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

1

Aliphatic Nitriles[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), Julie Klotzbach (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.

1. GENERAL INFORMATION FOR SELECTED ALIPHATIC NITRILES

In this chapter, the bases of the AEGL values for the following five aliphatic nitriles are described: acetonitrile, isobutyronitrile, chloroacetonitrile, propionitrile, and malononitrile. Information relevant to all five compounds is first presented, and is followed by separate sections on the individual chemicals.

1.1. Absorption, Distribution, Metabolism, and Excretion

Aliphatic nitriles are readily absorbed from the lung and gastrointestinal tract, resulting in systemic toxicity. Most of the systemic toxicity of these nitriles is mediated through hepatic and extrahepatic cytochrome P450 catalyzed oxidation of the carbon alpha to the cyano group producing a cyanohydrin and an aldehyde. The metabolically-liberated cyanide is then conjugated with thiosulfate to form thiocyanate and is excreted in the urine (NTP 1996). Studies containing nitrile-specific metabolism information were available for acetonitrile, propionitrile, and chloroacetonitrile and are described below. No chemical-specific metabolism studies were available for isobutyronitrile or malononitrile.

1.1.1. Acetonitrile

In humans, studies of smokers suggested that 91 ± 4% of the acetonitrile inhaled in cigarette smoke was retained and that a significant portion may have been retained in the mouth (Dalhamn et al. 1968). Also, human poisoning cases suggest that acetonitrile is well absorbed by both inhalation and dermal routes but provide little quantitative data (see Section 2.3.1).

Studies in monkeys, rats, and dogs have shown cyanide in the blood and thiocyanate in the urine following exposure to acetonitrile by injection or inhalation (Pozzani et al. 1959). The rate of cyanide release from acetonitrile is slower than for other nitriles (Ahmed and Farooqui 1982; see Section 1.4). Peak blood cyanide concentrations occurred 7.5-h after exposure to acetonitrile whereas peak levels occurred 1 h after exposure to comparable amounts of other nitriles or potassium cyanide. Also, the percentage of acetonitrile excreted in the urine as thiocyanate was lower than that for other nitriles, even when the initial dose was greater. These data suggest that the toxicity of acetonitrile is less than other nitriles because of its slower conversion to cyanide and thus more efficient detoxification to thiocyanate (NTP 1996).

Studies of male rats found free and conjugated cyanide and unchanged acetonitrile in various tissues after inhalation or intraperitoneal injection (Haguenoer et al. 1975). Ahmed et al. (1992) found acetonitrile and metabolites in the liver, kidney, gastrointestinal tract, gallbladder, and urinary bladder 5 min after administration of 2-[^{14}C]-acetonitrile to mice. At 24- and 48-h post-exposure, label was still detected in the liver and gastrointestinal tract, and delayed retention was noted in the male reproductive organs and brain.

Elimination acetonitrile occurs mainly through urinary excretion of unchanged chemical and free and bound hydrogen cyanide. Urinary excretion is greatest during the initial 24 h after dosing. However, after intraperitoneal injection, small amounts were detected in the urine of rats for up to 4 days post-exposure. Thiocyanate excretion was observed for up to 11 days post-exposure (Haguenoer et al. 1975). At high inhalation concentrations, unchanged acetonitrile may be eliminated by exhalation.

1.1.2. Propionitrile

Fromont et al. (1974) studied acute and repeated parenteral administration of propionitrile in relation to its distribution and biotransformation to cyanide in the rat. Lethal doses resulted in propionitrile accumulation in the kidneys, heart, testes, and liver, whereas cyanide concentrations were highest in the spleen, lungs, heart, and brain. Mumtaz et al. (1997) administered a tracer dose of 100 μCi/kg ^{14}C-propionitrile intravenously to female Sprague-Dawley rats, and killed selected animals 1-, 8-, or 24-h post-exposure. Within 1 h of administration, peak radioactivity was detected in the duodenum, kidneys, lungs, large intestine, plasma, erythrocytes, stomach, heart, and brain. The animals excreted approximately 5.3% of the dose within 24 h, with approximately equal amounts

in the expired air and urine and only trace amounts in the feces. The presence of radioactivity in the gastrointestinal tract for up to 24-h post-exposure suggested enterohepatic recirculation of propionitrile or metabolites. Subcellular fractions of liver, duodenum, and brain showed significant accumulation of radioactivity.

1.1.3. Chloroacetonitrile

Male Sprague-Dawley rats were administered chloroacetonitrile at 57 mg/kg by gavage (Pereira et al. 1984). Approximately 14% of the administered dose was excreted as thiocyanate in the urine within 24 h, suggesting that, as with other nitriles, chloroacetonitrile is metabolized via P450 catalyzed oxidation of the carbon alpha to the cyano group producing a cyanohydrin which leads to hydrogen cyanide.

Male Sprague-Dawley rats were administered [2-^{14}C]chloroacetonitrile intravenously (Ahmed et al. 1991). Within 12-h post-exposure, 51% of the radioactivity was excreted in the urine, 2.7% in feces, and 12% in expired air as $^{14}CO_2$. Only 0.8% of the administered dose was exhaled as unchanged chloroacetonitrile, and no unchanged chloroacetonitrile was excreted in the urine. Whole-body autoradiography for up to 48-h post-exposure showed persistent label in the thyroid, gastrointestinal tract, testes, brain, and eyes.

In vivo and in vitro studies suggest that chloroacetonitrile reacts extensively with glutathione and causes significant decreases in glutathione concentrations in treated rats (Ahmed et al. 1989) and mice (Jacob et al. 1998).

1.2. Mechanism of Toxicity

The toxicity of the aliphatic nitriles 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. Tissue concentrations of oxygen rise, resulting in increased tissue oxygen tension and a decreased unloading of oxyhemoglobin. Increased oxyhemoglobin in the venous blood may impart a flush to the skin and mucous membranes. As a consequence, oxidative metabolism 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. 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).

1.3. Concurrent Exposure Issues

As noted in Section 1.2, the selected aliphatic nitriles reviewed in this document share a common mechanism of toxicity through their biotransformation to cyanide. Therefore, caution should be noted regarding cumulative effects of exposure to multiple aliphatic nitriles.

Tanii and Hashimoto (1986) studied the effect of ethanol on the metabolism of 20 nitriles, including acetonitrile, isobutyronitrile, propionitrile, and chloroacetonitrile. 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 reached a maximum 13 h after oral administration of ethanol at 4.0 g/kg. Glucose at 7.0 g/kg was isocaloric to the ethanol dosage). The nitrile was added to the reaction mixture and the amount of cyanide released per minute per milligram of protein was determined. None of the nitriles were 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 consumption may enhance the acute toxicity of nitriles. The ethanol-to-glucose ratios ranged from 1.00 to 1.83 for the 20 nitriles tested. The ratios were 1.83 for acetonitrile, 1.20 for isobutyronitrile, 1.62 for propionitrile, and 1.54 for chloroacetonitrile.

Willhite and Smith (1981) found that subcutaneous pretreatment of mice with carbon tetrachloride (at a dose that effectively destroyed the metabolic capacity of the liver) protected mice against the lethal and toxic effects of intraperitoneally administered acetonitrile, propionitrile, and malononitrile. Survival of the carbon tetrachloride-treated mice compared with controls was attributed to decreased brain cyanide concentrations. Tanii and Hashimoto (1984) also found that mice pretreated intraperitoneally with carbon tetrachloride were less susceptible to the toxic effects of orally administered acetonitrile and propionitrile. In another study, Tanii and Hashimoto (1985) pretreated male ddY mice with olive oil or carbon tetrachloride and then orally administered malononitrile at doses 3-5 times greater than the LD_{50}. Mean survival times were increased and brain cyanide concentrations were decreased in the carbon tetrachloride-pretreated mice.

1.4. Structure-Activity Relationships

Because the acute toxicity of nitriles depends 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 α-carbon radical stability. Generally, the 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).

Dahl and Waruszewski (1987, 1989) examined the in vitro metabolism of acetonitrile, propionitrile, n-butyronitrile, isobutyronitrile, acrylonitrile, succinoni-

trile, and benzyl cyanide. Nasal maxilloturbinate, ethmoturbinate, and liver microsomes were prepared from 10-16-week-old male F344 rats. The microsomes and selected nitriles were incubated at 37°C for 30 min, the reaction was stopped by the addition of potassium hydroxide, and cyanide concentrations were measured. The rate of cyanide production varied with both the nitrile side chain and tissue source of the microsomes. Except in the case of acrylonitrile with maxilloturbinate microsomes, the maximum rate of cyanide production increased as the number of carbon atoms in the side chain increased. For ethmoturbinates, the rate of cyanide production was the lowest for acetonitrile and acrylonitrile (which had almost equal rates), followed by propionitrile, butyronitrile, isobutyronitrile, and succinonitrile (which had similar rates), and then benzyl cyanide. For maxilloturbinates, the rates were the lowest for acetonitrile, followed by propionitrile, isobutyronitrile and succinonitrile (which had similar rates), butyronitrile, benzyl cyanide, and acrylonitrile. For liver, rate were lowest for succinonitrile, followed by acetonitrile, propionitrile and butyronitrile (which had similar rates), isobutyronitrile, acrylonitrile, and benzyl cyanide.

Ahmed and Farooqui (1982) orally administered aliphatic nitriles or potassium cyanide at a single LD_{50} to male Sprague-Dawley rats. Animals were killed 1 h later and tissue and blood cyanide concentrations were measured. Hepatic and blood cyanide concentrations were highest for malononitrile, followed by propionitrile, potassium cyanide, butyronitrile, acrylonitrile, allylcyanide, fumaronitrile, and acetonitrile. The pattern in the brain differed in that potassium cyanide preceded malononitrile and propionitrile. Hepatic and brain cytochrome c oxidase were decreased and the decreases corresponded to measured cyanide concentrations.

Intraperitoneal LD_{50} values from studies of mice have been reported for several nitriles (Lewis 1996), allowing for the comparison of the relative toxicity of these compounds (see Table 1-1). These data are consistent with the information described above showing that the predicted rate of cyanide production (Dahl and Waruszewski1987, 1989; Devito 1996) and measured blood cyanide concentrations (Ahmed and Farooqui 1982) correlate with the intraperitoneal LD_{50} values.

TABLE 1-1 Intraperitoneal LD_{50} Values for Mice

Chemical	LD_{50}
Acetonitrile	521 mg/kg
Isobutyronitrile	Not available
Chloroacetonitrile	100 mg/kg
Propionitrile	34 mg/kg
Malononitrile	13 mg/kg
	Molar ratio of LD_{50} values:
Acetonitrile/Chloroacetonitrile	10
Acetonitrile/Propionitrile	21
Acetonitrile/Malononitrile	65

1.5. Species Sensitivity

Data on the aliphatic nitriles suggest that mice, guinea pigs, rabbits, dogs, and monkeys are more sensitive than rats to the effects of acetonitrile. Interspecies differences in acetonitrile toxicity may be due to the relative speed of cyanide formation and detoxification (NTP 1996). Thus, a slow rate of cyanide production that enables more efficient detoxification may account for the decreased sensitivity of the rat to acetonitrile. Although much metabolism data are available for rats and mice, direct comparisons of the rates between species are not possible because of differences in cyanide detection methods, different routes of administration, and units used in reporting data (for example, nmol/10^6 cells vs. ng/mg protein when comparing cyanide formed from isolated hepatocytes from rats vs. mice).

No studies that rigorously compared the acute toxicity of isobutyronitrile, propionitrile, or chloroacetonitrile in different species were found. However, available data suggest that mice are more sensitive to the toxic effects of these nitriles than rats. In an acute inhalation study of saturated atmospheres of isobutyronitrile (Tsurumi and Kawada 1971), 0/10 rats died after 4 min of exposure, 1/10 after 5 min, 4/10 after 6 min, 6/10 after 8 min, and 10/10 after 10 min. In studies with mice, 3/10 animals died after 0.5 min, 5/10 after 1 min, 7/10 after 1.5 min, and 10/10 after 2 min.

No deaths occurred in rats exposed to propionitrile at 690 ppm for 4 h, and the 4-h LC_{50} was 1,441 ppm (Younger Labs 1978). The 1-h mouse LC_{50} of 163 ppm (Willhite 1981) is approximately six times less than the concentration causing no deaths in rats exposed for 4 h. Finally, rat oral LD_{50} values for chloroacetonitrile are in the range of 180 to 220 mg/kg (Younger Labs 1976; Lewis 1996), whereas, the reported mouse oral LD_{50} is 139 mg/kg (Tanii and Hashimoto 1984).

1.6. Temporal Extrapolation

The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases can 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 available to derive an empirical value for n for acetonitrile only. An analysis of the acute inhalation lethality data for rats was conducted using the dose-response software of ten Berge (2006). This analysis used the concentration-specific data presented in the summary tables of lethal and sublethal effects of acetonitrile presented later in this chapter in Section 2.4.6, which allowed for the inclusion of all rat data except the DuPont (1968) study for which dose-specific data were not available. The value of n was estimated to be 1.550, with confidence limits of 0.539 and 2.560. Details of this analysis are presented in Appendix A. The exponent was rounded to 1.6, and was considered valid for scaling across time only for rat data because the rate of cyanide release from acetonitrile may vary between species.

Data were unavailable to determine an empirical value of n for isobutyronitrile, propionitrile, chloroacetonitrile, or malononitrile. In the absence of chemical-specific data, default values of n = 3 for extrapolation shorter durations and n = 1 for extrapolation to longer durations were used to provide AEGL values that are protective of human health (NRC 2001).

2. ACETONITRILE

2.1. Summary

Acetonitrile is a volatile, colorless liquid at ambient temperature and pressure (WHO 1993). It has a sweet, ether-like odor, with a reported odor threshold of 42 ppm (Ruth 1986). Mean ambient air concentrations of 0.000048 to 0.007 ppm have been reported, and slightly higher values were obtained for urban than for rural air. Single measurements taken before and after burning of brush and straw indicated a 10-fold increase in acetonitrile concentrations in air (WHO 1993).

The major use for acetonitrile is as an extraction and processing solvent in the pharmaceutical industry. Acetonitrile is also used as a process, extraction, and formulation solvent for agricultural chemicals, and in the extractive distillation of butadiene. It is also used as a mobile phase in high-performance liquid chromatography and in the separation of chiral systems. It also has minor uses as an intermediate in chemical manufacturing and in photographic applications.

The toxicity of acetonitrile is due to the metabolic liberation of cyanide and signs and symptoms are similar to those observed after cyanide exposure.

Slight chest tightness and cooling sensation in the lungs reported by one of three male volunteers exposed to acetonitrile at 40 ppm for 4 h (Pozzani et al. 1959) were used as the basis for AEGL-1 values. An interspecies uncertainty factor of 1 was applied because the critical study was conducted in humans. A factor of 1 was also applied for intraspecies variability, because the mild effects were judged to have occurred in a sensitive subject. No symptoms were reported by two other subjects exposed in the same manner, nor when the same subjects were exposed at 80 ppm for 4 h. A modifying factor of 3 was applied to account for the sparse database for effects relevant to AEGL-1. The 4-h AEGL-1 value of 13 ppm was held constant across the 10-min, 30-min, and 1-h durations because no human data were available exposure durations of less than 4 h; thus, time scaling to shorter durations could result in values that would eliciting symptoms above those defined by AEGL-1. A calculated value for an 8-h duration was 14 ppm, which is essentially equal to the 4-h AEGL-1 value of 13 ppm, so an 8-h AEGL-1 value was not recommended.

At nonlethal exposures, AEGL-2 effects, described as less than “moderate to marked pulmonary hemorrhage or congestion” were observed in rats (Pozzani et al. 1959). Since no-effect levels for AEGL-2 effects were not identified, AEGL-2 values could not be derived from the available data. Therefore, AEGL-2 values were estimated by dividing AEGL-3 values by 3.

The no-effect level for maternal and fetal mortality in pregnant rats exposed to acetonitrile at 1,500 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was used as the point of departure for deriving AEGL-3 values. Although the study involved repeated exposures, fetal death can occur during a narrow developmental window and does not necessarily require repeated exposures (Van Raaij et al. 2003). Therefore, the observation of increased fetal death after repeated gestational exposure was considered an appropriate end point for deriving AEGL-3 values. In addition, maternal lethality after repeated exposure during pregnancy is also relevant to AEGL-3 derivation, as pregnant animals may have increased sensitivity to acetonitrile compared with nonpregnant animals. An interspecies uncertainty factor of 10 was applied because no comparable data for similar exposures (repeated inhalation exposure during gestation) in other species were found. 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). Thus, the total uncertainty factor is 30. Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). This equation has been shown to describe the concentration-exposure duration relationship for many irritant and systemically acting vapors and gases. An empirical value for n of 1.6 was determined on the basis of rat lethality data that involved exposures to acetonitrile ranging from 15 min to 8 h. Time scaling was not performed for the 10-min AEGL-3 value, because of the uncertainty associated with time scaling a 6-h exposure to a 10-min value. Therefore, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value.

AEGL values for acetonitrile are presented in the Table 1-2.

TABLE 1-2 AEGL Values for Acetonitrile

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	NR[a]	Slight chest tightness and cooling sensation in lung (Pozzani et al. 1959)
AEGL-2 (disabling)	80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)	No-effect level for maternal and fetal lethality in rats (Saillenfait et al. 1993)

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

2.2. Introduction

Acetonitrile is a volatile, colorless liquid at ambient temperature and pressure (WHO 1993). It has a sweet, ether-like odor, with a reported odor threshold of 42 ppm (Ruth, 1986). Mean ambient air concentrations of 0.000048 to 0.007 ppm have been reported, and slightly higher values were obtained for urban than for rural air. Single measurements taken before and after burning of brush and straw indicated a 10-fold increase in acetonitrile concentrations in air (WHO 1993).

Acetonitrile is a combustion product of wood, straw, and other vegetation (WHO 1993). Commercially, most, if not all, acetonitrile produced in the United States is a byproduct of acrylonitrile synthesis by propylene ammoxidation. The amount of acetonitrile produced in an acrylonitrile plant is depends on the ammoxidation catalyst that is used; however, the ratio of acetonitrile:acrylonitrile is typically 2-3:100. Acetonitrile is then recovered as the water azeotype, dried, and purified by distillation. Current acetonitrile production information was not found. Acetonitrile can also be synthesized by other methods such as dehydration of an acetic acid and ammonia mixture, acetamide, or ammonium acetate; reaction of ethanol and ammonia at moderate temperatures in the presence of a metal catalyst; or the reaction of cyanogen chloride with methane, ketones, ethanol, alkylene epoxides, and paraffins or olefins (WHO 1993).

The major use for acetonitrile is as an extraction and processing solvent in the pharmaceutical industry. Acetonitrile is also used as a process, extraction, and formulation solvent for agricultural chemicals, and in the extractive distillation of butadiene. It is also used as a mobile phase in high-performance liquid chromatography and in the separation of chiral systems. It also has minor uses as an intermediate in chemical manufacturing and in photographic applications.

The chemical and physical properties of acetonitrile are presented in Table 1-3.

2.3. Human Toxicity Data

2.3.1. Acute Lethality

Case reports of lethality from acetonitrile exposure exist; however, specific information about exposure concentrations and durations are not available. Symptoms from acute exposure to acetonitrile before death include chest pain, gastric distress, skin discoloration, tachypnea, hypotension, general weakness, and absence of deep reflexes.

Grabois (1955) reported on 16 workers accidentally exposed to acetonitrile vapors while painting the inside walls of a storage tank. One worker died after two days exposure, two were seriously ill, and other workers experienced

TABLE 1-3 Chemical and Physical Data on Acetonitrile

Parameter	Data	Reference
Common name	Acetonitrile	HSDB 2009
Synonyms	Cyanomethane; ethanenitrile; nitrile of acetic acid; methyl cyanide; ethyl nitrile; methanecarbonitrile	WHO 1993
CAS registry no.	75-05-8	HSDB 2009
Chemical formula	CH_3CN	HSDB 2009
Molecular weight	41.05	HSDB 2009
Physical state	Colorless liquid	HSDB 2009
Boiling point	81.6°C	WHO 1993
Freezing point	-45°C	HSDB 2009
Flash point	5.6°C (open cup)	WHO 1993
Density/Specific gravity	0.78745 at 15°C/4°C	HSDB 2009
Solubility	Infinitely soluble in water; readily miscible with ethanol, ether, acetone, chloroform, carbon tetrachloride, and ethylene chloride; immiscible with saturated hydrocarbons (petroleum fractions)	WHO 1993, HSDB 2009
Vapor density	1.42 (air = 1)	HSDB 2009
Vapor pressure	88.8 mm Hg at 25°C	HSDB 2009
Conversion factors in air	1 ppm = 1.68 mg/m^3 1 mg/m^3 = 0.595 ppm	WHO 1993

less serious symptoms. In a follow-up report to this incident, Amdur (1959) reported that the tank capacity was 22,730 L (6 meters high and 2.75 meters at its greatest diameter). Due to the viscosity of the paint, it was thinned and heated to 25°C on the second work day; also, ventilation to the tank was stopped. The paint consisted of 30-40% acetonitrile and the thinner was 90-95% acetonitrile. Other components of the paint and thinner included phenolic resin primer, diethylene triamine, and mica. The one fatality was a 23-year-old male who had painted inside the tank for 12 h. He was asymptomatic when he returned home; however, he awakened shortly after midnight with malaise and chest pain. Nausea, vomiting, and spitting up blood preceded convulsions and coma. He was admitted to the hospital at 9:15 AM with shallow, irregular, and infrequent respiration; he died within 1 h of admission. Autopsy revealed cerebral, thyroid, hepatic, and splenic, and renal congestion, and a peach-pit odor of all tissues. Cyanide was detected in his blood, urine, gastric fluid, spleen, kidney, and lung. No cyanide was detected in his liver. The two workers who became seriously ill included a 35-year-old male who had painted inside the tank for 3 h and a 28-year-old male who had painted outside of the tank for 12 h. Both men felt well

when they returned home; however, during the night or the next day, both men were hospitalized with lightheadedness and semiconsciousness, chest pain, nausea, emesis, tachycardia, pallor, shallow or intermittent respiration, and loss of deep tendon reflexes. Both men recovered and returned to work in 10-20 days. Several other workers present at the work site sand-blasted and mixed paint, but were not involved in painting the tank. Symptoms in these individuals included nausea, headache, lassitude, weakness, and chest and abdominal tightness and pain.

Dequidt et al. (1974) reported the death of a 19-year-old male worker at a photography laboratory. He had handled acetonitrile in a closed vat for 2 days without problems; however, at the end of the second day, he poured an unknown amount of boiling water and acetonitrile on the floor to clean it. Four hours after work, he vomited and complained of nausea and epigastric pain. The next day he became comatose and had convulsions. Upon hospital admission, cyanide, thiocyanate, and acetonitrile were found in his blood and urine. He died 6 days post-admission despite treatment with dicobalt ethylenediaminetetraacetic acid (EDTA) and hydroxycolbalamine.

