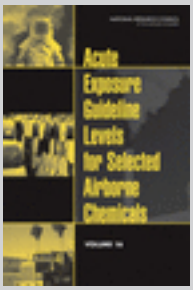

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VOLUME 16

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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

VOLUME 16

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

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

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

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

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

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

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

In November 1995, the National Advisory Committee (NAC)[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

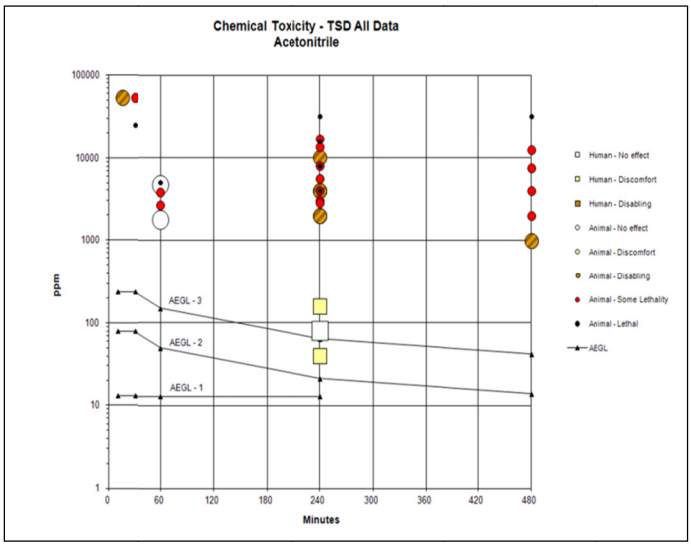

FIGURE D-1 Category plot of toxicity data and AEGL values for acetonitrile.

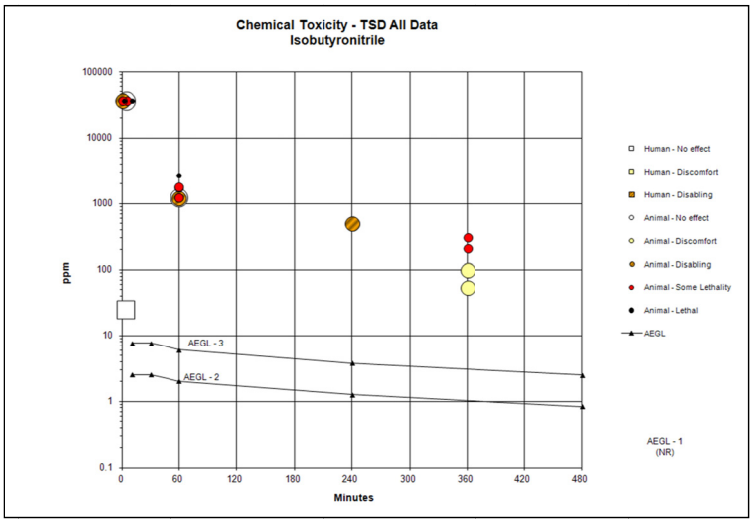

FIGURE D-2 Category plot of toxicity data and AEGL values for isobutyronitrile.

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

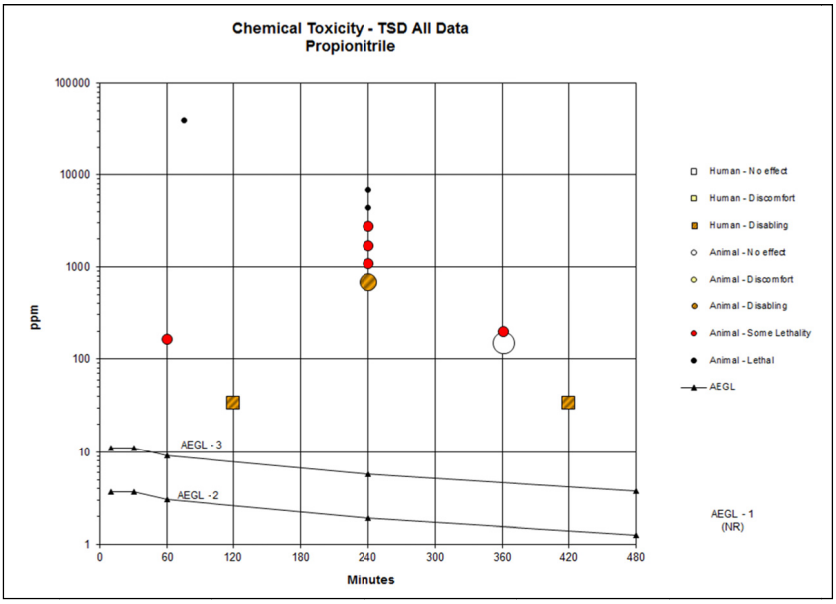

FIGURE D-3 Category plot of toxicity data and AEGL values for propionitrile.

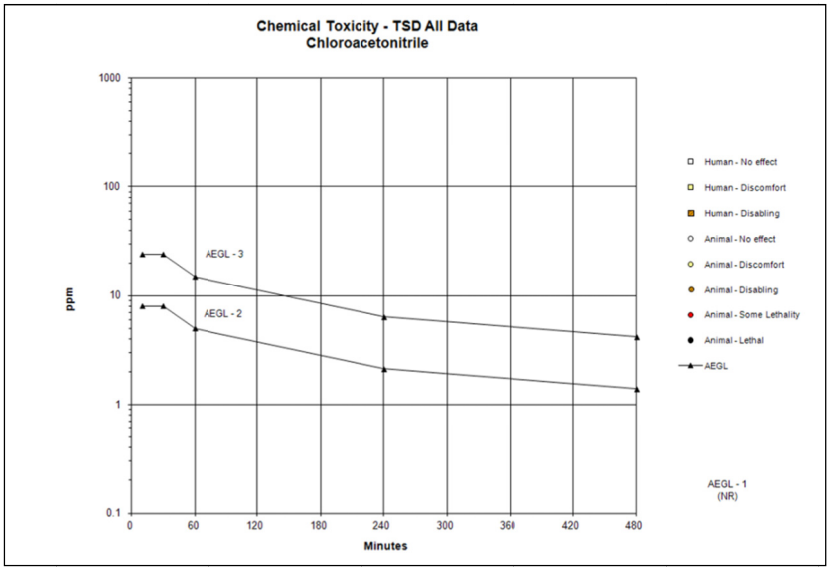

FIGURE D-4 Category plot of AEGL values for chloroacetonitrile.

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

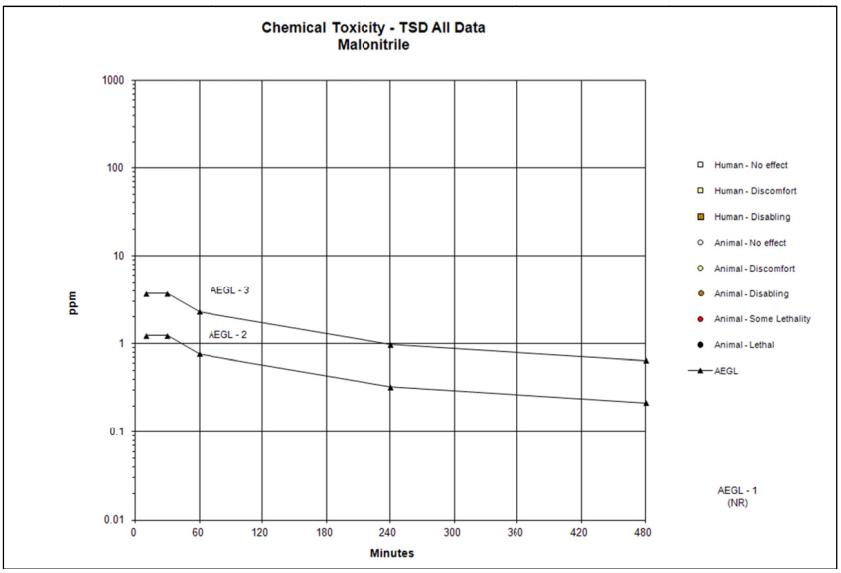

FIGURE D-5 Category plot of AEGL values for malononitrile.

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.

2

Benzonitrile[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

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

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

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

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

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

A study of mice exposed to benzonitrile at 890 ppm for 2 h was used as the basis of AEGL-3 values. Because one of seven mice died, further adjustment to estimate the lethal threshold was warranted. Typically, a 3-fold reduction of

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

AEGL values for benzonitrile are presented Table 2-1.

TABLE 2-1 AEGL Values for Benzonitrile

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (disabling)	11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)	Estimated lethal threshold in mice (MacEwen and Vernot 1974)

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

1. INTRODUCTION

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

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

TABLE 2-2 Physical and Chemical Data on Benzonitrile

Parameter	Data	Reference
Common name	Benzonitrile	IPCS 1999
Synonyms	Cyanobenzene, benzoic acid nitrile; phenyl cyanide	IPCS 1999
CAS registry no.	100-47-0	IPCS 1999
Chemical formula	C_6H_5 (CN)	IPCS 1999
Molecular weight	103.1	IPCS 1999
Physical state	Colorless liquid	HSDB 2003
Melting point	-12.8°C	IPCS 1999
Boiling point	190.7°C	IPCS 1999
Flash Point	75°C	IPCS 1999
Density/Specific gravity	1.010 at 25°C/15°C	HSDB 2003
Solubility	Poor solubility in water; miscible with organic solvents, soluble in alcohol, ether and acetone	HSDB 2003
Vapor density	3.6 (air = 1)	HSDB 2003
Vapor pressure	0.768 mm Hg at 25°C	HSDB 2003
Conversion factors in air	1 ppm = 4.22 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

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

2.2. Nonlethal Toxicity

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

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

Carcinogenicity studies of human exposure to benzonitrile were not available.

2.6. Summary

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

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

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

Groups of five male and five female young adult Charles River rats were exposed to benzonitrile at 0.8 or 8 mg/L (190 or 1,900 ppm) in a 70-L Plexiglas inhalation chamber for 4 h and observed for 14 days (Industrial Bio-Test 1970). An aerosol of undiluted benzonitrile was generated with an Ohio Ball-Jet Nebulizer. A stream of clean dry air was passed through the nebulizer and the resulting aerosol stream was mixed with additional dry air to obtain the final desired concentration. The test atmosphere was then introduced into the top of the exposure chamber, dispersed with a baffle plate, and exhausted at the bottom of the chamber. Air flow rates were measured with rotameters connected to the air supply line upstream of the aerosol; temperature and pressure of the test atmosphere were also measured. Average nominal concentrations were calculated by dividing the nebulizer weight loss by the total volume of air used during each exposure. No deaths, clinical signs, or effects on body weight were observed in the 0.8-mg/L group. At necropsy, no gross treatment-related effects were found in this group. Three females died after exposure at 8 mg/L; two deaths occurred 2 h after the end of the exposure period and one occurred on day 6. Six of the eight surviving rats lay prostrate 18 h after exposure; this effect persisted in two animals through day 4 and in one animal through day 6 (when death occurred). No adverse effects on body weight were noted. Necropsy of animals that died on the day of exposure showed minimal pulmonary hyperemia.

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

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

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

3.1.2. Mice

Groups of seven or 10 male CF-1 mice were exposed to benzonitrile at target concentrations of 900 ppm (saturated atmosphere) in a 30-L glass exposure chamber for 2 or 4 h and observed for 14 days (MacEwen and Vernot 1974). Measured concentrations were 890 ppm for the 2-h exposure and 700 ppm for the 4-h exposure. The benzonitrile atmosphere was produced by passing air through a fritted disc bubbler immersed in 200 mL of test material. The airflow through the bubbler was 10 L/min, and 9 min was necessary to achieve 95% saturation in the exposure chamber. The benzonitrile chamber concentration was continuously analyzed using a total hydrocarbon analyzer initially calibrated with several standard gas bags containing benzonitrile at 450 and 900 ppm in air. Irritation of the extremities was observed during the first hour of exposure, followed by poor coordination and labored breathing after 60-90 min. Prostration occurred at 2.5 h. All mice in the 4-h group died; three died on the day of exposure (including one during exposure at 3.5 h), three on day 1, and four on day 2. Only one mouse in the 2-h group died on day 2. Congestion accompanied by edema was found in the lungs of both exposure groups at necropsy. Mice exposed for 4 h also had hepatic congestion and sinusoidal dilation.

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

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

3.1.3. Rabbits

In an acute dermal toxicity study, two male and two female New Zealand white rabbits were administered undiluted benzonitrile at doses of 0.9, 1.4, 2.0,

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

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

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

3.2. Nonlethal Toxicity

No nonlethal toxicity studies of benzonitrile in animals were found.

3.3. Developmental and Reproductive Toxicity

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

3.4. Genotoxicity

Genotoxicity studies of animal exposure to benzonitrile were not available.

3.5. Carcinogenicity

Carcinogenicity studies of animal exposure to benzonitrile were not available.

3.6. Summary

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

4. SPECIAL CONSIDERATIONS

4.1. Metabolism

Hydrogen cyanide is not a metabolite of benzonitrile. The major metabolic pathway for benzonitrile is aromatic hydroxylation to cyanophenols. A small amount of the cyanophenol may then be hydrolyzed to benzoic acid. In rabbits, 50% of an orally administered dose of benzonitrile at 150 mg/kg was conjugated to cyanophenols, and 10% was excreted as benzoic acid. In rats, the in vivo microsomal hydroxylation of deuterated benzonitrile yielded primarily 4-hydroxybenzonitrile with 41% retention of deuterium (HSDB 2003). Although not documented, the structure of benzonitrile suggests that formation of an epoxide intermediate may occur; this may account for the hepatotoxicity observed in mice at necropsy by MacEwen and Vernot (1974).

4.2. Mechanism of Toxicity

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

4.3. Concurrent Exposure Issues

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

TABLE 2-3 Summary of Animal Toxicity Data on Benzonitrile

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

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

4.4. Structure-Activity Relationships

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

4.5. Species Differences

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

4.6. Concentration-Exposure Duration Relationship

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

5. RATIONALE FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

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

5.2. Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1 Values

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

6. RATIONALE FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

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

6.3. Derivation of AEGL-2 Values

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

TABLE 2-4 AEGL-2 Values for Benzonitrile

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

7. RATIONALE FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

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

7.3. Derivation of AEGL-3 Values

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

An interspecies uncertainty factor of 10 was applied. Mortality data reported by Agaev (1977) on benzonitrile suggest that rats and mice have similarly steep dose-response relationships (e.g., similar oral LD_{16}, LD_{50}, and LD_{84}), but the reported lack details about the methods, and no data on other species are available. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals. Application of this value, rather than a default of 10, is supported by the steep concentration-response curve for benzonitrile, which implies little individual variability. For example, the steepness of the curve is evident in mice exposed by inhalation to benzonitrile (10% mortality at 890 ppm for 2 h [ct = 1,780 ppm-h] vs. 100% mortality at 700 ppm for 4 h [ct = 2,800 ppm-h]) (MacEwen and Vernot 1974), in rats exposed orally (no mortality at 0.6 g/kg vs. 100% mortality at 2.0 g/kg) (Industrial Bio-Test 1970), and in rabbits exposed dermally (no mortality at 0.9 g/kg vs. 100% mortality at 1.4 g/kg) (Industrial Bio-Test 1970). The total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may

be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Insufficient data were available to derive an empirical value for n. Therefore, time scaling was performed using default values of n = 3 to extrapolate to shorter durations and n = 1 to extrapolate to longer durations to provide AEGL values that are protective of human health (NRC 2001). AEGL-3 values for benzonitrile are presented in Table 2-5, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

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

8.2. Other Standards and Guidelines

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

8.3. Data Adequacy and Research Needs

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

TABLE 2-5 AEGL-3 Values for Benzonitrile

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

TABLE 2-6 AEGL Values for Benzonitrile

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)
AEGL-3 (lethal)	34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)

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

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APPENDIX A

DERIVATION OF AEGL VALUES FOR BENZONITRILE

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

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

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

Derivation of AEGL-3 Values

Key study:	MacEwen, J.D., and E.H. Vernot. 1974. Acute inhalation toxicity of benzonitrile. Pp. 77-80 in Toxic Hazards Research Unit Annual Technical Report: 1974. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.
Toxicity end point:	Estimated 2-h lethality threshold in mice of 445 ppm
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n =1 for extrapolating to longer durations) $(445\ ppm)^3 \times 2\ h = 176{,}242{,}250\ ppm\text{-}h$ $(445\ ppm)^1 \times 2\ h = 890\ ppm\text{-}h$
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability
Modifying factor:	None

10-min AEGL-3:
$C^3 \times 0.167$ h = 176,242,250 ppm-h
C^3 = 1,055,342,814 ppm
C = 1,018 ppm
1,018 ÷ 30 = 34 ppm

30-min AEGL-3:
$C^3 \times 0.5$ h = 176,242,250 ppm-h
C^3 = 352,484,500 ppm
C = 706 ppm
706 ÷ 30 = 24 ppm

1-h AEGL-3:
$C^3 \times 1$ h = 176,242,250 ppm-h
C^3 = 176,242,250 ppm
C = 561 ppm
561 ÷ 30 = 19 ppm

4-h AEGL-3:
$C^1 \times 4$ h = 890 ppm-h
C^1 = 223 ppm
C = 223 ppm
223 ÷ 30 = 7.4 ppm

8-h AEGL-3:
$C^1 \times 8$ h = 890 ppm-h
C^1 = 111 ppm
C = 111 ppm
111 ÷ 30 = 3.7 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR BENZONITRILE

Derivation Summary

AEGL-1 VALUES

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

AEGL-2 VALUES

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

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

AEGL-3 VALUES

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

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

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

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

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

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

(Continued)

AEGL-3 VALUES Continued

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10, even though mortality data suggest that rats and mice have similarly steep dose-response relationships (e.g., similar oral LD_{16}, LD_{50}, and LD_{84}) (Agaev 1977), details of the study methods are lacking and no data on other species are available.
Intraspecies: 3, because steep concentration-response curves imply little individual variability. The steepness of the curve is evident in mice exposed by inhalation to benzonitrile (10% mortality at 890 ppm for 2 h [ct = 1,780 ppm-h] vs. 100% mortality at 700 ppm for 4 h [ct = 2,800 ppm-h]) (MacEwen and Vernot 1974), in rats exposed orally (no mortality at 0.6 g/kg vs. 100% mortality at 2.0 g/kg) (Industrial Bio-Test 1970), and in rabbits exposed dermally (no mortality at 0.9 g/kg vs. 100% mortality at 1.4 g/kg) (Industrial Bio-Test 1970).

Animal-to-human dosimetric adjustment: Insufficient data

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

Data adequacy: Sparse data set.

APPENDIX C

CATEGORY PLOT FOR BENZONITRILE

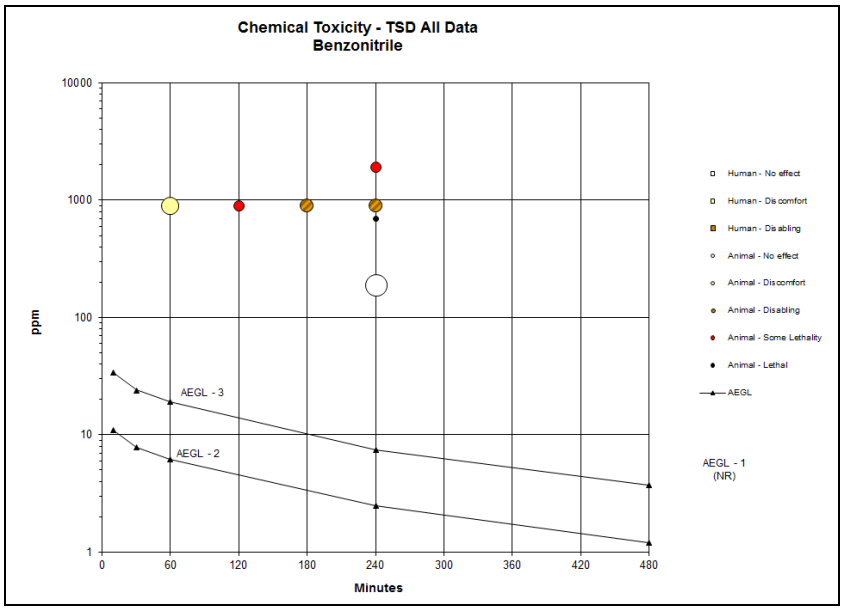

FIGURE C-1 Category plot of toxicity data and AEGL values for benzonitrile.

TABLE C-1 Data Used in Category Plot for Benzonitrile

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

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

3

Methacrylonitrile[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

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

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

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

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

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

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

A comparison of the 4-h LC_{50} values for several species suggest that mice and rabbits are more sensitive than rats and guinea pigs (Pozzani et al. 1968). No deaths were observed in mice or rabbits exposed to methacrylonitrile at 19.7 ppm for 4 h, so that concentration was selected as the point of departure for calculating AEGL-3 values. An intraspecies uncertainty factor of 3 was applied because studies of accidental and occupational exposures to hydrogen cyanide (the metabolically-liberated toxicant) indicate that there are individual differences in sensitivity to this chemical but that the differences are not expected to exceed 3-fold (NRC 2002). An interspecies uncertainty factor of 3 was applied because mice and rabbits are the most sensitive species. Thus, the total uncertainty factor is 10. The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on methacrylonitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min and 1h) and n = 1 to extrapolate longer durations (8-h) were used to estimate AEGL values that are protective of human health (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with time scaling a 4-h exposure to a 10-min value. AEGL values for methacrylonitrile are presented in Table 3-1.

1. INTRODUCTION

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

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

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

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

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

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

2.2. Nonlethal Toxicity

2.2.1. Experimental Studies

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

TABLE 3-1 AEGL Values for Methacrylonitrile

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (disabling)	1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)	Three-fold reduction of AEGL-3
AEGL-3 (lethal)	3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)	No effect level for lethality in mice and rabbits exposed to 19.7 ppm for 4 h (Pozzani et al. 1968)

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

TABLE 3-2 Physical and Chemical Properties of Methacrylonitrile

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

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

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

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

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

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

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

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

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

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

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

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

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

2.5. Carcinogenicity

Carcinogenicity studies of human exposure to methacrylonitrile were not available.

2.6. Summary

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

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

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

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

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

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

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

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

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

3.1.2. Mice

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

3.1.3. Guinea Pigs

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

3.1.4. Rabbits

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

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

3.1.5. Dogs

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

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

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

3.2. Nonlethal Toxicity

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

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

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

Source: Adapted from Pozzani et al. 1968.

3.3. Repeated-Dose Studies

3.3.1. Rats

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

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

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

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

3.3.2. Mice

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

3.3.3. Dogs

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

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

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

3.4. Developmental and Reproductive Toxicity

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

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

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

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

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

3.5. Genotoxicity

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

3.6. Carcinogenicity

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

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

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

3.7. Summary

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

4. SPECIAL CONSIDERATIONS

4.1. Absorption, Distribution, Metabolism, and Excretion

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

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

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

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

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

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

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

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

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

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

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

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

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

4.2. Mechanism of Toxicity

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

4.3. Concurrent Exposure Issues

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

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

4.4. Structure-Activity Relationships

Because the acute toxicity of nitriles depends on the ability to undergo cytochrome P450 mediated hydroxylation, on the carbon alpha to the cyano group (α-carbon), and because the hydroxylation is a radical-based reaction, acute toxicity of nitriles is related to the structural features that influence α-carbon radical stability. Generally, the nitriles that are metabolized most quickly or easily at the carbon atom alpha to the cyano group (α-carbon) are more toxic than nitriles metabolized more slowly at the α-carbon. Thus, the toxicity pattern, in decreasing order, with regard to the type of α-carbon radical formed following α-hydrogen abstraction is benzylic ≈ 3° > 2° >1°. The presence of a hydroxy or a substituted or unsubstituted amino group on the α-carbon increases toxicity, and the presence of these moieties at other carbon positions decrease acute toxicity (DeVito 1996).

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

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

4.5. Species Differences

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

4.6. Concentration-Exposure Duration Relationship

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

5. RATIONALE FOR AEGL-1 VALUES

5.1. Human Data Relevant to AEGL-1

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

5.2. Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1 Values

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

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

6. RATIONALE FOR AEGL-2 VALUES

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

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

6.3. Derivation of AEGL-2 Values

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

7. RATIONALE FOR AEGL-3 VALUES

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

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

TABLE 3-8 AEGL-2 Values for Methacrylonitrile

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

7.3. Derivation of AEGL-3 Values

A comparison of the 4-h LC_{50} values for the various species tested by Pozzani et al. (1968) suggest that mice and rabbits are sensitive species; the no-effect level for mice and rabbits of 19.7 ppm was selected as the point of departure for deriving AEGL-3 values. The no-effect level was chosen over the LC_{50} values because it is preferable to use an empirical value rather than estimating a no-effect level by adjusting an LC_{50} value. An intraspecies uncertainty factor of 3 was applied because studies of accidental and occupational exposures to hydrogen cyanide (the metabolically-liberated toxicant) indicate that there are individual differences in sensitivity to this chemical but that the differences are not expected to exceed 3-fold (NRC 2002). An interspecies uncertainty factor of 3 was applied because mice and rabbits are the most sensitive species. Thus, the total uncertainty factor is 10. The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on methacrylonitrile were insufficient for deriving an empirical value for n. Therefore, default values of n = 3 to extrapolate to shorter durations (30 min and 1h) and n = 1 to extrapolate longer durations (8-h) were used to estimate AEGL values that are protective of human health (NRC 2001). The 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value because of the uncertainty associated with time scaling a 4-h exposure to a 10-min value. AEGL-3 values for methacrylonitrile are presented in Table 3-9, and the calculations are presented in Appendix A.

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

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

TABLE 3-9 AEGL-3 Values for Methacrylonitrile

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

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

TABLE 3-10 AEGL Values for Methacrylonitrile

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	1.3 ppm (3.5 mg/m^3)	1.3 ppm (3.5 mg/m^3)	1.0 ppm (2.7 mg/m^3)	0.67 ppm (1.8 mg/m^3)	0.33 ppm (0.89 mg/m^3)
AEGL-3 (lethal)	3.9 ppm (11 mg/m^3)	3.9 ppm (11 mg/m^3)	3.1 ppm (8.5 mg/m^3)	2.0 ppm (5.5 mg/m^3)	0.99 ppm (2.7 mg/m^3)

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

8.2. Comparison with Other Standards and Guidelines

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

TABLE 3-11 Other Standards and Guidelines for Methacrylonitrile

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

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

8.3. Data Adequacy and Research Needs

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

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHYACRYLONITRILE

Derivation of AEGL-1 Values

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

Derivation of AEGL-2 Values

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

Calculations:

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

Derivation of AEGL-3 Values

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

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

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHACRYLONITRILE

Derivation Summary

AEGL-1 VALUES

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

AEGL-2 VALUES

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

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

AEGL-3 VALUES

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

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

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

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

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

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

Modifying factor: None

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

APPENDIX C

CATEGORY PLOT FOR METHACRYLONITRILE

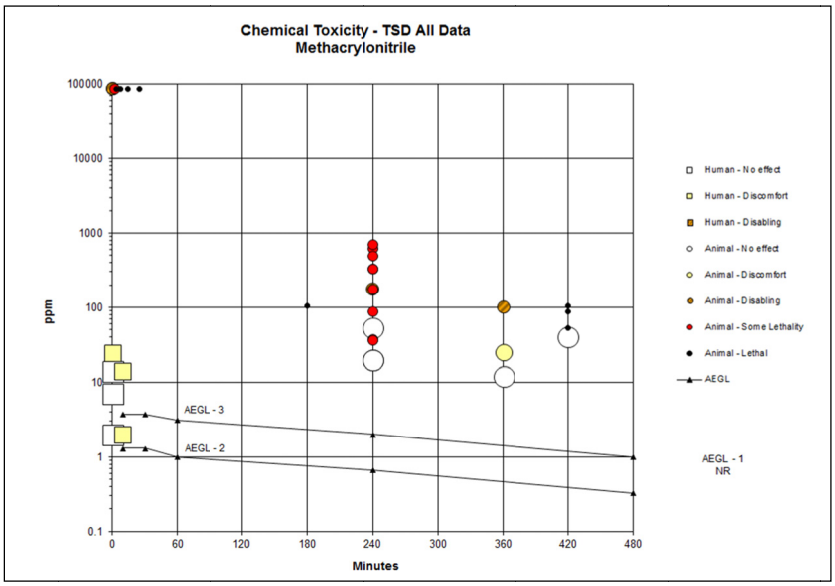

FIGURE C-1 Category plot of toxicity data and AEGL values for methacrylonitrile.

TABLE C-1 Data Used in Category Plot for Methacrylonitrile

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				1.3	10	AEGL	
AEGL-2				1.3	30	AEGL	
AEGL-2				1.0	60	AEGL	
AEGL-2				0.67	240	AEGL	
AEGL-2				0.33	480	AEGL	
AEGL-3				3.7	10	AEGL	
AEGL-3				3.7	30	AEGL	
AEGL-3				3.1	60	AEGL	
AEGL-3				2.0	240	AEGL	
AEGL-3				0.99	480	AEGL	
Pozzani et al. 1968	Human		1	2	1	0	
	Human		1	7	1	0	
	Human		1	14	1	0	
	Human		1	2	10	1	
	Human		1	14	10	1	
	Human		1	24	1	1	

(Continued)

TABLE C-1 Continued

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

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

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

4

Allyl Alcohol[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

[1]This document was prepared by the AEGL Development Team composed of Claudia Troxel (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Lisa Ingerman (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager Robert Benson (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).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Allyl alcohol is a colorless liquid that is a potent sensory irritant. Signs of intoxication following inhalation exposure to allyl alcohol vapor include lacrimation, pulmonary edema and congestion, and inflammation, hemorrhage, and degeneration of the liver and kidneys. Human data include studies of voluntary exposures to allyl alcohol for short durations and general descriptions of symptoms after accidental occupational exposures at unknown concentrations and durations. Animal data include a relatively recent detailed inhalation study in rats, studies in which only lethality was evaluated, studies of subchronic exposures, and single-exposure experiments in which only the RD_{50} (concentration that reduces the respiratory rate of test organisms by 50%) was measured.

