This PDF is available from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12870

Seventeenth Interim Report of the Committee on Acute Exposure Guideline Levels

ISBN
978-0-309-15139-9

80 pages
8 1/2 x 11
2010

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

More information | Find similar titles | Share this PDF

Visit the National Academies Press online and register for...

- Instant access to free PDF downloads of titles from the
  - NATIONAL ACADEMY OF SCIENCES
  - NATIONAL ACADEMY OF ENGINEERING
  - INSTITUTE OF MEDICINE
  - NATIONAL RESEARCH COUNCIL
- 10% off print titles
- Custom notification of new releases in your field of interest
- Special offers and discounts

Distribution, posting, or copying of this PDF is strictly prohibited without written permission of the National Academies Press.
Unless otherwise indicated, all materials in this PDF are copyrighted by the National Academy of Sciences.
Request reprint permission for this book

Copyright © National Academy of Sciences. All rights reserved.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

Seventeenth Interim Report of the Committee on Acute Exposure Guideline Levels

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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

Copyright © National Academy of Sciences. All rights reserved.

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 Numbers W81K04-06-D-0023 and EP-W-09-007 between the National Academy of Sciences and the U.S. Department of Defense and the U.S Environmental Protection Agency. 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.

This report is available online from the National Academies Press at http://www.nap.edu.

Copyright 2010 by the National Academy of Sciences. All rights reserved.

Printed in the United States of America.

Copyright © National Academy of Sciences. All rights reserved.

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

Copyright © National Academy of Sciences. All rights reserved.

Copyright © National Academy of Sciences. All rights reserved.

COMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

Members

DONALD E. GARDNER (*Chair*), Inhalation Toxicology Associates, Savannah, GA
EDWARD C. BISHOP, HDR Inc., Omaha, NE
LUNG CHI CHEN, New York University, Tuxedo, NY
FREDERIK A. DE WOLFF, Leiden University Medical Center (retired), Leiden, Netherlands
RAKESH DIXIT, MedImmune/AstraZeneca Biologics, Inc., Gaithersburg, MD
JEFFREY W. FISHER, University of Georgia, Athens, GA
FERNANDO HOLGUIN, University of Pittsburgh, Pittsburgh, PA
DAVID P. KELLY, E. I. du Pont de Nemours & Company , Newark, DE
MARGARET MACDONELL, Argonne National Laboratory, Argonne, IL
DAVID A. MACYS, U.S. Department of the Navy (retired), Oak Harbor, WA
FRANZ OESCH, University of Mainz, Mainz, Germany
NU-MAY RUBY REED, California Environmental Protection Agency, Sacramento, CA
GEORGE C. RODGERS JR., University of Louisville, Louisville, KY
RICHARD B. SCHLESINGER, Pace University, New York, NY
ROBERT SNYDER, Rutgers University, Piscataway, NJ

Staff

RAYMOND WASSEL, Senior Program Officer for Environmental Studies
KEEGAN SAWYER, Associate Program Officer
NORMAN GROSSBLATT, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects
ORIN LUKE, Senior Program Assistant

Sponsors

U.S. DEPARTMENT OF DEFENSE
U.S. ENVIRONMENTAL PROTECTION AGENCY

Copyright © National Academy of Sciences. All rights reserved.

COMMITTEE ON TOXICOLOGY

Members

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

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
RADIAH ROSE, Manager, Editorial Projects
TAMARA DAWSON, Program Associate

Copyright © National Academy of Sciences. All rights reserved.

BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY[1]

Members

ROGENE F. HENDERSON (*Chair*), Lovelace Respiratory Research Institute, Albuquerque, NM
RAMÓN ALVAREZ, Environmental Defense Fund, Austin, TX
TINA BAHADORI, American Chemistry Council, Arlington, VA
MICHAEL J. BRADLEY, M.J. Bradley & Associates, Concord, MA
DALLAS BURTRAW, Resources for the Future, Washington, DC
JAMES S. BUS, Dow Chemical Company, Midland, MI
JONATHAN Z. CANNON, University of Virginia, Charlottesville
GAIL CHARNLEY, HealthRisk Strategies, Washington, DC
RUTH DEFRIES, Columbia University, New York, NY
RICHARD A. DENISON, Environmental Defense Fund, Washington, DC
H. CHRISTOPHER FREY, North Carolina State University, Raleigh
J. PAUL GILMAN, Covanta Energy Corporation, Fairfield, NJ
RICHARD M. GOLD, Holland & Knight, LLP, Washington, DC
LYNN R. GOLDMAN, Johns Hopkins University, Baltimore, MD
JUDITH A. GRAHAM (retired), Pittsboro, NC
HOWARD HU, University of Michigan, Ann Harbor
ROGER E. KASPERSON, Clark University, Worcester, MA
TERRY L. MEDLEY, E. I. du Pont de Nemours & Company, Wilmington, DE
JANA MILFORD, University of Colorado at Boulder, Boulder
DANNY D. REIBLE, University of Texas, Austin
JOSEPH V. RODRICKS, ENVIRON International Corporation, Arlington, VA
ROBERT F. SAWYER, University of California, Berkeley
KIMBERLY M. THOMPSON, Harvard School of Public Health, Boston, MA
MARK J. UTELL, University of Rochester Medical Center, Rochester, NY

Senior Staff

JAMES J. REISA, Director
DAVID J. POLICANSKY, Scholar
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
SUSAN N.J. MARTEL, Senior Program Officer for Toxicology
ELLEN K. MANTUS, Senior Program Officer for Risk Analysis
EILEEN N. ABT, Senior Program Officer
RUTH E. CROSSGROVE, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects

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

Copyright © National Academy of Sciences. All rights reserved.

OTHER REPORTS OF THE
BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Hidden Costs of Energy: Unpriced Consequences of Energy Production and Use (2009)
Contaminated Water Supplies at Camp Lejeune—Assessing Potential Health Effects (2009)
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 (seven volumes, 2000-2009)
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)

Copyright © National Academy of Sciences. All rights reserved.

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

Copyright © National Academy of Sciences. All rights reserved.

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), Volume 7 (2009), Volume 8 (2009)
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)

Copyright © National Academy of Sciences. All rights reserved.

Preface

Extremely hazardous substances (EHSs)[2] can be released intentionally through terrorist activities or accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars or trucks transporting EHSs. EHSs can also be released because of improper storage or handling. 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 for exposure to airborne EHSs during accidental or intentional releases. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified some 400 EHSs on the basis of data on acute lethality 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 develop guidelines for establishing such levels. In response to that request, the National Research Council published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances,* published in 2001, provided updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the National Research Council Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 National Research Council guidelines reports, the NAC—consisting of members in EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academe, and other organizations in the private sector—has developed AEGLs for about 200 EHSs.

In 1998, EPA and DOD requested that the National Research Council independently review the AEGLs developed by the NAC. In response to that request, the National Research Council organized within its Committee on Toxicology the Committee on Acute Exposure Guideline Levels, which prepared the present report.

At its meetings, the committee hears presentations from NAC staff and its contractors on draft AEGL documents. At some meetings, the committee also hears presentations from the NAC's collaborators in other countries, such Germany and the Netherlands. The committee provides comments and recommendations on those documents to the NAC in its interim reports, and the NAC uses the comments to make revisions. The revised documents are presented to the committee by the NAC at later meetings until the committee concurs with the final draft documents. The revised documents are then published as appendixes in the committee's reports.

The present report is the committee's 17th interim report. It summarizes the committee's conclusions and recommendations for improving the NAC's AEGL documents for 17 chemicals: acetaldehyde, arsenic trioxide, benzene, 1,3-butadiene, butane, chloroacetaldehyde, chlorobenzene, hexane, jet propellant fuels 5 and 8, ketene, methylene chloride, oleum, propane, propionaldehyde,

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

Copyright © National Academy of Sciences. All rights reserved.

sulfuric acid, sulfur trioxide, and trichloroethylene. The report also summarizes the committee's conclusions and recommendations for improving the *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances,* published in 2001. Committee member Robert Snyder recused himself from discussion of the draft AEGL document for benzene.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and ensuring that the report meets institutional standards of 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 thank the following for their review of this report: Harvey Clewell, The Hamner Institutes for Health Sciences; Sammuel Kacew, University of Ottawa; and Kenneth Still, Occupational Toxicology Associates. Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Robert Goyer, University of Western Ontario. Appointed by the National Research Council, he was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the National Research Council.

The committee gratefully acknowledges the valuable assistance provided by the following: Iris Camacho and Ernest Falke, EPA; Sylvia Talmage, consultant to EPA; and Peter Bos, Joanne Nijhof, and Marcel van Raaij, the National Institute for Public Health and the Environment of the Netherlands.

The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful guidance and Raymond Wassel, project director, for his work on this project. Other staff members who contributed to this effort are Keegan Sawyer (associate program officer), Norman Grossblatt (senior editor), Mirsada Karalic-Loncarevic (manager, Technical Information Center), Radiah Rose (manager, Editorial Projects), and Orin Luke (senior program assistant). Finally, I 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

Copyright © National Academy of Sciences. All rights reserved.

Contents

Copyright © National Academy of Sciences. All rights reserved.

Copyright © National Academy of Sciences. All rights reserved.

Seventeenth Interim Report of the Committee on Acute Exposure Guideline Levels

BACKGROUND

In 1991, the U.S. Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) asked the National Research Council to provide technical guidance for establishing community emergency exposure levels (CEELs) for extremely hazardous substances (EHSs) pursuant to the Superfund Amendments and Reauthorization Act of 1986. In response to that request, the National Research Council published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances,* published in 2001, provided updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances.

The NAC was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. AEGLs developed by the NAC have a broad array of potential applications for federal, state, and local governments and for the private sector. AEGLs are needed for prevention of and emergency-response planning for potential releases of EHSs caused by accidents or terrorist activities.

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

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation or asymptomatic nonsensory effects. The effects are not disabling and are transient and reversible on cessation of exposure.

AEGL-2 is the airborne concentration 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 of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

THE CHARGE TO THE COMMITTEE

The National Research Council convened the Committee on Acute Exposure Guideline Levels to review the AEGL documents approved by the NAC. The committee members were selected for their expertise in toxicology; medicine, including pharmacology; industrial hygiene; biostatistics; and risk assessment.

Copyright © National Academy of Sciences. All rights reserved.

The charge to the committee is to review the proposed AEGLs for scientific validity, completeness, internal consistency, and conformance to the 1993 National Research Council guidelines report; review the NAC's research recommendations and—when appropriate—identify additional priorities for research to fill data gaps; and periodically review the recommended standard procedures for developing AEGLs.

This interim report presents the committee's conclusions and recommendations for improving the NAC's AEGL documents for 17 chemicals: acetaldehyde, arsenic trioxide, benzene, 1,3-butadiene, butane, chloroacetaldehyde, chlorobenzene, hexane, jet propellant fuels 5 and 8, ketene, methylene chloride, oleum, propane, propionaldehyde, sulfuric acid, sulfur trioxide, and trichloroethylene. It also summarizes the committee's conclusions and recommendations for improving the *SOP*).

ACETALDEHYDE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL technical support document (TSD) on acetaldehyde. A presentation on the TSD was made by Joanne Nijhof, of the Netherlands National Institute for Public Health and the Environment (RIVM). The following is excerpted from the executive summary of the TSD:

> Acetaldehyde is a colorless, highly volatile liquid at ambient temperature and pressure. . . . Available data for acetaldehyde included several recent human volunteer studies with very short exposure times, and two older volunteer studies with longer and more relevant exposure periods. Animal data were available for lethal and non-lethal endpoints in various species, and included also genotoxicity and carcinogenicity data. The AEGL-1 values are based on [a] human volunteer study . . . where workers experienced only mild respiratory irritation and no eye irritation following chamber exposure to acetaldehyde at a measured concentration of 134 ppm for 30 minutes. . . . The AEGL-2 values are based on histopathological changes observed in a study in rats. . . . The AEGL-3 values are based on 4-hour lethality data in rats.

General Comments

A revised document should be returned to the committee for review.

The committee recommends that the acetaldehyde and propionaldehyde TSDs be combined into one document because the observed effects are generally similar at comparable concentrations. The acetaldehyde TSD should provide more information on the metabolism of acetaldehyde in humans and its polymorphism. The AEGL-3 values for acetaldehyde were adopted for propionaldehyde.

The authors of the TSD state that the human exposure studies using aerosol exposures for durations of 2-4 min were not useful for AEGL derivations. Although the exposure durations of the studies were too short for this purpose, their results—bronchoconstriction and other respiratory airway effects—are certainly relevant to the uncertainty factor for intraspecies variability. That the experiments were done via mouth breathing does not invalidate their findings and relevance: a sizable fraction of people are primarily mouth breathers, and some may have nasal obstructions (such as colds) that result in mouth breathing. In addition, under substantial stress or exercise, as may occur during an emergency alert and evacuation order, breathing shifts to a mixture of nose and mouth breathing. Finally, even regular nose breathers will inhale some fraction of their respirations via the mouth. In an emergency situation, exposures may occur via the nose, the mouth, or both. Those exposure routes therefore are relevant for assessing the uncertainty factor (UF) or intraspecies variability.

A table should be developed to present the data from the human exposure experiments to facilitate review of exposure concentration and durations and the resulting health effects. It should be

Copyright © National Academy of Sciences. All rights reserved.

comparable with the tables developed for the lethal and nonlethal animal data. Such a table will also facilitate comparison with the proposed AEGL values.

Comments on AEGL-1 to AEGL-3 Derivations

AEGL-1: The committee agrees with an intraspecies UF of 3 but recommends that the interspecies UF be increased from 1 to 3. Stanek et al. (2001) mentions 25 ppm as a concentration above which vasodilation occurs. That must be considered an effect for AEGL-2 rather than AEGL-1. An AEGL-1 of 45 ppm is apparently too high. An intraspecies UF of 3 and an interspecies UF of 1 are insufficient. If the interspecies UF is increased to 3, that would lead to an AEGL-1 of 15 ppm for all exposure times, which accords better with the ACGIH TLV (Threshold Limit Value) for a 15-min short-term exposure limit (STEL) of 25 ppm. ACGIH adopted that TLV in 1993. It discarded the 8-h TWA and recommended a ceiling of 25 ppm (45 mg/m^3). ACGIH also notes that susceptible humans may develop allergic sensitization even at the latter concentration.

AEGL-2: The committee agrees with an intraspecies UF of 10 but recommends that the interspecies UF be 3. The reason is the potential effect of the acetaldehyde exposures on sensitive human subpopulations. The AEGL-2 derivation in the TSD does cite an interspecies factor but then uses a UF of 1 for interspecies variability, using a justification that is limited in the *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (referred to as *SOP* [NRC 2001]) to application to intraspecies UFs: from Section 2.5.3.4.1, p. 89, states that "if the toxicologic effects . . . are . . . less severe than those defined for the AEGL tier . . . an *intraspecies* UF less than 10-fold may be used" (emphasis added). In any case, 3, instead of 1, would have been a more reasonable choice for the UF less than 10. In the TSD, the AEGL-2 intraspecies UF of 10 is due to the existence of a susceptible human subpopulation and also represents the combined UF.

A choice of an interspecies UF of 3 is also more reasonable in light of the derivation of the AEGL-3.

AEGL-3: The committee agrees with an interspecies UF of 3 but considers the intraspecies UF of 3 to be too low.

According to the TSD, a factor of 3 for intraspecies extrapolation should be sufficient to protect sensitive human subpopulations. A larger factor is "considered not necessary given the typical irritative aldehyde toxic action by acetaldehyde." However, acetaldehyde has systemic effects in addition to local irritation, and these systemic effects are subject to polymorphic sensitivity in humans. The intraspecies UF should therefore be increased to 10. It is also more appropriate in light of the intraspecies UF of 10 in the AEGL2 derivation.

Specific Comments

Page 1, line 20: "Overall half-lives for acetaldehyde vary considerably" should be rewritten as "Overall environmental half-lives" or rather *disappearance*. In these documents, *half-life* usually refers to biologic half-life.

Page 2: The whole section on "Human Toxicity Data" is too limited and based on obsolete data. The section should be rewritten after a new literature search and consultation with a clinical toxicologist.

Page 3, line 35: "As a result of the polymorphism nearly half of the Japanese patients with asthma show bronchoconstriction after drinking alcohol, a phenomenon that is also known to occur in other Asian populations." The statement should be revised for greater clarity; it should indicate that bronchoconstriction occurs after systemic exposure via ingestion, not inhalation.

Page 4, line 13: Aerosol concentrations should be distinguished from vapor concentrations. The relevance of these data to the AEGL derivations should be given.

Page 6, lines 11-13: "At concentrations of 0.2 to 0.7% in the blood marked increases

Copyright © National Academy of Sciences. All rights reserved.

in heart rate, ventilation and calculated respiratory dead space were observed, as was a decrease in alveolar CO_2 levels." It should be noted that these effects also occur after heavy drinking.

Page 6, line 20: The authors state "No human studies on neurotoxicity were identified." It is likely that at least one of the many neurotoxic effects of ethanol abuse can be ascribed to the acetaldehyde metabolite. Please search again.

Page 6, lines 44 - 45: The statement "Overall IARC concluded that there is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde (IARC 1999)." should be rechecked. It is the committee's understanding that a more recent IARC monograph (vol. 96, still in process of publication) identified acetaldehyde as a "proven human carcinogen."

Page 7, line 48, through Page 8, line 3: The authors state "Finally the cat received 24500 mg/m^3 (13720 ppm) for 15 minutes. This produced lacrymation, sneezing, marked salivation, agitation, convulsions, screaming, marked dyspnea, prostration, anesthetization and finally death." Did the cats die during continued exposure or after discontinuation of exposure?

Page 8, line 44: "The 4-hour LC50 was calculated to be 30.6 grams/m^3 (17000 ppm)." Is 17,000 ppm vapor or aerosol?

Page 9, line 6: "concentrations ranged from 14,000 to 57,000 mg/m^3 (7840 to 31920 ppm)." Are the ppm values vapor or aerosol?

Page 14, lines 13-20: It is hard to believe that this 1985 paper is the only one on supposed neurotoxicity. Moreover, Na-K-ATPase is not specific for brain tissue. It is the motor of the sodium pump that is present in all mammal cells. If the authors did not compare brain Na-K-ATPase with activity in other organs, this cannot be listed as neurotoxicity. A more profound literature search on acetaldehyde neurotoxicity is necessary.

Page 17: In Section 3.6 on carcinogenicity, is it mere coincidence that mainly Dutch publications have been cited, such as Feron (1979) and Woutersen et al. (1986)?

Page 17, lines 22-24: "An acute rat inhalation study by Stanek et al. (2001) showed vasodilatation already at concentrations of 25 ppm but the toxicological significance of this effect is doubtful (it may represent a physiological protective response)." Vasodilatation at over 25 ppm can hardly be seen as a "physiological protective response" (protective against what?) but rather should be considered an AEGL-1 effect.

Page 18, lines 9-11: "Acetaldehyde is an intermediary in the normal catabolism of deoxyribose phosphate and various amino acids. A quantitatively much more important source of acetaldehyde in the body, however, is its formation through the action of alcohol dehydrogenase on ingested ethanol." Ethanol formation in the human intestine by microorganisms (Blomstrand 1971) also leads to acetaldehyde formation.

Page 18, line 24-26: "According to IPCS (1995) the conversion to acetic acid by aldehyde dehydrogenase constitutes the major biotransformation route for acetaldehyde. The acetate may enter into normal metabolism by the formation of acetyl-CoA, as is shown in the figure below." The AldDH step is also the rate-limiting step in ethanol metabolism.

Page 19, line 49, through Page 20, line 6: The TSD states Stanek and Morris (1999) studied the dose dependence of acetaldehyde detoxification by aldehyde dehydrogenase in nasal tissues in rats, observing that at concentrations of 300 ppm or higher (single exposure for 6 hours) the dose delivered to the nasal tissue equals or exceeds the capacity of the enzyme. This capacity limitation they regard as the explanation of their previously observed higher efficiency of acetaldehyde uptake in rat nasal tissue at 10 ppm compared to 300 or 1500 ppm. Stanek and Morris (1999) also determined DNA-protein cross links in the nasal respiratory after a single exposure to 1500 ppm for 6 hours, a concentration clearly in excess of the aldehyde dehydrogenase metabolic capacity in this tissue, but failed to find an increase. Thus they could not reproduce the finding by Lam et al. (1986) who detected increased crosslink formation in the same tissue after exposure to 1000 ppm for 6 hours. The second to last sentence refers to an increase. What increase was looked for?

Page 20, line 41: Does the fact that "no relevant data on species variability were identified" lead to the conclusion that no interspecies UFs have to be applied for this substance?

Copyright © National Academy of Sciences. All rights reserved.

Pages 23, line 34, through Page 24, line 7: After how many exposures was the degeneration of nasal epithelium observed by Appelman et al. (1982)?

Comment References

Appelman, L.M., R.A. Woutersen, and V.J. Feron. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology 23(4):293-307.

Blomstrand, R. 1971. Observations of the formation of ethanol in the intestinal tract in man. Life Sci. 10(10):575-582.

Feron, V.J. 1979. Effects of exposure to acetaldehyde in syrian hamsters simultaneously treated with benzo(a)pyrene or diethylinitrosamine. Prog. Exp. Tumor Res. 24:162-176.

IARC (International Agency for Research on Cancer). 1999. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide Part Two. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 71. Lyon France: IARC [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol71/index.php [accessed Jan. 19, 2010].

IPCS (International Programme on Chemical Safety). 1995. Acetaldehyde. Environmental Health Criteria 167. Geneva: World Health Organization [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc167.htm [accessed Jan. 19, 2010].

Lam, C.W., M. Casanova, and H.D. Heck. 1986. Decreased extractability of DNA from proteins in the rat nasal mucosa after acetaldehyde exposure. Fundam. Appl. Toxicol. 6(3):541-550.

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

Stanek, J.J., and J.B. Morris. 1999. The effect of inhibition of aldehyde dehydrogenase on nasal uptake of inspired acetaldehyde. Toxicol. Sci. 49(2):225-231.

Stanek, J.J., P.T. Symanowicz, J.E. Olsen, G. Gianutsos, and J.B. Morris. 2001. Sensory-nerve-mediated nasal vasodilatory response to inspired acetaldehyde and acetic acid vapors. Inhal. Toxicol. 13(9):807-822.

Woutersen, R.A., L.M. Appelman, A. van Garderen-Hoetmer, and V.J. Feron. 1986. Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 41(2):213-231.

ARSENIC TRIOXIDE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on arsenic trioxide (As_2O_3/As_4O_6). A presentation on the TSD was made by Peter Bos, of RIVM. The following is excerpted from the executive summary of the TSD:

> Arsenic trioxide (As_2O_3/As_4O_6) is a white, odorless powder of low aqueous solubility. . . . AEGL-1 values are not proposed, because there were no human or animal data available relating to AEGL-1 endpoints for arsenic trioxide. . . . No AEGL-2 effects were reported following acute inhalation exposure to arsenic trioxide. As an alternative, the AEGL-2 values are based on 1/3 of the AEGL-3 values. . . . The AEGL-3 values are based on lethality data in rats from a preliminary range-finding study of developmental toxicity.

General Comments

A revised document should be returned to the committee for review.

Several suggestions are offered to support the re-evaluation of the interim AEGL values. First, it seems unusual that many important papers from groups with a long history of research on arsenic are not

Copyright © National Academy of Sciences. All rights reserved.

mentioned in the TSD, including those by Lauwerys (such as Buchet and Lauwerys [1998]), Aposhian (1989, 1997), Centeno et al. (2002), and the recent review article on arsenic neurotoxicity by Vahidnia, van der Voet, and de Wolff (2007). The committee recognizes that considerable effort was involved in identifying a number of key studies when the TSD was being prepared and that the document summarizes many data well. However, additional relevant papers have become available since the TSD was prepared, so it would be useful for the authors of the TSD to conduct a new search of the peer-reviewed literature for references that would strengthen the AEGL derivations, including key work discussed in the current arsenic toxicologic profile from the Agency for Toxic Substances and Disease Registry (ATSDR 2007), which updates the 2000 profile cited in the TSD.

