Sixteenth Interim Report of the Committee on Acute Exposure Guideline Levels

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Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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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. Subsequently, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the NRC Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

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

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology 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 appendixes in the committee's reports.

The present report is the committee's sixteenth interim report. It summarizes the committee's conclusions and recommendations for improving NAC's AEGL documents for 26 chemicals: bromine pentafluoride, bromine trifluoride, carbon monoxide, chlorine pentafluoride, chloroacetone,

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

hexafluoroacetone, hydrogen bromide, hydrogen iodide, hydrogen selenide, metal phosphides[3] (aluminum phosphide, potassium phosphide, sodium phosphide, zinc phosphide, calcium phosphide, magnesium phosphide, strontium phosphide, and magnesium aluminum phosphide), nerve agent VX, propargyl alcohol, selenium hexafluoride, sulfur dioxide, sulfuryl chloride, trimethylbenzenes (1,3,5-, 1,2,4-, and 1,2,3-trimethylbenzene), and vinyl chloride. The report also summarizes the committee's conclusions and recommendations for improving the *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* published in 2001. Committee member David Kelly recused himself from discussion of the draft AEGL document for sulfuryl chloride.

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: A. Wallace Hayes, Harvard School of Public Health; Rogene F. Henderson, Lovelace Respiratory Research Institute; Charles R. Reinhardt, DuPont Haskell Laboratory (retired); and Andrew G. Salmon, California Environmental Protection Agency. Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario**.** 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 NRC.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Iris Camacho, Ernest Falke, and Robert Benson (all from EPA); Cheryl Bast, Sylvia Talmage, Carol Wood, and Robert Young (all from Oak Ridge National Laboratory).

The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful guidance. Raymond Wassel, project director for his work in this project. Other staff members who contributed to this effort are Keegan Sawyer (associate program officer), Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager, Technical Information Center), Radiah Rose (editorial projects manager), Patrick Baur (research assistant), Orin Luke (senior program assistant), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

[3]AEGL values for these eight metal phosphides were published with phosphine as an appendix in *Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 6.* The committee's comments on these chemicals are included in this document for the record.

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Sixteenth 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, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances.

The NAC was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. AEGLs developed by 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) review the NAC's research recommendations and identify additional 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 conclusions and recommendations for improving NAC's AEGL documents for 26 chemicals: bromine pentafluoride, bromine trifluoride, carbon monoxide, chlorine pentafluoride, chloroacetone, hexafluoroacetone, hydrogen bromide, hydrogen iodide, hydrogen selenide, metal phosphides[4] (aluminum phosphide, potassium phosphide, sodium phosphide, zinc phosphide, calcium phosphide, magnesium phosphide, strontium phosphide, and magnesium aluminum phosphide), nerve agent VX, propargyl alcohol, selenium hexafluoride, sulfur dioxide, sulfuryl chloride,

[4]AEGL values for these eight metal phosphides were published with phosphine as an appendix in *Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 6.* The committee's comments on these chemicals are included for the record in this document.

trimethylbenzenes (1,3,5-, 1,2,4-, and 1,2,3-trimethylbenzene), and vinyl chloride. The report also summarizes the committee's conclusions and recommendations for improving the *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* published in 2001.

BROMINE PENTAFLUORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on bromine pentafluoride (BrF_5). A presentation on the TSD was made by Sylvia Talmage, of Oak Ridge National Laboratory. The following is excerpted from the executive summary of the TSD.

> BrF5 is a strong oxidizing chemical that is used as a fluorinating agent and as an oxidizer in rocket propellant fuels. No data on human exposures were available. A single study provided information on lethal and nonlethal values for the rat. No information on time scaling could be ascertained from this study, although the data did indicate that the dose-response curve for lethality was steep. In the absence of empirical data, no AEGL-1 values were developed. …In the absence of data relevant to derivation of AEGL-2 values for BrF5, data for the structurally related chemical, chlorine pentafluoride (ClF5), were considered…. The AEGL-3 values are based on the highest nonlethal value from the one rat study.

General Comments

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

There is a paucity of toxicologic information for making a valid assessment for this chemical. There is little neurotoxicity information, and there is no reproductive and developmental, genotoxicity, carcinogenicity, or chronic toxicity data. Toxicologic studies that are available are 30 to 40 years old. Because there is a lack of data, the TSD should provide more discussion on why a modifying factor was not used to adjust for uncertainties in the overall database or for known differences in toxicity among structurally similar chemicals. One approach is to state that differences in toxicity were accounted for in the lower toxicity of BrF_5 compared with chlorine pentafluoride (ClF_5). In addition, time scaling in the TSD needs to be revised to be in agreement with the revised ClF_5 document.

Because the BrF_5 AEGL values are based on the ClF_5 TSD, and that TSD is compared to chlorine trifuoride (ClF_3), we recommend republishing the ClF_3 TSD (from AEGLs report, Volume 5) with bromine trifluoride (BrF_3) (see below), BrF_5, and ClF_5—possibly as an appendix so that it is easy to reference.

Specific Comments

Page 4, line 12: The text states, "In the absence of data relevant to derivation of AEGL-2 values for BrF_5, data for the structurally-related chemical, chlorine pentafluoride (ClF_5), were considered." Change "were considered" to "were used." If they were not used, then this statement is not needed.

Page 4, lines 19-21: The text states, "For chemicals with similar actions, such as HF and ClF_3, interspecies and intraspecies uncertainty factors (UFs) of 3 each for a total of 10 were shown to be protective of sensitive individuals." Provide better rationale for selecting the interspecies and intraspecies UF values. The rationale must be consistent with the standing operating procedures (SOP) (NRC 2001). The phrase "were shown to be protective of sensitive individuals" is a very strong statement. The

committee recommends reformulating the statement using the phrase "should be protective of sensitive individuals"

Page 9, lines 10-15: The TSD should explain how the 60-min LC_{50} of 375 ppm was calculated. From Table 2, at 500 ppm, there are no rat deaths at 40 min and 11 of 14 deaths at 50 min. This is a very steep concentration- response relationship between exposure time and effect. We suggest using the 60-min LC_{95} compared with the Table 2 ClF_5 values for monkeys at 215 ppm (50%) and 223 ppm (100%). CIF_5 is more toxic than BrF_5 and the LC_{95} for CIF_5 is better developed.

Page 9, lines 10-15: Using the data suggested in the previous comment, BrF_5 is closer to one-half the toxicity of ClF_5 as opposed to one-third.

Page 10, lines 21-22: The text states, "However, based on the limited data for BrF_5, the more conservative default time-scaling values for *n* of 3 and 1, respectively, for the shorter and longer exposure durations were considered." Change "were considered" to "were used" if they were used. If they were not used, then this statement is not needed.

Editorial Comments

Page 8, line 46: The text reads, "These limited data would indicate that BrF_5 is less toxic than ClF_5." Change "would indicate" to "indicate."

Page 11, line 13: The following statement needs to be revised**: "**In the absence of data relevant to derivation of AEGL-2 values for BrF5, data for the structurally-related chemical, ClF5, can be considered (Table 5)." Change "can be" to "were."

Page 12, line 41: "application of a modifying factor of 2 might be considered." Change "might be" to "was."

BROMINE TRIFLUORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on bromine trifluoride (BrF_3). The document was presented by Sylvia Talmage, of Oak Ridge National Laboratory. The following description is excerpted from the executive summary of the TSD.

> BrF3 is an extremely reactive and corrosive oxidizing agent used in nuclear reactor fuel processing; as a fluorinating agent; and, potentially, in rocket and missile fuels. No reliable information on toxicity to humans or experimental animals was located. In the absence of empirical information on BrF3, AEGL values were based on the chemical analogue, chlorine trifluoride (ClF3). Information on chemical reactivity and relative toxicity for the chlorine and bromine fluorides show that the chlorine fluorides are more reactive and more toxic than the bromine fluorides. Therefore, setting the BrF3 AEGL values equal to the 10 empirically-derived, more toxic ClF3 values is reasonable…. In the absence of chemical-specific data, the AEGL-1 value for BrF3 was based on structure activity relationships…. In the absence of chemical-specific data, the AEGL-2 values for BrF3 were based on structure-activity relationships… In the absence of chemical-specific data, the AEGL-3 values for BrF3 were based on structure-activity relationships.

General Comments

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

Because the BrF_3 AEGL values are based on the ClF_3 document, review the interim reports to document previous decisions in reference to apparently contradicting comments on ClF_3 during this

review of BrF_3. The committee recommends republishing the ClF_3 TSD (from AEGLs report, Volume 5) with BrF_3, BrF_5, and ClF_5, possibly as an appendix so that it is easy to reference.

Because there is a lack of data, the TSD should provide more discussion of why a modifying factor was not used to adjust for uncertainties in the overall database or for known differences in toxicity among structurally similar chemicals. One approach is to state that differences in toxicity were accounted for in the lower toxicity of BrF_3 compared with ClF_3.

Specific Comments

Page 4, lines 16-17: "Obvious" lacrimation is recommended to be taken at least as an AEGL-1 effect (marked discomfort). Thus, 1.17 ppm for 3 h would no longer be an AEGL-1 no-observed-effect level (NOEL) for chlorine trifluoride (page 10, lines 5-6). Thus, the 4-h and 8-h AEGL-1 bromine trifluoride values, which are defined in analogy to those of chlorine trifluoride, may have to be decreased. There should be a brief discussion on this point in the text (page 10 around line 7) where this "obvious" lacrimation is not even mentioned.

Page 4, lines 22: The text states, "Time scaling was not applied to the AEGL-1 as adaptation to slight sensory irritation occurs. Therefore, the calculated value of 0.12 ppm was used for all BrF3 AEGL-1 time points." Rhinorrhea and lacrimation are not signs of sensory irritations.

Page 4, lines 45-46: The unusual UF of 2 for interspecies variation should be justified or should be replaced by 3.

Page 7, lines 4-5 and 11-12: The text states, "Reaction with water produces a complex mixture of products including bromine, oxygen, and bromic and hydrofluoric acids (Braker and Mossman 1980).…Following fluorine inhalation, fluorine may be absorbed by the lungs, particularly following the formation of hydrofluoric acid by reaction with moisture in the lungs." Why is fluorine of interest? Either describe that it is formed from bromine trifluoride or omit the description of the toxicity of fluorine.

Page 10, lines 5-6: See remark regarding page 4, lines 16-17.

Page 10, line 9 and page 11, line 21: The text states, **"**(3 for interspecies differences [the dog was more sensitive than the rat]." For a reduction of the UF 10 to 3, it is not sufficient to use a species that is more susceptible than another species, but rather to use the most sensitive species.

Page 11, line 22: The text states, "An intraspecies UF of 3 is sufficient as these AEGL-2 values are considerably lower than those of HF." Explain why (e.g., in a similar way as done on page 10, lines 30-32).

Page 12, line 17: Should "chlorine trifluoride" replace "chlorine"?

Editorial Comments

Page 15, line 10: Should be spelled "Aanvaarde," not Aanv<u>aaa</u>rde.

Comment References

Braker, W. and A.L. Mossman. 1980. Bromine pentafluoride. In Matheson Gas Data Book, 6th ed. Lyndhurst, NJ: Matheson.

Lewis, R.J. 1996. Sax's Dangerous Properties of Industrial Materials. New York: Van Nostrand Reinhold.

CARBON MONOXIDE

At its meeting held on May 12-14, 2008, the committee discussed the AEGL technical support document (TSD) for carbon monoxide. No presentation was made on the revised TSD because only one issue remained to be addressed, as mentioned below. The following description is excerpted from the executive summary of the TSD.

> CO is a tasteless, non-irritating, odorless and colorless gaseous substance. The main source of CO production is the combustion of fuels. Exposure at the workplace occurs in blast furnace operations in the steel industry and when gasoline- or propane-powered forklifts, chain-saws or other machines are used in confined spaces, such as companies, tunnels and mines. Environmental exposure to CO can occur while traveling in motor vehicles (9-25 and up to 35 ppm), visiting urban locations with heavily traveled roads (up to 50 ppm), or cooking and heating with domestic gas, kerosene, coal or wood (up to 30 ppm) as well as in fires and by environmental tobacco smoke. Endogenous CO formation during normal metabolism leads to a background carboxyhemoglobin concentration (COHb) of about 0.5-0.8 %. Smokers are exposed to considerable CO concentrations leading to a COHb of about 3-8 %....Until very severe symptoms occur none or only nonspecific symptoms are noted. For this reason, AEGL-1 values were not recommended…. The derivation of AEGL-2 values was based on effects in patients with coronary artery disease…. The derivation of AEGL-3 values was based on observations in humans.

General Comment

The document can be finalized after more appropriate support is provided for why a carboxyhemoglobin (COHb) value of 40% was selected as the basis for the derivation of AEGL-3.

Comment References

Pach, J., L. Cholewa, Z. Marek, M. Bogusz, and B. Groszek. 1978. Various factors influencing the clinical picture and mortality in acute carbon monoxide poisoning [in Polish]. Folia Med. Cracov. 20(1):159-168.

