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

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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

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

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 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

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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)[1] 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 varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

AEGL-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) chemical-physical 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 no-observed-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

3

Methacrylonitrile[1]

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 predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]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).

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

Methacrylonitrile is a colorless liquid at ambient temperature and pressure. It has an odor similar to bitter almonds and may cause irritation or burning of the eyes and skin. It is metabolized to cyanide in the body and signs of exposure may include weakness, headache, confusion, nausea, vomiting, convulsion, dilated pupils, weak pulse, shallow and gasping breathing, and cyanosis (HSDB 2005). The same signs have been reported in humans exposed to hydrogen cyanide (Blanc et al. 1985).

Transitory irritation was noted by humans exposed to methacrylonitrile at 2 or 14 ppm for 10 min (Pozzani et al. 1968); however, the study was designed to assess sensory end points and did not examine potential systemic effects. Olfactory fatigue was also noted by the subjects exposed at 2 ppm or higher. Animal studies demonstrate a steep dose-response for lethality. For example, no deaths were observed in mice exposed to methacrylonitrile at 19.7 ppm and the LC_{50} is 36 ppm (Pozzani et al. 1968). Similarly in rats, a two-fold increase in concentration resulted in a 33% increase in mortality. Because of the poor warning properties of methacrylonitrile, AEGL-1 values are not recommended for this chemical.

No inhalation data consistent with the definition of AEGL-2 were available. Therefore, the AEGL-2 values for methacrylonitrile were based on a three-fold reduction of the AEGL-3 values. These values are considered estimates of a

threshold for irreversible effects and are considered appropriate given the steep concentration-response curve for methacrylonitrile.

A comparison of the 4-h LC_{50} values for several species suggest that mice and rabbits are more sensitive than rats and guinea pigs (Pozzani et al. 1968). No deaths were observed in mice or rabbits exposed to methacrylonitrile at 19.7 ppm for 4 h, so that concentration was selected as the point of departure for calculating AEGL-3 values. An intraspecies uncertainty factor of 3 was applied because studies of accidental and occupational exposures to hydrogen cyanide (the metabolically-liberated toxicant) indicate that there are individual differences in sensitivity to this chemical but that the differences are not expected to exceed 3-fold (NRC 2002). An interspecies uncertainty factor of 3 was applied because mice and rabbits are the most sensitive species. Thus, the total uncertainty factor is 10. The concentration-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 on methacrylonitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min and 1h) and n = 1 to extrapolate longer durations (8-h) were used to estimate AEGL values that are protective of human health (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with time scaling a 4-h exposure to a 10-min value. AEGL values for methacrylonitrile are presented in Table 3-1.

1. INTRODUCTION

Methacrylonitrile is a colorless liquid at ambient temperature and pressure. It has an odor similar to bitter almonds and may cause irritation or burning of the eyes and skin. It is metabolized to cyanide in the body and signs of exposure may include weakness, headache, confusion, nausea, vomiting, convulsion, dilated pupils, weak pulse, shallow and gasping breathing, and cyanosis (HSDB 2005). The acute toxicity of the organonitriles is due to the metabolic liberation of cyanide; cyanide interrupts cellular respiration by blocking electron transfer from cytochrome oxidase to oxygen (Smith 1996).

Methacrylonitrile is produced by vapor-phase catalytic oxidation of methallylamine, dehydration of methacrylamide, or by vapor-phase ammoxidation of isobutylene with ammonia. Methacrylonitrile is used as a copolymer with styrene and butadiene; as an intermediate in the preparation of acids, amides, amines, esters, and nitriles; and in elastomers, coatings, and plastics (HSDB 2005). It is a highly reactive unsaturated alkyl nitrile that readily polymerizes in the absence of a stabilizer. The commercial product contains hydroquinone monomethyl ether (50 ppm) as a stabilizer (Farooqui and Mumtaz 1991).

The estimated production capacity of methacrylonitrile in the United States in 1977 was 1-10 million pounds (EPA 1987). Approximately 425 workers were exposed annually to methacrylonitrile between 1980 and 1983 (NIOSH

1990). Methacrylonitrile has been identified as a component of mainstream cigarette smoke (3 µg/cigarette).

The physical and chemical properties of methacrylonitrile are presented in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Information concerning human fatalities following inhalation exposure to methacrylonitrile was not available.

2.2. Nonlethal Toxicity

2.2.1. Experimental Studies

Groups of 8-9 volunteers (ages 22-57 years) were exposed to a series of concentrations of methacrylonitrile for 1-min periods (Pozzani et al. 1968). The inhalation trials were conducted in a glass-lined 12.8-m^3 room from which air was exhausted at 2.5-3.2 m^3/min. Concentrations of methacrylonitrile in chamber air were monitored by gas chromatography. The intervals between each exposure period were at least 45 min. The subjects inhaled the same concentrations twice in the following sequence: 24, 14, 0, 7, 14, 24, 7, 2, 0, and 2 ppm. The subjects were unaware of the concentrations they were inhaling. Olfactory fatigue was reported by most subjects at concentrations of 7 and 14 ppm and by two subjects at 24 ppm. Most subjects exposed at 24 and 14 ppm detected an odor initially, but only half of the subjects could detect an odor at 7 ppm. None of the subjects could differentiate between the 0- and 2-ppm exposures. Results of this study are summarized in Table 3-3.

TABLE 3-1 AEGL Values for Methacrylonitrile

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)	1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)	Three-fold reduction of AEGL-3
AEGL-3 (lethal)	3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)	No effect level for lethality in mice and rabbits exposed to 19.7 ppm for 4 h (Pozzani et al. 1968)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 3-2 Physical and Chemical Properties of Methacrylonitrile

Parameter	Data	Reference
Synonyms	2-Methyl-2-propenenitile; methyl acrylonitrile; isoprene cyanide; isopropenylcarbonitrile; 2-cyano-1-propene; 2-cyanopropene; MAN; MeAN	Cohrssen 2001
CAS registry no.	126-98-7	Cohrssen 2001
Chemical formula	C_4H_5N	Cohrssen 2001
Molecular weight	67.09	Cohrssen 2001
Physical state	Colorless liquid	Farooqui and Mumtaz 1991
Melting point	-35.8°C	Farooqui and Mumtaz 1991
Boiling point	90.3°C	Farooqui and Mumtaz 1991
Flash point	13°C	Farooqui and Mumtaz 1991
Specific gravity	0.800 at 20°C	Farooqui and Mumtaz 1991
Solubility	2.5% in water; miscible with acetone, octane, and toluene	Farooqui and Mumtaz 1991; Hartung 1994
Vapor density	2.31 (air = 1)	Hartung 1994
Vapor pressure	65 mm Hg at 25°C	Farooqui and Mumtaz 1991
Conversion factors in air	1 ppm = 2.74 mg/m^3 1 mg/m^3 = 0.365 ppm	Hartung 1994

TABLE 3-3 Human Response to One-Minute Inhalation Exposures to Methacrylonitrile

	24 ppm	14 ppm	7 ppm	2 ppm	0 ppm
Number of subject inhalations	18	17	17	18	18
Incidence of odor detection, %	89	88	47	0	0
Incidence of throat irritation, %	22	0	0	0	0
Incidence of eye irritation, %	17	0	0	0	0
Incidence of nose irritation, %	6	0	0	0	0

Source: Pozzani et al. 1968. Reprinted with permission; copyright 1968, *Journal of Occupational and Environmental Hygiene*.

Two additional experiments were performed in a similar manner (Pozzani et al. 1968). Nine subjects were exposed to methacrylonitrile at 2 ppm for 10 min in one study, and seven subjects at 14 ppm for 10 min in the other study. Odor and irritation data were recorded at 1-min intervals during the exposures. These experiments indicate olfactory fatigue and irritation of a "transitory" nature. Results are summarized in Tables 3-4 and 3-5. Amoore and Hautala (1983) reported an odor threshold of 7 ppm for methacrylonitrile.

TABLE 3-4 Effects in Nine Subjects from Exposure to Methacrylonitrile at 2 ppm for 10 Minutes

Time (min)	Odor Detection	Eye Irritation	Tears	Nose Irritation	Throat Irritation
1	4	2	1	0	0
2	4	1	0	0	1
3	3	0	0	0	1
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	2	0
8	0	1	0	1	0
9	0	0	0	0	0
10	0	0	0	0	0

Source: Pozzani et al. 1968. Reprinted with permission; copyright 1968, *Journal of Occupational and Environmental Hygiene*.

TABLE 3-5 Effects in Seven Exposed to Methacrylonitrile at 14 ppm for 10 Minutes

Time (min)	Odor Detection	Eye Irritation	Tears	Nose Irritation	Throat Irritation
1	7	0	0	0	1
2	6	1	0	0	0
3	1	1	0	0	0
4	0	1	0	0	0
5	0	1	0	0	0
6	0	1	0	0	1
7	0	1	0	1	0
8	0	1	0	1	0
9	0	1	0	1	0
10	0	0	1	0	0

Source: Pozzani et al. 1968. Reprinted with permission; copyright 1968, *Journal of Occupational and Environmental Hygiene*.

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

Carcinogenicity studies of human exposure to methacrylonitrile were not available.

2.6. Summary

Only one human exposure study of methacrylonitrile was available. Approximately 6-22% of subjects exposed methacrylonitrile at 24 ppm for 1 min experienced nasal, throat, or ocular irritation. Irritation was also noted by a few subjects during the course of 10-min exposures at 2 or 14 ppm. No humans studies of the developmental and reproductive toxicity, genotoxicity, or carcinogenicity of methacrylonitrile were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

A group of four mature male rats (strain not specified) were exposed to a concentrated atmosphere of methacrylonitrile for up to 25 min (Younger Labs 1969). Vapors were produced by passing a stream of air through 106.0 g of methacrylonitrile in a 350-mL Erlenmeyer flask. Vapors from the flask passed into a 1-L bottle to remove droplets. The vapor then passed into the 35-L metal chamber. Air flow through the chamber was 4 L/min, the average chamber temperature was 74°F, and the average humidity was 58%. All animals died within 25 min after the start of exposure. Labored breathing, pawing at the face and nose, cyanosis, and collapse were observed during exposure. At necropsy, pulmonary and hepatic hyperemia, dilated coronary arteries, and aortic aneurysms were observed.

Groups of 10 young adult male ChR-CD rats were exposed to methacrylonitrile (most concentrations not reported, highest concentration was 625 ppm) for 4 h and observed for up to 14 days (DuPont 1968a). The test sample was uniformly metered by a syringe drive into a stainless steel T-tube whose internal temperature was above the boiling point of methacrylonitrile. A metered stream of air passing through the T-tube carried the vapors to the exposure chamber where the atmosphere was analyzed every half-hour by gas chromatography. Irregular respiration and hyperemia, followed by pale ears, unresponsiveness, tremors, convulsions, face-pawing, and lacrimation (at 625 ppm only), were

observed during exposure. Mild and erratic weight loss was initially observed, but was followed by normal weight gain after the exposure period. One animal died 1.5 h after the start of exposure and another died 15 min post-exposure. An LC_{50} of 440 ppm (380-510 ppm) was calculated. No other experimental details were reported.

Pozzani et al. (1968) exposed groups of six female Harlan-Wistar rats to methacrylonitrile at approximately 85,500 ppm (essentially saturated vapor) for 14, 7.5, 3.75, 1.88, 0.93, or 0.47 min. Mortality was 6/6, 6/6, 6/6, 1/6, 0/6, and 0/6, respectively. Deaths occurred during the 14-min exposure, within 1.5 h after the 7.5-min exposure, and within 24 h following the 3.75- and 1.88-min exposures. Prostration and loss of consciousness always preceded death, but also appeared in many survivors exposed for 1.88 min. The rats exposed for 0.93 min appeared normal during the exposure period, but showed prostration 0.5 h after the exposure, and remained in this condition for 2 h. Rats exposed for 0.47 min showed no clinical signs during or after exposure. No convulsions were observed in this study, and survivors gained weight normally during the 14-day observation period.

Pozzani et al. (1968) also exposed groups of six male and six female Harlan-Wistar rats to unspecified concentrations of methacrylonitrile for 4 h. Concentrations of methacrylonitrile in the inhalation chambers were determined by gas chromatography. Death was preceded by loss of consciousness and tonic-clonic convulsions. At necropsy, no discernible cause of death was found in animals that died, and no gross treatment-related effects were observed in animals surviving the 14-day observation period. Calculated LC_{50} values (328-700 ppm) are presented in Table 3-6.

In a repeated exposure, range-finding study, groups of six male and six female Harlan-Wistar rats were exposed to methacrylonitrile at 0, 20, 50, or 110 ppm for 7 h/day, 5 days/week for a total of 9 days (Pozzani et al. 1968). Concentrations of methacrylonitrile in the inhalation chambers were determined by gas chromatography. Two male rats in the 110-ppm group died during the first day; no convulsions were noted in these animals. No other rats in any exposure group exhibited clinical signs during the 9-day exposure period. No gross lesions were observed in the decedents or survivors, and survivors had normal body weight gains and normal liver and kidney weights at necropsy.

In an oral toxicity study, a 1% (w/v) solution of methacrylonitrile in water was intragastrically administered to groups of five non-fasted male Harlan-Wistar albino rats (Pozzani et al. 1968). An LD_{50} value of 0.24 g/kg was calculated (0.16-0.36 g/kg). Four of five rats administered 0.4 g/kg died on the day of dosing, and the fifth rat died overnight. Doses of 0.1 and 0.2 g/kg resulted in mortality of one of five rats in each group; deaths occurred overnight after dosing. In animals that died, prostration and convulsions were noted within 1.5 h after dosing. Survivors showed the same clinical signs, but to a lesser degree, and gained weight normally over the 14-day observation period.

3.1.2. Mice

Pozzani et al. (1968) exposed groups of six male A/J mice to unspecified concentrations of methacrylonitrile for 4 h. Concentrations of methacrylonitrile in the inhalation chambers were determined by gas chromatography. Death was preceded by loss of consciousness and tonic-clonic convulsions. At necropsy, no discernible cause of death was noted in animals that died, and no gross treatment-related effects were noted in animals surviving the 14-day observation period. A 4-h LC_{50} of 36 ppm was calculated (see Table 3-6).

3.1.3. Guinea Pigs

Pozzani et al. (1968) exposed groups of six male albino guinea pigs to unspecified concentrations of methacrylonitrile for 4 h. Concentrations of methacrylonitrile in the inhalation chambers were determined by gas chromatography. Death was preceded by loss of consciousness and tonic-clonic convulsions. At necropsy, no discernible cause of death was noted in animals that died, and no gross treatment-related effects were noted in animals surviving the 14-day observation period. A 4-h LC_{50} of 88 ppm was calculated (see Table 3-6).

3.1.4. Rabbits

Pozzani et al. (1968) exposed groups of four male albino rabbits to unspecified concentrations of methacrylonitrile for 4 h. Concentrations of methacrylonitrile in the inhalation chambers were determined by gas chromatography. Death was preceded by loss of consciousness and tonic-clonic convulsions. At necropsy, no discernible cause of death was noted in animals that died, and no gross treatment-related effects were noted in animals surviving the 14-day observation period. A 4-h LC_{50} of 37 ppm was calculated (see Table 3-6).

In a dermal toxicity study, undiluted methacrylonitrile was administered to groups of four male albino New Zealand white rabbits (Pozzani et al. 1968). The compound was kept in covered contact with clipped trunks for 24 h. An LD_{50} value of 0.32 mL/kg was calculated (0.19-0.51 mL/kg). All four rabbits treated with 0.5 mL/kg died within 3.45 h and were gasping or convulsing before to death. One rabbit administered 0.25 mL/kg gasped, convulsed, and died 2.66 h into the exposure. The three surviving rabbits treated with 0.25 mL/kg showed no clinical signs and gained weight normally over the 14-day observation period.

3.1.5. Dogs

Pozzani et al. (1968) exposed one female mongrel dog to methacrylonitrile at 106 ppm for 3 h. The concentration of methacrylonitrile in the inhalation chamber was determined by gas chromatography. Convulsions were observed

followed by death in 3 h. The investigators also exposed one female mongrel dog to methacrylonitrile at 106 ppm for 7 h. Vomiting, diarrhea, and convulsions were observed, and the dog died in 7 h. Finally, a female cocker spaniel was exposed to methacrylonitrile at 52.5 ppm for 7 h. Vomiting, convulsions, and loss of consciousness were observed within 7 h, and the dog died overnight. At necropsy, no discernible cause of death was apparent in any of the dogs.

In another study, DuPont (1968b) exposed young adult female beagles (number not specified) to methacrylonitrile at 40 or 87.5 ppm for 7 h. The test sample was uniformly metered by a syringe drive into a stainless steel T-tube whose internal temperature was above the boiling point of methacrylonitrile. A metered stream of air passing through the T-tube carried the vapors to the exposure chamber where the atmosphere was analyzed every half-hour by gas chromatography. No deaths or clinical signs were observed at 40 ppm. Vomiting, convulsions, unconsciousness, and irregular breathing were observed in dogs exposed at 87.5 ppm. Death occurred 5 h and 5 min post-exposure. No additional details were available.

3.2. Nonlethal Toxicity

No deaths or clinical signs were observed in guinea pigs exposed to methacrylonitrile at 52.5 ppm, in rabbits exposed at 19.7 ppm, or in mice exposed at 19.7 ppm for 4 h (Pozzani et al. 1968). No further details were available. Data from this study are summarized in Table 3-6.

TABLE 3-6 Effects in Animals Exposed to Methacrylonitrile for 4 Hours

Species (weight range)	Sex	LC_{50} (Concentrations that Caused Death) (ppm)	Comments
Rat (213-317 g)	Females	700 (213-2,327)	Loss of consciousness within 3 h; no deaths at 176 ppm.
Rat (95-72 g)	Females	496 (250-993)	Loss of consciousness within 3 h; no deaths at 176 ppm.
Rat (344-510 g)	Males	328 (208-516)	Loss of consciousness within 3 h; one death with convulsions at 176 ppm.
Rat (123-207 g)	Males	328 (231-594)	Loss of consciousness within 3 h; no deaths at 176 ppm.
Guinea Pig (585-1,035 g)	Males	88 (62-124)	No symptoms at 52.5 ppm.
Rabbit (2,356-4,290 g)	Males	37 (23-57)	No symptoms at 19.7 ppm.
Mouse (23-33 g)	Males	36 (25-43)	No symptoms at 19.7 ppm.

Source: Adapted from Pozzani et al. 1968.

3.3. Repeated-Dose Studies

3.3.1. Rats

Groups of 12 male and 12 female Harlan-Wistar rats were exposed to methacrylonitrile vapor at 0, 19.3, 52.6, or 109.3 ppm (measured by gas chromatography) for 7 h/day, 5 days/week for 91 days (Pozzani et al. 1968). Seven males died during the first day of exposure at 109.3 ppm and one male died on day 2 of exposure at 52.6 ppm. Loss of consciousness with no convulsions preceded death. Transient, decreased body-weight gain was observed at day 5 in mid-concentration females and high-concentration males and females. Relative liver weights were increased at the end of the study in mid-concentration males (10% increase) and high-concentration males (28% increase) and females (21% increase) compared with controls. However, no treatment-related effects were found in measurements of blood urea nitrogen, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), or alkaline phosphatase activities, and no correlative histopathology was observed. No other treatment-related effects were reported.

Both lethal and nonlethal effects were reported in a preliminary repeated-dose, range-finding study (Pozzani et al. 1968). This information is discussed in Section 3.1.1.

In a 13-week range-finding study, groups of 20 male and 20 female F344/N rats were administered methacrylonitrile at 0, 7.5, 15, 30, 60, or 120 mg/kg in deionized water by gavage 5 days/week (NTP 2000). Ten males and 10 females from each group were schedule to be killed on day 32 for interim evaluation. In this 32-day evaluation group, nine males exposed at 120 mg/kg died within the first week, but all high-dose female rats survived the 32-day period. Males in the 60-mg/kg group had decreased mean body weights (8% decrease compared with controls; $p \leq 0.01$) at the end of the 32-day period. The one surviving high-dose male also showed a decreased body weight (10% decrease compared with controls). Clinical findings at the 32-day evaluation included lethargy, lacrimation, ataxia, tremors, convulsions, and abnormal breathing in all treatment groups in a dose-related manner; these effects appeared within minutes of dosing and resolved several hours after dosing. Minimal, normocytic, normochromic anemia was found in males and females, as evidenced by dose-related decreases in hematocrit, hemoglobin concentration, and erythrocyte counts. (This anemia resolved in the 13-week evaluation group.) Decreased ($p \leq 0.01$) kidney and thymus weights were noted in males in the 60-mg/kg group at the 32-day evaluation. In females, stomach weights were increased ($p \leq 0.01$) in the 60- and 120-mg/kg groups, thymus weights were decreased ($p \leq 0.01$) in the 120-mg/kg group, and liver weights were increased ($p \leq 0.01$) in the 120-mg/kg group on day 32. Male and female rats in the 60-mg/kg groups and females in the 120-mg/kg groups showed increased ($p \leq 0.05$ or $p \leq 01$) incidences of nasal olfactory epithelial metaplasia on day 32. In females exposed at 60 and 120 mg/kg, an increased ($p \leq 0.05$) incidence of olfactory epithelial necrosis was also noted.

Among animals in the 13-week evaluation group, all males and one female in the 120-mg/kg group and two males in the 60-mg/kg group died during the first week of the study (NTP 2000). Males in the 60-mg/kg group and females in the 120-mg/kg group had lower ($p \leq 0.01$; 90% for males and 93% for females relative to controls) final body weights. Clinical findings were dose-dependent and included lethargy, lacrimation, ataxia, tremors, convulsions, and abnormal breathing; these effects appeared within minutes of dosing and resolved several hours after dosing. Increased ($p \leq 0.01$) liver and stomach weights were found in males in the 60-mg/kg group. In females, stomach weights were increased ($p \leq 0.01$) in the 60- and 120-mg/kg groups and thymus weights were decreased ($p \leq 0.01$) in the 120-mg/kg group. Males and females in the 60-mg/kg group and females in the 120-mg/kg group had increased incidences of nasal olfactory epithelial metaplasia.

3.3.2. Mice

In a 13-week range-finding study, groups of 20 male and 20 female $B6C3F_1$ mice were administered methacrylonitrile at 0, 0.75, 1.5, 3, 6, or 12 mg/kg in deionized water by gavage 5 days/week (NTP 2000). Ten male and 10 females from each group were scheduled to be killed on day 32 for interim evaluation. One male and one female exposed at 12 mg/kg died during week 3. There were no treatment-related differences in final mean body weight or body weight gain. Clinical findings including lethargy, ataxia, tremors, convulsions, and abnormal breathing in all treatment groups in a dose-related manner; these effects appeared within minutes of dosing and resolved 2-3 h after dosing. In the 32-day evaluation group, stomach weights of males treated with methacrylonitrile at 3 mg/kg or greater were increased (11-15%) and thymus weights of males in the 12-mg/kg group were decreased (23%) compared with controls. In animals in the 13-week evaluation group, stomach weights were increased (15%) only in the 12-mg/kg males. No treatment-related histopathology was found.

3.3.3. Dogs

In a repeated exposure, range-finding study, one female beagle (6.3 kg) was exposed to methacrylonitrile at 20 ppm for 7 h/day, 5 days/week for a total of 8 days (Pozzani et al. 1968). The concentration of methacrylonitrile in the inhalation chamber was determined by gas chromatography. The dog vomited on day 1 and experienced 20% weight loss by the eighth day of exposure. No other clinical signs were observed and no gross or microscopic lesions were found at necropsy.

Groups of three male beagles were exposed to methacrylonitrile vapor at 0, 3.2, 8.8, or 13.5 ppm (measured by gas chromatography) for 7 h/day, 5 days/week for 90 days (Pozzani et al. 1968). Convulsions and loss of motor con-

trol of the hind-limbs were observed in two dogs exposed at 13.5 ppm starting at day 39 of exposure. At necropsy, one of these dogs had histopathologic brain lesions, including demyelination of the corpus callosum. One dog exposed at 8.8 ppm exhibited marked, although transient, elevations in SGOT and SGPT values after 21 days of exposure, but the values were not reported. No other treatment-related effects were noted.

3.4. Developmental and Reproductive Toxicity

Saillenfait et al. (1993) exposed groups of 22 or 23 pregnant Sprague-Dawley rats to nominal concentrations of methacrylonitrile at 0, 12, 25, 50, or 100 ppm (analytic concentrations were 12 ± 0.6, 25 ± 1.3, 52 ± 2.1, or 106 ± 5.1 ppm, respectively) for 6 h/day on days 6-20 of gestation. The exposure was conducted in a 200-L stainless steel dynamic flow inhalation chamber. The chamber temperature was set at 23 ± 2°C and the relative humidity at 50 ± 5%. Vapors were generated by bubbling additional air through a flask containing the test compound and were mixed with filtered room air to achieve the desired concentration. The nominal concentrations were calculated from the ratio of the amount of test compound vaporized to the total chamber air flow during the exposure period. Analytic concentrations were determined once every hour during each 6-h exposure period using gas-liquid chromatography. No maternal deaths or other maternal effects were observed. There were no statistically significant, treatment-related effects on pregnancy rate, average number of implantations or live fetuses, fetal sex ratio, or incidences of nonsurviving implants or resorptions per litter across groups. At 100 ppm, there were non-statistically significant increases in the incidence of non-surviving implants and resorptions; the increases were influenced by the complete loss of one litter. Decreases in fetal weights per litter were observed in male (5.6%) and female (4.8%) fetuses. No treatment-related fetal malformations were observed.

Groups of 26 pregnant Sprague-Dawley rats were administered methacrylonitrile at 0, 5, 25, or 50 mg/kg/day in distilled water by gavage on gestation days 6-15 (George et al. 1996). Rats were killed on gestation day 20. There were no treatment-related maternal clinical signs, mortality, body weight effects, or effects on food or water consumption. Absolute and relative maternal liver weights were increased by 5-8% ($p < 0.05$) at necropsy in the mid- and high-dose groups; the investigators interpreted these changes as indicative of hepatic enzyme induction rather than a toxic response. There were no treatment-related effects on post-implantation loss, mean fetal body weight per litter, or morphologic development.

Groups of 26 pregnant New Zealand white rabbits were administered methacrylonitrile at 0, 1, 3, or 5 mg/kg/day in distilled water by gavage on gestation days 6-19 (George et al. 1996). Rabbits were sacrificed on gestation day 30. There were no treatment-related maternal clinical signs, mortality, body weight effects, effects on food or water consumption, or liver weight effects. There were no treatment-related effects on post-implantation loss, mean fetal

body weight per litter, or morphologic development. A decrease in the percentage of male fetuses per litter was noted in the high-dose group (40% vs 61% in control group; $p < 0.05$); however, there was no effect on total live litter size. Thus, this observation was considered to be of questionable toxicologic significance.

Groups of 4-5 pregnant Sprague-Dawley rats were administered methacrylonitrile at 150 mg/kg in olive oil by gavage on gestation day 10 (Saillenfait and Sabate 2000), and the dams were killed on gestation day 12. Clinical signs of toxicity and weight loss were observed in the dams. Misdirected allantois and trunk and caudal extremity were observed in 12.1% of the embryos (four of five litters affected) compared with 0% in controls. No alterations in embryo viability were observed.

3.5. Genotoxicity

Negative results were obtained in a sex-linked recessive lethal assay using *Drosophila melanogaster* larvae fed methacrylonitrile at 6,000 ppm (Zimmering et al. 1989). Negative results were also obtained in tests of reverse mutations both with and without metabolic activation (S-9 fraction) in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 exposed to methacrylonitrile at 100-10,000 μg/plate (Zeiger et al. 1987). No increase in the frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of male mice treated with methacrylonitrile at 6.25-25 mg/kg (Shelby et al. 1993).

3.6. Carcinogenicity

In a carcinogenicity study, groups of 50 male and 50 female F344/N rats were administered methacrylonitrile at 0, 3, 10, or 30 mg/kg in deionized water by gavage 5 days/week for 2 years (NTP 2001; Nyska and Ghanayem 2003). There were no treatment-related effects on survival or clinical signs. The investigators reported that mean body weights of the 30-mg/kg group were decreased compared with vehicle controls after week 21 for males (91-96% of control) and after week 37 for females (92-95% of control). No treatment-related neoplasms were observed. There was an increased incidence of nasal olfactory epithelial atrophy in high-dose males (0/50, 0/50, 0/49, and 48/50 for control, low-, mid-, and high-dose groups, respectively) and high-dose females (0/50, 0/50, 1/50, and 19/50 for control, low-, mid-, and high-dose groups, respectively). There was also an increased incidence of nasal olfactory epithelial metaplasia in high-dose males (0/50, 0/50, 0/49, and 47/50 for control, low-, mid-, and high-dose groups, respectively) and high-dose females (0/50, 0/50, 0/50, and 47/50 for control, low-, mid-, and high-dose groups, respectively). Increased incidences of cytoplasmic vacuolization occurred in the liver of males (14/50, 18/50, 23/50, and 28/49 for control, low-, mid-, and high-dose groups, respectively) and females (7/50, 14/49, 17/48, and 30/50 for control, low-, mid-, and high-dose groups,

respectively). NTP concluded that there was no evidence of carcinogenic activity in male or female F344/N rats treated with methacrylonitrile.

In a carcinogenicity study, groups of 50 male and 50 female $B6C3F_1$ mice were exposed to methacrylonitrile at 0, 1.5, 3, or 6 mg/kg in deionized water by gavage 5 days/week for 2 years (NTP 2001; Nyska and Ghanayem 2003). There were no treatment-related effects on survival, body weight, or clinical signs. There were no treatment-related increases in the incidences of neoplasms. NTP concluded that there was no evidence of carcinogenic activity in male or female $B6C3F_1$ mice treated with methacrylonitrile.

3.7. Summary

Animal toxicity data on methacrylonitrile are available for many species; however, experimental details are generally limited. Rats, mice, guinea pigs, rabbits, and dogs exposed to methacrylonitrile exhibited signs consistent with cyanide poisoning. Data suggest that rats are more resistant to the effect of methacrylonitrile than dogs, guinea pigs, rabbits, and mice. Four-hour LC_{50} values of 328-700 ppm have been reported for rats (DuPont 1968a; Pozzani et al. 1968), whereas 4-h LC_{50} values of 88, 37, and 36 ppm have been reported for guinea pigs, rabbits, and mice, respectively (Pozzani et al. 1968). Developmental toxicity studies in rats (Saillenfait et al. 1993; George et al. 1996) suggested concentration-related decreases in fetal weights in rats exposed via inhalation, but no frank effects. Genotoxicity data were negative, and there was no evidence of carcinogenicity in male or female F344/N rats or $B6C3F_1$ mice. Animal inhalation toxicity data on methacrylonitrile are summarized in Table 3-7.

4. SPECIAL CONSIDERATIONS

4.1. Absorption, Distribution, Metabolism, and Excretion

Methacrylonitrile is readily absorbed through the respiratory and gastrointestinal tracts and through the skin (Pozzani et al. 1968; Tanii and Hashimoto 1986; Farooqui and Mumtaz 1991; Ghanayem et al. 1992).

Ghanayem et al. (1992) described the time-course of tissue concentrations following administration of [2-^{14}C]-methacrylonitrile at 11.5, 58, or 115 mg/kg in water by gavage to male F344 rats. Dose-dependent concentrations of methacrylonitrile-derived radioactive label were highest in the adrenal glands, intestine, kidneys, liver, thymus, and urinary bladder. With the exception of the brain, the tissue/blood ratio of radioactive label concentrations in rats treated with 58 mg/kg was greater than 1.0 at 8-, 24-, and 72-h post-dosing. The concentration of label was consistently higher in the 115-mg/kg group and declined as a function of time to reach a minimal concentration at 72 h. Less than 3% of the administered dose remained in tissues 72-h post-dosing.

TABLE 3-7 Summary of Inhalation Toxicity Data on Methacrylonitrile in Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Single Exposure Studies				
Rat	85,500	0.47 min	No mortality (0/6)	Pozzani et al. 1968
Rat	85,500	0.93 min	No mortality (0/6)	Pozzani et al. 1968
Rat	85,500	1.88 min	17% mortality (1/6)	Pozzani et al. 1968
Rat	85,500	3.75 min	100% mortality (6/6)	Pozzani et al. 1968
Rat	85,500	7.5 min	100% mortality (6/6)	Pozzani et al. 1968
Rat	85,500	14 min	100% mortality (6/6)	Pozzani et al. 1968
Rat	85,500	25 min	100% mortality (4/4)	Younger Labs 1969
Rat	176	4 h	Loss of consciousness within 3 h; 1 male died with convulsions; no deaths in females	Pozzani et al. 1968
Rat	328	4 h	LC_{50}	Pozzani et al. 1968
Rat	440	4 h	LC_{50}	DuPont 1968a
Rat	496	4 h	LC_{50}	Pozzani et al. 1968
Rat	700	4 h	LC_{50}	Pozzani et al. 1968
Mouse	19.7	4 h	No mortality or symptoms	Pozzani et al. 1968
Mouse	36	4 h	LC_{50}	Pozzani et al. 1968
Rabbit	19.7	4 h	No mortality or symptoms	Pozzani et al. 1968
Rabbit	37	4 h	LC_{50}	Pozzani et al. 1968
Guinea pig	52.5	4 h	No mortality	Pozzani et al. 1968
Guinea pig	88	4 h	LC_{50}	Pozzani et al. 1968
Dog	40	7 h	No mortality	DuPont 1968b
Dog	52.5	7 h	100% mortality (1/1)	Pozzani et al. 1968
Dog	87.5	7 h	100% mortality	DuPont 1968b
Dog	106	7 h	100% mortality (2/2)	Pozzani et al. 1968

Rat	20	7 h/d, 5 d/wk, 9 d	No effects	Pozzani et al. 1968
Rat	50	7 h/d, 5 d/wk, 9 d	No effects	Pozzani et al. 1968
Rat	110	7 h/d, 5 d/wk, 9 d	33% mortality (2/6 males on day 1; no deaths in females)	Pozzani et al. 1968
Rat	19.3	7 h/d, 5 d/wk, 91 d	NOEL	Pozzani et al. 1968
Rat	52.6	7 h/d, 5 d/wk, 91 d	Day 1: no effects Day 2: 8% mortality (1/12 males) Day 5: body weight loss Day 91: increased liver weight	Pozzani et al. 1968
Rat	109.3	7 h/d, 5 d/wk, 91 d	Day 1: 58% mortality (7/12 males; no deaths in females)	Pozzani et al. 1968
Dog	20	7 h/d, 5 d/wk, 8 d	Day 1: vomiting Day 8: 20% body weight loss	Pozzani et al. 1968
Dog	3.2	7 h/d, 5 d/wk, 90 d	NOEL	Pozzani et al. 1968
Dog	8.8	7 h/d, 5 d/wk, 90 d	Days 1-20: no effects Day 21: increased SGOT and SGPT	Pozzani et al. 1968
Dog	13.5	7 h/d, 5 d/wk, 90 d	Days 1-38: no effects Day 39: convulsions; loss of hind-limb motor control	Pozzani et al. 1968
Developmental and Reproductive Study				
Rat	12	6 h/d, gestation days 6-20	Maternal: NOEL Fetal: NOEL	Saillenfait et al. 1993
	25		Maternal: NOEL Fetal: 5% decrease in body weight	
	50		Maternal: NOEL Fetal: 10% decrease in body weight	
	100		Maternal: NOEL Fetal: 13-15% decrease in body weight	

Abbreviations: LC_{50}, lethal concentration, 50% lethality; NOEL, no effect level; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Male Sprague-Dawley rats administered a single dose of [2-^{14}C]-methacrylonitrile at 100 mg/kg in safflower oil retained label in erythrocytes for more than 5 days after dosing (Cavazos et al. 1989). Peak concentration in erythrocytes occurred 3 h post-dosing. Approximately 70% of the label in the erythrocytes was localized in the protein fraction (membrane proteins and globin). Blood and urinary thiocyanate concentrations in these rats increased following the administration [2-^{14}C]-methacrylonitrile. The plasma thiocyanate concentration was increased from 26.3 µmol/L within 1 h to 87 µmol/L within 6 h. At day 5 post-dosing, the total urinary excretion of thiocyanate was 12% of the administered dose, whereas total urinary excretion of radioactivity was 43%, suggesting the presence of metabolites other than thiocyanate.

Methacrylonitrile is metabolized to an epoxide intermediate, 1-cyano-1-methoxyloxirane (Ghanayem et al. 1992). Studies in transgenic mice suggest that cytochrome P4502E1 (CYP2E1) is the primary enzyme responsible for the oxidative metabolism of methacrylonitrile; however, other cytochrome P450 enzymes are likely involved (Ghanayem et al. 1999). Although 1-cyano-1-methoxyloxirane was not identified in vivo, evidence based on the identity of methacrylonitrile metabolites in bile, urine, and expired air supports its formation in rats and mice. The 1-cyano-1-methoxyloxirane interacts with reduced glutathione, presumably via glutathione transferases, resulting in the formation of 1-(S-glutathionyl)-2-propanone, which was identified in the bile of male F344 rats administered methacrylonitrile by gavage (Ghanayem and Burka, 1996). Catabolism of the 1-(S-glutathionyl)-2-propanone results in the formation of N-acetyl-S-(2-hydroxypropyl)-L-cysteine, identified in the urine of rats administered methacrylonitrile (Ghanayem et al. 1992). Metabolism of 1-cyano-1-methoxyloxirane is considered the main pathway to cyanide release; cyanide is then converted to thiocyanate by rhodenese and excreted in the urine. Approximately 13% of the administered dose was recovered as thiocyanate in the plasma and urine of rats administered methacrylonitrile (Cavazos et al. 1989; Farooqui et al. 1992).

The [^{14}C]-acetone identified by Ghanayem et al. (1992) in rats administered [2-^{14}C]-methacrylonitrile may be the result of a nucleophilic attack of glutathione on the sulfur atom of the 1-(S-glutathionyl)-2-propanone intermediate. The acetone may also be the result of reductive metabolism of 1-cyano-1-methoxyloxirane.

Another metabolic pathway is direct conjugation of methacrylonitrile with reduced glutathione, resulting in the formation of 1-(S-glutathionyl)-2-cyclopropane, which has been identified in bile of rats administered methacrylonitrile by gavage (Ghanayem and Burka 1996). Degradation of 1-(S-glutathionyl)-2-cyclopropane yields N-acetyl-S-(2-cyanopropyl)-L-cystiene, which was identified in the urine of methacrylonitrile treated rats (Ghanayem et al. 1992).

Demby et al. (1993) showed that methacrylonitrile elimination in F344 rats occurs mainly in expired air and urine. Male F344 rats intravenously administered [2-^{14}C]-methacrylonitrile in saline at doses of 29, 58, or 116 mg/kg elim-

inated most of the chemical within 5 h. Within 24 h, 36% was exhaled as unchanged methacrylonitrile, 26% was exhaled as carbon dioxide, 17% was exhaled as acetone, and 16% was excreted in the urine as metabolites. In male F344 rats administered 58 mg/kg [2-^{14}C]-methacrylonitrile by gavage in water, 18% was exhaled as unchanged methacrylonitrile, 39% was exhaled as carbon dioxide, 13% was exhaled as acetone, and 22% was eliminated as urinary metabolites within 24 h (Demby et al. 1993).

Methacrylonitrile elimination by rats is dependent on dose, strain, and vehicle (Ghanayem et al. 1992). Male F344 rats were administered [2-^{14}C]-methacrylonitrile at 1.15, 11.5, or 115 mg/kg in water by gavage. The primary elimination route was in expired air as carbon dioxide. Rats administered 1.15 or 11.5 mg/kg exhaled 60-70% of the dose as carbon dioxide, whereas rats administered 115 mg/kg exhaled 25% of the dose as carbon dioxide and 40% as volatile organics (parent methacrylonitrile and acetone) within 72 h. Data suggest that methacrylonitrile metabolism was saturated at the highest dose. Urinary excretion accounted for 20-30% of the dose eliminated within 72 h. In another study, Cavazos et al. (1989) administered a single dose of methacrylonitrile at 100 mg/kg in corn oil by gavage to Sprague-Dawley rats; 43% of the dose was eliminated as urinary metabolites, 15% was eliminated in the feces, and 2.5% was exhaled as carbon dioxide. Ghanayem et al. (1992) noted that gavage administration of methacrylonitrile in corn oil rather than in water resulted in slower absorption and decreased elimination of unchanged methacrylonitrile.

4.2. Mechanism of Toxicity

The toxicity of methacrylonitrile is due to the metabolic release of cyanide. Cyanide interrupts cellular respiration by blocking the terminal step of electron transfer from cytochrome c oxidase to oxygen. As a consequence, tissue oxygen use may slow to a point where it cannot meet metabolic demands. This is particularly critical in the brain stem nuclei where lack of an energy source results in central respiratory arrest and death. Impairment of oxidative phosphorylation can also lead to an increased rate of glycolysis; however, the resultant pyruvate cannot be used via the cyanide-impaired Kreb's cycle resulting in the reduction of pyruvate to lactate and metabolic acidosis (Beasley and Glass 1998). Cyanide also stimulates chemoreceptors of the carotid and aortic bodies to produce a brief period of hyperpnea. Cardiac irregularities may occur, but death is due to respiratory arrest (Smith 1996).

4.3. Concurrent Exposure Issues

Tanii and Hashimoto (1986) studied the effect of ethanol on the metabolism of 20 nitriles, including methacrylonitrile. Male ddY mice were dosed orally with either ethanol (4.0 g/kg) or glucose (7.0 g/kg), killed by cervical dislocation 13 h later, and microsomes were then prepared from the livers. (A

preliminary study indicated that hepatic microsomal metabolizing activity for nitriles was at maximum 13 h after oral administration of ethanol at 4.0 g/kg. The glucose control was isocaloric to the ethanol dosage.) Methacrylonitrile was added to the reaction mixture, and the amount of cyanide released per minute per milligram of protein was determined. None of the nitriles was metabolized when incubation mixtures lacked nicotinamide adenine dinucleotide phosphate (NADPH). Ethanol treatment stimulated the metabolic rate of most nitriles compared with the glucose control, suggesting that ethanol may enhance the acute toxicity of nitriles. The ethanol/glucose ratios ranged from 1.00-1.83 for the 20 nitriles tested. The ratio for methacrylonitrile was 1.19.

4.4. Structure-Activity Relationships

Because the acute toxicity of nitriles depends on the 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 α-carbon radical stability. Generally, the nitriles that are metabolized most quickly or easily at the carbon atom alpha to the cyano group (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 decrease acute toxicity (DeVito 1996).

Methacrylonitrile is structurally similar to acrylonitrile, a known rat and probable human carcinogen (IARC 1987); however, there was no evidence of carcinogenic activity of methacrylonitrile in two-year studies in male or female F344/N rats or B6C3F1 mice (NTP 2001). As previously stated, the acute toxicity of the nitriles is due to metabolic liberation of cyanide. However, reaction with glutathione and reaction with DNA are likely involved in carcinogenicity. Conjugation lowers the concentration of glutathione in tissues and allows for nucleophilic attack (Ghanayem et al. 1985). Methacrylonitrile is less potent than acrylonitrile as a glutathione depleter (Day et al. 1988). In rats, a higher percentage of administered acrylonitrile was eliminated in urine as glutathione-derived mercapturic acids, and methacrylonitrile reacted less rapidly with tissue nucleophiles, based on differences in the concentration of radioactivity at the site of administration (Burka et al. 1994). With regard to DNA interaction, Guengerich et al. (1981) have shown that acrylonitrile does not directly react with DNA; the carcinogenic and mutagenic activity of acrylonitrile is attributable to the 2-cyanoethylene oxide, which is thought to react with DNA. The epoxide intermediate of methacrylonitrile may be less reactive with DNA (than the acrylonitrile intermediate) because a nucleophilic attack would be hindered by the methyl group on the adjacent carbon. Therefore, although a larger proportion of an ad-

ministered dose of methacrylonitrile may be metabolized via the epoxide intermediate, data suggest that the methacrylonitrile-derived epoxide is broken down and eliminated more efficiently that the acrylonitrile-derived epoxide intermediate. This is supported by the observation of greater exhalation of carbon dioxide by animals treated with methacrylonitrile compared with those treated with acrylonitrile.

4.5. Species Differences

Data suggest that rats are more resistant than mice, guinea pigs, and rabbits to the lethal effects of methacrylonitrile. Data suggest that metabolic liberation of cyanide from methacrylonitrile is species dependent (Farooqui et al. 1992). After rats, mice, and gerbils were administered methacrylonitrile at 100, 17, or 4 mg/kg (half the LD_{50}s for these species), respectively, the highest concentrations of cyanide were found in gerbils, followed by mice and then ratss. Maximum blood concentrations occurred 1 h after administration of methacrylonitrile in mice and gerbils, but after 3 h in rats. Cyanide concentrations returned to negligible levels by 24 h. In another study, Ghanayem et al. (1994) administered single gavage doses of ^{14}C-methacrylonitrile to male F344 rats and male B6C3F_1 mice. ^{14}C elimination in rats occurred primarily in expired air as unchanged methacrylonitrile, acetone, and carbon dioxide. The three major urinary metabolites identified were n-acetyl-S-(2-cyanopropyl)-L-cysteine, N-acetyl-S-(2-hydroxypropyl)-L-cysteine, and a deoxyuridine isomer. Rats excreted approximately 7% of the methacrylonitrile as N-acetyl-S-(2-hydroxypropyl)-L-cysteine, whereas mice excreted 49% of the administered dose as N-acetyl-S-(2-hydroxypropyl)-L-cysteine in the urine. Also, rats eliminated significantly more methacrylonitrile-derived carbon dioxide and deoxyuridine than mice. Tissue concentrations of radiolabel were consistently higher in rats than in mice, with the exception of the urinary bladder. It is likely that differences between rats and mice are due to a quantitative difference between them in forming the epoxide intermediate, higher efficiency of mice to conjugate the intermediate with glutathione, and a greater capacity of rats to degrade it to acetone and carbon dioxide.

