Fourteenth Interim Report of the Committee on Acute Exposure Guideline Levels

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

ISBN: 0-309-66072-6, 52 pages, 8 1/2 x 11, (2006)

Fourteenth 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

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

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

This project was supported by Contract No. 68-C-03-081 between the National Academy of Sciences 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.

Additional copies of this report are available from

The National Academies Press
500 Fifth Street, NW
Box 285
Washington, DC 20055

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

Printed in the United States of America

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

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

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

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

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

www.national-academies.org

COMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

COMMITTEE ON TOXICOLOGY

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

Staff

KULBIR S. BAKSHI, Program Director
EILEEN N. ABT, Senior Program Officer for Risk Analysis
SUSAN N. J. MARTEL, Senior Program Officer
ELLEN K. MANTUS, Senior Program Officer
AIDA NEEL, Program Associate
TAMARA DAWSON, Senior Program Assistant
ALEXANDRA STUPPLE, Senior Editorial Assistant
SAM BARDLEY, Librarian

BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY[1]

Members

JONATHAN M. SAMET *(Chair)*, Johns Hopkins University, Baltimore, MD
RAMÓN ALVAREZ, Environmental Defense, Austin, TX
JOHN M. BALBUS, Environmental Defense, Washington, DC
THOMAS BURKE, Johns Hopkins University, Baltimore, MD
DALLAS BURTRAW, Resources for the Future, Washington, DC
JAMES S. BUS, Dow Chemical Company, Midland, MI
COSTEL D. DENSON, University of Delaware, Newark
E. DONALD ELLIOTT, Willkie Farr & Gallagher LLP, Washington, DC
J. PAUL GILMAN, Oak Ridge National Laboratory, Oak Ridge, TN
SHERRI W. GOODMAN, Center for Naval Analyses, Alexandria, VA
JUDITH A. GRAHAM, American Chemistry Council, Arlington, VA
DANIEL S. GREENBAUM, Health Effects Institute, Cambridge, MA
WILLIAM P. HORN, Birch, Horton, Bittner and Cherot, Washington, DC
ROBERT HUGGETT, Michigan State University (emeritus), East Lansing
JAMES H. JOHNSON JR., Howard University, Washington, DC
JUDITH L. MEYER, University of Georgia, Athens
PATRICK Y. O'BRIEN, ChevronTexaco Energy Technology Company, Richmond, CA
DOROTHY E. PATTON, International Life Sciences Institute, Washington, DC
STEWARD T.A. PICKETT, Institute of Ecosystem Studies, Millbrook, NY
DANNY D. REIBLE, University of Texas, Austin
JOSEPH V. RODRICKS, ENVIRON International Corporation, Arlington, VA
ARMISTEAD G. RUSSELL, Georgia Institute of Technology, Atlanta
ROBERT F. SAWYER, University of California, Berkeley
LISA SPEER, Natural Resources Defense Council, New York, NY
KIMBERLY M. THOMPSON, Massachusetts Institute of Technology, Cambridge
MONICA G. TURNER, University of Wisconsin, Madison
MARK J. UTELL, University of Rochester Medical Center, Rochester, NY
CHRIS G. WHIPPLE, ENVIRON International Corporation, Emeryville, CA
LAUREN ZEISE, California Environmental Protection Agency, Oakland

Senior Staff

JAMES J. REISA, Director
DAVID J. POLICANSKY, Scholar
RAYMOND A. WASSEL, Senior Program Officer for Environmental Sciences and Engineering
KULBIR BAKSHI, Senior Program Officer for Toxicology
EILEEN N. ABT, Senior Program Officer for Risk Analysis
K. JOHN HOLMES, Senior Program Officer
SUSAN N.J. MARTEL, Senior Program Officer
SUZANNE VAN DRUNICK, Senior Program Officer
ELLEN K. MANTUS, Senior Program Officer
RUTH E. CROSSGROVE, Senior Editor

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

PREFACE

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars or trucks transporting EHSs, or intentionally through terrorist activities. These substances can also be released by improper storage and/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 of being exposed 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 approximately 400 EHSs on the basis of acute lethality data in rodents.

The National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances has developed acute exposure guideline levels (AEGLs) for approximately 150 EHSs to date. In 1998, EPA and the U.S. Department of Defense (DOD) requested that the National Research Council (NRC) independently review the AEGLs developed by the NAC. In response to that request, the NRC organized the Committee on Acute Exposure Guideline Levels. The NAC's *Standing Operating Procedures for Developing AEGLs for Airborne Chemicals* was reviewed by the committee and published in May 2001. That report provides step-by-step guidance for the derivation of AEGLs for hazardous chemicals. In December 2000, the committee's first report on specific chemicals, *Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 1*, was published by the NRC; Volumes 2, 3, and 4 in that series were published in 2002, 2003, and 2004, respectively; these four volumes contain AEGL documents on 18 chemicals. Thus far, the committee has provided comments on approximately 80 AEGL documents.

The committee meets two times each calendar year. At those meetings, the committee hears presentations from the NAC staff and its contractor—the Oak Ridge National Laboratory—on draft AEGL documents. At some meetings, the committee also hears presentations from NAC's collaborators from other countries, such as Germany. The committee provides comments and recommendations on those documents to NAC in its interim reports, and the NAC uses those comments to make revisions. The revised reports are presented by the NAC to the committee at subsequent meetings until the committee concurs with the final draft documents. The revised reports are then published as appendices in the committee's reports.

The present report is the committee's fourteenth interim report. It summarizes the committee's conclusions and recommendations for improving NAC's AEGL documents for 16 chemicals: xylenes; acetone; acetone cyanohydrin; carbon disulfide; allyl alcohol; acrolein; chloroform; peracetic acid; n,n-dimethylformamide; carbon tetrachloride; 1,2-dichloroethylene; sulfur dioxide; hydrazine; ethylenimine; propylenimine; and trichloroethylene.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and

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

critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Deepak K. Bhalla (Wayne State University), David W. Gaylor (Gaylor and Associates, LLC), and Sam Kacew (University of Ottawa).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by: Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Ernest Falke, Iris Camacho, and Marquea King (all from EPA); Cheryl Bast, Kowetha Davidson, Claudia Troxel, and Robert Young (all from Oak Ridge National Laboratory); and Jens-Uwe Voss of Germany. Aida Neel was the program associate, and Alexandra Stupple was the editor. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful guidance. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

William E. Halperin, *Chair*
Committee on Toxicology

Fourteenth 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 (NRC) 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, a committee of the NRC Committee on Toxicology prepared a report titled *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993). That report provides step-by-step guidance for the derivation of CEELs for EHSs.

In 1995, EPA, several other federal and state agencies, and several private academia organizations convened an advisory committee—the National Advisory Committee on Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances (referred to as the NAC)—to develop, review, and approve AEGLs (similar to CEELs) for up to 400 EHSs. 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 and emergency-response planning for potential releases of EHSs, either from accidents or as a result of terrorist activities.

THE CHARGE TO THE COMMITTEE

The NRC 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, pharmacology, medicine, industrial hygiene, biostatistics, and risk assessment.

The charge to the committee is to (1) review AEGLs developed by the NAC for scientific validity, completeness, and conformance to the NRC (1993) guidelines report, (2) identify priorities for research to fill data gaps, and (3) identify guidance issues that may require modification or further development based on the toxicologic database for the chemicals reviewed.

This interim report presents the committee's comments concerning the NAC's draft AEGL documents for 16 chemicals: xylenes (mixtures of ortho, para, and meta xylenes; meta-xylene predominates the mixture constituting 40-70% of the commercial mixture); acetone; acetone cyanohydrin; carbon disulfide; allyl alcohol; acrolein; chloroform; peracetic acid; n,n-dimethylformamide; carbon tetrachloride; 1,2-dichloroethylene; sulfur dioxide; hydrazine; ethylenimine; propylenimine; and trichloroethylene.

COMMENTS ON XYLENES

At its previous meeting, the committee reviewed the AEGL document on xylenes. The presentation was made by Claudia Troxel of Oak Ridge National Laboratory and James Dennison of Century Environmental Hygiene LLC. The committee recommends a number of revisions. A revised draft can be finalized if the recommended revisions are made appropriately.

General Comments

Based on discussion at the meeting, there was agreement among the committee members to use an interspecies uncertainty factor (UF) of 3 to derive the values for AEGL-2 and -3, because the physiologically based pharmacokinetic (PBPK) model used accounted for the oversensitivity of the animals in the experiment compared to humans.

The committee also recommended that a statement and a specific citation to the standard operating procedures (SOP) (including the specific section) should be added to explain why an intraspecies UF of 3 was selected, for both AEGL-2 and -3.

The committee recommended that new language should be added to describe why a "correction" factor was used to derive AEGL-2 and -3 values.

The committee also agreed with the approach used by the authors for time extrapolation and dose extrapolation and supported their findings and recommendations relative to the modeling. The committee believes that the methods used are accepted in the modeling community. However, since PBPK modeling is notorious for visualizing the uncertainties in dose-response relationships, further clarification is needed regarding how to handle the concept of "adequate fit," "model validation," and "poor fit." In addition, new text needs to be added describing how the specific PBPK model used to derive the AEGL values was evaluated and why it is considered to be a "valid" model for application in the derivation of AEGL values for xylenes.

Specific Comments

Page 41, lines 13-15. Eye irritation is not a sensory irritation (for example, bad smell is a sensory irritation to the olfactory system and glaring light is a sensory irritation to the vision).

Page 44, lines 25-32. Contradiction? Was an exposure of rats to 2,800 parts per million (ppm) xylene for 4 hours (h) a no-observed-effect level (NOEL) for prostration (lines 25-26), or did it produce prostration (line 32)? Or does "NOEL" in line 25 refer to death only and not to "reversible prostration"?

Editorial Comments

Page 5, line 9. Delete "age" (or "years old").

Page 31, Table 10. Add units (hours) to the Duration column.

Page 37, Section 4.3.2. Intraspecies Differences. The discussion of the two- to threefold range in humans is discussed in the SOP, but no references are provided here. Because this is an important point, add a reference to the SOP here so the reader understands that the basis for this statement is documented in the SOP. Add NRC 2001 (SOP manual) as a reference either at the end of the first or second paragraphs.

Page 48, line 35. Spell out what "EEL" stands for.

Scientific Comments in Response to the Initial Comments on Xylenes Discussion

Page 3, lines 12-15. This statement and consequent calculation is not justified. An elderly person being at greater risk for pharmacodynamic reasons (maximal sensitivity in newborn, pregnant, and

elderly) may have to run in an emergency situation irrespective of whether he is "the most physically active" or a rather physically inactive person. Thus, a pharmacokinetic component ("physical activity during exposure") may well add to a pharmacodynamic component (higher sensitivity). Also in the preceding lines (7-12), it is not clear whether "an intraspecies uncertainty factor of 3 includes both the pharmacokinetic and pharmacodynamic components. The corresponding corrections will also have to be made in the Executive Summary (page viii) and in the main text (page 45, lines 1-21).

Page 8, lines 14-16. This important point is still not incorporated in the text.

Specific/Editorial Comments

Page 3, lines 3-7. Unclear sentence. Is it meant to say, "because although it appears that similar central nervous system effects occur …"? (Same for present text on xylenes—for example, page viii, lines 37-39, and page 72, lines 8-10.)

When these changes are complete, the amended text of this technical summary document (TSD) should be sent to the committee for their approval.

The revised document can be finalized if the revisions recommended by the committee are made appropriately.

COMMENTS ON ACETONE

At its previous meeting, the committee reviewed the AEGL document on acetone. The document was presented by Jens-Uwe Voss of Germany.

General Comment

This is a well-documented report. A major issue is that acetone is a nontoxic compound. The fire and explosion hazard is considerably more important than the toxic hazard. Addressing the question of why AEGLs, and especially an AEGL-3, for this substance are needed at all is justified.

Specific Comments

Page vii, 1st and 7th paragraph. Conflicting data on odor level of 41-86 ppm versus the level of distinct odor awareness (LOA) 160 ppm.

Page viii, line 5. It is unlikely that inhalation exposure to high acetone concentrations in air will ever lead to toxicologically relevant blood concentrations.

Page 3, lines 5-6. Paint thinner is not acetone, although it may contain some. This case does not prove that oral acetone intake may be lethal. Is it necessary to cite all six reports by Litovitz et al.?

Page 3, line 23. Systemic acetone clearance is not rapid. Acetone, because of its relatively high water solubility, has a relatively high blood:air partition coefficient. As a result, its rate of exhalation is limited. The rate of metabolism of acetone is also limited, as is urinary excretion of the parent

compound. The elimination of acetone is quite slow when compared to more lipophilic solvents such as toluene (see Figure 4 in Bruckner and Peterson 1981).

Page 3, line 24. The word "excretion" should be replaced with "urinary excretion and exhalation."

Page 4, line 5. Comparable concentrations may be observed in diabetics and are not really alarming.

Page 4, lines 26-30. Acetylene is the most likely cause of coma in this case, not acetone.

Page 5, lines 5-15. These concentrations would be lethal for ethanol; apparently acetone is even less toxic than ethanol. A 6-month (mo) follow-up is too short a time to exclude neurodevelopmental complications.

Page 6, lines 24-30. The study of Nakaaki (1974) was poorly done, and its findings are uncertain. Therefore, it and its description should be deleted.

Page 9, line 15. What is 23-element clinical chemistry? Which parameters were actually included?

Page 9, line 28. The paper of Haggard et al. was published in 1944, not in 1994 (as in the text).

Page 13, line 25. Is "30-44" the age of workers or their number of years of acetone exposure?

Page 14, lines 39 sqq. Apparently, at a chronic exposure to 1,000 ppm, no excess mortality was observed. This corroborates the conclusion that acetone is nontoxic. See also page 19 where oral LD_{50}s are given in g/kg body weight.