Data from the study by Nielsen et al. (1984) were used as the basis of the AEGL-1 values for allyl alcohol. An RD_{10} of 0.27 ppm (30 min) in mice was used an estimate of the threshold for irritation. A total uncertainty factor of 3 was applied, as irritant effects are not expected to vary greatly between species or individuals. Time scaling was not applied because of the short duration of exposure.

The Kirkpatrick (2008) study in rats was selected as the basis for deriving AEGL-2 values. No-effect levels for disabling effects (reduced response to stimulus and gasping) from allyl alcohol were 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h; these values were used as the points-of-departure for the 1-,

4- and 8-h AEGL-2 values, respectively. A total uncertainty factor of 30 was applied. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether effects are due to allyl alcohol, one of its metabolites, or both. Furthermore, humans have genetic polymorphisms for aldehyde dehydrogenase. Time scaling was performed for the 10- and 30-min values using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.95 was derived from rat lethality data (see Appendix A).

AEGL-3 values for allyl alcohol are based on the calculated LC_{01} (lethal concentration, 1% lethality) values in rats of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} values were calculated using the ten Berge software program and rat mortality data from four studies (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008) (see Appendix A). As noted for AEGL-2, the ten Berge program estimated a value for n of 0.95 for time scaling. A total uncertainty factor of 30 was applied for the same reasons described for the AEGL-2 values.

A level of distinct odor awareness, which is the concentration above which more than half of the exposed population is predicted to experience at least a distinct odor intensity and about 10% will experience a strong odor intensity, could not be determined due to inadequate data. Although odor thresholds of 1.4 and 2.1 ppm have been reported for allyl alcohol, concurrent odor-threshold data for the reference chemical n-butanol (odor detection threshold 0.04 ppm) were not available.

AEGL values for allyl alcohol are presented in Table 4-1.

TABLE 4-1 AEGL Values for Allyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	Irritation threshold in mice (Nielsen et al. 1984)
AEGL-2 (disabling)	11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)	Gasping and reduced response to stimulus in rats (Kirkpatrick 2008)
AEGL-3 (lethal)	87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)	Estimated LC_{01} value in rats (McCord 1932; Smyth and Carpenter 1948;Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008)

1. INTRODUCTION

Allyl alcohol is a colorless liquid that is a potent sensory irritant. The chemical has a pungent, mustard-like odor, with a reported odor-recognition concentration of 0.78 ppm (Dunlap et al. 1958; HSDB 2013) and odor-detection threshold of 1.4-2.1 ppm (AIHA 1989). Primarily used in the production of allyl esters for use in resins and plasticizers, allyl alcohol is also used as an intermediate in the production of pharmaceuticals and other organic chemicals, as a fungicide and herbicide, in the production of glycerol and acrolein, and as a flavoring agent (Tabershaw et al. 1977; ACGIH 2001; O'Neil et al. 2006). Allyl alcohol is not currently registered for pesticide use in the United States, but approved pesticide uses may change periodically (HSDB 2013). Allyl alcohol is produced from the isomerization of propylene oxide at a high temperature using a lithium phosphate catalyst (Lyondell 2006; HSDB 2013). Acrolein is an intermediate in manufacturing processes and, therefore, may be a contaminant of allyl alcohol (Nagato 2004). Information on the production volume and sales quantities of ally alcohol was not available from the US Environmental Protection Agency's nonconfidential Chemical Data Reporting (EPA 2013a). The 2006 Inventory Update Rule estimated nonconfidential production volumes of allyl alcohol of 100-500 million pounds (EPA 2010). EPA's Toxic Release Inventory (EPA 2013b) reported a total environmental release and off-site waste transfer value of 484,955 pounds. Allyl alcohol is transported by rail, truck, ship, and aircraft (Lyondell 2006). In the atmosphere, allyl alcohol is degraded by reaction with photochemically-produced hydroxyl radicals. On the basis of a rate constant of 3.0×10^{-11} cu cm/molecule-sec at 25 ºC, the half-life for that reaction in the atmosphere is approximately 4.32 h (EPA 2013c). The physical and chemical properties of allyl alcohol are presented in Table 4-2.

Vaporized and liquid allyl alcohol is intensely irritating to intact skin, eyes, and mucous membranes. Contact of ally alcohol with the eye can produce corneal burns. Direct skin contact can produce first- and second-degree burns and can induce epidermal necrosis. At sufficiently high concentrations, inhaled allyl alcohol can induce pulmonary edema (Shell Chemical Corporation 1957). Human data included controlled studies with human volunteers; no lethality or epidemiologic data on allyl alcohol inhalation exposure were available. Studies addressing lethal and nonlethal toxicity of allyl alcohol in laboratory animals were available.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of death following inhalation exposure to allyl alcohol were found in the published literature. Toennes et al. (2002) reported a case of an individual dying within 100 min of ingesting a weed killer containing 85% (w/v)

allyl alcohol. Kononenko (1970) briefly described a case in which a man died within 90 min of ingesting allylic alcohol at approximately 150 mL; loss of consciousness was reported to occur 20 min after ingestion.

2.2. Nonlethal Toxicity

2.2.1. Acute Studies

Groups of five to seven volunteers, ranging in age from 19 to 39 years, were exposed to allyl alcohol for 5 min in an exposure room from one to three times per week over a total of 50 days (Dunlap et al. 1958). The 18,000-L exposure room had a revolving fan for mixing the vapor in the room. Vapor was generated by flash vaporization of allyl alcohol using a heat source. Five minutes of

TABLE 4-2 Chemical and Physical Properties of Allyl Alcohol

Parameter	Data	Reference
Synonyms	2-propen-1-ol; 1-propenol-3-ol; vinyl carbinol	O'Neil et al. 2006
CAS registry no.	107-18-6	ACGIH 2001
Chemical formula	C_3H_6O	O'Neil et al. 2006
Molecular weight	58.08	O'Neil et al. 2006
Physical state	Liquid	O'Neil et al. 2006
Color	Colorless	O'Neil et al. 2006
Melting point	-50°C	O'Neil et al. 2006
Boiling point	96-97°C	O'Neil et al. 2006
Freezing point	-129°C	HSDB 2013
Flash point	20.9°C	NIOSH 2011
Specific gravity (water = 1)	0.8540 at 20/4°C	NIOSH 2011; O'Neil et al. 2006
Solubility	Miscible with water, alcohol, chloroform, ether, petroleum ether	O'Neil et al. 2006
Vapor density (air = 1)	2.0	HSDB 2013
Vapor pressure	25.4 mmHg at 25°C;17 mmHg at 20°C	ACGIH 2001; HSDB 2013
Conversion factors in air	1 ppm = 2.42 mg/m^3 1 mg/m^3 = 0.413 ppm	ACGIH 2001; NIOSH 2011

vaporization and equilibration were allowed before the volunteers entered the room for the static exposure. Volunteers were exposed to allyl alcohol at 0.78, 6.25, 12.5, or 25.0 ppm; whether these concentrations were calculated or measured was not specified. Volunteers were prepared to describe their reactions by reviewing with them the different subjective sensations associated with a particular level of response, but the subject was not aware of the nature of the material. During the static exposure at 1-min intervals, they graded their ocular and nasal irritation, olfactory recognition, central-nervous-system effects, and pulmonary effects as absent, slight, moderate, severe, or extreme. A summary of the findings is presented in Table 4-3. After each exposure, the eyes of each subject were visually inspected, and physical examination of the chest was made at the end of the day's run or when the subject noted subjective symptoms. Olfactory recognition was noted as at least slight by five of six subjects at the lowest concentration of 0.78 ppm, and became at least moderate at 6.25 ppm in two of six subjects. At 12.5 ppm, nasal irritation of moderate or greater severity was experienced by four of seven volunteers, and all subjects described nasal irritation as moderate or greater at 25.0 ppm. Ocular irritation was slight in one of six and one of seven individuals at 6.25 and 12.5 ppm, respectively, and was moderate or greater at 25.0 ppm in all five exposed volunteers. The investigators described the ocular irritation at 25.0 ppm as severe, but it was not clear whether responses varied with repeated exposure. Separate from these tests with volunteers, Dunlap et al. (1958) described symptoms in workers who were exposed to "moderate" concentrations of allyl alcohol (concentrations not specified). Symptoms included lacrimation, retrobulbar pain, and blurred vision, which persisted for 24-48 h after exposure ended. No permanent damage to the cornea was reported.

Ten volunteers were exposed to allyl alcohol at 2 ppm for 1-3 min (Torkelson et al. 1959a). Groups of two or three volunteers entered a large exposure chamber once the desired concentration of allyl alcohol was achieved (methods described in Torkelson et al. 1959b). Half of the volunteers reported a distinct odor but no irritation. McCord (1932) commented that workers exposed to allyl alcohol (concentration, duration, and exposure situation not reported) had signs and symptoms of severe irritation of the mucous membranes, including edema, excessive secretions, conjunctivitis, and lacrimation, and that exposure at 5 ppm would produce some irritation. One worker was temporarily blinded by delayed corneal necrosis after exposure to the vapor, although the nature of the exposure was not described (Smyth 1956). The investigators reported that the primary toxic effect following exposure to allyl alcohol vapor is irritation manifested by pulmonary edema and disabling corneal injury.

Odor-detection threshold values for allyl alcohol reported by the American Industrial Hygiene Association (AIHA 1989) were 1.4 ppm (3.3 mg/m^3) and 2.1 ppm (5 mg/m^3). Those values are based on two studies (Katz and Talbert 1930; Dravnieks 1974) judged by AIHA to be acceptable.

TABLE 4-3 Summary of Sensory Responses to Ally Alcohol During 5-Minute Exposure

		Olfactory Recognition		Ocular Irritation		Nasal Irritation	
Concentration (ppm)	No. Subjects	Any Response[a]	≥ Moderate[b]	Any Response[a]	≥ Moderate[b]	Any Response[a]	≥ Moderate[b]
0.78	6	5	1	0	0	2	0
6.25	6	5	2	1	0	3	1
12.5	7	6	1	1	0	7	4
25.0	5	3	1	5	5[c]	5	5

Source: Adapted from Dunlap et al. 1958.
[a]Number of people showing any response.
[b]Number of people with responses greater than "slight."
[c]Response was graded as severe.

2.2.2. Epidemiologic Studies

Epidemiologic studies of human exposure to allyl alcohol were not available.

2.3. Developmental and Reproductive Toxicity

No human data on the developmental and reproductive toxicity of allyl alcohol were available.

2.4. Genotoxicity

No information on the genotoxicity of allyl alcohol in humans was available.

2.5. Carcinogenicity

No information on the potential carcinogenicity of allyl alcohol in humans was available.

2.6. Summary

There were no reported cases of human deaths following inhalation exposure to allyl alcohol, and no case reports of accidental occupational exposures. Volunteers exposed to allyl alcohol for 5 min reported nasal irritation at 12.5 ppm and severe ocular irritation at 25 ppm. Workers exposed to moderate concentrations (not specified) were reported to experience lacrimation, retrobulbar pain, and blurred vision. Odor-detection thresholds of 1.4 ppm and 2.1 ppm and an odor-recognition threshold of 0.78 ppm were reported for allyl alcohol.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

One monkey (sex not specified) exposed to allyl alcohol at 1,000 ppm died 4 h into the exposure (McCord 1932). Prior to death, the monkey vomited, had diarrhea, and appeared to be in severe pain. Necropsy revealed subcutaneous hemorrhage of the abdomen, petechial hemorrhage and inflammation of the intestine, a distended gastrointestinal tract, and hemorrhage of the spleen and kidneys. Inflammation was found in the brain, meninges, and blood vessels, and the lungs had edema with hemorrhagic exudate.

3.1.2. Rats

Groups of five male and five female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol vapor at measured concentrations of 0, 51, 220, or 403 ppm (nominal concentrations were 0, 50, 200, or 400 ppm) for 1 h; at 0, 22, 52, or 102 ppm (nominal concentrations were 0, 20, 50, or 100 ppm) for 4 h; or at 0, 10, 21, or 52 ppm (nominal concentrations were 0, 10, 20, or 50 ppm) for 8 h (Kirkpatrick 2008). All animals survived to the end of the study, except for one male rat exposed at 52 ppm for 8 h that died the day after exposure. The dead rat had severe ulceration and degeneration of the olfactory epithelium, mild hemorrhage and edema in the lungs, moderate to severe erosion of the epithelium in the larynx and trachea, and severe epithelial ulceration in the larynx. Further details are provided in Section 3.2.1.

Groups of six male Long-Evans rats were exposed to allyl alcohol at 40-2,300 ppm (individual concentrations not specified) for 1, 4, or 8 h to determine LC_{50} values (lethal concentration, 50% lethality) for allyl alcohol, (Dunlap et al. 1958). No mention was made of a concurrent control group. Exposures were conducted in a 19.5-L cylindrical glass chamber, and airflow was set at 8.6-12.9 L/min. Vapor concentrations of allyl alcohol were analyzed by drawing a sample of air through distilled water, adding bromine in acetic acid in the presence of mercapturic acetate as a catalyst, reducing the excess bromine with iodide, and then titrating the iodine with thiosulfate. The analyses showed that concentrations of allyl alcohol were 15-25% less than nominal concentrations. Animals were observed for at least 10 days after exposure. The uncorrected 1-, 4-, and 8-h LC_{50} values were 1,060, 165, and 76 ppm, respectively. Dunlap et al. (1958) conducted studies of different exposure routes with several species (inhalation [rats], intragastric administration [rabbit, mouse, and rat], intraperitoneal injection [mouse and rat], and percutaneous [rabbits]), but did not describe signs of toxicity and pathologic effects separately for the different exposure routes. Therefore, it was unclear whether some signs of toxicity were specifically related to inhalation exposure or were independent of the route of exposure. General

signs of toxicity in rats were lacrimation and tremors, with coma preceding death. Gross necropsy findings in both rats and rabbits (findings not presented separately) included pulmonary edema and congestion, visceral congestion, and discolored liver. Microscopic examination of rats and rabbits showed hepatic damage, including congestion of the periportal sinusoids, periportal necrosis, central pallor, and central necrosis. The kidneys of rats were swollen and discolored. A published abstract by Dunlap and Hine (1955) indicates that toxic signs and pathologic changes are not dependent on the route of exposure to allyl alcohol. The abstract states that allyl alcohol-induced lesions, such as necrosis, hemorrhage, and discoloration of the liver, discoloration of the kidneys, and congestion and hemorrhage of the intestines, did not vary with the route of administration. However, ocular and nasal irritation and profuse lacrimation were specifically noted for test of single 1-h inhalation exposures in rats (concentrations not specified), from which the 1-h LC_{50} value of 1,060 ppm was derived (also reported in Dunlap et al. 1958).

Six Sherman rats (sex not specified) were exposed to allyl alcohol vapor at 1,000 ppm for 1 h, and were observed for 14 days (Smyth and Carpenter 1948). No details about the exposure conditions were provided, exposure concentration was not confirmed by analytic methods, and no controls were used. Four of rats died. In another study by this group (Carpenter et al. 1949), a 4-h exposure to allyl alcohol at 250 ppm killed two of six, three of six, or four of six Sherman rats; no additional information was provided.

McCord (1932) exposed rats (strain and sex not specified) to several concentrations of allyl alcohol vapor for various durations. Six rats exposed at 1,000 ppm died 3 h into an intended 7-h exposure. Necropsy results were not described, but were reported to be similar to the findings in the monkey (see Section 3.1.1) and rabbits (see Section 3.1.4). (The primary findings in the monkey and rabbits were hemorrhage in the lungs, intestinal tract, bladder, and kidneys.) Four rats exposed at 200 ppm for 7 h/day died on the first or second day of exposure, and necropsy revealed similar findings. Four of five rats exposed at 50 ppm for 7 h/day died after approximately 30 days of exposure (it was inferred from the study description that exposures were conducted 7 days/week until termination). Necropsy information was not provided. No changes were observed in any of the control animals (number and treatment of controls not described).

Union Carbide and Carbon Corporation (1951) tabulated the mortality results of inhalation toxicity studies of allyl alcohol in rats. No information about controls, method of exposure, strain or sex of rats, analytic verification of concentrations, or period of observation was provided. The mortality results of the studies are presented in Table 4-4.

In a series of three experiments, groups of 10 Long-Evans male rats were exposed to allyl alcohol at 0, 1, 2, 5, 20, 40, 60, 100, or 150 ppm for 7 h/day, 5 days/week for a total of 60 exposures (Dunlap et al. 1958). Analyses of the vapor concentrations at 40 ppm and greater were within 10% of nominal concentrations (information on the measured concentrations at the lower concentrations

was not provided). Animals were observed daily and weighed weekly. After 90 days, the survivors were killed and necropsies were performed. Liver, kidneys, and lungs from all animals were weighed and examined microscopically. The thyroid, heart, thymus, pancreas, spleen, adrenal glands, testes, bladder, and brain were removed from every other animal and examined microscopically. Exposure to allyl alcohol at 1, 2, 5, and 20 ppm failed to produce any clinical signs of toxicity or abnormal gross or microscopic effects, although the animals in the 20-ppm group experienced a significant reduction in body weight gain. Rats exposed at 150 ppm exhibited gasping, severe depression, nasal discharge, and ocular irritation. All of the rats in the 150-ppm group died; four died during the first exposure, two after the first exposure, two during the second exposure, and two by the tenth exposure. The two rats surviving until the tenth exposure were lethargic, had red-rimmed eyes, and lost a third of their original body weight. Necropsy findings included hemorrhagic livers, pale and spotted lungs, and bloated gastrointestinal tracts. Slight congestion of the liver and lungs were found during microscopic evaluation. Rats exposed to allyl alcohol at 100, 60, or 40 ppm had similar but less intense signs, lesions, and microscopic findings. Six of the 10 rats exposed at 100 ppm died by the forty-sixth exposure, and the remaining rats were accidentally killed on exposure day 56. Gasping and muzzle rubbing occurred during the first few exposures at 60 ppm but disappeared thereafter, and persistent ocular discharge was observed throughout the experiment. The 60-ppm group also had statistically increased hepatic and renal weights, and one death occurred (day not specified). All signs of irritation in animals exposed at 40 ppm resolved after the first few exposures, but pulmonary weight was statistically increased at necropsy.

A toxicity data sheet by the Shell Chemical Corporation (1957) appears to include some of the same data that was published by Dunlap et al. (1958). Rats were exposed to allyl alcohol for 8 h at 1, 5, 10, 20, 40, 60, 100, or 150 ppm for a total of 60 exposures over 90 days (Shell Chemical Corporation 1957). Information on the strain, sex, and number of rats was not specified. No adverse effects were found in animals exposed at 20 ppm or less. Decreased growth and mild to moderate pulmonary congestion were found in the 40-ppm group. Animals in the 60-ppm group developed pulmonary congestion and increased renal and pulmonary weights, and one of 10 rats died. All animals exposed at 100 ppm died after 32 exposures and rats exposed at 150 ppm died after two exposures.

TABLE 4-4 Summary of Mortality Data in Rats Exposed to Allyl Alcohol

Concentration (ppm)	Time (h)	Deaths
200	1	0/10
1,000	0.5	1/6
1,000	1	4/6
1,000	2	6/6

Source: Union Carbide and Carbon Corporation 1951.

3.1.3. Mice

Union Carbide and Carbon Corporation (1951) tabulated the mortality results of inhalation toxicity studies of allyl alcohol in mice. No information about controls, method of exposure, strain or sex of mice, analytic verification of concentration, or the period of observation was provided. The mortality results of the studies are presented in Table 4-5.

Groups of 10 mice (strain and sex not specified) exposed to allyl alcohol between 2,450 and 26,000 ppm died within 165 and 24 min, respectively (Shell Chemical Corporation 1957). All animals developed spastic paralysis of the extremities, particularly of the hindlimbs, before dying convulsively. Necropsy results included irritation and inflammation of the respiratory tract and irritation and congestion of the liver, kidneys, and spleen. All mice exposed at 22,000 ppm for 10 min died (no other details provided). No deaths resulted when mice were exposed at 12,200 ppm for 10 min, but all died when exposed for another 10 min period (period of observation and time between exposures not specified). When mice were exposed daily to allyl alcohol at 2,450 ppm for 10 min, 10% of the animals died within three exposures and 30% were dead after nine exposures. Necropsy revealed irritation and inflammation of the respiratory tract and congestion of the gastrointestinal tract. Mice repeatedly exposed to allyl alcohol at 2,450 ppm developed severe ocular and nasal irritation.

3.1.4. Rabbits

When two rabbits (strain and sex not specified) were exposed to allyl alcohol at 1,000 ppm, one died 3.5 h into the exposure and the other died 4.25 h into the exposure (McCord 1932). The rabbits had rales, and fluid dripped from their noses and mouths. Pulmonary hemorrhage, hemorrhage and inflammation of the intestinal tract, bladder, and kidneys, and gaseous distention of the gastrointestinal tract were found in both rabbits at necropsy. One rabbit also had hemorrhaging of the eyes, opaque sclerae, and inflamed genitalia. In a second experiment, three rabbits were exposed to allyl alcohol at 200 ppm for 7 h/day.

TABLE 4-5 Summary of Mortality Data in Mice Exposed to Allyl Alcohol

Concentration (ppm)	Time (h)	Deaths
200	1	0/10
500	0.5	0/10
500	1	4/10
1,000	1	6/10
1,000	2	8/10
1,000	4	10/10

Source: Union Carbide and Carbon Corporation 1951.

Labored and noisy breathing and discharge from the nose and mouth were observed within 1 h of exposure. One rabbit convulsed and died after three days of exposure, a second rabbit died after six days of exposure, and the third died after 18 days of exposure. The noisy and labored breathing and oral and nasal discharge continued with the exposures. Necropsy of the animals revealed findings similar to those described above. In a third experiment, two rabbits were exposed to allyl alcohol at 50 ppm for 7 h/day. One rabbit died after 14 exposures, and the second was killed after 28 exposures. Necropsy of the rabbits revealed findings similar to those described above. No changes were observed in control animals (number and treatment of controls not specified).

Union Carbide and Carbon Corporation (1951) reported the mortality results of inhalation toxicity studies of allyl alcohol in rabbits. No information about controls, method of exposure, strain or sex of rabbits, analytic verification of concentrations, or the period of observation was given. None of the 10 rabbit exposed at 200 ppm for 1 h died, and no deaths occurred in four rabbits exposed at 500 ppm for 2 h. All four rabbits exposed to allyl alcohol at 500 pp m for 4 h died. The report also claimed that allyl alcohol at 3,400 ppm for 2-5 min will cause necrosis of the cornea of rabbits, but no data were included.

3.1.5. Guinea Pigs

Four guinea pigs were individually exposed to allyl alcohol in a bell jar, in which allyl alcohol was present in a petri dish below the jar (Adams 1958). The exact exposure concentrations were unknown. One guinea pig started to exhibit signs of irritation within 2 min of exposure, with lacrimation and exophthalmos developing soon thereafter. When the animal was removed after 30 min, marked lacrimation and exudation of serous fluid from the nose and mouth was observed, and the exophthalmos was pronounced. The guinea pig died 50 min post-exposure from respiratory failure. A second guinea pig was exposed in the bell jar until it died; death occurred after 55 min. Clinical signs included exophthalmos, lacrimation, and oral and nasal serous fluid exudate. A third guinea pig was exposed to allyl alcohol for 20 min. It also developed exophthalmos with lacrimation and nasal discharge, and died of respiratory failure 5 h post-exposure. A fourth guinea pig was exposed for 15 min and developed the same clinical signs as the others, but recovered and was still alive 6 days post-exposure.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of three male and three female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol at concentrations of 423 ppm or 638 ppm for 1 h, 114 ppm for 4 h, or 52 ppm for 8 h (Kirkpatrick 2008). Animals were examined for clinical signs 30 min into the exposure (all animals), 1 h into the

exposure (animals exposed for 4 and 8 h), 4 h into the exposure (animals exposed for 8 h), and within 1 h after exposure (all animals). Animals were observed for 6 days post-exposure and then killed without further examination. Animals were observed for mortality twice per day, body weight was recorded prior to exposure and on post-exposure day 5, and clinical examinations were performed daily. All animals survived to the end of the study, and no adverse effects on body weight were found. Clinical signs included gasping during and after exposure, labored respiration during exposure, and red and/or clear material around the mouth or nose and reddened limns after the exposure. The investigator noted that reddened limbs were considered an alcohol flush reaction caused by the presence of the aldehyde metabolite, acrolein. Thus, "alcohol flushing" observed in this study does not appear to be the result of a direct-acting irritant effect of allyl alcohol. One male rat exposed at 114 ppm for 1 h exhibited slight gait impairment at 1 h post-exposure; gait impairment was not observed in any other animals. A summary of the incidence of selected clinical observations from this study is presented in Table 4-6.

TABLE 4-6 Summary of Selected Clinical Observations in Rats Exposed to Allyl Alcohol

	1 h		4 h	8 h
Observation	423 ppm	638 ppm	114 ppm	52 ppm
Number of animals	6	6	6	6
Gasping				
Total affected	2	2	4	3
30-min into exposure	0	1	1	3
1 h into exposure	2	0	1	0
1 h post-exposure	0	1	3	0
Recovery period	0	0	0	0
Labored respiration				
Total affected	0	0	0	2
8-h into exposure	–	–	–	2
Recovery period	0	0	0	0
Reddend forelimbs				
Total affected	0	4	6	3
1 h post-exposure	0	4	6	3
Recovery period	0	0	0	0
Reddend hindlimbs				
Total affected	0	3	6	4
1 h post-exposure	0	3	6	4
Recovery period	0	0	0	0
Material around mouth/nose				
Total affected	3	5	4	2
1 h post-exposure	3	5	4	1
Recovery period	0	0	0	2

Source: Kirkpatrick 2008.

Groups of five male and five female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol vapor at measured concentrations of 0, 51, 220, or 403 ppm (nominal concentrations were 0, 50, 200, or 400 ppm) for 1 h; 0, 22, 52, or 102 ppm (nominal concentrations were 0, 20, 50, or 100 ppm) for 4 h; or 0, 10, 21, or 52 ppm (nominal concentrations were 0, 10, 20, or 50 ppm) for 8 h (Kirkpatrick 2008). Chamber concentrations were measured by gas chromatography at approximately 30-min intervals for the 1-h exposure, and at 60-min intervals for the 4- and 8-h exposures. Observations for clinical signs were performed 30 min into the exposure (all exposures), 1 h into the exposure (4- and 8-h exposures), and 4 h into the exposure (8-h exposure). Near the end of the exposure, response to a loud noise stimulus was tested by striking the cage. Clinical examinations, involving handling and open field arena observations, were performed immediately after the exposure, within an hour post-exposure, twice on day 1, and once daily until the end of the study. Body weight was recorded on days 0, 1, 6, and 13. When the animals were killed on day 14, blood was collected for analyses of hematology and clinical chemistry parameters; a complete gross necropsy was performed; liver, kidney and lung weights were recorded; and selected tissues (kidneys, larynx, liver, lungs, nasal tissues, trachea, and gross lesions) were processed and examined for histopathologic changes. All animals survived to the end of the study, except for one male rat exposed at 52 ppm for 8 h. The rat died the day after exposure, and death was attributed to ulceration of the respiratory and olfactory epithelium in the nasal passages, resulting in diminished breathing capacity and hypoxia. In the remaining rats, no exposure-related changes were observed in body weight, hematology or clinical chemistry parameters, or during gross necropsy or histopathologic examination of the kidneys, liver, or lungs.

Exposure to allyl alcohol at 51, 220, and 403 ppm for 1 h produced gasping in one female rat exposed at 403 ppm after 30 min of exposure (Kirkpatrick 2008). The incidences of alcohol flushing and material around the mouth exhibited a concentration-related increase at 220 and 403 ppm. A clear concentration-related response was not established in the novel stimulus/arousal response findings. Histopathologic examination of the nasal cavity revealed reversible changes. The incidence of chronic inflammation was increased at 202 and 403 ppm. Although the incidences of degeneration of the olfactory epithelium, metaplasia of olfactory epithelium, and hemorrhage did not follow a definitive concentration-related response, they were attributed to allyl alcohol because these effects were not found in control animals.

For the 4-h exposures, minimal clinical signs were observed in rats exposed to allyl alcohol at 22 ppm; only one animal exhibited material around the mouth (Kirkpatrick 2008). Exposure at 52 and 102 ppm produced a concentration-related increase in the number of animals exhibiting gasping, alcohol flushing, material around the mouth, and a reduced response to cage stimulus. An increased incidence of yellow material around the urogenital area was observed 1 h post-exposure in females of the 102-ppm group. Histopathologic examinations of the nasal cavity revealed reversible changes, including degeneration of

the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia.

