Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 16

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

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This project was supported by Contract No. W81K04-11-D-0017 and EP-W-09-007 between the National Academy of Sciences and the U.S. Department of Defense and the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-30096-4
International Standard Book Number-10: 0-309-30096-7

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, N.W., Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 3343313; Internet, http://www.nap.edu/.

Printed in the United States of America

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. 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 releases or intentional releases by terrorists. 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, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines 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 more than 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 (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the sixteenth volume *xiv Preface*

in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The

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

committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for selected aliphatic nitriles (interim reports 19b and 21b), benzonitrile (interim reports 19b and 21b), methacrylonitrile (interim reports 19a, 20a, and 21a), allyl alcohol (interim reports 10, 12, 14, 18, and 21a), hydrogen selenide (interim report 16), ketene (interim reports 17 and 21a), and tear gas (interim reports 19a and 21a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sidney Green (Howard University), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still (Portland State University), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim reports was overseen by David Gaylor (Gaylor and

Associates, LLC), Robert Goyer (University of Western Ontario [retired]), and David H. Moore (Battelle Memorial Institute). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges

Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 16

National Research Council Committee Review of Acute Exposure Guideline Levels for Selected Airborne Chemicals

This report is the sixteenth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[3] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term 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.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by

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

varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) 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 adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemicalphysical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when

available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the noobserved-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently SRC, Inc. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were then revised by NAC in response to the public

comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the committee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared fifteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b). This report is the sixteenth volume in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

2

Benzonitrile[4]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

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). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is

[4] This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Chemical Manager George Rodgers (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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.

Airborne concentrations below the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Benzonitrile is a colorless liquid at ambient temperature and pressure and has an odor of volatile almond oil. The liquid is irritating to the skin and eyes, and the vapor is irritating to the eyes, nose, and throat (HSDB 2003). Information on the toxicity of benzonitrile in humans is limited to a single case study of a nonlethal dermal and inhalation exposure (HSDB 2003). Symptoms included severe respiratory distress, tonic convulsions, and periods of unconsciousness which lasted for 75 min. The benzonitriles ioxynil (4-hydroxy-3,5-diiodobenzonitrile) and bromoxynil (4-hydroxy-3,5-dibromodobenzonitrile) are uncoupling agents (Ellenhorn 1997); however, the mechanism of toxicity of benzonitrile has not been established.

AEGL-1 values are not recommended for benzonitrile because of insufficient data.

Data on benzonitrile were also insufficient for calculating AEGL-2 values. Therefore, values were estimated by dividing the AEGL-3 values by 3. The steepness of the dose-response relationship makes it difficult to discern thresholds for impairment of escape (AEGL-2) and lethality (AEGL-3) from the available data.

A study of mice exposed to benzonitrile at 890 ppm for 2 h was used as the basis of AEGL-3 values. Because one of seven mice died, further adjustment to estimate the lethal threshold was warranted. Typically, a 3-fold reduction of the LC_{50} (lethal concentration, 50% lethality) would be used to extrapolate to a lethal threshold. However, an LC_{50} value was not available for benzonitrile. The 2-h study reported 14% mortality, which suggests the test concentration of 890 ppm is below the LC_{50}; therefore, a 2-fold adjustment was applied. The resulting adjusted value of 445 ppm was considered an estimate of the lethality threshold and used as the point of departure for deriving AEGL-3 values. An interspecies uncertainty factor of 10 was applied. Mortality data reported by Agaev (1977) on benzonitrile suggest that rats and mice have similarly steep dose-response relationships (e.g., similar oral LD_{16}, LD_{50}, and LD_{84}), but the reported lack details about the methods, and no data on other species are available. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals. This value is supported by the steep concentration-response curve for benzonitrile, which implies little individual variability. For example, the steepness of the curve is evident in mice exposed by inhalation to benzonitrile (10% mortality at 890 ppm for 2 h [ct = 1,780 ppm-h] vs. 100% mortality at 700 ppm for 4 h [ct = 2,800 ppm-h]) (MacEwen and Vernot 1974), in rats exposed orally (no mortality at 0.6 g/kg vs. 100% mortality at 2.0 g/kg) (Industrial Bio-Test 1970), and in rabbits exposed dermally (no mortality at 0.9 g/kg vs. 100% mortality at 1.4 g/kg) (Industrial Bio-Test 1970). The total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Insufficient data were available to derive an empirical value for n. Therefore, time scaling was performed using default values of n = 3 to extrapolate to shorter durations and n = 1 to extrapolate to longer durations to provide AEGL values that are protective of human health (NRC 2001).