Page 15, lines 40-41. It is stated that no reports of acetone-induced lethality were located, but Litovitz et al. (1999, 2001) recorded two such cases (See page 3, lines 6-11). It should be pointed out that each victim was also exposed to a variety of other chemicals present in the commercial products to which they were exposed.

Page 16, lines 23-25. Were the workers described by Smith and Mayers (1944) exposed to acetone and butanone (as stated here) or methyl ethyl ketone (MEK) as described in lines 10-16 on page 4 of the current document? MEK is the primary metabolite of 2-butanone. The parent compound and metabolite are more lipophilic than acetone and are thus more-potent CNS depressants.

Page 16, lines 36-38. It would be worthwhile to point out that, as expected, LC_{50}s are higher for shorter exposures.

Page 17, lines 9-11. The highest acetone exposure concentration (50,600 ppm) was lethal to some, but not all rats. Thus, the calculated 3-h LC_{50} of 55,700 ppm is reliable.

Page 19, line 23. Tanii et al. (1986) is not included in the References.

Page 20, line 1. Was this oral exposure?

Page 23, lines 6 and 22. Frantik's initials are given in the References as E.M. and E.L. for the 1994 and 1996 publications, respectively. Which is correct?

Page 23, lines 32-35. It is not necessary to include an account of the study by Garcia et al. (1978). The study design was flawed, and the findings were variable and of doubtful value.

Page 24, lines 29-30: The meaning of the latter part of this sentence is unclear. Did the depression in respiratory rate diminish/cease within a few minutes of cessation of acetone exposure?

Page 26, lines 14-15: How do fetal "variations" differ from fetal "malformations"?

Page 28, line 39: The carcinogenicity study of isopropanol should be included here.

Page 29, lines 22-23: Respiratory uptake of acetone is primarily dependent upon three factors: (1) respiratory rate; (2) cardiac output; and (3) blood:air partition coefficient. Acetone is a relatively water-soluble volatile organic chemical (VOC). It is therefore quite soluble in blood and is rapidly absorbed into the pulmonary (blood) circulation and distributed throughout the total body water. The large volume of distribution contributes to acetone's relatively slow clearance.

Page 30, lines 5-7. Blood:air partition coefficient (PC) is an indirect index of the water solubility of a VOC, as blood (especially plasma) is largely aqueous. It is best to avoid equating the terms blood:air and tissue:blood PC here in the text. Most tissues have a high water content, but their lipid content varies significantly. Acetone would, for example, have a relatively low tissue:blood PC for bone marrow, skin, adipose tissue, pancreas, etc. Dills et al. (1994) is not included in the References.

Page 30, lines 22-26. The authors should differentiate here between percentage uptake/retention and total systemic uptake of inhaled acetone. The document's authors' statements about the relationship between pulmonary ventilation rate and retention/uptake appear contradictory.

Page 30, lines 39-43. The low lipophilicity of acetone (relative to many other VOCs) contributes to its relatively slow uptake from blood into fat and other lipid-rich tissues, which in turn delays its pulmonary uptake, because of a high acetone concentration in venous blood returning to the pulmonary circulation. The influence of solubility on the rate of diffusion of acetone across alveolar/endothelial membranes should be minimal because acetone has a balance of lipid and water solubility, is uncharged, and has a low molecular weight.

Page 31, lines 3-8. It is right to assume that the 10 and 22 mg/kg values represent total absorbed dose, not venous blood concentration?

Page 32 line 7. Acetone monooxygenase is probably the same as CYP2E1 and is just another name for it.

Page 34, lines 2, 3, 13-14. Is the metabolic rate 2 mg/kg/h?

Page 34, lines 4-6. The meaning of the concluding sentence of the paragraph is not clear. Metabolic saturation is not an "all or none" phenomenon, but a progressively pronounced, dose-dependent process. The findings of Haggard et al. (1944) clearly show lower metabolic efficiency at higher blood acetone concentrations.

Page 36, Table 5. This table is confusing and should be replaced by a graphical representation of the data.

Page 37, lines 4-5. It should be pointed out here that fasting rats metabolize acetone more rapidly than fed rats because of CYP2E1 induction by fasting. Bruckner et al. (2002), for example, demonstrated that overnight fasting of rats causes lipolysis, which in turn results in increased formation of acetone and other ketone bodies. Acetone markedly induces hepatic CYP2E1 activity by stabilizing the existing isozyme, rather than by enhancing the synthesis of new enzymes.

CYP2E1, as previously described in the current document, is largely responsible for acetone metabolism. The complete reference to the aforementioned paper is as follows:

Bruckner, J.V., R. Ramanathan, K.M. Lee, and S. Muralidhara. 2002. Mechanisms of circadian rhythmicity of carbon tetrachloride hepatotoxicity. J. Pharmacol. Exp. Therap. 300:273-281.

Page 37, line 23. Acetone should not be characterized as moderately toxic. Extremely high concentrations of this endogenous compound are required to produce central nervous system (CNS) effects.

Page 37, lines 23-28. As described above, acetone induces CYP2E1, which is one of the P450s primarily responsible for metabolic activation of short-chain aliphatic halocarbons, including carbon tetrachloride, as shown by Bruckner et al. (2002). Items (ii) and (iii) are not applicable here.

Page 38, lines 2-5. Only some ketones is known to cause peripheral neuropathy at *chronic* exposure; this has no relevance for (acute) acetone exposure.

Page 38, lines 26-28. It is logical that neonatal rats would be more susceptible to the CNS depressant effects of the parent compound. Newborn rats' hepatic CYP2E1 metabolic capacity is much lower than that of human newborns.

Page 43, line 24. Were the papers of Geller et al. published in 1978 (as stated here in the text) or in 1979 (as stated in the References)?

Page 43, lines 29-35. The AEGL-1 is based on too low a NOAEL. An AEGL-1 is defined as "The airborne concentration above which … individuals could experience notable discomfort, irritation…" Studies (for example, Dick et al. 1988, 1989; Ernstgard et al. 1999) clearly showed that 250 ppm was a NOAEL for mucus membrane irritation in 10 subjects. Inhalation of 300 ppm is said to be slightly irritating by Nelson et al. (1943), although their study results may not be reliable. 500 ppm (for 6 h) produces subjective complaints of mucus membrane irritation by most subjects (Matsushita et al. 1969b; Nelson et al. 1943). A 4- or 8-h 1,000-ppm acetone exposure definitely produces subjective complaints of mucosal irritation, although adaptation occurs (Seebler et al. 1992a, b). Minimal CNS effects require higher exposure concentrations. Most 8-h occupational-exposure limits are 500 or 750 ppm (see page 51). Therefore, 500 ppm would be an appropriate AEGL-1 for each exposure duration (= 3× level of distinct odor awareness (LOA), although 300 ppm could be adopted if a more-conservative threshold were desired. A 500-ppm exposure would be in agreement with the "slight irritation" in the Matsushita paper.

Pages 44-49. There needs to be a clear explanation for why an interspecies UF of 1 was chosen for the derivation of AEGL-2 and -3. The current explanation is poorly worded and sounds too much like "the values were too high, and so we lowered the interspecies UF factor." There needs to be a more scientific basis for reducing the UF.

Page 45, lines 21-24. It should be noted that the PBPK model of Clewell et al. (2001) was validated for an extremely wide range (2,110-126,600 ppm) of inhaled acetone vapor concentrations in rats. Metabolic rate constants were determined for a wide range of inhaled acetone concentrations from 5,000 to 45,000 ppm. The model was validated for humans inhaling 100 and 500 ppm. Humans cannot be ethically subjected to high concentrations of acetone or other chemicals to obtain toxicokinetic data for PBPK model validation. Human metabolic rate constants for high acetone concentrations can be determined by in vitro experiments. Use of this PBPK model for time-scaling for humans would be preferable to the rather arbitrary ten Berge et al. (1986) methodology.

See Bruckner et al. (2004 J. Toxicol. Environ. Health A 67:621-634) for a comparison of the two approaches with trichloroethylene.

The key study is based on oral exposure in rats, which has nothing to do with inhalatory exposure in humans. Moreover, an intraspecies UF of 4.2 gives a false impression of precision.

Page 45, line 43. A more scientifically sound reason for using an interspecies factor of 1 would be the greater systemic absorption of inhaled VOCs by rats (than by humans). As noted previously, the three primary factors that govern the respiratory uptake of VOCs are (1) respiratory rate; (2) cardiac output; and (3) blood:air PC. (1) and (2) are significantly higher in rats than humans, resulting in the rat receiving a greater systemic dose of acetone (upon equivalent inhalation exposures of rats and humans) and therefore experiencing more-pronounced CNS depression. An interspecies factor would not be necessary if PBPK modeling were utilized.

Page 46, lines 1-7. Numerous clinical studies of a variety of inhaled anesthetics have clearly shown that there is modest (that is, two- to threefold) variability in the sensitivity of human subpopulations (including newborns, children, and the elderly). This principle is included in the SOP manual. This committee has consistently recommended the use of an intraspecies UF of 3 for CNS inhibitory effects of VOCs. This factor should be utilized rather than 4.2, a value derived from a single rodent study.

Page 47, lines 3-4. A little more information on the patient described by Ramu et al. (1978) should be provided here in the summary.

Page 47, lines 34-40. Selection of 12,600 ppm as the starting point for the derivation of AEGL-3 values results in 4- and 8-h values that human experiments (see lines 5-8) have shown produce only mucous membrane irritation and modest CNS depression. Adoption of the intermediate NOAEL or lethality (19,000 ppm) reported by Bruckner and Peterson (1981a) would result in more-reasonable AEGL-3 values.

Page 47, lines 41-42. As described above, rats will receive a greater systemic dose upon equivalent inhalation exposures of rats and humans to acetone.

Page 48, lines 1-2. There are a limited number of data points in Figure 2 from which to draw a conclusion about interspecies differences in blood acetone concentrations. Nevertheless, two things are clear: (1) Exercise, which produces increases in respiratory rate and cardiac output, substantially increases internal exposure to acetone (that is, blood concentrations)—see comments above about rats' higher respiratory rate and cardiac output. (2) At the 2,000-ppm exposure concentration, the resting rats have a higher blood acetone concentration than the exercising humans.

Page 48, lines 9-15. Again, it is preferable to use a human anesthesiology-based interspecies UF of 3 for CNS depression caused by VOCs.

Page 51, Table 12. (1) Remove TEEL 0, 1, 2, and 3 from the table because these concentrations are not documented and should not be used.

The 1-h AEGL-2 (3,200 ppm) was based on animal data. The emergency exposure limits (EEL) 8,500 ppm) was based on neurotoxicity studies in humans. Why did the NAC use animal data instead of human data?

COMMENTS ON ACETONE CYANOHYDRIN

At its previous meeting, the committee reviewed the AEGL document on acetone cyanohydrin. The document was presented by Jens-Uwe Voss of Germany.

General Comments

The major comments of the committee were addressed. The discussion of the mechanism of action for acetone cyanohydrin was revised. The AEGL-1 value is now based on hydrogen cyanide. All editorial comments were also appropriately addressed.

A revised document can be finalized if the committee's recommended revisions are made appropriately.

Revisions Recommended

The sentence footnoted on Tables 5, 6, 7, and 8, "Therefore always a mixed cyanide and acetone cyanohydrin exposure will result from acetone cyanohydrine release" should be deleted because it may not be a mixed exposure if all the material is converted to cyanide. Also, this sentence is not necessary; the explanation is adequate without it.

The phrase "be measured" should be deleted from the footnote sentence, and it should read "Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered."

Page 21. The figure is missing the AEGL-1 and -3 labels, and the AEGL-2 designation is misplaced.

COMMENTS ON CARBON DISULFIDE

At its previous meeting, the committee reviewed the revised AEGL document on carbon disulfide. The document was presented by Jens-Uwe Voss of Germany. A revised document can be finalized if the committee's recommended revisions are made appropriately.

Summary

The proposed AEGL values appear appropriate. Time scaling for derivation of the AEGL values appears appropriate. The use of UFs appears appropriate.

The document is generally well written. Many reports are reviewed, but the import of the data presented might be clearer if more-concise summaries of the individual reports were used along with summary data tables (for example, Table 4 on page 18). The discussion of developmental effects is quite good but should be condensed (Figure 1 is very helpful in this regard).

General Comments

This is, in general, a well-written document. It includes much valuable data, including interesting, hard-to-find literature. An adverse effect of this is that the technical support document (TSD) is very long—too long in places. It can be improved greatly by deleting a number of details and repetitions

(some phrases appear as many as three times). It could be pruned down to approximately 50% the present size without losing relevant information, which would result in improved readability.

Many reports are reviewed, but the import of the data presented might be clearer if more concise summaries of the individual reports were used along with summary data tables (for example, Table 4 on page 18). The discussion of developmental effects is quite good but should be condensed (Figure 1 is very helpful in this regard).

There are many spelling and grammatical errors in the report, which need to be corrected.

There is inconsistent use of units and a mix-up of generic and trade names. These should be harmonized. The metabolism of ethanol is not correctly described.

Although the SOP (pages 124-125) requires concentration to be expressed in the units used in the original text, an application of this would lead to confusion. In this TSD, the blood alcohol concentration is expressed as "0.75 ‰ (permil)." The Freundt et al. (1976b) paper uses the European convention for the units of blood alcohol concentration (BAC), which is, by the way, not followed in several European countries (g/L is preferred instead). The units in the United States would be expressed as %, mg/dL, or gm/100 mL. Given the target audience for the AEGLs, particularly the Executive Summary, it may be appropriate to insert an alternative unit in parentheses, for example, "level of 0.75 g/L (75 mg/dL)."