A 16-month-old boy (11.8 kg) ingested 15-30 mL of false nail remover ("Super Nail Off", 98-100% acetonitrile, 1-2 g/kg) (Caravati and Litovitz1988). The boy vomited approximately 20 min after ingestion. Assistance was sought from a poison control center; however, the product was mistaken for acetone-containing nail polish remover, and toxicity was expected to be minimal. During the night, the boy was breathing heavily and noisily; he was found dead in his crib the next morning, 12 h after ingestion. At autopsy, moderately severe pulmonary edema was found and cyanide was detected in his blood (3.1 mg/L) and brain (0.2 mg/kg).

2.3.2. Nonlethal Toxicity

2.3.2.1. Case Reports

Grabois (1955) and Amdur (1959) reported both lethal and nonlethal cases from inhalation exposure to acetonitrile. These case reports are presented above in Section 2.3.1.

Case reports of acetonitrile toxicity from dermal, inhalation, and oral exposure to false nail remover (98-100% acetonitrile) are also available. Caravati and Litovitz(1988) reported the case of a 2-year-old boy (12 kg) who spilled 30 mL of nail remover (98-100% acetonitrile) on himself and his bed. Eight hours after the exposure, he was moaning, poorly responsive, and had vomited. On arrival at the emergency room, an electrocardiogram showed sinus tachycardia. He responded to supportive treatment, and was discharged 3 days later in good condition.

Geller et al. (1991) reported the case of a 3-year-old boy who ingested 15-30 mL of nail tip glue remover containing 95% acetonitrile, and Kurt et al.

(1991) reported the case of a 2-year-old girl who had ingested 5-10 mL artificial nail glue remover containing 84% acetonitrile. Both children were asymptomatic for 11-14 h after the ingestions. They then became restless and vomited and the girl became comatose with tachycardia. After treatment, both children recovered and were discharged within 2 days.

2.3.2.2. Experimental Studies

Pozzani et al. (1959) exposed three male volunteers (ages 31-47 years) to acetonitrile at 40 ppm for 4 h in a 7,900-L chamber. Air was exhausted from the chamber at 1,400 L/min and chamber air temperature was kept below 76°F. A physician was available during the exposure period. Blood cyanide content was determined 19 days and 1 day prior to and immediately after the exposure. The thiocyanate content of 24-h urine samples was determined 19, 18, and 1 days before the test and immediately after. All subjects detected the odor of acetonitrile during the first 2-3 h, after which some olfactory fatigue was experienced. The two older subjects reported no subjective symptoms during or after the 4-h inhalation period, and there was no appreciable increase in urinary thiocyanate and no detectable blood cyanide. The youngest subject reported no adverse subjective response during the inhalation period, but experienced slight chest tightness that evening. The following morning, he reported a cooling sensation in the lung, which persisted for 24 h and was similar to that experienced when menthol was inhaled. There was no detectable blood cyanide in this subject, but a slight increase in urinary thiocyanate was found. The two older subjects were tested one week later with acetonitrile at 80 ppm for 4 h. No subjective symptoms were reported before or during the exposure, and no blood cyanide was detected after exposure. The urinary thiocyanate value of one subject was higher immediately before inhalation than after, and the values for the other subject were constant. Finally, nine days after the 80-ppm exposure, the same two subjects were tested with acetonitrile at 160 ppm for 4 h. One subject reported a slight transitory flushing of the face 2 h after inhalation and slight bronchial tightness 5 h later, which resolved overnight. Blood cyanide and urinary thiocyanate values were similar before and after exposure, and both subjects said that they would have no hesitation about being exposed at 160 ppm for another 4-h period.

2.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding acute human exposure to acetonitrile were not available.

2.3.4. Genotoxicity

Genotoxicity studies regarding acute human exposure to acetonitrile were not available.

2.3.5. Carcinogenicity

Carcinogenicity studies regarding human exposure to acetonitrile were not available.

2.3.6. Summary

Case reports of acetonitrile toxicity exist; however, exposure concentrations and durations were not available. Signs and symptoms from inhalation, dermal, and oral exposure to acetonitrile are similar and include chest pain, chest tightness, nausea, vomiting, tachycardia, short and shallow respiration, headache, restlessness, and seizures. Effects are primarily due to the metabolism of acetonitrile to cyanide, and blood cyanide and thiocyanate concentrations are increased after acute poisoning. Human case reports have indicated that the onset of symptoms is delayed for several hours after exposure (in contrast to the rapid toxicity of cyanide itself); this delay is consistent with the metabolism that must occur to release the cyanide moiety. Only one controlled experiment of the acute inhalation toxicity of acetonitrile was available, and no information about the potential human developmental and reproductive toxicity, genotoxicity or carcinogenicity was found.

2.4. Animal Toxicity Data

2.4.1. Acute Lethality

2.4.1.1. Rats

Groups of 10 male Sprague-Dawley rats were exposed to acetonitrile at 10,100, 13,600, 19,700, or 22,200 ppm for 4 h in a 20-L glass exposure chamber, followed by a 14-day observation period (Monsanto 1986). Metered air was bubbled through a heated (80°C) bubbler of the acetonitrile. This stream was diluted with air at 15 L/min prior to entering the exposure chamber. The acetonitrile exposure concentration was monitored continuously over the 4-h period using a gas analyzer, and the concentration of acetonitrile vapor was determined with a calibration curve. Animals were observed hourly during exposure and daily thereafter. Rats exposed at 10,100 ppm had hemorrhagic lungs, and rats exposed at higher concentrations had hemorrhagic lungs and corneal opacity. Mortality was 0/10 at 10,100 ppm, 1/10 at 13,600 ppm, 3/10 at 19,700 ppm, and 8/10 at 22,200 ppm. An LC_{50} of 19,950 ppm and an LC_{01} of 8,421 ppm were calculated.

Groups of 10 young adult male ChR-CD rats were exposed to acetonitrile (concentrations not specified) for 4 h and observed for up to 14 days (DuPont 1968). 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 the acetonitrile. 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, hyperemia, incoordination, and face pawing were observed at sublethal concentrations during exposure, and irregular respiration, hyperemia followed by pale ears, face pawing, incoordination, and unresponsiveness were observed at lethal concentrations during exposure. Mild to severe weight loss for 1-3 days, followed by normal weight gain, was observed after the exposure period at sublethal concentrations. Severe weight loss for 1-3 days, followed by normal weight gain, was observed after the exposure period at lethal concentrations. Deaths occurred from 3 h during exposure through 24-h post-exposure. An LC_{50} of 17,100 ppm (14,600-20,000 ppm) was calculated. No other experimental details were reported.

Haguenoer et al. (1975) exposed three rats to acetonitrile at 25,000 ppm; all rats died within 30 min after the start of exposure after exhibiting difficult breathing and cyanosis. Another group of three rats was exposed to acetonitrile at 2,800 ppm for 2 h/day for up to 5 days. All rats had labored breathing, temporary anuria, and diarrhea. After the third exposure, one rat died with lung and brain hemorrhage. After the fourth exposure, the remaining two rats had paralysis and decreased urinary excretion. One rat died at the start of the fifth exposure and the other died 2 h after the fifth exposure was completed. Both rats lost 45% of their body weight over the 5-day period.

Groups of 30 rats were exposed to acetonitrile at 4,000, 8,000, or 16,000 ppm for 4 h (UCC 1965). Mortality was 10% at 4,000 ppm, 33% at 8,000 ppm, and 57% at 16,000 ppm. No other details were available.

Pozzani et al. (1959) exposed groups of 12 male and 12 female Carworth Farms-Nelson rats to accurately metered acetonitrile vapor for 4- or 8-h periods at concentrations of 1,000 (8 h only), 2,000 (8 h only), 4,000, 8,000, 16,000, or 32,000 ppm. Prostration, usually followed by convulsive seizures, preceded death, and necropsy of decedents showed moderate to marked pulmonary hemorrhage or congestion. Some of the surviving animals also had these pulmonary effects at necropsy, but the effects were of less marked severity (described by as less than "moderate to marked pulmonary hemorrhage or congestion"). Mortality data and calculated LC_{50} values are presented in Table 1-4. The investigators also reported that 0/6 rats died when exposed to acetonitrile at 53,000 for 15 min, whereas 3/6 rats died when exposed at this concentration for 30 min.

A 13-week repeated exposure study (NTP 1996) described both lethal and nonlethal effects in rats; this study is described in Section 2.4.2.1.

2.4.1.2. Mice

Groups of 10 male CD-1 mice were exposed to five or six concentrations of acetonitrile ranging from 500-5,000 ppm for 60 min and observed for 14 days (Willhite 1981). Actual individual group exposure concentrations were not reported. Acetonitrile was mixed with a stream of dehumidified air (10 L/min) and

TABLE 1-4 Mortality in Rats Exposed to Acetonitrile for 8 and 4 Hours

Concentration	8 h		4 h	
(ppm)	Male	Female	Male	Female
1,000	0/12	0/12	–	–
2,000	0/12	1/12	–	–
4,000	1/12	1/12	0/12	0/12
8,000	6/12	1/12	3/12	0/12
16,000	12/12	9/12	3/12	6/12
32,000	12/12	12/12	12/12	12/12
LC_{50}	7,551 (5,975 to 9,542)	12,435 (11,036 to 14,011)	16,000 (12,450 to 20,5662)	16,000 (13,037 to 19,636)

Source: Pozzani et al. 1959. Reprinted with permission; copyright 1959, *Journal of Occupational and Environmental Medicine*.

delivered to a single pass 45-L glass inhalation chamber. Samples were collected every 5 min using a gas-tight syringe and were analyzed by gas chromatography. The mice exhibited dyspnea, tachypnea, gasping, tremors, convulsions, and corneal opacity 30-300 min following initial contact with acetonitrile. All mice exposed at 5,000 ppm died within 180 min of initial exposure and delayed deaths were observed for up to 3 days after exposure at lower (unspecified) concentrations. The livers of exposed mice were bright red compared with controls. An LC_{50} of 2,693 ppm (1,955-4,247 ppm) was calculated.

Groups of five male and five female Crl:CD-1 (ICR) BR mice were exposed to acetonitrile (>99.9%) vapor for 4 h via whole-body exposure methods (MPI 1998). Mean analytic concentrations determined by infrared spectrometer analysis were 3,039, 5,000, 4,218, and 3,568 ppm (Groups 1-4, respectively). Combined sex mortalities were 20, 80, 90, and 50%, respectively. All mortalities occurred on the day of exposure, except for a single male that died in the low-exposure group on post-exposure day 1. Clinical signs observed during the exposure and up to 4-h post-exposure included death, decreased activity, abnormal gait, loss of righting reflex, slow respiration, labored breathing, rapid respiration, gasping, cold-to-the-touch splayed limbs, leaning to the right, and yellow body surface staining. Surviving animals from Groups 2-4 were judged normal by study day 2. Clinical signs observed during the 14-day observation period for animals exposed at 3,039 ppm included death, decreased activity, and decreased defecation; survivors in this group were judged normal by study day 5. At necropsy, no test article-related macroscopic findings were observed in male or female mice. All tissues were considered to be within normal limits. A 4 h LC_{50} of was calculated to be 3,587 ppm, with 95% confidence limits of 2,938-4,039 ppm.

A 13-week repeated exposure study (NTP 1996) described both lethal and nonlethal effects in mice; this study is described in Section 2.4.2.2.

The oral LD_{50} for acetonitrile was estimated to be 269 mg/kg in male ddY mice (Tanii and Hashimoto 1984).

An intraperitoneal LD_{50} for acetonitrile of 521 mg/kg was reported for mice (Lewis 1996). No further information was available.

2.4.1.3. Rabbits

Pozzani et al. (1959) exposed groups of four male rabbits to accurately metered acetonitrile vapor for 4 h at concentrations of 1,000, 2,000, or 4,000 ppm. Prostration, usually followed by convulsive seizures, preceded death, and necropsy of decedents showed moderate to marked pulmonary hemorrhage or congestion. Some of the surviving animals had these pulmonary effects at necropsy, but the effects were of less marked severity. No rabbits died at 1,000 or 2,000 ppm, and all four rabbits died at 4,000 ppm. An LC_{50} of 2,828 ppm was calculated.

2.4.1.4. Guinea Pigs

Pozzani et al. (1959) exposed groups of six guinea pigs to accurately metered acetonitrile vapor for 4 h at concentrations of 4,000, 8,000, or 16,000 ppm. Both males and females were used, but were not equally distributed between groups. Prostration, usually followed by convulsive seizures, preceded death, and necropsy of decedents showed moderate to marked pulmonary hemorrhage or congestion. Some of the surviving animals had these pulmonary effects at necropsy, but the effects were of less marked severity. No guinea pigs died at 4,000 ppm; and all six guinea pigs in both the 8,000- and 16,000-ppm groups died. An LC_{50} of 5,655 ppm was calculated.

2.4.1.5. Dogs

Pozzani et al. (1959) also exposed groups of male dogs to accurately metered acetonitrile vapor for 4 h at concentrations of 2,000, 8,000, 16,000, or 32,000 ppm. Prostration, usually followed by convulsive seizures, preceded death, and necropsy of decedents showed moderate to marked pulmonary hemorrhage or congestion. Some of the surviving animals also showed these pulmonary effects, but the effects were of less marked severity. Mortality was 0/2 at 2,000 ppm, 0/1 at 8,000 ppm, 3/3 at 16,000 ppm, and 1/1 at 32,000 ppm.

2.4.2. Nonlethal Toxicity

2.4.2.1. Rats

Nonlethal effects in rats were reported by Pozzani et al. (1959). The protocol the study is described in Section 2.4.1.1, and nonlethal effects were described as less than marked pulmonary congestion or hemorrhage.

Five male and five female rats were exposed to acetonitrile at 4,760 ppm in a 200-L glass chamber for 1 h and observed for 14 days (Northview Pacific Labs 1989). One female lost weight, but all other rats gained weight during the follow-up period. No rats died, and there were no gross abnormalities observed at necropsy. No further experimental details were presented.

In a repeated-exposure study, groups of 15 male and 15 female Carworth Farms-Wistar rats were exposed to acetonitrile at 0, 166, 330, or 655 ppm for 7 h/day, 5 days/week for 90 days (Pozzani et al. 1959). Air was drawn from the 200-L exposure chamber at a rate of 125 L/min, and the acetonitrile concentrations were measured four times daily. There were no treatment-related deaths, or effects on body, liver, or kidney weights. Rats in the 166-ppm group had histocyte clumps in the alveoli (1/28), and those in the 330-ppm group exhibited bronchitis, pneumonia, and atelectasis (3/26). In rats exposed at 655 ppm, alveolar capillary congestion and focal edema (10/27, $p < 0.001$), accompanied by bronchial inflammation, desquamation, and hypersecretion of mucous, were observed. Tubular cloudy swelling of the kidneys (8/27, $p < 0.005$) and central cloudy swelling of the livers (7/27, $p < 0.04$) were also found at 655 ppm. No other treatment-related effects were noted.

In another repeated-exposure study, groups of 10 male and 10 female F344/N rats were exposed to acetonitrile at 0, 100, 200, 400, 800, or 1,600 ppm for 6 h/day, 5 days/week for 13 weeks (NTP 1996). Vapor was generated by pumping liquid acetonitrile from a reservoir into a stainless steel vaporizer heated to 177°F. The acetonitrile vapor was then mixed with filtered air, and the mixture drawn into a stainless steel distribution manifold, diluted to desired concentrations by adjusting compressed air pressure to the vacuum pumps, and delivered to the 1.7-m^3 exposure chambers. Chamber concentrations were monitored by gas chromatography, and calibration was accomplished by acquiring grab samples from each exposure chamber. The samples were analyzed against gravimetrically prepared standards using an off-line gas chromatograph. The time required to achieve 90% of target concentrations after the start of vapor generation was 15-17 min, and the time required for chamber concentration to decay to 10% of target after vapor generation was terminated was 12-14 min. In the 800-ppm group, one male died during the first week of exposure. In the 1,600-ppm group, death occurred in six males (four during week 1, one during week 2, and one during week 4) and three females (one during week 1 and two during week 2). Hypoactivity and ruffled fur were observed during the first week of the study in males exposed at 800 ppm and in both sexes exposed at 1,600 ppm. Additionally, ataxia, abnormal posture, and clonic convulsions were noted in 1,600-ppm males that died during week 1. Decreased body weight gains were noted at 1,600 ppm, and depression of the myeloid system and mild hypothyroidism were also noted at 1,600 ppm. Gross necropsy findings were limited to animals that died early and included red, dark, and mottled lungs, and red foci on the brain. Increased absolute and/or relative kidney, heart, and liver weights and decreased thymus weights were noted at 800 and 1,600 ppm. No effects were reported at concentrations of 400 ppm or lower.

2.4.2.2. Mice

In a repeated-exposure study, groups of 10 male and 10 female B6C3F$_1$ mice were exposed to acetonitrile at 0, 100, 200, 400, 800, or 1,600 ppm for 6 h/day, 5 days/week for 13 weeks (NTP 1996). The vapor generation and exposure monitoring were the same to those described for tests in rats in Section 2.4.2.1. All mice in the 1,600-ppm group died during the first 3 weeks of the study, and one female and one male exposed at 400 ppm and four females exposed at 800 ppm died before the end of the study. Hypoactivity and hunched rigid posture were observed during the first week of the study in the 800- and 1,600-ppm groups. Decreased body weight gains were noted only in 800-ppm males. In males exposed at 200 ppm or higher, an increase in absolute liver weights was found; relative liver weights were increased in males in all exposure groups. In females, absolute liver weight was increased at 800 ppm, and relative liver weight was increased at concentrations of 400 ppm or higher. In males exposed at 400 ppm or higher and in females exposed at 200 ppm or higher, areas of focal epithelial hyperplasia and ulceration were observed in the forestomachs. An increased incidence of cytoplasmic vacuolization was found in livers of males and females exposed to acetonitrile at 400 and 800 ppm. A lack of fatty degenerative change was observed in the X-zone of the adrenal cortex of females exposed at 800 and 1,600 ppm. No effects were reported in mice exposed at 100 ppm.

2.4.2.3. Dogs

Pozzani et al. (1959) exposed three male hybrid dogs to acetonicrile at 350 ppm for 7 h/day, 5 days/week for 91 days. The inhalation chamber was a 7,900-L cube from which air was exhausted at 1,400 L/min. Liquid acetonitrile was delivered at a constant rate from a dual syringe feeder into a heated Pyrex evaporator. The vapor was then introduced into the chamber under slight negative pressure. Daily inhalation concentrations were estimated from the amount of liquid acetonitrile consumed and the mean daily dilution airflow. The lack of animal housing facilities precluded an air control group. Decreased body weights were on days 3-72. Hematocrit and hemoglobin values were decreased during the first 5 weeks of the study, but returned to normal by the end of the 91-day inhalation period. Focal emphysema and alveolar septa proliferation were found at necropsy.

2.4.2.4. Monkeys

Pozzani et al. (1959) exposed three adult male Rhesus monkeys to acetonitrile at 350 ppm for 7 h/day, 5 days/week for 91 days. The exposure conditions were that same as those used in the tests in dogs described in Section 2.4.2.3. Bronchitis was noted during the 91-day inhalation period. Necropsy revealed

moderate hemorrhage of superior and inferior sagittal sinuses of the brain; however, this effect was considered an artifact of postmortem alteration due to tissue handling procedures.

Pozzani et al. (1959) also reported that one Rhesus monkey exposed to acetonitrile at 2,510 ppm for 7 h/day appeared normal after the first day of inhalation; however, this animal exhibited poor coordination followed by prostration and labored breathing during the second exposure. This monkey died a few hours later. In another experiment, Pozzani et al. (1959) exposed two monkeys at 660 ppm for 7 h/day. Poor coordination was observed in both monkeys during the second week of exposure. One animal vomited before death on day 23 of exposure.

2.4.3. Developmental and Reproductive Toxicity

In a developmental toxicity study (Mast et al. 1994), Sprague-Dawley rats were exposed to acetonitrile at 0, 100, 400, or 1,200 ppm for 6 h/day, 7 days/week. Each group consisted of 10 nonpregnant females (comparison group), 10 positively mated females for a distribution study evaluating maternal blood for acetonitrile and cyanide, and 33 positively mated females for evaluating developmental toxicity. Rats were exposed for 14 consecutive days (on days 6-19 of gestation for pregnant animals). The vapor generation and exposure systems were similar to those described for the 13-week rat and mouse studies (NTP 1996) described in section 2.4.2.1. In the 400-ppm group, a single dam died on gestational day 14 due to spontaneous cerebral hemorrhage; the study authors did not report any signs of toxicity or note any other adverse findings on necropsy in this animal. In the 1,200-ppm group, three animals were killed in a moribund state (one nonpregnant rat and two dams); they had severe clinical signs of toxicity (hypoactivity and emaciation). Therefore, it appears that the single death in the 400-ppm group was unlikely to be due to acetonitrile exposure. No treatment-related effects on body weights or reproductive indices at any treatment level were observed, and there were no significant increases in fetal malformations or variations. Measurement of acetonitrile and cyanide concentrations in maternal blood showed that the acetonitrile concentration in blood increased with the exposure concentration. Cyanide was detected only in the blood of animals in the 1,200-ppm group.

Willhite (1983) exposed groups of 6-12 pregnant Syrian Golden hamsters to acetonitrile at 0, 1,800, 3,800, 5,000, or 8,000 ppm for 1 h on day 8 of gestation. Acetonitrile was mixed with a stream of dehumidified air at a rate of 10 L/min and delivered to a 45-L glass inhalation chamber. Chamber concentrations were measured by gas chromatography. No maternal or offspring effects were found at 1,800 ppm. One dam exposed at 3,800 ppm had dyspnea, tremors, hypersalivation, ataxia, and hypothermia at the end of the exposure period and died 3 h post-exposure. No other maternal effects and no offspring effects were found at 3,800 ppm. All dams exposed at 5,000 ppm exhibited excessive saliva-

tion, and one dam had dyspnea, hypothermia, and tremors at the conclusion of exposure; this animal died 5 h later. Six abnormal fetuses were found in two litters from the 5,000-ppm group; malformations included exencephalyencephalocoele and rib fusions. Four dams exposed at 8,000 ppm had respiratory difficulty, lethargy, ataxia, hypothermia, ocular and nasal irritation, and gasping. Three of these hamsters developed tremors followed by deep coma, and died within 90 min after exposure. The offspring from five of nine surviving litters of the 8,000-ppm group had severe axial skeletal dysraphic disorders, and average fetal body weight was decreased compared with air controls. Overall, there was an increase in the number of abnormal fetuses in the 5,000- and 8,000-ppm groups compared with controls. Although lethality data are not available to compare the sensitivity of pregnant and nonpregnant hamsters, increased sensitivity to acetonitrile during pregnancy is possible.

