Twenty-first Interim Report of the Committee on Acute Exposure Guideline Levels: Part A

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Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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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-first interim report (Part A). It summarizes the committee's conclusions and recommendations for improving AEGL documents for the following chemicals and chemical classes: acrylonitrile, allyl alcohol, epichlorohydrin, ethylene chlorohydrin, ethylphosphorodichloridate, hexane, ketene, lewisite, mercaptans, methanesulfonyl chloride, methyl isothiocyanate, monoisocyanates, nitric acid, 3-quinuclidinyl benzilate, tear gas, titanium tetrachloride, trimehtylacetyl chloride, and vinyl acetate monomer.

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

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the NRC Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and ensuring that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), and Sam Kacew (University of Ottawa). 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.

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

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Twenty-first Interim Report of the Committee on Acute Exposure Guideline Levels: Part A

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 levels (AEGLs) 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 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.

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

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

THE CHARGE TO THE COMMITTEE

The NRC convened the Committee on Acute Exposure Guideline Levels to review the AEGL documents approved by NAC. The committee members were selected for their expertise in toxicology; medicine, including pharmacology and pathology; industrial hygiene; biostatistics; and risk assessment.

The charge to the committee is to (1) review the proposed AEGLs for scientific validity, completeness, internal consistency, and conformance to the NRC (1993) guidelines report; (2) review NAC's research recommendations and—when appropriate—identify additional priorities for research to fill data gaps; and (3) 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, epichlorohydrin, ethylene chlorohydrin, ethyl phosphorodichloridate, hexane, ketene, lewisite, mercaptans (ethyl mercaptan, methyl mercaptan, phenyl mercaptan, and tert-ocyl mercaptan), methanesulfonyl chloride, methyl isothiocyanate, monoisocyanates (n-butyl isocyanate, cyclohexyl isocyanate, ethyl isocyanate, and phenyl isocyanate), nitric acid, 3-quinuclidinyl benzilate, tear gas, titanium tetrachloride, trimethylacetyl chloride, and vinyl acetate monomer. These documents were reviewed by the committee at a meeting on May 2-4, 2012.

COMMENTS RELEVANT TO ALL AEGL TSDs

Sources for General Information

TSDs often cite references that are periodically updated (e.g., Patty's Industrial Hygiene, Merck Index), particularly in reference to chemical and physical properties. The most recent editions of these references should be used as much as possible to ensure that the most current information is being provided. Sometimes material in an earlier edition is revised in a later edition. In addition, information from common secondary sources should be verified by reviewing the primary references; if more current versions of the primary references are available, those newer references should be consulted for the most current information.

Extant Standards and Guidelines

The section in the TSDs on Extant Standards and Guidelines should provide substantive discussion of the comparison of AEGLs values and other relevant guidelines (see NRC 2001). Simple side-by-side comparisons of values are not adequate. It is particularly important to provide substantive context when there are substantial differences between the values. The discussion should examine possible reasons for the differences, such as (1) the documented quantitative derivation process for AEGLs compared with the processes used by other organizations, (2) different data requirements for the guidelines, (3) different target populations, (4) duration of exposure, (5) end point of concern (immediate vs delayed effects), and (6) other considerations. For example, occupational guidelines are intended to protect the working adult population from adverse effects from exposure to a chemical over a working lifetime, whereas AEGL values are intended to protect the general population (including sensitive subpopulations) from adverse effects from a one-time exposure to the chemical.

Because standards and guidelines are periodically updated, it is important that the most recent publication or listing of standards for each organization be consulted and referenced to document that the standard is still current. The discussion of the values should note the date the guideline was issued to provide historical context, and also reference the supporting (probably older) documentation of the standard.

Footnotes to the table on Extant Standards and Guidelines should indicate that ACGIH®, TLV®, AIHA®, and possibly other terms are registered trademarks.

ACRYLONITRILE

The committee reviewed the AEGL TSD on acrylonitrile that was presented by Julie Klotzbach of SRC, Inc. Table 1 presents a summary of the proposed AEGL values for acrylonitrile and their basis. The committee recommended that the basis for those AEGL values be re-evaluated, and that the revised TSD be reviewed again at a future meeting.

AEGL Comments

The committee is concerned that the developmental toxicity end points presented in Section 3.3 were not adequately considered in the selection of the point-of-departure for AEGL values for acrylonitrile. The argument that the results are inconsistent between the study by Murray et al. (1978), which found fetal malformations (lowest-effect level of 80 ppm, and a no-effect level of 40 ppm), and the study by Saillenfait et al. (1993), which reported lower fetal weight and negative absolute maternal weight gain (lowest-effect level [LOEL] of 25 ppm, and a no-effect level [NOEL] of 12 ppm), are not an adequate basis for excluding the end points from consideration. Consideration should be given to whether in vitro studies of embryotoxicity could help with interpretation of studies (e.g., Saillenfait et al.1992; 2004). If appropriate, it might be possible to translate the in vitro concentration from these studies to inhalation concentrations by applying the pharmacokinetic model described in EPA's 2011 toxicological review of acrylonitrile (EPA 2011). Below are comments on the use of developmental toxicity data specific to the AEGL-2 and AEGL-3 values.

AEGL-2 Values: In the TSD, an arbitrary threshold of 100 ppm was presumed for developmental toxicity, and was compared with the proposed 2-h AEGL point-of-departure of 305 ppm in adult nonpregnant rats in the study by Dudley and Neal (1942). However, further consideration should be given to reductions in maternal weight gain observed in both the Saillenfait et al. (1993) and Murray et al. (1978) studies, which had a LOEL range of 25-40 ppm and a NOEL of 12 ppm. In the Murray study, effect on maternal weight gain was evident at the first measurement, supporting the relevance of the end point to a single exposure scenario. Thus, the lower NOEL value from the Saillenfait study could be pertinent to AEGL-2 values if it is affirmed that there are no corresponding detrimental fetal effects.

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

Classification	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)	1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	1.5 ppm (3.3 mg/m^3)	No-effect level for notable discomfort (eye irritation) in human subjects (4.6 ppm, 8 h); UF = 3
AEGL-2 (disabling)	81 ppm (180 mg/m^3)	30 ppm (65 mg/m^3)	16 ppm (35 mg/m^3)	4.5 ppm (9.8 mg/m^3)	2.4 ppm (5.2 mg/m^3)	No-effect level for impairment of escape (tremors, convulsion) in rats (305 ppm, 2 h); UF = 36; n = 1.1 for time scaling
AEGL-3 (lethality)	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)	No-effect level for lethality (30-min, 1-h, and 8-h $BMCL_{05}$) in rats; UF = 36; n = 1.1 for time scaling

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

AEGL-3 Values: The proposed point-of-departure for AEGL-3 values was based on lethality in adult rats. However, severe fetal malformations that might lead to mortality after birth should be considered a pertinent end point for AEGL-3 values. The Murray et al. (1978) study involved oral and inhalation exposures, but only the inhalation data from the study was presented in the TSD. Consideration of the results from both the oral and inhalation studies provide clearer evidence of the teratogenic potential of acrylonitrile. For example, although not specifically noted for the inhalation data, the investigators reported that oral exposure resulted in multiple skeletal malformations, and that these same fetuses had visceral malformations. Moreover, sodium sulfide stain of the uterus found pregnancies in rats that appeared to be non-pregnant at an air concentration 80 ppm and at an oral dose of 65 mg/kg/day. The investigators stated that these data were not included in the report of fetal resorption incidences.