For the 8-h exposures, clinical effects were minimal in rats exposed at 10 and 21 ppm; a few animals had reddened limbs and material around the mouth, one rat at each concentration had yellow material around the urogenital area, and one rat in the 21-ppm group had rales/increased respiration (Kirkpatrick 2008). Exposure to allyl alcohol at 52 ppm for 8 h produced gasping, increased respiration, and red material around the mouth, yellow material around the urogenital area (three of 10 rats), and killed one male rat. The rat that died exhibited gasping, rales, and red material around the nose 1 h post-exposure, and rales and red material around the mouth and nose approximately 7 h before death. Reddened forelimbs were present in only a few animals. Clinical signs were generally noted 1 h post-exposure, and were resolved by the end of the recovery period. A concentration-related increase in the number of animals with a reduced response to cage stimulus was found in the 21- and 52-ppm groups. Histopathologic examination of the nasal cavity of rats exposed at 10 or 21 ppm revealed reversible changes, including degeneration of the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia. Exposure at 52 ppm produced similar but generally more severe lesions. Two rats (including the one that died) developed severe irreversible changes. The rat that died had severe ulceration and degeneration of olfactory epithelium, mild hemorrhage and edema in the lungs, moderate to severe erosion of the epithelium in the larynx and trachea, and severe epithelial ulceration in the larynx. Another male rat had severe, irreversible metaplasia and severe ulceration of the olfactory epithelium, along with the degeneration and subacute inflammation seen in almost all rats in the 52-ppm group.

Summaries of clinical signs and histopathologic findings from this study are presented in Tables 4-7 and 4-8, respectively.

3.2.2. Mice

Groups of four male Ssc:CF-1 mice were exposed to allyl alcohol at 0.42, 2.00, 4.55, or 18.10 ppm for 30 min to determine the RD_{50} for sensory irritation (Nielsen et al. 1984). RD_{50} values represent the concentration of an airborne sensory irritant that produces a 50% reduction in the respiratory rate, the decreased respiratory rate being caused by stimulation of the trigeminal nerve in the nasal mucosa. The mice were placed in a body plethysmograph attached to an exposure chamber such that the animal's head protruded into the chamber. Animals in the chambers were observed for 5-15 min to establish a baseline respiratory rate before beginning exposure to allyl alcohol. An RD_{50} of 3.9 ppm (95% C.I.: 2.4-6.5 ppm) was determined on the basis of the maximum decrease in respiratory rate within the first 10 min of exposure, and another value of 4.8 ppm (95% C.I.: 2.7-10.2 ppm) was determined on the basis of the mean value

TABLE 4-7 Summary of Clinical Signs in Rats Exposed to Ally Alcohol

	Concentration (ppm)											
	1 h				4 h				8 h			
End Point	0	51	220	403	0	22	52	102	0	10	21	52
No. animals	10	10	10	10	10	10	10	10	10	10	10	10
Clinical signs (total)												
Gasping	0	0	0	1	0	0	1	6	0	0	0	7
Rales/increased respiration	0	0	0	0	0	0	0	0	0	0	1	3
Reddened forelimbs	0	1	8	9	0	0	2	7	0	1	2	3
Reddened hindlimbs	0	1	7	9	0	0	2	6	0	0	1	0
Reddened ears	0	0	0	4	0	0	0	0	0	0	0	0
Red/clear material around mouth	0	0	3	5	0	1	3	8	2	3	2	8
Clinical signs (1 h post-exposure)												
Gasping	0	0	0	0	0	0	1	5	0	0	0	6
Rales/increased respiration	0	0	0	0	0	0	0	0	0	0	1	2
Reddened forelimbs	0	1	8	9	0	0	2	7	0	1	2	3
Reddened hindlimbs	0	1	7	9	0	0	2	6	0	0	1	0
Reddened ears	0	0	0	4	0	0	0	0	0	0	0	0
Red/clear material around mouth	0	0	3	5	0	1	3	8	0	1	3	8
Response to cage stimulus												
No reaction	2	0	6	3	0	0	2	4	0	0	3	4
Slight reaction	8	10	4	7	10	10	8	4	10	10	7	6
Energetic response (jump/vocalization)	0	0	0	0	0	0	0	2	0	0	0	0

Source: Kirkpatrick 2008.

TABLE 4-8 Summary of Selected Nasal Histopathologic Findings in Rats Exposed to Ally Alcohol[a]

	Concentration (ppm)											
	1 h				4 h				8 h			
End Point	0	51	220	403	0	22	52	102	0	10	21	52[b]
No. animals	10	10	10	10	10	10	10	10	10	10	10	10
Degeneration, olfactory epithelium												
Total	0	2	1	3	0	0	2	10	0	4	6	9
Minimal	–	0	0	2	–	–	2	3	–	1	1	1
Mild	–	2	1	0	–	–	0	5	–	3	4	1
Moderate	–	0	0	1	–	–	0	2	–	0	1	4
Severe	–	0	0	0	–	–	0	0	–	0	0	1
Severe, irreversible	–	0	0	0	–	–	0	0	–	0	0	2
Inflammation, chronic and subacute												
Total	3	2	4	9	0	7	7	8	3	7	9	10
Minimal	1	2	1	2	–	2	1	0	2	1	0	1
Mild	2	0	2	6	–	4	3	6	1	6	8	6
Moderate	0	0	1	1	–	1	3	2	0	0	1	3
Hyperplasia, goblet cell												
Total	1	2	2	1	0	1	5	4	0	4	4	5
Minimal	0	1	0	0	–	0	2	1	–	1	3	0
Mild	1	1	2	1	–	1	3	1	–	3	1	3
Moderate	0	0	0	0	–	0	0	2	–	0	0	2
Degeneration, respiratory epithelium												
Total	0	0	0	0	0	0	1	2	0	0	0	2

Minimal	–	–	–	–	–	–	1	0	–	–	–	0
Mild	–	–	–	–	–	–	0	2	–	–	–	0
Moderate	–	–	–	–	–	–	0	0	–	–	–	2
Metaplasia, olfactory epithelium												
Total	0	1	0	0	0	0	0	0	0	0	0	1
Mild	–	1	–	–	–	–	–	–	–	–	–	0
Severe, irreversible	–	0	–	–	–	–	–	–	–	–	–	1

[a]Summary of number of animals with lesion taking into account all six nasal levels; grade for each lesion is the highest grade for any of the six nasal levels.
[b]Results for the rat that died are included. Other effects found in this group that are not included in the table were severe, irreversible ulceration (two males) and severe erosion (one male) of the olfactory epithelium.
Source: Kirkpatrick 2008.

during the last 10 min of exposure. The onset of decreased respiratory rate occurred rapidly, plateaued within 10 min of exposure, and quickly subsided following termination of the exposure. Threshold values for irritation can be estimated using RD_{50} values. ASTM (2012) estimated a threshold value for allyl alcohol of 0.301 ppm based on 3% of the RD_{50} value. For this report the threshold for irritation was estimated by deriving an RD_{10} value of 0.27 ppm, using digitized data from Figure 2 of the Nielsen et al. (1984) report. Although studies of intravenous administration of allyl alcohol have demonstrated that conversion of allyl alcohol to acrolein is required to produce systemic toxicity (Serafini-Cessi 1972; Patel et al. 1983), the Nielsen et al. (1984) study did not find evidence of such a conversion in that there was no delay in the appearance, development, or resolution of the irritant response. However, no empirical data on the rates or extent of metabolism of allyl alcohol by pulmonary-tract tissues were presented. To determine if allyl alcohol produced pulmonary irritation at concentrations producing sensory irritation, concurrent exposures of tracheally cannulated mice to allyl alcohol were performed. Such exposure did not cause any pulmonary irritation at the RD_{50} concentration producing sensory irritation.

James et al. (1987) reported an RD_{50} for allyl alcohol of 2.5 ppm (2.0-3.2 ppm) in male ICR mice. Because the investigators used allyl alcohol to verify their experimental system with that of already published methods, no specific information was provided about how the RD_{50} was generated. Thus, it was inferred that the method was the same as that described for the test compound, methylisocyanate vapor. Exposures were performed in glass exposure chambers, and vapor concentrations were measured by a gas analyzer. Animals were observed in the chambers for 10 min to establish a baseline respiratory rate, and were then exposed to allyl alcohol for 30 min.

Groups of 10 male Swiss OF_1 mice were exposed to allyl alcohol at 2.4 or 6.4 ppm under three regimens: for 6 h/day for 4 days, for 6 h/day for 9 days (5 consecutive days the first week, 4 consecutive days the second week), or for 6 h/day, 5 days/week for 2 weeks (Zissu 1995). The target (nominal) concentrations were based on an RD_{50} value of 1.6 ppm, and 3 times the RD_{50} value of 4.8 ppm. Groups of five mice were used as controls. Histopathologic examination revealed lesions of the upper respiratory tract epithelium (hyperplasia, inflammatory infiltrates, and desquamation of epithelial cells) and olfactory epithelium (a slight loss of isolated sensory cells) in mice from the 2.4- and 6.4-ppm groups. The lesions were most severe in the group exposed for 4 days, and became less severe in the animals exposed for longer durations. No pathologic changes were found in the trachea or lungs of exposed animals. The target RD_{50} of 1.6 ppm was chosen from a published review (Bos et al. 1992) that summarized sensory irritation data for a large number of chemicals. The original reference (Muller and Greff 1984) investigated the correlation between selected physio-chemical parameters and sensory irritation for four chemical groups.

3.2.3. Dogs, Guinea Pigs, and Rabbits

Torkelson et al. (1959a) evaluated the toxicity allyl alcohol in rats, guinea pigs, rabbits, and dogs, but did not distinguish effects by species. Therefore, the results of this study are presented collectively in this section. Groups of 12 male and 12 female rats, nine male and nine female guinea pigs, and three male and three female rabbits were exposed repeatedly to ally alcohol vapor at 7 ppm (6.6-7.1 ppm) for 7 h/day for a total of 28 exposures and at 2 ppm (0.6-3.2 ppm) for 7 h/day for a total of 127-134 exposures (Torkelson et al. 1959a; methods reported in Torkelson et al. 1959b). In studies of dogs, one male and one female beagle were exposed to allyl alcohol at 2 ppm for 6 months. All exposures were conducted for 7 h/day, 5 days/week. Two control groups were used, a group exposed to air under similar test conditions and a group that was unexposed. None of the animals exposed to allyl alcohol at 7 ppm exhibited any clinical signs of toxicity or changes in body or organ weight, but microscopic examination found mild and reversible hepatic and renal degeneration in almost all animals. Livers had dilation of the sinusoids, cloudy swelling, and focal necrosis, and kidneys showed epithelial necrosis in the convoluted tubules, proliferation of the interstitial tissue, and changes similar to those seen in glomerulonephritis. Animals exposed at 2 ppm exhibited no measurable adverse effects as judged by clinical signs, mortality, body or organ weight, or gross and microscopic examination of tissues (noses not examined).

The potential of allyl alcohol to induce ocular damage was assessed in albino rabbits (Carpenter and Smyth 1946). Application of 0.02 mL of allyl alcohol into the eye resulted in an injury score of 5 on a 10-point scale, which was considered severe injury by the investigators. In another study, the eyes of New Zealand White rabbits were treated with 100 µL of allyl alcohol (Jacobs and Martens 1989). Mean scores of 2.8, 1.23, and 2.09 for erythema, chemosis, and corneal opacity (maximum possible scores of 3, 4, and 4, respectively) were recorded after 24, 48, and 72 h (scores for each time period were pooled). The mean percentage of corneal swelling was 76%.

3.3. Developmental and Reproductive Effects

No studies of reproductive and developmental effects in animals exposed to allyl alcohol by inhalation were found.

However, several oral exposure studies have been conducted. No evidence of reproductive toxicity (measured by changes in reproductive organ weights, sperm parameters, or number of implants) or dominant lethality was observed in male Sprague Dawley rats administered allyl alcohol at 25 mg/kg for 5-7 days/week for 33 weeks and mated with unexposed females during exposure weeks 1-11 (Jenkinson and Anderson 1990). Additionally, no significant alterations in the numbers of runts, gross abnormalities, or abnormal fetuses were observed. UNEP (2005) summarized two developmental and reproductive tox-

icity studies in rats exposed to allyl alcohol by gavage; neither study found significant alterations in malformations or variations in the offspring. A decrease in pup viability index was observed in the offspring of rats administered allyl alcohol at 40 mg/kg/day before mating and through lactation day 3 (males were also exposed before mating). The second study found no effect on pup viability, but found an increased frequency of total litter losses from exposure at 35 and 50 mg/kg/day on gestation days 9-19. In both studies, maternal toxicity (including mortality) was also observed at these concentrations. The first study also found an increase in estrous-cycle length and in the number of females with irregular estrous cycles in the group exposed at 40 mg/kg/day.

3.4. Genotoxicity

Allyl alcohol was mutagenic in cultured V79 cells using 6-thioguanine resistance as the measure of mutagenicity (Smith et al. 1990). At doses of 1 and 2 μM, the number of mutants per 106 survivors were 14 ± 8 and 37 ± 12, respectively, values similar to those produced by acrolein (Smith et al. 1990). A positive test was obtained in a modified Ames assay (tester strain TA100) without metabolic activation (750 revertants/μmole), but the mutagenic activity was greatly reduced with metabolic activation (approximately150 revertants/μmole) (Lutz et al. 1982). It has been suggested that bacterial alcohol dehydrogenase converts allyl alcohol to acrolein, which may be responsible for the mutagenic activity, and that the addition of the S9 mix inactivates acrolein by binding of the metabolite by the amino and sulfhydryl groups present in the mix (Lutz et al. 1982). Allyl alcohol tested positive for mutagenesis at concentrations of 50-300 μg/plate in the *Salmonella* tester strain TA1535 in the presence of hamster S9, but not in the presence of rat S9, and was cytotoxic at a concentration of 500 μg/plate (Lijinsky and Andrews 1980). Allyl alcohol was not mutagenic in strains TA1537, TA1538, TA98, or TA100 in the presence or absence of rat or hamster S9 (Lijinsky and Andrews 1980). Bignami et al. (1977) reported that allyl alcohol failed to increase the numbers of revertants in *Salmonella typhimurium* strains TA1535, TA100, TA1538, and TA98 (details not provided), and allyl alcohol did not induce point mutations in *Aspergillus nidulans*. Similarly, NTP (2006) found that allyl alcohol was not mutagenic in *S. typhmurium* strains TA97, TA98, TA100, or TA1535 with or without S9 metabolic activation. Intraperitoneal injections of allyl alcohol at 3-50 mg/kg/day did not increase the induction of micronucleated erythrocytes in rats (NTP 2006).

3.5. Carcinogenicity

Not enough data are available to provide a quantitative assessment of the carcinogenic potential of allyl alcohol. The carcinogenic potential of allyl alcohol has not been classified by EPA (2012a) or IARC. No evidence of carcinogenicity was found in a study in which male and female F344 rats were adminis-

tered allyl alcohol at 300 mg/L in drinking water for 106 weeks, or when 20 male Syrian golden hamsters were administered allyl alcohol at 2 mg in corn oil by gavage once a week for 60 weeks (Lijinsky and Reuber 1987). The median time-to-death and incidence of tumors was comparable in treated animals and controls. Further details, such as body- and organ-weight changes, were not provided.

Although no data are available to assess the potential for allyl alcohol to cause cancer, some of its metabolites are recognized carcinogens. EPA (2012b) has classified the allyl alcohol metabolite glycidaldehyde as a probable human carcinogen (B2) on the basis of an increased incidence of malignant tumors in rats and mice following subcutaneous injection of glycidaldehyde and of skin carcinomas following dermal application to mice. For acrolein, EPA (2003, p. 57) has determined that the "existing data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure."

3.6. Summary

A summary of acute animal lethality data is presented in Table 4-9, and summaries of acute and repeat-exposure nonlethality data in animals are presented in 4-10 and 4-11, respectively. Similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951).

Rats survived exposure to allyl alcohol at concentrations of 423 or 638 ppm for 1 h, 114 ppm for 4 h, or 52 ppm for 8 h (Kirkpatrick 2008). Clinical signs in all exposure groups included gasping during and after exposure, and material around the mouth and nose and alcohol flushing after exposure. Two rats exposed at 52 ppm for 8 h exhibited labored respiration during exposure. In another study, rats were exposed to allyl alcohol vapor at concentrations of 51, 220, or 403 ppm for 1 h; 22, 52, or 102 ppm for 4 h; or 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). All animals survived to study termination except for one male rat exposed at 52 ppm for 8 h. Reversible histopathologic changes were observed in the nasal cavity of exposed rats, and clinical signs included material around the mouth, alcohol flushing, and gasping. Exposure at higher concentrations at each duration generally resulted in increased incidences of clinical signs and histopathologic changes in the nasal cavity. Other data on nonlethal exposures to allyl alcohol included two RD_{50} studies in mice, in which RD_{50} values of 3.9 ppm and 2.5 ppm were reported (Nielsen et al. 1984; James et al. 1987). A few studies investigating the effects of repeated inhalation exposure in animals were available. One study found histopathologic lesions in the upper-respiratory-tract epithelium and olfactory epithelium of mice after exposure at 2.4 ppm for 6 h/day for 4 days, and the lesions decreased in severity in groups

TABLE 4-9 Summary of Acute Lethality Data in Laboratory Animals Exposed to Allyl Alcohol

Species	Concentration (ppm)	Exposure Duration	Deaths	Reference
Monkey	1,000	4 h	1/1	McCord 1932
Mouse	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Mouse	500	0.5 h	0/10	Union Carbide and Carbon Corporation 1951
	500	1 h	4/10	
Mouse	1,000	1 h	6/10	Union Carbide and Carbon Corporation 1951
	1,000	2 h	8/10	
	1,000	4 h	10/10	
Mouse	22,000	10 min	10/10	Shell Chemical Corporation 1957
	12,200	2 × 10 min	10/10 (after 2nd exposure)	
Rat	1,060	1 h	LC_{50}	Dunlap and Hine 1955; Dunlap et al. 1958
	165	4 h	LC_{50}	
	76	8 h	LC_{50}	
Rat	638	1 h	0/6	Kirkpatrick 2008
	423	1 h	0/6	
	114	4 h	0/6	
	52	8 h	0/6	
Rat	51	1 h	0/10	Kirkpatrick 2008
	220	1 h	0/10	
	403	1 h	0/10	
Rat	22	4 h	0/10	Kirkpatrick 2008
	52	4 h	0/10	
	102	4 h	0/10	

Rat	10	8 h	0/10	Kirkpatrick 2008
	21	8 h	0/10	
	52	8 h	1/10	
Rat	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Rat	1,000	0.5 h	1/6	Union Carbide and Carbon Corporation 1951
	1,000	1 h	4/6	
	1,000	2 h	6/6	
Rat	1,000	1 h	4/6	Smyth and Carpenter 1948
Rat	1,000	3 h	6/6 (during exposure)	McCord 1932
	200	2 × 7 h	4/4 (by end of 2nd exposure)	
	50	7 h/d for 30 d	4/5	
Rat	60	7 h/d, 5d/wk for 60 exposures	1/10 (by 60th exposure)	Dunlap et al. 1958
	100	7 h/d, 5d/wk for 60 exposures	6/10 (by 56th exposure)	
	150	7 h/d, 5d/wk for 60 exposures	10/10 (by 10th exposure)	
Rabbit	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Rabbit	500	2 h	0/4	Union Carbide and Carbon Corporation 1951
	500	4 h	4/4	
Rabbit	1,000	3.5 h	1/1	McCord 1932
	1,000	4.25 h	1/1	

TABLE 4-10 Summary of Acute Nonlethal Inhalation Data in Laboratory Animals Exposed to Allyl Alcohol

Species	Exposure Duration	Concentration (ppm)	Effects	Reference
Mouse	10 min	3.9	RD_{50}	Nielsen et al. 1984
Mouse	10 min	2.5	RD_{50}	James et al. 1987
Rat	1 h	638	Gasping, flushing[a], material around mouth/nose.	Kirkpatrick 2008
	1 h	423	Gasping, material around mouth/nose.	
	4 h	114	Gasping, flushing[a], material around mouth/nose.	
	8 h	52	Gasping, labored respiration, flushing[a], material around mouth/nose.	
Rat	1 h	51	Some flushing[a], olfactory degeneration and inflammation.	Kirkpatrick 2008
		220	Same as above (more affected); plus reduced response to stimulus, material around mouth/nose.	
		403	Same as above (more affected); plus gasping.	
Rat	4 h	22	One rat with material around mouth/nose, nasal inflammation.	Kirkpatrick 2008
		52	Same as above (more affected); plus gasping, some flushing[a], reduced response to stimulus, olfactory/respiratory degeneration.	
		102	Same as above (more affected); plus respiratory degeneration.	
Rat	8 h	10	One rat with flushing[a], material around mouth/nose.	Kirkpatrick 2008
		21	Same as above (more affected); plus reduced response to stimulus, some increased respiration and flushing[a], olfactory degeneration and inflammation.	
		52	1/10 died, gasping, irreversible nasal histopathologic changes.	

[a]Flushing characterized by reddened limbs/ears; considered an alcohol flush reaction caused by the presence of the aldehyde metabolite, acrolein.

TABLE 4-11 Summary of Nonlethal Inhalation Data in Laboratory Animals Exposed Repeatedly to Allyl Alcohol

Species	Exposure Duration	Concentration (ppm)	Effects	Reference
Mouse	6 h/d for 4 d	2.4	Histopathologic changes in upper respiratory tract epithelium (hyperplasia, inflammatory infiltrates, desquamation) and olfactory epithelium (slight loss of isolated sensory cells).	Zissu 1995
Rat	7 h/d, 5 d/wk for 60 exposures	1	No observed adverse effects.	Dunlap et al. 1958
		2	No observed adverse effects.	
		5	No observed adverse effects.	
		20	Reduced body weight gain.	
Rat	7 h/d, 5 d/wk for 90 d	40	Irritation (gasping, ocular irritation, nasal discharge) disappeared after first few exposures, increase pulmonary weight.	Dunlap et al. 1958
Rat	7 h/d, 5 d/wk for 90 d	60	Irritation (gasping, muzzle rubbing) disappeared after first few exposures, persistent ocular discharge, increased pulmonary and renal weights, 1/10 died after 4th exposure.	
Rat, guinea pig, rabbit	7 h/d, 5 d/wk for 127-134 exposures	7	Hepatic lesions (degeneration, dilation of sinusoids, cloudy swelling, focal necrosis) and renal lesions (degeneration, epithelial necrosis in convoluted tubules, proliferation of interstial tissue).	Torkelson et al. 1959a
Rat, guinea pig, rabbit	7 h/d, 5 d/wk for 28 exposures	2	No adverse effects.	Torkelson et al. 1959a

exposed for 9 days or 2 weeks (Zissu 1995). Rats repeatedly exposed by inhalation to allyl alcohol at 1, 2, 5, or 20 ppm had no gross signs of toxicity, but repeated exposures at 40 ppm resulted in transient irritation and increased pulmonary weight (Dunlap et al. 1958). Repeated inhalation exposure to allyl alcohol at 2 ppm for 7 h/day for a total of 28 exposures resulted in no measurable adverse effects in rats, guinea pigs, rabbits, and dogs (Torkelson et al. 1959a). Rats, guinea pigs, and rabbits exposed at 7 ppm for 7 h/day for a total of 127-134 exposures exhibited only mild and reversible microscopic hepatic and renal damage.

Other acute animal toxicity animal data focused on lethality. Mice, rats, and rabbits survived exposure to allyl alcohol at 200 ppm for 1 h; mice survived exposure at 500 ppm for 0.5 h, but not 1 h; and rabbits survived a 2-h but not a 4-h exposure at 500 ppm (Union Carbide and Carbon Corporation 1951). Exposure at 1,000 ppm for as little as 0.5 h and up to 4 h killed monkeys, mice, rats, and rabbits (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951). The only LC_{50} values available were based on tests that reported only target concentrations, and were unreliable because Dunlap et al. (1958) stated that actual concentrations ranged from 15-25% less than target concentrations. The uncorrected LC_{50} values in rats were 1,060 ppm for 1 h, 165 ppm for 4 h, and 76 ppm for 8 h. Repeated exposures of rats to allyl alcohol at 60, 100, or 150 ppm for 7 h/day, 5 days/week for 60 exposures resulted in mortality.

Only oral exposure studies on the potential developmental and reproductive toxicity of allyl alcohol were available. The studies found reproductive effects (decreased pup viability or total litter losses) at maternally toxic doses. Allyl alcohol was genotoxic in prokaryotic systems. No relevant data were available to assess the potential carcinogenicity of inhaled allyl alcohol. No evidence of carcinogenicity was observed in rats or hamsters orally administered allyl alcohol for 106 or 60 weeks, respectively.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Mechanism of Toxicity

Signs of toxicity in animals after acute and repeated inhalation exposure to allyl alcohol include lacrimation, pulmonary edema and congestion, gasping, alcohol flushing, material around the nose and mouth, and labored breathing. Histopathologic examination of rats after acute exposure to allyl alcohol revealed nasal lesions which progressed in incidence and severity with increasing duration and concentration, ultimately resulting in death due to reduced breathing capacity (Kirkpatrick 2008). These findings contrast with those found by McCord (1932) of pulmonary congestion leading to edema and compensatory emphysema, with degeneration of the cells in the convoluted tubules of the kidneys, liver, myocardium, ganglion cells of the spinal cord, and retina.

Mode-of-action information on allyl alcohol has focused on how the chemical causes periportal necrosis in the liver. It appears that this effect is more apt to occur after oral, intraperitoneal, or intravenous administration; thus, its relevance to effects after acute inhalation exposure is uncertain. Studies of the mechanism of allyl alcohol-induced liver necrosis and covalent binding to liver macromolecules found that metabolism of allyl alcohol to the reactive metabolite acrolein is required (Reid 1972; Serafini-Cessi 1972; Patel et al. 1983). This reaction is mediated by the cytosolic liver enzyme alcohol dehydrogenase (ADH) in the presence of NAD^+. The importance of ADH activity was exemplified in a study in which an ADH-negative strain of deer mice was resistant to allyl alcohol toxicity, while the ADH-positive strain of deer mice exhibited dose-dependent necrosis of periportal regions of the liver and increased plasma concentrations of lactate dehydrogenase, sorbitol dehydrogenase, and serum glutamate oxaloacetate transaminase activity 24 h after intraperitoneal injection (Belinsky et al. 1985). Another study found that old male rats were more susceptible to allyl alcohol-induced hepatotoxicity than young adult male rats because old rats had increased ADH activity (Rikans and Moore 1987). Acrolein can be detoxified to acrylic acid by further metabolism by aldehyde dehydrogenase or by conjugation with glutathione (Rikans 1987; Rikans and Moore 1987). Depletion of glutathione, followed by lipid peroxidation and hepatic necrosis, have been shown occur in both in vivo and in vitro studies of allyl alcohol (Badr et al. 1986; Belinsky et al. 1986; Jaeschke et al. 1987; Penttila et al. 1987; Miccadei et al. 1988; Penttila 1988; Pompella et al. 1988; Maellaro et al. 1990; Comporti 1991). Hormann et al. (1989) proposed that inactivation of thiol groups is critical for allyl alcohol hepatotoxicity on the basis of a study in which isolated rat hepatocytes exposed to allyl alcohol exhibited an initial rapid depletion of glutathione, followed by an increase in malondialdehyde, a decrease in protein sulfhydryl groups, and eventual loss of membrane integrity. When sulfhydryl compounds were added to the hepatocytes, however, hepatocytes were protected against cytotoxicity. Because mechanistic studies have reported that allyl alcohol-induced hepatotoxicity is also oxygen dependent, further experiments were conducted to elucidate which cell types are involved. It was determined that the presence of Kupffer cells is required to produce O_2-dependent hepatic necrosis (Przybocki et al. 1992).

Because one primary route of allyl alcohol exposure is inhalation, Patel et al. (1980) compared the metabolism of allyl alcohol in lung and liver preparations from male Holtzman rats. In the lungs, allyl alcohol was rapidly epoxidized to glycidol, and then further metabolized to glycerol, most likely by the action of epoxide hydrase. Allyl alcohol was not metabolized to the reactive metabolite acrolein because rat lungs do not contain appreciable ADH activity. Likewise, the amount of ADH activity in human lungs is only a small percentage of the ADH activity in liver; one study reported that ADH activity in the human lung was 1-8% of the ADH activity measured in liver (Moser et al. 1968). No study was available on the capability of rodent nasal and oral epithelial tissues to convert allyl alcohol to acrolein. It is currently unknown if the

parent alcohol is a direct irritant or if conversion to the acrolein metabolite is required to produce irritation. Liver preparations metabolized allyl alcohol to acrolein, acrylic acid, glycidaldehyde, and glyceraldehyde. It is unlikely that much glycidol and glycerol would be produced in the liver, as most of the hepatic allyl alcohol delivered dose would be converted to acrolein.

