Fifteenth Interim Report of the Committee on Acute Exposure Guideline Levels

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Fifteenth 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

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Preface

Extremely hazardous substances (EHSs)[2] 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 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.

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

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the U.S. Department of Defense (DOD), the U.S. Department of Energy, the U.S. Department of Transportation, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—developed acute exposure guideline levels (AEGLs) for approximately 200 EHSs.

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

At its meetings, the committee hears presentations from 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 NAC uses those comments to make revisions. The revised documents are presented by NAC to the committee at subsequent meetings until the committee concurs with the final draft documents. The revised documents are then published as appendices in the committee's reports.

The present report is the committee's fifteenth interim report. It summarizes the committee's conclusions and recommendations for improving NAC's AEGL documents for 16 chemicals (boron trifluoride, bromine, dimethyldichlorosilane, epichlorohydrin, ethylene oxide, furan, methyl ethyl ketone, methyl mercaptan, methyltrichlorosilane, nitric acid, nitrogen dioxide, nitric oxide, perchlormethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and trimethylchlorosilane) and 1 chemical mixture (jet fuel 8). The report also summarizes the committee's conclusions and recommendations for improving a draft white paper that proposes standard operating procedures for using physiologically based pharmacokinetic (PBPK) modeling as a tool in the AEGLs development program.

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

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 Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and ensuring 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: Harvey Clewell (The Hamner Institutes for Health Sciences), Sam Kacew (University of Ottawa), and Wallace Hayes (Harvard School of Public Health). 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 (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, Sylvia Talmage, Claudia Troxel, Carol Wood, and Robert Young (all from Oak Ridge National Laboratory); and James Dennison (Century Environmental Hygiene LLC).

We are grateful to past committee members James Bruckner (University of Georgia), John Doull (University of Kansas Medical Center), Kannan Krishnan (University of Montreal, Quebec, Canada), and Calvin Willhite (California Department of Toxic Substances Control) for providing comments to the committee on various technical support documents discussed in this report.

The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, Senior Program Officer for Toxicology for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Ruth Crossgrove (senior editor), Aida Neel (program associate), Korin Thompson (project assistant), Radiah Rose (senior editorial assistant), and Mirsada Karalic-Loncarevic (manager, Technical Information Center). 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

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Fifteenth 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, the National Advisory Committee on Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances (referred to as NAC) was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop AEGLs for high-priority, acutely toxic chemicals. AEGLs developed by 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, from accidents or terrorist activities.

THE CHARGE TO THE COMMITTEE

The NRC convened the Committee on Acute Exposure Guideline Levels to review the AEGL documents approved by 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 and supporting documentation developed by NAC for scientific validity, completeness, internal consistency, 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 NAC's draft AEGL documents for 16 chemicals (boron trifluoride, bromine, dimethyldichlorosilane, epichlorohydrin, ethylene oxide, furan, methyl ethyl ketone, methyl mercaptan, methyltrichlorosilane, nitric acid, nitrogen dioxide, nitric oxide, perchloromethylmercaptan, phosphorus oxychloride, phosphorus trichloride, and trimethylchlorosilane) and 1 chemical mixture (jet fuel 8). This interim report also includes the committee's comments regarding NAC's white paper on physiologically based pharmacokinetic (PBPK) modeling.

COMMENTS ON BORON TRIFLUORIDE

At its meeting held on January 17-19, 2007, the committee reviewed the revised AEGL technical support document (TSD) on boron trifluoride. The presentation was made by Claudia Troxel of Oak Ridge National Laboratory, and James Dennison of Century Environmental Hygiene, LLC.

General Comments

A revised draft TSD can be finalized if the recommended revisions are made appropriately. The primary difference between this version of the boron trifluoride TSD and the version the committee reviewed in 2002 is the addition of the 2005 report by A.M. Bowden (of the Huntingdon Laboratories), which was sponsored by Honeywell International (Bowden 2005). Although the Bowden report addresses the 4-hour (h) inhalation toxicity of boron trifluoride dihydrate rather than the dimethyl ether, the report is clearly relevant, and the authors have used its data to revise the AEGL-1. As discussed in the TSD, upon contact with even low levels of moisture in the air, boron trifluoride reacts to form the dihydrate. Boron trifluoride dihydrate is strongly corrosive to the eyes and skin of rabbits. The Bowden report was not included with a copy of the revised boron trifluoride document, but the document described the data in detail on pages 11 through 13. The Bowden report appears to be a well-conducted acute inhalation study from an established laboratory recognized for the quality of its toxicology studies.

The previous TSD on boron trifluoride raised a major concern for the committee because it used delayed irritancy (seen at 2 weeks after starting exposure) as the criterion upon which to base the AEGL-1. The Bowden data provide a better basis for the AEGL-1 and resolved the concern about using delayed irritancy. Additionally, the committee pointed out that in 1960 the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) committee set the TLV for boron trifluoride at 1 part per million (ppm) (2.8 mg/m^3) based partly on work that Bowden conducted on the Manhattan project at Rochester. Although these studies were not published, Stockinger and Spiegl (1953) discussed them. This is important for two reasons: (1) the only human data available for boron trichloride consist of one accidental exposure, and (2) the current AEGL-1 (2.5 mg/m^3) is much closer to Stokinger's and Spiegl's recommendation (2.8 mg/m^3) than the previous value (0.6 mg/m^3). The current AEGL-1 is also a better match for the Torkelson data where the NOAEL was 1.5 ppm (Torkelson et al, 1961).

The revised basis for establishing the AEGL-3 for boron trifluoride presented on page 27, uses the same data (Rusch et al. 1986) as the 2002 TSD but uses a different method (log-probit analysis with EPA benchmark dose software version 1.3.2) for interpretation of these data. Looking at the data presentation in Figure 1 (category plot on page 30) and in the probit plot on page 46, use of the different method seems reasonable and appropriate. The revised TSD provides more scientific and defensible AEGL values for boron trifluoride at all three levels.

Editorial Comments

The revised TSD corrects the typos found in the previous version and improves the wording in a few places.

The document is not consistent in its use of NOEL and NOAEL. For example, the summary on page vii says**, "**The AEGL-1 is based on a NOEL for irritation." In contrast, page 23 says**, "**The AEGL-1 is based on a NOAEL for irritation."

It would be helpful to the reader to add an explanation to the probit plot on page 46 (which has no log scale) to indicate how it relates to the log-probit analysis.

Comment References

Bowden, A.M. 2005. Boron Trifluoride Dihydrate Acute (Four-Hour) Inhalation Irritation Threshold Study in Rats. Conducted by Huntingdon Life Sciences Ltd., Cambridgeshire, England; Sponsored by Honeywell International, Inc., Morristown, NJ.

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COMMENTS ON BROMINE

At its meeting held on January 17-19, 2007, the committee reviewed the revised AEGL document on bromine. The document was presented by Sylvia Talmage of Oak Ridge National Laboratory.

General Comments

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

Specific Comments

Page 16, lines 9-13. In the first paragraph, it states that chlorine would penetrate to the lower respiratory tract more easily than bromine, and, therefore, chlorine would, produce lethality at a lower concentration than bromine. This statement is inconsistent with values for AEGL-3 listed in Table 8 on page 21. In this table, AEGL-3 values for chlorine are higher than those for bromine, suggesting that chlorine is less lethal than bromine at each time period. This relationship is consistent with TLV values noted below.

Page 18, lines 6-10. What is the justification for the statement that the uncertainty factor (UF) of 3 for intraspecies differences is appropriate when the mode of action is irritation rather than via biotransformation?

Page 19, lines 12-15. It states that asthmatic persons would be protected by an intraspecies UF of 3 because the concentration proposed for AEGL-2 "did not penetrate to the lower respiratory tract." Again, it is not clear whether no penetration occurred or whether some penetration occurred with no effect on normal tissue. In any case, there are receptors in the upper respiratory tract that can trigger an asthmatic attack, so the assumption that lack of any penetration into the lower respiratory tract of asthmatic persons would make this concentration "safe" for this population is not valid.

Page 21, Table 8. The TLVs for for fluorine, chlorine, and bromine are 1, 0.5, and 0.1 ppm, respectively, and the short-term exposure limits (STELs) (15 minutes [min]) are 2, 1, and 0.3 ppm, respectively. The rank order of relative toxicity for AEGLs-1 and -2 is, therefore, consistent with those values. There is, however, a disconnect for this order for AEGL-3, where chlorine appears to be the least toxic of the three halogens for each exposure duration.

Response to Comments

Page 2. It notes that data indicate that bromine is less toxic than chlorine and fluorine, and the reader is directed to Table 4 in the TSD. This table compares chlorine and bromine only and does not include fluorine. Furthermore, this statement is inconsistent with the rank order of the TLVs for these elements. In any case, the fact that bromine may be more soluble and therefore undergo more scrubbing in the upper respiratory tract is not a good rationale for why it may be less toxic than a less soluble chemical.

Editorial Comments

Page 18, lines 15 and 16. It states in this section that "…there was no penetration to the lower respiratory tract." There are no data to support this statement, so it should be changed to "…there is likely to be little penetration to the lower respiratory tract."

COMMENTS ON DIMETHYLDICHLOROSILANE

At its previous meeting held on January 17-19, 2007, the committee reviewed the revised AEGL document on dimethyldichlorosilane. The document was presented by Cheryl Bast of Oak Ridge National Laboratory.

General Comments

A revised document can be finalized if the committee's recommended revisions are made appropriately. The response to the comments has addressed the points raised; however, additional points have arisen. The rationale for deleting the comments regarding other toxic intermediates should be provided to the committee and should also be included in the response to the comments.

Section 8.3 should be revised to more clearly express the limitations in the data set and the assumptions made in light of the data limitations. The derivation of AEGLs 1-3 is heavily dependent on the AEGL derivation of hydrogen chloride and the assumption that the generation of 2 moles of hydrogen chloride for every mole of dimethyldichlorosilane accounts for the toxicity of the chemical. See comments below on methyltrichlorosilane. They are applicable to the document on dimethyldichlorosilane.

COMMENTS ON EPICHLOROHYDRIN

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on epichlorohydrin. The document was presented by Kowetha Davidson of Oak Ridge National Laboratory.

General Comments

Generally, this is a well-written document that requires a few major and some minor improvements. A revised document should be submitted to the committee for review.

The AEGL-1 (5.7 ppm throughout) up to the AEGL-3 for 4 h (43 ppm) and 8 h (30 ppm) are well below the level of distinct odor awareness (LOA) of 46 ppm. It may be advantageous to highlight (e.g., on page 6, line 10) the fact that odor is not an early warning aid for exposure to epichlorohydrin.

Page 43, lines 14 and 15. AEGL-2 values are summarized in Table 9. These values are supported by Wexler (1971) who stated that 20 ppm for 1 h is irritating to the eyes and nose. Clarify that irritation (at 20 ppm) is *not* an AEGL-2 end point and should not be used for AEGL-2 derivation.

Specific Comments

Page 6, line 21. Which species is referred to in the statement "Inhalation exposure of laboratory animals to epichlorohydrin causes effects similar to those reported for humans"?

Page 6, line 35. A UF of 3 (NA for interspecies sensitivity and 3 for intraspecies variability). Describe further the support for choosing a UF of 3.

Page 8, lines 5-7. In the table shown below and presented on page 8 of the TSD, 53 ppm (10-min AEGL-2) is *not* "a threefold reduction of AEGL-3" (570-ppm 10-min AEGL-3).

Proposed AEGL Values for Epichlorohydrin						
Classification	**10 minute**	**30 minute**	**1 hour**	**4 hour**	**8 hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	No effect level for irritation (UCC, 1983)
AEGL-2 (Disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	10 ppm (38 mg/m^3)	Three-fold reduction of AEGL-3 values
AEGL-3 (Lethal)	570 ppm (2155 mg/m^3)	160 ppm (605 mg/m^3)	72 ppm (272 mg/m^3)	43 ppm (163 mg/m^3)	30 ppm (113 mg/m^3)	Lethality threshold (Dietz et al., 1985; Laskin et al., 1980)

Page 9, line 9. The text states that "Epichlorohydrin is manufactured at three sites in the United States in Louisiana and Texas." Determine whether epichlorohydrin is produced outside the United States because AEGL documents are used in countries other than the United States.

Page 10, line 33. The text states that "Gardiner et al. (1993) reported a mean odor threshold of 10 ppm and an odor recognition level of 25 ppm. The odor threshold during and after a 5-min exposure of unconditioned personnel was 10-12 ppm for 50% of the subjects and 25 ppm for 100% of the subjects." Determine whether Gardiner et al. (1993) specify that the odor is recognized by individuals who have had previous exposure. If so, indicate that in the document.

Page 11, line 45. The text states that "Two years after the accident the patient complained of nonspecific epigastric pain; a clinical examination showed pronounced fatty liver, abnormal liver function, chronic asthmatic bronchitis, and essential hypertension (not related to exposure to epichlorohydrin)." Why mention hypertension here? Clarify whether there was a preexisting hypertension. If so, it should not be mentioned because it suggests an hypertensive effect of epichlorohydrin.

Page 15, lines 33 and 34. The text indicates that exposure to 20 ppm of epichlorohydrin for 1 h caused burning to the nose and mouth, 48 ppm for <2 h caused throat irritation that could last for 48 h, and >100 ppm caused pulmonary edema and 36 kidney lesions. This discussion may not be fully consistent with the odor threshold discussion on pages 10 and 11. For example, see Van Doorn et al. (unpublished report 2002).

Page 16, line 11. The text indicates that the unexposed workers also had a higher frequency of chromosome aberrations than the general population but not more cancers. Cancer epidemiology is treated in a separate chapter and is said to be inconclusive. Another sentence on the inconclusive evidence

for cancer should be inserted. The sentence on page 13, lines 36 and 37, could be inserted into this paragraph after the second sentence on line 5.