Saillenfait et al. (1993) exposed groups of 20 pregnant Sprague-Dawley rats to acetonitrile at nominal concentrations of 0, 900, 1,200, 1,500, or 1,800 ppm (analytic concentrations were 0, 1,000 ± 53.7, 1,287 ± 66.4, 1,592 ± 120.4, or 1,827 ± 138.5 ppm, respectively) for 6 h/day on days 6-20 of gestation. 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 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. Eight of 20 exposed females died (time-to-death not reported) in the 1,800 ppm group, and no other maternal deaths were observed. Maternal absolute weight gain was decreased ($p < 0.05$) to 60% of control values at 1,500 and 1,800 ppm. Increases ($p < 0.01$) in the mean percentage of nonsurviving implants and early embryonic resorptions were found in the 1,800-ppm group, and were accompanied by a decrease in mean number of live fetuses per litter. One litter was completely resorbed in a dam exposed at 1,800 ppm. No other treatment-related maternal or fetal effects were observed. Although this study involved repeated exposures, fetal death is relevant to AEGL values because fetal toxicity could result from a single exposure.

Results of an oral exposure study in pregnant rats show that acetonitrile can induce fetal toxicity after a single exposure (Saillenfait and Sabaté 2000). Pregnant Sprague-Dawley rats were administered a single oral dose of acetonitrile (2,000 mg/kg) on gestational day 10, and fetuses were examined for malformations on gestational day 12. Embryo viability was not affected, but abnormal development, including "overall poor and abnormal development" and misdirected allantois and trunk and/or caudal extremities were observed.

Johannsen et al. (1986) administered aqueous solutions of acetonitrile at concentrations of 0, 125, 190, or 275 mg/kg by gavage to pregnant rats on days 6-19 of gestation. Maternal body weights were decreased and death occurred in

high-dose dams; no other maternal effects were found at lower concentrations. Increases in early resorptions and post-implantation losses were found only in the high-dose group, and no teratogenic effects were found in any dose group.

Groups of 25 pregnant New Zealand white rabbits were administered acetonitrile at 0, 2.0, 15.0, or 30.0 mg/kg/day by gavage on days 6-18 of gestation (Argus Research Labs 1984). Rabbits in the high-dose group had decreased body weight gain and anorexia, and death occurred in five animals. Body weight was also decreased in the dames exposed at 15 mg/kg/day. A decrease ($p = 0.011$) in the average number of live fetuses in high-dose group was found, but no other fetal effects were noted in any dose group.

2.4.4. Genotoxicity

Acetonitrile did not induce mutations in *Salmonella typhimurium* (Mortelmans et al. 1986; Schlegelmilch et al. 1988; NTP 1996) or L5178Y mouse lymphoma cells with or without metabolic activation (S9). A weakly positive response was obtained in a sister-chromatid exchange assay in cultured Chinese hamster ovary cells only in the presence of S9 (NTP 1996). In another study, slight increases in sister-chromatid exchange frequency were found in cultured Chinese hamster ovary cells without S9 and slight increases in chromosomal aberrations occurred with S9 (Galloway et al. 1987). There was an increase in micronucleated normochromatic erythrocytes in peripheral blood samples from male mice exposed to acetonitrile for 13 weeks; however, the frequency was not affected in female mice treated similarly (NTP 1996). There was no increase in unscheduled DNA synthesis in rat hepatocytes in vivo or in vitro. Sex chromosome aneuploidy was induced in the oocytes of female *Drosophila melanogaster* fed acetonitrile as larvae or as adults (Osgood et al. 1991), and acetonitrile induced aneuploidy, but no point mutations or recombination, in *Sacchromyces cerevisiae* (Zimmermann et al. 1985).

2.4.5. Carcinogenicity

In a carcinogenicity study, groups of 56 male and 56 female F344/N rats were exposed to acetonitrile at 0, 100, 200, or 400 ppm for 6 h/day, 5 days/week for 2 years (NTP 1996). The vapor was generated by pumping liquid acetonitrile from a reservoir to a stainless steel vaporizer heated at 200°F. The acetonitrile vapor was then mixed with filtered air, and the mixture drawn into a stainless steel distribution manifold, diluted to desired concentrations by adjusting compressed air pressure to the vacuum pumps, and delivered to the 1.7-m^3 exposure chambers. Chamber concentrations were monitored by gas chromatography, and calibration was accomplished by acquiring grab samples from each exposure chamber. The samples were analyzed against gravimetrically prepared standards using an off-line gas chromatograph. The time to achieve 90% of target concentrations after the start of vapor generation was 10-15 min, and the time for

chamber concentration to decay to 10% of target after vapor generation was terminated was 14-17 min. No treatment-related effects on survival, mean body weights, organ weights, clinical signs, or hematological parameters were found. There was an increased incidence of hepatocellular adenoma (3/48), hepatocellular carcinoma (3/48), and hepatocellular adenoma or carcinoma combined (5/48) in male rats exposed at 400 ppm compared with controls (one carcinoma). The incidences of hepatocellular adenoma and carcinoma were within the ranges found for historical controls. However, the incidence of the adenoma or carcinoma combined (10%) slightly exceeded the range of the historical controls (2-8%). There were no exposure-related lesions in female rats. NTP concluded that there was equivocal evidence of carcinogenic activity in male F344/N rats based on marginally increased incidences of hepatocellular adenoma and carcinoma. There was no evidence of carcinogenic activity of acetonitrile in female rats exposed to acetonitrile at 100, 200, or 400 ppm.

In a carcinogenicity study, groups of 60 male and 60 female B6C3F_1 mice were exposed to acetonitrile at 0, 50, 100, or 200 ppm for 6 h/day, 5 days/week for 2 years (NTP 1996). The vapor generation and exposure systems were the same as those described above for the rat cancer bioassay. No treatment-related effects on survival, mean body weights, organ weights, clinical signs, or hematological parameters were found. There was a concentration-related increased incidence of squamous hyperplasia of the forestomach epithelium in all exposure groups. There were no treatment-related increases in the incidences of neoplasms. NTP concluded that there was no evidence of carcinogenic activity of acetonitrile in male or female B6C3F_1 mice exposed at 50, 100, or 200 ppm.

2.4.6. Summary

Acetonitrile produces toxic effects consistent with those observed with cyanide poisoning. Effects observed in experimental animals include labored breathing, dyspnea, hypoactivity, ataxia, abnormal posture, convulsions, and pulmonary histopathology. Prostration followed by seizures often precedes death. Both lethal and sublethal data indicate that mice, pregnant hamsters, guinea pigs, rabbits, dogs, and monkeys are more sensitive than rats to the effects of acetonitrile. Lethal effects of acetonitrile are summarized in Table 1-5 and sublethal effects are summarized in Table 1-6.

There was a significant and concentration-dependent increase in the number of abnormal fetuses in hamsters exposed to acetonitrile via inhalation. In rats and rabbits, acetonitrile was not toxic to fetuses at concentrations below those causing maternal toxicity; however, fetal death was observed under exposure conditions that produced maternal death. Although the developmental studies involved repeated exposures, fetal death is relevant AEGL values because fetal toxicity could result from a single exposure. Acetonitrile was not active in gene-mutation assays of bacteria or cultured mammalian cells; however, it was positive in assays

TABLE 1-5 Summary of Lethal Effects of Acetonitrile in Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Acute exposure				
Rat	53,000	15 min	No death	Pozzani et al. 1959
Rat	53,000	30 min	50% mortality (3/6)	Pozzani et al. 1959
Rat	25,000	30 min	100% mortality (3/3)	Haguenoer et al. 1975
Rat	4,000	4 h	10% mortality (3/30)	UCC 1965
Rat	8,000	4 h	33% mortality (10/30)	UCC 1965
Rat	16,000	4 h	LC_{50}	Pozzani et al. 1959
Rat	19,500	4 h	LC_{50}	Monsanto 1986
Rat	17,100	4 h	LC_{50}	DuPont 1968
Rat	16,000	4 h	57% mortality (17/30)	UCC 1965
Rat (male)	7,551	8 h	LC_{50}	Pozzani et al. 1959
Rat (female)	12,435	8 h	LC_{50}	Pozzani et al. 1959
Mouse	2,693	1 h	LC_{50}	Willhite 1981
Mouse	5,000	1 h	100% mortality (10/10)	Willhite 1981
Mouse	3,587	4 h	LC_{50}	MPI 1998
Hamster (pregnant)	1,800	1 h	No maternal death	Willhite 1983
Hamster (pregnant)	3,800	1 h	No embryo lethality	Willhite 1983
Hamster (pregnant)	3,800	1 h	16% mortality (1/6)	Willhite 1983
Rabbit	4,000	4 h	LC_{50}	Pozzani et al. 1959
Guinea pig	5,655	4 h	LC_{50}	Pozzani et al. 1959
Dog	16,000	4 h	100% mortality (3/3)	Pozzani et al. 1959
Dog	32,000	4 h	100% mortality (1/1)	Pozzani et al. 1959

Repeated exposure				
Mouse (female)	200	6 h/d, 5 d/wk, 13 wk	No death	NTP 1996
Mouse (male)	400	6 h/d, 5 d/wk, 13 wk	No death	NTP 1996
Rat (male)	400	6 h/d, 5 d/wk, 13 wk	No death	NTP 1996
Rat (pregnant and non-pregnant females)	400	6 h/d, 7 d/wk, gestational days 6-19	No death[a]	Mast et al. 1994
Mouse (female)	400	6 h/d, 5 d/wk, 13 wk	10% mortality (1/10)[b]	NTP 1996
Rat (female)	800	6 h/d, 5 d/wk, 13 wk	No death	NTP 1996
Rat (male)	800	6 h/d, 5 d/wk, 13 wk	10% mortality (1/10)[c]	NTP 1996
Mouse (male)	800	6 h/d, 5 d/wk, 13 wk	10% mortality (1/10)[d]	NTP 1996
Rat (female)	1,200	6 h/d, 7 d/wk, 14 exposures (mimicking gestational days 6-19)	10% mortality (1/10)[e]	Mast et al. 1994
Rat (pregnant)	1,200	6 h/d, 7 d/wk, gestational days 6-19	6% mortality (2/33) in dams[f]; no embryo lethality	Mast et al. 1994
Rat (pregnant)	1,500	6 h/d, gestational days 6-20	No maternal death or embryo lethality	Saillenfait et al. 1993
Rat (female)	1,600	6 h/d, 5 d/wk, 13 wk	30% mortality (3/10)[g]	NTP 1996
Rat (pregnant)	1,800	6 h/d, gestational days 6-20	40% mortality (8/20) in dams; embryo lethality[h]	Saillenfait et al. 1993

[a]One dam died on gestational day 14 due to spontaneous cerebral hemorrhage; this effect was probably unrelated to acetonitrile exposure.
[b]Death occurred during week 2.
[c]Death occurred during week 1.
[d]Death occurred sometime during weeks 6-13.
[e]Death occurred on gestational day 8.
[f]Deaths occurred on gestational days 15 and 19.
[g]Deaths occurred during weeks 1-2.
[h]Increase in mean percentage of nonsurviving implants and early embryonic resorptions; decrease in mean number of live fetuses per litter; total resorption of one litter. Time-to-death of dams was not reported.

TABLE 1-6 Summary of Sublethal Effects of Acetonitrile in Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Acute exposure				
Rat	4,000	4 h	Less than marked pulmonary congestion or hemorrhage.	Pozzani et al. 1959
Rat	1,000	8 h	Less than marked pulmonary congestion or hemorrhage.	Pozzani et al. 1959
Rabbit	2,000	4 h	Less than marked pulmonary congestion or hemorrhage.	Pozzani et al. 1959
Guinea pig	4,000	4 h	Less than marked pulmonary congestion or hemorrhage.	Pozzani et al. 1959
Dog	2,000	4 h	Less than marked pulmonary congestion or hemorrhage.	Pozzani et al. 1959
Monkey	2,510	7 h	No effect.	Pozzani et al. 1959
Repeated exposure				
Rat	2,800	2 h, up to 5 d	Labored breathing, temporary anuria, diarrhea.	Haguenoer et al. 1975
Rat	166	7 h/d, 5 d/wk, 90 d	Histiocyte clumps in alveoli.	Pozzani et al. 1959
Rat	330	7 h/d, 5 d/wk, 90 d	Bronchitis, pneumonia, atelectasis.	Pozzani et al. 1959
Rat	655	7 h/d, 5 d/wk, 90 d	Bronchial inflammation, desquammation, mucous hypersecretion, hepatic and renal lesions.	Pozzani et al. 1959
Rat	400	6 h/d, 5 d/wk, 90 d	No effect.	NTP 1996
Rat	800	6 h/d, 5 d/wk, 90 d	Hypoactivity, ruffled fur (wk 1), death (1/10 male), increased organ weights.	NTP 1996
Rat	1,600	6 h/d, 5 d/wk, 90 d	Hypoactivity, ruffled fur (wk 1), ataxia, abnormal posture, convulsions, decreased body weight, death, increased organ weights, gross lung and brain lesions.	NTP 1996
Mouse	100	6 h/d, 5 d/wk, 90 d	No effect.	NTP 1996
Mouse	200	6 h/d, 5 d/wk, 90 d	Increased liver weight; forestomach pathology.	NTP 1996
Mouse	400	6 h/d, 5 d/wk, 90 d	Increased liver weight, forestomach pathology, increased cytoplasmic vacuolization of liver, death.	NTP 1996

Mouse	800; 1,600	6 h/d, 5 d/wk, 90 d	Hypoactivity, hunched rigid posture, decreased body weight gain (in 800-ppm group only), increased liver weight, forestomach pathology, increased cytoplasmic vacuolization of liver, death.	NTP 1996
Dog	350	7 h/d, 5 d/wk, 90 d	Transitory decreases in body weight, transitory decreases in hemoglobin and hematocrit.	Pozzani et al. 1959
Monkey	350	7 h/d, 5 d/wk, 90 d	Bronchitis, moderate brain sinus hemorrhage.	Pozzani et al. 1959
Monkey	2,510	7 h/d, 2 d	Poor coordination, labored breathing, prostration, death.	Pozzani et al. 1959

designed to detect chromosome aberrations. There was equivocal evidence of carcinogenic activity in male F344/N rats based on marginally increased incidences of hepatocellular adenoma and carcinoma. There was no evidence of carcinogenic activity of acetonitrile in female F344/N rats or in male or female $B6C3F_1$ mice.

2.5. Data Analysis for AEGL-1

2.5.1. Human Data Relevant to AEGL-1

Pozzani et al. (1959) studied three male volunteers (ages 31-47) who inhaled acetonitrile at 40 ppm for 4 h. The two older subjects reported no subjective symptoms during or after the inhalation period. The youngest subject reported no adverse subjective response during exposure, but experienced slight chest tightness that evening. The following morning, he reported a cooling sensation in the lungs, which persisted for 24 h and was described as being similar to that experienced when menthol was inhaled. The two older subjects were exposed 1 week later to acetonitrile at 80 ppm for 4 h; no symptoms were reported. Nine days after the 80-ppm exposure, the same two subjects were exposed at 160 ppm for 4 h. One subject reported a slight transitory flushing of the face 2 h after inhalation and slight bronchial tightness 5 h later, which resolved overnight.

2.5.2. Animal Data Relevant to AEGL-1

Effects observed in experimental animals exposed to acetonitrile by inhalation are generally no-effect levels or more severe than those defined by AEGL-1.

2.5.3. Derivation of AEGL-1 Values

The slight chest tightness and cooling sensation in the lungs reported by one of three male volunteers exposed to acetonitrile at 40 ppm for 4 h (Pozzani et al. 1959) was selected as the basis for AEGL-1 values. An interspecies uncertainty factor of 1 was applied because the study involved humans. An intraspecies uncertainty factor of 1 was applied, because the mild effects are considered to have occurred in a sensitive subject since no symptoms were reported by two other subjects exposed at the same concentration or at a higher concentration of 80 ppm for 4 h. A modifying factor of 3 was applied to account for the sparse database. The resulting 4-h AEGL value of 13 ppm was held constant across the 10-, 30-min, and 1-h durations because no human data exist for periods of less than 4 h; thus, time scaling to shorter durations could yield values eliciting symptoms above those defined by AEGL-1. An 8-h AEGL-1 value was not derived because 13 ppm is essentially equal to the 8-h AEGL-2 value of 14 ppm. AEGL-1 values for acetonitrile are presented in Table 1-7, and the calculations are presented in Appendix B.

TABLE 1-7 AEGL-1 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	NR[a]

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

2.6. Data Analysis for AEGL-2

2.6.1. Human Data Relevant to AEGL-2

Case reports describing human poisonings from acetonitrile leading to effects consistent with the definition of AEGL-2 exist. However, due to the lack of reliable concentration and duration information, the data are not appropriate for deriving AEGL-2 values.

2.6.2. Animal Data Relevant to AEGL-2

Pulmonary congestion or hemorrhage, described by the investigators as less than "moderate to marked pulmonary hemorrhage or congestion" was observed in rats exposed to acetonitrile at 4,000 ppm for 4 h or at 1,000 ppm for 8 h, in rabbits exposed at 2,000 ppm for 4 h, in guinea pigs exposed at 4,000 ppm for 4 h, and in dogs exposed at 2,000 ppm for 4 h (Pozzani et al. 1959). These effects are considered to be AEGL-2 level effects. No-effect levels for these effects were not identified.

2.6.3. Derivation of AEGL-2 Values

At nonlethal concentrations, AEGL-2 level effects, described as less than "moderate to marked pulmonary hemorrhage or congestion" were observed in rats (Pozzani et al. 1959). Since no-effect levels for AEGL-2 level effects were not identified, the data are not appropriate for deriving AEGL-2 values. Therefore, AEGL-2 values were estimated by dividing AEGL-3 values by 3. AEGL-2 values for acetonitrile are presented in Table 1-8.

These values are considered protective because one of two human volunteers exposed to acetonitrile at 160 ppm for 4 h experienced only a slight transitory flushing of the face 2 h after exposure and slight bronchial tightness 5 h later, which resolved overnight. Blood cyanide and urinary thiocyanate values were similar before and after exposure (Pozzani et al. 1959). Also, mice, the species most sensitive to acetonitrile, exhibited no effects after repeated exposure at 100 ppm (6 h/day, 5 days/week for 90 days), and had only increased liver weight and forestomach pathology when exposed at 200 ppm (6 h/day, 5 days/week for 90 days) (NTP 1996).

TABLE 1-8 AEGL-2 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)

2.7. Data Analysis for AEGL-3

2.7.1. Human Data Relevant to AEGL-3

Human lethality data on acetonitrile were anecdotal and lacked reliable concentration and exposure duration information. Thus, those reports were not appropriate for establishing AEGL-3 values.

2.7.2. Animal Data Relevant to AEGL-3

Lethality studies of single exposures to acetonitrile are available for rats (Pozzani et al. 1959; DuPont 1968; UCC 1965; Haguenoer et al. 1975; Monsanto 1986), mice (Willhite 1981), pregnant hamsters (Willhite 1983), rabbits, guinea pigs, and dogs (Pozzani et al. 1959). The lowest nonlethal-effect concentration observed for a single exposure was 1,800 ppm in pregnant hamsters exposed for 1 h (Willhite 1983). Deaths were reported in male and female rats exposed repeatedly to acetonitrile at 800 and 1,600 ppm, respectively, during the first week of exposure (NTP 1996). Gestational exposure studies provide additional information on maternal death and embryo lethality. Maternal death and increased fetal resorptions were observed in rats exposed to acetonitrile at 1,800 for 6 h/day on gestational days 6-20, with a no-effect level for maternal and fetal death (resorptions) of 1,500 ppm for 6 h/day (Saillenfait et al. 1993). Maternal death, but not fetal death, was observed in rats exposed at 1,200 ppm for 6 h/day on gestational days 6-19 Mast et al. 1994).

2.7.3. Derivation of AEGL-3 Values

The no-effect level for maternal and fetal mortality in pregnant rats exposed to acetonitrile at 1,500 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was the point of departure for deriving AEGL-3 values. Although the study involved repeated exposures, fetal death can occur during a narrow developmental window and does not necessarily require repeated exposures (Van Raaij et al. 2003). Therefore, the observation of increased fetal death following repeated gestational exposure is considered appropriate for derivation of AEGL-3 values. In addition, although the study identified no-effect levels for mortality that were below those observed in studies of single exposures of nonpregnant animals, it is possible that sensitivity to acetonitrile may increase during pregnancy. The point of departure of 1,500 ppm is supported by observa-

tions of lethality in repeated exposure studies. In a 13-week study (6 h/day, 5 days/week), deaths were observed during the first week of exposure (number of days-to-death was not reported) in males exposed at 800 and 1,600 ppm and in females exposed at 1,600 ppm (NTP 1996). Two maternal deaths (on gestational days 15 and 19), but no fetal deaths, were observed in rats exposed at 1,200 ppm (6 h/day) on gestational days 6-19 (Mast et al. 1994). As noted above, embryonic death could occur after a single exposure. Thus, the 6-h no-effect level for fetal death of 1,200 ppm reported by Mast et al. (1994) supports the 6-h no-effect level for maternal and fetal lethality in the Saillenfait et al. (1993) study as the point of departure for deriving AEGL-3 values.

An interspecies uncertainty factor of 10 was applied because no comparable data were identified for similar exposures (repeated inhalation exposure during gestation) in other species. 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). Thus, the total uncertainty factor is 30. The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$ (ten Berge et al. 1986). An empirical value for n of 1.6 was used (see Section 1.6 and Appendix A for how the value was determined). Time scaling was not performed for the 10-min AEGL-3 value, because of the uncertainty associated with extrapolating a point of departure based on a 6-h exposure duration to a 10-min value. The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value. AEGL-3 values for acetonitrile are presented in Table 1-9, and the calculations are presented in Appendix B.

2.8. Summary of AEGLs

2.8.1. AEGL Values and Toxicity End Points

AEGL values for acetonitrile are presented in Table 1-10. Slight chest tightness and cooling sensation in the lungs of one of three human volunteers was used as the basis for the AEGL-1 values. Data were inadequate for deriving AEGL-2 values, so estimates were made by dividing the AEGL-3 values by 3. The no-effect level for maternal and fetal lethality (increased resorptions) in rats was the basis for the AEGL-3 values.