Similar reasoning applies to other differences in conventions (for example, the use of comma separators in large numbers [see page 1, line 18, where the Anglo-Saxon convention would write the number as 900,000 tons]). In these cases, the comma separator should be used to separate at thousands (that is, at every 10^3 increment).

The proposed AEGL-2 and -3 values appear appropriate. Time scaling for derivation of the AEGL values appears appropriate. The use of UFs for AEGL-2 and -3 appears appropriate. For AEGL-1, see comment at page 52.

Specific Comments

Page v, lines 8-9. Change to read "A wide range … was reported" (changed word underlined).

Page v, line 17. Change to read "toxicokinetic" (changed letter underlined). Make the same change elsewhere in the document for this spelling.

Page v, lines 18-19. Change to read "It ~~must~~ also must be taken."

Page v, line 26. Change to read "… may accumulate with repeated …" (changed word underlined).

Page v, line 33. Change to read "… on the CNS ~~already~~ led to an …."

Page vi, line 2. Change to read "… lacrimation …" (changed letter underlined). Make the same change elsewhere in the document for this spelling.

Page vi, line 4. Change to read "… difficulty in performing tasks …" (changed words underlined).

Page vi, line 12. Change to read "… person served as their own …" (changed words underlined). As an alternative to "their," "his or her" can be used.

Page vi, line 23. Change to read "… allele …" (added letter underlined). Make the same change elsewhere in the document for this spelling.

Page vi, line 34. Change to read "… derivation of the AEGL-2 …" (added words underlined).

Page vii, line 31. Change to read "Newark, DE" (changed letter underlined).

Page viii, line 22. Change to read "… lipid composition by …" (added letter underlined).

Page viii, lines 11, 18, and 27; page ix, line 7. These four references place the first initial of the last-cited author in front of the author's last name; all the other references place the initial after the last name (compare, for example, page viii, lines 11 and 14). For consistency, use the same format as in the other references cited. Review the references listed on pages 63-73 for similar consistency.

Page 1, line 5. Not everyone is familiar with decaying radish and will not recognize its smell. The smell of overcooked cauliflower will be better recognized. Change throughout the document and page 12, line 5.

Page 2, line 4. "Toxicity" rather than "lethality." The human toxicity data should be subdivided in 2.1 *acute* and 2.2 *chronic* (mostly occupational) toxicity. A division between lethal and nonlethal is unusual and incorrect. Neurotoxicity (both central and peripheral) is the most well-known effect of CS_2 and should be emphasized here. A concise review is Verberk in *Vinken & Bruyn's Handbook of Clinical Neurology, Vol. 64* (1994) pages 23-29, but any recent source of medical toxicology will do (like Dart 2004, pages 1182-1184, which gives a good scheme of CS_2 metabolism as well).

Page 3. Sections 2.1.1 and 2.2.1 have the same title. Clarify. Also, what is the rationale for including descriptions of noninhalation studies in the TSD?

Page 4, line 7. Is the concentration range 400-470,000 ppm, or 400,000-470,000 ppm?

Page 4, lines 10-11. The sentence currently reads "… measurement of cerebral flow showed reduced cortical flow in the right hemisphere." The presumption is that this refers to cerebral *blood* flow. If this is the case, change the sentence to state that.

Page 4, line 13. Remove "during consciousness."

Page 4, line 21. This sentence is unclear. Clarify.

Page 5, line 1. What are *bloody* bowel movements? State more precisely.

Pages 6-9. Although the Lehman (1894) paper is very interesting reading from a medico-historical point of view, the dedication of so many pages (with repetitions further in the TSD) is not necessary. One should realize that it is an open study with only two (nonblind) volunteers and no control group, with all the disadvantages linked to this experimental design. Moreover, the air concentrations of CS_2 were not monitored. The study is (justly) not used for the derivation of AEGL values and should therefore be condensed into no more than one or two paragraphs.

Page 5, line 7 and 14. "Psychic" should be replaced by either "neurologic" or "psychiatric."

Page 9, line 31. "Pharmako" and "toxiko" should read "pharmaco" and "toxico" throughout the document.

Page 9, line 32. Define "W."

Page 10, line 27 sqq. Is there anything known about differences in the elimination kinetics of alcohol between exposed and nonexposed workers? This is essential information because it could

discriminate between increased CNS sensitivity and decreased elimination as the mechanism of CS_2.

Liver enzyme nomenclature: GOT should be referred to as ASAT and GPT is called ALAT nowadays. Change throughout the document and on page 15, line 23).

Page 11, line 15 sqq. Apparently, CS_2 inhibits the second step of the ADH oxidative pathway. This should be mentioned because it explains the increased intolerance to alcohol in CS_2- exposed workers. Give a scheme of both ethanol oxidative pathways (ADH and CYP2E1) to clarify this.

Page 15, line 19. Replace "alcoholized subjects" with "subjects given alcohol."

Page 15, line 30, to page 16, line 8. Reduce quotation of Lehman and expend neurotoxicity data.

Page 19, line 36. Change "exsiccator" to "desiccator."

Page 22, Table 5. Some entries describe effects at different exposures or at different times during an exposure (see, for example, Frantik 1970 and McKenna and DiStafano 1977b). In instances like these, it would be much clearer to align the statements in the Effect column with the relevant entry in the Concentration or Exposure column(s).

Page 26, line 24. Change "trail" to "trial."

Page 28, line 21. Disulfiram is the generic name of Antabuse; the generic name should be used throughout, with the trade name in brackets when disulfiram is mentioned for the first time.

Page 48, line 1; page 49, line 17. Dithiocarbamates (change underlined). "The alcohol inducible isoenzyme": clarify. What is meant is that the CYP450 isoenzyme that can be induced by *ethanol* (never use *alcohol* where *ethanol* is meant). Here, a short survey of the two known pathways of ethanol metabolism should be given (the noninducible ADH-/AlDH-pathway and the inducible CYP2E1-pathway).

Page 48, line 22. P-450 dependent pathway is confusing; the P-450 isoenzyme in dependent on substrates (it is a mixed-function oxidase) and coenzymes, but not on itself.

Page 51, lines 3-20. These data are not relevant for the present TSD and should be deleted or condensed. It suffices when the disulfiram syndrome is mentioned only once in the paragraph where ethanol metabolism will be described.

Page 52, line 31; page 53, line 12. There is no consensus in the committee about the use of the key studies by Freundt et al. for derivation of the AEGL-1, because it is remarkable that this is based on data obtained in a population under the influence of alcohol. 0.7 g/L (70 mg/dL) cannot be described as "low to at most moderate" concentrations, because this concentration exceeds the legal limit for driving in most states and countries; several countries consider lowering this limit to 0.2 g/L (20 mg/dL) as it is in several European countries. Although the majority of the committee agrees with the use of this "sensitive subpopulation," more arguments should be given to defend this decision.

The UF of 10 is based on the fact that there is a population subgroup with atypical aldehyde dehydrogenase whose members are more sensitive to the disulfiram effect of CS_2 than "ordinary" ethanol consumers. In fact, sensitivity is now counted twice: once for alcohol consumption per se

and once for atypical metabolisers. In addition, it is unlikely that these atypical metabolisers will drink as much ethanol as ordinary metabolisers, because they feel unwell after drinking small amounts of alcohol. Additional exposure to CS_2 may contribute to them feeling unwell, but it does not justify a UF of 10; a UF of 3 would suffice. An additional advantage of lowering the UF to 3 is that the resulting values for AEGL-1 will be more in accordance with other exposure standards, the Threshold Limit Value (TLV) being 10 ppm.

Page 56, lines 2-14. Delete referral to the Lehman study because it is not used for the derivation of AEGL values.

Page 68, lines 5-6. The HSDB is now the National Library of Medicine Hazardous Substance Data Bank at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB/.

Scientific Comments

Derivation of AEGL-1

Page 53, lines 17-18. Change the phrase "… can be assumed not to cause …" to something like "… are unlikely to cause …." This is based on the wide range of odor sensitivity in the human population, the variability of reactions to odors, the data on odor perception on pages 12-13, and the information on the presence of malodorous impurities and the formation of decomposition (or reaction?) products in the presence of light and air (page 1, lines 2-6, and page 53, lines 19-22).

Derivation of AEGL-2

Page 55, lines 16-18. Is this a general statement (comparability of the effects in rodents and humans), or can it be made stronger by citing specific CS_2 data?

Page 55, lines 20-22. Cite the SOP manual as the source for this statement, with page number (NRC 2001, pages 79-80) and add the citation on page 57, line 2.

COMMENTS ON ALLYL ALCOHOL

At its previous meeting, the committee reviewed the AEGL document on allyl alcohol. The document was presented by Claudia Troxel, of Oak Ridge National Laboratory.

Major Issues

For the derivation of the AEGL-3 value, the committee recommends using two different end points—irritation and then systemic effects for longer-duration exposures. A UF of 3 will be used to account for interspecies differences. An intraspecies UF of 10 was selected, and then an adjustment factor of ⅓ was applied. The rationale was that the AEGL values with the adjustment are more consistent with the data primarily from repeat-dose studies that do not show significant effects at concentrations that would be derived without the adjustment. This awkward approach is not necessary. An intraspecies UF of 3 can be supported based on the available data set consisting of toxicology studies in six animal species (monkey, dog, rabbit, guinea pig, rat, and mouse). These studies provide consistent toxicologic findings. In addition, the mechanism of action has been reasonably well studied (see section 4.1 Metabolism and Mechanism of Action), because the reactive metabolite has been shown to be acrolein. The SOP manual

states that an intraspecies UF of 10 is appropriate when the mechanism of action is not known or studied (2.5.3.4.5). Further, the SOP manual states that UFs are derived based on the supporting data from human or animal studies (2.5.3.4.6). By doing this, there is no need to use an adjustment factor to derive the AEGL-3 value.

An additional modifying factor of 2 was used (page 21, line 26) for the 1-h AEGL to obtain the 4-h AEGL. The factor was only used for the derivation of the 4-h value from the 1-h value, and the 8-h value was held to the same concentration as the 4-h value. Rationale for these treatments are not provided. There is no clear basis for use of this factor. More importantly, the results are not consistent with the LC_{50} values in rats stated on page 5, line 11, to be 1,060, 165, and 76 ppm for the 1-, 4-, and 8-h exposures, respectively. The data from Dunlap et al. (1958) show a time dependency for acute toxicity for allyl alcohol from 1 to 8 h, and the modifying factor adjustment and subsequent flat-line treatment are not supported by the data. The committee recommends the use of the default extrapolation.

The basis is lacking for use of 5-minute (min) eye-irritation data to derive 4- and 8-h AEGL-2s on a compound where the toxicology data consistently show toxicity to the liver and kidney with increasing exposures from 1 to 8 h. Either provide a sound basis or do not extrapolate the data out to the prolonged exposures.

Appendix A. For AEGL-1 and AEGL-2, $C^n \times t = k$ was not used when using data from 5 min extrapolated to 10 min. The assumption is that this is because allyl alcohol is a direct-acting irritant. If this is the case, it should be stated as such; otherwise, $C^n \times t = k$ should be used.

Page 4, lines 3-6. Odor detection thresholds are available and described; however, no mention of an level of distinct odor awareness (LOA) is made. Provide the derivation of the LOA or the rationale for why the data do not permit one to be derived.

Page 35, line 27. The more common approach is to apply $C^n \times t = k$ and then apply the adjustment factor, rather than applying the adjustment factor to the concentration in $C^n \times t = k$.

Specific Comments

Page vi, lines 22-23. The number of positive respondents, and not the steepness of the dose-response curve, supports the factor of 3. Delete the reference to the steep dose-response curve.

Page vi, lines 29-30. Point of departure? Why not just call it the NOAEL?

Page 8, line 28. Make the following change: "Four guinea pigs were individually exposed in a bell jar, with allyl alcohol present in a petri dish below the jar (Adams 1958)."

Section 7.3. Same comments as the Executive Summary for AEGL-3.

Page 24. Category Plot. AEGL-3 line is not labeled. A review of this data is probably a better explanation for AEGL-3 than the adjustment factor of 3 and modifying factor of 2 argument. The values here indicate that the 4-h AEGL-3 has an overall factor of slightly less than 100 and just slightly greater than 10 at 7 h.

COMMENTS ON ACROLEIN

At its previous meeting, the committee reviewed the AEGL document on acrolein. The document was presented by Cheryl Bast, of Oak Ridge National Laboratory.

Summary

This TSD is short and succinct. The interim AEGL values appear reasonable given the data base used to derive them. The UFs used appear to be reasonable, based on the available data. Time scaling appears to be appropriate. The revised document can be finalized if the committee's recommended revisions are made appropriately.

Scientific Comments

Page 2, line 14; page 9, lines 33-34; page 10, lines 19-20; page 21, lines 44-45. The point of departure for the derivation of the AEGL-1 values is the eye irritation that was observed at 0.09 ppm. In principle, the starting point for derivation of an AEGL value should be a NOEL ("AEGL … is the … concentration above which it is predicted that …"). However, it is clear from Figure 4 in Weber-Tschopp et al. (1977) that this effect was extremely minimal (very much below the label "a little"). Thus, this point of departure appears to have been well selected. However, it must be clearly explained, and the effect should not be given in the text just as "irritation," but rather should be qualified as "very slight irritation."

Page 22, lines 10-11. "The threshold for these effects is 0.09 ppm" is not correct. No lower concentration was investigated; hence, what would have been observed at lower concentrations is not known. Replace with (for example) "lowest investigated dose."

Page 33, lines 44-45. Only (very slight) ocular irritation started at 0.09 ppm, not nasal and throat irritation (nasal irritation started at 0.15 ppm, and throat irritation started at 0.43 ppm).