Second, the committee suggests that the authors consider human data for derivation of the AEGL-3 and that relevance of toxicokinetic data be assessed with respect to study selection. For example, for arsenic, the rat is generally considered a poor model for humans (including permethylation and retention differences), and the rabbit is a better model; note that methylation has been considered to play a role in some detoxification processes because of the lower toxicity of metabolites, although more recently some have suggested that the converse might be indicated for specific end points. At higher exposure levels, some suggest that first-pass metabolism may be less of an issue. It has been reported that after exposures at high concentrations, much more arsenic trioxide is excreted compared with the typical high fraction of methylated compounds (Wang et al. 2004). That has suggested to some that oral data may provide useful context for higher inhalation exposure concentrations (which could be considered in this case as part of the AEGL-3 re-evaluation). In the same vein, intravenous data may offer useful insights for higher exposure concentrations. Some of the recent literature supports that concept. Thus, there are data, including some from studies published after the TSD was prepared, that suggest revisiting the AEGLs. The minimum lethal dose of arsenic trioxide has been reported to be 100-200 mg, and chelation treatment is recommended for arsenic exposure at over 50 mg (Dyro 2006a).

Third, the authors should consider human data to support derivation of the AEGL-2. For example, the authors might use data on the therapeutic use of arsenic trioxide (notably for acute promyelocytic leukemia [APL]) in forming the AEGL-2 rather then using a default 1/3 adjustment from an AEGL-3 that was derived from a rat study. The medical literature suggests that the common therapeutic dose of 0.15 mg/kg-d is generally well tolerated; for example, some have reported that such toxic effects as leukocytosis and skin hyperpigmentation are minimal. It is important that the updated literature search and later discussion in the TSD consider information regarding the severity and reversibility of toxic effects. For example, in some instances, therapy involving arsenic trioxide is simply indicated as "safe," or toxicity is identified as "minimal" without specific context regarding how serious or transient the toxic effects are. That applies notably to papers either that are publicly unavailable (and not yet acquired by the reviewer) or whose full form is in a foreign language. Examples of the first type include Ravandi et al. (2009), who indicate that therapy with arsenic trioxide is effective and safe; Pettersson et al. (2007), who state that "low doses of the drug can induce complete remission in patients with relapsed APL with minimal general toxicity"; and Douer and Tallman (2005), who state that "arsenic trioxide in the treatment of acute promyelocytic leukaemia is relatively safe with minimal side effects." Examples of the second type include Xu et al. (2009) and Jiao et al. (2009). Some authors—such as George et al. (2004), Pettersson et al. (2007), and Sweeney et al. (in press)—generally refer to toxicity as minimal or mild and transient, whereas others provide further specific information regarding severity and reversibility, including Matthews et al. (2006), Fox et al. (2008), and Hu et al. (2009). Note that some others report serious toxicity, whose context (including dose regimen and patient status) should also be considered. The TSD authors should carefully evaluate those and other relevant studies in the new literature review.

With respect to human variability (to support the intraspecies factor), treatment data exist for a range of ages, and this population subgroup that received therapeutic doses may be considered relatively sensitive given the subgroup's health conditions. It should also be considered that the blood concentration associated with the therapeutic dose has been indicated to be around 100-250 μg/L (which is roughly 3-7 times the biologic exposure index of 35 μg of arsenic per liter [ACGIH 2008]), whereas the reported blood concentration associated with fatality is about 4-10 times that concentration, 1,000 μg/L. Those

Copyright © National Academy of Sciences. All rights reserved.

data suggest a context for the steepness of the dose-response curve in moving to the AEGL-3. In evaluating human data, the shorter biologic half-life in blood makes urinary concentrations more useful in a biomonitoring context: 24-h concentrations of 100-400 μg were reported in most of 41 patients who had arsenic-induced peripheral neuropathy (Dyro 2006b). (Note: to estimate a rough blood concentration from that information on urinary concentrations, a general daily adult urine output may be considered to be around 1 L or more, depending on various factors; the study information should be pursued to support a specific calculation.) With respect to human variability and concurrent exposures for purposes of deriving AEGLs, chronic alcohol consumption (a sensitive subgroup indicator) appears to contribute to the development and severity of peripheral neuropathy (Dyro 2006b).

Fourth, the TSD authors should consider information on physiologically based pharmacokinetic (PBPK) models that have been developed for arsenic in a manner that was consistent with the general criteria identified in the PBPK modeling white paper prepared to support the AEGL derivation process (Dennison and Troxel [2006], pg. 6). Both the ATSDR (2007) toxicologic profile and the California EPA (CalEPA) technical support document for the arsenic reference exposure levels (OEHHA 2008) would serve as good overviews of the more recent literature on this topic (as well as the general toxicokinetics and mode of action). As summarized in those two documents, the PBPK suite includes the Mann model that evaluates inhalation of arsenic trioxide dust and addresses four chemical forms (two organic). The model has been validated with experimental data. That model was found to match observations well for 18 workers exposed at 10-1000 $\mu g/m^3$. Such information can frame the consideration of human data for the AEGLs. As suggested by the information on blood concentrations illustrated above, linkage of insights from PBPK models with such human data would seem to support a more inclusive consideration of data currently available for derivation of AEGLs (in contrast with basing the values on rodent data, whose relevance has not been clearly demonstrated).

Fifth, the TSD authors should further consider the relationship of the interim AEGLs to other established reference values and their bases, including the CalEPA acute and 8-h reference exposure levels, the National Institute for Occupational Safety and Health (NIOSH) concentration immediately dangerous to life or health (IDLH) (NIOSH 2005), and the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) military exposure guideline (MEG) for arsenic (CHPPM 2004). For example, the CalEPA (OEHHA 2008) information may offer insights into derivation options for the AEGL-1.

Finally, the cancer evaluation should be refined. The authors should clarify the EPA Integrated Risk Information System (IRIS) citations (the material should reflect current information rather than 1966 and 1997 references). The authors should consider related references (e.g., EPA 2005) regarding the draft slope factor, and they should also track the impending release of the updated arsenic assessment (see IRIS Track; the inorganic arsenic cancer assessment is expected to be finalized by March 2010 [EPA 2010]). EPA (2005) addresses increased susceptibility from early-life exposure to carcinogens that act via a mutagenic mode of action (MOA), emphasizing the period from birth (including lactational exposures) to adolescence (age, 16 years). In that guidance, EPA describes "focusing upon studies that define the potential duration and degree of increased susceptibility that may arise from childhood, defined as early-life (typically postnatal and juvenile animal) exposures." That definition is qualified; EPA notes that "prenatal (*in utero*) exposures are not part of the current analysis. Studies that have postnatal exposure were included (without adjustment) even if they also involved prenatal exposure." Thus, prenatal exposure may be reflected in the adjustment factors developed by EPA to address increased susceptibility. In any case, for carcinogens, it is useful to provide MOA context to address whether this further susceptibility could be an issue.

Specific Comments

Page vi, lines 11-15: (and parallel material in main text): "AEGL-1 values are not proposed, because there were no human or animal data available relating to AEGL-1 endpoints for arsenic trioxide.

Copyright © National Academy of Sciences. All rights reserved.

No AEGL-2 effects were reported following acute inhalation exposure to arsenic trioxide. As an alternative, the AEGL-2 values are based on 1/3 of the AEGL-3 values." The authors should reconsider the availability of relevant data for AEGL-1 and AEGL-2 after pursuing an additional literature search (see General Comments, above). They should also reconsider the study selection for the AEGL-3, taking human data into account. Note that if animal data were used, a UF of 10 seems much too low for interspecies and intraspecies variabililty combined (particularly given that the end point currently used is not an irritant effect). The greater sensitivity of the human to the effects of arsenic can be supported by referring to the summary plots of no-observed-adverse-effect levels (NOAELs) and lowest observed-adverse-effects levels (LOAELs) in the ATSDR profile. Available data indicate that an interspecies UF of 10 and an intraspecies UF of 10 would be much more appropriate.

Page 2, line 24, through Page 3, line 8: The literature cited in the "Oral Exposure" subsection of Human Toxicity Data (Section 2) is dated. More recent case reports are available; see, for example, Kim and Abel (2009) and Yilmaz et al. (2009).

Page 3, line 21: What are "arsenic fumes"? Was this an As_2O_3 aerosol? It might have been arsine (AsH_3), which has a toxicity profile different from that of As_2O_3.

Page 3, lines 47-50: "Przygoda et al. (2001) report the existence of a group of people (Styrians) in a region of Austria in the 17th century that were 'arsenic eaters.' They consumed arsenic trioxide in amounts of 300-400 mg per dose at a regular basis (every 2-3 days) over lifetime, to improve their health. They seemed to have had no adverse health effects." The TSD authors should check the current literature on the topic of tolerance, given the range of past and current (background) human exposures to arsenic. That would inform the adjustment for intraspecies (human) variability.

Page 4, line 46: "No human experimental studies with arsenic trioxide were located." Considerable literature exists on the experimental use of arsenic trioxide to treat patients for APL, which is now fairly routine; see, for example, Tallman and Altman (2009), Hu et al. (2009), and Ravandi et al. (2009). At least consider a reference to the section in which some earlier studies are cited (page 5, lines 36-42). In either case, it would be useful to provide more quantitative information from those studies. This body of literature goes beyond a handful of case reports to present safety information that addresses the human toxicity of arsenic trioxide, among age groups and in both males and females, that is considered useful in the evaluation of human data for the AEGLs. The potential utility of data from intravenous exposures is supported by several papers on toxicokinetics that consider multiple routes (combined with the fairly rapid absorption of roughly half the deposited fraction across the exchange boundary of the lung into the bloodstream); see Holland et al. (1959) and others, including the technical summaries published by the California Office of Environmental Health Hazard Assessment (OEHHA 2008) and ATSDR (2007). A number of end points have been assessed as part of the safety and efficacy evaluations for this treatment (ranging from toothache to cardiac effects).

Page 4, line 51: "Increased vasospastic reactivity in the fingers" is Raynaud's phenomenon (which also occurs in several autoimmune diseases). The sentence should be phrased ". . . showed increased vasospastic reactivity in the fingers (Raynaud's phenomenon)."

Page 6, lines 4-6: The two major target organs for acute arsenic toxicity in humans are the gastrointestinal tract and the peripheral nervous system (PNS) in patients who survive. This brief text is insufficient to deal with this issue. Moreover, no references are given here. The mechanism of arsenic effects on the PNS is well known; see, for example, Vahidnia et al. (2007). PNS toxicity is also the major effect of chronic exposure to As_2O_3. Therefore, neurotoxicity of this substance deserves much more attention. For the older literature and the historical context, see De Wolff and Edelbroek (1994).

Page 6, lines 28-36: Occupational exposure to atmospheric arsenic trioxide gives rise to increased incidences of lung cancer. This was found in studies among miners in China (Herz-Piciotto and Smith 1993), and among copper smelters in Montana (Lee-Feldstein 1986), Tacoma, WA (Pinto et al. 1977; Enterline and Marsh 1982; Enterline et al. 1987; Enterline et al. 1995) and Sweden (Järup et al. 1989; Sandström et al. 1989; Sandström and Wall 1993). Occupational exposure to other arsenic compounds (lead arsenate, calcium arsenate, copper acetoarsenite, and magnesium arsenate) in a

Copyright © National Academy of Sciences. All rights reserved.

pesticides factory also led to increased incidences of respiratory cancer (Ott et al. 1974). IARC (1987) concluded that there is sufficient evidence to classify the arsenic as a human carcinogen.

Consider including more recent information, as suggested in the general comments; for example, see note regarding Lubin et al. (2000, 2008) citations. Also note (regarding route-specific context) that Smith et al. (2009) indicate increased lung-cancer risk regardless of whether arsenic is ingested or inhaled.

Page 7, line 11, through Page 8, line 22: Section 3.1. The cat and mouse lethality data from early Flury experiments should be added to this section ahead of the rat data and other information that focuses on oral LD_{50}s, and the summary in Section 3.7 should be revised accordingly. The cat data seem particularly useful because the 1-h LC_{Lo} of 100 mg/m^3 for arsenic trichloride from Flury (1921), cited by NIOSH (1996), underlies the current NIOSH IDLH.

Page 10, line 23: The neurotoxicity section says "no data." It is unlikely that there are no data at all on neurotoxicity; a review of recent literature is recommended.

Page 13, line 13, to Page 18, line 6: The discussion under "Metabolism and Disposition" is somewhat dated. The TSD authors should update this section with key new information from the recent literature; see summaries in ATSDR (2007) and CalEPA (OEHHA 2008) noted in the general comments above.

Page 18, lines 7-18: As for the preceding comment, this section could benefit from a substantial update to reflect recent reviews, including Vahidnia et al. (2007), the summaries published by ATSDR (2007) and OEHHA (2008), and a number of recent publications in the primary literature. The updated information is expected to offer relevant insights for the AEGL derivations, for example, potentially to obviate a default 1/3 adjustment (for the AEGL-2) and inform better such factors as human variability (for example, with more recent information on polymorphisms).

Page 21, line 20: The proposed AEGL-3 is 11 mg/m^3, whereas the NIOSH recommended exposure limit-short term exposure limit (REL-STEL) (reported as arsenic) appears to be less than 0.1% of this level (Page 22). Can the enormous difference be justified?

Page 22, Table 9: The authors should consider including the Occupational Safety and Health (OSHA) concentrations that trigger requirements for respiratory protection in the comparison of AEGLs with other reference levels. Note that for such comparisons, it might be helpful to indicate the AEGL concentrations as milligrams of arsenic per cubic meter of air (mg/m^3), as was nicely presented for the occupational data summarized in Table 2). It may also be useful to clarify that the occupational limits are not presented in those sources as arsenic trioxide but that the conversions are as applied by the authors (check conversions).

Editorial Comments

Page 13, line 13, to Page 18, line 6: We suggest retitling this discussion "Toxicokinetics" (which would be expected to address absorption, distribution, metabolism, and elimination—ADME) and organizing it into subsections that distinguish human from animal data (either within the common ADME components or overall).

Page 18, line 25, to Page 19, line 7: Consider whether this information (updated) in Section 4.4.1, "Species Variability," is more suited for the toxicokinetics discussion (see editorial comment above for Page 13) because it discusses data on metabolism.

Page 19, line 13: "Sensibilisation" does not seem to be the correct term. Should the title read "Irritation and *Sensitization*?"

Page 23: NIOSH is ". . . Institute *for* Occupational . . .," and the IDLH is defined as ". . . life *or* health.")

Page 30, line 32: Marie Vahter's name is misspelled as "Vather."

Copyright © National Academy of Sciences. All rights reserved.

Comment References

ACGIH (American Conference of Governmental Industrial Hygienists). 2008. TLVs and BEIs: Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents, and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists Cincinnati, OH.

Aposhian, H.V. 1989. Biochemical toxicology of arsenic. Rev. Biochem. Toxicol. 10:265-299.

Aposhian, H.V. 1997. Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. Annu. Rev. Pharmacol. Toxicol. 37:397-419.

ATSDR (Agency for Toxic Substances and Disease Registry). 2007. Toxicological Profile for Arsenic. U.S. Department of Health and Human Services, Public Health Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf [accessed Jan. 19, 2010].

Buchet, J.P., and R. Lauwerys. 1988. Role of thiols in the in-vitro methylation of inorganic arsenic by rat liver cytosol. Biochem. Pharmacol. 37(6):3149-3153.

Centeno, J.A, F.G. Mullick, L. Martinez, N.P. Page, H. Gibb, D. Longfellow, C. Thompson, and E.R. Ladich. 2002. Pathology related to chronic arsenic exposure. Environ. Health Perspect. 110(Suppl. 5): 883-886.

CHPPM (U.S. Army Center for Health Promotion and Preventive Medicine). 2004. Chemical Exposure Guidelines for Deployed Military Personnel. Technical Guide 230, January 2004 Addendum. U.S. Department of Defense, Army Center for Health Promotion and Preventive Medicine [online]. Available: http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG230.pdf [accessed Jan. 26, 2010].

De Wolff, F.A., and P.M. Edelbroek. 1994. Neurotoxicity of arsenic and its compounds. Pp 283-291 in Handbook of Clinical Neurology, Vol. 64, P.J.Vinken, and G.W. Bruyn, eds. Amsterdam: Elsevier.

Dennison, J.E., and C. Troxel. 2006. PBPK Modeling White Paper. Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels (AEGL). November 16, 2006.

Douer, D., and M.S. Tallman. 2005. Arsenic trioxide: New clinical experience with an old medication in hematologic malignancies. J. Clin. Oncol. 23(10):2396-2410.

Dyro, F.M. 2006a. Arsenic: Treatment and medication. eMedicine, Dec. 6, 2006 [online]. Available: http://emedicine.medscape.com/article/1174215-treatment [accessed Jan. 19, 2010].

Dyro, F.M. 2006b. Arsenic: Differential Diagnosis. eMedicine, Dec. 6, 2006 [online]. Available: http://emedicine.medscape.com/article/1174215-diagnosis [accessed Jan. 19, 2010].

Enterline, P.E., and G.M. Marsh. 1982. Cancer among workers exposed to arsenic and other substances in a copper smelter. J. Am. Epidemiol. 116(6):895-911.

Enterline, P.E., V.L. Henderson, and G.M. Marsh. 1987. Exposure to arsenic and respiratory cancer: A reanalysis. Am. J. Epidemiol. 125(6):929-938.

Enterline, P.E., R. Day, and G.M. Marsh. 1995. Cancers related to exposure to arsenic at a copper smelter. Occup. Environ. Med. 52(1):28-32.

EPA (U.S. Environmental Protection Agency). 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC [online]. Available: http://www.epa.gov/ttn/atw/childrens_supplement_final.pdf [accessed Jan. 19, 2010].

EPA (U.S. Environmental Protection Agency). 2010. IRISTrack Report for Arsenic, Inorganic Assessment. Integrated Risk Information System, U.S. Environmental Protection Agency [online]. Available: http://cfpub.epa.gov/ncea/iristrac/index.cfm [accessed Jan. 19, 2010].

Flury, F. 1921. Arsentrichlorid. In Uber Kampfgasvergiftungen. IX. Lokal reizende Arsenverbindungen. Zeit. Ges. Exp. Med. 13:527-528 (as cited in NIOSH 1996).

Copyright © National Academy of Sciences. All rights reserved.

Fox, E., B.I. Razzouk, B.C. Widemann, S. Xiao, M. O'Brien, W. Goodspeed, G.H. Reaman, S.M. Blaney, A.J. Murgo, F.M. Balis, and P.C. Adamson. 2008. Phase 1 trial and pharmacokinetic study of arsenic trioxide in children and adolescents with refractory or relapsed acute leukemia, including acute promyelocytic leukemia or lymphoma. Blood 111(2):566-573.

George, B., V. Mathews, B. Poonkuzhali, R.V. Shaji, A. Srivastava, and M. Chandy. 2004. Treatment of children with newly diagnosed acute promyelocytic leukemia with arsenic trioxide: A single center experience. Leukemia 18(10):1587-1590.

Hertz-Piciotto, I., and A. Smith. 1993. Observations on the dose-response curve for arsenic exposure and lung cancer. Scand. J. Work. Environ. Health 19(4):217-226.

Holland, R.H., M.S. McCall, and H.C. Lanz. 1959. A Study of Inhaled Arsenic-74 in Man. Cancer Res 19: 1154-1156.

Hu, J., Y.F. Liu, C.F. Wu, F. Xu, Z.X. Shen, Y.M. Zhu, J.M. Li, W. Tang, W.L. Zhao, W. Wu, H.P. Sun, Q.S. Chen, B. Chen, G.B. Zhou, A. Zelent, S. Waxman, Z.Y. Wang, S.J. Chen, and Z. Chen. 2009. Long-term efficacy and safety of *all-trans* retinoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. Proc. Natl. Acad. Sci USA 106(9):3342-3347.

IARC (International Agency for Research on Cancer). 1987. Arsenic and arsenic compounds (Group 1). Pp. 100-105 in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7. Lyon: IARC [online]. Available: http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf [accessed Jan 20, 2010].

Järup, L., G. Pershagen, and S. Wall. 1989. Cumulative arsenic exposure and lung cancer in smelter workers: A dose-response study. Am. J. Ind. Med. 15(1):31-41.

Jiao, L., S.J. Wang, J.L. Zhuang, Y.Q. Zhao, D.B. Zhou, Y. Xu, B. Han, W. Zhang, M.H. Duan, N. Zou, T.N. Zhu, and T. Shen. 2009. Comparison of efficacy and adverse effects between arsenic trioxide and all-trans retinoic acid in patients with acute promyelocytic leukemia [in Chinese]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 31(5):555-558.

Kim, L.H., and S.J. Abel. 2009. Survival after a massive overdose of arsenic trioxide. Crit. Care Resusc. 11(1):42-45.

Lee-Feldstein, A. 1986. Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J. Occup. Med. 28(4):296-302.

Lubin, J.H., L.M. Pottern, B.J. Stone, and J.F. Fraumeni, Jr. 2000. Respiratory cancer in a cohort of copper smelter workers: Results from more than 50 years of follow-up. Am. J. Epidemiol. 151(6):554-565.

Lubin, J.H., L.E. Moore, J.F. Fraumeni, Jr., and K.P. Cantor. 2008. Respiratory cancer and inhaled inorganic arsenic in copper smelters workers: A linear relationship with cumulative exposure that increases with concentration. Environ. Health Perspect. 116(12):1661-1665.

Mathews, V., B. George, K.M. Lakshmi, A. Viswabandya, A. Bajel, P. Balasubramanian, R.V. Shaji, V.M. Srivastava, A. Srivastava, and M. Chandy. 2006. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: Durable remissions with minimal toxicity. Blood 107(7):2627-2632.

NIOSH (National Institute for Occupational Safety and Health). 1996. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLH): Arsenic (inorganic compounds, as As). National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/7440382.html [accessed Jan. 20, 2010].

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. Arsenic (Inorganic Compounds, as As). NIOSH Publication 2005-149. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0038.html [accessed Jan. 20, 2010].

OEHHA (Office of Environmental Health Hazard Assessment). 2008. Inorganic arsenic reference exposure levels. Pp. 68-127 in Appendix D.1 Summaries Using this Version of the Hot Spots Risk Assessment Guidelines, Air Toxics Hot Spots Risk Assessment Guidelines, Technical

Copyright © National Academy of Sciences. All rights reserved.

Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxicology and Epidemiology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA [online]. Available: http://www.oehha.org/air/hot_spots/2008/AppendixD1_final.pdf#page=68 [accessed Jan 19, 2010].

Ott, M.G., B.B. Holder, and H.L. Gordon. 1974. Respiratory cancer and occupational exposure to arsenicals. Arch. Environ. Health 29(5):250-255.

Pettersson, H.M., J. Karlsson, A. Pietras, I. Øra, and S. Påhlman. 2007. Arsenic trioxide and neuroblastoma cytotoxicity. J. Bioenerg. Biomembr. 39(1):35-41.

Pinto, S.S., P.E. Enterline, V. Henderson, and M.O. Varner. 1977. Mortality experience in relation to a measured arsenic trioxide exposure. Environ. Health Perspect. 19:127-130.

Przygoda, G., J. Feldmann, and W.R. Cullen. 2001. Historic review: The arsenic eaters of Styria: A different picture of people who were chronically exposed to arsenic. Appl. Organometal. Chem. 15(6):457-462.

Ravandi, F., E. Estey, D. Jones, S. Faderl, S. O'Brien, J. Fiorentino, S. Pierce, D. Blamble, Z. Estrov, W. Wierda, A. Ferrajoli, S. Verstovsek, G. Garcia-Manero, J. Cortes, and H. Kantarjian. 2009. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J. Clin. Oncol. 27(4):504-510.

Sandström, A., and S. Wall. 1993. Cancer incidence among male salaried employees at a smeltery in northern Sweden. Acta Oncol. 32(1):9-14.

