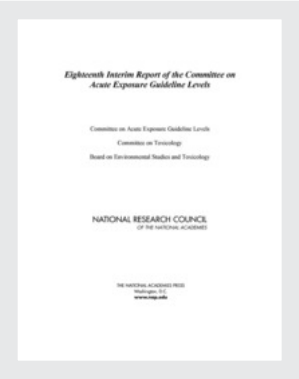

Eighteenth Interim Report of the Committee on Acute Exposure Guideline Levels

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Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars or trucks transporting EHSs, or 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 18th interim report. It summarizes 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,

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

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. Committee member David Kelly recused himself from discussion of the draft AEGL document for titanium tetrachloride.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: A. Wallace Hayes, Harvard School of Public Health; Sam Kacew, University of Ottawa; Joyce Tsuji, Exponent, Inc.; 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 authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Iris Camacho, Ernest Falke, and Robert Benson (EPA); Heather Carlson-Lynch, 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 and Keegan Sawyer, project director, for her work in this project. Other staff members who contributed to this effort are Susan Martel (senior program officer), Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (manager of editorial projects), and Tamara Dawson (senior program assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

Contents

Eighteenth 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 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.

ALLYL ALCOHOL

At its meeting held on June 15-18, 2010, the committee reviewed the technical support document (TSD) on allyl alcohol. 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:

> Allyl alcohol is a colorless liquid that is a potent sensory irritant. Signs of intoxication following inhalation exposure to allyl alcohol vapor include lacrimation, pulmonary edema and congestion, and inflammation, hemorrhage, and degeneration of the liver and kidney. . . . The AEGL-1 values are based upon nasal irritation as indicated by reversible nasal inflammation observed histologically in rats 14 days after exposure to 51 ppm allyl alcohol for 1 hour; 22 ppm for 4 hours, or 10 ppm for 8 hours. . . . The AEGL-2 was obtained by dividing the AEGL-3 by 3. . . . The AEGL-3 values are based on the calculated LC_{01} value in rats of 2600 ppm for 10 minutes, 820 ppm for 30 minutes, 400 ppm for 1 hour, 93 ppm for 4 hours, and 45 ppm for 8 hours.

Specific Comments

AEGL -1

Page vii, lines 15-18: The TSD notes, "An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because allyl alcohol is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species." Because effects other than direct-acting effects appear to be occurring, these uncertainty factors should be reviewed and additional justification provided.

Better justification is needed for using the Kirkpatrick (2008) study rather than the Dunlap et al. (1958) study for AEGL-1 values. Although the Kirkpatrick study is newer, it is in rats, and results are reported 14 days postexposure. Were any observations reported during or immediately post exposure? The Dunlap study used human volunteers, and the end points are relevant to deriving AEGL-1 values. Dunlap's results are supported by Torkelson et al. (1959) and McCord (1932).

Page 11, lines 4-6: "The incidences of alcohol flushing and material around the mouth exhibited a concentration-related increase at 220 and 403 ppm." Clarification is needed on whether alcohol flushing is a direct-acting irritant effect. In humans, alcohol flushing results from excess aldehyde in the blood from buildup of this metabolite, most commonly in individuals with the slow variant of the aldehdye dehydrogenase gene.

Page 21, lines 33-35: "It is currently not known if the parent alcohol is a direct irritant, or if conversion to the acrolein metabolite is required to produce irritation"; and **page 23, lines 12-15:** "Although the effect of mild irritation is generally not scaled across time, the empirical data indicate a time-response relationship for allyl alcohol-induced nasal irritation." The quoted statements indicate allyl alcohol goes through some metabolic transformation to the causative agent, which is inconsistent with other statements in the TSD saying that it is a direct-acting irritant.

Another example where mechanisms other than direct action by the chemical are indicated is when the default value of n = 3 was used to time-scale the 1-h AEGL-1 point of departure (POD) to 30 min. If lethality is on the continuum of effects, then the n from lethality studies should be used. Because the default values were used, it appears that the authors do not believe direct irritation is on the continuum of effects, indicating there are toxicodynamics influencing the toxicity. Such influence would not be expected for a direct-acting irritant.

Page 30, line 16 (also see page 31, Table 15): "The 8-hour AEGL-3 is comparable to the 15-min NIOSH STEL [National Institute of Occupational Safety and Health, short-term exposure limit]." The NIOSH STEL is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday. Using C^3 = 133 ppm (taken from in Appendix A in TSD) for AEGL-1, the 15-min AEGL-1 value is 8 ppm. This is twice the NIOSH level, which is for a healthy workforce and not the general public. The 8-ppm value requires additional explanation here or in the discussion of the AEGL-2 values.

AEGL -2

Page 11, lines 13-17: "Exposure to 52 and 102 ppm for 4 hours produced a concentration-related increase in the number of animals exhibiting gasping, alcohol flushing, material around the mouth, and a reduced response to cage stimulus, and an increased incidence of yellow material around the urogenital area was observed 1 hour post exposure in females exposed to 102 ppm. Histopathological examination of the nasal cavity revealed reversible changes, including degeneration of the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia." Are these AEGL-2 effects? If so, why was this study not used as the POD for AEGL-2?

Page 14, line 9: One-fifth of the RD_{50} (concentration of a substance that reduced the respiratory rate of test organisms by 50%) is a reasonable estimate for AEGL-2 values. How do the values compare with each other?

Page 31, Table 15: The 30-min AEGL-2 is 35% greater than NIOSH's immediately dangerous to life or health (IDLH) value. The explanation for the discrepancy should be explored.

AEGL -3

Page 28, lines 1-4: "An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because allyl alcohol is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species." Since there appear to be other than direct-acting effects occurring, the values of the uncertainty factors should be reviewed and better justified. If some of the tissue irritation and systemic effects are caused by metabolism of the alcohol to an aldehyde, the amount of irritation to the tissues might be affected by whether individuals have the slow or fast form of genetic polymorphisms for aldehyde dehydrogenase. Many tissues of the body have the capacity to metabolize alcohols and aldehdyes.

Page 30, line 16 (also see page 31, Table 15): "The 8-hour AEGL-3 is comparable to the 15-minute NIOSH STEL." Delete this observation, because 8-h values should not be compared with 15-min values.

Other Comments

Page viii, line 13: It is noted that the POD values are no-observed-effect levels (NOELs) as there were no clinical signs of nasal irritation; yet the end point noted in the AEGL table on page ix of the TSD indicates some irritation

Page viii, lines 17-18: Statements regarding the lack of interindividual variation to support the application of an uncertainty factor of 3 for intraspecies differences needs better justification. There is a wide range of responses to sensory irritants among individuals. The range is even evident from the study noted on page 3, lines 7-11, wherein all exposed individuals did not respond at the lower levels. The issue of the uncertainty factor related to variability is also present in Section 5.3 of the TSD.

Page 1, line 7: Delete mention of war gas, as such compounds are no longer manufactured per international treaty.

Page 6, lines 5-6: "(The primary findings in the rabbits and monkey were hemorrhage in the lungs, intestinal tract, bladder, and kidneys.)" These effects appear to be systemic and not completely related to a direct-acting irritant.

Page 18, Table 8: On the basis of the data, the mouse appears to be more sensitive than the rat.

Page 20, Special Considerations: Consider including discussion of the OH rate constant, given the fairly high reactivity of allyl alcohol with the hydroxyl radical (estimated half-life in air is shorter than the 8-h AEGL duration), and the potential role of associated fate products (e.g., regarding possible contribution to toxicity as human exposure duration increases to 8 h).

Page 22, lines 29-31: The sentence should be revised to make the distinction that, at lower concentrations, people with pre-existing lung disease might be at special risk to the pulmonary effects of allyl alcohol, but at very high concentrations, people with lung disease and healthy individuals will probably be affected similarly by the exposure.

Page 23, lines 33-34: Is acrolein contamination common in allyl alcohol? Is it possibly the causative agent of the observed ocular irritation?

Page 30, graph: What is the human disabling value?

Comment References

Dunlap, M.K., J.K. Kodama, J.S. Wellington, H.H. Anderson, and C.H. Hine. 1958. The toxicity of allyl alcohol. 1. Acute and chronic toxicity. A.M.A. Arch. Ind. Health 18(4):303-311.

Kirkpatrick, D.T. 2008. Acute Inhalation Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-hour Exposure Durations). WIL-14068. WIL Research Laboratories, LLC. Ashland, OH. Sponsored by Lyondell Chemical Company, Houston, TX.

McCord, C.P. 1932. The toxicity of allyl alcohol. J. Am. Med. Assoc. 98(26):2269-2270.

Torkelson, T.R., M.A. Wolf, F. Oyen, and V.K. Rowe. 1959. Vapor toxicity of allyl chloride as determined on laboratory animals. Am. Ind. Hyg. Assoc. J. 20(3):217-223.

bis-CHLOROMETHYL ETHER

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on bis-chloromethyl ether in conjunction with chloromethyl methyl ether (see below for comments on this chemical). The two TSDs are in good agreement and share some data. 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.

Specific Comments

AEGL-1

The committee agrees with the decision to not set AEGL-1 values.

AEGL-2

The committee recommends an uncertainty factor for intraspecies differences of 10 rather than 3 because BCME has a steep dose-response curve and might not be acting as a simple irritant gas.

AEGL-3

For the same reasons as above, the committee recommends the use of an uncertainty factor of 10 to account for intraspecies differences. The discussion in Section 7.3 of the derivation of the AEGL-3 values should also be revised to clarify that the 7-h exposure study supports the selection of the primary study.

Other Comments

Section 4.1 on metabolism and disposition should be expanded to briefly discuss likely metabolites.

The AEGL values will be well above the Threshold Limit Value (TLV) for BCME set by the American Conference of Governmental Industrial Hygienists. Thus, the reason for the differences between the AEGL values and the TLV should be added to the TSD.

CHLOROMETHYL METHYL ETHER

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on chloromethyl methyl 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, in

which rats and hamsters were exposed for 7 hours to 12.5-225 ppm CMME (content of BCME not given).

Specific Comments

The committee found that its previous recommendations for supporting the derivation of AEGLs for CMME were adequately addressed. The proposed AEGL-1, -2, and -3 values for CMME were approved.

Other Comments

Section 4.1 on metabolism and disposition should be expanded to include a brief discussion of the likely metabolic products, such as hydrogen chloride, formaldehyde, methanol, formic acid, and carbon dioxide.

HALOGEN FLUORIDES

At its meeting held on June 15-18, 2010, the committee reviewed the TSDs on chlorine pentafluoride, bromine pentafluoride, and bromine trifluoride. Presentations on the TSDs were made by Heather Carlson-Lynch, of Syracuse Research Cooperation.

The committee observed that the AEGL values for the three halogen fluorides are linked with each other and three other compounds, hydrogen fluoride, chlorine trifluoride, and chlorine dioxide, chemicals for which TSDs have already been published (NRC 2004, 2007). Thus, on the basis of the review of the TSDs at the meeting (see details below), and excerpted analyses below on related compounds, the committee strongly recommends publication of the halogen fluorides as a single document with chlorine trifluoride, chlorine dioxide, and hydrogen fluoride as appendixes or possibly republishing chlorine trifluoride and chlorine dioxide from Volume 5 of *Acute Exposure Guideline Levels for Selected Airborne Chemicals* and hydrogen fluoride from Volume 4 as chapters, as well as chapters on chlorine pentafluoride, bromine pentafluoride, and bromine trifluoride. Alternatively, it should be ensured that references are made throughout the document to hydrogen fluoride, chlorine trifluoride, and chlorine dioxide. Regardless of which approach is chosen, an expansion of the analysis below showing the dissociation paths of the different agents to explain the relative toxicities is important to understand the toxicities of these agents and should be provided in whatever document or documents are developed. This information belongs in Section 4 of the TSD, Special Considerations, and should also be included in the TSD's Executive Summary.

The following are excerpts from the TSD on chlorine trifluoride (NRC 2007) and are provided as the basis for the discussion of the dissociation paths and relative toxicities below:

- Chlorine trifluoride (ClF_3) is unstable in air and rapidly hydrolyzes to hydrogen fluoride (HF) and a number of chlorine-containing compounds, including chlorine dioxide (ClO_2). The toxic effects of ClF_3 are due, at least in part, to the actions of both HF and ClO_2.
- In the moist respiratory tract, ClF_3 is predicted to hydrolyze to ClOF, which further degrades to ClO_2F and ClF (Dost et al. 1974). ClO_2F rapidly hydrolyzes to ClO_2, HF, and ClO_x anions; the first two products predominate and are thought to be responsible for ClF_3 toxicity, as the ClO_x anions are relatively nontoxic.
- The chemical reactivity of the halogenated fluorine compounds in order of decreasing reactivity is chlorine pentafluoride (ClF_5) > ClF_3 > bromine pentafluoride (BrF_5) > iodine heptafluoride (IF_7) >

chlorine monofluoride (ClF) > bromine trifluoride (BrF_3) > bromine monofluoride (BrF) (Bailey and Woytek 1994).

