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

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

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 B). It summarizes the committee's conclusions and recommendations for improving AEGL documents for the following chemicals and chemical classes: aliphatic nitriles, benzonitrile, and methacrylonitrile.

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

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

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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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 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): aliphatic nitriles (acetonitrile, isobutyronitrile, propionitrile, chloroacetonitrile, and malononitrile), benzonitrile, and methacrylonitrile. These documents were reviewed by the committee at a meeting on May 2-4, 2012.

ALIPHATIC NITRILES

The committee reviewed the AEGL TSD on five aliphatic nitriles (acetonitrile, isobutyronitrile, propionitrile, chloroacetonitrile, and malononitrile) that was presented by Julie Klotzbach of SRC, Inc. Table 1 presents a summary of the proposed AEGL values for the aliphatic nitriles 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 clarifications and editorial changes are made.

General Comments

A statement of caution should be given for the cumulative effects of concomitant exposure to multiple aliphatic nitriles that share a common mechanism of toxicity through their biotransformation to cyanide.

For each of the aliphatic nitriles with extant standards and guidelines, more substantive discussion should be added about the basis for the differences between the AEGL values and other relevant guidelines. Simply presenting the other values without discussion is not sufficiently informative. See section on Comments Relevant to All AEGL TSDs in Part A of this report (NRC 2012) for guidance.

Acetonitrile

AEGL Specific Comments

The context for selecting the point-of-departure for AEGL-3 values should include the following data:

- Maternal deaths were observed after exposure to acetonitrile at 400 and 1,200 ppm in the NTP (1994) study
- Deaths of male rats exposed at 800 and 1,600 ppm and female rats at 1,600 ppm in the NTP (1996) study; the deaths that occurred during week 1 of the 13-week segment of the study are especially pertinent.

Because the number of days of exposure preceding death of these adult rats was not reported, the rationale for selecting a higher point-of-departure can be strengthened by emphasizing embryonic and fetal end points that could occur after a single exposure. Moreover, a no-effect level of 1,200 ppm for fetal effects in the NTP (1994) study also lends support for the 6-h point-of-departure of 1,500 ppm from the Saillenfait et al. (1993) study.

TABLE 1 Summary of Proposed AEGL Values for Five Aliphatic Nitriles Reviewed by the Committee

Classification	10 min	30 min	1 h	4 h	8 h	End Point, Derivation Factors
Acetonitrile						
AEGL-1 (nondisabling)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	Not recommended	Slight chest tightness and cooling sensation in lung (1 of 3 human volunteers at 40 ppm); MF = 3
AEGL-2 (disabling)	80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)	One third of AEGL-3 values
AEGL-3 (lethality)	240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)	No-effect level for maternal and fetal lethality in rats (1,500 ppm, 6 h); UF = 30; n = 1.6 for time scaling
Isobutyronitrile						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)	One third of AEGL-3 values
AEGL-3 (lethal)	7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)	No-effect level for maternal lethality (100 ppm, 6 h); UF = 30; default time scaling
Propionitrile						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)	One third of AEGL-3 values
AEGL-3 (lethal)	11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)	No-effect level for maternal and fetal mortality (50 ppm, 6 h); UF = 30); default time scaling
Chloroacetonitrile						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	8.0 ppm (25 mg/m^3)	8.0 ppm (25 mg/m^3)	5.0 ppm (15 mg/m^3)	2.1 ppm (6.5 mg/m^3)	1.4 ppm (4.3 mg/m^3)	Derived by analogy to AEGL-2 values for acetonitrile
AEGL-3 (lethal)	24 ppm (74 mg/m^3)	24 ppm (74 mg/m^3)	15 ppm (46 mg/m^3)	6.4 ppm (20 mg/m^3)	4.2 ppm (13 mg/m^3)	Derived by analogy to AEGL-3 values for acetonitrile
Malononitrile						
AEGL-1 (nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL-2 (disabling)	1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)	Derived by analogy to AEGL-2 values for acetonitrile
AEGL-3 (lethal)	3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)	Derived by analogy to AEGL-3 values acetonitrile

Accordingly, emphasis on fetal death should be reflected in the summary table on page II-35, Appendix II-B, where detailed data were given for maternal death but not fetal resorption/nonsurviving implants.