AEGL values for benzonitrile are presented Table 2-1.

TABLE 2-1 AEGL Values for Benzonitrile

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (disabling)	11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)	One-third of AEGL-3 values

AEGL-3 (lethal)	34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)	Estimated lethal threshold in mice (MacEwen and Vernot 1974)

a
Not recommended. Absence of AEGL-1 values does not imply that exposures below AEGL-2 values are without adverse effects.

1. INTRODUCTION

Benzonitrile is produced by vapor-phase catalytic ammoxidation of toluene, dehydrogenation of the Diels-Alder adduct of butadiene and acrylonitrile, or by reaction of benzoic acid with urea at 220-240°C in the presence of a metallic catalyst. It is used as an intermediate for rubber chemicals, and as a solvent for nitrile rubber, lacquers, and resins and polymers. It is also used as an additive in nickel-plating baths, for separating naphthalene and alkylphthalenes from nonaromatics by azeotropic distillation, as a jet fuel additive, in cotton bleaching baths, as a drying additive for acrylic fibers, and in the removal of titanium tetrachloride and vanadium oxytrichloride from silicon tetrachloride (HSDB 2003).

The physical and chemical properties of benzonitrile are presented in Table 2-2.

TABLE 2-2 Physical and Chemical Data on Benzonitrile

Parameter	Data	Reference
Common name	Benzonitrile	IPCS 1999
Synonyms	Cyanobenzene, benzoic acid nitrile; phenyl cyanide	IPCS 1999
CAS registry no.	100-47-0	IPCS 1999
Chemical formula	C_6H_5 (CN)	IPCS 1999
Molecular weight	103.1	IPCS 1999
Physical state	Colorless liquid	HSDB 2003
Melting point	-12.8°C	IPCS 1999
Boiling point	190.7°C	IPCS 1999
Flash Point	75°C	IPCS 1999
Density/Specific gravity	1.010 at 25°C/15°C	HSDB 2003

Solubility	Poor solubility in water; miscible with organic solvents, soluble in alcohol, ether and acetone	HSDB 2003
Vapor density	3.6 (air = 1)	HSDB 2003
Vapor pressure	0.768 mm Hg at 25°C	HSDB 2003
Conversion factors in air	1 ppm = 4.22 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Information on the toxicity of benzonitrile in humans is limited to a single occupational case study (HSDB 2003). A male worker was accidentally drenched (head and clothing) with benzonitrile. He was subsequently doused with water, but his clothing was not immediately removed. Immediately thereafter the worker collapsed into unconsciousness. He was subsequently bathed to remove dermal exposure, and became responsive for a short period, but exhibited respiratory distress. He then fell into deep unconsciousness and exhibited tonic contractions in the muscles of his arms and face. The tonic muscle contractions were alleviated following treatment with phenobarbitol and sodium thiosulfate. Under supplemental oxygen, he remained unconscious for approximately 75 min and gradually recovered and was released without apparent symptoms the following day. Air concentrations of benzonitrile experienced during the exposure were not reported. Dermal exposure to benzonitrile probably contributed to the absorbed dose.

2.2. Nonlethal Toxicity

An odor threshold of 2.9×10^{-5} mg/L (0.007 ppm) has been reported for benzonitrile (HSDB 2003).

2.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies of acute human exposure to benzonitrile were not available.

2.4. Genotoxicity

Genotoxic studies of acute human exposure to benzonitrile were not available.

2.5. Carcinogenicity

Carcinogenicity studies of human exposure to benzonitrile were not available.

2.6. Summary

No reports regarding lethality, nonlethal toxicity, developmental and reproductive toxicity, genotoxicity, or carcinogenicity on benzonitrile were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

A group of six male CFE rats was exposed to benzonitrile at 900 ppm (saturated atmosphere) in a 30-L glass exposure chamber for 4 h and observed for 14 days (MacEwen and Vernot 1974). The benzonitrile atmosphere was produced by passing air through a fritted disc bubbler immersed in 200 mL of test material. The airflow through the bubbler was 10 L/min, and 9 min was necessary to achieve 95% saturation in the exposure chamber. The chamber concentration of benzonitrile was continuously analyzed using a total hydrocarbon analyzer initially calibrated with several standard gas bags containing benzonitrile at 450 and 900 ppm in air. Irritation of the extremities was observed during the first hour of exposure, followed by poor coordination and labored breathing after 3 h. Prostration occurred at 3.5 h. Following the 14-day observation period, five of the six rats had weight gain that was below normal (data not presented). No treatment-related deaths occurred; however, microscopic examinations of the rats at the end of the 14-day observation period revealed multifocal areas of lymphoid hyperplasia with macrophage-containing foamy accumulations.