- In the monkey, ClF_3 is slightly less toxic than ClF_5 but 7 times more toxic than HF. (In all three species for which data are available, ClF_5 is almost exactly 10 times more toxic than HF.) In the rat and mouse, ClF_3 is approximately 4 times more toxic than HF.

On the basis of these observations, the committee recommends that the following discussion, suitably modified and expanded as appropriate, be included in any document or documents developed for the halogen fluorides.

ClF_5, ClF_3, BrF_5, BrF_3, HF, and ClO_2 are toxicologically related, and all produce the toxic effect at the point of absorption which is primarily related to the agent's physical form (vapor, mist, and aerosol). The relative toxicities of these agents are

$$ClO_2 > ClF_5 > ClF_3 > BrF_5 > BrF_3 > HF.$$

These toxicities could be expressed in terms of HF equivalents. ClF_3 is approximately 7 times more toxic than HF, and ClF_5 is approximately 10 times more toxic than HF. The relative toxicities indicate that ClO_2, an intermediate in the dissociation of ClF_x, plays a role in the toxicity of these agents. (In the moist respiratory tract, ClF_3 is predicted to hydrolyze to ClOF, which further degrades to ClO_2F and ClF [Dost et al. 1974]. ClO_2F rapidly hydrolyzes to ClO_2, HF, and ClO_x anions; the first two products predominate and are thought to be responsible for ClF_3 toxicity, as the ClO_x anions are relatively nontoxic.) If a similar path exists for bromine to form BrO_2, it is expected to be less toxic than ClO_2, as BrO_2 is less reactive than ClO_2.

Because the toxicity data for the individual chemicals are sparse, each chemical is compared with ClF_3, and the AEGL values are derived via or supported by the comparison, the Summary and Sections 2, 3, and 4 and much of Sections 5, 6, 7, and 8.3 should be straightforward to develop. Descriptions of the toxicity of ClF_3 should be reduced to cross-references to the relevant sections in the appendixes. Other redundancies could likewise be reduced. This consolidation would also strengthen the material in Section 8.3., as the larger data set generated by including all the halogen fluorides provides greater confidence. The other sections and the appendixes could be structurally awkward, so consolidation will be needed.

References to the ClF_3, ClO_2, and HF documents will need to be rechecked as the three halogen fluoride documents are combined into one document.

The summary table of AEGL values could either be a table for each compound or a table for each AEGL, the rows being the separate compounds.

As noted below in the section Comments Pertaining to All TSDs, better justification is needed for reducing the intraspecies factor to 3 for direct-acting irritants.

Below are comments on the specific halogen fluorides discussed at the June meeting.

Chlorine Pentafluoride

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

> Chlorine pentafluoride (ClF_5) is a strong oxidizer that was once considered for use as a missile propellant. No human data were available for development of AEGL values. . . . The AEGL-1 is based on empirical data as well as analogy with hydrogen fluoride (HF) and chlorine trifluoride (ClF_3). The empirical data point is a no-observed effect level for the endpoint of irritation of 3 ppm for 10 minutes in the rat. . . . The sensory irritation and reversible mild lung congestion observed in monkeys, rats, and mice following exposure to 30 ppm for 10 minutes, 20 ppm for 30 minutes, or 10 ppm for 60 minutes or following exposure of dogs to 30 ppm for 10 minutes meets the definition of the AEGL-2. . . . The AEGL-3 values are based on a lethality study with rats.

Specific Comments

AEGL-1

The TSD for ClF_5 proposes an AEGL-1 value of 0.30 ppm for exposure durations of 10 min, 30 min, and 1 h, but it does not apply the value to exposure durations of 4 h and 8 h. The rationale provided is that the value at those durations is similar to the corresponding AEGL-2 values. The committee recommends not setting any AEGL-1 values, as the sensory warnings are too close to AEGL-2 effects.

AEGL-2

The observation of "severe irritation" and "lung congestion" (on page 21, lines 27-34) are AEGL-2 effects. The observation of "irritation without pathology" (on page 22, lines 9-11) indicates changes below the definition of the AEGL-2 and, therefore, is suitable as a POD for AEGL-2 values. Using this POD will result in a 1-h AEGL-2 value being similar to the 1-h AEGL-1 value, which reinforces the recommendation above to not set AEGL-1 values.

AEGL-3

The committee approved the derivation of the AEGL-3 values for ClF_5.

Other Comments

Page 17, lines 29-31: "Although most review sources indicate that the reaction with water is violent, both Smith (1963) and Dost and Wang (1970) reported that the reaction with water is slow. (Slow reaction indicates poor scrubbing in the upper respiratory tract.)." The discrepancy noted in this sentence would benefit from further discussion. Some of the pathology reported in Section 3 indicates, in accordance with the parenthetical statement, that ClF_5 does indeed penetrate to the alveoli, and this information was used in the AEGL-2 derivation. The discrepancy might be resolved in Section 4 of a consolidated TSD that incorporates information on ClF_3, HF, and ClO_2.

Page 17, lines 42-44: The committee recommends retaining the text that states, "The authors stated that the toxicity of ClF_3 is comparable to that of ClO_2 on a chlorine equivalent basis and is comparable to that of HF on a fluorine equivalent basis." When taken in context of the relative toxicities of ClF_3, ClF_5, and HF, it adds to the discussion and was reported by the authors. This information (and the citation) belongs in Section 4 with the discussion on relative toxicities and mechanisms described above.

Page 18, lines 4-6: "These observations suggest that the effects of ClF_5 exposure may be more likely to be due to the direct irritation of the respiratory tract than to fluoride poisoning." This is a weak statement. The entire document is based upon direct action at the point of absorption. Can it not be stated that the effects are due to direct irritation of the respiratory tract and not due to fluoride poisoning? See page 24, lines 14-15. See also similar comments on BrF_5.

Page 19, lines 36-47, and page 20, lines 1-4: The revised section still does not provide a clear basis for the statement that concentration is more important than duration of exposure for effects other than irritation. The committee recommends rewriting the section to state that

> The data from the MacEwen and Vernot studies indicate that, at least for the direct irritant responses to ClF_5, concentration may be more important than exposure duration. However, for the other effects observed, the role of exposure duration versus concentration is difficult to interpret

because these studies provided few qualitative and quantitative details of the pathology findings. Discordant findings could be due to the dissociation to other agents or to a metabolic pathway.

Page 19, Section 4.4.2: The two paragraphs on susceptibility are found in each of the three halogen fluoride documents. The committee recommends keeping both paragraphs (some of the documents have one or both paragraphs deleted), as the information is relevant to all three compounds.

Page 20: The deletion of section Concurrent Exposure Issues would indicate that no relevant data are available (see Standing Operating Procedures [NRC 2001]).

Page 24, lines 13-17: The discussion of the relative toxicities of ClF_3, ClF_5, and HF should be moved to Section 4 (Special Considerations).

Page 24, line 21-23, and Table 13: In this section, the AEGL values for ClF_5 are compared with those for ClF_3 and HF. The AEGLs reported for ClF_3 in Table 13 are inaccurate and should be updated with the final published values (NRC 2007). The accompanying paragraph should be revised accordingly. (Specifically, the paragraph should note that the AEGL values for ClF_3 are *lower* than those for HF. There should also be discussion about the reason for the two compounds being more similar for longer-duration AEGLs than for shorter-duration AEGLs, including the fact that the relative toxicities of the compounds should be the same if tissue destruction is the end point, unless the saturation point has been reached and toxicokinetics become the driving factor.) The committee also recommends that a table of the AEGL values for ClO_2 be added to the TSD for completeness. ClO_2 is a breakdown product of ClF_5 and ClF_3 and probably accounts for why the two halogen chlorides are much more toxic than HF in terms of HF equivalents. The revised paragraphs comparing AEGL values for ClF_5 with those for ClF_3, HF, and ClO_2 should be moved to Section 4 (Special Considerations) rather than appear in Section 8 (Comparison with Other Standards and Guidelines), which should only consider values for ClF_5.

Page 25, Section 8.3: This section on data adequacy and research needs should be rewritten according to guidance in the Standing Operating Procedures (NRC 2001).

Bromine Pentafluoride

The following is excerpted from the Executive Summary of the TSD on BrF_5:

> Bromine pentafluoride (BrF_5) is a strong oxidizing chemical that is used as a fluorinating agent and as an oxidizer in rocket propellant fuels. No data on human exposures were available. A single study provided information on lethal and non-lethal values for the rat. . . . In the absence of empirical data, no AEGL-1 values were developed. . . . In the absence of data relevant to derivation of AEGL-2 values for BrF_5, data for the structurally-related chemical, chlorine pentafluoride (ClF_5), were used. . . . The AEGL-2 values for ClF_5 are based on a series of exposures with four species. . . . The AEGL-3 values for BrF_5 are based on the highest non-lethal value in the rat study of Dost et al. (1970), 500 ppm for 40 min.

Page 6, lines 35-37: Time-scaling for BrF_5 is based on a revised ClF_5 time-scaling factor. Footnote b of Table 3 (on page 7) should acknowledge that by noting that the 4-h and 8-h values were time-scaled from the 60-min value.

Page 9, lines 35-39, and page 10, line 2: Is this statement attributable to Darmer (1971) or to the NAC? If the NAC, the statement should be removed, as it is speculation.

Page 10, lines 4-8 and 12-13: The sentence on lines 4-8 should indicate the compound to which the rats were exposed, and the sentence on lines 12-13 should specify the concentration of BrF_5. Unlike ClF_5, in this study of BrF_5, Dost et al. (1968) reported fluoride in the bones and other organs. The TSD should build a case for no systemic effects from fluoride.

Page 10, lines 12-13: The statement that systemic effects are unlikely is appropriate, but a citation is needed to support it, especially since the preceding paragraph discusses the systemic distribution of fluoride as a result of BrF_5 exposure.

Page 10, lines 20-22: The discussion of relative chemical reactivity of halogenated fluorine compounds should be expanded when the TSDs on ClF_5, BrF_5, and BrF_3 are combined. The Bailey and Woytek (1994) study should be reviewed for information on specific relative toxicities.

Page 12, Section 4.4.2: The two paragraphs on susceptibility are found in each of the three halogen fluoride documents. The committee recommends keeping both paragraphs (some of the documents have one or both paragraphs deleted), as the information is relevant to all three compounds.

Page 16, Section 8.3: This section includes descriptive statements of the data used without assessment of data adequacy or of what, if any, additional research would be useful to improve the AEGLs. See Standing Operating Procedures (NRC 2001, page 53-57) for requirements.

Bromine Trifluoride

The following is excerpted from the Executive Summary of the TSD on BrF_3:

> Bromine trifluoride (BrF_3) is an extremely reactive and corrosive oxidizing agent used in nuclear reactor fuel processing; as a fluorinating agent; and, potentially, in rocket and missile fuels. . . . In the absence of empirical information on BrF_3, AEGL values were based on the chemical analogue, chlorine trifluoride (ClF_3). . . . The AEGL-1 values for ClF_3 are based on slight irritation as evidenced by rhinorrhea (nasal discharge) observed in two of two dogs during the first 3 hours of a 6-hour exposure to an average concentration of 1.17 ppm. . . . The AEGL-2 values for ClF_3 were based on signs of irritation (salivation, lacrimation, rhinorrhea, and blinking of the eyes) in two of two dogs exposed to a concentration of 5.15 ppm for 6 hours. . . . Lethality data for ClF_3 (1-hour LC_{50} values [concentrations of a substance that is lethal to 50% of test organisms in a given time]) were available for the monkey, rat, and mouse. . . . The AEGL-3 values were based on the highest 1-hour concentration that resulted in no deaths in monkeys.

No appendixes were included in this TSD.

Page 6, line 21: A study reporting "obvious" lacrimation in dogs, which was used to derive AEGL-1 values, should not be characterized as mild and transient. The somewhat late onset of the obvious lacrimation might have been due to a mechanism-based delay (e.g., the main responsible chemical species might have been a metabolite or dissociation product and not BrF_3 itself) or to an oversight of the onset at an earlier time point. Regardless, it was "obvious" and not mild when it was observed. Obvious lacrimation should be considered an AEGL-1 effect and not as a no-observed-adverse-effect level (NOAEL) for AEGL-1 (see Standing Operating Procedures [NRC 2001, page 41]).

Page 9, lines 13-14 and 24-25: The statement that systemic effects are unlikely is appropriate, but a citation is needed to support it.

Page 11, Section 4.4.2: These two paragraphs are found in each of the three halogen fluoride documents. The committee recommends keeping both paragraphs (some of the documents have one or both paragraphs deleted), as the information is relevant.

Page 13, line 37: The committee recommends using "lesser toxicity" rather than "lower toxicity" when comparing BrF_3 and ClF_3, as the latter description might be misinterpreted.

Page 17, Section 8.3: The Section states that there were no BrF_3 data. The inference is that structure-activity relationships are adequate to derive AEGL values using data from ClF_3 and other halogen fluorides and HF and that no further research is needed. If that is the case, then an explicit statement to that effect should be made in this section. See Standing Operating Procedures (NRC 2001, pages 53-57) for requirements.

Comment References

Bailey, W.I., and A.J. Woytek. 1994. Fluorine compounds, inorganic (halogens). Pp. 342-355 in Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 11, 4th Ed., Vol. 11. New York: John Wiley & Sons.

Darmer, K.I. 1971. The acute toxicity of chlorine pentafluoride. Pp. 291-300 in Proceedings of the 2nd Annual Conference on Environmental Toxicology, 31 August, 1 and 2 September 1971. AMRL-TR-71-120. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Dost, F.N., and C.H. Wang. 1970. Studies on Environmental Pollution by Missile Propellants. AMRL-TR-69-116. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH. January 1970.

Dost, F.N., D.J. Reed, A. Finch, and C.H. Wang. 1968. Metabolism and Pharmacology of Inorganic and Fluorine Containing Compounds. AMRL-TR-67-224, AD 681 161. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH. August 1968.

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Dost, F.N., D.J. Reed, V.N. Smith, and C.H. Wang. 1974. Toxic properties of chlorine trifluoride. Toxicol. Appl. Pharmacol. 27(3):527-536.

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

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

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Smith, D.F. 1963. Chlorine pentafluoride. Science 141(3585):1039-1040.

CARBON TETRACHLORIDE

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on carbon tetrachloride. 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:

> Carbon tetrachloride (CAS No. 56-23-5) is a colorless, nonflammable, heavy liquid only slightly soluble in water that is used as a laboratory and industrial solvent, an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and fire suppressant. . . . The AEGL-1 values were based upon a controlled exposure of human volunteer subjects to 76 ppm for four hours. . . . The AEGL-2 was also based upon human data from controlled exposure experiments in which subjects experienced CNS [central nervous system] effects characterized by headache, nausea and vomiting following 9-minute exposure to 1191 ppm carbon tetrachloride. . . . The AEGL-3 was based upon an estimated lethality threshold (1-hr LC_{01} of 5,135.5 ppm) using data from multiple studies on laboratory rats.

Specific Comments

AEGL-1

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

AEGL-2

The proposed POD for the AEGL-2 values for carbon tetrachloride was 1,191 ppm for 9 min, based on the report by Davis (1934). At this concentration, one of the four test subjects had headache, nausea, and vomiting at 9 min and could not tolerate longer exposure. The other three subjects also showed similar effects after 15 min of exposure.

Severe effects were also reported at 3-7 min of exposure to carbon tetrachloride at 12,800 ppm (page 11, line 19). These included dizziness, nausea, sleepiness, and throbbing headache (5-min exposure); nervousness, nausea, and listlessness (3-min exposure); and nausea, vomiting, dizziness, and sleepiness (7-min exposure) (page 11, lines 19-21). However, for this "experiment six" by Davis (1934), the study report stated that the unit for 12,800 ppm was by weight, whereas it was 2,382 ppm by volume. This issue should be investigated to ensure accurate presentation in the TSD.

Taken together, the Davis study reported that serious effects occurred in all test subjects either at 1,191 ppm for as little as 9 min of exposure or at a presumed concentration of 2,382 ppm for as little as 3 min of exposure to carbon tetrachloride. Thus, while the end points of headache, nausea, and vomiting are appropriate for the AEGL-2, the 9-min 1,191 ppm concentration is not a NOEL for the POD. It is recommended that either a different POD be selected or an uncertainty factor or modifying factor be applied to obtain an estimated NOEL for the POD.

It should also be noted that Davis (1934) reported that one of three test subjects had nausea, another had nausea and vomiting, and the third had a headache when exposed to carbon tetrachloride at 317 ppm for 30 min. A comparison of this value with the proposed 30-min AEGL-2 value of 250 ppm (based on a POD of 1,191 ppm) indicates insufficient assurance to meet AEGL-2 criteria, even without considering the potential for significantly greater alcohol-related sensitivity.

AEGL-3

It was not clear what the postexposure observation period was for the rats in the study by Adams et al. (1952). It was stated on page 16, line 16, that the surviving animals were killed one day after the termination of exposure. However, the study report stated that the surviving rats from acute exposures were ". . . observed for 2-3 weeks or until it was certain that they had fully recovered from the effects of the exposure." If the description in the TSD is correct, the deviation from the general protocol of a 14-day postexposure observation period for acute lethality studies should be addressed when deriving the POD for AEGL-3 at the LC_{01} (concentration with 1% lethality) from this study. This is a concern in light of a death reported in a worker 6 days after exposure to carbon tetrachloride (Norwood et al. 1950).

Serious considerations should be given to the reported effects in humans for the AEGL-3 determination. Compared with the proposed 10-min AEGL-3 value of 1,100 ppm, Davis (1934) reported that all three test subjects had nausea, vomiting, and headache 9 min after exposure to carbon tetrachloride at 1,190 ppm. In addition, the AEGL-3 is only 2-fold lower than 2,382 ppm, at which dizziness, nausea, sleepiness, and severe headache were observed within 3-7 min of exposure.

Additional comparisons to human data further illustrate the need for ensuring that the proposed AEGL-3 values for carbon tetrachloride provide adequate protection against death. For example, the proposed 8-h AEGL-3 of 220 ppm is only slightly lower than 250 ppm, the concentration at which a worker exposed for 6 h died (Norwood et al. 1950). The significance and extent of the worker's exposure level being "much higher" (page 10, lines 20-22) should be discussed in the following context: Two other coworkers exposed to the same level for 4 h only had very mild headaches and some dizziness (page 10, lines 16-17), although Davis (1934) reported severe nausea, vomiting, and headache in all three test subjects at carbon tetrachloride concentrations as low as 317 ppm for 30 min. This concentration is approximately 25% higher than the 250-ppm concentration reported by Norwood et al. but the responses were more severe.

Other Comments

The relevance of fetal toxicity to the determination of AEGLs should be discussed beyond its mere mention at the end of Section 3.3 (page 25, lines 18-19).

The discussion on the enhanced toxicity from alcohol consumption on page 36, lines 6-10, is inadequate on the basis of a single mention of the death of a worker reported by Norwood et al. (1950), where the exposure level was called into question on page 10 (see discussion of this issue provided under Comments for AEGL-3). Information readily available from reviews in the open literature should be presented.

A rationale should be given for considering the "ethanol-induced P-450" sensitive individuals for the derivation of AEGL-3 values but not for AEGL-1 and AEGL-2 values. Norwood et al. (1950) reported on a worker with heavy alcohol consumption who had headache and dizziness within 15 min of exposure while his coworker experienced less severe effects.

The reasons for significant differences between the AEGL values and pertinent time-specific standards recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) should be discussed in the text.

Comment References

Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister, and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. A.M.A. Arch. Ind. Hyg. Occup. Med. 6(1):50-66.

Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. J. Am. Med. Assoc. 103(13):962-966.

Norwood, W.D., P.A. Fuqua, and B.C. Scudder. 1950. Carbon tetrachloride poisoning: More regulation, more education needed. Arch. Ind. Hyg. Occup. Med. 1(1):90-100.

CHLOROFORM

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on chloroform. 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:

> Chloroform is a volatile liquid with a pleasant, nonirritating odor. The chemical is miscible with organic solvents but only slightly soluble in water. . . . AEGL-1 values were not recommended. Based upon the available data, attempts to identify a critical effect consistent with the AEGL-1 definition were considered tenuous and uncertain. . . . The AEGL-2 values for chloroform were based upon fetotoxicity in rats. . . . The AEGL-3 values for chloroform were based upon a 560-minute mouse LCt_{50} of 4500 ppm.

The committee found that the revised TSD appropriately addressed its comment from a previous meeting and is ready to be finalized.

CHLOROSILANES

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on 26 selected chlorosilanes. A presentation on the TSD was made by Heather Carlson-Lynch, 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. . . . Although chemical-specific data are not available for many of the title chlorosilanes, acute inhalation data from rat studies are available for structurally-similar chlorosilanes. . . . Hydrogen chloride is the only hydrolysis product released into the air. . . .Therefore, hydrogen chloride AEGL values were adopted as AEGL values for monochlorosilanes, AEGL values for dichlorosilanes were derived by dividing the hydrogen chloride AEGL values by a molar adjustment factor of two, AEGL values for the title trichlorosilanes were derived by dividing the hydrogen chloride AEGL values by a molar adjustment factor of three, and AEGL values for tetrachlorosilane were derived by dividing the hydrogen chloride AEGL values by a molar adjustment factor of four.

Specific Comments

The committee supports the consolidation of 26 chlorosilanes into one TSD. The proposed AEGL-1, -2, and -3 values for the chlorosilanes were approved.

Other Comments

Document Publication and Aggregation

Because the toxic effects of acute exposure to chlorosilanes seem adequately explained by the generation of and exposure to hydrogen chloride, consideration should be given to rewriting the chlorosilane TSD as an appendix or attachment to the hydrogen chloride TSD when the AEGL documents are reviewed for updating (the hydrogen chloride TSD was published in 2004). Such an approach was used in the past for the TSDs on phosphine and metal phosphides.

Document Harmonization

The following two comments suggest that the chlorosilanes TSD should be more carefully coordinated with the hydrogen chloride TSD. A sentence should be inserted stating that the reader should consult the published TSD on hydrogen chloride for additional information in the Executive Summary and in appropriate locations in the body of the TSD.

Page 19, line 3: The TSD on hydrogen chloride (NRC 2004) describes a human exposure resulting from a trichlorosilane spill, which is not mentioned in the chlorosilane TSD. This case report should be added because it involves a significant AEGL-2 level toxic effect, reactive airways dysfunction syndrome, which is relevant to the evaluation of the chlorosilanes.

Page 36, line 6: “The hydrogen chloride data set is fairly robust.” This statement needs to be rewritten, as this is not the way the TSD on hydrogen chloride describes the data set. The statements in Appendixes B and D of the chlorosilanes TSD for the derivation of the AEGL-2 values (specifically the discussion of data quality) are not consistent with the characterizations of the hydrogen chloride AEGLs. The hydrogen chloride TSD describes the confidence in the data as “moderate,” whereas the chlorosilanes TSD describes it as “good.”

The committee’s comments on the draft TSDs for individual chlorosilanes addressed concerns with Section 8.3 (Data Adequacy and Research Needs). Those comments focused on the uncertainties introduced by the sparseness of the database and the assumptions that were made, which affect the assessment of the adequacy of the data for deriving AEGL values. Some of these concerns are mitigated by aggregating the data on the 11 chlorosilanes tested, but others remain, especially the concerns associated with evidence on hydrogen chloride.

Utility of the Data Adequacy Section

Section 8.3, page 36: The requirements in the AEGL Standing Operating Procedures (Section 2.3.3) are not addressed. The procedures indicate that "this section reflects a 'best professional judgment' approach in the evaluation of the data adequacy and future research needs." Guidance is provided for addressing the issue of data adequacy and research needs and specifies the points to be addressed in the TSD. The chlorosilanes document is particularly suited for the tiered approach to data-adequacy assessment, as laid out in the procedures.

It would be more useful to have direct statements regarding data adequacy and research needs. Consider using phrasing such as the following:

- Data are therefore considered adequate for the derivation of AEGL values.
- Confidence in the AEGL values (especially those for AEGL-2 values) is moderate due to sparseness of the data and uncertainties due to assumptions
- No additional research is needed to refine the AEGL values.

Database Uncertainties and Their Acknowledgement

The database for the toxicity of the chlorosilanes is sparse. As stated above, the toxic effects of acute exposure to chlorosilanes seem adequately explained by the generation of and exposure to hydrogen chloride. However, the draft TSD includes only minimal information on other hydrolysis products or decomposition products, and no information was identified as to whether any toxicity information was related to them.

Although the draft TSD on chlorosilanes addressed the committee's previous recommendation that an explanation be provided for removing discussion of other toxic intermediates, the uncertainties associated with them remain and should be explicitly addressed. The following comments are related to this concern:

Cover, Title page, and Tables 2-27: The 26 chlorosilanes include three distinct groups that might (or might not) differ in their toxic properties. The largest group has only alkane substituent groups, the second group has one (or more) alkene or aromatic substituents, and the smallest group has chlorinated substituents. The assumption made in the draft TSD is that the acute toxicity is due to hydrogen chloride formed as a hydrolysis product, and the animal data support this assumption. The data were generated using 11 of the 26 chlorosilanes covered by the draft TSD, including two of the three that have alkene substituent groups. However, two chlorosilanes have aromatic substituents and two (including one of the aromatics) have chlorinated substituents, and none of these was among the tested compounds. This problem introduces some uncertainty regarding the degree to which the straightforward molar equivalent calculation will conservatively estimate the acute toxicity of these compounds. Practically speaking, their toxicities might not be changed appreciably; however, the uncertainty should be noted in Section 4.3 or 4.4 of the TSD.

Page 9, lines 8-11: Is there a citation for the statement that chlorosilanes react rapidly with water, steam, or moisture and decompose to form hydrogen chloride gas and silanols, which condense spontaneously to form highly cross-linked polymeric gels and for the statement that hydrogen chloride is the only hydrolysis product released into the air? The latter statement can lead to the inference that the only exposure possible is to the airborne hydrogen chloride. Review of the discussions on page 19, line 36, and on page 22, lines 19-20, indicates that if hydrolysis is not complete prior to the inhalation of a chlorosilane, hydrolysis and/or other reaction and/or decomposition products can form in biologic tissues. This process constitutes an exposure to these compounds. These products might not be limited to polymeric gels, which, if they form in airway tissues, might pose additional problems.

Page 19, line 36: Was the phrasing "Because chlorosilanes react with moisture to produce a variety of hydrolysis products . . . ." quoted from the referenced article? If from another source, provide a citation.

Page 21, Section 3.5: A statement should be inserted in this section to the effect that no information was found relating to the toxicity of silanols or other identified decomposition products (e.g., in the draft TSD for trimethylchlorosilane, reference is made to hexamethyldisilane). Alternatively, if toxicity information is identified for any of these products, a brief description should be added.

Extrapolation of Animal Data to Human Exposure

The committee questions the degree of conservatism of the exposure, dose, and effect model as addressed in the following comments.

Page 23, lines 30-37: Only passing reference is made to the distribution in the human population of nose breathers and mouth breathers, and the shift to mouth breathing with exercise or stress. Additional relevant information on this subject might be available that could help in assessing the uncertainty inherent in using data from rats (obligatory nose breathers) for AEGLs development; if so, it should be cited here.

Page 23, lines 41-43, and page 49: No sensitive subpopulations were identified, nor are any such identified in Section 4.4 of the hydrogen chloride TSD. However, the derivation of the AEGL-1 values for hydrogen chloride describes people who have asthma as being part of a sensitive subpopulation. The uncertainty factor for intraspecies variation was lowered to 1, because the POD was taken from a study that included asthmatic individuals. Asthmatics (and possibly others with sensitive airways) need to be discussed in Section 4.4.2.

Page 27, lines 17-18: In light of the statement on page 23, lines 25-27, that the mouse might not be a reliable model for humans because they appear to be more susceptible to the lethal effects of hydrogen chloride than other rodents or baboons, should the Nakashima et al. (1996) study in mice be cited here as being relevant to setting an AEGL-3 value, or should it be used as a supporting study in another location?

Comment References

Nakashima, H., K. Omae, T. Takebayashi, C. Ishizuka, H. Sakurai, K. Yamazaki, M. Nakaza, T. Shibata, M. Kudo, and S. Koshi. 1996. Acute and subacute inhalation toxicity of dichlorosilane in male ICR mice. Arch. Toxicol. 70(3-4):218-223.

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

EPICHLOROHYDRIN

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on epichlorohydrin. 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:

> Epichlorohydrin is a colorless liquid at room temperature; its vapor is explosive when mixed with air. It has a sweet, pungent or chloroform-like odor. . . . AEGL-1 values were derived from the no-effect level for irritation in four subjects exposed to epichlorohydrin vapor. . . . No specific effects consistent with the definition of AEGL-2 were reported in any of the studies on nonlethal effects. Therefore, AEGL-2 values were derived by reducing the AEGL-3 values by a factor of

3. . . . The 10-min, 30-min, and 1-hr AEGL-3 values were based on the 1-hr rat LC_{01} of 721 ppm. . . . The 4-hr AEGL-3 value was based on the 6-hr rat LC_{01} of 274 ppm. . . . The 8-hr AEGL-3 was based on a no-effect-level for death in rats in a repeated-exposure lifetime study.

Specific Comments

AEGL-1

The comment that response to sensory irritants is not expected to vary greatly among individuals (page 41, lines 13-18) is not correct. There is often wide variability in responses to such chemicals. The wording used to justify the use of an uncertainty factor of 3 for intraspecies variability should be modified to explain the reason for departing from the default value of 10 (see Standing Operating Procedures [NRC 2001, pages 87-88).

AEGL-2

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

AEGL-3

The National Institute for Public Health and the Environment (RIVM) in The Netherlands recently published a report (Ruijten 2009) in which the lethality studies used in the draft TSD as the basis of the AEGL-3 values for epichlorohydrin are considered more "uncertain" and "not qualitatively superior" to data from an unpublished study by Kimmerle (1967), which was cited in the RIVM report but not included in AEGL TSD. Those data include a 1-h NOAEL for lethality, plus lethal concentrations. The RIVM evaluation (using the ten Berge software) produced values in good agreement with reported data. This information might be useful in refining the derivation of the AEGL-3. The analysis in the RIVM report should be explicitly considered in the draft TSD with rationale given for accepting or rejecting it.

Confidence in the 8-h AEGL-3 value would be increased if alternative PODs were evaluated (that is PODs other than a no-effect level in a lifetime exposure study with total uncertainty factor of 1) in a manner similar to that done with the 6-h exposure data in the Laskin et al. (1980) study. See, for instance, the studies referenced in Ruijten (2009) or those listed in the Centers for Disease Control and Prevention's Registry of Toxic Effects of Chemical Substances (http://www.cdc.gov/niosh-rtecs/TX4AC4a0.html).

Other Comments

Responses to Previous Comments

In general, the responses were clear, and the changes made to the draft TSD were appropriate. Exceptions are noted in the following three items.

Page 15, lines 29-30 and 34-35: A previous comment dealt with chromosome aberrations and whether they are long-lived effects. The specific citation has been addressed, but disparate statements remain in these lines. An easy resolution might be to change the wording of line 35 to read "long-term *clinical* effects" or some similar phrasing.

Page 26, lines 7-10: Although the rewritten section on rat kidney damage (or the lack thereof) is responsive to previous comments, the wording is ambiguous. Is the conclusion that the observed changes are not toxicologically significant attributable to the authors of the study (Robinson et al. 1995) or to the professional judgment of the author(s) of the draft TSD? These two sentences should be rewritten to clarify this point.

Page 38, lines 28-29: The second sentence here begins "All three compounds," but the previous sentence merely lists the synonyms for epichlorohydrin, a single compound (unless the two optical enantiomers are counted separately). The first sentence should be reworded to emphasize and make explicit the point made here: "Structurally, epichlorohydrin can be related to either ethylene oxide or propylene oxide (i.e., either as chloromethyl ethylene oxide or as chlorinated propylene oxide)." The chemical nomenclature using "oxirane" can be discussed in the Introduction, if desired, but it adds nothing to this section.

Potential Carcinogenicity

Page 7, lines 41-46: The statement regarding the cancer unit risk for epichlorohydrin should disclose that it is for risks at the 1 in 10,000 level (10^{-4}), and should state that this is the level of risk most relevant for emergency exposure and response purposes (see Standing Operating Procedures, Section 2.8.4).

Page 13, lines 6-8: "The U.S. Environmental Protection Agency considered the human data to be inadequate for evaluating the carcinogenicity of epichlorohydrin (U.S. EPA 2006)." The sentence, although correct with regard to the human evidence, does not capture EPA's full evaluation. EPA's Integrated Risk Information System (IRIS) database shows that as of 1992 epichlorohydrin has been classified as a B2 carcinogen (probable human carcinogen, on the basis of sufficient evidence of carcinogenicity in animals). This statement should be added to the TSD.

Page 13, lines 21-22: The description of the International Agency for Research on Cancer (IARC) review of epichlorohydrin, as with the EPA IRIS citation above, is technically correct but substantively incomplete. The TSD should state that IARC categorized epichlorohydrin as "probably carcinogenic to humans (Group 2A)."

It is also noteworthy that the TLV for epichlorohydrin carries a carcinogen classification of A3 (confirmed animal carcinogen with unknown relevance to humans [since 1997]).

Page 58, Appendix B: The equation and calculations of the virtually safe dose and subsequent calculations should be checked for accuracy. The relevant AEGL values for noncancer effects should be presented in the table reporting the values associated with cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} to facilitate comparisons. It would be preferable to structure the table in the traditional format of presenting AEGL values: The exposure durations should be the column headings, and the AEGL values and cancer risk levels should constitute the row designations; entries should be sorted by ascending level of risk using the 1-h values.

Odor Issues

Section 2.2.1, page 10: Another useful reference for odor thresholds is Ruth (1986).

Page 10, lines 19-20, and PAGE 53, lines 26-27: Van Doorn et al. (2002) 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. A 2009 version of this report (Ruijten et al. 2009) has since been published, so the updated citation should be used.

Use of Tables to Present Data

Tables are important in examining and making comparisons of the data, especially when comparing the exposure conditions and results across several studies. Many studies (or useful data points) are discussed in the text but are not included in existing tables. For example, Table 3 does not include the studies by Freuder and Leake (1941) described on page 19 of the TSD or the Mobay Chemical Corporation (1983) study described on page 20.

Table 7 summarizes nonlethal effects, but mixes both single and repeat exposure studies. The data presentation would be easier to follow if these were separated into two tables. These tables should summarize all components of the studies regardless of where they are discussed in the text, unless good reason exists for excluding them (which should be clearly stated). Examples of places where one paper is discussed in multiple sections include the following:

- The results of the UCC (1983) study with rats are described on page 19, with monkeys (acute and repeated exposures) on page 25, and with dogs on page 31.
- The Mobay Chemical Corporation (1983) 5-day exposure studies with rats are described on page 19, with mice and guinea pigs on page 21, with rabbits on page 22, and with cats on page 23.
- The John et al. (1983) study with rabbits is described on page 22 and with rats on page 28.
- The Gage (1959) study with rats is described on page 28 and with rabbits on page 31.

Sometimes errors are introduced as summary tables are constructed, or useful data points are overlooked. For example,

- In Table 3, the approximate lethal concentration for the dog in the UCC (1983) study (430 ppm) was excluded.
- In Table 7, the Quast et al. rat study is cited as 1979b but is described on page 28 as 1979a.
- In Table 7, the Quast et al. (1979b) mouse study described on page 29 should include a note that there were 9 exposure days during the 12-day study period.

Concern about the utility of aerosol exposure data (or the comparability of vapor data with aerosol data) should not lead to exclusion of the data; it can be presented in a separate table(s) if there are several studies or appropriately annotated in existing tables.

General Comments

Page 42, line 33: "Studies using aerosols should not be used to derive AEGL values." It is unclear why aerosol data were excluded from consideration. The AEGL Standing Operating Procedures appear to support the use of such data. For example, the procedures state, "Therefore, no dosimetry adjustments have been made to date by the NAC-AEGL Committee for attaining human-equivalent doses in the development of AEGLs for gases, vapors, and aerosols" (p. 57). The implication is that AEGLs might be developed for aerosols. The procedures also state, "The determination of susceptibility entails the presence of observable changes in biochemical or physiologic processes reflecting dose-response relationships unique to a chemical (e.g., sulfur dioxide) or class of chemicals (e.g., acid aerosols)" (p. 81).

The TSD for titanium tetrachloride (discussed elsewhere in this report) involves an aerosol exposure; a second example is the metal phosphides (NRC 2008). A number of chemicals can occur as a vapor, an aerosol, or both (Perez and Soderholm 1991).

