Twenty-second Interim Report of the Committee on Acute Exposure Gudeline Levels

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

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 270 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 EPA staff and its contractor, SRC, Inc., on draft AEGL documents. The committee provides comments and recommendations on those documents in its interim reports, and EPA and SRC, Inc., use those comments to make revisions. The revised documents are presented by SRC, Inc., 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 twenty-second interim report. It summarizes the committee's conclusions and recommendations for improving AEGL documents for the following chemicals: acrylonitrile, allyl alcohol, boron tribromide, bromine chloride, cadmium, carbon tetrachloride, carbonyl fluoride, cyanide salts, diketene, ethyl benzene, germane, selected halogen fluorides (chlorine pentafluoride, bromine pentafluoride, and bromine trifluoride), hexafluoropropylene, hydrogen bromide

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

and hydrogen iodide, methacrylaldehyde, oxygen difluoride, pentaborane, stibine, styrene, tellurium hexafluoride, tetrafluoroethylene, thionyl chloride, and toluene.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the NRC Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and ensuring that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), and Judith Zelikoff (New York University School of Medicine). 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 [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the NRC.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Iris Camacho and Ernest Falke (U.S. Environmental Protection Agency), and Heather Carlson-Lynch, Gary Diamond, Lisa Ingerman, and Julie Klotzbach (SRC, Inc.).

The committee acknowledges Susan Martel, project director, for her work in this project. Other staff members who contributed to this effort are James Reisa, (director of the Board on Environmental Studies and Toxicology), 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.

Edward C. Bishop, *Chair*
Committee on Acute Exposure Guideline Levels

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Twenty-second 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 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. The NRC's previous name for acute exposure levels—community emergency exposure levels—was replaced by the term acute exposure guideline level (AEGL) to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

NAC[1] was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop AEGLs for high-priority, acutely toxic chemicals. AEGLs developed by NAC have a broad array of potential applications for federal, state, and local governments and for the private sector. AEGLs are needed for 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 [standard pressure] 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.

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

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 (e.g., general, inhalation, cardiovascular, reproductive, mechanistic, occupational); 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 published NRC guidelines; (2) review NAC's research recommendations and—when appropriate—identify additional priorities for research to fill data gaps; and (3) review periodically the recommended standard procedures for developing AEGLs.

This interim report presents the committee's conclusions and recommendations for improving the following AEGL technical support documents (TSDs): acrylonitrile, allyl alcohol, boron tribromide, bromine chloride, cadmium, carbon tetrachloride, carbonyl fluoride, cyanide salts, diketene, ethyl benzene, germane, halogen fluorides (chlorine pentafluoride, bromine pentafluoride, and bromine trifluoride), hexafluoropropylene, hydrogen bromide and hydrogen iodide, methacrylaldehyde, oxygen difluoride, pentaborane, stibine, styrene, tellurium hexafluoride, tetrafluoroethylene, thionyl chloride, and toluene. These documents were reviewed by the committee at a meeting on April 22-24, 2013.

ACRYLONITRILE

The committee reviewed the AEGL TSD on acrylonitrile that was presented by Gary Diamond of SRC, Inc. Table 1 presents a summary of the proposed AEGL values for acrylonitrile and their basis. The committee found that its previous comments on the TSD (NRC 2012) were adequately addressed, and agreed with the proposed derivation of the AEGL values. Just one remaining clarification with respect to the derivation of AEGL-2 values is needed.

AEGL Specific Comments

For AEGL-2 values, the committee agreed with the chosen point of departure (POD) and the derived values. However, support for an uncertainty factor of 2 for interspecies differences in toxicokinetics should be better justified. The current justification is based on physiologically-based pharmacokinetic (PBPK) model simulations by Sweeney et al. (2003), who based their predictions for humans on scaling of the metabolism from rats, but used no experimental data. More recently, Takano et al. (2010) published a PBPK model suggesting small differences (less than two-fold) between rats and humans. The advantage of the Takano model is that it is based on experimental data on metabolism (liver microsomes), but it also has the disadvantage of considering only oral exposure. Taken together, the two PBPK studies support an uncertainty factor of 2.

ALLYL ALCOHOL

The committee reviewed a proposal to change the approach to deriving AEGL-1 and AEGL-2 values for allyl alcohol presented by Julie Klotzbach of SRC, Inc. Table 2 presents a summary of proposed AEGL values. The committee agreed with the proposed AEGL-2 values, and the AEGL-3 values were approved at a previous meeting (NRC 2012). However, the committee recommends a few adjustments to how the AEGL-1 values were derived.

TABLE 1 Summary of Proposed AEGL Values for Acrylonitrile Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	NR	NR	NR	No-effect level for ocular irritation in humans (4.6 ppm, 8 h); total UF = 3 (intraspecies)
AEGL-2 (disabling)					
8.6 ppm (19 mg/m^3)	3.2 ppm (6.9 mg/m^3)	1.7 ppm (3.7 mg/m^3)	0.48 ppm (1.0 mg/m^3)	0.26 ppm (0.56 mg/m^3)	No-effect level for fetal toxicity (reduced fetal body weight) in rats (12 ppm, 6 h); total UF = 36 (interspecies = 6, intraspecies = 6); time scaling, n = 1.1
AEGL-3 (lethal)					
130 ppm (280 mg/m^3)	50 ppm (110 mg/m^3)	28 ppm (61 mg/m^3)	9.7 ppm (21 mg/m^3)	5.2 ppm (11 mg/m^3)	$BMCL_{05}$ for lethality in rats (1,784.0, 1,024.4, 185.8 ppm for 30 min, 1 h, 8 h, respectively); total UF = 36 (interspecies = 6, intraspecies = 6); time scaling, n = 1.1

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended; UF, uncertainty factor.

TABLE 2 Summary of Proposed AEGL Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
0.27 ppm	0.27 ppm	0.27 ppm	0.27ppm	0.27 ppm	RD_{10} (0.27 ppm) in mice; no UFs; no time scaling. Supportive evidence from human study.
AEGL-2 (disabling)					
11 ppm	3.5 ppm	1.7 ppm	0.73 ppm	0.33 ppm	No-effect levels for decreased response to stimulus and gasping in rats; total UF = 30 (interspecies= 3, intraspecies = 10); time scaling, n = 0.95.
AEGL-3 (lethal)					
87 ppm	27 ppm	13 ppm	3.1 ppm	1.5 ppm	LC_{01} values in rats; total UF = 30 (interspecies = 3, intraspecies = 10); time scaling, n = 0.95.

Abbreviations: LC_{01}, lethal concentration, 1% lethality; RD_{10}, concentration that reduces the respiratory rate by 50%; UF, uncertainty factor.

AEGL Specific Comments

The committee agreed with the approach of deriving AEGL-1 values for allyl alcohol by considering the studies of Nielsen et al. (1984) and Dunlap et al. (1958) together. The proposed AEGL-1 values on the basis of the Nielsen study are based on an RD_{10} (concentration that reduces the respiratory rate by 10%) of 0.27 ppm in mice. No uncertainty factors were applied, no time scaling was performed, and the values were held constant over the AEGL durations. Support for these values is provided by estimates of the AEGL-1 values based on human data from the Dunlap et al. (1958) study. Slight ocular irritation and mild-to-moderate nasal irritation were reported at 0.78 ppm for 5 min. If an uncertainty factor of 3 is applied for intraspecies variability, AEGL-1 values would also be 0.27 ppm. The committee agrees with the application of that uncertainty factor, and recommends that it also be used in calculating AEGL values on the basis of the Nielsen study. This will result in AEGL-1 values of 0.09 ppm for all AEGL durations. Also, relevant primary citations should be included in the TSD. (For example, 3% of the RD_{50} for allyl alcohol is listed as 0.301 ppm in ASTM [2012]).

Other Comments

A new literature search should be performed to update the information presented in the TSD. It also appears that some of the older literature has been overlooked; a few studies of ocular irritation (e.g., Jacobs 1992; Berry and Easty 1993) and renal toxicity (e.g., Hosohata et al. 2011) appear to have been omitted. Information can also be gleaned from assessment by other agencies, such as UNEP (2005) and EPA (2009, 2013a, 2013b). The most recent EPA compilations include brief summaries of the studies by Carpenter and Smyth (1946), Carpenter et al. (1949), and others.

Page 8, lines 5-9: The uses of allyl alcohol should be updated (the citations are from 1977-1996). For example, see information provided by LyondellBasell on its website (http://www.lyondellbasell.com). Also, check the accuracy of the statement that allyl alcohol is used as a fungicide and herbicide, because the Hazardous Substances Data Bank (HSDB) reference cited indicates that it was not registered for current use the United States.

Page 8, lines 9-17: The production of allyl alcohol should be updated (the citations are from 1977-1996). For example, the HSDB reference identifies another manufacturer from a 2011 directory, and recent information is also available from US patent summaries (Lin et al. 2011, Engelhard et al. 1976). The TSD citation regarding production (line 13) is nearly 20 years old; the HSDB link which was cited in the TSD for physicochemical properties included information on US production from 2002 (more than 50 to 100 million pounds), as well as for previous years, which indicate that production had at least doubled since 1990. Other sources provide more up-to-date information from LyondellBasell that production volume is between 100-500 million pounds (see EPA 2006). Similarly, the TRI data from 2000 should be updated with a more recent reference (see EPA 2013a). More recent information with respect to shipping (lines 16-17) should also be sought.

Page 8, line 20: Primary sources for atmospheric half-life should be referenced rather than HSDB. For example, the EPA High Production Volume Information System (EPA 2013b) identified information from several citations, such as the 1991 Handbook of Environmental Degradation Rates by Howard et al., which indicates a photo-oxidation half-life of 2.2 to 22 h, whereas Howard's 1989 Handbook indicated a range of 6 to 14.7 h; Grosjean et al. (1993) indicate a half-life on the order of 7.4 h or 0.3 days. The latter publication is also referenced by UNEP (2005).

Page 8, lines 27-28; page 9, lines 6-7; page 11, line 32: The statement that there are no reports of human fatalities is inaccurate (see Toennes et al. 2002 and Kononenko 1970).

Page 23, Section 3.3 (Developmental/Reproductive Effects): A relevant study by Jenkinson and Anderson (1990) should be added, as well as information summarized in UNEP (2005).

Page 24, Section 3.5 (Carcinogenicity): The citations are outdated with respect to EPA's classification, and the IARC determination should be cited. More recent publications may also be relevant (e.g., Wang et al. 2012).

Page 25, lines 20-22: Given that reproductive/developmental toxicity is not limited by the portal of entry, the restriction to "inhaled" ally alcohol is not warranted. (This is also true for similar statements about carcinogenicity.) All relevant information on allyl alcohol should be considered.

Pages 28-30, Section 4.1 (Metabolism and Mechanism of Toxicity): Relevant references appear to have been omitted from this section. An updated literature search should be performed, and recent compilations reviewed for relevant information on the mechanism of action of allyl alcohol (see UNEP 2005 and EPA 2009).

Page 30, Section 4.2 (Structure-Activity Relationships): More recent references should be consulted and added to this section (see Irvin 2006).

Pages 30-31, Section 4.3 (Susceptible Populations): A search should be conducted for more recent information, and the section should include consideration of other conditions, such as renal toxicity.

Page 38, Table 15; page 39, lines 1-36: The standards for allyl alcohol set by other organizations should be verified to ensure they reflect the most up-to-date values, and the supporting references updated accordingly. Given Japan's interest per sponsorship of the UNEP (2005) report, consider including the Japanese occupational exposure limit.

Pages 39-40, Section 8.3 (Data Adequacy and Research Needs): This section should be updated after the updated literature search is performed and more recent compilations of data are consulted (e.g., UNEP 2005, EPA 2009).

Relevant References

The following are several references that should be included in the updated TSD. Other relevant information should be sought through an updated literature search.

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Berry, M., and D.L. Easty. 1993. Isolated human and rabbit eye: Models of corneal toxicity. Toxicol. In Vitro 7(4):461-464.

Hosohata, K., H. Ando, Y. Fujiwara, and A. Fujimura. 2011. Vanin-1: A potential biomarker for nephrotoxicant-induced renal injury. Toxicology 290(1):82-88.

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Toennes, S.W., K. Schmidt, A.S. Fandiño, and G.F. Kauert. 2002. A fatal human intoxication with the herbicide allyl alcohol (2-propen-1-ol). J. Anal. Toxicol. 26(1):55-57.
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BORON TRIBROMIDE

The committee reviewed the AEGL TSD on boron tribromide that was presented by Lisa Ingerman of SRC, Inc. Table 3 presents a summary of the proposed AEGL values for boron tribromide and their basis. The committee agreed that its previous comments on the TSD (NRC 2011) were adequately addressed. It is appropriate to take one-third of the AEGL values for hydrogen bromide to determine AEGL values for boron tribromide, because three moles of hydrogen bromide are produced from hydrolysis of one mole of boron tribromide. However, the proposed AEGL values must be revised in light of changes to the AEGL values for hydrogen bromide specified later in this report.

BROMINE CHLORIDE

The committee reviewed the AEGL TSD on bromine chloride that was presented by Heather Carlson-Lynch of SRC, Inc. Table 4 presents a summary of the proposed AEGL values for bromine chloride and their basis. The committee agreed with the derivation of the proposed AEGL-2 and AEGL-3 values, but disagreed with the proposal to derive AEGL-1 values by analogy with chlorine.

General Comments

Bromine chloride is an unstable gas that spontaneously dissociates into a mixture of bromine chloride, bromine, and chlorine in a 60:20:20 ratio. When these gases come into contact with water (and presumably biological fluids), bromine chloride and the two halogens react to become their respective weak and strong acids:

$$2BrCl \leftrightarrow Br_2 + Cl_2 \;//\; Br_2 + H_2O \leftrightarrow HOBr + HBr \;//\; Cl_2 + H_2O \leftrightarrow HOCl + HCl$$
$$2BrCl + 2H_2O \leftrightarrow HBr + HOBr + HCl + HOCl$$

TABLE 3 Summary of Proposed AEGL Values for Boron Tribromide Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	0.33 ppm (3.4 mg/m^3)	Analogy with hydrogen bromide[a]
AEGL-2 (disabling)	33 ppm (340 mg/m^3)	14 ppm (140 mg/m^3)	7.3 ppm (75 mg/m^3)	3.7 ppm (38 mg/m^3)	3.7 ppm (38 mg/m^3)	Analogy with hydrogen bromide[a]
AEGL-3 (lethality)	250 ppm (2,600 mg/m^3)	83 ppm (850 mg/m^3)	40 ppm (410 mg/m^3)	10 ppm (100 mg/m^3)	10 ppm (100 mg/m^3)	Analogy with hydrogen bromide[a]

[a]AEGL values for hydrogen bromide are presented later in this document.