Pach, J., L. Cholewa, Z. Marek, M. Bogusz, and B. Groszek. 1979. Analysis of predictive factors in acute carbon monoxide poisoning. Vet. Hum. Toxicol. 21(Suppl.):158-159.

CHLORINE PENTAFLUORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on chlorine pentafluoride (ClF_5). The document was presented by Sylvia Talmage, of Oak Ridge National Laboratory. The following description is excerpted from the executive summary of the TSD.

> ClF5 is a strong oxidizer that was once considered for use as a missile propellant. No human data were available for development of AEGL values. Studies with the monkey, dog, rat, and mouse with exposure durations of 5 to 60 minutes were located. The relationship between exposure concentration and exposure duration in lethality studies with the rat was $C^2 \times t = k$…. The AEGL-1 is based on empirical data as well as analogy with hydrogen fluoride (HF) and chlorine

trifluoride (ClF3)…. The AEGL-2 values are based on a series of exposures with four species…The AEGL-3 values are based on a lethality study with rats.

General Comments

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

The author should explain the rationale for interspecies and intraspecies UFs throughout the document. The rationale for maintaining the same concentration for all time periods for AEGL-1 for direct acting irritants is that the effect is concentration- and not dose-dependent. Adaptation seems like a poor rationale, especially if irritation is on the continuum of other effects leading to death.

Specific Comments

Page 5, line 19: The text states, "The AEGL-1 for ClF_3 is 0.12 ppm (EPA 2003)." Instead of citing an EPA AEGL document, we recommend referencing the NRC publication for the ClF_3 AEGL-1 (NRC 2007).

Page 5, lines 31-32. The text states, "For chemicals with similar actions, such as HF and ClF_3, interspecies and intraspecies UFs of 3 each for a total of 10 *were shown to be protective of sensitive individuals*." The latter (italics) is a very strong statement. We recommend reformulating the statement to read, "should be protective of sensitive individuals" because AEGLs by definition account for sensitive individuals. Also, the TSD states "For chemicals with similar actions such as HF and ClF3, interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were shown to be protective of sensitive individuals. The same total uncertainty factor was applied to the ClF5 values." The TSD for ClF_5 should stand on its own for this chemical (i.e., all relevant information should be included within a chemicals TSD) and not refer back to the TSDs for HF and ClF_3, and it should properly explain the interspecies and intraspecies UFs and rationales.

Page 8, line 11: The text states, "chemical pneumonia was the cause of deaths that occurred during or immediately following exposure." The authors should change the term "chemical pneumonia" to "chemical pneumonitis". The author should also explain whether chemical pneumonitis is the cause of death during or immediately following exposure. A rapid onset of death due to chemical pneumonitis would speak to a highly reactive chemical and deserves additional comment in the TSD.

Page 8, Table 2: The data in Table 2 (acute lethality in monkeys) were graphed as a semi-log dose-response plot. The data for 30 min and 60 min revealed two parallel, sharply sloped lines from which the LD_{50} values could be derived, but the LD_{50} values from data for 15 min, although reported in the text, were more difficult to derive because the data do not readily form a straight line. That result should be addressed in the TSD.

Page 9, Table 3: In general, the exposure data for the animal studies are described as mean-value plus-or-minus "confidence limits." Clarify whether that means the range of values?

Page 16, lines 21-26: This paragraph seems to explain why fluoride is not a causative agent. We suggest re-wording this paragraph to distinguish between fluoride poisoning and 'physical reaction'. We also suggest re-wording this paragraph to explain that the effects of ClF_5 exposure are due to the physical reaction (direct irritation) and not fluoride poisoning.

Page 16, lines 36-38: The text states, "The authors stated that the toxicity of ClF_3 is comparable to that of ClO_2 on a chlorine equivalent basis and is comparable to that of HF on a fluorine equivalent basis." The statement does not add any clarity to the discussion and is confusing. We recommend deleting it.

Page 16, lines 45-46: The statement regarding the exothermic nature of hydrolysis of ClF_5 at higher concentrations is significant. It suggests that at higher concentrations the mechanism of tissue

damage may involve both the irritant activity of chlorine pentafluoride plus the effects of the released heat.

Page 18, lines 8-10: "Individuals under stress such as those involved in emergency situations and individuals engaged in physical activity will experience greater ClF_5 deposition and pulmonary irritation than individuals at rest. Furthermore, individuals who breathe through their mouths would be at greater risk." The same could be said for all chemicals. The statement is inherent in the AEGL definition and does not need further emphasis. We recommend the paragraph be deleted.

Page 18, lines 27-30: The statement "concentration is more important than duration" is contradicted by the monkey data on page 12, lines 40-41, where 10 ppm for 60 min produced effects and 30 ppm for 10 min did not. The author should resolve and explain this contradiction. See comment regarding page 21, lines 27-28.

Page 18, line 32: What is the relevance of the section titled "Concurrent Exposure Issues"? What concurrent exposures are discussed?

Page 18, lines 41-43: If the Threshold Limit Value (TLV) is based on the TLV for fluorides, it is irrelevant to this discussion based on the discussion on page 16, lines 21-26 (see comment above).

Page 19, Table 9: The discussion following Table 9—"AEGL-1 Values for Chlorine Pentafluoride"—explains the relative toxicities of ClF_3, ClF_5, and HF. However, the data for AEGL-1 are not consistent with these relative toxicities. The author should emphasize that the AEGL-1 is based on data for ClF_5. We suggest moving the discussion of relative toxicities to a different area or removing it entirely. It does not seem to add to the discussions and causes confusion because the TSD addresses why the real data are not in the same ratios as the relative toxicities. If the author judges that the discussion is relevant, it should be moved to Section 8.2, "Comparison with Other Standards and Guidelines."

Page 21, lines 27-28: The statement "concentration may be more important than exposure duration" is contradicted by the monkey data on page 12, lines 40-41, where 10 ppm for 60 min produced effects and 30 ppm for 10 min did not. The author should resolve and explain this contradiction. This problem occurs several times in the document. See comment for page 18, lines 27-30.

Page 23, lines 15-16: In the previous paragraph, the author states that the benchmark dose or concentration approach is inappropriate, yet it is referred to here. One of the two statements should be corrected or explained better.

Page 23, line 21: We recommend using n = 1.86 for time scaling. The exposure data have three significant figures.

Page 23, lines 30-34: It seems the text is trying to justify a correlation of toxicities between ClF_5 and HF when in fact empirical data were used to calculate the AEGL-3 for ClF_5. See comment regarding Page 19, Table 9.

Comment References

EPA (U.S. Environmental Protection Agency). 2003. Interim Acute Exposure Guideline Levels: Chlorine Trifluoride.

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

CHLOROACETONE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on chloroacetone. The document was presented by Cheryl Bast, of Oak Ridge National Laboratory. The following description is excerpted from executive summary of the TSD:

Chloroacetone has a pungent, suffocating odor similar to hydrogen chloride. It is toxic by inhalation, ingestion, and dermal contact and causes immediate lacrimation at low concentrations. Other effects from exposure to chloroacetone include contact burns of the skin and eyes, nausea, bronchospasm, delayed pulmonary edema, and death. It is produced by the direct chlorination of acetone. It has also been manufactured by reacting chlorine with diketene followed by boiling with water. It is used in the manufacture of couplers for color photography, as a photosensitizer for polyester-vinyl polymerization, as a fungicide/bactericide, and as an intermediate in the production of perfumes, antioxidants, and pharmaceuticals …Data were insufficient for derivation of AEGL-1 values for chloroacetone. No robust data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values were based upon a 3-fold reduction in the AEGL-3 values; this is considered an estimate of a threshold for irreversible effects.

General Comments

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

The key to the acute toxicity of chloroacetone is its severe irritant activity. Thus, an AEGL-1 value should be provided. That would best be accomplished by applying two correction factors to the human data (as sparse as it is): 3-fold for intraspecies variability and 3-fold for poor database.

Specific Comments

The authors need to provide a better discussion and justification for the selection of AEGLs 2 and 3. Re-examine the basis for presenting the same value for AEGL-3 (3.3 ppm or 13 mg/m^3) at both 4 and 8 h and for using the same values for AEGL-2 at 4 and 8 h (1.1 ppm or 4.2 mg/m^3). There is greater need for addressing the basis for the AEGL-3 because the end point is more critical. Also, consider adding Ruth (1986) as a reference.

A collation of odor threshold data for approximately 450 chemical substances is presented. The range of odor thresholds reported in the literature is shown along with any reported threshold of irritation to humans. These data can assist the industrial hygienist in determining when an "odor" may be in excess of the TLV, when use of an organic vapor respirator is not acceptable due to the lack of an odor warning at the end of a cartridge life, and where odors may not indicate a hazard due to extremely low odor thresholds, which may be well below the respective TLVs.

The oral LD_{50} values for rats and the dermal LD_{50} for rabbits are both 141 mg/kg. Please check those values for accuracy.

Page 9, lines 1-2: The text states, "The fumes, reported to be 4.7 ppm chloroacetone, produced immediate lacrimation and eye and upper respiratory tract irritation." The combination of the effects described here is likely to impair the ability to escape; that is, they reach the quality of AEGL-2 effects. They were observed in humans, albeit the report refers to one individual only.

Page 13, Section 3.6: Carcinogenesis data are conflicting: Robinson et al. (1989) treated SEN-CAR mice with chloroacetone followed by 12-*O*-tetra-decanoly-phorbol-13-acetate (TPA) and found no skin tumors. Searle (1966) reported that exposure of mice to chloroacetone and croton oil yielded skin tumors. A review of the detailed report might reveal differences in the studies to account for the conflicting results.

Page 14, lines 5-21: The text states, "Carcinogenicity data suggesting that chloroacetone may be a tumor initiator are also equivocal." Why use the word "equivocal" on line 21? The conditions (dose, number of animals, and so on) should be described (lines 5-6). See comment on page 13, Section 3.6.

Page 17, line 19: The text states, "No human data consistent with the definition of AEGL-1 were available." Why not use Sargent (1986) data for irritation (eye effects at 5 ppm) to establish AEGL-1?

Page 18, line 5ff: If what is said in the first specific comment above were taken as the basis for deriving the AEGL-2, the values given in this section would have to be reduced accordingly.

Page 19, lines 17-18: The text states, "The 4-hour value was also adopted as the 8-hour value because time scaling would yield an 8-hour AEGL-3 value approaching occupational standards." This is not a valid argument. If occupational experience shows that there is no problem with an exposure to 3.3 ppm for 8 h (or longer), that should be the argument. If that result is not known, the occupational standards may have to be recommended for reconsideration.

Page 19, lines 27-30: The committee recommends omitting the statement that these AEGL-3 values may be considered protective because the undetermined time period (line 28) may actually be small.

Comment References

Robinson, M., R.J. Bull, G.R. Olson, and J. Stober. 1989. Carcinogenic activity associated with halogenated acetones and acroleins in the mouse skin assay. Cancer Lett. 48(3):197-203.

Ruth J.H. 1986. Odor thresholds and irritation levels of several chemical substances: a review. Am. Ind. Hyg. Assoc. J. 1986. Mar 47(3):A142-151

Sargent, E.V., G.D. Kirk, and M. Hite. 1986. Hazard evaluation of monochloroacetone. Am. Ind. Hyg. Assoc. J. 47(7):375-378.

Searle, C.E. 1966. Tumor initiatory activity of some chloromononitrobenzenes and other compounds. Cancer Res. 26(1):12-17.

HEXAFLUOROACETONE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on hexafluoroacetone. The document was presented by Robert Young, of Oak Ridge National Laboratory. The following description is excerpted from the executive summary of the TSD:

> Hexafluoroacetone (HFA) is a colorless gas with a musty odor used in the synthesis of various polymers, medicinals, agriculture chemicals, and as an intermediate in various organic syntheses. HFA is highly reactive, reacting vigorously with water resulting in a series of hydrates (sesquihydrate, monohydrate, dihydrate) and ultimately producing a stable trihydrate. There are no inhalation exposure-response data for humans exposed to HFA and no information regarding an odor threshold…. Neither qualitative nor quantitative data were available for development of AEGL-1 values for HFA and none are recommended…. Evidence of developmental toxicity in rats occurred at lower exposures than did testicular effects and were selected as the critical effect for development of AEGL-2 values for HFA…. For AEGL-3, E. I du Pont & Co. studies in rats provided the most comprehensive data from which to develop AEGL-3 values.

General Comments

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

Specific Comments

Page 5, lines 35-36: The text states, "Testicular atrophy observed in male rats tended to be reversible upon removal from exposure and, therefore, not consistent with AEGL-2 effect severity."

Irreversibility is only one of three alternative/possible AEGL-2 criteria (NRC 2001, see page 42). Remove "not consistent with AEGL-2").

Page 12, line 19: The text states, "Severe testicular damage was also observed but reversible." Change to read, "Reversible testicular damage was observed in dogs at 12 ppm only." There were no testicular effects observed at 0.1 or 1 ppm.