Comment References

EPA (U.S. Environmental Protection Agency). 2006. Epichlorohydrin (CASRN 106-89-8). Integrated Risk Information System, U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/iris/subst/0050.htm [accessed Oct. 30, 2006].

Freuder, E., and C.D. Leake. 1941. The toxicity of epichlorohydrin. U. Calif. Pharmacol. 2(5):69-78.

Gage, J.C. 1959. The toxicity of epichlorohydrin vapour. Br. J. Ind. Med. 16(1):11-14.

John, J.A., J.F. Quast, F.J. Murray, L.G. Calhoun, and R.E. Staples. 1983. Inhalation toxicity of epichlorohydrin: Effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68(3):415-423.

Kimmerle, G. 1967. Toxicological Studies with Epichlorohydrin. Bayer AG Report No 479. Wuppertal, Bayer AG.

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

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

Mobay Chemical Corporation. 1983. Toxicological Studies with Epichlorohydrin. 8DS Submission. Doc. I.D. 878211473.

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.

Quast, J.F., J.W. Henck, B.J. Postma, D.J. Schuetz and M.J. Mckenna. 1979a. Epichlorohydrin – Subchronic Studies. I. A 90-day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats, and B6C3F1 Mice). Dow Chemical Co., Midland, MI. 8DS Submission, U.S. Environmental Protection Agency, Doc. I.D. 878210751.

Quast, J.F., J.W. Henck, B.J. Posma, et al. 1979b. Epichlorohydrin – Subchronic Studies. II. 12-Day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats and B6C3 F1 Mice). Dow Chemical Co., Midland, MI. 8DS submission, U.S. Environmental Protection Agency, Doc. I.D. 8783210753.

Robinson, B.L., D.E. Guinnup, J.E. Andrews, J.W. Allis, A. McDonald, J.C. Seely, T.J. Mohin, and J.E. Simmons. 1995. Hepatic and renal assessment of acute exposure to inhaled epichlorohydrin: Toxicological evaluation and exposure modeling. Inhal. Toxicol. 7(2):289-301.

Ruijten, M. 2009. Probit Function Technical Support Document. RIVM Report 20091015-Epichlorohydrin-Interim (15 October, 2009). National Institute for Public Health and the Environment, Bilthoven, The Netherlands [online]. Available: http://www.rivm.nl/milieuportaal/images/20091015-epichlorohydrin-interim.pdf [accessed Aug. 3, 2010].

Ruijten, M.W.M.M., R. von Doorn, A.Ph. van Harreveld. 2009. Assessment of Odour Annoyance in Chemical Emergency Management. RIVM Report 609200001. National Institute for Public Health and the Environment, Bilthoven, The Netherlands [online]. Available: http://www.rivm.nl/bibliotheek/rapporten/609200001.pdf [accessed Aug. 2, 2010].

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

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

Van Doorn, R., M. Ruijten, and T. van Harreveld. 2002. Guidance for the Application of Odor in 22 Chemical Emergency Response, Version 2.1, August 29, 2002. Public Health Service of Rotterdam, The Netherlands.

FORMALDEHYDE

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on formaldehyde. 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:

> Formaldehyde is a colorless flammable gas with a pungent, suffocating odor. . . . The AEGL-1 was based on a NOAEL for eye irritation in a single study with subjects whose eyes were sensitive to formaldehyde. . . . The AEGL-2 was based on the clinical study of Sim and Pattle

(1957). Twelve healthy male subjects inhaled 13.8 ppm for 30 minutes. . . . The AEGL-3 values were based on the highest non-lethal value for the rat following a 4-hour exposure to 350 ppm.

Specific Comments

AEGL-1

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

AEGL-2

Boja et al. (1985) reported decreased motor activity with 15 min of exposure to formaldehyde at 5 ppm. This study should be considered for the AEGL-2 derivations. Consideration should be given to whether the decreased motor activity could be a result of a behavioral or stress reaction to the odor or irritation.

AEGL-3

The 8-h AEGL-3 value for formaldehyde was set equal to the 4-h value because formaldehyde is well scrubbed in the nasal passages. Presumably the absorption data were derived from animal studies. The committee recommends that the TSD authors check whether the studies were performed at the proposed AEGL-3 values (35 ppm or above) and whether saturation could occur. In addition, there are substantial species differences in the anatomy and physiology of the nasal passages between rodents and humans, and their effects on the dosimetry of formaldehyde should be elaborated in more details.

It is also unknown whether tissue saturation could occur in human nasal passages, particularly at high concentrations and long exposure durations. If saturation occurred, formaldehyde could penetrate into the lower airways, resulting in a higher lung dose. The committee recommends that the nasal deposition models be reviewed (e.g., Conolly et al. 2003, 2004; Kimbell 2006; Schroeter et al. 2006) and that comparisons be made across species between lung dose at different rates and mode of breathing (nose versus mouth).

Page 8, line 19: Clarification is needed to explain why the Nagornyĭ et al. (1979) study (highest nonlethal effect in rats following 4-h exposure was 350 ppm) was selected for the POD when Carpenter et al. (1949) reported deaths (33-66%) following a 4-h exposure to formaldehyde at 250 ppm. Because there could be strain differences in their sensitivity to formaldehyde exposure, this information should be noted in Table 4 and 5.

Other Comments

Page 7, line 14: Since the general public is particularly concerned about the carcinogenic potential of formaldehyde, the carcinogenicity discussion in the Executive Summary should be expanded to include the exposure guideline values developed by EPA and the World Health Organization. The summary of the epidemiologic evidence appears to be overly generalized, and conclusions regarding carcinogenicity studies should be presented more cautiously. Some context on exposure concentrations at which carcinogenic effects are observed should also be provided.

Page 7, line 15: The statement that “formaldehyde is so highly reactive and rapidly metabolized/detoxified by the tissues of the nasal passages, inhalation is unlikely to result in cancers at remote sites” is inconsistent with the EPA (2010) draft IRIS assessment on formaldehyde. The IRIS

document makes the case that formaldehyde and its metabolites could be transported to the other organ systems. Another NRC committee is currently reviewing the IRIS document. Whether formaldehyde and its metabolites can be transported systemically is controversial and should be carefully considered and handled consistently in EPA's evaluations. An updated literature review on this topic should be performed.

Page 14-16: Table 3 in its current form is not very useful and informative. The Subjects/Effect column should be divided into separate Subjects and Effects columns so that the effects on healthy and sensitive subjects can be clearly delineated.

Comment References

Boja, J.W., J.A. Nielsen, E. Foldvary, and E.B. Truitt, Jr. 1985. Acute low-level formaldehyde behavioural and neurochemical toxicity in the rat. Prog. Neuro-Pshychophamacol. Biol. Psychiatry 9(5-6):671-674.

Carpenter, C.P., H.F. Smyth, and U.C. Pozzani. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyd. Toxicol. 31(6):343-346.

Conolly, R.B., J.S. Kimbell, D. Janszen, P.M. Schlosser, D. Kalisak, J. Preston, and F.J. Miller. 2003. Biologically motivated computational modeling of formaldehyde carcinogenicity in the F344 rat. Toxicol. Sci. 75(2):432-447.

Conolly, R.B., J.S. Kimbell, D. Janszen, P.M. Schlosser, D. Kalisak, J. Preston, and F.J. Miller. 2004. Human respiratory tract cancer risks of inhaled formaldehyde: Dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. Toxicol. Sci. 82(1):279-296.

EPA (U.S. Environmental Protection Agency). 2010. Toxicological Review of Formaldehyde – Inhalation Assessment (CAS No. 50-00-0) in Support of Summary Information on the Integrated Risk Information System (IRIS), Volumes I, II, III, and IV. U.S. Environmental Protection Agency, Washington, DC. June 2, 2010.

Kimbell, J.S. 2006. Nasal dosimetry of inhaled gases and particles: Where do inhaled agents go in the nose? Toxicol. Pathol. 34(3):270-273.

Nagornyĭ, P.A., Z.A. Sudakova, and S.M. Schablenko. 1979. General toxic and allergic action of formaldehyde [in Russian]. Gig. Tr. Prof. Zabol. 1:27-30.

Schroeter, J.D., J.S. Kimbell, M.E. Andersen, and D.C. Dorman. 2006. Use of a pharmacokinetic-driven computational fluid dynamics model to predict nasal extraction of hydrogen sulfide in rats and humans. Toxicol. Sci. 94(2):359-367.

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

HYDROGEN BROMIDE AND HYDROGEN IODIDE

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on hydrogen bromide and hydrogen iodide. A presentation on the TSD was made by Heather Carlson-Lynch, of Syracuse Research Corporation. The following is excerpted from the Executive Summary of the TSD:

> The hydrogen halides hydrogen bromide (HBr) and hydrogen iodide (HI) are colorless, corrosive, non-flammable gases. . . . No empirical data were available for HI. In the absence of data, the HI values were set equal to the HBr values. . . . The AEGL-1 was based on a study with six human volunteers exposed to 2, 3, 4, 5, or 6 ppm HBr for several minutes. . . . The point of departure for derivation of AEGL-2 values for HBr is the exposure of male rats to 1000 ppm for 30 minutes which resulted in lesions of the nasal passages. It could not be ascertained if the lesions were reversible. . . . The $BMCL_{05}$ of 1239 ppm, calculated from 1-hour lethality data for Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972), was selected as the point of departure to develop AEGL-3 values for HBr.

Specific Comments

AEGL-1

The committee approved the derivation of the AEGL-1 values for HBr and HI.

AEGL-2

The use of a modifying factor of 2 for the 30-min POD of 1,000 ppm is appropriately supported by the justification that "the severity of the lesions may exceed the definition of AEGL-2 and because this concentration is close to the calculated benchmark concentration with its lower confidence limit at a 5% extra risk ($BMCL_{05}$) of 1,239 ppm used as the point of departure for the AEGL-3." In addition, it should be noted that the reason for the closeness between the POD and the $BMDL_{05}$ might be that the rats in the study from which the POD was determined (Kusewitt et al. 1989) were killed within 8 to 24 h after a single exposure, instead of the 14-day post exposure observation period generally used for acute toxicity tests. The need for this protracted observation period is important because delayed death after acute exposure was noted in Section 3.1.1 (page 12, line 37) of the TSD.

The AEGLs values for HI were set equal to those for HBr because of the lack of data on HI. Consideration should be given to applying an additional modifying factor to the AEGL-2 and AEGL-3 values for HI because it is more unstable than HBr. The committee recommends that an additional modifying factor of 2 be applied to HI in addition to the modifying factor of 2 that was applied to HBr because of a lack of information on that compound, for a total modifying factor of 4.

AEGL-3

The committee approved the derivation of the AEGL-3 values for HBr and HI.

Other Comments

Page 6, lines 30-33, and page 16, lines 43-45: The discussions about toxicity in relation to solubility should be revised. A chemical that is highly soluble might not be less toxic than one that is less soluble. The relationship between solubility and toxicity often depends upon the exposure concentration. A highly soluble chemical might show disproportionate toxicity at higher concentrations when the upper airways become saturated and more reaches the lower airways.

Page 10, lines 1-2: Are not all ionic acids wholly in the ionic form in aqueous solution?

Page 12, line 41: The value for the "lower concentration" should be specified.

Page 13, lines 11-34: The specific anatomical localization of the numbered regions in the nasal cavity should be described.

Page 14, line 15-16: This sentence seems to suggest that the controls and exposed animals had similar lung lesions. Is that correct?

Page 16, lines 7-9: By definition, an irritant produces an effect at the site of contact. Therefore, it is only necessary here to note that HBr is an irritant. However, the next sentence noting that uptake and metabolism are not relevant to development of AEGL guidelines is too general a comment. Some irritants could have systemic effects, although for HBr this is not expected.

Page 16, lines 13-14: The sentence regarding iodine should be deleted because it does not provide adequate discussion of the speciation and amount of iodide absorbed or provide the context of the recommended upper limit of beneficial iodide intake.

Page 17, lines 8-12: These conclusions should be revised to be consistent with revisions to the document regarding the relation between solubility with toxicity.

Page 18, lines 23-27: The increased penetration of HBr and HI into the lower respiratory tract could also be due to switching from nasal to oronasal breathing under stress.

Page 19, lines 27-29: The comment that response to sensory irritants is not expected to vary greatly among individuals is not correct. There is often wide variability in responses to such chemicals. The wording used to justify the use of an uncertainty factor of 3 for intraspecies variability should be modified to explain the reason for departing from the default value of 10.

Page 21, lines 21-24: Although the steep dose-response curve might suggest little interindividual variability in a genetically identical group of animals, it might not do so in the more heterogeneous human population.

Page 25, Table 15: Given the steep dose response curve, the 30-min AEGL-2 value is not consistent with the IDLH value for HBr. The possible reason for the discrepancy should be discussed.

Comment References

Kusewitt, D.F., D.M. Stavert, G. Ripple, T. Mundie, and B.E. Lehnert. 1989. Relative acute toxicities in the respiratory tract of inhaled hydrogen fluoride, hydrogen bromide, and hydrogen chloride. Toxicologist 9:36.

MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72-62. AD 755 358. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

METHYL BROMIDE

At its meeting held on June 15-18, 2010, the committee reviewed the TSD on methyl bromide. 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:

> Methyl bromide is a colorless, nonflammable gas, with no taste or odor properties at low concentrations. . . . Methyl bromide has no odor or irritation properties at concentrations below those that define the AEGL-2. Therefore, an AEGL-1 was not established. . . . The AEGL-2 values are based on the NOAEL for neurotoxicity as evidenced by a lack of clinical signs in several studies with rats and dogs. . . . The AEGL-3 values were based on the $BMCL_{05}$ of 701 ppm in a 4-hour exposure of rats.

Specific Comments

AEGL-1

The study by the Japanese Ministry of Labor (1992) should be considered as a potential POD for AEGL-1 values on the basis of lacrimation observed in rodents.

The statement on page 37, line 16, that methyl bromide is not detectable at concentrations that are thresholds for tissue lesions or neurotoxicity should be put in context with the definition of AEGL-1.

AEGL-2

Consideration should be given to using the dog study (Newton 1994) to determine the POD for the AEGL-2 values because the dog is more relevant to humans. However, the study only had two dogs, so if the study is used as the basis for AEGL-2 values, a modifying factor should be applied to account for the small number of test animals.

AEGL-3

Consideration should be given to lowering the AEGL-3 value because of the steep dose-response curve observed for methyl bromide.

Other Comments

A paper by Johnson et al. (1993) on glutathione-*S*-tranferase isoenzymes in rat brain should be added to help explain the susceptibility of the rat brain to methyl bromide.

Comment References

IPCS (International Programme on Chemical Safety). 1995. Methyl Bromide. Environmental Health Criteria 166. Geneva: World health Organization [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc166.htm [accessed Aug. 3, 2010].

Japanese Ministry of Labour. 1992. Toxicology and Carcinogenesis Studies of Methyl Bromide in F344 Rat and BDF Mice (Inhalation Studies). Industrial Safety and Health Association, Japanese Bioassay Laboratory, Tokyo. 197 pp (as cited in IPCS 1995).

Johnson, JA., A. el Barbary, S.E. Kornguth, J.F. Brugge, and F.L. Siegel. 1993. Glutathione S-transferase isoenzymes in rat brain neurons and glia. J. Neurosci. 13(5):2013-2023.

Newton, P.E. 1994. An Up-and-Down Acute Inhalation Toxicity Study of Methyl Bromide in the Dog. Study No. 93-6067. Pharmaco LSR, East Millston, NJ.

METHYL CHLORIDE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on methyl 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:

> Methyl chloride is a substantially odorless, colorless gas with moderate flammability and explosiveness. . . . Because methyl chloride has no clearly defined odor or warning properties at concentrations that may be neurotoxic, an AEGL-1 is not recommended. The AEGL-2 values were based on several studies with rats; a monitoring study was used as support. . . . Data on lethality are limited to LC_{50} values for the mouse, a particularly sensitive species.

Specific Comments

AEGL-1

As noted in the TSD, the literature for deriving AEGL-1 values for methyl chloride is sparse. The committee recommends exploring the data in the paper by Ruth (1986), which might give an indication of a threshold for irritation that could be an appropriate POD for AEGL-1 values. Alternatively, the basis of the TLV-STEL of 100 ppm should be considered a potential POD.

AEGL-2

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

AEGL-3

Consideration should be given to whether it is appropriate to consider a single 6-h exposure to methyl chloride at 5,000 ppm as a POD on the basis of a repeated exposure study in which deaths were observed. If deemed appropriate, it might be preferable to use the Morgan et al. (1982) study because it appears that no deaths occurred in that study.

Comment References

Morgan, K.T., J.A. Swenberg, T.E. Hamm, Jr., R. Wolkowski-Tyl, and M. Phelps. 1982. Histopathology of acute toxic response in rats and mice exposed to methyl chloride by inhalation. Fundam. Appl. Toxicol. 2(6):293-299.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

NITRIC ACID

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on nitric acid. 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:

> Nitric acid is a highly corrosive, strongly oxidizing acid. . . . For derivation of the AEGL values, both human and animal data were utilized. For AEGL-1 a concentration of 0.53 ppm was adopted for all time points. . . . The derived AEGL-1 value is above the odor threshold which provides a warning of exposure before an individual could experience notable discomfort. . . . AEGL-2 and -3 values were based on a lethality study in rats. The point of departure is a NOAEL for AEGL-2 effects and would not be escape impairing; higher concentrations resulted in more severe clinical signs including partially closed eyes and lung noise. . . . AEGL-3 was based on an estimated LC_{01} calculated by a log-probit analysis from the lethality study in rats."

Specific Comments

AEGL-1

The committee recommends an uncertainty factor of 10 for intraspecies differences, because nitric acid exhibits a wide range of responses from healthy or asthmatic individuals and the Sackner and Ford (1981) study used healthy individuals.

AEGL-2

The transient body-weight loss used to derive AEGL-2 values is not an appropriate end point for this guideline level. The study reported partially closed eyes, a borderline AEGL-2 effect, and gasping at the next highest test concentration of 1,600 ppm, an AEGL-2 effect. Thus, the committee recommends a POD of 1,600 ppm for derivation of the AEGL-2 values for nitric acid.

AEGL-3

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

Other Comments

References to red fuming nitric acid (RFNA) should be removed and inserted into the TSD on oxides of nitrogen.

Nitric acid may exist in the following airborne forms: gas, vapor, mist, fume, and aerosol. The TSD should point out that mist will probably be scrubbed in the mouth or nasal passages, gas and vapor in the upper respiratory tract, and fume and aerosol in the alveolar region.

Page 9, lines 13-23: This case report involves the contact of nitric acid and zinc. Consideration should be given to the reaction of these compounds. Did the authors attribute the effects to only nitric acid? Because the reference was published in 1905, consideration should be given to deleting it.

Page 10, lines 15-21: This case report involved exposure to what was probably nitrogen monoxide (see TSD, page 11, line 37), so the committee recommends removing this reference because it does not involve exposure to nitric acid.

Page 13, line 19: Because all the studies involved exposures to nitric acid fumes, justification should be provided to apply these studies to the vapor and mist forms.

Page 15, lines 5-23: This study compared the toxicities of nitrogen dioxide, RFNA, and white fuming nitric acid (WFNA). Nitric acid produces a white fume, and RFNA (also known as IRFNA-inhibited red fuming nitric acid) produces a red fume, which is due to the nitrogen dioxide. It is likely that there are two different agents for WFNA and RFNA. As noted above, it would be appropriate to remove discussion of RFNA from this TSD.

Page 19, lines 21-28: Why was the Goldstein reference not discussed in Section 3 (Animal Toxicity Data)?

Comment Reference

Sackner, M.A., and D. Ford. 1981. Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function of normal and asthmatic adults, and preliminary results in normals exposed to nitric acid fumes. Am. Rev. Respir. Dis. 123(4):151.

NITROGEN DIOXIDE, NITROGEN TETROXIDE, AND NITRIC OXIDE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on nitrogen dioxide, nitrogen tetroxide, and nitric oxide. 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:

> Nitrogen oxide compounds occur from both natural and anthropogenic sources. . . . AEGL values were developed based on data for NO_2, the predominant form, and values are considered applicable to all nitrogen oxides. . . . For AEGL-1 a concentration of 0.5 ppm was adopted for all time points. . . . 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.

Specific Comments

The proposed AEGL-1, -2, and -3 values for nitrogen dioxide, nitrogen tetroxide, and nitric oxide were approved.

Other Comments

A summary of the information in Section 4.3 Chemical Transformation of Nitrogen Oxides should be included in the Executive Summary of the TSD. The information explains the relationships among the nitrogen oxides and provides support for combining the three compounds into a single TSD.

Pages 19-21, Section 2.2.2: EPA recently revised the ambient air quality standard for nitrogen dioxide, so the epidemiologic section might need to be updated to reflect this change. The concentrations of nitrogen dioxide that were associated with increased morbidity and mortality in the general public during air pollution episodes were generally very low, usually in the ppb range. The adverse health effects seen in these exposures were not likely due to only nitrogen dioxide but rather to other more toxic air pollutants. Nitrogen dioxide is more likely to serve as a surrogate and not the primary causative agent. In this particular case, the epidemiologic data might not be useful to derive AEGL values.

Page 53, line 26: The reaction arrow in the last equation should be changed to $N_2O_4 \rightarrow 2NO_2$, because this reaction only goes one way in the environment.

PIPERIDINE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on piperidine. 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:

> Piperidine is a cyclic pyridine that behaves like a secondary amine. It is a clear colorless flammable liquid that produces vapors that reach explosive concentrations at room temperature. . . . The AEGL-1 values were based on the no-effect-level (20 ppm for 6 hours) for nasal irritation in rats. . . .The AEGL-2 values were based on exposure of rats to piperidine at 200-ppm for 6 hours, which caused nasal irritation without salivation or evidence of eye irritation. . . . The AEGL-3 values were based on the LC_{01} calculated from a 4-hour acute inhalation study in rats.

Specific Comments

The proposed AEGL-1, -2, and -3 values for piperidine were approved.

Other Comments

The TSD should have consistency with units. It would be helpful to include both ppm and mg/m^3 information when possible for comparison across studies throughout the document. A good example of how this can be done appears on page 9, line 3, in discussing the BASF (1980) study.

The literature on the acute lethality of piperidine should be reviewed to determine whether any information on the cause of the deaths in rodents can be identified. The chemistry description should be verified. Is piperidine really a pyridine?

The skin contribution to body burden or effects of skin exposure should be evaluated. The workplace environmental exposure level (WEEL) set by the American Industrial Hygiene Association (AIHA) has a skin notation (even though AIHA used a different compound to establish the WEEL for piperidine), and the reason for the notation should be discussed.

Comment Reference

BASF. 1980. Determination of the Acute Inhalation Toxicity LC_{50} of Piperidine as Vapor in Sprague-Dawley Rats After a 4-Hour Exposure. BASF Gewerbehygiene und Toxikologie [unpublished data].

TITANIUM TETRACHLORIDE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on titanium tetrachloride. 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:

> Titanium tetrachloride is a colorless liquid that fumes when in contact with moist air. The odor of titanium tetrachloride has been described as penetrating, acrid, and irritating. . . .No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, derivation of an AEGL-1 is not recommended. . . . No acute toxicity data were relevant for derivation of an AEGL-2, so repeat-exposure studies were evaluated. . . . The mortality data by Kelly (1980) were used for the AEGL-3 derivation. This study was specifically designed to evaluate the mortality response for a wide range of exposure durations.

Specific Comments

AEGL-1

It would be helpful to reconsider whether AEGL-1 values could be established for titanium tetrachloride ($TiCl_4$). Consideration should be given to such data as the "no-clinical-effect levels" from repeat-exposure studies in animals and combining animal information with epidemiologic data, as well as insights from occupational benchmarks (e.g., from AIHA 2008). A further check should be made for an estimated chronic occupational exposure level for $TiCl_4$ (e.g., based on a starting point of $0.03*RD_{50}$).

Furthermore, for comparison it would be useful to assess the relative toxicity data for titanium dioxide (TiO_2) and hydrogen chloride (key transformation products in air). The re-evaluation of AEGL-1could be strengthened by developing a more integrated compilation of dose-response data to compare similar exposure durations and effect severities across species, as well as relative humidities.

Human data could offer additional context (such as data on the ship crew who passed through a $TiCl_4$ cloud this spring, see comment below). A committee member is aware of anecdotal information regarding measurements taken from an outdoor cloud at a chemical plant that had no apparent adverse effect on exposed workers. Those measurements indicated a $TiCl_4$ concentration on the order of 15-20 mg/m^3. There is no documentation of this personal anecdote, but it might provide some general context for a potential short-duration AEGL-1.