TABLE 4 Summary of Proposed AEGL Values for Bromine Chloride Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
0.50 ppm (2.4 mg/m^3)	0.50 ppm (2.4 mg/m^3)	0.50 ppm (2.4 mg/m^3)	0.50 ppm (2.4 mg/m^3)	0.50 ppm (2.4 mg/m^3)	Analogy with chlorine (NRC 2004a)
AEGL-2 (disabling)					
3.2 ppm (15 mg/m^3)	3.2 ppm (15 mg/m^3)	2.5 ppm (12 mg/m^3)	1.6 ppm (7.6 mg/m^3)	1.2 ppm (5.7 mg/m^3)	One-third of AEGL-3 values.
AEGL-3 (lethal)					
9.5 ppm (45 mg/m^3)	9.5 ppm (45 mg/m^3)	7.6 ppm (36 mg/m^3)	4.8 ppm (23 mg/m^3)	3.5 ppm (17 mg/m^3)	$BMCL_{05}$ for lethality in rats (39.5 ppm, 7 h); total UF = 10 (interspecies = 3, intraspecies =3); default time scaling.

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; UF, uncertainty factor.

Any scenario in which AEGL values would be used will involve exposure to a halogen-interhalogen mixture, not bromine chloride alone. The introduction to the TSD should make this explicit, along with the potential impact of relative humidity on the exposure mixture.

The dataset for bromine chloride consists of a single acute lethality study in rats. That study is weak; only six male rats per group were tested, and the investigators expressed uncertainty with respect to the composition of the exposure atmosphere and the actual exposure concentrations. Furthermore, the study was not peer reviewed.

AEGL Specific Comments

The committee disagrees with the proposal to establish AEGL-1 values on the basis of the AEGLs for chlorine. In the absence of relevant data specific to bromine chloride, no AEGL-1 values should be recommended.

The committee agrees with the proposed approach to deriving AEGL-3 values, but recommends that consideration be given to applying a modifying factor to account for the sparse database on bromine chloride. The committee agrees that AEGL-2 values can be determined by dividing the AEGL-3 values by 3.

Other Comments

Reference is made throughout the TSD that the toxicity of bromine chloride is expected to be between those of bromine and chlorine. A discussion of this hypothesis and the lack of data to confirm it should only be presented in Sections 4.3 (Structure-Activity Relationships), 8.1 (AEGL Values and Toxicity End Points), and 8.3 (Data Adequacy and Research Needs).

The description of the uncertainties associated with the concentrations of bromine chloride in the LC_{50} study by Dow Chemical Co. (1977) should be expanded. No attempt was made to speciate the components of the exposure, other than to note that bromine chloride is reported to be 40% dissociated; the ratio of the mixture would be 60:20:20 for bromine chloride, bromine, and chlorine, respectively. However, the discussion is presented in terms of exposure to bromine chloride, so it is uncertain whether the concentrations analyzed were 20, 40, 80, and 120 ppm of bromine chloride or a mixture of halogens. All rats showed symptoms of respiratory irritation at all exposure concentrations. Determination of the concentrations to which the rats were exposed was based on a separate, single exposure performed after the LC_{50} determination. This was further complicated by the evidence of stratification of concentrations

within the exposure chamber. The description of the "top", "middle", and "bottom" sampling positions were not otherwise described, and the breathing zone of the rats in context with these positions was not described in detail (e.g., duration of rearing behavior, which was interpreted as an escape response confirming the degree of concentration stratification). This information is important because the bottom concentration (91 ppm) during the exposure measurement experiment exceeded the LC_{17} value and appears to be close to the LC_{50}, and the top and middle concentrations (average of 42 ppm) were slightly (1-3 ppm) above the no-observed-adverse-effect level (NOAEL) and the calculated $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) value.

In the Section 4.3 (Structure-Activity Relationships), the toxicities of bromine and chlorine should be compared with bromine chloride to the extent possible. Lethality data seem to indicate that bromine chloride is as lethal as chlorine, whereas bromine is 1.4-2.3 times less lethal than chlorine. However, bromine appears to be more irritating to the upper respiratory tract than chlorine (NRC 2010a). The AEGL values for bromine chloride, bromine, and chlorine should be compared in Section 8.2 (Comparison with Other Standards and Guidelines).

In Section 8.3 (Data Adequacy and Research Needs), a recommendation should be made that acute toxicity studies of bromine chloride are needed to refine the AEGL-3 values and develop AEGL-1 and AEGL-2 values. Such studies should include analyses of the exposure atmospheres. Studies comparing bromine chloride, bromine, and chlorine would also be helpful.

CADMIUM

The committee reviewed the AEGL TSD on cadmium that was presented by Gary Diamond of SRC, Inc. Table 5 presents a summary of the proposed AEGL values for cadmium and their basis. The committee found the TSD to be unacceptable and in need of major revisions. The TSD presents data on different cadmium species without providing context regarding their solubility and particle size and the implications for interpreting and extrapolating data. None of the AEGL values were adequately justified.

The TSD should provide a discussion about the different cadmium species to which people may be exposed, and the relevance to understanding kinetics and lung toxicity. Cadmium oxide appears to be the most toxic species. The TSD should review the evidence as justification for focusing on that species to derive AEGL values. Exposure concentrations and AEGL values in the TSD should be expressed in terms of mg/m^3 of elemental cadmium, not as the individual test species. Some specific improvements needed include:

- Relevant new studies identified in an updated literature search should be added to the TSD and considered in deriving AEGL values, if appropriate. Data on *engineered* nanomaterials (e.g., Quantum dots) may be omitted from consideration, because these particles are usually produced in small quantities and risk of exposure to the general public is limited.
- Data on tissue burdens and urinary cadmium concentrations should be discussed to provide context for kinetic considerations (e.g., Lauwerys et al. 1979). Measurements from animals and humans should be compared.
- AEGL-1 values: It is unclear why a POD of 0.55 mg/m^3 was chosen, when other studies have reported effects such as petechial lung hemorrhages at 0.5 mg/m^3 (Buckley and Bassett 1987) and one death and biochemical lung changes at 0.45 mg/m^3 (Grose et al. 1987). The AEGL values are also lower than those reported to be associated with "metal fume fever" (described on page 11, lines 19-21 of the TSD).
- AEGL-2 values: It is unclear that the POD of 5.3 mg/m^3 is a NOAEL. The Buckley and Bassett (1987) study reported lung changes that persisted for at least 15 days after exposure. The Grose et al. (1987) study described severe pneumonitis in rats 72 h after exposure at 4.5 mg/m^3.

CARBON TETRACHLORIDE

The committee reviewed the AEGL TSD on carbon tetrachloride that was presented by Gary Diamond of SRC, Inc. Table 6 presents a summary of the proposed AEGL values for carbon tetrachloride and their basis. The committee agreed that its previous comments (NRC 2010b) were addressed, but recommends revisions to how the AEGL-2 and AEGL-3 values were derived.

AEGL Specific Comments

The committee agreed with the proposal not to establish AEGL-1 values.

TABLE 5 Summary of Proposed AEGL Values for Cadmium Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
0.13 mg/m^3	0.13 mg/m^3	0.10 mg/m^3	0.063 mg/m^3	0.041 mg/m^3	Respiratory irritation in rats (0.55 mg/m^3, 6 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-2 (disabling)					
1.4 mg/m^3	0.96 mg/m^3	0.76 mg/m^3	0.40 mg/m^3	0.20 mg/m^3	Overt respiratory tract irritation and pathology in rats (5.3 mg/m^3, 3 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-3 (lethal)					
8.5 mg/m^3	5.9 mg/m^3	4.7 mg/m^3	1.9 mg/m^3	0.93 mg/m^3	Threshold for lethality in rats (2-h LC_{50} of 112 mg/m^3); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: LC_{50}, lethal concentration, 50% lethality; UF, uncertainty factor.

TABLE 6 Summary of Proposed AEGL Values for Carbon Tetrachloride Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)					
45 ppm (280 mg/m^3)	29 ppm (180 mg/m^3)	22 ppm (140 mg/m^3)	13 ppm (82 mg/m^3)	9.5 ppm (60 mg/m^3)	Fetal toxicity (decreased body weight, shorter crown-to-rump length) in rats (300 ppm, 7 h, GD 6-15); total UF = 10 (intraspecies); MF = 3 (extrapolating from an effect level); time scaling, n = 2.5
AEGL-3 (lethal)					
1,100 ppm (6,920 mg/m^3)	680 ppm (4,227 mg/m^3)	520 ppm (3,270 mg/m^3)	300 ppm (1,887 mg/m^3)	220 ppm (1,384 mg/m^3)	Estimated LC_{01} in rats(5,153.5 ppm, 1 h); total UF = 10 (intraspecies); time scaling, n = 2.5

Abbreviations: GD, gestation day; LC_{01},lethal concentration, 1% response; MF, modifying factor; NR, not recommended; UF, uncertainty factor.

In examining the basis of the AEGL-2 values, the committee discovered a few methodology issues with the study by Schwetz et al. (1974) that were not identified in previous reviews of the TSD. Tests for the two dose (300 and 1,000 ppm) groups were conducted in two separate experiments, each with its own concurrent controls. The experimental variability over the three-fold dose range rendered these results inconclusive for identifying any fetal end points for deriving AEGL values. For example, when compared with concurrent controls, the incidence of delayed sternebral ossification was statistically significant only at 1,000 ppm, with a substantially lower incidence in the concurrent control group; however, when the control data were combined, total skeletal abnormalities (predominantly delayed ossification) was significant only at 300 ppm. Similarly, compared with the combined controls, fetal subcutaneous edema (potentially pertinent to acute exposure scenarios) was only significant at 300 ppm; however, no significant increase in total soft tissue abnormalities was detected at either dose. Data on each set of concurrent controls and for individual litters were unavailable for further analysis.

The committee concluded that the Schwetz et al. study should not be used as the basis for deriving AEGL-2 values. No gross abnormalities at either test concentration were found, and a clear dose-response relationship in skeletal and soft-tissue anomalies was lacking. Findings of lower fetal body weight and shorter crown-rump length are likely to be associated with the sustained lower maternal weight over gestation days 6-15.

Several studies in humans (page 15, Table 2) were considered for establishing a POD for AEGL-2 values. Considering the database on acute exposures in humans and the severity of end points observed at concentrations ranging from 317 to 2,382 ppm for fractions of an hour, the committee recommended that the 4-h exposure at 76 ppm in the Davis (1934) study be considered as the POD for AEGL-2 values. That starting point is based on a NOAEL for effects on the central nervous system (CNS) and liver. Use of this POD will result in AEGL-2 values that will also be protective of possible fetal effects that could occur at maternal exposures as low as 300 ppm for 7 h (estimated POD of 100 ppm for 7 h) throughout gestation days 6-15 in rats (Schwetz et al. 1974). Time scaling should be performed for all the AEGL durations (with n = 2.5, as described in the TSD).

For AEGL-3 values, the committee recommends that an uncertainty factor for interspecies differences be based on modeling of the LC_{50} values for carbon tetrachloride, which would yield a factor of 1.5.

CARBONYL FLUORIDE

The committee reviewed the AEGL TSD on carbonyl fluoride that was presented by Julie Klotzbach of SRC, Inc. Table 7 presents a summary of the proposed AEGL values for carbonyl fluoride and their basis. The committee approved the proposed AEGL values with a few clarifications and modifications.

TABLE 7 Summary of Proposed AEGL Values for Carbonyl Fluoride Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)					
0.35 ppm (0.95 mg/m^3)	0.35 ppm (0.95 mg/m^3)	0.28 ppm (0.76 mg/m^3)	0.17 ppm (0.46 mg/m^3)	0.087 ppm (0.23 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)					
1.0 ppm (2.7 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.83 ppm (2.2 mg/m^3)	0.52 ppm (1.4 mg/m^3)	0.26 ppm (0.70 mg/m^3)	$BMCL_{05}$ for lethality in rats (5.2 ppm, 4 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended; UF, uncertainty factor.

AEGL Specific Comments

The committee agrees that no AEGL-1 values should be recommended. The rationale should acknowledge that if AEGL values were to be derived from the limited data on no-effect levels of carbonyl fluoride, the AEGL-1 values would be very close to the AEGL-2 values for the 10- and 30-min durations and higher than the AEGL-2 values for the longer durations.

The committee agrees that it is appropriate to derive AEGL-2 values by taking one-third of the AEGL-3 values. It might also be useful to show that deriving AEGL-2 values from the limited data on carbonyl fluoride (e.g., NOAEL for dyspnea) would result in higher values than those proposed. Given the steep exposure-response curve, that approach would provide less margin for error.

Other Comments

Page 8, lines 5-6; page14, lines 10-11: The argument that the steep concentration-response curve of carbonyl fluoride is an indication of a little variation in toxic effects within a population is not appropriate. The steeper the concentration-response curve is, the larger the resulting differences in effect from increases in concentration and from factors that increase susceptibility. The argument should be omitted, even though it is identified as an appropriate consideration in the Standing Operating Procedures (NRC 2001, Section 2.5.3.4.4).

Page 12, line 39, and following pages: The discussions in Sections 3.7, 4.1, 4.2, and 4.3 refer to phosgene, hydrogen fluoride, and pyrolysis products of polytetrafluoroethylene. This is helpful for understanding what is known regarding the toxicity of carbonyl fluoride, but no comparisons are made to the AEGLs developed for hydrogen fluoride or phosgene. A comparison of the AEGL values for these chemicals with those of carbonyl fluoride would be helpful.