TABLE 1-9 AEGL-3 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)

TABLE 1-10 AEGL Values for Acetonitrile

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	NR[a]
AEGL-2 (disabling)	80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)
AEGL-3 (lethal)	240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)

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

2.8.2. Other Standards and Guidelines

Exposure standards and guidelines for acetonitrile have been established by several organizations (see Table 1-11). The 30-min immediately dangerous to life or health value (IDLH) of 500 ppm is substantially higher than 10- and 30-min AEGL-3 values. The AEGL-3 values are based on a no-effect level for lethality in rats, whereas the IDLH value is based on an acute inhalation study in humans showing that a 4-h exposure to acetonitrile at 160 ppm caused flushing and a feeling of chest constriction (Pozzani et al. 1959) and exposure at 500 ppm (duration not specified) caused irritation to the nose and throat. The recommended exposure limit of the National Institute for Occupational Safety and Health and the threshold limit value of the American Conference of Governmental Industrial Hygienists of 20 ppm are based on human data showing that exposure to acetonitrile at 40 ppm for 4 h caused no effects in two volunteers and the sensation of cooling in the lungs and slight tightness of the chest in a third volunteer (Pozzani et al. 1959). The permissible exposure limit of the Occupational Safety and Health Administration of 40 ppm is based on the risks of organic cyanide poisoning and liver and respiratory tract injuries associated with exposure to acetonitrile. The German maximum workplace concentration for acetonitrile was derived from a 2-year study in rats showing a dose-dependent increase in basophilic foci in the liver at concentrations of 100 ppm and higher. The basis of the Dutch maximal accepted concentration for acetonitrile was not found.

2.8.3. Data Adequacy and Research Needs

Data were adequate for deriving AEGL-1 and AEGL-3 values for acetonitrile, and AEGL-2 values were based on the AEGL-3 values. However, human data include just one experimental study and several anecdotal reports, so additional supporting data for AEGL-1 values in humans or animals are needed. Animal data are available for several species, with the vast majority of studies using the rat. The animal data suggest that, as with other nitriles, the rat is more resistant to the toxic effects of acetonitrile than are other species. For other nitriles, data suggest that this interspecies difference is due to the rate of metabolic

cyanide liberation. However, no definitive data are available to explain this interspecies difference for acetonitrile.

TABLE 1-11 Other Standards and Guidelines for Acetonitrile

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	NR[a]
AEGL-2	80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)
AEGL-3	240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)
IDLH (NIOSH)[b]	500 ppm (840 mg/m^3)	–	–	–	–
TLV-TWA (ACGIH®)[c]	–	–	–	–	20 ppm (34 mg/m^3)
REL-TWA (NIOSH)[d]	–	–	–	–	20 ppm (34 mg/m^3)
PEL-TWA (OSHA)[e]	–	–	–	–	40 ppm (70 mg/m^3)
MAK (Germany)[f]	–	–	–	–	20 ppm (34 mg/m^3)
MAC (The Netherlands)[g]	–	–	–	–	40 ppm (70 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]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The IDLH for acetonitrile is based on acute inhalation toxicity data in humans; comment is made in supporting documentation that this may be a conservative value.

[c]TLV-TWA (threshold limit value—time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) 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.

[d]REL-TWA (recommended exposure limit—time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011a) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/wk.

[e]PEL-TWA (permissible exposure limit—time-weighted average, Occupational Safety and Health Administration) (29 CFR 1910.1000 [1999]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 8 h/d, 40 h/wk.

[f]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2012) is defined analogous to the ACGIH TLV- TWA.

[g]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.

3. ISOBUTYRONITRILE

3.1. Summary

Isobutyronitrile is a colorless liquid at ambient temperature and pressure. It has an almond-like odor 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 (EPA 1985). These same signs have been reported in humans exposed to hydrogen cyanide (Blanc et al. 1985).

Data were insufficient to derive AEGL-1 values for isobutyronitrile. Data were also insufficient for deriving AEGL-2 values for isobutyronitrile, so the values were estimated by dividing AEGL-3 values by 3.

The no-effect level for maternal mortality in pregnant rats exposed to isobutyronitrile at 100 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was used as the point of departure for deriving AEGL-3 values for isobutyronitrile. Although the Saillenfait et al. (1993) study involved repeated exposures, the day on which the dams died and the number of exposures at the next highest dose (200 ppm) that preceded death were not reported; therefore, it is possible that the deaths could have resulted from a single exposure. The study identified no-effect levels for mortality that were lower than those observed in studies involving single exposures to nonpregnant animals; this might reflect a higher sensitivity of pregnant animals to the lethal effects of isobutyronitrile. Therefore, the no-effect level of 100 ppm for maternal toxicity (mortality) is considered appropriate for deriving 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 10 was also applied because no comparable studies of similar exposures (repeated inhalation exposure during gestation) in other species were available. Thus, the total uncertainty factor is 30. Time scaling was performed using 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 isobutyronitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min, 1h, and 4 h) 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 6-h exposure to a 10-min value.

The AEGL values for isobutyronitrile are presented in Table 1-12.

TABLE 1-12 AEGL Values for Isobutyronitrile

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)	2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)	No-effect level for maternal lethality (Saillenfait et al. 1993)

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

3.2. Introduction

Isobutyronitrile is a colorless liquid at ambient temperature and pressure. It has an almond-like odor and may cause irritation or burning of the eyes and skin.

Isobutyronitrile is produced from isobutyraldehyde by cyanation with ammonia. It is used in organic synthesis, as a catalyst in the polymerization of ethylene, as an intermediate for insecticides, and as a gasoline additive (HSDB 2003a).

The chemical and physical properties of isobutyronitrile are presented in Table 1-13.

3.3. Human Toxicity Data

3.3.1. Acute Lethality

Information concerning death in humans following inhalation exposure to isobutyronitrile is not available.

3.3.2. Nonlethal Toxicity

3.3.2.1. Case Report

A 44-year-old man was occupationally exposed to isobutyronitrile while filling a tank (Thiess and Hey 1969). He became unconscious, exhibited tonic and clonic movements of the arms, had a soft thready pulse, exhibited dilated pupils, had shallow and gasping breathing, and secreted viscous, glossy mucous from glands of the oropharyngeal area. He was admitted to the hospital, and his

TABLE 1-13 Chemical and Physical Data for Isobutyronitrile

Parameter	Data	Reference
Common name	Isobutyronitrile	HSDB 2003a
Synonyms	2-Methylpropanenitrile; 1-cyano-1-methylethane; 2-cyanopropane; 2-methylpropionitrile; dimethylacetonitrile; isopropyl cyanide; propanoic acid, 2-methyl-, nitrile	HSDB 2003a
CAS registry no.	78-82-0	HSDB 2003a
Chemical formula	C_4H_7N	HSDB 2003a
Molecular weight	69.1	HSDB 2003a
Physical state	Colorless liquid	HSDB 2003a
Melting point	-71.5°C	HSDB 2003a
Boiling point	103.9°C	HSDB 2003a
Density/Specific gravity	0.7704 at 20°C	HSDB 2003a
Solubility	Slightly soluble in water; soluble in alcohol and ether	HSDB 2003a
Vapor density	2.38 (air = 1)	HSDB 2003a
Vapor pressure	32.7 mm Hg at 25°C	HSDB 2003a
Conversion factors in air	1 ppm = 2.83 mg/m^3 1 mg/m^3 = 0.35 ppm	NIOSH 2011b

condition worsened; tonic and clonic movements continued and were accompanied by clenched teeth, a cold sweat on the forehead, and cyanosis. He was treated with norepinephrine, amyl nitrite, sodium nitrite, and sodium thiosulfate, followed by lobeline and phenobarbital. He improved within 5-10 min of treatment, and regained consciousness 4 h after the exposure. He complained of a headache for a few days. He was discharged from the hospital 14 days after the accident. The report did not provide estimates of the exposure concentration or duration.

Zeller et al. (1969) reported that two workers exposed to isobutyronitrile experienced headache, dizziness, and vomiting 10-60 min after exposure. The severity of symptoms reportedly varied with concentration and exposure duration; however, no concentration or duration information was reported.

An exposure of "a few minutes" to isobutyronitrile at estimated concentrations of 20-25 ppm during a spill did not produce symptoms of cyanide poisoning (AIHA 1992).

3.3.3. Developmental and Reproductive Toxicity

Developmental and reproductive studies regarding acute human exposure to isobutyronitrile were not available.

3.3.4. Genotoxicity

Genotoxicity studies regarding acute human exposure to isobutyronitrile were not available.

3.3.5. Carcinogenicity

Carcinogenicity studies regarding human exposure to isobutyronitrile were not available.

3.3.6. Summary

Data concerning human exposure to isobutyronitrile are limited to occupational case reports lacking exposure concentration and duration information. The reports indicate that clinical signs are consistent with those of cyanide poisoning. No human studies of the developmental or reproductive toxicity, genotoxicity, or carcinogenicity of isobutryonitrile were available.

3.4. Animal Toxicity Data

3.4.1. Acute Lethality

3.4.1.1. Rats

Groups of five male and five female CRL:CD(SD)BR rats were exposed to isobutyronitrile at target vapor concentrations of 1,200, 1,800, or 2,700 ppm for 1 h, followed by a 14-day observation period (Katz 1986). Exposures were conducted in 420-L stainless steel and glass inhalation chambers maintained under negative pressure and at 13 air changes per hour. Vapors were generated by metering the test material dropwise into a heated glass bead-packed column supplied with metered dried, oil-free compressed air. Chamber concentrations were determined four times per hour by an infrared analyzer equipped for automated sampling and analysis. Temperature and humidity were determined twice per hour and test material distribution was determined initially by measurement from numerous chamber positions and then from a fixed reference position. Actual mean exposure concentrations were 1,248 ± 62 ppm, 1,778 ± 16 ppm, and 2,709 ± 34 ppm for the 1,200-, 1,800-, and 2,700-ppm groups, respectively. All animals exposed at 1,800 and 2,700 ppm exhibited lethargy during exposure; the effect was minor at 1,800 ppm, whereas rats in the 2,700-ppm group developed gait disturbances followed by narcosis. Lethargy was observed in 1,800- and 2,700-ppm animals for up to 24 h after exposure. No clinical signs were noted at 1,200 ppm. Mortality was 1/5 (males) and 0/5 (females) at 1,200 ppm; 4/5 (males) and 1/5 (females) at 1,800 ppm; and 5/5 (males) and 3/5 (females) at 2,700 ppm. All deaths occurred within 48-h post-exposure. One-hour LC_{10} val-

ues of 1,143 ppm and 1,630 ppm were calculated for males and females, respectively; the combined LC_{10} was 1,173 ppm. A combined LC_{01} of 677 ppm was also calculated. No treatment-related histopathologic effects were reported.

As an adjunct to the above study, groups of four male CRL:CD(SD)BR rats were exposed to isobutyronitrile at target vapor concentrations of 0, 1,200, 1,800, or 2,700 ppm for 1 h (Eastman Kodak 1986a). The exposures were conducted using the same method as the study by Katz (1986). Pulmonary function tests (lung volume and capacity, ventilation, dynamic compliance, and airway resistance) were performed on the day before and the day after exposure. Animals were killed on day 7, and no necropsies were performed. All four animals from the 2,700-ppm group and two of four animals from the 1,800-ppm group died before pulmonary function tests could be performed. The small sample size and high mortality prevented statistical analysis of the pulmonary function data. However, "appreciable" differences were noted between pre- and post-exposure values for the four 1,200-ppm and two surviving 1,800-ppm rats. Differences were noted in expiratory reserve volume, residual volume, dynamic compliance (up to 76% decrease), and forced expiratory volume (FEV) 10%.

In another study, five male and five female CRL:CD(SD)BR rats were similarly exposed to a isobutyronitrile at a target vapor concentration of 1,200 ppm for 1 h (Eastman Kodak 1986b). Actual mean vapor concentrations were 1,233 ± 15 ppm for males and 1,177 ± 53 ppm for females. One male died within 1 day following exposure. No other effects were reported.

Tsurumi and Kawada (1971) exposed groups of 10 rats (sex and strain not specified) to a nominally saturated atmosphere (approximately 37,000 ppm at 20°C) of isobutyronitrile for up to 10 min. Surviving animals were observed for 24 h, and the fraction of deaths occurring as a function of exposure duration was recorded (see Table 1-14).

Tsurumi and Kawada (1971) administered single intraperitoneal or oral doses of isobutyronitrile to groups of six female Wistar rats, and the animals were observed for 72 h. Clinical signs included clonic movements and decreased respiratory frequency and depth, followed by complete respiratory failure and death. An intraperitoneal LD_{50} of 190 mg/kg and oral LD_{50} of 100 mg/kg were calculated.

3.4.1.2. Mice

Tsurumi and Kawada (1971) exposed groups of 10 mice (sex and strain not specified) to a nominally saturated atmosphere (approximately 37,000 ppm at 20°C) of isobutyronitrile for up to 10 min. Surviving animals were observed for 24 h, and the fraction of deaths occurring as a function of exposure duration was recorded (see Table 1-14).

TABLE 1-14 Deaths within 24 Hours of Exposure to Isobutyronitrile at Nominal Saturation of 37,000 ppm

Species	Exposure Duration (min)	Mortality
Rats	4.0	0/10
	5.0	1/10
	6.0	4/10
	8.0	6/10
	10.0	10/10
Mice	0.25	0/10
	0.5	3/10
	1.0	5/10
	1.5	7/10
	2.0	10/10

Source: Data from Tsurumi and Kawada 1971.

Tsurumi and Kawada (1971) administered single intraperitoneal doses of isobutyronitrile ranging from 0.4 to 0.8 mg/kg to groups of male mice, and the animals were observed for 72 h. Clinical signs included clonic movements and decreased respiratory frequency and depth, followed by complete respiratory failure 20-30 min after injection and death. The lethal dose could not be determined due to the potency of the compound and the difficulty of administering smaller doses.

The oral LD_{50} for isobutyronitrile was estimated to be 25 mg/kg in male ddY mice (Tanii and Hashimoto 1986).

3.4.1.3. Rabbits

Rabbits (sex, strain, age, and number not reported) were administered isobutyronitrile intravenously to assess effects on cardiac function (Tsurumi and Kawada 1971). At doses below 0.01 mg/kg, no effects were noted. At doses above 0.01 mg/kg, decreased blood pressure, blood flow, and respiration were noted. A dose of 0.1 mg/kg resulted in death within 30-40 min after exposure.

3.4.2. Nonlethal Toxicity

Smyth et al. (1962) reported that exposure of six rats to isobutyronitrile at a nominal concentration of 500 ppm for 4 h resulted in no mortality. No other details were available.

In a repeated-exposure study, groups of 10 male and 10 female Wistar rats were administered isobutyronitrile once a day for 14 days either by intraperitoneal injection (23.2 or 38.6 mg/kg) or orally (0.2 g/kg). No clinical signs or death were

reported. Males in the 0.2 g/kg-group had decreased mean body weights, and males and females exposed at 0.2 g/kg had slightly increased stomach, liver, and adrenal weights compared with controls. Rats in the 38.6 mg/kg-group had parenchymous liver degeneration (Tsurumi and Kawada 1971).

3.4.3. Developmental and Reproductive Toxicity

Saillenfait et al. (1993) exposed groups of 21 pregnant Sprague-Dawley rats to isobutyronitrile at nominal concentrations of 0, 50, 100, 200, or 300 ppm (analytic concentrations were 54 ± 2.3, 98 ± 10, 208 ± 12.4, or 308 ± 18.6 ppm, respectively) for 6 h/day on days 6-20 of gestation. Exposures were 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 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. One of 21 exposed females died in the 200-ppm group, and 3 of 21 females died in the 300-ppm group. The day on which the animals died and number of exposures that occurred prior to death were not reported. No treatment-related effects on maternal absolute body weights or body weight gain on gestation days 6-20 were found. There were also no treatment-related effects on pregnancy rate, number of implantations or live fetuses, or sex ratio across groups. A significant ($p < 0.01$) increase in the incidence of embryonic resorptions was observed at 300 ppm compared with the concurrent controls. A concentration-related decrease in fetal weight was observed in females in the 200-ppm group (8% lower than control, $p < 0.05$) and males and females in the 300-ppm group (14-16% lower than controls, $p < 0.05$). The only major malformation observed was a unilateral hydronephrosis at 300 ppm. There was no evidence of reproductive or developmental toxicity in the absence of maternal toxicity.

3.4.4. Genotoxicity

Studies of the genotoxic potential of isobutyronitrile were not available.

3.4.5. Carcinogenicity

No information concerning the carcinogenicity of isobutyronitrile in animals was available.

3.4.6. Summary

One-hour LC_{10} values for isobutyronitrile of 1,143 and 1,630 ppm for male and female rats, respectively, have been reported (Katz 1986). On the basis of this data, the combined LC_{10} for rats is 1,173 ppm, and the combined LC_{01} is 677 ppm. Clinical signs in rats included lethargy, gait disturbances, and narcosis. Pulmonary function effects were evidenced by changes in expiratory reserve volume, residual volume, dynamic compliance (up to 76% decrease), and $FEV_{10\%}$ (Eastman Kodak, 1986a). Acute inhalation of saturated atmospheres of isobutyronitrile suggest that mice are more sensitive than rats (Tsurumi and Kawada 1971). Clinical signs from oral, intraperitoneal, and inhalation exposure to isobutyronitrile are consistent with those seen in cyanide poisoning. In a developmental toxicity study, Saillenfait et al. (1993) observed an increase in the incidences of nonsurviving implants and embryonic resorptions at 300 ppm compared with controls, concentration-related decreases in fetal weight at 200 and 300 ppm, and unilateral hydronephrosis at 300 ppm. Maternal deaths were observed at 200 and 300 ppm; no maternal or fetal effects were found at 50 or 100 ppm. No genotoxicity or carcinogenicity data on isobutyronitrile were available.

3.5. Data Analysis for AEGL-1

3.5.1. Human Data Relevant to AEGL-1

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

3.5.2. Animal Data Relevant to AEGL-1

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

3.5.3 Derivation of AEGL-1 Values

Data were insufficient to derive AEGL-1 values for isobutyronitrile. Because the available data do not suggests a particularly steep concentration-response curve for this chemical, it was considered inappropriate to estimate AEGL-1 values by dividing the AEGL-2 values by 3. Therefore, AEGL-1 values are not recommended for isobutyronitrile.

3.6. Data Analysis for AEGL-2

3.6.1. Human Data Relevant to AEGL-2

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

3.6.2. Animal Data Relevant to AEGL-2

No maternal or fetal effects were observed in pregnant rats exposed to isobutyronitrile at 50 or 100 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993); however, maternal lethality was observed in dams exposed at 200 ppm.

3.6.3. Derivation of AEGL-2 Values

The no-effect level of 100 ppm for maternal or fetal effects in pregnant rats exposed to isobutyronitrile for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was not considered an appropriate basis for deriving AEGL-2 values because lethality was observed in the dams exposed at the next highest concentration (200 ppm). Furthermore, although the Saillenfait et al. (1993) study involved repeated exposures and identified no-effect levels for mortality that were below those observed in studies of single exposures of non-pregnant animals, it is possible that sensitivity to isobutyronitrile could increase during pregnancy. Therefore, the no-effect level of 100 ppm for maternal and fetal toxicity (mortality) is not an appropriate end point for AEGL-2 values. No other data identifying a point of departure for derivation of AEGL-2 values were identified. Therefore, AEGL-2 values were derived by dividing AEGL-3 values by 3. AEGL-2 values for isobutyronitrile are presented in Table 1-15.

3.7. Data Analysis for AEGL-3

3.7.1. Human Data Relevant to AEGL-3

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

3.7.2. Animal Data Relevant to AEGL-3

One-hour LC_{10} values for isobutyronitrile of 1,143 and 1,630 ppm for male and female rats, respectively, have been reported (Katz 1986). On the basis of this data, the combined LC_{10} for rats is 1,173 ppm, and the combined LC_{01} is 677 ppm. In a study of repeated exposure to iosbutyronitrile, the no-effect level for lethality in pregnant rats exposed for 6 h/day on gestational days 6-20 was 100 ppm (Saillenfait et al. 1993); maternal lethality was observed in dams exposed at 200 ppm.

TABLE 1-15 AEGL-2 Values for Isobutyronitrile

10 min	30 min	1 h	4 h	8 h
2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)

3.7.3. Derivation of AEGL-3 Values

The no-effect level of 100 ppm for maternal mortality in pregnant rats exposed to isobutyronitrile for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was selected as the point of departure for deriving AEGL-3 values. Although the study involved repeated exposures, the day on which the dams died and the number of exposures at the next higher dose (200 ppm) that occurred prior to death were not reported. Therefore, it is possible that the deaths could have resulted from a single exposure. The Saillenfait et al. (1993) study identified no-effect levels for mortality that were below those observed in studies with single exposures of nonpregnant animals; this may reflect a higher sensitivity of pregnant animals to lethal effects of isobutyronitrile. Therefore, the no-effect level of 100 ppm for maternal toxicity (mortality) was considered an appropriate end point for 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 10 was also applied because no comparable studies of similar exposures (repeated inhalation exposure during gestation) in other species were available. Thus, the total uncertainty factor is 30. Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). This equation has been shown to describe the concentration-exposure duration relationship for many irritant and systemically acting vapors and gases. Data on iosbutyronitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min, 1h, and 4 h) 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 6-h exposure to a 10-min value. AEGL-3 values for isobutyronitrile are presented in Table 1-16, and the calculations are presented in Appendix B.

3.8. Summary of AEGLs

3.8.1. AEGL Values and Toxicity End Points

The AEGL values for isobutyronitrile are presented in Table 1-17. Data were insufficient to derive AEGL-1 values. Data were also inadequate for deriving AEGL-2 values, so they were estimated by dividing the AEGL-3 values by 3. A no-effect level for maternal mortality and increased fetal resorptions in pregnant rats exposed to isobutyronitrile on gestational days 6-20 was used as the basis of AEGL-3 values.

TABLE 1-16 AEGL-3 Values for Isobutyronitrile

10 min	30 min	1 h	4 h	8 h
7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)

TABLE 1-17 AEGL-3 Values for Isobutyronitrile

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)	2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)
AEGL-3 (lethal)	7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)

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

3.8.2. Other Standards and Guidelines

Standards and guidelines for short-term exposures to isobutyronitrile are presented in Table 1-18. The emergency response planning guideline 1 (ERPG-1) of 10 ppm is based on the lowest odor threshold reported for methacrylonitrile (no odor threshold reported for isobutyronitrile). The ERPG-2 of 50 ppm is based on a weight-of-evidence approach that considered data from acute and subchronic studies in rats and symptoms reported in workers. The ERPG-3 of 200 ppm is based on an LC_{10} value from an acute exposure study in rats (Katz 1986). The National Institute for Occupational Safety and Health's recommended exposure limit of 8 ppm is based on evidence that selected nitrile compounds are metabolized to cyanide ion which causes numerous systemic effects.

3.8.3. Data Adequacy and Research Needs

Data were insufficient to derive AEGL-1 values for isobutyronitrile. Only one set of well-conducted animal studies and one developmental toxicity study were available as a basis for deriving AEGL-2 and AEGL-3 values.

4. PROPIONITRILE

4.1. Summary

Propionitrile is a selective solvent used commercially in hydrocarbon separation and in petroleum refining. It has served as a raw material in manufacturing pharmaceuticals and as a setting agent for resins (NIOSH 1978). Propionitrile is a colorless liquid at ambient temperature and pressure. It has a pleasant

TABLE 1-18 Standards and Guidelines for Isobutyronitrile

	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	2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)
AEGL-3	7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)
ERPG-1 (AIHA)[b]	–	–	10 ppm (28 mg/m^3)	–	–
ERPG-2 (AIHA)[b]	–	–	50 ppm (140 mg/m^3)	–	–
ERPG-3 (AIHA)[b]	–	–	200 ppm (570 mg/m^3)	–	–
REL-TWA (NIOSH)[c]	–	–	–	–	8 ppm (22 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]ERPG (emergency response planning guidelines, American Industrial Hygiene Associations) (AIHA 1992, 2013).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for isobutyronitrile is based on odor data on methacrylonitrile.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for isobutyronitrile is based on rat LC_{10} and pulmonary function data.

ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for isobutyronitrile is based on rat LC_{10} data.

[c]REL-TWA (recommended exposure limit—time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011b) is defined as a time-weighted average concentrations for up to a 10-h workday during a 40-h workweek.

pleasant, ethereal, sweetish odor and may cause irritation or burning of the eyes and skin. It is metabolized to cyanide in the body. Depending on the level of exposure, signs of intoxication may include weakness, headache, confusion, nausea, vomiting, convulsion, dilated pupils, weak pulse, dyspnea, and cyanosis (HSDB 2002). These clinical signs are similar to those that have been reported in people exposed to hydrogen cyanide (Blanc et al. 1985), although the time course for propionitrile intoxication is more protracted.

Chemical-specific data were insufficient to derive AEGL-1 values for propionitrile, so no values are recommended. Data on propionitrile were also

insufficient to derive AEGL-2 values, so AEGL-2 values were derived by dividing AEGL-3 values by 3.

The threshold level for maternal mortality and increased fetal resorptions in pregnant rats exposed to propionitrile at 150 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was used as the point of departure for deriving AEGL-3 values for propionitrile. Although the study involved repeated exposures, fetal death can occur during a narrow developmental window and does not necessarily require repeated exposures (Van Raaij et al. 2003). Therefore, the observation of increased fetal resorptions following repeated gestational exposure is considered a relevant end point for deriving 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 10 was also applied because no comparable studies of similar exposures (repeated inhalation exposure during gestation) in other species were available. Thus, the total uncertainty factor is 30. Time scaling was performed using 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 propionitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min, 1h, and 4 h) 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 6-h exposure to a 10-min value.

AEGL values for propionitrile are presented in Table 1-19.

TABLE 1-19 AEGL Values for Propionitrile

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)	3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)	No-effect level for maternal and fetal mortality (Saillenfait et al. 1993)

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

4.2. Introduction

Propionitrile is a colorless liquid at ambient temperature and pressure. It has a pleasant, ethereal, sweetish odor and may cause irritation or burning of the eyes and skin.

Propionitrile is produced using a copper or nickel catalyst in selective hydrogenation of acrylonitrile, as a by-product during the electroreduction of acrylonitrile to form adiponitrile, or may be prepared by dehydration of propionamide or by distillation of ethyl sulfate and concentrated aqueous potassium cyanide (Thompson 1972; ITTI 1977; NIOSH 1978). It is used as a solvent in petroleum refining, as a raw material in drug manufacturing, and in manufacturing cyanoacetates (HSDB 2002).

The chemical and physical properties of propionitrile are presented in Table 1-20.

4.3. Human Toxicity Data

4.3.1. Acute Lethality

Information concerning death in humans following inhalation exposure to propionitrile was not available.

TABLE 1-20 Chemical and Physical Data for Propionitrile

Parameter	Data	Reference
Common name	Propionitrile	HSDB 2002
Synonyms	Cyanoethane, ether cyanatus; ethyl cyanide; hydrocyanic ether; propanenitrile; propionic nitrile; propiononitrile; propylnitrile	HSDB 2002
CAS regsitry no.	107-12-0	HSDB 2002
Chemical formula	C_3H_5N	HSDB 2002
Molecular weight	55.08	HSDB 2002
Physical state	Colorless liquid	HSDB 2002
Melting point	-91.8°C	HSDB 2002
Boiling point	97.2°C	HSDB 2002
Density/Specific gravity	0.7818 at 20°C/4°C	HSDB 2002
Solubility	In water, 1.03×10^5 mg/L at 25°C; miscible with alcohol, ether	HSDB 2002
Vapor density	1.9 (air = 1)	HSDB 2002
Vapor pressure	47.4 mm Hg at 25°C	HSDB 2002
Conversion factors in air	1 ppm = 2.25 mg/m^3 1 mg/m^3 = 0.437 ppm	NIOSH 2011c

4.3.2. Nonlethal Toxicity

4.3.2.1. Case Reports

A healthy 55-year-old man noticed that a pump in the chemical plant where he worked had a leaking pipe fitting (Bismuth et al. 1987). He entered the area to repair the leak wearing protective gloves but no respirator or other protective clothing. The pump was connected to a liquid propionitrile source and the worker inhaled propionitrile vapors and was exposed dermally to the liquid. He rapidly lost consciousness and developed metabolic acidosis consistent with cyanide poisoning. He was treated with intravenous hydroxycobalamin and sodium thiosulfate, and his symptoms resolved within 1 h. No exposure concentration or duration was reported.

Scolnick et al. (1993) describe cases of two male workers (ages 28 and 34 years) exposed to propionitrile at an organic chemical plant. Their assignment was to treat waste discharge containing ammonia and water by stirring it to make a slurry suitable for disposal. They wore protective clothing, boots, and gloves but did not respirators. The 28-year-old occasionally had to bend within 2-3 inches of the slurry, and was found collapsed after approximately 7 h of exposure. Upon arrival at the hospital, he was deeply comatose, and within 10 min he experienced tonic/clonic, generalized seizures. Since cyanide poisoning was suspected, he was treated with sodium nitrite followed by sodium thiosulfate approximately 90 min after he arrived at the hospital. He regained consciousness shortly thereafter and no further seizures occurred. He was ventilated when a chest X-ray indicated bilateral interstitial infiltrates. (By this time, chemical plant officials had notified the hospital that a contaminant of unreacted propionitrile overlaying the waste slurry had been detected). Because of continuing complaints of lethargy and headache, the patient was treated with hyperbaric oxygen. He was released from the hospital 48 h later with resolving pneumonia. He continued to complain of severe headaches and dizziness for the next 30 days. No remarkable symptoms reported at the 6-month follow-up exam. The 34-year-old worker complained of headache, nausea, and dizziness after 2 h of working in the same area. He left the work area, vomited, and went to the cafeteria to lay down. He was found confused and disoriented 5 h later, and was taken to the same emergency room as the 28-year-old worker. He had a bad headache and nausea and vomited once. His chest X-ray was normal; however, his blood cyanide level was elevated 6 h after admission. He received the cyanide antidote and was discharged 24 h later and had an uneventful recovery. Ambient air sampling of the work area performed shortly after the men were discovered measured propionitrile at 33.8 ppm. Analysis of the slurry indicated 80% propionitrile.

4.3.3. Developmental and Reproductive Toxicity

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

4.3.4. Genotoxicity

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

4.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to propionitrile were not available.

4.3.6. Summary

Only case reports of human exposure to propionitrile are available. A total of three men were occupationally exposed to propionitrile, and developed signs consistent with cyanide poisoning. They all recovered after treatment for cyanide poisoning. No human studies of the developmental or reproductive toxicity, genotoxicity, or carcinogenicity of propionitrile were available.

4.4 Animal Toxicity Data

4.4.1. Acute Lethality

4.4.1.1. Rats

Groups of five male and five female Sprague-Dawley rats were exposed to propionitrile at 690, 1,100, 1,700, 2,800, 4,400, or 6,900 ppm for 4 h (Younger Labs 1978). Animals were placed in a cage (9” × 16” × 7”) suspended in the middle of a 210-L drum-like chamber. The chamber was equipped with a circulating fan (6” blade) and a glass window at one end for viewing. The sample was introduced into the chamber through a special port with a No. 27 needle. As the sample was introduced into the chamber it was spread toward the surface areas to facilitate evaporation. The fan was operated at maximum speed during introduction of the sample and for an additional 2 min, and then turned off. The rats were observed for signs of toxicity during exposure and surviving animals were observed for 14 days. The average chamber temperature was 24-25°C and average humidity was 70%. Salivation, lethargy, weakness, tremors, convulsions, collapse, and death were observed during exposure. Macroscopic examination of decedents found hemorrhagic lungs,

liver discoloration, and acute gastrointestinal inflammation. The viscera of animals surviving the 14-day follow-up period appeared normal. An LC_{50} of 1,441 ppm was calculated. Mortality data from this study are summarized in Table 1-21.

In another study, lethargy, labored breathing, tremors, convulsions, collapse, and death were observed in a group of six male Sprague-Dawley rats exposed to propionitrile at 39,432 ppm for 1.25 h (Younger Labs 1979). Chamber temperature was 26°C and humidity was 80%. Hemorrhagic lungs and gastrointestinal inflammation were observed at necropsy. No other experimental details were available.

Smyth et al. (1962) reported that two of six rats died after being exposed to a nominal concentration of propionitrile at 500 ppm for 4 h.

4.4.1.2. Mice

Groups of 10 male CD-1 mice were exposed to five or six concentrations of propionitrile ranging from 70-400 ppm for 60 min (Willhite and Smith 1981). Actual individual group exposure concentrations were not reported. Propionitrile (99%) was mixed with a stream of dehumidified air (10 L/min) and delivered to a single pass 45-L glass inhalation chamber. Samples were collected every 5 min using a gas-tight syringe and concentrations were analyzed by gas chromatography. The mice exhibited dyspnea, tachypnea, gasping, tremors, convulsions, and corneal opacity 30-300 min after initial contact with propionitrile. All mice in the 400-ppm group died within 180 min of initial contact, and delayed deaths were observed up to 3 days after exposure to lower (unspecified) concentrations. The livers of exposed mice were bright red compared with controls. Gross and histopathologic examination of pulmonary tissues from mice exposed to lethal concentrations of propionitrile showed no marked difference compared with air-exposed controls. An LC_{50} of 163 ppm (95% confidence limit = 116-211 ppm) was calculated.

TABLE 1-21 Mortality in Sprague-Dawley Rats Exposed to Propionitrile for 4 Hours

	Males		Females	
Concentration (ppm)	Mortality	Time to death	Mortality	Time to death
690	0/5	–	0/5	–
1,100	5/5	<4 h (n =1); 1 d (n = 4)	0/5	–
1,700	5/5	<4 h (n = 2); 1 d (n = 1); 2 d (n = 1); 13 d (n = 1)	0/5	–
2,800	5/5	<4 h	3/5	<4 h (n = 1); 1 d (n = 2)
4,400	5/5	<4 h	5/5	1 d
6,900	5/5	<4 h	5/5	<4 h

Source: Adapted from Younger Labs 1978.

An oral LD_{50} for propionitrile was estimated to be 36 mg/kg in male ddY mice (Tanii and Hashimoto 1984).

An intraperitoneal LD_{50} of 34 mg/kg for mice was reported (Lewis 1996). No further information was available.

4.4.2. Nonlethal Toxicity

No information concerning nonlethal toxicity from inhalation exposure to propionitrile was available. However, several single- or repeated-exposure subcutaneous studies at 2-5 mg/kg document the production of duodenal ulcers in rats (Szabo and Selye 1972; Dzau et al. 1975; Giampaolo et al. 1975; Haith et al. 1975). Male rats were more resistant than female rats to these ulcerogenic effects (Robert et al. 1975). The development of the propionitrile-induced ulcers is associated with enhanced gastric acid output, delayed gastric emptying (Szabo et al. 1976), and the accumulation of highly acidic gastric juice (Szabo et al. 1977). Vagotomy eliminated the occurrence of propionitrile-induced ulcers, and hypophysectomy decreased the incidence of the lesions (Haith et al. 1975). No clinical reports of duodenal ulcer associated with occupational exposure to propionitrile were found.

4.4.3. Developmental and Reproductive Toxicity

Saillenfait et al. (1993) exposed groups of 22-23 pregnant Sprague-Dawley rats to propionitrile at nominal concentrations of 0, 50, 100, 150, or 200 ppm (analytic concentrations were 0, 52 ± 4.9, 97 ± 7.7, 151 ± 13.9, or 200 ± 15.4 ppm, respectively) for 6 h/day on days 6-20 of gestation. Exposures were 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. Two of 22 females died in the 200-ppm group, and no other maternal deaths were observed; the day on which the animals died or the number of exposures that occurred prior to death were not reported. There were no treatment-related effects on maternal absolute body weight or body weight gain on gestation days 6-20. No treatment-related effects on pregnancy rate, number of implantations or live fetuses, or sex ratio across groups were found. A significant ($p < 0.01$) increase in the incidences of nonsurviving implants and embryonic resorptions was observed at 200 ppm compared with controls. One litter was completely resorbed at 200 ppm. A concentration-related decrease in fetal weight was observed and was statistically significant in 200-ppm males ($p < 0.01$) and females ($p < 0.05$). These decreases

amounted to 11-13% of the control values. No treatment-related fetal malformations were observed. Although this study involved repeated exposures, fetal death is a relevant end point for deriving AEGL values because fetal toxicity could result from a single exposure. In addition, although the study identified no-effect levels for mortality that were below those observed in studies of single exposures of nonpregnant animals, it is possible that sensitivity to propionitrile could increase during pregnancy.

Results of an oral exposure study in pregnant rats show that propionitrile can induce fetal toxicity after a single exposure (Saillenfait and Sabaté 2000). Pregnant Sprague-Dawley rats were administered a single oral dose of propionitrile (180 mg/kg) on gestational day 10, and fetuses were examined for malformations on gestational day 12. Embryo viability was not affected, but abnormal development, including "overall poor and abnormal development" and misdirected allantois, trunk, and caudal extremities, was observed.

A single parenteral administration of propionitrile at 0.54-1.51 mmol/kg during the early primitive streak stage of pregnancy in Syrian Golden hamsters induced dose-dependent signs of intoxication (intense dyspnea, incoordination, hypothermia, salivation, and convulsions with opisthotonis) (Willhite et al. 1981a). Frank malformations (encephalocele, bifurcated ribs, and fused ribs) were observed at doses which also caused clear signs of maternal intoxication and increased mortality. Propionitrile induced mesodermal shrinkage, collapse, decreased mitotic figures, and necrobiosis. Malformations of the central nervous system were accompanied by congenital defects of the basisphenoid and basioccipital (Willhite et al. 1981b). Propionitrile-induced maternal and developmental toxicity was prevented by prophylactic and repeated thiosulfate injections. Decreases in circulating and brain cyanide concentrations after thiosulfate administration and the fact that thiosulfate prevented maternal and developmental toxicity, suggest that metabolically liberated cyanide was responsible for the observed effects (Willhite and Smith 1981).

Johannsen et al. (1986) administered aqueous solutions of propionitrile at concentrations of 0, 20, 40, or 80 mg/kg by gavage to pregnant rats on days 6-19 of gestation. Maternal body weights were decreased and one death occurred in high-dose dams; no maternal effects were noted at lower concentrations. Increases in early resorptions and post-implantation losses and decreases in fetal body weight were noted only in the high-dose group, and no teratogenic effects were found in any dose group.

4.4.4. Genotoxicity

Propionitrile (0.03 to 30 µmol/plate) did not induce reverse mutations either with or without metabolic activation (S-9 fraction) in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537. It was also negative in *Escherichia coli* strain Sd-4-73 when tested at concentrations of 0.01-0.025 mL/plate (EPA 1985). Propionitrile induced mitotic chromosome loss in *Sac-*

chromyces cerevisiae strain D61.M (Whittaker et al. 1989) and mitotic chromosome gain in strain BR1669 (Whittaker et al. 1990). Sex chromosome aneuploidy was induced in oocytes of female *Drosophila melanogaster* fed propionitrile as larvae or as adults (Osgood et al. 1991). Propionitrile may interfere with tubulin assembly in vitro, thereby inducing chromosome malsegregation with no effect on recombination or mutation. Propionitrile was negative for sister chromatid exchanges and chromosome aberrations both with and without metabolic activation in cultured Chinese hamster ovary cells (Loveday et al. 1990).

4.4.5. Carcinogenicity

No information concerning the carcinogenicity of propionitrile was found.

4.4.6. Summary

Rats and mice exposed to propionitrile exhibited signs of toxicity consistent with cyanide poisoning. A 4-h rat LC_{50} of 1,441 ppm (Younger Labs 1978) and a 1-h mouse LC_{50} of 163 ppm (Willhite 1981) were calculated. Subcutaneous administration of propionitrile induced duodenal ulcers in rats. No reproductive or developmental toxicity was found in the absence of maternal toxicity. Genotoxicity data were generally negative, except for chromosome loss or gain. No carcinogenicity data on propionitrile were found.

4.5. Data Analysis for AEGL-1

4.5.1. Human Data Relevant to AEGL-1

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

4.5.2. Animal Data Relevant to AEGL-1

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

4.5.3. Derivation of AEGL-1 Values

Chemical-specific data were insufficient to derive AEGL-1 values for propionitrile. Because the available data do not suggests a particularly steep concentration-response curve for this chemical, it was considered inappropriate to estimate AEGL-1 values by dividing the AEGL-2 values by 3. Therefore, AEGL-1 values are not recommended for propionitrile.

4.6 Data Analysis for AEGL-2

4.6.1. Human Data Relevant to AEGL-2

A worker exposed to propionitrile at approximately 34 ppm for 2 h experienced headache, nausea, and dizziness (Scolnick et al. 1993). After leaving the work area, he vomited and was found confused and disoriented 5 h later.

4.6.2. Animal Data Relevant to AEGL-2

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

4.6.3. Derivation of AEGL-2 Values

The headache, nausea, and dizziness reported in the worker exposed to propionitrile at approximately 34 ppm for 2 h are considered AEGL-2 level effects. However, because a no-effect level was not identified, these data are not appropriate for deriving AEGL-2 values. Therefore, AEGL-2 values were derived by dividing the AEGL-3 values by 3 (NRC 2001). The AEGL-2 values for propionitrile are presented in Table 1-22. These values are below the concentration of 34 ppm (2-h exposure) shown to produce disabling effects in an exposed worker (Scolnick et al. 1993).

4.7. Data Analysis for AEGL-3

4.7.1. Human Data Relevant to AEGL-3

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

4.7.2. Animal Data Relevant to AEGL-3

Saillenfait et al. (1993) observed maternal deaths in pregnant rats exposed to propionitrile at 200 ppm for 6 h/day on days 6-20 of gestation. An increase in the incidences of nonsurviving implants and embryonic resorptions was observed at 200 ppm compared with controls, and a concentration-related decrease in fetal weights was also observed in the offspring of the 200-ppm group. No maternal deaths or developmental effects were observed at 150 ppm. A 4-h LC_{50} of 1,441 ppm was calculated for Sprague-Dawley rats (Younger Labs 1978). The highest concentration causing no mortality was 690 ppm. A 1-h LC_{50} of 163 ppm was calculated for male CD-1 mice (Willhite 1981). No concentration-response data were available for this study.

TABLE 1-22 AEGL-2 Values for Propionitrile

10 min	30 min	1 h	4 h	8 h
3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)

4.7.3. Derivation of AEGL-3 Values

The threshold level for maternal mortality and increased fetal resorptions in pregnant rats exposed to propionitrile at 150 ppm for 6 h/day on gestational days 6-20 (Saillenfait et al. 1993) was used as the point of departure for deriving AEGL-3 values for propionitrile. Although the study involved repeated exposures, fetal death can occur during a narrow developmental window and does not necessarily require repeated exposures (Van Raaij et al. 2003). Therefore, the observation of increased fetal resorptions following repeated gestational exposure is considered a relevant end point for AEGL-3 values. The no-effect level of 150 ppm for fetal death was the point of departure. 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 10 was also applied because no comparable studies of similar exposures (repeated inhalation exposure during gestation) in other species were available. Thus, the total uncertainty factor is 30. Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). This equation has been shown to describe the concentration-exposure duration relationship for many irritant and systemically acting vapors and gases. Data on propionitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min, 1h, and 4 h) 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 6-h exposure to a 10-min value. AEGL-3 values for propionitrile are presented in Table 1-23, and the calculations are presented in Appendix B.

4.8. Summary of AEGLs

4.8.1. AEGL Values and Toxicity End Points

AEGL values for propionitrile are presented in Table 1-24. Data were insufficient to derive AEGL-1 values. Data were also insufficient for AEGL-2 values, so values were estimated by dividing the AEGL-3 values by 3. A no-effect level for maternal mortality and increased fetal resorptions in pregnant rats exposed to propionitrile on gestational days 6-20 was used as the basis for the AEGL-3 values.

TABLE 1-23 AEGL-3 Values for Propionitrile

10 min	30 min	1 h	4 h	8 h
11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)

TABLE 1-24 AEGL Values for Propionitrile

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)	3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)
AEGL-3 (lethal)	11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)

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

4.8.2. Other Standards and Guidelines

Only one other exposure standard for propionitrile was found (see Table 1-25). The National Institute for Occupational Safety and Health's recommended exposure limit (time-weighted average) of 6 ppm is based on evidence that selected nitrile compounds are metabolized to cyanide ion, which causes numerous systemic effects.

4.8.3. Data Adequacy and Research Needs

Data were insufficient to derive AEGL-1 values for propionitrile. Data were also insufficient for AEGL-2 values, so they had to be estimated from the AEGL-3 values. Only limited animal data were available from which to derive AEGL-3 values.

5. CHLOROACETONITRILE

5.1. Summary

Chloroacetonitrile is a colorless liquid at ambient temperature and pressure. It has a pungent odor and may cause irritation or burning of the eyes, skin, and respiratory tract. It is metabolized to cyanide in the body and signs of intoxication may include weakness, headache, dizziness, confusion, nausea, vomiting, convulsion, dilated pupils, weak pulse, tachypnea, dyspnea, and cyanosis (HSDB 2013).

TABLE 1-25 Standards and Guidelines for Propionitrile

	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	3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)
AEGL-3	11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)
REL-TWA (NIOSH)[b]	–	–	–	–	6 ppm (14 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]REL-TWA (recommended exposure limit - time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011c) is defined as a time-weighted average concentrations for up to a 10-h workday during a 40-h workweek.

Chemical-specific inhalation data on chloroacetonitrile were insufficient for deriving AEGL values. Therefore, a relative potency approach was used to estimate AEGL-2 and AEGL-3 values for chloroacetonitrile on the basis of comparison with acetonitrile. In the absence of inhalation data on chloroacetonitrile, comparison was based on the intraperitoneal toxicity of the two chemicals. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, AEGL-2 and AEGL-3 values for acetonitrile were divided by 10 to approximate AEGL-2 and AEGL-3 values for chloroacetonitrile. AEGL-1 values were not derived by this method because of the uncertainty associated with applying a relative potency estimate based on lethality to AEGL-1 effects. AEGL values for malononitrile are presented in Table 1-26.

5.2. Introduction

Chloroacetonitrile is a colorless liquid at ambient temperature and pressure. It has a pungent odor and may cause irritation or burning of the eyes, skin, and respiratory tract.

Chloroacetonitrile is produced commercially by the high-temperature chlorination of acetonitrile (IARC 1991). It has been used as a fumigant and is an organic intermediate in the manufacture of the insecticide fenoxycarb and the cardiovascular drug guanethidine. Occupational exposure to chloroacetonitrile may occur via inhalation or dermal contact at workplaces where chloroacetonitrile is used or produced (HSDB 2013). Halogenated acetonitriles have been detected in chlorinated drinking water in several countries as a result of the reaction of chlorine with natural organic substances present in untreated water (IARC 1999).

The chemical and physical properties of chloroacetonitrile are presented in Table 1-27.

TABLE 1-26 AEGL Values for Chloroacetonitrile

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)	8.0 ppm (25 mg/m^3)	8.0 ppm (25 mg/m^3)	5.0 ppm (15 mg/m^3)	2.1 ppm (6.5 mg/m^3)	1.4 ppm (4.3 mg/m^3)	Based on AEGL-2 values for acetonitrile
AEGL-3 (lethal)	24 ppm (74 mg/m^3)	24 ppm (74 mg/m^3)	15 ppm (46 mg/m^3)	6.4 ppm (20 mg/m^3)	4.2 ppm (13 mg/m^3)	Based on AEGL-3 values for acetonitrile

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

TABLE 1-27 Chemical and Physical Data on Chloroacetonitrile

Parameter	Data	Reference
Common name	Chloroacetonitrile	HSDB 2013
Synonyms	Monochloromethyl cyanide; monochloroacetonitrile; chloromethyl cyanide	HSDB 2013
CAS registry no.	107-14-2	HSDB 2013
Chemical formula	C_2H_2ClN	HSDB 2013
Molecular weight	75.50	HSDB 2013
Physical state	Colorless liquid	HSDB 2013
Boiling point	126.5°C	HSDB 2013
Density/Specific gravity	1.1930 at 20°C	HSDB 2013
Solubility	In water, $>1 \times 10^5$ mg/L (temperature not specified); soluble in hydrocarbons and alcohols	HSDB 2013
Vapor density	2.61 (air = 1)	HSDB 2013
Vapor pressure	8 mm Hg at 20°C	HSDB 2013
Conversion factors in air	1 ppm = 3.09 mg/m^3 1 mg/m^3 = 0.323 ppm	

5.3. Human Toxicity Data

5.3.1. Acute Lethality

Information concerning death in humans following inhalation exposure to chloroacetonitrile is not available.

5.3.2. Nonlethal Toxicity

Information concerning nonlethal toxicity in humans following inhalation exposure to chloroacetonitrile is not available.

5.3.3. Developmental and Reproductive Toxicity

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

5.3.4. Genotoxicity

Genotoxicity studies of acute human exposure to chloroacetonitrile were not available.

5.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to chloroacetonitrile were not available.

5.4.6. Summary

No human studies of the lethal toxicity, nonlethal toxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity of chloroacetonitrile were available.

5.4. Animal Toxicity Data

5.4.1. Acute Lethality

5.4.1.1. Rats

Groups of two or three male and two or three female Sprague-Dawley rats were administered single doses of chloroacetonitrile at 126, 158, 200, or 251 mg/kg by gavage and observed for up to 14 days (Younger Labs 1976). Decreased appetite and activity (1-2 days in survivors), increasing weakness, tremors, convulsions, collapse, and death were observed in the three highest dose groups. Lung hyperemia, slight liver discoloration, and gastrointestinal inflammation were found in decedents at necropsy. Surviving rats had no abnormal findings at necropsy. Mortality incidence was 0/5 at 126 mg/kg, 2/5 at 158 mg/kg, 4/5 at 200 mg/kg, and 5/5 at 251 mg/kg. An LD_{50} for chloroacetonitrile of 180 mg/kg was calculated.

An oral LD_{50} of 220 mg/kg for rats was reported (Lewis 1996). No further information was available.

5.4.1.2. Mice

The oral LD_{50} for chloroacetonitrile was estimated to be 139 mg/kg in male ddY mice (Tanii and Hashimoto 1984).

An intraperitoneal LD_{50} of 100 mg/kg for mice was reported (Lewis 1996). No further information was available.

5.4.1.3. Rabbits

One or two New Zealand white rabbits were administered single 24-h dermal doses of chloroacetonitrile at 100, 158, 200, 251, or 376 mg/kg and observed for up to 14 days (Younger Labs 1976). Decreased appetite and activity (2-3 days in survivors), rapidly increasing weakness, tremors, convulsions, dyspnea, collapse, and death were observed in the three highest dose groups. Hemorrhagic lungs, liver, and spleen, kidney discoloration, ruptured gall bladders, and gastrointestinal inflammation were found in decedents at necropsy. Surviving rabbits had no abnormal findings at necropsy. Mortality incidence was 0/1 at 100 mg/kg, 0/1 at 158 mg/kg, 2/2 at 200 mg/kg, 1/1 at 251 mg/kg, and 1/1 at 376 mg/kg.

Younger Labs (1976) reported that chloroacetonitrile was corrosive to the eyes of New Zealand white rabbits.

5.4.2. Nonlethal Toxicity

No information concerning the nonlethal toxicity of chloroacetonitrile in animals was available.

5.4.3. Developmental and Reproductive Toxicity

Thirty pregnant Long-Evans rats were administered chloroacetonitrile at 55 mg/kg by gavage on days 7-21 of gestation (Smith et al. 1987). The litters were culled to six to eight pups on postnatal day 6 and were further culled to four pups at weaning. These pups were observed until 41-42 days of age. One of the treated dams died, and there was a decrease in maternal weight gain (13% decrease; $p < 0.05$) during treatment. There was no effect on pregnancy, resorptions, pup survival, or pup growth after birth. Litter weight at birth was decreased (8% decrease; $p < 0.05$) compared with controls.

5.4.4. Genotoxicity

Chloroacetonitrile at concentrations of 5.0-160 µmol/plate did not induce reverse mutations either with or without metabolic activation (S-9 fraction) in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (Bull et

al. 1985). Similar results were obtained when the chemical was tested at concentrations of 10-3,333 μg/plate (Mortelmans et al. 1986). Chloroacetonitrile at concentrations of 15.8-950 μM was negative in a sister chromatid exchange assay using Chinese hamster ovary cells with metabolic activation, and was positive without metabolic activation at concentrations of 52-158 μM (Bull et al. 1985). Micronuclei were induced in the erythrocytes of newt larvae exposed for 12 days to chloroacetonitrile at 1.25-5 μg/mL (LeCurieux et al. 1995); however, mice administered chloroacetonitrile for 5 days had neither micronuclei in bone marrow (Bull et al. 1985) nor abnormal sperm morphology at doses of 12.5, 25, or 50 mg/kg/day (Meier et al. 1985). Chloroacetonitrile at 3 mM was weakly positive in a DNA strand break assay in cultured human lymphoblastic cells (Daniel et al. 1986).

5.4.5. Carcinogenicity

Groups of 10-week-old female A/J mice were administered chloroacetonitrile at 10 mg/kg in 10% Emulphor by gavage three times per week for 8 weeks (Bull and Robinson 1985). A control group of 40 mice were treated with 10% Emulphor. Survival at the end of the study was 31/40 for controls and 28/40 for the chloroacetonitrile-treated animals. Lung adenomas occurred in 3/31 control animals and 9/28 treated animals; the average numbers of tumors per mouse were 0.1 for controls and 0.43 for mice administered chloroacetonitrile.

In an initiation-promotion study, groups of 40 female Sencar mice were treated dermally with chloroacetonitrile at 200, 400, or 800 mg/kg in 0.2 mL of acetone three times per week for 2 weeks (Bull et al. 1985). Three groups of 40 mice served as controls and were treated with only acetone. Two weeks after the last chloroacetonitrile application, mice were treated topically with 12-O-tetradecanoylphorbol 13-acetate (TPA) at 1 μg three times per week for 20 weeks. Animals were observed for 1 year. Combined incidences of papillomas and carcinomas was 11/38 in the low-dose group ($p < 0.001$), 11/37 in the mid-dose group ($p < 0.01$), and 6/38 in the high-dose group. Incidences were 1/34, 3/37, and 5/34 for the three control groups.

In another experiment, groups of 40 female Sencar mice were treated dermally with chloroacetonitrile at 800 mg/kg in 0.2 mL of acetone three times per week for 24 weeks (Bull et al. 1985). A group of 40 mice served as a control and were treated with only acetone. No tumors were observed; however, the duration of the observation period was not stated.

5.4.6. Summary

Inhalation toxicity data for chloroacetonitrile were not available, and other animal toxicity data are sparse. Animals exposed to chloroacetonitrile by oral and dermal routes exhibited signs consistent with cyanide poisoning. Rat oral LD_{50} values of 180 mg/kg (Younger Labs 1976) and 200 mg/kg (Lewis, 1996)

have been reported. In mice, an oral LD_{50} of 139 mg/kg (Tanii and Hashimoto 1984) and an intraperitoneal LD_{50} of 100 mg/kg were reported (Lewis 1996). No reproductive or developmental toxicity was noted in rats in the absence of maternal toxicity. Genotoxicity data were equivocal. An increase in the incidence of lung adenomas was found in mice treated orally with chloroacetonitrile; however, IARC (1991) concluded that there is inadequate evidence of carcinogenicity of chloroacetonitrile in experimental animals.

5.5. Special Considerations

5.5.1. Other Available Data

Little data are available to evaluate the toxicity of chloroacetonitrile. Chloroacetonitrile is oxidized in vitro to cyanide in the presence of a myeloperoxidase/hydrogen peroxide/chloride (Abdel-Naim and Mohamadin 2004), which provides data to support a common mechanism of toxicity for chloroacetonitrile and other aliphatic nitriles (e.g., metabolic release of cyanide; see Section 1.2). Oxidation of chloroacetonitrile to cyanide also has been demonstrated in vivo in rats following oral administration (Lin et al. 1986). Results of an oral gestational exposure study in rats show increased fetal resorptions and alterations in skeletal development in dams exposed at 50 mg/kg on gestational days 6-18 (Ahmed et al. 2008). Results are consistent with findings of gestational exposure studies on acetonitrile (see Section 2.4.3), isobutyronitrile (see Section 3.4.3), and propionitrile (see Section 4.4.3), in which rats were exposed via inhalation on gestational days 6-20. Distribution of chloroacetonitrile to fetal tissues was demonstrated following a single intravenous administration of ^{14}C-labeled chloroacetonitrile to pregnant rats on gestational day 13 (Jacob et al. 1998).

5.6. Data Analysis for AEGL-1

5.6.1. Human Data Relevant to AEGL-1

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

5.6.2. Animal Data Relevant to AEGL-1

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

5.6.3. Derivation of AEGL-1 Values

Chemical-specific data were insufficient for deriving AEGL-1 values for chloroacetonitrile. Therefore, AEGL-1 values are not recommended.

5.7. Data Analysis for AEGL-2

5.7.1. Human Data Relevant to AEGL-2

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

5.7.2. Animal Data Relevant to AEGL-2

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

5.7.3. Derivation of AEGL-2 Values

Chemical-specific inhalation data were insufficient to derive AEGL-2 values for chloroacetonitrile. However, data from other routes of exposure (oral, intraperitoneal, and dermal) are available. A relative potency approach was used to approximate AEGL-2 values for chloroacetonitrile on the basis of comparison with acetonitrile.

In the absence of inhalation data, the intraperitoneal route is considered the most appropriate for approximating inhalation toxicity values because both routes involve entry into the organism through a semipermeable membrane (peritoneal membrane and alveolar membrane) before diffusion into the blood. Furthermore, the magnitude and rate of effect for the different routes of administration (in descending order) are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical (Eaton and Gilbert 2008). Intraperitoneal toxicity data are available for acetonitrile and propionitrile for comparison, but a judgment was made to use acetonitrile because the overall database on this chemical is more robust (includes toxicity data and data to derive a value for the exponent "n" for time scaling) than for propionitrile. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, the AEGL-2 values for acetonitrile were divided by 10 to approximate the AEGL-2 values for chloroactonitrile. The AEGL-2 values for chloroacetonitrile are presented in Table 1-28.

5.8. Data Analysis for AEGL-3

5.8.1. Human Data Relevant to AEGL-3

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

TABLE 1-28 AEGL-2 Values for Chloroacetonitrile

10 min	30 min	1 h	4 h	8 h
8.0 ppm (25 mg/m^3)	8.0 ppm (25 mg/m^3)	5.0 ppm (15 mg/m^3)	2.1 ppm (6.5 mg/m^3)	1.4 ppm (4.3 mg/m^3)

5.8.2. Animal Data Relevant to AEGL-3

No animal data on chloroacetonitrile consistent with the definition of AEGL-3 were available.

5.8.3. Derivation of AEGL-3 Values

Chemical-specific inhalation data were insufficient to derive AEGL-3 values for chloroacetonitrile. Therefore, the relative-potency approach used to derive AEGL-2 values (described in Section 5.7.3) was also used to estimate AEGL-3 values. Because chloroacetonitrile is estimated to be approximately 10 times more toxic than acetonitrile, the AEGL-3 values for acetonitrile were divided by 10 to approximate AEGL-3 values for chloroacetonitrile. The AEGL-3 values for chloroacetonitrile are presented in Table 1-29.

5.9. Summary of AEGLs

5.9.1. AEGL Values and Toxicity End Points

Chemical-specific data were insufficient for deriving AEGL values for chloroacetonitrile. Therefore, AEGL-2 and AEGL-3 values were determined on the basis of chloroacetonitrile's relative potency to acetonitrile. AEGL-1 values were not derived by this method because of the uncertainty associated with applying a relative-potency estimate based on lethality to effects defined by AEGL-1. The AEGL values for chloroacetonitrile are presented in Table 1-30.

5.9.2. Other Standards and Guidelines

No other standards or guidelines for chloroacetonitrile were found.

5.9.3. Data Adequacy and Research Needs

Chemical-specific data were insufficient to derive AEGL values for chloroacetonitrile. AEGL-2 and AEGL-3 values for chloroacetonitrile were determined on the basis of its relative potency to acetonitrile.

TABLE 1-29 AEGL-3 Values for Chloroacetonitrile

10 min	30 min	1 h	4 h	8 h
24 ppm (74 mg/m^3)	24 ppm (74 mg/m^3)	15 ppm (46 mg/m^3)	6.4 ppm (20 mg/m^3)	4.2 ppm (13 mg/m^3)

TABLE 1-30 AEGL Values for Chloroacetonitrile

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)	8.0 ppm (25 mg/m^3)	8.0 ppm (25 mg/m^3)	5.0 ppm (15 mg/m^3)	2.1 ppm (6.5 mg/m^3)	1.4 ppm (4.3 mg/m^3)
AEGL-3 (lethal)	24 ppm (74 mg/m^3)	24 ppm (74 mg/m^3)	15 ppm (46 mg/m^3)	6.4 ppm (20 mg/m^3)	4.2 ppm (13 mg/m^3)

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

6. MALONONITRILE

6.1. Summary

Malononitrile is a white powder at ambient temperature and pressure, and can cause irritation or burning of the eyes and skin. It is metabolized to cyanide in the body and signs of intoxication may include weakness, headache, dizziness, confusion, nausea, vomiting, convulsion, dilated pupils, weak pulse, tachypnea, dyspnea, and cyanosis. The systemic toxicity of malononitrile is due to the metabolic release of cyanide and the onset of symptoms may be delayed for up to several hours (HSDB 2003b).

Chemical-specific inhalation data were insufficient to derive AEGL values for malononitrile. Therefore, a relative potency approach was used to estimate AEGL-2 and AEGL-3 values for malononitrile on the basis of comparison with acetonitrile. In the absence of inhalation data on malononitrile, comparison was based on the intraperitoneal toxicity of the two chemicals. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, malononitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the AEGL-2 and AEGL-3 values for acetonitrile were divided by 65 to approximate AEGL-2 and AEGL-3 values for malononitrile. AEGL-1 values were not derived by this method because of the uncertainty associated with applying a relative potency estimate based on lethality to AEGL-1 effects. The AEGL values for malononitrile are presented in Table 1-31.

6.2. Introduction

Malononitrile is a white powder at ambient temperature and pressure and can cause irritation or burning of the eyes and skin. The systemic toxicity of malononitrile is due to the metabolic release of cyanide and the onset of symptoms may be delayed for up to several hours (HSDB 2003b).

TABLE 1-31 AEGL Values for Malononitrile

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)	1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)	Based on AEGL-2 values for acetonitrile
AEGL-3 (lethal)	3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)	Based on AEGL-3 values for acetonitrile

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

Malononitrile is produced batchwise by elimination of water from cyanoacetamide with phosphorus pentachloride, and can also be produced from chloronitrile, methylnitrile, hydrogen cyanide, cyanochloride, and acetonitrile at temperatures above 700°C. Malononitrile is the hydrolysis product of 2-chlorobenzylizene (CS-tear gas) used for self-defense. It is used as a lubricating oil additive, and in the synthesis of thiamine, anticancer agents, acrylic fibers, and dyes (HSDB 2003b).

HSDB (2003b) reported that approximately 1,200 workers were potentially exposed to malononitrile in 1981-1983, and that occupational exposure may occur by dermal contact.

The chemical and physical properties of malononitrile are presented in Table 1-32.

6.3. Human Toxicity Data

6.3.1. Acute Lethality

Information concerning death in humans following inhalation exposure to malononitrile was not available.

6.3.2. Nonlethal Toxicity

6.3.2.1. Case Reports

In the late 1940s malononitrile was used as an experimental treatment for schizophrenia and depression. The premise was that malononitrile might stimulate the formation of proteins and polynucleotides in nerve tissue and thus restore normal function. Hyden and Hartelius (1948) administered a 5% malononitrile solution intravenously to 66 patients at doses of 1-6 mg/kg. The number of doses administered to each patient varied from 3 to 17; injections were made two or three times per week. Each infusion lasted from 10 to 60 min. Tachycar-

dia was noted 10-20 min after infusion of malononitrile in all 66 patients. Facial redness, nausea, vomiting, shivering, cold hands and feet, muscle spasms, and numbness were also reported. Convulsions occurred in two patients. Cardiac collapse occurred in one patient with a history of congenital heart defect. Hartelius (1950) then administered a 5% malononitrile solution intravenously at an average dose of 2.4 mg/kg to nine patients. The number of doses administered to each patient varied from 3 to 12, over a period of 24 days. Each infusion lasted 48 min. Facial redness, tachycardia, and congestive flow of blood to the head were observed throughout treatment.

MacKinnon et al. (1949) administered a 5% malononitrile solution intravenously at a dose of 2 mg/kg to nine patients. Patients received 10 doses over 2-3 weeks. Clinical signs were similar to those described above; however, no convulsions occurred. Nausea recurred several hours after treatment.

Myers et al. (1950) administered a 5% malononitrile solution intravenously to 66 patients at doses ranging from 3 to 6 mg/kg. Each infusion lasted from 21 to 60 min. Effects during treatment included flushing of the face (appearing within 5 min and increasing throughout treatment), tachycardia (appearing with 10-15 min), nausea (appearing within 20-25 min), and vomiting (appearing within 30 min). Patients were described as restless and acutely distressed. Veins of the head and neck were distended and extremities were cold. Systolic blood pressure was increased and pulse was decreased.

TABLE 1-32 Chemical and Physical Data on Malononitrile

Parameter	Data	Reference
Common name	Malononitrile	HSDB 2003b
Synonyms	Methylene cyanide; propanedinitrile; cyanoacetonitrile; dicyanomethane; malonic acid dinitrile; malonicdinitrile	HSDB 2003b
CAS registry no.	109-77-3	HSDB 2003b
Chemical formula	$C_3H_2N_2$	HSDB 2003b
Molecular weight	66.06	HSDB 2003b
Physical state	White powder	HSDB 2003b
Melting point	32°C	HSDB 2003b
Boiling point	218-219°C	HSDB 2003b
Density/specific gravity	1.19 at 20°C/4°C	HSDB 2003b
Solubility	In water, 1.33×10^5 mg/L at 25°C; soluble in acetone, benzene, chloroform	HSDB 2003b
Vapor pressure	0.200 mm Hg at 22°C	HSDB 2003b
Conversion	1 ppm = 2.70 mg/m^3	NIOSH 2011d

6.3.3. Developmental and Reproductive Toxicity

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

6.3.4. Genotoxicity

Genotoxicity studies of acute human exposure to malononitrile were not available.

6.3.5. Carcinogenicity

Carcinogenicity studies of human exposure to malononitrile were not available.

6.3.6. Summary

The only human studies available on malononitrile involved the intravenous administration of malononitrile as an experimental treatment for mental illness. Clinical signs included tachycardia, facial redness, headache, nausea, vomiting, cold extremities, muscle spasms, and convulsions. No human studies on the developmental or reproductive toxicity, genotoxicity, or carcinogenicity of malononitrile were available.

6.4. Animal Toxicity Data

6.4.1. Acute Lethality

6.4.1.1. Rats

American Cyanamid (1988) reported a 2-h LC_{50} of 57 ppm for rats. No details of the experiment were available, and the reported value could not be verified.

Hicks (1950) administered intraperitoneal injections of malononitrile at 5-10 mg/kg to 26 young adult rats at 2-4 h intervals for 1-2 days. Four rats died during the exposure period, and 15 of the surviving rats had brain lesions, including necrosis of instriatal neurons, demyelinating lesions of the optic tract and nerve, and lesions of the cerebral cortex, at necropsy. Renal tubular necrosis, ventricular myocardial changes, and pulmonary edema were also found in some rats.

6.4.1.2. Mice

Panov (1969) exposed groups of six mice (strain and sex not specified) to malononitrile at 3-110 ppm for 2 h in a dynamic chamber at 29-30°C. The concentration of malononitrile was measured colorimetrically twice during the experiment. Mice developed signs of restlessness and increased respiration rates shortly after exposure, followed by lassitude, cyanosis, decreased respiration rate, incoordination, trembling, and convulsions. Death occurred in two mice.

Fifty percent of mice exposed to malononitrile at 74-110 ppm for 2 h died. Mice exposed at 89 ppm for 2 h developed hyperemia, had increased lung, kidney, and brain weights, and had decreased liver weight compared to air-exposed controls. No further details were provided (Panov1969).

Mice administered a single oral dose of malononitrile at 5 mg/kg showed "general intoxication", but no deaths occurred. Morality was 60-80% in mice administered malononitrile at single oral doses of 20-30 mg/kg, and 100% died when administered 40-50 mg/kg (Panov 1969). An LD_{50} of 18.6 mg/kg was calculated. No further experimental details were available.

An intraperitoneal LD_{50} of 13 mg/kg was reported for mice (Lewis 1996). No further information was available.

6.4.1.3. Rabbits

Panov(1969) administered a 5% malononitrile solution to the eyes of six rabbits. Tearing, hyperemia of the conjunctiva, and spasm and swelling of the eyelids occurred in all rabbits. Respiratory impairment, convulsions, and death occurred in four of the rabbits.

6.4.2. Nonlethal Toxicity

Panov (1970) exposed groups of 10 rats (strain and sex not specified) to malononitrile at 0 or 13 ppm for 2 h/day for 35 days in a dynamic chamber at 29-30°C. The concentration of malononitrile was measured at 2-day intervals by determining the amount of nitrogen with Nessler reagent. Effects observed in treated animals included increased relative lung weights at the end of the study, increased reticulocyte counts on day 7 (34 in treated group vs. 14.1 in control group) and day 35 (27.9 in treated group vs. 10.3 control group), and increased respiration.

6.4.2.1. Mice

Panov (1969) reported that a single dermal application of malononitrile (concentration and duration not reported) to the tails of mice (number, sex, and strain not stated) resulted in restlessness, rapid respiration, and slight cyanosis of

the mucosa of the lips and extremities. The symptoms reportedly subsided following removal of the chemical by washing.

6.4.3. Developmental and Reproductive Toxicity

No information concerning the developmental or reproductive toxicity of malononitrile was available.

6.4.4. Genotoxicity

No information concerning the genotoxicity of malononitrile was available.

6.4.5. Carcinogenicity

No information concerning the carcinogenicity of malononitrile was available.

6.4.6. Summary

The few animal toxicity studies on malononitrile suggest that the chemical can produce central nervous system, respiratory, and cardiovascular effects in animals; however, no quantitative inhalation data were available. No studies of the reproductive developmental toxicity, genotoxicity, or carcinogenicity of malononitrile were found.

6.5. Data Analysis for AEGL-1

6.5.1. Human Data Relevant to AEGL-1

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

6.5.2. Animal Data Relevant to AEGL-1

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

6.5.3. Derivation of AEGL-1 Values

Chemical-specific data were insufficient to derive of AEGL-1 values for malononitrile. Therefore, AEGL-1 values are not recommended.

6.6. Data Analysis for AEGL-2

6.6.1. Human Data Relevant to AEGL-2

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

6.6.2. Animal Data Relevant to AEGL-2

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

6.6.3. Derivation of AEGL-2 Values

Chemical-specific inhalation data were insufficient to derive AEGL-2 values for malononitrile. However, data from other routes of exposure (oral and intraperitoneal) are available. A relative potency approach was used to approximate AEGL-2 values for malononitrile on the basis of comparison with acetonitrile.

In the absence of inhalation data, the intraperitoneal route is considered the most appropriate for approximating inhalation toxicity values because both routes involve entry into the organism through a semipermeable membrane (peritoneal membrane and alveolar membrane) before diffusion into the blood. Furthermore, the magnitude and rate of effect for the different routes of administration (in descending order) are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical (Eaton and Gilbert 2008). Intraperitoneal toxicity data are available for acetonitrile and propionitrile for comparison, but a judgment was made to use acetonitrile because the overall database on this chemical is more robust (includes toxicity data and data to derive a value for the exponent "n" for time scaling) than for propionitrile. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, malononitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the AEGL-2 values for acetonitrile were divided by 65 to approximate the AEGL-2 values for malononitrile. The AEGL-2 values for malononitrile are presented in Table 1-33.

6.7. Data Analysis for AEGL-3

6.7.1. Human Data Relevant to AEGL-3

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

TABLE 1-33 AEGL-2 Values for Malononitrile

10 min	30 min	1 h	4 h	8 h
1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)

6.7.2. Animal Data Relevant to AEGL-3

A 2-h LC_{50} of 57 ppm for rats was reported (American Cyanamid 1988). However, no experimental details were available, and the reported value could not be verified.

6.7.3. Derivation of AEGL-3 Values

Chemical-specific inhalation data were insufficient to derive AEGL-3 values for malononitrile. Therefore, the relative-potency approach used to derive AEGL-2 values (described in Section 6.6.3) was also used to estimate AEGL-3 values. Because malononitrile is estimated to be approximately 65 times more toxic than acetonitrile, the AEGL-3 values for acetonitrile were divided by 65 to approximate AEGL-3 values for malononitrile. The AEGL-3 values for malononitrile are presented in Table 1-34.

6.8. Summary of AEGLs

6.8.1. AEGL Values and Toxicity End Points

Chemical-specific data were insufficient for deriving AEGL values for malononitrile. Therefore, AEGL-2 and AEGL-3 values were determined on the basis of malononitrile's relative potency to acetonitrile. AEGL-1 values were not derived by this method because of the uncertainty associated with applying a relative-potency estimate based on lethality to effects defined by AEGL-1. The AEGL values for malononitrile are presented in Table 1-35.

6.8.2. Other Standards and Guidelines

Only one other exposure standard for malononitrile was found (see Table 1-36). The National Institute for Occupational Safety and Health's recommended exposure limit (time-weighted average) of 3 ppm is based on evidence that selected nitrile compounds are metabolized to cyanide ion, which causes numerous systemic effects.

TABLE 1-34 AEGL-3 Values for Malononitrile

10 min	30 min	1 h	4 h	8 h
3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)

TABLE 1-35 AEGL Values for Malononitrile

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)	1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)
AEGL-3 (lethal)	3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)

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

TABLE 1-36 Other Standards and Guidelines for Malononitrile

	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	1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)
AEGL-3	3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)
REL-TWA (NIOSH)[a]	–	–	–	–	3 ppm (8.1 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]REL-TWA (recommended exposure limits—time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011d) is defined as a time-weighted average concentrations for up to a 10-h workday during a 40-h workweek. Values is based on relative toxicity (subcutaneous exposure) to isobutyronitrile.

6.8.3. Data Adequacy and Research Needs

Chemical-specific data were insufficient to derive AEGL values for malononitrile. AEGL-2 and AEGL-3 values for malononitrile were determined on the basis of its relative potency to acetonitrile.

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APPENDIX A

CALCULATION OF THE TIME-SCALING EXPONENT "N"

Concentration vs Time Analysis Using DoseResp

TABLE A-1 Lethality in Rats After Acute Inhalation of Acetonitrile

Concentration (ppm)	Minutes	Exposed	Dead
53,000	15	6	0
53,000	30	6	3
25,000	30	3	3
4,000	240	30	3
8,000	240	30	10
32,000	240	30	17
10,100	240	10	0
13,600	240	10	1
19,700	240	10	3
22,200	240	10	8
4,000	240	24	0
8,000	240	24	3
16,000	240	24	9
32,000	240	24	24
1,000	480	24	0
2,000	480	24	1
4,000	480	24	2
8,000	480	24	7
16,000	480	24	21
32,000	480	24	24

Selection of trials from number 1 through 20

Transformation of variables
Concentration ppm is transformed logaritmically!
Minutes is transformed logarithmically!
Probit model used without background response correction!
Variable 1 = conc ppm
Variable 2 = minutes
Chi-Square = 67.02
Degrees of Freedom = 17
B 0 = -1.124E+01 Student t for B 0 = -3.623
B 1 = 1.225E+00 Student t for B 1 = 5.456
B 2 = 7.907E-01 Student t for B 2 = 2.932

Variance B 0 0 = 9.617E+00
Covariance B 0 1 = -6.255E-01
Covariance B 0 2 = -6.557E-01
Variance B 1 1 = 5.042E-02
Covariance B 1 2 = 2.636E-02
Variance B 2 2 = 7.274E-02

The prediction of the model is not sufficient. Use for estimation of the 95% confidence limits.

Student t with 17 degrees of freedom

Correction for variances Chi-Squares/Degrees of Freedom = 3.943

The prediction of the model is not sufficient. Use for estimation of the 95% confidence limits Student t with 17 degrees of freedom

Correction for variances Chi-Squares/Degrees of Freedom = 3.943

Student t = 2.110

Estimation of ratio between regression coefficients

Ratio between regression coefficients
conc ppm and minutes

Ratio = 1.550

Confidence limits
0.539 2.5

APPENDIX B

DERIVATION OF AEGL VALUES FOR SELECTED ALIPHATIC NITRILES

Acetonitrile

Derivation of AEGL-1 Values

Key study:	Pozzani, U.C., C.P. Carpenter, P.E. Palm, C.S. Weil, and J.H. Nair. 1959. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1:634-642.
Toxicity end point:	Slight chest tightness and cooling sensation in the lung reported by one of three volunteers exposed to acetonitrile at 40 ppm for 4 h.
Time scaling:	Value held constant across the 10-min to 4-h durations.
Uncertainty factors:	1 for interspecies differences 1 for intraspecies variability
Modifying factor:	3 because of the sparse database
Calculations:	
10-min AEGL-1:	Set equal to the 4-h AEGL-1 of 13 ppm
30-min AEGL-1:	Set equal to the 4-h AEGL-1 of 13 ppm
1-h AEGL-1:	Set equal to the 4-h AEGL-1 of 13 ppm
4-h AEGL-1:	40 ppm ÷ 3 = 13 ppm
8-h AEGL-1:	Not recommended

Derivation of AEGL-2 Values

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

Calculations:

10-min AEGL-2:	240 ppm ÷ 3 = 80 ppm
30-min AEGL-2:	240 ppm ÷ 3 = 80 ppm
1-h AEGL-2:	150 ppm ÷ 3 = 50 ppm
4-h AEGL-2:	64 ppm ÷ 3 = 21 ppm
8-h AEGL-2:	42 ppm ÷ 3 = 14 ppm

Derivation of AEGL-3 Values

Key study:	Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.
Toxicity end point:	No-effect level for maternal and fetal lethality (1,500 ppm for 6 h/d on gestational days 6-20).
Time scaling:	$C^{1.6} \times t = k$ $(1{,}500 \text{ ppm})^{1.6} \times 6 \text{ h} = 7.24 \times 10^5$ ppm-h
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability

Calculations:

10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 240 ppm
30-min AEGL-3:	$C^{1.6} \times 0.5 \text{ h} = 7.24 \times 10^5$ ppm-h $C^{1.6} = 1.45 \times 10^6$ ppm C = 7,089 ppm 7,089 ÷ 30 = 240 ppm
1-h AEGL-3:	$C^{1.6} \times 1 \text{ h} = 7.24 \times 10^5$ ppm-h $C^{1.6} = 7.24 \times 10^5$ ppm C = 4,597 ppm 4,596 ÷ 30 = 150 ppm
4-h AEGL-3:	$C^{1.6} \times 4 \text{ h} = 7.24 \times 10^5$ ppm-h $C^{1.6} = 1.81 \times 10^5$ ppm C = 1,933 ppm 1,933 ÷ 30 = 64 ppm

8-h AEGL-3: $C^{1.6} \times 8\ h = 7.24 \times 10^5$ ppm-h
$C^{1.6} = 9.05 \times 10^4$ ppm
C = 1,253 ppm
1,253 ÷ 30 = 42 ppm

Isobutyronitrile

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

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

Calculations:

10-min AEGL-2: 7.6 ppm ÷ 3 = 2.5 ppm

30-min AEGL-2: 7.6 ppm ÷ 3 = 2.5 ppm

1-h AEGL-2: 6.1 ppm ÷ 3 = 2.0 ppm

4-h AEGL-2: 3.8 ppm ÷ 3 = 1.3 ppm

8-h AEGL-2: 2.5 ppm ÷ 3 = 0.83 ppm

Derivation of AEGL-3 Values

Key study: Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Toxicity end point: No maternal mortality (100 ppm, 6 h/d on gestational days 6-20)

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)
$(100\ ppm)^3 \times 6\ h = 6.00 \times 10^6$ ppm-h
$(100\ ppm)^1 \times 6\ h = 600$ ppm-h

Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability

Calculations:

10-min AEGL-3:	Set equal to the 30-min AEGL-3 values of 7.6 ppm
30-min AEGL-3:	$C^3 \times 0.5$ h = 6.0×10^6 ppm-h $C^3 = 1.20 \times 10^7$ ppm C = 229 ppm 229 ÷ 30 = 7.6 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 6.0×10^6 ppm-h $C^3 = 6.00 \times 10^6$ ppm C = 182 ppm 182 ÷ 30 = 6.1 ppm
4-h AEGL-3:	$C^3 \times 4$ h = 6.0×10^6 ppm-h $C^3 = 1.50 \times 10^6$ ppm C = 114 ppm 114 ÷ 30 = 3.8 ppm
8-h AEGL-3:	$C^1 \times 8$ h = 600 ppm-h C^1 = 75 ppm C = 75 ppm 75 ÷ 30 = 2.5 ppm

Propionitrile

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

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

Calculations:

10-min AEGL-2:	11 ppm ÷ 3 = 3.7 ppm
30-min AEGL-2:	11 ppm ÷ 3 = 3.7 ppm
1-h AEGL-2:	9.1 ppm ÷ 3 = 3.0 ppm

4-h AEGL-2:	5.7 ppm ÷ 3 = 1.9 ppm
8-h AEGL-2:	3.8 ppm ÷ 3 = 1.3 ppm

Derivation of AEGL-3 Values

Key study:	Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz, J. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.
Toxicity end point:	No maternal or fetal mortality (150 ppm, 6 h/d on gestational days 6-20)
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) $(150 \text{ ppm})^3 \times 6 \text{ h} = 2.03 \times 10^7$ ppm-h $(150 \text{ ppm})^1 \times 6 \text{ h} = 900$ ppm-h
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability
Calculations:	
10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 11 ppm
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 2.03 \times 10^7$ ppm-h $C^3 = 4.05 \times 10^7$ ppm C = 343 ppm 343 ÷ 30 = 11 ppm
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 2.03 \times 10^7$ ppm-h $C^3 = 2.02 \times 10^7$ ppm C = 273 ppm 273 ÷ 30 = 9.1 ppm
4-h AEGL-3:	$C^3 \times 4 \text{ h} = 2.03 \times 10^7$ ppm-h $C^3 = 5.06 \times 10^6$ ppm C = 172 ppm 172 × 30 = 5.7 ppm
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 900$ ppm-h $C^1 = 112$ ppm C = 112 ppm 112 ÷ 30 = 3.8 ppm

Chloroacetonitrile

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

No chemical-specific data were available to derive AEGL-2 values for chloroacetonitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-2 values were divided by 10 to approximate AEGL-2 values for chloroacetonitrile.

Calculations:

10-min AEGL-2:	80 ppm ÷ 10 = 8.0 ppm
30-min AEGL-2:	80 ppm ÷ 10 = 8.0 ppm
1-h AEGL-2:	50 ppm ÷ 10 = 5.0 ppm
4-h AEGL-2:	21 ppm ÷ 10 = 2.1 ppm
8-h AEGL-2:	14 ppm ÷ 10 = 1.4 ppm

Derivation of AEGL-3 Values

No chemical-specific data were available to derive AEGL-3 values for chloroacetonitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-3 values were divided by 10 to approximate AEGL-2 values for chloroacetonitrile.

10-min AEGL-3:	240 ppm ÷ 10 = 24 ppm
30-min AEGL-3:	240 ppm ÷ 10 = 24 ppm
1-h AEGL-3:	150 ppm ÷ 10 = 15 ppm
4-h AEGL-3:	64 ppm ÷ 10 = 6.4 ppm
8-h AEGL-3:	42 ppm ÷ 10 = 4.2 ppm

Malononitrile

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

No chemical-specific data were available to derive AEGL-2 values for malononitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-2 values were divided by 65 to approximate AEGL-2 values for malononitrile.

Calculations:

10-min AEGL-2:	80 ppm ÷ 65 = 1.2 ppm
30-min AEGL-2:	80 ppm ÷ 65 = 1.2 ppm
1-h AEGL-2:	50 ppm ÷ 65 = 0.77 ppm
4-h AEGL-2:	21 ppm ÷ 65 = 0.32 ppm
8-h AEGL-2:	14 ppm ÷ 65 = 0.22 ppm

Derivation of AEGL-3 Values

No chemical-specific data were available to derive AEGL-3 values for malononitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-2 values were divided by 65 to approximate AEGL-3 values for malononitrile.

Calculations:

10-min AEGL-3:	240 ppm ÷ 65 = 3.7 ppm
30-min AEGL-3:	240 ppm ÷ 65 = 3.7 ppm
1-h AEGL-3:	150 ppm ÷ 65 = 2.3 ppm
4-h AEGL-3:	64 ppm ÷ 65 = 0.98 ppm
8-h AEGL-3:	42 ppm ÷ 65 = 0.65 ppm

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR SELECTED ACRYLONITRILES

Derivation Summary for Acetonitrile

AEGL-1 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	13 ppm (22 mg/m^3)	NR[a]

Key reference: Pozzani, U.C., C.P. Carpenter, P.E. Palm, C.S. Weil, and J.H. Nair. 1959. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1:634-642.

Test species/Strain/Number: Humans, 3 adult males

Exposure route/Concentrations/Durations: Inhalation; 40, 80, 160 ppm for 4 h

Effects: 40 ppm: slight chest tightness and cooling sensation in lungs (1/3); 80 ppm: no effects (0/2); 160 ppm: slight transitory flushing of the face 2 h after exposure and slight bronchial tightness 5 h later, which resolved overnight (1/2).

End point/Concentration/Rationale: Slight chest tightness and cooling sensation at 40 ppm.

Uncertainty factors/Rationale:
Interspecies: 1
Intraspecies: 1, mild effect is considered to have occurred in a sensitive subject because no symptoms were reported by two other subjects exposed to the same regimen and no effects were report in subjects exposed at 80 ppm for 4 h.

Modifying factor: 3, because of sparse database for AEGL-1 effects.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Concentration held constant across the 10-min to 4-h durations. No human data on exposures of durations less than 4 h are available; thus, time scaling to shorter durations could yield values eliciting symptoms above those defined by AEGL-1. An 8-h AEGL-1 value was not recommended because 13 ppm is essentially the same as the 8-h AEGL-2 value of 14 ppm.

Data adequacy: Human data were used to derive the AEGL-1 values. Values are considered protective because no effect occurred in other subjects exposed at higher concentrations.

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

AEGL-2 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
80 ppm (130 mg/m^3)	80 ppm (130 mg/m^3)	50 ppm (84 mg/m^3)	21 ppm (35 mg/m^3)	14 ppm (24 mg/m^3)

Data adequacy: In the absence of specific data on acetonitrile to determine AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3.

AEGL-3 Values for Acetonitrile

10 min	30 min	1 h	4 h	8 h
240 ppm (400 mg/m^3)	240 ppm (400 mg/m^3)	150 ppm (250 mg/m^3)	64 ppm (110 mg/m^3)	42 ppm (71 mg/m^3)

Key reference: Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Test species/Strain/Sex/Number: Rats, Sprague-Dawley, pregnant females, 20 per group

Exposure route/Concentrations/Duration: Inhalation; 900, 1,200, 1,500, or 1,800 ppm for 6 h/d on gestational days 6-20

End point/Concentration/Rationale: No-effect level for maternal and fetal lethality (1,500 ppm for 6 h)

Effects:

Concentration	Maternal mortality	Implants per litter (mean ± SD)	Sites per litter (mean ± SD)
0 ppm	0/20	4.40 ± 6.26	4.40 ± 6.26
900 ppm	0/20	4.61 ± 5.30	4.28 ± 4.92
1,200 ppm	0/20	3.68 ± 5.95	3.68 ± 5.96
1,500 ppm	0/20	4.40 ± 4.77	4.03 ± 4.82
1,800 ppm	8/20	21.78 ± 38.68[a]	21.78 ± 36.68[a]

[a]Significantly different from control, $p < 0.01$.

Uncertainty factors/Rationale:
Interspecies: 10, default value was applied because no comparable data were identified for similar exposures (repeated inhalation exposure during gestation) in other species.
Intraspecies: 3, because human accidental and occupational exposures indicate that there are individual differences in sensitivity to hydrogen cyanide (the metabolically-liberated toxicant), but potential differences in susceptibility among humans are not expected to greater than three-fold (NRC 2002). Furthermore, application of a default uncertainty factor of 10 would result in AEGL-3 values that would be inconsistent with the database (220 ppm for 1 h, 93 ppm for 4 h, and 60 ppm for 8 h are values in the range of concentrations (40-160 ppm) causing only minor effects in humans [Pozzani et al. 1959]).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$, where $n = 1.6$ (derived from rat lethality data for exposure durations ranging from 15 min to 8 h). Time scaling was not performed for the 10-min AEGL value because of the uncertainty associated with extrapolating a point-of-departure based on a 6-h exposure to a 10-min value. The 10-min AEGL-3 value was set equal to the 30-min AEGL value.

Data adequacy: Well-conducted study with appropriate end point for AEGL-3 values.

Derivation Summary for Isobutyronitrile

AEGL-1 Values for Isobutyronitrile

The data on isobutyronitrile were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Isobutyronitrile

10 min	30 min	1 h	4 h	8 h
2.5 ppm (7.1 mg/m^3)	2.5 ppm (7.1 mg/m^3)	2.0 ppm (5.7 mg/m^3)	1.3 ppm (3.7 mg/m^3)	0.83 ppm (2.3 mg/m^3)

Data adequacy: In the absence of specific data on isobutyronitrile to determine AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3.

AEGL-3 Values for Isobutyronitrile

10 min	30 min	1 h	4 h	8 h
7.6 ppm (22 mg/m^3)	7.6 ppm (22 mg/m^3)	6.1 ppm (17 mg/m^3)	3.8 ppm (11 mg/m^3)	2.5 ppm (7.1 mg/m^3)

Key reference: Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Test species/Strain/Sex/Number: Rats, Sprague-Dawley, pregnant females, 21 per group

Exposure route/Concentrations/Durations: 50, 100, 200, or 300 ppm for 6 h on gestational days 6-20

End point/Concentration/Rationale: No maternal death at 100 ppm for 6 h

Effects:

Concentration	Maternal mortality
50 ppm	0/21
100 ppm	0/21
200 ppm	1/21
300 ppm	3/21

A statistically significant increase in fetal resorptions was observed in dams exposed at 300 ppm.

Uncertainty factors/Rationale:
Interspecies: 10, default value was applied because no comparable data were identified for similar exposures (repeated inhalation exposure during gestation) in other species.
Intraspecies: 3, because human accidental and occupational exposures indicate that there are individual differences in sensitivity to hydrogen cyanide (the metabolically-liberated toxicant), but potential differences in susceptibility among humans are not expected to greater than three-fold (NRC 2002).

Modifying factor: None

Animal-to-human dosimetric adjustment: Insufficient data

(Continued)

AEGL-3 Values for Isobutyronitrile Continued

Time scaling: $C^n \times t = k$, where default values of n = 3 for extrapolation to the 10- and 30-min durations and n = 1 for extrapolation to the 4- and 8-h 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 6-h exposure to a 10-min value.
Data adequacy: Database is sparse.