Sandström, A.I., S.G. Wall, and A. Taube. 1989. Cancer incidence and mortality among Swedish smelter workers. Br. J. Ind. Med. 46(2):82-89.

Smith, A.H., A. Ercumen, Y. Yuan, and C.M. Steinmaus. 2009. Increased lung cancer risks are similar whether arsenic is ingested or inhaled. J. Expo. Sci. Environ. Epidemiol. 19(4):343-348.

Sweeney, C.J., C. Takimoto, L. Wood, J.M. Porter, W.C. Tracewell, M. Darwish, D.M. D'Andrea, and S.C. Remick. In press. A pharmacokinetic and safety study of intravenous arsenic trioxide in adult cancer patients with renal impairment. Cancer Chemother. Pharmacol.

Tallman, M.S., and J.K. Altman. 2009. How I treat acute promyelocytic leukemia. Blood 114 (25):5126-5135.

Vahidnia, A., G.B. van der Voet, and F.A. de Wolff. 2007. Arsenic neurotoxicity: A review. Hum. Exp. Toxicol. 26(10):823-832.

Wang, Z., J. Zhou, X. Lu, Z. Gong, and L.X Chris. 2004. Arsenic speciation in urine from acute promyelocytic leukemia patients undergoing arsenic trioxide treatment. Chem. Res. Toxicol. 17(1):95-103.

Xu, S.N., J.P. Chen, J.P. Liu, and Y. Xia. 2009. Arsenic trioxide in combination with all-trans retinoic acid for acute promyelocytic leuikemia: A systematic review and meta-analysis [in Chinese]. Zhong Xi Yi Jie He Xue Bao. 7(11):1023-1034.

Yilmaz, Y., E. Armagan, O.F. Olmez, M. Esen, N. Alkis, and E. Dolar. 2009. Acute arsenic self-poisoning for suicidal purpose in a dentist: A case report. Hum. Exp. Toxicol. 28(1):63-65.

BENZENE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on benzene. A presentation on the TSD was given by Marcel van Raaij, of RIVM. The following is excerpted from the executive summary of the TSD:

> Benzene (or benzol, the old name for the commercial product benzene) is a clear colorless liquid with a characteristic sweet odor at low concentrations and disagreeable and irritating at high levels. . . . For AEGL-1, both CNS effects and eye and airway irritation are relevant effects. It is expected that mild CNS effects will be the first noticeable effects of benzene exposure and that irritation occurs only at higher exposures or are due to co-exposure to other substances.

Copyright © National Academy of Sciences. All rights reserved.

> Therefore, the AEGL-1 values should be based on mild CNS effects. . . . The most prominent effect of acute benzene exposure, therefore, is CNS depression. Because this is a continuum from very slight dizziness to narcosis, the level that impairs escape should be identified for AEGL-2 derivation. . . . The observed NOEL for mortality of 5,940 ppm for a 4h exposure of rats…is taken as starting point AEGL-3 development. . . . The resulting AEGL-3 values are in good agreement with the limited quantitative human experiences from occupational and accidental exposures. In addition, these values are considered to be protective also for sudden cardiac arrest due to cardiac sensitization.

General Comments

A revised document should be submitted to the committee for review.

Several suggestions are made to improve discussion of the health end points associated with benzene exposure in the chemical TSD:

Cancer risk. The authors should present the results of a literature search conducted according to the approach described in the *SOP* document and include necessary cautions for the interpretation of the results.

Hematotoxicity. The dismissal of hemotoxicity as a valid AEGL end point needs more thorough coverage and sufficient justification.

Developmental effects. The TSD should provide results of a literature search regarding leukemia.

Cardiotoxicity. The relevance of cardiotoxicity should be discussed in the context of the general population, especially those who are being treated for heart conditions.

Specific Comments

AEGL-1: The point of departure (POD) is based on the report by Srbova et al. (1950) of a toxicokinetic study that did not include the evaluation of toxic effects. Because of the lack of other relevant human data, that POD should be supported by observations in animals, for example, "milk licking activity" at 100 ppm reported by Dempster et al. (1984). An additional uncertainty factor should be considered for the POD to account for the limitations in using the Srbova et al. study for this purpose.

The proposed AEGL-1 levels are higher than other regulatory standards as listed in Section 8.2. Please note the comments for Page 73, Section 8.3, regarding the need to update and amend the list, which will show a substantial difference between AEGL-1 levels and current standards.

AEGL-2: The selection of POD. Consideration should be given to the following data:

> The 4,000 ppm from the Molnar et al. (1986) study for a 4-h period is based on the decrease in locomotor activity after a period of increase. In this context, a 1-h exposure is already sufficient to elicit such a response. On Page 31, line 16, it was stated that the decreased activity occurred at all exposure times (1, 2, 3, and 4 h) at 5,940 ppm, which was noted as the narcotic threshold. Thus, the 4,000-ppm concentration would more appropriately be the POD for 1 h, not 4 h.

- The TSD did not deem increased activity an AEGL-2 end point (Page vii, lines 29-30). However, it should be noted that in the Molnar et al. study, increased locomotor activity at 2,000 ppm was accompanied by incoordination and tremors (Page 31, lines 15-19). The significance of those end points should be considered.
- A lower narcosis threshold was also reported in mice at 900 ppm for 6 h (Page 34, line 4).
- The proposed AEGL-2 may be discussed in the context of Drozd and Bockowski (1967) (Page 7 of the TSD), who indicated that workers had to leave the room for a few minutes at an estimated

Copyright © National Academy of Sciences. All rights reserved.

concentration of 750 ppm for 30 min and 1,500 ppm for 50 min from the start. Specifically, in light of the "escaping" behavior, would the 30-min AEGL-2 at 1,100 ppm be adequate?

Page 13, lines 29-35: It is unclear how the concerns about maternal exposure to childhood leukemia may affect the AEGL determination. Concerns raised by other regulatory agencies—for example, OEHHA (2001) as cited and the EPA (2002) IRIS—should be addressed here instead of a mere reference to the tabulated information in Appendix C.

Page 15, lines 6-19: The first sentence referred to the presence of sister-chromatid exchange (SCE) at low exposures. However, the study described actually showed negative results in SCE. There was actually an indication of possible effects on chromosomal aberrations. A more thorough discussion is needed.

Page 20, lines 20-25: It is unclear how the emergency exposure guidance levels (EEGLs) were calculated. If it is important in the context of the TSD here and according to *SOP*, could more computational information be included in an appendix?

Page 53, line 11: It is stated here that fetal tissue concentrations were generally much lower than the maternal concentrations. However, that appears to be inconsistent with Page 52, line 24, which states that concentrations in "cord blood may be equal or higher than those in maternal blood".

Page 54, line 15: We suggest adding the following reference, which is of substantial importance in this context: Snyder, R., T. Chepiga, C.S. Yang, H. Thomas, K. Platt, and F. Oesch. 1993. Benzene metabolism by reconstituted cytochromes P450 2B1 and 2E1 and its modulation by cytochrome b5, microsomal epoxide hydrolase, and glutathione transferases: Evidence for an important role of microsomal epoxide hydrolase in the formation of hydroquinone. Toxicol. Appl. Pharmacol. 122(2):172-181.

Page 60, lines 11-12: "Although a study of limited design, Thackara et al. (1979) investigated the response of circulating cells." Please explain what this is.

Page 60, lines 19-21: "From metabolism studies with monkeys, it appears that these species produce less polyhydroxylated rings or muconic acid in their urine than mice which might indicate reduced sensitivity of primates." Please explain why there is lower production of polyhydroxylated rings.

Page 61, line 6: The notion that susceptibility factors play a role primarily in chronic toxicity and are less relevant to AEGLs needs clear support. ATDSR (2007) stated that "workers with polymorphisms for both negligible NQ01 activity and rapid CYP2E1 activity exhibited greater than 7-fold increased risk of benzene poisoning than workers not expressing these polymorphisms." The same conclusion is given in EPA's 2002 IRIS support document.

Page 63, line 38: "in all these cases co-exposure to other substances cannot be excluded." To how many lines before this statement does this refer? Does the statement include or exclude the first-mentioned study ("The most controlled human study")?

Page 66, Lines 8-11: With regard to the text, "Some observations from epidemiological studies reporting that 'peak' exposure or 'high level' exposure may render a relatively higher risk than low dose chronic exposure should be placed in this perspective. In these studies 'peak exposure' is rather defined relative to general long-term exposure levels of <10 ppm and refers to (incidental) additional peak exposures of about 30 to 100 ppm," more information on the epidemiologic data would aid understanding of single vs multiple exposure and peak vs prolonged exposure. Specifically, more discussion is needed to clarify the duration of the "peak exposure" (for example, a few minutes or hours), the frequency of "peaks, the duration of long-term exposure (e.g., daily, weekly yearly, how many years), the certainty of this long term exposure being below 10 ppm, and the cancer incidence outcome."

Page 69, lines 4-7: The definition of AEGL-2 (see preface to the AEGL values of the individual substances), "the . . . concentration . . . above which . . . irreversible *or* [emphasis added] other serious, long-lasting adverse health effects": Either the severity of the reported effect, and as a consequence the argument here, should be that the observed reduction in the numbers of circulating cells is not sufficient to constitute a serious adverse health effect or the observed reduction should be accepted as an AEGL-2 effect.

Copyright © National Academy of Sciences. All rights reserved.

Page 69, line 26: ". . . Dempster et al. (1984) in mice are considered to be below an AEGL-2 endpoint." What end point did the study show to be considered as below an AEGL-2 end point?

Page 72, line 6: The TSD stated in Section 3.2.3, "Rats": "Injection of a higher dose of 20 µg/kg bw aconitine after inhalation at 0.2 ml benzene induced severe effects between minute 4 and 16 (ventricular fibrillation, asystole and death)." Is research needed to determine whether aconitine at 20 µg/kg of body weight is equipotent to clinically used potassium channel blockers? If so, do we, on the basis of this interaction, have an AEGL-3 effect of benzene?

Page 73, Section 8.3, "Comparison with Other Standards and Criteria": The comparison table should be updated; for example, the current American Conference of Governmental Industrial Hygienists threshold limit value (TLV) time weighted-average (TWA) is 0.5 ppm; the STEL is 2.5 ppm, skin, A1 human carcinogen. Other useful information should also be added to this list, such as the OSHA STEL, ceiling, and 10-min peak. It is noted that the proposed 10-min AEGL-1 at 130 ppm is higher than OSHA's ceiling and peak.

Page 96, lines 35-36: "For comparison, the EEGL values derived by NRC in 1986 were 38 ppm for 24h and 912 ppm for 1h. (for a risk level of 10^{-4}). The SMAC value based on carcinogenicity (risk 10^{-4}) was 12 ppm for 24h (NRC 1996)." These EEGL estimates should be explained because they are different from those presented in the TSD.

Editorial Comments

Please use a consistent unit risk number, either 2.5 or 2.6 x 10^{-2} $(ppm)^{-1}$.

Page 6, line 5: What does "±" in front of 3400-4900 ppm mean?

Page 30, line 25: Reference?

Page 41, Table 14: Time to effects in the Molnar et al. (1986) study should be added under "Major effect and comments."

Page 41, Table 14: The 90% confidence interval of 98 ppm given by Frantik et al. (1994) should be included.

Page 41, Table 14: The citation for Kaminski et al. (1970) should be added to the blank under "Reference."

Page 53, metabolism flow chart: In "Phenylmercapturic acid," a double bond is missing (the structure that is drawn on the right side of phenylmercapturic acid is prephenylmercapturic acid, which is converted by dehydration to phenylmercapturic acid; the latter step introduces the double bond that is missing.

Page 65, lines 44-45: "First, the Standing Operating Procedures for AEGL development states that at present AEGL values based on carcinogenicity are not developed because of reasons explained in the *SOP* (NRC 2001)." Please specify a section of *SOP*.

Page 69, Line 21-22: "In mice, 8h exposure at 5020 ppm induced reversible prostration." Cite a reference.

Comment References

ATSDR (Agency for Toxic Substances and Disease Registry). 2007. Toxicological Profile for Benzene. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp3-p.pdf [accessed Jan. 20, 2010].

Dempster, A.M., H.L. Evans, and C.A. Snyder. 1984. The temporal relationship between behavioral and hematological effects of inhaled benzene. Toxicol. Appl. Pharmacol. 76(1):195-203.

Copyright © National Academy of Sciences. All rights reserved.

Drozd, J., and E.J. Bockowski. 1967. Acute benzene poisoning. J. Occup. Environ. Med. 9(1):9-11.
EPA (U.S. Environmental Protection Agency). 2002. Toxicological Review of Benzene (Noncancer Effects) (CAS No. 71-43-2) in Support of Summary Information on the Integrated Risk Information System (IRIS). October 2002 [online]. Available: http://www.epa.gov/iris/toxreviews/0276-tr.pdf [accessed Jan. 20, 2010].
Frantik, E., M. Hornychova, and M. Horvath. 1994. Relative acute neurotoxicity of solvents: Isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ. Res. 66(2): 173-185.
Kaminski, M., A. Karbowski, and J. Jonek. 1970. Some histochemical renal changes in mice during acute poisoning with benzene. Folia Histochem. Cytochem. 8(1):63-75.
Molnar, J., K.A. Paksy, and M. Naray. 1986. Changes in the rat's motor behaviour during 4-hr inhalation exposure to prenarcotic concentrations of benzene and its derivates. Acta Physiol. Hung. 67(3):349-354.
NRC (National Research Council). 1996. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.
OEHHA (Office of Environmental Health Hazard Assessment). 2001. Prioritization of Toxic Air Contaminants – Children's Environmental Health Protection Act: Benzene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. October 2001[online]. Available: http://www.oehha.org/air/toxic_contaminants/pdf_zip/benzene_final.pdf [accessed Jan. 20, 2010].
Snyder, R., T. Chepiga, C.S. Yang, H. Thomas, K. Platt, and F. Oesch. 1993. Benzene metabolism by reconstituted cytochromes P450 2B1 and 2E1 and its modulation by cytochrome b5, microsomal epoxide hydrolase, and glutathione transferases: Evidence for an important role of microsomal epoxide hydrolase in the formation of hydroquinone. Toxicol. Appl. Pharmacol. 122(2):172-181.
Srbova, J., J. Teisinger, and S. Skramovsky. 1950. Absorption and elimination of inhaled benzene in man. Arch. Ind. Hyg. Occup. Med. 2(1):1-8.
Thackara, J.W. et al. 1979. Twelve-Week Inhalation Toxicity Study of Benzene on Seven Species of Animals. API Med. Res. Publ. 27-30765. Prepared by Bio/dynamics, Inc., for American Petroleum Institute, Washington, DC.

1, 3-BUTADIENE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on 1,3-butadiene. A presentation on the TSD was given by Peter Bos, of RIVM. The following is excerpted from the executive summary of the TSD:

> 1,3-Butadiene (butadiene) is a highly volatile, colorless gas with a mildly aromatic odor. . . . Clear species differences exist in susceptibility in 1,3-butadiene toxicity . . . humans will be more comparable to rats with respect to 1,3-butadiene toxicity than to mice. . . . The derivation of AEGL-1 values is based on the study by Carpenter et al. (1944). Two human subjects were exposed to 1,3-butadiene concentrations of 2000 ppm for 7 hours, 4000 ppm for 6 hours, or to 8000 ppm for 8 hours; all exposures were interrupted for a one-hour lunch break in the middle of the exposure period (Carpenter et al. 1944). Subjective symptoms reported at 2000 and 4000 ppm included slight smarting of the eyes and difficulty in focusing. . . . Two studies were considered relevant for AEGL-2, the study with human volunteers . . . and a 3-month exposure study in rats. . . . No effects defined by AEGL-2 were observed in either study. . . . Although both studies lead to approximately similar AEGL-2 values the use of human data is preferable to the rat data. . . . AEGL-3 is based on the acute lethality study by Shugaev (1969). Rats were exposed for 4 hours and a 4-hour LC_{50} of 128,000 ppm was reported.

Copyright © National Academy of Sciences. All rights reserved.

General Comments

A revised document should be returned to the committee for further review.

No clear discussion was found in the TSD of whether and why carcinogenicity should be considered in the derivation of AEGL-2. The calculation in Appendix C, "Carcinogenicity Assessment," would lead to AEGL-2 values that deviate widely (sometimes by 2 orders of magnitude) from the interim AEGL-2 values in the section "Derivation of AEGL-2." To avoid providing the reader with an unwarranted impression of risk, it would be preferable to state that after a single exposure of the more sensitive rodent species (the mouse) to very high doses of butadiene, no cancer was observed but that the risk of a carcinogenic response in humans after a single exposure has not been accurately determined. Therefore, in the case of butadiene, extrapolation of cancer incidence after lifelong exposures down to acute AEGL exposure times appears to be misleading, and no calculation is performed in Appendix C. This point needs a clear discussion.

It also appears to be inappropriate to combine data from an epidemiologic study and an animal study in the cancer calculation. An additional factor of 2 is used in the cancer calculation to account for mammary gland tumors in rodents when the human leukemia epidemiologic data are used as a basis of the calculation. This point also needs a clear discussion.

Specific Comments

Page 1, line 2 (also Page 5, lines 22-24): "This chapter is based on IARC 1999." A new IARC monograph on butadiene is available**:** IARC Monograph 97 (2008), which is based on the IARC working-group meeting of June 2007; it would be preferable to base the TSD on the more recent data.

Page 3, lines 2-4: "This study is poorly reported and is considered of doubtful significance (also considering the observations by Carpenter et al. (1944) described below)." State what in the Carpenter et al. paper supports the conclusion that the results of Ripp are of doubtful significance.

Page 3, lines 33-35: It was considered that peak exposures rather than cumulative exposures may be associated with the observed increase in non-Hodgkin lymphoma (NHL), although no data on the occurrence of peak exposures were available. That is crucial with regard to whether the observation is relevant for the derivation of AEGL values. If no data on the occurrence of peak exposures were available, it should be discussed whether there are other valid arguments for the consideration that peak exposures rather than cumulative exposures may be associated with the observed increase in NHL or whether this is an empty speculation and should not be considered for the derivation of AEGL values.

Page 5, lines 8-9: "IARC (1999) considered the increase in *hprt* mutations in lymphocytes conflicting." Please explain this statement further. This comment also pertains to Page 5, line 33.

Page 10, line 4: At the outset of the section on developmental and reproductive, it should be stated that the loss of maternal weight was considered a toxic effect and had a confounding effect on interpretation of the results.

Page 10, lines 20-52, and Page 11, lines 1-9: These paragraphs are confusing and need to be rewritten. The key to the paragraphs is that although some changes appeared to be related to dosing with butadiene, maternal toxicity appeared to have confounded the outcome. In addition, mean and standard-deviation (SD) values should be reported.

Page 11, line 33-34: "Flow cytometric analysis of spermatogonial cells revealed a statistically significant decrease depletion of the round and elongated spermatid compartments which paralleled the effects on testis weight." The sentence is confusing. What is meant by "statistically significant decrease depletion"?

Page 14, line 19, through Page 15, line 50: We suggest shortening of the section on carcinogenicity. There is much evidence that butadiene is a carcinogen, and this aspect of its activity can be handled by using the usual regulatory approach, that is, slope factor, risk assessment, and so on.

Copyright © National Academy of Sciences. All rights reserved.

However, it has less significance for the purpose of AEGL derivation. A shortened version summing up the data would be preferable to a detailed accounting of each chronic bioassay.

Page 14, line 22: The phrase "only the most important studies are studied" is unclear.

Page 15, lines 1-4: "In an additional study groups of 60 male B6C3F1 mice and 60 male NIH Swiss 1 mice, 4-6 weeks of age, were exposed to 0 or 1250 ppm (2760 mg/m^3) butadiene for 6 h/d, 5 d/w for 52 weeks (Irons et al. 1989). An additional group of 50 male B6C3F1 mice was exposed similarly to 1,3-butadiene for 12 weeks and held for the remainder of the study. All animals were killed after 52 weeks." What were the results of the described study?

Page 17, line 32: "These experiments showed that 1,3-butadiene is readily taken up." From where is butadiene taken up, and where does it go?

Page 17, lines 39-43: "Groups of three animals per species were withdrawn from exposure at 2, 4, and 6 hours of exposure for analyses of metabolites in blood. Immediately after exposure groups of four animals per species were placed in metabolism cages and excreta were collected up to 65 hours postexposure. The animals in the metabolism studies were exposed to 7 ppm 1,3-butadiene and higher." That description is unclear. What was the group size? What was the administered dose?

Page 18, line 50, through Page 19, line 13: The discussion in the section on metabolism could be shortened with a summary of the pathway and comments on important interspecies differences as they may be related to toxicity or carcinogenicity. Details of each study do not help in calculating AEGL values.

Page 19, line 45: "Mice consistently had the highest enzyme activities." Which enzyme activities? The statement is true for epoxidation, but for hydration it is the other way round, and this is crucial for species differences in the toxication-detoxication ratio.

Page 22, line 21: The statement "while in rats hormonal influences may play an important role," is unclear. Please explain further.

Page 22, line 34-36: The statement about "enzyme-mediated hydrolysis" is unclear. Epoxide hydrolase does not mediate hydrolysis. Hydrolysis is a chemical process in which a molecule is cleaved into two parts by the addition of a molecule of water. That is not the case here. Hydrolysis is distinct from hydration. In hydration, the hydrated molecule does not lyse (break into two new compounds).

Page 22, line 40: "However, carcinogenic endpoints are not relevant for AEGL-derivation." This statement is not completely true, and the issue should be discussed more objectively.

Page 23, lines 5-6: "Therefore, it can be concluded that mice are extremely susceptible to 1,3-butadiene and humans will be more equal to rats"… The phrase "will be" exceeds the present state of safe knowledge. See the first sentence of the preceding paragraph: "As to carcinogenicity, it has been argued that mice may be a more relevant model for humans in terms of site specificity, in that 1,3-butadiene induces tumors of the lymphohematopoietic system in both mice and humans (EPA 2002a)." And see the second sentence of the next chapter: "Large differences in metabolic rates for specific steps in the biotransformation of 1,3-butadiene have been observed (in humans), in some cases the rate of formation was similar to that in mice."

Page 24, lines 36-38: If the complaints at 2,000 and at 4,000 ppm were minor (with which, in light of the facts discussed, the committee agrees) and at 8,000 ppm there were no complaints, effects occurring at all those values may be rightly considered to be less than those corresponding to AEGL-1 effects. Thus, 8,000 ppm appears to be an objectively more defensible POD. "However, since only two humans were exposed, an intraspecies factor of 3 is considered appropriate": an intraspecies UF of 10 is more appropriate. The following facts should be viewed in combination: the reported complaints are in fact most objectively considered as sub-AEGL-1, allowing a reduction of the standard UF of 10 to 3 (*SOP* Section 2.5.3.4.1); but only two individuals were exposed, so the UF should be increased to the standard UF of 10.

Page 25, lines 33-43: This section describes "maternal growth retardation and fetal effects" and potential male fertility effects after butadiene exposure. Do the end points described in this section (if they would occur after a single exposure) constitute AEGL-2 effects?

Copyright © National Academy of Sciences. All rights reserved.

Page 26, lines 1-6 and lines 28-32: The cause of death in mice in the 1979 Crouch et al. paper is not known. Therefore, it may not be safely assumed that mice are an inappropriate model for humans with respect to the lethal effects of butadiene and that the much higher sensitivity of mice (compared with the rat) to lethal effects of butadiene may simply be disregarded (see also last sentence of Section 4.3, "Mechanisms of Toxicity": "No data are available with respect to the mechanism of action with respect to non-carcinogenic end points in acute exposures"). To be protective for humans, a lower concentration than the one that was lethal in mice (first deaths on treatment with butadiene at 1,250 ppm 6 h/d 5 d/week for up to 14 weeks) should be chosen as a starting point for deriving the AEGL-2 (or as support for the AEGL-2 value derived from the human data) rather than the much higher concentration that caused no effects in the rat (8,000 ppm 6 h/d 5 d/week for 3 months) (or leave out this "support" by the rat study).