Page 17, lines 5-6: The NIOSH and ACGIH® STEL values exceed the AEGL-3 values for the 10-min and 30-min durations by a factor of 5, and the 8-h TWA values exceed the AEGL-3 value for 8 h by almost an order of magnitude. An explanation about what might account for the differences should be added (NRC 2001, Appendix J).

Page 17, Section 8.3: The section on Data Adequacy and Research Needs should also acknowledge the lack of animal data to derive AEGL-1 and AEGL-2 values. A recommendation should be added that additional studies on genotoxicity and reproductive and developmental toxicity would also help to strengthen the basis of the AEGL values for carbonyl fluoride.

A discussion that pyrolysis of polytetrafluoroethylene yields high amounts of carbonyl fluoride should be added to the summary of the TSD, as well as the introductory section. Information should be included that pyrolysis products are composed of a large number of compounds, can be of variable composition, and pose significant analytic challenges. Pyrolysis products of polytetrafluoroethylene include a number of highly toxic compounds in addition to carbonyl fluoride, including perfluoroisobutylene, which is approximately 10-fold more toxic than phosgene (Patocka and Bajgar 1998; IPCS 2004). Because the Scheel et al. (1968a) study involved exposure to carbonyl fluoride and other compounds pyrolized from polytetrafluoroethylene, the study should be used only to support the uncertainty factor of 3 for interspecies variability, for reasons noted in Section 8.3 of the TSD.

CYANIDE SALTS

The committee reviewed the AEGL TSD on sodium cyanide, potassium cyanide, and calcium cyanide that was presented by Heather Carlson-Lynch of SRC, Inc. Table 8 presents a summary of the proposed AEGL values for the three cyanide salts and their basis. The committee approved the AEGL values, and made a few suggestions for clarifications before the document is finalized.

TABLE 8 Summary of Proposed AEGL Values for Selected Cyanide Salts Reviewed by the Committee[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Sodium cyanide						
AEGL-1 (nondisabling)	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3	Based on AEGLs for hydrogen cyanide (NRC 2002)
AEGL-2 (disabling)	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3	
AEGL-3 (lethality)	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3	
Potassium cyanide						
AEGL-1 (nondisabling)	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3	Based on AEGLs for hydrogen cyanide (NRC 2002)
AEGL-2 (disabling)	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3	
AEGL-3 (lethality)	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3	
Calcium cyanide[b]						
AEGL-1 (nondisabling)	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3	Based on AEGLs for hydrogen cyanide (NRC 2002)
AEGL-2 (disabling)	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3	
AEGL-3 (lethality)	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3	

[a]These airborne concentrations will produce equivalent AEGL values for hydrogen cyanide.
[b]Although the adjusted oral lethlity value for calcium cyanide in rats is much greater (suggesting a less toxic compound) than would be expected on a molar basis for cyanide, the production of two moles of hydrogen cyanide was assumed per mole of calcium cyanide.

Other Comments

The report should include a discussion of hydrolysis of the cyanide salts to provide a more robust foundation for the assumption of complete and instantaneous decomposition of these compounds. That this assumption probably results in more conservative AEGL values should be indicated. It would also be useful to add some discussion of case reports from accidental releases from cyanide salt storage or use, especially cases that resulted in exposure to aerosols.

In Tables 9-11, the AEGL values for the cyanide salts should also be expressed in terms of cyanide to allow direct comparison with the exposure standards set by other agencies.

The risk of intoxication by dermal exposure to the cyanide salts should be summarized. Useful sources for summarized information include Montelius (2001) and SCOEL (2010).

DIKETENE

The committee reviewed the AEGL TSD on diketene that was presented by Heather Carlson-Lynch of SRC, Inc. Table 9 presents a summary of the proposed AEGL values for diketene and their basis. The committee agreed with the proposal not to derive AEGL-1 values, and the approach of basing the AEGL-2 values on the AEGL-3 values. However, revisions to the derivation of the AEGL-3 values are needed.

TABLE 9 Summary of Proposed AEGL Values for Diketene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)					
11 ppm (38 mg/m^3)	7.7 ppm (26 mg/m^3)	6.0 ppm (21 mg/m^3)	1.5 ppm (5.2 mg/m^3)	0.77 ppm (2.6 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)					
33 ppm (110 mg/m^3)	23 ppm (79 mg/m^3)	18 ppm (62 mg/m^3)	4.5 ppm (15 mg/m^3)	2.3 ppm (7.9 mg/m^3)	$BMCL_{05}$ for lethality in rats (181 ppm, 1 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended; UF, uncertainty factor.

AEGL Specific Comments

The committee agreed that the data on diketene were inadequate to derive AEGL-1 value. The same was true for AEGL-2 values, and the committee agreed with the proposal to derive AEGL-2 values by dividing the AEGL-3 values by 3.

In the derivation of AEGL-3 values, the committee recommends that the uncertainty factor for interspecies differences be increased to 10. The proposed factor of 3 is not consistent with the mortality rate observed in guinea pigs in comparison with other species (Sections 3.1.3 and 4.4.1). A modifying factor of 2-5 is also recommended because of the poor database on diketene.

The AEGL values for ketene and how they were derived should be compared with the AEGL values for diketene to ensure consistency and that the relationship between the two compounds is appropriately reflected in the values.

Other Comments

More detailed information on the decomposition products of diketene should be added to the TSD to provide more context with respect to the toxicity of ketene. Diketene decomposition at temperatures greater than 200ºC under anhydrous conditions results in some ketene formation (Bui et al. 2007), so potential for thermal decomposition is an important concern that could affect the derivation of AEGL-3 values, because ketene is a more potent toxicant than diketene.

ETHYLBENZENE

The committee reviewed the AEGL TSD on ethylbenzene that was presented by Lisa Ingerman of SRC, Inc. Table 10 presents a summary of the proposed AEGL values for ethylbenzene and their basis. The committee approved the proposed AEGL-1 values, but recommends revisions to how the AEGL-2 and AEGL-3 values were derived.

AEGL Specific Comments

The committee recommends that the study by Bardodej and Bardodejova (1961) be used to derived the AEGL-2 values for ethylbenzene. In that study, some of the 11 individuals exposed to ethylbenzene at 180 ppm for 8 h complained of irritation of the upper respiratory tract and eyes, and headache and sleepiness near the end of exposure. Transient feelings of drunkenness were also reported. A POD of 180 ppm is further supported by the pharmacokinetic study by Engström et al. (1984), in which

no effects were reported in volunteers exposed to ethylbenzene at 150 ppm for 4 h. An uncertainty factor of 3 for intraspecies variability is appropriate. Because the POD reflects acute CNS effects likely caused by the parent chemical and because ethylbenzene in blood (and brain) reaches a steady state after about 2 h (Åstrand et al. 1978), no time scaling is needed between the 2- and 8-h durations. Default time scaling should be applied for shorter durations.

The committee approved the proposed approach to deriving AEGL-3 values, with the exception that it recommends that the PBPK model simulate light exercise (50W) rather than rest. This will reduce the AEGL-3 values by about a factor of two.

Other Comments

A summary of the study by Åstrand et al. (1978) should be added to the TSD to support the use of it for time scaling.

GERMANE

The committee reviewed the AEGL TSD on germane that was presented by Julie Klotzbach of SRC, Inc. As illustrated in Table 11, data on germane were insufficient to derive AEGL values, so a proposal was made to adopt the AEGL-2 and AEGL-3 values for the related compound arsine and not establish any AEGL-1 values.

The committee disagrees that there is an adequate scientific basis for using the arsine values, and recommends that the AEGLs program retract the interim values for germane.

TABLE 10 Summary of Proposed AEGL Values for Ethylbenzene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	33 ppm (144 mg/m^3)	Highest no effect level in humans (100 ppm, 8 h); total UF = 3 (intraspecies)
AEGL-2 (disabling)					
2,900 ppm (13,000 mg/m^3)	1,600 ppm (7,000 mg/m^3)	1,100 ppm (4,800 mg/m^3)	660 ppm (2,900 mg/m^3)	580 ppm (2,500 mg/m^3)	No effect level for narcosis in rats (1,500 ppm, 4 h); UF = 3 (intraspecies); PBPK model for time scaling
AEGL-3 (lethal)					
4,700 ppm (20,400 mg/m^3)	2,600 ppm (11,000 mg/m^3)	1,800 ppm (7,800 mg/m^3)	1,000 ppm (4,400 mg/m^3)	910 ppm (4,000 mg/m^3)	Highest nonlethal concentration in rats (2,000 ppm, 6 h/day, 3 days; UF = 3 (intraspecies); PBPK model for time scaling

Abbreviations: PBPK, physiologically based pharmacokinetic; UF, uncertainty factor.

TABLE 11 Summary of Proposed AEGL Values for Germane Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	0.30 ppm (0.96 mg/m^3)	0.21 ppm (0.67 mg/m^3)	0.17 ppm (0.54 mg/m^3)	0.040 ppm (0.13 mg/m^3)	0.020 ppm (0.064 mg/m^3)	Arsine AEGL-2 values adopted (NRC 2000)
AEGL-3 (lethality)	0.91 ppm (2.9 mg/m^3)	0.63 ppm (2.0 mg/m^3)	0.50 ppm (1.6 mg/m^3)	0.13 ppm (0.42 mg/m^3)	0.060 ppm (0.19 mg/m^3)	Arsine AEGL-3 values adopted (NRC 2000)

HALOGEN FLUORIDES

The committee reviewed the AEGL TSD on chlorine pentafluoride, bromine pentafluoride, and bromine trifluoride that was presented by Heather Carlson-Lynch of SRC, Inc. Table 12 presents a summary of the proposed AEGL values for the three halogen fluorides and their basis. The committee agreed that its previous comments (NRC 2010b) have been adequately addressed, but recommends that the POD used to derive the AEGL-2 values for chlorine pentafluoride be re-evaluated before the document is finalized. All of the other AEGL values were appropriately justified.

TABLE 12 Summary of Proposed AEGL Values for Selected Halogen Fluorides Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Chlorine pentafluoride						
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Insufficient warning properties
AEGL-2 (disabling)	1.8 ppm (9.6 mg/m^3)	1.0 ppm (5.3 mg/m^3)	0.5 ppm (2.7 mg/m^3)	0.24 ppm (1.3 mg/m^3)	0.17 ppm (0.91 mg/m^3)	Sensory irritation in monkey, dog, rat, mouse (10 ppm for 3 min, 5 ppm for 60 min); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.9
AEGL-3 (lethality)	21 ppm (112 mg/m^3)	12 ppm (64 mg/m^3)	8.0 ppm (43 mg/m^3)	3.9 ppm (21 mg/m^3)	2.7 ppm (14 mg/m^3)	Highest nonlethal concentration in rats (80 ppm, 1 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.9
Bromine pentafluoride						
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	1.8 ppm (12 mg/m^3)	1.0 ppm (7.2 mg/m^3)	0.5 ppm (3.6 mg/m^3)	0.24 ppm (1.7 mg/m^3)	0.17 ppm (1.2 mg/m^3)	Set equal to AEGL-2 values for chlorine pentafluoride
AEGL-3 (lethality)	79 ppm (565 mg/m^3)	55 ppm (393 mg/m^3)	33 ppm (236 mg/m^3)	8.3 ppm (59 mg/m^3)	4.2 ppm (30 mg/m^3)	Highest nonlethal concentration in rat (500 ppm, 40 min); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
Bromine trifluoride						
AEGL-1 (nondisabling)	0.12 ppm (0.67 mg/m^3)	0.12 ppm (0.67 ppm mg/m^3)	0.12 ppm (0.67 ppm mg/m^3)	0.12 ppm (0.67 ppm mg/m^3)	0.12 ppm (0.67 ppm mg/m^3)	Set equal to AEGL values for chlorine trifluoride (NRC 2007)
AEGL-2 (disabling)	8.1 ppm (45 mg/m^3)	3.5 ppm (20 mg/m^3)	2.0 ppm (11 mg/m^3)	0.70 ppm (3.9 mg/m^3)	0.41 ppm (2.3 mg/m^3)	
AEGL-3 (lethality)	84 ppm (470 mg/m^3)	36 ppm (200 mg/m^3)	21 ppm (120 mg/m^3)	7.3 ppm (41 mg/m^3)	7.3 ppm (41 mg/m^3)	

Abbreviations: NR, not recommended; UF, uncertainty factor.

AEGL Specific Comments

The characterization of the critical study (MacEwen and Vernot 1972) for deriving AEGL-2 values for chlorine pentafluoride has ambiguities throughout the TSD; in some cases the effects are described as mild and reversible and in others as severe. For example, effects are described as sensory irritation and reversible mild lung congestion that meet the definition of AEGL-2 (page 32, lines 30-33). It is unclear from this description whether the effects are suitable for identifying PODs or exceed the definition of AEGL-2. The description on page 32, lines 14-24, suggests the effects are severe. Because the TSD identifies the next lower concentration as a NOAEL for AEGL-2 end points, one can infer that the sensory irritation and lung congestion were considered "serious" effects. The description of the MacEwen and Vernot study should be revised throughout the TSD to better characterize the effects in context with the definition of the AEGL-2 levels (see NRC 2001 for guidance).

Other Comments

Pages 10-11: In this section, halogen fluorides are described as likely to hydrolyze rapidly in the moist respiratory tract, that the mechanism by which they exert their acute toxicity is by direct irritation and corrosion, and that at high concentrations they penetrate the lungs. This contrasts with the characterization in the TSD on bromine (NRC 2010a, Section 4.3) that the more water soluble halogens are scrubbed higher in the respiratory tract and are thus more likely to produce irritation than those with lower water solubility. Conversely, the latter are more likely to penetrate more deeply and be more toxic to the lung. Is there any information for the halogen fluorides to support this generalization in the TSD?

In the derivation of AEGL values, part of the rationale for applying an uncertainty factor of 3 for intraspecies variability is that halogen fluorides exhibit a steep concentration-response relationship. The extent to which this justification applies to assessing variability within an outbred, wild-type population is questionable. This justification should be removed from the TSD. The factor of 3 is still appropriate because of the direct-acting nature of the halogen fluorides.

HEXAFLUOROPROPYLENE

The committee reviewed the AEGL TSD on hexafluoropropylene that was presented by Heather Carlson-Lynch of SRC, Inc. Table 13 presents a summary of the proposed AEGL values for hexafluoropropylene and their basis. The committee recommends that the basis of all the AEGL values be reanalyzed and that better justification be provided to support the selection of uncertainty factors.