Groups of five male and five female young adult Charles River rats were exposed to benzonitrile at 0.8 or 8 mg/L (190 or 1,900 ppm) in a 70-L Plexiglas inhalation chamber for 4 h and observed for 14 days (Industrial Bio-Test 1970). An aerosol of undiluted benzonitrile was generated with an Ohio Ball-Jet Nebulizer. A stream of clean dry air was passed through the nebulizer and the resulting aerosol stream was mixed with additional dry air to obtain the final desired concentration. The test atmosphere was then introduced into the top of the exposure chamber, dispersed with a baffle plate, and exhausted at the bottom of

the chamber. Air flow rates were measured with rotameters connected to the air supply line upstream of the aerosol; temperature and pressure of the test atmosphere were also measured. Average nominal concentrations were calculated by dividing the nebulizer weight loss by the total volume of air used during each exposure. No deaths, clinical signs, or effects on body weight were observed in the 0.8-mg/L group. At necropsy, no gross treatment-related effects were found in this group. Three females died after exposure at 8 mg/L; two deaths occurred 2 h after the end of the exposure period and one occurred on day 6. Six of the eight surviving rats lay prostrate 18 h after exposure; this effect persisted in two animals through day 4 and in one animal through day 6 (when death occurred). No adverse effects on body weight were noted. Necropsy of animals that died on the day of exposure showed minimal pulmonary hyperemia.

Agaev (1977) reported the following lethal concentrations of benzonitrile in white rats: LC_{84} = 1,071 ppm, LC_{50} = 929 ppm, and LC_{16} = 738 ppm. Exposure duration and other experimental details were not reported.

In an acute oral toxicity study, two male and two female albino Charles River rats were administered undiluted benzonitrile by gavage at single doses of 0.6, 0.9, 1.4, or 2.0 g/kg and observed for 14 days (Industrial Bio-Test 1970). Dose-related clinical signs included hypoactivity, muscular weakness, ruffled fur, prostration, dyspnea, and lacrimation. Mortality was 0/4 at 0.6 g/kg, 2/4 at 0.9 g/kg, 3/4 at 1.4 g/kg, and 4/4 at 2.0 g/kg. An oral LD_{50} of 1.0 ± 0.2 g/kg was calculated.

Agaev (1977) reported the following lethal doses for a one-time exposure to a 50% solution of benzonitrile in sunflower oil in white rats: LD_{84} = 2,350 mg/kg, LD_{50} = 1,500 mg/kg, and LD_{16} = 650 mg/kg. No other experimental details were reported.

3.1.2. Mice

Groups of seven or 10 male CF-1 mice were exposed to benzonitrile at target concentrations of 900 ppm (saturated atmosphere) in a 30-L glass exposure chamber for 2 or 4 h and observed for 14 days (MacEwen and Vernot 1974). Measured concentrations were 890 ppm for the 2-h exposure and 700 ppm for the 4-h exposure. The benzonitrile atmosphere was produced by passing air through a fritted disc bubbler immersed in 200 mL of test material. The airflow through the bubbler was 10 L/min, and 9 min was necessary to achieve 95% saturation in the exposure chamber. The benzonitrile chamber concentration was continuously analyzed using a total hydrocarbon analyzer initially calibrated with several standard gas bags containing benzonitrile at 450 and 900 ppm in air. Irritation of the extremities was observed during the first hour of exposure, followed by poor coordination and labored breathing after 60-90 min. Prostration occurred at 2.5 h. All mice in the 4-h group died; three died on the day of exposure (including one

during exposure at 3.5 h), three on day 1, and four on day 2. Only one mouse in the 2-h group died on day 2. Congestion accompanied by edema was found in the lungs of both exposure groups at necropsy. Mice exposed for 4 h also had hepatic congestion and sinusoidal dilation.

Agaev (1977) reported the following lethal concentrations for benzonitrile in white mice: LC_{84} = 595 ppm, LC_{50} = 429 ppm, and LC_{16} = 167 ppm. Exposure duration and other experimental details were not reported.

Agaev (1977) reported the following lethal doses for a one-time exposure to a 50% solution of benzonitrile in sunflower oil in white mice: LD_{84} = 2,350 mg/kg, LD_{50} = 1,400 mg/kg, and LD_{16} = 650 mg/kg. No other experimental details were reported.