Page 13, line 1: The text states, "absolute body weights adjusted to eliminate the products of conception." Explain for the lay reader what is meant by "eliminate the products of conception."

Page 14, lines 5-8: Are the "3,600 ppm for 4 hours without lethality" in reality 3,600 ppm for 30 min? That would appear plausible based on page 10, lines 13-14, and page 10, Table 3 (line 27), where all rats survived an exposure of 30 min to 3,600 ppm.

Page 15, lines 37-38: The text states, "data for animals regarding effects consistent with AEGL-2 severity are lacking." However, lines 42-44 present "evidence of developmental toxicity in rats" as the "critical effect for development of AEGL-2." These statements should be reconciled.

Page 15, lines 41-42: Change the wording to read, "Testicular atrophy in male rats was observed only after exposure to hexachloroacetone at 12 ppm and not after exposure at 1 ppm or 0.1 ppm." (and omit "and, therefore, not consistent with AEGL-2 severity"). See comment, page 15, lines 37-38.

Page 16, lines 14-16 and page 17, lines 18-20: The variable, *n*, for time scaling should either be based on data with the compound under consideration (which should be explained in each of these instances), or a value of 3 (not 1) should be used for scaling from longer to shorter time periods (NRC 2001, see page 105).

Page 17, lines 11-14: Justify the reduction of the interspecies UF from 10 to 3. Is no significant contribution by metabolism to uncertainty expected?

Comment References

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

HYDROGEN IODIDE AND HYDROGEN BROMIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on hydrogen iodide (HI) and hydrogen bromide (HBr). The document was presented by Sylvia Talmage, of Oak Ridge National Laboratory. The following description is excerpted from the executive summary of the TSD:

> HBr and HI, are colorless, corrosive, non-flammable gases. HBr fumes strongly in moist air. It is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl). It is extremely soluble in water, forming a strong acid that is available as 48 or 68% solutions. HBr is used both as a reagent and a catalyst in a variety of organic reactions; it is also used for the preparation of numerous bromide compounds. Anhydrous HBr is shipped in high pressure steel cylinders. HI is unstable at room temperatures and above, slowly decomposing to hydrogen and iodine. It is extremely soluble in water, forming a strong fuming acid, hydriodic acid. The acid is decomposed by light…. No empirical data were available for HI. In the absence of data, the HI values were set equal to the HBr values…. The AEGL-1 was based on a study with six human volunteers exposed to 2, 3, 4, 5, or 6 ppm HBr for several minutes… The AEGL-2 values for the 30-minute, 1-, 4-, and 8-hour time points were based on severe nasal histopathology in rats exposed to 1300 ppm HCl or HBr for 30 minutes… The benchmark dose approach, specifically the BMCL05, was used to develop AEGL-3 values for HBr and HI.

General Comments

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

Specific Comments

Page 6, line 15: The text states, "An uncertainty factor of 3 was applied for intraspecies extrapolation since the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals. Justification needs to be provided for the use of an uncertainty factor of 3. Note that the SOP indicates the default should be 10.

Page 9, line 36: The Amoore and Hautala (1983) study reported that odor of HBr was detected by all individuals at 2 ppm. Thus, it is not a threshold as stated on line 36 but could be a lowest-observed-adverse-effect level (LOAEL). Also, on page 10, line 24, it states that the threshold for irritation was 3.0 ppm. Is this a threshold or LOAEL?

Page 11, line 25: What is meant by "thrombosis of vessels"?

Page 11, lines 30-32: The text states, "No lung or tracheal injury was evident for any of the chemicals, although accumulations of inflammatory cells and exudates in the trachea and lungs following the exposure to hydrogen chloride (HCl) indicated that this chemical may not be as well scrubbed in the nasal passages as HF and HBr." The observation of injury in the trachea or lungs for HCl is clearly related to the difference in minute volume, so the comment about less effective scrubbing, given the solubility of HCl, should be deleted.

Page 12, lines 27-29: The text states, "Microscopically, fibrinonecrotic tracheitis, necrosis of the mucosa of the major bronchus, and polymorphonuclear neutrophils in scattered alveoli were observed. However, quantitatively, the lung lesions were not significantly different from those of the cannulated control group." The way this is written indicates that there was no difference between exposed and control animals. To avoid confusion, the details of the lesions (lines 27-28) should be deleted, and a statement about the lack of difference in controls should be added.

Page 14, line 17: The text states, "Hydrogen bromide is a site of contact irritant." This wording is confusing (HBr is not a "site"). The committee suggests revising it to read, "HBr is an irritant at the site of contact."

Page 14, lines 23-31: The text states, "Iodine is an essential nutrient required for development and functioning of the thyroid gland. No information on the metabolism of HI was located. Ingested iodine is readily absorbed from the gastrointestinal tract into the blood. Approximately one-third of normally ingested iodine, 1 mg/week, is taken up by the thyroid gland. The remaining two-thirds are rapidly cleared by the kidneys. The kidney clearance rate of iodide ion is 35 mL/min, far greater than the 1 mL/min clearance of chloride ion. Excess iodine absorbed from the blood into the thyroid is synthesized into the thyroid hormones thyroxine and triiodothyronine, which are stored as a hormone-thyroglobulin complex (Guyton 1976). Ingested amounts of 2 to 4 mg of iodine have been fatal (O'Neil et al. 2001)."

Most of this information applies to ingested iodine and may not apply to effects from inhaled HI following reaction in the respiratory tract. Therefore, this paragraph, with the exception of the first two sentences, should be deleted.

Page 15, lines 29-30: **The** text states, "Thus, it is likely that HBr and HI are more effectively scrubbed in the nasal cavity than HCl, resulting in less penetration to the lungs and less severe toxicity there." The comment about scrubbing may be too strong based on the slight differences in solubility of HI, HBr, and HCl. The differences are so insignificant in relation to scrubbing potential that effectively there would be no significant difference in scrubbing potential in the upper respiratory tract. See comment, page 11, lines 30-32.

Page 15, line 38: What is the basis for the statement that HI is predicted to be the least toxic of the group being discussed (HI, HBr, HCl, and HF)? Please elaborate.

Page 16, lines 30-32: The text states, "Individuals under stress such as those involved in emergency situations and individuals engaged in physical activity will experience greater HBr or HI deposition and pulmonary irritation than individuals at rest." The sentence should be rewritten as follows: "Individuals under stress, such as those involved in emergency situations or individuals engaged in physical activity, will likely experience increased penetration of HBr or HI into the lower respiratory tract due to increased minute volumes, with the potential for increased irritant response, compared with individuals at rest.

Page 17, lines 18-20: The text states, "The 3 ppm was divided by an intraspecies uncertainty factor of 3 because the threshold for sensory irritation is not expected to vary greatly among individuals." This sentence is contradictory to the comment in Section 4.4.2. about the potential for increased sensitivity of asthmatics (page 16, lines 26-27). Again, stating 3 ppm is a no-observed-adverse-effect level (NOAEL) is not correct based on the definition of NOAEL. It could be a LOAEL, however. See comment, page 9, line 36.

Page 17, line 22: What is the basis for the assertion that adaptation to slight irritation occurs? Please elaborate.

Page 17, lines 39-40: The text states, "The 1-ppm value is considered protective of asthmatics. At low concentrations, HBr is well scrubbed in the upper nasal passages." Although the 1-ppm value may be protective of asthmatics, the justification for that statement is not valid. There are receptors in the upper respiratory tract that could trigger an asthmatic attack if stimulated, so having a chemical that is well scrubbed in the upper tract is not sufficient justification for assuming that asthmatics will not be preferentially affected by that chemical. See also comments on page 11, lines 30-32, and page 15, lines 29-30.

Sections 6.2 and 6.3. Why was 1,300 ppm selected as the basis for AEGL 2 when there was some mortality at this level but none at 1,000 ppm?

Page 18, lines 35 -37. The text states, "A modifying factor of 3 was applied to account for the sparse database of effects defined by AEGL-2, and because the effects observed at the concentration used to derive AEGL-2 values were somewhat severe." Justification needs to be provided for the use of an uncertainty factor of 3, instead of a default value of 10.

Page 18, lines 37- 39: The text states, "An uncertainty factor of 3 was applied for intraspecies extrapolation because the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals (NRC 2001)." The statement does not allow for the potential for increased susceptibility of asthmatics. See comment, page 17, lines 39-40.

Page 18, Table 9 Summary: The nasal lesion study of Stavert et al. (1991) suggests that the order of toxicity would be HF and HCl > HBr. However, if the HBr AEGLs are added to this table, the ordering is problematic in that the values of AEGLs 2 and -3 for HBr are greater than those for HF but similar to those for HCl.

Page 19, lines 5-19: The following paragraph from the TSD is difficult to follow and it should be revised for greater clarity. Many of the sentences are not clearly related to previous ones. Also, the text should indicate why mice were not chosen because of their greater susceptibility relative to rats.

> The benchmark dose approach, specifically the BMCL05, was used to develop AEGL-3 values for HBr and HI. The basis for the values was the 1-hour lethality data for Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972). The mouse data were not chosen because mice may be more susceptible than other rodents to respiratory irritants. The 1-hour BMCL05 was 1239 ppm (Appendix C) and the BMC01 was 1456 ppm (data not shown). The more conservative 1-hour BMCL05 of 1239 ppm was chosen as the point of departure. A total UF of 10 was applied: 3 for interspecies differences and 3 for differences in human sensitivity. Action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001). The interspecies UF of 3 is sufficient as additional uncertainty or modifying factors would lower the longer-term AEGL-3 values to the AEGL-2 values. The basis for time-scaling was data for the slightly more toxic chemical, HCl. The resulting 30-minute value of 100 ppm was time

scaled to shorter and longer time periods using an n value of 1 (where $C^n \times t = k$) (Tables 12 and 13). Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 8-hour AEGL-3 was set equal to the 4-hour AEGL-3, as was done for HF and HCl (NRC 2004). Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

Page 22, line 30: The text states, "data were available to derive both AEGL-2 and AEGL-3 values." What is the strength of these data?

Comment References

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-289.

Guyton, A.C. 1976. Textbook of Medical Physiology, 5th Ed. Philadelphia: W.B. Sanders.

MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL TR-72-62. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH. August 1972.

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

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

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2001. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th Ed. Whitehouse Station, NJ: Merck.

Stavert, D.M., D.C. Archuleta, M.J. Behr, and B.E. Lehnert. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol.16(4):636-655.

HYDROGEN SELENIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on hydrogen selenide (H_2Se). The document was presented by Carol Wood, of Oak Ridge National Laboratory. The following description is excerpted from the executive summary of the TSD:

> H_2Se is a gas with a disagreeable odor at room temperature. It has a density higher than air and is formed by the reaction of acids or water with metal selenides. Although elemental selenium has a wide variety of uses in industry, agriculture, and pharmaceuticals, H_2Se has no commercial use… AEGL-1 values are not recommended. No data with the appropriate endpoints were found in either the human or animal studies…. Data were insufficient to calculate AEGL-2 values…. AELG-3 values were based on an estimated LC01 of 66 ppm obtained by a log-probit analysis of data from a 1-hour LC_{50} study in Wistar rats

General Comments

Taking the comments below into account, the document can be finalized if the committee's recommended revisions are made.

The AEGL derivation appears appropriate given the very limited database, although the resulting values are higher than other similar standards. Time scaling used a value of *n* that was calculated from appropriate data, and the calculations were presented in the document. The use of UFs appears appropriate.

The discussion of the mechanism of toxicity for selenium and its compounds in Section 4.2 of the TSD should be coordinated or harmonized with the related discussion in the selenium hexafluoride TSD.

The discussions of effects or studies with little or no direct application to the acute effects that are relevant to development of AEGLs should be reviewed for the value they add to the TSD. See, for example, much of the discussion of epidemiologic studies and of metabolism and disposition.

Specific Comments

Page 9, line 31 (Table 1): By convention in industrial hygiene, conversions are done at normal temperature and pressure (25°C and 1 atm) (see SOP Section 2.9.3). The molecular weight of H_2Se = 80.98. The conversion factors should be

$$1 \text{ ppm} = 3.3 \text{ mg/m}^3 \text{ and } 1 \text{ mg/m}^3 = 0.3 \text{ ppm}.$$

The values listed by the ATSDR are for the selenium component of H_2Se, not for the gas itself, as stated in its Table 4-2. Since the focus of the AEGLs is on exposure to the H_2Se gas, it would be more precise to use the values calculated with the molecular weight of the gas.

Page 21, Section 5.3: Consider using or reviewing the level of the OSHA/NIOSH standard of 0.05 ppm to establish AEGL-1.

Page 26, Table 8: AEGL-2 andAEGL-3 values are significantly higher than other existing standards. Comment on why such differences exist between the 1-h AEGL-2 value and the ERPG-2 (emergency response planning guidelines) value and between the 30-min AEGL-3 value and the IDLH (immediately dangerous to life and health) value.

Comments on Dudley and Miller Studies

Because the Dudley and Miller (1937, 1941) were not used in the determination of AEGL values, the discussion of their work should be reduced somewhat in the document, otherwise their work appears to carry substantial weight because of the amount of space devoted to it.