AEGL Specific Comments

A systematic reassessment of the POD for AEGL-1 values for hexafluoropropylene should be conducted on the basis of the following considerations. First, the rat appears to be relatively insensitive to hexafluoropropylene compared with other species; so, it would be more appropriate to consider candidate PODs from studies of more sensitive species. Second, although the proposed POD represents a no-effect level for a subclinical effect (renal toxicity), the CNS effects reported in a repeated exposure study might be a more relevant end point to consider. Given that CNS effects are typically acute effects, relevant studies should be evaluated for more information with respect to the timing at which the CNS effects are observed. Because no human data are available, it is reasonable to consider that an effect relevant to AEGL-1 values (such as headache) might occur at the POD (or at lower concentrations) from animals studies. If no appropriate data are available, an option would be to not establish any AEGL-1 values.

TABLE 13 Summary of Proposed AEGL Values for Hexafluoropropylene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
150 ppm (920 mg/m^3)	67 ppm (410 mg/m^3)	40 ppm (240 mg/m^3)	14 ppm (85 mg/m^3)	8.3 ppm (51 mg/m^3)	Absence of renal toxicity in rats (140 ppm, 4 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.33
AEGL-2 (disabling)					
350 ppm (2,100 mg/m^3)	150 ppm (920 mg/m^3)	91 ppm (560 mg/m^3)	32 ppm (200 mg/m^3)	19 ppm (120 mg/m^3)	Reversible nephrosis and altered renal function in rats (320 ppm, 4 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.33
AEGL-3 (lethal)					
1,800 ppm (11,000 mg/m^3)	800 ppm (4,900 mg/m^3)	480 ppm (2,900 mg/m^3)	170 ppm (1,000 mg/m^3)	100 ppm (600 mg/m^3)	$BMCL_{05}$ for lethality in rats (1,677 ppm, 4 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.33

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; UF, uncertainty factor.

A similar reanalysis of the POD for AEGL-2 values should also be performed. Adding a summary table of nonlethal toxicity data to the TSD would facilitate making species comparisons and selecting the appropriate POD.

The POD for AEGL-3 values appears to be too high. There are differences in sensitivity to hexafluoropropylene across species, with the rat appearing to be less sensitive than the mouse, guinea pig, or rabbit. Thus, the committee recommends that the basis of the AEGL-3 values be reconsidered by performing a more systematic evaluation of all relevant lethality data, with more context provided for findings across studies. Adding a summary table of lethality data to the TSD would facilitate making species comparisons and selecting the appropriate data set.

For all the AEGL values, it is important to justify the selection of the uncertainty factors. A factor of 10 for interspecies differences should be supported by evidence of variability specific to hexafluorpropylene across species. For intraspecies variability, the TSD should discuss the substantial polymorphisms in several glutathione transferases and in several P450s, as well as the substantial differences between children and adults relevant to metabolism. Further, it appears that the glutathione transferase activity ratios are incorrectly represented in the TSD. Consideration should be given to the fact that study animals are inbred and humans are not. Thus, the response range for test species is more limited, so it is inappropriate to compare an average for a rat with a reported “average” for humans (the lower 1-10% should be considered for humans given their known variability). The TSD on tetrafluoroethylene is a helpful model in terms of the basic issues to address and the discussion of the uncertainty factors.

Other Comments

Page 20, lines 6-7: Is a reason provided for why initial mutagenic activity assays were positive but subsequent tests were not? A publication by the Japan Bioassay Research Center (2006) should be added to the TSD.

An updated literature search should be performed to identify more recent information about the production of hexafluoropropylene, to verify that the standards set by other organizations are still accurate, and to identify additional publications that might be relevant to deriving AEGL values.

Section 8.3 (Data Adequacy and Research Needs): This section should be revised to more accurately reflect the data needs. As currently written, the section suggests that all that is needed is to reaffirm the precision of the AEGL-1 and AEGL-2 values.

HYDROGEN BROMIDE AND HYDROGEN IODIDE

The committee reviewed the AEGL TSD on hydrogen bromide and hydrogen iodide that was presented by Lisa Ingerman of SRC, Inc. Table 14 presents a summary of the proposed AEGL values for these two chemicals and their basis. For hydrogen bromide, the committee approved the proposed AEGL-1 values, but recommends revisions to how the AEGL-2 and AEGL-3 values were derived.

The AEGL values for hydrogen iodide are based on those for hydrogen bromide. The committee found there was inadequate evidence to support this approach, and recommended that the TSD be restricted to an analysis of just hydrogen bromide. The committee recommends that the proposed AEGL values for hydrogen iodide be retracted by the AEGLs program and that no values be proposed. The committee was uncomfortable with basing values for hydrogen iodide on those for either hydrogen bromide or hydrogen chloride, because hydrogen iodide is the strongest of the halide acids and there are no specific data on hydrogen iodide on which to base AEGL values.

AEGL Specific Comments

The committee considered three options for deriving AEGL-2 values for hydrogen bromide: using a POD of 1,300 ppm (severe nasal lesions in the rat) for 30 min from a study by Stavert et al. (1991); adopting the AEGL-2 values for hydrogen chloride (based on studies by Stavert et al. 1991 and Barrow et al. 1977) because it and hydrogen bromide appear to have similar toxicity and the data on hydrogen chloride are more robust; or taking one-third of the AEGL-3 values for hydrogen bromide. The Stavert study was judged to be weak (see discussion below), so the committee recommends that the third option of dividing AEGL-3 values by 3 be used to derive the AEGL-2 values.

The committee evaluated four options for deriving AEGL-3 values for hydrogen bromide: using a $BMCL_{05}$ of 1,230 ppm from the MacEwen and Vernot (1972) study as the POD; using one-third (952 ppm) of the LC_{50} value (2,858 ppm) from the same study as the POD; using one-half of the concentration (1,300 ppm) that produced severe nasal lesions in rats after 30 min in the study by Stavert et al. (1991), which also reported 8% death; or adopt the AEGL values for hydrogen chloride (based on Vernot et al. 1977) because it and hydrogen bromide appear to have similar toxicities. The committee agreed that the first proposal was the best option. The selection of the POD could be strengthened by acknowledging that if the 1-h POD is extrapolated to 30 min, the concentration would be nearly two-fold higher than the concentration associated with death in the Stavert et al. (1991) study. The committee disagreed with the proposal to set the 8-h AEGL-3 value equal to the 4-h value; time scaling should be performed instead.

Other Comments

A discussion about the difficulties of the study by Stavert et al. (1991) study and why it was not used to determine a POD for AEGL-2 and AEGL-3 values should be added to the TSD. This study was the basis of the AEGL values for hydrogen chloride, which is why the option of basing AEGL values for hydrogen bromide on those for hydrogen chloride was not selected. The number of animals used to test hydrogen bromide and hydrogen chloride is not known, and only one concentration was tested. Deaths were reported for both chemicals—8% mortality with hydrogen bromide and 6% with hydrogen chloride.

The TSD should discuss the AEGLs values for hydrogen bromide in context with the AEGLs established for hydrogen chloride and hydrogen fluoride.

METHACRYLALDEHYDE

The committee reviewed the AEGL TSD on methacrylaldehyde that was presented by Heather Carlson-Lynch of SRC, Inc. Table 15 presents a summary of the proposed AEGL values for methacryaldehyde and their basis. The committee agreed with the proposed AEGL-1 values, but recommended revisions to how the AEGL-2 and AEGL-3 values were derived.

TABLE 14 Summary of Proposed AEGL Values for Hydrogen Bromide and Hydrogen Iodide Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Hydrogen bromide						
AEGL-1 (nondisabling)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	Threshold for nasal irritation in humans (3 ppm); UF = 3 (intraspecies)
AEGL-2 (disabling)	100 ppm (330 mg/m^3)	43 ppm (140 mg/m^3)	22 ppm (73 mg/m^3)	11 ppm (36 mg/m^3)	11 ppm (36 mg/m^3)	Hydrogen chloride values adopted (NRC 2004b)
AEGL-3 (lethality)	740 ppm (2,442 mg/m^3)	250 ppm (825 mg/m^3)	120 ppm (396 mg/m^3)	31 ppm (102 mg/m^3)	31 ppm (102 mg/m^3)	$BMCL_{05}$ for lethality in rats (1,239 ppm, 1 h); UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1
Hydrogen iodide						
AEGL-1 (nondisabling)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	Analogy with hydrogen bromide
AEGL-2 (disabling)	50 ppm (260 mg/m^3)	22 ppm (120 mg/m^3)	11 ppm (58 mg/m^3)	5.5 ppm (29 mg/m^3)	5.5 ppm (29 mg/m^3)	Analogy with hydrogen bromide; MF = 2
AEGL-3 (lethality)	370 ppm (1,900 mg/m^3)	130 ppm (680 mg/m^3)	60 ppm (310 mg/m^3)	16 ppm (84 mg/m^3)	16 ppm (84 mg/m^3)	Analogy with hydrogen bromide; MF = 2

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; MF, modifying factor; UF, uncertainty factor.

TABLE 15 Summary of Proposed AEGL Values for Methacrylaldehyde Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
0.20 ppm (0.60 mg/m^3)	0.20 ppm (0.60 mg/m^3)	0.20 ppm (0.60 mg/m^3)	0.20 ppm (0.60 mg/m^3)	0.20 ppm (0.60 mg/m^3)	Increased blink frequency in humans (0.189 ppm, 20 min); no UFs
AEGL-2 (disabling)					
3.5 ppm (9.8 mg/m^3)	3.5 ppm (9.8 mg/m^3)	2.8 ppm (7.8 mg/m^3)	1.8 ppm (5.0 mg/m^3)	1.1 ppm (3.1 mg/m^3)	Sensory and respiratory tract irritation in rats (15.3 ppm, 6 h/day, 13 wk); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-3 (lethal)					
5.9 ppm (17 mg/m^3)	5.9 ppm (17 mg/m^3)	4.7 ppm (13 mg/m^3)	2.9 ppm (8.1 mg/m^3)	1.9 ppm (5.3 mg/m^3)	One-third of lethal concentration in rats (25.7 ppm, 6 h, 5 d/wk, 2 wk); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: UF, uncertainty factor.

AEGL Specific Comments

The proposed AEGL-1 values for methacrylaldehyde were appropriate. Clarification on how blink frequency and perceived irritation were measured in the critical study should be added.

The basis of the AEGL-2 values should be changed to use a POD of 5 ppm from the studies by Coombs et al. (1992, 1994). At that concentration, rats exhibited ocular irritation, decreased respiratory rate, and had upper-respiratory-tract lesions. The latter effects were reversible, so they are not considered AEGL-2 effects. The POD is also less than one-third of the LC_{90}. Because the basis of the AEGL-2 values are irritant effects, no time scaling should be performed; a single value should be used for all the exposure durations.

The proposed AEGL-3 values should be revised to use a NOAEL for lethality of 19 ppm (Coombs et al. 1994) as the POD, rather than adjusting the LD_{90} by one third. The NOAEL is supported by the Coombs et al. (1992) study, in which no rats died when exposed to methacrylaldehyde at 15.3 ppm.

OXYGEN DIFLUORIDE

The committee reviewed the AEGL TSD on oxygen difluoride that was presented by Gary Diamond of SRC, Inc. Table 16 presents a summary of the proposed AEGL values for oxygen difluoride and their basis. The committee agreed with the proposal not to derive AEGL-1 values and to base AEGL-2 values on the AEGL-3 values. However, modifications are needed to explain how the AEGL-3 values were derived.

AEGL Specific Comments

The committee agreed that the data on oxygen difluoride were insufficient for deriving AEGL-1 values. This is also true of the AEGL-2 values, and the committee agreed with the proposal to derive AEGL-2 values by dividing the AEGL-3 values by 3. The discussion in support of this approach focuses on pulmonary, hematologic, and clinical chemistry data, and could be expanded and strengthened by including the following points:

- Section 6.2: The study in monkeys also included effects indicative of escape impairment (described in section 3.2.1 of the TSD), which also precludes using the data to identify a POD for AEGL-2 values.
- The data presented in Tables 2-5 indicates the exposure-response curve for lethality is steep. This should be cited in support of using a fraction of the AEGL-3 values (NRC 2001).
- The margin of safety afforded by the proposed values should be discussed. The signs and symptoms in the Deichmann and Gerarde (1969) study of respiratory-tract irritation and pulmonary edema and hemorrhage were reported to occur in humans after exposure to oxygen difluoride at 0.5 ppm for several hours. These effects should be compared with the pathology results from non-lethal exposure of rhesus monkeys. Although the Diechmann and Gerarde study is not specific, it involves an exposure concentration and duration relevant to AEGL-2 values. Also, all the occupational standards are set at or below the level reported in that study.

For AEGL-3 values, the committee recommends that the interspecies uncertainty factor be increased to 3. Despite the reduction in toxicity as the size of the test species increased, the data on the larger species (dogs and monkeys) are from a single study from 1945 that used a small number of test animals (two males and two females per group). The committee also recommends the use of a modifying factor 3 to account for the sparse data set.

Other Comments

A study by Harrison and MacKenzie (1973) that examined the ultrastructural pathogenesis of lesions produced in rats exposed to oxygen difluoride should be added to the TSD.

Page 10, lines 20-21, and page 11, lines 19-20: The exposure durations of the studies described in these sections are characterized as being “several” or “a few” hours. Quantitative information should be provided, if available.

TABLE 16 Summary of Proposed AEGL Values for Oxygen Difluoride Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	4.3 ppm (9.5 mg/m^3)	1.6 ppm (3.5 mg/m^3)	0.83 ppm (1.8 mg/m^3)	0.24 ppm (0.53 mg/m^3)	0.13 ppm (0.29 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethality)	13 ppm (29 mg/m^3)	4.7 ppm (10 mg/m^3)	2.5 ppm (5.5 mg/m^3)	0.71 ppm (1.6 mg/m^3)	0.38 ppm (0.84 mg/m^3)	$BMCL_{05}$ for lethality in monkeys (7.48 ppm, 1 h); UF = 3 (intraspecies); time scaling, n = 1.1

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; UF, uncertainty factor.

Page 17, Section 4 (Special Considerations): A subsection on sensitive subpopulations, similar to the section in the TSD on halogen fluorides, should be added. People with pre-existing lung disease might be at particular risk for delayed pulmonary effects from an acute exposure to oxygen difluoride.

Page 18, Section 4.3 (Structure-Activity Relationships): In addressing relative toxicities, it should be clarified that all comparisons are based on lethality data. The footnote in Table 8 is not adequate to convey this information. The discussion should specifically reference AEGL-3 values and not AEGL values generally. Relevant information on the non-lethal toxicity of other fluorinated compounds should be added, if available.

Page 22, Section 8.2 (Comparison with Other Standards and Guidelines): A substantive discussion of the differences between the AEGL values and other standards for oxygen difluoride must be added to the TSD (NRC 2001, Appendix J). Some of the values are substantially lower than the proposed AEGL values and the reasons for the differences should be explained. Table 13 should be updated by removing the Dutch MAC value. In 2004, the Health Council of the Netherlands found the toxicologic database on oxygen difluoride too weak to justify a health-based occupational exposure limit and concluded that the MAC value was too high (Health Council of the Netherlands 2004).

PENTABORANE

The committee reviewed the AEGL TSD on pentaborane that was presented by Gary Diamond of SRC, Inc. Table 17 presents a summary of the proposed AEGL values for pentaborane and their basis. The committee agreed with the proposal not to derive AEGL-1 values, but recommended that the basis of the AEGL-2 and AEGL-3 values be reanalyzed.

AEGL Specific Comments

Whether the POD for deriving AEGL-2 values for pentaborane is a NOAEL is questionable. The Weir et al. (1964) study reported no effects in dogs after a single 60-min exposure to pentaborane at 1.4 ppm. However, the study by Weeks et al. (1964) found that pentaborane at 5.2 ppm for 15 min produced delays in tests of conditioned avoidance response in at least some dogs. The cumulative exposure in these scenarios was similar; 84 ppm-min in the Weir et al. study and 78 ppm-min in the Weeks study. A discussion of this comparison should be added to the TSD to acknowledge the possible uncertainty with the POD. The TSD should also acknowledged that AEGL-2 effects occur below the odor threshold for pentaborane, an AEGL-1 effect.

TABLE 17 Summary of Proposed AEGL Values for Pentaborane Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
NR	NR	NR	NR	NR	
0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)	No observed effect level for CNS effects in dogs (1.4 ppm, 1 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.3
2.8 ppm (7.2 mg/m^3)	1.2 ppm (3.1 mg/m^3)	0.70 ppm (1.8 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	$BMCL_{05}$ for lethality in rats (7.0 ppm, 1 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.3

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; CNS, central nervous system; UF, uncertainty factor.

The uncertainty factors used in the derivation of the AEGL-2 values should also be reconsidered. Because the experimental data do not provide much information on test species age or gender variation in response to pentaborane, the proposed factor of 3 to account for interspecies differences should be increased to 10. The uncertainty factor for intraspecies variability should also be increased to 10, because most of the human studies involved exposures of adult males and it is uncertain whether potentially more susceptible groups would be adequately protected by an uncertainty factor of 3. Furthermore, the proposed AEGL values are 5-50 times higher than most of the other exposure guidelines for pentaborane.

The discussion of time scaling to derive AEGL-2 values should note that neurotoxic effects are on the continuum of effects leading to death (e.g., tremors, convulsions, apprehension). This will provide additional support for how time scaling was performed on the basis of LD_{50} data.

For derivation of AEGL-3 values, the reason that studies with mice were not used should be justified. In Section 7.2 (page 32, lines 11-13), mice are identified as having LC_{50} values consistently lower than those of other species. This would typically result in mice being characterized as the most sensitive species (as detailed in Section 4.4.2) and the data used to derive AEGL values. Yet in this instance mice are characterized as "overly sensitive" and are not used to derive AEGL values. Table 7 (page 19) does not appear to support the characterization of mice being consistently more sensitive. For exposure durations for which LC_{50} values were calculated, mice are more sensitive than dogs or rats by a factor of 2 for a 15-min or shorter exposure (except rats for 5 min), but are comparably sensitive for a 60-min exposure. These values do, however, agree with the characterization on page 32, line 29, that LC_{50} values varied less than three-fold among species.

Other Comments

Table 15: A PEL-STEL for pentaborane was established by OSHA in 1989. However, the courts vacated the rule in 1992, which eliminated the PEL-STEL. The value should be removed from the table or a footnote added to indicate that this value is no longer in effect.

STIBINE

The committee reviewed the AEGL TSD on stibine that was presented by Lisa Ingerman of SRC, Inc. Table 18 presents a summary of the proposed AEGL values for stibine and their basis. The committee agreed with the proposal not to derive AEGL-1 values. Because a number of relevant studies on stibine were identified that should be added to the TSD, the committee recommended the AEGL-2 and AEGL-3 values be reconsidered in context with the new information before they are finalized.

TABLE 18 Summary of Proposed AEGL Values for Stibine Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	
AEGL-2 (disabling)					
4.2 ppm (21 mg/m^3)	2.9 ppm (15 mg/m^3)	1.5 ppm (7.7 mg/m^3)	0.36 ppm (1.8 mg/m^3)	0.18 ppm (0.92 mg/m^3)	No effect level for irreversible toxicity in rats and guinea pigs (29.1 ppm, 30 min); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-3 (lethal)					
28 ppm (140 mg/m^3)	19 ppm (97 mg/m^3)	9.6 ppm (49 mg/m^3)	2.4 ppm (12 mg/m^3)	1.2 ppm (6.1 mg/m^3)	Highest nonlethal concentration in rats and guinea pigs (191 ppm, 30 min); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: UF, uncertainty factor.

AEGL Specific Comments

The committee recommends that the basis of the AEGL-2 andAEGL-3 values be re-evaluated in light of additional information on stibine and more careful consideration of the result in context with the definition of the AEGL levels. Below are some specific examples.

Page 16, Sections 6.2. and 6.3: In the key study (Price et al. 1979), exposure to stibine at 191 ppm for 30 min was described as producing "…minimal renal tubular calcification damage considered to be a precursor to irreversible lesions …" and "… eye irritation and closure … [and] generalized depressed activity, but none were judged to have an impaired ability to escape." The next lower test concentration was selected to derive AEGL-2 values because it was "… the highest exposure without an AEGL-2 effect" [emphases added]. These descriptions are ambiguous in the context of the definition of AEGL-2 effects: "… the threshold between reversible effects and …serious or irreversible health effects or effects that impair escape … above [which] there is an increasing likelihood that people may become disabled or are increasingly likely to experience serious or irreversible health effects" [emphasis added] (NRC 2001, page 42). Description of such effects is used in the TSD to reject 191 ppm as a POD for stibine. Justification for this decision should be reconsidered or strengthened by clarifying the ambiguity of the described effects. For example, on page 16, lines 42-44: delete the two sentences referring to ocular irritation and depressed activity unless the link is made to the threshold for impaired ability to escape. Otherwise, because the investigators indicate the effects are below AEGL-2 effects, addressing them without this context could create some confusion. Also, indicate more clearly that the minimal renal tubular calcification in and of itself was a serious or irreversible health effect. Consideration should also be given to the fact that POD for AEGL-3 values is 191 ppm, so its use in deriving AEGL-2 values would be conflicting, especially if the relevance of the effects to AEGL-2 values is uncertain.

For both the AEGL-2 and AEGL-3 values, the committee recommends that an uncertainty factor of 10 be applied to account for interspecies differences because of the evidence of differences in sensitivity among cats, dogs, guinea pigs, and rodents with respect to effects other than direct contact irritation. A factor of 3 for intraspecies variability is appropriate. In addition, a modifying factor is recommended because of the sparse data on stibine; a factor of 2 or 3 might be appropriate, depending on a review of additional data on stibine that is not currently in the TSD, including data on adverse effects other than direct contact irritation.

Other Comments

An updated literature search is needed to ensure that the document reflects the most current and complete information on stibine.

Page 7, lines 3-5; page 8, Introduction: Clarification of how stibine is produced is needed. For example, the statement "Nascent hydrogen is required for its production" might be replaced with "Stibine is a gas that forms when antimony is treated with, or comes in contact with, acids" (e.g., see DeWolff 1995).

Page 7, lines 7-10: provide more information beyond the single statement that "Stibine is also a hemolytic poison." The level of detail should be similar to that provided for pulmonary effects, given that many references identify hemolysis as a key issue (see Section 3.1.1: "Hemoconcentration, pulmonary congestion and edema were cited as the cause of death.") For example, in a review and description by ATSDR (1992), pulmonary edema reflects contact irritation in the lung and has been identified as a contributing factor to the death of rats and guinea pigs exposed to stibine as reported in the Price et al. (1979) study. Hemolysis was identified in the delayed deaths of guinea pigs, with irreversible morphological changes followed by hemoglobinuria and anemia. Other studies also identify hemolysis as a key effect. To illustrate, CDC (2013) relate arsine and stibine, indicating that "signs and symptoms occur 2-24 h after exposure and result from massive hemolysis. These signs and symptoms include generalized weakness, dark urine, jaundice, and dyspnea. Oliguria and renal failure often occur 1 to 3 days after exposure."

Similarly, from HPA (2012): "The health effects of arsine and stibine are similar. The characteristic toxic effect of both arsine and stibine is haemolysis (rupture of red blood cells). The onset of symptoms may be delayed for several hours. Inhalation of arsine or stibine may cause headache, malaise, weakness, dizziness, dyspnoea, anaemia, red staining of the conjunctiva, dark red urine, abdominal pain, nausea and vomiting. Renal failure, liver damage and pulmonary oedema may occur 24-48 h post exposure. Exposure to high concentrations may lead to death." Also, DeWolff (1995) indicates: "Acute inhalation of the volatile hydride stibine (for which an occupational limit of 0.1 ppm (0.5 mg/m^3) has been defined) may lead to haemolytic anemia and acute renal failure." In addition, from Elkins (1950): "Antimony hydride, stibine (SbHs), is a highly toxic gas similar to arsine. ... Its effects, primarily blood changes and liver damage, are similar to those of arsine."

Page 7, lines 10-11: Relevant human case reports of exposure to stibine appear to be available. See ATSDR (1992) and other sources, including Fairhall and Hyslop (1947): "Possible stibine poisoning was associated with exposure to gases produced by quenching hot antimony metallic dross containing aluminum with water. Three exposed employees became ill within a few hours with complaints of weakness, headache, nausea, severe abdominal and lumbar pain, and hematuria; the hemolytic effect on blood was the 'most outstanding laboratory finding." Given that stibine is an antimony compound, context could be provided by considering data on people exposed to antimony. DeWolff (1995) indicates "Haemolysis, myoglobinuria, haematuria, renal failure, nausea, vomiting, and headache have been reported in humans after inhalation."

Page 7, lines 11-13: Provide context for the statement that air samples provide data regarding human exposure. For example, specify concentrations of stibine in different types of factories.

Page 7, lines 33-42: Revise discussion here and other relevant portions of the TSD to reflect changes in the uncertainty factors and to acknowledge the hemolytic effects and potential for human variability, such as among subgroups with kidney conditions. As discussed in the comments on carbonyl fluoride, the argument that a steep concentration-response is an indication of little toxic variation within a population is not appropriate and should be removed.

Page 8, Introduction: Provide more current information about the uses of stibine. For example, HPA (2012) reports that "Both arsine and stibine are used in the semiconductor industry as doping agents in the manufacture of microchips. Industrial processes may lead to accidental formation, including overcharging lead storage batteries."

Page 9, Table 2: More current references should be used for the chemical and physical properties for stibine (for example, see SER 2013a). It appears that HSBD (misspelled in the TSD) has not been updated in the last several years. Considering the comparisons made to arsine and phosphine in the TSD, it might be useful include data on those chemicals in the table to allow for comparisons. (See ATSDR [1992] and other syntheses for example tabulations for antimony and compounds, including stibine.)

Page 9, lines 22-24 (in Section 2.2, Epidemiologic Studies): Include information from additional studies by Young (1979) and others, such as described in ATSDR (1992) and other, more recent syntheses.

Page 10, Section 2.3 (Neurotoxicity): This section only refers to one study that assessed cholinesterase and acetylcholinesterase activity in the presence of stibine, referring to human plasma, human red blood cells, and mouse neuronal cells. Additional relevant information in other references regarding CNS effects should be included. Some references that refer to activity in red blood cells vs. plasma when considering stibine as an antimony compound, include: Voegtlin et al. (1920), Fairhall and Hyslop (1947), DOD (2005), and HPA (2012).

Page 10, line 43 (Section 2.4, Developmental/Reproductive Toxicity): Given that stibine is an antimony compound, provide context for antimony and other related compounds as indicated.

Page 10, line 47 (Section 2.4, Genotoxicity): Data on antimony and other related compounds should be considered for inclusion in this section. Also, why is "relevant to the derivation of AEGLs" included?

Page 11, line 3 (Section 2.6, Carcinogenicity): Data on antimony and other related compounds should be considered for inclusion in this section.

Page 11, Section 2.7 (Summary): This brief summary appears to only relate to Section 2.2 and reflects limited information (e.g., other exposure concentrations have been identified that were not reflected in that section). Revise to provide the summary all of the information on human toxicity, including any new information added regarding antimony compounds.

Page 12, lines 42-43; page 13, lines 19-20; and page 16, lines 32-33 and lines 40-41: The first two text callouts describe the Price et al. (1979) findings regarding renal effects after exposure to stibine at 191 ppm for 30 min as renal tubular dilation and calcific debris in the renal pelvis, whereas the next two text locations add descriptors of the damage and draw conclusions about the severity of the damage, described as "minimal renal tubular calcification damage considered a precursor to irreversible lesions." and "renal tubular dilation and calcification that would result in scarring." Clarification is required regarding the description on page 16: (1) a descriptor is used that is not supported by the earlier description of the experimental findings ("minimal" renal tubular damage); (2) the conclusions drawn are not clearly evident from the earlier descriptions ("considered a precursor to irreversible lesions" and "would result in scarring"); and (3) the change from "tubular dilation and calcific debris" to "tubular calcification damage" and "tubular dilation and calcification" does not appear to be synonymous descriptions.