Human Toxicity Data

Page 9, line 33. This is the first mention of an exposure concentration of 0.09 ppm. Because this experiment, and this value in particular, is used to derive the AEGL-1, it would be helpful to construct a table of the time points at which concentrations were measured during the "continuous" exposure experiment and the concentrations measured. This would also help interpret the data on eye blink rate presented at the bottom of the page and continuing onto page 10.

Page 9, line 46, to page 10, line 1. The phrasing can be interpreted to mean that eye blink rate was significantly different from control values only at the time point when the concentration was 0.26 ppm. If the rate was significantly different from that point on in the experiment, change the sentence to read "… the increase became significant ($p < 0.01$) once the concentration reached 0.26 ppm acrolein" (changed words underlined). (Compare to phrasing at page 10, lines 9-10.)

Page 10, Table 2. The title refers to subjective effects but has entries for blinking rate and respiratory rates, which are objective measures. The committee recommends deleting the word "subjective" from the title and from the title of Table 3 on page 11. Also, change the entries in the List of Tables on page 6.

Page 11, line 30. Does "no clear concentration-response" mean no significant difference?

Page 11, lines 32-34. Is this the conclusion of the authors of the study (Darley et al. 1960)? If so, change it to read, "The authors concluded that …." If this is the conclusion drawn by the author(s) of the AEGL document, it might be better to state that the conditions of the study did not allow distinguishing between slight irritation caused by other constituents of the greenhouse air, or even air movement in the eye mask, and that caused by acrolein at 0.06 ppm. This phrasing would be more appropriate given the statement on page 22, lines 23-24.

Animal Toxicity Data

Page 19, line 17; page 20, line 5. Why equivocal? Genotoxic substances rarely are positive in all genotoxicity tests, because of the specificities of the individual tests.

Page 21, lines 7-8. Adduct formation of acrolein with glutathione, cysteine, and other thiols may, on one hand, ameliorate the toxicity of acrolein (as is stated in the text) but may also substantially contribute to the toxicity of acrolein (by depletion of such important cellular molecules). This is expected to be fundamentally different at different doses of acrolein: protective at low doses of acrolein, substantially contributing to toxicity at high doses.

Data Analysis for Proposed AEGL-1

The approach and values are supported by the data.

Page 21, lines 44-45. Only ocular irritation is stated to occur as a result of exposure to 0.09 ppm on page 9, lines 33-36. Add the exposure duration to this statement and to page 22, lines 10-11.

Data Analysis for Proposed AEGL-2

The point of departure for the derivation of the AEGL-2 of a decrease in respiration in humans exposed to 0.3 ppm for 1 h is appropriate.

The use of 3 for intrapsecies uncertainty is based on the rationale that irritation is not thought to differ among individuals; however, there is little basis given for the decrease in respiration to be assumed to be attributed solely to local irritation, because it could involve a central response. If available, provide the evidence for a decrease in respiration to be mechanistically a result of local irritation. There are several reasons for the use of 3 as the intraspecies UF. Alternative scientific explanations include the sensitivity of the methods used; the fact that the point-of-departure effect was only a very small detectable decrease in respiration; the lack of evidence of marked variability across the study group, including women; and the fact that at twice the concentration, respiration was still only slightly decreased.

Page 22, lines 30-31. Add the exposure concentration(s) and duration(s) to this statement.

Page 23, lines 14-16. The derivation of n = 1.2 needs to be presented in an appendix as indicated in the SOP manual (see §2.7.5, §3.1, and Appendix G).

The AEGL-2 is based on respiratory irritation (lines 3-10). The derivation of the time-scaling factor *n* is based on lethality. The source of the data for this derivation (Ballantyne et al. 1989, page 12)

should be cited here. A statement should also be made that the underlying mechanism of action for both the AEGL-2 effect and lethality are considered to be sufficiently similar as to permit the application of the value of *n* from lethality data, as described throughout §2.7.5. to §2.7.8. of the SOP manual, pages 98-110.

Data Analysis for Proposed AEGL-3

Use of 3 for the interspecies UF is appropriate, but the rationale should be changed to be science based. It is more appropriate to base the value on the fact that the toxicity data is fairly consistent across five species of animals (SOP manual section 2.5.3.2.3) and that the values obtained are more consistent with the human data available (SOP manual, section 2.5.3.2.8).

The use of 3 for intraspecies UF is based on the steep dose response in the rat, but the intraspecies UF is for variability in humans, not rats. Based on human and animal data from five species, the mechanism was not thought to vary (SOP manual, section 2.5.3.4.4). Further use of a higher value for the intraspecies UF would result in a value that would conflict with the actual human data available (SOP manual, section 2.5.3.4.6).

Summary of Proposed AEGLs

Page 26, lines 48-50; page 27, lines 1-2. Are there specific studies that can be recommended?

Other Scientific Issues

Cancer discussion in Section 3.5 for acrolein does not contain the carcinogenicity information for acrolein that was included in the cancer discussion for allyl alcohol (page 12). The information should be fully described.

Page 23, line 5. There is an error. The study by Weber-Tschopp et al. (1977) did not expose humans to 0.6 ppm for 1 h.

Editorial Recommendations

In the Weber-Tschopp et al. study, the authors used three exposure protocols. The first one they call "continuous." It was continuous exposure in the sense that acrolein was continuously present—however, it was not at constant but at continuously increasing concentrations (last paragraph in Methods). Thus, it was not what would be understood by labeling it simply "continuous" without explanation or qualification (perhaps explain at first occurrence and subsequently have the term in quotes). This should be clarified throughout the document starting with page 8, line 32.

Page 2, line 1. For consistency call this "Executive Summary."

Page 2, line 7. What should "biocide" indicate in addition to " herbicide, algicide, slimicide"?

Page 2, line 27. Change "full" to "default" when referring to a UF of 10, here and elsewhere in the document.

Page 3, line 2. Change to read "It is unlikely that people exposed to…" (changed words underlined). Make the same change at page 24, line14, and on page B-4, line 20.

Page 6, line 9. Change to read "Subjective Effects in Human Subjects" (reversed words underlined).

Page 7, line 35. Place comma between acetone and benzene.

Human Toxicity Data

Page 8, line 9. Probably bronchial lumen is meant.

Page 8, line 41. Replace the colon with a comma.

Page 9, lines 4-9. Clarify the description of the second experiment. It is 5 repeat, 1.5 min exposures with 8 min in between. The current text is not clear.

Page 9, line 16. Change "uL" to "uL."

Page 10, line 2 and 8; Table 2, footnote. The 1-h exposure is called "prolonged." Ordinarily, this would not be the term to use for an exposure of this duration unless it is being used to indicate the subjective experience of breathing acrolein vapor. Not using the word is suggested.

Page 12, line 12. "... containing no verifiable concentration and time parameters": this is an apparent contradiction to page 8, lines 5-6.

Page 13, Table 4. The entry for Time To Death for an exposure of 4 h to 9.1 ppm shows 1-13 d. Should this be 1-3 d, or does it indicate a late death? The description of the experiment on page 12 is not clear about the duration of the postexposure observation period.

Page 18, line 37. Eliminate the hyphens in "intra-septal" and "intra-alveolar."

Page 19, line 44. Drop "and."

Page 20, line 18. Replace "epoxide hydrase" with "epoxide hydrolase."

Page 22, line 12. Cite the SOP manual, page 90, §2.5.3.4.4, for this conclusion. Inserting the sentence at lines 23-24 at this point more directly supports the use of the intraspecies UF of 3.

Page 22, lines 14-15. Cite the SOP manual, page 106, for this conclusion.

Page 23, lines 10-11. Cite the SOP manual, page 90, §2.5.3.4.4, for this conclusion.

Page 23, lines 17-18. Cite the SOP manual, page 106, for this conclusion.

Page 26, lines 31-42. This material appears to be redundant and should be deleted.

References

Check the alignment and indentation of the entries for consistency.

Page 27, lines 6-7. Verify completeness of citation.

Page 27, lines 9-10. The Web version of this document may not be generally available. It might be best to cite the hard-copy version for general reference.

Page 27, lines 20-21. The citation appears incomplete. What is the book title? Is 234 a page number? "Ed." should not be capitalized.

Page 28, line 28. Do not capitalize "and."

Page 28, lines 40-41. The IPCS INCHEM is now available online at http://www.inchem.org/, and this would be a good general reference, more accessible than a print document (although it's a big database, and a more specific URL would be helpful in finding the material being cited here).

Page 29, line 19. This extra line can be deleted.

Page 29, lines 37-38. This reference is now available online at http://www.cdc.gov/niosh/idlh/idlh-1.html.

Page 29, lines 40-41. This reference is now available online at http://www.cdc.gov/niosh/npg/npg.html.

Page 30, lines 4-5. Do not capitalize "and."

This reference document states that this reference is cited in AIHA 1989, but that reference is not in this bibliography.

Page 30, lines 7-8. There appears to be one or more words missing from the title of this article.

Page 30, lines 10-11. Is this reference also available online, perhaps through the IPCS INCHEM database?

Appendices

Review the alignment and indentation of entries in Appendices A and B.

Page A-2, line 12. It might be easier to simply say "for all exposure durations" rather than listing each of the exposure times for the AEGL-1 values.

Pages A-3 and A-4. As used on these two pages (and the previous one), some abbreviations for minutes and hours use a period and some do not. For consistency and clarity, do not use the period.

Page B-2, line 11. Although it is obvious what the exposure route is, the title for this box on the form calls for it to be stated explicitly (same for page B-3), and this is done on page B-4.

Page B-3, line 13. State the "rationale" explicitly for this entry.

Page B-4, line 7. Delete "concentration."

Page B-4, lines 9-11. This information belongs in the next box, End Point/Concentration/Rationale.

Page B-4, lines 22-25. Put material in parentheses at the end of the sentence for better clarity.

Page B-4, lines 28-30. Refer to derivation and graph in appendix to be added for time scaling.

Page C-2. The ppm scale is not correct below 1 because the zeros should be labeled 0.1 and 0.01. The label for AEGL-2 line has "2" missing.

The human data described from the Weber-Tschopp et al. (1977) experiment with exposures up to 40 min need to be added.

COMMENTS ON CHLOROFORM

At its previous meeting, the committee reviewed the AEGL document on chloroform. The document was presented by Robert Young, of Oak Ridge National Laboratory. The document can be finalized if the committee's recommended revisions are made appropriately.

Major Comments

There is one item that requires further discussion. This has to do with the treatment of developmental toxicity data (Schwetz 1974) as it relates to the key study that was used to derive AEGL-2 values. Some committee members thought that, in light of the PBPK data showing that humans are less susceptible to the effects of chloroform, that the data could support higher AEGL-2 values. Others thought that the AEGL-2 values were appropriately conservative.

A conservative interpretation of developmental toxicity data is that the effects can occur as a result of a brief window of exposure. This has been demonstrated experimentally with several chemicals and was demonstrated early on in the classic case of thalidomide. Many (including the Emergency Response Planning [ERP] Committee) believe that this approach is most applicable with frank teratogenic effects (for example, cleft palate, exencephaly, anophthalmia) occurring during organogenesis.

A second approach is to take into consideration the fact that most developmental toxicity studies involve a chemical exposure over the entire gestation period. In the case of chloroform, in Schwetz et al. (1974), there was a group of findings that could have been secondary to repeated toxic insult or to maternal toxicity, with the resultant developmental variations, such as wavy ribs and delayed ossification, that can occur as a result of toxicity and delayed development. In these cases, it was suggested that these effects should be considered to be a result of repeated exposure rather than a single exposure.

The committee suggested that the NAC consult with an experienced developmental toxicologist about this issue. Bryan Hardin, of the National Institute for Occupational Safety and Health (NIOSH), was one experienced person that was suggested because he has broad experience in developmental toxicology and emergency planning. Another name was Carol Kimmel of EPA. Another developmental toxicologist is Eve Mylchreest of DuPont, who is quite experienced.

The following are some questions that should be addressed:

- When should the window approach be used, and when should we take into consideration the repeat-dose nature of these developmental studies? Should the approach depend on the effects observed?
- What if the developmental effects occur in the presence of maternal toxicity?

- How should we treat pre-implantation and implantation losses such as those seen at 300 ppm in the Schwetz et al. study?

Specific Comments

Page 6. This seems to be a deviation from format. There is no Executive Summary that is numbered with small roman numerals.

Page 6, lines 7-11. Make the following change:

> AEGL-1 values were not recommended. Based upon the available data, attempts to identify a critical effect consistent with the AEGL-1 definition were considered tenuous and uncertain. Exposures of humans to concentrations approaching those inducing narcosis or possibly causing hepatic and renal effects (AEGL-2 effects) are not accompanied by overt signs of symptoms. Furthermore, the odor of chloroform is not unpleasant or irritating.

Page 25, line 31. It's suggested that the following be added: "At 100 ppm, frank teratogenic effects (that is, imperforate anus and acaudia [missing tail] were observed in three litters)."

Page 25, Table 5. Under total gross anomalies, the 100 ppm column, the incidence should be 3/23.

COMMENTS ON PERACETIC ACID

At its previous meeting, the committee reviewed the AEGL document on peracetic acid. The revised document was presented by Kowetha Davidson, of Oak Ridge National Laboratory. The revised document can be finalized if the committee's recommended revisions are made appropriately.

Summary

This is a well-written, concise document based on well-performed key studies. It is applauded that these studies were traced, because they have not been published in the "open" literature. The proposed AEGL values appear appropriate given the limited data base for their derivations, except for some uncertainty regarding the severity of effects anticipated at the shorter AEGL-3 exposure durations and their potential impacts (as addressed below). Time scaling for derivation of the AEGL-3 values appears appropriate. The use of UFs appears appropriate.

General Scientific Comments

The proposed AEGL values are all derived from unpublished, non-peer-reviewed reports. Is there a mechanism (for example, posting them on a Web site) to make these documents generally available? If the documents are or can be made available, the location(s) where they can be accessed should be included as part of the bibliographic reference (for example, EPA Docket No. xxxx, at URL xyz, or ORNL Web site URL xyz).