To this end, take out the detail on Table 2, and report the LC_{50} values in a paragraph.

Second, there is a section in the ERPG support document (AIHA 2002) that could be adapted for this document that captures the problems with the Dudley and Miller studies:

> In light of the 1989-1993 data which appears to result from a well conducted study with modern techniques, the previous acute inhalation work, conducted about 50 years earlier, may have overestimated the acute inhalation toxicity of hydrogen selenide. The whole body exposures, with the presence of animal excreta in the chambers, could have resulted in an underestimation of the H2Se chamber concentrations. In addition, the presence of selenium or selenium compounds on the fur of the exposed animals would have resulted in relatively high oral doses occurring through preening and perhaps skin permeation. The combination of possibly erroneously low chamber concentrations in the older studies coupled to oral/dermal exposure could explain the overestimation of inhalation toxicity. Finally, guinea pigs may be somewhat more susceptible to H2Se exposure than rats. All of this could explain the order of magnitude differences between the two studies done about 50 years apart.

Editorial Comments

Page 5, line 42: The sentence should state, "Lethality studies were conducted in pairs of Wistar rats." Add "pairs of" to existing sentence.

Page 9, lines 3-4: The text states, "It has a density higher than air…." Change to read "density greater than air"

Page 10, line 41: Ensure that the spelling of the word "tachypnea" is consistent throughout.

Page 12, line 23. The citation for the statement, "Irritation occurs at or below the odor threshold" should be added.

Page 17, lines 43-45: To support the relevance of the other absorption, distribution, metabolism, and excretion studies cited, the Medinsky et al. (1981) reference should be discussed near the beginning of this paragraph rather than at the end.

Page 18, line 1: The text states, "In blood, selenium is rapidly taken up by erythrocytes, metabolically altered in the RBC…." Define what the phrase "metabolically altered" means in this context.

Page 18, line 8: Consider adding a sentence at the end of this paragraph that indicates that Lu et al. (1995) provides a brief review of the selenium metabolic pathways.

Page 19, Figure 1: Verify that all the data points from the two studies are on the graph, and connect the dots to improve clarity.

Page 20, lines 22-26: The text states**, "**Therefore it appears that the concentration that causes death is reached quickly and is relatively flat over a range of duration. This supports the possible mechanisms of toxicity in which high concentrations that result in severe irritation cause death by pulmonary edema, whereas the liver can compensate for exposure to lower concentrations of a long duration." The points being made by these two sentences are not clear. They should be improved by referring to Figure 1 or to a separate graph.

Page 21, lines 17-18: To improve clarity, change sentence to read "for pulmonary edema resulting from irritation after…cessation of exposure." Add "resulting from irritation." In addition, provide citation for pulmonary edema occurring at this AEGL-1.

Page 23, line 4: The text states, "While the 8-hour value is only slightly higher than the reported odor threshold, it is considered reasonable because of the potential for cumulative liver damage from extended exposure." This sentence seems to have no relevance to the discussion of the AEGL-3 and should be omitted.

Page 25, lines 11-12: Change to read "0.002 ppm (0.005 mg/m^3)" because the California values are given in units of micrograms per cubic meter. It is worth noting that the California values were set using Dudley and Miller (1937 and 1941) and did not cite the Zwart and Arts (1989) and the Zwart et al. (1992) studies.

Page 28, lines 10-12: Insert URL for this reference (http://oehha.ca.gov/air/acute_rels/allAcRELs.html).

Page 30, lines 21-25: There are two citations to EPA's IRIS distinguished only by different dates. The specific document being cited should be identified in each case.

Reference Comments

If a document or a database is available on line (other than a journal article), the URL should be provided to improve ease of access.

In the reference list, provide URLs for the ATSDR toxicological profile, California-EPA acute RELs, the IPCS EHCs, NIOSH IDLHs and Pocket Guide, NTP bioassays, OSHA standards, and EPA IRIS.

If there is a citation of a common secondary source, check for 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, workplace environmental exposure limits (WEELs), and ERPGs, which can change and even withdraw certain values or the references used to support them. Also ensure that, for exposure limits and guidelines, the citation is either to the value or to the documentation.

In this reference list, the more recent versions of the secondary sources used are ACGIH TLVs and their documentation, AIHA ERPGs, Patty's Toxicology (the fifth edition is current), Matheson Gas Data Book, the German maximum workplace concentration (MAK) values, the Netherlands maximum accepted concentration (MAC) values, the Merck Index, and the Catalog of Teratogenic Agents.

When citing a secondary reference or database, consider whether citing the primary source of the data would be better.

Comment References

AIHA (American Industrial Hygiene Association). 2002. Emergency Response Planning Guidelines. Hydrogen Selenide. Fairfax, VA: AIHA Press. 6 pp.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Toxicological Profile for Selenium. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. September 2003 [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp92.pdf [accessed May 8, 2009].

Dudley, H.C., and J.W. Miller. 1937. Toxicology of selenium. IV. Effects of exposure to hydrogen selenide. Public Health Rep. 52(36):1217-1231.

Dudley, H.C., and J.W. Miller. 1941. Toxicology of selenium. VI. Effects of subacute exposure to hydrogen selenide. J. Ind. Hyg. Toxicol. 23(10):470-477.

EPA (U.S. Environmental Protection Agency). 1991. Integrated Risk Information System. Retrieved online 3/18/2003.

EPA (U.S. Environmental Protection Agency). 1993. Integrated Risk Information System. Retrieved online 3/18/2003.

Lu, J., C. Jiang, M. Kaeck, H. Ganther, S. Vadhanavikit, C. Ip, and H. Thompson. 1995.
Dissociation of the genotoxic and growth inhibitory effects of selenium. Biochem. Pharmacol. 50(2):213-219.

Medinsky, M.A., R.G. Cuddihy, W.C. Griffith, and R.O. McClellan. 1981. A simulation model describing the metabolism of inhaled and ingested selenium compounds. Toxicol. Appl. Pharmacol. 59(1):54-63.

OSHA (Occupational Safety and Health Administration). 1999. Table Z-1—Limits for Air Contaminants. CFR 29, Section 1910.1000, p. 13.

Zwart, A., and J.H.E. Arts. 1989. Acute (1-hour) Inhalation Toxicity Study with Hydrogen Selenide in Rats. Report No. V 89.463. Zeist, The Netherlands: TNO-CIVO Institutes.

Zwart, A., J.H.E. Arts, W.J. ten Berge, and L.M. Appleman. 1992. Alternative acute inhalation toxicity testing by determination of the concentration-time-mortality relationship: Experimental comparison with standard LC_{50} testing. Regul. Toxicol. Pharmacol. 15(3):278-290.

METAL PHOSPHIDES

At its meeting held on May 12-14, 2008, the committee reviewed AEGLs technical support documents (TSD) that were developed for eight metal phosphides: aluminum phosphide, potassium phosphide, sodium phosphide, zinc phosphide, calcium phosphide, magnesium phosphide, strontium

phosphide, and magnesium aluminum phosphide. The following description is excerpted from the executive summary of the TSD:

> Metal phosphides are solids and are typically used as fumigants against insects and rodents in stored grain. The metal phosphides react rapidly with water and moisture in the air or stored grain to produce phosphine gas. It is the phosphine gas which is responsible for acute toxicity, and the rate of phosphine generation is dependent on ambient temperature and humidity and the chemical structure of the phosphide…. In the absence of appropriate chemical-specific data for aluminum phosphide, zinc phosphide, calcium phosphide, potassium phosphide, magnesium phosphide, sodium phosphide, strontium phosphide, or magnesium aluminum phosphide, the AEGL-2 and AEGL-3 values for phosphine will be used to obtain AEGL-2 and AEGL-3 values, respectively, for the title metal phosphides…. Because AEGL-1 values for phosphine are not recommended (due to insufficient data), AEGL-1 values for the title metal phosphides are also not recommended.

General Comments

Because the acute toxicity of the eight phosphides results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based on phosphine AEGLs. For this reason, AEGL values for the eight metal phosphides were published with phosphine as an appendix in *Acute Exposure Guideline Levels for Selected Airborne Chemicals*, Volume 6 (NRC 2008).

The comments below are included for the record.

The metal phosphides are solids that generate phosphine gas in the presence of moisture. The TSD reasonably concludes that exposure to phosphine gas is responsible for acute toxicity related to metal phosphides. Previously, the committee concluded that the phosphine AEGL values are adequately supported by the phosphine TSD.

Therefore the AEGL values for metal phosphide compounds can be included in the phosphine document published in AEGLs volume 6. In doing so, the following aspects should be addressed in the revised phosphine document:

- A description of the chemical reactions and molar ratios of phosphine generated from metal phosphides, as presented in the metal phosphides TSD of November 2007.
- The concentrations of the metal phosphides that generate phosphine at concentrations equivalent to the AEGL values for phosphine should be given, where the phosphine values are reported in parts per million and the metal phosphide values are in milligrams per cubic meter.
- Better justification than is currently provided in the metal phosphide TSD that the metal components are not expected to be a factor in toxicity of these compounds. Note that in the case history developed by Garry et al. (1993) a very high concentration of aluminum in the blood was observed (713 ng/mL; normal range up to 10 ng/mL). In this one case, the metal apparently could not be neglected.
- Estimate the exposure concentrations of metals expected to occur with the release of metal phosphides in amounts that are sufficient to reach phosphine AEGL values. Indicate whether the resulting metal concentrations would pose a significant toxic threat.

Add the following references to the document: Garry et al. (1993), Verma et al. (2007), and Shadnia et al. (2008).

Editorial Comments

Page 10, line 12, and page 24, line 40: Change "Hendrickx" to "Heynderickx."

Comment References

Garry, V., Good, P.F., Manivel, J.C., Perl, D.P. 1993. Investigation of a fatality from nonoccupational aluminum phosphide exposure: measurement of aluminum in tissue and body fluids as a marker of exposure. J. Lab. Clin. Med. 122: 739-747.

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

Shadnia, S., O Mehrpour, and M Abdollahi. 2008**.** Unintentional Poisoning by Phosphine Released from Aluminum Phosphide. Hum. Exp. Toxicol. 27:87-89. Available: http://het.sagepub.com/cgi/content/abstract/27/1/87?eaf.

Verma, S., S Ahmad, N Shirazi, SP Barthwal, D Khurana, M Chugh, and HS Gambhir. 2007. Acute pancreatitis: a lesser-known complication of aluminum phosphide poisoning. Hum. Exp.Toxicol. 26:979-981. Available: http://het.sagepub.com/content/vol26/issue12/.

NERVE AGENT VX

AEGL values for nerve agent VX were published in *Acute Exposure Guideline Levels for Selected Airborne Chemicals*, Volume 3 (NRC 2003), but more recent information regarding this chemical has become available (see Benton et al. 2006a,b; Genovese et al. 2007). At the AEGL committee meeting held on May 12-14, 2008, Robert Benson, of the U.S. Environmental Protection Agency, discussed the extent to which the information supports the current AEGL values. According to Mr. Benson, the information validates the approach used to develop the AEGL values for VX as published in NRC (2003), and the information indicates that the published AEGL values (NRC 2003) are adequately protective. He presented the following summary points:

- AEGL-1 values developed using data of Benton et al. (2006a) would eliminate the need for a modifying factor and lead to the use of a VX-specific *n* of 1.65 (for miosis) resulting in slightly greater (8-h value is slightly lower) but operationally equivalent values compared with the AEGL-1 values in NRC (2003) (see Table 1).
- Data (Benton et al. 2006a; Genovese et al. 2007) would result in slightly increased AEGL-2 values (operationally equivalent) due to an interspecies UF of 3 vs. 1 and a time-scaling *n* value of 1.65 vs. 2 (see Table 2). Like the published values, the new values would address peripheral neuromuscular effects as well as miosis.
- Data from Benton et al. (2006b) would justify elimination of the modifying factor for a sparse database. Using a time scaling *n* of 0.92 instead of 2 would result in slightly lower values for the 4-h and 8-h durations but slightly higher values for the durations of 1 h and less (see Table 3). However, the *n* of 0.92 may be a function of percutaneous absorption.

Mr. Benson asked the committee to recommend how to proceed in light of this new information.

General Comments

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

For AEGL-2, use an interspecies UF of 10 instead of the proposed 3 because human ataxias are complex, comprising more than 20 types (including spinal, locomotoric, central nervous system, sensoric, and muscular) that are not displayed in the rat ataxia model (See Furtado et al. 1998; Margolis 2002; Viau and Boulanger 2004.

Prepare a document showing the new values with an explanation that more recent data specific to VX are now available. Provide the tables of AEGL values showing the data published in NRC (2003) and the values based on the more-recent information, including use of an interspecies UF of 10 for AEGL-2. The document should also discuss whether the AEGL values for VX in NRC (2003) should be revised after the more-recent data are taken into account. The document should then be submitted to the committee for review. The document should be published whether or not the current AEGL values are revised.