Derivation Summary for Propionitrile

AEGL-1 Values for Propionitrile

The data on propionitrile were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Propionitrile

10 min	30 min	1 h	4 h	8 h
3.7 ppm (8.3 mg/m^3)	3.7 ppm (8.3 mg/m^3)	3.0 ppm (6.8 mg/m^3)	1.9 ppm (4.3 mg/m^3)	1.3 ppm (2.9 mg/m^3)

Data adequacy: In the absence of specific data on propionitrile to determine AEGL-2 values, estimates were made by dividing the AEGL-3 values by 3.

AEGL-3 Values for Propionitrile

10 minute	30 minute	1 hour	4 hour	8 hour
11 ppm (25 mg/m^3)	11 ppm (25 mg/m^3)	9.1 ppm (20 mg/m^3)	5.7 ppm (13 mg/m^3)	3.8 ppm (8.6 mg/m^3)

Key reference: Saillenfait, A.M., P. Bonnet, J.P. Gurnier, and J. de Ceaurriz, J. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Test species/Strain/Sex/Number: Rats, Sprague-Dawley, pregnant females, 22-23 per group

Exposure route/Concentrations/Durations: Inhalation, 50, 100, 150, or 200 ppm for 6 h on gestational days 6-20

End point/Concentration/Rationale: No maternal death or increase in fetal resorptions (150 ppm for 6 h)

Effects:

Concentration	Maternal mortality
50 ppm	0/22
100 ppm	0/23
150 ppm	0/22
200 ppm	2/23

A statistically significant increase in fetal resorptions was observed in dams exposed at 200 ppm.

Uncertainty factors/Rationale: Interspecies: 10, default value was applied because no comparable data were identified for similar exposures (repeated inhalation exposure during gestation) in other species. Intraspecies: 3, because human accidental and occupational exposures indicate that there are individual differences in sensitivity to hydrogen cyanide (the metabolically-liberated toxicant), but potential differences in susceptibility among humans are not expected to greater than three-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 the 10- and 30-min durations and n = 1 for extrapolation to the 4- and 8-h 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 6-h exposure to a 10-min value.
Data adequacy: Database is sparse.

Derivation Summary for Chloroacetonitrile

AEGL-1 Values for Chloroacetonitrile

The data on chloroacetonitrile were insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Chloroacetonitrile

10 min	30 min	1 h	4 h	8 h
8.0 ppm (25 mg/m^3)	8.0 ppm (25 mg/m^3)	5.0 ppm (15 mg/m^3)	2.1 ppm (6.5 mg/m^3)	1.4 ppm (4.3 mg/m^3)

Data adequacy: No chemical-specific data were available to derive AEGL-2 values for chloroacetonitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-2 values were divided by 10 to approximate AEGL-2 values for chloroacetonitrile.

AEGL-3 Values for Chloroacetonitrile

10 min	30 min	1 h	4 h	8 h
24 ppm (74 mg/m^3)	24 ppm (74 mg/m^3)	15 ppm (46 mg/m^3)	6.4 ppm (20 mg/m^3)	4.2 ppm (13 mg/m^3)

Data adequacy: No chemical-specific data were available to derive AEGL-3 values for chloroacetonitrile. Mouse intraperitoneal LD_{50} data suggest that, on a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile (see Table 1-1). Therefore, the acetonitrile AEGL-3 values were divided by 10 to approximate AEGL-3 values for chloroacetonitrile.

Derivation Summary for Malononitrile

AEGL-1 Values for Malononitrile

The data on malononitrile are insufficient for deriving AEGL-1 values, so no values are recommended.

AEGL-2 Values for Malononitrile

10 min	30 min	1 h	4 h	8 h
1.2 ppm (3.3 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.77 ppm (2.1 mg/m^3)	0.32 ppm (0.87 mg/m^3)	0.22 ppm (0.59 mg/m^3)

Data adequacy: No chemical-specific data are available to derive AEGL-2 values for malononitrile. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, malononitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the AEGL-2 values for acetonitrile were divided by 65 to approximate AEGL-2 values for malononitrile.

AEGL-3 Values for Malononitrile

10 min	30 min	1 h	4 h	8 h
3.7 ppm (10 mg/m^3)	3.7 ppm (10 mg/m^3)	2.3 ppm (6.2 mg/m^3)	0.98 ppm (2.7 mg/m^3)	0.65 ppm (1.7 mg/m^3)

Data adequacy: No chemical-specific data are available to derive AEGL-3 values for malononitrile. Intraperitoneal LD_{50} data from studies of mice suggest that, on a molar basis, malononitrile is approximately 65 times more toxic than acetonitrile (see Table 1-1). Therefore, the AEGL-3 values for acetonitrile were divided by 65 to approximate AEGL-3 values for malononitrile.

APPENDIX D

CATEGORY PLOTS FOR SELECTED ALIPHATIC NITRILES

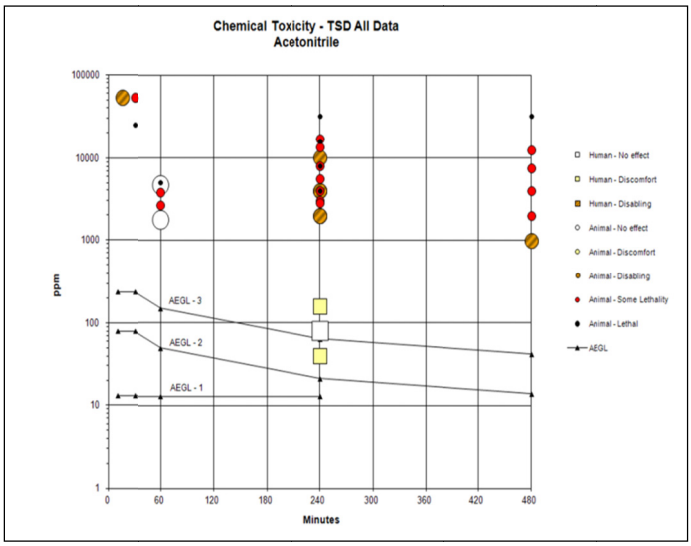

FIGURE D-1 Category plot of toxicity data and AEGL values for acetonitrile.

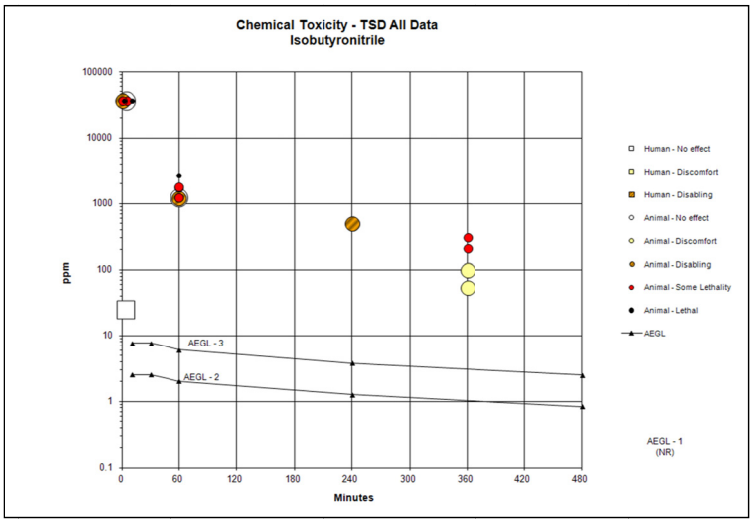

FIGURE D-2 Category plot of toxicity data and AEGL values for isobutyronitrile.

TABLE D-1 Data Used in Category Plot for Acetonitrile

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				13	10	AEGL	
AEGL-1				13	30	AEGL	
AEGL-1				13	60	AEGL	
AEGL-1				13	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				80	10	AEGL	
AEGL-2				80	30	AEGL	
AEGL-2				50	60	AEGL	
AEGL-2				21	240	AEGL	
AEGL-2				14	480	AEGL	
AEGL-3				240	10	AEGL	
AEGL-3				240	30	AEGL	
AEGL-3				150	60	AEGL	
AEGL-3				64	240	AEGL	
AEGL-3				42	480	AEGL	
Pozzani et al. 1959	Dog	Male	1	2,000	240	2	Pulmonary congestion or hemorrhage
Pozzani et al. 1959	Dog	Male	1	16,000	240	3	100% mortality (3/3)
Pozzani et al. 1959	Guinea pig		1	4,000	240	2	Pulmonary congestion or hemorrhage
Pozzani et al. 1959	Guinea pig		1	5,655	240	SL	LC_{50}
Pozzani et al. 1959	Guinea pig		1	8,000	240	3	100% mortality (6/6)
Willhite 1983	Hamster	Female	1	1,800	60	0	No maternal death
Willhite 1983	Hamster	Female	1	3,800	60	SL	Mortality (1/6); no signs of toxicity in others

Willhite 1983	Hamster	Female	1	3,800	60	0	No embryo lethality
Pozzani et al. 1959	Human	Male	1	40	240	1	n = 3, no subjective symptoms, slight chest tightness followed by a cooling sensation in lungs
Pozzani et al. 1959	Human	Male	1	80	240	0	n = 2, no subjective symptoms
Pozzani et al. 1959	Human	Male	1	160	240	1	n = 2, slight transitory flushing of the face, slight bronchial tightness
MPI 1998	Mouse	Both	1	3,039	240	SL	20% mortality (2/10)
Willhite 1981	Mouse		1	2,693	60	SL	LC_{50}
Willhite 1981	Mouse		1	5,000	60	3	100% mortality (10/10)
Pozzani et al. 1959	Rabbit		1	2,000	240	2	Pulmonary congestion or hemorrhage
Pozzani et al. 1959	Rabbit		1	2,828	240	SL	LC_{50}
Pozzani et al. 1959	Rabbit		1	4,000	240	3	100% mortality (4/4)
DuPont 1968	Rat	Male	1	17,100	240	SL	LC_{50}
Haguenoer et al. 1975	Rat		1	25,000	30	3	100% mortality (3/3)
Monsanto 1986	Rat		1	10,100	240	2	Hemorrhagic lungs
Monsanto 1986	Rat		1	13,600	240	SL	Mortality (1/10), hemorrhagic lungs, corneal opacity
Northview Pacific Labs 1989	Rat	Both	1	4,760	60	0	1/5 females lost weight, no mortality or gross abnormalities
Mast et al. 1994	Rat	Female	14	1,200	360	0	No embryo lethality
Mast et al. 1994	Rat	Female	13	1,200	360	SL	6% (2/33) in dams
NTP 1996	Rat	Male	65	400	360	0	No death
NTP 1996	Rat	Female	65	800	360	0	No death
NTP 1996	Rat	Male	65	800	360	SL	10% mortality (1/10)

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Pozzani et al. 1959	Rat	Both	1	1,000	480	2	Pulmonary congestion or hemorrhage
Pozzani et al. 1959	Rat	Both	1	2,000	480	SL	Mortality (1/24), pulmonary congestion or hemorrhage
Pozzani et al. 1959	Rat	Both	1	4,000	240	2	Pulmonary congestion or hemorrhage
Pozzani et al. 1959	Rat	Both	1	4,000	480	SL	Mortality (2/24), pulmonary congestion or hemorrhage
Pozzani et al. 1959	Rat	Male	1	7,551	480	SL	LC_{50}
Pozzani et al. 1959	Rat	Both	1	8,000	240	SL	Mortality (7/12)
Pozzani et al. 1959	Rat	Female	1	12,435	480	SL	LC_{50}
Pozzani et al. 1959	Rat	Both	1	32,000	240	3	100% mortality (24/24)
Pozzani et al. 1959	Rat	Female	1	32,000	480	3	100% mortality (24/24)
Pozzani et al. 1959	Rat		1	53,000	15	2	No death
Pozzani et al. 1959	Rat		1	53,000	30	SL	50% mortality (3/6)
Saillenfait et al. 1993	Rat	Female	14	1,500	360	0	No maternal death or embryo lethality
Saillenfait et al. 1993	Rat	Female	14	1,800	360	3	40% (8/20) mortality in dams, embryo lethality
UCC 1965	Rat		1	4,000	240	SL	10% mortality (3/30)

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

TABLE D-2 Data Used in Category Plot for Isobutyronitrile

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				2.5	10	AEGL	
AEGL-2				2.5	30	AEGL	
AEGL-2				2.0	60	AEGL	
AEGL-2				1.3	240	AEGL	
AEGL-2				0.83	480	AEGL	
AEGL-3				7.6	10	AEGL	
AEGL-3				7.6	30	AEGL	
AEGL-3				6.1	60	AEGL	
AEGL-3				3.8	240	AEGL	
AEGL-3				2.5	480	AEGL	
Katz 1986	Rat	Male	1	1,248	60	SL	Mortality (1/5)
Katz 1986	Rat	Male	1	2,709	60	3	Mortality (5/5)
Katz 1986	Rat	Female	1	1,248	60	0	No clinical signs
Katz 1986	Rat	Female	1	1,778	60	SL	Mortality (1/5)

(Continued)

TABLE D-2 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Eastman Kodak 1986a	Rat	Male	1	1,200	60	2	"Appreciable" differences noted in expiratory reserve volume, residual volume, dynamic compliance (up to 76% decrease), and FEV 10%
Eastman Kodak 1986a	Rat	Male	1	1,800	60	SL	Mortality (2/4)
Eastman Kodak 1986a	Rat	Male	1	2,700	60	3	Mortality (4/4)
Eastman Kodak1986b	Rat	Male	1	1,233	60	SL	Mortality (1/5)
Smyth et al. 1962	Rat		1	500	240	2	No mortality, no details provided
Tsurumi and Kawada 1971	Rat		1	37,000	4	0	Mortality (0/10), no other effects described
Tsurumi and Kawada 1971	Rat		1	37,000	5	SL	Mortality (1/10), no other effects described
Tsurumi and Kawada 1971	Rat		1	37,000	10	3	Mortality (10/10), no other effects described
Tsurumi and Kawada 1971	Mouse		1	37,000	0.25	2	Mortality (0/10), no other effects described
Tsurumi and Kawada 1971	Mouse		1	37,000	0.5	SL	Mortality (3/10), no other effects described
Tsurumi and Kawada 1971	Mouse		1	37,000	2	3	Mortality (10/10), no other effects described
AIHA 1992	Human		1	25	3	0	An exposure of a few minutes to estimated concentrations of 20-25 ppm from a isobutyronitrile spill did not produce symptoms of cyanide poisoning

Saillenfait et al. 1993	Rat	Female	15	50	360	1	Gestation days 6-20
Saillenfait et al. 1993	Rat	Female	15	100	360	1	Gestation days 6-20
Saillenfait et al. 1993	Rat	Female	15	200	360	SL	Gestation days 6-20, mortality (1/21), decrease in fetal weight
Saillenfait et al. 1993	Rat	Female	15	300	360	SL	Gestation days 6-20, mortality (3/21), increased embryonic resorptions, decreased fetal weight, unilateral hydronephrosis

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

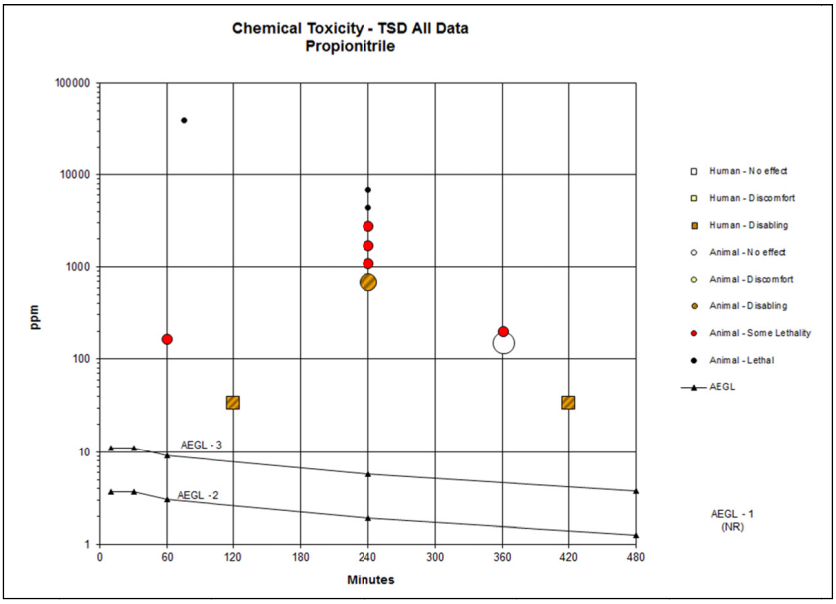

FIGURE D-3 Category plot of toxicity data and AEGL values for propionitrile.

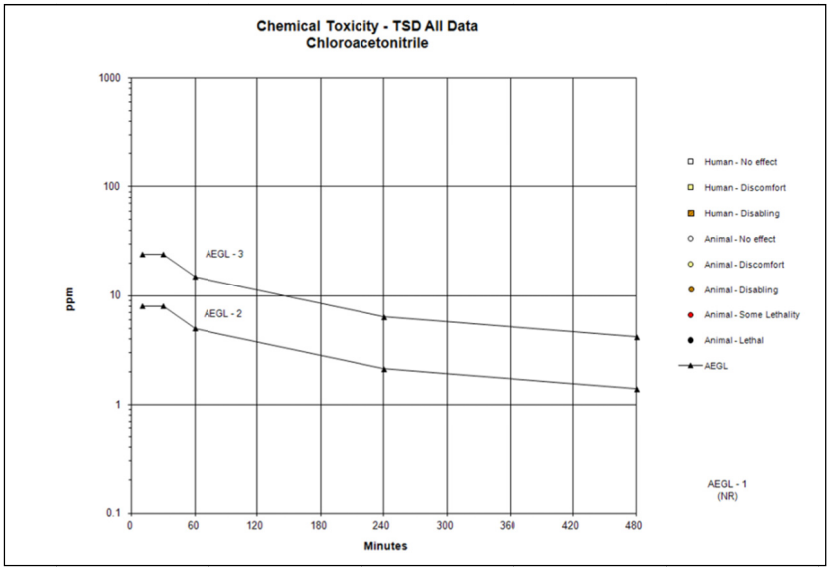

FIGURE D-4 Category plot of AEGL values for chloroacetonitrile.

TABLE D-3 Data Used in Category Plot for Propionitrile

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				3.7	10	AEGL	
AEGL-2				3.7	30	AEGL	
AEGL-2				3.0	60	AEGL	
AEGL-2				1.9	240	AEGL	
AEGL-2				1.3	480	AEGL	
AEGL-3				11	10	AEGL	
AEGL-3				11	30	AEGL	
AEGL-3				9.1	60	AEGL	
AEGL-3				5.7	240	AEGL	
AEGL-3				3.8	480	AEGL	
Saillenfait et al. 1993	Rat	Female	14	150	360	0	No maternal or fetal death
Saillenfait et al. 1993	Rat	Female	14	200	360	SL	Maternal death (2/23) and increased embryo lethality (increased mean % non-surviving implants/litter, increased mean % resorption sites/litter)

(Continued)

TABLE D-3 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Younger Labs 1978	Rat	Both	1	690	240	2	Salivation, lethargy, weakness, tremors, convulsions
Younger Labs 1978	Rat	Male	1	1,100	240	SL	Mortality (5/10), salivation, lethargy, weakness, tremors, convulsions, collapse and death
Younger Labs 1978	Rat	Male	1	1,700	240	SL	Mortality (5/10), salivation, lethargy, weakness, tremors, convulsions, collapse, death
Younger Labs 1978	Rat	Male	1	2,800	240	SL	Mortality (8/10), salivation, lethargy, weakness, tremors, convulsions, collapse, death
Younger Labs 1978	Rat	Both	1	4,400	240	3	Mortality (10/10), salivation, lethargy, weakness, tremors, convulsions, collapse, death
Younger Labs 1978	Rat	Both	1	6,900	240	3	Mortality (10/10), salivation, lethargy, weakness, tremors, convulsions, collapse, death
Younger Labs 1979	Rat	Male	1	39,432	75	3	Mortality (6/6)
Lewis 1996	Mouse		1	34		SL	Intraperitoneal LD_{50}
Tanii and Hashimoto 1984	Mouse	Male	1	36		SL	Oral LD_{50}
Willhite and Smith 1981	Mouse	Male	1	163	60	SL	LC_{50}
Scolnick et al. 1993	Human	Male	1	33.8	120	2	Headache, nausea, dizziness
Scolnick et al. 1993	Human	Male	1	33.8	420	2	Coma, seizures, bilateral interstitial infiltrates (lungs), lethargy, headaches, dizziness

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

TABLE D-4 Data Used in Category Plot for Chloroacetonitrile

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				8.0	10	AEGL	
AEGL-2				8.0	30	AEGL	
AEGL-2				5.0	60	AEGL	
AEGL-2				2.1	240	AEGL	
AEGL-2				1.4	480	AEGL	
AEGL-3				24	10	AEGL	
AEGL-3				24	30	AEGL	
AEGL-3				15	60	AEGL	
AEGL-3				6.4	240	AEGL	
AEGL-3				4.2	480	AEGL	

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

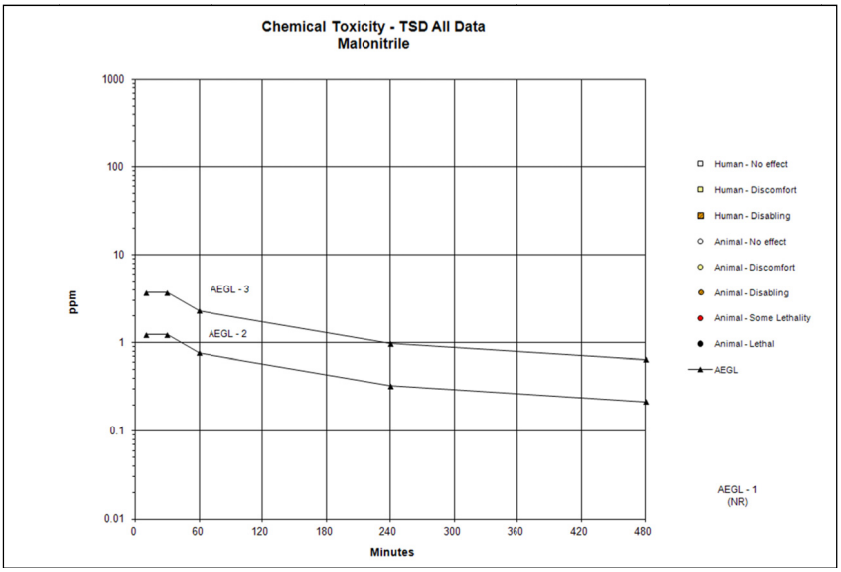

FIGURE D-5 Category plot of AEGL values for malononitrile.

TABLE D-5 Data Used in Category Plot for Malononitrile

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				1.2	10	AEGL	
AEGL-2				1.2	30	AEGL	
AEGL-2				0.77	60	AEGL	
AEGL-2				0.32	240	AEGL	
AEGL-2				0.22	480	AEGL	
AEGL-3				3.7	10	AEGL	
AEGL-3				3.7	30	AEGL	
AEGL-3				2.3	60	AEGL	
AEGL-3				0.98	240	AEGL	
AEGL-3				0.65	480	AEGL	

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