There is some question as to whether AEGLs for peracetic acid alone can be proposed, given that peracetic acid apparently never appears unaccompanied by hydrogen peroxide and acetic acid, compounds with similar irritant and corrosive properties. Exposures to peracetic acid alone are therefore most unlikely, and in fact, appear to occur in commercial mixtures of these three compounds, along with other compounds which may be proprietary. Because peracetic acid is chemically unstable, the relative concentrations of the various corrosive components also may vary.

In this case, peracetic acid appears to be the most toxic of the components, but there is some uncertainty regarding potential contributions by one or more of the other components to the toxic effects seen. Does this uncertainty need to be addressed in the values of the UF used or by use of a modifying factor (MF), or perhaps by retitling the document Peracetic Acid Solutions or something similar?

How important is it to obtain the composition information for mixtures when only the ingredient of concern is reported?

In this context, the inclusion of the third paragraph of the Introduction and of Section 4.4.4 is very helpful.

Specific Scientific Comments

Page 2, Table 1. Proxitane formulations are listed as synonyms although the name clearly refers to a mixture. Is this name commonly used as a synonym? Would it be more accurate to add a box to the table for trade names because others are referred to in the document?

The conversion box should indicate that the equation is valid at 25°C, or at normal temperature and pressure (NTP. The SOP, § 2.9.3. on pages 122-123, specifies that NTP is to be used.

The conversion equation is in error; it appears that the units have been reversed. For peracetic acid at NTP, 1 ppm = 3.110 milligrams per cubic meter (mg/m^3), and 1 mg/m^3 = 0.321 ppm.

Page 3, lines 6-23. The Fraser and Thorbinson (1986) report is used to derive both the proposed AEGL-1 and -2 values.

The material used was called Peratol, which had a specified concentration of peracetic acid but no other composition information. Has anyone obtained the composition information to verify that it was similar to the other trade name products studied (for comparison purposes) and that there were no unusual components that may have affected the effects reported? This also applies to Persteril, discussed on page 7, Section 3.1.2.

The analytical method used is not described, only referred to by a method number (Interox analytical method number S 15200 M 42C), and the concentrations are reported as "ppm (as H_2O_2)." Has anyone obtained a copy of this method and checked that the results it produces are comparable to methods used in other analytical methods (for example, Janssen 1989a)? Based on the citation for McDonagh (1997), Interox is a component of the Solvay corporation.

The SOP manual (pp. 124-125) requires concentration to be expressed in the units used in the original text. In describing the findings from Fraser and Thorbinson (1986) in which all concentrations are expressed as ppm, the values have been converted to mg/m^3, and ppm values are not used. Although there is value in providing the converted values for ready comparison, especially because other references use concentrations expressed only in mg/m^3, the original values need to be preserved, as prescribed by the SOP manual.

Page 5, lines 30-34. While it appears that peracetic acid is more toxic, how likely is it that exposure will occur in the absence of the other significant components of most commercial mixtures (acetic acid and hydrogen peroxide)? Since both peracetic acid and acetic acid seem to act on their common target organ, the respiratory tract, in a similar manner, is it appropriate to address this question? See, for example, page 16, line 30, where the mouse RD_{50} (dose that causes a 50% respiration rate decrease) for acetic acid is reported as 400 mg/m^3; although the Janssen (1989a) study used rats, this value was exceeded by a factor of 5 or more in each exposure that produced mortality. One way to address this is to note that the RD_{50} for peracetic acid in rats is about 22 mg/m^3, as stated on page 9, line 27, and that the exposures in this study exceeded that by a factor of more than 14.

Similar consideration might be given to hydrogen peroxide. See, for example, Table 4 on page 7, where the exposure for Group B animals exceeds one-half the LD_{50} for this compound.

Page 10, line 40. Exposure is identified as being 7.2-72.0 mg/m^3 for 4 h. This needs to be described better. Was this a constantly increasing exposure concentration? This value from the Benes et al. (1966) article is cited later in the document (page 19, lines 16-17), and the ambiguity regarding the concentration makes it difficult to place in context.

Page 15, Section 4.2. This would be a good place to refer to any data or the specific section in the SOP manual that supports the assertion that effects of exposure to corrosive and irritant materials like peracetic acid are expected to be similar across species and within populations, the justification used to support the selection of UFs of 3 in the derivation of all proposed AEGLs.

Page 15, Section 4.4.3. The derivation of *n* should be shown, either in the text here or in an appropriate place in an appendix, because it is used in the calculation of the AEGL-3 values, whose derivation calculations are shown.

Page 17, lines 27-28. Is this statement about the inconsistency of depression of respiratory rates in rats exposed to irritants based on the results cited in the previous sentences, or is it a conclusion based on data reported elsewhere? If the latter, what is the reference?

As a follow-on: line 39 refers to the effects reported in lines 25-27 as marginal. Is this an editorial opinion, or is there a basis (that is, data that can be cited) for this characterization (that a depression of respiratory rates by one-third to almost one-half is marginal)?

Page 18, lines 20-21. The exposure period should be 1 h and 10 min if the sequence used here is the determinant: 55 min at 6.23 mg/m^3, then 15 min at 7.79-9.35 mg/m^3. If the next exposure segment is included, then an additional 10-15 min of exposure to 6.35 mg/m^3 can be added, for a total exposure time at these concentrations of 1 h and 20-25 min.

Page 20, lines 24. The Janssen experiments were nose-only exposures, whereas in an actual exposure situation, humans will be total-body exposed, with the aerosol mix affecting other mucosae in addition to those in the respiratory tract. Serious irritation of the conjunctivae, which can be expected at these higher concentrations, may interfere with the ability to escape, thereby increasing the potential exposure duration. While this effect has been accounted for in setting the AEGL-2 value by using human exposure data, the impact of this effect should be addressed in setting AEGL-3 values. Compare the effects of exposure to 6.23 mg/m^3 for 1 h, as described on page 19, lines 20-25, with the AEGL-3 values for 10, 30, and 60 min. This effect may or may not be relevant but should be addressed in the description and justification of the derivation. It is notable that this rationale has been used by National Institute for Occupational Safety and Health (NIOSH) in revising immediately dangerous to life or health (IDLH) values (see, for example, acetic acid).

Pages 21-22, Section 8.2. The discussion of the Solvay Emergency Exposure Indices indicates that these values were developed, using ECETOC methodology, by the manufacturer for accidental releases. Is there information available about whether these values are for application to occupational populations or to the general public?

Page 22, Section 8.3. Should additional studies be recommended, at very low concentrations, using asthmatic humans? Should additional studies be recommended using high-purity peracetic acid rather than commercial mixtures?

Editorial Recommendations

Page 4, list of Tables. Tables 4 and 9 are missing from the list. The summary table of proposed AEGL values on page 6 of the Preface is listed first; confusion engendered by listing this table on page 6 before Table 1 on page 2 would be avoided by having the Preface page numbers shown in Roman numerals.

Throughout the document, concentrations are referred to as "x.xx mg peracetic acid/m^3." In a document on peracetic acid, it is acceptable (and easier to read) to use "mg/m^3" unless referring to several other chemicals and their concentrations in the same context.

Page 2, lines 29-30. The description of the report by McDonagh (1997) refers to measurements of airborne peracetic acid concentrations without indicating whether the peracetic acid was a vapor or aerosol. Since the distinction is made later (page 3, lines 45-46), it should be mentioned here as well.

Page 2, line 37. The concentration listed here is the only one cited from this reference (McDonagh 1997) that is listed only in mg/m^3. All others are cited in ppm with the equivalent mg/m^3 in parentheses. This should be changed for consistency and ease of reading.

Page 3, lines 25-26. Change to read "of peracetic <u>acid</u> began … observed physiological response<u>s</u>" (inserted word and inserted letter underlined).

Page 3, lines 25-31. The bulk of this paragraph repeats almost word for word the entries in Table 2. Would it not be better to refer to the table for the data and describe it here as "over the course of 45 min, the concentrations declined to below the detectable limit; the severity of the observed effects declined during this period as well," or some similar description?

Page 5, line 33. The parenthetical expression should refer to Section 4.4.4 on page 16, not Section 4.3.

Page 6, line 28. Drop the virgule (/) at the end of the line.

Page 10, Tables 6 and 7. In other tables, the exposure groups were arranged to show increasing exposure to peracetic acid; but in these tables, the groups were left in numerical order. Is there a specific reason? If not, it would be more useful to present these tables in the same way as the other tables—that is, in ascending order of peracetic acid exposure concentration.

Page 10, line 40. The article being summarized is identified in the first sentence of the paragraph in almost every other case. This makes it easy to scan the document to find a particular reference and its summary information. Move the citation from page 11, line 2 (very end of paragraph), forward to this location. This comment also applies to page 12, lines 43-45, and to page 13, lines 4-13.

Page 13, line 26. The paragraph to this point summarizes lethality data. For ease in reading and comprehension, start a new paragraph here that summarizes the nonlethality data.

Page 16, line 11. The text indicates that 227 ppm is an LD_{50} for mice. Checking the reference (online, see citation below), this value is reported as an LD_{Lo} (lowest dose that causes lethality).

Page 20, line 15. Change to read "peracetic acid/m^3 <u>for</u> the 1-hour…" (inserted word underlined).

Page 20, line 28. Change to read "peracetic acid/m^3 <u>for 60 min</u>" (inserted words underlined).

Page 21, line 24. Was the value of *n* estimated or calculated?

Page 21, Table 12. Include, for the AEGL-3 values, the concentrations in ppm; do the same on page 31.

Page 22. There is an American Conference of Industrial Hygienists (ACGIH) 2004 reference and an ACGIH 1991b reference. Is the "b" needed?

Page 23. The HSDB is now the National Library of Medicine Hazardous Substance Data Bank at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB/.

Page 24. The NIOSH IDLH database is also an online database at http://www.cdc.gov/niosh/idlh/idlh-1.html.

Is there a free-access online site for the Registry of Toxic Effects of Chemical Substances (RTECS) database that can be inserted here?

Page 27, line 31. Change to read "AEGL-2 derived" (changed numeral underlined).

Page 28, line 5. Change to read "Highest nonlethal concentration" (changed prefix underlined).

Page 28, line 15. Change to read "individuals are not" (inserted word underlined).

Page 29, line 15. Change to read "…/Number: humans—two subjects (I)…" (shifted word underlined).

Page 30, line 13. Is it appropriate to add "(but tolerable for 2 min)"?

Page 30, line 27. The phrase used here is "a concentration thought to approximate mild irritation." Is this the right phrasing given the description on page 19, lines 22-23 and 29-31?

Page 31, line 22. Change to read "individuals are not expected" (added word underlined).
The phrasing here is inconsistent with page 20, lines 36-39; if the phrasing here was correct, then a UF of 10 would be more logical than the proposed UF of 3.

COMMENTS ON N,N-DIMETHYLFORMAMIDE

At its previous meeting, the committee reviewed the AEGL document on n,n-Dimethylformamide (DMF). The document was presented by Claudia Troxel, of Oak Ridge National Laboratory. The revised document can be finalized if the committee's recommended revisions are made appropriately.

Summary

The proposed AEGL values appear appropriate given the limited data base for their derivations. Support for the derivation of the AEGL values is sufficient, but the question of the utility of AEGL-2 values that are only half the AEGL-3 values should be addressed. Time scaling appears appropriate, and the use of UFs appears appropriate. Recommendations need to be made for specific additional research to improve the AEGLs, given the paucity of the data base.

General Scientific Comments

The proposed AEGL values are all derived from a single unpublished, non-peer-reviewed report. Is there a mechanism (such as posting on a Web site) to make this document generally available? If the document is or can be made available, the location(s) where it can be accessed should be included as part of the bibliographic reference (for example, EPA Docket No. xxxx, at URL xyz, or ORNL Web site URL xyz).

Reference to specific liver enzyme tests and values vary throughout the document, depending on the age of the study cited. While the older terms should be used because they are in the source documents, in accordance with the spirit of the SOP manual, the current terminology should be appended in parentheses for the sake of clarity. For example, on page 5, the old abbreviations SGOT and SGPT are used (lines 9-10); these should be changed to ASAT and ALAT, respectively. The same holds for ALT (ALAT) and AST (ASAT) on lines 16-29 and throughout the document.

Specific Scientific Comments

Introduction

Page 2, Table 1. Because of the significant change in the saturated vapor concentration with a small change in ambient temperature (see page 9, line 22), it would be appropriate to have an entry in this table for both of these values (saturated vapor concentrations at 20°C and 25°C) to indicate the rapid change that occurs with this chemical—an increase of one-third over this commonly encountered 5°C change in temperature.

If the data are available, additional values for the saturated vapor concentration at 35°C (95°F) and 45°C (113°F) should be determined to assess the potential impact on the use of the AEGL values. If the potential impact appears significant, a note to that effect should be added in the text for reasons analogous to noting the potential for significant skin absorption to contribute to the overall exposure.

Page 21, lines 7-17. It might be useful after this discussion of the saturable metabolism of DMF, to insert a short discussion about DMF inhibiting its own metabolism and that of its metabolites (Mraz et al. 1993). This would be the appropriate context and would not detract from the mention of these findings and their application to the excretion of AMCC on page 22, lines 3-5.

Page 21, lines 21-23. Is there a way to present this information on quantitative differences in absorption across routes of exposure in the previous section ("Absorption and Distribution") on page 20?

Page 23, Figure 1. While the pathways as diagrammed in Gescher 1993 are cited and shown, they are not as useful in following the discussion of the postulated toxic intermediate as Figure 1 is from Mraz et al. 1993. This latter diagram is much clearer regarding the alternative pathways and the formation of the postulated toxic intermediate and provides structural information that helps in following the discussion. For improved clarity, the Mraz et al. pathway should be substituted for the Gescher one.

Page 24, lines 8-22. The basic metabolism of ethanol is a two-step process involving a noninducible ADH/AldDH pathway. The first step is the oxidation of ethanol by alcohol dehydroxygenase to acetaldehyde. The second step is the oxidation of acetaldehyde by aldehyde dehydrogenase to acetic acid. This is the step inhibited by, inter alia, disulfiram and most likely by DMF (with the exact mechanism being unknown), thereby causing a disulfiram-like effect. An unrelated second

pathway involves CYP2E1, which is inducible and which also leads to the formation of acetic acid. The interpretation advanced by Mraz et al. (1993, citing Terelius et al. 1991, reference 45 in the Mraz et al. article) that DMF inhibition of CYP2E1 leads to an increase in acetaldehyde (lines 21-22) is open to debate. It is also possible that it could lead to a decrease as CYP2E1 is supposed to also oxidize ethanol to acetaldehyde.

Pages 26-27, Section 6.3, Derivation of AEGL-2. Setting the AEGL-2 values at half the AEGL-3 values requires consideration of the ability to distinguish between the two in the field. The values may be too close to separate, leading the emergency planner in practice to always take measures conforming with the AEGL-3 definition. This issue should at least be mentioned in this section.

Page 27, line 6. Would it be reasonable to include the human data from Kimmerle and Eben 1975b in this statement? The argument made on page 28, lines 23-27, for AEGL-3 values applies equally as well here for AEGL-2 values.

Pages 27-29, Section 7.3, Derivation of AEGL-3. Human data presented in earlier sections indicates that DMF is a human hepatotoxicant (see page vii, line 15, and page 4, lines 21-26 and 37-42). While these observations were of occupationally exposed workers, the effects described are serious. Toxic liver injury may evolve to chronic aggressive hepatitis and cirrhosis of the liver, a lethal condition. This hepatotoxicity has to be taken into account in the risk assessment of this substance, even for acute exposures. While the discussion of the UFs applied to the key study for the AEGL-3 on pages 27-28 addresses many of the hepatotoxicity issues, it may be useful to insert a summary statement on page 27, line 31, such as "… intraspecies variability. The total uncertainty factor of 30, in conjunction with the available human experimental data and the supporting animal data (both cited below), should protect against all but hypersensitive human hepatotoxic effects."

Page 28, line 23. Kimmerle and Eben (1975b) report the 4-h exposure concentration as 87 ± 25 ppm (a range of 62-112 ppm). In this context, and that of the next paragraph in the text as well as the values in Table 10, it may be useful to present the confidence interval.

Page 29, Table 11. Given the potentially significant contribution to the total absorbed dose that skin exposure presents (refer to human incident reports in Section 2.2.2 and the monkey study by Hurtt et al. 1991), the table should have a footnote that reiterates the information in the Executive Summary, page viii, lines 39-40.

Page 32, Section 8.3. With the database being so limited, should additional studies be recommended that would refine the AEGL database?

Page 44, line 17. This is the only place the odor threshold is described as being above the AEGL-2 (see page 2, lines 21-26, for values). Which value for the odor threshold is being used here, and which AEGL-2 time period is referred to?

Editorial Recommendations

Page vi, list of tables. Change to read "Summary of Proposed AEGL Values for ~~Name of~~ Dimethyl<u>f</u>ormamide" (deleted words in strikethrough, added letter underlined). Make the same changes in the table on page ix.

For the listing for Table 12, would it be desirable to change to "Guidelines for DMF"? If so, the entry for the table on page 31 should also be changed.

Page vii, line 31. Change to read "such as these, a factor of 2 was used" (added words underlined).

The same change can be made on page 27, line 5.

Page 14, line 3. Change to read "at 2 and 4 weeks" (changed word underlined).

Page 14, line 11. Change to read "and it was not stated" (changed word underlined).

Page 18, Table 5. Check entries in the Effect column for consistency in format and punctuation. In the Duration column for the mouse data, use only a single "2 h" entry (as in Table 6).

Page 20, line 34. Change to read "used for gas-chromatographic analysis" (changed word underlined).

Page 21, line 3. Change to read "toxic lesion or by conjugation with" (changed word underlined). The construction of this sentence is awkward. To improve, break it into two sentences. For example, "Another pathway … intermediate(s). This intermediate could then generate a toxic lesion, or be conjugated with … and ultimately form the urinary metabolite …."

Page 23, line 18. Delete the phrase "at this time." It is redundant.

Page 27, line 1. Change to read "which may be reflected" (changed word underlined).

Page 29, Table 11. Change the table title to read "Summary of AEGL Values for DMF…" (added words underlined). Make the same change on page iv.

Page 30, Figure 2. The markers for the Human—No Effect data points for 2 h and 4 h do not appear to match up with the data presented on page 2, lines 32-34, and page 3, lines 1-3.

Page 31, Table 12. Change the table title to read "… and Guidelines for DMF" (changed word underlined). Make the same change on page iv.

References

General Note: If a document is available online (other than a journal article), the URL should be provided.

Page 33, lines 2-5. Is this a citation of the TLVs themselves or of the documentation?

Page 33, line 18. Delete "1983." It's repeated from the previous line.

Page 36, lines 20-21. Does this sentence constitute a part of the citation? If not, and if the information is worth retaining, it should be in a footnote; otherwise, it should be deleted. If a change is made, the same change should be applied to the citation in the Reference list on page ix.

Page 37, lines 8-9. The NIOSH Pocket Guide to Chemical Hazards is also online at http://www.cdc.gov/niosh/npg/npg.html.

Page 37, lines 10-13. The NIOSH IDLH database is also online at http://www.cdc.gov/niosh /idlh/idlh-1.html.

Page 37, line 20. Check the spelling of "half-life" in the article title; was it really spelled "half-live"?

Page 37, line 26. The OSHA Air Contaminants list (Table Z-1) is online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Page 38, line 18. The EPA IRIS database is online at http://www.epa.gov/iris/index.html.

Page 38, lines 19-21. Is this document accessible online?

Appendix A

Page 42, Derivation of AEGL-3. Use a comma as a thousands separator in the large figures here for ease of reading.

The straightforward math here is easy to follow, but is there a reason (such as consistency with other documents) to retain the derivation calculations in log format?

Appendix B

Page 46, line 23. Change to read "and it has <u>been</u> demonstrated" (inserted word underlined).

Page 47, line 4. Change to read "Using <u>this</u> default value" (changed word underlined).

COMMENTS ON CARBON TETRACHLORIDE

At its previous meeting, the committee reviewed the AEGL document on carbon tetrachloride (CCl_4). The revised document was presented by Robert Young, of Oak Ridge National Laboratory. The document needs to be revised. The committee will review the revised document at its future meeting.

Main Comments

An interspecies UF of 1 was used to derive the AEGL-3 values. The committee disagrees with this determination. However, if a clear description can be give of why, in this instance, this value was selected, the committee would accept the result. This explanation needs to include the rationale that the mouse species used in the key study is much more sensitive than humans for this measured effect (lethality). Some estimates are that the mouse may be as much as 50 times more sensitive than humans. On this basis, the toxicokinetic component of the default interspecies UF of 10 would certainly be no greater than 1. At the same time, there remains some uncertainty about the toxicodynamic component of the UF. However, since the mechanism of action for this compound is fairly well understood, this factor is likely to be some value less than 3. Whatever this value might be, it will be more than compensated for by the factor used to account for the greater sensitivity of the mouse compared to the human in the toxicokinetic component of the UF.

In this explanation, it is important to document the sensitivity of the mouse compared to the human. Only one study, Stewart 1961, cited the evidence that rats metabolize CCl_4 faster than humans. Additional papers need to be included and cited as the basis for this decision.

PBPK models are used to justify and support the conclusion that rats are more sensitive than humans. Yet the committee has not agreed on any guidelines for the use of PBPK models in the derivation of AEGL values. Important questions, such as which PBPK models should be used in the derivation of AEGLs and what criteria, such as validation, need to be met before the results from a model can be used, need to answered and included as part of the SOP manual.

The statement by Paustenbach (see the Jan. 2005 TSD draft) that the Paustenbach model "predicted that at concentrations up to 100 ppm, rats, monkeys, and humans metabolize and eliminate carbon tetrachloride in a similar manner" was challenged and removed from the text. Why was this done? Is this statement a quote directly from Paustenbach or a paraphrase by the authors of the technical support document (TSD)? What's not clear here is what exactly the author said. This is important because this statement contradicts the general statement made in the application of the UF of 1 that mice are much more sensitive than humans. Also, it contradicts the use of the PBPK models as support for this statement. The statement also points out that different models can lead to different conclusions.

The discussion of the potential cancer risks of CCl_4 is still not well written or complete. The three risk values required by the SOP manual have still not been derived. They should be added to the document. There is only one estimate in Appendix C. The explanation in the text for why the potential carcinogenicity of CCl_4 was not considered in the derivation of the AEGL values is still vague and inconsistent between the Executive Summary and the text (Executive Summary, page 3, lines 10-15; page 27, line 35, to page 28, line 16; and page 37, line 31-35). The discussion in the Executive Summary states that "AEGLs based on non carcinogenic toxicity endpoints were more applicable for human health protection." It's not clear why the noncancer risks are more "applicable." The discussion in the text is equally vague, stating that "quantitative data regarding a carcinogenic response following inhalation exposure to carbon tetrachloride were not available" (page 35, lines 39-40). The discussion in Appendix C is no better (page D-1 [should be C-1], last paragraph).

The point here is that the Executive Summary and text (as well as Appendix C) should discuss briefly that CCl_4 may cause cancer, that the data on inhalation is limited and that although there were sufficient data to calculate risk estimates, these risk estimates were sufficiently low as to not impact on the AEGLs derived using other, more appropriate end points.

The intraspecies UF used for AEGL-1 and -2 was 3. The reasoning given for AEGL-1 is "an UF of 3 for protection of sensitive individuals was applied to account for variability in possible CNS effects." The text goes on to say why this is appropriate, but the statement cited above is poorly written and should be restated, perhaps something along the lines of "a UF of 3 was selected because CNS-mediated effects are not metabolism-mediated and exhibit limited variability among individuals and thus should be sufficient to protect most individuals."

The text for selecting a UF of 3 for AEGL-2 states that "the adjustment for uncertainty regarding individual variability is limited to 3 because CNS-mediated effects are not metabolism-mediated and exhibit limited variability among individuals." This is also awkward, but it makes more sense than the text for AEGL-1. Rewrite both statements so that they are consistent and more straightforward.

There is still no discussion in the revised TSD about the sensitivity of children or adults other than those sensitized by alcohol in regard to exposure to CCl_4 (See Section 4.4, page 30). This section should address the potential impact of exposure to CCl_4 on children and on sensitive individuals other than those sensitized by alcohol.

Specific Comments

Page 9, lines 10-14. The committee has previously pointed out that it is not possible for the victim described by Norwood et al. (1950) to have inhaled as low a concentration of $CC1_4$ as 250 ppm. It is not necessary for the document's authors to provide an alternative estimation. They should, however, include a qualitative description, based on the pertinent comments the committee provided previously, of why the exposure level calculated by Norwood et al. (1950) is unlikely. "At a minimum it should state this is calculated exposure."

Page 28, lines 15-16. The abbreviation IARC should be followed with a period. The following sentence should read "The NTP has classified carbon tetrachloride as reasonably anticipated to be a human carcinogen."

Page 31, line 39. The title of subsection 4.4.2 might be amended to include the phrase "potentially susceptible subpopulations" or some such term.

Page 32, lines 5-7. Some specific examples involving CYP2E1 inducers, in addition to ethanol, should be included here. Other alcohols and ketones, such as isopropanol and acetone, are good CYP2E1 inducers and potentiate the acute hepatotoxicity of $CC1_4$. Bruckner et al. (2002 J. Pharmacol. Exp. Therap. 300:273-281), for example, found a pronounced circadian rhythmicity in the susceptibility of rats to liver damage by $CC1_4$. Lipolysis during overnight fasting (while asleep) produced acetone, which results in higher CYP2E1 concentrations by reversibly binding to and stabilizing the existing isozyme. Subpopulations with ketosis (for example, diabetics, obese persons, people who have fasted for 12-48 h) are at greater risk of tissue injury by $CC1_4$ and other short-chain aliphatic halocarbons that are metabolically activated by CYP2E1. Note: the intraspecies UF of 10 also protects these groups.

Page 32, line 23. The question was raised again at a previous committee meeting about the potential susceptibility of children and the elderly to $CC1_4$. See the committee's previous comments about children's potential risks (that is, the comments indexed to page 30, lines 15-21, in the first draft of this document). The elderly should be less susceptible to acute hepatic injury by $CC1_4$, because liver CYP2E1 activity diminishes gradually during aging. It should be kept in mind, however, that some elderly (such as alcoholics and those with hepatitis) will have less hepatic functional reserve because of cirrhosis.

Page 33, lines 31-35. It is recommended that these sentences be replaced with the following: "A UF of 3 was selected because CNS-mediated effects are produced by the parent compound (that is, are not metabolite induced). Extensive experience in anesthesiology with similar volatile organic chemicals has revealed limited variability among individuals and age groups (Gregory et al. 1969; de Jong et al. 1975; Stevens et al. 1975). Thus, an intraspecies UF of 3 should protect most individuals."

Similarly, rewrite the corresponding statement about selection of an intraspecies UF of 3 for calculation of AEGL-2s on page 35, lines 10-12.