Page 14, Section 3.4 (Genotoxicity), line 15: The information provided in this section is limited. Relevant comparisons of the differences in genotoxicity of stibine and arsine are provided in the study by Andrewes et al. (2004), and a number of relevant studies are cited. The section should be expanded to reflect this information.

Page 14, Table 3: Include more information from additional references including but not limited to those reflected in these comments. Webster (1946) indicates that the first well-regarded experiment with pure stibine gas was performed by Stock and colleagues (citing several references). Fairhall and Hyslop (1947) also address the validity issue: "Probably the earliest experiment of significance with pure stibine were those made by Stock and Guttman in 1904. The few experimental investigations which had been made prior to this date were very likely invalidated as a result of the impurity of the materials used, animals being subjected either to atmospheres of pure hydrogen or to gases containing arsine. Stock and Guttman clearly demonstrated the toxicity of antimony hydride. They found that in order to produce death of white mice, an exposure of 3 hours 52 minutes in an atmosphere containing 100 p.p.m. of arsine was necessary, compared with 1 hour and 42 minutes for stibine." (There is precedent for using such early studies; see AEGL values for the chloroarsenicals and lewisite.)

Page 14, Section 3.5 (Carcinogenicity), line 19: Provide related context for antimony (e.g., see statements in ATSDR (1992), Andrewes et al. (2004), and other sources regarding cancer classifications.

Page 14, lines 23-25 (Summary): The summary does not provide sufficient detail; it refers to the preceding section and a table of effects (which is incomplete). The summary should be revised to be more informative.

Page 15, Section 4.1 (Metabolism and Disposition): The section does not provide an adequate description of the data. The study by Kentner et al. (1995) should be described in more detail, and additional references should be added. For example, see descriptions provided in Smith et al. (1948), Bailly et al. (1991), DeWolff (1995), IPCS (1996), Montelius (2000), Sundar and Chakravarty (2010), HPA (2012), EPA (2012), and ICRP (2012).

Page 15, Section 4.2 (Mechanism of Toxicity): Additional references should be sought from recent compilations of the data on stibine (for example, OSHA [2004]; HPA [2012]). Older literature also appears to have relevant information (for example, Webster [1946]; DeWolff [1995]).

Page 15, lines 25-26 (Section 4.3, Structure-Activity Relationships): Revise this one-sentence section to clarify which stibine regulations are based on arsine, to provide information beyond the statement of similar acute mortality in rats (notably effects other than mortality), and to present additional information regarding analogues (considering antimony trioxide as well as other volatile hydrides). Some studies have reported that the Stock and Guttman study provide evidence that stibine killed mice more than twice as quickly as arsine (Fairhall and Hyslop 1947).

Page 15, Section 4.4.1 (Species Variability): Provide additional context from other references that indicate species differences, rather than limiting the information to only two citations. Given that stibine is an antimony compound, provide context with respect to that chemical as indicated (see references cited in ICRP 2012). Data are also available from the study by Webster (1946).

Page 15, line 41 (Section 4.4.2, Unique Physicochemical Properties): The relevance of this one-sentence section is unclear ("Nascent hydrogen is required for the formation of stibine.") Replace or delete.

Page 15, lines 46-48 (Section 4.4.3, Concurrent Exposure): Provide justification for the statement that "It is assumed that concurrent exposure with other chemicals, especially arsine, could increase the severity of the effects of an exposure to stibine."

Page 15: A section on susceptible populations should be added to the TSD. That section would be expected to include discussion of groups with respiratory conditions and kidney conditions. Also, discuss differences in male and female mortality from the Price et al. (1979) study.

Page 16, line 12: Clarify that lesions observed in the animals at this concentration were "reported to be" not treatment related.

Page 16, Section 6.2, lines 30-31 and 33-34: These two sentences appear contradictory with regard to whether the effects were irreversible. Regarding the POD, provide (and consider) additional context provided by the data from Fairhall and Hyslop (1947), Stock and Guttman (1904), and others, such as the estimated median 1-h lethal dose for one-week-old chicks (25-30 ppm), and dog and cat mortality at 40-45 ppm.

Page 19, lines 4 and 12: These two sentences are incorrect: "All currently available standards and guidelines are shown in Table 8" and "No other standards or guidelines are available for stibine (antimony hydride)." First, the most "current" citation for the standards and guidelines in this table appears to be from 8 years ago, with some references being even older. Second, a number of other occupational exposure limits (OELs) exist. For example, see SER (2013), which includes OELs for Switzerland, Belgium, Spain, and other countries (0.1 ppm), as well as the OELs for Sweden, Norway, Finland, and Denmark (lower value, 0.05 ppm).

Pages 19 and 21-22, Table 8 and references: The citations are out of date; current references should be cited and all information presented in Table 8 should be checked and updated as indicated. Values in mg/m^3 should be included in this table where identified with the given standard or guideline. In the reference list, the URLs of online sources should be verified just prior to submitting the revised TSD and the access dates should be provided. Considering the toxicity comparisons made to similar

chemicals, notably arsine and phosphine, it would be useful for the TSD to provide a table with side-by-side comparisons of the extant standards for those compounds, at least in the appendix.

Page 19, line 23, through page 20, line 2: The 2005 reference of the American Industrial Hygiene Association cited in the TSD is outdated. Of particular note is the update of the emergency response planning guidelines (ERPGs) set from several years ago (2009), in which arsine and stibine were identified as among the 15 chemicals with new or revised documents.

Page 19, line 8; page 20, lines 20-22; page 22, lines 5-6. A new (modified) system for OELs was established in The Netherlands in 2007, which requires updating the information in the text and in Table 8 and cited references. The Dutch Health Council's Expert Committee on Occupational Standards recommends health-based values (similar to the U.S. NIOSH or ACGIH®), with SDU Uitgevers as the publisher/distributor; the Social and Economic Council of the Netherlands (SER) provides OELs online (see SER [2007, 2013a]) .

Page 20, lines 26-35 (Section 8.3, Data Adequacy and Research Needs): This section should be rewritten in light of new information that is added to the TSD. In lines 26-27, revise to clarify the availability of "actual concentration and/or duration parameters to which workers have been exposed". In lines 32-33, clarify "The animal data are sufficient for showing lethality and non-incapacitating exposures" considering that the lack of data for an AEGL-1 is not addressed. Also, in lines 34-35, clarify "Data on exposure durations would be useful in the development of more precise temporal extrapolation" which implies the extrapolation is at least somewhat precise (when in fact the default approach was used). Given that the draft AEGLs were derived from pulmonary irritant effects while substantial uncertainty exists with regard to the role of hemolytic effects, the rationale for additional data on hemolytic effects should be made explicit here.

Relevant References

The following are several references that should be included or expanded upon in the updated TSD. Other relevant information should be sought through an updated literature search.

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STYRENE

The committee reviewed the AEGL TSD on styrene that was presented by Lisa Ingerman of SRC, Inc. Table 19 presents a summary of the proposed AEGL values for styrene and their basis. The committee agreed with the proposed AEGL-1 values, and recommended a few adjustments to how the AEGL-2 and AEGL-3 values were derived.

AEGL Specific Comments

For AEGL-2 values, the POD (376 ppm) is based on a study in humans in which two subjects reported "feeling of being inebriated" (Stewart et al. 1968). Because that feeling was not further characterized (e.g., slightly, moderately, or heavy inebriation), it should be considered potentially escape-impairing. The next lower concentration from the study (216 ppm) would be a better choice for the POD. The committee disagrees with the argument presented in the TSD (pages 54-55) that an uncertainty factor of 3 is adequate to account for intraspecies variability. Conditions of heavy exercise may indeed not be expected to last for hours. However, conditions of escape from an accident may be equivalent to at least moderate exercise, which experimentally led to a five-fold increase in styrene concentration in the blood. Moreover, although the range of individual differences in susceptibility to direct-acting irritants may be expected to be relatively small, the Standing Operating Procedures (NRC 2001, Section 2.5.3.3.4) indicates that a default of 10 is generally used to account for the potential broad range of human susceptibility to respiratory irritants. Although the TSD makes a case that workers exposed to styrene have not exhibited signs of CNS depression that would affect their ability to escape, consideration should be given to the possibility of adaptation to the exposure and the "healthy worker effect." Results from worker populations may not be protective to naïve victims of an accident. Therefore, the committee recommends an uncertainty factor of 10 for intraspecies variability.

For AEGL-3 values, the committee agreed with the proposed POD, but recommended that the uncertainty factor for intraspecies variability be increased to 10 for the same reasons specified above for AEGL-2 values. An uncertainty factor of 1 for interspecies differences is adequate because kinetic modeling has shown that rats absorb more styrene into their blood stream than humans.

Other Comments

In many places in the TSD, statements are made that mice are more sensitive to styrene than rats and that rats are more sensitive than humans. This is true only for reactive metabolite-mediated effects, not for CNS effect or for irritation.

Page 42, paragraph 4: Are the concentration ratios in blood divided by those in air (as specified in the first few sentences) or in air divided by those in blood (as specified in the last sentence)?

New data are available on the genotoxicity, ototoxicity, and effects on color vision caused by styrene (see Montelius 2010 for a more recent summary). Although this information will not affect the AEGL values, it should be used to update the TSD to give a better characterization of the evidence on those effects.

TELLURIUM HEXAFLUORIDE

The committee reviewed the AEGL TSD on tellurium hexafluoride that was presented by Julie Klotzbach of SRC, Inc. Table 20 presents a summary of the proposed AEGL values for tellurium hexafluoride and their basis. The committee agreed with the proposal not to derive AEGL-1 values, and with deriving AEGL-2 values from the AEGL-3 values. However, the AEGL-3 values for tellurim hexafluoride should be modified.

AEGL Specific Comments

The committee agrees the data on tellurium hexafluoride are inadequate to establish AEGL-1 values. It might be useful to add consideration of how AEGL values were established for other hexafluorides, such as selenium hexafluoride and uranium hexafluoride, to the TSD.

TABLE 19 Summary of Proposed AEGL Values for Styrene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	20 ppm (85 mg/m^3)	NOAEL for slight irritation in humans (20 ppm, 3 h); no UFs
AEGL-2 (disabling)					
230 ppm (980 mg/m^3)	160 ppm (680 mg/m^3)	130 ppm (550 mg/m^3)	130 ppm (550 mg/m^3)	130 ppm (550 mg/m^3)	NOAEL for CNS effects in humans (376 ppm, 1 h); total UF = 3 (intraspecies); default time scaling to shorter durations
AEGL-3 (lethal)					
1,900 ppm (8,090 mg/m^3)	1,900 ppm (8,090 mg/m^3)	1,100 ppm (4,690 mg/m^3)	340 ppm (1,450 mg/m^3)	340 ppm (1,450 mg/m^3)	$BMCL_{05}$ for lethality in rats (3,400 ppm, 4 h); total UF = 10 (interspecies = 3, intraspecies = 3); time scaling, n = 1.2

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; CNS, central nervous system; NOAEL, no observed adverse effect level; UF, uncertainty factor.

TABLE 20 Summary of Proposed AEGL Values for Tellurium Hexafluoride Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)					
0.032 ppm (0.32 mg/m^3)	0.002 ppm (0.22 mg/m^3)	0.018 ppm (0.18 mg/m^3)	0.011 ppm (0.11 mg/m^3)	0.0057 ppm (0.056 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)					
0.096 ppm (0.95 mg/m^3)	0.067 ppm (0.66 mg/m^3)	0.053 ppm (0.52 mg/m^3)	0.033 ppm (0.33 mg/m^3)	0.017 ppm (0.17 mg/m^3)	Highest nonlethal concentration in rabbits, guinea pigs, rats, mice (1 ppm, 4 h); total UF = 3 (intraspecies), MF = 10; default time scaling

Abbreviations: MF, modifying factor; UF, uncertainty factor.

Estimating AEGL-2 values by taking one-third of the AEGL-3 values is justified and consistent with the Standing Operating Procedures (NRC 2001). However, the discussion of the available data for AEGL-2 values should be expanded to consider approaches used for other metal hexafluorides and to note similarities with respect to renal toxicity relevant to this AEGL level (which differs from the pulmonary effect underlying the AEGL-3 values). Information regarding human variability and reproductive toxicity summarized in IPCS (1998) should also be considered.

For AEGL-3 values, the committee disagrees with the proposal to use an uncertainty factor of 1 for interspecies differences. The study by Kimmerle (1960) in mice, rats, guinea pigs, and rabbits is cited in support of this value. The number of animals tested was small (only 1-4 animals per group) and only adult male animals appear to have been used. Thus, it is inappropriate to conclude that differences between laboratory species and the diverse human population are minimal on the basis of this study. A time-scaling approach should be determined after considering information about mode of action for renal and pulmonary effects and how AEGL values were derived for other hexafluorides.

Other Comments

Throughout the TSD and especially in Section 4.4 (Other Relevant Information), consideration should be given to information on tellurium as a toxic moiety. Relevant information on other hexafluorides should also be added to provide needed context, particularly in the absence of data on tellurium hexafluoride.

The study by Kimmerle (1960) is discussed in several section of the TSD. The sections should acknowledge the limitations and uncertainties associated with the study, particularly with respect to the small number of animals tested. For example, the number of animals should be specified in Table 3, in the discussion of structure-activity relationships on page 11 (lines 1-9), in the discussion of species variability on page 11 (lines 31-34), and elsewhere.

Page 7, Section 2.2.2 (Case Report): Additional information from case reports is available from a survey of workers conducted by Steinberg et al. (1942).

Pages 8-9, Section 3 (Animal Toxicity Data): A discussion about the toxicity of tellurium (in ionic and elemental form) should be added to this section, because it is the other component of potential toxicity in addition to hydrogen fluoride, and could help explain the relative toxicities between different hexafluorides. Relevant information should also be added to Section 4.2 (Mechanism of Toxicity).

Page 10, Section 3.4 (Developmental/Reproductive Toxicity): A study by Duckett (1970) on the fetal effects from exposure to tellurium should be added to this section. This study indicates a potential role of tellurium as a toxic moiety.