Comment References

Benton, B.J., J.M. McGuire, D.R. Sommerville, et al. 2006a. Low-level effects of VX vapor exposure on pupil size and cholinesterase levels in rats. Ch. 5, pp. 91-108 in Inhalation Toxicology, 2nd Ed., H.A. Salem and S.A. Katz, eds. Boca Raton, FL: CRC Press, Taylor & Francis Group.

Benton, B.J., J.M. McGuire, D.R. Sommerville, et al. 2006b. Effects of whole-body VX vapor exposure on lethality in rats. Inhal. Toxicol. 18:1091-1099.

Furtado S., S. Das, O. Suchowersky. 1998. A review of the inherited ataxias: recent advances in genetic, clinical and neuropathologic aspects. Parkinsonism & Related Disorders Dec; 4(4):161-169.

Genovese, R.F., B.J. Benton, E.H. Lee, et al. 2007. Behavior and biochemical evaluation of sub-lethal inhalation exposure to VX in rats. Toxicology 232 (104):109-118.

Margolis R. L. 2002. The spinocerebellar ataxias: order emerges from chaos. Current Neurology and Neuroscience Reports. Sep; 2(5):447-56.

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

Viau M., Boulanger Y. 2004. Characterization of ataxias with magnetic resonance imaging and spectroscopy. Parkinsonism & Related Disorders. Aug;10(6):335-351.

PROPARGYL ALCOHOL

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL document on propargyl alcohol. The document was presented by Robert Young, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> Propargyl alcohol is a moderately volatile three-carbon acetylenic alcohol with a geranium-like odor. It is used as a chemical intermediate, solvent stabilizer, soil fumigant, and corrosion inhibitor. Annual production in the United States has been estimated at 0.5 to 2.8 million pounds…. The AEGL-1 values for propargyl alcohol were based upon a 6-hour exposure to 25.3 ppm which was without significant effects… Because exposure of mice to 88 ppm, 6 hrs/days for 4 days resulted in severe histopathologic changes in the olfactory region, a single 6-hour exposure was considered an estimation of a threshold for serious histological changes in olfactory tissue and served as the POD for AEGL-2 development…. A BMCL05 of 584 ppm (2-hour exposure) derived from mouse lethality data was selected as the POD for AEGL-3 derivation.

TABLE 1 AEGL-1 Values for VX (mg/m^3) Presented for Discussion by the NRC Committee

	10 min	30 min	1 h	4 h	8 h	POD	Interspecies UF	Intraspecies UF	Modifying factor	*n*	Reference
Published	0.00057	0.00033	0.00017	0.00010	0.000071	Relative potency to GB (GB POD was EC_{50} for miosis in adult female rats)	1: miosis response to nerve agent vapor is similar across species	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality and miosis data)	NRC 2003
New data	0.00070	0.00036	0.00020	0.00010	0.000066	EC_{50} for miosis in adult female rats: 10 min: 0.007mg/m^3 1 h: 0.002 mg/m^3 4 h: 0.001 mg/m^3	1: as above	10: as above	1: well-conducted study with VX	1.65: VX miosis data	Benton et al. 2006a
	0.0072	0.0042	0.0029	0.0015	0.0010	Relative potency to GB (GB POD was miosis, dyspnea, RBC-ChE inhibition, SFEMG changes in human volunteers) 0.5 mg/m^3 for 30 min	1: human data	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality and miosis data)	NRC 2003
	0.015	0.0076	0.0050	0.0022	0.0014	Pinpoint pupils, NOEL for ataxia in rats: 0.15 mg/m^3 for 1 h	3: even though miosis is similar across species and argues for a UF of 1, a 3 is applied to protect against ataxia. Also, allows for better separation from AEGL-3 values and more protective AEGL-2 values.	10: as above	1: well-conducted study with VX	1.65: VX miosis data (Benton et al., 2006a)	Genovese et al. 2007

TABLE 1 Continued

	10 min	30 min	1 h	4 h	8 h	POD	Interspecies UF	Intraspecies UF	Modifying factor	*n*	Reference
	0.029	0.015	0.010	0.0052	0.0038	Relative potency to GB (GB POD was female rat LC_{01} values between 10 min and 6 h	3: mechanism of toxicity is same in rodents and humans	10: Some individuals possess abnormally low levels of blood cholinesterase and carboxyesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents	3: sparse VX database	2: GB lethality data)	NRC 2003
	0.108	0.032	0.018	0.0041	0.0019	LC_{01} in female rats: 10 min: 3.24 mg/m^3 1 h: 0.525 mg/m^3 4 h: 0.123 mg/m^3	3: as above	10: as above	1: well-conducted study with VX	0.92: VX rat lethality data	Benton et al. 2006b

Abbreviations: ChE, Cholinesterase; GB, nerve agent GB; LC_{01}, concentration of a substance that is lethal to 1% of test organisms in a given time; *n*, in the equation $C^n \times t = k$; POD, point of departure; RBC, red blood cells; SFEMG, single fiber electromyography; UF, uncertainty factor;
Source: Robert Benson, U.S. Environmental Protection Agency, 2008, unpublished material.

General Comments

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

Propargyl alcohol is undoubtedly an irritant (also causing hyperplasia of nasal epithelium), but a paucity of animal and human data makes it difficult to assess its toxicologic properties. There are virtually no data on developmental and reproductive toxicity, genotoxicity, or carcinogenicity. As an alcohol, this agent is expected to cause some degree of central nervous system depression as well as some hepatotoxicity. Extended exposure could result in respiratory and renal toxicity.

The proposed AEGL values and their derivation appear appropriate given the database. Time scaling also appears appropriate. However, the UFs used and their derivation requires some modification.

In deriving the AEGL-1 and -2 values, the intraspecies UF was set at 3. The rationale given was that "for simple direct-contact irritation, individual variability is not expected to vary more than 3-fold" (p. 18, lines 10-11, of the TSD; similarly on p. 19, lines 27-28). The rationale is probably true for the histopathologic lesions seen. However, it may not be true for the physiologic effects produced by exposure to respiratory tract irritants, such as propargyl alcohol. Such effects may retard the ability of an exposed person to escape, and the effects warrant assessing whether there may be sensitive human subpopulations, which should be addressed in Section 4.4.1, on p. 17 of the TSD. This concern is discussed in the standing operating procedures (SOP) in Section 2.5.3.3.4, p. 87 (NRC 2001), in the context of the magnitude of the intraspecies UF. If the default UF of 10 for respiratory irritants, as identified in the SOP, is not going to be used, a more robust justification is required.

Specific Comments

Page 13, lines 25-36: The Zissu (1995) study described in Section 3.2.2 on p. 13 of the TSD was selected as the key study for deriving the proposed AEGL-1 and -2 values. The study was designed to evaluate *histopathologic* effects produced by repeated inhalation of irritant chemicals at concentrations based on the RD_{50} for each chemical. The fact that respiratory tract irritation occurs should be included in the discussion sections of the TSD. If it is not used in the derivations, the reasons should be discussed in the TSD.

At the very least, the presence of an irritation effect is a strong supporting factor in the selection of concentrations for AEGL-2 (see SOP Section 2.2.2.2.2), as the RD_{50} can affect the ability to escape especially for sensitive subpopulations. The point of departure for deriving the AEGL-2 values was the RD_{50} in the Zissu study. Not including a known acute effect for "an estimation of a threshold for serious histological changes" (TSD, page 19, line 12) has to be justified.

This respiratory irritant effect also should be considered in the selection of concentrations for AEGL-1 (see SOP Section 2.2.2.1.3 and Section 2.2.2.1.4). Zissu (1995) discusses Kane et al. (1979) in the Introduction of that document, concluding with the selection of the exposure levels to be used in his experiments. In the Kane et al. report, $0.3 \times RD_{50}$ is proposed as an intermediate exposure level, in the context of various occupational exposure limits, between $0.1 \times RD_{50}$ ("definite but tolerable sensory irritation") and $1.0 \times RD_{50}$ ("intolerable sensory irritation"). The irritation level at $0.3 \times RD_{50}$ was recommended for use by military personnel and astronauts (a *less* sensitive subpopulation) in a fashion analogous to the AEGL-2 (quotation in Kane et al. [1979] from the Committee on Toxicology [1964]).

Because the proposed AEGL-3 values exceed the $0.3 \times RD_{50}$ value (for 4- and 1-h exposures), or exceed the RD_{50} value (30- and 10-min exposures), some discussion is warranted as to why the exceedances are not a concern, especially for potential sensitive subpopulations.

Page 16, lines 19-40, and page 17, lines 4-6; Discussions of metabolism and disposition (p. 16, Section 4.1), mechanism of toxicity (p. 16, Section 4.2), and susceptible populations (p. 17, Section 4.4.1) should be reviewed for relevance to understanding the derivations of the proposed AEGL values. The information as presented is interesting but is not tied to the AEGLs derivation. The discussions in

Sections 6.2, 6.3, 7.3, 8.1, the summary, and the appendixes also should be reviewed to reduce material not relevant to the derivation of the AEGL-2 values.

Page 17, lines 21-33: The section "Animal Data Relevant to AEGL-1" (p. 17, Section 5.2) begins by stating, "Both acute exposure and multiple exposure studies in animals are available that describe nonlethal effects…." The rest of the paragraph cites four multiple-exposure studies, three of which are subchronic exposures. Reword the first sentence of the paragraph, replacing "exposure and" with "and subchronic" to read, "Both acute and subchronic multiple exposure studies …"

Page 18, line 3: The severity of the histopathologic effects seen in the BASF (1992a) study at various concentrations should be characterized on page 12 using a descriptor, such as mild, moderate, or severe. The results of this study could be used more explicitly in supporting the derivation of the proposed AEGL-1 and -2 values because similar histopathologic effects were seen in a second species at exposure levels and durations comparable to the Zissu (1995) study, especially if the histopathologic effects were less severe at the lower concentration. The effects seen in the Zissu study were the same at all durations, and the longest duration was longer than the BASF (1992a) study.

Pages 18-19, Section 6.3: In the discussion of the derivation of AEGL-2 (TSD Section 6.3, pp. 18-19), the statement is made (p. 18, line 40) that "These studies … do not provide definitive data for a single acute exposure to propargyl alcohol." That statement may be true for histopathologic effects, but, at least in the case of the Zissu (1995) paper, it is not true for physiologic effects relevant to impairment of escape. Insert the word "histopathologic" before the word "data."

Editorial Comments

Cover page: The chemical structure shown is not an alcohol.

Page 9, lines 19-20: The text states, "Gross pathology examination of animals that died revealed evidence of liver toxicity." The previous sentence states that only one animal died. Revise to eliminate the conflict.

Page 9, lines 26-30: This paragraph should come after the first paragraph in this section (3.1.1. Rats). It currently breaks up the three-paragraph description of the BASF (1965) studies. Moving it also places it in chronologic sequence.

Page 12, line 11: Change to read "signs were noted for…."

Page 12, line 19: Change to read "200-ppm group and both genders…."

Page 12, line 36: The NTP study is cited here as "unpublished"; elsewhere it is cited as "in press". Choose one to be consistent (it might have a citable date before finalizing the TSD).

Page 12, line 41: Change "Table 2" to "Table 3."

Page 13, line 25: Change to read "airborne chemicals, ~~one phase of~~ which included…." The reference does not indicate that there were other phases of this study not reported in the reference itself.

Page 14, line 12: Change to "Table 3" to "Table 4."

Page 16, Section 4.1: Use of a graphic would make the discussion of metabolites much easier to follow.

Page 16, line 26: Change to read "*N*-acetyl-~~yl~~cysteine…."

Page 16, line 30: Change to read "catalase pathway ~~resulted~~ produced…."

Page 16, line 40: Do not italicize the "1" and the "a" in "2-propyn-1-al."

Page 17, Section 4.4.3: Given the default approach for selecting a time-scaling exponent, *n*, described here, is Appendix B "Time Scaling Calculations" necessary?

Page 17, line 26: Which BASF study is referred to here? If both, cite as "BASF 1992a,b."

Page 19, line 2: Change to read "BASF 1992a,b"

Page 19, lines 9-11: The dependent clause of the second sentence appears on first reading to be redundant, given the first sentence, and is thus confusing. Reword the first two sentences of this paragraph for clarity.

Page 19, line 10: Insert the citation for this study (Zissu 1995) after the first sentence rather than on line 16.

Page 21, lines 10-11: Change to read "for the respective AEGL severity levels. The AEGL-1 values…." Alternatively, change to read "thresholds for each respective AEGL severity level. The…."

Reference Comments

If a document or a database is available on the internet (other than a journal article), the URL should be provided to improve ease of access for the reader, either an index page for a collection of documents or the specific page for the referenced document, along with the date accessed. The addresses of some web sites are changed periodically; therefore, the index page URLs listed below should be verified:

ATSDR (Agency for Toxic Substances and Disease Registry) publications, including the Toxicological Profiles, are at: http://www.atsdr.cdc.gov/toxpro2.html.