3.1.3. Rabbits

In an acute dermal toxicity study, two male and two female New Zealand white rabbits were administered undiluted benzonitrile at doses of 0.9, 1.4, 2.0, or 3.0 g/kg and observed for 14 days (Industrial Bio-Test 1970). The test substance was applied to the clipped skin, covered with impervious plastic sheeting, and allowed to remain in contact with the skin for 24 h. The rabbits were fitted with collars to prevent oral ingestion of the benzonitrile. Local skin irritation was characterized as barely perceptible to pale red erythema and slight edema at the end of the 24-h exposure period; the dermal irritation subsided during the first week. Dose-related clinical signs included salivation, muscular weakness, ataxia, prostration, tremors, and loss of righting reflex. Mortality was 0/4 at 0.9 g/kg and 4/4 at 1.4, 2.0, and 3.0 g/kg, suggesting a very steep dose-response curve. An acute dermal LD_{50} of 1.2 ± 0.1 g/kg was calculated. Necropsy of animals that died from treatment found consolidation of the lungs, watery fluid in the peritoneal cavity, and hyperemia of kidneys.

In an ocular irritation study, 0.1 mL of undiluted benzonitrile was instilled into the right eye of five New Zealand white rabbits; the left eyes served as scoring controls (Industrial Bio-Test 1970). The cornea, iris, and palpebral conjunctiva were graded according to the Draize method after 1 min, after 1, 24, and 72 h, and after 7 days following instillation. Benzonitrile was graded as mildly irritating. Transient iridal and conjunctival irritation (redness grade 2, swelling grade 1, and discharge grade 2) was observed within 1 min after instillation. Irritation peaked at 1 min and subsided over the following 24-72 h.

In a primary skin irritation study, 0.5 mL of undiluted benzonitrile was applied to the shaved abraded or unabraded skin of four New Zealand white rabbits (Industrial Bio-Test 1970). The test sites were covered with gauze and plastic sheeting and remained in place for 24 h. No irritation was found 24- or 72-h post-treatment.

3.2. Nonlethal Toxicity

No nonlethal toxicity studies of benzonitrile in animals were found.

3.3. Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies of animal exposure to benzonitrile were not available.

3.4. Genotoxicity

Genotoxicity studies of animal exposure to benzonitrile were not available.

3.5. Carcinogenicity

Carcinogenicity studies of animal exposure to benzonitrile were not available.

3.6. Summary

Animal toxicity data are limited to acute lethality studies in rats, mice, and rabbits. The data suggest that mice are more sensitive than rats to the effects of benzonitrile administered by inhalation; however, oral lethality data suggest that mice and rats have similar sensitivities. Clinical signs included labored breathing, poor coordination, hypoactivity, salivation, lacrimation, muscular weakness, and dyspnea. No developmental and reproductive, genotoxicity, or carcinogenicity data on benzonitrile were available. Animal data on benzonitrile are summarized in Table 2-3.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism

Hydrogen cyanide is not a metabolite of benzonitrile. The major metabolic pathway for benzonitrile is aromatic hydroxylation to cyanophenols. A small amount of the cyanophenol may then be hydrolyzed to benzoic acid. In rabbits, 50% of an orally administered dose of benzonitrile at 150 mg/kg was conjugated to cyanophenols, and 10% was excreted as benzoic acid. In rats, the in vivo microsomal hydroxylation of deuterated benzonitrile yielded primarily 4hydroxybenzonitrile with 41% retention of deuterium (HSDB 2003). Although not documented, the structure of benzonitrile suggests that formation of an

epoxide intermediate may occur; this may account for the hepatotoxicity observed in mice at necropsy by MacEwen and Vernot (1974).

4.2. Mechanism of Toxicity

No information regarding the mechanism of toxicity of benzonitrile was found. The benzonitriles, ioxynil (4-hydroxy-3,5-diiodobenzonitrile) and bromoxynil (4-hydroxy-3,5-dibromodobenzonitrile), are uncoupling agents (Ellenhorn 1997); however, the mechanism of toxicity of benzonitrile has not been established.