Page 10, Section 4.1 (Metabolism and Disposition): More information on tellurium hexafluoride and its hydrolysis products should be presented. The IPCS (1998) reference cites some relevant papers.

Table 8: Clarification of whether the exposure guidelines from other organizations are based on tellurium concentration measurements or tellurium hexafluoride should be specified. This should also be done throughout the document.

Section 8.3 (Data Adequacy and Research Needs): This section should be expanded to appropriately reflect the substantial uncertainties with the database on tellurium hexafluoride. Issues include lack of information on the contribution of hydrolysis products to toxicity (similar to the situation with other hexafluorides) and unknown mechanisms for the reproductive effects found in rats.

TETRAFLUOROETHYLENE

The committee reviewed the AEGL TSD on tetrafluoroethylene that was presented by Heather Carlson-Lynch of SRC, Inc. Table 21 presents a summary of the proposed AEGL values for tetrafluoroethylene and their basis. The committee agreed with the selected PODs for the AEGL values, but recommends modifications to the uncertainty factors.

TABLE 21 Summary of Proposed AEGL Values for Tetrafluoroethylene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
270 ppm (1,100 mg/m^3)	270 ppm (1,100 mg/m^3)	220 ppm (900 mg/m^3)	140 ppm (570 mg/m^3)	90 ppm (370 mg/m^3)	No adverse renal effects in rats and mice (1,200 ppm, 6 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-2 (disabling)					
690 ppm (2,800 mg/m^3)	690 ppm (2,800 mg/m^3)	550 ppm (2,200 mg/m^3)	340 ppm (1,400 mg/m^3)	230 ppm (940 mg/m^3)	NOAEL for renal necrosis (3,000 ppm, 6 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling
AEGL-3 (lethal)					
4,200 ppm (17,000 mg/m^3)	4,200 ppm (17,000 mg/m^3)	3,300 ppm (13,000 mg/m^3)	2,100 ppm (8,500 mg/m^3)	1,000 ppm (4,100 mg/m^3)	$BMCL_{05}$ for lethality in hamsters (20,822 ppm,4 h); total UF = 10 (interspecies = 3, intraspecies = 3); default time scaling

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NOAEL, no observed adverse effect level; UF, uncertainty factor.

AEGL Specific Comments

The uncertainty factors used to derive AEGL values for tetrafluoroethylene are inadequately justified. A factor of 3 is proposed to account for species differences in glutathione (GSH)-mediated metabolism of tetrafluoroethylene. However, these data are based on cytosolic measurements of GSH. The metabolism of tetrafluoroethylene is mediated by a specific GSH-*S*-transferase (GST) located in cell membranes (Odum and Green 1984), so free enzyme or substrate levels in the cytoplasm have less to do with the metabolism than the activity of the membrane-bound enzyme. Therefore, the data on cytosolic GSH isoenzyemes should not form the basis for any conclusions regarding interspecies differences. If no data are available on GSH isoenzymes in cell membranes to help inform consideration of interspecies differences, a default factor of 10 should be used.

The proposed factor of 3 for intraspecies variability is insufficient to address the uncertainty associated differences in humans, particularly with respect to children. A factor of 10 should be used.

Other Comments

Page 19, line 36: reference is made to a reactive “thiol”; a more accurate characterization is a reactive “metabolite”.

Page 20, line 26: the metabolism of tetrachloroethylene is described as being exclusively by CYP-450 epoxidation. This is incorrect. The chemical is also metabolized by GSH isoenzymes.

Page 20, line 28: the statement that tetrachloroethylene causes kidney damage and not liver damage is not correct. Lash and Parker (2001) indicate that both organs are damaged.

THIONYL CHLORIDE

The committee reviewed the AEGL TSD on thionyl chloride that was presented by Julie Klotzbach of SRC, Inc. Table 22 presents a summary of the proposed AEGL values for thionyl chloride and their basis. The committee agreed with the approach to deriving the AEGL values, but recommends that additional information be considered to determine whether alternate derivations might be more appropriate or whether slight adjustments to the calculations might be made before the TSD is finalized.

TABLE 22 Summary of Proposed AEGL Values for Thionyl Chloride Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
NR	NR	NR	NR	NR	
AEGL-2 (disabling)					
4.0 ppm (19 mg/m^3)	2.7 ppm (13 mg/m^3)	2.2 ppm (11 mg/m^3)	0.53 ppm (2.6 mg/m^3)	0.27 ppm (1.3 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)					
12 ppm (58 mg/m^3)	8.2 ppm (40 mg/m^3)	6.5 ppm (32 mg/m^3)	1.6 ppm (7.8 mg/m^3)	0.82 ppm (4.0 mg/m^3)	$BMCL_{05}$ for lethality in rats (196 ppm, 1h); total UF = 30 (interspecies = 3, intraspecies = 10); default time scaling

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended; UF, uncertainty factor.

AEGL Specific Comments

The committee agreed with the proposal not to recommend AEGL-1 values for thionyl chloride. The discussion should mention that in an emergency situation, exposure is likely to be to the hydrolysis products of thionyl chloride—sulfur dioxide and hydrogen chloride. Therefore, AEGL-1 values for those chemicals should be presented in the TSD, with corresponding relative humidity and stoichiometric information, to provide relevant context.

The committee also agreed with the approaches to deriving AEGL-2 and AEGL-3 values. The importance of relative humidity and the range that could be encountered in release situations should be discussed. Additional information brought to light as part of the re-review of animal studies (see below) should be considered to assess whether an alternate approach to deriving AEGL values is appropriate. In the current derivation of AEGL-3 values, the statement that the intraspecies uncertainty factor is protective of asthmatics and other sensitive populations should be deleted unless further justification can be provided. A factor of 10 was applied to address asthmatics alone in the derivation of AEGL values for sulfur dioxide, and there appears to be gender differences in sensitivity to thionyl chloride.

Other Comments

Page 6, lines 4-5: Because of the importance of hydrolysis to the toxicity of thionyl chloride, quantitative context for the rate of hydrolysis should be provided.

Page 6, lines 8-16; page 8, lines 20-24: The discussion should be revised to avoid the impression that nothing is known about the mechanism of toxicity of thionyl chloride; information is available and are well supported by related studies. The revision should also cover nonlethal toxicity and reflect the input provided in a previous review by the committee (NRC 2011): "Thionyl chloride hydrolyses upon contact with water yielding sulfur dioxide and hydrogen chloride, and most, if not all, of the effects of thionyl chloride are likely caused by these hydrolysis products. However, the concentration-effect relationship for inhaled thionyl chloride may differ from that for inhaled sulfur dioxide and hydrogen chloride, as the former exposure will result in deeper deposition in the respiratory tract and more severe effects. This notion is supported by the lower rat LC_{50} values obtained at low relative humidity (Nachreiner 1993), as compared to higher humidity (Pauluhn 1987)." Information on the effect of relative humidity on thionyl chloride hydrolysis should be included. For example, the companion publications by Driver et al. (2003) and Johnson et al. (2003) report rapid hydrolysis of thionyl chloride in air upon contact with water (and no decomposition in the absence of water), with a hydrolysis half life of several hours or more at lower relative humidities compared with a half life of less than 9 min at higher relative humidity (e.g., 50%). In addition, supporting context for this mechanism of toxicity should be provided by discussing the similar findings with sulfur dioxide (as highlighted in NRC [2010c] and the primary literature).

Page 6, lines 39-40: In summarizing the Pauluhn (1987) study, clarify the context for the relative humidity range presented. From the study description, it appears that four distinct relative humidities are reported for the input air (29, 38, 47, and 51%), and four for the chamber exhaust (48, 53, 51, 54, and 54%); each represents the average of three measurements taken at the beginning, middle, and end of the given exposures. Thus, the actual range of relative humidities across these exposures (five concentrations) is unknown. The highest average relative humidity reported for the chamber exhaust (54%) was associated with the two highest concentrations, while the lowest average relative humidity reported for the chamber exhaust (48%) corresponded to the lowest concentration. Both are similar, on the order of 50%. Also, mention of this study (in line 39) should refer to the 1987 study (not the 1983 study). The other study by Pauluhn (1986), a 4-h exposure study cited in Pauluhn (1987), should be mentioned in the summary of the lethality studies (page 7, first paragraph).

Page 6, lines 42-44: The justification for deriving AEGL-2 values by dividing AEGL-3 values by 3 should make it clear that this is a general approach for chemicals with a steep concentration-response curve for lethality and not because of data specific to thionyl chloride.

Page 7, lines 1-6: Include the 4-h Pauluhn (1986) data, and check the inputs to the benchmark calculations to confirm those estimates are appropriate.

Page 7, lines 7-10: Justify the statement that the animal model is appropriate (e.g., per citation); male outbred CD rats served as the animal model for sulfur dioxide (Cohen et al. 1973), whereas male and female Wistar rats serve as the basis for the AEGL-3 derivations for thionyl chloride. Also, clarify that the mechanism of action for direct-acting irritants of the eyes and respiratory tract is not expected to substantially differ across species.

Page 8, lines 14-15: Replace the qualitative comparison to hydrolysis of phosgene (unless relevance is justified) with quantitative information to support the statement in line 14 that hydrolysis is very rapid.

Page 9, Table 2 (Chemical and Physical Properties): The HSDB "2013" reference is misleading because information for this chemical in that database has not been updated for years; check other standard sources, as it appears other values have been reported. Given its importance to the inhalation toxicity of thionyl chloride, hydrolysis rates should be included in the table.

Page 10, lines 8-9 (Section 2.2.2, Case Reports): Delete the statement that the case reports lack exposure and duration data. Duration data are provided in the summary by Grieco (1962) and in EPA/OPPT (2000).

Page 10, lines 29, 32, 36-37, 39 (Section 2.2.2, Case Reports): Clarify that the first worker was "entirely well *4 years after the exposure*" (line 29) to avoid the impression that corticosteroids returned the patient to normal health after the six-month therapy period. Clarify that the second worker (from the same factory) was admitted to the *ophthalmology department for his corneal burns* (line 32), *developed a spontaneous pnuemothorax with progressive respiratory failure, developed atelectasis and repeated lung infections*, and continued to be *severely* ill, was *considered to have* end-stage lung disease *and was sent to a transplant center for a heart-lung transplantation but during the wait his conditions gradually* improved (lines 36-37), and he *subsequently underwent bilateral corneal transplantation for blindness due to his chemical corneal injury* (line 39).

Page 10, line 43, to page 11, line 2: Regarding the summary of the USEPA/OPPT (2000) case report, the TSD should explain that the worker had entered an area where another employee (who was on supplied air) was rinsing out emptied thionyl chloride-containing drums with water. This will illustrate the relevance of this case report. The TSD should also provide additional relevant information regarding the symptoms, notably "*impaired cerebellar function -- ataxia, markedly* impaired hand-eye coordination, slurred speech; *significantly impaired* memory (*short, intermediate and long term);* and impaired *executive function and* judgment. All clinical signs improved dramatically during the first 6 hours following exposure. *Twenty-four hours after the exposure, cerebellar function and standard memory/executive/judgment screening tests were within normal limits; however, no baseline data for the employee were available.* At 72 hours post exposure, *all subjective concerns were completely resolved*".

Page 11, lines 17-18 (Section 2.4, Developmental/Reproductive Toxicity): This section should indicate whether any relevant data are available on the hydrolysis products sulfur dioxide or hydrogen chloride.

Page 11, line 22 (Section 2.5, Genotoxicity): The section currently indicates that there are no data "relevant to the derivation of AEGL values for thionyl chloride". Clarification is needed on whether there are any genotoxicity data. This section should also indicate whether any relevant data are available on sulfur dioxide or hydrogen chloride.

Page 11, line 26 (Section 2.6, Carcinogenicity): This section should indicate whether any relevant data are available on sulfur dioxide or hydrogen chloride.

Page 11, lines 30-33 (Section 2.7, Summary): Correct the statement about the lack of exposure and duration data regarding lethal and nonlethal human exposures to thionyl chloride. Also, bronchiolitis obliterans and blindness from corneal burns should be included in the description of effects.

Pages 11-12 (Section 3.1.1, Rats): This section should include information for the 4-h exposure duration study by Pauluhn (1986), which is referenced in the Pauluhn (1987) study. This section should also include the data from Flury and Zernik (1931), which Kinkead and Einhaus (1984) cite in support of the reported lethality for cats from a 20-min exposure to thionyl chloride at 17.5 ppm. That report was dismissed because the concentration appeared inconsistent with their rat data. However, because of thionyl chloride's rapid hydrolysis, the toxicity results reflected exposure to sulfur dioxide and hydrogen chloride; only 11 ppm was measured at the highest test concentration, whereas concentrations of sulfur dioxide and hydrogen chloride were calculated to be 661 ppm and 1,322 ppm, respectively. The difference in toxicity might at least in part reflect the deeper deposition in the lung and greater effect severity for thionyl chloride (presumably studied by Flury and Zernik) compared with the hydrolysis products essentially tested by Kinkead and Einhaus. The TSD should provide the cat data and discuss potential explanations for differences.

Page 11, line 45, to page 12, line 11 (Section 3.1.1, Kinkead and Einhaus): This summary is misleading because of confusion about the data for thionyl chloride and for its two hydrolysis products. In the first sentence, clarify that although the original chemical was 99% pure thionyl chloride, the rats were exposed to the hydrolysis products. Also clarify that the exposure concentrations listed (page 12, line 5) are calculated values (not measured concentrations) and that they reflect sulfur dioxide plus hydrochloric acid, not thionyl chloride. Furthermore, most deaths occurred within 24 h after exposure ended, and the calculated LC_{50} of 1,480 ppm is for sulfur dioxide and hydrochloric acid. The calculated LC_{50} for thionyl chloride was much lower (500 ppm; 95% confidence limits: 420-660 ppm). This estimated lethal concentration is very similar to the LC_{50} identified from the Nachreiner study, and its much lower value suggests that the calculated values for the $BMCL_{05}$ (196 ppm) and BMC_{01} (227 ppm) should be much lower than presented.