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 for derive an empirical value of n for methacrylonitrile. To obtain conservative and protective AEGL values in the absence of a chemical-specific scaling exponent, temporal scaling was performed using default values of $n = 3$ for extrapolating to shorter durations and $n = 1$ for extrapolating to longer durations.

5. RATIONALE FOR AEGL-1 VALUES

5.1. Human Data Relevant to AEGL-1

Approximately 6-22% of subjects exposed to methacrylonitrile at 24 ppm for 1 min experienced nasal, throat, or ocular irritation. Transitory nasal, throat, or ocular irritation was also noted during the course of 10-min exposures at 2 or 14 ppm (Pozzani et al. 1968).

5.2. Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1 Values

Data from the Pozzani et al. (1968) study were considered unsuitable for deriving AEGL-1 values for methacrylonitrile. The study was designed to assess sensory response to methacrylonitrile vapors in humans and did not evaluate potential systemic effects. Since the toxicity of methyacrylonitrile is due to the release of cyanide, basing AEGLs on a study that only examined sensory end points may not be protective. Methacrylonitrile does not have adequate warning properties. Olfactory fatigue was observed after a few minutes of exposure to methacrylonitrile at 2 ppm (Pozzani et al. 1968). Studies in animals demonstrate a steep dose-response for lethality. No deaths or symptoms of toxicity were observed in mice exposed at 19.7 ppm for 4 h (Pozzani et al. 1968); however, the LC_{50} is 36 ppm. In a repeated-dose study in rats, no deaths were observed in rats exposed at 50 ppm for 7 h/day for 9 days, and two of six male rats died on the first day of exposure at 110 ppm (Pozzani et al. 1968).

AEGL-1 values are not recommended for methacrylonitrile due to its poor warning properties.

6. RATIONALE FOR AEGL-2 VALUES

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

No animal data on methacrylonitrile consistent with the definition of AEGL-2 were available.

6.3. Derivation of AEGL-2 Values

No inhalation data on methacrylonitrile consistent with the definition of AEGL-2 are available. Therefore, the AEGL-2 values for methacrylonitrile were estimated by dividing the AEGL-3 values by 3. The resulting values are considered estimates of thresholds for irreversible effects and are considered appropriate given the steep concentration-response curve for methacrylonitrile. For example, in mice, the 4-h no-effect level is 19.7 ppm and the LC_{50} is 36 ppm. Similar results were found in studies of rabbits; the 4-h no-effect level is 19.7 ppm and the LC_{50} is 37 ppm. In guinea pigs, the 4-h no-effect level was 52.5 ppm and the LC_{50} was 88 ppm (Pozzani et al. 1968). Although the 10-min AEGL-2 value is below the concentration range where only minor irritation was reported in humans (Pozzani et al. 1968), this value is considered appropriate given the lack of warning properties for this chemical. AEGL-2 values for methacrylonitrile are presented in Table 3-8, and the calculations are presented in Appendix A.

7. RATIONALE FOR AEGL-3 VALUES

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

Many 4-h LC_{50} values for methacrylonitrile have been reported: 440 ppm for male ChR-CD rats (DuPont 1968a), 496 ppm and 700 ppm for female Wistar rats (Pozzani et al. 1968), 328 ppm for male Wistar rats (Pozzani et al. 1968), 36 ppm for male A/J mice (Pozzani et al. 1968), 37 ppm for male rabbits (Pozzani et al. 1968), and 88 ppm for male albino guinea pigs (Pozzani et al. 1968). Loss of consciousness within 3 h of exposure and one death preceded by convulsions was observed in male rats exposed to methacrylonitrile at 176 ppm for 4 h (Pozzani et al. 1968). In another study of male rats (presumably younger than the previous study based on body weight) and in two studies of female rats, loss of consciousness was also observed within 3 h of exposure, but no deaths were observed (Pozzani et al. 1968). No deaths were observed in mice or rabbits exposed to methacrylonitrile at 19.7 ppm for 4 h (Pozzani et al. 1968).

TABLE 3-8 AEGL-2 Values for Methacrylonitrile

10 min	30 min	1 h	4 h	8 h
1.3 ppm ($3.5\ mg/m^3$)	1.3 ppm ($3.5\ mg/m^3$)	1.0 ppm ($2.7\ mg/m^3$)	0.67 ppm ($1.8\ mg/m^3$)	0.33 ppm ($0.89\ mg/m^3$)

7.3. Derivation of AEGL-3 Values

A comparison of the 4-h LC_{50} values for the various species tested by Pozzani et al. (1968) suggest that mice and rabbits are sensitive species; the no-effect level for mice and rabbits of 19.7 ppm was selected as the point of departure for deriving AEGL-3 values. The no-effect level was chosen over the LC_{50} values because it is preferable to use an empirical value rather than estimating a no-effect level by adjusting an LC_{50} value. An intraspecies uncertainty factor of 3 was applied because studies of accidental and occupational exposures to hydrogen cyanide (the metabolically-liberated toxicant) indicate that there are individual differences in sensitivity to this chemical but that the differences are not expected to exceed 3-fold (NRC 2002). An interspecies uncertainty factor of 3 was applied because mice and rabbits are the most sensitive species. Thus, the total uncertainty factor is 10. The concentration-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 on methacrylonitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min and 1h) and n = 1 to extrapolate longer durations (8-h) were used to estimate AEGL values that are protective of human health (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with time scaling a 4-h exposure to a 10-min value. AEGL-3 values for methacrylonitrile are presented in Table 3-9, and the calculations are presented in Appendix A.

The 10-min AEGL-3 value of 3.9 ppm is lower than the concentration (14 ppm) resulting in transient irritation in humans exposed for 10 min (Pozzani et al. 1968); although a similar value would be calculated if the human data were used (a point of departure of 14 ppm and an intraspecies uncertainty factor of 3 would yield a value of 4.6 ppm). Given the steep dose-response for lethality in animals (e.g., no deaths in mice exposed at 19.7 ppm and an LC_{50} of 36 ppm) and the lack of odor warning properties, the AEGL values are considered protective of human health.

The AEGL values for methacrylonitrile are presented in Table 3-10. AEGL-1 values are not recommended due to the poor warning properties of methacrylonitrile. Data on methacrylonitrile were inadequate for deriving AEGL-2 values, so estimates were based on a three-fold reduction in AEGL-3 values. AEGL-3 values were based on a no-effect level for lethality in mice.

TABLE 3-9 AEGL-3 Values for Methacrylonitrile

10 min	30 min	1 h	4 h	8 h
3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

TABLE 3-10 AEGL Values for Methacrylonitrile

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)	1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)
AEGL-3 (lethal)	3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for short-term exposures to methacrylonitrile are presented in Table 3-11.