4.3. Concurrent Exposure Issues

Tanii and Hashimoto (1984) studied the acute toxicity and effect of carbon tetrachloride on the metabolism of 20 nitriles, including benzonitrile, in male ddY mice. All of the test nitriles liberated cyanide in vivo and in vitro except for benzonitrile. Groups of 10 male ddY mice were dosed orally with either carbon tetrachloride or olive oil, and then treated with the nitrile 24 h later. Pretreatment with carbon tetrachloride clearly enhanced the toxicity of benzonitrile (100% mortality with carbon tetrachloride vs. no mortality with olive oil). However, pretreatment with carbon tetrachloride either reduced or had little effect on the toxicity of nitriles that metabolically liberate cyanide.

TABLE 2-3 Summary of Animal Toxicity Data on Benzonitrile

Species	Concentration or Dose	Exposure Duration	Effect	Reference
Inhalation Studies				
Rat	190 ppm	4 h	No-observed-effect level	Industrial Bio-Test 1970
Rat	900 ppm	1 h	Irritation of extremities	MacEwen and Vernot 1974
Rat	900 ppm	3 h	Labored breathing, poor coordination	MacEwen and Vernot 1974
Rat	900 ppm	4 h	No mortality (0/6), decreased weight gain	MacEwen and Vernot 1974
Rat	1,900 ppm	4 h	30% mortality (3/10); two died after 2 h, one died on day 6 post-exposure	Industrial Bio-Test 1970
Mouse	700 ppm	4 h	100% mortality (10/10)	MacEwen and Vernot 1974
Mouse	890 ppm	2 h	14% mortality (1/7)	MacEwen and Vernot 1974
Oral Studies				
Rat	0.6 g/kg	Single gavage	No mortality (0/4); hypoactivity, ruffled fur, muscular weakness, prostration, dyspnea, lacrimation	Industrial Bio-Test 1970
Rat	0.9 g/kg	Single gavage	50% mortality (2/4); hypoactivity, ruffled fur, muscular weakness, prostration, dyspnea, lacrimation	Industrial Bio-Test 1970
Rat	1.4 g/kg	Single gavage	75% mortality (3/4); hypoactivity, ruffled fur, muscular weakness, prostration, dyspnea, lacrimation	Industrial Bio-Test 1970
Rat	2.0 g/kg	Single gavage	100% mortality (4/4); hypoactivity, ruffled fur, muscular weakness, prostration, dyspnea, lacrimation	Industrial Bio-Test 1970
Rat	650 mg/kg	Single gavage	LD_{16}	Agaev 1977
Rat	1,500 mg/kg	Single gavage	LD_{50}	Agaev 1977

Rat	2,350 mg/kg	Single gavage	LD_{84}	Agaev 1977
Mouse	650 mg/kg	Single gavage	LD_{16}	Agaev 1977
Mouse	1,400 mg/kg	Single gavage	LD_{50}	Agaev 1977
Mouse	2,350 mg/kg	Single gavage	LD_{84}	Agaev 1977
Dermal Studies				
Rabbit	0.9 g/kg	4 h	0% mortality (0/4); muscular weakness, prostration, salivation, ataxia, tremors, loss of righting reflex	Industrial Bio-Test 1970
Rabbit	1.4 g/kg	24 h	100% mortality (4/4); muscular weakness, prostration, salivation, ataxia, tremors, loss of righting reflex	Industrial Bio-Test 1970
Rabbit	2.0 g/kg	24 h	100% mortality (4/4); muscular weakness, prostration, salivation, ataxia, tremors, loss of righting reflex	Industrial Bio-Test 1970
Rabbit	3.0 g/kg	24 h	100% mortality (4/4); muscular weakness, prostration, salivation, ataxia, tremors, loss of righting reflex	Industrial Bio-Test 1970

4.4. Structure-Activity Relationships

Because the acute toxicity of most nitriles is dependent on their ability to undergo cytochrome P450 mediated hydroxylation, on the carbon alpha to the cyano group (α-carbon), and because the hydroxylation is a radical-based reaction, acute toxicity of nitriles is related to the structural features that influence αcarbon radical stability. Generally, nitriles that are metabolized most quickly or easily at the α-carbon are more toxic than nitriles metabolized more slowly at the α-carbon. Thus, the toxicity pattern, in decreasing order, with regard to the type of α-carbon radical formed following α-hydrogen abstraction is benzylic ≈ 3° > 2° > 1°. The presence of a hydroxy or a substituted or unsubstituted amino group on the α-carbon increases toxicity, and the presence of these moieties at other carbon positions decreases acute toxicity (DeVito 1996). Benzonitrile is not metabolized to cyanide in vivo or in vitro (Tanii and Hashimoto 1984).