AEGL-2

It would be helpful to reconsider the AEGL-2 values (including the POD) in light of available data, including data on overt ocular and nonescape-impairing, reversible respiratory tract irritation (see Standing Operating Procedures [NRC 2001], Section 2.2.2.2.2) for relevance to acute exposures. As with the AEGL-1, fuller data integration would strengthen this evaluation, including information relevant to species variability and related chemicals, as it is not clear that the various data support reducing the interspecies and intraspecies uncertainty factors to 3. This possibility is especially of interest given the variability introduced by relative humidity, as well as consideration of nanoscale materials.

AEGL-3

It would be helpful to reconsider the AEGL-3 values (including the POD) in light of available data, including studies not yet cited in the TSD. As with the AEGL-2 comments, these data include information relevant to species variability and related chemicals as well as other factors, as it is not clear that the various data support lowering both the interspecies and intraspecies uncertainty factors to 3. For example, it might be useful to compile NOAELs from lethality studies for integrated evaluation. According to the Standing Operating Procedures (NRC 2001, page 44), if the AEGL value is estimated by dividing an LC_{50} value by 3 (or some other divisor), then the slope of the exposure-response curve or enough data points should be given to support the division by 3 (or some other divisor). This process would extend to consideration of other lethality data beyond those summarized in the study cited.

Other Comments

Outdated Information

The TSD contains a good amount of helpful information but would benefit from updates in a number of areas to reflect more current and complete information. It appears that all references specific to $TiCl_4$ are more than 10 years old. (The only citations from this century are three older AIHA references for the emergency response planning guideline [ERPG] and WEEL values, and the 2004 NRC AEGL volume that contains a report on hydrogen chloride.) Topics for which updates are suggested are production and use, including nanoscale material; transformation products; human data; and variability. The updated information will help inform a re-evaluation of the AEGL derivations, for which some notes are offered below.

Production and Use, Including Nanoscale Materials

Page vi, lines 3-7 (Executive Summary), and page 1, lines 5-10 (Introduction): The information on production and use is dated and should be updated. For example, ITA (2008) noted a "growing global demand for high-purity $TiCl_4$ in innovative applications," while an industry report to the SEC from this spring (TIMET 2010) recognized this area's growth, while acknowledging recent economic turmoil: "Over the last ten years, titanium mill product demand in the military, industrial and emerging market sectors has increased, primarily due to the continued development of innovative uses for titanium products in these industries. Over the last several years, we, and the industry as a whole, have experienced significantly increased demand with periods of increased volatility."

Given the importance of $TiCl_4$ to the production of titanium metal and other compounds anticipated for expanded applications and more widespread use, it would be helpful to update both the production and application context. The TSD states, "Titanium tetrachloride is used . . . as a military smoke screen." Is this still the case? If it is no longer developed and used for this purpose, it would be helpful to revise the text.

From a review of the considerable amount of more recent literature (see EPA [2009] and public submittals to the e-docket associated with this EPA report and many other studies since the older data reflected in the TSD), the emergence of nanoscale materials appears to be an important consideration for these AEGLs. $TiCl_4$ is a key intermediate in the production of titanium and oxides. Thus, it would be useful to address nanoscale implications, considering both toxicokinetics (including distribution) and toxicodynamics. (Nanoscale production and use could be addressed in Chapter 1, while toxicologic information could be presented within the toxicity discussions and in Chapter 4 as Special Considerations.)

Transformation Products and Toxicity Contributions

Page vi, lines 4-7 (Executive Summary); page 1, lines 10-17 (Chapter 1); page 15, lines 7-8, and repeated at lines 37-38 (Chapter 4): The TSD does a good job of emphasizing the formation of hydrogen chloride; the brief description of fate products could benefit from even more direct context for airborne releases of $TiCl_4$ and human exposures. For example, beyond increased hydrogen chloride formation under conditions of high relative humidity, exposure to water following an airborne release notably includes contact with perspiration and tears.

It would also be helpful if the discussion of $TiCl_4$ transformation products could focus on air more specifically, as the TSD seems to blur this context a bit in having only provided sequential reactions in water (page 1, lines 11-14). The source provided for the reactions is more than 45 years old and was translated from Russian. More recent standard sources for reactions in air could be tapped.

Most important, TiO_2 is not identified in the fate discussion despite being rapidly formed when $TiCl_4$ is released to air. It is especially important to clearly identify this compound, given the relevance of associated toxicity data (not only relative to $TiCl_4$ for similar exposure durations but also in light of the considerable number of recent publications on nano-TiO_2). It would be useful to present a comparison of data for $TiCl_4$ and its two key transformation products that form quickly in air, together with interpretations regarding relative toxicities (including data from Kelly [1978] cited in Archuleta and Stocum [1993]), side by side with toxicity data for nano-TiO_2 to consider possible insights regarding relative toxicity.

EPA's health and environmental research online (HERO) database (EPA 2010) might be useful as part of this check of more recent potentially relevant toxicity data (including the ability to search for information specifically for TiO_2). NIOSH also has a draft assessment of TiO_2 that should be considered.

Human Data

More information has become available since the studies cited in the TSD (which are from 1998 and earlier). For example, Roy et al. (2003) discuss over 470 exposure incidents with $TiCl_4$ between 1990 and 1999, 13 of which involved evacuation, injuries, or deaths; the authors also noted a small tanker leak in 2001 that affected workers and others nearby (see citations in that publication). Even more recent incidents involving transportation accidents (2008) and chemical plant releases (2010) suggest that AEGLs are especially needed in light of the recent identification that $TiCl_4$ production and use is an anticipated "growth area."

In March, a 48-year-old worker exposed to $TiCl_4$ died within 2 weeks following an explosion at a United Kingdom facility (Daily Mail Reporter 2010; ENS 2010; Grimsby Telegraph 2010; HSE 2010); the company had previously been fined for $TiCl_4$ releases, including in 2006 and 2009. Although a temporary restricted fly zone was established in the area of the cloud, a vessel on the adjacent river sailed through it before controls were put in place. The crew received medical checks and had no indication of adverse effects (ENS 2010). These exposures might suggest a general context for the short-duration AEGL-1, taken together with the rough estimation made by committee members familiar with this issue that a visible cloud indicates a concentration on the order of 10 mg/m^3 (or higher). A search of the scientific and medical literature should be performed to determine whether relevant information to support these observations is available.

The United Kingdom tragedy was followed in April by the evacuation of a Louisiana community due to the release of $TiCl_4$ from a ruptured pipeline at a local chemical plant (New Orleans News 2010; Times-Picayune 2010). Although no quantitative exposure data were found in news reports for these recent incidents, a more structured pursuit of such information might be fruitful, and additional injury and mortality information could be reflected in an updated section on human data.

In addition to updating the human toxicity content with more current information, it would also strengthen the TSD to provide more information from specific key studies that were cited, such as Chen and Fayerweather et al. (1992).

Variability and Uncertainty Factors

A more integrated discussion and reconsideration of variability and uncertainty factors would be useful. For example, consider the current application of uncertainty factors for the AEGL-3, which reflect only a factor of 3 for interspecies and intraspecies variability, respectively. (Variability might be considered somewhat moderated under chronic conditions, and it might be less of a factor for the acute durations addressed by AEGLs.) The severity of effect is known to vary substantially with relative humidity, so consideration of perspiration and other factors relevant to "individual" hydrolysis is needed.

In addition, people with underlying respiratory conditions (such as those with asthma or chronic obstructive pulmonary disease), whose numbers are a nontrivial fraction in the U.S. population, are susceptible to exacerbated effects from exposure to $TiCl_4$ and its transformation products in air. Thus, to use only a factor of 3 to account for human variability, including sensitive subgroups, would need better justification, particularly in light of the potential need for further adjustments to address transformation products (and possibly nanoscale material).

For animals, acute lethality data for dogs illustrate variability within this species alone, as do the rat data of Burgess (1977) presented in Table 4. Also, a comparison of rat and mouse LC_{50} data (Archuleta and Stocum 1993) suggest that interspecies differences could be roughly 9-fold. Thus, available data even within and across animal (nonhuman) species suggest similar questions regarding the use of 3 for the interspecies uncertainty factor.

Archuleta and Stocum (1993) summarized the findings of the 2-year rat inhalation study by Lee et al. (1986) (exposure to $TiCl_4$ at 0.1-10 mg/m^3 [and hydrolysis products], 6 h/day, 5 days/week) as revealing no abnormal clinical signs, body-weight changes, or excess mortality. Further, the pulmonary

response at 1.0 mg/m^3 was presented as typical of that seen for a nuisance dust; for comparison, the Occupational Safety and Health Administration's limit for TiO_2 as a nuisance particulate is 10 times higher (10 mg/m^3). At a concentration of 10 mg/m^3 for $TiCl_4$, Archuleta and Stocum (1993) noted that the rat pulmonary response suggests chronic exposure might result in upper respiratory tract irritation and possibly acute or chronic bronchitis. Compared with the other primary fate product, $TiCl_4$ is considered more toxic than hydrogen chloride because it can penetrate to the deep lung where it can then hydrolyze to hydrogen chloride and cause further damage (as reflected in the TSD in other cited papers). These authors also noted that the intermittent low-level exposures to $TiCl_4$ (0.1-1 mg/m^3) did not result in progressive or cumulative changes in lungs of workers. It would be helpful to integrate relevant data in a table to help support the determinations regarding variability and uncertainty factors applied for the AEGL derivations.

It would also be useful to revisit related wording in various sections, including 4.4.1 and 4.4.2. For example, in Section 4.4.1, additional explanation on why $TiCl_4$ is expected to react more highly in the nasal cavity of rats than humans is needed. Section 4.4.2 should include references to studies that have considered the potential for increased susceptibility or sensitivity (e.g., Archuleta and Stocum 1993), and the document would be strengthened by not limiting this evaluation to $TiCl_4$ (e.g., given the key role of hydrogen chloride).

RD_{50}

We suggest updating the references and checking the Alarie (2002) paper to verify statements presented in the TSD. It might also be helpful to consider the usefulness of the RD_{50} (exposure concentration producing a 50% respiratory rate decrease) to support reanalysis and checks of the AEGL derivations. (Note related context from the hydrogen chloride AEGLs.)

Reproductive and Developmental Effects, Genotoxicity, and Cancer Information

A literature search should be performed to determine whether any new information is available on the reproductive and developmental effects, genotoxicity, and carcinogenicity of $TiCl_4$. It would also be helpful to consider the main fate products of $TiCl_4$, as these might constitute coexposures because of their rapid formation in air. In light of more recent applications of $TiCl_4$, it would also be helpful to consider nanoscale titanium.

Comment References

AIHA (American Industrial Hygiene Association). 2008. Case Study 11: Chemical substitution; Process containment. Pp. 156-157 in Demonstrating the Business Value of Industrial Hygiene: Methods and Findings from the Value of the Industrial Hygiene Profession Study. American Industrial Hygiene Association, May 22, 2008 [online]. Available: http://www.aiha.org/votp_NEW/pdf/votp_report.pdf [accessed July 28, 2010].

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TOLUENE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on toluene. 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:

> Toluene is a colorless, flammable liquid with a pungent floral or aromatic odor. . . . The AEGL-1 was based on the preponderance of data from clinical and occupational exposures and from metabolism studies with human subjects that indicated an 8-hour exposure to 200 ppm was without an effect that exceed the AEGL-1 definition, i.e., notable discomfort. . . . The AEGL-2 is based on narcosis which would impair the ability to escape. The point of departure was the NOAEL for narcosis in a 70-minute exposure of Long-Evans rats to 2400 ppm. . . . The AEGL-3 was based on a NOAEL for lethality in a study with the rat. A 2-hour exposure to 6250 ppm was not lethal but produced prostration in rats.

Specific Comments

AEGL-1

The discussion of the selection of the POD should be rewritten to be consistent with the definition of an AEGL-1. Specifically, the discussion should state that an exposure for 8 h to toluene at 200 ppm is a NOEL or is below an AEGL-1 effect, such as notable discomfort (rather than as "an effect that exceeds the AEGL-1 definition"). Such revisions are need on page 61, lines 18-21 and lines 42-44, and in the corresponding section in the Summary on page 7, lines 25-26.

Better support is needed for using an uncertainty factor of 1 for intraspecies differences. The populations in the clinical studies should be reviewed for how well they might represent the general population, and consideration should be given to whether there are any subgroups, such as children, who might be more susceptible.

AEGL-2

The committee approved the derivation of the AEGL-s values for toluene.

AEGL-3

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

Other Comments

The TSD reflects a top notch effort for the physiologically based pharmacokinetic (PBPK) modeling. All model development and extrapolations were performed using acceptable methods. However**,** the authors of the TSD are encouraged to review EPA's recent IRIS technical support document on toluene, which used a five-compartment PBPK model. Consideration should be given to

whether this model might lead to a more accurate estimation by being more comprehensive than the four-compartment model used in the AEGL derivations.

In the TSD's Executive Summary, there are three sections on AEGL-1 values. The first and the third sections can remain as written. However, the long middle section cites many different studies to make points about concentrations of exposure, how representative study populations are of the general public, and the effects of exercise on toluene blood concentrations. This information should be presented more succinctly to support what appears to be the main message, which is that no effects were observed after 5 days of exposure to toluene at 100 ppm in clinical settings but that exercise can more than double the blood concentration of toluene.

Page 13, line 8: The statement that aplastic anemia in two subjects indicated "that the toluene was contaminated with benzene" is too strong. Contamination with other chemicals is possible but should not be presented so definitively. A more objective statement would be that the effect might *possibly* indicate contamination with benzene.

Page 63, lines 18-20: An explanation of "minimum alveolar concentration" is needed. The discussion should reference Section 4.4.2 (Intraspecies Variability) rather than Section 4.4.1 (Interspecies Variability).

It should be mentioned that the IDLH value is much lower than the 30-min AEGL-3 value, and the possible reason for the difference should be discussed in the TSD.

In the appendix, the information given in the pharmacokinetic figures (on the ordinates, within the figures, and in the figure legends; e.g., Figures C-6, C-9, C-10, and C-11) is not sufficient to be self-explanatory to nonspecialists (and without expecting the reader to refer to the original literature). Simple clarifications should be made if possible.

TRIMETHYLBENZENES

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, 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:

> Trimethylbenzene (TMB) isomers, including 1,3,5-TMB, 1,2,4-TMB, and 1,2,3-TMB, are common components of fuels and mixed hydrocarbon solvents. . . . The most appropriate animal data for derivation of AEGL-1 are the neurotoxicity studies. . . . Limited data were available for derivation of AEGL-2 values. Rats repeatedly exposed to 2000 ppm for 6 hours exhibited irritation, respiratory difficulty, lethargy, and tremors (Gage 1970); therefore, 2,000 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.

Specific Comments

The proposed AEGL-1 and AEGL-2 values for the trimethylbenzenes were approved. The committee agrees with the decision not to set AEGL-3 values for these compounds.

Comment Reference

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

VINYL ACETATE MONOMER

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on vinyl acetate monomer. 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:

> Vinyl acetate (VA) [CASRN 108-05-4] is a colorless, flammable liquid with low solubility in water. . . . The AEGL-1 is based on a human study in which inhalation exposure of humans to 4-20 ppm for 2 minutes resulted in minimal or slight throat irritation, exposure to 20 ppm for 4 hours produced persistent slight throat irritation, and exposure to 34 ppm for 2 hours resulted in persistent throat irritation. . . . exposure of rats for 6 hours to 1000 ppm represents a NOAEL for an AEGL-2. . . . Because the reported lethality data were unreliable, the AEGL-3 values are based on the same point of departure as the AEGL-2.

Specific Comments

AEGL-1

The determination of AEGL-1 for vinyl acetate should consider that, at the proposed 10-min value of 6.7 ppm, hoarseness was reported by Deese and Joyner (1969) for the same period of exposure but at lower concentrations of 4.2 and 5.7 ppm. Slight eye irritation in one of three individuals was reported at concentrations of vinyl acetate at 5.7 or 6.8 ppm. However, the usefulness of this report is questionable because it was a self survey of subjective symptoms (page 16, lines 1-4). It should be noted that these end points are not unobservable and, therefore, are not entirely subjective. It should also be noted that the results from this study, along with consideration of odor threshold, form the basis for setting the ERPG-1 (page 41, Table 19).

AEGL-2

The POD for vinyl acetate of 1,000 ppm for 6 h from the study by Bogdanffy et al. (1997) in rats was used for establishing the AEGL-2 (page 7, line 31). The study reported that lesions of the olfactory epithelial cells, characterized by degeneration, necrosis, and exfoliation, occurred at 600 and 1,000 ppm. However, 1,000 ppm was selected as the NOEL because of the presumed reversibility of these end points. It should be noted that these end points are sufficiently severe and appropriate for the AEGL-2. The adverseness of the effects should not be dismissed by their presumed reversibility (see discussion under Other Comments). Thus, a POD should be at a level without those effects.

The application of a total uncertainty factor is presented on page 36, line 44, to page 37, line 3. Ample support is first provided for applying a factor of 10 for intraspecies differences. This factor is followed by a decision to lower it to 3 because, if a value of 10 is used, the resulting AEGL-2 values would be lower than concentrations of vinyl acetate that did not result in serious adverse health effects in human volunteer studies. Better justification is needed for lowering the uncertainty factor for intraspecies differences from 10 to 3. Part of the reason for not using human data as the basis of the AEGL-2 values was that nasal histopathologic end points were not examined or followed up in human studies. By this same reasoning, these data should not serve as support for reducing the intraspecies uncertainty factor.

AEGL-3

The description for the AEGL determination needs clarification. It states that "the 4-hour mortality data provided by Smyth and Carpenter (1973 . . . produce $BMCL_{05}$ values ranging from 226 ppm in mice to 1791 ppm in rats. The 226-ppm value appears unreasonable in context of other available data. For example, a group of 10 mice survived exposure to [vinyl acetate] for 6 h/day, 5 days/week, for 4 weeks" (page 38, lines 22-26). First, no concentration was given for the mice that survived the vinyl acetate exposure. Second, the argument for the unacceptable $BMDL_{05}$ in mice is unconvincing. Presuming that the mice were exposed to vinyl acetate at 226 ppm for 6 h/day, 5 days/week, for 4 weeks, the $BMCL_{05}$ would mean that 95% of the exposed mice are expected to survive, this being the lower end of the 95% confidence interval. Hence, survival of 10 mice in a group of 10 does not convincingly argue for the unreasonableness of $BMCL_{05}$ at 226 ppm. Even if the exposure was for 6 h and given repeatedly, the outcome between acute versus repeated exposure would depend on the end-point-specific mechanism or mode of action, which could entail recovery between the daily exposure or the development of tolerance.

It was stated that "because the exposure concentrations in the Smyth and Carpenter (1973) study were not measured, but corrected using a curve based on gas chromatographic analysis of calculated concentrations, it is possible that the exposure concentrations reported are not accurate. Therefore, these data were not used for derivation of the AEGL-3" (page 42, lines 31-35). However, data from the same study were used in deriving the AEGL-1 values. This apparent discrepancy about the data criteria should be addressed.

The TSD proposed to use the same POD for AEGL-3 as used for AEGL-2 values (1,000 ppm for 6 h), but handled the uncertainty factors differently. As with the AEGL-2 derivation, an uncertainty factor of 3 was applied for interspecies sensitivity but an uncertainty factor of 1 (instead of 3) was applied for intraspecies variability. In light of the discussion about the lack of evidence for the reversibility of nasal olfactory epithelial lesions (see discussion under Other Comments), and the expected revision of the POD for AEGL-2, the POD for AEGL-3 should be reevaluated and justification provided for the selection of the uncertainty factor to account for intraspecies differences.

Other Comments

Olfactory epithelial degeneration, necrosis, and exfoliation reported by Bogdanffy et al. (1997) in rats were the end points for AEGL-2 and AEGL-3 values. Although the study did not include a recovery phase, the lesions were judged as reversible based on a personal communication with S.R. Frame (2004). However, without data, such communication should not be viewed as providing definitive evidence. A full recovery of olfactory epithelia would include regeneration of the same cell type and not mere unspecified cell replacement. Thus, reversibility for these end points from vinyl acetate exposure can only be noted as "presumed reversible" at best.

Revisions are needed to reconcile the following statements:

- The text on page 35, lines 18-19, states, "Human exposure to 20 ppm resulted in one of three individuals reporting persistent slight throat irritation." However, the text on page 35, line 23, states that 20 ppm was used to derive AEGL-1 values because "exposure to 20 ppm represents a no-effect level for notable discomfort."
- The text on page 35, lines 27-28, states, "Because irritation is considered a threshold effect and therefore should not vary over time, the AEGL-1 value is not scaled across time . . . . However, both time and exposure level seem to be an important descriptor elsewhere. For example, the text on page 35, lines 19-22, states, "While exposure to 34 ppm for 2 h resulted in one of three individuals complaining of persistent throat irritation, exposure to 72 ppm for 4 h resulted in irritation severe enough that the exposed subjects expressed an unwillingness to work at this concentration."

The reason for significant differences between AEGL values and pertinent time-specific standards recommended by ACGIH should be discussed in the text.

Comment References

Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(4):331-350.

Deese, D.E., and R.E. Joyner. 1969. Vinyl acetate: A study of chronic human exposure. Am. Ind. Hyg. Assoc. J. 30(5):449-457.

Smyth, H.F., and C.P. Carpenter. 1973. Initial Submission: Vinyl Acetate: Single Animal Inhalation and Human Sensory Response with Cover Letter Dated 08/27/92. Carnegie-Mellon Institute. Submitted by Union Carbide Corporation. Doc. No. 88-920010328.

VINYL CHLORIDE

At its meeting held on June 15-18, 2010, the committee reviewed the AEGL TSD on vinyl chloride. A presentation on the TSD was made by Bob Benson, of the U.S. Environmental Protection Agency. The following is excerpted from the Executive Summary of the TSD:

> Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. . . . The AEGL-1 was based on the study . . . with 4-7 volunteers, two individuals experienced mild headache during 3.5 and during 7.5 hours (3.5 hours, 0.5 hours break, 3.5 hours) of exposure to 491 ppm…. The AEGL-2 was based on prenarcotic effects observed in human volunteers. . . . The AEGL-3 was based on cardiac sensitization and the no effect level for lethality.

Specific Comments

The proposed AEGL-1, -2, and -3 values for vinyl chloride were approved.

Other Comments

Better justification is needed for using an uncertainty factor of 1 for interspecies differences in deriving the AEGL-3 values. A short discussion of the dog cardiac-sensitization model and how it is specifically designed to maximize cardiac response should be added (see paper by Brock et al. 2003). Arrhythmias can be seen in mice, but it is very difficult to interpret because the heart rate can be 500-700 beats per minute.

The TSD should mention whether the Single Exposure Carcinogen Database was consulted for relevant information.

The table in Appendix C, which presents AEGL values on the basis of carcinogenic effects, should also include the relevant AEGL values that are based on noncancer effects to allow for easier comparison. It would be preferable to structure the table in the traditional format of presented AEGL values (that is, the exposure durations should be the column headings and the AEGL values should constitute the row designations).

Comment Reference

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

COMMENTS PERTAINING TO ALL TSDs

For all TSDs, when 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.

It is important that the TSD summaries be updated to reflect revisions to the main text of the TSDs.

For chemicals thought to be direct-acting respiratory irritants, an uncertainty factor of 3 to account for intraspecies differences is often used rather than a default factor of 10. This is usually supported by a statement that response to sensory irritants is not expected to vary greatly among individuals. However, there is often wide variability in responses to such chemicals. Better justification and supporting references should be provided for departing from the default value of 10 (see Standing Operating Procedures [NRC 2001, pages 87-88]).

Comment Reference

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

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	acute exposure guideline level
AIHA	American Industrial Hygiene Association
ATSDR	Agency for Toxic Substances and Disease Registry
BCME	bis-chloromethyl ether
$BMCL_{05}$	benchmark concentration with its lower confidence limit at a 5% extra risk
CAS	chemical abstracts service
CASRN	chemical abstracts service registry number
CEELs	community emergency exposure levels
CMME	chloromethyl methyl ether
EHS	extremely hazardous substances
EPA	U.S. Environmental Protection Agency
ERPG	emergency response planning guidelines
HBR	hydrogen bromide
HI	hydrogen iodide
HERO	health and environmental research online
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life or health
IRIS	Integrated Risk Information System
LC_{50}	concentration of a substance that is lethal to 50% of test organisms in a given time
MF	modifying factor
NAC	National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBPK	physiologically based pharmacokinetic
POD	point of departure
RD_{50}	concentration of a substance that reduced the respiratory rate of test organisms by 50%
RFNA	red fuming nitric acid
RIVM	Netherlands National Institute for Public Health and the Environment
STEL	short-term exposure limit
TMB	trimethylbenzene
TLV	Threshold Limit Value
TSD	technical support document
VA	vinyl acetate
VC	vinyl chloride
WFNA	white fuming nitric acid
WEEL	workplace environmental exposure limit