It is noteworthy that the investigators concluded that ". . . it is unlikely that the malformations were caused by maternal toxicity alone since there was no apparent correlation between the degree of toxicity seen in the individual dams and the occurrence of malformation in their offspring, and the types of malformations seen in this study have not occurred at an increased incidence in previous studies in this laboratory in which rats were stressed to an even greater degree" (p. 551). Thus, the investigators' conclusion of a NOEL of 40 ppm is relevant for AEGL-3 values. There is some degree of uncertainty that detrimental fetal effects with low historical occurrence (e.g., omphalocele) were present at 40 and 80 ppm, although the increase was not statistically significant.

ALLYL ALCOHOL

The committee reviewed the AEGL TSD on allyl alcohol that was presented by Julie Klotzbach of SRC, Inc. Table 2 presents a summary of the proposed AEGL values for allyl alcohol and their basis. The committee also reviewed a submission from Lyondell Chemical Company (2012) on the study it performed to support the derivation of AEGL values.

AEGL Specific Comments

The committee agreed that the AEGL-3 values for allyl alcohol were appropriately derived, but recommended revisions to the derivation of the AEGL-2 and AEGL-1 values before the TSD is finalized.

For the AEGL-2 values, the committee disagreed with the proposal to use the rat study by Kirkpatrick (2008). The ocular irritation reported in the human volunteer study by Dunlap et al. (1958) should be regarded as an AEGL-2 effect. In that study, one of seven subjects reported slight ocular irritation at 12.5 ppm for 5 min, and five of five reported moderate or more marked ocular irritation at 25 ppm for 5 min. Considering 12.5 ppm as the NOEL for moderate to marked ocular irritation and applying an uncertainty factor of 3 for intraspecies variability, the upper limit of AEGL-2 values is 4 ppm. That value is relevant to the 10-min AEGL, and can be adopted for the 30-min and 1-h values. AEGL-2 values for the longer durations should be calculated as one-third of the AEGL-3 values.

For the AEGL-1 values, the committee found the Dunlap study was too limited to provide the sole basis for AEGL-1 values. Instead, the measurements of sensory irritation in mice for a variety of allyl derivatives should be used (see Nielsen et al. 1984; Nielsen and Bakbo 1985). Those studies report an RD_{50} value (concentration that reduces the respiratory rate by 50%) for allyl alcohol of 3.9 ppm. A point-of-departure can be estimated by calculating 3% of the RD_{50} value (see Nielsen et al. 1984). The sensory irritation studies by Nielsen et al. show that the different allyl derivatives, including allyl alcohol and its aldehyde metabolite acrolein, are equally potent (have approximately equal RD_{50} values). Furthermore, the time courses for respiratory depression are very similar for the alcohol and the aldehyde. Collectively, this suggests that the sensory irritation is caused by the allyl moiety and not by the metabolism from alcohol to aldehyde. Thus, no uncertainty factors are needed to calculate the AEGL-1 values. Because sensory irritation is an almost instantaneous effect, the same value can be applied for all exposure durations. The AEGL-1 value of 0.12 ppm is in a similar range as that for acrolein (0.03 ppm) and close to the TLV® (0.5 ppm).

EPICHLOROHYDRIN

The committee reviewed the AEGL TSD on epichlorohydrin that was presented by Heather Carlson-Lynch of SRC, Inc. Table 3 presents a summary of the proposed AEGL values for epichlorohydrin and their basis. The committee agreed that its previous comments (NRC 2011) on the TSD have been adequately addressed, and that the TSD can be finalized for publication after some editorial clarifications are made.

Other Comments

In the discussion of AEGL-2 values, a statement is made (page 43, line 31) that a decrease in respiratory rate was not considered a relevant end point for AEGL-2 values. A rationale should be added to the TSD to support this statement.

Editorial Comments

Page 26, Table 4, footnote a: The unit for temperature should be added.

Page 41, Figure 1: The figure should be reviewed to verify that it appropriately represents the data.

Page 48, Section 8.2: The discussion of other standards and guidelines for epichlorohydrin should be reorganized to discuss the guidelines that are most analogous to the AEGLs values (e.g., ERPG, IDLH) first. The discussion about the TLV® for epichlorohydrin should indicate that one of the bases for the value is upper-respiratory-tract irritation observed in the study by Gage (1959). In that study, a lowest-observed-adverse-effect level of 16 ppm was found for rabbits and 17 ppm for rats, and 9 ppm was a no-observed-adverse-effect level.

TABLE 2 Summary of Proposed AEGL Values for Allyl Alcohol Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	0.62 ppm (1.5 mg/m^3)	0.62 ppm (1.5 mg/m^3)	0.62 ppm (1.5 mg/m^3)	Not recommended	Not recommended	Slight to moderate nasal and slight ocular irritation (6.25 ppm); UF = 10
AEGL-2 (disabling)	11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)	No-effect level for disabling effects in rats (gasping, reduced response to stimulus); UF = 30; n = 0.95 for time scaling
AEGL-3 (lethal)	87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)	Estimated LC_{01} value in rats; UF = 30; n = 0.95 for time scaling

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	No effect level for irritation; UF = 10
AEGL-2 (disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)	Three-fold reduction of AEGL-3 values, except for 10-min value
AEGL-3 (lethal)	570 ppm (2200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)	Lethality threshold; UF = 10; n = 0.87 for time scaling

Page 50, References: The reference list should be cross-checked with the text to eliminate discrepancies. For example, there are references in the text for two NIOSH publications in 2003, but only one citation is provided in the reference list. On line 9, the superscript 7s should be replaced by the symbol for a registered trademark (®).

Page 56, line 34: The reference for EPA's carcinogenicity assessment of epichlorohydrin should make it clear that it refers to an assessment conducted in 1994. As currently presented, the reference only indicates that the IRIS database was accessed in 2012.

Page 62: Consideration should be given to reorganizing the table that compares AEGLs values with cancer risk-based values to present the values in ascending order by concentration. In this case, the 10^{-6} values would be presented between the AEGL-1 and AEGL-2 values, and the 10^{-5} and 10^{-4} values would be presented after the AEGL-3 values.

ETHYL PHOSPHORODICHLORIDATE

The committee reviewed the AEGL TSD on ethyl phosphorodichloridate that was presented by Lisa Ingerman of SRC, Inc. Table 4 presents a summary of the proposed AEGL values for ethyl phosphorodichloridate and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSD have been adequately addressed, and that the document can be finalized for publication.

Editorial Comments

Page 6, line 9: replace "estimated" with "obtained."

Page 13, line 17: replace "delayed clinical findings" with "delayed clinically manifested effects."

Page 15,line 25: clarify what is meant by ". . . yields a better concentration-response relationship."

ETHYLENE CHLOROHYDRIN (2-CHLOROETHANOL)

The committee reviewed the AEGL TSD on ethylene chlorohydrin that was presented by Julie Klotzbach of SRC, Inc. Table 5 presents a summary of the proposed AEGL values for ethylene chlorohydrin and their basis. The committee agreed that its previous comments on the TSD (NRC 2011) have been adequately addressed, but made a few additional recommendations for improving the document before it is published.

AEGL Specific Comments

The committee recommended that more explanation be provided about why AEGL-1 values were not derived. It would appear that the AEGL-1 values would be much lower than the AEGL-2 values, and options might be explored on ways to reduce the AEGL-2 values.

Other Comments

Section 3.1.1: Two studies of acute lethality in rats are discussed in this section. The two-orders-of-magnitude difference in lethality values is significant and warrants a discussion of the possible reasons for the difference. It appears that the exposures in the Ambrose (1950) study were probably substantially higher than reported because (1) the bubbler could have produced significant amounts of aerosol in addition to the vapor, (2) the bubbler was above room temperature at 40ºC, whereas the temperature of the exposure delivery system and exposure chamber were likely around 25ºC (not specified), and (3) the

saturated vapor concentration of ethylene chlorohydrin at 20ºC is about 6,500 ppm and would be higher at 25ºC and 40ºC. A mixed aerosol/vapor exposure seems likely, even with the air flow being ≤570 ml/min. Edits to the discussion might include: "Air was passed through this tower and into the exposure chamber (neither air temperature nor air flow was specified, but air flow was noted as never exceeding 570 ml/min). No indication (other than the air flow value) was given that the possibility of aerosolization of the test material was considered. The inhalation exposure concentrations associated with specific dilutions of ethylene chlorohydrin in water were not measured or estimated (whether vapor phase, aerosol, or mixed) in the study report."

The section of the TSD on extant standards and guidelines require the following revisions and verifications:

- Table 9: All of the extant standards and guidelines and their values and definitions should be verified. For example, several of the guidelines are described as time-weighted averages in the "Guideline" column, but then have a "ceiling" notation associated with the value presented. A review of the most recent ACGIH® (2012) publication on TLV®s indicates that there is TLV-STEL but not a TLV-TWA for ethylene chlorohydrin.
- In Table 9, ceiling limits should be presented in a way that shows they cross all the AEGL durations. The entry into the Guideline column should include appropriate notation that it represents a ceiling value (e.g., REL-C, TLV-C).
- In Table 9, skin notations should be specified in the footnotes rather than in the tables to avoid confusion about their meaning.
- Page 18, lines 1-2: The MAK documentation should be consulted to verify that the value does *not* represent a ceiling concentration. Notation of a peak limitation "II (1)" suggests that the value is the functional equivalent of a ceiling notation (DFG 2012).

TABLE 4 Summary of Proposed AEGL Values for Ethyl Phosphorodichloridate Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.37 ppm (2.4 mg/m^3)	0.25 ppm (1.7 mg/m^3)	0.20 ppm (1.3 mg/m^3)	0.13 ppm (0.86 mg/m^3)	0.063 ppm (0.40 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	1.1 ppm (7.3 mg/m^3)	0.76 ppm (5.0 mg/m^3)	0.60 ppm (4.0 mg/m^3)	0.38 ppm (2.5 mg/m^3)	0.19 ppm (1.3 mg/m^3)	Four-hour threshold for lethality ($BMCL_{05}$ of 38 ppm) in rats; UF = 100; default time scaling

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)	Nonlethal effects in mice (280 ppm for 120 min); UF = 100; default time scaling

- The MAC value from the Netherlands should be checked for relevant notations (e.g., ceiling value, skin notation).
- The footnotes to Table 9 should be revised to reflect the revisions made in response to the preceding bullets. Also, the PEL-TWA and MAK values should be defined according to their respective agencies. Those values are currently described as being analogous to the TLV-TWA. However, the definition of the TLV-TWA will not appear in the revised set of footnotes because such a value for ethylene chlorohydrin not been established by ACGIH®.
- Page 18, line 8: "value" should be added after IDLH.

The discussion of database adequacy gives a misleading impression that the database on ethylene chlorohydrin is fairly robust (e.g., "the animal data are sufficient for describing lethal and nonlethal exposures"), when the database for deriving AEGL-3 values for ethylene chlorohydrin is relatively weak. The animal database consists of one dose-ranging study that used a small number of animals. Although a decision was made to use the study to derive AEGL-3 values in the absence of other data, an impression should not be given that the database on lethality was adequate.

Editorial Comments

Table 1: The saturated vapor concentration should be calculated (see Perez and Soderholm [1991] for formulae).

Page 10, line 44: "low" should be "flow."

Page 11, lines 4-5: ". . . and that ~~for~~ most exposure~~s~~-related deaths occurred following . . ."

Page 11, line 24: "death" should be "cause."

Page 13, line 29: Delete "the" before ethylene chlorohydrin.

Page 13, line 32: The citation to the study in rabbits should be added (i.e., NTP 1983b).

Page 14, lines 16-17: Specify that "Radio-labeled" carbon dioxide was detected, to clarify that the carbon dioxide was one of the metabolites of the radio-labeled ethylene chlorohydrin.

Page 15, line 45: The heading for this section should be changed to Inter- and Intra-Species Variability, because more than just species differences are covered.

Page 17, lines 23-24: The sentence should be moved to line 14, after the first sentence. This will allow for a better transition to the discussion of the lethality data.

Page 17, line 29: The sentence should cite Table 9 (not Table 10).

Page 18, lines 7: The sentence should be revised to be: "The AEGL-2 value for 30 minutes is comparable but less than the NIOSH IDLH, as would be expected from the differences between the respective target populations." The subsequent phrase and sentence on lines 8-11 can be deleted since they simply repeat the definition of IDLH and AEGL-2 values.

References: The references should be cross-checked with the text to ensure accuracy. Several references appear in the reference list but do not seem to be referenced in the text (e.g., AIHA® 2006, Budavari et al. 1996). There are some discrepancies in the years cited in the text and those in the reference list (e.g., HSDB 2012 in Table 1, but HSDB 2007 in reference list).

HEXANE

The committee reviewed the AEGL TSD on hexane that was presented by Julie Klotzbach of SRC, Inc. Table 6 presents a summary of the proposed AEGL values for hexane and their basis. The committee agreed that its previous comments (NRC 2010a) on the TSD have been adequately addressed, and that the document can be finalized for publication after a few editorial changes are made.

Editorial Comments

There appear to be conflicting results of studies considered as a basis for deriving AEGL-3 values. Thus, an explanation should be added to the TSD that the Raje et al. (1984) study was preferred over the Swann et al. (1974) study because the quality of the study was better and there were concerns about one death occurring in the Swann study.

Animal lethality data should be included in the category plot on page 42.

KETENE

The committee reviewed the AEGL TSD on ketene that was presented by Lisa Ingerman of SRC, Inc. Table 7 presents a summary of the proposed AEGL values for ketene and their basis. The committee agreed that its previous comments (NRC 2010a) on the TSD have been adequately addressed, and that the document can be finalized for publication after a few editorial changes.

Editorial Comments

The structural formula for ketene should be corrected. It currently shows the carbonyl carbon with an incorrect valence state.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	See below[b]	See below[c]	See below[c]	See below[c]	See below[c]	No lethality in rats; UF = 10; default time scaling for the 10-min value

[a]The proposed value is greater than 10% of the lower explosive limit of hexane in air of 1.1 % (11,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.
[b]The proposed 10-min AEGL-3 value of 12,000 ppm (42,000 mg/m^3) is greater than the lower explosive limit of hexane in air of 1.1 % (11,000 ppm). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
[c]The proposed value is greater than 50% of the lower explosive limit of hexane in air of 1.1 % (11,000 ppm). Therefore, extreme safety considerations against hazard of explosion must be taken into account. The respective calculated AEGL-3 values for 30-min, 1-h, 4-h, and 8-h are similar: 8,600 ppm (30,000 mg/m^3).

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)	Nonlethal concentration to mice (1 ppm, 7 h); UF = 10; default time scaling

Page 6, line 5 and lines 7-8: The two sentences begin with the same clause and could give the impression that an inadvertent duplication occurred. Consideration should be given to rephrasing or combining the two sentences.

Page 27, Section 4.3.2: This section on intraspecies variability and susceptible subpopulations should begin with a statement that the only indication of potential intraspecies sensitivity was in the variability of time-to-death at certain exposure parameters, and that this was not considered strong enough in the absence of other data to warrant concern about a potential sensitive subpopulation. The discussion should also note that there is a similar lack of information for the structurally analogous chemical phosgene.

Page 27, lines 8-10, and page 30, line 24: Statements regarding "Considering the potential for sensitive human subpopulations" in the context of discussing the uncertainty factor for intraspecies differences should be removed because the phrasing is ambiguous. The Standing Operating Procedures for developing AEGL values indicates that an uncertainty factor of 10 is the appropriate default value for respiratory irritants, unless data exist to support a different value. In the case of ketene, an uncertainty factor of 3 is justified because (1) there appears to be no indication in either the ketene or phosgene literature (as cited in NRC [2002]) of a sensitive human population, (2) ketene produces minor respiratory irritation in animals, and (3) the only indication of intraspecies variability appears to be in the time-to-death data.

Page 31, lines 16-17: The statement that the AEGLs values for ketene and phosgene are "generally consistent" should be qualified. Although the 8-h values are very similar, there are much larger differences for the shorter durations (e.g., 7.5-fold difference between the 10-min AEGL-2 values, 15-fold difference between the 10-min AEGL-3 values). The supporting discussion should note the differences in the available data used to obtain the exponents for the time-scaling equations.

Page 32, lines 13-14: The 8-h AEGL value for ketene is 5.5 times *lower* (not higher) than the TWA occupational values.

Table 12: The table includes several rows for values derived by other agencies, but no entries appear. The values should be inserted, if available, or the rows deleted.

LEWISITE

The committee reviewed the AEGL TSD on lewisite that was presented by Julie Klotzbach of SRC, Inc. Table 8 presents a summary of the proposed AEGL values for lewisite and their basis. The committee agreed that its previous comments (NRC 2011b) on the TSD have been adequately addressed, and that the document can be finalized for publication.

Editorial Comments

Page 19, line 6: Change to "According to a secondary source . . . "

Page 25, line 37: Change Frank to Franke.

Page 25, line 38: Change to "Office of the Assistant Chief of Staff for Intelligence"

MERCAPTANS

The committee reviewed the individual AEGL TSDs on ethyl mercaptan, methyl mercaptan, phenyl mercaptan, and tert-octyl mercaptan that were presented by Lisa Ingerman of SRC, Inc. Table 9 presents a summary of the proposed AEGL values for the four mercaptans and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSDs have been adequately addressed, and that the documents can be finalized for publication after a few editorial clarifications are made.

TABLE 8 Summary of Proposed AEGL Values for Lewisite Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.15 ppm (1.3 mg/m^3)	0.055 ppm (0.47 mg/m^3)	0.030 ppm (0.25 mg/m^3)	0.0083 ppm (0.070 mg/m^3)	0.0044 ppm (0.037 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	0.46 ppm (3.9 mg/m^3)	0.16 ppm (1.4 mg/m^3)	0.087 ppm (0.74 mg/m^3)	0.025 ppm (0.21 mg/m^3)	0.013 ppm (0.11 mg/m^3)	Dog LC_{01} values

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Ethyl Mercaptan						
AEGL-1 (nondisabling)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	1.0 ppm (2.5 mg/m^3)	No-effect level for respiratory changes associated with odor avoidance in rabbits; UF = 10
AEGL-2 (disabling)	150 ppm (380 mg/m^3)	150 ppm (380 mg/m^3)	120 ppm (310 mg/m^3)	77 ppm (200 mg/m^3)	37 ppm (94 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	450 ppm (1100 mg/m^3)	450 ppm (1100 mg/m^3)	360 ppm (910 mg/m^3)	230 ppm (580 mg/m^3)	110 ppm (280 mg/m^3)	LC_{01} in mice; UF = 10; default time scaling
Methyl Mercaptan						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	40 ppm (80 mg/m^3)	29 ppm (57 mg/m^3)	23 ppm (43 mg/m^3)	14 ppm (28 mg/m^3)	7.3 ppm (14 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	120 ppm (240 mg/m^3)	86 ppm (170 mg/m^3)	68 ppm (130 mg/m^3)	43 ppm (85 mg/m^3)	22 ppm (43 mg/m^3)	LC_{01} in rats; UF = 10; default time scaling
Phenyl Mercaptan						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	1.0 ppm (4.5 mg/m^3)	0.70 ppm (3.2 mg/m^3)	0.53 ppm (2.4 mg/m^3)	0.33 ppm (1.5 mg/m^3)	0.17 ppm (0.77 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	3.0 ppm (14 mg/m^3)	2.1 ppm (9.5 mg/m^3)	1.6 ppm (7.2 mg/m^3)	1.0 ppm (4.5 mg/m^3)	0.52 ppm (2.3 mg/m^3)	LC_{01} in rats; UF = 10; default time scaling
tert-octyl Mercaptan						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.77 ppm (4.6 mg/m^3)	0.77 ppm (4.6 mg/m^3)	0.60 ppm (3.6 mg/m^3)	0.40 ppm (2.4 mg/m^3)	0.19 ppm 1.1 mg/m^3)	One-third the AEGL-3 values
AEGL-3 (lethal)	2.3 ppm (14 mg/m^3)	2.3 ppm (14 mg/m^3)	1.8 ppm (11 mg/m^3)	1.2 ppm (7.2 mg/m^3)	0.58 ppm (3.5 mg/m^3)	Threshold for lethality ($BMCL_{05}$) in female rats; UF = 10; default time scaling

Editorial Comments on Ethyl Mercaptan

Page 8, Table 1: Because vapor pressure and saturated vapor concentration vary with temperature, the temperature for the calculated saturated vapor concentration should be added.

Page 12, line 3: A citation and reference for the Litchfield and Wilcoxon method should be added.

Page 20, Table 10: Several occupational standards and guidelines are noted to be ceiling values, which is pertinent to all time points. The table should clarify this by entering the ceiling value for all the exposure durations.

Page 17, line 9: "Terrible" should be Terribile.

Page 17, line 36: Capitalize the "l" in the first use of AEGL, and delete colon after second use of AEGL in the sentence.

Page 18, line 43: Rephrase "mice yielded" to "mice exposures yielded."

In the discussion of the AEGL-3 values, clarification is needed of the statement that mouse data provides "a better concentration-response curve" than rat data.

Page 20: The discussion of occupational standards for ethyl mercaptan should provide more context for why they differ from the AEGL values (see earlier section on Comments Relevant to All TSDs). For example, the sentence on lines 29-30 could be revised as follows: ". . .the ACGIH® documentation (2004) states that the TLV® value is based on the very limited human data indicating irritation of the mucous membranes, lacrimation, and the central nervous system effects seen at 4 ppm, but is more experience based than experimentally derived."

Page 22, lines 29-30: Reference for the 1978 NIOSH citation is incomplete.

Editorial Comments on Methyl Mercaptan

Page 9, Table 1: The temperature for the vapor pressure and calculated saturated vapor concentration for methyl mercaptan should be added. Several of the table entries have citations for a 1991 ACGIH® publication. There is no corresponding reference in the Reference List, and a review of more recent publications by ACGIH® indicate that the methyl mercaptan documentation was updated in 2004. The chemical property values, such as vapor pressure, should be verified using more current references. A reference is also not provided for the citation to an AIHA® publication.

Page 13, line 14: Rephrase the sentence as follows: ". . . 20-liter static exposure chamber . . ." to make it clear that these chambers were not flow-through systems.

Page 23, Table 10: The citation for the OSHA permissible exposure limit should be the most recent Federal Register notice in which the limit is recorded. The other standards should be referenced accordingly (see section above on Comments on All AEGLs TSDs)

References: ACGIH® (1991) is cited in the text but does not have a corresponding reference. AIHA® (2001) is cited in the text, but a 1999 publication appears in the reference list. The following references do not appear to be cited in the text: Swedish Work Authority (2005), U.S. EPA (1994), Van Doorn et al. (2002), and Zieve et al. (1984).

Comments on Phenyl Mercaptan

The chemical and physical data reported for phenyl mercaptan should be verified. The entries in the table are attributed to the HSDB (Hazardous Substances Data Bank) in 2006. A check of the database in May 2012 indicates that some of the values have been updated or may have been improperly recorded (e.g., the vapor pressure in the TSD is identified as 1 mm Hg at 25ºC, but the HSDB database currently reports it to 1.93 mm Hg at 25ºC).

Page 9, line 17: A citation and reference for the Litchfield and Wilcoxon method should be added.

In the discussion of the AEGL-3 values, clarification is needed of the statement that rat data provides "a better concentration-response curve" than mouse data.

The entry in Table 9 (Extant Standards and Guidelines) for the NIOSH REL is a ceiling value and should be shown to be applicable across all the exposure durations. Footnote b of the table should be

restricted to defining the German MAC as analogous to the ACGIH® TLV®. The fact that the TLV® was changed in 2004 is already covered in the text, and is not appropriate for the footnote.

Page 18, line 19: Delete "established a" from the sentence.

References: Add the appropriate references to NRC (2001) and AIHA® (1995), which are cited in the text. The O'Neil reference does not appear to be cited in the text.

METHANESULFONYL CHLORIDE

The committee reviewed the AEGL TSD on methanesulfonyl chloride that was presented by Lisa Ingerman of SRC, Inc. Table 10 presents a summary of the proposed AEGL values for methanesulfonyl chloride and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSD have been adequately addressed, and that the document can be finalized for publication after a few editorial changes are made.

Editorial Comments

In Section 3.1 on acute animal toxicity, the type of detector used for the gas-chromatographic analysis in the Pennwalt Corporation study is identified as GC/FIC. That may be a typographical error of GC/FID. If not, the method should be further described.

Page 9, lines 41-43: The sentence is unclear.

The reference to RTECS (1997) should be reviewed to verify that it is accurately cited. It might be appropriate to specify that RTECS is a database of the Centers for Disease Control and Prevention.

METHYL ISOTHIOCYANATE

The committee reviewed the AEGL TSD on methyl isothiocyanate that was presented by Heather Carlson-Lynch of SRC, Inc. Table 11 presents a summary of the proposed AEGL values for methyl isothiocyanate and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSD have been adequately addressed, and that the document can be finalized for publication after a few editorial revisions are made.

Editorial Comments

The citations for unpublished studies should provide information on how the studies can be obtained (e.g., National Technical Information Service, EPA docket), or indicate that the study details came from a secondary source. For example, the reference to the Russell and Rush (1996) study should clarify whether the study results were obtained directly or were obtained from a previous EPA data evaluation record (currently referenced as EPA 2006a). Another study in question is the one by Jackson et al. (1981).

The website link provided in the reference list for EPA (2006b) no longer provides access to the document. An updated website link should be provided, if available.

Page 21: A reference is not provided for Dourson (2010). It is also not clear whether the reference is being used to support the assertion that ocular irritation is a more sensitive end point than nasal or mucous membrane irritation as a general statement or as specific to methyl isothiocyanate.

Page 20, lines 33-34: The discussion about susceptible subpopulations should indicate that no data on this topic were found. This will clarify that the statement that individuals with respiratory diseases may be particularly sensitive methyl isothiocyanate is based on the direct-acting irritant properties of the chemical.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.40 ppm (1.9 mg/m^3)	0.40 ppm (1.9 mg/m^3)	0.21 ppm (0.98 mg/m^3)	0.053 ppm (0.25 mg/m^3)	0.026 ppm (0.12 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	1.2 ppm (5.6 mg/m^3)	1.2 ppm (5.6 mg/m^3)	0.62 ppm (2.9 mg/m^3)	0.16 ppm (0.75 mg/m^3)	0.078 ppm (0.37 mg/m^3)	4-hour rat $BMCL_{05}$ of 15.5 ppm; UF = 100; default time scaling

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	0.27 ppm (0.81 mg/m^3)	Highest concentration without notable discomfort (eye irritation) in humans; UF = 3
AEGL-2 (disabling)	21 ppm (63 mg/m^3)	21 ppm (63 mg/m^3)	17 ppm (51 mg/m^3)	10 ppm (30 mg/m^3)	5.3 ppm (16 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	63 ppm (190 mg/m^3)	63 ppm (190 mg/m^3)	50 ppm (150 mg/m^3)	31 ppm (94 mg/m^3)	16 ppm (47 mg/m^3)	Highest 4-h nonlethal concentration in rats; UF = 3; default time scaling

MONOISOCYANATES

The committee reviewed the AEGL TSD on four monoisocyanates—n-butyl isocyanate, cyclohexyl isocyanate, ethyl isocyanate, and phenyl isocyanate—that was presented by Heather Carlson-Lynch of SRC, Inc. Table 12 presents a summary of the proposed AEGL values for those monoisocyanates and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSD have been adequately addressed, and that the document can be finalized for publication.

NITRIC ACID

The committee reviewed the AEGL TSD on nitric acid that was presented by Julie Klotzbach of SRC, Inc. Table 13 presents a summary of the proposed AEGL values for nitric acid and their basis. The committee agreed that its previous comments (NRC 2010b) on the TSD have been adequately addressed, and that the document can be finalized for publication.

3-QUINUCLIDINYL BENZILATE

The committee reviewed the AEGL TSD on 3-quinuclidinyl benzilate that was presented by Lisa Ingerman of SRC, Inc. Table 14 presents a summary of the proposed AEGL values for 3-quinuclidinyl benzilate and their basis. The committee agreed that its previous comments (NRC 2011a) on the TSD have been adequately addressed and that the document can be finalized for publication after a few editorial clarifications are made.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Ethyl isocyanate						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient warning properties; systemic effects possible at concentrations lower than those associated with irritation.
AEGL-2 (disabling)	0.20 ppm (0.58 mg/m^3)	0.065 ppm (0.19 mg/m^3)	0.034 ppm (0.099 mg/m^3)	0.0085 ppm (0.025 mg/m^3)	0.0040 ppm (0.012 mg/m^3)	Based on AEGL-2 values for methyl isocyanate; MF = 2
AEGL-3 (lethality)	0.60 ppm (1.7 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.10 ppm (0.29 mg/m^3)	0.025 ppm (0.073 mg/m^3)	0.013 ppm (0.038 mg/m^3)	Based on AEGL-3 values for methyl isocyanate; MF = 2
Cyclohexyl isocyanate						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient warning properties; systemic effects possible at concentrations lower than those associated with irritation.
AEGL-2 (disabling)	0.20 ppm (1.0 mg/m^3)	0.065 ppm (0.33 mg/m^3)	0.034 ppm (0.17 mg/m^3)	0.0085 ppm (0.043 mg/m^3)	0.0040 ppm (0.020 mg/m^3)	Based on AEGL-2 values for methyl isocyanate; MF = 2
AEGL-3 (lethal)	0.60 ppm (3.1 mg/m^3)	0.20 ppm (1.0 mg/m^3)	0.10 ppm (0.51 mg/m^3)	0.025 ppm (0.13 mg/m^3)	0.013 ppm (0.066 mg/m^3)	Based on AEGL-3 values for methyl isocyanate; MF = 2
n-Butyl isocyanate						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient warning properties; systemic effects possible at concentrations lower than those associated with irritation.
AEGL-2 (disabling)	0.10 ppm (0.41 mg/m^3)	0.10 ppm (0.41 mg/m^3)	0.083 ppm (0.34 mg/m^3)	0.053 ppm (0.21 mg/m^3)	0.026 ppm (0.11 mg/m^3)	One-third AEGL-3 values
AEGL-3 (lethal)	0.31 ppm (1.3 mg/m^3)	0.31 ppm (1.3 mg/m^3)	0.25 ppm (1.0 mg/m^3)	0.16 ppm (0.65 mg/m^3)	0.078 ppm (0.32 mg/m^3)	No mortality in rats, 14 ppm, 4 h; UF = 30; MF = 3; default time scaling
Phenyl isocyanate						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient warning properties; systemic effects possible at concentrations lower than those associated with irritation.
AEGL-2 (disabling)	0.012 ppm (0.058 mg/m^3)	0.012 ppm (0.058 mg/m^3)	0.0096 ppm (0.047 mg/m^3)	0.0061 ppm (0.030 mg/m^3)	0.0030 ppm (0.015 mg/m^3)	One-third AEGL-3 values
AEGL-3 (lethal)	0.036 ppm (0.18 mg/m^3)	0.036 ppm (0.180 mg/m^3)	0.029 ppm (0.14 mg/m^3)	0.018 ppm (0.088 mg/m^3)	0.0091 ppm (0.044 mg/m^3)	$BMCL_{05}$ (1.64 ppm) from rat 4-h study; UF = 30; MF = 3; default time scaling

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	No-effect level for notable discomfort (changes in pulmonary function: vital capacity, respiratory resistance, and FEV_1) in humans of 1.6 ppm; UF = 10
AEGL-2 (disabling)	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)	No-effect level for inability to escape (eye closure) in rats of 470 ppm for 1 h; UF = 3; default time scaling
AEGL-3 (lethal)	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)	No-effect level for lethality (estimated LC_{01} of 919 ppm) in rats; UF = 10; default time scaling

TABLE 14 Summary of Proposed AEGL Values for 3-Quinuclidinyl Benzilate Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	Not recommended	Not recommended	Estimated threshold for incapacitation in human volunteers (20 mg-min/m^3); UF = 10; MF = 3; default time scaling
AEGL-3 (lethal)	1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	Not recommended	Not recommended	Estimated lethality threshold (3,700 mg-min/m^3); UF = 100; MF = 3; default time scaling

Editorial Comments

For the AEGL-2 values, context and a rationale should be provided for why one-third of the ICT_{50} (a concentration-time product causing incapacitation of 50% of the test subjects) was used to determine the point-of-departure.

TEAR GAS

The committee reviewed the AEGL TSD on tear gas that was presented by Lisa Ingerman of SRC, Inc. Table 15 presents a summary of the proposed AEGL values for tear gas and their basis. The committee recommends a few changes in how those AEGL values were derived.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	Estimated no-effect level for impaired ability to escape (ocular/nasal/throat irritation, cough in humans); UF = 3; MF = 3
AEGL-3 (lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3	Threshold for lethality (LC_{01}) in rats; UF = 10; n = 0.70 for time scaling

AEGL Specific Comments

The committee suggests that military handbooks on warfare agents be consulted for relevant information on tear gas that might be used as a basis for AEGL values (e.g., Langford 2004; Gupta 2009).

For the AEGL-2 values, consideration should be given to whether the effects observed in the Beswick study are from irritation or if other mechanisms are involved. Nausea was observed in the study, which raises the possibility of systemic toxicity. If other mechanisms are involved, it will not be appropriate to apply the same AEGL value to all durations.

The committee has reconsidered its previous recommendation that an uncertainty factor of 3 for intraspecies variation in the derivation of AEGL-2 and AEGL-3 values not be supported by the fact that responses of volunteers with conditions such as jaundice, hepatitis, or peptic ulcer were similar to those of "normal" volunteers when exposed to tear gas. It recommends that the discussion in the previous draft be reinstated, and expanded to include important relevant information that in the study by Punte et al. volunteers included people with seasonal allergies and asthma.

Editorial Comments

Section 6.1: The description of the Beswick study should be edited to make it clear how many subjects were exposed. This will clarify that the subsequent description of symptoms occurred in other subjects exposed at the same concentrations.

TITANIUM TETRACHLORIDE

The committee reviewed the AEGL TSD on titanium tetrachloride that was presented by Heather Carlson-Lynch of SRC, Inc. Table 16 presents a summary of the proposed AEGL values for titanium tetrachloride and their basis. The committee found that its previous comments on the TSD (NRC 2010b) were not adequately addressed, and continues to recommend further systematic evaluation of existing information, including a more thorough consideration of relevant literature to provide context for the derivation of AEGL values in the TSD. The committee judged that the TSD should be reviewed again before finalization.

AEGL Specific Comments

The TSD for titanium tetrachloride continues to propose no AEGL-1 values on the basis that no relevant data are available. It would be helpful to reconsider the previous comments regarding this

proposal (see NRC 2010b), including the suggestion to check for potentially relevant studies that have not yet been reflected in the TSD. For example, some references noted in the previous comments did not appear to have been considered in the revised TSD, and others not explicitly identified in those comments are also not yet reflected. Such information could potentially support the derivation of AEGL-1 values. It may also be helpful to consider context from relevant occupational benchmarks, evaluations, and derivations from the National Institute for Occupational Safety and Health (Moseley et al. 1980; NIOSH 2009), including documentation related to a transformation product of titanium tetrachloride (e.g., NIOSH 2011) and information on concentrations at which a visible cloud would form, as human exposures were reported for such cases without adverse health effects.

SRC did not pursue the committee's previous suggestion of using an RD_{50}-based approach to derive AEGL-1 values because no RD_{50} estimate for mice was identified and because the RD_{50} for rats produced AEGL-1 values that exceed the point of departure for AEGL-2 values. However, the committee suggests that this approach be revisited by considering relative toxicities of transformation products that would be formed immediately upon release of titanium tetrachloride, in the same manner as is done for similar chemicals (e.g., others that form hydrogen chloride upon release). RD_{50} values for hydrogen chloride are available (see NRC 2009). Such information taken together with information provided in Kelly (1980) for relative toxicities of titanium tetrachloride and hydrogen chloride (accounting for stoichiometry), as well as other data not yet reflected in the TSD, may suggest a basis for deriving AEGL-1 values. Furthermore, the point of departure for the AEGL-2 values warrants revisiting, because it is from a repeat inhalation study (see discussion below). It may be helpful to review other relevant applications of the RD_{50} approach (e.g., see NRC 2009).

The TSD should provide a more integrated compilation of dose-response data to facilitate evaluation of effect severities across species, exposure durations, and end points, including consideration of fate products and variations in relative humidity. Such a compilation in tabular form might help to clarify options for derivation of AEGL-1 values.

For the AEGL-2, SRC proposed two options that are based on a 4-week exposure study (Kelly 1979). The committee disagrees with the statement that "acute animal toxicity data are not appropriate for AEGL derivation," and recommends that its previous comments on the use of repeat-exposure studies for deriving AEGL-2 values be considered again. The study by Kelly (1980) appears to be relevant, and more detailed information about toxic symptoms at individual concentrations could be sought by contacting the investigator. Relevant context might also be found in the NRC AEGLs report for hydrogen chloride (NRC 2004) and a more recent derivation of a 1-hour emergency exposure guidance level (NRC 2009).

TABLE 16 Summary of Proposed AEGL Values for Titanium Tetrachloride Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	17 mg/m^3	17 mg/m^3	7.7 mg/m^3	1.6 mg/m^3	0.72 mg/m^3	No-effect level for irreversible or other serious, long-lasting health effects or an impaired ability to escape (10 mg/m^3 for 6 h/d, 5 d/wk for 4 wk) UF = 10; n = 0.88 for time scaling
AEGL-3 (lethal)	95 mg/m^3	33 mg/m^3	14 mg/m^3	5.1 mg/m^3	2.3 mg/m^3	One-third of rat LC_{50} values; UF = 30; n = 0.88 for time scaling

Consideration should be given to using an intraspecies uncertainty factor of 10 in deriving AEGL-2 and AEGL-3 values, given that the specific mode of action is not yet clearly defined. Furthermore, variability in particle sizes can affect both toxicokinetics and toxicodynamics. With formation of titanium oxide and oxychlorides upon release of the tetrachloride, recent studies have characterized the impact of particle size (vs. concentration) on differential clearance, distribution, and relative toxicity for very small particles. (For example, K.P. Lee, H.J. Trochimowicz, C.F. Reinhardt, and others have assessed translocation of fine/ultrafine titanium dioxide particles following inhalation exposure in rats, while R. Kumazawa and others have assessed the effects of these small particles on neutrophil function.)

Given the variability issues noted above, consideration should be given to whether the default approach of calculating an LC_{01} based on one-third the LC_{50} values is appropriate. A tabulated presentation of relevant data across species (beyond rats), exposure durations, end points, and effect levels would facilitate such an evaluation.

Other Comments

A short discussion should be added about nanoscale particles formed in the air and lungs (vs. those formed by milling), and that nanoscale titanium dioxide is likely to be a coexposure with titanium tetrachloride.

Page 6, lines 5-12, and page 9, lines 1-14: Production information should be updated with more recent information. For example, the reference cited in the current draft to support the statement that titanium tetrachloride "is still used in the production of military smoke screens" is more than ten years old. It would be useful to qualify such statements per the time frame indicated or refer to other recent reviews (e.g., EPA 2009).

Page 6, lines 40-42: The substantial role of humidity in the toxicity of titanium tetrachloride and its transformation products should receive more emphasis (including quantitative context) to ensure that humidity is appropriately accounted for in the event of a release.

Page 6, line 45 to page 7, line 6: The discussion should clarify that histopathology was only performed on the respiratory tract in the Kelly (1980) study.

Page 7, lines 12-13: The discussion should acknowledge that clinical effects in rats exposed at 10 mg/m^3 returned to normal after the 2-week recovery period, whereas rats exposed at 5 mg/m^3 had results similar to controls (which suggest a no adverse effect level).

Page 7, lines 20-21: The discussin should clarify that collagenized fibrosis still remained 12 months post-exposure, especially in the respiratory bronchioles and adjoining alveolar walls.

Page 8, Table S.1, lines 20-25 (footnotes): Differential toxicity implications of both relative humidity and nanoscale titanium should be discussed further in the text (not just in footnotes to the table), including more quantitative context, to support practical implementation of AEGL values.

Page 20, lines 24-25: It is unclear why this section is proposed for deletion. As noted earlier, further consideration should be given to using RD_{50}s as a basis for AEGL-1 values.

Page 22, lines 10-20: Titanium dioxide has been identified as an immediate transformation product of titanium tetrachloride. Recent toxicity studies of this chemical might provide information on potential mode of action and joint toxicity of titanium tetrachloride with its conversion products.

Page 23, lines 1-2: More recent references should be included to support the statement that "the toxic effects of titanium tetrachloride are unlikely to be similar to those induced by either titanium dioxide or HCl alone." Relevant information includes quantitative context from Kelly (1979), the role of oxychlorides and fine/ultrafine particles, and joint toxicity. In addition, studies on differential clearance and translocation beyond the respiratory tract would also be relevant.

Page 23, lines 7-13 (Species Variability): More quantitative context should be provided in the discussion of species variability. Such context would include considering the potential impacts of

toxicokinetic differences among species on joint toxicity and interpretation of available studies. A summary table of data relevant to species variability would be very helpful to facilitate comparisons.

Page 23, lines 16-21 (Susceptible Populations): This statement appears to support an uncertainty factor of 10 because of lack of information on mode of action and susceptibility, in addition to the variable humidity and variations in sizes and forms of the transformation products, as affected by the nature of the release and the exposure setting (e.g., see Roy et al. 2003 and Kapias and Griffiths 2005). A literature search should be conducted for relevant information to inform the interspecies adjustment (for example, see general susceptibility considerations noted by Testud and Lambert-Chhum [2004] and others).