4.5. Species Differences

One study of inhalation exposure to benzonitrile suggests that rats are more resistant than mice to its lethal effects (MacEwen and Vernot 1974). Another study of the oral lethality of benzonitrile suggests that mice and rats have similar sensitivities (Agaev 1977), but details of the study methods were lacking.

4.6. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were inadequate to derive an empirical value of n for benzonitrile. To obtain conservative and protective AEGL values in the absence of a chemical-specific scaling exponent, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.

5. RATIONALE FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data on benzonitrile consistent with the definition of AEGL-1 were available.

5.2. Animal Data Relevant to AEGL-1

No animal data on benzonitrile consistent with the definition of AEGL-1 were available.

5.3. Derivation of AEGL-1 Values

Data on benzonitrile are insufficient to derive AEGL-1 values; therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below AEGL-2 values are without adverse effects.

6. RATIONALE FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on benzonitrile consistent with the definition of AEGL-2 were available.

6.2. Animal Data Relevant to AEGL-2

Studies conducted in rats and mice show steep dose-response relationships which makes it difficult to discern thresholds for AEGL-2 and AEGL-3 effects from the sparse data (MacEwen and Vernot 1974). For example, in mice, exposure to benzonitrile at 890 for 2 h ($C^n \times t = 1{,}780$ ppm-h) resulted in 14% (1/7) mortality whereas exposure at 700 ppm for 4 h (2,800 ppm-h) resulted in 100% mortality, with prostration occurring at 2.5 h and 10% (1/10) mortality at 3.5 h. In rats, exposure at 900 ppm for 3 h (2,700 ppm-h) resulted in labored breathing and impaired coordination; however, an additional 30 min of exposure at 900 ppm resulted in prostration, but no deaths in rats.

6.3. Derivation of AEGL-2 Values

Given the steepness of the dose-response relationship and uncertainty in distinguishing the threshold for AEGL-2 and AEGL-3 effects, AEGL-2 values were derived based on a 3-fold reduction of the AEGL-3 values. The AEGL-2 values for benzonitrile are presented in Table 2-4, and the calculations for these AEGL-2 values are presented in Appendix A.

TABLE 2-4 AEGL-2 Values for Benzonitrile

10 min	30 min	1 h	4 h	8 h
11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)

7. RATIONALE FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on benzonitrile consistent with the definition of AEGL-3 were available.

7.2. Animal Data Relevant to AEGL-3

Animal data on benzonitrile consistent with the definition of AEGL-3 are sparse. No deaths were observed in rats exposed to benzonitrile at 190 ppm for 4 h (Industrial Bio-Test 1970) or at 900 ppm for 4 h (MacEwen and Vernot 1974). One of 10 mice died when exposed at 890 ppm for 2 h (MacEwen and Vernot 1974).

7.3. Derivation of AEGL-3 Values

The available data offer two options for deriving the AEGL-3 value. One option is to use the 3.5-h exposure at 900 ppm that resulted in prostration but no deaths in rats as the point of departure. The second option is to base the AEGL-3 values on the 2-h exposure at 890 ppm that resulted in 14% (1/7) mortality in mice. The second option was chosen because it results in lower AEGL-3 values. Because some lethality in mice was observed at 890 ppm, the concentration was adjusted to estimate the lethal threshold. Typically, a 3-fold reduction of the LC_{50} would be used to extrapolate to a lethality threshold. However, an LC_{50} value for benzonitrile is not available. The 2-h study reported 14% mortality, which suggests the test concentration of 890 ppm is below the LC_{50}; therefore, a 2-fold adjustment was applied. The resulting adjusted value of 445 ppm was considered an estimate of the lethality threshold and used as the point of departure for deriving AEGL-3 values.

An interspecies uncertainty factor of 10 was applied. Mortality data reported by Agaev (1977) on benzonitrile suggest that rats and mice have similarly steep dose-response relationships (e.g., similar oral LD_{16}, LD_{50}, and LD_{84}), but the reported lack details about the methods, and no data on other species are available. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals. Application of this value, rather than a default of 10, is supported by the steep concentration-response curve for benzonitrile, which implies little individual variability. For example, the steepness of the curve is evident in mice exposed by inhalation to benzonitrile (10% mortality at 890 ppm for 2 h [ct = 1,780 ppm-h] vs. 100% mortality at 700 ppm for 4 h [ct = 2,800 ppm-h]) (MacEwen and Vernot 1974), in rats exposed orally (no mortality at 0.6 g/kg vs. 100% mortality at 2.0 g/kg) (Industrial Bio-Test 1970), and in rabbits exposed