Editorial Comments

The spelling errors of "Saillenfait" should be corrected throughout the TSD.

Page II-20, Table II-3: data from the Saillenfait et al. (1993) and NTP (1994, 1996) studies should be added. For the NTP (1996) study, the time-to-death for male and female rats should be specified, if possible.

Page II-26, Table II-9: the IDLH (immediately dangerous to life and health) value of 840 should expressed as mg/m^3 not ppm.

Appendix II-B, page II-35: In the "Effects" row of the table, the data on resorptions and nonsurviving implants at 1,800 ppm were for rats not hamsters.

Appendix II-C: Data from the Saillenfait et al. (1993) and NTP (1994) studies should be added to the category plot and data list.

Add the citation of van Raaij et al. (2003) regarding the window of vulnerability for fetal effects in the section on acetonitrile, as well as in the reference section.

Isobutyronitrile

In several places, the lowest exposure concentration for maternal death in the Saillenfait et al. (1993) study was reported to be 150 ppm (for example, see page III-12, line 28 and 35; page III-13, line 15). The correct concentrations used in this study were 200 and 300 ppm.

Page III-25, Appendix III-C: For the sake of consistency, the data from the Saillenfait et al. (1993) study should be reported as nominal concentration of 200 and 300 ppm rather than analytic concentrations of 208 and 308 ppm. The distinction has already been made in the study description on page III-11.

Page III-15: The AIHA (2002) citation was not mentioned in the text.

Propionitrile

Appendix IV-C, page IV-25: The data from the study by Saillenfait et al. (1993) should be added to the category plot and database.

Chloroacetonitrile

Page V-22: The dose units for chloroacetonitrile administered to rats in the Younger Labs (1976) study should be in mg/kg not in ppm.

Page V-23: The citation for Hashimoto (1984) should be Tanii and Hashimoto (1984).

Malononitrile

The committee had no specific comments on malononitrile.

BENZONITRILE

The committee reviewed the AEGL TSD on benzonitrile that was presented by Heather Carlson-Lynch of SRC, Inc. Table 2 presents a summary of the proposed AEGL values for benzonitrile and their basis.

The committee agreed that its previous comments (NRC 2011b) on the TSD have been adequately addressed, but recommended one substantive change to the AEGL values. Specifically, the uncertainty factor for interspecies differences should be 10 instead of 3. The TSD currently cites small differences in the toxicity of benzonitrile in rats and mice in the study by Agaev (1977) to support a factor of 3. However, the study lacks adequate detail about the methods, and differences between two rodent species give no indication of differences between rodents and humans. Thus, an uncertainty factor of 3 cannot be justified. After the AEGL values for benzonitrile are recalculated and the supporting text revised, the committee agreed that the TSD can be finalized.

METHACRYLONITRILE

The committee reviewed a presentation of proposed AEGL values for methacrylonitrile by Heather Carlson-Lynch of SRC, Inc. Revisions to the originally proposed AEGL-2 and AEGL-3 values were required because of a transcription error in the data of the key study, and revisions to the AEGL-1 values were proposed after further consideration of the warning properties of the chemical. The proposed AEGL values and options considered are presented in Table 3. The committee agreed that after the TSD is revised to incorporate the proposed changes, it can be finalized for publication.