NLM (National Library of Medicine) TOXNET databases, including the Hazardous Substances Data Base (HSDB) are at: http://toxnet.nlm.nih.gov/.

IPCS (International Programme on Chemical Safety) publications, including the Environmental Health Criteria, are at: http://www.inchem.org/.

NIOSH (National Institute for Occupational Safety and Health) publications and databases, including the immediately dangerous to life and health (IDLH) values and documentation, are at: http://www.cdc.gov/niosh/database.html.

NTP (National Toxicology Program) publications and reports, including Study Reports and the Report on Carcinogens, are at http://ntp.niehs.nih.gov/.

OSHA (Occupational Safety and Health Administration) Occupational Safety and Health Standards in Title 29 of the CFR are at http://www.osha.gov/pls/oshaweb/owasrch.search_form?Page_doc_type=STANDARDS&Page_toc_level=0.

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 certain values or the references used to support them can be withdrawn. For exposure limits and guidelines, ensure that the citation clearly is either to the value or to the documentation. In this reference list, the more recent versions of the secondary sources used are the following:

ACGIH, 2007. Documentation of the Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs). Pub. No. 0100Doc. American Conference of Governmental Industrial Hygienists, , Cincinnati OH.

Alternatively, ACGIH, 2007. Documentation of the Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs), with Other Worldwide Occupational Exposure Values on CD-ROM.. Pub. No. 0107CD, American Conference of Governmental Industrial Hygienists, Cincinnati OH.

ACGIH, 2008. 2008 TLVs and BEIs. Pub. No. 0108, American Conference of Governmental Industrial Hygienists, Cincinnati OH.

Bevan C., 2001. Ketones, Alcohols, Esters, Epoxy Compounds, Organic Peroxides. Vol. VI, Ch. 78: Monohydric alcohols, C7 to C18, aromatic and other alcohols. Section N.32: Propargyl

Alcohol. In Bingham E, Cohrssen B, Powell CH, eds. (2001). Patty's Toxicology, 5th Ed. New York: John Wiley & Sons.

O'Neil M.J., Heckelman P.E., Koch C.B., and Roman K.J. 2006. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 14th Ed. Merck Research Laboratories, a Division of Merck & Co., Inc., Whitehouse Station NJ. 2,520 pp.

Page 24, lines 16-17: Is this reference (NCI 1996) cited in the TSD? Is this a complete citation? It seems to be an entry in a larger document or a web page entry that could be expanded.

Page 24, line 33: Verify that the page cited is correct (p. 7898).

Comment References

BASF AG. 1965. Bericht über die Prüfung der Inhalationstoxizität von Propargylalkohol im Vergleich zu Allylalkohol. Study No.XIII/62-63. Gewerbehygienisch-Pharmakologisches Institut.

BASF AG. 1992a. Range-Finding Study: Study on the Inhalation Toxicity of Propargyl Alcohol as a Vapor in Rat, 14-Day Study. Project No. 3610969/88060, BG No. 116. BASF AG, Department of Toxicology, Ludwigshafen, FRG.

BASF AG. 1992b. Study on the Inhalation Toxicity of Propargyl alcohol as a Vapor in Rats, 90-Day Test. Project No. 5010969/88100, BG No. 116. BASF AG, Department of Toxicology, Ludwigshafen, FRG.

Committee on Toxicology. 1964. Basis for Establishing Emergency Inhalation Exposure Limits Applicable to Military and Space Chemicals. National Academy of Sciences-National Research Council, Washington DC (as cited in Kane et al. 1979).

Kane, L.E., C.S. Barroe, and Y. Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40(3):207-229.

NCI.(National Cancer Institute). 1996. Summary of Data for Chemical Selection: Propargyl Alcohol CAS No. 107-19-7. Prepared for NCI by Technical Resources International, Inc., under Contract No. NO1-CB-50511. August 1996 [online]. Available: http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/PropargylAlcohol.pdf [accessed May 11, 2009].

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

Zissu, D. 1995. Histological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207-213.

SELENIUM HEXAFLUORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL document on selenium hexafluoride (SeF_6). The document was presented by Cheryl Bast, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> Selenium hexafluoride is a colorless, irritating gas. It is insoluble in water, but decomposes slowly in moisture to form hydrogen fluoride and selenium oxide. It is corrosive and severely irritating to skin, eyes, and causes respiratory distress and pulmonary edema; the irritation is immediate, but pulmonary edema may be delayed several hours. Selenium hexafluoride is used as a gaseous electric insulator…. A NOEL for irritation in the guinea pig, rabbit, rats, and mice (1 ppm for 4-hours) (Kimmerle, 1960) was used to derive AEGL-1 values…. In the absence of empirical data, the AEGL-3 values were divided by 3 to obtain AEGL-2 values for selenium

hexafluoride…. The highest concentration causing no mortality in the guinea pig, rabbit, rats, and mice (5 ppm for 4-hours) (Kimmerle, 1960) was used to derive AEGL-3 values.

General Comments

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

This agent is an irritating gas and may cause respiratory distress and pulmonary edema. No data are available on reproductive and development toxicity, and no studies are available on either genotoxicity or carcinogenicity. Respiratory-compromised individuals (e.g., persons with asthma) would be particularly sensitive to selenium hexafluoride.

The interim AEGL values and their derivation appear appropriate given the very sparse database. Use of the default approach in the absence of relevant data for time scaling is also appropriate. However, the use of UFs and modifying factors requires some adjustment.

The committee encourages the author to cross-reference between this TSD and the one for H_2Se, as much of the discussion on the mechanisms of toxicity of Se compounds are common to both.

Selenium Oxide Toxicity

In several places in the TSD, reference is made to the decomposition of SeF_6 (slowly) in water to form HF and SeO (e.g., see page 11, lines 4-5, and page 13, lines 18-19, of the TSD). Although HF toxicity and its probable contribution to SeF_6 toxicity are discussed, no discussion of SeO toxicity is provided beyond the speculation on page 13, lines 30-33, which does not address the acute irritant or corrosive effects from SeO exposure (e.g., see the Hazardous Substances Data Bank [HSDB]). Such a discussion is important to help clarify (to the extent possible) the relative contributions of SeF_6, HF, and SeO (and possibly other Se compounds) to the observed toxicity, especially as the potential effects of the "selenium moiety" are cited as helping to justify the development of AEGL values. Because selenium has several valence states, the exact composition of the "selenium moiety" (Se_xO_y) may not be clear (unless the moiety has been determined analytically, in which case that information should be cited). The ATSDR Toxicological Profile (ATSDR 2003) has some relevant chemistry information.

The delayed pulmonary edema cited on page 11, lines 8-9, of the TSD appears to be very similar to the effect described for exposure to selenium oxide fume (HSDB 2005, as cited in Thienes and Haley 1972). Consider describing data used to set SeO TLV levels and comparing them with SeF_6 levels for clarification.

HSDB (2009) identifies selenious acid as "monohydrated selenium dioxide (H_2SeO_3). The author should consider using the following reference, which indicates that selenium dioxide "decomposes" to selenious acid in water: Ellenhorn, M.J. 1997. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning,* 2nd Ed.*,* CD-ROM. Baltimore: Williams and Wilkins.

Interspecies and Intraspecies UFs

There are few data on SeF_6 and apparently no human data at all, but the interspecies differences in toxicity seem small. There is some potential for a sensitive human subpopulation (TSD, Section 4.4.2), and there is some uncertainty as to the exact nature of the reactive species of SeF_6 that produces the observed toxic effects (see above). Given this degree of uncertainty, an interspecies UF of 3, an intraspecies UF of 3, and a modifying factor of 3 may express this range of uncertainty more appropriately. Therefore, the AEGL-1 and AEGL-3 derivation paragraphs should be modified. An issue to be addressed is distinguishing between "irritation effects" and "corrosive effects"; because concentrations increase from below AEGL-1 to AEGL-3, irritation may predominate at lower

concentrations and corrosive effects at higher concentrations. Selection of the UFs should be based on the specific effect of concern at the level of concern. See the discussion in SOP Section 2.5.3.3.4, especially the top half of page 87, and Sections 2.5.3.2.3 and 2.5.3.4.4 on pages 72 and 90. Additional support for lowering the modifying factor from 10 to 3 can be provided by having more information on selenium moiety.

Enzymatic Effects

Reference is made in several places in the TSD to the potential role of the effect of selenium and its compounds on the activity of one or more enzymes (see, e.g., page 13, lines 30-33). These effects undoubtedly occur; however, the only data for acute toxic effects is from Kimmerle (1960). The relevance of these enzymatic effects would be strengthened (and uncertainty therefore reduced) if the effects noted by Kimmerle, and their time course, could be compared (type of effect produced, time course, and so forth) with selenium-produced enzymatic effects (the rate of hydrolysis would affect this), especially if they differed from the acute effects produced by selenium oxides or selenious acid. This is particularly important in supporting the time-scaling decisions in deriving the proposed AEGL-1 values. In the absence of information beyond that presented, the committee recommends modifying the text on page 15, line 22 (and elsewhere in the document), to read "any potential ~~enzymatic~~ effects resulting from the selenium moiety." This change is relevant not only to the hypothesized enzymatic effects for which no data are presented but also to the effects from the Se_xO_y formed by hydrolysis and the acute effects for which there is human anecdotal information (HSDB).

Editorial Comments

Cover Sheet. The formula for SeF_6 does not normally have a dash between the Se and the F.

Page 15, line 7: Change "port-of-entry" to "portal of entry". The former is where trade goods enter a country by ship or airplane. Correct as necessary elsewhere in the document.

Reference Comments

Page 18, lines 24-25: The date of the Toxicological Profile cited (ATSDR 2001) is for the draft released for public comment. The final published version, according to the ATSDR web site, is dated September 2003.

If a document or a database is available on line (other than a journal article), the URL should be provided to improve ease of access for the end user with either an index page for a collection of documents or the specific page for the referenced document, along with the date accessed. The index page URLs listed below should be used and updated as appropriate, as the addresses of some web sites are changed periodically. For this TSD, listed references include the following:

ATSDR (Agency for Toxic Substances and Disease Registry) publications, including the Toxicological Profiles, are at: http://www.atsdr.cdc.gov/toxpro2.html.

NLM (National Library of Medicine) TOXNET databases, including the Hazardous Substances Data Base (HSDB) are at http://toxnet.nlm.nih.gov/.

IPCS (International Programme on Chemical Safety) publications, including the Environmental Health Criteria, are at http://www.inchem.org/.

NIOSH (National Institute for Occupational Safety and Health) publications and databases, including the immediately dangerous to life and health (IDLH) values and documentation, are at http://www.cdc.gov/niosh/database.html.

OSHA (Occupational Safety and Health Administration) Occupational Safety and Health Standards in Title 29 of the CFR are at http://www.osha.gov/pls/oshaweb/owasrch.search_form?Page_doc_type=STANDARDS&Page_toc_level=0

If there is a citation of a common secondary source, check 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 certain values or the references used to support them can be withdrawn. For exposure limits and guidelines, ensure that the citation clearly is either to the value or to the documentation. In this reference list, more recent versions of the secondary sources used are

ACGIH. 2007. Documentation of the Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs). Pub. No. 0100Doc, American Conference of Governmental Industrial Hygienists, Cincinnati OH.

Alternatively, ACGIH. 2007. Documentation of the Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs), with Other Worldwide Occupational Exposure Values on CD-ROM. Pub. No. 0107CD. American Conference of Governmental Industrial Hygienists, Cincinnati OH.

ACGIH. 2008. 2008 TLVs and BEIs. Pub. No. 0108. American Conference of Governmental Industrial Hygienists, Cincinnati OH.

O'Neil, M.J., P.E. Heckelman, C.B. Koch, and K.J. Roman, eds. 2006. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th Ed. Whitehouse Station, NJ: Merck.

Comment References

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Toxicological Profile for Selenium. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. September 2003 [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp92.pdf [accessed May 8, 2009].

Ellenhorn, M.J. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, 2nd Ed. Baltimore: Williams and Wilkins.

HSDB (Hazardous Substances Data Bank). 2005. Selenium dioxide (CASRN 7446-08-4): Human health effects. TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/ [accessed May 11, 2009].

HSDB (Hazardous Substances Data Bank). 2009. Selenious acid (CASRN 7783-00-8). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/ [accessed May 11, 2009].

Kimmerle, G. 1960. Comparative study of the inhalation toxicity of sulfur-, selenium-, and tellurium hexafluorides [in German]. Arch. Toxikol. 18:140-144.

Thienes, C., and T.J. Haley. 1972. P. 209 in Clinical Toxicology, 5th Ed. Philadelphia: Lea & Febiger (as cited in HSDB 2005).