dermally (no mortality at 0.9 g/kg vs. 100% mortality at 1.4 g/kg) (Industrial Bio-Test 1970). The total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Insufficient data were available to derive an empirical value for n. Therefore, time scaling was performed using default values of n = 3 to extrapolate to shorter durations and n = 1 to extrapolate to longer durations to provide AEGL values that are protective of human health (NRC 2001). AEGL-3 values for benzonitrile are presented in Table 2-5, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for benzonitrile are presented in Table 2-6. AEGL-1 values are not recommended due to insufficient data. AEGL-2 values were estimated by dividing the corresponding AEGL-3 values by 3, and AEGL-3 values were based on lethality data from studies of mice.

8.2. Other Standards and Guidelines

No other standards and guidelines for short-term exposures to benzonitrile were found.

8.3. Data Adequacy and Research Needs

No human data on benzonitrile were found and animal data were sparse. AEGL-1 values were not derived. AEGL-2 and AEGL-3 values were derived; however, it was necessary to apply a modifying factor, partly because of the sparse data base.

TABLE 2-5 AEGL-3 Values for Benzonitrile

10 min	30 min	1 h	4 h	8 h
34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)

TABLE 2-6 AEGL Values for Benzonitrile

Classification	10 min	30 min	1 h	4 h	8 h

AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)
AEGL-3 (lethal)	34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)

[a] Not recommended. Absence of AEGL-1 values does not imply that exposures below AEGL-2 values are without adverse effects.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR BENZONITRILE

Derivation of AEGL-1 Values

The data on benzonitrile were insufficient for deriving AEGL-1 values.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values for benzonitrile, AEGL-3 values were divided by 3 to estimate AEGL-2 values.

10-min AEGL-2:	34 ppm ÷ 3 = 11 ppm
30-min AEGL-2:	24 ppm ÷ 3 = 7.8 ppm
1-h AEGL-2:	19 ppm ÷ 3 = 6.2 ppm
4-h AEGL-2:	7.4 ppm ÷ 3 = 2.5 ppm
8-h AEGL-2:	3.7 ppm ÷ 3 = 1.2 ppm

Derivation of AEGL-3 Values

Key study:	MacEwen, J.D., and E.H. Vernot. 1974. Acute inhalation toxicity of benzonitrile. Pp. 77-80 in Toxic Hazards Research Unit Annual Technical Report: 1974. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.
Toxicity end point:	Estimated 2-h lethality threshold in mice of 445 ppm
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n =1 for extrapolating to longer durations) $(445\ ppm)^3 \times 2\ h = 176{,}242{,}250\ ppm\text{-}h$ $(445\ ppm)^1 \times 2\ h = 890\ ppm\text{-}h$
Uncertainty factors:	10 for interspecies differences

	3 for intraspecies variability
Modifying factor:	None
10-min AEGL-3:	$C^3 \times 0.167$ h = 176,242,250 ppm-h C^3 = 1,055,342,814 ppm C = 1,018 ppm 1,018 ÷ 30 = 34 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 176,242,250 ppm-h C^3 = 352,484,500 ppm C = 706 ppm 706 ÷ 30 = 24 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 176,242,250 ppm-h C^3 = 176,242,250 ppm C = 561 ppm 561 ÷ 30 = 19 ppm
4-h AEGL-3:	$C^1 \times 4$ h = 890 ppm-h C^1 = 223 ppm C = 223 ppm 223 ÷ 30 = 7.4 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 890 ppm-h C^1 = 111 ppm C = 111 ppm 111 ÷ 30 = 3.7 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR BENZONITRILE

Derivation Summary

AEGL-1 VALUES

The data on benzonitrile were insufficient for deriving AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)

Data adequacy: In the absence of specific data on benzonitrile to determine AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3. These values are considered estimates of the threshold for impaired ability to escape and are considered appropriate given the steep concentration-response curve for benzonitrile.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)

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

Test species/Strain/Number: Mouse, CF-1, 7 or 10 males/group

Exposure route/Concentrations/Durations: Inhalation, 700 ppm for 4 h or 890 ppm for 2 h

Effects:
700 ppm for 4 h: 100% mortality (10/10) 890
ppm for 2 h: 14% mortality (1/7)

End point/Concentration/Rationale: Estimated lethality threshold of 445 ppm. Typically, a 3-fold reduction of the LC_{50} would be used to estimate a lethal threshold. However, an LC_{50} value for benzonitrile was not available. The 2-h exposure to benzonitrile at 890 ppm resulted in 14% lethality, which suggests this concentration is below the LC_{50}; therefore, a 2-fold adjustment was applied to estimate a 2-h lethality threshold of 445 ppm.