Page 35, lines 13-14; page 37, lines 1-5. Use of the ten Berge et al. (1986) approach frequently results in underestimation of 4- and 8-h AEGLs for VOCs when extrapolating from shorter to longer exposure periods. See Boyes et al. (2000 Environ. Health Perspec. 108[Suppl. 2]:317-322) and Bruckner et al. (2004 J. Toxicol. Environ. Health A 67:621-634) for illustrations of this phenomenon with trichloroethylene. $CC1_4$, in an oral dose as low as 1 mg/kg, is a suicide inhibitor (that is, its reactive metabolites destroy cytochrome P450s) (Fisher et al. 2004 Environ. Toxicol. Pharmacol. 16:93-105) in mice. Thus, despite an increase in the systemically absorbed dose over time, much of the additional $CC1_4$ cannot be metabolized. As a result, blood and brain concentrations of $CC1_4$ (the parent compound) would not reach near steady-state as many VOCs do, but would continue to increase through an 8-h exposure. This phenomenon supports the progressive decrease in AEGL-2 values, because they are based upon CNS and/or local effects caused by the parent compound. Conversely, since suicide inhibition reduces metabolic activation of $CC1_4$ to free radicals and other reactive metabolites, liver damage should not become much more pronounced at the later exposure times. Sanzgiri et al. (1997) reported that rats inhaling CCl_4 at 1,000 ppm for 2 h received a total (absorbed) dose of 179 mg/kg. This and far lower doses will rapidly destroy hepatic P450s and thereby be protective from acute hepatotoxicity. Thus, it would be quite reasonable to "flat line" the 1-, 4-, and 8-h AEGL-3s (that is, keep all three at 500 ppm).

Page 36, lines 16-19 and 21-26. The NAC should provide a clearer, more-comprehensive explanation of why the NAC decided that it was unnecessary to apply an interspecies UF in deriving AEGL-3s. The information provided in lines 16-19 is not very pertinent to this decision and is probably not necessary. Rats eliminate $CC1_4$ somewhat faster than larger species because rats metabolize and exhale it more rapidly. Of greater relevance, it has been well established that upon equivalent inhalation exposures, rats achieve significantly higher tissue doses than do humans (Paustenbach et al. 1998) because of the rats' higher blood:air PC (Gargas et al. 1989) and higher alveolar ventilation rate, cardiac output, and liver perfusion rate (Brown et al. 1997 Toxicol. Ind. Health 13:407-484). More importantly, rats metabolically activate $CC1_4$ to a greater extent (~47-fold according to Delic et al. 2000) than do humans. If one follows this reasoning, mice should be more sensitive to $CC1_4$ hepatotoxicity than rats because mice achieve higher body burdens upon inhalation of $CC1_4$ and metabolically activate more than do rats. Indeed, Gomez et al. (1975 Toxicol. Appl. Pharmacol. 34:102-114) observed that $CC1_4$-induced liver necrosis was much more intense in mice than in comparably exposed rats. The foregoing strongly argues that the toxicokinetic component of the interspecies UF should be considerably less than 1. At the same time, there remains some uncertainty about the toxicodynamic component. The general mechanism whereby $CC1_4$ causes hepatocytoxicity, however, is well understood and is not believed to vary substantially across species. If there were a toxicodynamic difference, it should be more than compensated for by the recognized toxicokinetic component.

The authors might point out that a PBPK model could have been used for interspecies extrapolations and time scaling in the AEGL derivations, but the decision was made to use reported model simulations to support adoption of an interspecies UF of 1.

The NAC provided a white paper on utilization of PBPK modeling for establishing AEGLs, but there was little opportunity for it to be reviewed by the committee. Selected members of the committee have agreed to provide comments on this first draft of the white paper. It is important that criteria be established for selection of the most appropriate PBPK model and that standard guidelines be followed in the use of such models. This information should be submitted to the committee for a full review and then be incorporated into the SOP manual.

Page 37, lines 31-35. The International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) carcinogenicity classifications have yet to be added here or on page 27, lines 33-41. Once the data of Nagano et al. (1998) have been evaluated, remember to derive and include a three-range cancer risk from 10^{-4} to 10^{-6}. Provide more-specific reasoning in the Executive Summary and text as to why AEGLs for $CC1_4$ are based on noncancer risks rather than theoretical cancer-risk estimates. It would be worthwhile to note that the AEGLs based on noncancer end points are more protective than AEGLs based on cancer-risk estimates, if this turns out to be the case.

Detailed Comments

Page 8, line 5. Explain the word anthelmintic, because it has been explained in the Executive Summary.

Page 8, line 11. Delete the second date on the ATSDR reference (should be just 2003, not 1993).

Page 18, line 8. The word "times" should be singular.

Page 19, line 34. Replace "in was" with "were."

Page 28, lines 3-6. This new sentence is poorly written. The committee's comment was in regard to the appropriateness of using chronic studies to derive AEGLs, not to the appropriateness of using chronic exposures to derive cancer-risk estimates.

Page 37, line 3. Appendix 3 should be Appendix B.

Appendix B. Correct page numbers (listed as C-1, C-2, etc.).

Appendix C. Three risk values should be calculated here, not just one.

COMMENTS ON 1,2-DICHLOROETHYLENE

At its previous meeting, the committee reviewed the AEGL document on 1,2-Dichloroethylene. The document was presented by Cheryl Bast, of Oak Ridge National Laboratory. The revised document can be finalized if the recommended revisions are made appropriately.

General Comment

Use of the ten Berge et al. (1986) approach and adoption of a value of 1 for the exponent *n* (as a default) frequently results in underestimation of 4- and 8-h AEGLs (that is, overestimation of risks) for VOCs when extrapolating from shorter exposure periods. See Bruckner et al. (2004 J. Toxicol. Environ. Health A 67:621-634) for an illustration of this phenomenon with trichloroethylene (TCE). For most well-metabolized VOCs, such as TCE, blood concentrations rapidly attain near steady-state during inhalation exposures. As a consequence, adverse effects typically only increase modestly with time for the longer exposure periods (once near steady-state is reached). *Cis*- and *trans*-dichloroethylene (DCE) are unique in that they are suicide inhibitors (that is, the epoxide metabolite of each isomer interacts with and inhibits cytochrome P4502E1 [the P450 isozyme that mediates biotransformation of DCE to the epoxide]) (Lilly et al. 1998). *Trans*-DCE is a more potent suicide inhibitor than *cis*-DCE. As a result, blood and brain concentrations of DCE should continue to increase during prolonged exposures, rather than reaching near steady-state. The parent compounds are responsible for producing CNS depression, the toxic effect of interest. Thus, the AEGLs should progressively decrease, as is the case with AEGL-2s and -3s in the current document.

COMMENTS ON SULFUR DIOXIDE

At its previous meeting, the committee reviewed the AEGL document on sulfur dioxide (SO_2). The revised document was presented by Cheryl Bast, of Oak Ridge National Laboratory.

Overall Comment

The NRC committee on AEGLs concluded that this is a well-written document and had only relatively minor suggestions for improvement. A revised document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

The committee concurs with comments and responses below unless otherwise noted by additional comments.

Page ii, line 34. Have any casualties/anaphylactic reactions been reported in asthmatics at low exposure?

Response: No causalities/anaphylactic responses were reported in the referenced literature.

Page 1, line 25. Add "co-exposure" before respirable particles at beginning of sentence.

Response: Revised as suggested.

Page 3, line 32. Because bronchiolar obstruction was still present 4 years (y) after the accident, the airway

Response: Text revised (the word "reversible" has been deleted).

Page 4, line 1. What is "destructing bronchitis"?

Response: Text revised (the word "destructing" has been deleted).

Page 5, line 6. In the London case, 1.3 ppm was the peak SO_2 concentration at which people died. This could lead to the conclusion that 1.3 ppm is an AEGL-3, whereas this document proposes 16-42 ppm for AEGL-3 and 0.75 ppm for AEGL-2. This discrepancy should be explained.

Response: A statement has been added referring the reader to Section 4.4, showing that particulate matter and other pollutants enhance the effects of SO_2. The concentration of particulate matter in the London episode was too great to measure.

Page 5, lines 8-9. Change sentence to "The excess deaths were attributed to bronchitis or to other impairments of the respiratory tract."

Response: Text revised as suggested.

Page 7, lines 8-9. The increase in sensitivity to SO_2 odor at the end of exposure is remarkable and opposite to, for example, dioxane and H_2S, where the sensitivity of the olfactory system decreases after a certain time. Is this logical?

Response: This is not logical. The reference was consulted, and the text has been modified, as follows, to reflect what is actually reported by the study authors.
"Unpleasant odor was reported more frequently ($p < 0.05$) at the end of the exposure to SO_2 at 4 ppm than <u>before exposure</u> ~~at the beginning of this exposure period~~."

Page 13, lines 40-41. If changes were shown to be statistically significant, how can it be difficult to ascertain the exact magnitude of the effect?

Response: The data are reported graphically, and it is difficult to read the exact magnitude (percent change) from the graphs. A statement to this effect has been added to the text.

Page19, line 6. Insert "ambient" before "air pollution."

Response: Text revised as suggested

Section 3.1. Do we really need all these animal data when there are so many human data available?

Response: These data are included for completeness and are useful because animal data are used for derivation of AEGL-3 values.

Section 4.4. This section does not seem to have a place in the document, because the data described is not used for derivation of AEGLs.

Response: Section 4.4 has been retained because this section explains that concurrent exposures to other pollutants or particulate matter enhance the effects of SO_2. It is important to retain this information to help explain the apparent discrepancy of the peak SO_2 concentration noted in the London case and AEGL-2 and -3 values.

The committee agrees with the response and would further note that this information is of value to the end users of the AEGLs because it alerts them to additional factors to consider as they apply the SO_2 AEGLs.

Section 4.5. Delete from text as explained below.

Response: Section 4.5 has been deleted as suggested.

Derivation of AEGL-1

It must be realised that effective concentrations in asthmatics are highly dependent upon the severity of the disease in the subjects being tested, the extent of medication use, etc. Thus, one study may show an effect at a concentration showing no effect in another study merely because of differences in subjects. Asthmatics are a highly variable group in terms of response to exposure to irritants, much more so than normal individuals exposed to the same atmospheres. Furthermore, most controlled clinical studies generally use subjects who are not the most severe. Based upon all this, the committee concludes that the value for AEGL-1 of 0.25 ppm is too high and should be reduced to account for susceptibility differences in the most sensitive population, namely asthmatics. The committee suggests a value of 0.2 ppm at the highest. The committee agrees that the time should be held constant for all the time points.

This comment also applies to page 19, line 16. The committee agrees with the response and would further note that this information is of value to the end users of the AEGLs because it alerts them to additional factors to consider as they apply the SO_2 AEGLs.

Response: The AEGL-1 values have been revised to 0.20 ppm for all time points. The justification in the appropriate text and tables in the technical support document (TSD) have been revised as follows:

"AEGL-1 values were based on the weight of evidence from human asthmatic data suggesting that ~~0.25~~ 0.20 ppm may be a ~~threshold~~ NOEL for bronchoconstriction in exercising asthmatics. No treatment-related effects were noted in asthmatics exposed to 0.2 ppm for 5 min (Linn et al. 1983b), 0.25 ppm for 10-40 min (Schacter et al. 1984), 0.25 ppm for 75 min (Roger et al. 1985), 0.5 ppm for 10-40 min (Schacter et al. 1984), or 0.5 ppm for 30 min (Jorres and Magnussen 1990). However, an increase in airway resistance (SRaw) of 134-139% was observed in exercising asthmatics exposed to 0.25 ppm for 5 min (Bethel et al. 1985); the increase in SRaw in this study, but not in the other studies, may be attributed to the lower relative humidity (36%) in the Bethel et al. (1985) study compared to the other studies (70-85%). No uncertainty factors were applied because the weight-of-evidence approach utilized studies from a sensitive human population, exercising asthmatics. At relatively low concentrations, the role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to SO_2 at 0.75 ppm for 3 h exhibited increases in SRaw of 322% 10 min into exposure, 233% 20 min into the exposure, 26% 1 h into exposure, 5% 2 h into exposure, and a decrease of 12% at the end of the 3-h exposure period. These data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10 min and increases minimally or resolves beyond 10 min of exposure. Therefore, AEGL-1 values for SO_2 were held constant across all time points. Exposure to concentrations at the level of derived AEGL-1 values is expected to have no effect in healthy individuals but are consistent with the definition of AEGL-1 for asthmatic individuals."

Furthermore, the committee recommends that the Comparative Indices table (Table 6) not be included in the document. This table could be misleading. For example, while an increase in SRaw of 200% may not be of concern in normals, it would surely be of concern in someone with pre-existing respiratory disease. Thus, the comment on page 28, line 2, that a change of 134-139% is mild to moderate should be deleted from the text.

Response: Table 6 and Section 4.5 have been deleted as suggested.

Derivation of AEGL-2

The argument above for AEGL-1 applies here as well. Changes in airway resistance of almost 600% are not necessarily of little consequence to an asthmatic.

Response: The AEGL-2 values have been revised to 0.75 ppm for all time points. The justification in the appropriate text and tables in the TSD have been revised as follows:
"AEGL-2 values were based on the weight of evidence from human asthmatic data suggesting that ~~1.0~~ 0.75 ppm induces moderate, but reversible, respiratory response in exercising asthmatics for exposure durations of 10 min to 3 h ~~5- to 75-minutes. The same response was observed at 0.75 ppm for 10-minutes to 3-hours. Asthmatics developed increased airway resistance of 102% to 580% after exposure to 1.0 ppm SO2~~ (Roger et al. 1985; Balmes et al. 1987; Kehrl et al.1987). No uncertainty factors were applied, because the weight-of-evidence approach utilized studies from a sensitive human population, exercising asthmatics. At relatively low concentrations, the role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. For example, asthmatics exposed to SO_2 at 0.75 ppm for 3 h exhibited increases in SRaw of 322% 10 min into exposure, 233% 20 min into the exposure, 26% 1

h into exposure, 5% 2 h into exposure, and a decrease of 12% at the end of the 3-h exposure period. These data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10 min and increases minimally or resolves beyond 10 min of exposure. Therefore, AEGL-2 values for SO_2 were held constant across all time points. ~~time for the 10-min, 30-min, and 1-hr values. Because the maximum duration for a 1.0 ppm exposure of asthmatics was 75-minutes, and data were available at 0.75 ppm for up to 3 hours, the 4- and 8-hour AEGL-2 values were held constant at 0.75 ppm.~~ Exposure to concentrations at the level of derived AEGL-2 values is expected to have no effect in healthy individuals but are consistent with the definition of AEGL-2 for asthmatic individuals."