Page 12, lines 13-22 (Section 3.1.1, Pauluhn): Check the unit conversions presented in the TSD, as Pauluhn reported concentrations in mg/m^3 and provided a conversion factor to indicate ppm. Clarify that the listed LC_{50} (converted from 6,200 mg/m^3 reported by Pauluhn) is an approximate value. This value was calculated from the geometric mean of the concentrations for groups 3 and 4, and was the delineation point between no fatalities and deaths in 4 of 5 animals (both sexes), with signs in group 3 of dyspnea and apathy that did not reverse within the subsequent 14- day observation period. Also incorporate the 4-h LC_{50} data summarized from the Pauluhn (1986) study, which converts to 1,117 ppm (95% confidence limits: 884-1,411) based on the data summarized in Pauluhn (1987) and the conversion factor provided therein.

Page 12, lines 34-40 (Section 3.1.1, Nachreiner): This text should be corrected and clarified (and edited). Confidence limits should be provided to better characterize the study (see the summary on page 5 of Nachreiner [1993]). The reported relative humidity was approximate; it could not be monitored during exposure using the nose-only apparatus. The description should also indicate that mouth breathing was observed for all test groups, provide information regarding post-exposure time to death, and acknowledge mean concentrations, as well as issues related to the controls.

Page 12, line 42, to page 13, line 3: Revise this interpretation to reflect the correct LC_{50} value calculated for thionyl chloride by Kinkead and Einhaus (1984), to provide the correct relative humidity data corresponding to the exposure concentrations, and to include the Pauluhn (1986) data. Provide context for higher toxicity at lower relative humidity as outlined in previous comments (less hydrolysis in ambient air prior to inhalation resulting in deeper deposition of thionyl chloride in the lung, where hydrolysis to sulfur dioxide and hydrogen chloride produces greater direct contact effects of those corrosive irritants with local tissue compared with the result when hydrolysis products are inhaled at the outset).

Ensure that the important role of relative humidity is clearly presented. See the study summaries for sulfur dioxide in NRC (2010c). For example, the discussion explains that the increased response identified in Bethel et al. (1985) compared with other studies may be attributed to the lower relative humidity for that study (35% vs. 70-85%). Similarly, the summary of Rahlenbeck and Kahl (1996) describes controlling for humidity to assess the relationship between mortality and air pollution. The key study by Linn et al. (1985) used for the AEGL-1 values specifically addresses the role of relative humidity (as well as temperature). The study found that respiratory effects were more severe at lower humidity regardless of temperature. (The response at lower humidity and temperature is more than double that at higher humidity and temperature.) Discussion of Table 9 should provide a summary of toxicity data for sulfur dioxide and hydrogen chloride that includes relative humidity data.

Page 13, lines 5-12. Provide additional information on the rate of thionyl chloride hydrolysis to address the differences indicated here. Correct the statement that additional information was not identified (lines 11-12). For example, see Driver et al. (2003) and related resources. Such data indicate that the rate estimated by Nachreiner is reasonable. Correct the statement that Kinkead and Einhaus did not detect any parent compound (lines 7-8), as described in the study and reflected in the comment on pages 11-12 (Section 3.1.1, Rats), which indicates that thionyl chloride was measured at the highest test concentration. Also, provide the further context from Kinkead and Einhaus (1984), who describe: “Sampling for thionyl chloride analysis was done once during each exposure. The chamber was allowed to achieve a stable total chloride contaminant concentration as indicated by the chloride ion electrode analysis before impinger sampling was initiated.” Thus, among other factors, it is reasonable to consider that the sampling may not have begun within 5 min of the start of the exposure, which could alone explain the results given the rapid hydrolysis of thionyl chloride at the average relative humidities indicated for those exposure conditions (in particular because the concentrations clearly ranged higher per the average representing three measurements during the 1-h period).

Page 14, Table 3: Include additional lethality data, such as from Pauluhn (1986) and Flury and Zernik (1931), with qualification as indicated. Correct the calculated LC_{50} and BMC values for the Kinkead and Einhaus (1984) to reflect their calculated LC_{50} for thionyl chloride. Correct the discrepancy in the last row (highest concentration) of the Pauluhn entry, which shows 5/5 male, 5/5 female, and 10/10 combined mortality, whereas the text in the “Effects at Lethal Exposure” column states 90% mortality, and the report appears to indicate that only 4/5 females died. Given the differences per sex in the Nachreiner study (and also at the highest concentration in the Pauluhn study), provide mortality percentages for males and females separately in the “Effects at Lethal Exposure” column to facilitate comparisons between studies. If an average is also intended to be given, rather than a combined average, present the mortality percentage for males to represent the more sensitive subgroup.

Page 15, line 37 (Section 3.3, Developmental/Reproductive Toxicity): The section should be revised to address the hydrolysis products of thionyl chloride that would be distributed systemically. For example, see corresponding discussion in the AEGL TSD for sulfur dioxide (NRC 2010c).

Page 15, line 41 (Section 3.4, Genotoxicity): The section should be revised to address the hydrolysis products of thionyl chloride that would be distributed systemically. For example, see corresponding discussion in the AEGL TSD for sulfur dioxide (NRC 2010c).

Page 15, line 45: (Section 3.5, Carcinogenicity): Revise the sentence “There are no data to suggest that thionyl chloride is a carcinogen.” If any data exist they should be provided, otherwise state

no data were found. Also address the hydrolysis products, which would be distributed systemically. For example, see the corresponding discussion in the AEGL TSD for sulfur dioxide (NRC 2010c).

Page 16, lines 6-7 (Section 3.6, Summary): Revise to correct the values as indicated (such as the LC_{50} value calculated for thionyl chloride by Kinkead and Einhaus). Include the LC_{50} value identified in Pauluhn (1987) from Pauluhn (1986), which are described as corresponding in order of magnitude to the value calculated in the 1987 study. Clarify what the calculated value represents and provide the corresponding relative humidities.

Page 16, lines 13-20 (Section 4.1, Metabolism and Disposition): Revise the text to clarify that following inhalation of thionyl chloride and its hydrolysis to sulfur dioxide and hydrogen chloride in the lung, these two products enter the blood stream (across the exchange boundary of the respiratory system) and are distributed throughout the body.

Page 16, lines 24-42 (Section 4.2, Mechanism of Toxicity): Revise the text to address previous comments. Correct the LC_{50} information and include additional relevant data, including from Pauluhn (1986). Ensure that the correct relative humidity is clearly identified for each key value, and provide more supporting context for humidity considerations.

Page 17, lines 8-9 (Section 4.3, Structure-Activity Relationships): Revise the text to acknowledge the roles of sulfur dioxide and hydrogen chloride.

Page 17, lines 15-21 (Section 4.4.1, Susceptible Populations): Revise the text to provide context for direct-acting irritants. Information should be included on thionyl chloride, in addition to that for sulfur dioxide. Gender differences should also be discussed, given that it is mentioned elsewhere and serves as part of the rationale for the intraspecies uncertainty factor. Information about gender differences in the rapid hydrolysis products of thionyl chloride should be included. More specific (at least semiquantitative) information should be provided, including data from the key human study underlying the AEGL-1 and AEGL-2 values for sulfur dioxide and relevant information on hydrogen chloride.

Page 18, Section 6.2, lines 10-19 (Summary of Animal Data Relevant to AEGL-2): The discussion should be revised to better characterize the data from the candidate Pauluhn (1987) study, such that the study can at least serve to support the AEGL-2 values estimated by scaling from the AEGL-3 values.

Page 18, lines 23-35 (Section 6.3, Derivation of AEGL-2): Revise this section in response to previous comments, including the comments regarding page 6, lines 8-16, 39-40, and 42-44, as well as comments that identify corrections and clarifications regarding the characterization of information from the respective animal studies. The relative humidity value (and its basis) corresponding to each exposure concentration estimate should be provided. In light of the revisions, ensure that appropriate data and assumptions underlie the AEGL-3 values, and present the correct nonlethal toxicity data. Discuss the data underlying the AEGL-2 values for sulfur dioxide and hydrogen chloride to provide supporting context for the AEGL-2 values for thionyl chloride.

Page 19, lines 10-16 (Section 7.2): Provide further context for these data (e.g., see comments regarding page 12, lines 34-40), including information on the estimated relative humidities and additional lethality data.

Page 19, lines 20-25: Correct values and provide further context, as identified in previous comments (for example, the comments regarding page 12, lines 42-ff).

Page 19, lines 31-33, and Appendix D: The current EPA benchmark dose software is version 2.4, from April 2013. Check input values and assumptions and compare with the current model.

Page 19, lines 36-38: Revise per comments on page 7, lines 7-10.

Page 19, lines 38-46: Revise per comments on the same text elsewhere.

Page 20, lines 28 and 35 (Section 8.2, Comparison with Other Standards and Guidelines): Verify the accuracy of the information presented in this section. A number of other occupational exposure limits (OELs) exist. For example, see SER (2013b), which includes OELs for Switzerland, Belgium, Spain, Norway, Finland, and Denmark (including limits of about 5 mg/m^3 for 15-min exposures). Standards expressed in mg/m^3 should be presented in those units.

Page 20, lines 29-30: The MAC is referenced but no value is provided in Table 8; provide the status of the MAC and, if available, reinstate the MAC definition in the table and footnote on page 25.

A new (modified) system for OELs was established in The Netherlands in 2007, which requires updating the information in the text, Table 8, and cited references. The Dutch Health Council's Expert Committee on Occupational Standards recommends health-based values; the Social and Economic Council of the Netherlands (SER) provides OELs online (see SER [2013b]).

Page 20, lines 24-25: Explain how the AEGL values are consistent with current standards and guidelines.

Page 21, Table 9: The AEGL values for thionyl chloride should be included in the table to facilitate comparisons between the parent chemical and its hydrolysis products. Summary information on how the values were derived (for example, the end point, species, uncertainty factors), as well as relative humidity information should be included. In addition, identify the stoichiometric context for hydrogen chloride (to clarify that two moles are generated per mole thionyl chloride).

Page 22 (Section 8.3, Data Adequacy and Research Needs): Correct the first sentence (claiming human data do not contain duration information). In the second sentence, indicate that quantitative concentration-response data are a key gap. The third sentence is unclear in terms of human evidence that supports the toxicologic end points identified in animal studies (the reverse is more standard). The next sentences (lines 8-10), states "Quantitative animal data are available from three studies that demonstrate a respiratory response similar to that observed in humans." This appears to contradict other statements that the effects in animals are relatively severe and thus not useful for deriving AEGL-1 or AEGL-2 values, whereas human end points such as bronchiolitis obliterans and blindness are not reflected in animals. The statement in lines 14-16 that only 1-h studies are available should be corrected. Finally, the last sentence should be corrected because good information is available regarding the relationship between the hydrolysis rate of thionyl chloride and relative humidity.

Page 24, lines 18-19: Update and check the benchmark dose modeling inputs and outputs per the spring 2013 version of the model.

Page 28, lines 21-23; and page 33, summary table (UF/Rational entry): These two statements appear contradictory: "Results of the Nachreiner (1993) study indicate males are more sensitive than females" and "data on a sensitive population are lacking for thionyl chloride." Also, verify that the results of the Nachriener (1993) study indicate male Wistar rats are more sensitive than females. Provide context for gender differences in humans with respect to the hydrolysis products of thionyl chloride, notably sulfur dioxide in exercising asthmatics.

Page 28, lines 25-26; and page 33, summary table (UFs/rationale row): Delete the sentence regarding the intraspecies uncertainty factor being protective of asthmatics and other sensitive populations unless it can be justified. A factor of 10 was applied to address asthmatics alone in the derivation of AEGL values for sulfur dioxide (NRC 2010c), and there is some indication of gender differences in response to thionyl chloride.

Page 35, Table D-1: Include the relative humidity information to provide that important context for the lethality data.

Page 42, table: A title should be provided for the table to indicate the data presented were used in the category plot. In the column for Sex, it is unclear what the entry of "B" indicates (both sexes?).

TOLUENE

The committee reviewed the AEGL TSD on toluene that was presented by George Woodall of the U.S. Environmental Protection Agency. Table 23 presents a summary of the proposed AEGL values for toluene and their basis. The committee agreed that its previous comments on the TSD (NRC 2010b) were addressed, and that most of the proposed AEGL values were appropriately derived. The committee recommends that one data set be re-reviewed for its relevance to deriving AEGL-1 values before the document is finalized.

TABLE 23 Summary of Proposed AEGL Values for Toluene Reviewed by the Committee

10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)					
67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	No effect level for notable discomfort and neurologic effects (200 ppm, 8 h);total UF = 3 (intraspecies)
AEGL-2 (disabling)					
1,400 ppm (5,200 mg/m^3)	760 ppm (2,800 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)	NOAEL for decrement in neurologic function (1,600 ppm, 34 min); total UF = 3 (intraspecies); PBPK model for time scaling
AEGL-3 (lethal)					
See below[a]	5,200 ppm (19,500 mg/m^3)	3,700 ppm (13,800 mg/m^3)	1,800 ppm (6,800 mg/m^3)	1,400 ppm (5,100 mg/m^3)	NOAEL for lethality (6,250 ppm, 2 h); total UF = 3 (intraspecies); PBPK model for time scaling

[a]The 10-min AEGL-3 value of 10,000 ppm (37,500 mg/m^3) is higher than 50% of the lower explosive limit of toluene in air (14,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

Abbreviations: NOAEL, no observed adverse effect level; PBPK, physiologically based pharmacokinetic; UF, uncertainty factor

AEGL Specific Comments

Page 60, lines 42-43, and page 61, lines 18-19: The sentences should be revised to indicate that 200 ppm is a NOAEL for AEGL-1 effects. As currently written ("an effect that exceeds the definition of AEGL-1"), the sentences suggest that the concentration is a NOAEL for AEGL-2 effects.

Page 65, lines 22-23: Toluene at 100 ppm is reported to produce fatigue, drowsiness, headache, dizziness, and feelings of intoxication. These effects are relevant to AEGL-1 values, but do not appear to have been considered for deriving AEGL-1 values. The data should be included in the discussion of relevant to studies to AEGL-1 effects, and a determination made on whether they are suitable for deriving AEGL-1 values.

Other Comments

A brief description of the toxicokinetic model of Benignus et al. (2006) should be provided.

Because data on ethanol are cited in support of the AEGL-2 values for toluene, consideration should be given to including a table that compares air concentrations of toluene and ethanol that are associated with decrements in neurologic function.

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