(Continued)

AEGL-3 VALUES Continued

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10, even though mortality data suggest that rats and mice have similarly steep dose-response relationships (e.g., similar oral LD_{16}, LD_{50}, and LD_{84}) (Agaev 1977), details of the study methods are lacking and no data on other species are available.
Intraspecies: 3, because steep concentration-response curves imply little individual

variability. The steepness of the curve is evident in mice exposed by inhalation to benzonitrile (10% mortality at 890 ppm for 2 h [ct = 1,780 ppm-h] vs. 100% mortality at 700 ppm for 4 h [ct = 2,800 ppm-h]) (MacEwen and Vernot 1974), in rats exposed orally (no mortality at 0.6 g/kg vs. 100% mortality at 2.0 g/kg) (Industrial Bio-Test 1970), and in rabbits exposed dermally (no mortality at 0.9 g/kg vs. 100% mortality at 1.4 g/kg) (Industrial Bio-Test 1970).

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; default values of n = 3 to extrapolate to shorter durations (10 min, 30 min, and 1 h) and n = 1 to extrapolate to longer durations (4 and 8 h) to provide AEGL values that would be protective of human health (NRC 2001).

Data adequacy: Sparse data set.

APPENDIX C

CATEGORY PLOT FOR BENZONITRILE

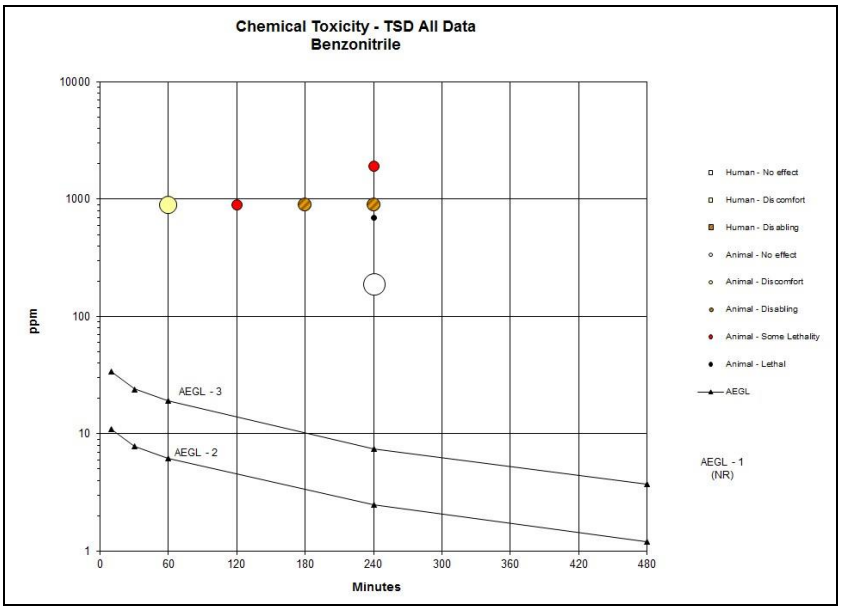

FIGURE C-1 Category plot of toxicity data and AEGL values for benzonitrile.

TABLE C-1 Data Used in Category Plot for Benzonitrile

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				11	10	AEGL	
AEGL-2				7.8	30	AEGL	
AEGL-2				6.2	60	AEGL	
AEGL-2				2.5	240	AEGL	
AEGL-2				1.2	480	AEGL	
AEGL-3				34	10	AEGL	
AEGL-3				24	30	AEGL	
AEGL-3				19	60	AEGL	
AEGL-3				7.4	240	AEGL	
AEGL-3				3.7	480	AEGL	
Industrial Bio-Test 1970	Rat		1	190	240	0	No-observed-effect level
MacEwen and Vernot 1974	Rat		1	900	60	1	Irritation of extremities
MacEwen and Vernot 1974	Rat		1	900	180	2	Labored breathing, poor coordination
MacEwen and Vernot 1974	Rat		1	900	240	2	No mortality (0/6), decreased weight gain
Industrial Bio-Test 1970	Rat		1	1,900	240	SL	30% mortality (3/10)
MacEwen and Vernot 1974	Mouse		1	700	240	3	100% mortality (10/10)
MacEwen and Vernot 1974	Mouse		1	890	120	SL	14% mortality (1/7)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal