy metabolism and show a constant expression level, a limited intraspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values within individual species is small because the reported LD_{50} values for different species varied within each species by less than a factor of 2 (see Table 3-4). Some variation is indicated by the finding that repeated oral exposure of rats to 120 mg/kg/d led to death in 8 of 10 males but only in 3 of 10 females (Daniel et al. 1991). The contribution to death of local effects in the respiratory tract upon inhalation is unknown.

At lower concentrations that do not lead to systemic effects, MCAA is irritating to the eye and mucosal surfaces. The mechanism for this effect may involve both local lowering of the pH value and local metabolic blockage by enzyme inhibition. A limited interindividual variability can be assumed for this local effect because it involves direct effects on the tissue (acidity) or effects on highly conserved enzymes, which are expected not to differ considerably between individuals.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Clariant GmbH (unpublished material, 2000) found no respiratory tract irritation, effects on lung function parameters, or irritation of skin and mucous membranes in more than 33 workers potentially exposed to MCAA concentrations of less than 0.13 ppm for 3 h and 0.31 ppm for 7 h.

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm). (For this study, an exposure time of 1 min was stated in Izmerov et al. 1982.) The experimental details were not stated by the authors and, therefore, evaluation of the studies is impossible.

Reported odor thresholds are 0.01 ppm (cited from unpublished correspondence from Dow Chemical Co. in AIHA [1993]) and 0.045 ppm (Oelert and Florian 1972). (In the latter study, it was unclear if the value was cited from the literature or measured by the authors.)

5.2. Animal Data Relevant to AEGL-1

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate.

After exposure of rats and guinea pigs to MCAA at 5.8 and 20.8 mg/m³ (1.5 and 5.4 ppm) over a period of 4 months (probably continuous exposure; exact exposure conditions were not stated by the authors), slightly reduced body weights, effects on metabolism (reduced oxygen uptake and lower rectal body temperature) and kidney function (reduced chloride concentration in urine and hemoglobinemia), and inflammatory alterations of respiratory organs were found in the high-dose group. In the low-dose group, only very slight effects (lower oxygen uptake, lower rectal temperature, and lower urine chloride concentration) were found (Maksimov and Dubinina 1974).

5.3. Derivation of AEGL-1

No definitive study was available for the derivation of AEGL-1 values (Table 3-5). The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (unpublished material 2000) was not considered an adequate basis for the derivation, because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about 1 to 2 measurements per year was considered insufficient. Therefore, due to insufficient data, AEGL-1 values were not recommended.

Because of the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body weight of 70 kg and 0.05% as 500 mg/L, this oral exposure corresponds to a daily dose of 500 mg/L × 0.3 L/d × 1/70 kg = 2.1 mg/kg/d.

TABLE 3-5 AEGL-1 Values for Monochloroacetic Acid

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

[a]Not recommended because of insufficient data.

6.2. Animal Data Relevant to AEGL-2

Dow Chemical Co. (1987) exposed a group of six female and six male Fischer 344 rats to MCAA vapor by inhalation for 1 h. The targeted concentration was 1,000 ppm, and the nominal concentration was 964 ppm; however, the analytic concentration of MCAA vapor during exposure was found to be 66 ppm. It was stated that a concentration of 1,000 ppm could not be achieved because of "substantial recrystallization of MCAA in the presence of room temperature (23°C) air." During exposure, all rats squinted and appeared "slightly lethargic" (stated in the text) or "lethargic" (stated in the tables). During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remaining period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

6.3. Derivation of AEGL-2

For the derivation of AEGL-2 values, the study of MCAA in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 h resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system. No severe effects occurred. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (that is, before the air stream entered the chamber) or whether uptake of recrystallized MCAA might have occurred by routes other than inhalation (e.g., dermal and oral uptake after deposition on the hair). In case of an additional exposure, the measured air concentration of 66 ppm is regarded as a conservative exposure assumption. The AEGL-2 values were based on a 1-h exposure to 66 ppm.

Time scaling using the equation $C^n \times t = k$ was done to derive the other exposure duration-specific values. Due to lack of a definitive dataset, an n of 3 was used in the exponential function for extrapolation from the experimental period (1 h) to shorter exposure periods, and an n of 1 was used for extrapolation to longer exposure periods. The calculations of exposure concentrations scaled to AEGL-2 time periods are shown in Appendix A.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability (1) because the effect level was considered below that of an AEGL-2; (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects (see section 4.4.1); and (3) because of the limited toxicodynamic variability, as the enzymes inhibited by MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and

because of the limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species. The values are listed in the Table 3-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No reports on deaths after inhalation of MCAA are available in the literature. Fatal cases and life-threatening poisonings in workers have been described after skin contact (Kulling et al. 1992; BUA 1994; IUCLID 1996); however, exact doses have not been reported.

Only one study reporting lethality after oral uptake was located: Feldhaus et al. (1993) and Rogers (1995) reported the case of a 5-year-old girl who was accidentally given 5-6 mL of an 80% MCAA containing wart remover, resulting in a dose of MCAA at 4.0-4.8 g (corresponding to 200-240 mg/kg), assuming a body weight of 20 kg. The girl died 8 h post-ingestion despite medical intervention. An autopsy revealed diffuse gastric erosions, fatty liver, and pulmonary and cerebral edema. The postmortem MCAA concentration in serum was 100 mg/L (this concentration corresponds to an MCAA concentration of about 75 mg in serum, assuming a serum volume of 750 mL) as determined by gas chromatography/mass spectroscopy.

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body weight of 70 kg and 0.05% as 500 mg/L, this oral exposure corresponds to a daily dose of 500 mg/L × 0.3 L/d × 1/70 kg = 2.1 mg/kg/d.

7.2. Animal Data Relevant to AEGL-3

Maksimov and Dubinina (1974) reported an LC_{50} in rats of 180 (146-221) mg/m³ (46.8 ppm) for 4 h without providing experimental details. Assuming a body weight of 0.3 kg for rats and a pulmonary absorption rate of 100% and deriving a respiration rate using the allometric relationship published by EPA (1988),

$$\text{ventilation rate (m}^3\text{/d)} = 0.80 \times \text{body weight (kg)}^{0.8206} \text{ (EPA 1988).}$$
$$\text{ventilation rate} = 0.80 \times 0.3^{0.8206} = 0.298 \text{ m}^3\text{/d.}$$

TABLE 3-6 AEGL-2 Values for Monochloroacetic Acid

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)

The corresponding dose can be calculated as

$$\text{dose (mg/kg)} = \text{exp. conc. (mg/m}^3\text{)} \times \text{ventilation rate (m}^3\text{/d)} \times \text{exp. time (d)} \times 1/\text{body weight (kg)}.$$

$$\text{dose} = 180\ \text{mg/m}^3 \times 0.298\ \text{m}^3\text{/d} \times 4/24\ \text{d} \times 1/0.3\ \text{kg} = 29.8\ \text{mg/kg}.$$

Hercules (1969a,b) reported that exposure of rats, mice, and guinea pigs to MCAA-saturated vapor generated at 75°C (reported nominal concentrations 7,020-8,060 ppm) for up to 10 min resulted in irritation (mild lacrimation, nasal discharge), dyspnea, and lung hyperemia but did not cause lethality. Because no experimental details, especially no analytic concentrations, were reported, these studies provide little meaningful information.

Oral LD_{50} data are presented in Table 3-4. Hoechst AG (1979a) administered doses of MCAA at 0, 40, 63, 100, and 160 mg/kg to groups of 10 female Wistar rats using gavage of 1% (w/v) solutions of MCAA in water. Using Probit analysis, an LD_{50} of 90.4 (95% CI 73.6-112) mg/kg was calculated by the authors. The very high LD_{50} of 580 mg/kg for neutralized MCAA solution found in rats by Maksimov and Dubinina (1974) will not be considered further (1) because this value is much higher than other values reported for neutralized MCAA solutions (see Table 3-4), which are similar to non-neutralized MCAA solutions; and (2) due to inadequate data presentation, neutralization by addition of sodium hydroxide (solid or as solution) to the acidic MCAA solution cannot be excluded; this could give rise to high pH either locally in the solution or temporarily due to overtitration and thus cause nucleophilic substitution (hydrolysis) of the chlorine moiety in MCAA, resulting in reaction to the much less toxic glycolic acid.

7.3. Derivation of AEGL-3

For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available.

Although oral lethality data in animals are available, these were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point to a possible role of local effects: (1) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; (2) MCAA can bind to sulfhydryl groups (Yllner 1971; Hayes et al. 1973; van Hinsbergh and Vermeer 1994), for example, those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and (3) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies.

Experimental findings support a possible local effect on the respiratory tract: (1) the available inhalation studies report effects on the respiratory tract,

that is, Hercules (1969a) reported lacrimation, nasal discharge, dyspnea and lung hyperemia in rats, and Maksimov and Dubinina (1974) reported inflammation in the respiratory organs, tracheal catarrh, bronchitis, and bronchopneumonia in rats; and (2) MCAA causes severe local damage to skin and eyes (Hoechst AG 1979e, 1988d; see section 4.2).

Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina 1974), data presentation is inadequate. Because pathologic findings were not reported, it remains unknown whether rats died from local lung-tissue destruction or from systemic toxicity (that is, acidosis affecting CNS or heart). With respect to systemic effects, it could be argued that the rat LC_{50} value of 46.8 ppm for 4 h (Maksimov and Dubinina, 1974), corresponding to a dose of 29.8 mg/kg (see section 7.2), is not supported by studies reporting oral LD_{50} values of about 90 mg/kg for rats (see Table 3-4 and Figure 3-1). However, as discussed above, a higher toxicity of MCAA for the inhalation route compared with the oral route cannot be ruled out. The data presented in Figure 3-1 suggest that upon inhalation exposure, lethal effects might occur at lower doses compared with oral exposure.

Inhalation studies using MCAA esters revealed no mortality after 4 h of exposure at up to 210 or 250 ppm (Torkelson et al. 1971; Hoechst AG 1988a). These data were not considered relevant for the derivation of AEGL-3 values; compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure.

Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina, 1974) and the uncertainties of a route-to-route extrapolation, no AEGL-3 values were derived (Table 3-7).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 3-8. They were derived using the following key studies and methods.

No relevant studies of adequate quality were available for the derivation of the AEGL-1 value. Therefore, due to insufficient data, AEGL-1 values were not derived.

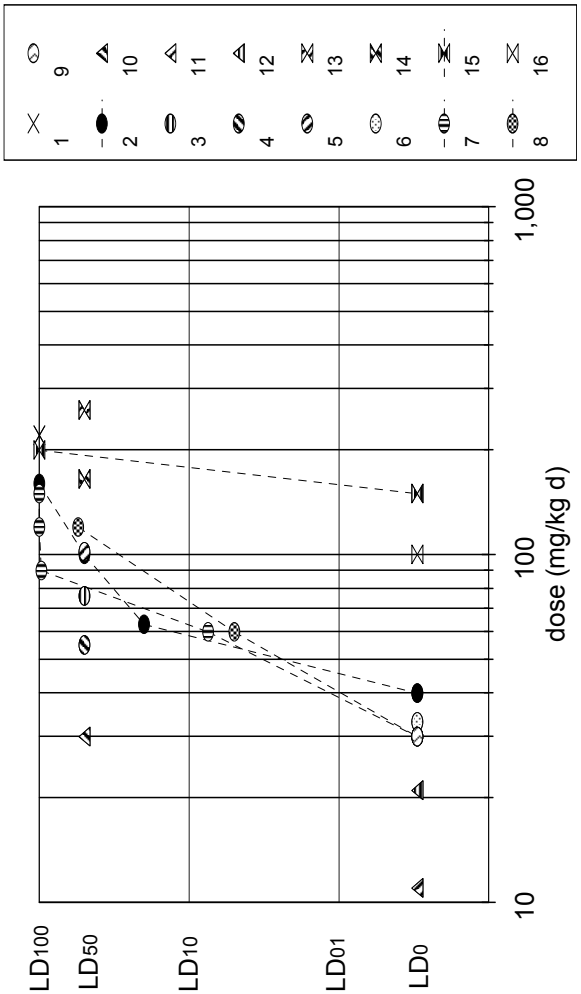

FIGURE 3-1 Relationship between MCAA dose and lethal effects. All exposures (including single and repeated inhalation exposures and single oral exposures) were converted to daily doses. LD_0 designates a NOEL for lethality. (1) Human case, single oral exposure (Feldhaus et al. 1993; Rogers 1995); (2) rat, single oral exposure (Hoechst AG 1979a); (3) rat, oral LD_{50} (Woodard et al. 1941); (4) rat, oral LD_{50} (Maksimov and Dubinina 1974); (5) rat, oral LD_{50} (Berardi 1986); (6) rat, subacute oral exposure (Johnson et al. 1998); (7) rat, subchronic oral exposure (Bryant et al. 1992; NTP 1992); (8) rat, subchronic oral exposure (Daniel et al. 1991); (9) rat, chronic oral exposure (NTP 1992); (10) rat, inhalation LC_{50} (Maksimov and Dubinina 1974); (11) rat, acute inhalation exposure (Dow Chemical Co. 1987); (12) rat, subchronic inhalation exposure (Maksimov and Dubinina 1974); (13) mouse, oral LD_{50} (Berardi 1986); (14) mouse, oral LD_{50} (Morrison and Leake 1941); (15) mouse, subchronic oral exposure (Bryant et al. 1992; NTP 1992); (16) mouse, chronic oral exposure (NTP 1992).

TABLE 3-7 AEGL-3 Values for Monochloroacetic Acid

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a]Not recommended because of insufficient data.

TABLE 3-8 Summary of AEGL Values for Monochloroacetic Acid[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	N.R.[b]	N.R.	N.R.	N.R.	N.R.
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.

[a]Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid, and fatal intoxications have been observed when 10% or more of the body surface was involved.
[b]Not recommended because of insufficient data.

The AEGL-2 was based on a single inhalation study in rats (Dow Chemical Co. 1987) in which eye squint and lethargy were observed in rats exposed at 66 ppm for 1 h. A total uncertainty factor of 10 was used. Other exposure-duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods due to the lack of suitable experimental data for deriving the concentration exponent.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data, AEGL-3 values were not derived.

All inhalation data are summarized in Figure 3-2. The data were classified into severity categories chosen to fit into definitions of the AEGL health effects. The category severity definitions are "no effect;" "discomfort;" "disabling;" "lethal;" and "some lethality" (animals that did not die at an experimental lethal concentration at which other animals died). Note that the AEGL-2 values are designated as triangles.

8.2. Comparison with Other Standards and Criteria

Existing limit and guideline concentrations are shown in Table 3-9. The occupational exposure limits for Sweden is 1 ppm (with skin notation) and a STEL of 2 ppm (with skin notation) (KEMI 1994). Maksimov and Dubinina (1974) recommended 1 mg/m³ (0.26 ppm) as the Russian occupational exposure limit.

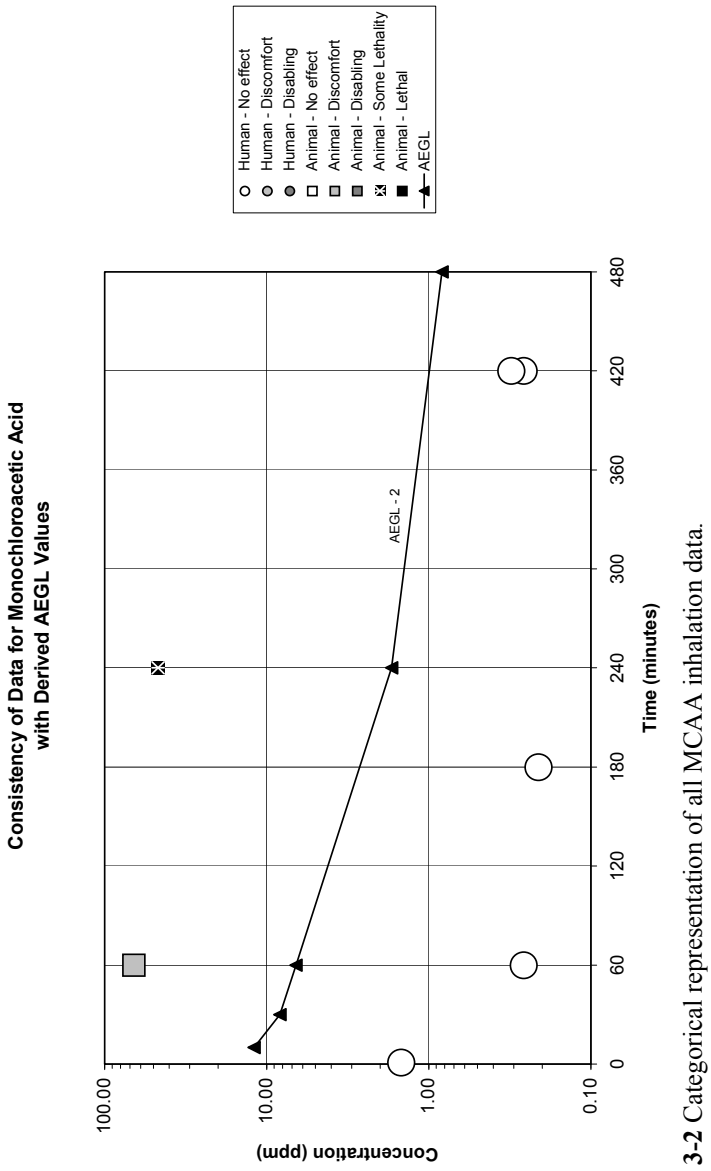

FIGURE 3-2 Categorical representation of all MCAA inhalation data.

TABLE 3-9 Extant Standards and Guidelines for Monochloroacetic Acid

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	N.R.	N.R.	N.R.	N.R.	N.R.
AEGL-2	12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm
AEGL-3	N.R.	N.R.	N.R.	N.R.	N.R.
REL-TWA (AIHA)[a]					0.26 ppm 1 mg/m³
STEL (AIHA)[b]	1.0 ppm (4 mg/m³) for 15 min				
MAK (Germany)[c]					1.0 ppm
MAC-Peak Category (The Netherlands)[d]					1.0 ppm (4 mg/m³)

[a]AIHA TWA (American Industrial Hygiene Association 1993) is defined as 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.
[b]AIHA STEL (American Industrial Hygiene Association 1984) (AIHA 1993) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday.
[c]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association]) is defined analogous to the ACGIH Threshold Limit Value–time-weighted average (TLV-TWA). The peak category is 1; MCAA has a skin notation (BMAS 2000).
[d]MAC (maximaal aanvaarde concentratie [maximal accepted concentration–peak category]) (MSZW 2004) is defined analogous to the AIHA TWA.
Abbreviation: N.R., not recommended.

8.3. Data Adequacy and Research Needs

Definitive, high-quality studies assessing health effects of MCAA after single or repeated inhalation exposure in humans or experimental animals are not available. Due to insufficient data, AEGL-1 and AEGL-3 values were not derived.

The derivation of AEGL-2 was based on a single 1-h inhalation exposure study on rats using a single concentration.

Single inhalation exposure studies focusing on lethal effects in animals and irritative effects in animals and humans would allow for more precisely defining the thresholds for the three AEGLs.

9. REFERENCES

AIHA (American Industrial Hygiene Association). 1993. Monochloroacetic Acid. Workplace Environmental Exposure Levels. American Industrial Hygiene Association, Fairfax, VA.

Berardi, M.R. 1986. Monochloroacetic Acid Toxicity in the Mouse Associated with Blood-Brain Barrier Damage. Ph.D. Dissertation. Rutgers, State University of New Jersey, New Brunswick, NJ.

Berardi, M., and R. Snyder 1983. Toxicity and pharmacokinetics of monochloroacetic acid. Pharmacologist 25:228 (as cited in BG Chemie 1993).

Berardi, M.R., R. Snyder, R.S. Waritz, and K.R. Cooper. 1987. Monochloroacetic acid toxicity in the mouse associated with blood-brain barrier damage. Fundam. Appl. Toxicol. 9(3):469-479.

BG Chemie (Berufsgenossenschaft der Chemischen Industrie). 1993. Monochloressigsäure. Toxikologische Bewertungen Nr. 23. Berufsgenossenschaft der Chemischen Industrie, Heidelberg.

Bhat, H.K., M.F. Kanz, G.A. Campbell, and G.A. Ansari. 1991. Ninety day toxicity study of chloroacetic acids in rats. Fundam. Appl. Toxicol. 17(2):240-253.

Bhunya, S.P., and P. Das. 1987. Bone marrow chromosome aberration and sperm abnormality in mice in vivo induced by monochloroacetic acid (MCA). Chromsome Inf. Serv. (42):28-30.

BIBRA (The British Industrial Biological Research Association). 1997. Toxicity Profile: Chloroacetic Acid. TNO BIBRA International Ltd., Carshalton, Surrey, UK.

BMAS (Bundesministerium für Arbeit und Soziales). 2000. Grenzwerte in der Luft am Arbeitsplatz. TRGS 900. In Gefahrstoffe: Kommentar zu Chemikaliengesetz und Gefahrstoffverordnung, Band 2, Lieferung 4/00, M. Nöthlichs, ed. Berlin, Germany: Erich Schmidt.

Bryant, B.J., M.P. Jokinen, S.L. Eustis, M.B. Thompson, and K.M. Abdo. 1992. Toxicity of monochloroacetic acid administered by gavage to F344 rats and B6C3F1 mice for up to 13 weeks. Toxicology 72(1):77-87.

BUA (Beratergremium für Umweltrelevante Altstoffe). 1994. Monochloressigsäure, Natriummonochloracetat, BUA-Stoffbericht 127. Stuttgart: Hirzel.

Christiansen, M., and S. Dalgaard-Mikkelsen. 1961. Toxic effects of monochloroacetic acid on geese. Acta Pharmacol. Toxicol. 18:179-182 (as cited in BG Chemie 1993).

Christofano, E.E., J.P. Frawley, H.L. Reed, and K.L. Keplinger. 1970. Skin exposure to monochloroacetic acid. Am. Ind. Hyg. Assoc. J. 31(2):35.

Dalgaard-Mikkelsen, S., and F. Rasmussen. 1961. Toksiciteten af monokloracetat for kvaeg. Nord. Vet. Med. 13:271-279.

Daniel, F.B., M. Robinson, J.A. Stober, N.P. Page, and G.R. Olson. 1991. Ninety-day toxicity study of sodium monochloroacetate in Sprague-Dawley rats. Toxicology 67(2):171-185.

DeAngelo, A.B., F.B. Daniel, B.M. Most, and G.R. Olson. 1997. Failure of monochloroacetic acid and trichloroacetic acid administered in the drinking water to produce liver cancer in male F344/N rats. J. Toxicol. Environ. Health 52(5):425-445.

DHHS (U.S. Department of Health and Human Services). 2008. Chloroacetic Acid (79-11-8). TRI Release: 2004. TOXMAP, Specialized Information Services. National Institutes of Health, U.S. Department of Health and Human Services [online]. Available: http://toxmap.nlm.nih.gov/toxmap/main/index.jsp [accessed June 9, 2008].

Dow Chemical Co. 1976. Study of Monochloroacetic Acid: Pharmacokinetics, Metabolism and Potential Antidotes. Dow Chemical Company, Midland, MI.

Dow Chemical Co. 1987. Monochloroacetic Acid: An Acute Vapor Inhalation Limit Study with Fischer 344 Rats. Dow Chemical Company, Midland, MI.

ECB (European Chemicals Bureau). 2005. Monochloroacetic Acid (MCAA). CAS No: 79-11-8. EINECS No: 201-178-4. Summary Risk Assessment Report. Institute for Health and Consumer Protection, European Chemicals Bureau, Ispra, Italy [online]. Available: http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/mcaasum320.pdf [accessed June 9, 2008].

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1999. Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3). Joint Assessement of Commodity Chemicals No. 38. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium [online]. Available: http://staging.idweaver.com/ECETOC/Documents/JACC%20038.pdf [accessed June 16, 2008].

Elf Atochem. 1995. Acute Intravenous Toxicity in Male Rats with Monochloroacetic Acid. CIT study No. 12052 TAR (as cited in ECETOC 1999).

EPA (U.S. Environmental Protection Agency). 1988. Recommandations for and Documentation of Biological Values for Use in Risk Assessment. EPA/600/6-87/008. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH. February 1988 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855 [accessed June 10, 2008].

Feldhaus, K., D. Hudson, D. Rogers, R.S. Horowitz, J. Brent, R.C. Dart, and H. Gomez. 1993. Pediatric fatality associated with accidental oral administration of monochloroacetic acid (MCA). Vet. Hum. Toxicol. 35:344.

Greim, H., ed. 1998. Monochloressigsäure. In Gesundheitsschädliche Arbeitsstoffe: Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsamm-lung 26. Lfg. Weinheim: WILEY-VCH Verlag.

Hercules. 1969a. Acute Vapor Inhalation Toxicity Study on Monochloroacetic Acid. IBT report No. N7789 (as cited in ECETOC 1999).

Hercules. 1969b. Acute Vapor Inhalation Toxicity Study on Monochloroacetic Acid. IBT report No. N7646 (as cited in ECETOC 1999).

Hayes, F.D., P.J. Gehring, and J.E. Gibson. 1972. Studies on the acute toxicity of monochloroacetic acid in rats. Toxicol. Appl. Pharmacol. 22(2)303 (Abstract No. 76).

Hayes, F.D., R.D. Short, and J.E. Gibson. 1973. Differential toxicity of monochloroacetate, monofluoroacetate, and monoiodoacetate in rats. Toxicol. Appl. Pharmacol. 26(1):93-102.

Hoechst AG. 1979a. Akute orale Toxizität von Monochloressigsäure VA 2308 an weiblichen Ratten. Report No. 232/79, Hoechst AG, Pharma Forschung Toxikologie (as cited in ECOTOC 1999).

Hoechst AG. 1979b. Akute orale Toxizität von Monochloressigsäureäthylester an weiblichen Ratten. Report No. 237/79. Hoechst AG, Pharma Forschung Toxikologie. 29.5.1979.

Hoechst AG. 1979c. Akute orale Toxizität von Monochloressigsäuremethylester an weiblichen Ratten. Unpublished report No. 139/79. Hoechst AG, Pharma Forschung Toxikologie. 30.3.1979.

Hoechst AG. 1979d. Akute subcutane Toxizität von Monochloressigsäure VA 2308 an weiblichen Ratten. Report No. 233/79. Hoechst AG, Pharma Forschung Toxikologie (as cited in ECETOC 1999).

Hoechst AG. 1979e. Haut- und Schleimhautverträglichkeit von Monochloressigsäure VA 2308 an Kaninchen. Report No. 235/79. Hoechst AG, Pharma Forschung Toxikologie (as cited in ECETOC 1999).

Hoechst AG. 1988a. Monochloressigsäuremethylester Inhalation im strömenden Gemisch an männlichen und weiblichen SPF-Wistar-Ratten - 4 h - LC 50. Unpublished report No. 88.0041. Hoechst AG, Pharma Forschung Toxikologie und Pathologie. 7.3.1988.

Hoechst AG. 1988b. Chloressigsäuremethylester - Subakute Inhalation (20 Applikationen in 28 Tagen) an SPF-Wistar Ratten. Unpublished report No. 88.0233. Study conducted for Berufsgenossenschaft der chemischen Industrie, by Hoechst AG, Pharma Forschung Toxikologie und Pathologie. 13.4.1988.

Hoechst AG. 1988c. Natriummonochloracetat. Prüfung der akuten dermalen Toxizität and der Wistar-Ratte. Report No. 151/88. Hoechst AG, Pharma Forschung Toxikologie und Pathologie (as cited in ECETOC 1999).

Hoechst AG. 1988d. Natriummonochloracetat. Prüfung auf Augenreizung am Kaninchen. Report No. 88.0109. Hoechst AG, Pharma Forschung Toxikologie und Pathologie (as cited in ECETOC 1999).

IPCS /CEC (International Programme on Chemical Safety and the Commission of the European Communities). 1994. Chloroacetic acid. ICSC: 0235. International Chemical Safety Cards. International Programme on Chemical Safety and the Commission of the European Communities [online]. Available: Http://www.cdc.gov/niosh/ipcsneng/neng0235.html [accessed June 10, 2008].

IUCLID (International Uniform Chemical Information Database), 1996. Data Set, CD-ROM, 1st Ed. European Commission, European Chemicals Bureau, Joint Research Centre, Ispra, Italy.

Izmerov, N.F., I.V. Sanotsky, and K.K. Sidorov. 1982. Toxicometric Parameters of Industrial Toxic Chemicals under Single Exposure. Centre of International Projects, GKNT, Moscow.

Johnson, P.D., B.V. Dawson, and S.J. Goldberg. 1998. Cardiac teratogenicity of trichloroethylene metabolites. J. Am. Coll. Cardiol. 32(2):540-545.

Kaphalia, B.S., H.K. Bhat, M.F. Khan, and G.A. Ansari. 1992. Tissue distribution of monochloroacetic acid and its binding to albumin in rats. Toxicol. Ind. Health 8(1-2):53-61.

KEMI (Kemikalieninspektionen). 1994. SIDS Dossier on the OECD HPV Chemical Monochloroacetic Acid (MCA). Kemikalieninspektionen, National Chemicals Inspectorate, Solna, Sweden.

Knapp, P. 1923. Zur Frage der Keratitis traumatica infolge Einwirkung von Gasen. Schweizerische medizinische Wochenschrift 4, 702 (as cited in OECD 1996)

Kulling, P., H. Andersson, K. Boström, L.A. Johansson, B. Lindström, and B. Nyström. 1992. Fatal systemic poisoning after skin exposure to monochloroacetic acid. J. Toxicol. Clin. Toxicol. 30(4): 643-652.

Maksimov, G.G., and O.N. Dubinina. 1974. Materials of experimental substantiation of maximally permissible concentration of monochloroacetic acid in the air of production area [in Russian]. Gig. Tr. Prof. Zabol. 9:32-35.

Mitroka, J.G. 1989. Monochloroacetic Acid Lethality in the Rat in Relation to Lactic Acid Accumulation in the Cerebrospinal Fluid. Ph.D. Dissertation, Rutgers, State University of New Jersey, New Brunswick, NJ.

Morrison, J.L., and C.D. Leake. 1941. Monochloroacetic acid as a food and beverage stabilizer. Univ. Calif. Pub. Pharmacol. 1:397-421 (as cited in NTP 1992).

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

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

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

NTP (National Toxicology Program). 1992. Toxicology and Carcinogenesis Studies of Monochloroacetic Acid (CAS No. 79-11-8) in F344/N Rats and B6C3F$_1$ Mice. Technical Report No. 396. NIH 92-2851. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC.

OECD (Organization for Economic Cooperation and Development). 1996. Chloroacetic Acid (79-11-8). Pp. 118-124 in Screening Information Data Set (SIDS) for High Production Volume Chemicals, Vol. III, Part 3. Geneva: United Nations Environment Programme Chemicals [online]. Available: http://www.chem.unep.ch/irptc/sids/OECDSIDS/79118.pdf [accessed June 13, 2008].

Oelert, H.H., and T. Florian. 1972. Detection and evaluation of odor nuisance from diesel exhaust gases. Staub Reinhalt. Luft 32(10):20-31.

Rodionova, R.P., and N.G. Ivanov. 1979. Comparison of the level of irritant properties of industrial toxins [in Russian]. Tok. Nov. Prom. Khim. Vesh. 15:58-63;145-150 (as cited in ECOTOC 1999).

Rogers, D.R. 1995. Accidental fatal monochloroacetic acid poisoning. Am. J. Forensic Med. Pathol. 16(2):115-116.

Rozman, K.K. 2000. The role of time in toxicology or Haber's c × t product. Toxicology 149(1):35-42.

Ruty, J., R.J. Millischer, J.C. Contassot, M. Vincenti, and J. Jouglard. 1988. Monochloroacetic acid: A report of systemic poisoning from percutaneous absorption. Pp. 145-148 in Occupational Health in the Chemical Industry: 22th ICOH (International Commission on Occupational Health)-Congress, September 27-October 2, 1987, Sydney, Australia. Copenhagen, Denmark: World Health Organization.

Smith, K.M., J.L. Randall, E.J. Read, and J.A. Stober. 1990. Developmental effects of chloroacetic acid in the Long-Evans rat. Teratology 41(5):593 (Abstract P164).

Torkelson, T.R., C.D. Kary, M.B. Chenoweth, and E.R. Larson. 1971. Single exposure of rats to the vapors of trace substances in methoxyflurane. Toxicol. Appl. Pharmacol. 19(1):1-9.

USITA (U.S. International Trade Administration). 2004. Industry Trade Data and Analysis. U.S. International Trade Administration, U.S. Department of Commerce [online]. Available: http://ita.doc.gov/td/industry/otea/trade-detail/Latest-December/Imports/29/291540.html

van Hinsbergh, V.W.M., and M. Vermeer. 1994. Toxicity of Monochloroacetic Acid on Human Endothelial Cells and Rat Heart Mitochondria: Third interim report. Gaubius Laboratory TNO-GP, Leiden, The Netherlands (as cited in Greim 1998).

Weast, R.C., ed. 1984. CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data, 64th Ed. Boca Raton: CRC Press.

Woodard, G., S.W. Lange, K.W. Nelson, and H.O. Calvery. 1941. The acute oral toxicity of acetic, chloroacetic, dichloroacetic and trichloroacetic acids. J. Ind. Hyg. Toxicol. 23(2):78-82.

Yllner, S. 1971. Metabolism of chloroacetate-1-^{14}C in the mouse. Acta Pharmacol. Toxicol. 30(1-2):69-80.

Xu, X., and C.P. Weisel. 2003. Inhalation exposure to haloacetic acids and haloketones during showering. Environ. Sci. Technol. 37(3):569-576.

APPENDIX A

TIME-SCALING CALCULATIONS FOR AEGLS

AEGL-2 VALUES

Key study:	Dow Chemical Co. 1987
Toxicity end point:	Rats were exposed for 1 hat an analytic MCA concentration of 66 ppm, no other concentrations were tested. During exposure all rats squinted and appeared slightly lethargic.
Scaling:	$C^3 \times t = k$ for extrapolation to 30 min and 10 min $k = 66^3$ ppm$^3 \times 1$ h = 287,496 ppm^3-h $C \times t = k$ for extrapolation to 8 h and 4 h $k = 66$ ppm $\times 1$ h = 66 ppm-h
Uncertainty factors:	Combined uncertainty factor of 10. 3 for interspecies variability 3 for intraspecies variability
Calculations:	
10-min AEGL-2	$C^3 \times 0.167$ h = 287,496 ppm^3-h C = 119.85 ppm 10-min AEGL-2 = 119.85 ppm/10 = 12 ppm (47 mg/m^3)
30-min AEGL-2	$C^3 \times 0.5$ h = 287,496 ppm^3-h C = 83.15 ppm 30-min AEGL-2 = 83.15 ppm/10 = 8.3 ppm (33 mg/m^3)
1-h AEGL-2	C = 66 ppm 1-h AEGL-2 = 66 ppm/10 = 6.6 ppm (26 mg/m^3)
4-h AEGL-2	$C \times 4$ h = 66 ppm-h C = 16.50 ppm 4-h AEGL-2 = 16.50 ppm/10 = 1.7 ppm (6.7 mg/m^3)
8-h AEGL-2	$C \times 8$ h = 66 ppm-h C = 8.25 ppm 8-h AEGL-2 = 8.25 ppm/10 = 0.83 ppm (3.3 mg/m^3)

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR MONOCHLOROACETIC ACID

Derivation Summary for Monochloroacetic Acid

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

Reference: Not applicable.

Test Species/Strain/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale:
No definitive study was available for the derivation of AEGL-1 values. The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (unpublished material 2000) was not considered an adequate basis because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about one to two measurements per year was considered insufficient. Therefore, due to insufficient data, AEGL-1 values were not recommended.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Adequate human or animal data relevant for the derivation of AEGL-1 values are not available.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm

Key Reference: Dow Chemical Company. 1987. Monochloroacetic acid: An acute vapor inhalation limit study with Fischer 344 rats. Unpublished report, Dow Chemical Company, Midland, USA.

Test Species/Strain/Sex/Number: Rat/Fischer 344/6 female and 6 male.

Exposure Route/Concentrations/Durations: Inhalation/66 ppm (analytic concentration)/1 h

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm

Effects: During all exposures, all rats (12/12) showed eye squint and slight lethargy. While in the text the expression "slight lethargy" is used, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

End Point/Concentration/Rationale: For the derivation of AEGL-2 values, the study in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 h resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system, but no severe effects. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (that is, before the air stream entered the chamber) or whether uptake of recrystallized MCAA by routes other than inhalation (e.g., dermal and oral uptake after deposition on the hair) might have occurred. In case of an additional exposure, the measured air concentration of 66 ppm and be regarded as a conservative exposure assumption. The AEGL-2 values were based on a 1-h exposure to 66 ppm.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3, because (1) the effect level was considered below that of an AEGL-2, (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects, and (3) because of the limited toxicodynamic variability as the enzymes inhibited by MCAA do not vary considerably within and between species.

Intraspecies: 3, because of the limited toxicokinetic variability with respect to local effects and limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: The exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

Data Adequacy: The only available single inhalation study in animals was used for the derivation of AEGL-2 values. In this study, neither different exposure concentrations nor different exposure durations were used. The derived values are supported by an older subchronic toxicity study in humans who had daily oral exposures to MCAA.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

Reference: Not applicable.

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

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available.

Although oral lethality data in animals are available, they were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point at a possible role of local effects: (1) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; (2) MCAA can bind to sulfhydryl groups, for example, those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and (3) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies. Experimental findings support a possible local effect on the respiratory tract: (1) the available inhalation studies report effects on the respiratory tract, and (2) MCAA causes severe local damage to skin and eyes.

Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina, 1974), data presentation is inadequate. Because pathologic findings were not reported, it remains unknown whether rats died from local lung tissue destruction or from systemic toxicity (that is, acidosis affecting CNS or heart).

Inhalation studies using MCAA esters were not considered relevant for the derivation of AEGL-3 values; compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure.

Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina 1974) and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Adequate animal data relevant for the derivation of AEGL-3 values are not available.