Page 27, lines 14-22: Similarly, the cause of death in mice in the 1969 Shugaev and 1979 Crouch et al. papers is not known. Therefore, it may not be safely assumed that mice are an inappropriate model for humans with respect to the lethal effects of butadiene. Some more thorough discussion may be helpful.

Page 27, lines 25-28: "A higher UF would lead to unrealistically low values for AEGL-3 in comparison with the experiment by Carpenter et al. (1944) who reported that two humans showed no clear signs of toxicity during exposure to 8000 ppm for a total of 8 hours." That is not a convincing reason. It may be preferable to use the last two sentences of the paragraph ("The in vitro . . .") as primary (first-mentioned) arguments, followed by the above (". . . unrealistically low values . . .") marked as supportive.

Page 27, line 29: "The *in vitro* data obtained with human tissue samples show that overall the bioformation rate in human liver is rather comparable to that in rats." What is meant by "bioformation"?

Page 27, line 40-42: "Approximately 90 percent of the values of *n* range between n = 1 and n = 3. Consequently, these values were selected as the reasonable lower and upper bounds of *n* to use when data are not available to derive a value of *n*." What value was selected for *n*, and why?

Editorial Comments

Definitions of *target concentration, actual concentration, measured concentration*, and *analytical concentration* need to be added to the introduction. As it is, the differences among the terms are unclear.

It is unclear throughout the text what it means for a result to be "positive" or "negative." The meanings of those terms need to be explained when they are used, or they should be replaced with clearer descriptions of data results.

Page 11, line 37 through Page 12, line 10: "Summary and Conclusions on Developmental/ Reproductive Toxicity." This section is key to understanding the studies reported above but could be lost on a reader who tries to decipher the individual studies before reading the summary provided here. The section on reproductive toxicity (beginning on Page 10, line 3) should be reorganized so that the summary precedes the more detailed discussion of individual studies.

Page 12, lines 28-47: We suggest omitting the three paragraphs on in vitro and in vivo genotoxicity studies. The material is covered better in Table 4.

Page 12, lines 44: "Dominant lethal mutations were especially found in mice although only after repeated exposure." What is meant by "especially"?

Page 13, line 25-26: "1,3-Butadiene was also consistently genotoxic in germ cells of mice, but not in the single assay in rats identified." The sentence seems incomplete. What is meant by "rats identified"?

Page 16, line 1, through Page 17, line 15: The data in this section have already been discussed in detail. The summary can be shortened to a few bullet points.

Page 23, line 43: "They" exposed two males to 1,3-butadiene at 2,000 ppm 1,3-butadiene 7 h, 4,000 ppm for 6 h, and 8,000 ppm for 8 h. Who are "they"? Ripp (1967) or Carpenter et al. (1944)?

Copyright © National Academy of Sciences. All rights reserved.

Page 26, line 5: The reference to "Chapter 4" is incorrect. Which chapter is this section referring to?

Page 27, line 33-35: "The value of (41,000/3=) 13,700 ppm for 4 hours was extrapolated across time periods using $C^n \times t\ k = n$ with default values n = 1 for extrapolation to longer time periods and n = 3 for extrapolation to shorter time periods." The statement "The value of (41,000/3=) 13,700 ppm" is unclear.

Comment References

Carpenter, C.P., C.B. Shaffer, C.A. Weir, and H.F. Smyth. 1944. Studies on the inhalation of 1,3-butadiene. J. Ind. Hyg. Toxicol. 26:69-78.

Crouch, C.N., D.H. Pullinger, and I.F. Gaunt. 1979. Inhalation toxicity studies with 1,3-butadiene 2. 3-month toxicity study in rats. Am. Ind. Hyg. Assoc. J. 40(9):796-802.

EPA (US Environmental Protection Agency). 2002a. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. October 2002 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54499#Download [accessed Jan. 22, 2009].

IARC (International Agency for Research on Cancer). 1999. 1.3-Butadiene. Pp. 109-225 in Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide, Part 1. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol. 71. Lyon, France: IARC [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf [accessed Jan. 22, 2010].

IARC (International Agency for Research on Cancer). 2008. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol. 97. Lyon, France: IARC [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol97/mono97.pdf [accessed Jan. 22, 2010].

Irons, R.D., H.P. Cathro, W.S. Stillman, W.H. Steinhagen, and R.S. Shah. 1989. Susceptibility to 1,3-butadiene-induced leukemogenesis correlates with endogenous ecotropic retroviral background in the mouse. Toxicol. Appl. Pharmacol. 101(1):170-176.

Ripp, G.K. 1967. Sanitary validation of the maximum permissible concentration of divinyl in atmospheric air. Pp. 33-54 in Biologicheskoe deystvie i gigienicheskoe znachenie atmosfernykh zagryazneniy, V.A. Ryazanova, ed. Moscow: Izdatel'stvo Meditsina [translation prepared for U.S. Environmental Protection Agency PB-212].

Shugaev, B.B. 1969. Concentrations of hydrocarbons in tissues as a measure of toxicity. Arch. Environ. Health. 18(6):878-882.

BUTANE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on butane. A presentation on the TSD was given by Peter Bos, of RIVM. The following is excerpted from the executive summary of the TSD:

> Butane is a colorless gas with a faint disagreeable odor, although it is considered to be odorless by some. . . . The AEGL-1 derivation is based on observations in a study with volunteers on the warning properties of short exposures to butane. . . . It is concluded that 10,000 ppm (10-min exposure) can be regarded as a boundary for drowsiness. . . . The AEGL-2 values are based on a study with guinea pigs exposed for 2 hours to a butane concentration varying between 50,000 and 56,000 ppm. . . . Animals sowed a "dazed appearance" but were able to walk. Therefore, the

Copyright © National Academy of Sciences. All rights reserved.

> effects are considered not to be serious enough to impair escape and the lower value in this range (i.e. 50,000 ppm) is used as starting point for the derivation of AEGL-2. . . . The AEGL-3 derivation is based on an acute exposure study with rats and mice. . . . The 2-hour LC_{01} for mice is chosen as starting point for AEGL-3 derivation, as it is the lowest value in a possibly more susceptible species.

General Comments

A revised document should be returned to the committee for further review.

Specific Comments

Page 3, lines 43-44: The TSD indicates that 10,000 ppm for 10 min caused drowsiness; the statement is contradicted by another statement that indicates that 10,000 ppm caused no symptoms. Which statement is correct?

Page 3, lines 49-50: Section 2.3, "Neurotoxicity," was left blank. Several case reports presented in Section 2.2.1 are related to intentional or accidental exposure to butane and suggest neurotoxicity; these should be described here.

Page 6, Line 21-22: Section 3.2, "Nonlethal Toxicity": Concentration related decreases in cardiac output and left ventricular pressure were observed, starting at 5,000 ppm in dogs. How should this information be used in adjusting AEGL-1?

Editorial Comments

Page 3, line 42: The sentence starting with "Although it was reported in a table" is unclear. Please change the sentence to read "Although a table in the report stated that exposure at 10,000 ppm for 10 min caused drowsiness, this was contradicted by a statement in the text stating that 10-min exposure at 10,000 ppm caused no symptoms."

CHLOROACETALDEHYDE

At its meeting on October 27-29, 2009, the committee reviewed the TSD on chloroacetaldehyde. The document was presented by Joanne Nijhof, of RIVM. The following is excerpted from the summary of the TSD:

> Chloroacetaldehyde is a colorless, volatile liquid with an acrid, penetrating odor. . . . The toxicity database on chloroacetaldehyde is poor. . . . The AEGL-1 derivation is based on nasal and eye irritation in animals. . . . The AEGL-2 values are based on impaired lung function in rats as the most relevant effect. . . . Two studies with acute lethality [AEGL-3] data are available. . . . The data show a steep concentration-response curve for mortality, a shift from zero to 100% mortality was already observed in case of doubling the exposure concentration or time.

General Comments

The document is generally well presented, and the committee takes no issue with the numbers derived. The document can be finalized if several revisions are made:

Copyright © National Academy of Sciences. All rights reserved.

1. Consider using the statement in the Dow report concerning human irritation at 10 ppm as supporting data for the AEGL-1 value after application of an intraspecies UF of 3: Dow Chemical Company. 1952. The report of The Dow Chemical Company. In Toxicity of Chloroacetaldehyde. NTIS Report No. 8EHQ-0392-28338 (microfiche no.OTS0536151). National Technical Information Service, Springfield, VA.
2. Provide a somewhat more complete description of the use of a modifying factor of 2 for AEGL-2. Refer to *SOP*.
3. In the discussion of human data as related to ifosfamide and cyclophosphamide, include discussion of renal toxicity, also thought to be related to chloroacetaldehyde. Some of the references are cited but only in Section 4.2. Consider including some of the discussion in Section 2. Also consider adding these references in this section: Yaseen et al. (2008) and Dubourg et al. (2002). The latter addresses younger and older susceptible populations.

Specific Comments

Page 2, lines 25-27: What does "SE" refer to, and is it necessary to report it?

Page 2, lines 27-28: Sentence beginning with "Several other reports have also concluded." Cite this reference: Rieger C et al. (Anti-Cancer Drugs 2004; 15: 347-50), which discusses risk factors for central nervous system (CNS) injury.

Page 5, lines 45-47: The logic of this explanation is not clear. Is this a conclusion offered by the study authors? If so, the sentence should be rephrased to make that clear.

Page 9, lines 29-32: This paragraph is not very clear. Is it saying that inhalation would probably not cause toxicity other than to the lung? There don't seem to be any data to support or refute that conclusion. One might argue that ifosfamide toxicity to brain, kidney, or bladder suggested that the substance survives long enough to circulate effectively to other organs. The first sentence also needs revision for clarity.

Page 10, lines 14-16: The TSD authors should examine a recent publication on nephrotoxicity by Hanly L et al. (Expert Opin Drug Safety 2009; 8[2]:155-68), which gives a good review of mechanisms (oxidative stress), and so on. They should also cite articles by Skinner R et al. (Br. J. Cancer 2000; 82:1638-45), Loebstein R et al. (J Clin Pharmacol. 1999; 39:454-61), and Aleksa K et al. (Pediatr Nephrol 2001; 16:1153-8) on the issue of age dependence, which is not so clear. Current thinking is that chloroacetaldehyde is formed in the kidney and that this metabolism is probably age-dependent.

Page 16, line 39: Delete the editorial statement "We don't have Einsatztoleranzwert levels, so skip at this time."

Comment References

Aleksa, K., C. Woodland, and G. Koren. 2001. Young age and the risk for ifosfamide-induced nephrotoxicity: A critical review of two opposing studies. Pediatr. Nephrol. 16(12):1153-1158.

Dow Chemical Company. 1952. The report of The Dow Chemical Company. In Toxicity of Chloroacetaldehyde. NTIS 8EHQ-0392-28338. (Microfiche No.OTS0536151). Springfield, VA: National Technical Information Service.

Dubourg, L., P. Tanière, P. Cochat, G. Baverel, and C. Michoudet. 2002. Toxicity of chloroacetaldehyde is similar in adult and pediatric kidney tubules. Pediatr. Nephrol. 17(2):97-103.

Hanly, L., N. Chen, M. Rieder, and G. Koren. 2009. Ifosfamide nephrotoxicity in children: A mechanistic base for pharmacological prevention. Expert Opin. Drug Saf. 8(2):155-168.

Loebstein, R., G. Atanackovic, R. Bishai, J. Wolpin, S. Khattak, G. Hashemi, M. Gobrial, S. Baruchel, S. Ito, and G. Koren. 1999. Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. J. Clin. Pharmacol. 39(5):454-461.

Copyright © National Academy of Sciences. All rights reserved.

Rieger, C., M. Fiegl, J. Tischer, H. Ostermann, and X. Schiel. 2004. Incidence and severity of ifosfamide-induced encephalopathy. Anti-Cancer Drug 15(4):347-350.
Skinner, R., S.J. Cotterill, and M.C.G. Stevens. 2000. Risk factors for nephrotoxicity after ifosfamide treatment in children: A UKCCSG Late Effects Group study. Br. J. Cancer 82(1):1636-1645.
Yaseen, Z., C. Michoudet, G. Baverel, and L. Dubourg. 2008. Mechanisms of the ifosfamide-induced inhibition of endocytosis in the rat proximal kidney tubule. Arch. Toxicol. 82(9):607-614.

CHLOROBENZENE

At its meeting on October 27-29, 2009, the committee reviewed the AEGL TSD on chlorobenzene. A presentation on the TSD was given by Joanne Nijhof, of RIVM. The following is excerpted from the executive summary of the TSD:

> Chlorobenzene is a flammable liquid with a high vapor pressure and a medium solubility in water. . . . The database for chlorobenzene is rather poor and many data are limitedly described in reviews or summaries. . . . The AEGL-1 values are based on two kinetic studies with [human] volunteers. . . . There are no adequate human data for derivation of AEGL-2. Some studies with experimental animals report subtle CNS effects but are difficult to interpret with respect to their relevance for humans and for AEGL-2 derivation. . . . The most appropriate point of departure is the absence of AEGL-2 related effects in rats and guinea pigs exposed to 2990 ppm for 30 min. . . . The data in rats and guinea pigs . . . are considered to provide the most appropriate point of departure for AEGL-3 derivation, i.e. no mortality in rats and guinea pigs after exposure to 7970 ppm for 30 min.

General Comments

The TSD can be finalized when the following comments have been adequately addressed.

Specific Comments

Page vi, line 4 (also Page 1, line 2): "Chlorobenzene is a flammable liquid with a high vapor pressure and a medium solubility in water." "Medium solubility" needs to be defined.

Page vi, line 12: "several original papers were unavailable." What does that mean? Was the search insufficient, or are there no copies anywhere?

Page vi, lines 32-33: "Since the described effects at 60 ppm include irritation and CNS depression, the 8-hour AEGL-1 value of 10 ppm is considered appropriate for all time-points." In the sentences (lines 24-27) that precede that statement, CNS depression was not listed as an observed effect. Was CNS depression observed?

Page 2, line 1: What does "indications" mean in "indications of exposure levels"?

Page 2, line 27: "Knecht: personal communication, 2005)." To whom was the personal communication made?

Page 2, lines 36-37: "In the IRPTC summary (1988) individual EEG changes were described both at the time of inhaling and as near- and long-term effects." What are "individual EEG changes"?

Page 3, lines 5-9: "Only limited information is available stating that exposure to 220 to 660 ppm was bearable for hours, 1200 ppm for an unknown period induced clear narcosis, 2400 - 2900 ppm induced unsteady movement, tremors and convulsions within one hour but no more severe damage; 3700 ppm caused mortality and pulmonary hemorrhage was seen after 7 hours; 8000 ppm for 2 hours induced signs of narcosis after 30 minutes and mortality after the end of the exposure period." The committee is

Copyright © National Academy of Sciences. All rights reserved.

not sure how narcosis is used in this context. Did the cats experience respiratory failure due to CO_2 retention? That usually occurs after prolonged respiratory failure, which is what one would expect in the setting of pulmonary hemorrhage.

Page 4, lines 4-5: "Groups of 5 rats per sex were whole body exposed to mean analytical concentrations of 2990 (SD: 53), 5850 (1350) or 7970 (355) ppm chlorobenzene for 30 min." Was the SD given for only one dose? Do all the parenthetical numbers represent SDs? If so, please make that explicit.

Page 5, lines 8- 9: "Only limited information is available stating that exposure to 220 to 660 ppm was bearable for hours and exposure to 1200 ppm for an unknown period induced clear signs of narcosis." Why use "bearable" for cat exposures?

Page 5, lines 9-11: "cats that inhaled 2400-2900 ppm developed unsteady movement, tremors and convulsions within one hour but no severe damage." Define "no severe damage."

Page 6, line 12: Please clarify how "narcosis" is being used in this context. See previous comment for Page 3, lines 5-9.

Page 6, line 18: "male adult albino SPF, n = 4 per group." Please indicate that "SPF" means specific-pathogen free.

Page 10, line 1, through Page 11, line 32: There is too much emphasis on genotoxicity. Not all this material is necessary. Please carefully revise and condense this section.

Page 11, lines 3-4: "According to BUA (1990) this might be due to contamination of the DNA with RNA or proteins." What is the evidence for that statement?

Page 12, lines 18-20: "In both species an effect of 30 or 37.5%, respectively was found at 610 ppm (4-hour)." Clarify what the values 30 and 37.5% refer to.

Page 13, lines 12-14: "Ogata and Shimada (1983) determined the metabolites excreted in the urine (working hours) of two workers exposed to 0.84 ppm for 415 minutes or 0.5 ppm for 228 minutes and compared it to the estimated intake." What were the results of that study?

Page 14, lines 4-12: "Recently, a physiologically based pharmacokinetic model was developed by Thrall et al. (2004) for the respiratory absorption, distribution, metabolism and elimination of chlorobenzene in the rat and evaluated against real-time exhaled breath data.

"A physiologically based pharmacokinetic model was developed by Kumagai and Matsunaga (1995) to relate the inhalation exposure of workers to the urinary excretion of 4-chlorocatechol. The model was compared to data reported by others. The results indicate that the pharmacokinetic model can be used to estimate the urinary concentrations of 4-chlorocatechol." Is there a need to discuss the models? If not, why cite them?

Page 14, line 23: Explain the phrase "correlated to a concentration of 70 ± 31 mM."

Page 14, lines 31-36: "This suggests that the toxicity to liver and kidney and probably also the toxicity to the white blood cells (or bone marrow) is due to reactive metabolites. The reactive epoxides are normally removed by the enzymatic reaction with glutathione or by epoxide hydratase. Repeated exposure can therefore result in glutathione depletion. A decrease in glutathione can result in an increase in covalent binding and toxicity. This would indicate that repeated exposure can have more severe effects than a single exposure." Are there data to support that conclusion?

Page 14, lines 50-51: "Only dichlorobenzene was more toxic." What does "more toxic" mean in this context?

Page 16, lines 13-15: "Flicker fusion values were significantly decreased at the end of exposure period of 3 hours in the morning, indicating lowered perception." What does "lowered perception" mean?

Page 16, lines 18-19: "None of the probands made complaints." Because some readers may not be familiar with the term "probands," please include an alternative term, such as "subjects."

Page 16, line 30-31: "These concentrations were not expected to influence normal locomotor activity or to induce behavioral excitation." Provide evidence to support that statement.

Page 16, lines 37-38: The TSD states that "De Ceaurriz et al. (1983) determined the ID50 for the decrease in the duration of immobility in the 3-minute 'behavioral despair' swimming test at 804 ppm. This effect is considered to be a subtle change in neurobehavior and therefore the ID50 to be a sub AEGL-2 concentration." Indicate who considers the effect to be a subtle change.

Copyright © National Academy of Sciences. All rights reserved.

Page 17, lines 3-9: Perhaps more weight should be given to the animal studies.

Page 17, lines 7-8: "The most appropriate point of departure is the absence of AEGL-2 related effects in rats and guinea pigs exposed to 2990 ppm for 30 min." More justification should be provided for ignoring effects seen at lower doses.

Page 18, line 18-20: "However, the results of Bonnet et al. (1982) are not in line with the results of Rebert et al. (1995) who did not report deaths in rats exposed for 5 days for 8 hour per day to chlorobenzene concentrations ranging from 1000 to 2400 ppm." What rat strains are being referred to?

Editorial Comments

In describing test results, "negative" and "positive" can be ambiguous. Such descriptions of test results need to be replaced with clear terms.

Page 10, line 1, through Page 11, line 32: The genotoxicity section needs to be condensed and copyedited.

Page 11, lines 2-3: The sentence beginning with "Chlorobenzene binds covalentely" needs to be more specific.

Page 11, line 8: "Negative in an oral micronucleus test" is not a sentence. Please rewrite.

Page 11, lines 10-16: It is unclear what "negative" and "positive" tests results indicate. Does "negative" mean that micronuclei were not found? Please reword the description of these test results.

Page 16,-lines 40-41: No information is given to support this statement. Should there be a citation?

Comment References

Bonnet, P., Y. Morele, G. Raoult, D. Zissu, and D. Gradiski. 1982. Determination of the median lethal concentration of the main aromatic hydrocarbons in the rat [in French]. Arch. Mal. Prof. 43(4):461-465.

BUA (GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance). 1990. Chlorobenzene. BUA Substance Report 54. Weinheim, Germany: VCH. November 1990.

De Ceaurriz, J., J.P. Desiles, P. Bonnet, B. Marignac, J. Muller, and J.P. Guenier. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol. Appl. Pharmacol. 67(3):383-389.

IRPTC (International Register of Potentially Toxic Chemicals). 1988. Chlorobenzenes (Chlorobenzene, Dichlorobenzene, Trichlorobenzene). Scientific Reviews of Soviet Literature of Toxicity and Hazards of Chemicals No. 108. Moscow: GKNT.

Kumagai, S., and I. Matsunaga. 1995. Effect of variation of exposure to airborne chlorobenzene on internal exposure and concentration of urinary metabolite. Occup. Environ. Med. 52(1):65-70.

Ogata, M., and Y. Shimada. 1983. Differences in urinary monochlorobenzene metabolites between rats and humans. Int. Arch. Occup. Environ. Health 53(1):51-57.

Rebert, C. S., R.W. Schwartz, D.J. Svendsgaard, G.T. Pryor, and W.K. Boyes. 1995. Combined effects of paired solvents on the rat's auditory system. Toxicology 105(2-3):345-354.

Thrall, K.D., A.D. Woodstock, and M.R. Kania. 2004. Development of a Physiologically Based Pharmacokinetic Model for Chlorobenzene in F-344 rats. J. Toxicol. Environ. Health A 67(7):525-536.

Copyright © National Academy of Sciences. All rights reserved.

HEXANE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on hexane. The document was presented by Peter Bos, of RIVM. The following description is excerpted from the executive summary of the TSD:

> *n*-Hexane is a colorless liquid with a slightly disagreeable, gasoline-like odor. . . . Due to insufficient human and animal data addressing the level of effects defined by AEGL-1 no AEGL-1 values are recommended. The AEGL-2 values are based on a kinetic study with groups of 3 male Fischer 344 rats. . . . It was stated that at the highest concentration of 10,000 ppm animals showed a reduced respiration associated with narcosis. Considering all data available this effect is considered to be below the definition of AEGL-2; the 10,000 ppm exposure concentration is therefore used as point of departure for AEGL-2. . . . The AEGL-3 derivation is based on a kinetic study with male Sprague-Dawley rats. . . . Although the study focused on blood hexane concentrations, it was mentioned that only the rats exposed for 25 and 30 min showed visible signs of toxicity, i.e., ataxia and decreased motor activity, but no deaths. From these results, a 30-min exposure to 86,222 ppm is chosen as point of departure for AEGL-3.

General Comments

A revised document should be submitted to the committee for review.

Specific Comments

Page 6, lines 2-12: The study that is described here is dismissed in the TSD section "Derivation of AEGL-values" as being unsuitable because of confounding by stress. State why that is the case (conditions in which AEGL-values will be used in practice probably often involve stress).

Page 21, lines 44-46: "However, this study was concluded not to be relevant for AEGL-derivation because mice were exposed under stress." If that is also true for Swann et al. (1974), the argument for disregarding the results of Fühner (1921) and Lazarew (1929) mentioned immediately above—"oxygen concentrations will have decreased and the CO_2 level will have increased"—is stronger for disregarding the results of Swann et al. (1974) rather than the argument concerning stress, in that stress may be a realistic condition in emergency situations.

Page 23, lines 22-24: "A 6-hour exposure to 10,000 ppm was reported to induce reduced respiration associated with narcosis in rats (Bus et al. 1982)." Page 23, lines 31-33: "It is, therefore, concluded that the effects observed by Bus et al. (1982) at an exposure level of 10,000 ppm are below the definition of AEGL-2." Page 24, line 6**:** "Point of departure for AEGL-2 is the 6-hour exposure to 10,000 ppm (Bus et al. 1982)." Narcosis impairs the ability to escape and hence *is* an AEGL-2 effect and should not be included with effects expected to occur at concentrations *below* those associated with AEGL-2 effects.

Page 24, lines 6-11: The TSD states that "a total UF of 3 is considered sufficient for toxicokinetic and toxicodynamic differences between individuals and interspecies differences." According to Section 2.5.3.2.3 of *SOP*, "if evidence is available indicating that the mechanism . . . is not expected to differ significantly among species, an interspecies UF of 3 is generally used." Section 2.5.3.4.4 of *SOP* states: "mechanism of action . . . such that the response . . . by different subpopulations is unlikely to differ

Copyright © National Academy of Sciences. All rights reserved.

significantly, an intraspecies UF of 3 is generally used." Hence, an interspecies UF of 3 and an intraspecies UF of 3, resulting in a total UF of 10 (not 3), are sufficient (instead of the standard total UF of 100).

Page 18, lines 28-30: "The following results supported this hypothesis: (1) increased liver weight/body weight ratio caused by a 10% decrease in body weight." A decrease in body weight does not constitute an argument to support enzyme induction.

Page 19, line 53: "many other metabolites were found with only little species differences between human, rat, mouse, rabbit." The next sentence shows remarkable species differences: "2,5-dimethylfuran and γ-valerolactone could be demonstrated in urine of man and rat, but not in urine of rabbit and monkey." Please explain the apparent contradiction.

Editorial Comments

Executive Summary, Page vi, line 23: "margin" should be "ratio" between toxic (narcosis) dose and lethal dose. Moreover, the statement contradicts the statement on line 38: "reduced respiration (which is associated with narcosis) is considered to be below the definition of AEGL-2." That means that the author considers narcosis (or at least narcosis-associated effects on respiration) as a sub-AEGL2 whereas the narcosis dose and lethal dose are very close. That should be reconsidered or at least rephrased to deal with the apparent contradiction.

Page 4, lines 48-49, to Page 5, lines 1-2: "No mortality was reported in these studies, not even at exposure levels of 86,222 ppm for 30 min (male Sprague-Dawley rats; whole body exposure) and 48,280 ppm for 10 h (female albino rats; whole body exposure; purity of *n*-hexane not given)." Which of the abovementioned four studies does this refer to?

Page 7: The section on nonlethal toxicity should be divided into two sections, one on acute and one on chronic, to make the material more accessible. Moreover, the data on neurotoxicity should be moved to the next section (see below).

Page 9, line 6: "numerous inflammatory were seen." Numerous inflammatory *cells* . . . ?

Page 11, Section 3.3: *n*-Hexane is primarily an important neurotoxicant (after chronic exposure). Its major metabolite, 2,5-hexanedione, interferes with neurofilament phosphorylation status and thus impairs axonal transport. It is insufficient to say "See under nonlethal toxicity." Although the neurotoxicity of hexane may be primarily a chronic effect and therefore not affect the AEGLs, it should be addressed more thoroughly than in this draft TSD. Moreover, whether neurotoxicity occurs only after chronic exposure and is not a long-term effect of a single high exposure should be discussed.

Page 18, line 32: Define "DCPIP."

Page 18, lines 50-51: "The newly described 4,5-dihydroxy-2-hexanone was the second metabolite." What does that mean? The second-most abundant metabolite?

Page 21, lines 34-36: "No adverse signs were reported but it is not clear whether these effects were actually asked for. Similarly, no clinical signs were reported by workers exposed to 8-h concentrations of up to 325 ppm." Give literature citations for those two sentences.

Page 25, line 16: "Point of departure for AEGL-3 is the 30-min exposure to 86,222 ppm." Exposure of which species?

Comment References

Bus, J.S., D. Deyo, and M. Cox. 1982. Dose-dependent disposition of *n*-hexane in F-344 rats after inhalation exposure. Toxicol. Sci. 2(5):226-229.

Fühner, H. 1921. The narcotic effects of gasoline and its components (pentane, hexane, heptane, octane) [in German]. Biochem. Z. 115:235-261.

Copyright © National Academy of Sciences. All rights reserved.

Lazarew, N.W. 1929. The toxicity of various hydrocarbon vapours [in German]. Arch. Exp. Pharmakol. 143:223-233.

Swann, H.E., B.K. Kwon, G.K. Hogan, and W.M. Snellings. 1974. Acute inhalation toxicology of volatile hydrocarbons. Am. Ind. Hyg. Ass. J. 35(9):511-518.

JET PROPELLANT FUELS 5 AND 8

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on jet propellant fuels 5 and 8. The document was presented by Silvia Talmage, of Summitec Corporation. The following description is excerpted from the executive summary of the TSD:

> Jet propellant (JP) fuels, used in military and civilian aircraft, are complex mixtures of aliphatic and aromatic hydrocarbons made by blending various distillate stocks of petroleum. The primary military fuel for land-based military aircraft is JP-8. . . . JP-5 was developed by the U.S. Navy for shipboard service. The composition of JP-8 and JP-5 is basically that of kerosene (with additives) and they have similar chemical and physical characteristics. This document focuses on the toxicity of JP-8 with some attention to the chemically similar JP-5. The AEGL-1 was based on the sensory irritation . . . wherein an RD_{50} (the concentration that reduced the respiratory rate of Swiss-Webster mice by 50%) was measured for JP-8 of 2876 mg/m^3 vapor plus aerosol. . . . The AEGL-2 is based on inhalation studies with rats and mice that demonstrate exposure to 1100 mg/m^3 of JP-8 failed to elicit signs of intoxication or central nervous system depression. . . . Based on the likelihood that airborne concentrations of JP-8 aerosol and vapor sufficient to cause death cannot be sustained under ambient conditions, an AEGL-3 was not derived.

General Comments

The document can be finalized after the following comments are satisfactorily addressed.

Page 5, lines 26-29: Change these sentences to "However, emergency exposures are expected to be in the form of vapor exposures that result from spills, whereas aerosols are relevant only to occupational exposures during aircraft-foam removal operations or aircraft cold starts. Studies that addressed the toxicity of jet fuel only in the aerosolized form were not used to derive AEGL values." The change will explain the most likely exposure scenario and put the aerosol occupational exposure in context. Make similar changes in other locations in the document as appropriate.

Add citations to the following references:

1. Tremblay, R.T., S.A. Martin, and J.W. Fisher. In press. Novel characterization of the aerosol and gas phase composition for aerosolized jet fuel atmospheres. Inhalation Toxicology.
2. Martin, S.A., K.F. Brunson, C. Kendrick, R.T. Tremblay, and J.W. Fisher. In press. Characterization of a nose-only inhalation exposure system for hydrocarbon mixtures and jet fuels. Inhalation Toxicology.

Comment References

Martin, S.A., K.F. Brunson, C. Kendrick, R.T. Tremblay, and J.W. Fisher. In press. Characterization of a nose-only inhalation exposure system for hydrocarbon mixtures and jet fuels. Inhalation Toxicology.

Copyright © National Academy of Sciences. All rights reserved.

Tremblay, R.T., S.A. Martin, and J.W. Fisher. In press. Novel characterization of the aerosol and gas phase composition for aerosolized jet fuel atmospheres. Inhalation Toxicology.

KETENE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on ketene. The document was presented by Joanne Nijhof, of RIVM. The following description is excerpted from the executive summary of the TSD:

> Ketene is a colorless gas with a sharp, penetrating odor that can be detected at 12 ppm but not at 1 ppm. . . .The AEGL-1 values are based on a repeated dose study . . . on the mouse. . . Since the results of the other studies available are rather in agreement, [this] study is considered to provide an appropriate point of departure for AEGL-setting (at all levels: AEGL-1, AEGL-2, and AEGL-3). . . . The predominant nonlethal effects induced by ketene included sneezing, coughing, salivation, nasal discharge, frothy fluid from the mouth, irregular and labored respiration, and lethargy (effects predominantly related to the lungs and the brain). Since no effects were observed in mice exposed for 7 hours (= 420 min) to 1 ppm, this exposure level is chosen as point of departure for AEGL-1. . . . lethal concentrations caused severe damage to the lungs, [so] it cannot be ruled out that severe lung damage was induced by the first 4.5-hour exposure to 12 ppm. These effects fall under the endpoints as defined by AEGL-2. . . . A 4.5-hour exposure to 12 ppm (the next lower exposure concentration) did not result in deaths. . . . Therefore, the 4.5 hour (= 270 min) exposure to 12 ppm is considered to provide a threshold for lethal effects caused by ketene exposure and is chosen as point of departure for AEGL-3.

General Comments

A revised document should be submitted to the committee for review.

The proposed AEGL-2 and AEGL-3 values are based on a single experiment used as the POD and an assumption regarding the toxic effect produced. Although well stated, the assumption affects the selection of modifying and uncertainty factors.

The authors of the key study compared the toxic effects of ketene with those of phosgene. Because the toxicity database on ketene is so sparse, it would be helpful to provide more information regarding the similarities and to discuss what is known about phosgene toxicity that may be useful in assessing a ketene exposure. For example, the phosgene literature may be helpful in determining the potential for the existence of a subpopulation that is particularly sensitive to ketene. The phosgene literature may also be helpful in assessing the degree of intraspecies variability of ketene's effects and the influence that that might or should have on the selection of the intraspecies UF. Both those points are raised in specific comments below. Reference to the phosgene AEGL TSD would highlight a ready source of additional information for the TSD reader.

The authors of the key study emphasized the existence of a latent period before the onset of serious toxic effects or lethality. That is an important aspect of ketene toxicity and one that is relevant to emergency-response planners, in addition to first responders, the target audience for the TSD. The comments below include suggestions as to appropriate locations in the document for that aspect of ketene toxicity to be mentioned.

The existence of a latent period also presents some complications in evaluating the toxic effects in a repeated-dose experiment; it influences the selection of the POD and the values of the UFs. In the key mouse exposure, it is not possible to determine whether the single 4.5-h exposure at 12 ppm alone would have produced lethality. The authors of the TSD briefly allude to that uncertainty in their discussion of intraspecies variability and susceptible subpopulations, but for the derivation of the AEGL values they

Copyright © National Academy of Sciences. All rights reserved.

assume that no deaths would have occurred (they state that assumption very clearly). However, the nature of the toxic effect and the steepness of the dose-response curve in light of the variability in time to death suggest the possibility of the lethality mentioned above, as do the observations in mice, rats, and guinea pigs at the various doses (concentration × time values) shown in Tables 3 and 4 of the key study. Because the result of that one experiment is used as the POD for both the AEGL-2 and AEGL-3 values, greater confidence could be placed in the derivations if more detailed support for the assumption (and the associated UFs) were provided. The comparison with phosgene toxicity, recommended above, and with the phosgene AEGL values and their derivations would also be supportive.

Specific Comments

Summary: Insert a few sentences describing the latent period and its similarity to phosgene's latent period.

Page 16, line 7: Considering the mode of action of ketene and the similarity of its effects to those produced by phosgene, relevant information from the first paragraph in the "Introduction" on Page 1 could be presented here to support the analogy. A brief discussion of phosgene mode and mechanism of toxicity would supplement the sparse database on ketene; this could be extracted and condensed from the phosgene TSD.

Page 16, lines 42-46: The authors of the key study highlighted the similarity of ketene's toxic effects to the toxic effects of phosgene. Review the literature on phosgene (including its TSD) to determine whether there is information on subpopulations (such as people who have asthma) that may be susceptible to effects of phosgene exposure. If it exists, evaluate the information for its applicability to and influence on ketene AEGL derivations. If no information is available, insert a statement that the review was done and no susceptible populations were identified.

Page 16, lines 42-46: "No information was located on intraspecies variability and susceptible populations concerning the toxicity of ketene. However, in all lethality studies available (Cameron and Neuberger 1937, Wooster *et al.* 1947, Treon et al. 1949, Mendenhall and Stokinger 1959) great differences were reported in the times of death in animals exposed to certain doses of ketene. Therefore, intraspecies variability might be expected." This paragraph, particularly the last sentence, seems to indicate that there may be wide variability in the general population with respect to sensitivity to the effects of ketene. It appears to contradict the basis of an intraspecies UF of 3 for all three AEGL tiers. The discrepancy (variability vs intraspecies UF of 3) needs to be resolved. See also the next comment.

Page 18, lines 43-45: "Further, considering the mode of action to be a direct action of the parent at the port of entry (alveolar damage) and considering the similarities in toxicity between the species tested an intraspecies factor of 3 is considered adequate." In selecting the appropriate UFs, the use of the most sensitive species (mouse), a steep dose-response curve, and a mode of action that is unlikely to differ substantially among species (portal-of-entry damage to the alveoli by the parent compound) all support selecting a factor of 3 for both interspecies and intraspecies UFs. The similarity of the toxic effect in all the species tested supports the choices. However, more confidence could be placed in the selection of the UF of 3 if two points were addressed: the point raised in the comment regarding Page 16, lines 42-46, and the comparison with phosgene. If the review of the phosgene literature suggested above indicates that there may be a subpopulation (such as people who have asthma) sensitive to the effects of ketene, greater justification for the intraspecies UF of 3 will be required. See the discussion in *SOP* in Section 2.5.3.3., particularly on Pages 75 (last paragraph), 80-81, and 86-88. The relevant guideline is Section 2.5.3.4.4 on Page 90.

Page 19, lines 32-36: "Although the time of death during the second exposure is not given, these deaths are considered to be caused by the second subsequent exposure. However, since it was stated by Treon et al. (1949) that lethal concentrations caused severe damage to the lungs, it cannot be ruled out that severe lung damage was induced by the first 4.5-hour exposure to 12 ppm." The phrasing of those two sentences should be reconsidered in light of the recommendation above to highlight the latency of

Copyright © National Academy of Sciences. All rights reserved.

ketene's toxic effect and its similarity to phosgene. The current phrasing can be read as only weakly supporting the similarity between the two chemicals.

Page 19, lines 33-34: "these deaths are considered to be caused by the second subsequent exposure." It is not clear whether that conclusion is that of the study's authors; if so, the attribution should be made clear.

Page 20, lines 1-5: "It is concluded from the study by Treon et al. (1949) that a 4.5-hour exposure to 12 ppm did not result in deaths. Deaths occurring during exposure on the second exposure day are considered to be caused by the second subsequent exposure. Since it was stated by Treon et al. (1949) that lethal concentrations caused severe damage to the lungs, it cannot be ruled out that severe lung damage was induced by the first 4.5-hour exposure to 12 ppm." See comment above regarding Page 19, lines 32-36.

Page 20, lines 2-9: The guidance on using modifying factors (MFs) (*SOP* Section 2.6, Pages 91-92) is limited and is essentially captured by the statement that "the [MF] 'reflects professional judgment on the entire data base available for the specific agent' and is applied on a case by case basis." An accepted alternative approach applies a fraction of the AEGL-3 value in the absence of specific data on an AEGL-2 effect (*SOP* Section 2.2.2.2.3, Page 43). The defensibility of the approach chosen (use of an MF vs one-third of the AEGL-3 value) hinges on the understanding of the toxic effect: is it an AEGL-2 effect, or is it an AEGL-3 effect that required more than a 4.5-h exposure to be manifested? In this case, the practical result is the same in that the MF chosen is 3; however, it may be preferable to cite the ambiguity inherent in the database and use the "one-third of the AEGL-3 value" approach. If the use of an MF is retained, a stronger justification for the value of 3 should be presented, inasmuch as the *SOP* guidance provides for choosing a value between 1 and 10 (and note item 2 in Section 2.6.2.).

Page 20, lines 9 and 23: These sentences address the POD for developing the AEGL-2 values; however, the first states that it is 4 ppm, and the second that it is 12 ppm. The latter value is directly from the experimental data in the key study, whereas the former was derived after an MF was applied to the experimental data. *SOP* defines the POD as "a toxicologic value . . . obtained for use in AEGL calculations" (Section 2.3.2, Page 52). In other words, the POD is 12 ppm. The distinction between the 12-ppm POD and the modified value of 4 ppm needs to be made clear here and throughout the TSD because the same experimental exposure study is being used to derive both the AEGL-2 and AEGL-3 values. See also the comment regarding Page 29, line 7, below.

Page 20, lines 25- 27: See comment above for Page 18, lines 43-45, regarding potential sensitive subpopulations and the intraspecies UF. Modify as necessary.

Page 21, lines 20-23: See comment above for Page 20, lines 9 and 23. Revise if changes are made in the AEGL-2 derivation that affect the AEGL-3 POD.

Page 21, lines 30-32: "Approximately 90 percent of the values of *n* range between n = 1 and n = 3. Consequently, these values were selected as the reasonable lower and upper bounds of *n* to use when data are not available to derive a value of *n*." The key study appears superficially to have sufficient data to permit calculation of a value for *n*. A statement that describes why the data are insufficient for that purpose would be helpful for the reader who is not familiar with time scaling.

Page 21, lines 34-35: "Since the AEGL-3 values are derived from a longer exposure time of 4.5 hours, the AEGL-3 value for the 10-min exposure is set equal to the AEGL-3 value of the 30-min exposure." As supporting information for the 10-min value, it could be noted that applying the total UF of 10 to the mouse static exposure data (no deaths after a 10-min exposure at 25 ppm) produces the same result.

Page 21, line 41: See comment above for Page 18, lines 43-45, regarding potential sensitive subpopulations and the intraspecies UF. Modify as necessary.

Page 22, line 8: A comparison of the ketene AEGL values with those for phosgene would also be instructive, given the key study's emphasis on the comparable nature of the toxic effects produced.

Page 29, line 7: The POD is identified as an exposure of 4.5 h at 4 ppm. In fact, no such exposure was described by Treon et al.; rather, this value is the result of applying an MF of 3 to the 12-ppm

Copyright © National Academy of Sciences. All rights reserved.

exposure. That needs to be explicitly stated, perhaps on line 5 where the toxicity end point is listed. See also the comment for Page 20, lines 9 and 23, above.

Editorial Comments

Consider using the structural formula as providing more information, especially inasmuch as Table 1 shows the chemical formula.

Review the material presented in the summary paragraphs that address the key study and the derivation of the AEGL tiers to determine whether the relevant information can be presented more succinctly. (Compare, for example, with the Executive Summary for propionaldehyde.)

Page vi, line 3: Insert the CAS number after "Ketene." The corrected sentence should read "Ketene (CAS No. 463-51-4) is a colorless gas. . . ." See *SOP* Section 3.1, page 125.

Page vi, lines 3-17: This paragraph should be reduced. Retain lines 3-9, and delete the balance of the first paragraph. That will keep the information that is likely to be of most interest to the target audience, emergency-response planners and first responders.

Page vi, lines 28-29: "In general, severe effects are absent in animals that survive exposure." This might be a good place to mention the latent period and the similarity to phosgene.

Page viii, Table "Summary of AEGL Values for Ketene": *SOP*, Section 2.9.1, indicates that AEGL values should be rounded to two significant figures. Review the values in the table (and in the derivation sections of the TSD) and adjust as needed.

Page 1, Table 1: Although they are excellent references, the *Merck Index* and the *Kirk-Othmer Encyclopedia of Chemical Technology* are not widely accessible. If the information cited is not peculiar to one of those, consider using something widely accessible, such as the on-line U.S. National Library of Medicine (NLM) databases or the equivalent European Union (EU) on-line databases. When citing these, indicate which database is being referred to (for example, ToxLine) and the date when accessed.

Page 1, lines 8-9: "In water it reacts preferentially with amino groups, phenolic OH-groups and SH groups, even at 0 C." The sentence seems to be contradicted by the entry in Table 1 that states that ketene is not soluble in water. The apparent discrepancy should be resolved.

Page 16, lines 13-14: Insert "and in the delay of onset of its effects on the respiratory system (Treon et al. 1949)," after "Ketene resembled phosgene in its mode of toxic action." See the comment above on emphasizing this aspect of ketene's toxicity.

Page 17, line 1: "Irritation and Sensibilisation." Is there a better term to use here than *sensibilisation*? Do you mean *sensitization*?

Page 17, lines 1-33: This section is a good summary of irritation effects. However, the studies are well described above, and the salient effects are extracted in the derivation sections below, so this section might not be needed.

Page 17, lines 17-18: "These results indicated that ketene is irritating for the eyes and nose, but not for the skin." This summary sentence should provide some statement about the likelihood of irritation at the AEGLs, for example, no irritation was noted in any species at [insert appropriate concentration and duration values].

Page 17, lines 25 and 33: The references here are to Tables 7 and 6, respectively, but Table 7 lists the AEGL-1 values and Table 6 lists nonlethal effects. Are the correct tables being referred to?

Page 23, lines 9-10: "The general standards focus on the prevention of adverse effects on the lungs and the brain. No AEGL-1 values are recommended." Does that perhaps mean that no standards equivalent to the AEGL-1 have been set? The way it is phrased, it is contradicted by Tables 7 and 10.

Page 23, lines 12-17: "The TLV is based on the reasoning that 1ppm was tolerated for several weeks up to 6 months without apparent injury in several animal species (Treon et al. 1949). A concentration of 5 ppm was interpreted as the lowest concentration productive of a clinically relevant physiological response. Finally, it was stated that ketene had similarities in its mechanism of action to that

Copyright © National Academy of Sciences. All rights reserved.

of phosgene (TLV of 0.1 ppm), but appeared to be less toxic on a chronic basis than phosgene. Based on these considerations an 8-h TLV-TWA of 0.5 ppm with a STEL of 1.5 ppm was recommended." That is a summary of the development of the TLV for occupational exposure to ketene. Does it provide useful background information for understanding the derivation of the AEGLs?

Pages 24-25: Validate references to and descriptions of the various standards and guidelines, and cite the current versions.

Page 26, lines 4-5 and lines 14-15: The two references cite the *Kirk-Othmer Encyclopedia of Chemical Technology*, but the first cites the second edition and the second the third edition. Does the second edition contain material (such as the Hasek article cited) that is not in the third edition? If not, both places in the text should cite the third edition.

Comment References

Cameron, G.R., and A. Neuberger. 1937. Ketene as a noxious gas. J. Pathol. Bacteriol. 45:658-660.

Mendenhall, R.M., and H.E. Stokinger. 1959. Tolerance and cross-tolerance development to atmospheric pollutants ketene and ozone. J. Appl. Physiol. 14:923-926.

Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to air-borne ketene. J. Ind. Hyg. Toxicol. 31:209-219.

Wooster, H.A., C.C. Lushbauch, and C.E. Redemann. 1947. The inhalation toxicity of ketene and ketene dimmer. J. Ind. Hyg. Toxicol. 29:56-57.

METHYLENE CHLORIDE

At its meeting on October 27-29, 2009, the committee reviewed the AEGL TSD on methylene chloride. The document was presented by Peter Bos, of RIVM. The following description is excerpted from the executive summary of the TSD:

> Methylene chloride (or dichloromethane: DCM) is a clear colorless, highly volatile liquid with a sweet-pleasant odor, although the odor has also been described as penetrating ether-like. . . . The AEGL-1 is based on the observation in humans . . . that exposure concentrations of 868 and 986 ppm (n=3) may lead to light-headedness and difficulties in enunciation. Those effects were absent at a 1-h exposure to 514 (n=3) or 515 ppm (n=8). Several experimental studies with volunteers have addressed neurobehavioral endpoints that are sensitive subtle effects that may be indicative of more severe effects at higher exposure concentrations but are actually not AEGL-2 effects in themselves. . . . Since no data were available that adequately addresses AEGL-2 endpoints, the highest concentration of 751 ppm (for 230 min) was used as point of departure for AEGL-2 (CNS-effects). . . . No human data that adequately address the level of effects defined by AEGL-3 were retrieved. Evaluation of mortality due to CNS-related effects will be based on animal mortality data.

General Comments

A revised document should be submitted to the committee for review.

The TSD is very thorough and complete, but it needs reorganization to lead the reader through the mechanisms of toxicity better and to explain clearly the change in toxic end points of methylene chloride between CNS effects after shorter exposure to cardiac effects after longer exposure because of the

Copyright © National Academy of Sciences. All rights reserved.

formation of carboxyhemoglobin (COHb) from methylene chloride metabolism. The committee recommends describing the toxic mechanisms by using the figures from the PowerPoint presentation at the October meeting. The figures should be presented in the same format as in Section 4.3, "Mechanism of Toxicity," and the material in that section should be moved to the beginning of Section 2.

The executive summary should be condensed and focused on the salient issues of the chemical and the AEGL values. It is much too long and should be condensed to one or two pages. Summary Table 2 is confusing because two toxic end points were used to set AEGL values. The table should show only final values (now seen in boldface), and values not used should be removed. The authors can provide the end points used to establish each AEGL value. That can be aided by consistently presenting methylene chloride effects first followed by changes in COHb concentrations. Refer to the National Research Council AEGL Volume 8 (NRC 2009), which contains material on carbon monoxide whenever COHb concentrations are discussed as the rationale for the AEGL. It is a documented and established source for COHb concentrations for AEGL-2 and AEGL-3 PODs.

AEGL-1: A better explanation of the selection of the key study is needed. Explain why Stewart et al. (1972) was selected over other studies. It is not clear why the 2-h LOAEL of 195 ppm from the purportedly well-performed study by Putz et al. (1979) was not considered as the POD. In the Putz et al. study, hand-eye coordination, peripheral light response time, and auditory vigilance task (AVT) were statistically significant (Page 10, lines 11-13). On the basis of those data, the 1-h 200-ppm AEGL-1 value may not be protective against AEGL-1 effects. If the Putz et al. study were used as the POD, a 4-h AEGL-1 value can also be derived.

AEGL-2: Satisfactory as written.

AEGL-1 and AEGL-2 Physiologically Based Pharmacokinetic Modeling: The physiologically based pharmacokinetic (PBPK) modeling approach used to develop the AEGL-1 and AEGL-2 is excellent. However, comparison of results of PBPK with the available human data is needed. If the comparison yields model-derived AEGL values inconsistent with the human data (that is, values that are not protective when compared with the human data), explain the discrepancies. As examples, see specific comments below for Page 8, lines 41-42, and Page 57.

AEGL-3: The selection of the POD of 11,000 ppm in rats needs better justification. Because AEGLs are single lifetime exposures, use of multiple-exposure data is not recommended except if there are insufficient single-dose data or in the possible case of fetotoxicity. In the case of methylene chloride, there appear to be sufficient animal data, as presented in Table 6, to define a POD, specifically, data on the guinea pig at 5 h and the rat at 4 h. However, it should be noted that in a multiple-exposure study one rabbit died after a single exposure at 9,464 ppm. The committee recommends that the TSD authors review the original studies cited in the National Toxicology program (NTP) reports.

A single human case of no postsurgery complaint (Page 54, line 7) at an estimated 7,000-9,333 ppm for 3 h was used to support the AEGL-3 value. It is arguable that, because of the sparseness of human data, animal data should be used. Thus, the single case with an estimated concentration under tight medical supervision should not be used again to support the final AEGL-3 value.

On Page 8, line 48, the average COHb in three subjects 1 h after a 2-h exposure at 986 ppm was 10.1%; It was 15% in one subject. The pre-exposure baseline was 1-1.5% (ATSDR 2000). Thus, it appears that a human 2-h AEGL-3 for 15% COHb would not be too far from 986 ppm. In this comparison, the 4-h AEGL-3 of 5,300 ppm would be inadequate.

For the methylene chloride effects, the argument that differences in mortality between rats and humans appear to be small is a lighting-rod argument and needs additional explanation or deletion. Emphasizing the use of the human PBPK model to minimize the difference in pharmacokinetics between rats and humans to decrease the interspecies factor from 3 to 1 is acceptable. We recommend that the TSD authors discuss the reduction of 3 to 1 by explaining that the end-point brain concentration of methylene chloride was decreased by one-third in the PBPK model.

Copyright © National Academy of Sciences. All rights reserved.

Specific Comments

Page vi, lines 9-11: The production data are outdated. Some Internet sources of updates are EPA's *Chemical Summary for Methylene Chloride (Dichloromethane)* from the Office of Pollution Prevention and Toxics (1994) and ATSDR's *Toxicological Profile for Methylene Chloride* (2000).

Page vii, lines 38-39: Are these effects consistent with CNS effects or with carbon monoxide exposure?

Page vii, lines 44-46: "Because the calculated AEGL-1 values at 4- and 8-h (160 and 140 ppm, respectively) are at or above the corresponding AEGL-2 values, no AEGL-1 for these time periods can be recommended." Those values are below the ones stated in the next paragraph not to cause CNS problems. At what concentration does the PBPK model indicate blood saturation and therefore no time effect?

Page vii, lines 50-52: "No effects on reaction time, short term memory, or numerical ability were observed in humans exposed for 4 subsequent 30-min periods to 250, 500, 750, and 1000 ppm DCM, respectively (Gamberale et al. 1975)." Please explain why the TSD authors are using multiple-exposure data.

Page viii, lines 1-4: "The effects are indicative of subtle changes which are neither irreversible nor will cause a serious impairment of escape, and, therefore, are regarded as sub AEGL-2 effects." Could these be considered AEGL-1 effects?

Page viii, lines 4-8: Did the TSD authors consider using the anesthetic data for AEGL-2 in the PBPK model?

Page viii lines 8-13: "Since susceptibility for gross CNS-depressing effects do not vary by more than a factor of 2-3, an intraspecies uncertainty factor of 3 would normally have been used. However, in this case the CNS-effects observed at 751 ppm are very mild and occur at any exposure that is far below that which would cause effects that would impair the ability to escape. Therefore, the intraspecies uncertainty factor was reduced to 1. The human PBPK-model was used to calculate the AEGL-2 values resulting in a maximum brain concentration of 0.137 mM for an exposure of 10 and 30 minutes." It seems that the TSD authors are trying to justify a number. It also seems as though the wrong AEGL-2 POD is being used. How does this compare with one-third of the AEGL-3 POD?

Page viii, lines 26-29: "An interspecies factor of 1 is considered to be sufficient since the differences in susceptibility regarding mortality between species appear to be very small and because a human PBPK-model is used to calculate the external human exposure." Use of a UF of 1 for death as the end point seems too liberal and not adequately justified.

Page 2, lines 15-16: "Because of increasing concern and/or more strict legislation its use in consumer products has declined." What is the current production rate?

Page 2, lines 19-20: "Mean outdoor air concentrations of up to approximately 11 ppb have been reported, with incidental maximum values of about 200 ppb." Under what conditions were those mean outdoor concentrations reported? After a spill? In normal air pollution?

Page 2, lines 32-33: "A recent study by Takeshita et al. (2000) showed that postmortem uptake of DCM vapor may occur." Describe the relevance of that sentence.

Page 4, lines 21-42: The major issue that is not resolved is whether increased concentrations of COHb due to methylene chloride exposures can be a cause of death and, if so, under what exposure conditions. The TSD seems to document CNS depression, but the information on COHb is more anecdotal. This needs to be resolved.

Page 8, lines 41-42: The text states that at 986 ppm, two of three subjects had light-headedness, and one had difficulty in enunciating clearly 1 h after exposure. That suggests that 1,000 ppm for 1-h AEGL-2 would be inadequate.

Page 8, line 48: The average COHb in three subjects 1 h after a 2-h exposure at 986 ppm was 10.1%; it was 15% in one subject. The pre-exposure baseline was 1-1.5% (ATSDR, 2000). Thus, it appears that a human 2-h AEGL-3 for 15% COHb would not be too far from 986 ppm. In this comparison, the 4-h AEGL-3 at 5,300 ppm would be inadequate.

Copyright © National Academy of Sciences. All rights reserved.

Page 10, lines 11-13: In the Putz et al. (1979) study, hand-eye coordination, peripheral light response time, and AVT were statistically significant. On the basis of those data, the 1-h 200-ppm AEGL-1 may not be low enough. If used as a POD, a 4-h AEGL-1 can also be derived.

Page 10, lines 13-14: The TSD text indicates that "The performance for the first two parameters were worse after 4 hours of exposure to DCM than after CO exposure." What conclusions are drawn from that statement?

Page 11, line 1: "The reports described in this section do not reveal any clear effect of DCM exposure up to 751 ppm on neurobehavioral parameters." This summary's mention of no clear effect up to 751 ppm may be confusing inasmuch as 514 ppm is used as a POD for deriving the AEGL-1. Also, is the exposure up to 751 ppm for an 8-h work shift?

Page 11, lines 47-49: The heart does not appear to be a target organ for methylene chloride exposures.

Page 14, lines 28-32: "DCM has been used in the 1920s and for sometimes afterwards for its anesthetic or analgesic properties. It was reported that it can lead to narcosis within 30 min at concentrations of about 2 Vol.%. Exposure to an estimated concentration of 7000-9333 ppm for 3-h induced a light narcosis satisfactory for surgical procedures. The narcotic dose appeared to be very close to the toxic dose. An average amount of 26.6 g DCM has been satisfactorily used as an obstetric analgesic." Why not use this as the AEGL-3 and one-third of it as the AEGL-2?

Page 14, lines 42-44: "It is noted that in some cases high COHb levels up to 40% are measured without serious complaints. The reported COHb levels could not be linked to effects in a dose-related way in any of these cases." On the basis of that information, why was COHb concentration chosen as an end point?

Page 16, lines 42-47: "Groups of 20 white Swiss mice were exposed to actual DCM concentrations of 11,485, 13,730, 13,126, and 15,400 ppm for 7 h (Svirbely et al. 1947). A steep dose-response was observed with death rates of 0/20, 2/20, 4/20, and 18/20, respectively." It looks as though the death rate is flat to a threshold and then spikes quickly. A comment would be appropriate.

Page 17, line 29, and Table 3: We recommend using a table that summarizes all the LC_{50} exposure data, times, results, and so on, to justify better the statement of a steep lethality curve.

Page 17, lines 32-33: "The dose-response relation for lethality is very steep, with an increase in mortality from 0 to 100% within a twofold increase in exposure concentration." That statement is not supported by the data presented in the TSD.

Page 26, lines 5-7: "CO is known to readily cross the placenta and is reported to be eliminated at a slower rate than from the maternal circulation. The developing fetus may be more susceptible to CO than the mother. Hence, a risk may also be present following exposure to DCM (Bentur et al. 1994)." The issue should be methylene chloride first and then carbon monoxide.

Page 27, lines 1-2: "The respective blood CO concentrations were comparable, 167 and 160 nmol/mL (4.7 and 4.5 μg/mL)." What would the value be if expressed as percent COHb (the unit used to present all the other data)?

Page 31, line 39, through Page 32, line 19: These paragraphs describe methylene chloride carcinogenicity assessments (lifetime risk to humans) conducted by EPA, the World Health Organization, and the EU. What does that mean for a single exposure?

Page 32, lines 39-40: "The predominant effect of a single exposure to DCM is CNS-depression (see Table 3 for summary). No large interspecies differences in response appear to be present." If the TSD authors are referring to Table 3, "no large interspecies differences" is true for three species of rodents. However, what about humans, nonhuman primates, dogs, and so on?

Page 36, Table 7: Table 7 lists peak COHb concentrations in humans after a single methylene chloride exposure. They seem much lower than those reported after accidental exposures. Is it possible that the accidental-exposure data are in error?

Page 37, lines 14-15: "The DCM concentrations in exhaled breath were approximately twofold higher during and after 200 ppm exposure compared to 100 ppm exposure values." Does that mean that absorption is a percentage of methylene chloride?

Copyright © National Academy of Sciences. All rights reserved.

Page 37, lines 36-37: "Approximately 70 to 100% was excreted with the first urine sample collected within 30 min postexposure." Is the sentence referring to a metabolite or to methylene chloride itself?

Page 37, lines 47-49: "Further, despite the fact that this pathway becomes saturated, very high levels of up to 50% COHb have been reported in specific cases (section 2.2.1)." Are the data suspect?

Page 46, line 3: The data do not seem to support the statement "COHb formation, via biotransformation to CO" as important.

Page 47, lines 40-41: "As pointed out previously, clear interspecies differences in metabolic rate exist, predominantly in the rate of the GST-pathway that is much higher in mice hepatocytes compared with other species." Previously, the TSD stated that there is not much difference among species (see comment for Page 32, lines 39-40).

Page 49, lines 30-41: Winneke (1974) should be cited in this section for further support. The reference is Winneke, G. 1974. Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance. Pp. 130-144 in Behavioral Toxicology: Early Detection of Occupational Hazards, C. Xintaras, B.L. Johnson, and I. de Groot, eds. DHEW (NIOSH) 74-126. U.S. Department of Health, Education and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Washington, DC.

Page 51, lines 15-17: "An exposure level of 4% COHb was also considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness, and dyspnea." The effects listed seem to be attributable primarily to CNS depression, not increased COHb. Also, the text should be revised so as not to imply that 4% COHb provides protection against acute neurotoxic effects—instead of causing the effects.

Page 51, lines 22-29: This paragraph describes CNS depression as "the second relevant endpoint for DCM" exposure. Is CNS depression the primary or secondary effect? It seems that it would be the primary effect.

Page 51, lines 44-45: "The effects observed are not considered to be severe enough to cause a serious impairment of escape, and, therefore, are regarded as sub AEGL-2 effects." Are the effects indicative of an NOAEL?

Page 53, lines 37-41: Was any UF applied? If so, state and discuss.

Page 54, line 7: A single human case of no postsurgery complaint at an estimated 7,000-9,333 ppm for 3 h was used to support the AEGL-3. It is arguable that because of the sparseness of human data, animal data should be used. This single case with an estimated concentration under tight medical supervision should not be used again to support the final AEGL-3.

Page 54, line 31-41: Delete text beginning with "However Heppel et al. (1944)." We recommend using only single-exposure studies. Table 6 seems to provide sufficient data to support a POD from the results of methylene chloride exposure (no COHb).

Page 57: The AEGL-2 for an 8-h exposure is above both the permissible exposure limit and the TLV for healthy workers. AEGLs should protect the general population, including infants and sensitive subpopulations. Please explain why the AEGL-2 for an 8-h exposure is higher than the suggested occupational exposure limits.

Editorial Comments

Page viii, Table: For the table "Summary of Proposed Values for Methylene Chloride," follow the table format given in *SOP*. Column 1 should combine an AEGL with its associated generic descriptor (for example, "nondisabling"). The specific effect (that is, "CNS effects") should be described in the last column, "Endpoint (Reference)."

Page 2, lines 33-38: The animal data need to be moved to the animal section.

Page 8: In Section 2.2.2, "Experimental Studies," show a summary table of the results.

Copyright © National Academy of Sciences. All rights reserved.

Page 8, lines 30-31: "100 min (2-h exposures)." Is it 100 or 120 min?

Page 10, line 40, through Page 11, line 3: Why isn't this included in the occupational studies?

Page 25, lines 23-24: Reference?

Page 26, Table 4:

1. A number of relevant studies should be added, including Flury and Zernik (1931), on dogs (6,100 ppm, 2 h, light narcosis) and mice (14,000 ppm, 8-15 min); Landry et al. (1981), on rats (8,000 ppm, 6 h, tremors); and Nuckolls (1933), on guinea pigs (wide range of concentrations and exposure periods).
2. Include the durations of exposure: Balmer et al. (1976), 5 days; and Heppel et al. (1944), 7.5 weeks, 6 months, and 1-h effects on monkeys at 9,464 ppm.
3. Add to Ulanova and Yanovskaya (1959) the effect of "paralysis."

Page 32, lines 26-27: Percent of what?

Page 33, Table 6:

1. Under "Nonlethality Data" and "Effect," add the specific effects.
2. Add Bonnet et al. (1980)—13,000 ppm, 1/12 dead after 6 h.
3. NTP (1986), mouse study results**:** Are these data correct? It is suspicious that one could measure the concentrations that accurately and that the deaths would increase from 0 to over 50% with only a 1% increase in concentration. Please examine the original study.

Page 34, lines 16-38: This is repeated text. Delete.

Page 37, lines 51-53: This is not a complete sentence. Also, many of the exposures in Section 2.2.1 involved methanol and acetone.

Page 51, lines 8-12: Refer to the 2009 National Research Council report on AEGLs (Volume 8).

Page 52, Section 6.2 (also Page 54, Section 7.1): Refer to the National Research Council carbon monoxide AEGL in Volume 8.

Page 52, lines 28-29: Sentence says "increase," but the COHb level is set at 4%, not an increase of 4%.

Page 52, lines 40-42: An "increase" in the data is not apparent. Rephrase the text to state simply they are higher.

Page 53, lines 49-51: Delete sentences beginning with "Therefore, the interspecies uncertainty factor was" and ending with "would conflict with these data."

Page 53, lines 2-7: Begin new paragraph with the text beginning with "The toxic end point of interest" and move it to follow the paragraph ending on line 35 with "surgical procedures (3-h exposure to ≥7000 ppm)."

Page 54, lines 12-18: Refer to Table 6. Note that the NTP report shows dramatic increases in deaths with only a 1% change in concentration. This seems suspicious. See comments above for Table 6.

Page 55, lines 6-7: Delete sentence beginning with "AEGL-3 values will be derived for."

Page 55, lines 19- 23: Replace text beginning with "Regarding mortality due to CNS-depression" with "Due to a lack of reliable exposure data associated with human deaths, no adequate…"

Page 55, lines 32-33: The argument is stronger if based strictly on the use of the human PBPK model rather than using the starting comment that differences in mortality among species appear to be small. Switch the sequence of the arguments stressing use of the human PBPK.

Comment References

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for Methylene Chloride (Update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. September 2000 [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp14.pdf [accessed Jan. 25, 2010].

Balmer, M.F., F.A. Smith, L.J. Leach, and C.L. Yuile. 1976. Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. Am. Ind. Hyg. Assoc. J. 37(6):345-352.

Copyright © National Academy of Sciences. All rights reserved.

Bentur, Y., E. Zalzstein, and G. Koren. 1994. Occupational exposures known to be human reproductive toxins. Pp. 399-424 in Maternal-Fetal Toxicology: A Clinician's Guide, 2nd Ed, G. Koren, ed. New York: Marcel Dekker.

Bonnet, P., J.M. Francin, D. Gradisky, G. Raoult, and D. Zissu. 1980. Détermination de la concentration léthale50 des principaux hydrocarbures aliphatiques chlorés chez le rat. Arch. Mal. Prof. 41:317-321.

EPA (U.S. Environmental Protection Agency). 1994. Chemical Summary for Methylene Chloride (Dichloromethane). Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. August 1994 [online]. Available: http://www.epa.gov/chemfact/s_dcm.txt [accessed Jan. 25, 2010].

Flury, F., and F. Zernik. 1931. Methylenchlorid. Pp. 311-312 in Schädliche Gase, Dämpfe, Nebel, Rauch- und Staubarten. Berlin: Verlag von Julius Sprenger.

Gamberale, F., G. Annwall, and M. Hultengren. 1975. Exposure to methylene chloride. II. Psychological functions. Scand. J. Work Environ. Health 1(2):95-103.

Heppel, L.A., P.A. Neal, T.L. Perrin, M.L. Orr, and V.T. Porterfield. 1944. Toxicology of dichloromethane (methylene chloride). I. Studies of effects of daily inhalation. J. Ind. Hyg. Toxicol. 26(1):8-16.

Landry, T.D., J.D. Burek, T.J. Bell, and E.L. Wolfe. 1981. Methylene chloride: An acute inhalation toxicity study in rats. Midland, MI: Dow Chemical Company (Internal report).

NRC (National Research Council). 2009. Acute Exposure Guideline Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: The National Academies Press.

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP-TR-306. U.S. Department of health and human Services, Public Health Service, National Institute of Health, Bethesda, MD.

Nuckolls, A.H. 1933. The Comparative Life, Fire, and Explosion Hazards of Common Refrigerants. Misc. hazards No. 2375. Chicago, IL: National board of Fire Underwriters, Underwriter's Laboratories.

Putz, V.R., B.L. Johnson, and J.V. Setzer. 1979. A comparative study of the effects of carbon monoxide and methylene chloride on human performance. J. Environ. Pathol. Toxicol. 2(5):97-112.

Stewart, R.D., T.N. Fisher, M.J. Hosko, J.E. Peterson, E.D. Baretta, and H.C. Dodd. 1972. Experimental human exposure to methylene chloride. Arch. Environ. Health 25(5):342-348.

Svirbely, J.L., B. Higman, W.C. Alford, and W.F. von Oettingen. 1947. The toxicity and narcotic action of mono-chloro-mono-bromo-methane with special reference to inorganic and volatile bromide in blood, urine and brain. J. Ind. Hyg. Toxicol. 29:382-389.

Takeshita, H, K. Mogi, T. Yasuda, S. Mori, Y. Nakashima, T. Nakajima, H. Akuzawa, S. Nakajo, Y. Hirota, and K. Kishi. 2000. Postmortem absorption of dichloromethane: A case study and animal experiments. Int. J. Legal Med. 114(1-2):96-100.

Ulanova, I.P., and B.I. Yanovskaya. 1959. Changes in the ascorbic acid content of the internal organs of white rats in response to the action of chlorinated hydrocarbons. II. Effect of methylene chloride. Bull. Exp. Biol. Med. 48(1):846-849.

Winneke, G. 1974. Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance. Pp. 130-144 in Behavioral Toxicology: Early Detection of Occupational Hazards, C. Xintaras, B.L. Johnson, and I. de Groot, eds. DHEW (NIOSH)74-126. U.S. Department of Health, Education and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Washington, DC.

Copyright © National Academy of Sciences. All rights reserved.

PROPANE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on propane. A presentation on the TSD was given by Peter Bos, of RIVM. The following is excerpted from the executive summary of the TSD:

> Propane is a colorless and odorless gas. . . . The AEGL-1 derivation is based on observations in a study with volunteers on the warning properties of short exposures to propane. . . . The anesthetic potency for propane is estimated to be lower than for butane [therefore] the AEGL-1 values for propane should therefore not be lower than those for butane, which are based on the same study. The AEGL-2 derivation is based on cardiac sensitization. In a well-performed cardiac sensitization test beagle dogs were exposed to a propane concentration. The same study as for AEGL-2 is used as starting point for AEGL-3.

General Comments

This document can be finalized if the committee's recommended revisions are made.

Specific Comments

Page xi, Line 48 (also Page 8, line 38, and Page 10, line 8): The statement that "the dog is a good model for the human heart" remains controversial in toxicology inasmuch as there are cases in which the dog is not very sensitive. We recommend revising the text to say that because the dog is a sensitive model of cardiac sensitization and no substantial interspecies differences have been observed among various animal species, a combined factor of 3 was used to account for interspecies and intraspecies uncertainty or differences in susceptibility.

Page 5, line 10: "Neurotoxicity." This section was left blank. Case reports have suggested neurotoxicity and should be mentioned, although limitations should also be described.

Page 7, lines 8-10: "Because of consistency reasons the AEGL-1 values for propane are derived in a similar way as for butane. The reasoning for butane for time-scaling is therefore also considered applicable to propane and is summarized below." If the butane data are poor, that statement is not justified.

Page 8, lines 38- 39: These sentences describe the dog model for the human heart as "a conservative test." Explain why it is considered a conservative test.

Page 8, lines 39-40: How many dogs were studied? In Section 7.2, lines 29-36, it appears that two or seven of 12 responded. The UF is not well justified if only 12 dogs were studied and two or seven responded. Please clarify.

Page 10, lines 8-10: "Because the dog appears to be a good model for the human heart, an interspecies UF of 1 was applied. Because this is a conservative test, an intraspecies UF of 3 was applied to protect sensitive individuals." Statistics do not support a UF of 1 (see suggested additional information below for Page 8, line 27, and Page 9, line 31).

Editorial Comments

Make certain that any reference to butane is correct and that there is no ambiguity in statements.

Copyright © National Academy of Sciences. All rights reserved.

Page 1, line 22: Clarify that the "autoerotic fatalities" are considered to be accidental deaths involving inhalation of propane.

Page 2, lines 7-8: "A few reports provide information of quantitative (Pragst et al. 1991; Graefe et al. 1999) or qualitative (Haq and Hameli 1980) propane concentrations in tissues." This sentence is unclear and should be rewritten.

Page 2, lines 20-46: Section 2.2.2, "Experimental Studies," is too wordy and should be shortened.

Page 2, lines 20-23: If the number of subjects in each case is important, that information should be clearly described at the outset. Otherwise, delete the section beginning with "eight volunteers" and ending with "9 days over 2 weeks."

Page 3, lines 3-5: The sentence beginning with "Although several publications" needs further explanation.

Page 3, lines 46-50, and Page 4, lines 1-8: Is so much detail needed?

Page 3, lines 48-40: The sentence beginning with "Actual concentrations" needs further explanation.

Page 5, Line 16: The section "Genotoxicity" indicates that "Propane appears to be negative in the Ames test." We suggest revising the text to read as follows: "Propane was found to be negative for reverse mutations in the Ames test."

Page 6, line 32: "For the low exposure group, the butane concentration. . . ." Propane or butane?

Page 6, lines 48-50: The sentence beginning with "Firstly, the concentration-response." This will depend on the quality of the data on butane. If they are equally skimpy for butane, this statement is not justified.

Page 7, line 29 (also line 40): What is "effect-size?"

Page 8, lines 27-31, and Page 9, lines 31-36: These sentences should be reworded for clarity. We suggest using the following revised wording**:** "The cardiac-sensitization potential of propane was evaluated in beagles exposed in a protocol developed by Reinhardt et al. (1971). Briefly, just before the exposure, dogs received injections of epinephrine, and each group of six to 12 dogs was exposed to a different concentration of propane for 5 min, at which time a challenge injection of epinephrine was administered, and electrocardiography was used to evaluate the presence of cardiac sensitization. Under those exaggerated conditions, none of six dogs exposed at 50,000 ppm showed cardiac effects, but two of 12 dogs exposed at 100,000 ppm showed effects, and seven of 12 dogs exposed at 200,000 ppm showed effects. Those findings were confirmed in a similar study (Clark and Tinston 1982) in which groups of four to seven dogs per dose were exposed to several propane concentrations, and this resulted in an EC_{50} for cardiac sensitization of 180,000 ppm (95% confidence interval, 120,000-260,000 ppm)."

Page 8, lines 35-37: We suggest replacing the first sentence with the following text: "The relevant cardiac-sensitization study used an optimized conservative model in the beagle. The test involved the injection of epinephrine into the dog before and during exposure at very high concentrations. The administered epinephrine was given at a dose rate about 10 times higher than that calculated to occur in humans in times of stress (Brock et al. 2003). Although the model is very sensitive, it is relevant to humans because humans exposed to high concentrations of several substances may develop cardiac arrhythmias."

Comment References

Brock, W.J., G.M. Rusch, and H.J. Trochimowicz. 2003. Cardiac sensitization**:** Methodology and interpetation in risk assessment. Regul. Toxicol. Pharmacol. 38(1): 78-90.

Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some haligenated and non-halogenated hydrocarbons. Hum. Exp. Toxicol. 1(3):239-247.

Copyright © National Academy of Sciences. All rights reserved.

Graefe, A., R.K. Müller, R. Vock, H. Trauer, and H.J. Wehran. 1999. Fatal propan-butane poisoning [in German]. Arch. Kriminol. 203(1-2):27-31.

Haq, M.Z., and A.Z. Hameli. 1980. A death involving asphyxiation from propane inhalation. J. Forensic Sci. 25(1):25-28.

Pragst, F., M. Prügel, J. Vogel, and S. Herre. 1991. Investigation of two fatal cases caused by inhalation of propane and chloroethane. Schmiedeberg's Arch. Pharmacol. 344 (Suppl 2): R127. [Abstract].

Reinhardt, C.F., A. Azar, M.E. Maxfield, P.E. Smith Jr., and L.S. Mullin. 1971. Cardiac arrhythmias and aerosol "sniffing". Arch Environ. Health 22(2):265-279.

PROPIONALDEHYDE

At its meeting held on October 27-29, 2009, the committee reviewed the AEGL TSD on propionaldehyde. A presentation on the TSD was given by Joanne Nijhof, of RIVM. The following is excerpted from the executive summary of the TSD:

> Propionaldehyde is a low-boiling, colorless liquid. . . . Toxicity and mortality data are limited. The main effects in animal studies were irritation of the airways at low concentrations and CNS effects and mortality at higher concentrations. . . . The AEGL-1 derivation is based on the effects described in [a] human volunteer study. . . . Mild irritation of the mucosal surface was found at the only tested concentration of 134 ppm after a 30 minutes exposure. . . . The AEGL-2 derivation is based on the combined repeated dose and reproduction toxicity study. . . . The AEGL-3 derivation is not based on data from experiments with propionaldehyde because the available data are very limited and/or of doubtful quality. The data on propionaldehyde was considered to be insufficient for AEGL-3 setting. Qualitative much better data were available for the related substance acetaldehyde.

General Comments

A revised document should be submitted to the committee for review.

The TSDs for propionaldehyde and acetaldehyde should be combined into one document, and the revised document should be submitted to the committee for review. A recent example of such combination is the combination of the phosphine and metal phosphides TSDs into one document (see AEGL Volume 7, NRC 2009).

The database on propionaldehyde is very sparse. On the basis of the reported effects, it appears that a reasonable justification can be developed for the hypothesis that the toxicities of acetaldehyde and propionaldehyde are similar and that acetaldehyde data therefore can be used to derive propionaldehyde AEGLs. However, support for that hypothesis as it is presented in the current TSD is minimal; more information needs to be presented to justify the use of the acetaldehyde data in this way. Note that contrary data must be identified and addressed because such data can affect the uncertainties inherent in the comparison.

An important issue not currently addressed for propionaldehyde is the potential for subpopulations that could be sensitive to propionaldehyde exposure and the influence of this on the values selected for UFs. Comparison with acetaldehyde effects should assist in assessing that potential.

The committee understands that the issue of the utility of RD_{50} data for derivation of AEGLs is being addressed by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances. For the purposes of the propionaldehyde TSD, the available RD_{50} data should be discussed with regard to their application to propionaldehyde toxicity and their utility for deriving or supporting AEGLs.

Copyright © National Academy of Sciences. All rights reserved.

Specific Comments

Page 2, line 42: Given the 34% concentration, was this an oxygen-deprivation effect, or could oxygen deprivation have contributed to the effects seen?

Page 3, lines 16 and 24: As above.

Page 3, Table 2: Add acute-lethality data to the table from Smyth et al. (1951), 16,000 ppm, 2.5 h, 6/6 dead and 4,000 ppm, 4 h, 0/6 dead; Izmerov et al. (1982), 8,938 ppm, LC_{50}; and Driscoll 1993, 2,592 ppm for 20 days, 0 deaths.

Page 4, Line 18: Given the discussion of the RD_{50} below, it might be helpful to note that 72 ppm is about 1% of the RD_{50}.

Page 5, lines 34-35: Was the mouse strain used by Alarie 1981 reported? If so, it should be noted here.

Page 5, line 48: It might be helpful to note that these values are about 32% and 23% of the respective RD_{50} values. Also, because this refers to concentrations that were "without an effect on the respiratory rate," confirm that the correct values were obtained from the regression line.

Page 6, Table 3: Insert text to indicate that Salem and Cullumbine (1960) saw irritation responses were seen in rabbits, mice, and guinea pigs and that Egle (1972) saw cardiac effects at 8,440 and 84,440 ppm.

Page 7, line 3: Parental effects should be described above in the relevant toxicity section; only the specific effects on reproduction and development should be here (except for reference to maternal toxicity that had a bearing on fetal effects).

Page 7, lines 5-6: The range-finding study data cited here do not appear in the text of the reference provided. Is there a separate source? If so, it should be cited.

Pages 9-11: These sections should be used to expand on and justify the hypothesis that propionaldehyde is similar in toxicity to acetaldehyde. This argument is central to the derivation of the AEGL-3 values and supports the AEGL-2 and AEGL-1 values (compare the proposed values for both chemicals). It is of specific concern that there is no discussion of the potential subpopulations that are particularly sensitive to the effects of exposure to propionaldehyde. Because the TSD relies on comparison with acetaldehyde to derive the AEGL-3 values, and these effects, if present, would influence the AEGL-2 and possibly the AEGL-1, some discussion of acetaldehyde-sensitive subpopulations (see the acetaldehyde TSD) and their implication for propionaldehyde-sensitive subpopulations is required. The discussion should also be reflected in the derivation sections below.

Page 9, lines 17-20: It is clear what happens to the aldehyde in the first half of this paragraph, but is there information on what happens when the thiohemiacetal is formed?

Page 9, line 22: Two studies are described in some detail, and a summary paragraph is provided. Although interesting, that amount of detail does not add to the understanding of the AEGLs inasmuch as the effects described are not connected in this discussion to the AEGL end points and the derivation of AEGL values. The two paragraphs detailing the studies could be deleted, and the summary paragraph should be expanded somewhat to cite and briefly describe the two studies, with more emphasis and detail on what their findings mean for the development of the AEGL values.

Page 10, line 4: The discussion in this paragraph makes an argument regarding the utility of RD_{50} data for setting AEGL values. Although useful, it is misplaced here; the discussion should focus on RD_{50} values for propionaldehyde and their relationship both to other toxic end points for propionaldehyde (and acetaldehyde) and to the derivation of AEGL-2 values. Consider condensing and relocating to the section of the TSD that discusses the rationale for setting AEGL values. Note the relevant comments below that refer to Page 12, line 28, and Page 13, lines 8-11.

Page 10, lines 12-14: This is a good conclusion to the discussion, but then RD_{50} data are discussed in the "Summary of Animal Data Relevant to AEGL-1." That seems inconsistent with the point of discussion in this paragraph, that RD_{50} data are not useful.

Page 10, lines 29-30: Two things should be considered in evaluating the Smyth et al. (1951) data: because one set of results that differs does not necessarily call into question all other results, specific

Copyright © National Academy of Sciences. All rights reserved.

justification for rejecting data is required; and Smyth et al. also did an oral LD_{50} study and reported that acetaldehyde was much less toxic than propionaldehyde—acetaldehyde LD_{50}, 1,930 mg/kg, and propionaldehyde LD_{50}, 1.4 mg/kg. The latter involved a different route of exposure and may indicate an important difference between chemicals and be a factor in assessing the degree of uncertainty in basing AEGL derivations on close analogy with acetaldehyde. The data from Salem and Cullumbine (1960) should also be discussed here because these aerosol exposures resulted in lethal effects at concentrations (1,207 ppm for 4-5 h) much lower than those reported by other studies that used vapor exposures, including that of Smyth et al. (1951).

Page 10, lines 32-35: Sim and Pattle (1957) could be cited in support, given their (brief and sketchy) description of the effects of the sequence of acetaldehyde, propionaldehyde, butyraldehyde, and isobutyraldehyde.

Page 12, lines 13-14: There is a terminologic issue here in how to describe "mild (sensory) irritation"—as an AEGL-1 end point or as a sub-AEGL-1 effect. Compare, for example, *SOP* Page 41, lines 9 and 27-28, and Page 42, line 12, with *SOP* Page 32, lines 11-15, and the diagram on Page 33. The "weight of the evidence" indicates that mild (sensory) irritation is considered a sub-AEGL-1 effect and is a toxicologic end point suitable for deriving AEGL-1 values. See specifically the first two paragraphs (Page 40) of *SOP* Section 2.2.2.1, and compare with the brief description in Sim and Pattle (1957). To reduce potential confusion, we suggest modifying the sentence to read ". . . severity of this effect is less than the AEGL-1 level, and. . . ."

Page 12, lines 16-17: *SOP* Section 2.5.3.4.4 calls for a description of the mode of action, in this case direct irritation, and a discussion of *why* the response is unlikely to differ. The latter discussion is not present, but *SOP* calls for it (this is also true for the equivalent interspecies UF). It is particularly important for direct-acting irritants for which there is some question of whether there may be sensitive subpopulations; see *SOP,* Page 87, on respiratory irritants, such as sulfur dioxide, and appropriate UFs.

Page 12, line 28: RD_{50} data are presented as relevant to the AEGL-1 on Page 12, lines 2-5, but no RD_{50} data are presented as relevant to the AEGL-2, for which it might be much more relevant. That is inconsistent. The data are described in the section "Animal Toxicity Data" and should be addressed here, even if they are not used for the derivation. Because the RD_{50} end point addresses a specific AEGL-2 effect, impairment of escape ability (*SOP* Section 2.2.2.2, Page 42), how the RD_{50} data on propionaldehyde (and on acetaldehyde) fit with the other AEGL-2-relevant data should be discussed here. If the data are not used for the AEGL-2 derivation, the specific reasons should be detailed. See the comment for Page 10, line 4, above.

Page 13, line 7: The Driscoll range-finding data are referred to but without citation; see comment above for Page 7, lines 5-6, regarding the source of the data.

Page 13, lines 8-11: No acute-exposure studies were deemed adequate for the derivation of AEGL-2s, apparently because no adverse effect was considered except histologically demonstrated damage to the nasal epithelium (see Page 17, lines 27-30). Although multiple-exposure studies have been used to derive AEGLs (*SOP* Section 2.5.3.2.9, Page 74), and end points that were neither incapacitating nor irreversible have been used (*SOP* Section 2.2.2.2.2, Page 43), more consideration should be given to the results of the other acute-exposure studies reviewed, if only to indicate the extent to which the results of the studies are (or are not) consistent with the proposed AEGL-2s.

The propionaldehyde data do not meet the specific test for setting AEGL-2s by using a fraction of the better-supported AEGL-3s (see *SOP* Section 2.2.2.2.3, Page 43), but the fact that one-third of the proposed AEGL-3s are very similar to the derived AEGL-2s provides some additional confidence in the derivation. Additional support from among the propionaldehyde acute-exposure studies, perhaps the RD_{50} data and studies reported in the acetaldehyde TSD, should be identified.

The reference to the TSD for acetaldehyde should be expanded to include citations, including the citation of the study referred to in that TSD and listing the Web site for the TSD for easy access (http://www.epa.gov/opptintr/aegl/pubs/acetaldehyde_%20interim_12_2008.v1_pdf.pdf).

Page 14, lines 2-13: This discussion indicates that the Salem and Cullumbine (1960) data are of poor quality and are not used for the derivation of AEGL-3s. This is the only statement regarding the

Copyright © National Academy of Sciences. All rights reserved.

quality of these data, and some support for the assertion should be offered. Note that the data from this study reported in Table 4 of the TSD are consistent with the hypothesis that the toxicity of propionaldehyde is similar to but somewhat less than that of acetaldehyde. It may be worth comparing the data points from that study with the AEGL-3s**:** Salem and Cullumbine used 2,868 mg/m^3 or 1,207 ppm and had 100% mortality in rabbits and mice after 4-5 h of exposure; the AEGL-3s are 1,100 ppm for 30 min and 530 ppm for 4 h. Although they are insufficient by themselves for deriving AEGL-3s, some explanation should be provided as to how they affect the derivation or why they do not.

Page 14, lines 15-20: This paragraph lays out an appropriate approach to the derivation of the AEGL-3s. The argument needs to be strengthened; see the comment above for Pages 9-11, "Special Considerations," on expanding the comparison with acetaldehyde. By elaborating on and providing support for the argument that acetaldehyde and propionaldehyde are comparable in toxicity, the assertion on line 19 can be justified. Note that data that do not support this argument and the uncertainties introduced by the data must be addressed.

Page 17, lines 30-31: This last sentence raises the question of whether there are sufficient data to set AEGL-2 and AEGL-3 values (AEGL-1 is based on adequate human data), inasmuch as the one good study is a repeated-dose or subchronic study used for AEGL-2 derivation. Data on propionaldehyde were deemed unsuitable for deriving AEGL-3s, and these were set by assuming that the chemical is no more toxic than acetaldehyde and adopting its values.

Page 32, Appendix D: Perceptible odor can be helpful in providing initial warning, and calculating a level of odor awareness (LOA) provides some quantitation for a typically qualitative measure. However, it is important to note that habituation to odors does occur and is sometimes complicated by temporary loss of the sense of smell. If an LOA is provided, a cautionary note should accompany it.

Editorial Comments

Cover Page: Consider using the structural formula to provide more information, especially inasmuch as Table 1 shows the chemical formula.

Executive Summary: The general approach is good, but the detail in the derivation paragraphs, such as the time-scaling, could be reduced.

Page 1, lines 3-4: Confirm that the phrasing "an addition of nucleophiles, an oxidation and a reduction" is the correct description of the chemical process.

Page 1, Table 1: Consider including the saturated vapor concentration, which can be calculated if the vapor pressure is available; see Perez, C. and S. C. Soderholm (1991). Some Chemicals Requiring Special Consideration When Deciding Whether to Sample the Particle, Vapor, or Both Phases of an Atmosphere. Appl Occup Environ Hyg 6(10): 859-864. The *Merck Index* and *Beratergremium für umweltrelevante Altstoffe* are excellent references but are not widely accessible. If the information cited is also provided in other references, consider using something that is widely accessible, such as the on-line U.S. National Library of Medicine (NLM) databases or their EU equivalents. When citing these, indicate which database (e.g., ToxLine) and the date accessed.

Odor: suffocating odor: Was any source identified for this description or any indication of relative concentration? Nothing is stated in the section on human toxicity, nor is it addressed in Appendix D.

Explosive: Use the abbreviation UEL instead of the phrase "Upper explosion limit."

Conversion factors: When calculated by NTP with the standard industrial-hygiene value of 24.45 for RxT (the product of the gas constant in the ideal gas law and absolute temperature), slightly different values are obtained**:** 1 mg/m^3 = 0.42 ppm and 1 ppm = 2.38 mg/m^3. Consider recalculating these, at least in the cases in which it is easy to do, rather than accepting the value in a reference. Throughout

Copyright © National Academy of Sciences. All rights reserved.

the text, where values in ppm are provided in addition to values in mg/m^3, if the values are provided by the author of the reference, consider recalculation to verify that the calculation was done correctly.

Page 2, line 18: For chemicals with limited databases, such as this one, it may be helpful to the reader to include at the beginning a summary statement regarding whether and to what extent studies directly relevant to setting AEGL values were found, for example, studies that dealt with acute dose-effect relationships or repeated-dose studies that included first-day observations. The two summary slides from the presentation to the committee ("Toxicological Database for Propionaldehyde" Parts 1 and 2) provide a good basis for this kind of summary statement. The second and third paragraphs of the Executive Summary also do a good job of summarizing.

Page 8, lines 7-8: The source of the genotoxicity data is listed as "as cited in BUA 1996"; were the primary references not available to cite directly?

Page 8, line 48: Insert the concentration that guinea pigs were exposed to here, or state that it was the same as for mice and rabbits.

Page 10, Table 4: In the first cell, check the spelling of "deference" and the concentration units. In the last row, express the concentrations in full rather than in scientific notation. Include the Appelman (1982) data.

Page 12, line 38: Driscoll (1993) identifies the high concentration as 1,522 ppm; see page 14 of that report.

Page 13, line 35: Insert the calculated ppm value for comparison. Indicate the extent of mortality in mice and rabbits (100%?) inasmuch as mortality in guinea pigs is listed as 15%.

Page 15, line 9: The TLV for propionaldehyde was proposed by ACGIH in 2000 and adopted in 2002. Consult the current *Documentation of the Threshold Limit Values and Biological Exposure Indices* . References used were Steinhagen and Barrow (1984), Gage (1970), and studies from Bushy Run Research Center, which may be the ones cited as Driscoll (1993).

Page 17, lines 1 and 6: The current ACGIH TLVs are listed in *The 2009 TLVs and BEIs* booklet; the current documentation for these values is the *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 7th edition, 2001, with supplements for 2002-2009.

Page 19, line 4: What is the reference "GKNT"? If it stands for the Center for International Projects, that should be indicated by placing the letters in parentheses.

Page 19, lines 19-20: This database is now available on line through the NIOSH databases Web site, http://www.cdc.gov/niosh/database.html.

Page 19, line 21: The NLM toxicology databases are accessible through the Environmental Health and Toxicology web site, http://sis.nlm.nih.gov/enviro.html. The specific database used should be indicated.

Appendix C
Derivation Summary Tables

AEGL-2: Exposure Route/Concentrations/Durations Block, and Effects Block: The high concentration is shown as 1,453 ppm, whereas the reference shows 1,533 ppm.

Page 32, line 4: What is the meaning of "established at III"?

Page 32, line 16: Citations for this and the other standards mentioned in this appendix would be appropriate, including Web sites if available.

Page 32, line 21: "a Level 1 odor threshold" should be defined, or the specific reference or standard should be indicated; as phrased now, it is not clear whether it refers to the Japanese triangle method or the NVN2820 standard.

Copyright © National Academy of Sciences. All rights reserved.

Comment References

ACHIH (American Conference of Governmental Industrial Hygienists) 2001. Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Alarie, Y. 1981. Dose-response analysis in animal studies: Prediction of human responses. Environ. Health Perspect. 42: 9-13.

BUA (Beratergremium für umweltrelevante Altstoffe). 1996. Propionaldehyd (CAS-Nr. 123-38-6). BUA substance report No. 195. Stuttgart: S. Hirzel Verlag.

Driscoll, C.D. 1993. Propionaldehyde: Combined Repeated-Exposure and Reproductive/Developmental Toxicity Study in CD Rats. Report No. 91U0086. Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc., Export, PA. April 6, 1993 [online]. Available: oaspub.epa.gov/eims/eimscomm.getfile? p_download_id=471833 [accessed Jan. 26, 2010].

Egle, J.L. Jr. 1972. Effects of inhaled acetaldehyde and propionaldehyde on blood pressure and heart rate. Toxicol. Appl. Pharmacol. 23(1): 131-135

Gage J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27(1): 1-18.

Izmerov, N.F., I.V. Sanotsky, and K.K. Sidorov. 1982. Pp. 9-12, 102 in Toxicometric Parameters of Industrial Toxic Chemicals under Single Exposure. Center of International Projects, Soviet State Committee for Science & Technology (GKNT), Moscow.

NRC (National Research Council). 2009. Acute Exposure Guidelines for Selected Airborne Contaminants, Volume 7. Washington, DC: The National Academies Press.

Perez, C. and S. C. Soderholm. 1991. Some chemicals requiring special consideration when deciding whether to sample the particle, vapor, or both phases of an atmosphere. Appl Occup Environ Hyg 6(10): 859-864.

Salem H., and H. Cullumbine. 1960. Inhalation toxicities of some aldehydes. Toxicol. Appl. Pharmacol. 2:183-187.

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

Smyth, H.F.,Jr., C.P. Carpenter, and C.S. Weil. 1951. Range-finding toxicity data: List IV. A.M.A.Arch. Ind. Hyg. Occup. Med. 4(2): 119-122.

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

SULFURIC ACID, SULFUR TRIOXIDE, AND OLEUM

At its meeting on October 27-29, 2009, the committee reviewed the TSD on sulfuric acid, sulfur trioxide, and oleum. The document was presented by Marcel van Raaij, of RIVM. The following is excerpted from the summary of the TSD:

> Sulfuric acid is one of the most produced chemicals in the world. It is a strong inorganic acid that is mainly used in the production of phosphate fertilizers. . . . The AEGL-1 values are based on respiratory irritation observed in many human volunteer studies at concentrations higher than 0.2 mg/m324. . . . Considering the database of more than 600 subjects tested for symptoms, the level of 0.2 mg/m^3 is chosen as the point of departure for AEGL-1. . . . The AEGL-2 values are based on the absence of severe or disabling acute effects in the large number of experimental human volunteer studies as well as in the available occupational studies. . . . The AEGL-3 values are based on animal data, in absence of human lethality data. . . . The acute health effects of sulfuric acid (H2SO4), sulfur trioxide (SO3), and oleum are discussed in one TSD because sulfur trioxide and oleum will eventually be converted into sulfuric acid. Oleum (fuming sulfuric acid) is a mixture of sulfuric acid with up to 80% free sulfur trioxide.

Copyright © National Academy of Sciences. All rights reserved.

General Comments

A revised document should be submitted to the committee for review.

For AEGL-1, the concentration of sulfuric acid that can induce a change in specific airway resistance (SR_{aw}) should be considered. Changes in SR_{aw} are considered to be changes in airway function. Although a person may not feel the increase in SR_{aw}, it is nonetheless a functional change that should not be ignored. It is not known whether changes in SR_{aw} during an emergency could be augmented by other physiologic conditions and lead to incapacitation.

The source of the comment that intra-individual variability of SR_{aw} can be as high as 80% (Page 25, line 18 et seq.) is not clear. That also applies to the statement that a 20% change in forced expiratory volume in 1 second (FEV_1) is needed to elicit discomfort. The TSD authors do note that effects on SR_{aw} were observed mainly when people who had asthma withheld medication, but such people do not necessarily take medication all the time, so it is possible that exposure to acid could affect them during a release episode by altering SR_{aw} to a point that causes discomfort. The authors need much stronger justification for not using SR_{aw} as a relevant index for setting AEGL-1 that takes sensitive populations into account.

Sulfuric acid has been shown to produce alterations in mucociliary clearance. The authors disregard that effect because the changes were not consistent. However, in both humans and animals, sulfuric acid has been shown to produce faster mucociliary clearance at low concentrations consistently and retardation of clearance at high concentrations. Retardation of mucus clearance could lead to mucus plugging in the small airways and to functional change in people who have lung diseases, such as asthma and chronic bronchitis.

AEGL-2 was based on occupational exposure in a lead-acid battery plant (el Sadik et al.1972). The rationale of using the factory concentration is that the workers could tolerate sulfuric acid up to 31 mg/m^3 without discomfort. It is not mentioned that the size of the acid droplets in the occupational-exposure scenario may not be the same as that from an acid release or especially from a sulfur trioxide release. It is well known that the toxicity of sulfuric acid varies with particle size. Acid particles in the battery plants tend to be larger than 1 μm, whereas those of acid formed from sulfur trioxide will be in the accumulation mode, below 1 μm. There is a potential for deeper lung penetration and greater effects with the latter than with the former. The derivation of AEGL-2 should consider the effects of sulfuric acid if particles were smaller, and the UF should be 10 here and for intersubject variability.

Many of the animal toxicity studies were conducted with whole-body exposure conditions in which ammonia from feces and urine could neutralize the sulfuric acid aerosols. The toxicity studies should be divided into ones that used nose-only exposure and ones that used whole-body exposure. If toxicity was different between the two kinds of exposure, the lowest concentration that can produce an effect should be used.

Development of AEGL values for a particular chemical typically does not consider other chemicals, but sulfuric acid is very reactive and, on release into the environment, reacts with many substances with which it comes into contact. The reaction products, which may contain many toxic metals and other materials, could be more toxic than the sulfuric acid itself. Because there is no study that can be used as a guideline, the best approximation of such mixtures was probably the acidic atmospheres that occurred during severe air-pollution episodes, such as the 1952 London fog episode. During that episode, the increased mortality was associated with increased sulfuric acid concentrations. The AEGL should take that into consideration.

The hydrogen ion concentration is thought to be responsible for the adverse effects of sulfuric acid. The AEGLs for sulfuric acid should be compared with those established for other acids, such as nitric acid and hydrochloric acid. Because sulfuric acid is present as droplets and could penetrate deeper into the lung than vapors of nitric acid and hydrochloric acids, it is believed that sulfuric acid could be the most toxic of these acids. The authors should search to see whether studies have compared the health effects of these acids and determine whether sulfuric acid is the most toxic of them.

Copyright © National Academy of Sciences. All rights reserved.

Specific Comments

Page 3, lines 9-14: The case study (in Trinidad) by Daisly and Simmons (1999) is not relevant to the normal, airborne route of exposure to acid, so it should not be described in the document.

Page 25, lines 23- 27: What is the source of the comment that intra-individual variability of SR_{aw} can be as high as 80%? The same question applies to the statement that a 20% change in FEV_1 is needed to elicit discomfort. The authors do note that effects on SR_{aw} were observed mainly when people who had asthma withheld medication, but such people do not necessarily take medication all the time, so it is possible that exposure to acid could affect them during a release episode by altering SR_{aw} to a point that causes discomfort. The authors need much stronger justification for not using SR_{aw} as a relevant index for setting AEGL-1 that takes sensitive populations into account.

Page 49, lines 27-45: Section 4.3.5. The effects of coexposure to other pollutants is not considered in setting the AEGLs, so this section should be deleted. Background concentrations are not complete. There are data for peak concentrations of acid in some areas, and these should be reported so that they can be compared with AEGL-1, which is fairly low.

Page 50, lines 2-11: Section 5.1. It is stated that Avol et al. (1979) found no signs of irritation in people who had asthma at 0.1 mg/m^3, but they did find that two of six showed increased airway resistance.

Page 50, line 20: Section 5.3. The basis of AEGL-1 seems sound and consistent with previous irritant AEGLs. However, we suggest that AEGL-1 be reduced somewhat given that SR_{aw} was altered in one-third of people who had asthma in the Avol et al. study noted above. SR cannot be ignored as a relevant end point for setting AEGL-1, at least in justifying its value.

Page 52, Table 8: This table makes the issue confusing. We presume that the numbers are moles of each specific acid. Given that sulfuric acid delivers 2 moles of H+ per mole of acid whereas the others deliver only 1, it seems that sulfuric acid is much more potent than the other acids. That does not support the idea that the effect of the acids is due solely to delivery of H+ to airway surfaces. One might think that only twice as many moles of HCl would be needed. So, that raises the question of what is actually responsible for the irritant effects of the compounds.

Page 52, lines 27-30: The authors note that although effects were seen at 2 mg/m^3 in people who had asthma, the symptoms were relieved by using medication. One cannot assume that during a release people who have asthma will be thinking about taking their medication. They may be incapacitated before that.

Page 53, lines 28-50: Section 6.3. TLVs and occupational studies are not good PODs for AEGLs, because they generally are relevant only to healthy workers. This had been discussed at prior meetings of this committee. Thus, a no-effect level at a TLV or other occupational exposure should not be assumed to apply to sensitive populations. AEGL-2 needs to reconsidered because it is based on occupational exposure, and there needs to be strong justification for assuming that the proposed concentration will not affect people who have asthma, for example. Furthermore, the intraindividual variation should be 10, not 3, because there is wide variation in asthmatic response, and controlled studies do not examine people who have severe asthma.

Page 53: Section 6.3, "Derivation of AEGL-2": The AEG-2 value was based on results of El Sadik et al. (1972), but there is no mention that the acid droplets in the occupational-exposure scenario may not be the same size as those from an acid release or especially from a sulfur trioxide release. Acid particles in the battery plants tend to be larger than 1 μm, whereas those of acid formed from sulfur trioxide will be in the accumulation mode, below 1 μm. Thus, there is a potential for deeper lung penetration and for greater effects with the latter than with the former. Furthermore, the UF should be 10 here, as well for intersubject variability.

Page 55, Table 10: Same comments as above for Table 8 on Page 52.

Page 58, Table 15: The authors should explain the difference between AEGL-3 and ERPG-3.

Copyright © National Academy of Sciences. All rights reserved.

Editorial Comments

Page 4, line 32, through Page 25, line 25: The organization of Section 2.2.2 needs to be simplified. Pages of tabular material are followed by detailed discussion of some studies. Then, beginning on Page 25, there are subsections that appear to be summaries of the tables or studies. The summaries should all be integrated into Section 2.7, "Summary of Human Data."

Page 44, line 1, through Page 5, line 37: Section 3.6 is difficult to follow, especially the subsection "Pathologic Changes of the Respiratory Tract." We suggest that the TSD authors prepare a table of exposure concentrations and durations to summarize the material in a way that allows the reader to compare effects at different levels and times.

Page 48, line 1: The name of Section 4.3.3, "Intraspecies Variability/Susceptible Populations," does not seem to reflect its content. Perhaps it should be called "Effect of Ammonia on Acid Response."

Comment References

Avol EL., M.P.Jones, R.M. Bailey, N.M.Chang, M.T.Kleinman, W.S.Linn, K.A.Bell, and J.D.Hackney. 1979. Controlled exposures of human volunteers to sulfate aerosols. Health effects and aerosol characterization. Am. Rev. Respir. Dis. 120(2): 319-27.

Daisley, H., and V. Simmons. 1999. Forensic analysis of acute fatal poisonings in the southern districts of Trinidad. Vet. Hum. Toxicol. 41(1): 23-25

el-Sadik, Y.M., H.A. Osman, and R.M. el-Gazzar. 1972. Exposure to sulfuric acid in manufacture of storage batteries. JOM 14(3): 224-226.

TRICHLOROETHYLENE

At its meeting on October 27-29, 2009, the committee reviewed the TSD on trichloroethylene (TCE). The document was presented by Marcel van Raaij, of RIVM. The following is excerpted from the summary of the TSD:

> Trichloroethylene is a colorless, highly volatile liquid at ambient temperature and pressure. It has a sweet, chloroform-like odor. . . . Following exposure to trichloroethylene humans primarily experience central nervous system effects and irritation. At high concentrations cardiac arrhythmias have also occurred. . . . The AEGL-1 derivation is based on the exposure of volunteers to 300 ppm for 2 hours. . . . The AEGL-2 derivation is based on the same study. . . . At 1000 ppm for 2 hours the subjects reported light-headedness, dizziness, or lethargy. In addition reduced neurobehavioral performance was detected at this concentration, most importantly reduced performance in the pegboard test. Although significant in themselves, these effects are not escape-impairing. Thus the concentration of 1000 ppm for 2 hours is considered an adequate starting point for AEGL-2 effects in humans. . . . The AEGL-3 value is based on the acute mouse mortality study. . . . The NOEL from this study is 4600 ppm for 4 hours.

General Comments

A revised document should be submitted to the committee for review.

The current document is 8 years old, and the authors need to update it and, if necessary, use new published data to derive AEGL values.

Copyright © National Academy of Sciences. All rights reserved.

The PODs for AEGL values need better justification. Specifically, the selection of the AEGL-1 POD needs to be transparent, given the human studies of TCE reported. There is some concern that a lower TCE POD could have been selected.

AEGL-1: POD at 2-h NOAEL of 300 ppm; PBPK at an arterial blood TCE concentration of 4.78 mg/L.

A POD of 300 ppm may be too high.

- Although the effect is reported as marginal, an incidence of one of eight volunteers would still be the LOAEL, not NOAEL.
- On the basis of Pages 3-7 of the TSD, the following data indicated lower LOAELs:

15 min:	95.8 ± 8.2 ppm (abnormal ECG with ventricular extrasystoles) (Konietzko et al. 1975c)
50-70 min:	100 ppm (reaction time) (Gamberale et al. 1976)
2 h:	27 ppm (nose and throat mucous membrane irritation, drowsiness), 81 ppm (headache), LOAEL of 201 ppm (dry throat) (Nomiyama and Nomiyama 1977)
≥2 h:	198-199 ppm (dry throat, throat irritation) (Stewart et al. 1970)
2.5 h:	75 ppm (suppression of sinus arrhythmia) ((Ettema and Zielhuis 1975; Ettema et al. 1975)
4 h :	110 ppm (slight dizziness) (Salvini et al. 1971)
≤4h:	110-114 ppm (impaired Flanagan test) (Stewart et al. 1974)

- A 3.5-h NOEL of 50 ± 11 ppm for auditory evoked brain potential was noted in a study by Winneke et al. (1976).
- It was noted on Page 4 of the TSD that ATSDR used the POD of the LOAEL of 200 ppm from the Stewart et al. (1970) study which reported eye and throat irritation, fatigue, and drowsiness. Using ATSDR's LOAEL of 200 ppm and its uncertainty of 3 (ATSDR 1997), a NOAEL would be 67 ppm. The 1977 study by Nomiyama and Nomiyama provides some support for that estimated NOAEL, specifically, headache at 81 ppm and drowsiness at 27 ppm (as reported in the TSD on page 3).
- Alcohol-enhanced TCE effects are noted on Page 6 of the TSD for 2 h at 200 ppm (Windemuller and Ettema 1978). ATSDR also noted increase in heart and breathing rates at that concentration. Concomitant alcohol ingestion cannot be excluded from consideration for the general population.

AEGL-2: POD at 2-h NOAEL of 1,000 ppm; PBPK @Ca = blood TCE at 18.3 mg/L.

AEGL-2 is based on light-headedness, dizziness, or lethargy in combination with reduced performance in neurobehavioral tests of volunteers at 1,000 ppm for 2 h (Vernon and Ferguson 1969). These are noted as "sub" AEGL-2. A lower threshold can be found with similar end points. The following are summarized from Pages 3-7.

2 h	LOAEL of 300 ppm (NOAEL, 100 ppm) (Howard Dolman and steadiness test) (Vernon and Ferguson 1969)
2.5 h	LOAEL of 150 ppm (suppressed sinus arrhythmia) (Ettema and Zielhuis 1975; Ettema et al. 1975)
4 h	LOAEL of 201 ppm (NOAEL, 81 ppm) (dizziness, anorexia, skin irritation), LOAEL of 100 ppm (slight dizziness) (Nomiyama and Nomiyama 1977)

AEGL-3: POD at 4-h NOAEL of 4,600 ppm in mice.

- The rationale for selecting the POD from the mouse study by Friberg et al. (1953) was that the benchmark-dose approach for obtaining the 95th lower bound of LC_{05} from the Adams et al. (1951) study

Copyright © National Academy of Sciences. All rights reserved.

results in too low an AEGL-3. It is noted that taking the NOAEL approach, the 4-h NOAEL would be 4,800 ppm from the Adams et al. study of rats—not very different from the chosen POD of 4,600 ppm in mice.

- The proposed AEGL-3 for 30 min is 6,100 ppm. The AEGL-2 for 30 min is 620 ppm for 30 min and 960 ppm for 10 min. Please indicate whether it is a concern that the AEGL-3 is higher than the NIOSH IDLH of 1,000 ppm.

The authors used an unpublished human PBPK model for TCE to derive AEGL-1 and AEGL-2 values. The human model was not validated against kinetic data. For the committee to accept PBPK-derived dosimetrics for time extrapolations, the models need to be published or undergo a documented peer review.

The AEGL-2 human PBPK dosimetric was blood TCE. A primary metabolite, trichloroethanol (TCOH), is known to be responsible for CNS depression. A human PBPK model by Ted Simon (*Regulatory Toxicology and Pharmacology*, Volume 26, Issue 3, December 1997, Pages 257-270, Combining Physiologically Based Pharmacokinetic Modeling with Monte Carlo Simulation to Derive an Acute Inhalation Guidance Value for Trichloroethylene) uses both blood TCE and blood TCOH. The authors need to use TCE and TCOH as dosimetrics for deriving AEGL-2 values.

The AEGL-3 human PBPK model efforts were not useful and were abandoned in the TSD. That is probably because the dosimetric required in the PBPK model is TCOH, not TCE. The exposure conditions could result in saturation of the rate of formation of TCOH and lead to a different AEGL-3 profile for time extrapolations. Simulations should be redone to address that shortcoming. If there is still a problem (too high exposure to TCE), the PBPK modeling approach should not be used.

Because in utero developmental effects—rat hydrocephalus at 500 ppm for 7 h/day in Belilies at al. (1980) and total litter loss at 100 ppm for 4 h/day in Healy et al. (1982; see Page 29 of the TSD)—can occur after a single day of maternal exposure during the window of vulnerability, the concerns regarding pregnant women should be adequately addressed. Other end points of oral exposures—such as decreased number of myelinated fibers in rat offspring hippocampus in Isaacson and Taylor (1989) and neurobehavioral effects in mice in Fredriksson et al. (1993; see page 30 of the TSD)—also point to the need to address those concerns.

Specific Comments

There should be results of a literature search conducted on carcinogenicity following *SOP* guidelines and criteria.

Page 1, lines 21-22: What are the times associated with the use of TCE as an anesthetic?

Page 8, Table 2: Data from Konietzko et al. (1975c) study (see I. AEGL-1 section above) should be included in the table, and please include time to effects.

Comment References

Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister, and D.D. Irish. 1951 Vapor toxicity of trichloroethylene determined by experiments on laboratory animals. A.M.A. Arch. Ind. Hyg. Occup. Med. 4(5): 469-481.

ATSDR (Agency of Toxic Substances and Disease Registry). 1997. Toxicological Profile for Trichloroethylene (Update). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency of Toxic Substances and Disease Registry, Atlanta, GA. September 1997 [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf [accessed Jan. 26, 2010].

Copyright © National Academy of Sciences. All rights reserved.

Beliles, R.P., D.J. Brusick, and J. Mecler. 1980. Teratogenic-Mutagenic Risk of Workplace Contaminants: Trichloroethylene, Perchloroethylene and Carbon Disulfide. NIOSH Contract Report No. 210-77-0047. NTIS PB-82 185-075. U.S. Department of Health and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cinccinnatti, OH.

Ettema, J.H., and R.L. Zielhuis. 1975. Effect of alcohol, carbon monoxide and trichloroethylene inhalation on mental capacity. Int. Arch. Occup. Environ. Health 35(2):117-132.

Ettema, J.H., L. Kleerekoper, and J.W.C. Duba. 1975. Study of mental stresses during short-term exposure to trichloroethylene. Staub Reinhalt. Luft 35:409-410.

Fredriksson, A., B.R. Danielsson, and P. Eriksson. 1993. Altered behavior in adult mice orally exposed to tri- and tetrachloroethylene as neonates. Toxicol. Lett. 66(1):13-19.

Friberg, L., B. Kylin, and Å. Nyström. 1953. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyridine-alkali reaction. Acta Pharmacol. Toxicol. 9(4):303-312.

Gamberale, F., G. Annwall, and B.A. Olson. 1976. Exposure to trichloroethylene. III. Psychological functions. Scand. J. Work Environ. Health 2(4):220-224.

Healy, T.E., T.R. Poole, and A. Hopper. 1982. Rat fetal development and maternal exposure to trichloroethylene 100 ppm. Br. J. Anaesth. 54(3):337-341.

Isaacson, L.G., and D.H. Taylor. 1989. Maternal exposure to 1,1,2-trichloroethylene affects the myelin in the hippocampal formation of the developing rat. Brain Res. 488(1-2):403-407.

Konietzko, H., I. Elster, P. Schomann, and H. Weichardt. 1975c. Felduntersuchungen in Lösunsmittelnbetrieben. 4. Mitteilung: Herzrhythmustörungen durch Trichloräthylen. Zentralblatt für Arbeitsmedizin und Arbeitsschutz 5:139-141Nomiyama, K., Nomiyama, H. (1977) Dose-response relationship for trichloroethylene in man. *International Archives of Occupational Environmental Health* 39, 237-248.

Nomiyama, K., and H. Nomiyama. 1977. Dose-response relationship for trichloroethylene in man. Int. Arch. Occup. Environ. Health 39(4):237-248.

Salvini, M, S. Binaschi, and M. Riva. 1971. Evaluation of the psychophysiological functions of humans exposed to trichloroethylene. Br. J. Ind. Med. 28(3):293-295.

Simon, T.W. 1997. Combining physiologically based pharmacokinetic modeling with Monte Carlo simulation to derive an acute inhalation guideline value for trichloroethylene. Regul. Toxicol. Pharmacol. 26(3): 257-270.

Stewart, R.D., H.C. Dodd, H.H. Gay, and D.S. Erley. 1970. Experimental human exposure to trichloroethylene. Arch. Environ. Health 20(1):64-71.

Stewart, R.D., C.L. Hake, A.J. Lebrun, J.H. Kalbfleisch, P.E. Newton, J.E. Peterson, H.H. Cohen, R. Struble, and K.A. Busch. 1974. Effects of trichloroethylene on behavioral performance capabilities. Pp. 96-129 in Behavioral Toxicology: Early Detection of Occupational Hazards, C. Xintaras, B.L. Johnson, and I. de Groot, eds. DHEW (NIOSH)74-126. U.S. Department of Health, Education and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Washington, DC.

Vernon, R.J., and R.K. Ferguson. 1969. Effects of trichloroethylene on visual motor performance. Arch. Environ. Health 18(6):894-900.

Windemuller, F.J.B., and J.H. Ettema. 1978. Effect of combined exposure to trichloroethylene and alcohol on mental capacity. Int. Arch. Occup. Environ. Health 41(2):77-85.

Winneke, G., U. Kramer, and J. Kastka. 1976. Zur Beeinflussung pschomotorischer Leistungen durch Alkohol und durch Verschiedene Lösungsmitteldämpfe. Pp. 99-110 in Adverse Effects of Environmental Chemicals and Psychotropic Drugs, Vol. 2. Neurophysiological and Behavioral Tests, M. Horvath, ed. Amsterdam: Elsevier.

Copyright © National Academy of Sciences. All rights reserved.

STANDING OPERATING PROCEDURES

Before developing AEGLs for individual chemicals, the NAC developed the guidelines document *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* (referred to as *SOP*), which documents the procedures, methods, criteria, and other guidelines used by the NAC in the development of AEGLs. The information contained in *SOP* is based on guidance provided by the National Research Council in its guidelines report (NRC 1993). *SOP* was reviewed by the National Research Council AEGLs committee and published by the National Research Council (NRC 2001).

In addition to reviewing AEGL documentation developed by the NAC, the National Research Council committee is charged to identify guidance issues from time to time that may require modification or further development on the basis of the toxicologic database for chemicals reviewed. The committee provides the following recommendation to the NAC for updating and improving *SOP* and TSDs.

General Comments

"Mechanism of Toxicity" is Section 4.2 of the TSD as a subsection of Section 4, "Special Considerations." In light of the review of methylene chloride, in which the mechanism of toxicity is key to understanding the data and the development of the AEGL values, the committee recommends the following change to *SOP*: make "Mechanism of Toxicity" Section 2, "Mechanism of Toxicity," and renumber the later sections (such as Section 3, "Human Toxicity Data").

Copyright © National Academy of Sciences. All rights reserved.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists, a member-based organization for advancement of occupational and environmental health.
ATSDR	Agency for Toxic Substances and Disease Registry, a federal public health agency of the U.S. Department of Health and Human Services
AVT	auditory vigilance task
BEI	biologic exposure index
CalEPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CEEL	Department of Health and Human Services community emergency exposure levels
CHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
DCM	dichloromethane (also known as methylene chloride)
DOD	U.S. Department of Defense
DOT	U.S. Department of Transportation
CNS	central nervous system
COHb	carboxyhemoglobin
EEG	electroencephalography
EEGL	emergency exposure guideline level
EHS	extremely hazardous substance
EPA	U.S. Environmental Protection Agency
FEV_1	forced expiratory volume in 1 second
IARC	International Agency for Research on Cancer
ICPS	International Programme on Chemical Safety
IDLH	immediately dangerous to life or health
IRIS	Integrated Risk Information System
LC_{50}	concentration of a substance that is lethal to 50% of test organisms in a given time
LD_{50}	dose of a substance that is lethal to 50% of test organisms in a given time
LOEL	lowest-observed-effect level
LOAEL	lowest observed-adverse-effect level
MEG	military exposure guideline
MF	modifying factor
NAC	National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTIS	National Technical Information Service
NTP	National Toxicology Program
OEHHA	California Office of Environmental Health Hazard Assessment
ORNL	Oak Ridge National Laboratory

Copyright © National Academy of Sciences. All rights reserved.

OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PNS	peripheral nervous system
POD	point of departure
RBC	red blood cell
RD_{50}	concentration of a substance that reduced the respiratory rate of test organisms by 50% REL reference exposure level
RIVM	Netherlands National Institute for Public Health and the Environment
SD	standard deviation
SOP	*Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*
SR_{aw}	specific airway resistance
STEL	short-term exposure limit
TCE	trichloroethylene
TCOH	trichloroethanol
TLV	Threshold Limit Value
TSD	technical support document
UF	uncertainty factor
WEEL	workplace environmental exposure limit

Copyright © National Academy of Sciences. All rights reserved.