With the change in the AEGL-2 value from 1.0 ppm to 0.75 ppm, the references cited also have to be changed.

Is the phrasing in the response above "0.75 ppm induces moderate, but reversible, respiratory response in exercising asthmatics for exposure durations of 10 min to 3 h … consistent with the definition of AEGL-2 for asthmatic individuals" consistent with the phrasing on page 19, lines 15-18?

Table 2: The AEGL-3 is almost twice the level of the emergency response planning guideline (ERPG) 3. Thus, the latter seems to be more conservative. Some comment on this should be made. Similarly, the IDLH is more than twice the ERPG-3 value. In this case, the latter seems to be much more conservative.

Page 30. The AEGL-3 is extremely high in comparison to AEGL-2. Are there any examples of other substances the committee reviewed where such a high AEGL-3-to-AEGL-2 ratio exists? At first sight, the ERPG-3 seems to be more reasonable.

Response: The approximate 30-fold difference between AEGL-2 and AEGL-3 values (at 1 h) is a function of the availability of an extremely sensitive AEGL-2 end point (asthmatic human data) and utilization of animal data for AEGL-3 values. (AEGL-3 values were derived using a lower 95% confidence limit, per the SOP manual.) Also, the data-derived time scaling exponent *n* is 4, suggesting a flat concentration-response curve. In cases where the concentration-response curve is steep, the AEGL-2 and AEGL-3 values are often very close together. Therefore, it follows that in cases where the curve is flat, values may be further apart.

The ratio of 1-h AEGL-3-to-AEGL-2 values for sulfur mustard (published in Vol. 3) is 16. This large difference is also a function of the use of a sensitive human end point for AEGL-2 and of mouse lethality data for AEGL-3 values.

The ratio of 1-h AEGL-3-to-AEGL-2 values for chloroform is approximately 80. This large difference is also a function of the use of an exceptionally sensitive AEGL-2 end point, that of developmental toxicity.

Several ERPG values also have relatively large ERPG-3-to-ERPG-2 ratios (5/100 chemicals have ratios between 17-100). This is also a function of an exceptionally sensitive ERPG-2 end point. For example, the ratio of chloroform ERPG-3-to-ERPG-2 values is 100, a result of use of developmental toxicity data for ERPG-2 derivation.

Conclusions of the Committee

The AEGL-1 should be 0.2 ppm across the time scale.
The AEGL-2 should be 0.75 ppm throughout.

The AEGL-3 remains as proposed *provided* a good justification for these values can be given.

Given the discussion during the committee meeting on the final day of the meeting and the rationale developed as a result, the committee is in concurrence with the values for the AEGLs that emerged.

Editorial Comments

Page 1, line 22. Bronchiolitis is misspelled.

Page 1, line 25. Add "of the respiratory cycle" after expiratory phase.

Page 3, lines 28-29. The terms do not have to be capitalized, only the initials.

Page 4, line 2. What is emphysema of the mediastinum or skin?

Page 5, lines 31-32. Are these concentrations correct?

Page 7, lines 9-10. This does not seem to make sense.

Page 7, line 19. What specific activity of the macrophage was altered?

Page 8, line 41. Is the 20% an increase?

Page 13, line 9. Exercised is misspelled.

Page 14, lines 23-24. This sentence is unclear.

Page 14, line 34. Bronchodilator is misspelled.

Page 15, lines 3 and 21. Sraw should be SRaw.

Page 15, line 15. Effects peak within 10 min of what?

AEGL-3. There is a large differential between AEGLs-2 and -3 because of the use of human data for one and animal data for the other. However, it does appear that the animals are not as sensitive as humans to pulmonary functional effects from exposure. Thus, if this is extrapolated to lethal concentrations, then a higher concentration would result in death in animals compared to humans, and the AEGL-3 may have been set too high.

COMMENTS ON HYDRAZINE

At its previous meeting, the committee reviewed the AEGL document on hydrazine. The revised document was presented by Robert Young, of Oak Ridge National Laboratories.

Overall, the committee agrees the AEGL values are appropriate and supported by the data, but the explanations for UFs and MFs are confusing and inconsistent. UFs are used for inter- and intraspecies variability. MFs are for data-quality issues, including suspect concentrations such as those associated

with hydrazine at low concentrations. A revised document can be finalized if the committee's recommended revisions are made appropriately.

Major Issues

Page 5, line 45 to end of paragraph. Note the paragraph below. The 0.1 ppm value was correctly applied to all durations, not just 1 h, 30 min, and 10 min, because it is a direct-acting irritant. If a total UF of 10 was applied to 0.4, wouldn't that yield a value of 0.04? Did the NAC apply a factor of 3—not 3 × 3? Also, does the "variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism" impact direct-acting irritation? If not, then this seems to be irrelevant.

Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, the 0.1 ppm AEGL-1 value derived for the 8-h duration was applied to the 1-h, 30-min, and 10-min durations. A total UF of 10 was applied to the 0.4 ppm concentration to derive the AEGL-1 values. A UF of 3 was applied for interspecies variability because the surface-contact irritation by the highly reactive hydrazine is not likely to vary greatly among species and because a nonhuman primate was the test species. A UF of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals. Additionally, variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism has been shown to vary approximately twofold.

Page 6, lines13-15 and lines 27-30. Here is the response to this same issue. Variability in the data is not a reason for a UF. It should be an MF.

Comment: The presentation of the UF remains a problem. For irritants and direct-acting chemicals (and the case is made for hydrazine-induced irritation as the primary basis for AEGL-1 and - 2), inter- and intraspecies UF adjustments generally need a factor of 3 for each, for a total of 10. This was done for AEGL-1. However, for AEGL-2, "an uncertainty factor of 10 for interspecies variability was applied to account for the high degree of variability in the data due to the extreme reactivity of hydrazine that compromised exposure concentration measurements." What does this have to do with interspecies variability, especially when hydrazine appears to be a direct-acting material? Although an interspecies UF of 10 may be reasonable, the rationale of uncertainty of the data is not a UF issue. Uncertainty in the data should be addressed with an MF. The response provided to the comment in Section 6.3 that the nasopharyngeal area of rats and humans are different should be discussed here. This concept is very helpful in distinguishing hydrazine from a simple irritant.

Response**:** As noted, an interspecies UF of 3 is more appropriate and is typically used for direct-contact irritants such as hydrazine. Although the uncertainties regarding species variability may be indirectly the result of uncertainties inherent in exposure measurements of early studies, such deficiencies are more appropriately data-quality issues. Therefore, the AEGL-2 and -3 values are now derived using an interspecies UF of 3 and an MF of 3 for data inadequacies resulting from difficulties in accurately measuring exposure concentrations in older studies. Although newer studies (Health Research Council [HRC] and Latendresse et al.'s work) apparently resolved this issue (both studies used rats), older data in other species are still compromised by possibly inaccurate exposure data. Additionally, an MF of 2 has been retained for AEGL-2 development because of the paucity of data on AEGL-2-specific critical effects.

Page 29, lines 17-21. Same issue.

Editorial

Page 5, line 3. Add "of" between "pressure" and "14.4."

Page 5, lines 16-20. Delete this paragraph because it addresses methylated hydrazines, which have their own technical support documents, and the information is irrelevant.

Page 5, lines 24-27. The following is stating hydrazine is a direct-acting irritant because it is highly reactive. Why not simply state this?
"The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate port-of-entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine per se is a plausible determinant of acute port-of-entry toxic effects."

Page 5, lines 32-35. Recommend restating the following paragraph as follows:
"Because there were no data to empirically derive the chemical-specific exponent, the default values of n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points were used in the $C^n \times t = k$ equation in accordance with the SOP manual."
This is better than the following:

"To obtain AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation."

COMMENTS ON ETHYLENIMINE

At its previous meeting, the committee reviewed the AEGL document on ethylenimine. The revised document was presented by Kowetha Davidson, of Oak Ridge National Laboratory. The document can be finalized if the committee's recommended revisions are made appropriately.

Scientific Comments

Page 4, item 25. The logic for why the 4-h value is taken as the point of departure for the derivation of the AEGL-2 (NOAEL or respiratory difficulties in the guinea pig) although after 8 h no respiratory difficulties were observed has to be explained. For example, "The logical point of departure for derivation of the AEGL-2 would be the NOAEL for respiratory difficulties after exposure of guinea pigs for 8 h. However, this would lead to values irresponsibly close to life-threatening AEGL-3 concentrations, at some time points even surpassing the AEGL-3 values. It was therefore decided to take the next-shorter exposure duration of 4 h because this was also a clear NOEL for respiratory difficulties in the guinea pig").

Page 3, Section 2.2.1. Odor Threshold – This section defines the odor threshold for ethylenimine as being 2.0 ppm. This value is repeated in the executive summary, and on page 6, line 1. Yet the Level of Distinct Odor Awareness (LOA) is derived based on an odor threshold of 0.6980. However, there is no discussion in the text to explain why the odor threshold used to derive the LOA is not 2.0 ppm as defined in section 2.2.1 or why it is 0.698. There needs to be some discussion here to address this apparent discrepancy. Perhaps the easiest way to do this would be to include 0.698 in a range of reported odor thresholds and to provide a rationale for why this number was selected for the derivation of the LOA.

There are several similar statements regarding the potential carcinogenicity of ethylenimine in the Executive Summary, page vi, line 35-36, in the footnote to the Summary table, and in the text on page 22, lines 27-28; page 34, lines 38-39; and page 35, lines 35-36. These statements, generally expressed as "AEGL values do not account for the carcinogenic potential of ethylenimine," are open-ended and can be interpreted in different ways (and are likely to be). Suggest adding the reason *why* the AEGLs values (2 and 3) do not take into account the potential carcinogenicity of ethylenimine—for example, "because no adequate data were available for the derivation of quantitative carcinogenicity potencies."

Editorial Comments

Page 3, line 26; page 32, lines 12-24. The use of four decimals suggests an accuracy of the odor threshold (OT_{50}) determination that is not realistic (at least drop the last zero?).

Page 3, lines 20-27; page 32. The method for how the level of distinct odor awareness was derived from the OT_{50} is quoted as the guidance provided by van Doorn et al. (2002). However, the list of references gives no indication where the reader can find this article.

Page 4, line 6. Place comma after "nausea."

The reasoning for the selection of the intra- and interspecies UFs used to derive the AEGL-3 values is discussed in several places in the text. In every instance, the text simply states that the reasoning for the selection of the UFs is "based on the same rationale described for AEGL-2 derivation." In the Executive Summary (page vi), this shorthand is acceptable because the discussion of the reasoning for the selection of the UF for the AGEL-2 values is spelled out on the same page (in the prior paragraph). However, in the text (pages 21-22) and in the Appendix (page 35), where the derivation of the AEGL-3 values is described in detail, it is recommended that the entire rationale be repeated so that the reader does not have to go hunting for the reasoning behind the selection of the UFs for AEGL- 2. This shorthand is not appropriate in this instance.

COMMENTS ON PROPYLENIMINE

At its previous meeting, the committee reviewed the AEGL document on propylenimine. The revised document was presented by Kowetha Davidson, of Oak Ridge National Laboratory. The document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comment

Page 4, lines 27-37; response to comments, item 6. Because the NAC believes that values based on AEGL-2 NOAELs were unreasonably low, it used a relative-potency approach compared to ethylenimine with appropriate MFs to develop AEGL-2 values. While seemingly valid, the explanation needs to be more straightforward as provided in response to comments. The explanation in Section 6.3 is more clear and consistent. The confusing point is the sentence describing the calculations from the NOAEL. The committee recommends deleting this. But still unanswered is why was the geometric mean used rather than the arithmetic mean?

COMMENTS ON TRICHLOROETHYLENE

The committee's preliminary comments on pharmacokinetic modeling of TCE are attached. The TCE AEGL document was withdrawn from review by the NAC at the meeting.

- A basic (and brief) discussion about drug (maybe anesthesia) kinetics and how the practice of medicine and drugs is based on understanding the blood or tissue concentrations is needed to show that other established disciplines use pharmacokinetic information to predict effects.
- Some basic explanation of the physiology of the body—what happens when a chemical is inhaled and how it gets to tissues—is needed. What governs the rate of uptake, distribution, and elimination? Slant discussion so it helps to explain the structure of a PBPK model.
- State and restate that the intended purpose is to predict the blood or tissues concentrations associated with exposures to chemicals and that the predicted internal exposure is thought to be a better representation of exposure than air concentration (C). Perhaps show an example of calculated AEGL values with a PBPK model and, using $C^n \times T = k$, point out which physiologic processes are accounted for in the PBPK model that were not accounted for in the air-concentration-extrapolation methodology.
- UFs remain a great concern. What is the NAC guidance on the use of intra- and interspecies UFs? How well do the simulations have to fit the data points to be a good fit (variability)? A discussion of current practices would be helpful. Should any statistical procedures be implemented to address this? For example, if 10 infants, 10 teenagers, 10 adult males, and 10 pregnant females are all exposed for 10 min to chemical X, what is the expected range of blood concentrations? If unknown, what UF would be applied, and what is the basis for this factor?