TABLE 3-11 Other Standards and Guidelines for Methacrylonitrile

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)
AEGL-3	3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)
TLV-TWA (ACGIH)[b]	–	–	–	–	1 ppm (3 mg/m^3)
REL-TWA (NIOSH)[c]	–	–	–	–	1 ppm (3 mg/m^3)
MAC (The Netherlands)[d]	–	–	–	–	1 ppm (3 mg/m^3)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.
[b]TLV-TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2003]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[c]REL-TWA (recommended exposure limit–time-weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA.
[d]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands [MSZW 2004]) is defined analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

Human data on methacrylonitrile are limited to one experimental study. Animal data are available for several species, with the vast majority of studies having been conducted in the rat. The animal data suggest that, as with other nitriles, the rat is more resistant to the toxic effects of methacrylonitrile than are other species. This interspecies difference may be due to the rate of metabolic cyanide liberation.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHYACRYLONITRILE

Derivation of AEGL-1 Values

AEGL-1 values are not recommended due to the poor warning properties of methacrylonitrile. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

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

Calculations:

10-min AEGL-2:	3.9 ppm ÷ 3 = 1.3 ppm
30-min AEGL-2:	3.9 ppm ÷ 3 = 1.3 ppm
1-h AEGL-2:	3.1 ppm ÷ 3 = 1.0 ppm
4-h AEGL-2:	2.0 ppm ÷ 3 = 0.67 ppm
8-h AEGL-2:	0.99 ppm ÷ 3 = 0.33 ppm

Derivation of AEGL-3 Values

Key study:	Pozzani, U.C., E.R. Kinkead, and J.M. King. 1968. The mammalian toxicity of methacrylonitrile. Am. Ind. Hyg. Assoc. J. 29(3):202-210.
Toxicity end point:	No mortality in mice exposed for 4 h at 19.7 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) $(19.7 \text{ ppm})^3 \times 4 \text{ h} = 30{,}581 \text{ ppm-h}$ $(19.7 \text{ ppm})^1 \times 4 \text{ h} = 78.8 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability

10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 3.9 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 30,581 ppm-h C^3 = 61,162 ppm C = 39.4 ppm 39.4 ÷ 10 = 3.9 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 30,581 ppm-h C^3 = 30,581 ppm C = 31.3 ppm 31.3 ÷ 10 = 3.1 ppm
4-h AEGL-3:	C × 4 h = 78.8 ppm-h C = 19.7 ppm 19.7 ÷ 10 = 2.0 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 78.8 ppm-h C^1 = 9.9 ppm C = 9.9 ppm 9.9 ÷ 10 = 0.99 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHACRYLONITRILE

Derivation Summary

AEGL-1 VALUES

AEGL-1 values are not recommended due to the poor warning properties of methacrylonitrile. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)

Data adequacy: Data consistent with the definition of AEGL-2 were not available. AEGL-2 values for methacrylonitrile were estimated by dividing the AEGL-3 values by 3. These values are considered estimates of thresholds for irreversible effects and are considered appropriate given the steep concentration-response curve for the chemical. For example, in the mouse, the 4-h no-effect level is 19.7 ppm and the LC_{50} is 36 ppm. In the rabbit, the 4-h no-effect level is 19.7 ppm and the LC_{50} is 37 ppm. In the guinea pig, the 4-h no-effect level is 52.5 ppm and the LC_{50} is 88 ppm (Pozzani et al. 1968).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)

Key reference: Pozzani, U.C., E.R. Kinkead, and J.M. King. 1968. The mammalian toxicity of methacrylonitrile. Am. Ind. Hyg. Assoc. J. 29(3):202-210.

Test species/Strain/Sex/Number: Mouse, A/J, males, 6/group

Exposure route/Concentrations/Durations: Inhalation, 19.7 ppm and other unspecified concentrations for 4 h

End point/Concentration/Rationale: No deaths or symptoms at 19.7 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because mice are a sensitive species.
Intraspecies: 3, because studies of accidental and occupational exposures to hydrogen cyanide (the metabolically-liberated toxicant) indicate that there are individual differences in sensitivity to this chemical but that the differences are not expected to exceed 3-fold (NRC 2002).

Modifying factor: None

Animal-to-human dosimetric adjustment: Insufficient data
Time scaling: $C^n \times t = k$, where default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations were used to calculate AEGL values that are protective of human health (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with extrapolating a point-of-departure based on a 4-h exposure to a 10-min value.
Data adequacy: End point consistently observed in numerous experiments.

APPENDIX C

CATEGORY PLOT FOR METHACRYLONITRILE

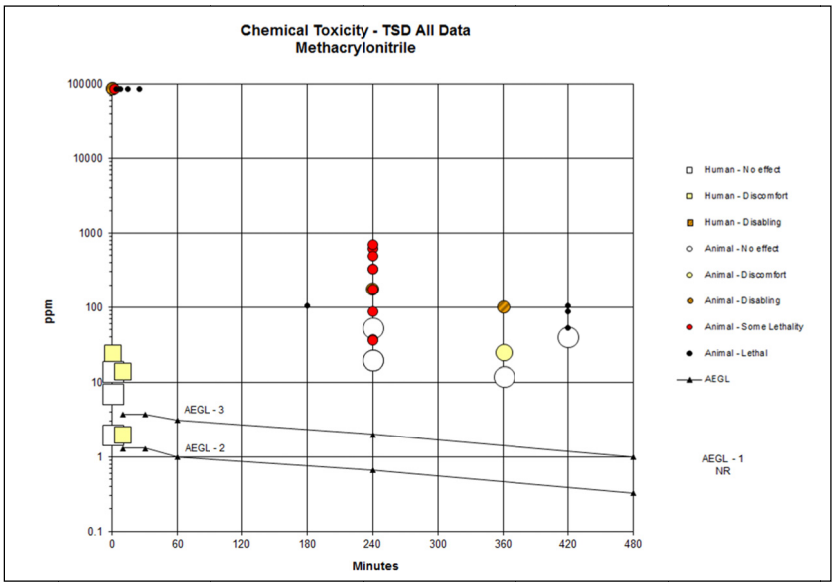

FIGURE C-1 Category plot of toxicity data and AEGL values for methacrylonitrile.

TABLE C-1 Data Used in Category Plot for Methacrylonitrile

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				1.3	10	AEGL	
AEGL-2				1.3	30	AEGL	
AEGL-2				1.0	60	AEGL	
AEGL-2				0.67	240	AEGL	
AEGL-2				0.33	480	AEGL	
AEGL-3				3.7	10	AEGL	
AEGL-3				3.7	30	AEGL	
AEGL-3				3.1	60	AEGL	
AEGL-3				2.0	240	AEGL	
AEGL-3				0.99	480	AEGL	
Pozzani et al. 1968	Human		1	2	1	0	
	Human		1	7	1	0	
	Human		1	14	1	0	
	Human		1	2	10	1	
	Human		1	14	10	1	
	Human		1	24	1	1	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Younger Labs 1969	Rat	Males	1	625	240	SL	Mortality (2/10)
Pozzani et al. 1968	Rat	Females	1	85,500	0.47	2	No mortality (0/6)
	Rat	Females	1	85,500	0.93	2	No mortality (0/6)
	Rat	Females	1	85,500	1.88	SL	17% mortality (1/6)
	Rat	Females	1	85,500	3.75	3	100% mortality (6/6)
	Rat	Females	1	85,500	7.5	3	100% mortality (6/6)
	Rat	Females	1	85,500	14	3	100% mortality (6/6)
	Rat	Females	1	85,500	25	3	100% mortality (4/4)
	Rat		1	176	240	2	Loss of consciousness, no mortality
	Rat		1	176	240	SL	1 male died
	Rat	Females	1	700	240	SL	LC_{50}
	Rat	Females	1	496	240	SL	LC_{50}
	Rat	Males	1	328	240	SL	LC_{50}
	Rat	Males	1	328	240	SL	LC_{50}
	Guinea pig	Males	1	88	240	SL	LC_{50}
	Rabbit	Males	1	37	240	SL	LC_{50}
	Mouse	Males	1	36	240	SL	LC_{50}
Pozzani et al. 1968	Dog	Females	1	106	180	3	Mortality (1/1)
	Dog	Females	1	106	420	3	Mortality (1/1)
	Dog	Females	1	52.5	420	3	Mortality (1/1)

DuPont 1968b	Dog	Females	1	40	420	0	No mortality
	Dog	Females	1	87.5	420	3	100% mortality
Pozzani et al. 1968	Guinea pig		1	52.5	240	0	
	Rabbit		1	19.7	240	0	
	Mouse		1	19.7	240	0	
Saillenfait et al. 1993	Rat	Both	1	12	360	0	
	Rat	Both	1	25	360	1	
	Rat	Both	1	100	360	2	

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