Page 23, lines 37-40 (Concurrent Exposure Issues): This section should be revised to better explain the nature and importance of the concurrent exposure issue, which is inherent to any release of titanium tetrachloride.

Page 24, Section 4.4.5 (Factors Affecting Toxicity of Titanium Tetrachloride: Nanoscale Uses and Humidity): This section whould be revised so the implications of both nanoscale titanium particles and humidity are clear and can be incorporated in the practical implementation of the AEGLs if titanium tetrachloride is released (particularly if the area happens to be very humid).

Page 24, lines 36-37: Regarding the statement that no odor threshold data are available, some context may exist (e.g., see the indicator in AIHA® 2011). Additional information might now be available on titanium tetrachloride because of its use in nanoscale titanium dioxide production.

Page 26, lines 1-2: To avoid a possible misinterpretation that 10 mg/m^3 is a no-observed adverse-effect level, it would be useful to acknowledge the results of clinical lab tests for that exposure group, and to explain dose-dependent acute inflammation of the respiratory tract after 20 days of exposure (6 hours per day, 5 days a week for 4 weeks).

Page 26, lines 16-17: The following sentence seems more relevant to AEGL-1 values: "Because of the irritating properties of this chemical, the AEGL-2 should be based on irritation." The data should be reassessed for relevance to the AEGL-2 bases.

Page 26, lines 44-47: "An intraspecies uncertainty factor of 3 was chosen because the mechanism of action, direct contact irritation, is not expected to vary greatly among subpopulations." This statement may not adequately reflect the available data. Furthermore, the mechanism of action may not be clearly known (e.g., see comments on the previous draft TSD).

Page 27, lines 10-32: For the AEGL-2 derivation, consideration should be given to how values for hydrogen chloride were derived in NRC (2009). An uncertainty factor of 10 could be considered based on variability across species and the potential for differential susceptibility in humans. The committee recommends that AEGL-2 values not be derived by dividing the AEGL-3 values by 3, given that relevant data exist. See page 29, lines 33-35, regarding the indication that species differences in the transport and deposition of titanium oxide hydrates and/or oxychloride particles (that are postulated to deliver irritant hydrogen chloride to the deep lungs) cannot be ruled out. The same logic applies for using that uncertainty factor of 10 to derive the AEGL-2 values.

Page 30, lines 14-16: The following sentence could be interpreted as somewhat misleading: "Although no clinical signs were reported at this concentration, exposure to the next higher concentration (resulting in labored breathing) approached the lethality threshold concentration." It is important to clarify that the next higher concentration is substantially higher (representing the widest dose spacing of the study). The statement also contrasts with opposite argument that seems to be made earlier (see page 26, lines 19-23) in stating that it is unclear whether the effect was only seen after repeated exposures, in which case it could be considered a no-effect level for AEGL-2 end points.

Page 31, Table 13 (line 5): More recent references should be used to support current standards and guidelines. For example, the AIHA® ERPGs are still cited in the TSD as a 2004 reference, while a more current source is available.

Page 31, lines 1-2 and 20-25: The following statement in the TSD only applies to the molar basis: "The Kelly (1980) study reported a 16-fold higher potency of titanium tetrachloride compared to that expected from HCl alone." On a weight basis, Kelly indicates the difference is 4-fold.

Page 32, Section 8.3 (Data Adequacy and Research Needs): A valuable opportunity seems to exist with regard to contacting the author of the key studies (Kelly) for information that could potentially address limitations noted in this section, and provide further insight for the derivation of improved AEGLs for titanium tetrachloride.

Editorial Comments

Values and unit conversions should be checked to ensure technical accuracy and consistency. It is unclear that it is appropriate for all values to be presented in mg/m^3, so further rationale should be provided for why this was done.

Page 7, line 9: Clarify that the "measured concentrations" were 4-week averages that ranged higher and lower over that time.

Page 9, lines 31-33: The following statement should be revisited: "Animal studies in rats, mice, and dogs are available but the studies are of limited usefulness because of poor reporting of experimental procedures and results, or because they were repeated exposure studies," given that the Kelly (1980) study was well-designed and conducted and that the Kelly (1979) repeated-exposure study was used to derive AEGL values.

Examples of Potentially Relevant References Not Cited in TSD

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TRIMETHYLACETYL CHLORIDE

The committee reviewed the AEGL TSD on trimethylacetyl chloride that was presented by Lisa Ingerman of SRC, Inc. Table 17 presents a summary of the proposed AEGL values for trimethylacetyl chloride and their basis. The committee agreed that its previous comments on the TSD (NRC 2011a) were adequately addressed, and that the document can be finalized for publication after a few clarifications are made.

Other Comments

For clarity, the TSD should include the rationale for exploring whether data on phosgene could be used in the development of AEGL values for trimethylacetyl chloride, and should explain why the phosgene data were not used. Considerations should also be given to moving the comparison of the AEGLs values for trimethylacetyl chloride and phosgene from Section 8.2 (Comparison with Other Standards and Guidelines) to Section 8.1 (AEGLs Values and Toxicity End Points).

Editorial Comments

Page 5, line 13: delete "the" before "a mouse study."
Page 7, lines 4-6: consider splitting the sentence into two sentences.
Page 11, line 14: add "exposure" after "Phosgene."
Page 11, line 25: the uncertainty factor is 10 not 9.

VINYL ACETATE MONOMER

The committee reviewed the AEGL TSD on vinyl acetate monomer that was presented by Heather Carlson-Lynch of SRC, Inc. Table 18 presents a summary of the proposed AEGL values for vinyl acetate monomer and their basis. The committee agreed that its previous comments (NRC 2010b) on the TSD have been adequately addressed, and that the document can be finalized for publication after a few editorial clarifications are made.

Editorial Comments

Section 6.3: In the discussion of AEGL-2 values, the olfactory degeneration/necrosis should not be described as "reversible," because there are no data to support that contention.

Page 7, line 5, and page 39, line 35: Suggest the following revisions for clarity: "Application of a higher total uncertainty factor of 30 would reduce the AEGL-3 values below concentrations that—albeit at shorter exposure durations—did not result in serious health effects . . .Data in human volunteers showed no serious health effects as . . .."

The reference to Frame (2004) is a personal communication and should be cited as such in the text rather than the reference list.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.070 ppm (0.34 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)	6-h exposure causing no mortality in the rat (78 ppm); UF 100; MF = 3; default time scaling

TABLE 18 Summary of Proposed AEGL Values for Vinyl Acetate Monomer Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
AEGL-1 (nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	No-effect level for notable discomfort in humans (20 ppm, 4 h); UF = 3
AEGL-2 (disabling)	46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)	No-effect level for serious, long-lasting histopathologic nasal lesions in rats (200 ppm, 6 h); UF = 10; default time scaling
AEGL-3 (lethal)	230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)	Highest nonlethal concentration in rats or mice (1,000 ppm, 6 h/day, 28 days); UF = 10; default time scaling

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