TABLE 2 Summary of Proposed AEGL Values for Benzonitrile 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)	33 ppm (140 mg/m^3)	24 ppm (100 mg/m^3)	19 ppm (80 mg/m^3)	7.3 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)	No effect level for impairment of escape (one-third of AEGL-3)
AEGL-3 (lethal)	100 ppm (420 mg/m^3)	71 ppm (300 mg/m^3)	56 ppm (240 mg/m^3)	22 ppm (93 mg/m^3)	11 ppm (46 mg/m^3)	No effect level for lethality (estimated lethal threshold in mice, 445 ppm, 2 h); UF = 10 (3 × 3)

TABLE 3 Summary of Proposed AEGL Values for Methacrylonitrile 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	Poor odor warning properties
AEGL-2 (disabling)	To be determined	To be determined	To be determined	To be determined	To be determined	One-third of AEGL-3 values
AEGL-3 (lethal): Option 1	7.3 ppm	7.3 ppm	5.8 ppm	3.6 ppm	1.8 ppm	One-third of the 4-h LC_{50} of 109 ppm in rats; UF = 30; default time scaling
AEGL-3 (lethal): Option 2[a]	3.9 ppm	3.9 ppm	3.1 ppm	2.0 ppm	0.99 ppm	4-h nonlethal concentration of 19.7 ppm in mice and rabbits; UF = 10; default time scaling

[a]Option supported by the committee.

AEGL Specific Comments

SRC proposed not establishing AEGL-1 values because it is not clear that methacrylonitrile has adequate warning properties. The committee supports this proposal. As part of the rationale for not using the human data in the study by Pozzani et al. (1968), which was a basis for proposing AEGL-1 values in the past, the TSD should note that the focus of the study was sensory effects and it was not designed to detect systemic effects. The study also reported that the test subjects showed olfactory fatigue after a few minutes of exposure to methacrylonitrile at 2 ppm, which supports that the chemical has poor odor warning properties.

SRC discovered that the point-of-departure for calculating AEGL-3 values for methacrylonitrile had to be revised because of an error in reporting that no deaths occurred in rats exposed to methyacrylonitrile at 176 ppm in the study by Pozzani et al. (1968). One male rat died at that concentration. A reevaluation of the toxicity database led to the following observations. For a 4-h exposure, the margin between the LC_{50} (lethal concentration, 50% lethality) and the no-effect level for lethality is narrow in mice (36 ppm vs 19.7 ppm) and rabbits (37 ppm vs 19.7 ppm). The same pattern is demonstrated in other test species, albeit at slightly higher concentrations. For example, there were no deaths of dogs at 40 ppm for 7 h, but 100% death at 52.5 ppm. One dog vomited at 20 ppm. Although rats appear to be less sensitive, the wide range of 4-h LC_{50} values (378-700 ppm) is alarming when considering the narrow margin for lethality observed in other test species.

SRC presented two options for recalculating the AEGL-3 values (see Table 3). The committee judged that Option 2 was the better approach for deriving AEGL-3 values, because the overall database supported a point-of-departure of 19.7 ppm and it is preferable to use an empirical no-effect level rather than estimating a no-effect level by adjusting an LC_{50} value (as was done in Option 1). The committee supports SRC's proposal to derive AEGL-2 values by calculating one-third of the AEGL-3 values, because of the lack of data to support a point-of-departure for AEGL-2 end points.

Editorial Comments

Page 13, Table 5, and page 18, Table 6: Tables should be corrected to indicate that one rat died within 3 h after exposure to methacrylonitrile at 176 ppm.

Page 16, lines 17-19: The description of fetal body-weight reduction appears to be in error, because it refers to acrylonitrile not methacrylonitrile. The Saillenfait et al. (1993) study reported lower fetal body weight occurred only at 100 ppm and was accompanied by lower maternal weight gain.

Page 18, Table 6: (1) The table should indicate that there were no deaths in dogs (not 100% mortality) after exposure to methacrylonitrile at 40 ppm for 7 h; (2) the entry in the "Effects" column for rats exposed at 110 ppm should indicate that the 17% mortality was on day 1, and that mortality was 33% (2 of 6 rats) in males; and (3) the entry in the "Effects" column for rats exposed at 109.3 ppm should indicate that the 28% mortality was on day 1, and that mortality was 58% (7 of 12 rats) in males.

Appendix C: The text should be corrected to indicate that the death of one rat was observed at 176 ppm.

REFERENCES

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