SULFUR DIOXIDE

At its meeting held on May 12-14, 2008, the committee reviewed the revised AEGL technical support document (TSD) on sulfur dioxide (SO_2). The document was presented by Cheryl Bast, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> SO_2 is a colorless gas at ambient temperature and pressure. It can be detected by taste at concentrations of 0.35-1.05 ppm and has a pungent, irritating odor with an odor threshold of 0.67-4.75 ppm. SO_2 is used in the production of sodium sulfite, sulfuric acid, sulfuryl chloride, thionyl chloride, organic sulfonates, disinfectants, fumigants, glass, wine, industrial and edible protein, and vapor pressure thermometers. It is also used during the bleaching of beet sugar, flour, fruit, gelatin, glue, grain, oil, straw, textiles, wood pulp, and wood. Sulfur dioxide is also used in leather tanning, brewing and preserving, and in the refrigeration industry. It is a by-product of ore smelting coal, and fuel-oil combustion, paper manufacturing, and petroleum refining… AEGL-1 values were based on the weight-of-evidence from human asthmatic data… AEGL-2 values were based on the weight-of-evidence from human asthmatic data… The AEGL-3 values were based on a calculated BMLC05 in rats exposed to SO2 for 4-30 hours (573 ppm).

General Comments

The TSD can be made final after several editorial comments are satisfactorily addressed.

Previously, the committee had several concerns about the derivation of the interim AEGL-3 values. In response, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances provided additional supporting information and applied time scaling to the derivation.

The committee reviewed the NAC's proposed modifications to the SO_2 TSD. The new interim AEGL-3 values and supporting information respond adequately to the committee's concerns, and are acceptable as written. Several editorial recommendations are provided below.

Reference Comments

If a document or a database is available on line (other than a journal article), the URL should be provided to improve ease of access.

If a reference of a common secondary source is cited, check for a more recent version that contains the material to be referenced, verify the information being referenced, and cite the most recent version. This is especially appropriate for annually updated sources, such as the TLVs, WEELs, or ERPGs, which can change and certain values or the references used to support them can be withdrawn. For exposure limits and guidelines, ensure that the citation clearly is either to the value or to 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, Cincinnati OH.

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

Page 19, lines 15-17: Shertzer H.G. 2001. Organic Sulfur Compounds, Vol. VII, Ch. 94, pp. 681-765, Section 33, Perchloromethyl Mercaptan. In Patty's Toxicology. 2001. Bingham, E., Cohrssen. B., and Powell, C.H., eds., 5th Ed., Vols. 1-8. New York: John Wiley & Sons.

SULFURYL CHLORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the revised AEGL technical support document (TSD) on sulfuryl chloride. The document was presented by Robert Young, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> Sulfuryl chloride, a colorless to light yellow liquid with a pungent odor, is used as chlorinating, sulfonating, and chlorosulfonating agent in organic synthesis. It is generally used in closed systems, thereby limiting exposure potential…. Data were insufficient for development of AEGL-1 values…. Because lethality threshold estimates tended to be less than nonlethal experimental exposures and because of the apparent steep exposure-response curve for sulfuryl chloride, AEGL-2 values were estimated by a three-fold reduction of the AEGL-3 values… A 4-hour BMCL05 of 70.1 ppm calculated from the Haskell Laboratory study was used as the POD for deriving AEGL-3 values.

General Comments

This document can be finalized.

Given the limitations of the data in Table 4 and that many of the available studies are terse and of poor quality, the committee agrees that the data are insufficient to develop an AEGL-1 value. The committee agrees with the results obtained in deriving AEGL-2 and AEGL-3 values, as shown in the TSD.

TRIMETHYLBENZENES (1,3,5, 1,2,4, AND 1,2,3-TMB)

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on trimethylbenzenes. The document was presented by Carol Wood, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> Trimethylbenzene (TMB) isomers, including 1,3,5-TMB, 1,2,4-TMB, and 1,2,3-TMB, are common components of fuels and mixed hydrocarbon solvents. Together with other compounds of the same empirical formula, these flammable and explosive hydrocarbons are referred to as the C9 aromatics. TMB isomers are clear, colorless liquids that are insoluble in water. Little difference in toxicity has been observed between the TMB isomers. Since occupational exposures are likely to involve more than one isomer, regulatory standards that have been established are for the individual isomers and any mixture thereof…. even though the point of departure may be based on data from an individual isomer, the resulting AEGL values are considered applicable to all three TMB isomers…. The most appropriate animal data for derivation of AEGL-1 are the neurotoxicity studies.... The most appropriate animal data for derivation of AEGL-2 were those of Gage (1970)…. Data are insufficient for derivation of AEGL-3 values for TMB.

General Comments

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

The major effect of short-term exposure to these compounds is neurotoxicity, which is discussed on pages 5, 11, 12, 13, and 15 of the TSD. The document should discuss the neurotoxicity in a single

section instead of in multiple places. The executive summary should be revised to contain less detailed information.

The question of hematotoxicity, originally dismissed by Gerarde (1960) because of the suspicion that the trimethylbenzenes were contaminated with benzene, should be revisited. If more recent data suggest that there is a hematotoxic effect of trimethylbenzenes, that effect should be reported.

The committee recommends using an additional UF of 3 to account for polymorphic metabolism of the trimethylbenzenes. Elimination of trimethylbenzene by exhalation is often much faster than by metabolism. Please verify the applicability of this observation by evaluating published information on the pharmacokinetics of trimethylbenzenes. The blood-air partition coefficient values are quite high; thus, elimination by exhalation may be less than by metabolism for certain exposure conditions. Evaluate elimination by exhalation relative to elimination by metabolism in light of the AEGL trimethylbenzene concentrations. If exhalation dominates, then metabolic clearance is less important.

AEGL-2

The reported 2,000-ppm exposure concentration in the Gage (1970) paper is not reliable for this purpose. All AEGL-2 values are based on this reported exposure level. The exposure level was not measured, and is considered nominal. Also, the term "saturated concentration" is used in the TSD. This is a very difficult level to achieve experimentally without forming aerosol droplets. Please provide justification for selection of this concentration.

Specific Comments

Page 11, lines 7-14: Acute, subacute, and subchronic exposure data are under the heading "Acute Lethality." Revise the text to discuss these data in their appropriate sections. Acute exposure data and data illustrating exposure-response times longer than acute are mixed up under the heading, "Acute Lethality". Revise the text to discuss these data in their appropriate sections.

Page 12, lines 6-7: The text states, "Saturated atmospheres (estimated by weight loss as 2,000 ppm) were obtained by passing air through the liquid…." Does the parenthetical refer to weight loss of the animals or the chemical? Please clarify.

Page 13, lines 22-23: The text states, "Within one minute of removal from the chamber, each animal was measured for propagation and maintenance of the electrically evoked seizure discharge." What parameter of the "electrically evoked seizure discharge" was measured and why?

Page 14, line 28: The text states, "Fetal body weight was reduced at 500 ppm." Can 500 ppm be considered as the LOAEL for developmental toxicity?

Page 21, lines 13-18: Line 18 states that the differences in response to exposure may have been due to repeated versus single application, but lines 14 and 17 does not state whether these exposures were repeated or single applications. The duration of exposure should be given on line 14.

Page 21, lines 39-44: Are these key publications (Korsak et al. 1995; Korsak and Rydzynski 1996) subchronic exposure studies or not? If they are, can they be considered a proper starting point for acute exposure guidelines levels?

Page 23, line 3: An exposure resulting in "respiratory difficulty" leads to impairment of escape, certainly in combination with lethargy. See comment about page 23, lines 19-20.

Page 23, lines 19-20: The text states, **"**The point of departure is a no-effect-level for AEGL-2, however, the endpoints considered could lead to an impaired ability to escape." This is a contradiction: Impairment to escape is an AEGL-2 effect, not an AEGL-2 NOEL. See comment about page 23, line 3.

Page 24. lines 13-14: The text states, "AEGL 3 values are given in Table 5." Rephrase so as not to suggest that AEGL-3 values are recommended in the table.

Comment References

Korsak, Z., K. Rydzyski, and J. Jajte. 1997. Respiratory irritative effects of trimethylbenzenes: an experimental animal study. Int. J. Occup. Med. Environ. Health 10:303-311.

Korsak, Z. and K. Rydzyski. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health 9:341-349.

Korsak, Z., R. Dwiercz, and K. Rydzyski. 1995. Toxic effects of acute inhalation exposure to 1,2,4-trimethylbenzene (pseudocumene) in experimental animals. Int. J. Occup. Med. Environ. Health 8:331-337.

Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 24:1-18.

Gerarde, H.W. 1960. Toxicology and Biochemistry of Aromatic Hydrocarbons. Amsterdam: Elsevier.

VINYL CHLORIDE

At its meeting held on May 12-14, 2008, the committee reviewed the AEGL technical support document (TSD) on vinyl chloride. The document was presented by Robert Benson, of Oak Ridge National Laboratory. The following description was excerpted from the executive summary of the TSD:

> Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms, tanks etc. Its worldwide production is approximately 27,000,000 tons. Most is polymerized to PVC. Combustion of VC in air produces carbon dioxide and hydrogen chloride. Odor thresholds of VC were reported in the range of 10 to 25,000 ppm. Validated studies providing a quantitative odor recognition and detection limit are not available. Therefore, a Level of Odor Awareness (LOA) can not be derived… The AEGL-1 was based on the study of 4-7 volunteers, two individuals experienced mild headache during 3.5 and during 7.5 hours (3.5 hours, 0.5 hours break, 3.5 hours) of exposure to 491 ppm.... The AEGL-2 was based on prenarcotic effects observed in human volunteers.... The AEGL-3 was based on cardiac sensitization and the no effect level for lethality.

General Comments

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

Time Scaling

Page 66 of the TSD indicates, "Regarding the three different endpoints and the data obtained for mice and guinea pigs values for *n* were in the range of 1.44 to 2.6 (1.44; 1.46; 1.8; 2.0; 2.1; 2.6; arithmetic mean: 1.9 +/- 0.4). Based on these data, it is justified to use a value of $n = 2$ for the time extrapolation for AEGL-2 (CNS effects) and AEGL-3 (cardiac sensitization) values up to two hours."

Because time scaling involves a log-log transformation of a plot of concentration versus time, it is not correct to take the arithmetic average. Instead, pick the value for *n* in the equation $C^n \times t = k$, without basing the selection on an arithmetic average.

1. Because AEGL-1 and AEGL-2 are both based on central nervous system (CNS) effects, consider using one of the log-log time-scaling plots.
2. Conversely, because AEGL-3 is not based on a CNS effect, consider using a CNS derived plot for *n*.

Cancer Determination

On the basis of the following comments, reevaluate the data and develop a sound rationale for single-exposure cancer risk as a driver for AEGL-3 in accordance with Section 2.8 of the standing operating procedures (NRC 2001). Development of AEGLs for vinyl chloride is an anomalous case relative to other chemicals, and the serious ramifications of exposure to vinyl chloride should be considered by AEGLs users. The TSD should provide a very clear discussion of the cancer-risk conclusions.

These AEGL values appear to be very conservative and could pose problems for the users of this document. Usually, the single-exposure cancer calculations demonstrate that even with very conservative assumptions there appears to be little risk of cancer from a single exposure. This risk gives comfort to the community in an exposure. In this case, with these low numbers, the opposite may occur, and people might be needlessly alarmed because there are substantial uncertainties in calculating a cancer risk from a single exposure to vinyl chloride.

How do vinyl chloride AEGLs compare with other known human carcinogens for which we have developed AEGLs (e.g., benzene)?

Although Appendix C of the TSD presents a very good discussion, the reader will probably find it easier to understand the bases for the conclusions in the TSD (use of method C) if the same format were used for each calculation method. Specifically, the section on relevancy should be similar and follow the format of method C. The discussion addresses why method C applies to the AEGL exposure scenario. There is no relevancy for methods A and B, and the relevancy for method D does not relate to the AEGL exposure scenario.

Specific Comments

Section 6, Rationale and Proposed AEGL-2

The study by Tatrai and Ungvary (1981) provides evidence of liver damage after 2 h of exposures. The TSD does not discuss why it discounts this study and bases the AEGL-2 on Lester et al. (1963). This study focuses on CNS effects; was liver damage reviewed in this study?

Page 38, lines 36-42: This paragraph discusses selection of 2 h for steady-state time without any supporting information. This information is provided on page 60, lines 27-42. The committee recommends that the author add this discussion to page 38 also.

Page 38, line 42 to page 39, lines 1-2: The text states, “However, the resulting AEGL-2 values may not provide a sufficient margin of safety to avoid mutational events or malignancies after short-term exposure to VC.” This assertion needs additional discussion. The TSD implies that carcinogenicity may be an issue but does not provide any explanation. The committee recommends that the author refer to Appendix C and state that these levels are lower than the carcinogenic-risk exposure levels. The author should discuss the fact that there are toxicodynamic and toxicokinetic effects for carcinogenicity because a VC metabolite is the apparent causative agent.

Section 7, Rationale and Proposed AEGL-3

Page 40, line 10: The text states, “A total uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.” Add that this is an intraspecies UF.

Page 40, lines 10-12: The text states, “As the challenge with epinephrine and the doses of epinephrine used represent a conservative scenario, no interspecies uncertainty factor was used.” The argument for an interspecies UF of 1 needs more justification. Currently, the TSD implies that there is no

difference in toxicodynamics between humans and animals for vinyl chloride. More information is needed to support that conclusion.

Page 42: The category plot indicates that there is at least a 100-fold concentration difference for similar effects. The author should highlight this in a short discussion.

Page 44, lines 35-36: The text states, "AEGL-2 values are based on animal experiments regarding CNS-effects." The TSD should be revised to indicate that AEGL-2 values are based on human data (Lester et al. 1963), not animal data as stated.

Page 44, Section 8.3: The TSD author should monitor any ongoing health studies of people exposed to vinyl chloride due to the Schoenebeck, Germany, train accident. This exposure is very relevant to the development of vinyl chloride AEGL values.

Comment References

Lester, D., L.A. Greenberg, and W.R. Adams. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am. Ind. Hyg. Assoc. J. 24:265-275.

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti, and D. Carretti. 1981. Carcinogenicity bioassays of vinylchloride monomer: A model of risk assessment on an experimental basis. Environ. Health Perspect. 41:3-29.

Maltoni, C., G. Lefemine, A. Ciliberrti, G. Cotti, and D. Carretti. 1984. Experimental Research on Vinyl Chloride Carcinogenesis, Vol. 2. Archives of Research on Industrial Carcinogenesis. Princeton, NJ: Princeton Scientific Publishers.

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

Tatrai, E., and G. Ungváry. 1981. On the acute hepatotoxicity of inhaled vinyl chloride. Acta Morphol. Acad. Sci. Hung. 29(2-3):221-226.

STANDING OPERATING PROCEDURES

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

In addition to reviewing AEGL documentation developed by NAC, the NRC committee is -charged to identify guidance issues from time to time that may require modification or further development based on the toxicologic database for chemicals reviewed. The committee provides the following recommendations to NAC for updating and improving the SOP and TSD documents.

General Comments

SOP Review and Revisions: The SOP should be reviewed by the NAC SOP Working Group, as prescribed on pages 22-23 and 29-30 of the SOP, and the document should be revised every 5 years. The NRC committee will recommend inclusion of new toxicology methods as applicable and will provide corrections and additions to the SOP as part of the AEGL review process. Some recommendations might require an out-of-cycle revision of the SOP.

Minimum data requirements for setting AEGL values: There are TSDs with very sparse databases to support the development of AEGL values. For example, AEGLs for selenium hexafluoride are based on the data from only one study. Provide guidance in the SOP on minimum data requirements.

"Data Adequacy and Research Needs": The information provided in this section of TSDs is usually of very little value and is usually very terse. The SOP, Section 2.3.3, specifies a number of points to be discussed in this section of the TSDs. Data adequacy is sometimes addressed in developing a modifying factor but without any detail given beyond a statement such as "sparse database." Actual research needs usually are not discussed. Standardized descriptions of specific needed information should be routinely included in this section.

AEGLs Review and Revisions: AEGL values should be reviewed every 5 years by the NAC; this process should be documented in the public record. AEGLs should be updated if new data are available that challenge the scientific credibility of the final AEGLs, as specified in the SOP on page 28. When documents are reissued/reprinted, AEGL TSD review dates should be noted in the document even if no changes are made and changes should be annotated as such in the text. These modifications should be made to the online versions as well.

Specific Comments

Distinguishing between AEGL-1 and AEGL-2 effects: Provide multiple examples in the SOP to help distinguish between AEGL-1 and AEGL-2 effects. Place emphasis on defining what constitutes "impairment of escape," especially for sensitive subpopulations. Discuss possible situations where an effect is judged to meet AEGL-1 criteria for the general population but meets AEGL-2 criteria for a specific subpopulation.

Level of distinct odor awareness (LOA): Describe when a LOA can and should be calculated and what data are needed. When a LOA is developed, calculations should be presented in an appendix to the TSD.

Odor detection: Use odor detection as a basis for AEGL-1 development when acceptable. Perceptible odor can help provide initial warning and be used to calculate a LOA, which provides some quantification for a typically qualitative parameter. However, 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.

Physiologically based pharmacokinetic (PBPK) modeling: Provide guidance on how to incorporate results from PBPK modeling into AEGLs development. The guidance should illustrate cases for which it is appropriate to use the PBPK approach.

Calculation of benchmark dose: Provide additional discussion on when a benchmark concentration can or should be calculated. Describe what data are needed for the calculation. Present example calculations in an appendix (see, for example, the AEGL TSD for propargyl alcohol).

Neurotoxicity end points: "Neurotoxicity" is not a singular effect. It encompasses a very wide range of effects—both central and peripheral—which are dependent on disparate pathways. Provide ample descriptive information in the TSDs to better define these types of end points.

RD_{50}: The SOP should address the use of RD_{50} data in the development of AEGL-1 and AEGL-2.

UF of 1: Discuss when use of an UF of 1 is applicable for interspecies and for intraspecies data.

Repeated-dose studies: Provide guidance on how to incorporate data from repeated-dose studies for AEGL development, both to support acute single-dose studies and for cases in which only repeated-dose studies are available.

Sensory irritants: AEGL values should remain constant across time for cases in which sensory irritation is the effect, as specified in the SOP on p. 107. This primarily applies to AEGL-1 but could also apply to AEGL-2. A UF of 10 is generally used to account for potentially large differences in human susceptibility to respiratory irritants (Section 2.5.3.3.4 of the SOP document). However, it is possible that

a lower UF (e.g., 3-5) could be supported if reliable data are available (see the recommendation regarding RD_{50}). Revisions to the SOP should explore whether there are sufficient data to support generalization regarding sensory irritants. It will also be necessary to distinguish between sensory irritants and irritants that also cause nonsensory toxic responses, especially with regard to considerations for time-scaling.

Solvents causing CNS effects: Revisions to the SOP should include consideration of whether generalizations can be applied to solvents that cause CNS effects. An important consideration is whether AEGL-2 and AEGL-3 values for such solvents 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 lipophilic, the quicker the equilibrium). The relationship $C^n \times t = k$ does not apply in these cases. At some point, the compound reaches saturation. The time must be determined with pharmacokinetic modeling to estimate blood concentration. If there is no pharmacokinetic model, provide guidance on use of observations of effects at the concentration of concern. Developers of AEGL values should not extrapolate from the short-term (less than equilibrium time) to the longer duration. For CNS depression in which the compound is direct acting (not metabolites), small animals reach equilibrium more quickly than humans, and this difference should be considered in determining an appropriate interspecies UF.

Saturated vapor concentration: This property would be a useful addition to the chemical and physical properties table in the TSD and would not be difficult to calculate if the data were available (see Perez and Soderholm 1991).

Skin absorption: This type of absorption can complicate efforts to assess absorbed dose, even in acute exposures, for some chemicals. Guidance is needed on how to account for this factor in the development of AEGL values.

Modifying factors: Section 2.6 of the SOP gives a very terse discussion of modifying factors. Expand this section to provide further guidance.

Use of existing standards: Include Threshold Limit Value–short-term exposure limits (TLV-STELs) in the 10-min block of Table 8 of the TSDs and any ceiling and skin notations. Mention other similar standards, for example, California EPA acute reference exposure levels (RELs).

Aerosol vs. vapor concentrations: Nonvolatile chemicals are generally suspended in the atmosphere as aerosols; concentrations are usually reported in units of milligrams per cubic meter. Volatile chemicals may be present as a vapor (reported in units of parts per million), an aerosol, or both. The form of the chemical to which humans are exposed can affect the extent of the toxic effects that may occur. Nonvolatile chemicals are generally suspended in the atmosphere as aerosols; concentrations are usually reported in units of milligrams per cubic meter. Volatile chemicals may be present as a vapor (reported in units of parts per million), an aerosol, or both. If both forms of the chemical are present, assessment of exposure requires combining the measured concentrations from different sampling methods to account for the two forms. The measurements might have to be converted before combining if they are not reported in the same units.

Precision of calculations: Provide guidance on the impact of UFs and modifying factors on the precision needed in deriving AEGL values.

Time scaling and use of the $C^n \times t$ equation: Discuss when rounding is acceptable or indicate that the discussion in SOP, Section 2.9.1 on rounding of AEGL values is to be followed for rounding of *n* values as well ("Precision of Calculations"). When *n* is calculated, show data and calculations in an appendix of the TSD. In addition, because modelers will use them, the equations should be given in an appendix with the applicable time bounds.

Comments on Document Format and Presentation

Target Audience: Chapter 3 of the SOP addresses the overall format and content of SOPs. This chapter also should indicate that the various sections of the TSD will have different target audiences, who will be reading the TSD under different circumstances and looking for specific information. By defining

these parameters, authors can structure the presentation (e.g., format, language, and level of detail presented) to the appropriate audience. The following comments on document format and presentation provide specific recommendations toward that end.

Length of TSDs: Some TSDs are excessively long, not because there is so much relevant data, but because the presentation has not been limited to information focused on deriving AEGL values.

TSD format: Consider a revised format for TSDs that would make the document easier for the intended audience to read and understand. A modified outline format, using subparagraphs with indentation, bullets, or other ways to set off specific elements may be helpful. A single paragraph that consumes half a page or more is almost certainly too long—and far too common in the TSDs.

TSD summary: Authors of TSDs should not only cut-and-paste from various sections of the document to form a summary. The summary should be phrased differently from the text of the document as the readership of summaries is broader than that for the TSD itself, and the summary is likely to be read under different circumstances.

Redundancy across sections: TSDs often have a paragraph or two (usually very long) on the derivation of each AEGL values, and there is an appendix providing an AEGL derivation summary (with a structured form that typically covers a whole page). Could these sections be combined? Separately, there is an appendix showing the calculation of *n*, and there is an appendix on the calculation of each AEGL for each time point. Could these be combined? Other examples of redundant materials or presentations exist. If some repetition is desirable, consider whether cross-referencing would be acceptable (e.g., "see calculation in Appendix Q" or "see discussion on page Z").

Category plots: State in the SOP that category plots will be generated by TSD developers to summarize data used to develop AEGL values. Also, indicate that an illustration should be provided by TSD developers to compare observed effects with the AEGL-1, AEGL-2, and AEGL-3 effects.

Comments on Use of References

Use of secondary sources, papers cited by others: If a reference of a common secondary source is cited, check for a more recent version that contains the material to be referenced, verify the information being referenced, and cite the most recent version. Sometimes material in an earlier edition is dropped a later edition or is updated. This is especially appropriate for annually updated sources, such as the TLVs, WEELs, or ERPGs, which can change and certain values or the references used to support them can be withdrawn.

If the primary article is not accessible, the citation should indicate something like "article x, as summarized in article y." This is not necessary when citing a secondary source, such as a widely used standard reference or handbook.

Reference citing: If a document or a database is available online (other than a journal article), the URL should be provided to improve ease of access for the end user with either an index page for a collection of documents or the specific page for the referenced document, along with the date accessed.

Comment References

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

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

Perez, C., and S.C. Soderholm. 1991. Some Chemicals Requiring Special Consideration When Deciding Whether to Sample the Particle, Vapor, or Both Phases of an Atmosphere. Appl. Occup. Environ. Hyg. 6(10):859-864.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists, a member-based organization for advancement of occupational and environmental health.
AEGL	acute exposure guideline level
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.
ATSDR	Agency for Toxic Substances and Disease Registry, a federal public health agency of the U.S. Department of Health and Human Services
BrF_5	bromine pentafluoride
BrF_3	bromine trifluoride
CEEL	community emergency exposure level
ChE	Cholinesterase
ClF_5	chlorine pentafluoride
ClF_3	chlorine trifuoride
CNS	central nervous system
COHb	carboxyhemoglobin
EHS	extremely hazardous substance
EPA	U.S. Environmental Protection Agency
ERPG	emergency response planning guideline
GB	nerve agent GB
h	hour
HBr	hydrogen bromide
HCl	hydrogen chloride
HF	hydrogen fluoride
HI	hydrogen iodide
HSDB	Hazardous Substances Data Bank
H_2Se	hydrogen selenide
H_2SeO_3	monohydrated selenium dioxide
IDLH	immediately dangerous to life and health
LC_{01}	concentration of a substance that is lethal to 1% of test organisms in a given time

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
LOAEL	lowest-observed-adverse-effect level
MAC	maximaal aanvaarde concentratie (maximum accepted concentration)
MAK	maximale argeitsplatzkonzentration (maximum workplace concentration)
min	minute
NAC	National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances
NIOSH	National Institute for Occupational Safety and Health
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
POD	point of departure
ppm	parts per million
RBC	red blood cell
RD_{50}	concentration of a substance that reduced the respiratory rate of test organisms by 50%
REL	reference exposure level
SO_2	sulfur dioxide
SeF_6	selenium hexafluoride
SeO	selenium oxide
SFEMG	Single Fiber Electromyography
SOP	standard operating procedure
STEL	short-term exposure limit
TLV	Threshold Limit Value
TMB	trimethylbenzene
TPA	12-*O*-tetra-decanoly-phorbol-13-acetate
TSD	technical support document
UF	uncertainty factor
WEEL	workplace environmental exposure limit