Page 19, line 13. Check the calculation of this unusually high LC_{50} (979 mg/m^3) and re-examine its consistency through different studies.

Page 26, lines 8 and 9 versus lines 10-12. Contradictory to each other? "The only evidence of kidney damage in young rats was … and lowered blood urea nitrogen (BUN)" versus "The only effect in the exposed adult rats … was a decreased BUN … No evidence of kidney toxicity was observed in the adult rats."

Page 26, line 22. The text states that "Bromosulfophthalein (BSP) removal from the blood was decreased at all three concentrations on the day of exposure. BSP is used to assess liver function, particularly biliary function." However, the BSP test is obsolete as a liver function test.

Page 38, line 28. The text states, "Epichlorohydrin is a chloromethyl substituted oxirane (ETO) or chlorinated methyloxirane (propylene oxide)." To avoid confusion, reword the sentence to show that "oxirane" and "ethylene oxide" (ETO) refer to the same substance.

Page 41, line 26. Note that 5.7 as shown in the table below and on page 41is far below the LOA of 46 ppm.

TABLE 8. AEGL-1 Values for Epichlorohydrin

10 minutes	30 minutes	1 hour	4 hours	8 hours
5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)	5.7 ppm (21 mg/m^3)

Page 42, lines 25 and 26. The text mentions that severe kidney toxicity was observed in rats exposed to 150 ppm of epichlorohydrin gas mixture for 1 h. Explain why "severe kidney toxicity" was not taken as a basis for deriving AEGL-2 (instead of dividing AEGL-3 by 3).

Page 43, lines 7 and 8. Perhaps this statement should be rephrased: "No definitive data were available for deriving AEGL-2 values from studies with humans or animals." However, the author should explain why severe kidney toxicity is not "definitive data."

Page 42, lines 36-38. The text states, "Because kidney damage was observed after a single inhalation exposure to epichlorohydrin, clinical signs alone are considered inadequate for evaluating animal toxicity after inhalation exposure to epichlorohydrin vapor." The statement is unclear. Is kidney damage not a "clinical sign"? For development of AEGLs, we are mainly interested in single inhalation exposure as is the case here.

Page 43, lines 14 and 15. The text states, "AEGL-2 values are summarized in Table 9. These values are supported by Wexler (1971) who stated that 20 ppm for 1 h is irritating to the eyes and nose." The committee suggests adding the word "only" between "is" and "irritating" to help clarify that irritation is not considered an AEGL-2 effect but is considered an effect below an AEGL-2.

Editorial Comments

Page 6, lines 34 and 35. Make a full sentence.

Page 6, line 39. "to become more severe with increasing time …."

Page 9, line 9. Is epichlorohydrin produced outside the U.S.? (This AEGL document is intended to be used internationally.)

Page 11, lines 12 and 13. Lefaux (1968) was before Wexler (1971) and should be mentioned first.

Page 14, lines 27-29. Unclear.

Page 14, line 40. Probably exposure "to epichlorohydrin" is meant.

Page 15, line 10. What is an "epoxy-producing unit"?

Page 15, line 16. Give years. Not every reader will know which years were the early years of operation of the Shell Chemical facility at Dear Park, Texas.

Page15, line 20. "Finnish," not "Finish."

Page 15, line 30. "irritation," not "Irritation."

Page 16, lines 1 and 2 versus lines 7-9 are contradictory: Chromosome aberrations are as long lived as the cells in which they occur and some lymphocytes are long-lived. Perhaps the sweeping statement "not been associated with any long-lasting effects" in lines 1 and 2 should be deleted.

Page 27, line 2; page 29, line 14; and page 31, line 2. "for 6 hours 5 days per week for 14 days."

Page 30, lines 9-14. The exposure is given in the same sentence first in ppm, then in mg/m^3, then again in ppm. The units should be consistent.

Page 34, line 11. *Escherichia coli*.

Page 34, lines 12, 13, and 14. If epichlorohydrin is more effective as a mutagen without "metabolism," it means that the metabolism leads to inactivation, not activation. Perhaps it would be best to replace "without metabolic activation" with "in absence of an exogenous metabolizing system."

Page 34, line 19. Sram et al.

Page 35, line 8. systemic but mainly portal-of-entry effects.

Page 37, lines 15 and 16. Mention the known metabolites.

Page 38, line 28. Define the abbreviation ETO: ethylene oxide (= oxirane).

Page 41, lines 19 and 26. Note that 5.7 is far below the LOA of 46 ppm.

Page 42, line 8. Wrong table number.

Page 42, lines 36-38. Rephrase the text for greater clarity. For AEGLs, we are mainly interested in single inhalatory exposure.

Pages 44, lines 22-23, and 45, lines 8-10: Which long-term study?

Page 44, line 26. "factor of 3" (no full stop after "of").

Page 44, line 27. "and rabbits was from" (not "The range ... ranged from …").

Page 45, line 1. "the AEGL-3 values."

Page 45, line 7. "an AEGL-3 value of 19."

Page 45, line 9. If we understand this statement correctly, it would be clearer for the reader if "over a lifetime" were added ("the exposure concentration of 30 ppm (6-h duration) over a lifetime that caused no lethality …").

Pages 54, line 24, and 55, line 5. Mention species.

Page 55, lines 41 and 42. Unclear.

Page 62. Legend not legible (may be just a problem of copying).

Comment References

Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC50 Determination in Fischer-344 Rats. Lake Jackson Research Center, Health and Environmental Sciences–Texas, Dow Chemical U.S.A., Freeport, TX.

Gardiner, T.H., J.M. Waechter, and D.E. Stevenson. 1993. Epoxy compounds. Pp. 329-444 in Patty's Industrial Hygiene and Toxicology, 4th Ed., Vol. 2, Pt. A: Toxicology, G.D. Clayton, and F.E. Clayton, eds. New York: John Wiley & Sons.

Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.

UCC (Union Carbide Corporation). 1983. Epichlorohydrin Repeated Inhalation, Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. RI-UP-HEASD 8S SU HS FN Submission. U.S. Environmental Protection Agency, Doc. I.D. 878212138.

Wexler, B. 1971. Determination of epichlorohydrin contamination in an industrial facility for the manufacturing of epoxy resins [in Romanian]. Mater. Plast. 8:322-323.

COMMENTS ON ETHYLENE OXIDE

At its meeting held on January 17-19, 2007, the committee reviewed the revised AEGL document on ethylene oxide. The document was presented by Kowetha Davidson of Oak Ridge National Laboratory.

General Comments

A revised draft can be finalized if the recommended revisions are made appropriately.

Specific Comments

Page 62, lines 10-12, 31, 32, and 35-39. 100 ppm is proposed as the NOAEL although it states that "fetal body weight was slightly, but significantly decreased." Presumably this significant decrease is considered as biologically insignificant. If so, give the percentage of the decrease (and, if possible, give a literature quotation that confirms that such a percentage decrease of fetal body weight is considered biologically insignificant). However, if the decrease in fetal body weight in question is considered biologically significant, 100 ppm cannot be taken as the NOAEL.

Page 64, lines 1 and 2. AEGL-2 was based on neurotoxicity and developmental toxicity studies, but time extrapolation for AEGL-2 was done using rat lethality data and ten Berge's equation (ten Berge et al. 1986). This is acceptable if the former are on the continuum of effects finally leading to lethality (e.g., all of them alkylation-driven). If so, it should be stated that these effects are on the continuum, and it should describe the basis of the conclusion. If not, the default values should not be used.

Page 88, lines 4-6. The word "neuropathy" should be crossed out. Distal axonal degeneration is the morphological basis of the neuropathy, which in turn must be of extracellular origin (supposedly myelin damage through ETO-induced oxidation). Axonal degeneration and neuropathy are not synonymous. Also, the sentence should be improved for clarity. What does "respectively" refer to?

Editorial Comments

Page 6, line 14. The phrase "dose in mg/kg bw" does not make sense in this context. Omit or qualify by saying, e.g., "internal dose in mg/kg bw at given external dose"if that is what is meant.

Page 8, line 4. Omit the phrase "the vapor density indicates that it is heavier than air" because it may be misleading.

Page 9, line 16. Correct the flammability value. Range is from 3% to 100%, as stated in the text.

Page 35, lines 7 and 20. Write out "Maximum nerve conduction velocity" in full and omit abbreviation "MCV" because term occurs only twice.

Page 40, line 34. Change to read "conducted a developmental toxicity *study* in mice…."

Page 40, line 41. Change to read "see Table 16" (not Table 15).

Page 41, line 17. Change to read "length reduction at 2,100."

Page 57, line 20. Change to read "with heterozygous."
Page 58, line 3. Unclear. What are "newborn adult levels"?
Page 58, line 16. Unclear. What is "proportionally similar"?
Page 58, lines 21 and 22. Something is missing in the sentence "The genotypic diversity…."
Page 62, line 44. Change to read "were significantly increased".
Page 63, line 27. Change to read "the dosimetry" (instead of dosmetric).
Page 63, line 28. Change to read "not expected to differ" (omit the word "be").
Page 65, line 30. Change "Deah" to "Death".
Page 87, line 35. The phrase "dose in mg/kg bw" does not make sense in this context. Omit or qualify by saying, e.g., "internal dose in mg/kg bw at given external dose" if that is what is meant.
Page 89, line 20. The phrase "dose in mg/kg bw" does not make sense in this context. Omit or qualify by saying, e.g., "internal dose in mg/kg bw at given external dose" if that is what is meant.

Comment Reference

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

COMMENTS ON FURAN

At its meeting held on January 17-19, 2007, the committee reviewed the revised AEGL document on furan. The document was presented by Claudia Troxel of Oak Ridge National Laboratory.

General Comments

The authors have provided a good-faith response to the previous review and addressed nearly all of the areas of concern. The revised document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

Page vii, line 29. This line states that the key study "actually evaluated the acute inhalation toxicity of several chemicals," giving rise (from the text, as written) to the interpretation that the Terrill et al. (1989) study examined mixed furan, 2-methyl furan, furfuryl alcohol, and furfural exposures rather than individual studies of each congener. Please drop the text that describes chemicals other than furan. They have no bearing on the furan AEGL as Section 3.1.2 describes the results of the furan inhalation trials.
Page vii, lines 20 and 21. This provides no useful information ("Therefore, the differences in furan kinetics in humans could be compared to those in rodents."). Page vii provides a description of the interspecies 10-fold factor utilized in AEGL-2 and AEGL-3 derivations, but it is not clear why the available PBPK parameters were not used for the interspecies dose scaling and why the authors relied upon a default factor of 10. Please either revise (or at least compare and contrast) the derivation to incorporate results of interspecies furan extrapolation using the published PBPK parameters or explain why the PBPK approach for extrapolation of the rat data to humans is not useful here and why the interspecies dose extrapolation should be conducted using a default UF. At a minimum, the text should state and explain the margin of exposure (as summarized on page 19, lines 11-14) and indicate why a

dose of furan metabolites in human liver at AEGL-2 and AEGL-3 of 1.7 ppm or 4.8 ppm for 4 h is within the acceptable risk range.

Page 1, line 17. The first sentence of the second paragraph on page 1 is incomplete. It is important that the public understand furan is a ubiquitous material present in cooked foods (snacks, biscuits, bread crust, roasted wheat flour, roasted coffee beans) (Becalski et al. 2005; Zoller et al. 2007). The U.S. Food and Drug Administration (FDA) carried out a large survey of various foods to determine their furan content and found concentrations ranged from nondetectable to 100 ppb (http://www.cfsan.fda.gov/~dms.furanexp/sld09.htm). FDA calculations found that mean daily furan exposure ranged from 0.26 µg/kg-day for adults to 0.41 µg/kg-day for infants. It is important to point out that for most people, coffee is the primary source of furan exposure and that coffee brews from espresso-type machines (considered to have the best aroma) had the highest amounts of furan compared with other brews.

Page 2, line 23. The NTP (1993) report referenced is badly dated as human exposure data. The annual production quantities and numbers of facilities that produce, handle, or otherwise consume furan should be revisited. Move the references to furan exposure from the section on "Nonlethal Toxicity" to the section dealing with environmental exposure. It appears Section 2.2 could be rewritten to state, "No data were available regarding acute nonlethal toxicity of furan."

Page 9, lines 38-40. Move or enhance the descriptions of the rats that inhaled 100, 500, 1,050 or 3,850 ppm to the section on nonlethal toxicity. Do the Kedderis et al. (1993) and Kedderis and Held (1996) publications provide descriptions of the health and/or behavior of the rats used in the kinetic studies that could be used to support or detract from the AEGL-2 and AEGL-3 values derived from the Terrill (1989) data? Because the rats used in the kinetic studies survived their single 4-h exposures to as high as 208 ppm without apparent ill effect (page 10, line 6) or even up to 3,850 ppm (page 9, line 40), how can one justify a 4-h AEGL-2 of <2 ppm and a 4-h AEGL-3 of <5 ppm unless there is an over-riding carcinogenic concern? As carcinogenicity was not considered (page 19), it is not clear how the AEGLs are justified when the rats used in controlled inhalation studies conducted at up to 4 h survived exposures with "initial" concentrations of as great as 3,850 ppm (page 9, line 40)? It may be that the proposed AEGLs are more the consequence of the concentrations (to 2,851 ppm) and duration (1 h) used in the Terrill protocol than the fact that groups of three rats can tolerate up to 3,850 ppm for 4 h (Kedderis et al., 1993).

Page 10, lines 4-7. In discussing the results of the Terrill report, move or enhance the descriptions of the rats that inhaled furan for 4 h at 52, 107 or 208 ppm (12 rats/group). Also, refer to comment from page 9, lines 38-40.

Page 19, lines 6-8. This discussion is weak. Where a material can induce nongenotoxic changes that lead to production of tumors, it is usually implied that the mode of action can be handled by a threshold or sigmoid dose-response relationship, and it does not follow that "it is not expected that a one-time exposure up to 8 h would induce cancer." Rather, the reader needs to know whether the metabolized dose to the target organ (liver) has a margin of safety at the AEGL-2 and AEGL-3 values that is sufficiently large so that other noncarcinogenic factors (body weight reduction) can drive the furan AEGL.

Editorial Comments

Page vii, line 35. Delete "Toxicity signs during exposure"; change to: "Signs of furan intoxication during exposure included…"

Page viii, line 17. The Terrill report was not inadequate because "the study actually evaluated the acute inhalation toxicity of several chemicals"; rather, the description of the results was not as precise as the reader might wish.

Page 10, line 29. Change to "Michaelis-Menten".

Comment References

Becalski, A., D. Forsyth, V. Casey, B.P. Lau, K. Pepper, and S. Seaman. 2005. Development and validation of a headspace method for determination of furan in food. Food Addit. Contam. 22(6): 535-540.

Kedderis, G.L., and S.D. Held. 1996. Prediction of furan pharmacokinetics from hepatocyte studies: Comparison of bioactivation and hepatic dosimetry in rats, mice and humans. Toxicol Appl Pharmacol. 140(1):124-130.

Kedderis, G.L., M.A. Carfagna, S.D. Held, R. Batra, J.E. Murphy, and M.L. Gargas. 1993. Kinetic analysis of furan biotransformation by F-344 rats in vivo and in vitro. Toxicol. Appl. Pharmacol. 123(2):274-282.

NTP (National Toxicology Program). 1993. Toxicology and Carcinogenesis Studies of Furan (CAS No. 110-00-09) in F344N rats and B6C3F1 Mice (Gavage Studies). Technical Report 402. NIH 93-2857. U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Terrill, J.B., W.E. van Horn, D. Robinson, and D.L. Thomas. 1989. Acute inhalation toxicity of furan, 2-methylfuran, furfuryl alcohol, and furfural in the rat. Am. Ind. Hyg. Assoc. J. 50(5):A359-A361.

Zoller, O., F. Sager, and H. Reinhard. 2007. Furan in food: Headspace method and product survey. Food Addit. Contam. 24(Suppl. 1):91-107.

COMMENTS ON JET FUEL 8

At its meeting held on January 17-19, 2007, the committee reviewed the revised AEGL document on jet fuel 8. The document was presented by Sylvia Talmage of Oak Ridge National Laboratory.

General Comments

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

With all the references to JP-5, why not include JP-5 in the title? The claim is made that JP-5 is a subset of JP-8. Page 8, lines 11-16, describe the distillation specification for JP-5. Provide the same for JP-8 to validate that JP-5 is a subset of JP-8.

Also, there is a need to address the source of benzene. The committee suggests incorporating the following information as an explanation for benzene:

— Only the studies of Carlton and Smith (2000) discuss benzene exposures measured during maintenance operations on military aircraft fuel tanks. The exposures were measured inside the fuel tanks or on personnel removing foam from the tanks. The later operation involves the generation of aerosols as the foam is pulled out of the tank. Benzene is more water soluble than other jet fuel components and concentrates in the small amount of water remaining after many refuelings. This can result in measurable benzene concentrations during these operations even though the levels of benzene in the bulk fuel are not detectable (see Appendix A). Benzene is not a component of concern for JP-8 AEGLs.

— Aerosols are not generated during refueling operations. Aerosols will only be developed during aircraft foam removal operations (occupational exposure) or aircraft engine cold starts (occupational exposure).

— While these exposures are based on reported mixed aerosol and vapor concentrations, the primary exposure is to the vapor. Exposure to aerosols will probably result in deep lung

deposition. Therefore, AEGLs based on mixed aerosol and vapor exposures are more conservative than those based on gas-phase exposures. However, aerosol concentrations of 10 mg/m^3 result in a visible cloud. These concentrations and higher will result in liquid deposition on surfaces.

— For JP-8, the typical aromatic hydrocarbons in JP-8 are the polycyclic aromatics and not the lighter aromatics, such as benzene, toluene, xylenes, and ethyl benzene found in gasoline. Refer to the analysis in Appendix A.

Specific Comments

Page 5, lines 21 and 22. What is the rationale for aerosolized fuel to cause immune system effects more than fuel vapor?

Page 5, lines 37-39. Stating the concentration can be tolerated over all AEGL-1 exposures is reverse logic from the general rule for TSDs that AEGL concentrations should remain constant across time where irritation is the effect. This primarily applies to AEGL-1 but could also apply to AEGL-2. This rule is not based on a toleration effect but rather on the effects not being concentration-dependent.

Page 5, lines 41-43. The argument on uptake is valid for solvents for CNS effects. It does not apply for irritants.

Page 7, lines 6 and 7. The general rule for solvents that cause CNS effects is that AEGL-2 and AEGL-3 should remain relatively constant over a time exceeding 1 h because of blood equilibrium concentrations. The time to equilibrium depends on the blood solubility of the compound (the more lipophillic, the quicker the equilibrium). The ten Berge (1986) equation does not apply. At some point, the compound reaches saturation. This must be determined with pharmacokinetic modeling to estimate blood concentration. If there is no pharmacokinetic model, observations need to be included on the effects at the concentration of concern. Extrapolations cannot be made from the short term (less than equilibrium time) to the longer duration.

Page 16, lines 31-37. Include the carcinogenicity data on kerosene (ATSDR 1998). Because JP-8 is essentially kerosene with additives, the results of animal bioassays of kerosene should be summarized in this section.

Page 17, lines 16 and 17. JP-8 particles are most commonly generated during start-up of cold jet engines.

Page 18, lines 3-5. Did MacEwen and Vernot (1985) report eye irritation in mice and rats exposed for 1 h to 625 ppm as stated in the TSD? This seems unlikely, if the undiluted fuel was not irritating to the eyes.

Page 31, lines 3-5. Could the increase in grip strength over the 65-day interval between exposure and testing merely have been due to muscle growth during this period?

Page 39, line 32. The TSD does not address the committee's suggestion to mention a potential relationship between male-rat-specific nephropathy and nephrocarcinogenicity.

Page 43, lines 17 and 18. The committee suggests using the Alarie (1981) rationale but deleting the parenthetical explanation "(essentially applying a 3-fold reduction to approach an AEGL-1 concentration and intraspecies and interspecies factor of 1 [based on greater uptake in rodents] and 3, respectively)". The manner in which this is stated is confusing and appears the author is trying to apply a UF explanation where it does not apply. We suggest explaining the Alarie approach includes appropriate UFs in going from a rodent RD_{50} to slight irritation in humans. Perhaps expanding on the number of chemicals that Alarie investigated will provide additional support.

Page 43, lines 20-24. Recommend deleting the rest of the paragraph: "In addition, Schaper (1993) … the AEGL-1." This is an interesting correlation but irrelevant. A 30-fold reduction of the RD_{50} leads to the TLV for an irritant. Multiplying the TLV by 3 yields the AEGL-1 but it is undesirable to establish this relationship between TLV and AEGL-1.

Pages 43, line 37, and 44, line 5. Delete the rest of the paragraph:
"If the 1000 mg/m^3 value … protective for humans."
Page 43, Section 5.3. Here is a suggested discussion on the derivation of AEGL-1:

The AEGL-1 is based on the sensory irritation study of Whitman et al (2001), specifically the RD_{50} for JP-8 of 2,876 mg/m^3. This is a robust study based on aerosol and vapor atmospheres in accordance with the ASTM E981-84 method. According to Alarie (1981), reducing the RD_{50} by 10-fold results in an exposure concentration of the JP-8 mixture that produces some sensory irritation to humans that is tolerable for hours to days. This is consistent with an AEGL-1 effect. The resulting value is 290 mg/m^3. Because primary irritation is a concentration effect independent of time, the 290 mg/m^3 value was applied to all AEGL-1 exposure durations (Table 5; Appendix B).

The primary volatile components of JP-8 present in the vapor phase, the *n*-alkane solvents in the C9 to C12 range, are not primary irritants. As indicated in Table 3, there were no other adverse clinical effects in animal studies with repeated exposure to JP-8 vapor at 1,000 mg/m^3 (MacEwen and Vernot 1985; Mattie et al. 1991; Briggs 2001; Rossi et al. 2001). Rossi et al. (2001) did report some changes in brain neurotransmitter activities. Applying an interspecies UF of 1 (chosen because the uptake of these chemicals is higher in rodents than in humans [Gargas et al., 1989]) and an intraspecies UF of 3 (chosen to account for potential differences in human susceptibility to sensory irritation) results in a value of 330 mg/m^3. This supports the value of 290 mg/m^3 determined using the RD_{50} study of Whitman, et al. Figure 1 is a category plot of animal toxicity data and AEGL values.

Page 44, Section 6. Is this based on irritation or CNS effect (page 6, lines 18 and 19)? The committee is unaware of only the CNS depression results from the Rossi et al. (2001) study, which is a repeat exposure study. Regarding the supporting studies:

— Biggs (2001), vapor only, repeat exposures, no reproduction effects.
— Mattie et al. (1991), 90-day continuous exposure, looking for renal effects, no effects.
— Rossi et al. (2001), whole-body, repeat exposures 6 h/day, 5 days/week for 6 week, minor CNS effects.
— Wolfe et al. (1996), vapor and aerosol, vapor, aerosol, single 4-h exposure, no change in body weights, eye and upper respiratory irritation.

Page 46, Section 7. The committee agrees with this explanation.

Editorial Comments

Page 17, line 8. Include the word "relatively" between "are" and "low."
Page 28, lines 2 and 3. The second half of the sentence here should be amended to read "and may reflect coverage of all of the nasal tissue."
Page 39, lines 19 and 20. Rewrite this sentence to read as follows: "α2u-Microglobulin nephropathy is unique to male rats. This protein is not synthesized in humans (EPA1991). Therefore, this adverse effect is not relevant to human exposures to jet fuels."
Page 40, lines 21 and 22. This sentence should be revised as follows: "Aromatic amines, the substrates for *N*-acetyltransferases, are not major constituents of JP-8."

Comment References

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

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. Toxicological Profile for JP-5 and JP-8. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp121.pdf.

Briggs, G.B. 2001. Evaluation of Military Fuel Potential to Produce Male Reproductive Toxicity. Presented at the International Conference on the Environmental Health and Safety of Jet Fuel, August 8-11, 2001, San Antonio, TX.

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COMMENTS ON METHYL ETHYL KETONE

At its previous meeting, the committee reviewed the revised AEGL document on methyl ethyl ketone. The document was presented by Sylvia Talmage of Oak Ridge National Laboratory.

General Comments

The author did an excellent job in responding to the comments on the previous, first version of this TSD. Taking the comments below into account, the document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

Page 15, lines 8-14. This section should be left out if methyl ethyl ketone (MEK) was involved only sporadically or not at all. As is, it gives the impression that these serious neurological birth defects were caused exclusively by MEK.

Page 21, lines 29-31. MEK is an inducer of the cytochrome P450-2B and -2E families.

Page 32, lines 12 and the following. Do not use "MAC" as an abbreviation for minimum alveolar concentration; it is a well-known abbreviation of maximum accepted concentration in the workplace, and is, therefore, confusing.

Editorial Comments

Page 5, line 41. The text states, "The AEGL-2 was based on the absence of neurobehavioral effects on the first day of the subchronic study of Cavender et al. (1983)." The text should be revised to indicate that the AEGL-2 was based on an exposure concentration that did not result in neurobehavorial effects on the first day of the subchronic study of Cavender et al. (1983). The wording avoids saying the level is based on the absence of an effect.

Page 33, line 15. Change to read "MEK itself does not…."

Page 43, line 20. "Aanvaarde", *not* "Aanvaaarde."

Page 50, line 43. "Opdam" *not* "Oipdam."

Comment Reference

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg, and E.J. Gralla. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fundam. Appl. Toxicol. 3(4):264-270.

COMMENTS ON METHYL MERCAPTAN

At its previous meeting held on January 17-19, 2007, the committee reviewed the AEGL document on methyl mercaptan. The document was presented by Cheryl Bast of Oak Ridge National Laboratory.

General Comments

The proposed AEGL values appear appropriate given the limited database for their derivations. Support is sufficient for the derivation of the AEGL values. Time scaling and the use of UFs appear appropriate. More specific recommendations could be made for specific additional research to improve the AEGLs, given the paucity of the database. A revised document should be submitted to the committee for review.

Although the database is sparse, the studies that exist are consistent. Good agreement was noted between the two rat 4-h LC_{50} tests. There was less, but still acceptable, agreement between those results and the rat 1-h LC_{50} test. Good agreement was noted between the two rat short-term exposure studies (15-30 min) and between those and the LC_{50} studies. The one mouse 4-h LC_{50} test is consistent with the rat studies and with the observations in the mouse bone marrow red-blood-cell micronucleus assay.

The key study for AEGL-2 values, the 1996 Elf Atochem report (see page 17 of the TSD), should have been posted in its entirety on the NAC/AEGL web site at cira.ornl.gov, rather than only in the

summary. If the bulk was prohibitive, the relevant material could be excerpted and posted, including the Methods and References sections. Handwritten notations on the summary refer to pages 11 and 18; presumably these had relevant material. Compare the informational value of this summary to that of the posted key article for the AEGL-3 values.

Specific Comments

Page 10, line 6. This section is titled "Nonlethal Toxicity" but addresses only studies defining odor detection and/or thresholds (except for the one study discussed on page 11). Would this material be more appropriately included in the Introduction section, perhaps after Table 1?

Page 11, line 3. If available, any details regarding the "clinical symptoms" should be reported here, even if the exposures were to a mixture of similar chemicals.

Page 14, lines 20-23. The suggested explanation of the increase of total blood protein as probably due to dehydration is plausible but not the decrease in serum albumin. This appears rather indicative of liver damage, even in the absence of gross lesions visible by standard histopathological investigation. Decreased serum albumin levels could also reflect mild kidney (glomerular) toxicity with resultant albuminurea. These other possibilities are important, because of the statement that the "AEGL-2 values are considered protective because rats exposed to 57-ppm methyl mercaptan 7 h/day, 5 days/week for 3 months experienced only decreased body weight" on page 18, line 6.

Page 15, lines 30-38. The discussion of mechanisms would be clearer if the active moiety for this effect, presumably the hydrosulfide anion, is identified. This would also strengthen the flow of the discussion from metabolism to mechanism to structure-activity relationships (SARs).

Page 16, line 2. The duration of exposure to hydrogen sulfide in the DuPont (1992) study should be stated, as should the number of deaths and the number of subjects.

Page 16, lines 10-11. Are the toxic effects referred to and methyl mercaptan's facilitating role the result of acute exposure(s)? Are they observed acutely, after a delay, or are they chronic?

Page 16, lines 14 and 15. The text indicates that "based upon the limited available data, a definitive assessment of species variability is not possible." Although this may be true in a narrow sense, the discussion regarding mechanism of action in Section 4.2 supports a reasonable conclusion that wide variations in susceptibility are unlikely and that the dose-response curves for acute effects are likely to be relatively steep. This would also support the selection of an interspecies UF of 3.

Page 17, lines 1-6. The LOA is very low, which may be helpful in providing initial warning; however, nothing is mentioned regarding habituation to this odor and the possibility of temporary loss of smell as complicating factors. This may also support not using the LOA in deriving an AEGL-1. A note regarding this issue could (also) be included in Appendix C: "Even though methyl mercaptan has an extremely unpleasant odor, at high concentrations, olfactory desensitization or fatigue occurs. Therefore, odor and symptoms of irritation may not adequately provide warning of high concentrations of methyl mercaptan (Shertzer, 2001)."

Page 18, line 6. Refer to the comment above regarding page 14, lines 20-23. Change to read, "experienced only decreased body weight and decreased serum albumin …."

Page 19, line 12. Refer to the comment above regarding page 14, lines 20-23. Change to read, "experienced only decreased body weight and decreased serum albumin …." Do the same on page B-3, line 39 and page B-5, line 4.

Page 19, lines 24-34. The discussion notes the steepness of the dose-response curve for lethality and the narrow concentration range across which effects occur, from NOAEL to LC_{50}, and places in that context the acknowledgement that the values for the 8-h AEGL-2 and AEGL-3 are essentially identical. This discussion should also note that the spread between AEGL-2 and AEGL-3 values for shorter time periods (except for 10 min) is also narrow and about half that derived for the equivalent hydrogen sulfide (H_2S) values. Because the rationale for selection of UFs is based on methyl mercaptan being similar to, but less toxic than, H_2S, this apparent inconsistency should be noted and addressed.

Page 22, lines 20-23. The first two sentences translate clearly to research recommendations. The third sentence should be expanded to a set of more specific recommendations to identify the specific data to be generated.

Page B-3, line 39. Refer to the comment above regarding page 14, lines 20-23. Change to read, "experienced only decreased body weight and decreased serum albumin …."

Page B-5, line 4. Refer to the comment above regarding page 14, lines 20-23. Change to read, "experienced only decreased body weight and decreased serum albumin …."

Appendix C: Derivation of the Level of Distinct Odor Awareness (LOA). Perceptible odor can be helpful in providing initial warning, and calculating a LOA provides some quantitation for a typically qualitative parameter. However, whenever the warning properties of odors are mentioned, it is important to note that habituation to odors does occur, sometimes accompanied by the temporary loss of smell as a complicating factor. If a LOA is provided, a cautionary note should accompany it. This may also support not using the LOA in deriving an AEGL-1.

Editorial Comments

Page 2, lines 24-44. See comments regarding page 17, lines 23-33.

Page 2, lines 24-27. Two studies are referred to here: one in mice and the other in rats. The phrasing in the parenthetical on line 27 starts out somewhat ambiguously. To improve clarity, change the parenthetical to read "(in a study in rats [Tansy et al. 1981], 600 ppm … 675 ppm—4 h LC_{50}; 429 ppm—4 h LC_{01}) …."

Page 2, line 32. Insert a space between "to" and "17 ppm".

Page 2, line 41. The parenthetical statement that was opened on line 31 needs to be closed here.

Page 3, lines 7-29. See comments regarding Section 7.3 below (page 18, line 23 to page 19, line 19).

Page 3, line 15. Remove one of the parentheses after 1981.

Page 3, lines 19-21. Which species was used to develop each of these values?

Page 9, line 14. "Odor" is the last value listed in the table. This is not a physical or chemical value in the common use of these terms. Because odor is addressed on page 8, lines 10 and 11, it can be deleted here. Also, see the comment in the "Specific Comments" section regarding page 10, line 6.

Page 9, line 32. Delete period after "arteries."

Page 10, lines 20-41. Many of the values reported here are <0.001 ppm. The use of scientific notation would make it easier to identify just how much less (as on line 35).

Page 10, lines 26 and 27. It is most likely that this investigator expressed concentration measurements and results of calculations in units of mg/m^3. Assuming NTP conditions, the value listed for ppm is incorrect; it should be 0.00025 ppm.

Page 10, line 35. The odor threshold reported here is two orders of magnitude lower than others in this section. Is that a typographical error or is it correct?

Page 11, line 36. This study had an unusual set of exposure concentrations, and the reader could easily assume a typographical error had been made regarding the two 700-ppm exposure groups. A note explaining that there were two separate exposure groups at this concentration would help avoid confusion. This also applies to Table 3 on page 12.

Page 11, line 39. Should "15 pdi" be "15 psi"?

Page 11, line 41. For clarity, change to read "pump. For this 4-h exposure, the LC_{50} calculated value …."

Page 11, line 43. For emphasis, change to read, "Data are summarized in Table 3, where the strength of the dose-response relationship can be readily seen."

Page 13, lines 19-25. The exposure duration is stated as "15 minutes *or less*" [emphasis added]. The CD_{50} value stated in lines 22-23 does not state a duration of exposure explicitly, nor does the CD_{00} on

line 25. Although it can be inferred that the duration of exposure is 15 min, it would reduce ambiguity if stated explicitly.

Page 15, lines 10-14. This summarization is awkwardly written and difficult to follow. Parallelism of construction is very important in writing these results. A graphic would be even better.

Page 15, lines 13 and 14. The statement "no rats died … [at] 500 ppm and all rats died at 750 ppm" gives the impression of an investigation using a reasonable number of animals. This would be more accurately phrased as "none of the two rats died ... and both rats died …."

Page 15, line 23. Presumably, the form found in the urine was not $^{35}SO_4$ but $^{35}SO_4^{2-}$.

Pages 15, line 43, and 16, line 1. The comment above regarding page 15, lines 13 and 14 also applies here. Change to read, "none of the 2 rats died …."

Page 17, line 17. Insert the species (mice) for clarity.

Page 17, lines 19 and 20. See comment above addressing page 2, lines 24-27.

Page 17, lines 23-33. Discussion in this paragraph is interrupted by an extensive parenthetical discussion, which contains another parenthetical data presentation (lines 30-31). The material presented is important but the manner of presentation disrupts the flow of information and distracts attention. Is there not a better way to word this?

Page 17, line 26. The word "unreasonable" conveys more than one meaning; this might be better phrased, "it is very unlikely that people exposed"

Page 17, lines 30 and 31. Identify the species used to derive the LC_{50} values.

Page 18, lines 5 and 6. The protective nature of the AEGL-2 values is also supported by the occupational exposure experience referred to on page 11, lines 1-5. This would also be relevant for the 8-h AEGL-3 value on page 19, lines 11 and 12.

Page 18, lines 30-39. Discussion in this paragraph is interrupted by an extensive parenthetical discussion, which contains another parenthetical data presentation (lines 36-38). The material presented is important but the manner of presentation disrupts the flow of information and distracts attention. Is there not a better way to word this?

Page 18, lines 23 and 26. The LC_{01} is given two (slightly) different values on these lines; this should be clarified or changed. Verify that the same value is used throughout the text.

Page 18, line 25. For clarity and smoothness, change to read "lethal response curve <u>in this study</u> (600 ppm …."

Page 18, line 37. Identify the species used to derive the LC_{50} values.

Page 19, line 31. There was no exposure at 675 ppm; this was the calculated LC_{50} . The lowest exposure group to experience 100% mortality was at 700 ppm. This changes the dose-range to 1.75-fold.

Page 19, lines 32 and 33. The exposure period for the 258-ppm and the 512-ppm exposures was 6 h. There is some ambiguity created by waiting to state the exposure duration until late in the sentence. Recommend that the approach used in the preceding sentence be used here: "Furthermore, in mice exposed to methyl mercaptan for 6 h, only shallow breathing …."

Page 22, line 4. The page number is probably in error, see note below on this reference (page 24, lines 24 and 25).

Page 22, line 6. The 2006 TLV could be used as the citation.

Pages 23-25. References: If a document is available online (other than a journal article), the URL should be provided to improve ease of access to the document.

— ATSDR Toxicological Profiles are available on line at http://www.atsdr.cdc.gov/toxpro2.html.
— NIOSH IDLH database is on line at http://www.cdc.gov/niosh/idlh/idlh-1.html.
— NIOSH Criteria Documents, Occupational Hazard Assessments, Special Hazard Reviews and Joint Occupational Health Documents are available on line at http://www.cdc.gov/niosh/critdoc2.html.
— OSHA1993 revocation of the 1989 update to the PELs is online at http://www.osha.gov/pls/oshaweb/owadisp.showdocument?ptable=FEDERALREGISTER&p_id=13306.

— OSHA Air Contaminants list (Table Z-1) is on line at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Also, if there is a citation of a common secondary source, check to see if there is a more recently updated version, verify the information being referenced there, and cite the most recent version that contains the material to be referenced. This is especially appropriate for annually updated sources such as the TLVs, WEELs, or ERPGs, which can change and even withdraw certain values. Also ensure that, for exposure limits and guidelines, the citation clearly is either to the value or to the documentation (See Comment References section below).

Page 23, lines 5 and 6. Change from the 1991 version to the 2004 version of the documentation, which was updated that year for methyl mercaptan.

Page 23, lines 32-34. The DFG 2005 MAK (maximale argeitsplatzkonzentration [maximum workplace concentration]) values are in Report No. 41, not 35.

Page 23, line 48. Expand the reference to read "Matheson (1983). Guide to Safe Handling of Compressed Gases (GSHCG), 2nd ed. Matheson Gas Products, Inc., East Rutherford NJ."

Page 24, lines 14-16. References to NIOSH (and other government agency) documents generally read "NIOSH (date). Title, etc." and include the publication number (for the IDLHs, the web site indicates NTIS Pub. No. PB-94-195047, May 1994).

Page 24, lines 24 and 25. The *Federal Register* page number shown is 6 digits, unlikely for June even now. The citation should be 58 Fed. Regist. 35338-35351 (30 June 1993).

Page 24, lines 45 and 46. Is this the complete citation for this reference?

Page 25, line 4. Is there a title for this paper?

Page 25, lines 6 and 7. Use complete citation as shown in the Standard Operating Procedures (SOP).

Page 25, lines 9 and 10. Is this the complete citation for this reference?

Pages A-3 and A-4. For ease in reading the calculated values, use standard U.S. convention for separating digits in groups of three (i.e., thousands) by inserting commas.

Page B-2, line 14. To what does the "(1)" refer?

Page B-2, line 15. For consistency, change "Not applicable" to "NA".

Page C-2, line 11. Insert a space after "ppm."

Comment References

Bloom, J.C., and J.T. Brandt. 2001. Toxic responses of the blood. Pp. 389-417 in Casarett & Doull's Toxicology: The Basic Science of Poisons, 6th Ed., C.D. Klaassen, ed. New York: McGraw-Hill.

Deichmann, W.B., and H.V. Gerarde. 1973. Toxicology of Drugs and Chemicals, 4th Rev. Ed. New York: Academic Press.

Pohanish, R.P. 2002. Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens, 4th Ed. Norwich NY: William Andrew Publishing/Noyes.

Shertzer, H.G. 2001. Organic sulfur compounds. Pp. 681-765 in Patty's Toxicology, Vol. 7. Glycols and Glycol Ethers/Synthetic Polymers/Organic Sulfur Compounds/Organic Phosphates, 5th Ed., E. Bingham, B. Cohrssen, and C.H. Powell, eds. New York: John Wiley & Sons.

COMMENTS ON METHYLTRICHLOROSILANE

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on methyltrichlorosilane. The document was presented by Cheryl Bast of Oak Ridge National Laboratory.

General Comments

The response to the comments has addressed most of the points raised. The minor comment regarding the formatting of the mortality data on page 4 appears to be corrected, although no underscore was apparent on that page on the copy provided. The revised document can be finalized if the committee's recommended revisions are made appropriately.

The rationale for the deletion of consideration of other toxic intermediates needs to be provided in the response to the comments.

The derivation of AEGLs 1-3 for methyltrichlorosilane is heavily dependent on the AEGL derivation of hydrogen chloride (HCl) and the assumption that the generation of 3 moles of HCL for every mole of methyltrichlorosilane accounts for toxicity of the chemical. The first draft had included language about other toxic decomposition products, and, therefore, this would not be consistent with AEGL derivation based on analogy with HCl. The committee asked that this inconsistency be addressed. A possible solution was not to link the AEGL derivation to that of HCl but to permit the AEGL values at longer exposure times to be based on the values derived from the standard methodology. However, in the revision, statements regarding these toxic products have been deleted. Also deleted is the comment that the "confidence in the AEGL values was at best moderate." In this revised document, the AEGLs are consistent with those based on the HCl generation alone. No uncertainty is expressed that may be due to other toxic intermediates.

The document is internally consistent as revised, and the AEGL values derived are acceptable as long as the assumption that the toxicity can be accounted for wholly on the basis of the moles of HCl that are produced is accepted. The reason for deleting the statements regarding other toxic intermediates is not given in the response to the comments. It is unclear on what basis the statements were deleted. It is worthwhile to have the basis for the record provided to the committee in the response to the comments. This information would provide assurance that the approach taken for the derivation of the AEGLs is correct and would increase the transparency of the process.

Section 8.3 should be revised. The revision to this section does not reflect the data limitations or the assumptions. It gives the impression that there is a high degree of confidence in the AEGL values, whereas there are several data limitations and uncertainties that should be acknowledged.

The HCl database is not "robust" as stated in the revised document (page 12, line 34) and this word should be deleted. The human study on exercising asthmatic individuals included only 10 individuals, and they were exposed for only 45 min. Data for longer exposure times are lacking. These data are used to set the AEGL-1 values up to 8 h and reduce the inter- and intraspecies uncertainty from 100 to 1. Further, it is assumed in setting the AEGL-1 that the effect of methyltrichlorosilane is based only on the molar equivalent HCl produced, and this assumption should be noted. Compounds with limited data sets should be revisited at a shorter frequency than those with robust data sets.

The AEGL-2 and -3 values are based on a rat study whose concentrations were given as nominal concentrations and the exposure period only 1 h. Adjustments were made in the derivations to rationalize the results with the HCl AEGLs 1-3 values. Limitations in the animal toxicology database on methyltrichlorosilane and the assumption of toxicity based on only HCl should be noted.

Given these issues, the confidence in the AEGL values seems less than implied. The committee recommends that this section be revised to indicate the limitations in the data available and the assumptions made in the derivation of the AEGLs.

COMMENTS ON NITRIC ACID

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on nitric acid. The document was presented by Carol Wood of Oak Ridge National Laboratory.

General Comments

Because nitric acid (HNO_3), nitrogen dioxide (NO_2), nitric oxide (NO) are reactants or products of the same chemical reactions, the committee recommends these be sections of the same chapter within the AEGL publication. A revised document should be submitted to the committee for review.

The committee recommends that the authors expand their explanation of the basis for expressing AEGL values in units of ppm (in addition to units of mg/m^3) and the extent to which it is a conservative (protective) approach, given that the aerosol is more toxic because particles reach the deep lung. Also, the authors should discuss and provide examples of the likely exposure scenario and indicate whether the exposure is more likely to be to nitric acid as a vapor or aerosol.

Nitric acid is highly soluble in water and, therefore, should be a primary irritant in the upper respiratory effect. HNO_3, NO_2, and NO have related and complicated chemistry. It appears NO_2 is the primary route of exposure, but the dose is delivered when NO_2 converts to HNO_3 in the deep lung. The committee recommends that the document be revised to explain the chemistry and the relationships with the toxicologic observations as they apply to AEGLs.

Throughout the document there are references to various physical states (vapors, fumes, gaseous acids, etc). A brief explanation of each of those terms should be given in the definition section beginning on page 23 of the technical support document. The authors should ensure that each of the terms is used unambiguously.

Specific Comments

Page 4, lines 22-25. The basis of the AEGL-2 and AEGL-3 values is a lethality study with an aerosol route of exposure. This is not a likely emergency exposure scenario.

Pages 4, line 42, and 5, line 1. For AEGL-2, if HNO_3 is a direct acting irritant, then the scaling is not appropriate. Is it really direct-acting tissue destruction rather than simple irritation?

The SOP indicates that for irritation, AEGL concentrations should remain constant across time where irritation is the effect. This primarily applies to AEGL-1 but could also apply to AEGL-2.

— Irritants: Default UF of 10 will be used. However, the UF probably will drop to 3-5 based on the data. The irritant effect (upper airway versus deep lung) is dependent on the water solubility.

Page 6, lines 25 and 26. There are a number of reports of human occupational exposure to HNO_3 that are not limited to measures of nitrogen oxides. The authors need to add these reports to the TSD.

Page 9, lines 11-22. There are many epidemiology studies that have assessed the role of airborne acidity, measured as H+, on various health outcomes. If it is assumed that any biological effect of inhaled inorganic acid in ambient air is due to H+ rather than to the anion (there is much evidence that this is probably true), then the authors should have included all such studies. It is not clear why they only chose the ones they did for inclusion in the TSD.

Page 11, line 21. The authors noted that there was no consistent pattern of concentration by time for the described study. However, what this limited study does suggest is that time may be more important than concentration.

Page 11, lines 39-41. If the exposure is to particles, reporting the exposure in ppm is not acceptable.

Page 12, line 6. It notes that there were no differences between the genders. Differences in what?

Page 12, lines 21-34. Does white fuming nitric acid (WFNA) have a higher LC_{50} because it does not generate as much NO_2?

Page 12, lines 28-30. The authors note that because the dose-response curves for nitrogen dioxide and red fuming nitric acid (RFNA) were parallel, there is a similar mode of action for the two gases. What

is the justification for this statement? Is it not possible that the two chemicals act via different modes but have a similar relationship between exposure and response?

Page 15, lines 14-16. HNO_3 has been used to produce changes in the lungs in animal models of obstructive lung disease. The sentence needs to be reworded.

Page 15, Section 4.1. NO_2 is direct acting in the lungs. This section is really not relevant here because the absorption and the distribution of HNO_3 probably differ from those of NO_2. It cannot be assumed that they are the same, as some toxicology studies indicate otherwise.

Page 17, line 4. The sentence is not quite true. What the cited study noted was that water particles in the lungs may act as vectors for adsorption of HNO_3 and carry the substance deep into the deep lung. Any reaction with NO_2 was not mentioned in the paper on which the authors base their comment.

Page 17, lines 14-16. Although the "course of toxicity" may be identical, the levels producing the effect may be different.

Page 17, line 22. The authors based the AEGL-1 on 1.6 ppm and use a UF of 3 for intraspecies differences (page 19, line 6). However, on page 17 they note a study in which exposure of asthmatic individuals to 0.05 ppm resulted in some decrease in pulmonary function. The proposed AEGL value of 0.53 is 10 times the concentration at which pulmonary function seemed to be affected in asthmatic subjects. Thus, it is not clear that there is an adequate safety margin in the proposed value for AEGL-1.

Page 17, lines 37 and 38. The TSD indicates that the Lehmann and Hasagawa (1913) study *suggest* humans have irritation and a long latency period before inflammation appears. Is there any supporting evidence for this? Also, this sentence does not agree with the first sentence (line 29) which states there are no species differences in toxic response to acute inhalation exposure to HNO_3.

Page 18, line 3. The first sentence states, "Epidemiologic studies indicate that asthmatics are more sensitive to acidic atmospheres." Evidence of any enhanced susceptibility of asthmatics to ambient particles is not definitive. Because effects are not consistent across studies, the authors should change the first sentence to "Epidemiologic studies indicate that asthmatic individuals may be more sensitive…."

Page 18, lines 37-39. Why is the Lehmann and Hasagawa study not reported here instead of in the AEGL-3 section (page 20)?

Page 19, line 34. Omit "LC_{50}". State only, "AEGL-2 values were those from the 1987 DuPont study."

Page 20, line 6. Weight loss is not an AEGL-2 effect. It should not impair escape, and it is reversible.

Page 20, lines 20-22. The proposed AEGL-2 for 10 and 30 min is much higher than the existing STEL, MAK, and STV (short-term value). In addition, the IDLH is 25 ppm, and the AEGL-2 is 30 ppm. Explain and justify.

Page 20, line 36. The response reported in Lehmann and Hasagawa (1913) is not an AEGL-3 effect.

Page 21, lines 31-33. Explain why the proposed 30-min and 8-h AEGL-3 values are much higher than the IDLH.

Editorial Comments

Page 4, lines 22-32. Omit this paragraph. Too much detail for summary, and the next two paragraphs covers the subject adequately.

Page 6, lines 30 and 31. Change the sentence as follows: "The chemical contributes to acid deposition (or acid rain). Nitric acid is a large contributor to acid deposition in the in the western United States compared to the eastern states (NARSTO 2004)."

Page 16, lines 14-23. Delete this paragraph. It is discussing nitric oxide, not nitric acid.

Comment Reference

NARSTO. 2004. Particulate Matter Assessment for Policy Makers: A NARSTO Assessment. McMurry, M. Shepherd, and J. Vickery, eds. Cambridge, UK: Cambridge University Press.

COMMENTS ON NITROGEN DIOXIDE

At its meeting, January 17-19, 2007, the committee reviewed the AEGL document on nitrogen dioxide. The document was presented by Carol Wood of Oak Ridge National Laboratory.

General Comments

Because nitric acid (HNO_3), nitrogen dioxide (NO_2), nitric oxide (NO) are reactants or products of the same chemical reactions, the committee recommends these be sections of the same chapter within the AEGL publication. A revised document should be submitted to the committee for review.

AEGL-1: The AEGL-1 value of 0.5 ppm is based on Kerr et al. (1978, 1979). However, other studies discussed in the TSD contradict that value by showing effects at lower levels. The committee recommends reevaluation of AEGL-1 in light of the other studies. The committee also recommends consideration of the lower values for the longer exposure periods.

AEGL-2: The committee concurs with the AEGL-2 values.

AEGL-3: The committee recommends using the animal lethality study of Hine (1970), as the study for point of departure and the Henry et al. (1969) study as supporting study. Reassess the interspecies UFs used.

Specific Comments

Page 5, line 13. The committee suggests adding "… NO_2 increases susceptibility to infection due to alterations in host pulmonary defense mechanisms (Gardner et al 1969)." They showed that rabbits exposed to levels of NO_2 from representative ambient concentration to 60 ppm demonstrated increased numbers of polymorphonuclear leukocytes (PMNs) in lung washings (levels as low as 8 ppm caused significant increase in PMNs and the peak infiltration of PMNs was found to occur between 6 and 9 h after exposure, as well as an inhibition of phagocyte activity following a 3-h exposure to 10 ppm).

Page 5, line 27. "0.5 ppm was considered a no-adverse effect level for asthmatic"? What about the Orehek et al. (1976) study? Exposure for 60 min to 0.1 ppm resulted in 3 of 20 subjects having increased specific airway resistance, and in 13 of 20 subjects there was increased sensitivity to a bronchoconstrictor.

Page 5, lines 29 and 30. "Time scaling was not done because effects at this concentration will appear immediately and not progress in severity with continued exposure." This is not the issue. Primary irritation depends on the concentration of a substance present in the breathing zone of an individual and does not depend on the dose presented over time.

Whether effects at a concentration will appear immediately and not progress in severity with continued exposure depends on the effect. For example, using the infectivity model, the effect was clearly shown at 0.5, 1.5, 3.5, 7.0, 14, and 28 ppm (increase in mortality did increase with time). See Gardner et al. (1979). These studies examine the effects of continuous and intermittent exposure to determine the relationship between biological response and length of exposure to a wide range of concentrations. Using the curves presented, one can examine the relationship between level of effect, concentration, and time.

Page 6, lines 8-22. This is not an end point appropriate for an AEGL-2 (all reversible effects).

Page 6, lines 24-36. From the description, it would appear that these are effects for an AEGL-2 level, NOT for AEGL -3. This was primarily an infectivity study. Were these effects seen in monkeys also exposed to the *Klebsiella* infection? Were the effects reported by Henry et. al. (1969) reversible?

Page 6, lines 38-42. The Norwood and Henry studies were not lethality studies. Should not the author use the animal lethality data for dog, rabbit, guinea pig, rat, and mouse from Hine (1970)?

Page 7, lines 27 and 28. In the description of the Henry study, you should add to the table: fibrosis, edema of cardiac tissue, and necrosis of the liver.

Page 10, lines 12 and 13. The text says: "NO_2 is a major component of smog." Because NO_2 can react readily in the atmosphere and convert to other compounds, the statement should be revised to say, "NO_2 is a major contributor to smog."

Page 12, lines 10-15. This information is fairly useless and should be deleted from the TSD.

Page 12, Section 2.2. The authors might consider adding the following: "A 10-min exposure to 4-5 ppm (to healthy individuals) resulted in increased expiratory and inspiratory flow resistance, which was greatest 30 min after the exposure ended (Abe 1967)."

Page 15, line 39. This line states, "indoor air quality may be more significant than ambient air quality," but on the next page (page 16, line 1), the text states that evidence was insufficient to find a positive association between NO_2 exposure and health effects in infants and children. The paragraph should indicate why indoor air may be more significant than outdoor air in this context.

Pages 14-16, Section 2.2.2. There are more recent epidemiology studies that have implicated NO_2 in adverse health effects, and these should be included in this section.

Page16, line 9. The text states that odor threshold for NO_2 was 0.4 ppm, but the next sentence states that 33% of volunteers perceived odor at 0.12 ppm and 62 % at 0.22 ppm. The text should acknowledge the conflicting information.

Page 16, line 16. "Low-level exposure…." is not a good term to use. What does "low-level" mean? For example, line 23 states that 1.5 ppm resulted in significant fall in FEV_1. Some might think this is low.

Page 17, line 30. What is meant by "overall" enzyme levels in bronchoalveolar lavage fluid (BALF)? Which enzymes?

Page 17, line 35. Was the exposure duration for 20 min, or was clearance stopped for 20 min?

Page 19, line 1. What is "initial" specific airway resistance?

Page 20, line 25. Please provide a concentration for immediate irritation.

Page 20. lines 25-27. Adding concentrations that caused this effect is suggested. It has little value without levels of exposure.

Page 20, line 27. There is concern about the statement that bronchiolitis obliterans developed because this effect also occurred "many years later" (page 12, line 35). Was this effect reported in any other human or animal study?

Page 20, lines 34-38. Provide a basis for concluding that increases in respiratory illnesses are probably due to NO_2 in combination with other pollutants. There is evidence that NO_2 alone can have such an effect. What is the source for the conclusion in the text?

Page 21, line 2. The text states, "It should be noted that in the studies which found statistically significant changes with NO_2 exposure, the differences were <10% and of questionable biological significance even for 3 asthmatics." The value of <10% seems to be inconsistent with the reported changes noted earlier in pulmonary function tests of asthmatic persons. Please explain.

Page 22, line 13. This line states, "Mortalities were first observed at 75 ppm for 60 mins," but you should mention that at 2 h, there were no mortalities at 75 ppm.

Page 23, line 1-4. The animals were from 5 to 60 days old, and 17-27 animals in each age group were exposed. This description is too broad. What were the age groupings?

Page 24, line 28. "2 days" from what?

Page 28, line 5 and the following. The authors might want to include discussion of Selegrade et al. (1981). The study used vitamin-C-deficient and normal guinea pigs that were exposed to various

concentrations of NO_2 (0.4, 1.0, 3.0, and 5.0 ppm). The researchers found that 72 h of exposure did not alter the protein or lipid content of lung lavage fluid, but exposure of vitamin-C-deficient animals to the same concentrations of NO_2 caused increases in lavage protein and lipids at all concentrations except the lowest one (0.4 ppm). At 5.0 ppm, 50% of the exposed vitamin-C-deficient animals died. At 5.0 ppm, effects could be seen in the vitamin-C-deficient animals even when the exposure period was shortened to 3 h.

Page 29, line 34 and the following. The authors might want to comment on Gardner at al. (1977). The study provided measured results of the effects of various durations of exposure to different NO_2 concentrations (7, 14, and 28 ppm) on the alteration in pulmonary cell population (increased PMNs).

Page 30, line 39. Maigetter et al. (1978) showed that phytohemagglutinin (PHA) and lipopolysaccharide (LPS) responses from mice exposed to NO_2 were generally depressed when the mice were exposed continuously, 24 h per day, to 940 $\mu g/m^3$ (0.5 ppm) and to 188 $\mu g/m^3$ (0.1 ppm) with daily 3-h peaks (5 days per week) to either 470 $\mu g/m^3$ (0.25ppm), 940 $\mu g/m^3$ (0.5ppm) or 1,880 $\mu g/m^3$ (1.0 ppm) (Maigetter et al. 1978).

Page 32, lines 13 and 14. Are these percentages correct? The way the text is written, it seems that the higher level of exposure resulted in less effect than did the lower level of exposure.

Page 32, line 14. The authors might want to add or comment on Illing et al. (1980). In that study, exercised mice exposed to 3 ppm had a significant enhancement in mortality over nonexercised mice.

Page 33, line 8. The authors might want to add or comment on Miller at al. (1980). The study found that acute exposure to NO_2 at 0.25 ppm caused a significant increase in sleeping time due to an influence of NO_2 on pentobarbital-induced sleep. Because pentobarbital-induced sleeping time is determined by hepatic mixed function oxidate activity, NO_2 may alter some aspect of xenobiotic metabolism.

Page 37, lines 16-19. Is the take-home message of this text intended to be that smaller animals have a greater min-volume per unit body mass than do larger animals? If so, such a statement should be included with appropriate citations.

Page 38, lines 28-29. This statement is not necessarily true for all end points. For example, Bauer et al. (1985) noted changes in pulmonary function tests at 0.3 ppm for 4 h, indicating that duration of exposure may be a factor.

Page 39, lines 1-15. Many similar studies were done with the *Streptococcus* organism. See some of the studies discussed above. For example, look at: Gardner et al. (1979), which presents data on continuous and intermittent exposure to determine the relationship between biological response and length of exposure to a wide range of NO_2 concentrations. Using those results, relationships between level of effect, concentration, and time can be determined. Also, studies were conducted and curves were generated that displayed relationships between the effects of various durations of exposure to various concentrations of NO_2 (7 , 14, and 28 ppm) on the alteration in pulmonary cell population (increased PMNs) (Gardner et al. 1977). The Gardner paper also showed percentage mortality of mice (using the infectivity model) versus length of exposure (numerous time points ranging from 15 min to 12 months) at concentrations of NO_2 of 0.5, 1.5, 3.5, 7.0, 14, and 28 ppm.

Page 39, Section 5.1. Consider the paper by Larsen et al (1979), who used infectivity studies to determine what would be the increase in infectivity in individuals living in polluted areas of Chicago at the concentrations producing increased mortality in mice. The conclusion was that if men were exposed to NO_2 at concentrations equivalent to the lethal dosages administered to mice, one would expect increased morbidity rather than increased mortality.

Page 44, lines 32 and 33. The structure of the respiratory tract between humans and monkeys is not as similar as implied here.

Page 43, line 4. The AEGL-2 level being proposed for 30 min (15 ppm) is very close to the immediately dangerous to life and health (IDLH) level of 20 ppm for 30 min. Indicate whether this is a matter of concern.

Page 44, lines 31 and 32. This text states, “Because the end point in the monkey study is below the definition of AEGL-3….” Actually, the effects reported were marked changes in lung structure,

collapsed alveolar septa, and so forth, which falls within the AEGL-2 definition of "exposed to life-threatening health effects."

Editorial Comments

Pages 7-9. Why are references presented after the summary?
Page 12, line 20. Insert "occupational" after "manifestation."
Page 14, line 17. Are these numbers odds ratios or relative risks?
Page 15, lines 19-23. This sentence needs to be reconstructed.
Page 15, line 39. Change "ambient" to "outdoor."
Page 36, line 2. Change "theory" to "hypothesis."
Page 37, line 40-42. This sentence does not make sense.

Comment References

Abe, M. 1967. Effects of mixed SO_2-NO_2 gas on human pulmonary function: Effects of air pollution on the human body. Bull. Tokyo Med. Dent. Univ.14(4):415-433.

Bauer, M.A., Utell, M.J., Morrow, P.E., Speers, D.M., and Gibb, F.R. 1985. Route of inhalation influences airway responses to 0.30 ppm nitrogen dioxide in asthmatic subjects. Am. Rev. Respir. Dis. 131:A171.

Gardner, D.E., R.S. Holzman, and D.L. Coffin. 1969. Effect of nitrogen dioxide on pulmonary cell population. J. Bacteriol. 98(3):1041-1043.

Gardner, D.E., D.L. Coffin, M.A. Pinigin, and G.I. Sidorenko. 1977. Role of time as a factor in the toxicity of chemical compounds in intermittent and continuous exposures. Part I. Effects of continuous exposure. J. Toxicol. Environ. Health 3(5-6):811-820.

Gardner, D.E., F.J. Miller, E.J. Blommer, and D.L. Coffin. 1979. Influence of exposure mode on toxicity of NO_2. Environ. Health Perspect. 30:23-29.

Illing, J.W., F.J. Miller, and D.E. Gardner. 1980. Decreased resistance to infection in exercised mice exposed to NO_2 and O_3. J. Toxicol. Environ. Health 6(4):843-851.

Kerr, H.D., Kulle, T.J., McIlhany, M.L., and Swidersky, P. 1978. Effects of nitrogen dioxide on pulmonary function in human subjects. An environmental chamber study. Report: ISS EPA/600/1-78/025; Order no. PB-281 186, 20 pp.

Kerr, H.D., Kulle, T.J., McIlhany, M.L., and Swidersky, P. 1979. Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. Environ. Research 19:392-404.

Larsen, R.I., D.E. Gardner, and D.L. Coffin. 1979. An air quality data analysis system for interrelating effects, standards, and needed source reductions: Part 5. NO_2 mortality in mice. J. Air Pollut. Control Assoc. 29(2):133-137.

Maigetter, R.Z., J.D. Fenters, J.C. Findlay, R. Ehrlich, and D.E. Gardner. 1978. Effect of exposure to nitrogen dioxide on T and B cells in mouse spleens. Toxicol. Lett. 2:157-161.

Miller, F.J., J.A. Graham, J.W. Illing, and D.E. Gardner. 1980. Extrapulmonary effects of NO_2 as reflected by pentobarbital-induced sleeping time in mice. Toxicol. Lett. 6(4-5):267-274.

Orehek, J., J.P. Massari, P. Gayrard, C. Grimaud, and J. Charpin. 1976. Effect of short-term low level NO_2 exposure on bronchial sensitivity of asthmatic patients. J. Clin. Invest. 57(2): 301-307.

Selgrade, M.K., M.L. Mole, F.J. Miller, G.E. Hatch, D.E. Gardner, and P.C. Hu. 1981. Effects of NO_2 inhalation and vitamin C deficiency on protein and lipid accumulation in the lung. Environ. Res. 26(2):422-437.

COMMENTS ON NITRIC OXIDE

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on nitric oxide. The document was presented by Carol Wood of Oak Ridge National Laboratory.

General Comments

Because nitric acid (HNO_3), nitrogen dioxide (NO_2), nitric oxide (NO) are reactants or products of the same chemical reactions, the committee recommends these be sections of the same chapter within the AEGL publication. A revised document should be submitted to the committee for review.

There is a need to address the potential for public exposure to NO. The combined TSD for HNO_3, NO_2, and NO should address the likelihood of elevated exposures to NO resulting from episodic releases of bulk NO or other chemicals that react to form NO. If there is a potential for public exposure to high concentrations of NO, the combined TSD for HNO_3, NO_2, and NO needs to address the toxicology of NO to a greater extent and reconsider the default to NO_2 AEGL values because NO converts to NO_2.

Specific Comments

Page 5, line 23. This line states, "exposures below 80 ppm NO should not constitute a health hazard." However, at 50 ppm, there was increase lung weight, and at 25 ppm, there were histopathologic changes. Please explain.

Page 12, lines 13 and 14. A better way to state this would be that NO attenuated any bronchoconstriction due to methachol.

Page 18, lines 11 and 12. Can changes in behavior be used for AEGL-1?

Page 19, lines 24 and 25. This line states, "Lethality studies … were confounded by possible NO_2 contamination…." This result was not reported in all studies. In a study using rats by Stavert and Lehnert (1990) and in a study using mice by Pfleser (1935), there were deaths with no evidence of lung injury, increase in lung weight, or histopathologic changes. Because those effects are associated with NO_2 and not with NO, their absence indicates there was no confounding by NO_2. The results of those studies should be considered in setting the AEGL-3 for NO.

Page 23, Section 4.3. Change title of section to "Chemical Transformation of Nitrogen Oxides."

Page 25, line 12. This line refers to only one abstract (Wilhelm et al. 1998); however, there is another one (Mihalko et al. 1998;). Although they are only abstracts, they report effects in dogs that may be relevant to AEGL-1 (decreased arterial oxygen) at 320-ppm and 640-ppm exposure and AEGL-3 effect (death) at 640 ppm.

Page 27, lines 16-20. The descriptions of the results of Pflesser (1935) and Stavert and Lehnert (1990) in the TSD indicate that NO_2 was not a contaminant.

Editorial Comments

Page 18, line 36. Correct spelling of histological.

Comment References

Mihalko, P.J., C.R. Hassler, R.R. Moutvic, T. Vinci, R.L. Hamlin, and S.J. Waters. 1998. Effects of inhaled nitric oxide on cardiovascular and pulmonary function in the dog. Toxicologist 42:250.

Pflesser, G. 1935. The significance of nitric oxide in poisoning by nitrous gases. Naunyn-Schmiedeberg Arch. Exp. Pathol. Pharmakol. 179:545-547. (German) Cited in NIOSH, 1976.

Stavert, D.M. and B.E. Lehnert. 1990. Nitric oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for brief periods. Inhal. Toxicol. 2:53-67.

Wilhelm, J.A., P. Veng-Pedersen, P.J. Mihalko, and S.J. Waters. 1998. Pharmacokinetic modeling of methemoglobin concentration-time data in dogs receiving inhaled nitric oxide. Toxicologist 42:213.

COMMENTS ON PERCHLOROMETHYL MERCAPTAN

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on perchloromethylmercaptan. The document was presented by Claudia Troxel of Oak Ridge National Laboratory.

General Comments

The proposed AEGL values and their derivation appear appropriate, given the very limited database. Time scaling and the use of UFs appear appropriate. Recommendations need to be made for specific additional research to improve the AEGLs, given the paucity of the database. Responses to comments from the committee are considered sufficient unless otherwise noted. The revised document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

Page 1, Table 1. Include additional vapor pressure value: 3 torr at 20°C (citation is: Shertzer 2001; see reference section below). Additional information for boiling point entry:

Decomposition products include chlorine and oxides of chlorine and sulfur (citation is Shertzer 2001). Current citation is ACGIH (1991); however, ACGIH (2006) does not mention decomposition.

Pages 3-5, Section 3. There is an unpublished study mentioned in Shertzer (2001) identifying skin absorption as a potential issue:

> Skin irritation studies in guinea pigs indicated severe skin irritation and absorption of the material through the skin; animals that received 2.5 ml/kg died within 2 days (Eastman Kodak, TSCA Section 8E submission, TSCATS Accession No. 42513, Fiche No. 0533569, 1961).

See also the Althoff (1973) reference on pages 1, 3, and 13, which reports that the clothes of the person who died were contaminated with liquid perchloromethyl mercaptan; the clothes of the two survivors apparently were not. Refer also to the editorial comments for the Executive Summary and Sections 2.6 and 7.1.

Although this is very limited information, a footnote to Table 7 and/or mention in the discussion in Section 8.1 as potentially affecting the application of the AEGL values should be considered. Alternatively, some statement indicating why possible skin absorption is not addressed should be included.

Page 7, lines 32 and 33. When considering the phrase "respiratory nasal epithelial changes," if available, a more complete description of the nature of these changes should be included.

Page 10, lines 23 and 24. Is quoting the SOP in this case sufficient to meet the spelled-out requirement there for a "discussion" of why the mechanism is likely not to differ?

Page 10, lines 28 and 29. Does the text mean that a repeat-exposure study reduces the uncertainty regarding the occurrence of the minor epithelial changes? A clarification of this statement would be helpful.

Page 12, line 11. Can the use of the term "reasonable" be better justified? The committee is not disagreeing with the conclusion but wonders why a factor of 3 is any more (or less) reasonable than a factor of 5, for example? This same question applies to the use of this term in the Executive Summary (page viii, line 4) and Appendix B (page 31, line 14).

Page 18, line 14. The last sentence is not relevant to this paragraph and can be deleted. Recommendations regarding specific research needs and their priorities are needed. (For example, should reproductive studies be done before dog or monkey studies defining nonlethal effects thresholds?)

Editorial Comments

Page vii, lines 9 and 10. Change to read "Human data were ~~generally limited to~~ described only in secondary sources; case reports describing respiratory and topical exposures …."

Page vii, line 28. Change to read "the end point is a no-effect level for perchloromethyl mercaptan as a respiratory irritant."

Page viii, lines 4 and 5. Change to read "The divisor of 3 is reasonable based on the ~~steepness of the~~ strong dose-response relationship~~curve~~ for lethality~~; no rats died following exposure to 9 ppm for 1 hour, while 7/10 died at 18 ppm~~."

Page viii, lines 35-44. Change to read "1971)~~. T~~Therefore, ~~that concentration~~ 9 ppm was selected as …. All exposed ~~animals~~ rats ~~eye~~ developed ocular and mucosal irritation within 5 min ~~after~~ of initial exposure~~, and~~; dyspnea, …. Necropsy revealed inflamed ~~mouth~~ oral and nasal … a direct irritant, and ~~is therefore~~ the mechanism is not expected to differ ~~significantly~~ among species … effects of exposure appear ~~to be~~ related to a direct ~~irritant effect~~ tissue irritation at the point of contact, and ~~irritant~~ these effects …."

Page ix, line 2. Change to read "indication of relatively little variation …."

Page ix, lines 15-20. Change to read "appears to be ~~a~~ direct ~~irritant effect~~ contact irritation, it is … but rather the AEGL-3 concentration represents ~~the~~ a threshold for …. Therefore, the irritation is sufficiently severe ~~enough~~ that continued exposure would ~~result in~~ produce increased and likely irreversible damage … longer to shorter durations of exposure ~~periods~~, respectively."

Page 3, lines 5-7. Change to read "~~One fatality f~~Following exposure to an unknown concentration of ~~pechloromethyl~~ perchloromethyl mercaptan vapors and skin contact with the liquid, one fatality occurred due to ~~resulted from~~ massive hemorrhagic pulmonary edema, accompanied by simultaneous heart, circulatory, and kidney collapse …."

Page 3, line 17. Change to read "When averaged ~~together~~, the 1-h LC_{50} for male~~s~~ and female~~s~~ Sprague-Dawley rats (combined) is …"

Page 5, line 27. Change to read "~~Necrospy~~ Necropsy …."

Page 5, line 31. Change to read "included gross ~~findings of~~ mucus …."

Page 6, lines 4 and 5. Change to read "by Gage was ~~confounded~~ compromised by … including: ~~the~~ lack of …."

Page 6, lines 8-21. Change to read "exposed to perchloromethyl mercaptan at a nominal … study ~~should~~ can be used … results section of the study report were mostly … mercaptan to the ~~gassing~~ exposure chamber. The (legible) summary section ~~(which was legible) did not~~ failed to discuss or ~~even~~ mention control animals, ~~leading one to believe~~ suggesting that control animals were not assigned.~~This was unfortunate because there were questions about the animals' health.~~ … infestation and ~~had~~ findings … bronchopneumonia~~,~~; … septicemia~~,~~; and the … not already present prior to or at the start of ~~the~~ exposure~~s~~ … presented together below.

Page 6, lines 22-31. Change to read "exposure. ~~Toxicity s~~Signs … respiration. ~~As already stated, the g~~Guinea pigs … guinea pig ~~had~~ developed fibrotic … dogs died as a result of their exposure. The dogs

~~exhibited~~ developed excessive lacrimation … stools.~~It is reiterated~~ [Note that at least one of the dogs … infection.~~]~~ … Microscopic examination of their lungs … appearance.~~I~~ and, in some areas, the alveolar walls ~~had~~ ruptured …."

Page 6, lines 36 and 37. Change to read "… mercaptan ~~tested positive for~~ was mutagenic~~ity~~ in a number of *in vitro* ~~genotoxicity~~ assays …."

Page 7, lines 3-8. Change to read "kinase locus in cultured L5178Y … mercaptan ~~did not induce~~ failed to increase chromosomal aberrations … in cultured Chinese hamster … activation and ~~did not induce~~ there was no increase in micronuclei … mice in ~~the~~ a micronucleus assay …."

Page 7, lines 21-37. Change to read "mercaptan exposure ~~were extremely~~ are very limited … 1971). ~~Unfortunately, t~~The severity of ~~these~~ those signs at this concentration and at the higher concentrations (which resulted in mortality) was not provided;~~, and a~~ no control group was ~~not~~ included. … Mild nasal epithelial changes were observed in rats … 0.580 ppm, consisting of ~~decreased~~ reduced body weight … 1987). No ~~effects~~ such changes were observed in rats ~~subchronically exposed to~~ that inhaled 0.014 or 0.079 ppm for 70-72 days (Knapp … (1952) are ~~limited in usefulness~~ of little use because the protocols used were ~~confounded~~ fundamentally compromised by several factors."

Page 7, lines 38-40. Change to read "Perchloromethly mercaptan was generally ~~tested positive for~~ mutagenic~~ity~~ in standard in vitro test systems … mercaptan exposure to cause … reproductive ~~effects~~ toxicity or to ~~induce neoplasia~~ increase carcinogenic risk.

Page 9, line 3. Change to read "This fact ~~would~~ explains the deeper lung damage after HCl exposure compared with …."

Page 9, lines 7-13. Change to read "were not used ~~for~~ in the derivation … Although ~~there are~~ acute toxicity data are available … the ~~toxicity~~ potency of perchloromethyl mercaptan is ~~much~~ greater than that of ~~the congener as seen when examining lethality data~~ methyl mercaptan. In rats, ~~the 1-hour LC_{50}~~ the highest nonlethal concentration of perchloromethly mercaptan is 9 ppm for 1 h, and the 1-h LC_{50} is reported as 11, 13, or 16 ppm~~, and the highest nonlethal concentration is 9 ppm for 1 hour with the next concentration of 18 ppm for 1 hour resulting in 7/10 rats dying within 24 hours of exposures~~. By way of comparison, the highest nonlethal concentration of methyl mercaptan in rats is 400 ppm for 4 h …."

Page 10, lines 2-13. Change to read "appropriate ~~for use in~~ deriving … provided, and ~~it was~~ the report stated that dyspnea, gasping, and signs of acute depression … 1.15 ppm resulted in objective clinical signs of intoxication (haircoat … in the nose) (Knapp …."

Page 10, lines 27 and 28. Change to read "(SOP 2.5.3.4.4.) ~~(no deaths … Company, 1971)~~."

Page 10, line 30. Change to read "level for ~~an irritant~~ irritation."

Page 11, line 27. Change to read "by Gage are of limited ~~in usefulness~~ utility."

Page 11, lines 28-36. Change to read "0.13 ppm developed ~~only~~ mild … next higher concentration ~~of~~ (1.15 ppm) developed … rats exposed ~~for~~ 6 h … highest exposure concentration ~~of~~ (0.58 ppm) (Knapp … present until ~~later in the~~ study duration increased (salivation … compared with the controls ~~were minimal, and~~ included ~~decreases~~ reductions in …."

Page 12, lines 8-12. Change to read "Insufficient data ~~were~~ are available to derive ~~AEGL-2~~ values consistent with the AEGL-2 definition. ~~Available s~~Studies that … concentrations ~~did not report~~ failed to describe adverse health effects consistent with ~~the definition of~~ an AEGL-2 end point … values ~~are~~ were derived … based on ~~the steepness of~~ the steep … lethality~~: no rats … 18 ppm~~."

Page 13, lines 10 and 11. Change to read "describing exposure~~s~~ to ~~unquantifiable~~ unquantified concentrations … mercaptan and the likelihood these accidents involved both skin and respiratory tract contact with the material (Althoff …."

Page 13, line 26. Change to read "there was no increase in mortality … Therefore, ~~that concentration~~ 9 ppm was selected …."

Page 13, lines 29-30. Change to read "5 minutes after initial exposure … depression" were ~~also~~ observed …."

Page 14, line 15. Change to read "mechanism of action responsible for death appears to be ~~a~~ direct ~~irritant effect~~ contact irritation in the lung, it is …."

Page 14, line 35. Change to read "~~are summarized~~ is presented …."

Page 15, lines 13-18. Change to read "repeat-exposure study~~, which~~ … This end point represents … the AEGL-2 values ~~are~~ were obtained … for lethality. ~~Also at this concentration~~ At the no-effect level for increased mortality, exposed animals ~~exhibited~~ developed eye and … revealed inflamed ~~mouth~~ oral and nasal mucosa."

Page 15, line 28. Change to read "~~A useful~~ One way…."

Page 15, lines 29-32. Where are these code numbers used in the text? This paragraph refers to the Category Plot on page 16, but these codes do not appear to be used there or elsewhere outside the SOP. The codes 1,2,3 and NL can be left out.

Pages 15, line 37, and 16, line 1. Change to read "From this plot, ~~one sees~~ it is evident that AEGL values are below any exposure concentration in animals resulting in ~~any~~ adverse effects, and should therefore be protective of human health.

Page 16, Figure 1. Parts per million values less than 1 have been either rounded or truncated to 0.

Page 17, line 11. The entry for IDLH should be in the "30 minute" column. It looks like two cells have been joined or combined.

Pages 19-21. If a document is available online (other than a journal article), the URL should be provided to improve ease of access. In this reference list, add the following:

Page 20, lines 6-9. The NIOSH IDLH database is also online at http://www.cdc.gov/niosh/idlh/idlh-1.html.

Page 20, lines 10-12. The NIOSH Pocket Guide to Chemical Hazards is also online at http://www.cdc.gov/niosh/npg/npg.html.

Page 20, line 13. The OSHA Air Contaminants list (Table Z-1) is also online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Page 21, lines 13 and 14. The EPA AEGLs list is online at http://www.epa.gov/oppt/aegl/pubs/chemlist.htm.

If there is a citation of a common secondary source, check to see if there is a more recent version, verify the information being referenced therein, and cite the most recent version that contains the material to be referenced. This is especially appropriate for annually updated sources such as the TLVs, WEELs or ERPGs, which can change and even withdraw certain values or the references used to support them. For exposure limits or guidelines, also ensure that the citation clearly refers to either the value or the documentation. In this reference list, the more recent versions of the secondary sources used are the following:

Page 19, lines 2-4. ACGIH, 2006a. Documentation of the Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs). American Conference of Governmental Industrial Hygienists, Inc. (ACGIH), Cincinnati OH.

Page 19, lines 5-7. ACGIH, 2006b. 2006 TLVs and BEIs. American Conference of Governmental Industrial Hygienists, Inc. (ACGIH), Cincinnati OH.

Page 19, lines 15-17. Shertzer H.G., 2001. Organic Sulfur Compounds. Vol. VII, Ch. 94, § 33, Perchloromethyl Mercaptan. Pp. 681-765 in Bingham E., Cohrssen B., Powell C.H., eds. (2001). Patty's Toxicology (5th Edition) Volumes 1-8. John Wiley & Sons, New York NY.

Page 19, lines 10-12. Does this report have a title? How many pages? [N.B.: for reports like this one, and for various unpublished company reports cited below, the standard citation form includes the number of pages, as with the citation for Knapp and Thomassen, 1987]

Page 19, lines 20 and 21. Is this the complete report title?

Page 23, line 5. Change to read "the effects are those of mild irritation" [alternative choice: minor]. Change recommended based on the discussion on page 14, lines 14-18; using "mild" or "minor" will distinguish irritation at the AEGL-1 concentrations from that at higher concentrations.

Page 27. For consistency across documents, application of UFs should be after calculation of the time scaling equation, rather than integrated into it. This is a stylistic recommendation, not an algebraically substantive one.

Page 27, line 4. What does "this document" mean here?

Responses to Committee's Comments on the Previous Document

Page 1. "The NAC did not feel a modifying factor was needed." Is there a justification for this position, rather than just a feeling?

Page 2. The committee concurs that the two chemicals are sufficiently different to warrant no SAR comparison. A statement to that effect in the TSD would be useful.

Page 3. The committee concurs with the response to the committee's comment about odor and ocular and respiratory tract irritation. However, the point raised regarding highlighting the intensity and nociceptive properties of the odor remain valid. This point should be presented as a footnote to Table 7.

Page 7, Section 5.2. The committee concurs; however, the rationale for selecting the Knapp et al. (1987) study has not been explicitly stated in the response to the committee's comment.

COMMENTS ON PHOSPHORUS OXYCHLORIDE

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on phosphorus oxychloride. The document was presented by Robert Young of Oak Ridge National Laboratory.

General Comments

The committee finds that this document is good and has convincing reasons not to propose AEGL-1 and AEGL-2 values. Previously, there was concern about the high interspecies UF of 10 and a proposal for lowering it to 3. The author has convinced the committee that the interspecies UF of 10 should be retained. A total UF of 30 is justified.

After taking the comments shown below into account, the document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

Pages 11, line 39, and 12, line 2. The only concern that remains is a statement on page 11 in Section 7.3 that contact irritation as a toxic mechanism would not vary greatly among individuals, and, therefore, the UF of 3 for intraspecies differences was used. For other chemicals, there are data that justify a UF of 10. For sulfur dioxide, e.g., there is a factor 10 difference in concentration for response between nonasthmatic and asthmatic individuals. Thus, the statement made in the TSD might not be universally true and might depend on the specific chemical. In the case of phosphorous oxychloride, the intraspecies UF of 3 appears to result in a reasonable value for the AEGL-3, which seems in line with other published standards.

COMMENTS ON PHOSPHORUS TRICHLORIDE

At its meeting held on January 17-19, 2007, the committee reviewed the AEGL document on phosphorus trichloride. The document was presented by Robert Young of Oak Ridge National Laboratory.

General Comments

The committee finds that this revision is responsive to the comments made on the original submission. The major difference with the first submission is that time scaling for the AEGL-1 value has now been skipped for reasons mentioned on page 9. The committee agrees with this decision.

After taking the comments shown below into account, the document can be finalized if the committee's recommended revisions are made appropriately.

Specific Comments

Page 9, lines 17-20. A point on page 9 that needs some clarification is the rationale for intraspecies UF of 3. The authors state that the UF was 'limited' to a value of 3 because the main effect of the chemical appears to be due to hydrogen chloride and phosphonic acid resulting from dissociation. Please indicate why this chemical reaction should limit the UF.

Page 9, lines 20 and 21. This indicates that effects from direct contact of dissociation products are likely to be similar for any epithelial surface. This is, however, unlikely to be true if skin is compared with the eye or bronchial epithelium, for example. Possibly, *mucosa* is meant instead of *epithelium*.

COMMENTS ON PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING (PBPK)

At its meeting held on January 17-19, 2007, the committee reviewed the document on physiologically based pharmacokinetic modeling (PBPK). The document was presented by James Dennison of Century Environmental Hygiene, LLC.

General Comments

PBPK models have gained acceptance over the last decade for use in dose-response assessments and risk assessments. This timely white paper lays out how PBPK models can be used in the AEGL development process. The report is generally well written and should be useful in implementing the application of these models to derive AEGLs, where feasible. After taking the comments shown below into account, the document can be finalized if the committee's recommended revisions are made appropriately. The concerns of the reviewers are as follows.

A more basic introduction on PBPK modeling is needed. Particularly, it would be helpful if the document could include

1. A basic (and brief) discussion about drug (maybe anesthesia) kinetics and how the practice of medicine and drugs is based on understanding the blood levels or tissue levels. This shows that other established disciplines use pharmacokinetic information to estimate effects.

2. Basic physiology of the body. What happens when a chemical is inhaled, and how does it get to tissues? What governs the rate of uptake, distribution, and elimination? Focus discussion, so the structure of a PBPK model can be understood.

3. State and restate that the intended purpose is to estimate the concentrations in blood or tissues associated with exposures to chemicals and that the estimated internal concentration 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 using $C^n \times T = k$ and point out which physiological

processes are accounted for in the PBPK model that were not accounted for in the air concentration extrapolation methodology.

The use of the term standard operating procedure (SOP) appears overstated. The document provides general guidance and uses toluene as an example for how PBPK models could be used. SOP infers more refined step-by-step procedures than are outlined in this document. This is a guidance document, not an SOP for PBPK modeling and AEGL derivation.

The white paper should make clear that only peer-reviewed PBPK models are to be used in the process. If modification to the model structure or description is made, then it should undergo peer review before being used for AEGL derivation. This document also should make it clear from the outset that the use of PBPK models is only intended for AEGLs associated with systemic effects.

Reevaluate the emphasis on the inclusion of exercise physiology in these models. Changes in physiological parameters relevant to exposure (e.g., breathing rate) are not accounted for currently in setting the AEGLs. Therefore, the proposed consideration of exercise physiology in PBPK models intended for AEGL application (e.g., of different levels of physical activity at different AEGLs) would appear to be inconsistent with the current practice of guideline setting. PBK models should be executed under the conditions of light-to-moderate level of human activity; sedentary conditions should not be used.

A plot of the dosimetrics as a function of time and dose might be useful. If the dosimetrics for each chemical are plotted in this way, readers can readily grasp the relationships between exposure or administered dose and internal dose. Some guidance should also be provided on the choice of dose surrogates, particularly for acute effects.

The use of interspecies UFs to adjust dosimetrics other than administered dose should be clarified. The authors should clearly indicate that application of UF to the internal dose is the scientifically defensible approach—particularly, given that the AEGL development probably deals with nonlinear kinetics in several situations. In addition, provide guidance on the use of intraspecies 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 should be applied and what is the basis for this factor?

Specific Comments

Page 13, lines 7-10. It is the other way around. Metabolism is often dominated by more than one enzyme; their relative impact depends on the concentration of the substance to be metabolized. For example, enzyme X might dominate at relatively low concentrations (e.g., AEGL-2 concentrations), and enzyme Y might dominate at relatively high concentrations (e.g., AEGL-3 concentrations). Their relative abundance across species is often drastically different. Therefore, modeling of just one enzyme may lead to grossly wrong values in either the low concentration or the high concentration range.

Editorial Comments

Page 12, lines 10-21. This sentence is unclear.

Page 22, line 14: Unclear what “the present order” is. To facilitate reading, state which sequence is meant here.

COMMENTS ON TRIMETHYLCHLOROSILANE

At its meeting held on January 17-19, 2007, the committee reviewed the document on trimethylchlorosilane. The document was presented by Cheryl Bast of Oak Ridge National Laboratory.

General Comments

The proposed AEGL values and support for their derivation appear appropriate given the limited database. Given the proposed mode or mechanism of action, reliance on the HCl database and the AEGLs derived from it is appropriate. Appendix E and the discussion of molar ratios in Sections 4.3, 6.3, and 7.3 are helpful. Time scaling and the use of uncertainty and modifying factors appear appropriate. A revised document should be submitted to the committee for review.

As was mentioned in the comments on the TSD for methyltrichlorosilane earlier in this report, the revised TSD for trimethylchlorosilane, should explain why toxic intermediates are not considered.

A total UF of 100 for AEGL-3 seems high; please provide some justification.

Recommendations need to be made for specific additional research to improve the AEGLs, given the paucity of the database.

Specific Comments

Page. iii, line 9. There are two 1-h LC_{50} rat studies—Dow (1999a) and Kolesar et al. (1987).

Page iii, lines 23 and 24. In table on page v, effects of "reversible lacrimation, corneal opacity, rales, gasping and nasal discharge" is *not* an AEGL-2 effect.

Page 4, Summary. Explain why the Dow (1999a) LC_{50} = 4,257 was selected rather than that of Kolesar et al (LC_{50} = 2,928).

Pages 6, line 41-44, and 7, lines 1-5. "Comparison of human vs rodent and differences in breathing." The authors need to cite papers to support the concluding statement on lines 5 and 6, that humans are more sensitive than rodents to HC1 or irritants.

Page 6, lines 35-37. The mice data reported should be vetted to justify not using this species for AEGL development and perhaps guinea pigs (lines 38 and 39). Only the data sets for rats are presented and then used by the authors. A reader would need to obtain these mice papers to determine their relevance. The critical studies have been selected, but the process of getting there should be provided.

Page 9, lines 6 and 7. The ratio of HCl to trimethylcholorsilane needs to be rewritten so that it is easier to understand. Were the two AEGL values simply compared (after assumptions about UF values) to derive the ratio? This is important because it shows the relationship between the HCl values and this chemical, which is primarily based on HC1. If this is correct, rewrite text to state clearly the intent to use HCl values as guideline values.

Page 8, Section 6.3. The language seems convoluted. Perhaps, the text should state the assumptions that were used to be consistent with the database on HCl and show the results. More detailed discussion of the calculations and their inconsistency could be shown in a table and discussed in an appendix.

Page 7. Derivation of AEGL-1. If the AEGL-1 and the ERPG (stated on page 11) are all based on HCl, why are the numbers not the same.

Page. 8, line 20. Clinical effects observed are reversible and not an AEGL-2 effect. Page iii, line 23, lists lacrimation, corneal opacity, rales, gasping, and nasal discharge.

Page 9, lines 11 and 12. Intraspecies UF of 3. Can the underlying rationale for 3 vs 10 be explained more clearly?

Page 10, line 17. The rationale for setting the 8-h AEGL-3 value equal to the 4-h value is not provided and must be presented here.

Page 11, Section 8.3. No specific research needs for trimethylchlorosilane are identified. Is the last sentence intended to indicate that no further research is needed?

Editorial Comments

Pages iii-iv. Much of the material in the paragraphs on the AEGL-2 and AEGL-3 values is there to explain the rationale for selecting specific values for UFs and illustrating the consequences of using other values. This is all explained in the text; for the purposes of a *summary*, it could be left out.

Page 1. Insert a molecular structure diagram here (or wherever appropriate) for comparison purposes with the other silanes for which AEGLs are being developed.

Page 3, line 20. The term "fiducial limits" should be replaced with the more commonly used "confidence limits."

Page 9, line 25. Change "subjective" to "were not quantified."

Page 11, lines 8-11. In Table 7, the lines demarking the cells for ERPG values are missing. While these values are by definition for exposures up to 1 h, the lack of the lines could be inferred to indicate that the values are valid for longer time periods as well. For the WEEL ceiling value, either no cell lines should be used (as is), or the same value should be in each cell (as with the AEGL-1 value).

Pages 12 and 13, Section 9. If a document is available online (other than a journal article), the URL should be provided to improve ease of access:

— EPA EHS Chemical Profiles are online at http://yosemite.epa.gov/oswer/ceppoehs.nsf/EHS_Profile?openform.
— NLM TOXNET databases, including the HSDB, are online at http://toxnet.nlm.nih.gov/.

If there is a citation of a common secondary source, check to see if there is a recently updated version, verify the information being referenced there, and cite the most recent version that contains the material to be referenced. This is especially appropriate for annually updated sources such as the TLVs, WEELs, or ERPGs, which can change and even withdraw certain values. For exposure limits and guidelines, also ensure that the citation clearly refers to either the value or the documentation (see Bingham et al. 2001).

Pages A1-A3. This material is redundant with the paragraph on the derivation of AEGL-1 values on page 7, line 30, which does not refer to Appendix A. It seems the appendix is redundant, and it can be dropped.

Page C-2, line 17. Change "insufficient data" to "not relevant."

Page D2. The category plot is missing an axis.

Comment Reference

Bingham, E., Cohrssen, B., Powell, C.H. (2001). Patty's Toxicology (5th Edition) Volumes 1-8. John Wiley & Sons, New York NY.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL-1	The airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure
AEGL-2	The airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape
AEGL-3	The airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death
AEGLs	acute exposure guideline levels
ATSDR	Agency for Toxic Substances and Disease Registry
BALF	bronchoalveolar lavage fluid
BSP	bromosulfophthalein
BUN	blood urea nitrogen
CD_{50}	coma induction in 50% of subjects
CEELs	community emergency exposure levels
CNS	central nervous system
DFG	Deutsche Forschungsgemeinschaft
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy
EHS	extremely hazardous substance
EPA	U.S. Environmental Protection Agency
ERPG	emergency response planning guidelines
ETO	ethylene oxide
FEV_1	forced expiratory volume in the first second
h	hour
HNO_3	nitric acid
IDLH	immediately dangerous to life and health
JP-8	jet fuel (or jet propellant) number 8
LC_{50}	concentration of a substance that is lethal to 50% of test organisms in a given time
LD_{50}	dose of a substance that is lethal to 50% of test organisms in a given time
LOA	level of distinct odor awareness
LPS	lipopolysaccharide
m^3	cubic meters
MAK	maximale argeitsplatzkonzentration [maximum workplace concentration]
MEK	methyl ethyl ketone
mg	milligram

min	minute
NAC	National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances
NIOSH	National Institute for Occupational Safety and Health
NO	nitric oxide
NO_2	nitrogen dioxide
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
NTP	National Toxicology Program
ORNL	Oak Ridge National Laboratory
PBPK	physiologically based pharmacokinetic
PHA	phytohemagglutinin
PMN	polymorphonuclear leukocyte
ppm	parts per million
RBC	red blood cell
RD_{50}	concentration of a substance that reduced the respiratory rate of test organisms by 50%
RFNA	red fuming nitric acid
SAR	structure-activity relationship
SOP	standard operating procedure
STEL	short-term exposure limit
STV	short-term value
TLV	Threshold Limit Value
TSD	technical support document
UF	uncertainty factor
URL	uniform resource locator for the Internet
WEEL	workplace environmental exposure limit
WFNA	white fuming nitric acid