Nineteenth Interim Report of the Committee on Acute Exposure Guideline Levels: Part A

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Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars or trucks transporting EHSs, or they can be released 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. It provided updated procedures, methods, 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 considering acute adverse health effects to develop AEGL values.

Using the 1993 and 2001 NRC guideline 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, Syracuse Research Cooperation, on draft AEGL documents. At some meetings, the committee also hears presentations from NAC's collaborators from other countries. The committee provides comments and recommendations on those documents in its interim reports to NAC, 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 19th interim report. It summarizes the committee's conclusions and recommendations for improving NAC's AEGL documents for the following chemicals and chemical classes: acrylonitrile, benzonitrile, boron tribromide, BZ (3-quinuclidinyl benzilate),

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

chloroarsenicals, chloroformates, bis-chloromethylether, chloromethylether, chlorosilanes (26 selected compounds), cyanogen, ethyl mercaptan, hexafluoroacetone, lewisites, mercury vapor, nitric acid, nitric oxide, nitrogen dioxide, nitrogen tetroxide, oleum, phenyl mercaptan, propargyl alcohol, selenium hexafluoride, silane, sulfer trioxide, sulfuric acid, tear gas, tert-octyl mercaptan, tetramethoxy silane, thionyl chloride, trimethoxysilane, trimethylbenzenes (1,2,4-; 1,2,5-;and 1,3,5-TMB), and vinyl 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: Harvey Clewell, Hamner Institutes for Health Sciences; James McDougal, Wright State University; and Judith Zelikoff, New York University.

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 author committee and the NRC.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Iris Camacho, Ernest Falke, and Robert Benson (EPA); Gary Diamond, Mark Follansbee, Lisa Ingerman, and Julie Klotzbach (Syracuse Research Corporation); and George Rusch (Honeywell International, Inc.).

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

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

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Nineteenth 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; it provided updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances for assessing acute adverse health effects.

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 emergency-response planning for potential releases of EHSs, from accidents or terrorist activities.

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

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

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

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

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; medicine, including pharmacology and pathology; industrial hygiene; biostatistics; and risk assessment.

The charge to the committee is to (1) review the proposed AEGLs for scientific validity, completeness, internal consistency, and conformance to the NRC (1993) guidelines report; (2) review NAC's research recommendations and—when appropriate—identify additional priorities for research to fill data gaps; and (3) periodically review the recommended standing operating procedures (SOP) for developing AEGLs.

This interim report presents the committee's conclusions and recommendations for improving NAC's AEGL documents for 25 chemicals**:** allyl alcohol, bis-chloromethyl ether, chloromethyl methyl ether, bromine pentafluoride, bromine trifluoride, chlorine pentafluoride, carbon tetrachloride, chloroform, chlorosilanes (26 selected compounds), epichlorohydrin, formaldehyde, hydrogen bromide, hydrogen iodide, methyl bromide, methyl chloride, nitric acid, nitric oxide, nitrogen dioxide, nitrogen tetroxide, piperidine, titanium tetrachloride, toluene, trimethylbenzenes (1,2,4-; 1,2,5-; and 1,3,5-TMB), vinyl acetate monomer, and vinyl chloride.

ACRYLONITRILE

At its meeting held on October 26-29, 2010, the committee reviewed the technical support document (TSD) on acrylonitrile. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Nonlethal effects of occupational exposure to AN [acrylonitrile] include headache, nasal and ocular irritation, thoracic discomfort, nervousness and irritability.… The AEGL-1 values were based on the absence of effects in informed human volunteer subjects (6 males) exposed for 8 hours to 4.6 ppm AN.… The 4.6 ppm value is recommended for all AEGL-1 exposure durations…. The AEGL-2 values were based upon slight transient effects in rats exposed to 305 ppm AN for 2 hours…. The AEGL-3 values were derived using 30-minute, 1-, 4-, and 8-hour $BMCL_{05}$ estimates of lethality threshold.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

The point of departure (POD) of 4.6 ppm is based on six male toxicologist volunteers 28-45 years old (Jakubowski et al. 1987). A discussion of the uncertainty associated with the POD should include considerations that the focus of this study was for the metabolism of arylonitrile, not for identifying acute toxicity. In additions, considerations should be given for the small sample size, and the male-only adult subjects.

Further, it should be clearly stated that the volunteers for the Jakubowski study were toxicologists working in the same laboratory as the lead authors, as this raises some ethical concerns. Yet, as three studies (Jakubowski, Sakurai, and personal communication) indicate a similar effect level, the committee agrees with the choice of the Jakubowski study for AEGL-1. Also see "Other Comments" regarding Page 10, lines 10-12, regarding the use of "personal communication" as supporting evidence.

Page 6, lines 13-14 (also see page 15, line 11): Since children may be more sensitive to acute inhalation, given that the POD was based on observations in adult males, the decision for not applying an intraspecies uncertainty factor (UF) to derive the AEGL-1 needs either adequate justification or revision.

Page 30, Section 5.1, Human Data Relevant to AEGL-1 (also see page 31, lines 14-35): The TSD also enlisted three ranges of occupational exposure as lending support to the proposed AEGL-1

when an intraspecies UF of 3 is applied. In addition to the inconsistent use of applying the intraspecies UF here but not for the 4.6 ppm above, additional considerations are needed for each listed range of exposure. They are listed below:

- **Page 30, line 42; page 31, line 2 and lines 18-21:** A range of 12 to 15 ppm for ocular irritation and headache in occupational exposure was based on a NAC/AEGL personal communication. However, no data are presented in TSD for review. These data need to be presented in the AN document.
- **Page 10, lines 30-42:** A range of 10 to 20 ppm was based on a survey of workers reported by Sakurai et al. (1978). The associated toxicities were headache, nervousness, fatigue, nausea, and insomnia. Some of these effects may have exceeded the threshold end points for AEGL-1 and warrant additional modification factor. Moreover, the TSD attributed additional confidence to this range of exposure because the surveyed workers were routinely exposed to AN. However, it is not clear that these end points would occur only after repeated exposure, especially since the overall data presented throughout the TSD indicate that these effects are not all cumulative with repeated exposure. In fact, the rationale for holding one AEGL-1 value for all durations of exposure would indicate otherwise.
- **Page 5, lines 5-12 (also see page 30, lines 35-37):** A third range of 16 to 100 ppm for 20-45 min was taken from Wilson et al. (1948). The associated toxicities were dull headache, fullness in the chest, mucous membrane irritation (including eyes, nose, and throat), apprehension, and nervous irritability (Wilson et al. 1948). It is not clear how all of these effects are determined to be "of greater sensitivity than the AEGL-1 definition," as stated on page 30, line 37, especially when compared with the end point for AEGL-2, for example, slight ocular and nasal irritation. Please provide additional discussion.

AEGL-2

Page 32, lines 25-26: The POD was based on a 2-h exposure to 305 ppm that resulted in slight transient ocular and nasal irritations in rats. These end points are apparently milder than the effects reported in the three sets of concentration ranges used to support the derivation of AEGL-1.

The end points of developmental toxicity and other systemic effects (e.g., hearing loss) as detailed in Other Comments should be considered together with irritation end points selected for use for the proposed AEGL-2.

Page 32, line 27-28: The meaning is unclear for the following sentence: "The interspecies uncertainty factor was limited to 3 because a non-human primate is considered a more relevant model than rodents." This statement should be supported with an explicit comparison between the two species and the humans. Then, data from the former should be used if it is a preferred species for the POD. The choice of associated interspecies UF should subsequently be justified.

Due to the lack of quality data from humans, the POD for AEGL-2 is based on data from laboratory animals. However, some of the human data may be useful for bounding the AEGL-2. For example, 60 of the 144 acute AN poisoning cases evaluated by Chen et al. (1999) were reported on page 10, line 19-21, to be from exposures at 18-258 ppm. A closer look at the publication indicates that 18 of the 60 cases were exposed at 40-79 mg/m^3 (18-36 ppm) for 1.0-3.5 h. Apparently, dizziness, headache, feebleness, and chest tightness occurred in all these cases because these effects occurred in 100% of the 144 cases. Because these effects may impair the ability to escape, it would be prudent to consider setting the AEGL-2 values below 18 ppm for up to 4 h unless adequate justification can be given to exclude this set of data.

AEGL-3

Page 33, lines 37-38: The interspecies UF was limited to 3 on the basis of the physiologically based pharmacokinetic (PBPK) model results. However, the description for the rationale is incomplete, and supporting data are insufficiently presented for its justification. Specifically, the rationale for the interspecies UF of 3 was only given later in the AEGL-3 table on page 59, that is, it "is considered sufficient to account for possible toxicodynamic/metabolism differences." This explanation should also be included here for the sake of completing the concept. Also, the Kedderis and Fennel 1996 paper from a CIIT publication was cited on page 33, line 41, as demonstrating similar AN and cyanoethylene oxide (CEO) dose metrics between humans and rats. However, no data were presented in the TSD for review, and the CIIT report cannot be located for review. More important, the results of PBPK modeling by Sweeney et al. (2003) showed that instead of being similar, the brain AN and brain and blood CEO concentrations estimated in humans are generally 2-fold higher than in rats exposed to AN at 2 ppm for 8 h or at continuous 0.4 ppm exposure. Thus, if the intraspecies UF of 3 is needed for pharmacodynamic variability, an additional 2-fold uncertainty would be needed to account for the pharmacokinetic differences.

Other Comments

The list of end points for the study by Wilson et al. (1948) was given multiple times throughout the TSD; however, they were not consistently described. Please harmonize the descriptions of this study.

Tables 2 to 7: Orient entries in these tables consistently regarding the dose or exposure level (e.g., low to high) and exposure duration (e.g., short to long).

Tables 8 to 10: Add exposure regimen "6 h/day, GD 6-15" to the table title or the footnote study citation.

Page 6, line 15, to page 7, line 2: reference citations are needed for the data mentioned

Page 10, lines 10-12 (also see page 31, lines 1-2 and lines 18-21): The TSD states "Additional reports (see NAC/AEGL, personal communication) affirmed that occupational exposure at 12 to 15 ppm resulted in ocular irritation and headache." The use of personal communication for supporting information on human exposure is not appropriate for this document unless the information is publically available. Section 2.3.2 of the Standing Operating Procedures (SOP) requires that data on humans must be "used from sources that are publicly available," (page 53). Is this study now published? If the study has since been published, please provide the appropriate reference. If it has not been published, the public source for the "NAC/AEGL personal communication" should be given in Section 9 references.

Page 10, Section 2.2, Nonlethal Toxicity: This section includes a mixture of different study types, some of which do not necessarily reflect toxicity. The first paragraph (lines 2-4) on odor threshold should not be in this section. Perhaps, it could be in the Introduction. The case studies and perhaps the epidemiologic studies also should not be in a section called Nonlethal Toxicity.

Page 11, Section 2.3, Developmental and Reproductive Effects: The presentation of developmental toxicity should be expanded to ensure adequate protection against potential developmental effects from acute maternal exposure. For example, fetal morphogenic alterations from a single maternal oral exposure during the gestation period were reported at 100 mg/kg in rats (Saillenfait and Sabate 2000) and at 80-120 mg/kg in hamsters through the intraperitoneal (i.p.) route (Willhite et al. 1981). These data are not included in the TSD arguably because they are not from inhalation studies. However, the Willhite et al. (1981) and its companion study by the same researchers were included in the propionitrile TSD. A more fundamental concern is that developmental effects are pertinent systemic toxicity end points, especially since Section 4.1(pages 27-28) indicated that AN is rapidly absorbed after inhalation exposure, with 52% to 91.5% retention. Please provide additional discussion on these issues.

Although maternal toxicity was present at fetal toxicity levels, distinction should be made between the reversibility of many observed maternal effects versus irreversibility of the developmental

effects. This distinction could affect the selection of the POD for AEGL-2 and AEGL-3. For example, in the Murray et al. (1978) study, maternal weight gain (Table 8, page 22) apparently recovered after its severe suppression of the initial two to three 6-h/day exposures (that is, 95% lower weight gain at 40 ppm and weight loss at 80 ppm). However, fetal effects of omphalocele, anterior displaced ovaries, missing vertibrae, short tail, and trunk (Table 10; page 23) are permanent.

Page 12, lines 11-13: "The authors, however, reported that the overall results supported the null hypothesis for AN-induced effects in people living in the vicinity of the AN factory." What was the actual null hypothesis? Please include this information in the TSD.

Page 15, Section 3.1, Acute Lethality and Page 20, Section 3.2, Nonlethal Toxicity: Present the animal toxicity data for lethality and nonlethal toxicity in consistent order according to the test species (e.g., monkey, rat, dog, and guinea pig,)

Page 15, lines 10-12: "Although no exposure terms are available and information is limited, children appeared to be more susceptible than adults in the same exposure conditions." If no exposure terms are available, how can one conclude that children are more susceptible than adults for the same exposure? Please provide an explanation for this statement.

Page 25, line 44: "Group II" was not specified before this point. Could this be the "Group II" mentioned in line 35?

Page 26, lines 17-18: The sentence "The increased mortality for the 20-ppm females was the result of early sacrifice due to benign mammary gland tumors" needs clarification. Did the benign tumors cause them to be moribund and warranted early sacrifice?

Page 26, lines 28- 29: "The frequency of Zymbal's gland tumors was significantly increased (11/100; $p < 0.05$) in both male and female animals…." The sentence needs revision. The incidence of 11/100 given here is only for the males, not for "both males and females"

Page 26, lines 34-36: "Based on astrocytoma incidence data reported by Quast et al. (1980), Felter and Dollarhide (1997) reported a calculated risk range from 8.5 × 10-6 to 1.1 × 10-5, which yields a 1 × 10-4 risk specific concentration of 9 $\mu g/m^3$ from chronic exposure based upon the LED_{10}." This sentence is awkward. What exposure scenario is associated with the given risk? Also, the expression "1 × 10^{-4} risk specific concentration of 9 ug/m^3" is awkward. Is this "unit risk"? If so, please use the term "unit risk".

Page 27, Table 12, Tumor Type and Incidence Data for Rats Exposed to AN Vapor: Do these data include interim sacrifices? This should be clarified so that they would not be directly used for modeling cancer potency.

Page 27, lines 2-24, Section 3.6: Reference citations are needed for the data mentioned

Page 27, lines 22-23: "Results of inhalation exposure cancer bioassays have shown that AN is carcinogenic in rat brain, spinal cord, Zymbal's gland, tongue, and nonglandular stomach." There is no report of stomach tumors in this TSD. Either delete stomach from this list or add the appropriate data into the document.

Page 29, lines 21-22: Enhanced noise-induced hearing loss was reported by Fechter et al. (2003) in rats shortly after receiving 40 mg/kg through subcutaneous injection. This systemic effect was apparently not tested through the inhalation route but should be discussed in the document and included as an end point for AEGL considerations.

Page 27, lines 30-31: "AN with absorption exhibiting a biphasic pattern….": What is a biphasic pattern?

Page 31, lines 21-22: "It is reasonable to assume that for AEGL-1 severity effects, individual variability in the response to AN would vary no more than 3-fold…." Is it reasonable to assume based on the occupational exposure studies? If so, provide a sentence to state this explicitly with appropriate justification.

Page 31, lines 25-27: "This is slightly lower than the no effect level of 10 ppm noted in the occupational exposure findings but is appropriate for the general public who may not be accustomed to acrylonitrile exposure as would workers." On the basis of what scientific evidence? The appropriate reference(s) should be provided. If references are unavailable this sentence should be deleted.

Page 32, Section 6.3, Derivation of AEGL-2 Values: The section indicates that the AEGL-2 value is based on rats (line 25), but then goes on to state, "interspecies uncertainty factor was limited to 3 because a non-human primate is considered a more relevant model than rodents, dogs or cats" (lines 27-29). This is somewhat confusing. Perhaps the justification for the UF of 3 needs to be rephrased to state "because variation was observed across the different species." Otherwise, if primate data are more relevant, why is rodent data being used to derive the AEGL-2 values?

Page 32, lines 29- 31: "The intraspecies uncertainty factor was limited to 3 because the effects associated with acute irritation effects of AN are not likely to vary greatly among individuals and because metabolism may be of limited relevance regarding such effects." What is the basis for the comment on line 31 that metabolism may be of limited relevance.

Page 34, Section 8.2, Comparisons with other Standards and Guidelines: A discussion for the 2-fold difference between the proposed 30-min AEGL-3 (180 ppm) and the corresponding immediately dangerous to life or health (IDLH) (85 ppm) is needed.

Comment References

Chen, Y., C. Chen, S. Jin, and L. Zhou. 1999. The diagnosis and treatment of acute acrylonitrile poisoning: A clinical study of 144 cases. J. Occup. Health 41(3):172-176.

Fechter, L.D., S.F. Klis, N.A. Shirwany, T.G. Moore, and D.B. Rao. 2003. Acrylonitrile produces transient cochlear function loss and potentiates permanent noise-induced hearing loss. Toxicol. Sci. 75(1):117-123.

Felter, S.P., and J.S. Dollarhide. 1997. Acrylonitrile: A reevaluation of the database to support an inhalation cancer risk assessment. Regul. Toxicol. Pharmacol. 26(3):281-287.

Jakubowski, M., I. Linhart, G. Pielas, and J. Kopecky. 1987. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br. J. Ind. Med. 44(12):834-840.

Kedderis, G.L., and T.R. Fennell. 1996. Development of a Physiologically Based Description of Acrylonitrile Dosimetry. CIIT Activities 16(1), January 1996.

Murray, F.J., K.D. Nitschke, J.A. John, A.A. Crawford, J.S. Murray, L.W. Rampy, and B.A. Schwetz. 1978. Teratologic Evaluation of Inhaled Acrylonitrile Monomer in Rats. Toxicological Research Laboratory, Dow Chemical, Midland, MI.

Quast, J.F., D.J. Schuetz, M.F. Balmer, T.S. Gushow, C.N. Park, and M.J. McKenna. 1980. A Two-Year Toxicity and Oncogenicity Study with Acrylonitrile Following Inhalation Exposure of Rats. Prepared by Toxicology Research Laboratory, Dow Chemical, Midland, MI., for the Chemicals Manufacturing Association, Washington, DC.

Saillenfait, A.M., and J.P. Sabate. 2000. Comparative developmental toxicities of aliphatic nitriles: In vivo and in vitro observations. Toxicol. Appl. Pharmacol. 163(2):149-163.

Sakurai, H., M. Onodera, T. Utsunomiya, H. Minakuchi, H. Iwai, and H. Mutsumura. 1978. Health effects of acrylonitrile in acrylic fibre factories. Br. J. Ind. Med. 35(3):219-225.

Sweeney, L.M., M.L. Gargas, D.E. Strother, and G.L. Kedderis. 2003. Physiologically based pharmacokinetic model parameter estimation and sensitivity and variability analyses for acrylonitrile disposition in humans. Toxicol. Sci. 71(1):27-40.

Willhite, C.C., V.H. Ferm, and R.P. Smith. 1981. Teratogenic effects of aliphatic nitriles. Teratology 23(3):17-23.

Wilson, R.H., G.V. Hough, and W.E. McCormick. 1948. Medical problems encountered in the manufacture of American-made rubber. Ind. Med. Surg. 17(6):199-207.

BENZONITRILE

At its meeting held on October 26-29, 2010, the committee reviewed TSD on benzonitrile. A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

Benzonitrile is a colorless liquid at ambient temperature and pressure and has an odor of volatile oil of almonds. The liquid is irritating to the skin and eyes, and the vapor is irritating to the eyes, nose, and throat…. AEGL-1 values are not recommended for benzonitrile because of insufficient data…. The AEGL-2 was based on labored breathing and poor coordination in rats exposed to 900 ppm for 3 hours…. The exposure of mice to 890 ppm for 2 hours resulting in 1/7 deaths was used as the basis of AEGL-3.

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

AEGL-Specific Comments

AEGL-1

Page 6, lines 6-9 (also see page 8, lines 5-8): "Symptoms of acute poisoning with benzonitrile are similar to those produced by other uncoupling agents, such as pentachlorophenol and dinitrophenol, and include fatigue, excessive sweating, thirst, pyrexia, anxiety, tachycardia, and hyperventilation. Symptoms may resolve on cessation of exposure. (HSDB 2003)." If these symptoms have been observed in humans, many of which are consistent with the AEGL-1 defintions, why do the authors state on page 15 that "no human data consistent with the definition of AEGL-1 were available." HSDB is a secondary source. The authors should evaluate the primary source for these data and reassess whether the AEGL-1 value can be derived. If human data are in fact unavailable, the authors should consider whether data from "other uncoupling agents" could be used to derive AEGL-1 values for benzonitrile if acute effects are indeed similar across these agents.

AEGL-2

Page 9, lines 28-39 (also see page 10, lines 29-42): In addition to poor coordination and labored breathing that occurred in rats and mice in the MacEwen and Vernot (1974) study described in Section 3.1, the authors reported the progression to prostration with an additional 30 min of exposure; that is, for 3.5 h at 900 ppm in rats and for 2.5 h in mice presumably at 700 ppm. Poor coordination and prostration data are pertinent to the derivation of AEGL-2 and should be added to the toxicity description in this section and in Table 2. However, is labored breathing an AEGL-2 end point? The TSD notes that, in mice exposed at 700 ppm for 4 h, "Congestion accompanied by edema was noted in the lungs of both exposure groups at necropsy." In humans, labored breathing may equate to respiratory failure, which in cases, depending on the severity, may not be reversible without medical intervention. Please discuss whether labored breathing may be a more appropriate end point for AEGL-3

Page 15, line 29-30 states that a 2-fold modifying factor is used to "account for the sparse data base and potential delayed hepatic effects…." Although these are pertinent reasons for using a modifying factor, other crucial considerations are missing in this discussion. It is important to note that poor coordination is an end point to be prevented at the AEGL-2 because it can impair escape. The progression into prostration with only an additional 30 min of exposure lends further support for escape impairment (see details in Other Comments below). Thus, the use of a modifying factor should be sufficient for ensuring that these overt effects will not be likely to occur. To achieve sufficiency, at least two additional factors should be considered. One factor is the incidence of poor coordination at 900 ppm. Although the frequency of occurrence is not given in the study report, it appears to be prevalent for both rats and mice under the study conditions. The other factor is the extremely steep time-response relationship, showing progression into prostration with only an additional 30 min of exposure. Taken together, the modifying factor of 2 is probably not adequate. The authors should consider a modifying factor of 3 instead.

AEGL-3

In selecting the POD at 890 ppm for 2 h that resulted in 14% fatality in mice (MacEwen and Vernot 1974), it should be noted that all 10 mice died at 700 ppm for 4 h. Of these, one died at 3.5 h of exposure. Thus, the default time-dose adjustment that brings the POD for 4 h at 445 ppm does not appear to be sufficiently low, as it is only 1.6-fold [=700/445] below a level that resulted in 100% death.

Other Comments

Cover page: Please provide the chemical structure on the title page.

The reference HSDB (2003) is cited repeatedly in the Executive Summary and throughout the document (For example, page 8, lines 5, 8, and 17). Instead of citing the summary data, it is preferable that the original literature be reviewed and cited. Use of summary data gives the false impression that research was conducted more recently than in actuality.

Page 7, Table S 1: Please indicate the exposure duration for the POD in the AEGL summary table when its concentration is mentioned

Page 9, line 38-39: The sentence "However, multifocal areas of lymphoid hyperplasia.…" is incomplete. Please revise it.

Page 12, Table 2: The following items need to be revised in Table 2:

- Inhalation Section—In the rat exposure study (1900ppm) by Industrial Bio-Test (1970), the "Effect" cell should include the following sentence "two died at 2 h after exposure, one died on day 6 postexposure" in order to clarify that two post-exposure time points are included in "30% Mortality (3/10)."
- Inhalation section—Provide information on mice effects from the MacEwen and Vernot (1974) study at the same level of detail as done for the rats, that is, indicate the irritation of extremities at the first hour of exposure, poor coordination, and labored breathing after 60-90 min. Also indicate that the one death at 890 ppm occurred on day 2.
- Oral section—Unify all entries of dose in the unit of mg/kg.

Page 10, lines 12-13: "Agaev (1977) reported the following 'lethal concentrations for one-time exposure' of benzonitrile in white rats: LC_{84} = 1,071 ppm, LC_{50} = 929 ppm, and LC_{16} = 738 ppm." Please specify that the duration of exposure for the lethal concentrations was given.

Comment References

Agaev, F.B. 1977. Experimental substantiation of the maximum allowable concentration of benzonitrile for the air of the workplace [in Russian]. Gig. Tr. Prof. Zabol. 6:34-37.

HSDB (Hazardous Substances Data Bank). 2003. Benzonitrile (CASRN 100 -47-0). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Dec. 8, 2010].

Industrial Bio-Test. 1970. Acute Toxicity Studies on Benzonitrile. Report to Velsicol Chemical Co. OTS 0571101.

MacEwen, J.D. and E.H. Vernot. 1974. Acute inhalation toxicity of benzonitrile. Pp. 77-80 in Toxic Hazards Research Unit Annual Technical Report: 1974. AMRL-TR-74-78. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.

BORON TRIBROMIDE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on boron tribromide. A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Based on the knowledge that boron tribromide hydrolyzes into hydrogen bromide, the boron tribromide AEGL-1 was based on the AEGL-1 value for hydrogen bromide…. No human or animal data on boron tribromide were available to derive AEGL-2 values. Therefore, the AEGL-2 values for boron tribromide were based on the AEGL-2 values for hydrogen bromide. For hydrogen bromide, the AEGL-2 values for the 30-minute, 1-, 4-, and 8-hour time points were based on severe nasal histopathology as well as low mortality in rats exposed to 1300 ppm hydrogen bromide or hydrogen chloride for 30 minutes…. The 10-minute AEGL-2 for hydrogen bromide was based on the RD_{50} (a decrease in the respiratory rate of 50%) of 309 ppm during a 10-minute exposure of male Swiss-Webster mice to hydrogen chloride…. No human or animal data on boron tribromide were available to derive AEGL-3 values.… The AEGL-3 values were derived by dividing the hydrogen bromide AEGL-3 values by three. The hydrogen bromide AEGL-3 values were based on 1-hour lethality data in a study with rats.
>
> A revised document should be returned to the committee for review.

AEGL-Specific Comments

AEGL-1

The committee approved the derivation of AEGL-1 values for boron tribromide.

AEGL-2

The TSD correctly notes that human and animal data were unavailable for the derivation of hydrogen bromide values. The TSD authors used hydrogen bromide values to develop AEGL values for boron tribromide "[b]ased on the knowledge that boron tribromide hydrolyzes into hydrogen bromide. The committee is concerned that the 10-min hydrogen bromide (HBr) AEGL-2 value (150 ppm), used as the basis for AEGL-2 derivation of boron tribromide, may cause escape impairment to sensitive individuals. Stavert et al. (1991) stated that there is no quantitative difference between the toxicity of hydrogen chloride (HCl) and HBr. The 10-min HBr AEGL-2 value is 50% higher than the HCl value (100 ppm). In addition, the only human data on HBr irritation shows nasal and throat irritation at 6 ppm. The HBr AEGL-2, 10-min value is 25 times the nasal irritation level in healthy humans. We do not have information about the sensory effects of HBr at these concentrations, but we do have an RD_{50} (concentration that reduces the respiratory rate by 50%) for HCl of about 300 ppm. The committee suggests using the HCl AEGL-2 values across the board for HBr AEGL derivation with a rationale for using the more robust HCl database; also mention that this database is supported by the more limited HBr database. This change would significantly affect only the 10-min HBr AEGL-2 value and subsequently the boron tribromide AEGL-2,10-min value because the other AEGL-2 values for HCl and HBr are essentially the same.

AEGL-3

The committee approved the derivation of the AEGL-3 values for boron tribromide.

Other Comments

Page 8, Table 2: Vapor pressure data should be reported in the same units (either torr or mmHg, not both). Choice of unit should be consistent across all AEGL documents.

Comment References

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.

BZ

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on agent BZ (3-quinuclidinyl benzilate). A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Data in humans did not define no-effect exposures or exposures that would result in effects consistent with the AEGL-1 definition. Therefore, AEGL-1 values for BZ are not recommended. For AEGL-2 development, a 3-fold reduction of the ICt_{50} value of 60.1 mg-min/m^3 (60.1 mg-min/m^3 ÷ 3 = 20 mg-min/m^3 or 4 mg/m^3; equivalent to 0.004 mg/L) was considered an estimate of the threshold for incapacitating effects.… Due to the lack of data regarding longer exposure durations and uncertainties regarding the effects of such exposures, AEGL-2 values for 4-hour and 8-hours were not recommended…. The AEGL-3 values for BZ were derived using 3,700 mg-min/m^3 as the point-of-departure. This is a 10-fold reduction of the LCt_{50} value for monkeys…
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

The authors should reconsider derivation of an AEGL-1 value or provide a better explanation for not deriving an AEGL-1 value. The committee finds that an AEGL-1 derivation may be possible by using the 95% lower-confidence ED_{50} (dose of a substance causing an effect in 50% of the exposed population) for Total Response Inventory (TRI) 4.0 effects in humans (page 10, Section 2.2, Nonlethal Toxicity) as an appropriate POD. If the lower-confidence ED_{50} for TRI 4 is used as a POD, please consider (a) UF = 1 for interspecies because it is based on human data; or (b)UF = 10 for intraspecies due to the range of toxic effects (primarily psychological). In considering use of the 4.0 TRI, that authors should investigate variability in the TRI data and whether the 95% CI is too low, particularly with an intraspecies UF of 10. In considering use of the 4.0 TRI, that authors should investigate variability in the TRI data and whether the 95% CI is too low, particularly with an intraspecies UF of 10.

AEGL-2

The ICT_{50} (concentration and time of an exposure that incapacitates 50% of an exposed population) is an AEGL-2 effect. The authors should consider the lower 95% confidence level of the ICT_{50} (41.3 mg-min/m^3) or, if available, the 99% lower confidence level of the ICT_{50} for AEGL-2 derivation. This is also supported by the lower 95% confidence limit (66.2 mg-min/m^3) for the ED_{50} (90.5 mg-min/m^3) for TRI 4.0 effects. The TRI 4.0 effects are mild and below those of an AEGL-2 effect.

The authors should consider using an intraspecies UF of 10. The uncertainty in dosimetric parameters seems to support an UF of 10. If the authors choose to leave the UF at 3, a better justification is needed.

Because of the short 5-min exposure period, the authors could consider dropping the 1-h value for AEGL 2. If that is done, discussion needs to be added explaining the rationale.

AEGL-3

Page 20, line 45, to page 21, line 3: "Although a 3-fold reduction of the LC_{50} (lethal concentration in 50% of exposed population) is routinely considered an appropriate estimate of the lethality threshold for chemicals with known steep exposure-response relationships (NRC 2001), little is known about the exposure-response curve for BZ. Therefore, the 10-fold reduction is considered more defensible." A 10-fold reduction deviates from the SOP. Please review SOP Section 2.2.2.3.2 for applicability. The committee recommends a 3-fold reduction from data on the most sensitive species with the most appropriate uncertainty factors. If the experimental conditions do not apply, the authors should identify a different POD.

The authors should consider using an intraspecies UF of 10. The uncertainty in dosimetric parameters and toxic end points support an UF of 10. If left at 3, better justifcation is needed.

The authors should eliminate the modifying factor. Modifying factors represent an adjustment for uncertainties in the overall database or for known differences in toxicity among structurally similar chemicals. Although not a rich database, there are no apparent uncertainties for lethality with the exception of the short durations (see comment on AEGL-3 1-h value below).

Because of the short 5-min exposure period, the authors should consider dropping the 1-h value for AEGL 3. If that is done, discussion needs to be added explaining the rationale.

Other Comments

The accepted abbreviation for the Department of the Army is 'DA'. Replace DoA with DA throughout the TSD.

Page 7, lines 18-19: What is the basis for the statement "the anticholinergic mechanism by which BZ operates is not likely to vary by an order of magnitude"?

Page 8, lines 12-13; page 10, lines 11-12. The authors cite the following reference: "Hoenig, S.L. 2007. Compendium of Chemical Warfare Agents. New York: Springer." Is this reference peer reviewed? If possible, the authors should cite the source document rather than a compendium.

Page 10, lines 23-24: The sentence "Test candidates were also selected based upon evaluation by the Minnesota Multiphasic Personality Inventory and results of psychological interviews" seems out of place. It describes how candidates were selected, while the previous sentence discusses how tests were conducted. The sentence should be placed in the appropriate context near the beginning of the paragraph.

Page 11. lines 2-3: Was there any discussion of deposition and release from clothing contributing to exposure?

Page 11, lines 5-8: "These experiments were conducted using a series of suspensions and solutions of BZ, including an acetone solution, Freon 11 suspension, methylene chloride solution, pyrotechnic mix, and a water solution." With the exception of water, all of these carriers have toxic effects. Was there any discussion of interactions with the carriers or any reason to suspect interactions?

Page 11, lines 21-34; The authors should add some discussion on ED_{50} and ICT_{50}.

Page 12, line 27: What is the basis of "regardless of exposure route"? It appears the only exposure was inhalation.

Page 18, Section 6, Data Analysis for AEGL-2: This section is very confusing due to the different units (e.g., mg/kg, µg/kg, and mg/m^3) and different end points used in comparisons. The different units also make the AEGL-2 table (page 20, Table 8) difficult to interpret relative to the text. The authors should revise this section to improve clarity.

Page 19, lines 38-40: "Data with which to assess the exposure-time relationship are not available. The experiments conducted by Ketchum and colleagues were of very short durations; 6-8 minutes of animal exposures and possibly no more than 5 minutes for the tests with human volunteers." The difference between 5 and 8 min is a wide swing when evaluating and extrapolating exposure data. This should be addressed more fully and could be a reason in selecting a modifying factor for the human data (although the duration appears to be short, it is known).

Comment References

Hoenig, S.L. 2007. Incapacitating agents: Agent-BZ. Pp. 73-76 in Compendium of Chemical Warfare Agents. New York: Springer.

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

CHLOROACETONE

At its meeting held on October 26-29, 2010, the committee reviewed TSD on chloroacetone. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> 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 corresponding AEGL-3 values; this is considered an estimate of a threshold for irreversible effects…. A 1-hour male rat $BMCL_{05}$ (lethality threshold) of 131 ppm was used as the basis of the AEGL-3 value.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

The authors concluded that data were insufficient for the derivation of AEGL-1 values. However, the Sargent et al. (1986) study in humans (discussed on page 9, lines 14-33) reported evidence for lacrimation, eye and respiratory tract irritation, all of which are typical AEGL-1 effects. Using the same data, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) has been set since 2003 at 1.0 ppm as a ceiling value. The TLVs are being used to protect the health of workers exposed during an 8-h working day. The TLV was set to prevent sensory and

respiratory irritation from chloroacetone as a direct irritant, and the value has not changed since 2003; this supports the use of Sargent et al. 1986 to derive an AEGL-1 value. Since the TLV is a human standard for a direct irritant, UFs of 1 for interspecies and intraspecies can be supported. On the basis of the TLV, the committee recommends using the 1.0-ppm AEGL-1 value for all time periods.

AEGL-2

The use of one-third of the AEGL-3 value is appropriate if there is a steep dose response. It should be so stated as part of the rationale. However, the calculated 4- and 8-h values are at or below the 8-h TLV value. Because the AEGL-3 value is calculated from the $BMCL_{05}$ (benchmark concentration with its lower confidence limit at a 5% extra risk), the data must exist to plot and calculate n.

Although 3 is generally accepted for intra- and interspecies UFs, the dermal LD_{50} (lethal dose to 50% of the exposed population) seems to indicate a systemic toxicity component in addition to the irritation (see Other Comments below). The potential for systemic toxicity needs further discussion.

While time-scaling from 1 h to 8 h is acceptable, there should be additional supporting information. Again, with the probable systemic toxicity, is time-scaling appropriate? A rationale could be that we are recommending a lower value.

The 8 h AEGL-2 (for irreversible, long-lasting adverse health effects) is half the TLV (1.0 ppm) for the same exposure period and the 4-h AEGL-2 is just above the TLV. The authors need to provide a better justification for the AEGL-2 values when workers can function at similar TLV levels.

AEGL-3

The 8-h AEGL-3 of 1.6 ppm is not even twice the TLV ceiling value of 1.0 ppm for irritation. This issue needs recognition, and the authors need additional rationale for the 8-h AEGL-3 value.

Other Comments

Chloroacetone does not exhibit typical direct-acting irritant toxicity. There is a sex difference in susceptibility (page 14 lines 33-34), and the dermal toxicity effects are not localized. Discuss how the dermal LD_{50} is supportive of direct irritation as the mechanism of toxicity. It is unlikely that the rabbits died of direct irritation of the skin. They seemed to have had systemic effects (ataxia and discharge from the mouth) that do not seem to be an outcome of direct irritation. If there are systemic effects, modify the language on mechanism of action. The values seem appropriate as evidenced by the category plots, but the rationale does not seem to be supported by the data (there appears to be more than direct irritation occurring).

Page 14, line 41-42: "Chloroacetone showed tumor-initiating potential in male and female mice.…" Is chloroacetone a cancer initiator or a promoter?

Page 9, line 6 and 10**:** Prentiss (1937) is a compendium. If possible, the authors should cite the source document rather than this compendium.

Page 17, line 23: change AEGL-3 to AEGL-2.

Comment References

Prentiss, A.M. 1937. P. 121 in Chemicals in War. New York: McGraw Hill.

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CHLOROARSENICALS

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on adamsite (DM), ethyldichloroarsine (ED), methyldichloroarsine (MD), phenyldichloroarsine (PD), and diphenylchloroarsine (DA). A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation.

AEGL-Specific Comments are provided for each individual chloroarsenical. Technical and general comments for the entire document are combined in Other Comments.

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

Adamsite

The following is excerpted from the Executive Summary of the TSD:

> Studies with human volunteer subjects affirm nasal and ocular irritation as the primary effect from short term low level exposure to DM [adamsite]…. The human experience data reported by Lawson and Temple (1922) and analyzed by Craighill and Folkoff (1922) were the most relevant for AEGL-1 development.… AEGL-2 values were developed using data … for monkeys exposed to DM at various concentration-time regimens and exhibiting various physiological/behavioral responses (hyperactivity, blinking, nasopharyngeal irritation, ocular irritation) and gross pathological effects (tracheal, bronchial and pulmonary edema).… AEGL-3 values were based upon data in monkeys.

AEGL-Specific Comments

AEGL-1

Page 7, line 46, to page 8, line 2: The authors state "Because the effects were likely of greater severity than would be considered consistent with the definition of AEGL-1 (i.e., 60-minute exposure to 0.14 mg/m^3 was a tolerance limit), the exposure concentration was reduced three-fold to approximate an exposure (0.047 mg/m^3) resulting in effects of less severity and more consistent with those associated with AEGL-1." Decreasing the concentration by one-third to determine a concentration resulting in effects of less severity is an unsual approach. How did the authors determine that the effects are less severe? The committee recommends using the data from Tables 7 and 9, which leads to a concentration of 2.2 mg-min/m^3 for tolerance. Table 7 also leads to 0.9 mg-min/m^3 for lacrimation. Either of these could be used as a lowest-observed-adverse-effect level (LOAEL) and divided by an acceptable UF (e.g., 3) to go from LOAEL to no-observed-adverse-effect level (NOAEL).

The committee recommends the following concerning AEGL-1 UFs:

- UF = 1 for interspecies because human data are used.
- UF = 3 for intraspecies. The present argument supporting UF-3 is weak. The argument should be re-stated "A UF of 3 was applied to account for individual variability" without additional explanation.

The modifying factor of 3 for LOAEL to NOAEL needs additional explanation. Evaluate different modifying factors based on the different PODs (tolerance or lacrimation) suggested above.

AEGL-2

The exposure study in monkeys (Striker et al. 1967a,b) does not address escape impairment. The authors should explore the human data (Lawson and Temple 1922) in more detail for a more appropriate AEGL-2 POD.

AEGL-3

The committee recommends using the McNamara et al. (1969) exposure concentration of 279 mg/m^3 for 46 min (12,834 mg-min/m^3) for development of AEGL-3 values. McNamara et al. (1969) is supported by Striker et al. (1967b) who had exposure to DM at 330 mg/m^3 for 40 min (13,200 mg-min/m^3).

A lower UF for intraspecies variability is typically used for direct-acting irritants. However, because the lethality studies do not indicate the cause of death, it is uncertain whether direct irritation was the cause of death. The committee recommends either of the following alternatives: (1) a UF of 3 for intraspecies variability and a modifying factor of 3 for poor quality of data and uncertainty in the mechanism of lethality; or (2) a UF of 3 for intraspecies variability and a modifying factor of 10 for poor quality of data and uncertainty in the mechanism of lethality. The choice of a modifying factor is dependent upon the author's knowledge of the data set.

Diphenylchloroarsine

The following is excerpted from the Executive Summary of the TSD:

> Data were unavailable with which to develop AEGL-1 and AEGL-2 values for DA [diphenylchloroarsine]…. Due to the quantitatively and qualitatively poor data base for DA, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended. The AEGL-3 values for DA were based upon the rat data reported in MMW (1918) which are supported by similar findings in rabbits and cats (MMW 1918).

AEGL-Specific Comments

AEGL-1

Page 9, line 27-29 (also page 22 lines 13-14, and page 42, lines 27-28): The authors conclude that the nasal irritation threshold (1.5 mg/m^3) observed in humans (Macy 1932) cannot be used for the development of AEGL-1. Although the data are sparse, it is unclear why the data cannot be used. The authors should consider using the nasal irritation threshold as the POD for AEGL-1.

AEGL-2

AEGL-2 values were developed based on AEGL-3 values. See comment for AEGL-3 regarding uncertainty and modifying factors. A change in the AEGL-3 value will affect the derivation of AEGL-2 values.

Page 9, lines 29-31: "Due to the quantitatively and qualitatively poor database for DA, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended."

This statement misleading and should be deleted because the authors chose to derive an AEGL-2 by extrapolation from AEGL-3.

There is very limited human data on DA (only the one study). The dog data is not reliable and the guinea pig is much more sensitive to irritants than humans and, therefore, this data should not be used as the basis as an AEGL-2 endpoint. Without data to base derivation on, how can escape impairment be determined? The nose and throat irritation presented in the Macy 1931 study did not provide information on how these thresholds were determined. Discuss this information in light of the AEGL-2 values being derived from 1/3 AEGL-3.

AEGL-3

A lower UF for intraspecies variability is typically used for direct-acting irritants. However, becaue the lethality studies do not indicate the cause of death, it is uncertain whether direct irritation was the cause of death. The committee recommends either of the following alternatives: (1) a UF of 3 for intraspecies variability and a modifying factor of 3 for poor quality of data and uncertainty in the mechanism of lethality; or (2) a UF of 3 for intraspecies variability and a modifying factor of 10 for poor quality of data and uncertainty in the mechanism of lethality. The choice of a modifying factor is dependent upon the author's knowledge of the data set.

Ethyldichloroarsine

The following is excerpted from the Executive Summary of the TSD:

> Data were unavailable with which to develop AEGL-1 and AEGL-2 values for ED [ethyldichloroarsine].… AEGL-2 values (10-minute, 30-minute and 1-hour only) for ED were estimated as a three-fold reduction of the AEGL-3 values…. AEGL-3 values for 10 and 30 minutes, and 1 hour were developed based on a lethality threshold estimated as a 3-fold reduction of a mouse 10-minute LCt_{50}... Limited data and uncertainties in extrapolating to exposure durations 24-fold and 48-fold greater than the 10-minute experimental time frame, preclude development of the 4-hour and 8-hour AEGL-3 values.

AEGL-Specific Comments

AEGL-1

The committee agrees that there are insufficient data at this time to derive AEGL-1 values for ethyldichloroarsine.

AEGL-2

AEGL-2 values were developed based on AEGL-3 values. See comment for AEGL-3 regarding uncertainty and modifying factors. A change in the AEGL-3 value will affect derivation of AEGL-2 values.

Page 10, line 19-21: "Due to the deficient data base for ED, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended." This statement is confusing because the authors chose to calculate an AEGL-2 value from AEGL-3 (page 10, lines 21-23). Please explain your rationale for developing an AEGL-2 if extrapolation from AEGL-3 values is not recommended.

AEGL-3

Page 10, lines 25-36: "AEGL-3 values for 10 and 30 minutes, and 1 hour were developed based on a lethality threshold estimated as a 3-fold reduction of a mouse 10-minute LCt_{50} of 1555.5 mg • min/m^3…." What is the basis for reducing the LCt_{50} by one-third to achieve a lethality threshold? In the critical effect, the NRC (2001) SOP recommends reducing the LC_{50} not the LCt_{50} by one-third. This appears to be a typographical error because Section 7.3 on derivation of AEGL-3 for ED (page 51, lines 21-23) states, "AEGL-3 values for 10 and 30 minutes and 1 hour could be developed based on a lethality threshold estimated as a 3-fold reduction of this LC_{50} (i.e., 51.8 mg/m^3)." Please correct the error.

A lower UF for intraspecies variability is typically used for direct-acting irritants. However, because the lethality studies do not indicate the cause of death, it is uncertain whether direct irritation was the cause of death. The committee recommends either of the following alternatives: (1) a UF of 3 for intraspecies variability and a modifying factor of 3 for poor quality of data and uncertainty in the mechanism of lethality; or (2) a UF of 3 for intraspecies variability and a modifying factor of 10 for poor quality of data and uncertainty in the mechanism of lethality. The choice of a modifying factor is dependent upon the author's knowledge of the data set.

Methyldichloroarsine

The following is excerpted from the Executive Summary of the TSD:

> Data were insufficient for development of AEGL-1 values or by extrapolation from AEGL-2 values…. AEGL-2 values for MD [methyldichloroarsine] were estimated as a three-fold reduction of the AEGL-3 values…. The AEGL-3 values for MD were developed using the multiple time-point dog lethality data.

AEGL-Specific Comments

AEGL-1

The committee agrees that there are insufficient data at this time to derive AEGL-1 values for methyldichloroarsine.

AEGL-2

AEGL-2 values were developed based on AEGL-3 values. See comment for AEGL-3 regarding uncertainty and modifying factors. A change in the AEGL-3 value will affect derivation of AEGL-2 values.

AEGL-3

A lower UF for intraspecies variability is typically used for direct-acting irritants. However, because the lethality studies do not indicate the cause of death, it is uncertain whether direct irritation was the cause of death. The committee recommends either of the following alternatives: (1) a UF of 3 for intraspecies variability and a modifying factor of 3 for poor quality of data and uncertainty in the mechanism of lethality; or (2) a UF of 3 for intraspecies variability and a modifying factor of 10 for poor

quality of data and uncertainty in the mechanism of lethality. The choice of a modifying factor is dependent upon the author's knowledge of the data set.

Phenyldichloroarsine

The following is excerpted from the Executive Summary of the TSD:

> Data were unavailable with which to develop AEGL-1 or AEGL-2 values for PD [phenyldichloroarsine].… The AEGL-2 values for PD were estimated as a three-fold reduction of the AEGL-3 values. The AEGL-3 values for PD were derived by assuming a 3-fold reduction of the mouse 10-minute LC_{50} of 330 mg/m^3.

AEGL-Specific Comments

AEGL-1

The committee agrees with the authors that there are insufficient data to derive AEGL-1 values for PD.

AEGL-2

Unlike the other chlorarsenicals, PD produces skin blisters. This difference needs to be discussed. The human health effects data are derived from a secondary source, and some values are predicted.

AEGL-2 values were developed based on AEGL-3 values. See comment for AEGL-3 regarding uncertainty and modifying factors. A change in the AEGL-3 value will affect derivation of AEGL-2 values.

AEGL-3

The AEGL-3 value is based on the reported median lethal dose in humans (2,600 mg/m^3), which is a predicted value; this approach may not be acceptable. Consider a benchmark calculation based on the animal data as a more appropriate method.

A lower UF for intraspecies variability is typically used for direct-acting irritants. However, because the lethality studies do not indicate the cause of death, it is uncertain whether direct irritation was the cause of death. The committee recommends either of the following alternatives: (1) a UF of 3 for intraspecies variability and a modifying factor of 3 for poor quality of data and uncertainty in the mechanism of lethality; or (2) a UF of 3 for intraspecies variability and a modifying factor of 10 for poor quality of data and uncertainty in the mechanism of lethality. The choice of a modifying factor is dependent upon the author's knowledge of the data set.

Other Comments

The TSD should show the chemical structures on the front page and again in Section 4.3.

The committee recommends restructuring the TSD animal data by chemical rather than by animal species. Doing so will support the lack of data and generally make it easier to follow the information provided.

The Executive Summary should be revised to discuss the relative potencies of the chloroarsenicals (see also comment above on AEGL-2 for PD). Discussing relative potency in the Executive Summary would be helpful to the reader.

Because the chloroarsenicals are vomiting agents, a succinct discussion of vomiting as an escape impairment needs to be provided (also see comment below for page 41, lines 5-11).

Where possible, compare the estimated AEGL values across time scales to determine whether differences in concentration × exposure time are consistent with the expected comparative toxicity of the chemicals in terms of structure-activity relationships as an additional check for reasonableness, given the sparseness of data for most chloroarsenicals.

Page 7, lines 23-25: Provide a more specific citation other than NRC (2001) for what "informed consent" means to avoid confusion with post-World War II standards. Citing the specific section and pages in the NRC (2001) report that apply to older studies would be helpful.

Page 8, lines 7-8: The statement "Available data suggest that exposure duration may be more relevant than exposure concentration with respect to DM" is not apparent from the data in Table 9 and is counter to a direct irritant. Please provide an explanation for this statement or delete it.

Page 14, line 6-7: "Although varying in their toxic manifestation and potency…." This phrase is inconsistent with the rest of the TSD, which indicates that toxic manifestation is irritation for all agents. Please clarify the discrepancy.

Page 14, lines 34- 35: "The hydrolysis of solid adamsite is generally considered negligible due to the formation of an oxide coating.…" What is the DM hydrolysis product? Show the reaction pathways in Section 4.3.

Page 31, lines 13-14: "Lethality thresholds (10-min LC_{01}) values were also calculated using the method of Litchfield and Wilcoxon (1949)." This statement is misleading. The paragraph is discussing research conducted by Wells in 1924, well before the cited method was available. Please clarify.

Page 41, lines 5-11: The paragraphs discuss "vesicant potency," "toxic vesicant-potential," and "vesicant agent" in relationship to dichloroarsines. Where did vesicant come in? Vesicants generally cause longer-term effects than indicated by the other descriptions of these agents in this document. A better explanation of why DM is a vesicant needs to be included. Only PD causes blisters as reported. DM is a vomiting agent.

Page 45, lines 7-10: Sullivan and Krieger (1992) is a compendium. If possible, the authors should cite the source document rather than this compendium. Citing the compendium gives the false impression that research was more recent than actually conducted. What is the original source?

Page 83: The category plot "Chemical Toxicity—TSD All Data Adamsite" includes data for animal deaths at exposures between AEGL-1 and AEGL-2. Please provide an explanation for lethality at AEGL-1 and AEGL-2.

Comment References

Craighill, M.D., and C.M. Folkoff. 1922. A Digest of Reports Concerning the Toxic Effect of Diphenylaminechloroarsine on Man and Laboratory Animals. EA-CD-145. Edgewood Arsenal, Aberdeen Proving Ground, MD. April 1922.

Lawson, W.E., and J.W. Temple. 1922. Report on Relation between Concentration and Limit of Tolerance for Diphenylaminochloroarsine and the Development of a Continuous Flow Apparatus for Testing. EA-CD-92. Edgewood Arsenal, Aberdeen Proving Ground, MD. January 1922 (as cited in Craighill and Folkoff 1922).

Litchfield, J.T., and F. Wilcoxon. 1949. Simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96(2):99-113.

Macy, R. 1932. Constants and Physiological Action of Chemical Warfare Agents. EATR-78. Edgewood Arsenal, Aberdeen Proving Ground, MD. July 1932.

McNamara, B.P., E.J. Owens, J.T. Weimer, T.A. Ballard, and F.J. Vocci. 1969. Toxicology of Riot Control Chemicals - CS, CN, and DM. Technical Report EATR 4309. AD0862075. U.S. Army Medical Research Laboratory, Edgewood Arsenal, Aberdeen Proving Ground, MD.

MMW (Ministry of Munitions of War). 1918. Report Upon Certain Gases and Vapours and Their Physiological Effects. London: HMSO.
NRC (National Research Council). 1984. Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Vol. 2. Cholinesterase Reactivators, Phychochemicals, and Irritants and Vesicants. 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.
Striker, G.E., C.S. Streett, D.F. Ford, L.H. Herman, and D.R. Helland. 1967a. A Clinicopathological Study of the Effects of Riot Control Agents on Monkeys. III. Diphenylaminochloroarsine (DM) Grenade. Technical Report 4070. U.S. Army Medical Research Laboratory, Edgewood Arsenal, Aberdeen Proving Ground, MD (as cited in NRC 1984).
Striker, G.E., C.S. Streett, D.F. Ford, L.H. Herman, and D.R. Helland. 1967b. A Clinicopathological Study of the Effects of Riot Control Agents on Monkeys. V. Low Concentrations of Diphenylaminochloroarsine (DM) or o-Chlorobenzylidine Malononitrite (CS) for Extended Periods. Technical Report 4072. U.S. Army Medical Research Laboratory, Edgewood Arsenal, Aberdeen Proving Ground, MD (as cited in NRC 1984).
Sullivan, J.B., and G.R. Krieger, eds. 1992. Pp. 995-999 in Hazardous Materials Toxicology: Clinical Principles of Environmental Health. Baltimore: Williams and Wilkins.
Wells, W.J.H.B. 1924. The Effect of Humidity upon the Toxicity of Methyldichloroarsine on Mice. Report No. E.A.M.R.D. 23. War Department, Chemical Warfare Service, Edgewood Arsenal, Aberdeen Proving Ground, MD. April 18, 1924.

CHLOROFORMATES

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on 13 selected chloroformates. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. Technical and general comments for the entire document are combined below in "Other Comments."

This document can be finalized when the committee comments are addressed adequately.

Methyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for derivation of AEGL-1 values for methyl chloroformate…. The AEGL-2 values for methyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The calculated 4-hour $BMCL_{05}$ value in rats (42.4 ppm) (Hoechst 1986) was used as the point-of-departure for methyl chloroformate AEGL-3 values.

Ethyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for derivation of AEGL-1 values for ethyl chloroformate…. The AEGL-2 values for methyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… One-third of the most conservative 1-hour LC_{50} value in rats (145 ppm × 1/3 = 48 ppm) (Vernot et al. 1977) was used as the point-of-departure for ethyl chloroformate AEGL-3 values.

Propyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for derivation of AEGL-1 values for propyl chloroformate.… The AEGL-2 values for propyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The calculated 1-hour rat $BMCL_{05}$ of 216 ppm (Bio-Test Laboratories Inc. 1970a) was used for deriving AEGL-3 values.

Isopropyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for derivation of AEGL-1 values for isopropyl chloroformate…. The AEGL-2 values for isopropyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values…. One-third of the 1-hour LC_{50} value in rats (300 ppm × 1/3 = 100 ppm) (Bio Test Laboratories, Inc. 1970b) was used as the point-of-departure for isopropyl chloroformate AEGL-3 values.

Allyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for allyl chloroformate.… The AEGL-2 values for allyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The calculated 1-hour rat $BMCL_{05}$ of 21 ppm (Stillmeadow Inc. 1987) was used for deriving AEGL-3 values.

n-Butyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for *n*-butyl chloroformate.… The AEGL-2 values for *n*-butyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… One-third of the concentration where 4/10 rats died after a 1-hour exposure to *n*-butyl chloroformate (200 ppm × 1/3 = 66.7 ppm) (BASF 1970) was used as the point-of-departure for *n*-butyl chloroformate AEGL-3 values.

Benzyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for benzyl chloroformate.… The AEGL-2 values for benzyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The experimental concentration causing no deaths in rats (18.6 ppm) after a 4-hour exposure (BASF 1990a) was used as the point-of-departure for benzyl chloroformate AEGL-3 values.

Phenyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for phenyl chloroformate.… The AEGL-2 values for phenyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The 4-hour rat $BMCL_{05}$ of 3.6 ppm from the combined BASF (1990b) and Hoechst (1989) studies was used as the point-of-departure for phenyl chloroformate AEGL-3 values.

2-Ethylhexyl Chloroformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for 2-ethylhexyl chloroformate.… The AEGL-2 values for 2-ethylhexyl chloroformate were based upon a 3-fold reduction in the AEGL-3 values.… The 4-hour male rat $BMCL_{05}$ of 18.1 ppm from the BASF (1985) study was used as the point-of-departure for 2-ethylhexyl chloroformate AEGL-3 values.

Ethyl Chlorothioformate

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for the derivation of AEGL-1 values for ethyl chlorothioformate.… The AEGL-2 values for ethyl chlorothioformate were based upon a 3-fold reduction in the AEGL-3 values.… An estimated 4-h rat lethality threshold of 15 ppm (1/3 the 4-hour LC_{50}: 1/3 × 45 ppm = 15 ppm) (Stauffer 1983) was used for deriving AEGL-3 values for ethyl chlorothioformate.

AEGL-Specific Comments

The committee approved the AEGL-1, AEGL-2, and AEGL-3 derivations for the selected chloroformates.

Other Comments

The references are somewhat dated (e.g., 5 years or older) and many appear to be indirect sources (e.g., HSDB, in which original data sources are older still). The authors should check the current literature to ensure that statements in the document are still valid—see Section I.8, pages I-11 to I-12; Section II.7, pages II-19 to II-21; Section III.7, pages III-13 to III-14; Section IV.7, p. IV-12; Section V.7, pages V-15 to V-16; Section VI.7, p. VI-10; Section VII.7, pages VII-13 to VII-14; Section VIII.7, pages VIII-10 to VIII-11; Section IX.7, p. IX-13; Section X.7, p. X-10; Section XI.7, pages X-11 to X-12. It would be useful to conduct a quick check of the current literature to ensure that the TSD reflects current knowledge, and that statements within each chapter are still valid.

A summary table should be added to the introductory chapter (Chapter 1: General Information for Selected Chloroformates) that lists all 12 chemicals in this class and the corresponding AEGL values for the time exposures. The authors should include relevant AEGLs to place values for chloroformates in context with chemicals for which toxicity comparisons have been made, as indicated by the fate discussion in the literature. For example, the discussion should include AEGL values and other relevant

information on phosgene, since chloroformates are formed from the reaction of phosgene with alcohols (page 12, line 11). The authors should also consider adding relevant information about hydrogen chloride (HCl) and other relevant chemicals, since chloformates hydrolyze to HCl and other parent compounds in water or moist air (page 12, lines 29-30). This information could be inserted in a new section for "Special Considerations" (often included in TSDs, e.g., see Section 4 of the TSD for mercury vapor). Also see the comment about providing these values in the combined summary table for the AEGLs. This consideration of fate products (notably HCl) may also have implications for a potential AEGL-1; see the first sentence and table in each of the executive summaries for Chapters II-XI, as well as companion text and tables for the AEGL-1 within topical sections of each chapter (e.g., Sections II.3.3, III.3.3, IV.3.3, and so on; Sections II.6, III.6, IV.6, and so on; and Appendixes A and B in each chapter: "Derivation of AEGL-1 Values" and "Derivation Summary," respectively).

Section I.1 (General Chemical and Physical Properties), pages. I-4 to I-10: This section contains very little text. More information would be useful to provide context for the summary tables and derivation of AEGLs in the subsequent chapters. In particular, it would be useful to include specific information on the fate of chloroformates (including persistence and half-life) to frame additional context regarding toxicity information for fate products that could also be present with the parent chemical within 8 h of a release. It would also be useful to highlight this specific information in Section I.5, pg. I-11 (concurrent exposure issues). Furthermore, it would be useful to check reported vapor pressures (per temperature) against nominal concentrations considered for AEGL derivations (e.g., for isopropyl chloroformate); see Section I.1, Table I-4, page I-6; and Section V.2.6, page V-11, Table V-4, and the text associated with that summary.

Page I-4, Section 1.1: Given the unusual nature of this document in addressing so many chloroformates and given the repetition of the same basic categories in the tables, the authors should consider presenting a combined table that identifies key properties across these compounds (e.g., for evaporation, flash points). It could also be informative to present such properties as a bar graph to highlight key similarities and differences.

Pages I-4 to I-10, Sections 1.1 to 1.4: These sections contain main summary tables. Additional (short) text would be useful to provide context for the summary tables. In particular, the authors should include specific information on the fate of chloroformates to frame additional context regarding toxicity information for fate products that could also be present with the parent chemical within 8 h of a release.

Section I.6, page I-11, lines 9-15: As indicated per the check of more recent literature (see the comment above), the committee suggests revisiting statements regarding the toxic effect not being expected to vary greatly between species or individuals; for example, consider animal data for isopropyl chloroformate (Section V.2, pg. V-11, Table V-4, and the text that precedes this summary).

Page I-10, lines 23-29; and Section I.7, page I-11, lines 19-27: It would seem useful to explicitly address the issue of delayed onset of pulmonary effects (and need for treatment to address severity as indicated, per human data from more recent literature; see comment above). This issue would also be useful to keep in mind in the parallel discussions for specific AEGL derivations (e.g., for Chapter XI [ethyl chlorothioformate], Section XI.4.3, pages XI-9 to XI-10).

Page III-7, lines 17-18: As indicated by the check of more recent literature (see comment above), the committee suggests addressing potential implications for humans of carcinogenicity information for ethyl chloroformate.

Page IV-8, lines 27-36: Consider using this information from standard ocular irritant testing to inform the irritant end point, as potentially providing context not only for the AEGL-1 but also for the AEGL-2. Also, consider an adjustment for this relatively reactive compound (propyl), noting that a modifying factor was used for the AEGL-3 but not the AEGL-2. (Regarding consistency in applying modifying factors within and across derivations, see the following comment.)

Page IV-11, lines 11-13; and page IV-19, AEGL-3 derivation table: The modifying factor entry is 2, with a "justification" that would also apply to a number of other compounds and other AEGLs (e.g., AEGL-2) where it has not been used. For example, consider Chapter VIII (benzyl chloroformate) and derivation summary tables on pages VIII-16 and VIII-17. We suggest checking the consistency in

how the modifying factor was or was not applied across these compounds, while ensuring adherence to the SOP, and we suggest explaining the inconsistencies or revising the applications to achieve consistency. Perhaps consider adding language to the introductory chapter to address this issue (e.g., in Section I.4).

Regarding other available benchmarks, a number of sections indicate that no (other) values have been established, a possibility that does not appear to reflect current information; for example, see page II-19, lines 13-14 (methyl); page III-13, line 10 (ethyl); page VII-10, line 16 (isobutyl and sec-butyl); page VIII-10, line 15 (benzyl); page IX-12, line 21 (phenylpage) page X-10, line 20 (2-ethylhexyl); page XI-11, line 14 (ethyl chlorothioformate). We suggest checking emergency response planning guidelines (ERPGs) (e.g., for methyl and ethyl chloroformate) and workplace environmental exposure limits (WEELs) (e.g., for benzyl, phenyl, isobutyl, sec-butyl, and 2-ethylhexyl chloroformate and for ethyl chlorothioformate) for additional information and whether the scientific bases of these benchmarks can be provided for potential insights.

Comment References

BASF. 1970. n-Butylchlorokohlensaureester-Gewerbetoxikologische Vorprufung Report No. XIX352. BASF Aktiengesellschaft, Gewerbehygienisch-Pharmakologisches Institut.

BASF. 1985. Acute Inhalation Toxicity LC_{50} for a 4-hour Exposure (Rats), Vapor Test of 2-Ethylhexyl Chloroformate. BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 8, 1985.

BASF. 1990a. Study on the Acute Inhalation Toxicity LC_{50} of Benzyl Chloroformate as a Vapor in Rats, 4-hour Exposure. Project No 13I0674/887075. BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. February 15, 1990.

BASF. 1990b. Study on the Acute Inhalation Toxicity LC_{50} of Phenyl Chloroformate as a Vapor in Rats, 4-hour Exposure. Project No 13I0675/887076. BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Ludwigshafen, Germany. January 18, 1990.

Bio-Test Laboratories, Inc. 1970a. Acute Toxicity Studies on n-Propyl Chloroformate. IBT No. A8345. Report to PPG Industries, Inc., Pittsburg, PA

Bio-Test Laboratories, Inc. 1970b. Acute Vapor Inhalation Toxicity Study with IPCF in Albino Rats. IBT No. N9129. Report to PPG Industries, Inc., Pittsburg, PA.

Hoechst. 1986. Chloroformic Acid Methyl Ester. Inhalation Toxicity in the Flow through System in Male and Female SPF Wistar Rats: 4-hour LC_{50}. Report No. 86.0432. Hoechst Pharmaceutical Research Toxicology. April 11, 1986.

Hoechst. 1989. Chloroformic Acid Phenyl Ester. Aerosol Inhalation Toxicity in Male and Female SPF Wistar Rats: 4-hour LC_{50}. Report No. 89.0761. Hoechst Pharmaceutical Research Toxicology. April 26, 1989.

Stauffer. 1983. Initial Submission: Acute Inhalation Toxicity of Ethyl Chlorothioformate in Rats with Cover Letter Dated 08/28/92. Report No. T-10712. Stauffer Chemical Company, Farmington, CT. Submitted by ICI Americas, Inc., to U.S. Environmental Protection Agency, Washington, DC. Microfiche No. OTS05384564.

Stillmeadow. 1987. Rat Acute Inhalation Toxicity: Allyl Chloroformate. Project No. 4438-86. Stillmeadow, Inc., Houston, TX, February 19, 1987. Submitted by PPG Industries, Inc., Chicago, IL, to U.S. Environmental Protection Agency, Washington, DC. Microfiche No. OTS0536028.

Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2):417-423.

CHLOROSILANES

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on 26 selected chlorosilanes. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Chlorosilanes contain one or more chlorine atoms covalently bonded to a silicon atom; the maximum Cl:Si ratio is four…. Data suggest that the acute toxicity of chlorosilanes is largely explained by the hydrogen chloride hydrolysis product…. Based on these data, and in the absence of appropriate chemical-specific data for the chlorosilanes considered in this document, the hydrogen chloride AEGLs were used to derive the chlorosilane AEGLs.
>
> This document can be finalized when the committee comments are adequately addressed.

AEGL-Specific Comments

The committee approved the AEGL-1, AEGL-2, and AEGL-3 derivations for the 26 selected chlorosilanes.

Other Comments

A recommendation in the Eighteenth Interim Report of the Committee on Acute Exposure Guidelines (NRC 2010) regarding publishing the chlorosilanes TSD with the HCl document was not intended to delay publication; it was intended for consideration at such a time as the HCl document was reviewed, revised, and reissued.

The Data Adequacy and Research Needs section as revised can serve as an excellent example of the intent for this section, as defined in the SOP on pages 53-57.

Page 15, Lines 14-22: In support of the "HCl-is-the-toxic-moiety hypothesis," the TSD discusses a 1-h LC_{50} study done with HCl. For clarity and completeness in referencing this study, the discussion should indicate that this was an unpublished study done in the same laboratory as that described in Jean et al. 2006 (see page 520, column 2 of the article).

Comment References

Jean, P.A., R.H. Gallavan, G.B. Kolesar, W.H. Siddiqui, J.A. Oxley, and R.G. Meeks. 2006. Chlorosilane acute inhalation toxicity and development of an LC_{50} prediction model. Inhal. Toxicol. 18(8):515-522.

NRC (National Research Council). 2010. Eighteenth Interim Report of the Committee on Acute Exposure Guideline Levels. Washington, DC: The National Academies Press.

BIS-CHLOROMETHYL ETHER

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on bis-chloromethyl ether. A presentation on the TSD was made by Mark Follansbee, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Bis-chloromethyl ether (BCME) is a man-made chemical that is a severe respiratory, eye, nose, and skin irritant that can lead to pulmonary edema and congestion, corneal necrosis, dyspnea, and death…. AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals. The AEGL-2 was based on a study in which rats were exposed for 7 hours to 0.7, 2.1, 6.9, or 9.5 ppm BCME, and hamsters were exposed for 7 hours to 0.7, 2.1, 5.6, or 9.9 ppm BCME, followed by lifetime observation…. AEGL-3 values were derived from the single-exposure scenario of a

study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures of 1 ppm BCME followed by lifetime observation.

The BCME document can be finalized.

AEGL-Specific Comments

The committee approved the derivation of AEGL-1, AEGL-2, and AEGL-3 values for BCME.

CHLOROMETHYL ETHER

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on chloromethyl ether. A presentation on the TSD was made by Mark Follansbee, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Chloromethyl methyl ether (CMME) is a man-made chemical that is highly flammable and a severe respiratory tract, eye, nose, and skin irritant…. AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. AEGL-2 values for technical grade CMME were based on an acute toxicity study in which rats and hamsters were exposed to 12.5-225 ppm CMME (content of BCME not given) for 7 hours and observed for 14 days…. AEGL-3 values were based on the same study as the AEGL-2 values.
>
> The CMME document can be finalized.

AEGL-Specific Comments

The committee approved the derivation of AEGL-1, AEGL-2, and AEGL-3 values for CMME.

CYANOGEN

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on cyanogen. A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> The hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. This approach is supported by cyanogen irritation in humans.… In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to derive AEGL-2 values for cyanogen.… Experimental concentrations causing no deaths in rats (McNerney and Schrenk 1960) were used as points-of-departure for the 10-minute, 30-minute, and 1-hour AEGL-3 values…. A modifying factor of 2 was applied to the 1-hour AEGL-3 value to derive the 4- and 8-hour AEGL-3 values.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

The committee approves the derivation of AEGL-1 values for cyanogen.

AEGL-2

The committee approves the derivation of AEGL-2 values for cyanogen.

AEGL-3

A 7.5-minute at 2,000 ppm from McNerney and Schrenk (1960) is used as the POD for the 10-minute AEGL-3. The committee is concerned that this POD does not adequately protect against death. In the McNerney and Schrenk study, 100% death occurred at the 2,000ppm after 15 minutes of exposure. The steepness of this dose-time-response relationship between 7.5 and 15 minutes indicates that the 2,000 ppm non-lethality for 7.5-min is not sufficient for protecting against death for a 10-minute exposure. This is further supported by the dose-time plot presented in the Figure 1 of McNerney and Schrenk's report in which "area of no mortality" was marked. A 10-minute exposure at 2,000 ppm is outside of the area of no mortality. Thus, instead of using the 7.5-min POD for 10-min, information from this plot should be used to derive a lower POD for 10 minute AEGL-3.

Other Comments

Page 8, Table S.1: The values of AEGL-1 are for *cyanide* and need to be converted to *cyanogen.*

Page 8, Table S 1: Please include the POD with its associated exposure duration and end point in this summary table

Page 14, lines 33-34: "HCN interupts celluar respiration by blocking electron transfer from cytochrome oxidase to oxygen." This statement is inaccurate. Please revise it to say "...blocking electron transfer from NADPH to oxygen, which is catalyzed by cytochrome oxidase." This statement also applies to the mechanism of toxicity for cyanide (lines 38-40). In addition, there is no slowing of metabolism but in fact increased glycolysis, lack of pyruvate utilization in the Kreb's cycle, and consequent formation of lactate, resulting in lactic acidosis. Hyperpnea also results from severe metabolic acidosis.

Page 19, Table 9: Footnote designation for MAC and MAK are mislabeled.

Comment References

McNerney, J.M., and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 21(2):121-124.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: The National Academies Press.

HEXAFLUOROACETONE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on hexafluoroacetone (HFA). A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> 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.
>
> This document can be finalized provided that the following comments are adequately addressed.

AEGL-Specific Comments

The committee approved the derivations of AEGL-1, AEGL-2, and AEGL-3 values for HFA.

Other Comments

Page 6, lines 25-27: The sentence "Testicular atrophy observed in male rats tended to be reversible upon removal from exposure and, therefore, not consistent with AEGL-2 effect severity" is incorrect and should be rewritten as "Testicular atrophy observed in male rats tended to be reversible upon removal from exposure." See related comment below (page 17, lines 8-10).

Page 17, line 4-5: The authors incorrectly state that "exposure-response data for animals regarding effects consistent with AEGL-2 severity are limited to mild or transient developmental effects in rats." As discussed on Page 17, lines 14-15, the "significant decrease in live fetuses/litter, total resorptions/litter and mean fetal weight," are neither mild nor transient effects. The statement on page 17, line 4, beginning with "exposure-response data for animals" should be deleted.

Page 17, lines 8-10: The authors incorrectly state that "testicular atrophy observed in male rats tended to be reversible upon removal from exposure and, therefore, not consistent with AEGL-2 effect severity." There are AEGL-2 effects that do not need to be irreversible: "serious, long-lasting adverse health effects" and "impaired ability to escape." The phrase "and, therefore, not consistent with AEGL-2 effect severity" should be deleted. See related comment above (page 6, lines 25-27).

LEWISITES

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on lewsites 1, 2, and 3. A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Appropriate data were not available for derivation of AEGL-1 values for lewisite-1 (L-1), lewisite-2 (L-2), or lewisite-3 (L-3)…. No inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for lewisite-1, were based upon a 3-fold reduction in the AEGL-3 values for L-1…. AEGL-2 values for L-1 were adopted as AEGL-2 values for the mixture of L-1, L-2, and L-3…. The AEGL-3 values for lewisite-1 (L-1) were based on dog lethality data…. AEGL-3 values for L-1 were adopted as AEGL-3 values for the mixture of L-1, L-2, and L-3.

A revised document should be submitted to the committee for review

AEGL-Specific Comments

AEGL-1

The committee approved the derivation of AEGL-1 values for lewisites.

AEGL-2

Page 23, lines 9-10: The TSD states that animal data were not available for deriving AEGL-2 values. The authors should consider whether the human (Ottinger et al. 1973) and animal (Gates et al. 1946) studies reporting ocular irritation and lesions on page 11, lines 19-20 (and in Table 4), and page 17, lines 28-34 (and in Table 7), can be used as the POD. The ocular irritation and lesions are an AEGL-2 impairment-of-escape effect supported by both human and animal data. The effect concentrations were 30, 150 and 600 mg-min/m^3, for rabbits, humans, and dogs, respectively. Without a modifying factor of 2 in the derivation (see comment below), the AEGL-2 values are the following:

Min	10	30	60	240	480
AEGL-2 mg-min/m^3	13	14	15	17	18
AEGL-3 mg-min/m^3	39	42	44	50	53

If a modifying factor of 2 is not used, the human ocular irritation data should be contrasted to the rabbit data and should be used in support of the AEGL-2 data. If these data are not used to support AEGL-2 values, discussion is needed in the AEGL-2 derivation section as to why this information was not used.

Page 23, lines 19-21: "Additionally, a modifying factor of 2 was applied to account for the sparse data set for effects defined by AEGL-2." A modifying factor of 2 is inappropriate for the derivation of AEGL-2. In the absence of specific data used to determine an AEGL-2 value, one-third of the AEGL-3 value was used to establish the AEGL-2 value. This approach is used when the data indicate a steep exposure-based relationship based on data for effects below the AEGL-2 value and lethal-effect value, which is the case for lewisite. Section 2.6.1 of the SOP states "Hence, the modifying factors represent an adjustment for uncertainties in the overall database or for known differences in toxicity among structurally similar chemicals." The data for AEGL-3 appears sufficient and AEGL-2 is derived from AEGL-3 in accordance with the SOP. No further modification is recommended.

AEGL-3

The committee approves the derivation of AEGL-3 values for lewisites.

Other Comments

Throughout the document the agent is commonly referred to as lewisite with no distinction on L-1, L-2, or L-3. The committee recommends renaming the document "Lewisite" and describing the

contaminants as occurring during manufacturing. Additional support for this approach is provided on page 21, lines 3-4: "The toxicity of L-2 and L-3 is reportedly comparable to L-1 (Lindberg et al. 1997)." The TSD should only note distinctions if a discussed study makes a distinction.

The SOP (pages 124-125) requires inserting parts-per-million values when milligrams-per-cubic-meter concentrations are used in the primary literature. As all the literature on lewisite is in milligrams per cubic meters, this would require extensive and distracting changes. Consider whether the intent of the SOP can be met by limited use of parts-per-million values, by including them in the AEGL values table, the Executive Summary, and the conversion values in Table 2.

The text of the TSD, in multiple locations, uses both "aerosol" and "vapor" when referring to exposures. See for example, page 10, Table 2-Conversion Factors, "aerosol atmosphere"; page 12, lines 1-7, "varying concentrations of lewisite vapor"; page 13, lines 16-22, "vapor"; and page 3, Table 4, "Summary of Data for Humans Exposed to Lewisite Vapor." Articles being summarized or quoted should be checked to ensure that the correct term is used in each case. Where the words are from the TSD's author, ensure that the term used is correct for the context. Except under controlled conditions, exposure of a civilian population is likely to be primarily to a vapor unless the source is under pressure; even then, aerosol generation is likely to include a substantial vapor component. (Please note the comment below regarding saturated vapor concentration.)

Page 8, lines 33- 34: "Exposure will be to these compounds and to potential hydrolysis products, sodium arsenite and arsenic acid." Please include the chemical formulas for sodium arsenite and arsenic acid.

Page 10, Table 2: At 25^{o}C and 1 atm: 1 mg/m^3 = 0.118 ppm, and 1 ppm = 8.48 mg/m^3.

Page 10,Table 2: During discussions at the October 26-29, 2010 meeting "volatility" was equated with "evaporation rate." However, there is no time component shown in Table 2. A brief literature search did not produce a specific definition for volatility, though it appears to be connected to vapor pressure, and the values shown are similar to the calculated saturated vapor concentration. The parameter "volatility" is not typically provided in AEGL documents, and the authors should consider removing volatility from the table since its relative importance is ambiguous.

Page 7, Table S1 and pages 22-25, Tables 9-12: Please insert the parts-per-million-equivalent values into these tables. The SOP (page 125) states "If the data are expressed in milligrams per cubic meter (mg/m^3) or other units, then state the concentration as expressed in the data source and add the ppm values in parentheses."

Page 11, lines 18-20: The source of these data is cited as Ottinger et al. 1973; however, this is not the original source. The problem with using this citation is that it gives the false impression that data was gathered more recently (1973) when testing probably occurred during World Wars I or II. Please make an effort to locate the original source and cite it accordingly in the document.

Page 15, lines 20-33 and Table 6: This paragraph outlines the findings from Armstrong et al. (1923) on dogs. Table 6 indicates that the number of dogs differs per exposure group. Please add to the text that the number of dogs differed from group to group and the reason why.

Page 15, lines 24-25: "In dogs exposed for 30-minutes or longer, frequent retching, vomiting, extreme salivation, labored breathing, inflammation of the entire respiratory tract were noted.…" Inflammation of the entire respiratory tract was probably not noted at the same time as the other clinical signs but during necropsy. The phrase regarding this information should be moved into the following sentence beginning with "At necropsy in animals.…" unless Armstrong 1923 states it differently.

Page 20, lines 6- 7: "Lewisite is readily absorbed through the mucous membranes, and because of its lipophilicity, is also readily absorbed through the skin (HSDB 2004)." Is this a primary source? This is a definitive statement that requires supporting data.

Page 20, lines 7 and 17: HSDB (2004) and Goldman and Dacre (1989) appear to be secondary references. Whenever possible, the authors should cite the primary source. If the primary source cannot be located, these citations need to be identified as secondary sources. Secondary references give the false impression that data are more recent than they actually are. In addition, they should not be given equal weighting as primary references.

Page 21, lines 12-14: "On the basis of trivalent arsenic content, lewisite was 6.5 times more toxic than the inorganic sodium arsenite, and the clinical signs and times of death and recovery differed between the compounds." Is trivalent arsenic or sodium arsenite the causative form that reacts with the thiols? If one of these compounds is not a causative agent, why include comparative toxicity?

Page 21, line 17: The sentence discusses "sodium arsenate-treated rabbits." Is this correct? If so, insert the chemical formula Na_3AsO_4, because it is not referenced elsewhere, and the preceding and following sentences are both discussing arsenite.

Page 21, lines 27-29: "This suggests that there is relatively little species variability with respect to lethal response to lewisite inhalation exposure, as would be expected for such a corrosive substance." Why is species variability expected with a corrosive substance, direct-irritant effect? This sentence needs additional explanation, as it seems counter to the arguments for direct-irritant effects among species.

Page 24, line 10-12: "Points-of-departure will be the calculated LC_{01} values: 38.7 mg/m^3 for the 10-minute value, 14.0 mg/m^3 for the 30-minute value, 7.4 mg/m^3 for the 1-hour value, 2.1 mg/m^3 for the 4-h value, and 1.1 mg/m^3 for the 8-hour AEGL-3 value." Calculations to derive these values (dog LC_{01} values) should be shown in the appendix for the derivation of AEGL-3.

Page 24, lines 13-14: This sentence discusses the application of a UF of 3 for intra- and interspecies variability. Insert a reference to Table 7 (page 19) for supporting data.

Page 24, Section 8.3, Derviation of AEGL-3: The values are reported in milligrams per cubic meter. Please include parts per million in parentheses. Using the values in Table 2 for vapor pressure and molecular weight, the conversion factors at 25ºC are 1 mg/m^3 = 0.118 ppm, and 1 ppm = 8.48 mg/m^3 (rounded). Note that the saturated vapor concentration at 25ºC, using the Table 2 values, is 3,794 mg/m^3 = 447 ppm, indicating the potential to generate concentrations much higher than the AEGL-3 values very rapidly. This potential should be noted in the TSD.

Page 25, Lines 9-11, Section 8.3 (Data Adequacy and Research Needs): Change to read: "Animal data were adequate to determine AEGL-3 values. Although most studies were dated, mouse and dog lethality … other species." Insert a new sentence: "No data were available to determine AEGL-2 values."

Appendix C: Correct the Y-axis in the category plot. Two points are labeled "0 (zero)".

Comment References

Armstrong, G.C. 1923. The toxicity of M-1 by inhalation for dogs. Chapter II in The Toxicity, Pathology, Chemistry, Mode of Action, Penetration, and Treatment for M-1 and its Mixtures with Arsenic Trichloride, Part 1. ADB954935. Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923.

Gates, M., J.W. Williams, and J.A. Zapp. 1946. Arsenicals. Pp. 83-114 in Chemical Warfare Agents and Related Chemical Problems, Vol. 1, Parts I. Summary Technical Report of Division 9. National Defense Research Committee, Office of Scientific Research and Development, Washington, DC.

Goldman, M., and J.C. Dacre. 1989. Lewisite: Its chemistry, toxicology, and biological effects. Rev. Environ. Contam. Toxicol. 110:75-115.

HSDB (Hazardous Substances Data Bank). 2004. Lewisite (CASRN 541-25-3). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Mar.15, 2004].

Lindberg, G., P. Runn, S. Winter, and A. Fallman. 1997. Basic Information on Lewisite: A Chemical Warfare Agent with Effects Similar to Mustard Gas. FOA-R-96-00238-4.5-SE. Defense Research Establishment, Division of NBC Defense, Umea, Sweden.

Ottinger, R.S., J.L. Blumenthal, D.F. Dal Porto, G.I. Gruber, M.J. Santy, and C.C. Shih. 1973. Recommended Methods of Reduction, Neutralization, Recovery, or Disposal of Hazardous Wastes, Vol. VII. Propellants, Explosives, Chemical Warfare. EPA-670/2-73-053g. National Environmental Research, U.S. Environmental Protection Agency, Cincinnati, OH.

MERCAPTANS

At its meeting held on October 26-29, 2010, the committee reviewed the TSDs on ethyl mercaptan, methyl mercaptan, phenyl mercaptan, and tert-octyl mercaptan. Presentations of the TSDs were made by Mark Follansbee, of Syracuse Research Corporation.

Ethyl Mercaptan

The following is excerpted from the Executive Summary of the TSD:

> Ethyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis…. AEGL-1 values were based on a NOEL for irritation in rabbits exposed to 10 ppm for 20 minutes.… AEGL-2 values for ethyl mercaptan were based upon a 3-fold reduction in the AEGL-3 values.… AEGL-3 values were based on a calculated LC_{01} (2250 ppm) in mice exposed to ethyl mercaptan for 4 hours.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

Page 16, line 33 (also page 7, Table S 1, and Appendix B): The POD for AEGL-1 is identified as 10 ppm, which is characterized as a NOEL for irritation in rabbits exposed for 20 min. Just prior to that (page 16, lines 28-29), this effect is characterized as "no significant effect". However, the description of the experimental results (page 13, lines 26-28) described effects at 10 ppm without characterizing their significance (e.g., author's statement to that effect). Additional information is needed to characterize these findings as a NOEL rather than a LOAEL.

Page 19, Table 9: The AEGL-1 values are higher by a factor of 2 than the occupational exposure limits shown. Some discussion in the text would be appropriate to clarify why the general population exposure is being set higher than an occupational exposure limit.

NIOSH (1978) derived sufficient quantitative information from the Katz and Talbert (1930) publication to either set or support the recommended exposure limit (REL) values. Review these references, the case report and the human experimental data to determine if an exposure-response estimate, even a rough one, can be identified to either derive an AEGL-1 based on human data or to support the values derived from animal data.

AEGL-2

Page 17, line 13: The authors report that animal data were not available for deriving AEGL-2 values. Reassess the cited literature, in particular, Fairchild and Stokinger (1958), Zieve et al. (1974), and Shibata (1966a,b) to determine whether data are sufficient to either derive values or support default values rather than rely on the default procedure. If distinct levels of exposure (which are given) cannot be equated with distinct occurrence of the effects sufficiently for AEGL value derivation or support, perhaps they can provide at least some indication of AEGL-2 effects, information that may also be helpful to the end user.

Pages 1, line 26, to Page 12, line 21: The Fairchild and Stokinger (1958) paper may have data for exposure groups that did not experience mortality; these data, if available, might be useful to identify,

as a minimum, AEGL-2 effects and possibly exposure-response relationships. For instance, page 11, lines 36-39, describes clinical signs from a study on mice, and page 12, lines 5-8, describes clinical signs from a study on rats.

Page 12, line 26 to page 13, line 13: The Zieve et al. (1974) study of 15-min exposures in rats describes central nervous system (CNS) effects that would be relevant to escape impairment. Please consider using these data in deriving AEGL-2 values. See also the comment on the Shibata study below.

Page 13, lines 21-25: The Shibata (1966b) study in rabbits describes changes in respiratory parameters for a short exposure period (1,000 ppm for 20 min). These effects may have AEGL-2 consequences for asthmatics and others with compromised respiratory systems. If ese data are otherwise acceptable, AEGL-2 values might be derived except for 4-h and 8-h time periods; alternatively, the data might be supportive of the values derived using the default procedure. Please consider these data in deriving AEGL-2 values.

AEGL-3

Page 18. lines 4-6: Regarding the selection of the data from mice as the POD for AEGL-3, it could also be noted (perhaps parenthetically) here that the mouse was the more sensitive species. This could be more fully stated in lines 10-12 when used to justify the interspecies UF of 3, with perhaps a cross-reference to Section 4.5.

Page 18, Section 7.3: The values proposed for AEGL-3 10- and 30-min values are about a factor of 4 higher than that used in Shibata (1966a). This factor is noted on page 18, lines 20-23. Elsewhere, and several times, it is emphasized that ethyl mercaptan has a steep concentration-response curve; that is, the distance between no effects and very serious effects is a relatively small increment in concentration. Derivation of the AEGL-3 values is from the 4-h lethality data time-scaled via the standard procedure. Greater confidence in the degree of conservatism of the values for short exposure periods could be provided by noting that the results of the Zieve et al. (1974) study (30,000 ppm for 15 min, no coma and loss of righting reflex) provide additional support for the protective nature of the AEGL-3 values.

Other Comments

The authors can be complimented for their excellent and critical review of the literature, their analysis of the data, and their establishment of scientifically defensible AEGLs.

Page 6, lines 36-39 and lines 43-46: "(a 4 hour exposure to 2600 ppm caused 40% lethality in mice, the 4-h mouse LC_{50} value was 2770 ppm and at 3573 ppm for 4 hours 100% of mice died; the 4-h rat LC_{01} value was 3808 ppm and the 4-h rat LC_{50} value was 4740 ppm)." This information is useful information for the derivation of the AEGL-2 and -3 values, but this parenthetical is out of place in an Executive Summary. A brief summary of these data would be good, but is not necessary. This level of detail is not appropriate for an Executive Summary. The parenthetical should be deleted or summarized.

Page 6, line 41, to page 7, line 19: This paragraph simply repeats the derivation of the AEGL-3 values from the text of the document (page 18, lines 3-31). Readers are not looking for this kind of information in an executive summary. This paragraph should be revised to summarize the information that was essential to derive the AEGL-3 values.

Page 8, Table 1: Given the data in the table, the calculated saturated vapor concentration is about 58%, indicating great potential to generate toxic concentrations very quickly in an emergency. This potential should be discussed in the TSD.

Pages 8-10, Section 2.2.1: This section discusses very small numbers (such as 0.00026 and 0.00076 ppm). The authors should consider the use of scientific notation to make comparisons easier.

Page 14, lines 38-39: "It was hypothesized that oxidation converted the thiol to the sulfide and then to the sulfone." Although it is evident from the context what the specific components of the

metabolic pathway are, the term "sulfide" can be ambiguous. Verify that Snow (1957) used the specific phrasing shown, or revise the sentence to be more specific.

Page 15, line 12: The phrase "caused an increased reduction in the mitochondria " is ambiguous. What was increased, and compared with what? Consider alternative phrasing to clarify.

Page 15, Section 4.3: Insert the Comparative Toxicity of the Mercaptans table from the tert-octyl mercaptan TSD. This table is very useful for comparing relative potency across the different mecaptan compounds.

Page 16, lines 34-37: The POD for AEGL-1 is direct irritation. UFs of 3 for both intra- and interspecies are justified based on common mechanism of action and effects that do not vary greatly (PK and PD factors), and are supported by the fact that higher values would result in AEGL-1 values at odds with information from human exposures. The following wording change is recommended: "Uncertainty factors of 3 each were applied to account for interspecies and intraspecies variability because direct-acting irritation is not expected to differ substantially between species or between individuals. These values are considered sufficient"

Page 17, lines 21-23, and page 18, lines 7-10: "(a 4 hour exposure to 2600 ppm caused 40% lethality in mice, the 4-h mouse LC_{50} value was 2770 ppm and at 3573 ppm for 4 hours 100% of mice died; the 4-h rat LC_{01} value was 3808 ppm and the 4-h rat LC_{50} value was 4740 ppm)." To improve readability, consider replacing the material in the parenthetical with a reference to Table 4, "Mortality of Mice and Rats Exposed to Ethyl Mercaptan for 4 Hours," on page 12.

Page 18, lines 17-19: "The 4-hour rat LC_{50} value for ethyl mercaptan was 4740 ppm (Fairchild and Stokinger 1958), whereas, the 4-hour LC_{50} value for hydrogen sulfide was 444 ppm (Tansy et al. 1981).]" Replace the material in square brackets with a cross-reference to Section 4.3., the comparative toxicity table.

Page 18, lines 24-30: This information repeats what is detailed in Section 4.6. Either replace with a reference to Section 4.6. (e.g., "Time-scaling was done as described in Section 4.6.") or delete Section 4.6. Having both is redundant.

Page 19, line 13: "NIOSH (1996) REL is a 15-min TWA exposure that should not be exceeded at any time during a workday." A definition of "REL" was not apparent on cursory review of the NIOSH IDLH Web site. A better source would be the NIOSH Pocket Guide to Chemical Hazards online at http://www.cdc.gov/niosh/npg/pgintrod.html. The REL is defined at the Exposure Limits link.

Page 21, lines 37-38: Van Doorn et al. is cited as the source for determining the level of distinct odor awareness, but the reference is to an unpublished report with no other source information. As cited, this reference is of limited use: Now that the 2009 version of this report has been published, the citation should be updated to Ruijten et al. (2009) (see below in Comment References for the full citation).

Page 29, Appendix D: Does this plot include the Zieve et al. (1974) data? If not, please revise the plot. In addition, a subtitle or footnote should be added saying that the decimal is lost on this log-scale plot.

Comment References

Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Katz, S.H., and E.J. Talbert. 1930. Intensities of Odors and Irritating Effects of Warning Agents for Inflammable and Poisonous Gases. U.S. Department of Commerce, Bureau of Mines Technical Paper 480. Washington DC: U.S. Government Printing Office.

NIOSH (National Institute for Occupational Safety and Health). 1978. Occupational Exposure to n-Alkane Monothiols, Cyclohexanethiol, and Benzenethiol. Criteria for a Recommended Standard DHEW (NIOSH)78-213. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1996. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLH): NIOSH Chemical Listing and Documentation of Revised IDLH

Values (as of 3/1/95)-Ethyl Mercaptan. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. August 1996 [online]. Available: http://www.cdc.gov/niosh/idlh/75081.html [accessed Dec. 13, 2010].

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH. September 2005 [online]. Available: http://www.cdc.gov/niosh/npg/ [accessed Dec. 13, 2010].

Ruijten, M.W.M.M., R.van Doorn, and A.P. van Harreveld. 2009. Assessment of Odour Annoyance in Chemical Emergency Management. RIVM Report 609200001/2009. RIVM (National institute for Public Health and the Environment), Bilthoven, The Netherlands [online]. Available: http://www.rivm.nl/bibliotheek/rapporten/609200001.pdf [accessed Dec.13, 2010].

Shibata, Y. 1966a. Studies on the influence of ethyl mercaptan upon the living body: III. Inhalation experiment of ethyl mercaptan gas in the human body [in Japanese]. Shikoku Acta Med. 22:844-850.

Shibata, Y. 1966b. Studies on the influence of ethyl mercaptan upon the living body: II. On the respiratory function and clinical findings in rabbits which inhaled ethyl mercaptan gas [in Japanese]. Shikoku Acta Med. 12:136-145.

Snow, G.A. 1957. The metabolism of compounds related to ethanethiol. Biochem J. 65(1):77-82.

Tansy, M.F., F.M. Kendall, J. Fantasia, W.E. Landin, R. Oberly, and W. Sherman. 1981. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health 8(1-2):71-88.

Van Doorn, R., M.W. Ruijten, and T. Van Harreveld. 2002. Guidance for the Application of Odor in Chemical Emergency Response, Version 2.1, August 29, 2002. Presented at the NAC/AEGL Meeting, September 2002, Washington, DC.

Zieve, L., W.M. Doizaki, and F.J. Zieve. 1974. Synergism between mercaptans and ammonia or fatty acids in the production of coma: A possible role for mercaptans in the pathogenesis of hepatic coma. J. Lab. Clin. Med. 83(1):16-28.

Methyl Mercaptan

The following is excerpted from the Executive Summary of the TSD:

Data were insufficient for derivation of AEGL-1 values for methyl mercaptan…. AEGL-2 values were based on shallow breathing and hypoactivity in mice exposed to 258 ppm methyl mercaptan for 6 hours…. AEGL-3 values were based on the calculated LC_{01} (430 ppm) for rats exposed for four hours.

A revised document should be submitted to the committee for review

AEGL-Specific Comments

AEGL-1

The committee agrees that data are insufficient at this time for the derivation of AEGL-1 values for methyl mercaptan.

AEGL-2

Page 8, line 12 to Page 9, line 2: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is not uncommon in humans and is more prevalent among African-Americans. The case report described mentions that the affected individual was G6PD deficient. If there is reason to suspect that this condition

was contributory to the outcome, assess whether the intraspecies UF of 3 is sufficient to protect more sensitive individuals.

AEGL-3

The committee approves the derivation of AEGL-3 values for methyl mercaptan.

Other Comments

The authors can be complimented for their excellent and critical review of the literature, analysis of the data and establishment to scientifically defensible AEGLs. A number of revisions have been made to this document in response to previous reviews. The authors have responded to these comments adequately.

If all the mercaptans are combined into a single document or published in a single volume, the document should include some discussion about their relative toxicities.

Page 15, lines 12-15: Nephrotoxicity, specifically a disturbance of glomerular filtration, could also explain the effects noted here and should be included in this sentence.

Phenyl Mercaptan

The following is excerpted from the Executive Summary of the TSD:

> Phenyl mercaptan depresses the central nervous system and affects the respiratory center, similar to hydrogen sulfide, producing death by respiratory paralysis…. AEGL-1 values are not recommended for phenyl mercaptan due to insufficient data. No robust data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for phenyl mercaptan were based upon a 3-fold reduction in the AEGL-3 values…. AEGL-3 values were based on a calculated LC_{01} (10.3 ppm) in rats exposed to phenyl mercaptan for 4 hours.

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

AEGL-Specific Comments

AEGL-1

The authors should reconsider whether sufficient data exist to set AEGL-1 values. Both the ACGIH TLV and the National Institute for Occupational Safety and Health (NIOSH) REL are set at 0.1 ppm (a value below the derived AEGL-2 values). The documentation of these values (the primary sources) should be reviewed to determine whether the data used would be adequate to derive AEGL-1 values. The NIOSH authors appear to have found sufficient information in Katz and Talbert (1930) to set or at least support an exposure standard. This study is also cited in the phenyl mercaptan document on page 8, lines 12-20. The Katz and Talbert publication should be reviewed in conjunction with the NIOSH criteria document to determine whether quantitative exposure-response data are present that are adequate to derive AEGL-1 and/or AEGL-2 values or to support values otherwise derived. If not, a discussion needs to be added to Section 8.2 Comparison with Other Standards and Guidelines (page 17), particularly because headache and dizziness have been reported in humans, as well as ocular, throat, and nasal irritation and some clinical signs in animals.

AEGL-2

Based on the 8-h TWA values used to control chronic occupational exposures listed in Section 8.2., the AEGL-2 values should be reassessed. These recommendations have been applied for many years without reports of adverse effects due to exposure at these levels. Although the current ACGIH value is slightly more than half the AEGL-2 value, until 2004 it was the same as the current Dutch maximum accepted concentration (MAC) value, which is almost three times the AEGL-2 value. Note also that these TWAs permit excursions above the average value: "Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded."

Although the statement is made that there were no animal data for derivation of AEGL-2 values (page 15, lines 14-15), several studies reported effects at exposure concentrations that did not cause lethality and that therefore might be useful for deriving AEGL-2 values. These studies are on (1) page 9, lines 38-41 and 44-46; (2) page 10, Table 3, first entry and lines 14-17 and 20-21; and (3) page 10, lines 31-32, and page 11, lines 1-2.

The Fairchild and Stokinger paper, items 1 and 2, should be reviewed to ensure that distinct levels of exposure (which are given) are not associated with distinct occurrence of these effects—the phrasing used in the TSD allows the opposite inference, especially given the entry in Table 3. Note that item 3, the Stauffer Chemical Company study, does cite specifics. If these data are indeed not adequate for deriving AEGL values, a more detailed explanation should be provided.

AEGL-3

The committee approves the derivation of AEGL-3 values for phenyl mercaptan.

Other Comments

Page 6, line 22, to Page 7, line 4: The Executive Summary discussion of AEGL-3 repeats the text from page 16 on derivation of the AEGL-3. The Executive Summary should briefly summarize the information essential to derive the AEGL-3 values, not repeat it verbatim.

Page 8, Table 1: Given the molecular weight and vapor pressure listed here, insert the calculated saturated vapor concentration (SVC): 1,316 ppm (5,930 mg/m^3).

Page 13-14, Section 4.3, Structure-Activity Relationships: Insert the Comparative Toxicity of the Mercaptans table from the tert-octyl mercaptan document.

Page 14, lines 18-19: "data suggest that mice and rats are of similar sensitivity with regard to lethality from inhalation." The data presented by Fairchild and Stokinger (1958) in their Table III on page 181 of the paper may be less supportive than this statement suggests. The 48-h LC_{50} values are reasonably close, but comparing the time to death values in the table would support a conclusion that mice were more sensitive, at least to the onset of effects and death, even if the ultimate result (the 15-day LC_{50}) was similar. Consider a change in phrasing to capture this distinction.

Page 15, line 17: "is considered appropriate given the extremely steep concentration-response curve." Is the slope more steep than those for other similar chemicals (e.g., tert-octyl mercaptan)? Either delete "extremely" or provide some justification for this statement.

Page 16, lines 15-19: Replace with a cross-reference to Section 4.3.

Comment References

Fairchild, E.J., and H.E. Stokinger. 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J. 19(3):171-189.

Katz, S.H., and E.J. Talbert. 1930. Intensities of Odors and Irritating Effects of Warning Agents for Inflammable and Poisonous Gases. U.S. Department of Commerce, Bureau of Mines Technical Paper 480. Washington DC: U.S. Government Printing Office.

NIOSH (National Institute for Occupational Safety and Health). 1978. Occupational Exposure to n-Alkane Monothiols, Cyclohexanethiol, and Benzenethiol. Criteria for a Recommended Standard DHEW (NIOSH)78-213. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH.

Stauffer Chemical Company. 1969. Acute Inhalation LC_{50} Study of Thiophenol in Male and Female Rats with Cover Letter Dated 05/06/94. Submitted by Zeneca Specialties to U.S. Environmental Protection Agency, Washington, DC. Document No. 86940000970. Microfiche No. OTS0557380.

Tert-octyl Mercaptan

The following is excerpted from the Executive Summary of the TSD:
Data were insufficient for derivation of AEGL-1 values for tert-octyl mercaptan. Therefore, AEGL-1 values are not recommended. In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to derive AEGL-2 values for tert-octyl mercaptan…. A 4-hour $BMCL_{05}$ value of 11.5 ppm calculated from combined female rat data (Atochem 1982) was used as the point-of-departure (POD) for AEGL-3 values. This is considered a threshold for lethality calculated from the most sensitive test animals (females).

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

AEGL-Specific Comments

The authors are complimented for their analysis of the data and establishment of scientifically defensible AEGL values, considering the sparse database.

AEGL -1

The authors should investigate the sources used by Hazardous Substances Data Base (2006), which states in the Introduction (page 9, lines 5-7) that tert-octyl mercaptan "is moderately irritating to the eyes, and may cause headache, nausea, vomiting, and central nervous system effects, resulting in dizziness, convulsions, unconsciousness, and respiratory depression." If dose and time of exposure are extractable from those sources, they should be evaluated for the derivation of AEGL-1 values.

AEGL-2

The committee approves the derivation of AEGL-2 values for tert-octyl mercaptan.

AEGL-3

The committee approves the derivation of AEGL-3 values for tert-octyl mercaptan.

Other Comments

Studies that focus on nonlethal effects are not available for some chemicals, and a database derivation of AEGL-2 values cannot be developed. The default procedure of dividing the AEGL-3 values is used in these cases, including for tert-octyl mercaptan. This procedure, however, provides no information on the types of disabling and/or escape-impairing effects that may be of concern to the end user. Another source of data may sometimes be available, however, and should be considered. Lethality studies frequently have exposure groups that have no deaths but have signs of toxicity from which they recover during the observation period and show no gross abnormalities at necropsy. These data are typically reported, and should be explored to determine their suitability either for deriving AEGL-2 values or for supporting the values obtained through the default procedure. Page 17, lines 13-18, of this TSD is a good example of the latter. A conceptually similar approach may also be useful in identifying AEGL-1 effects and deriving data-based values. This comment is offered as an observation; it is not meant to cause change in AEGL values derived for tert-octyl mercaptan. Discussion is invited to improve the AEGL development process.

Page 7, lines 14-20: This information is useful for the derivation of the AEGL-2 and -3 values, but this parenthetical is out of place in an executive summary. The first sentence of this paragraph captures the essence; a second sentence could elaborate and provide some summary data, but detailing the studies' results here is not appropriate for an executive summary.

Page 7, Lines 22-46: This paragraph repeats the derivation of the AEGL-3 values from the text of the document. It is not the kind of information expected by those who read an executive summary. This paragraph should briefly summarize the information that was essential to derive the AEGL-3 values

Page 10, Lines 28-35: "Clinical signs included respiratory stimulation, followed by CNS stimulation initially characterized by a 'threshold effect' consisting of localized minimal convulsive movements in the form of repeated facial and ear twitches. Propulsive and retropulsive thrusts of the trunk were also observed, followed by circumscribed clonic convulsions limited to the forebody and forelimbs, resulting in a sitting position while pawing in the air. This was followed by generalized clonic seizures of fore- and hind-limbs causing a loss of upright position. Exophthalmus with conjunctival congestion and salivation accompanied the seizures. Muscle relaxation, irregular labored breathing, and coma preceded death." It is not clear from the wording whether *all* exposure groups experienced the described respiratory and CNS effects. Please explicitly state if all or some of the exposure groups experienced these effects. If review of data indicates that some exposure groups did not experience symptoms, consider whether this information could be used to establish AEGL-2 values (the effects reported exceed AEGL-1). See also the first paragraph above under 'Other Comments'.

Page 10, Table 2: Are the "Seizures observed within 45 min-1.5 h; average of 2 mild seizures" the "threshold effect" mentioned in line 29? If so, this concentration should be included in the text.

Page 11, lines 9-10: "Clinical signs were noted in females at 29 ppm and above and included seizing the wire mesh bottom...." What was the concentration in males? Please include this concentration in the document or state if the concentration was not noted for males.

Page 11, lines 9-13: Since female mortality was reported at two concentrations of less than 29 ppm, were there no clinical signs noted in the animals that died? The current phrasing leads to the inference that the animals died without warning.

Page 12, line 20-21: "Clinical signs included convulsions, with females affected more frequently and with greater severity than males." Were clinical signs noted in *all* exposure groups given in lines 14-15? If not, please clarify for which exposure groups the clinical signs were observed.

Page 15, Table 7: The table titled Comparative Toxicity of Mercaptans is very useful. This table should be included in the Structure-Activity Relationship section of each mercaptan document for which it provides information, in particular ethyl-, methyl-, and phenylmercaptan documents discussed during the October 27-30 meeting.

Page 17, lines 13-18: "The AEGL-2 values are considered protective. No effects (clinical signs or mortality) were noted in male and female rats exposed to 7 ppm tert-octyl mercaptan for 4 hours

(Atochem 1982). Using the 7 ppm concentration as a POD and applying time scaling and uncertainty factors as proposed, yields 10- and 30-minute values of 1.4 ppm, a 1-h value of 1.1 ppm, a 4-hour value of 0.70 ppm, and an 8-hour value of 0.35 ppm, values slightly higher than the proposed AEGL-2 values." This discussion is instructive, but could provide more useful information on potential AEGL-2 effects. Rewording the second sentence of this paragraph as follows would indicate both the not-necessarily-lethal clinical signs of concern as well as their proximity to lethal concentrations: "An exposure of 7 ppm for 4 h produced no observable effects in either male or female rats, whereas an exposure of 12 ppm for 4 h produced both clinical effects (tremors and clonic convulsions in all exposed animals) as well as 10% mortality in female rats (Atochem 1982)." This statement does not change the POD, or the AEGL-2 values but does provide information to the end user beyond the values themselves

Comment References

Atochem (Atochem North America, Inc). 1982. Initial Submission: Final Report on a Study to Establish an LC50 Concentration of *t*-Octyl Mercaptan in Adult Sprague-Dawley Rats of Both Sexes (Final) with Attachments and Letter. Submitted to U.S. Environmental Protection Agency, Washington, DC. Microfiche No. OTS0534952.

HSDB (Hazardous Substances Data Bank). 2006. *t*-Octyl Mercaptan (CASRN 141-59-3). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Feb. 27, 2008].

MERCURY VAPOR

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on mecury vapor. A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Mercury vapor has no odor. At low concentrations, there are no sensory or irritant warning properties. Therefore, AEGL-1 values are not recommended. Although maternal exposures were for 2 hours/day for 10 days, a single 2-hour exposure of pregnant Long-Evans rats to 4 mg/m^3 mercury vapor (Morgan et al. 2002) was used as the point of departure for the AEGL-2…. The AEGL-3 values were based on a single 1-hour exposure of male Wistar rats to 26.7 mg/m^3
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

Page, 31 line 44, to Page 31, line 1: "Because there are no signs of notable discomfort or irritation at low concentrations, and studies that document asymptomatic, non-sensory effects that meet the definition of an AEGL-1 are not available, AEGL-1 values 1 are not recommended." The authors should reconsider the studies discussed on page 23, Section 4.1, and reassess whether sufficient information is available to develop AEGL-1 values. For example, consider the biokinetic studies in concert with other human data, particularly the Shelnitz study. Note that assumptions for the Shelnitz et al. study (page 31, lines 31-32) should be checked, including the inhalation rate used; scaling 20 m^3/24 h to 3/4 h may suggest a resting/sleeping rate.

AEGL-2

The committee approves the derivation of AEGL-2 values for mercury vapor.

AEGL-3

The committee is concerned about the choice of Livardjani et al. (1991) as the basis for the AEGL-3 development. The reported exposure level of 26.7 mg/m^3 at 22°C exceeds the saturation concentration of 16 mg/m^3 (page 8, Table 1). This makes the true exposure level questionable. The authors should discuss this apparent discrepancy in the TSD (no explanation was found in the Livardjani paper). One way to check whether the reported exposure concentration is reasonable would be to compare ambient air concentrations with blood concentrations in the Livardjani et al. stludy with other rat studies (e.g., Falnoga et al 1994).

Another issue with use of Livardjani et al. (1991) relates to the time-scaling up from 1-h exposures, given the steepness of the dose-response curve. That is, 20 of 32 rats died when exposed to effectively the same concentration at 2 h vs. 1 h. This concern is also mindful of the potential for delayed onset of serious effects, illustrated by the tragic death of Professor Karen Wetterhahn from diethyl mercury, for which toxicity benchmarks are of a similar order as those for mercury vapor (Witt 1991).

Other Comments

The references are fairly dated (the most recent is from 2005), and a number reflect indirect sources. For example, see Section 2 (Human Toxicity Data), page 9, lines 25-26: "Studies on the toxicity of mercury vapor have been reviewed by Friberg and Vostal (1972), EPA (1995), ACGIH (1996), ATSDR (1999), AIHA (2002), and WHO (2003)." A substantial number of other and more recent studies on mercury exposure are available, including human toxicity data. Although the document was updated in 2010, it does not appear a new literature search was conducted. The authors should check the current literature to ensure that statements in the document are still valid. In addition, updating the literature will ensure the document represents a current state of knowledge (ranging from use to toxicity to benchmarks).

Throughout the document the authors should take care in indicating adjustment for nose-only exposures; many AEGL-2 values are based on rat studies, without distinct adjustment for nose-only breathing. Uptake is only one part of toxicokinetics, as taken into account in the overall adjustment.

Page 24, lines 9-24: The TSD should more clearly state that the Sandborgh-Englund et al. (1998) study did not investigate potential health effects, only the toxicokinetics. The statement "No adverse effects were reported" on page 23, line 45, is still correct.

Page 9, Section 2 Human Toxicity Data: It would be useful to add that an acute exposure can lead to acute respiratory distress syndrome and chemical pneumonitis (see Lim et al. 1998 and Moromisato et al. 1994). It would also be useful to include more recent data (as indicated in Other Comments), also considering ocular and cardiovascular effects.

Page 9, lines 5-12: The first sentence of Section 2 on Human Toxicity, "Mercury vapor is odorless (ATSDR 1999)", (line 5) should be deleted or moved, as it does not address toxicity. Similarly, most of the text in the next paragraph (lines 7-12) does not appear to address toxicity and should be deleted or moved to a more appropriate section.

Page 9, line 15: The committee suggests deleting "corrosive" to simply read "acute bronchitis." Corrosive bronchitis is not standard or accepted clinical terminology).

Page 11, Section 2.3 Neurotoxicity: We suggest adding information from other (including more recent) literature regarding effects on the central and peripheral nervous systems, as potential context for informing AEGL derivations.

Page 12, Section 2.5 Genotoxicity: As described for Neurotoxicity above, it would be useful to add more recent information.

Page 12, lines 35-37: It is not clear what is meant by "for rats exposed in utero to 1.8 mg/m^3 during PND 2-3," given that PND is post-natal day.

Page 13, Section 2.6, Carcinogenicity: It may be helpful to provide a more recent reference (e.g., NTP's 11th Report on Carcinogens, among others). Also see Editorial Comment 5.

Page 13, lines 7-11: "The U.S. EPA identified a LOAEL for systemic effects of 0.025 mg/m^3 (0.003 ppm) for chronic (8 hours/day) exposures. The critical effects were hand tremor, increases in memory disturbance, and slight subjective and objective evidence of autonomic dysfunction. A NOAEL was not identified." Section 2.6 discusses carcinogenicity. It is not clear why these sentences are included in this section on carcinogenicity. We suggest they be discussed in a different section.

Page 29, Section 4.4.1, Species Variability: The authors should compare species variability based on additional information beyond the earlier studies cited in the TSD. A literature search to update the information may be needed.

Page 29, 35-38: "Exposure of rats during fetal development comprises a subchronic exposure.Ten days of exposure for 2 hours/day for a total of 20 hours over a 20 day gestation period (Morgan et al. 2002) comprises 4% of the rat gestational period; whereas, the same exposure scenario comprises 0.3% of the human gestation period of 270 days." The last sentence may confuse the reader. Simple time-scaling is not useful, given different windows of susceptibility for various effects. The committee suggests that the sentence is either deleted to avoid confusion or that the issue be addressed with specific context for key end points relevant to mercury vapor exposure.

Page 31, Section 4.4.4, Concurrent Exposure Issues: The authors should further discuss the implications of ethanol (ETOH) to improve the consideration of clinical consequences of joint ETOH and mercury exposure. ETOH is a very strong factor for the reduction of alveolar lining fluid levels of reduced glutathione. On the basis of that alone, one would expect mercury to be more toxic in subjects with concomitant ETOH abuse, especially habitual users.

Page 36-37, Section 8.2, Comparison with Other Standards and Guidelines: Check the text and Table 12 for consistency. For example, permissible exposure level (PEL) (page 36, line 7) and emergency exposure guidance level (EEGL) (page 37, lines 5-9) are not included in Table 12. Also, given that the ACGIH Biological Exposure Index (BEI) for creatinine in urine is identified, it would seem useful to also identify the BEI for mercury in blood. In addition, the authors should consider discussing other peer-reviewed agency benchmarks, such as the CalEPA acute reference exposure levels (RELs); the scientific bases of these values and the associated citations should be identified whenever possible. Citations are not consistently provided in the text. As a note, a considerable number of additional occupational benchmarks also exist (beyond the German and Dutch values); it would be useful to at least acknowledge that fact in the text to avoid implying that those are the only non-U.S. levels established.

Page 37, Table 12: According to the SOP (pages 124-125), data should be presented in parts per million. Given that the AEGLs (and several other values) are provided in milligrams per cubic meter, it would seem useful to also list the ERPGs and spacecraft maximum allowable concentrations (SMACs) in milligrams per cubic meter, moving the parts per million for all values into parentheses.

Page 46, line 5: "Because mercury vapor has no odor or warning properties, AEGL-1 values are not recommended." Given that odor is only one factor considered in deriving an AEGL-1, this statement is inaccurate (see similar text on page 6, lines 27-28 and Table S.1.) Please revise the sentence.

Comment References

ACGIH (American Conference of Governmental Industrial Hygienists). 1996. Mercury, all forms except alkyl. In Documentation of the Threshold Limit Values and Biological Exposure Indices, Supplement to the Sixth Ed. Cincinnati, OH: ACGIH.

AIHA (American Industrial Hygiene Association). 2002. The AIHA Emergency Response Planning Guidance and Workplace Environmental Exposure Level Guidelines Handbook. Fairfax, VA: AIHA Press.
ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological Profile for Mercury (Update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. March 1999 [online]. Available: http://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf [accessed Dec. 14, 2010].
EPA (U.S. Environmental Protection Agency). 1995. Mercury, Elemental (CASRN 7439-97-6). Integrated Risk Information System, U.S. Environmental Protection Agency [online]. Available: http://epa.gov/iris/subst/0370.htm [accessed Dec. 14, 2010].
Falnoga, I., A. Mrhar, R. Karba, P. Stegnar, M. Skreblin, and M. Tusek-Znidaric. 1994. Mercury toxicokinetics in Wistar rats exposed to elemental mercury vapor: Modeling and computer simulation. Arch. Toxicol. 68(7):406-415.
Friberg, L., and J.J. Vostal. 1972. Mercury in the Environment: An Epidemiological and Toxicological Appraisal. Cleveland, OH: CRC Press.
Lim, H.E., J.J. Shim, S.Y. Lee, S.H. Lee, S.Y. Kang, J.Y. Jo, K.H. In, H.G. Kim, S.H. Yoo, and K.H. Kang. 1998. Mercury inhalation poisoning and acute lung injury. Korean J. Intern. Med. 13(2):127-130
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METHACRYLONITRILE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on methacrylonitrile. A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> The AEGL-1 was based on transitory nasal, throat or ocular irritation in humans exposed to 2 ppm methacrylonitrile for 10 minutes…. No inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for methacrylonitrile were based upon a

2-fold reduction in the AEGL-3 values…. The loss of consciousness, with no mortality noted, in rats exposed to 176 ppm for 3 hours was used as the basis of AEGL-3.

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

AEGL-Specific Comments

AEGL-1

The authors should re-evaluate the use of the Pozzani study for the derivation of AEGL-1 values. With a very small number of subjects, which were exposed for 10 1-min periods intermittently during an 8-h exposure period (45 min between exposures), is it possible to conclude that the level for AEGL-1 remains fairly constant even after 8 h of exposure? This seems uncertain, and it provides very little information about any health effects that could arise due to a *cumulative and continuous* exposure at low levels.

AEGL-2

See the comment below for AEGL-3.

AEGL-3

Developmental end points should be considered for use in selecting the POD. Developmental effects are pertinent systemic toxicity end points for AEGL-2 and AEGL-3 (van Raaij et al. 2003, 2009). The consideration for windows of susceptibility for fetuses supports the use of NOELs from repeated dosing during organogenesis for single-day acute toxicity scenarios. This exposure is supported by the fetal effects from a single-day maternal exposure by Saillenfait and Sabate (2000). It is important to distinguish the concurrent maternal effects that are reversible from the irreversible fetal effects (e.g., embryonic or fetal resorption) when they are end points of different level of AEGL. Also, see Other Comments below regarding developmental toxicity.

When using developmental end points, the consideration for applying the typical interspecies UF of 10 (page 24, line 30) would not be constrained by the 14-ppm benchmark from Pozzani et al. (1968), which was not designed to study these end points.

Other Comments

Cover page: Please provide the chemical structure on the title page.

Page 7, Table S 1: Please include the POD with its associated exposure duration and end point in this summary table.

Page 16, Section 3.4, Developmental/Reproductive Toxicity: The presentation of developmental toxicity in Section 3.4 should be expanded. Greater detail from the study by Saillenfait et al. (1993)could provide data on the increase in mean resorption site per litter and decrease in mean live fetuses per litter at 100 ppm (6 h/day during GD 6-20). Although these effects are reported as not statistically significant, the resorption was 3-fold higher than that in the controls. Thus, the 100-ppm can be considered as close to the highest NOEL for the fetal death end point. A developmental study in rats by Saillenfait and Sabate (2000) should also be included in this section. Fetal morphogenic alterations from a single maternal oral exposure on GD 10 was reported at 150 mg/kg in rats.

Page 20, Section 4.2: The explanation regarding mechanism of toxicity is not worded correctly In fact, the uncoupling of the respiratory chain and inability to transfer electrons from NADPH to oxygen, results in reduced tissue oxygen utilization. During this time, metabolic processes continue (do not slow down as stated) and even increase, such as glycolysis. Lines 40-41 state that "oxidative metabolism may slow to a point where it cannot meet metabolic demands"; however, pyruvate cannot be utilized via the Krebs cycle, and thus is metabolized to lactate. This process generates a severe lactic acidosis, which can be fatal. Please revise this section. See Beasley and Glass (1998) for additional information.

Comment References

Beasley, D.M.G., and W.I. Glass. 1998. Cyanide poisoning: Pathophysiocology and treatment recommendations. Occup. Med. 48(7):427-431.

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van Raaij, M., P. Janssen, J. Nijhof, P. Bos, and A. Piersma. 2009. The Relevance of Endpoints in Developmental Toxicity Studies for Acute Limit Setting. AEGL June 2007 Update. RIVM (National Institute of Public Health and the Environment), Bilthoven, The Netherlands. (Presented to NAS/AEGL Committee on October, 2009).

NITROGEN DIOXIDE, NITROGEN TETROXIDE, AND NITRIC OXIDE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on nitrogen dioxide (NO_2), nitrogen tetroxide (N_2O_4), and nitric oxide (NO). A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Since NO_2 is the most ubiquitous and the most toxic of the oxides of nitrogen, AEGL values derived from NO_2 toxicity data are considered applicable to all oxides of nitrogen.… For AEGL-1 a concentration of 0.5 ppm was adopted for all time points. Although the response of asthmatics to NO_2 is variable, asthmatics were identified as a potentially susceptible population…. Human data were also used as the basis for AEGL-2. Three healthy male volunteers experienced definite discomfort from exposure to 30 ppm for 2 hours…. AEGL-3 values were based on animal data and supported by a human case report. Exposure of monkeys to 50 ppm for 2 hours was used to derive the AEGL-3 values.
>
> This document can be finalized.

AEGL-Specific Comments

The committee approves the derivation of the AEGL-1, AEGL-2, and AEGL-3 values for NO_2, N_2O_4, and NO.

PROPARGYL ALCOHOL

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on propargyl alcohol. A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> The AEGL-1 values for propargyl alcohol were based upon a 6-hour exposure to 25.3 ppm which was without significant effects based upon histological assessments.… Because exposure of mice to 88 ppm, 6 hours/day 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 $BMCL_{05}$ of 573 ppm (2-hour exposure) derived from mouse lethality data reported by Stasenkova and Kochetkova (1966) was selected as the POD for AEGL-3 derivation.
>
> This document can be finalized provided that the following comments are adequately addressed.

AEGL-Specific Comments

The committee approves the derivation of AEGL-1, AEGL-2, and AEGL-3 values for propargyl alcohol.

Other Comments

Page 9, Table 1: Given the values in the table, the calculated saturated vapor concentration is about 15,800 ppm at 20°C (see Perez and Soderholm 1991). This would be a useful addition to the table, with the potential to generate very high concentrations relative to the AEGL-3 values noted in the derivation section.

Page 32, Appendix B: This is a good write-up, but it is primarily background material that is also found in the SOP. The essential information, that there are no data to calculate n, so the default time-scaling procedure is used, is also presented in the text. Appendix B adds nothing of value and can be deleted.

Comment References

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.

Stasenkova, K.P., and T.A. Kochetkova. 1966. Toxicological characteristics of propargyl alcohol [in Russian]. Toksikol. Novykh. Prom. Khim. Veshchestv. 8:97-111.

SELENIUM HEXAFLUORIDE

At its meeting held on October 26-29, 2010, the committee reviewed theTSD on selenium hexafluoride. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> 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.

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

AEGL-Specific Comments

AEGL-1

Page 14, lines 26-28: "The limited data of Kimmerle (1960) suggest that the acute toxicity of selenium hexafluoride is similar among rabbits, guinea pigs, rats, and mice. This would be expected for a corrosive/severely irritating chemical." Is selenium hexafluoride a direct irritant or a systemic toxicant? AEGL-1 values are time-scaled (page 15, lines 38-43), but common practice for direct-acting irritants is to maintain a constant concentration across all time (see interim report 16 discussion of Sensory Irritants on pages 35-36) . Please address the time-scaling issue and provide supporting rationale within the TSD.

AEGL-2

Page 18, Table 8: The 8-h AEGL-2 (0.028 ppm) is lower than the Occupational Health and Safety Administration (OSHA), NIOSH, and ACGIH occupational standards (all three adopted 0.05ppm). Please discuss and provide justification for this difference.

AEGL-3

The committee approves the derivation of AEGL-3 values for selenium hexafluoride.

Other Comments

Throughout the document, change "selenium moiety" to "selenium and selenium compounds."

Page 11, line 23: The statement "No information on human exposure was available" appears inaccurate because of the human exposure information on page 13, lines 37-40 (see comment below) Which is true? The statement should be revised to say that there are no concentration data associated with exposure outcomes.

Page 13, lines 37-40: "Acute exposure to selenium oxide fumes causes headache, burning sensation of the nostrils accompanied by sneezing and dizziness, bronchospasm, and severe dyspnea. Symptoms of metal fume fever are noted approximately twelve hours post-exposure, followed by prolonged bronchitis and pneumonitis." Where is this information coming from? Please provide the appropriate reference(s) for this information.

Page 13, lines 44-47: "The exact mechanism of toxicity of selenium and selenium compounds, including the selenium oxide hydrolysis product, is unknown …One possible mechanism for systemic selenium toxicity is an effect on enzyme activities either by inactivation of sulfhydryl enzymes, interference of glutathione metabolism, or substitution for sulfur in biomolecules." Is there any reason to suspect systemic toxicity rather than point of entry effects? This would seem to be of concern from more long-term, low-concentration exposures than from an acute exposure.

Page 14, lines 37-39: "Individuals under stress, such as those involved in emergency situations and those engaged in physical activity, will experience greater selenium hexafluoride deposition and

pulmonary irritation than individuals at rest." This is an obvious statement and does not need to be stated. Please delete it.

Page 17, lines 17-18, and page 18, lines 36-37: "A modifying factor of 3 will be applied to account for potential effects of the selenium moiety and the sparse database." The database for selenium hexafluoride has a lot more information than others where we have, appropriately, not used a modifying factor of 3. As noted on page 13, line 5, only one animal study addresses selenium hexafluoride exposure, but the study included multiple animal species and multiple exposure concentrations. The authors should reword the justification for a modifying factor, as "a modifying factor of 3 will be applied to account for potential effects of selenium and selenium compounds."

Page 19, Section 9 References: Please correct the ACGIH references. The organization's name is the American Conference of Governmental Industrial Hygienists.

Comment References

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

NRC (National Research Council). 2009. Sixteenth Interim Report of the Committee on Acute Exposure Guideline Levels. Washington, DC: The National Academies Press.

SILANE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on silane. A presentation on the TSD was made by Mark Follansbee, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Silane can ignite spontaneously in room air and can cause explosions making it difficult to conduct studies safely. AEGL -1 values were determined from a study in which male mice were exposed to 1000 ppm silane for 1, 2, 4 or 8 hours. The NOAEL for irritation was 1,000 ppm.…AEGL-2 values were derived from a 4 hour acute inhalation study in mice.… AEGL-3 values were based on a 4 hour mouse inhalation study; 5000 ppm was the concentration that induced irreversible microscopic renal lesions and was the no-effect level for lethality.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

Page 14, lines 22-24: "While this is a gas with suspected irritating properties as demonstrated in mouse stuides, it also has a distinct repulsive odor, which would likely limit exposure, thus decreasing the possibility for substantial inhalation." AEGL-1 values (10 min, 30 min, and 1 h) were set based on a mouse irritation study; however, the "repulsive odor" most likely would be the driver for AEGL-1. The definition for AEGL-1 includes "notable discomfort", but without odor data or quantitative human information, AEGL-1 values cannot be derived. The committee suggests that AEGL-1 values be identified as "not recommended" across all time points.

AEGL-2

The committee approved the derivation of AEGL-2 values for silane.

AEGL-3

The committee approved the derivation of AEGL-3 values for silane.

Other Comments

Page 5, lines 25-26: "At the next higher concentration, 5000 ppm, renal lesions were noted after both the two day and two week observations, making 2500 ppm the NOEL for irreversible effects at 4 hours." Please clarify that at 5,000 ppm, no reversibility was observed *during the 2-week observation period*, rather than call the renal lesions "irreversible".

SULFURIC ACID, OLEUM, AND SULFUR TRIOXIDE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on sulfuric acid, oleum, and sulfur trioxide. A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary and Introduction of the TSD:

> In essence, the health effects of sulfuric acid are related to the direct irritation of the respiratory tract…. The AEGL-1 values are based on respiratory irritation observed in many human volunteer studies at concentrations higher than 0.2 mg/m^3…. The AEGL-2 values are based on the absence of severe or disabling acute effects in the large number of experimental human volunteer studies as well as in the available occupational studies…. The AEGL-3 values are based on animal data, in the absence of human lethality data…. The acute health effects of sulfuric acid (H_2SO_4), sulfur trioxide (SO_3), and oleum are discussed in one TSD because sulfur trioxide and oleum are converted to sulfuric acid at ambient conditions.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

Although the values for all three AEGL levels appear to be reasonable, the rationale that the authors used to reach these numbers is not well-justified and, in some cases, not correct. The authors need to revise the rationale for the issues outlined in Other Comments below.

Other Comments

The rationale of citing only three air-pollution epidemiologic studies in this Interim TSD is not clear. There are many similar studies that were applicable to the derivation of AEGLs that need to be included for discussion.

The number of human subjects participating in sulfuric acid studies exceeds 1,000. However, only the results of 96 healthy and 85 asthmatic subjects were summarized in the Interim TSD. Justification is needed to explain why other studies were excluded. Perhaps a summary of the other studies needs to be included. Notably missing studies are Utell (1983) and Koenig (1983).

Page 4, lines 7-6: "The author linked these increases to the high ambient sulfur trioxide concentrations...." Please clarify whether the ambient sulfur trioxide concentrations resulted from accidental release or persistent industrial effluent. This case report could be relevant to AEGL development if sulfur trioxide release was accidental.

Page 4, lines 37-39: The authors describe the studies as of "adequate quality" (line 39) which suggests that these studies are acceptable, but could have been conducted or reported in a better manner. Is this the intention of the authors? If the studies were well-conducted, they should be described as "high quality."Also, it is unclear why these specific studies were described in such detail (page 4, line 42- page 6, line 49), particularly if they are only of "adequate" quality. The authors should consider providing an overview summary of the data in the tables. For example, say that exposures for x to y hours at concentrations of a to b did not affect PFT in normal adults, and so forth. Perhaps consider moving Section 2.7 to this discussion.

Page 5, lines 47-51: Please revise the description of the Linn et al. study (1989) to say that the particles were fog particles and hypo-osmotic. They were not regular acid droplets.

Page 7, lines 19-23: "There was a significant difference in the incidence of chronic bronchitis/chronic bronchial asthma between the workers and controls. The VC was not affected by exposure. The FEV_1 decreased by 82 ml (an estimated decrease of 2%) during the shift of exposed workers, but this decrease is small compared to the normal diurnal variation in FEV_1 of approximately 10%." The authors should distinguish functional change in a population vs. individual change. Since diurnal variation or other variations most likely occurred in both the control and exposed groups, a small, statistically significant change when compared with the controls should be treated as relevant, even though physiologically, it may not be important.

Page 7, lines 25-37: Could the lack of effect be due to the healthy worker effect? Also, larger particles are not effective in inducing pulmonary toxicity. Hygroscopic growth would probably result in these particles being deposited in the nasopharyngeal region, not deep in the conducting or respiratory airways. It is a mistake to use the results of fog acid particle studies to say that size is not a factor. Those fog particles are hypo-osmotic and contain little acid. If left in dry air, they will become submicrometer in size. The larger particles found in the lead acid plants were more likely to be concentrated acid and to absorb water vapor readily.

Page 27, lines 8-10: Epidemiologic studies of acid aerosol should be a separate section or not discussed at all. For other epidemiologic studies, see Chen et al. (2007) (full citation provided below).

Page 27, lines 37-46: These two paragraphs are confusing. They include assessments of both epidemiologic studies in the general public and occupational studies without distinguishing which of these demonstrated associations between sulfuric acid exposure and cancer. Please revise this section to make it clear whether both types of studies demonstrated a causal relationship or whether a relationship is observed in just one type of study.

Page 28, lines 17-19: "Studies examining lung function in healthy and asthmatic individuals found statistically significant alterations in several parameters.... However, the magnitude of the alterations were within normal variation." These sentences do not make sense. If the changes were within normal variation than how can they be statistically significantly associated with acid exposure? Please clarify.

Page 27, lines 19-25: "However, the magnitude of the alterations were within normal variation. For FEV_1, changes of less than 12% in an individual are not considered clinically significant (Pellegrino et al. 2005). Measurements of airway resistance and conductance have a relatively poor reproducibility (Tattersfield and Keeping 1979). Hruby and Butler (1975) reported a diurnal variation of 40% of the mean for SRAW readings for a group of 6 subjects; Tattersfield and Keeping (1979) reported that other studies have found 12-17% variation in day-to-day readings. Thus, changes in SRAW and SGAW of less

than 20% were considered to be within the range of normal variation." Clinical significance is more applicable to assessment of whether an adverse effect is meaningful for an individual subject. However, in control studies, statistical significance should be treated differently (see above).

Page 28, line 32-33: "Conflicting results between individual studies may have been due to differences in the tracer aerosol particle size (Spektor et al. 1989)" This comment is misleading. Tracer particle size differences may have resulted in different studies measuring clearance from different regions of the respiratory tract. Please revise this comment.

Page 28, line 34-35: "The increased mucociliary clearance observed at lower sulfuric acide concentrations may be due to subthreshold irritation...." What is subthreshold irritation? If exposure resulted in a change in some function, how can it be subthreshold? In addition, both increased and decreased clearance indicates an effect, and the justification for excluding increased clearance rate is not valid.

Page 28, lines 40-46: This section describes the results of occupational studies, and the comment that "the concentrations in these studies would not induce severe short-term toxic effects or impair the subjects' ability to escape" is misleading. In general, the particle size of the acid in occupational settings would be much larger than that during some exposure to the general population. Thus, there could be short-term effects at some of these occupational concentrations with smaller-sized acid particles. Please revise this section to discuss possible toxicity caused by smaller-sized particles.

Page 45, Section 4.2: There were studies that investigated how sulfuric acid affects intracellular pH regulation that may be relevant to cellular function and macrophage phagocytosis and may be applicable to physiologic change.

Page 46, lines 33-39: The Interim TSD dismissed many studies using guinea pigs as an animal model. Although it is debatable to dismiss guinea pigs as a super-sensitive model not applicable to humans (including those who have asthma), some studies that had used this species to investigate the effect of particle size and mechanisms should be included. It is possible that a super-sensitive human population exists and could respond to sulfuric acid similar to guinea pigs. Better justification is needed to exclude data derived using guinea pig.

Page 49, line 20-48: The authors dismiss several controlled clinical studies with changes that were smaller than "normal" physiologic range. The "normal" physiologic range that was measured during routine medical examinations and would be influenced by many factors—environment where these measurements were taken, environmental factors that subjects experienced prior to these measurements, and other host factors. However, in controlled clinical studies, many of these factors were minimized, and any changes seen that were different from the controls' changes should be taken as changes induced by the exposure. Furthermore, even though the changes from the controls were not clinically significant, changes in respiratory parameters over a control group have significance because there must be a mechanistic influence caused by exposure that leads to these changes. The document should be revised to reflect these comments.

Page 49, line 26, to page 55, line 2: "Although some conflicting results have been reported, increases in mucociliary clearance have generally been observed at exposures of 0.1 to 0.5 mg/m^3; increase in clearance, which is likely due to subthreshold irritation, was not considered an AEGL-1 effect" The change in mucus clearance produced by sulfuric acid is similar to that produced by cigarette smoke exposure, that is, low-concentration accelerated clearance and high-concentration retarded clearance. Both types of change should be considered irritant effects. Mucus clearance is a sensitive end point, and changes in this parameter have been shown to be reproducible (rather than erratic as described in the Interim TSD) across species in response to such irritants as sulfuric acid aerosol and cigarette smoke. The concentrations that elicit changes in mucus clearance should be included in the derivation of AEGLs.

Page 50, line 34: "However, this termination does not necessarily reflect an impaired ability to escape." Perhaps if the exposure continued for a bit at this concentration, there would be impaired ability to escape. This sentence should be revised to reflect this possibility.

Page 50, line 36: "Occupational data indicate that workers can complete their normal work shifts at sulfuric acid concentrations of 26-25 mg/m^3 (El-Sadik et al. 1972),". This statement is not relevant and should be deleted. The particle size in this study is large and not relevant to real-world exposure scenarios.

Page 51, line 20: "The results of the study by Linn et al. (1989) do not provide an adequate point of departure for AEGL-2 because of the worst case exposure conditions and because the termination by some of the subjects was due to sub-AEGL-2 effects:" The authors note that four asthmatic subjects in the Linn study could not complete one or more of the exposures (page 6, lines 25-27). Although control conditions (exercise) also produced symptoms in asthmatic subjects, it is not clear whether these four subjects completed all exercise period during the control experiments. If the four subjects were able to complete the control experiments, but not the acid exposures, the Linn study is very relevant to setting AEGL-2 values. Please clarify which experiments the four were able to complete.

Page 52, Section 6 (Data Analysis for AEGL-2): The authors dismiss the notion that the size of sulfuric acid particles can be a factor in toxicity, and cited Linn et al. (1989) as evidence. Citing Linn's study to say size is not relevant is not correct. There are many studies that showed that size matters, especially for sulfuric acid. Linn et al. (1989) was investigating acid fog particles with particle sizes ranging from 1 to 20 μm, however, these particles need to be produced at 100% relative humidity to maintain their size and would be very different from those produced in the acid battery plants where up to 20-μm size particles were present. Particles in the Linn study were also hypo-osmotic, which produced very different effects from those of normally hyper-osmotic sulfuric acid droplets. It is not only inappropriate to use industrial exposure to extrapolate to exposure to the general public, it is very difficult to conclude that particle size has no effect. Those particles measured in the battery plants would have grown to even larger particles and would be deposited on the upper airway without ever reaching the lower airways. There were several studies specifically investigating particle size, and these studies need to be included in this document. Discussions of size-dependent toxicity of sulfuric acid aerosol should reference Lippmann et al. (1987) (full citation provided below).

Page 52, lines 36-37: "... no irreversible or disabling effects were observed follwing acute exposure to 20.8 mg/m^3 for 30 minutes or 39.4 mg/m^3 for 60 minutes (Sim and Pattle 1957)." The issue of particle-size differences is not addressed at all, and it can make a significant difference when setting the AEGL. If the size is large, most deposition would be in the upper respiratory tract, and this factor could have less impact on escape potential than deposition in the lower tract, especially for those who have asthma.

Comment References

Chen, L.C., G.D. Thurston, and R.B. Schlesinger. 2006. Acid aerosols as a health hazard. Pp. 111-161 in Air Pollution and Health, J. Ayres, R.L. Maynard, and R. Richards, eds. London: Imperial College Press.

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

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Spektor, D., B.M. Yen, and M. Lippmann. 1989. Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. Environ. Health Perspect. 79:167-172.
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Utell, M.G., Morrow P.E., Speers D.M., Darling J., and R.W. Hyde. 1983. Airway responses to sulfate and sulfuric acid aerosols in asthmatics. An exposure-response relationship. Am. Rev. Respir. Dis. 128(3):440-450.

TEAR GAS

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on tear gas. A presentation on the TSD was made by Lisa Ingerman, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> The AEGL-1 values were based on human exposure to 1.5 mg/m^3 for 90 minutes (Punte et al. 1963). All four subjects could tolerate the exposure, but experienced eye and nose irritation and headache…. The AEGL-2 values were based on human exposure to 1.5 mg/m^3 for 90 minutes (Punte et al. 1963). All four subjects could tolerate the exposure, but experienced eye and nose irritation and headache…. AEGL-3 values were based on the threshold for lethality at each AEGL-3 exposure duration calculated using the probit-analysis based dose-response program.
>
> A revised document should be returned to the committee for review.

AEGL-Specific Comments

AEGL-1

The committee is concerned that the existing AEGL-1 values lack sound scientific foundation and supporting studies. The TSD authors should evaluate the following alternatives for the derivation of AEGL-1, and provide adequate justification for their choice in the TSD:

1. Justify selection of the modifying factor. Page 43, lines 7-9: "Because the observed effects are above those defined by AEGL-1, a modifying factor of 10 will be applied to reduce the point-of-departure from a LOAEL to a NOAEL for AEGL-1 effects." Section 2.6.2 (page 92) of the SOP states that in "instances in which the adverse effects used to set the AEGL value are more severe than those described in the AEGL definitions," a modifying factor of 2 or 3 should be considered. Why did the authors choose a modifying factor of 10? Reduction from LOEL to NOEL using a modifying factor of 10 instead of 2 or 3 needs additional justification.
2. Select an alternate POD. Page 10, lines 11-14: "In a review article, Blain (2003) reported a TC_{50} (defined as the concentration required to obtain no more than a perceptible effect on 50% of the population exposed to the gas for 1 minute) of 0.004 mg/m^3 for ocular irritation and 0.023 mg/m^3 for airway irritation." The authors should consider the TC_{50} of 0.004 mg/m^3 for perceptible effects as a reasonable POD for AEGL-1 values, if the original article can be referenced.
3. Do not recommend AEGL-1 values. On the basis of the chosen PODs, the difference in AEGL-1 and AEGL-2 effects and in recommended concentrations is small. However, there is a large increase in concentration (approximately 50 times) leading to AEGL-3 effects. Rather than using a modifying factor, the authors should consider not providing an AEGL-1.

AEGL-2

The Punte et al. (1963) study of four human subjects was used to develop AEGL-2 values. The exposure time was short, but data were inconsistent among the four individuals. Ocular irritation developed in 20 min of 24 min in two individuals and in 70 min of 75 min for the remaining two individuals. This result indicates a wide time diversity in susceptibility. The authors report that "all four subjects could tolerate the exposure, but experienced eye and nose irritation and headache." (page 44, lines 7-8, and elsewhere). AEGL-2 effects include "irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape." Are the effects described in the Punte study a LOAEL for AEGL-2 effects? If the TLV ceiling is listed as 0.05 ppm, why is there such discrepancy between the AEGL 2 value and the TLV ceiling? It would seem that the health effect is more an intolerance to tear gas based on the individual susceptibilities of the four subjects. With ocular irritation at 20 min, how would it affect escape? Would it have an impairement affect on escape?

The ERPG-2 is one-fifth the proposed AEGL-2 value but is based on the same end point. The basis for the ERPG-2 should be reviewed to determine whether the assumption of no individual variability is sufficiently robust and whether the intraspecies UF of 3 is appropriate in this case. Evaluate this in light of the 30-min AEGL-2 being less than the IDLH. Could it be that at exposures greater than 30 min effects other than direct irritating effects come into play? This discussion needs to address the category plots on page 64. For animals, disabling effects (AEGL-2) and death (AEGL-3) overlap. How does this overlap relate to human exposures?

The authors should reconsider Beswick et al. (1972) for the development of AEGL-2 values (pages 14-15).The Beswick study included more subjects than Punte et al. (1963), and some subjects experienced nausea and vomiting in addition to occular irritation.

AEGL-3

The authors should consider whether a benchmark concentration approach could be used to derive AEGL-3 values (see SOP, Section 2.2.1).

Other Comments

Page 8, lines 5 and 8: The authors use a time-scaling value of 0.704. Is this an appropriate number of significant figures? SOP 2.9.1 Mathematical Rounding of AEGL Values states two significant figures for AEGLs; this factor should also apply to time-scaling.

Page 9, line 38: "When released to the air CS will exist in both vapor and aerosol form (HSDB 2005)" What is the aerosol particulate size distribution? The size distribution is an important factor affecting toxic effect location. Also, the Hazardous Substances Data Bank is a secondary reference. What is the primary source for this information? Whenever possible, the primary source should be cited.

Page 44, Section 7, Data Analysis for AEGL-3: Provide a table summarizing the AGEL-3 value derived from each species compared with the value derived from the high-end human exposures based on case reports. The narrative provides a description of this analysis, but it is not easy to compare across species. In addition, please explain why the guinea pig is more sensitive than the other species.

Page 46, Section 8.2, Comparison with Other Standards and Guidelines: The authors need to provide some discussion regarding the considerable differences in some of the values in comparison to the derived AEGLs. For example, the IDLH value is so much different from the AEGL values; the ERPG-3 value is twice the AEGL-3 value. Please provide an explanation.

Page 43, lines 11-13 (also page 44, lines 9-13, and page 45, lines 23-27): Delete the sentence about the UF of 3 being supported by responses of individuals with jaundice, hepatities, or peptic ulcers. The sentence is confusing and irrelevant.

Appendix B: Please show the plot for the time-scaling.

Comment References

Beswick, F.W., P. Holland, and K.H. Kemp. 1972. Acute effects of exposure to orthochlorobenzylidene malononitrile (CS) and the development of tolerance. Br. J. Ind. Med. 29(3):298-306.

Blain, P.G. 2003. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. Toxicol. Rev. 22(2):103-110.

HSDB (Hazardous Substances Data Bank). 2005. 2-Chlorobenzalmalononitrile (CASRN 2698-41-1). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed Feb. 28, 2008].

Punte, C.L., E.J. Owens, and P.J. Gutentag. 1963. Exposures to ortho-chlorobenzylidene malononitrile: Controlled human exposures. Arch. Environ. Health 6:366-374.

THIONYL CHLORIDE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on thionyl chloride. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> Data are not available from human or animal studies to derive AEGL-1 values. Therefore, AEGL-1 values are not recommended. Rats exposed to 71 ppm thionyl chloride for one hour experienced swollen noses and dyspnea (Pauluhn 1987). These are toxic responses but not irreversible or incapacitating effects and will not impair ability to escape. The AEGL-2 values are derived from this data…. The AEGL-3 values were based upon the highest concentration causing no lethality in rats exposed to thionyl chloride for one hour.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

As stated in the TSD (page 8, lines 20-22), thionyl chloride hydrolyzes upon contact with water, yielding sulfur dioxide and hydrogen chloride. Most, if not all, of the effects of thionyl chloride are probably caused by these hydrolysis products. The authors should consider developing AEGL-1 values based on SO_2 data.

AEGL-2

There are two primary data sets best suited to develop both AEGL-2 and AEGL-3 values—the Pauluhn study (page 12, lines 5-14) and the Nachreiner study (page 12, lines 16-26). AEGL-2 values should be recalculated based on the Nachreiner study. As noted in the TSD, there appears to be a relationship between LC_{50} and the relative humidity used in the experiment, lower humidity leading to increased toxicity and lower LC_{50} values. This finding suggests that either the parent compound is more toxic than the hydrolysis products or that the delay in hydrolysis (half-life of 5 min at 53% relative humidity per Nachreiner) leads to deeper deposition in the lungs of the hydrolysis products. Both possibilities regarding hydrolysis should be discussed in the text. Because of these possibilities, the

Nachreiner study, with the lowest humidity, is probably a better POD; the Pauluhn study could be used as support.

AEGL-3

The committee recommends the use of Pauluhn (1987) for development of AEGL-3 values. Please see comment above under AEGL-2.

Other Comments

Page 8, lines 20-23: Thionyl chloride hydrolyzes upon contact with water, yielding sulfur dioxide and hydrogen chloride, and most, if not all, of the effects of thionyl chloride are probably caused by these hydrolysis products. However, the dose-effect (or concentration-effect) relationship for inhaled thionyl chloride may differ from that for inhaled sulfur dioxide and hydrogen chloride, as the former exposure will result in deeper deposition in the respiratory tract and more severe effects. This notion is supported by the lower rat LC_{50} values obtained at low relative humidity (Nachreiner 1993), as compared with higher humidity (Pauluhn 1987).

Page 15, lines 6-8: "Following inhalation, sulfur dioxide is distributed throughout the body after dissolving into surface fluid. Some remains in the respiratory system for a week or more following exposure." Please explain how SO_2 can remain in the lung for a week or more.

Page 15, Section 4.2 (Mechanism of Toxicity): On the basis of data from the three main studies indicating a toxicity difference related to relative humidity, the following paragraphs should be added to the discussion:

Sulfur dioxide acts on the respiratory system via stimulation of bronchoconstriction and mucus secretion in the upper airways. It injures cells lining the airway passages and causes mucus-secreting goblet cells to proliferate. These two events result in airway narrowing and increased airflow resistance (Costa 2001).

Inhaled hydrogen chloride irritates the respiratory tract following a latency period of several hours. Following exposure, the epithelial barrier in the alveolar zone breaks down and begins to leak, causing pulmonary edema (Witschi and Last 2001)."

Page 16, Section 6 (Data Analysis for AEGL-2): Three additional items should be inserted into the discussion on AEGL derviation: (1) the equation showing the hydrolysis reaction of thionyl chloride; (2) a summary table comparing the Kinkead and Einhaus (1984), Pauluhn (1987), and Nachreiner (1993) studies and including the relative humidity present in each; and (3) a table of the AEGL values for HCl and SO_2 (currently a part of Table 8).

Page 16, lines 36-38, and page 18, lines 9-11: "An uncertainty factor of 10 was used for intraspecies variation due to the wide variability in response to sulfur dioxide between healthy and asthmatic humans." The gender difference noted in the Nachreiner study (page 12. lines 20-22) should be listed as support for the intraspecies UF of 10 used.

Comment References

Costa, D.L. 2001. Air pollution. Pp. 979-1012 in Casarett & Doull's Toxicology: The Basic Science of Poisons, 6th Ed., C.D. Klaassen, ed. New York: McGraw-Hill.

Kinkead, E.R., and R.L. Einhaus. 1984. Acute Toxicity of Thionyl Chloride Vapor for Rats. AFAMRL-TR-84-069. ADA148952. Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Nachreiner, D.J. 1993. Thionyl Chloride: Acute Vapor Inhalation Toxicity Study in Rats. Union Carbide Chemicals and Plastics Company, Inc., Export, PA.

Pauluhn, J. 1987. Study for Acute Inhalation Toxicity in Rats in Accordance with OECD Guideline No. 403 (Exposure: 1 × 1 Hour). Bayer AG Report No. 15403. Leverkusen, Germany: Bayer AG.
Witschi, H.R., and J.A. Last. 2001. Toxic responses of the respiratory system. Pp. 515-534 in Casarett & Doull's Toxicology: The Basic Science of Poisons, 6th Ed., C.D. Klaassen, ed. New York: McGraw-Hill.

TRIMETHOXYSILANE AND TETRAMETHOXY SILANE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on trimethoxysilane and tetramethoxysilane. A presentation on the TSD was made by Mark Follansbee, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> AEGL-1 values were not derived for either trimethoxysilane or tetramethoxysilane because of limited data. AEGL-2 values for trimethoxysilane were derived by taking 1/3 of AEGL-3 values.… AEGL-3 values were determined by using mortality data from 1 and 4 hour LC_{50} rat inhalation studies…. AEGL-2 values for tetramethoxysilane were derived from a repeat dose inhalation study in which rats were exposed for 6 hours/day, 5 days/week for 28 days at concentrations up to 45 ppm…. AEGL-3 values were derived from an LC_{50} 4-hour rat inhalation study.
>
> A revised document should be submitted to the committee for review.

AEGL-Specific Comments

AEGL-1

AEGL-1 values were not derived for either trimethoxysilane or tetramethoxysilane because of limited data. A recommendation is to consider developing AEGL-1 values based on AEGL-2 values by using an UF between 3 and 10. This comment is largely discretionary.

The 1-h ERPGs for trimethoxysilane were recently (2010) set at 0.5 ppm based on a 90-day exposure study in rats. The authors should review the supporting literature for the ERPG as a possible source to support the development of AEGL-1 values.

AEGL-2

The committee approves the derivation of AEGL-2 values for trimethoxysilane.

Page 21, lines 36-37: For tetramethoxysilane "A total uncertainty factor of 30 was used. Three was used for the interspecies uncertainty factors because in a five-day inhalation study with trimethoxysilane, a structural analog, effects were similar in rats, mice and hamsters." A UF of 3 may be overly conservative, given the similarity in effects across species. The committee suggests that the authors use a UF of 1 for interspecies.

AEGL-3

The committee approves the derivation of AEGL-3 values for trimethoxysilane.

Page 23, lines 15-17: For tetramethoxysilane, a UF of 3 was used for interspecies, although "in a five-day inhalation study with trimethoxysilane, a structural analog, effects were similar in rats, mice and hamsters." A UF of 3 may be overly conservative. The committee suggests that a UF of 1 be used instead.

This number is also supported by evidence from the Kolesar et al. (1989) (used to derive the AEGL-2 values) study in which rats survived a 28-day, 6 h/day exposure at 30 ppm (although rats died at 45 ppm).

Comment References

Kolesar, G.B., W.H. Siddiqui, R.G. Geil, R.M. Malczewski, and E.J. Hobbs. 1989. Subchronic inhalation toxicity of tetramethoxysilane in rats. Fundam. Appl. Toxicol. 13(2):285-295.

TRIMETHYLBENZENES

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on 1,3,5-trimethylbenzene, 1,2,4-trimethylebenzene, and 1,2,3-trimethylbenzene. A presentation on the TSD was made by Julie Klotzbach, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> For derivation of AEGL values, all available data for the individual TMB isomers were considered…. The most appropriate animal data for derivation of AEGL-1 are the neurotoxicity studies (Korsak et al. 1995, Korsak and Rydzyński 1996)…. Rats repeatedly exposed to 2000 ppm for 6 hours exhibited irritation, respiratory difficulty, lethargy, and tremors (Gage 1970); therefore 2000 ppm was chosen as the basis for deriving the 10-min, 30-min, 1-hour, 4-hour, and 8-hour AEGL-2 values…. Data are insufficient for derivation of AEGL-3 values for TMB. One study showing lethality in rats did not include data adequate for a concentration-response assessment.
>
> This document can be finalized.

AEGL-Specific Comments

The committee approves the derivation of the AEGL-1, AEGL-2, and AEGL-3 values for trimethylbenzenes.

Comment References

Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27(1):1-18.
Korsak, Z., and K. Rydzyński. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health 9(4):341-349.
Korsak, Z, R. Swiercz, and K. Rydzynski.1995. Toxic effects of acute inhalation exposure to 1,2,4-trimethylbenzene (pseudocumene) in experimental animals. Int. J. Occup. Med. Environ. Health 8(4):331-337.

VINYL CHLORIDE

At its meeting held on October 26-29, 2010, the committee reviewed the TSD on vinyl chloride. A presentation on the TSD was made by Ernest Falke, of the U.S. Environmental Protection Agency. The following is excerpted from the Executive Summary of the TSD:

> 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 time of onset of headaches is not clearly stated and was assumed to be after 3.5 hours…. The AEGL-2 was based on prenarcotic effects observed in human volunteers. After 5 minute exposure to 16,000 ppm VC [vinyl chloride], 5 of 6 persons showed dizziness, lightheadedness, nausea, and visual and auditory dulling…. The AEGL-3 was based on cardiac sensitization and the no effect level for lethality.
>
> This document can be finalized.

AEGL-Specific Comments

The committee approves the derivation of the AEGL-1, AEGL-2, and AEGL-3 values for vinyl chloride.

COMMENTS PERTAINING TO ALL TSDS

Whenever substantial discrepancies are found between AEGL values and other guideline values (e.g., IDLHs, STELs, and WEELs), the possible reasons should be explored and discussed in the text. The SOP, Appendix J, page 201, states, "A summary discussion of important comparisons should be presented in the text and the values for recognized standards and guidelines, if available, should be presented in the table."

Reliance on review articles and compendia appears to have increased. The SOP states that the primary literature must be used (SOP, page 51) for key studies, supporting data, and information important to the derivation of an AEGL value. If the summarization of findings from a primary reference as described in a secondary source is used, the citation needs to be clear that it is not coming from the primary literature, that is, a paper "as cited in." If a reference is unpublished, the citation should make clear how the information can be obtained by others.

The authors need to make sure the literature on the chemicals have been updated for documents that have been several years in the AEGL-development process. The date of the most recent literature review should be included in the TSD.

The chemical structure of the compounds should be included on the title page of every TSD.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	acute exposure guideline level
AN	acrylonitrile
ATSDR	Agency for Toxic Substances and Disease Registry
BCME	bis-chloromethyl ether
BEI	Biological Exposure Index
$BMCL_{05}$	benchmark concentration with its lower confidence limit at a 5% extra risk
BZ	3-quinuclidinyl benzilate
CEEL	community emergency exposure level
CEO	cyanoethylene oxide
CMME	chloromethyl methyl ether
DA	diphenylchloroarsine
ED	ethyldichloroarsine
ED_{50}	the dose of a substance that causes an effect in 50% of the exposed population
EHS	extremely hazardous substances
EPA	U.S. Environmental Protection Agency
ERPG	emergency response planning guidelines
H_2SO_4	sulfuric acid
HBr	hydrogen bromide
HCl	hydrogen chloride
HFA	hexafluoroacetone
ICt_{50}	concentration and time of a substance that causes incapacitation to 50% of an exposed population
IDLH	immediately dangerous to life or health
IRIS	Integrated Risk Information System
L	liter
L-1	lewisite-1
L-2	lewisite-2
L-3	lewisite-3
LC_{01}	lethal concentration to 1% of the exposed population
LC_{50}	concentration of a substance that is lethal to 50% of the exposed population
LCt_{50}	concentration and time of a substance that is lethal to 50% of the exposed population
LOAEL	lowest-observed-adverse-effect level
m^3	cubic meter
MAC	maximum accepted concentration
MAK	maximum workplace concentration
MD	methyldichloroarsine
Mg	milligram
min	minute
mmHg	millimeters of mercury

NAC	National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances
NIOSH	National Institute for Occupational Safety and Health
NO	nitric oxide
NO_2	nitrogen dioxide
N_2O_4	nitrogen tetroxide
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
OSHA	Occupational Health and Safety Administration
PBPK	physiologically based pharmacokinetic
PD	phenyldichloroarsine
POD	point of departure
ppm	part per million
RD_{50}	concentration of a substance that reduces the respiratory rate of test organisms by 50%
REL	recommended exposure limit (NIOSH)
SMAC	spacecraft maximum allowable concentration
SO_3	sulfur trioxide
SOP	standing operating procedures
STEL	short-term exposure limit
TMB	trimethylbenzene
TLV	Threshold Limit Value
TRI	Toxics Release Inventory
TSD	technical support document
UF	uncertainty factor
WEEL	workplace environmental exposure limit