No quantitative information was available on systemic absorption and distribution of allyl alcohol following inhalation exposure. Although studies investigating intravenous administration of allyl alcohol demonstrated that conversion of allyl alcohol to acrolein was required to produce toxicity, the study by Nielsen et al. (1984) did not find evidence of such a conversion occurring; there was no delay in the appearance, development, or disappearance of the measured irritant response in mice. The in vitro study by Patel et al. (1980) demonstrated that the lungs will not metabolize allyl alcohol to the reactive metabolite acrolein, and it is unknown how much of the allyl alcohol will be distributed to the liver where the metabolic conversion will occur. The study investigating lung pathology in mice following repeated exposure at an RD_{50} concentration did not investigate whether any pathologic changes had occurred in other organs such as the liver and kidney (Zissu 1995). Therefore, it is unknown whether inhalation exposure at lower concentrations of allyl alcohol will produce toxicity confined to the lungs, or if some systemic toxicity will also be produced. It should again be noted that subchronic exposure of rats, guinea pigs, and rabbits to allyl alcohol at 2 ppm did not result in any measurable adverse effects (Torkelson et al. 1959a).

4.2. Structure-Activity Relationships

Groups of four male Ssc:CF-1 mice were exposed by inhalation to allyl acetate, allyl alcohol, allyl ether, or acrolein to evaluate the sensory and pulmonary irritation of propene derivatives (Nielsen et al. 1984). The four derivatives did not vary much in their ability to elicit sensory irritation as assessed by RD_{50} measurements; the RD_{50}s were 2.9, 3.9, 5.0, and 2.9 ppm, respectively. However, when the potency was expressed in terms of the thermodynamic activity, acrolein was 10 times more potent than the other three derivatives. Further experiments in which tracheally cannulated mice were exposed to the respective RD_{50} concentrations of the propene derivatives did not reveal any pulmonary irritation.

A number of studies investigating a homologous series of nonreactive alcohols demonstrated that both the odor and nasal pungency thresholds and ocular irritation thresholds in normosmics and nasal pungency thresholds in anosmics decreased with increasing chain length (Cometto-Muniz and Cain 1990, 1993, 1994, 1995). Although quantitative structure-activity relationship equations have been developed to predict nasal pungency, a condition of the equations is that the volatile organic compounds must be nonreactive (Abraham et al. 1996, 1998). Allyl compounds are reactive and are specifically excluded. If one

uses the algorithm to predict the potency of a reactive compound, the predicted minimum potency will be less than the observed potency.

NTP (2006) conducted studies comparing the toxicity of allyl alcohol, allyl acetate, and acrolein in male and female rats and mice exposed via gavage for 14 weeks, in an effort to discern the role of metabolism to acrolein in the toxicity of the other two compounds. Apart from one female rat exposed at 6 mg/kg that was killed moribund, all rats and mice survived exposure at doses up to 25 mg/kg (rats) or 50 mg/kg (mice). In contrast, all rats exposed at 10 mg/kg and all mice exposed at 20 mg/kg acrolein died. Rats exposed to allyl acetate survived at doses up to 50 mg/kg (all died at 100 mg/kg), and all but one female mouse survived exposure at up to 32 mg/kg. The forestomach was the primary organ affected by all three compounds. Exposure to allyl alcohol resulted in minimal to mild squamous epithelial hyperplasia in rats and mice at doses up to 50 mg/kg. Exposure to acrolein at doses of 10 mg/kg and higher resulted in more severe lesions of necrosis, hemorrhage, and chronic active inflammation in rats and mice. These more severe lesions were also seen at the highest doses of allyl acetate (100 mg/kg in rats or 62.5 mg/kg or higher in mice). NTP (2006) suggested that the forestomach toxicity of allyl alcohol and allyl acetate may have resulted from their metabolism to acrolein in the forestomach.

Renal toxicity was not observed in either species or with any of the three test compounds in the oral subchronic study (NTP 2006). Allyl alcohol was hepatotoxic to mice and female rats, and allyl acetate also resulted in hepatotoxicity in both species, while acrolein did not. NTP (2006) postulated that the reaction of acrolein with gut contents reduced its systemic bioavailability and, thus, its hepatotoxic potential, whereas the bioavailability of allyl alcohol and allyl acetate would not have been similarly affected due to these compounds' lower reactivity.

4.3. Susceptible Populations

Exposure at high concentrations of inhaled allyl alcohol can produce pulmonary congestion, edema, and compensatory emphysema, so it is likely that people with pulmonary conditions would be at increased risk of such effects (McCord 1932). People with pre-existing pulmonary disease might be at special risk to the pulmonary effects of allyl alcohol at lower concentrations; however, at high concentrations, people with pulmonary disease and healthy individuals will probably be affected similarly. Allyl alcohol exposure can result in hepatotoxicity, so individuals with compromised hepatic function may also be at an increased risk. More specifically, variations in the amount of ADH or glutathione will influence the extent of hepatotoxicity. This is due to the fact that allyl alcohol-induced hepatotoxicity depends on the conversion of allyl alcohol to acrolein by ADH (Serafini-Cessi 1972; Patel et al. 1983). Acrolein is then detoxified by further metabolism to acrylic acid by aldehyde dehydrogenase or by conjugation with glutathione (Rikans 1987; Rikans and Moore 1987). Hepatic

damage can also be influenced by bacterial infections, as demonstrated in a study reporting that allyl alcohol-treated rats pretreated with bacterial endotoxin experienced enhanced hepatic damage compared with rats given allyl alcohol alone (Sneed et al. 1997). Allyl alcohol exposure can also result in renal damage; thus, individuals with pre-exisiting renal conditions may be at an increased risk.

4.4. Concentration-Exposure Duration Relationship

The experimentally-derived exposure values in toxicity studies are scaled to the AEGL durations using the concentration-time relationship given by the equation $C^n \times t = k$, where C is concentration, t is time, and k is a constant. The value of the exponent n generally ranges from 0.8 to 3.5, and should be derived empirically from acute inhalation toxicity experiments, in which both the concentration and exposure duration are variables (ten Berge et al. 1986). For the AEGL-3 values, the LC_{01} values for each AEGL duration were calculated by the ten Berge software program using all available individual rat mortality data (see Appendix A); the ten Berge program estimated an n value of 0.95.

4.5. Other Relevant Information

An in vitro study conducted by Berry and Easty (1993) compared the corneal toxicity of allyl alcohol in isolated rabbit and human eyes and found a similar degree of ocular damage in both species.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Five of six human volunteers exposed to allyl alcohol for 5 min reported olfactory recognition at the lowest concentration of 0.78 ppm (Dunlap et al. 1958). Nasal irritation was reported as slight in two of six subjects exposed at 0.78 ppm and three of six subjects exposed at 6.25 ppm for 5 min. Nasal irritation of moderate or greater severity was reported in one of six subjects exposed to allyl alcohol for 5 min at 6.25 ppm, in four of seven volunteers exposed at 12.5 ppm, and in all five subjects exposed at 25 ppm. Slight ocular irritation was reported by one of six and one of seven individuals exposed for 5 min at 6.25 or 12.5 ppm, respectively. Severe ocular irritation was reported by all five volunteers exposed to allyl alcohol at 25 ppm for 5 min. Data from this study were not used to derive AEGL-1 values, because of the short exposure duration and uncertainties about the exposures, but the data are supportive of the AEGL-1 values. Humans reported severe ocular irritation at 25 ppm for 5 min, and rats exposed at 600 ppm for 1 h did not exhibit any signs of ocular irritation (Dunlap et al. 1958; Kirkpatrick 2008). Ocular irritation noted by the human volunteers was possibly the result of acrolein contamination.

5.2. Animal Data Relevant to AEGL-1

Exposure to allyl alcohol at 51 ppm for 1 h, at 22 ppm for 4 h, or at 10 ppm for 8 h produced reversible histopathologic changes in the nasal cavity of rats, including degeneration of the olfactory epithelium, chronic inflammation, and goblet cell hyperplasia (Kirkpatrick 2008). Clinical signs included material around the mouth and alcohol flushing. Exposure at higher concentrations at each duration resulted in increased incidences of histopathologic changes in the nasal cavity, gasping, and reduced reaction to cage stimulus. A study in mice identified an RD_{50} (concentration that reduces respiratory rate by 50%) of 3.9 ppm (30 min) (Nielsen et al. 1984). This test quantitatively measures irritant effects as indicated by a reflex decrease in respiration (ASTM 2012). An RD_{10} value of 0.27 ppm was calculated to estimate the threshold for irritation.

5.3. Derivation of AEGL-1 Values

Data from the Nielsen et al. (1984) study in mice were used as the basis for deriving AEGL-1 values. An RD_{10} value of 0.27 ppm (30 min) was an estimate of the threshold for irritation. A total uncertainty factor of 3 was applied, as irritant effects are not expected to vary greatly between species or individuals. Time scaling was not applied due to the short duration of exposure. The AEGL-1 values are supported by results of the Dunlap et al. (1958) study. If AEGL-1 values had been based on human data from that study, AEGL-1 values would have been 0.27 ppm (point of departure of 0.78 ppm, a total uncertainty factor of 3, and no time scaling).

AEGL-1 values for allyl alcohol are presented in Table 4-12, and the calculations are presented in Appendix B.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Slight nasal irritation was reported by two of six human volunteers exposed to allyl alcohol for 5 min at 0.78 ppm and three of six subjects exposed at 6.25 ppm (Dunlap et al. 1958). Nasal irritation of moderate or greater severity was reported in one of six subjects exposed at 6.25 ppm, by four of seven volunteers exposed at 12.5 ppm, and in all five subjects exposed at 25 ppm. Slight ocular irritation was reported by one of six and one of seven individuals exposed for 5 min at 6.25 or 12.5 ppm, respectively. Severe ocular irritation was reported by all five volunteers exposed at 25 ppm for 5 min. These data were not used to derive AEGL-2 values, because of the short exposure duration and uncertainties about the exposures. Although humans reported severe ocular irritation at 25 ppm for 5 min, and rats exposed at 600 ppm for 1 h did not exhibit any signs of ocular irritation (Dunlap et al. 1958; Kirkpatrick 2008). Ocular irritation noted by the human volunteers was possibly the result of acrolein contamination.

TABLE 4-12 AEGL-1 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)

6.2. Animal Data Relevant to AEGL-2

Rats were exposed to allyl alcohol vapor at concentrations of 0, 51, 220, or 403 ppm for 1 h, 0, 22, 52, or 102 ppm for 4 h, and 0, 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). In studies of 1-h exposures, minimal effects were observed at 51 ppm. At concentrations of 220 and 430 ppm, reduced responses to stimulus, concentration-related increases in alcohol flushing, material around the mouth, and chronic inflammation in the nasal cavity were found. Olfactory epithelium degeneration and goblet cell hyperplasia were present in 1-3 rats at all concentrations, and one rat exposed at 403 ppm exhibited gasping during exposure. In rats exposed for 4 h, 22 ppm produced material around the mouth in one rat, goblet cell hyperplasia in one rat, and chronic inflammation in the nasal cavity. Exposure at 52 and 102 ppm generally resulted in concentration-related increases in alcohol flushing, material around the mouth, gasping, reduced response to cage stimulus, olfactory and respiratory epithelium degeneration, chronic inflammation in the nasal cavity, and goblet cell hyperplasia. In rat exposed for 8 h, clinical effects were minimal at 10 and 21 ppm (a few rats had alcohol flushing, material around the mouth, one rat at each concentration had yellow material around the urogenital area, and one rat in the 21-ppm group had rales/increased respiration). One rat in the 52-ppm group died. A concentration-related increase in the number of animals with a reduced response to cage stimulus was observed at 21 and 52 ppm. Histopathologic examination of the nasal cavity of rats exposed at 10 or 21 ppm revealed reversible changes, including degeneration of the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia. Exposure at 52 ppm produced similar but generally more severe lesions.

Other inhalation data were not appropriate for deriving AEGL-2 values. In a study by Dunalp et al. (1958), rats were exposed repeatedly to allyl alcohol at 20, 40, or 60 ppm for 7 h. No measurable adverse effects were found in the 20-ppm group. At 40 ppm, irritation (which resolved after the first few exposures) and increased lung weight were observed. At 60 ppm, irritation evidenced by gasping and muzzle-rubbing (which disappeared after the first few exposures), persistent ocular discharge, and one death were observed.

6.3. Derivation of AEGL-2 Values

The Kirkpatrick (2008) study in rats was selected as the basis for deriving AEGL-2 values for allyl alcohol. No-effect levels for disabling effects (reduced response to stimulus and gasping) were 51 ppm for 1 h, 22 ppm for 4 h, and 10

ppm for 8 h. These values were used as the points-of-departure for the 1-, 4- and 8-h AEGL-2 values, respectively. A total uncertainty factor of 30 was applied. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether the disabling effects are due to allyl alcohol, one of its metabolites, or both. Also, humans have genetic polymorphisms for aldehyde dehydrogenase. Time scaling was performed for the 10- and 30-min AEGL values using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.95 was derived from rat lethality data (see Appendix A).

AEGL-2 values for allyl alcohol are presented in Table 4-13, and the calculations are presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on allyl alcohol were relevant for deriving AEGL- value3. No reports of death following accidental exposure to allyl alcohol were found.

7.2. Animal Data Relevant to AEGL-3

Groups of five rats per sex were exposed to allyl alcohol vapor at concentrations of 0, 51, 220, or 403 ppm for 1 h, at 0, 22, 52, or 102 ppm for 4 h, and at 0, 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). All animals survived to study termination except for one male rat exposed at 52 ppm for 8 h. The rat died the day after exposure, and death was attributed to ulceration of the respiratory and olfactory epithelium in the nasal passages, resulting in diminished breathing capacity and hypoxia. Another male rat had irreversible nasal histopathologic lesions. The histopathologic changes that were observed in the nasal cavities of all other exposed rats were considered reversible. In a preliminary study by Kirkpatrick (2008), groups of three rats per sex were exposed to allyl alcohol at concentrations of 423 ppm or 638 ppm for 1 h, 114 ppm for 4 h, and 52 ppm for 8 h. All animals survived to study termination. Clinical signs in all exposure groups included gasping during and after exposure, material around the mouth and nose, and alcohol flushing after the exposure. Two rats exposed at 52 ppm for 8 h exhibited labored respiration during exposure. Histopathologic examinations were not performed.

Mice, rats, and rabbits survived exposure to allyl alcohol at 200 ppm for 1 h. Mice survived exposure to allyl alcohol at 500 ppm for 30 min but not for 1 h. Rabbits survived a 2-h but not a 4-h exposure to allyl alcohol at 500 ppm (Union

Carbide and Carbon Corporation 1951). Exposure to allyl alcohol at 1,000 ppm for as little as 30 min and up to 4 h killed monkeys, mice, rats, and rabbits (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951). Dunlap et al. (1958) reported 1-, 4-, and 8-h LC_{50} values in rats of 1,060 ppm, 165 ppm, and 76 ppm, respectively (actual exposure concentrations were 15-25% less than the target concentrations, but no corrected concentrations were provided).

7.3. Derivation of AEGL-3 Values

AEGL-3 values are based on the calculated LC_{01} values for allyl alcohol in rats of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} estimates were calculated using the ten Berge software program and rat mortality data from four studies (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008) (see Appendix A). The ten Berge program estimated an n = 0.95 for time scaling. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether lethal effects are due to allyl alcohol, one of its metabolites, or both. Furthermore, humans have genetic polymorphisms for aldehyde dehydrogenase. AEGL-3 values for allyl alcohol are presented in Table 4-14, and the calculations are presented in Appendix B.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of AEGL values for allyl alcohol is presented in Table 4-15. AEGL-1 values are based on the RD_{10} value in mice, which was an estimate of the threshold for irritation.AEGL-2 values are based on no-effect levels for disabling effects observed in rats. AEGL-3 values for allyl alcohol are based on LC_{01} estimates calculated using the ten Berge software program and rat mortality data from several studies.

TABLE 4-13 AEGL-2 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)

8.2. Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to allyl alcohol are presented in Table 4-16.

8.3. Data Adequacy and Research Needs

Human data available for allyl alcohol AEGL derivations are limited. In one study from 1958, humans were exposed to allyl alcohol for only 5 min and nose and eye irritation was recorded (Dunlap et al. 1958). The study results are of limited utility due to the short exposure duration, and are questionable in the context of other study results. Humans reported severe eye irritation at 25 ppm for 5 min, while rats exposed to 600 ppm for 1 h did not exhibit any signs of eye irritation. It is possible that the eye irritation noted by the human volunteers was the result of acrolein contamination. The only other human data available are case reports of corneal damage (Smyth 1956) and occupational accounts of pulmonary edema, conjunctivitis, and lacrimation after exposures to unknown concentrations, frequencies, or durations (McCord 1932).

Major data gaps include the lack of lifetime inhalation carcinogenicity bioassays on allyl alcohol and the lack of in vivo assays for clastogenicity or confirmatory evidence of genotoxicity. The NAC recognizes the potential for ally alcohol to be a carcinogen, considering the evidence that allyl alcohol can be metabolized to acrolein. However, at this time there are not enough data to provide a quantitative assessment of the carcinogenic potential of allyl alcohol. In order to determine whether the pronounced upper respiratory tract irritation (McCord 1932; Dunlap et al. 1958) is due to the parent molecule or to its irritant/carcinogenic aldehyde metabolites (acrolein, glycidaldehyde) (Beauchamp et al. 1985), pharmocokinetic and disposition data in target tissues are necessary. Fundamental research including quantification and extrapolation of irritant response for ally alcohol and related material is lacking.

TABLE 4-14 AEGL-3 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

TABLE 4-15 AEGL Values for Allyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)
AEGL-2 (disabling)	11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)
AEGL-3 (lethal)	87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

TABLE 4-16 Standards and Guidelines for Allyl Alcohol

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	0.09 ppm (0.22 mg/m^3)	–	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)
AEGL-2	11 ppm (27 mg/m^3)	–	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)
AEGL-3	87 ppm (210 mg/m^3)	–	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)
IDLH (NIOSH)[a]	–	–	–	20 ppm	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	–	0.5 ppm (1.21 mg/m^3) [skin]
PEL-TWA (OSHA)[c]	–	–	–	–	–	2 ppm (5 mg/m^3) [skin]
REL-TWA (NIOSH)[d]	–	–	–	–	–	2 ppm (5 mg/m^3) [skin]
REL-STEL (NIOSH)[e]	–	4 ppm (10 mg/m^3) [skin]	–	–	–	–
MAK (Germany)[f]	–	–	–	–	–	Not established; carcinogenicity category 3
MAC (The Netherlands)[g]	–	–	–	–	–	2 ppm (5 mg/m^3)

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health [NIOSH 1994, 2011]) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The ILDH value for allyl alcohol is based on severe ocular irritation in humans exposed at 25 ppm (Dunlap et al. 1958).

[b]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2013]) 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. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.

[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Safety and Health Administration `[(29 CFR 1910.1000) [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 8 h/day, 40 h/week. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.

[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.
[e]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.
[f]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2012) is defined analogous to the ACGIH TLV-TWA. Carcinogenicity category 3B is defined as: "Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data. In vitro test or animal studies have yielded evidence of carcinogenicity that is not sufficient for classification of the substance in one of the other categories. The classification of Category 3 is provisional. Further studies are required before a final decision can be made. A MAK value can be established provided no genotoxic effects have been detected."
[g]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

A level of distinct odor awareness (LOA), which represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity and about 10 % of the population will experience a strong odor intensity, could not be determined due to inadequate data. Although odor thresholds for allyl alcohol have been reported (1.4 ppm and 2.1 ppm), concurrent odor threshold data for the reference chemical n-butanol (odor detection threshold 0.04 ppm) were not available.

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APPENDIX A

DERIVATION OF LC_{01} VALUES AND TIME-SCALING EXPONENT FOR ALLY ALCOHOL

Filename: allyl alcohol for Log Probit Model
Date: 13 November 2008 Time: 14:07:13

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	51	60	10	0
2	220	60	10	0
3	403	60	10	0
4	22	240	10	0
5	52	240	10	0
6	102	240	10	0
7	10	480	10	0
8	21	480	10	0
9	52	480	10	1
10	200	60	10	0
11	1,000	30	6	1
12	1,000	60	6	4
13	1,000	120	6	6
14	1,000	60	6	4
15	1,000	180	6	6
16	638	60	6	0
17	423	60	6	0
18	114	240	6	0
19	52	480	6	0

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 6.50
Degrees of freedom = 16
Probability model = 9.82E-01

Ln(Likelihood) = -7.40

B 0 = -2.7460E+01	Student t = -3.3238
B 1 = 2.9303E+00	Student t = 4.2466
B 2 = 3.0760E+00	Student t = 3.3390

Variance B 0 0 = 6.8256E+01
Covariance B 0 1= -5.6297E+00
Covariance B 0 2 = -7.5164E+00
Variance B 1 1 = 4.7615E-01
Covariance B 1 2 = 6.0522E-01
Variance B 2 2 = 8.4867E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.953
Lower limit (95% CL) = 0.758
Upper limit (95% CL) = 1.147

Estimation of Conc ppm at response of 1%
Minutes = 480
Point estimate Conc ppm = 4.482E+01 for response of 1%
Lower limit (95% CL) Conc ppm = 2.858E+01 for response of 1%
Upper limit (95% CL) Conc ppm = 6.399E+01 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 240
Point estimate Conc ppm = 9.279E+01 for response of 1%
Lower limit (95% CL) Conc ppm = 6.111E+01 for response of 1%
Upper limit (95% CL) Conc ppm = 1.180E+02 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 60
Point estimate Conc ppm = 3.976E+02 for response of 1%
Lower limit (95% CL Conc ppm = 2.194E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 5.115E+02 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 30
Point estimate Conc ppm = 8.232E+02 for response of 1%
Lower limit (95% CL) Conc ppm = 3.833E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 1.154E+03 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 10
Point estimate Conc ppm = 2.608E+03 for response of 1%
Lower limit (95% CL) Conc ppm = 8.960E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 4.347E+03 for response of 1%

APPENDIX B

DERIVATION OF AEGL VALUES FOR ALLYL ALCOHOL

Derivation of AEGL-1 Values

Key study:	Nielsen, G.D., J.C. Bakbo, and E. Holst. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. Toxicol. 54(4):292-298.
Toxicity end point:	RD_{10} = 27 ppm (estimated threshold for irritation)
Time scaling:	Not applied
Uncertainty factors:	3, because irritant effects are not expected to vary greatly between species or individuals
Calculation:	0.27 ppm ÷ 3 = 0.090 ppm (applied to all AEGL-1 durations)

Derivation of AEGL-2 Values

Key study:	Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.
Toxicity end point:	No effect level for disabling effects: 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h
Time scaling:	Performed for the 10- and 30-min values. $C^n \times t = k$, where n = 0.95 (derived from rat lethality data; see Appendix B) $C^{0.95} \times t = k$ $(51 \text{ ppm})^{0.95} \times 1 \text{ h} = 42 \text{ ppm-h}$
Uncertainty Factors:	3 for interspecies differences 10 for intraspecies variability
Calculations:	
10-min AEGL-2:	$C^{0.95} \times 0.0167 \text{ h} = 42 \text{ ppm-h}$ $C^{0.95} = 251 \text{ ppm}$ C = 336 ppm 336 ÷ 30 = 11 ppm

30-min AEGL-2: $C^{0.95} \times 0.5$ h = 42 ppm-h
$C^{0.95}$ = 84 ppm
C = 106 ppm
106 ÷ 30 = 3.5 ppm

1-h AEGL-2: 51 ppm ÷ 30 = 1.7 ppm

4-h AEGL-2: 22 ppm ÷ 30 = 0.73

8-h AEGL-2: 10 ppm ÷ 30 = 0.33

Derivation of AEGL-3 Values

Key studies: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.

McCord, C.P. 1932. The toxicity of allyl alcohol. J. Am. Med. Assoc. 98(26):2269-2270.

Smyth, H.F., and C.P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30(1):63-68.

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem Regarding a Letter About Toxicity Studies with Allyl Alcohol, Union Carbide and Carbon Corporation, New York, January 29, 1951. Subbmited by DuPont, Wilmington, DE to EPA with cover letter dated October 27, 1992. EPA Document No. 88-920009857. Microfische No. OTS0571508.

Toxicity end point: Calculated LC_{01} values: 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h.

Time scaling: A point of departure for each AEGL exposure duration was calculated using ten Berge program; the program calculated an n value 0.95 (see Appendix B).

Uncertainty factors: 3 for interspecies differences
10 for intraspecies variability

Calculations:

10-min AEGL-3:	2,600 ppm ÷ 30 = 87 ppm
30-min AEGL-3:	820 ppm ÷ 30 = 27 ppm
1-h AEGL-3:	400 ppm ÷ 30 = 13 ppm
4-h AEGL-3:	93 ppm ÷ 30 = 3.1 ppm
8-h AEGL-3:	45 ppm ÷ 30 = 1.5 ppm

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR ALLY ALCOHOL

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)

Key reference: Nielsen, G.D., J.C. Bakbo, and E. Holst. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. Toxicol. 54(4):292-298.

Test species/Strain/Sex/Number: Mice, Ssc:CF-1; 4 males per group

Exposure route/Concentrations/Durations: Inhalation (head only), 0.42, 2.00, 4.55, or 18.10 ppm for 30 min

Effects: Reduction in respiratory rate, RD_{50} = 3.9 ppm; RD_{10} = 0.27 ppm

End point/Concentration/Rationale: Estimate of irritation threshold, RD_{10} = 0.27 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 3, irritant effects are not expected to vary greatly between species or individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: None

Data adequacy: Data are adequate to derive AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)

Key reference: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-Hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.

Test species/Strain/Sex/Number: Rats, Crl:CD(DS), 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 51, 220, or 403 ppm for 1 h, 22, 52, or 102 ppm for 4 h, and 10, 21, or 52 ppm for 8 h.

Effects:

Duration	Concentration	Effects
1h	51 ppm	Alcohol flush and nasal irritation.
	220 ppm	Same as at 51 ppm, plus decreased response to stimulus.

Duration	Concentration	Effects
	403 ppm	Same as at 220 ppm, plus gasping.
4 h	22 ppm	Clear red material around mouth.
	52 ppm	Same as at 22 ppm, plus nasal irritation, gasping, and reduce response to stimulus.
	102 ppm	Same as at 52 ppm.
8 h	10 ppm	Alcohol flush and nasal irritation.
	21 ppm	Same as at 10 ppm, plus gasping and reduced response to stimulus.
	52 ppm	Same as at 21 ppm.

End point/Concentration/Rationale: No-effect level for AEGL-2 effects; 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h.

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3, similar 1-h no-effect levels for lethality reported for rats (200-423 ppm), mice (200 ppm), and rabbits (200 ppm).
Intraspecies: 10, unknown if effects of allyl alcohol are due to parent compound, metabolites, or both. Also, accounts for genetic polymorphisms for aldehyde dehydrogenase in humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: Performed for the 10- and 30-min values. $C^n \times t = k$, where n = 0.95 (derived from rat lethality data; see Appendix B).

Data adequacy: Data sufficient to derive AELG-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

Key references: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-Hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC, Ashland, OH.

McCord, C.P. 1932. The toxicity of allyl alcohol. J. Am. Med. Assoc. 98(26):2269-2270.

Smyth, H.F., and C.P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30(1):63-68.

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem Regarding a Letter About Toxicity Studies with Allyl Alcohol, Union Carbide and Carbon Corporation, New York, January 29, 1951. Subbmited by DuPont, Wilmington, DE to EPA with cover letter dated October 27, 1992. EPA Document No. 88-920009857. Microfische No. OTS0571508.

Test species/Strain/Sex/Number: Rat (see table below for number of animals for each study)

(Continued)

AEGL-3 VALUES Continued

Exposure route/Concentrations/Durations: Inhalation, 10-1,000 ppm for 1-8 h

Effects:

Concentration (ppm)	Minutes	Exposed	Responded	Reference
51	60	10	0	Kirkpatrick 2008
220	60	10	0	Kirkpatrick 2008
403	60	10	0	Kirkpatrick 2008
22	240	10	0	Kirkpatrick 2008
52	240	10	0	Kirkpatrick 2008
102	240	10	0	Kirkpatrick 2008
10	480	10	0	Kirkpatrick 2008
21	480	10	0	Kirkpatrick 2008
52	480	10	1	Kirkpatrick 2008
200	60	10	0	Union Carbide and Carbon Corporation 1951
1,000	30	6	1	Union Carbide and Carbon Corporation 1951
1,000	60	6	4	Union Carbide and Carbon Corporation 1951
1,000	120	6	6	Union Carbide and Carbon Corporation 1951
1,000	60	6	4	Smyth and Carpenter 1948
1,000	180	6	6	McCord 1932
638	60	6	0	Kirkpatrick 2008
423	60	6	0	Kirkpatrick 2008
114	240	6	0	Kirkpatrick 2008
52	480	6	0	Kirkpatrick 2008

End point/Concentration/Rationale: Estimated lethality thresholds, LC_{01}s of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} values calculated using log-probit model of ten Berge (see Appendix B).

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3, similar 1-h no-effect levels for lethality reported for rats (200-423 ppm), mice (200 ppm), and rabbits (200 ppm).
Intraspecies: 10, unknown if effects of allyl alcohol are due to parent compound, metabolites, or both. Also, accounts for genetic polymorphisms for aldehyde dehydrogenase in humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: A point of departure for each AEGL exposure duration was calculated using ten Berge program; program calculated an n value 0.95 (see Appendix B).

Data adequacy: Data were adequate to derive AEGL-3 values. The most recent study with measured concentrations of allyl alcohol reported minimal mortality; therefore, mortality data from earlier studies with less than adequate analytic techniques were included.

APPENDIX D

CATEGORY PLOT FOR ALLYL ALCOHOL

A useful way to evaluate AEGL values in the context of empirical data is presented in Figure D-1. For this plot, toxic responses were placed into severity categories. The severity categories fit into definitions of the AEGL health effects of no effects, discomfort, disabling, some lethality (an experimental concentration at which some of the animals died and some did not), and lethal. The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The doses often span a several orders of magnitude, especially when human data are available. Therefore, the concentration in the plot is placed on a log scale. The graph in Figure D-1 plots the AEGL values for allyl alcohol and acute human and animal toxicity data for the chemical.

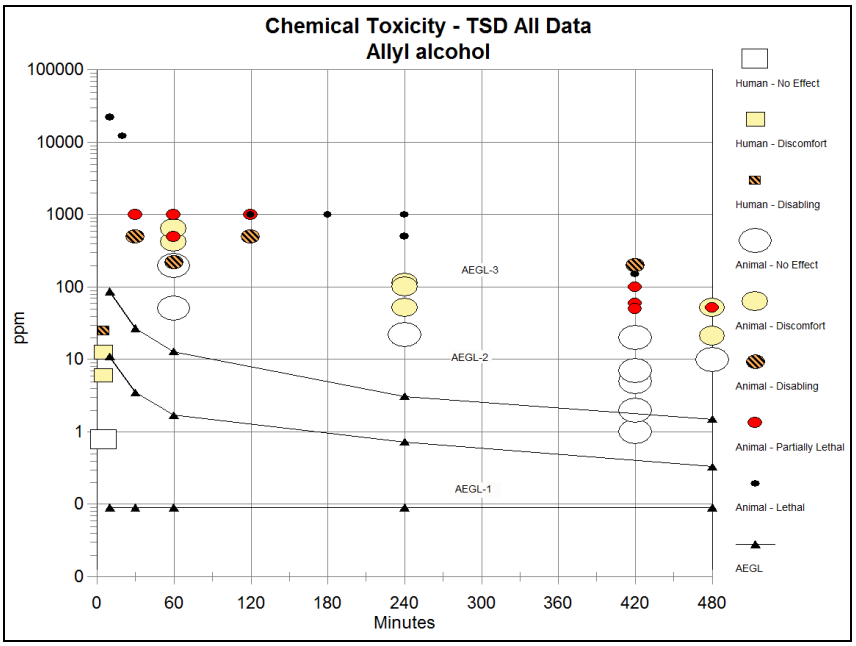

FIGURE D-1 Category plot of toxicity data and AEGL values for allyl alcohol.

TABLE D-1 Data Used in Category Plot for Allyl Alcohol

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				0.090	10	AEGL	
AEGL-1				0.090	30	AEGL	
AEGL-1				0.090	60	AEGL	
AEGL-1				0.090	240	AEGL	
AEGL-1				0.090	480	AEGL	
AEGL-2				11	10	AEGL	
AEGL-2				3.5	30	AEGL	
AEGL-2				1.7	60	AEGL	
AEGL-2				0.73	240	AEGL	
AEGL-2				0.33	480	AEGL	
AEGL-3				87	10	AEGL	
AEGL-3				27	30	AEGL	
AEGL-3				13	60	AEGL	
AEGL-3				3.1	240	AEGL	
AEGL-3				1.5	480	AEGL	
Dunlap et al. 1958	Human			0.78	5	0	
Dunlap et al.1958	Human			6	5	1	
Dunlap et al. 1958	Human			12.5	5	1	
Dunlap et al. 1958	Human			25	5	2	Severe ocular irritation
Dunlap et al. 1958	Rat	Both	1	60.0	420	SL	
Dunlap et al. 1958	Rat	Both	1	100.0	420	SL	

Dunlap et al. 1958	Rat	Both	1	150.0	420	3	
Dunlap et al. 1958	Rat		1	20.0	420	0	
Dunlap et al. 1958	Rat		1	1.0	420	0	
Dunlap et al. 1958	Rat		1	2	420	0	
Dunlap et al. 1958	Rat		1	5	420	0	
Kirkpatrick 2008	Rat	Both	1	51	60	0	
Kirkpatrick 2008	Rat	Both	1	423	60	1	
Kirkpatrick 2008	Rat	Both	1	220	60	2	
Kirkpatrick 2008	Rat	Both	1	638	60	1	
Kirkpatrick 2008	Rat	Both	1	114.0	240	1	
Kirkpatrick 2008	Rat	Both	1	22	240	0	
Kirkpatrick 2008	Rat	Both	1	52.0	480	1	
Kirkpatrick 2008	Rat	Both	1	52.0	240	1	
Kirkpatrick 2008	Rat	Both	1	102.0	240	1	
Kirkpatrick 2008	Rat	Both	1	10.0	480	0	
Kirkpatrick 2008	Rat	Both	1	21.0	480	1	
Kirkpatrick 2008	Rat	Both	1	52.0	480	SL	Mortality (1/10)
McCord 1932	Monkey		1	1,000	240	3	Mortality (1/1)
McCord 1932	Rat		1	1,000	180	3	Mortality (6/6)
McCord 1932	Rat		1		420		Mortality (4/4)
McCord 1932	Rat		1	50.0	420	SL	Mortality (4/5)

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
McCord 1932	Rat	Both	1		420		Mortality (4/4)
Shell Chemical Corp. 1957	Mouse		1	22,000	10	3	Mortality (10/10)
Shell Chemical Corp. 1957	Mouse		1	12,200	20	3	Mortality (10/10)
Smyth and Carpenter 1948	Rat		1	1,000	60	SL	Mortality (4/6)
Torkelson et al. 1959a,b	Dog	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Guinea Pig	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Guinea Pig	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Rabbit		1	200.0	420	2	
Torkelson et al. 1959a,b	Rabbit	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Rabbit	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Rat	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Rat	Both	1	2.0	420	0	
Union Carbide and Carbon Corporation 1951	Mouse		1	200	60	0	
Union Carbide and Carbon Corporation 1951	Mouse		1	500	30	2	
Union Carbide and Carbon Corporation 1951	Mouse		1	500	60	SL	Mortality (4/10)
Union Carbide and Carbon Corporation 1951	Mouse		1	1,000	60	SL	Mortality (6/10)
Union Carbide and Carbon Corporation 1951	Mouse		1	1,000	120	SL	Mortality (8/10)

Union Carbide and Carbon Corporation 1951	Mouse		1	1,000.0	240	3	Mortality (10/10)
Union Carbide and Carbon Corporation 1951	Rabbit	Both	1	500	120	2	
Union Carbide and Carbon Corporation 1951	Rabbits		1	500.0	240	3	Mortality (4/4)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	30	SL	Mortality (1/6)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	60	SL	Mortality (4/6)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	120	3	Mortality (6/6)

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

5

Hydrogen Selenide[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 Carol Wood (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), and Chemical Managers Nancy Kim (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances) and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Hydrogen selenide is a gas with a disagreeable odor at room temperature. It is formed by the reaction of acids or water with metal selenides (Malczewska-Toth 2012). Although elemental selenium has a wide variety of uses in industry, agriculture, and pharmaceuticals (ATSDR 2003), hydrogen selenide has no commercial use (Malczewska-Toth 2012).

Hydrogen selenide is highly irritating to the respiratory tract and effects progress to pulmonary edema, bronchitis, and bronchial pneumonia (Glover 1970; IPCS 1987; Malczewska-Toth 2012). Initial effects in exposed workers are signs of respiratory irritation, include tearing, running nose, coughing, sneezing, and chest tightness. The compound is oxidized to elemental selenium when it comes into contact with mucus membranes and appears as a red precipitate (Dudley and Miller 1937, 1941; Glover 1970; Zwart and Arts 1989). A distinct garlic odor of the breath has been reported in people accidentally exposed to selenium or selenium compounds and is most likely the result of the excretion of dimethyl selenide in expired air (ATSDR 2003).

No reports of human death after exposure to hydrogen selenide were found in the literature. AIHA (1989) reports an odor threshold of 0.3 ppm for hydrogen selenide. Olfactory fatigue occurs quickly at that concentration, and anecdotal reports indicate that workers exposed to hydrogen selenide at concentrations greater than 1.5 ppm experienced nasal and throat irritation that was

severe enough that they could not remain at work, but that workers were able to tolerate 0.3 ppm for several minutes without noticeable effects (Dudley and Miller 1941).

Dudley and Miller (1937, 1941) performed a series of experiments in which groups of 16-32 guinea pigs (sex and strain not specified) were exposed whole body to various concentrations of hydrogen selenide for 10-480 min and monitored for 30 days. Concentration-related clinical signs of toxicity at concentrations greater than 6.3 ppm included pawing at the nose and eyes, copious mucus from the nasal passages, and difficulty breathing. Marked weight loss was apparent, with recovery in survivors beginning 8 days after exposure. Animals that died within 48 h exhibited respiratory and circulatory failure, whereas those dying after 5 days or later had few acute respiratory symptoms but exhibited bronchial pneumonia for extended periods. The calculated 1-h LC_{50} (lethal concentration, 50% lethality) was 3.6 ppm, and 100% lethality occurred at 6.0 ppm. The main finding during histopathologic examination was fatty deposition in the liver and, to a lesser extent, in the kidney; splenic enlargement due to hyperplasia of the lymphoid tissue was also found. Hepatic lesions, but no increase in mortality, were observed at concentrations as low as 1.2 ppm for 30-60 min and the lesions generally resolved 17-20 days after exposure.

Lethality studies were conducted in pairs of Wistar rats exposed nose-only to various concentrations of hydrogen selenide for different durations, followed by a 14-day observation period (Zwart and Arts 1989; Zwart et al. 1992). In one experiment, no deaths occurred after exposure at 117 ppm for 4 or 15 min, but one animal died after exposure for 7.5 min; thus, 117 ppm for 15 min or less might be a threshold for death. In another experiment, groups of five male and five female Wistar rats were exposed to hydrogen selenide at 47-74 ppm for 1 h. Most deaths occurred within 2 days after exposure. Concentration-related clinical signs observed after exposure was stopped included piloerection, red discoloration of the fur, cyanosis, half-closed eyes, red nasal discharge, mouth breathing, moist or dry rales, and apnea. Surviving animals had body weight loss or reduced weight gain throughout the observation period. For example, at 47 ppm, no deaths occurred but four males and two females lost weight throughout the 14-day observation period. Necropsy revealed gas in the stomach or intestines of animals that died during the study and red discolored, atelectatic, edematous, or spongy, swollen, and/or spotted lungs with irregular surface in almost all decedents and survivors. A 1-h LC_{50} of 72 ppm was calculated (Zwart and Arts 1989; Zwart et al. 1992). Examination of the data used to calculate the 1-h LC_{50} shows a steep dose-response curve (0% mortality at 47 ppm, 20% at 71 ppm, and 60% at 74 ppm).

AEGL-1 values are not recommended for hydrogen selenide, because no animal or human data on appropriate end points were found. Data were insufficient to calculate the level of distinct odor awareness for the chemical because the basis of the reported odor threshold of 0.3 ppm was not documented.

Data were also insufficient to calculate AEGL-2 values for hydrogen selenide. In the absence of specific data for determining an AEGL-2 value, one-third of the AEGL-3 values can be used to establish AEGL-2 values (NRC 2001). This approach is justified because the lethality data in rats indicate a steep concentration-response relationship.

AEGL-3 values for hydrogen selenide were based on an estimated LC_{01} of 33 ppm, obtained by a log-probit analysis of data from experiments in Wistar rats (Zwart and Arts 1989; Zwart et al. 1992). Values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). A value of n = 2.5 was calculated by probit analysis of all of the available lethality data in the rat. A total uncertainty factor of 100 was applied (10 for interspecies differences and 10 for intraspecies variability). The intraspecies factor of 10 was selected to address uncertainty about the mechanism of action for the marked body-weight loss exhibited by some surviving rats and whether this reflected a moribund state. An interspecies factor of 10 was used, because data were available in only two species and the limited data suggest that the rat might not be the most sensitive species.

AEGL values for hydrogen selenide are presented in Table 5-1.

1. INTRODUCTION

Hydrogen selenide is a gas with a disagreeable odor at room temperature. It has a density greater than that of air and is formed by the reaction of acids or water with metal selenides (Malczewska-Toth 2012). Although elemental selenium has a wide variety of uses in industry, agriculture, and pharmaceuticals (ATSDR 2003), hydrogen selenide has no commercial use (Malczewska-Toth 2012).

Hydrogen selenide is highly irritating to the respiratory tract with effects progressing to pulmonary edema, bronchitis, and bronchial pneumonia (Glover 1970; Malczewska-Toth 2012). The compound is oxidized to elemental selenium when it comes into contact with mucus membranes, and appears as a red precipitate (Dudley and Miller 1937, 1941; Glover 1970; Zwart and Arts 1989). The breath of people accidentally exposed to selenium or selenium compounds has been reported to have a distinct garlic odor, most likely the result of excretion of dimethyl selenide in expired air (ATSDR 2003).

The chemical and physical properties of hydrogen selenide are listed in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human lethality following exposure to hydrogen selenide were found in the available literature.

TABLE 5-1 AEGL Values for Hydrogen Selenide

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)	0.22 ppm (0.73 mg/m^3)	0.15 ppm (0.48 mg/m^3)	0.11 ppm (0.37 mg/m^3)	0.064 ppm (21 mg/m^3)	0.048 ppm (0.16 mg/m^3)	One-third of the AEGL-3 values
AEGL-3 (lethal)	0.67 ppm (2.2 mg/m^3)	0.44 ppm (1.5 mg/m^3)	0.33 ppm (1.1 mg/m^3)	0.19 ppm (0.63 mg/m^3)	0.14 ppm (0.48 mg/m^3)	Calculated 1-h LC_{01} in rats (Zwart and Arts 1989; Zwart et al. 1992)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.
Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.

TABLE 5-2 Chemical and Physical Properties of Hydrogen Selenide

Parameter	Value	Reference
Synonyms	Dihydrogen selenide, selenium hydride, selenium dihydride, selane	ATSDR 2003
CAS registry no.	7783-07-5	O'Neil et al. 2006
Chemical formula	H_2Se	
Molecular weight	80.98	O'Neil et al. 2006
Physical state	Colorless gas	ATSDR 2003
Melting point	-65.73°C	O'Neil et al. 2006
Boiling point	-41.3°C	O'Neil et al. 2006
Liquid density (water = 1)	2.12 at -42°C/4°C	O'Neil et al. 2006
Solubility in water	377 mL/100 mL at 4°C	O'Neil et al. 2006
Vapor density (air = 1)	2.80	Yaws 2001
Vapor pressure	9,120 mm Hg (12 atm) at 30.8°C	ATSDR 2003; O'Neil et al. 2006
Conversion factors	1 ppm = 3.3 mg/m^3 1 mg/m^3 = 0.3 ppm	NIOSH 2011

2.2. Nonlethal Toxicity

Odor thresholds for hydrogen selenide are reported to range from 0.0005 to 3.6 ppm, with irritation reported at 1.8 ppm; the odor was described as decayed horseradish (Ruth 1986). AIHA (1989) lists the odor threshold as 0.3 ppm. Olfactory fatigue occurs quickly at this concentration (Dudley and Miller 1941).

2.2.1. Case Reports

Dudley and Miller (1941) reported that workers exposed to concentrations of hydrogen selenide greater than 1.5 ppm experienced nasal and throat irritation that was so severe that they could not remain at work. Workers were able to tolerate 0.3 ppm for several minutes without noticeable effects. However, these observations were reported in the discussion section of the paper without a citation or information on any associated sampling or analysis.

Twenty-five workers engaged in various metal etching, buffering, and polishing operations were exposed to hydrogen selenide in a large workroom (Buchan 1947). A reaction of selenious acid in the ink with metal was identified as the source of the hydrogen selenide. The breath of all of the exposed workers had a distinct garlic odor, but five had recently eaten food containing garlic. Only five complained of symptoms, including nausea, vomiting, metallic taste in the mouth, dizziness, extreme lassitude, and fatigue. No correlation was found between symptoms and urinary concentrations of selenium. Air samples were taken at six sites in the room; although a visible precipitate was observed on the filter paper, the measured concentration of hydrogen selenide did not exceed the detection limit of 0.2 ppm for the titrometric method. Additional details of the analytic methods were not described. However, the possibility that the highest concentrations were reached close to the breathing zone of the workers was noted by the authors. A review chapter describing this study (Glover et al. 1979) reported that "Five cases of subacute industrial selenosis were reported as due to exposure to less than 0.07 mg/m^3 of H_2Se"; however, that concentration appears to be an erroneous conversion from the detection limit of 0.2 ppm (the correct conversion would be 0.7 mg/m^3).

Other early reports of symptoms in workers exposed to hydrogen selenide have been summarized by Glover (1970) and IPCS (1987). Initial effects are of respiratory irritation and include tearing, running nose, coughing, sneezing, and tightness of the chest. A latent period of several hours may follow, after which pulmonary edema occurs. Affected workers all had complete recovery, but no exposure concentrations were measured. A chemist exposed to a "high concentration" of hydrogen selenide developed hyperglycemia that was controllable by increasing doses of insulin (Rosenfeld and Beath 1964; Malczewska-Toth 2012).

Banerjee et al. (1997) described effects in 31 workers exposed to "toxic fumes" produced during refining or recovery of scrap metal. The initial clinical presentation included intense cough, suffocation, burning, severe water discharge from eyes, cyanosis, tachypnea, tachycardia, and severe bronchospasm. Most workers recovered within 7 days; however, four with respiratory diseases associated with heavy smoking (one with acute respiratory distress syndrome, one with bilateral emphysema, two with chronic obstructive pulmonary disease) were treated for more than 3 weeks. Blood selenium concentrations did not correlate with symptoms; only four samples had selenium concentrations in the range of 71-189 µg/L on the first day. Selenium was confirmed in soil and wall-scratch samples from the incident site but no exposures could be determined.

Workers were exposed to selenium fume while smelting scrap aluminum contaminated with metallic selenium (Clinton 1947). A reddish cloud was released into the plant when the contents of a furnace were stirred in preparation for pouring; no concentrations were measured and the author estimated that no worker was exposed for more than 2 min. All exposed workers had intense irritation of the eyes, nose, and throat and headache developed several hours later. In addition, one worker with potentially higher exposure developed severe dyspnea 8-12 h after the accident. All workers appeared completely well in 3 days.

A 24-year old male was accidentally exposed to hydrogen selenide while transferring the gas from one cylinder to another (Schecter et al. 1980). Immediate symptoms included burning of the eyes and throat and was followed by coughing and wheezing. He was hospitalized 18 h later due to recurrent cough and dyspnea. Chest X-ray revealed pneumomediastinum and subcutaneous emphysema. Results of most pulmonary function tests returned to predicted levels within 30 days of the accident. However, abnormalities in flows at 50% and 25% of vital capacity persisted for up to 3 years.

A female college student was exposed to hydrogen selenide gas at least once a week for one year while working in a research laboratory (Alderman and Bergin 1986). She complained of chronic diarrhea and abdominal pain, had conjunctivitis and nasal stuffiness, and six dental caries had recently developed. She also had granular conjunctivitis, breath with a distinct garlic-like odor, and prominent transverse ridges of the fingernails. Chronic selenosis was diagnosed, which resolved after exposure ended. No exposure measurements were made in the research laboratory.

Another report described exposure of a researcher once a week for 2 years to selenium vapors produced by evaporation of pure selenium in an evacuated container (Ducloux et al. 1976). Symptoms included eczema of the face, weakness, and bronchitis. No other details were given.

2.2.2. Epidemiologic Studies

No epidemiologic studies of exposure to hydrogen selenide were found.

2.3. Neurotoxicity

No information regarding the neurotoxicity of hydrogen selenide in humans was found.

2.4. Developmental and Reproductive Toxicity

No information regarding the developmental or reproductive toxicity of hydrogen selenide in humans was found.

2.5. Genotoxicity

No information regarding the genotoxicity of hydrogen selenide in humans was found.

2.6. Carcinogenicity

No information regarding the carcinogenicity of hydrogen selenide in humans was found. A study of smelter workers found that those who died of lung cancer had lower selenium concentrations than either controls or workers who died of other causes (Gerhardsson et al. 1986). EPA (1993) has judged that selenium and selenium compounds are not classifiable as to their carcinogenicity in humans because of inadequate human data and inadequate evidence of carcinogenicity in animals. However, the agency found the evidence on selenium sulfide to be sufficient for classifying it as a probable human carcinogen classification.

2.7. Summary

Hydrogen selenide is highly irritating to the respiratory tract with effects progressing to pulmonary edema, bronchitis, and bronchial pneumonia (Glover 1970; Malczewska-Toth 2012). Irritation occurs at or below the odor threshold (Ruth 1986).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Guinea Pigs

Dudley and Miller (1937, 1941) performed a series of experiments in which groups of 16 or 32 guinea pigs (sex and strain not specified) were exposed whole body to various concentrations of hydrogen selenide (0.001- 0.57 mg/L or 0.3-171 ppm) for 10, 30, 60, 120, 240, or 480 min and were monitored for 30 days. Chamber atmospheres were calibrated prior to exposures and analytic concentrations were measured by weighing precipitated selenium from air samples. Clinical signs of toxicity from exposure at concentrations of 0.021 mg/L (6.3 ppm) or higher included pawing at the nose and eyes, copious mucus from the nasal passages, and difficulty breathing. At concentrations less than 0.021 mg/L (6.3 ppm) for up to 8 h, nasal discharge was less marked and severe ocular and nasal irritation were not observed; difficulty breathing was not observed until 24 h after exposure. Decomposition of the chemical by the mucus in the nasal passages resulted in a deposit of red, amorphous selenium on the nose and head of the animals. Marked weight loss was apparent with recovery in sur-

vivors beginning 8 days after exposure. Animals that died within 48 h exhibited respiratory and circulatory failure whereas those that died after 5 days or later had few acute respiratory symptoms but exhibited bronchial pneumonia for extended periods. More importantly, even for concentrations greater than the LC_{50}, the majority of deaths occurred more than 5 days after exposure; the peak occurred at 8-10 days, which likely corresponded to evidence of hepatic damage (see discussion of histopathologic findings below).

The investigators did not report LC_{50} values; however, on the basis of the lethality data from the study, LC_{50} values were calculated to be 0.34, 0.020, 0.012, 0.012, 0.012, and 0.0054 mg/ L (102, 6.0, 3.6, 3.6, 3.6, and 1.6 ppm) for 10, 30, 60, 120, 240, and 480 min, respectively. A few animals (1-3) died in each of the control groups, so the reliability of these data and the calculated LC_{50} values is uncertain. Regardless, a marked increase in deaths (resulting in more than 35% lethality) was consistently seen at 3.3-3.6 ppm for durations of 30-240 min.

Histopathologic examinations were performed on the animals used in the lethality studies (Dudley and Miller 1937, 1941), but severity scores were not determined. The main finding was fatty deposition in the liver and, to a lesser extent, in the kidney. Splenic enlargement due to hyperplasia of the lymphoid tissue was also found. Hepatic lesions, but no increase in mortality, were observed at concentrations as low as 1.3 ppm for 30-60 min. Fatty changes became progressively more severe for up to 10 days and generally resolved by 17-20 days after exposure. Slight to moderate thickening of the alveolar wall was found in the lung of almost all animals and acute pneumonia that progressed to bronchopneumonia occurred in about half of the animals. Most importantly, the severity of the pathologic lesions was more closely related to the amount of time between exposure and death than to the concentration or duration of exposure.

3.1.2. Rats

Two lethality studies were conducted in Wistar rats exposed nose-only to various concentrations of hydrogen selenide for different durations followed by a 14-day observation period (Zwart and Arts 1989; Zwart et al. 1992). The mortality results are summarized in Table 5-3. Test atmospheres were measured by atomic absorption spectrometry. In the first experiment (Study A or $C \times t$ study), groups of one male and one female rat were exposed at concentrations of 0.13-2.9 g/m^3 (39-870 ppm) for durations of 4-120 min. At 0.39 g/m^3 (117 ppm), no deaths occurred following exposures for 4 and 15 min, but one animal died during the observation period following exposure for 7.5 min; thus, 117 ppm for 15 min or less may be a threshold for death. Nearly all animals exposed to hydrogen selenide at 78 ppm or greater for 30 min or more died. At a concentration of 39 ppm, no animals died following exposure for up to 60 min, but one of two died following exposure for 84 or 120 min. Most deaths occurred within 2 days

after exposure. Concentration-related clinical signs included piloerection, red discoloration of the fur, cyanosis, half-closed eyes, red nasal discharge, mouth breathing, moist or dry rales, and apnea. For animals exposed at 39 ppm, "breathing problems" recurred during week 2 of the observation period. Surviving animals had body weight loss or reduced weight gain throughout the observation period. Necropsy revealed gas in the stomach or intestines of animals that died during the study and red discolored, atelectatic, edematous, or spongy, swollen, and/or spotted lungs with irregular surface in almost all decedents and survivors. The authors reported a 1-h LC_{50} of 0.18 g/m^3 (54 ppm).

In the second experiment (Study B or 1-h LC_{50} study), groups of five male and five female Wistar rats were exposed nose-only to hydrogen selenide at 0.155, 0.235, or 0.245 g/m^3 (47, 71, or 74 ppm) for 1 h. Clinical signs, effects on body weight, and gross findings were similar to those described above for the first experiment. At 0.155 g/m^3 (47 ppm), four males and two females had body weight loss throughout the 14-day observation period. A 1-h LC_{50} of 0.24 g/m^3 (72 ppm) was calculated (Zwart and Arts 1989; Zwart et al. 1992). Examination of the data used to calculate the 1-h LC_{50} shows a steep concentration-response curve (see Table 5-3).

On the basis of marked body weight loss among survivors (which suggested the animals were moribund) during the observation periods of both experiments, the investigators postulated that the LC_{50} estimates would have been lower if the observation periods had been longer. However, extending the observation period was not considered ethical due to the condition of the animals. Zwart and Arts (1989) suggested that animals that lost weight during days 8-14 of the observation period could be considered "dead", and estimated that this approach would yield a 1-h LC_{50} of 0.06-0.07 g/m^3 (18-21 ppm).

TABLE 5-3 Lethality in Rats Exposed to Hydrogen Selenide

Concentration	4-20 min	30 min	60 min	120 min
Study A (C × t study)				
0.13 g/m^3 (39 ppm)	NR	0/2	0/2	1/2
0.26 g/m^3 (78 ppm)	NR	2/2	2/2	2/2
0.39 g/m^3 (117 ppm)	1/6	2/2	2/2	NR
1.41 g/m^3 (423 ppm)	10/10	NR	NR	NR
2.90 g/m^3 (870 ppm)	8/8	2/2	NR	NR
Study B (1-h LC_{50} study)				
155 g/m^3 (47 ppm)	NR	NR	0/10	NR
235 g/m^3 (71 ppm)	NR	NR	2/10	NR
245 g/m^3 (74 ppm)	NR	NR	6/10	NR

Abbreviations: LC_{50}, lethal concentration, 50% lethality; NR, not reported.
Source: Zwart and Arts 1989; Zwart et al. 1992.

3.2. Nonlethal Toxicity

Groups of five young, female albino rats were exposed to selenium fumes produced by passing a current through tungsten wire wound in a cone and filled with chips of selenium (Hall et al. 1951). The exposure concentration, particle size, and chemical form were not specified. Exposures were for 2-16 min and animals were killed 1-16 days following exposure. At necropsy, lung weights were increased and hemorrhage with scattered emphysematous and atelectatic areas were observed. Little evidence of repair was apparent up to 16 days after exposure.

3.3. Neurotoxicity

No evidence of a narcotic or anesthetic effect was seen in guinea pigs exposed to lethal concentrations of hydrogen selenide for up to 8 h (Dudley and Miller 1937, 1941).

3.4. Developmental and Reproductive Toxicity

No information on the developmental or reproductive toxicity of hydrogen selenide in animals was found. Selenium or selenium compounds have produced defects in the chick when applied to the air cell, and decreased live births and pup size in mice when administered orally or by injection; no adverse effects have been found in hamsters or monkeys (Shepard 2010).

3.5. Genotoxicity

No information on the genotoxicity of hydrogen selenide was found. Sodium selenite and sodium selenide, which are metabolized to hydrogen selenide, induced DNA single-strand breaks and growth inhibition in a mouse mammary carcinoma cell line (Lu et al. 1995). Hydrogen selenide was not measured in the culture medium.

3.6. Chronic Toxicity and Carcinogenicity

No information on the chronic toxicity or carcinogenicity of hydrogen selenide in laboratory animals was found. In studies of selenium sulfide and Selsun (2.5% selenium sulfide), no evidence of carcinogenicity was found following dermal application of either compound to the skin of male and female ICR mice three times per week for 86-88 weeks (NTP 1980 a,b). However, these studies were considered inadequate because of their short duration due to the limited lifetime of the test stain of mice.

3.7. Summary

Lethality studies in guinea pigs and rats show a steep concentration-response relationship for hydrogen selenide. Clinical signs in both species were indicative of severe irritation and pulmonary lesions were observed at necropsy. Exposures at high concentrations for a short duration resulted in death from pulmonary edema. In contrast, deaths in studies with longer durations occurred over a relatively flat concentration range and were most likely secondary to hepatic damage. Effects in the liver were identified in guinea pigs but these lesions resolved in surviving animals. Livers from rats were not examined microscopically.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information on the metabolism and disposition of hydrogen selenide was found. However, the absorption, distribution, metabolism, and excretion of selenium have been reviewed elsewhere (Sunde 1990; ATSDR 2003); salient information is briefly reviewed in this section. In the dog, inhaled selenious acid aerosol was rapidly and almost completely absorbed whereas the metal aerosol was less rapidly absorbed. Selenium from both aerosols was distributed similarly to the liver, kidney, spleen, and heart and had a biologic half-life of 30-40 days; the main route of excretion was via the urine (Weissman et al. 1983). Results from inhalation studies of selenious acid or selenium aerosols in the rat confirm that, once absorbed, selenium from both compounds is distributed and excreted in an identical manner (Medinsky et al. 1981).

In blood, selenium is rapidly taken up by erythrocytes and metabolized to a form that binds to plasma proteins (Lee et al. 1969; Gasiewicz and Smith 1978). The uptake and release was shown to be dependent on glutathione and resulted in depletion of erythrocyte glutathione (Gasiewicz and Smith 1978). When some other forms of selenium are metabolized, hydrogen selenide may be formed as an intermediate through reduction of a selenopersulfide by glutathione reductase (Gasiewicz and Smith 1978). A brief review of selenium metabolic pathways indicates the intermediate formation of hydrogen selenide from inorganic forms of selenium (Lu et al. 1995). Hydrogen selenide formed in this manner may either be incorporated into cellular selenoproteins or further metabolized by methylation before elimination. Methylation of selenium results in the formation of dimethyl selenide, the compound found in exhaled air that is likely responsible for the garlic-breath odor commonly reported in exposed persons (ATSDR 2003). Selenium is excreted in the urine, feces, and expired air (ATSDR 2003).

4.2. Mechanism of Toxicity

The mechanism of toxicity (including pulmonary edema and marked body weight loss) following acute exposure to hydrogen selenide is unknown.

The mechanism of toxicity of selenium and selenium compounds is likely to vary depending on the individual compound (IPCS 1987; ATSDR 2003). One possible mechanism for selenium toxicity is via alteration of enzyme activities, such as inactivation of sulfhydryl enzymes or the succinic dehydrogenase system, interference with glutathione metabolism, or substitution for sulfur in biomolecules (IPCS 1987; ATSDR 2003). Whether these effects may contribute to the toxic effects of hydrogen selenide is unknown.

Examination of the lethality data in guinea pigs (Dudley and Miller 1937, 1941) and rats (Zwart and Arts 1989; Zwart et al. 1992) suggests that hydrogen selenide may exert effects via at least two distinct mechanisms of toxicity. For guinea pigs, it appears that exposures at high concentrations for a short duration result in death due to pulmonary edema as a result of severe irritation. Clinical signs of irritation were observed in the animals. This part of the concentration-response curve is very steep. In contrast, deaths in studies with longer durations occurred over a relatively flat concentration range and were most likely secondary to liver damage. As noted earlier in Section 3.1.1, most deaths occurred more than 5 days after exposure when hepatic damage was greatest. Glutathione depletion by high concentrations of selenium may play a contributing role in the observed hepatic damage.

In Figure 5-1, LC_{50} values for guinea pigs with respect to exposure duration are compared with data on partial lethality in rats (only a 1-h LC_{50} was available for rats). The observation that deaths occur at a threshold concentration at longer durations is also suggested to some degree by data from rats (Zwart and Arts 1989; Zwart et al. 1992); however, the small number of rats (2/concentration) exposed for durations other than 60 min limit the confidence in lethality data for other time points.

4.3. Structure Activity Relationships

Toxicities of the various selenium compounds vary widely depending on the individual compound; hydrogen selenide is one of the most toxic due to its irritant properties (ATSDR 2003).

4.4. Other Relevant Information

4.4.1. Species Variability

Data on hydrogen selenide were available for only two species. Estimated 1-h LC_{50} values for the guinea pig and rat were 3.6 and 72 ppm, respectively. Although these two values suggest significant species differences, other differ-

ences (including whole-body vs. nose-only exposure, different analytic techniques, and differences in the post-exposure observation duration) between the studies make it difficult to draw direct comparisons between the LC_{50}s. Furthermore, in the guinea pig studies, one to three control animals died, raising additional questions as to the reliability of the data. The guinea pig study, which was conducted more than 70 years ago, involved whole body exposures (Dudley and Miller 1937, 1941) that could have resulted in oral exposure to elemental selenium from grooming, as well as percutaneous absorption. The higher total dose from all routes of exposure could have contributed to the hepatic lesions and delayed deaths in guinea pigs. In the more recent rat study, the animals were exposed nose-only (Zwart and Arts 1989; Zwart et al. 1992), eliminating potential exposure by other routes. In addition, the guinea pig study measured concentrations of hydrogen selenide by weighing precipitated selenium, whereas the rat study used atomic absorption spectrometry. Direct measurement of the test atmospheres is probably a more accurate method of determining exposure concentrations. Finally, the guinea pigs were observed for up to 30 days, whereas the rats were observed for only 14 days. All but a few of the guinea pig deaths occurred within the first 15 days in the 1-h study, indicating that the increased observation period probably had limited impact on the value of the LC_{50}; however, a longer observation period in the rat study might also have lead to a slightly lower LC_{50} value. In summary, while the available data suggest that the guinea pig may be more sensitive to hydrogen selenide, conclusions are difficult to draw because of the differences in the exposures, analytic techniques, and observation periods used in the two studies.

4.4.2. Susceptible Populations

In the experiments with guinea pigs (Dudley and Miller 1937, 1941), no significant differences in death rates were found between young animals (body weights 189-283 g) and older animals (body weights 451-701 g) or between males and females exposed to hydrogen selenide.

Epidemiologic studies of populations living in areas with high dietary intakes of selenium suggest that children are less susceptible to selenium intoxication than adults, as 97% of selenosis cases are in individuals more than 18 years of age (ATSDR 2003).

4.4.3. Concentration-Exposure Duration Relationship

As discussed in Section 4.2 and shown in Figure 2-1, lethality data from studies of guinea pigs and the rats suggest two possible mechanisms of action: one that is operant at high concentrations with brief exposures and one that is operant at lower concentrations with longer exposures. Although limited, the data indicate that the first mechanism exhibits a steep concentration-time relationship with a strong time component, whereas the mechanism at lower concen-

trations and longer durations appears to be primarily dependent on concentration. These concentration-time relationships may be explained by the postulated mechanisms of toxicity; exposure at high concentrations results in severe irritation and causes death by pulmonary edema, whereas the liver can compensate for exposure at lower concentrations and of a long duration, and only when a threshold concentration is exceeded are mortalities seen.

The observed concentration-exposure duration relationships pose a challenge in identifying a suitable approach for time scaling AEGL values. AEGL values are scaled to the various durations from experimentally derived values using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and the value of n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Zwart and Arts (1989) derived a value for n (b_1/b_2) of 1.98 from probit analysis of lethality data (Study A, which examined the time and concentration [C × t] relationship for hydrogen selenide) in rats using both concentration and time as variables.

An argument could be made for making separate estimates of n for the two distinct concentration-duration relationships suggested by the guinea pig and rat data; however, many of the data points for shorter exposure durations were associated with 100% mortality, and the numbers of animals (n = 2) in the groups were too small to provide a reliable estimate of n. An alternative to the n value estimated by Zwart and Arts (1989) can be calculated by probit analysis of the combined lethality data from Study A and Study B (1-h LC_{50}study, which used 10 rats/concentration). The value of n is 2.5 on the basis of the combined data. This estimate makes use of the more robust lethality data from Study B, in addition to the data on the concentration-time relationship from Study A. Although this estimate for n might yield lower concentrations than the data might suggest when extrapolating from longer to shorter durations, such extrapolations will be conservative. Furthermore, the empirical value of 2.5 is close to the default value of 3 that is used to extrapolate from longer to shorter durations in the absence of data to estimate an empirical value of n.

4.4.4. Concurrent Exposure Issues

Total body burden of selenium would potentially be of concern only for chronic hydrogen selenide exposures. No other concurrent exposure issues for acute exposures were identified.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data for calculating AEGL-1 values for hydrogen selenide were available. Dudley and Miller (1941) reported anecdotally that workers were able to tolerate a concentration of 0.3 ppm for several minutes without noticeable effects. According to the authors, olfactory fatigue occurred quickly at this con-

centration. However, the report did not provide a citation for this observation, nor any information on sampling or analysis of workplaces to support the statement.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data for calculating AEGL-1 values for hydrogen selenide were available.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended for hydrogen selenide. No human or animal data on appropriate end points were available. Data for calculating the level of distinct odor awareness for hydrogen selenide were insufficient because the reported odor threshold of 0.3 ppm was based on an anecdotal report.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data for calculating AEGL-2 values for hydrogen selenide were available. Dudley and Miller (1941) reported that workers exposed at concentrations greater than 1.5 ppm experienced nasal and throat irritation severe enough that they could not remain at work. The duration of exposure was not reported, so it was assumed that effects were immediate. However, as noted earlier, the statements by Dudley and Miller (1941) were not supported by a citation or any information on sampling or analysis of workplaces.

6.2. Summary of Animal Data Relevant to AEGL-2

In lethality studies of hydrogen selenide, histopathologic examinations were performed on guinea pigs (Dudley and Miller 1937, 1941), but severity scores were not specified. The main finding was fatty deposition in the liver and, to a lesser extent, in the kidney; splenic enlargement due to hyperplasia of the lymphoid tissue was also found. Hepatic lesions, but no increase in mortality, were observed at concentrations as low as 1.3 ppm for 30-60 min. Fatty changes became progressively more severe for up to 10 days and generally resolved with 17-20 days after exposure.

6.3. Derivation of AEGL-2 Values

Data for calculating AEGL-2 values were not available. Hepatic lesions in the guinea pig resolved if the exposure was not lethal. According to the AEGL

standing operating procedures (NRC 2001), in the absence of specific data for determining an AEGL-2 value, one-third of the AEGL-3 values can be used to establish AEGL-2 values. This approach is justified because the lethality data indicate a steep concentration-response curve, as discussed in Section 4.4.3. AEGL-2 values for hydrogen selenide are presented in Table 5-4.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No reports of human lethality following exposure to hydrogen selenide were found.

7.2. Summary of Animal Data Relevant to AEGL-3

Data relevant to determining AEGL-3 values for hydrogen selenide include those from guinea pig (Dudley and Miller 1937, 1941) and rat (Zwart and Arts 1989; Zwart et al. 1992) lethality studies. As described in Section 4.4.1, the guinea pig lethality data (Dudley and Miller 1937, 1941) had a number of uncertainties because the exposures were whole-body instead of nose-only (leading to potential oral and dermal exposure in addition to inhalation), less precise analytic methods to estimate exposure concentrations, and unexplained mortalities in the controls. Consequently, the rat lethality studies were selected for deriving AEGL-3 values.

In the rat studies of 60-min exposures, no animals died at 47 ppm, but 2/10 died at 71 ppm and 6/10 died at 74 ppm. Most deaths occurred within 2 days after exposure. Concentration-related clinical signs included piloerection, red discoloration of the fur, cyanosis, half-closed eyes, red nasal discharge, mouth breathing, moist or dry rales, and apnea. Most surviving animals had body weight loss throughout the observation period. Necropsy revealed gas in the stomach and intestines of premature decedents and red discolored, atelectatic, edematous, or spongy, swollen, and spotted lungs with irregular surface in almost all decedents and survivors.

7.3. Derivation of AEGL-3 Values

To derive AEGL-3 values for hydrogen selenide, two options were considered for identifying a point of departure and time-scaling value. For time scaling, the equation $C^n \times t = k$ was used, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). For the first option, the point of departure was an LC_{01} of 66 ppm (calculated by log-probit analysis) and n was 2.0, on the basis of data from the 1-h LC_{50} experiment (Zwart and Arts 1989). However, calculation of AEGL

TABLE 5-4 AEGL-2 Values for Hydrogen Selenide

10 min	30 min	1 h	4 h	8 h
0.22 ppm (0.73 mg/m^3)	0.15 ppm (0.48 mg/m^3)	0.11 ppm (0.37 mg/m^3)	0.064 ppm (0.21 mg/m^3)	0.048 ppm (0.16 mg/m^3)

values on the basis of those estimates results in a predicted LC_{01} of 47 ppm at 120 min, which is inconsistent with data that show that a lower concentration of 39 ppm resulted in 1/2 deaths after 120 min of exposure (Zwarts and Art 1989). Thus, it appears that this approach would not be adequately protective.

The second option involved combining data from two experiments to estimate the point of departure and the value of n. The two experiments were a C × t study (Zwarts et al. 1992) and 1-h LC_{50} study (Zwarts and Arts 1989). From the combined data, an LC_{01} of 33 ppm and an n of 2.5 are estimated. This approach yields a 120-min LC_{01} of 25 ppm, which is below the observed lethal concentration of 40 ppm. The combined data were analyzed in total (28 observations) and after excluding data at 1,410 mg/m^3 and higher; mortality was 100% (2/2) at those concentrations, so the data provided little value to the analysis. Both analyses yielded the same 1-h LC_{01} and n value. A total uncertainty factor of 100 was applied. A factor of 10 for interspecies differences was used because data were available only on two species and the limited data indicate that the rat may not be the most sensitive (see Section 4.4.1). A value of 10 for intraspecies variability was applied because of uncertainty with respect to the mechanism of action for the marked body weight loss exhibited by some surviving rats in the second week of observation, and uncertainty as to whether this body weight loss reflected a moribund state. AEGL-3 values for hydrogen selenide are presented in Table 5-5.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for hydrogen selenide are summarized in Table 5-6. AEGL-1 values are not recommended because symptoms in workers have been reported at concentrations at or below the odor threshold and because values based on irritation may not account for the delayed onset of pulmonary edema. Data on hydrogen selenide were inadequate for calculating AEGL-2 values, so estimates were made taking one-third of the AEGL-3 values. For AEGL-3 values, a 1-h LC_{01} calculated from mortality data in rats was used to derive values.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to hydrogen selenide are presented in Table 5-7. The concentration that is immediately dangerous to life and health (IDLH) is 1 ppm (NIOSH 1994), which is

higher than the 30-min AEGL-3 value of 0.44 ppm. The supporting documentation of the IDLH value indicates that it is based on acute inhalation data in humans, and cites Dudley and Miller (1941) and Glover et al. (1979) but does not provide details of the derivation.

TABLE 5-5 AEGL-3 Values for Hydrogen Selenide

10 min	30 min	1 h	4 h	8 h
0.67 ppm (2.2 mg/m^3)	0.44 ppm (1.5 mg/m^3)	0.33 ppm (1.1 mg/m^3)	0.19 ppm (0.63 mg/m^3)	0.14 ppm (0.48 mg/m^3)

TABLE 5-6 AEGL Values for Hydrogen Selenide

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)	0.22 ppm (0.73 mg/m^3)	0.15 ppm (0.48 mg/m^3)	0.11 ppm (0.37 mg/m^3)	0.064 ppm (0.21 mg/m^3)	0.048 ppm (0.16 mg/m^3)
AEGL-3 (lethal)	0.67 ppm (2.2 mg/m^3)	0.44 ppm (1.5 mg/m^3)	0.33 ppm (1.1 mg/m^3)	0.19 ppm (0.63 mg/m^3)	0.14 ppm (0.48 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.

TABLE 5-7 Standards and Guidelines for Hydrogen Selenide

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.22 ppm	0.15 ppm	0.11 ppm	0.064ppm	0.048 ppm
AEGL-3	0.67 ppm	0.44 ppm	0.33 ppm	0.19 ppm	0.14 ppm
ERPG-1 (AIHA)[a]			Not appropriate		
ERPG-2 (AIHA)			0.2 ppm		
ERPG-3 (AIHA)			2.0 ppm		
IDLH (NIOSH)[b]		1 ppm as Se			
TLV-TWA (ACGIH)[c]					0.05 ppm as Se
REL-TWA (NIOSH)[d]					0.05 ppm as Se
PEL-TWA (OSHA)[e]					0.05 ppm as Se
MAK (Germany)[f]					0.006 ppm
MAC (The Netherlands)[g]					0.025 ppm

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 2002, 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.

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 protection action.
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.
[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.
[c]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 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 2011) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[e]PEL-TWA (permissible exposure limit - time weighted average, Occupational Safety and Health Administration) (29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH TLV-TWA.
[f]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2012) is defined analogous to the ACGIH TLV-TWA.
[g]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration]) Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004), is defined analogous to the ACGIH TLV-TWA.

The emergency response planning guidelines (ERPGs) for hydrogen selenide are slightly higher than the corresponding AEGL values. AIHA (2002, 2013) derived an ERPG-3 of 2 ppm, noting that this value is higher than a concentration associated with acute intoxication of five workers (citing Buchan 1947) but well below the 1-h LC_{50} values of 51-72 ppm in rats (based on Zwart and Arts 1989 and Zwart et al. 1992). The ERPG-2 of 0.2 ppm was based on the statements by Dudley and Miller (1941) that 0.3 ppm was tolerated by healthy workers without irritation for several minutes and that 1.5 ppm was irritating to the eye and nose. An ERPG-1 was not set because the ERPG-2 was below the odor threshold of 0.3 ppm (AIHA 2002, 2013).

The current occupational exposure limit reported by the American Conference of Governmental Industrial Hygienists (ACGIH), the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health, and German Research Association is 0.05 ppm (as selenium) whereas the value reported by The Netherlands is 0.025 ppm (RTECS 2009). Documentation for the ACGIH threshold limit value indicates only that the value was set to "minimize the potential for irritation, gastrointestinal effects, and the onset of chronic hydrogen selenide-related disease" (ACGIH 2001). The

OSHA standard for hydrogen selenide was derived in 1978, but the supporting documentation (29 CFR 1910.1000 [2006]) does not describe how the value was derived.

In addition to the guidelines presented in Table 5-7, the state of California has adopted 0.002 ppm (0.005 mg/m^3) as the acute reference exposure level for hydrogen selenide (CalEPA 2007). This concentration is based on data from studies in guinea pigs by Dudley and Miller (1937, 1941).

8.3. Data Adequacy and Research Needs

Little human or animal data on hydrogen selenide are available. Although symptoms in humans were well described, case reports did not include reliable exposure concentrations. Two well-conducted animal lethality studies were available, but the study in guinea pigs suffered from a variety of limitations, including potential exposure via multiple routes, use of a more uncertain analytic technique to estimate exposure concentrations, and unexplained control mortalities (see Section 4.4.1). Thus, it is difficult to draw conclusions regarding species differences (if any).

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APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values

AEGL-1 values for hydrogen selenide are not recommended. No animal or human data on appropriate end points were found. A level of distinct odor awareness could not be calculated because the reported odor threshold of 0.3 ppm was not documented. In addition, AEGL-1 values based on irritation may not account for delayed onset of pulmonary edema.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values and because hydrogen selenide has a steep concentration-response relationship, AEGL-3 values were divided by 3 to estimate AEGL-2 values (NRC 2001).

Calculations:

10-min AEGL-2:	0.67 ppm ÷ 3 = 0.22 ppm
30-min AEGL-2:	0.44 ppm ÷ 3 = 0.15 ppm
1-h AEGL-2:	0.33 ppm ÷ 3 = 0.11 ppm
4-h AEGL-2:	0.19 ppm ÷ 3 = 0.064 ppm
8-h AEGL-2:	0.14 ppm ÷ 3 = 0.048 ppm

Derivation of AEGL-3

Key studies:	Zwart, A., and J.H.E. Arts. 1989. Acute (1-hour) Inhalation Toxicity Study with Hydrogen Selenide in rats. Report No. V 89.463. Zeist, The Netherlands: TNO-CIVO Institutes. Zwart, A., J.H.E. Arts, W.J. ten Berge, and L.M. Appleman. 1992. Alternative acute inhalation toxicity testing by determination of the concentration-time-mortality relationship: Experimental comparison with standard LC_{50} testing. Regul. Toxicol. Pharmacol. 15(3):278-290.
Toxicity end point:	1-h LC_{01} of 33 ppm, calculated by log-probit analysis of the combined lethality data from the two experiments in rats (1-h LC_{50} study and C × t study).

Time scaling:	$C^n \times t = k$ (n = 2.5, based on probit analysis of the combined lethality data)
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability
Modifying factor:	None
Calculations:	
10-min AEGL-3:	$C^{2.5} \times 0.167$ h = 6,255.829 ppm-h C = (6,255.829 ppm-h ÷ 0.167 h)$^{1/2.5}$ = 67.04 ppm 67.04 ÷ 100 = 0.67
30-min AEGL-3:	$C^{2.5} \times 0.5$ h = 6,255.829 ppm-h C = (6,255.829 ppm-h ÷ 0.5 h)$^{1/2.5}$ = 43.54 ppm 43.54 ÷ 100 = 0.44
1-h AEGL-3:	C = 33 ppm 33 ÷ 100 = 0.33 ppm
4-h AEGL-3:	$C^{2.5} \times 4$ h = 6,255.829 ppm-h C = (6,255.829 ppm-h ÷ 4 h)$^{1/2.5}$ = 18.95 18.95 ÷ 100 = 0.19 ppm
8-h AEGL-3:	$C^{2.5} \times 8$ h = 6,255.829 ppm-h C = (6,255.829 ppm-h ÷ 8 h)$^{1/2.5}$ = 14.36 ppm 14.36 ÷ 100 = 0.14

APPENDIX B

DERIVATION SUMMARY FOR HYDROGEN SELENIDE

AEGL-1 VALUES

AEGL-1 values for hydrogen selenide are not recommended because of insufficient data. No animal or human data on appropriate end points were found. A level of distinct odor awareness could not be calculated because the reported odor threshold of 0.3 ppm was not documented. In addition, AEGL-1 values may not account for pulmonary edema, which may occur from exposures resulting in irritation after a latency period.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.22 ppm	0.15 ppm	0.11ppm	0.064 ppm	0.048 ppm

Data adequacy: No data with appropriate end points for deriving AEGL-2 values were available. Therefore, one-third of the AEGL-3 values were used to estimate AEGL-2 values (NRC 2001).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.67 ppm	0.44 ppm	0.33 ppm	0.19 ppm	0.14 ppm

Key references:
Zwart, A., and J.H.E. Arts. 1989. Acute (1-h) Inhalation Toxicity Study with Hydrogen Selenide in Rats. Report No. V 89.463. Zeist, The Netherlands: TNO-CIVO Institutes.
Zwart, A., J.H.E. Arts, W.J. ten Berge, and L.M. Appleman. 1992. Alternative acute inhalation toxicity testing by determination of the concentration-time-mortality relationship: Experimental comparison with standard LC_{50} testing. Regul. Toxicol. Pharmacol. 15(3):278-290.

Test species/Strain/Number: Rat (males and females), Wistar, 2-10 per group

Exposure route/Concentrations/Durations: Nose-only; 39-870 ppm; 4-120 min

Effects: Mortality (incidence); clinical signs of irritation occurred at all concentrations
≥ 423 ppm for ≥4 min: 2/2
117 ppm for 4 min: 0/2
117 ppm for 7.5 min: 1/2
117 ppm for 15 min: 0/2
117 ppm for 30 min: 2/2
78 ppm for 30 min: 2/2
39 ppm for 30 min: 0/2
39 ppm for 42 min: 0/2
117 ppm for 60 min: 2/2
78 ppm for 60 min: 2/2
74 ppm for 60 min: 6/10

71 ppm for 60 min: 2/10
47 ppm for 60 min: 0/10
39 ppm for 60 min: 0/2
78 ppm for 60 min: 2/2
78 ppm for 84 min: 2/2
39 ppm for 84 min: 1/2
39 ppm for 120 min: 1/2
78 ppm for 120 min: 2/2

End point/Concentration/Rationale: LC_{01} of 33 ppm, calculated by log-probit analysis of combined data from the two studies

Uncertainty factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10; data are available in only two species, and the rat is not the most sensitive species
Intraspecies: 10; although the steepness of concentration-response relationship indicates little individual variation, this factor was applied to account for the uncertainty with respect to the mechanism for and long-term implications of marked body weight loss in surviving rats

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$ where $n = 2.5$. Empirical value of n calculated from log probit analysis of rat lethality data combined from the two studies.

Data adequacy: Limited data are available for hydrogen selenide. AEGL-3 values were based on a well-conducted and documented study. Exposures were by nose-only administration, which eliminated potential confounding exposure routes.

APPENDIX C

CATEGORY PLOT FOR HYDROGEN SELENIDE

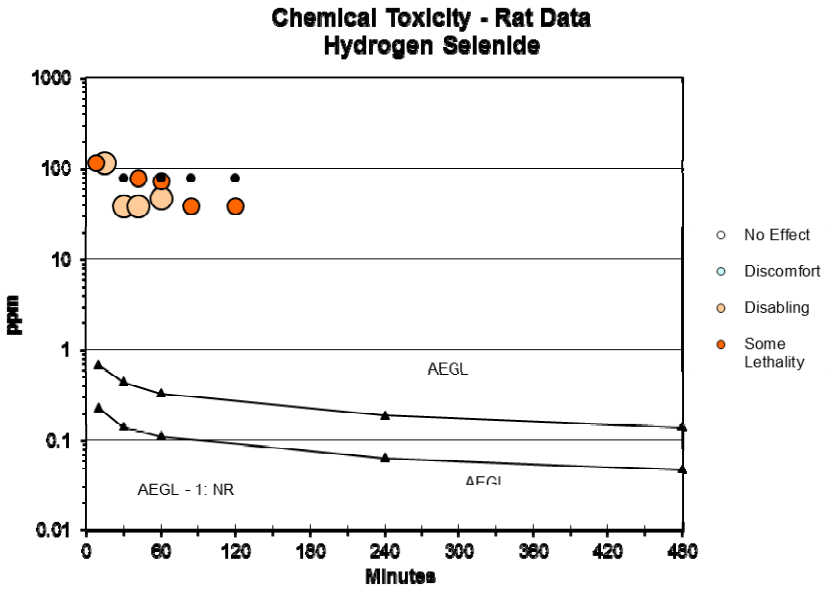

FIGURE C-1 Category plot of toxicity data and AEGL values for hydrogen selenide. Note: There are no documented human data on hydrogen selenide; anectodal information reported by Dudley and Miller (1941) is considered unreliable because no citation was provided nor did the authors indicate sampling or analysis methods to supporting their statements. Guinea pig data are not included because a large number of deaths occurred in the control groups for this study.

TABLE C-1 Data Used in Category Plot for Hydrogen Selenide

Source	Species	Sex	No. exposures	ppm	Minutes	Category	Effect
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				0.22	10	AEGL	
AEGL-2				0.14	30	AEGL	
AEGL-2				0.11	60	AEGL	
AEGL-2				0.064	240	AEGL	
AEGL-2				0.048	480	AEGL	
AEGL-3				0.67	10	AEGL	
AEGL-3				0.44	30	AEGL	
AEGL-3				0.33	60	AEGL	
AEGL-3				0.19	240	AEGL	
AEGL-3				0.14	480	AEGL	
	Rat	M/F	1	117	7.5	SL	Mortality 1/2
	Rat	M/F	1	117	15	2	Pilerection, red discoloration of fur, blue discoloration of limbs, half-closed eyes, red nasal discharge, mouth breathing, moist or dry rales, apnea, body weight loss

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. exposures	ppm	Minutes	Category	Effect
	Rat	M/F	1	39	30	2	Clinical signs as above
	Rat	M/F	1	78	30	3	Mortality 2/2
	Rat	M/F	1	39	42	2	Clinical signs as above
	Rat	M/F	1	78	42	SL	Mortality1/2
	Rat	M/F	1	47	60	2	Clinical signs as above
	Rat	M/F	1	72	60	SL	LC_{50}
	Rat	M/F	1	78	60	3	Mortality 2/2
	Rat	M/F	1	39	84	SL	Mortality 1/2
	Rat	M/F	1	78	84	3	Mortality 2/2
	Rat	M/F	1	39	120	SL	Mortality 1/2
	Rat	M/F	1	78	120	3	Mortality 2/2

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

6

Ketene[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 Peter Bos (RIVM, The Dutch National Institute of Public Health and the Environment), Lisa Ingerman (SRC, Inc.), Chemical Manager James Holler (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Ketene is a colorless gas with a sharp, penetrating odor that can be detected at a concentration of 12 ppm but not at 1 ppm. It is an unstable, readily polymerizing compound and cannot be stored in the gaseous state. Ketene reacts with water to form acetic acid, and the reaction is accelerated by the presence of alkali; it will acetylate amino groups, phenolic hydroxyl groups, and sulfhydryl groups in aqueous solution (Cameron and Neuberger 1937). It is soluble in acetone, benzene, ether, and chloroform wherein it can react with a variety of compounds, such as amines, alcohols, and acids. Ketene is used as an acetylating agent in chemical synthesis, especially in synthesis of acetic acid and acetate esters.

Human data on the acute toxicity of ketene are not available. Neurotoxicity, developmental and reproductive toxicity, genotoxicity, and carcinogenicity have not been examined in humans.

Five studies examined the toxicity of ketene in various animal species. These studies indicate that the inhalation route of exposure is of particular concern for ketene and that the chemical has similarities to phosgene in clinical effects and mode of action. Ketene is a respiratory poison that can exhibit delayed toxicity to alveolar structures (mainly capillaries) to produce death by pulmonary edema. Ketene has been shown to acetylate free amino (and other functional) groups of proteins in aqueous solution. Like phosgene, the pulmonary effects of inhalation exposure to ketene may be manifested in the absence of direct irri-

tation by ketene or its breakdown product, acetic acid. For all species tested, the toxicologic profile of ketene is similar. Ketene is lethal at high concentrations; at lower concentrations, minor irritation during exposure and central nervous system impairment have been observed. However, severe damage to the lungs (at the alveolar level) may manifest as long as 24 h after exposure. The central nervous system effects are likely due to cerebral anoxia secondary to alveolar damage. Toxicity is greatest in mice, followed by rats, guinea pigs, cats, and rabbits. Ketene appears to exhibit a steep concentration-response relationship.

Data were insufficient for deriving AEGL-1 values for ketene. No human or animal data on AEGL-1 severity effects following exposure to ketene were available. No overt signs of toxicity were observed in mice exposed at 1 ppm for 7 h in a repeated-exposure study (Treon et al. 1949). Pulmonary damage was reported at the end of the exposure period; however, whether pulmonary damage would occur following a single exposure is unknown. Because of the uncertainty of whether the lowest concentration tested (1 ppm) would result in effects which exceeded the AEGL-1 definition, derivation of AEGL-1 values is not recommended for ketene. Although ketene reportedly has a distinct, penetrating floral odor (Health Council of the Netherlands 2001), neither an odor threshold nor a level of odor awareness are available. Thus, whether odor detection and minor irritation would provide adequate warning of ketene exposure is uncertain, especially given the potential for sensitive subpopulations (asthmatics) and delayed severe pulmonary toxicity (including lethality) after ketene exposure.

Data on AEGL-2 severity effects in humans and animals were not available. As discussed in consideration of AEGL-1 values, uncertainty is associated with using the lowest test concentration of 1 ppm in the repeated-exposure study in mice (Treon et al. 1949) to derive AEGL-2 values. Therefore, AEGL-2 values for ketene were based on a 3-fold reduction of AEGL-3 values. This approach is used to estimate a threshold for irreversible effects and is considered appropriate given the apparent steep concentration-response curve for ketene (lethality in mice was 0/10 at 1 ppm for 7 h; 7/10 at 23 ppm for 30 min; and 10/10 at 50 ppm for 50 min).

AEGL-3 values are based on the mouse studies of Treon et al. (1949). A 50-min exposure to ketene at 50 ppm caused 100% mortality in mice. A 30-min exposure at 23 ppm was lethal to 7/10 mice, but a 2-h exposure at this concentration was 100% lethal. A 4.5-h exposure at 12 ppm (the next lower test concentration) did not result in deaths, but 3/7 mice died during a 5.5-h exposure at the same concentration on the subsequent day of exposure. Because the time of death during the second exposure was not reported, whether the deaths were a delayed effect of the first exposure or caused by the second exposure is uncertain. In a second repeated-exposure study (Treon et al. 1949), no deaths occurred in mice after a single 7-h exposure at 1 ppm and 1/10 mice died 3 days after the tenth exposure. The concentration of 1 ppm was considered a threshold for lethal effects caused by a single exposure to ketene and was chosen as the point of departure for calculating AEGL-3 values. A total uncertainty factor of 10 was used. Mice appeared to be the most susceptible species, so an interspecies factor

of 3 was considered adequate to account for interspecies differences. An intraspecies factor of 3 was used because the mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations and used an intraspecies uncertainty factor of 3 in the derivation of the AEGL-2 and AEGL-3 values (NRC 2002). AEGL-3 values were derived by time scaling according to the equation $C^n \times t = k$, using default values of n = 3 to extrapolate from longer to shorter durations and n = 1 to extrapolate from shorter to longer durations. The 10-min AEGL-3 value was set equal to the 30-min value because of the uncertainty associated with extrapolating a 7-h point of departure to a 10-min AEGL value.

The AEGL values for ketene are presented in Table 6-1.

1. INTRODUCTION

Ketene is a colorless gas (Hasek 1981; Taylor 1950; HSDB 2005) with a sharp, penetrating odor (Health Council of the Netherlands 2001) that can be detected at 12 ppm but not at 1 ppm (Treon et al. 1949). It is an unstable, readily polymerizing compound (Hasek 1981; HSDB 2005), and cannot be stored in the gaseous state. Ketene reacts with water to form acetic acid, and the process is accelerated by the presence of alkali (Treon et al. 1949). It is soluble in acetone, benzene, ether, and chloroform (Cameron and Neuberger 1937). When in a solution of inert solvents, ketene can react with a variety of compounds, such as amines, alcohols, and acids. Ketene reacts with water to form acetic acid and will acetylate amino groups, phenolic hydroxyl groups, and sulfhydryl groups in aqueous solution (Cameron and Neuberger 1937). Ketene polymerizes slowly at 0°C and more quickly at room temperature. Polymerization is catalyzed by pyridine, dust particles, and rubber (Cameron and Neuberger 1937).

Ketene is manufactured by pyrolysis of acetic acid at 700-800°C under reduced pressure (10-50 kPa or 0.1-0.5 atm) (Hasek1981). A phosphate ester is injected to provide an acidic catalyst. After removal of water and unconverted acetic acid, gaseous ketene is absorbed immediately in an appropriate reaction medium (e.g., acetic anhydride is prepared by passage into a mixture of acetic acid and anhydride). Very pure ketene is best obtained from pyrolysis of acetic anhydride.

In the laboratory, ketene is prepared easily in a “ketene lamp”, in which acetone vapors are passed over an electrically-heated tungsten wire at about 700°C (Cameron and Neuberger 1937; Hasek1981). The major problem with this production is contamination of ketene with large amounts of methane produced in equivalent amounts (Cameron and Neuberger 1937) and other gaseous byproducts. If the temperature is increased further, ketene decomposes into ethylene and carbon monoxide. A substantially better product is obtained by pyrolysis of diketene (the commercially available dimer of ketene) or acetic anhy-

dride, the latter material easily affords a ketene stream of better than 99% purity (Hasek 1981).

Ketene is used as an acetylating agent in chemical synthesis, especially of acetic acid and acetate esters (Health Council of the Netherlands 2001). The chemical and physical properties of ketene are presented in Table 6-2.

2. HUMAN TOXICITY DATA

No human data on ketene were found.

TABLE 6-1 AEGL Values for Ketene

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)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)	One third of AEGL-3 values (NRC 2001)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)	Nonlethal exposure of mice, 1 ppm for 7 h (Treon et al. 1949)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. A penetrating odor was reported for ketene, but neither an odor threshold nor a level of odor awareness are available. Therefore, whether the distinct floral odor of ketene will be noticeable by individuals is unclear.

TABLE 6-2 Chemical and Physical Properties for Ketene

Parameter	Value	Reference
Synonyms	Ethenone; carbomethene	HSDB 2005
CAS registry no.	463-51-4	HSDB 2005
Chemical formula	C_2H_2O	HSDB 2005
Molecular weight	42.04	HSDB 2005
Physical state	Gas	HSDB 2005
Color	Colorless	HSDB 2005
Odor	Penetrating	HSDB 2005
Melting point	-150°C	HSDB 2005
Boiling point	-56°C	HSDB 2005
Solubility	Fairly soluble in acetone	HSDB 2005
Vapor density (air = 1)	1.45	HSDB 2005
Vapor pressure	1.4×10^4 mm Hg at 25°C	HSDB 2005
Conversion factors	1 mg/m^3 = 0.582 ppm 1 ppm = 1.719 mg/m^3	NIOSH 2011

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

Treon et al. (1949) exposed (whole body) monkeys (one animal per concentration, sex and strain not specified) to ketene at nominal concentrations of 50, 200, 750, and 1,500 ppm for 10 min under static conditions. The desired atmosphere was obtained by introducing a calculated volume of freshly generated ketene gas (purity: 98-99%) into the chamber. At the lowest concentration of 50 ppm, the exposed monkey survived without noteworthy signs of intoxication. At higher concentrations, all monkeys died within 7.67, 1.95, and 0.6 h after exposure, respectively (see Table 6-3). Symptoms of toxicity were similar at the various concentrations, but the onset of symptoms was shorter with higher concentrations. The only sign of intoxication during exposure was coughing at 1,500 ppm. Toxicity was characterized by dyspnea (rapid and labored breathing) and cyanosis culminating in fatal edema of the lungs (nasal discharge, slightly sanguineous fluid expelled from the mouth). Death was preceded by evidence of irritation (probably anoxic) of the central nervous system, which included lethargy, weakness, laying down inside position, closed eyes, and convulsive movements of the head. The observed clinical effects were confirmed by evidence of gross and microscopic pathologic changes in the lungs (generalized alveolar edema and congestion, occasional cases of an emphysematous condition at the periphery of the lobes, and distended alveolar spaces with fluid) and brain (meningeal and cerebral edema and congestion, accompanied by neuronal chromatolysis indicating the presence of cerebral anoxia). No significant changes in other organs were found.

Treon et al. (1949) exposed one monkey (sex and strain not specified) to ketene at 23 ppm for 4 h on two consecutive days and one monkey received 14 exposures of 1 ppm for 7 h/day, 5 days/week, followed by another 55 exposures after a 9-day interval (see Table 6-4). At the start of each experiment, ketene (purity: 98-99%) was injected in the chamber from a syringe to obtain the desired concentration. Because no analytic method was available to measure such low concentrations, estimates were calculated from measurements of the rate at which ketene flowed from the reservoir into a measured air stream (nominal concentrations). During the first 4-h exposure period, the monkey exposed at 23 ppm showed adverse clinical effects, including irritation of the eyes, coughing, and lethargy, especially signs related to the lungs and brain. Clinical effects were more pronounced during the second 4-h exposure (some nasal discharge, irregular and labored respiration, more severe coughing, and frothy fluid from the mouth). It was unclear whether microscopic examinations were performed on the tissues of this animal, but it was reported that in general all test species, except guinea pigs, showed alveolar edema and acute pulmonary congestion after repeated exposure to ketene at concentrations above 12 ppm. The monkey recovered and survived. No clinical signs were observed in the monkey exposed repeatedly to ketene at 1 ppm.

TABLE 6-3 Acute Lethality Data from Studies of Animals Exposed to Static Concentrations of Ketene for 10 Minutes

Concentration (ppm)	Mortality	Time of death (h)
Monkeys (n = 1)		
50	0/1	–
200	1/1	7.67
750	1/1	1.95
1,500	1/1	0.6
Cats (n = 1)		
200	0/1	–
750	1/1	2.83[a]
1,250	1/1	58.7
1,500	1/1	17
Rabbits (n = 1-2)		
200	0/2	–
250	0/2	–
375	0/2	–
500	0/2	–
750	0/2	–
1,000	1/2	0.8
1,250	2/2	2.8 and 3.07
1,500	1/1	1.3
Guinea pigs (n = 2)		
100	0/2	–
200	0/2	–
250	0/2	–
375	0/2	–
500	1/2	5.5
750	1/2	1.6
1,000	2/2	2.0 and 6.0
1,250	2/2	2.16 and 9.1
Rats (n = 2)		
100	0/2	–
200	0/2	–
250	0/2	–
375	2/2	3.25 and 9.67
500	2/2	4.45 and 6.75
750	2/2	3.7 and 5.5
1,000	2/2	2.0 and 2.6
1,250	2/2	0.95 and 1.95
Mice (n = 10-20)		
25	0/10	–
50	8/20	1.1-7.75 (6 mice); 16.2-16.4 (2 mice)
75	10/10	1.5-4.5 (7 mice); 12-22.5 (2 mice); 60 (1 mouse)
100	10/10	1.05-3.05 (9 mice); 7.5-16 (1 mouse)

[a]The cat had an obstruction of the bowel.
Source: Adapted from Treon et al. 1949.

TABLE 6-4 Acute Lethality Data from Studies of Animals Exposed to Dynamic Concentrations of Ketene for 10 Minutes

	Intended Exposure			
Concentration (ppm)	(time/day)	(day)	Mortality	Time of Death
Monkeys (n = 1)				
23	4 h	2	0/1	–
1	7 h	14	0/1[a]	–
1	7 h	55	0/1[a]	–
Cats (n = 1-2)				
23	4 h	2	0/1	–
23	6.5 h	2	0/1	–
12	4.5-6 h[b]	15	1/1	After fifth exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Rabbits (n = 4-5)				
50	50 min	1	0/4	–
53	100 min	1	3/4	1.87-3.57 h (2 rabbits), 135.5 h (1 rabbit)
23	4 h	2	4/4	1.5-8 d after second exposure
23	6.5 h	2	2/4	24 min after first exposure and during second exposure
12	4.5-6 h[b]	15	4/4	During or after fifth exposure (3 rabbits); during ninth exposure (1)
1	7 h	14	0/4	–
1	7 h	55	3/5	During ninth exposure (1 rabbit); after twenty-third exposure (1 rabbit); after thirty-ninth exposure (1 rabbit)
Guinea pigs (n = 2)				
50	50 min	1	0/2	–
53	100 min	1	2/2	4.04 and 4.32 h
23	120 min	1	0/2	–

Guinea pigs (n = 2)				
23	4 h	2	2/2	Less than 7.3 h after first exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Rats (n = 2)				
50	50 min	1	0/2	–
53	100 min	1	2/2	1.37 and 3.04 h
23	4 h	2	0/2	–
23	6.5 h	2	2/2	0 and 55 min after first exposure
12	4.5-6 h[b]	15	1/2	After sixth exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Mice (n = 7-10)				
50	50 min	1	10/10	0-94 min (7 mice); 5.25-8.25 h (3 mice)
53	100 min	1	10/10	0-92 min
23	30 min	1	7/10	1.05-4.2 h (5 mice); 7 h (1 mouse), 16 h (1 mouse)
23	120 min	1	10/10	1.85-6.85 h
23	4 h	2	10/10	During first exposure (3 mice); less than 7 h after first exposure (7 mice)
12	4.5-6 h[b]	15	4/7	During second exposure (3 mice); during seventh exposure (1 mouse)
1	7 h	14	1/10	3 days after tenth exposure
1	7 h	55	1/10	1 day after forty-ninth exposure

[a]The same monkey was exposed in both of these experiments, with a 9-day interval between them.
[b]Animals were exposed for 4.5 h on the first day, 5.5 h on the second day, and 6 h on each of 13 other days for 5 days per week.
Source: Adapted from Treon et al. 1949.

3.1.2. Cats

Wooster et al. (1947) exposed groups of 1-2 cats (sex and strain not specified) to ketene vapor (purity not specified). The amount of ketene generated per minute was determined at the beginning and the end of exposure by titration method to calculate the mean ketene concentration during exposure. Cats were exposed (whole body) for 10 min to mean concentrations of 233 ppm (0.40 g/m^3; n = 1), 367 ppm (0.63 g/m^3; n = 2), 623 ppm (1.07 g/m^3; n = 2), and 815 ppm (1.40 g/m^3; n = 1); the observation period was 15 days. Cats showed no signs of irritation during exposure, but salivated profusely. Mortality rates of 0/1, 1/2, 2/2, and 1/1, respectively, were found (see Table 6-5). Cats died within 12 h. Deaths were preceded by convulsive seizures, during which animals gasped for breath. Necropsy revealed trachea and bronchi containing foam and hyperemic lungs containing lobules filled with edema fluid. Microscopically, the perivascular connective tissue of the bronchial and bronchiolar vessels was very edematous, as were many alveoli. No changes in the epithelium of the airways or other organs were found. Toxicity was reported in a general way for several species and without reference to exposure concentrations.

Treon et al. (1949) exposed four cats (one animal per concentration, sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 750, 1,250, and 1,500 ppm for 10 min under static conditions. The lowest concentration that caused death was 750 ppm, although it was noticed that the cat had an obstruction of the bowel. Times of death are presented in Table 6-3. Cats displayed signs of illness only after a latency period much longer than that observed for any of the other species tested. Referring to all species tested, general toxicity of ketene was reported to be characterized by dyspnea and cyanosis culminating in fatal edema of the lungs. Death was preceded by evidence of irritation (probably anoxic) of the central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 750 ppm.

Treon et al. (1949) exposed cats (one or two cats per concentration, sex and strain not specified) to ketene at nominal concentrations ranging from 1 to 23 ppm for a various number of exposures (see Section 3.1.1 for technical details and Table 6-4 for information on exposure conditions). No mortality was seen in cats exposed at 1 ppm for up to 55 days or in cats exposed for two successive days at 23 ppm (4- or 6.5-h exposures). The only cat that died had received five exposures at 12 ppm for 4.5-6 h. Cats exposed to ketene at 12 or 23 ppm for several hours on successive days exhibited sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, and labored respiration. Convulsions preceded death in the case of the cat exposed at 12 ppm.

3.1.3. Rabbits and Guinea Pigs

Cameron and Neuberger (1937) studied the noxious properties of ketene in guinea pigs (number, sex, and strain not specified). Ketene was prepared accord

TABLE 6-5 Acute Lethality Data from Studies of Animals Exposed to Ketene for 10 Minutes

Concentration (ppm)	Mortality	Time of Death or Observation Period
Cats (n = 1-2)		
233	0/1	15 d
367	1/2	8-12 h
623	2/2	26 min and 8-12 h
815	1/1	135 min
Rabbits (n = 2)		
652	0/2	10 d
Guinea pigs (n = 2-4)		
367	2/4	8-12 h
	3/4	3 d
623	4/4	8-12 h
652	2/2	8-12 h
Rats (n = 4)		
122	0/4	10 d
250	4/4	150 min
774	4/4	135 min
Mice (n = 20-24)		
70	9/20	115 min
	20/20	240 min
122	16/20	180 min
	18/20	3 d
192	20/20	115 min
349	11/20	55 min
	20/20	80 min
815	24/24	60 min

Source: Adapted from Wooster et al. 1947.

ing to the method of Herriott (1934.) Methane was produced in equivalent amounts using this method, but the authors stated that methane could be ignored because very high concentrations were known to be without effect on white mice. In some experiments (not further specified) ketene was passed through ice-cold liquid paraffin to remove acetone. The exposure chamber was an 18-L glass vessel containing a fan and perforated for some inlets and outlets (glass tubes). The use of rubber was minimized to prevent polymerization of ketene. The system ensured that ketene entered within 30 seconds after commencing the experiment and allowed the concentration to be measured during exposure. A titration method was used, but no details about when the measurements were taken or how many were made were provided. Guinea pigs were exposed (whole body) for 5 min to ketene at 200-300 ppm (whether these were actual or nominal

concentrations was not specified). All animals died within 2-4 h after exposure (see Table 6-6). Animals were quiet, stretched out or huddled together, and showed somewhat decreased respiration, but no obvious dyspnea until 10-15 min before death. Marked dyspnea, violent jumping, clonic spasms, coma, and death with obvious pulmonary edema were observed. The bronchi were unaffected. There was no blistering or burning of the skin or mucous surfaces. Effects on other organs included dilated right hearts, slightly congested brains, and markedly congested arteries and veins accompanied by edema of their walls and sometimes marked hemorrhages. No changes were found in the other organs or tissues, apart from terminal venous congestion. Fetuses from pregnant animals were reported to be unaffected, but no details were provided.

Wooster et al. (1947) exposed two rabbits (sex and strain not specified) for 10 min to a mean nominal concentration of ketene at 652 ppm (1.12 g/m^3) (see Section 3.1.2 for technical details). Both animals survived the 10-day observation period (see Table 6-5). Toxicity results were discussed without reference to species or exposure concentration. It was generally reported that only a few signs of irritation and slight lacrimation during exposure were observed, and that animals tended to keep their eyes closed.

Wooster et al. (1947) exposed groups of four, four, and two guinea pigs (strain and sex not specified) for 10 min to mean nominal concentrations of ketene (purity not given) at 367 ppm (0.63 g/m^3), 623 ppm (1.07 g/m^3), and 652 ppm (1.12 g/m^3), respectively (see Section 3.1.2 for technical details). All animals in the two highest exposure groups died 8-12 h after exposure (see Table 6-5). Two of four guinea pigs in the lowest exposure group died during that timeframe, and a third animal died within 3 days. Signs of irritation and slight lacrimation during exposure were reported. Toxicity symptoms preceding death was similar to those described for the cat, with effects predominantly on the lungs and central nervous system (see Section 3.1.2 for technical details). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

TABLE 6-6 Acute Lethality Data in Several Animal Species

Concentration (ppm)	Exposure Duration (min)	Mortality (%)	Time of Death (min)
Guinea pigs (n = unknown)			
200-300	5	100	120-250
Rats (n = unknown)			
200-300	5	100	90-100
Mice (n = 120 mice [total])			
100	5	100	50-250
200-300	5	100	35-65
200-300	20	100	20-65
2,000	20	100	20-103

Source: Adapted from Cameron and Neuberger 1937.

Treon et al. (1949) exposed eight groups of rabbits (two animals per concentration except for one animal in the highest exposure group, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 200, 250, 375, 500, 750, 1,000, 1,250, and 1,500 ppm for 10 min under static conditions. Mortality data are presented in Table 6-3. The lowest lethal concentration was 1,000 ppm; times of death were 0.8 h (1,000 ppm), 2.8 and 3.07 h (1,250 ppm), and 1.3 h (1,500 ppm). Animals that died exhibited coughing, blinking of the eyes, and a slight increase of respiratory rate during exposure. A more severe toxic state developed after latent periods of variable duration, depending on the concentration. Toxicity preceding death was similar that that described for monkeys (see Section 3.1.1 for technical details), with affects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 1,000 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed seven groups of rabbits (4-5 animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Exposure at 50 ppm for 50 min was not lethal to four rabbits, but three of four rabbits died after a 100-min exposure at 53 ppm. A 6.5-h exposure at 23 ppm killed one of four rabbits, and a second animal died during exposure on day 2. Further, all four rabbits died after a 4-h exposure at 23 ppm on two consecutive days. After repeated exposure to ketene at 12 ppm and 23 ppm, the following signs of respiratory illness followed by brain damage were seen: sneezing, rubbing noses, holding heads up and back, labored respiration (also seen in animals that died at 1 ppm), and running movements of the legs. Surviving animals exposed at 1 ppm exhibited no signs of respiratory illness. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen in animals after repeated exposures at 12 ppm and higher.

Treon et al. (1949) exposed eight groups of guinea pigs (two animals per concentration, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 500 ppm, and 100% mortality occurred at 1,250 ppm. Compared with other the species tested, guinea pigs that died exhibited greater individual variability in the length of the latent period prior to the onset of respiratory distress. Otherwise the response of guinea pigs was of the same general type as that of the other species. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with effects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 500 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed six groups of guinea pigs (two animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and time of

death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or a 2-h exposure at 23 ppm. After a 100-min exposure at 53 ppm or a 4-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before signs of respiratory illness were observed was lengthened as the ketene concentration decreased. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen in animals after repeated exposures to ketene at 23 ppm and higher.

3.1.4. Rats

Cameron and Neuberger (1937) tested the effects of 5-min exposures to ketene (purity not specified, but equivalent amounts of methane were reported to be present) at 200-300 ppm on albino rats (number, sex, and strain not specified). Exposure conditions were comparable those used for guinea pigs (see Section 3.1.3 for technical details). All animals died within 90-100 min after exposure (see Table 6-6). Animals were quiet, stretched out or huddled together, and showed somewhat decreased respiration but no obvious dyspnea until 10-15 min before the end of exposure. Toxicity preceding death was similar to that described for guinea pigs (see Section 3.1.3), with effects predominantly on the lungs and central nervous system but also on the heart, arteries, and veins. There was no blistering or burning of the skin or mucous surfaces. No changes were found in the other organs or tissues, apart from terminal venous congestion. It was reported that fetuses from pregnant animals appeared unaffected, but details were not provided.

Wooster et al. (1947) exposed three groups of four rats (sex and strain not specified) for 10 min to mean nominal concentrations of ketene (purity not specified) at 122 ppm (0.21 g/m^3), 250 ppm (0.43 g/m^3), and 774 ppm (1.33 g/m^3) (see Section 3.1.2 for technical details). In the lowest exposure group, all animals survived the 10-day observation period (see Table 6-5). In general, only a few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed. In the two highest exposure groups, all animals died within 150 or 135 min, respectively. Toxicity preceding death was similar to that described for the cat, with effects predominantly on the lungs and central nervous system affected (see Section 3.1.2). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

Treon et al. (1949) exposed eight groups of rats (two animals per concentration, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 375 ppm (100% mortality). Rats that died developed severe respiratory distress after latent periods of variable duration, depending on the concentration. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with ef-

fects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 375 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed seven groups of rats (two animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or 4-h exposures on two consecutive days at 23 ppm. After a 100-min exposure at 53 ppm or a 6.5-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before any signs of respiratory illness were observed lengthened as the ketene concentration decreased. Effects on respiration (irregular and labored respiration, gasping, and prostration) were further shown to be dependent on exposure duration. At 23 ppm, no respiratory effects were observed after two exposures of 4 h, but were observed after a single exposure for 6.5 h. At 50-53 ppm, effects were seen after 100 min, but not after 50 min. At 12 ppm, effects on respiration and on the brain (tremors) were seen after the fifth exposure. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen following repeated exposures at 12 ppm and higher.

3.1.5. Mice

Cameron and Neuberger (1937) studied the 5 min-effects of ketene (purity not specified, but equivalent amounts of methane were reported to be present) in more detail using four groups of fully grown male and female white mice (120 mice; strain, sex, and number per group were not specified) under experimental conditions described for guinea pigs (see Section 3.1.3 for technical details and Table 6-6 for information on exposure conditions). All animals died within 4 h, and had variable survival times within and across the groups (see Table 6-6). The investigators were unable to obtain an accurate estimate of the lower range toxicity of ketene, but had reason to believe that a concentration of less than 100 ppm was fatal to mice. Mice that died within 30 min immediately became quiet on exposure and crouched together lying stretched on their bellies. Within 5 min, respiration became more rapid and labored and sometimes noses and eyes were rubbed. After about 10 min, a little frothy fluid appeared at the mouth and nose and respiration became irregular, with the animals often gasping and showing more frequently shallow and rapid breathing. Animals made violent leaps or ran around for a few seconds, then felt on their sides with limbs extended, making jerky movements of their hind limbs. Respiration became slower and deeper, much fluid poured from the nose and mouth, the animal passed into deep coma, and death occurred in 20-30 min from the onset. When mice died after 2-4 h, animals were very quiet, stretched out or huddled together, and showed somewhat decreased respiration but no obvious dyspnea until 10-15 min before death. Toxicity preceding death was similar to that described for guinea pigs (see Section 3.1.3 for technical details), with effects predominantly on the lungs, central

nervous system, the heart, arteries, and veins. There was no blistering or burning of the skin or mucous surfaces. No changes were found in the other organs or tissues, apart from terminal venous congestion. It was reported that fetuses from pregnant animals appeared unaffected, but details were not provided.

Wooster et al. (1947) exposed five groups of 20-24 mice (sex and strain not specified) for 10 min to mean nominal concentrations of ketene (purity not specified) of 70 ppm (0.12 g/m^3), 122 ppm (0.21 g/m^3), 192 ppm (0.33 g/m^3), 349 ppm (0.6 g/m^3), and 815 ppm (1.4 g/m^3) (see Section 3.1.2 for technical details). During exposure only a few signs of irritation and slight lacrimation were reported. Animals tended to keep their eyes closed. With the exception of the 122-ppm group, 100% mortality occurred in the treatment groups. The duration of survival decreased with increasing concentrations (see Table 6-5). At 122 ppm, two animals survived through an observation period of 3 days. Toxicity preceding death was similar to that described for the cat, with effects predominantly on the lungs and central nervous system affected (see Section 3.1.2 for technical details). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

Treon et al. (1949) exposed four groups of mice (10-20 per group, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 25, 50, 75, and 100 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 50 ppm, and 100% mortality occurred at 75 ppm and higher. Within the various exposure groups, great variability in time of death was found. Animals that died remained fairly active during exposure. After latent periods of variable duration, the response of mice was of the same general type as that of other species. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with effects predominantly in the lungs and central nervous system affected. No significant changes in other organs were found.

Treon et al. (1949) exposed eight groups of mice (7-10 per group, sex and strain not specified) to nominal ketene concentrations ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. The lowest concentration with acute lethality was 12 ppm (4.5-6 h/day); three of seven mice died during the second exposure period. At 23 ppm, mortality rates of 7/10 and 10/10 were found after 30 min in the groups exposed for 2 and 4 h, respectively. Exposure of 50-100 min at 50-53 ppm resulted in 100% mortality. Clinical effects were dependent on exposure duration. At 12 ppm, only slight nasal irritation was observed after 4.5 h of exposure, followed by labored respiration after the following 5.5 h. At concentrations of 23 ppm and higher, effects were seen on respiration and the brain (convulsions). Animals that died in the 1-ppm group showed some labored respiration. Microscopic evidence of alveolar edema and acute pulmonary congestion were observed in mice following repeated exposures at 12 ppm and higher.

Mendenhall and Stokinger (1959) exposed (whole body) groups of 6-30 male white mice of the HLA (Hamilton Labs., Hamilton, O.) strain for 10 min to ketene at concentrations of 1.1-39.0 ppm to investigate mortality. Ketene was generated with a ketene mantle and the concentration of ketene, methane, and other gases in the effluent was estimated by absorption of ketene in alkali (99.8% efficiency) and measuring the time required for neutralization. Assuming that each molecule of ketene formed was accompanied by 1 molecule of methane, it was calculated that the gas mixture was comprised of 42.0% methane, 42.0% ketene, and 16.0% other gases (mean ketene concentration: s.d. 2.17%, n = 10 analyses). It was assumed that animals were exposed to this mixture. During actual runs, the ketene concentration was estimated spectrophotometrically (precision better than 5%). Exposure of 15 mice in the chamber under usual testing conditions did not show interference with the test for ketene (no effects of exudates on the ketene reagent). This test was part of a tolerance study in which mice exposed to ketene were challenged by a second ketene or ozone exposure after a lapse of some days. The lowest lethal concentration was 5.4 ppm (6.7% mortality). The lowest concentration with 100% mortality was 18.4 ppm. Mortality rates varied from 0$ to 20% at 5.4-11.4 ppm and from 50% to 100% at 14.4-39.0 ppm. Time of death varied between 6 h and "in the second week" post-exposure. An LC_{50} of 16.5 ppm for a 10-min exposure was reported, with confidence limits of 8.8 and 31 (p = 0.05). This estimate of the toxicity of ketene at 10 days after exposure was made by assuming that none of the animals died after the third day as a result of ketene exposure. Death was preceded by concentration-dependent effects on the lungs, with edema starting at 11.4 ppm. The following effects were confirmed by histologic examination conducted (3 h to 4 days post-exposure) in a parallel experiment: no significant changes at 5.8 ppm, marked capillary congestion at 7.2 ppm, and marked capillary engorgement, some patchy edema with hemorrhages, and superficial desquamation of the bronchial tree at 9 ppm.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Treon et al. (1949) exposed (whole body) four monkeys (one animal per concentration, sex and strain not specified) to ketene at initial nominal concentrations of 50, 200, 750, and 1,500 ppm for 10 min under static conditions. The desired atmosphere was obtained by introducing a calculated volume of freshly generated ketene gas (purity: 98-99%) into the chamber. At the lowest concentration of 50 ppm, the exposed monkey survived (see Table 6-3) without noteworthy signs of intoxication. The higher concentrations were all lethal.

Treon et al. (1949) exposed one monkey to ketene at 23 ppm for 4 h on two consecutive days and another monkey received 14 exposures of 1 ppm for 7 h/day, 5 days/week followed by another 55 exposures after a 9-day interval (see

Table 6-4). The sex and strain of the monkeys were not specified. At the start of each experiment, ketene (purity: 98-99%) was injected into the chamber from a syringe to obtain the desired concentration. Because no analytic method was available to measure these low concentrations, the ketene concentrations were calculated from measurements of the rate at which ketene flowed from the reservoir into a measured air stream (nominal concentrations). The monkey exposed at 23 ppm showed some adverse clinical effects, especially related to lungs and brain (irritation of the eyes, some coughing, and some lethargy) during the first 4-h exposure period. Clinical effects were more pronounced during the second 4-h exposure period (some nasal discharge, irregular and labored respiration, more severe coughing, and frothy fluid from the mouth). It was not clear whether a microscopic examination was performed on this animal, but it was reported in general that all species tested, except guinea pigs, showed alveolar edema and acute pulmonary congestion after repeated exposure to ketene concentrations above 12 ppm. The monkey recovered and survived. No clinical signs were observed in the monkey repeatedly exposed at 1 ppm.

3.2.2. Cats

Wooster et al. (1947) exposed four groups of cats (sex and strain not specified; 1-2 animals/group) to ketene vapor (purity not given). The amount of ketene generated per minute was determined at the beginning and the end of exposure by titration method to calculate the mean ketene concentration during exposure. Cats were exposed (whole body) for 10 min to ketene at mean concentrations of 233 ppm (0.40 g/m^3; n = 1), 367 ppm (0.63 g/m^3; n = 2), 623 ppm (1.07 g/m^3; n = 2), and 815 ppm (1.40 g/m^3; n = 1); the observation period was 15 days. Cats showed no signs of irritation during exposure, but salivated profusely. No deaths occurred at the lowest concentration of 233 ppm (see Table 6-5). Although the description of toxic effects is not detailed, it appeared that surviving animals did not suffer from serious effects.

Treon et al. (1949) exposed four cats (one animal per concentration; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 750, 1,250, and 1,500 ppm for 10 min under static conditions. The highest nonlethal concentration was 200 ppm (see Table 6-3). Cats had signs of illness only after a latency period much longer than that observed in any of the other species tested, but whether slight signs of toxicity occurred at 200 ppm was not reported. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 750 ppm.

Treon et al. (1949) exposed cats (one or two per concentration; sex and strain not specified) to nominal ketene concentrations of 1-23 ppm for a various number of exposures (see Section 3.1.1 for technical details and Table 6-4 for information on exposure conditions). No mortality was seen in cats exposed at 1 ppm for up to 55 days or in cats exposed for two successive days at 23 ppm (4- or 6.5-h exposures). Cats exposed at 12 or 23 ppm for several hours on succes-

sive days exhibited sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, and labored respiration.

3.2.3. Rabbits and Guinea Pigs

Wooster et al. (1947) exposed two rabbits (sex and strain not specified) for 10 min to ketene at a mean nominal concentration of 652 ppm (1.12 g/m^3) (see Section 3.1.2 for technical details). Both animals survived the 10-day observation period (see Table 6-5). Toxicity results were discussed without reference to species or exposure concentration. It was generally reported that only few signs of irritation and slight lacrimation during exposure were observed. Animals tended to keep their eyes closed.

Wooster et al. (1947) exposed three groups of four, four, and two guinea pigs (strain and sex not specified) for 10 min to ketene (purity not specified) at mean nominal concentrations of 367 ppm (0.63 g/m^3), 623 ppm (1.07 g/m^3), and 652 ppm (1.12 g/m^3), respectively (see Section 3.1.2 for technical details). Only one animal exposed at the lowest concentration survived the 3-day observation period (see Table 6-5). Although the description of toxic effects was not very detailed, it appeared that surviving animals did not suffer from serious effects. In general, only few signs of irritation and slight lacrimation during exposure were reported.

Treon et al. (1949) exposed eight groups of rabbits (two animals per group except for one animal in the highest exposure group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 250, 375, 500, 750, 1,000, 1,250, and 1,500 ppm for 10 min under static conditions. The mortality data and times of death are presented in Table 6-3. The highest concentration without mortality was 750 ppm. Surviving rabbits did not show noteworthy signs of intoxication.

Treon et al. (1949) exposed seven groups of rabbits (four or five animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Exposure at 50 ppm for 50 min was not lethal, but three of four rabbits died after a 100-min exposure at 53 ppm. All rabbits exposed at 1 ppm for 7 h/day for 14 exposures survived. These animals exhibited no signs of respiratory illness. Although toxicity was described without specific reference to animal species or concentrations, the description suggested that no severe effects were seen in surviving animals.

Treon et al. (1949) exposed eight groups of guinea pigs (two animals per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The highest nonlethal concentration was 375 ppm. Surviving animals did not show noteworthy signs of intoxication.

Treon et al. (1949) exposed six groups of guinea pigs (two animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or a 2-h exposure at 23 ppm. The time that elapsed before any signs of respiratory illness lengthened as the ketene concentration decreased. Although toxicity was described without specific reference to animal species or concentrations, the description suggested that no severe effects were seen in surviving animals.

3.2.4. Rats

Wooster et al. (1947) exposed three groups of four rats (sex and strain not specified) for 10 min to ketene (purity no specified) at mean nominal concentrations of 122 ppm (0.21 g/m^3), 250 ppm (0.43 g/m^3), and 774 ppm (1.33 g/m^3) (see Section 3.1.2 for technical details). Only the rats in the lowest exposure group survived the 10-day observation period (see Table 6-5). Although the description of toxic effects is not detailed, it appeared that surviving animals did not suffer from serious effects. In general, only few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed.

Treon et al. (1949) exposed eight groups of rats (two animals per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The highest concentration without mortality was 250 ppm. Surviving rats rubbed their noses during exposure, and later exhibited vigorous breathing associated with signs of moisture of the respiratory passages (rales).

Treon et al. (1949) exposed seven groups of rats (two animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure ato 50 ppm or 4-h exposures on two consecutive days at 23 ppm. After a 100-min exposure at 53 ppm or a 6.5-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before any signs of respiratory illness were observed lengthened as the ketene concentration decreased. Effects on respiration (irregular and labored breathing, gasping, and prostration) were further shown to depend on exposure duration. At 23 ppm, no respiratory effects were observed after two exposures of 4 h, but were observed after a single exposure of 6.5 h. At 50-53 ppm, effects were seen after 100 min, but not after 50 min. The description of toxicity suggested that no severe effects were seen in surviving animals.

3.2.5. Mice

Wooster et al. (1947) exposed five groups of 20-24 mice (sex and strain not specified) for 10 min to ketene (purity no specified) at mean nominal concentrations of 70 ppm (0.12 g/m^3), 122 ppm (0.21 g/m^3), 192 ppm (0.33 g/m^3), 349 ppm (0.6 g/m^3), and 815 ppm (1.4 g/m^3) (see Section 3.1.2 for technical details; see Table 6-7). Only two animals from the 122-ppm group survived the observation period of 3 days (see Table 6-5). Although the description of toxic effects is not very detailed, it appeared that surviving animals did not suffer from serious effects. Only a few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed.

Treon et al. (1949) exposed four groups of mice (10-20 mice per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 25, 50, 75, and 100 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. Only at the lowest concentration of 25 ppm was no mortality found. Surviving mice at 25 ppm had labored and irregular respiration and appeared lethargic for several hours; effects after a 10-min exposure at 50 ppm were similar but more severe.

Treon et al. (1949) exposed eight groups of mice (7-10 animals per group; sex and strain not specified) to ketene at nominal concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Mortality was observed at all concentrations; however, there was latency in pulmonary toxicity. The lowest concentration with acute lethality was 12 ppm (4.5-6 h/day): all mice survived the first 4.5-h exposure period, but three of seven mice died during the second 5.5 h. Slight nasal irritation was found after the first exposure, and was followed by labored respiration after the second exposure. Two animals died after exposure at 1 ppm, but only after repeated (10 and 49 times) 7-h exposures; surviving animals exhibited no overt signs of respiratory illness. The time that elapsed before any signs of respiratory illness lengthened as the ketene concentration decreased.

Mendenhall and Stokinger (1959) exposed (whole body) groups of 6-30 male white mice of the HLA (Hamilton Labs., Hamilton, O.) strain for 10 min to ketene at concentrations of 1.1-39.0 ppm to investigate mortality (see Section 3.1.5 for technical details). It was assumed that animals were exposed to a gas mixture calculated to be comprised of 42.0% methane, 42.0% ketene, and 16.0% other gases (mean ketene concentration: s.d. 2.17%, n = 10 analyses). During actual runs, the ketene concentration was estimated spectrophotometrically (precision better than 5%). No mortality was found in the two lowest exposure groups of 1.1 and 5.0 ppm, as well as in some groups exposed to ketene at 5.4-11.4 ppm (0-20% mortality). At higher concentrations, mortality was 50-100% (see Section 3.1.5). Time of death varied between 6 h and “in the second week” post-exposure. At variable lethal/nonlethal concentrations (parallel experiment;

5.8-11.4 ppm), histologic examination of the lungs performed 3-6 h post-exposure showed capillary congestion at 7.2-9 ppm and increased water content at 11.4 ppm.

3.3. Neurotoxicity

Evidence of neurotoxicity is discussed in conjunction with the studies described in Section 3.2.

TABLE 6-7 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	LOAEL Without Lethality (ppm)	Exposure Duration	Effect	Reference
Monkey	23	4 h/d, 2 d	Effects related to the lungs and brain (first exposure: irritation of the eyes, some coughing, some lethargy; second exposure: some nasal discharge, irregular and labored respiration, more severe coughing, frothy fluid from the mouth). Alveolar edema, acute pulmonary congestion.	Treon et al. 1949
Cat	233	10 min	Profuse salivation, no signs of irritation, no serious effects.	Wooster et al. 1947
Cat	23 23 12	4 h/d, 2 d 6.5 h/d, 2 d 4.5-6 h/d, 2 d	Sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, labored respiration.	Treon et al. 1949
Rabbit	652	10 min	Only few signs of irritation, slight lacrimation, closed eyes.	Wooster et al. 1947
Rat	122	10 min	No serious effects, a few signs of irritation and slight lacrimation, closed eyes.	Wooster et al. 1947
Rat	100	10 min	Nose rubbing during exposure, vigorous breathing associated with signs of moisture of the respiratory passages (rales).	Treon et al. 1949
Mouse	122	10 min	No serious effects, a few signs of irritation and slight lacrimation during exposure.	Wooster et al. 1947
Mouse	25	10 min	Labored and irregular respiration, lethargy for several hours.	Treon et al. 1949

3.4. Developmental and Reproductive Toxicity

No studies on the development or reproductive toxicity of ketene were found. However, the mortality study of Cameron and Neuberger (1937) reported that fetuses from pregnant guinea pigs, rats, and mice appeared to be unaffected after ketene exposure (see Sections 3.1.3., 3.1.4., and 3.1.5). No details on the experimental conditions of the developmental study were given.

3.5. Genotoxicity

Jensen et al. 1951) reported that ketene was negative in the Neurospora back-mutation test using the double mutant adenineless, colonial W.40a strain (recovered from the adenineless strain from Beadle's stock crossed to the colonial growing strain 70007A). Additionally, they cited an earlier report by Rapoport (1947, in Russian) that ketene was mutagenic in *Drosophila*.

3.6. Carcinogenicity

No reports on the carcinogenicity ketene were found.

3.7. Summary of Animal Data

Four studies conducted with experimental animals exposed to ketene are available, but the studies are old and the results are not described in great detail.[2] The reports of Cameron and Neuberger (1937), Wooster et al. (1947), and Mendenhall and Stokinger (1957) only involve 5- or 10-min exposures and the exposure concentrations are not always well-described. Wooster et al. (1947) only describe their results in general terms without reference to specific species or concentrations. Treon et al. (1949) provide results of longer exposure periods (several hours to several weeks), but they only report calculated (nominal) concentrations of ketene. The results of Treon et al. (1949) are adequate for deriving AEGL values because the study used ketene of high purity (98-99%), dynamic exposure conditions, longer exposure durations (up to 7 h), and wide concentration ranges for both lethal and nonlethal effects.

The toxicologic profile of inhalation exposure to ketene is generally similar among species tested, involving minor irritation and some central nervous system impairment during exposure, lethality at high exposure concentrations, and severe damage to the lungs (at the alveolar level) that may be manifest as long as 24 h after exposure (Cameron and Neuberger 1937; Potts et al. 1949;

[2]A fifth study by Potts et al. (1949) examined the acute toxicity of ketene (0.5 mg/L [500 mg/m^3 or 291 ppm]) in rats and mice (n = 8). However, the study examined only 1.5-min exposures and was poorly described.

Treon et al. 1949). The minor irritation during exposure may be due to the liberation of acetic acid (Potts et al. 1949), and the central-nervous-system effects reported are likely due to cerebral anoxia secondary to alveolar damage (Treon et al. 1949). Toxicity of ketene is greatest in mice, followed by rats, guinea pigs, cats, and rabbits (Treon et al. 1949).

The inhalation route of exposure is of particular concern for ketene. The available information indicates that the mode of action for ketene is similar to phosgene, which causes delayed toxicity to alveolar structures (mainly capillaries) and produces death by pulmonary edema (Cameron and Neuberger 1937; Potts et al. 1949). In general, severe effects are absent in animals that survive the initial exposure to ketene; however, latent pulmonary toxicity, similar to that observed following phosgene exposure, may result in lethality. In addition, the pulmonary histopathology following ketene exposure was characterized by Potts et al. (1949) as being "severe phosgene poisoning" by the pathologist. A steep concentration-response relationship appeared to be present for ketene.

Data on the developmental and reproductive toxicity, genotoxicity, and carcinogenicity of ketene are in adequate to draw conclusions.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No reports on the metabolism of ketene were found.

4.2. Mechanism of Toxicity

As noted above in Section 3.7, clinical signs and pathologic effects of ketene following inhalation exposure are similar to phosgene, involving death at high concentrations and minor irritation during exposure with some lethality after a latency period at lower concentrations. Ketene, like phosgene, acetylates free amino groups of proteins in aqueous solution (Cameron and Neuberger 1937; Potts et al. 1949). Potts et al. (1949) also provided some evidence that phosgene and ketene may affect enzymatic activity in lung cells in a similar way, suggesting that their modes of action could be similar. Similar to phosgene, the delay in toxicity observed with ketene results from the acylation of essential functional groups of enzymes and proteins in the lung rather than direct irritation by ketene or metabolites (Sciuto 2005). Ketene produces acetic acid as a breakdown product, whereas phosgene produces hydrochloric acid (Potts et al. 1949).

4.3. Structure Activity Relationships

Cameron and Neuberger (1937) grouped ketene (C_2H_2O) with arsines (AsH_3) and phosgene ($COCl_2$) as very poisonous gases, and suggested that phosgene was the most toxic, followed by ketene then arsine (fatal concentra-

tions were >25, ±100, and 250 ppm, respectively). Ketene resembled phosgene in its mode of toxic action (see Section 4.2).

4.3.1. Species Variability

From the static inhalation studies of Treon et al. (1949) (see Section 3.1), there was evidence of a marked difference in the relative susceptibility to ketene among the animal species tested when mortality was the end point. As shown in Table 6-8, two 10-min exposure studies showed that mice were the most susceptible to ketene, followed by monkeys, rats, guinea pigs, cats, and rabbits. Furthermore, a 5-min exposure study by Cameron and Neuberger (1937) had supportive results. Time to death after an exposure to ketene at 200-300 ppm was shortest for mice (35-36 min) followed by rats (90-100 min) and guinea pigs (120-250 ppm).

Differences in species susceptibility were also seen under dynamic inhalation conditions (Treon et al. 1949) (see Section 3.1). Comparison of the lowest acute exposure conditions resulting in lethality (see Table 6-4) indicated that mice (12 ppm for ≥4.5 h) were the most susceptible, followed by guinea pigs (23 ppm for 4 h), rats (23 ppm for 6.5 h) and rabbits (23 ppm for 6.5 h), and cats (12 ppm for 4.5-6 h, after fifth exposure). No monkeys died in this study. Although the relative susceptibility was somewhat different from above, the mouse was the most sensitive species in all studies.

TABLE 6-8 Susceptibility to Ketene

Species	Highest Concentration That Did Not Induce Fatal Pulmonary Edema	Lowest Concentrations That Induced Edema and Congestion of the Pulmonary Alveoli Followed by Death
Data from 10-min Exposure Study by Treon et al. (1949)		
Mouse	25 ppm	50 ppm
Monkey	50 ppm	200 ppm
Rat	250 ppm	375 ppm
Guinea pig	375 ppm	500 ppm
Cat	200 ppm	750 ppm
Rabbit	750 ppm	1,000 ppm
Data from 10-min Exposure Study by Wooster et al. (1947)		
Mouse	Unknown	≤70 ppm
Rat	122 ppm	250 ppm
Guinea pig	Unknown	≤367 ppm
Cat	233 ppm	367 ppm
Rabbit	≥652 ppm	Unknown

4.3.2. Intraspecies Variability and Susceptible Populations

No human data are available on the toxicity of ketene which can be used to evaluate intraspecies variability or identify susceptible populations. The probable mode of action for ketene toxicity (binding to macromolecules in the lung) is unlikely to vary greatly among individuals. A sensitive human subpopulation was not identified in the available literature on phosgene (NRC 2002), which has a similar mode of action.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data on ketene were available.

5.2. Animal Data Relevant to AEGL-1

Four studies were available on the acute toxicity of ketene in experimental animals, but they were rather old and sometimes lack sufficient details (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). Only the study by Treon et al. (1949) was carried out with ketene of high purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). It was not always clear whether actual or nominal concentrations were reported. Further, toxicity results are not always clearly related to a specific exposure concentration or duration, exposures mostly are of short duration, and exposure concentrations were not regularly measured. No reports on metabolism and mechanism of toxicity were found. Exposures of less than 10 min are of little use for setting AEGLvalues for durations of more than 30 min, but can be used as supporting information for the 10-min AEGL values. Thus, the most appropriate study is the one by Treon et al. (1949), in which several animal species were exposed to ketene concentrations ranging from 1 to 53 ppm for various exposure durations (10 min to 7 h).

Effects reported in the four studies were predominately related to the lungs and brain, and included sneezing, coughing, salivation, nasal discharge, frothy fluid from the mouth, irregular and labored respiration, and lethargy (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). These effects were dependent on both the exposure concentration and duration. Histopathologic effects found in the lungs included alveolar edema and acute pulmonary congestion. Furthermore, irritation of the eyes, lacrimation, and closed eyes during exposure were reported. Serious effects on the lungs and brain ultimately led to death. Mice appeared to be the most susceptible animal species among those tested. No overt signs of toxicity were observed in

mice exposed to ketene for 7 h at 1 ppm, the lowest concentration tested (Treon et al. 1949). However, the investigators noted that animals repeatedly exposed at 1 ppm exhibited varying degrees of interstitial fibrosis, leukocytic and histiocytic infiltration, atelectasis, and emphysema. It is not known if a single 7-h exposure at 1 ppm would also result in pulmonary damage. As shown in other experiments by Treon et al. (1949), inhalation exposure to ketene can result in latent pulmonary toxicity. Mice exposed at 25 ppm for 10 min (static exposure) showed labored and irregular breathing and appeared lethargic for several hours.

5.3. Derivation of AEGL-1 Values

It was not possible to develop AEGL-1 values for ketene with any scientific rigor. No overt signs of toxicity were observed in mice exposed to ketene at 1 ppm for 7 h; however, the investigators noted serious pulmonary effects following repeated exposure at this concentration. However, it is unknown whether the pulmonary damage occurred following a single exposure or resulted from repeated exposure. Due to the uncertainty of whether the lowest concentration tested (1 ppm) would result in effects which exceeded the AEGL-1 definition, derivation of AEGL-1 values is not recommended for ketene.

Although ketene reportedly possesses a distinct, penetrating floral odor (Health Council of the Netherlands 2001), neither an odor threshold nor a level of odor awareness are available. Thus, it is uncertain whether odor detection and minor irritation would provide adequate warning of ketene exposure, given the potential for sensitive subpopulations (asthmatics) and for delayed, severe pulmonary toxicity (including lethality) associated with ketene exposure.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on ketene were available.

6.2. Animal Data Relevant to AEGL-2

Of the four lethality studies available on the acute toxicity of ketene (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959), only the study by Treon et al. (1949) was carried out with ketene of high purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). Whether actual or nominal concentrations were reported in these studies was unclear. The nonlethal effects report in these studies included sneezing, coughing, salivation, nasal discharge, ocular irritation, frothy fluid from the mouth, irregular and labored respiration, and lethargy (Cameron and Neuberger

1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). The effects were predominantly related to the lungs and the brain, and were dependent on the concentration and exposure duration. Histopathologic findings in the lungs included alveolar edema and acute pulmonary congestion. Serious effects on the lungs and brain ultimately led to death. Mice appeared to be the most susceptible species. In the Treon et al. (1949) study, no overt signs of toxicity were observed in mice exposed to ketene at1 ppm for 7 h or at 12 ppm for 4.5 h (the next higher exposure concentration); however, 3/7 mice that were subsequently exposed to ketene the next day at 12 ppm for 5.5 h died. It is unknown if a single exposure at either concentration would result in latent lung damage. Serious lung damage was reported in mice repeatedly exposed to ketene at 1 ppm (Treon et al. 1949).

6.3. Derivation of AEGL-2 Values

Effects on the lungs observed in acute exposure studies of ketene in rodents are the adverse effects most relevant to deriving AEGL-2 values (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). Although Treon et al. (1949) identified concentrations that did not result in overt signs of toxicity or mortality following a single exposure, it is unknown whether these concentrations would result in latent lung damage. Thus, the data were considered unsuitable for deriving AEGL-2 values. In the absence of relevant data, the AEGL-2 values were estimated by taking 3-fold reduction of the AEGL-3 values (NRC 2001). This reduction is considered an estimate of a threshold for irreversible effects and appropriate because of the apparent steep concentration-response relationship (lethality was 0/10 at 1 ppm for 7 h, 7/10 at 23 ppm for 30 min; 10/10 at 50 ppm for 50 min). The AEGL-2 values for ketene are presented in Table 6-8.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on ketene were available.

7.2. Animal Data Relevant to AEGL-3

Of the four lethality studies on the acute toxicity of ketene (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959), only the study by Treon et al. (1949) was carried out with ketene of known purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). Whether actual or nominal concentrations of ketene were reported in these studies was not always clear.

TABLE 6-8 AEGL-2 Values for Ketene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm 0.050 mg/m^3)

Mice appeared to be the most susceptible animal species. A 50-min exposure to ketene at 50 ppm caused 100% mortality in mice. A 30-min exposure at 23 ppm was lethal to 7/10 mice, but a longer exposure of 2 h at this concentration was lethal to all 10 mice. A 4.5-h exposure to ketene at 12 ppm (the next lower concentration) did not result in deaths, although 3/7 mice died during a 5.5-h exposure at 12 ppm on the subsequent day (Treon et al. 1949). In a repeated-exposure study, no deaths were observed in mice exposed to ketene at 1 ppm for 7 h (Treon et al. 1949), but 1/10 mice died 3 days after the tenth exposure.

In the Treon et al. (1949) study, no overt signs of toxicity were observed in mice exposed to ketene at 1 ppm for 7 h or at 12 ppm for 4.5 h (the next higher concentration). However, 3/7 mice died during a subsequent exposure at 12 ppm for 5.5 h the next day

7.3. Derivation of AEGL-3 Values

No mortality in mice exposed to ketene at 1 ppm for 7 h in the Treon et al. (1949) repeated-exposure study was selected as the basis of the AEGL-3 values. Although no mice died after a 4.5-h exposure at 12 ppm, 3/7 died during a second exposure for 5.5 h. Because the time of death during the second exposure was not reported, whether the deaths were a delayed effect of the first exposure or caused by the second subsequent exposure is uncertain. Due to this uncertainty, the 1 ppm was selected as the point of departure for calculating AEGL-3 values for ketene. Because mice appeared to be the most susceptible species, an interspecies uncertainty factor of 3 was considered adequate. An intraspecies uncertainty factor of 3 was considered adequate because the mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, a chemical which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations. AEGL-2 and AEGL-3 values derived for phosgene used an intraspecies uncertainty factor of 3 (NRC 2002). Thus, a total uncertainty factor of 10 was used to calculate the AEGL-3 values for ketene.

Time scaling was performed using the equation $C^n \times t = k$, where the value of n ranges from 0.8 to 3.5 (ten Berge et al. 1986; NRC 2001). The mortality and time-to-death information in the study by Treon et al. (1949) were inadequate for deriving an empirical value of n. The lowest mortality for a single exposure was 70% (at 23 ppm for 30 min), followed by 100% (four of the five test concentrations that could be used for a derivation resulted in a 100% response). In the absence of adequate data, default values of n = 3 (for extrapolation from a

7-h exposure to 30 min, 1 h, and 4 h) and n = 1 (for extrapolation from a 7-h exposure to 8 h) were used. Because of the uncertainty associated with extrapolating a 7-h exposure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value. The AEGL-3 values for ketene are presented in Table 6-9.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for ketene are presented in Table 6-10.

Reports vary concerning the relative toxicity of ketene and phosgene. For example, Potts et al. (1949) report that "the toxicity of ketene for mice seems 20 times as great as that of phosgene" (1.5-min exposure at 500 mg/m^3 [291 ppm] killed 7/8 mice), whereas Treon et al. (1949) reported that "the toxicity of ketene appears to be of the same order of magnitude as that of phosgene". Information from the American Conference of Governmental Industrial Hygienists (ACGIH 2012) suggests that ketene is less toxic on a chronic basis than phosgene (report includes secondary citation to Treon et al. 1949). A comparison of the AEGL-3 values for ketene (Table 6-10) and phosgene (Table 6-11; NRC 2002) is difficult because of differences in the exposure duration associated with the points of departure (7 h for ketene vs. 10 and 30 min for phosgene) and the different n values used for time scaling (default values of n = 3 or n = 1 for ketene vs. n = 1 for all durations for phosgene). However, the 8-h AEGL-3 values, which were both calculated using n = 1 for time scaling, are similar for ketene and phosgene.

TABLE 6-9 AEGL-3 Values for Ketene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

TABLE 6-10 AEGL Values for Ketene

	Exposure Duration				
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)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

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

TABLE 6-11 AEGL Values for Phosgene

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)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)	One third of AEGL-3 values (NRC 2001)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)	Nonlethal exposure of mice, 1 ppm for 7 h (Treon et al. 1949)

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

8.2. Comparison with Other Standards and Guidelines

No emergency response planning guidelines have been set for ketene. The immediately dangerous to life or health (IDLH) value for ketene is 5 ppm, and is based on acute inhalation toxicity data in humans and animals (NIOSH 1994). NIOSH (1994) remarked that 5 ppm is the lowest concentration that produces a clinically-relevant physiologic response. Furthermore, it noted that this may be a conservative value due to the lack of relevant acute toxicity data on workers exposed to ketene at concentrations greater than 5 ppm. The 30-min AEGL-2 value, based on a 3-fold reduction in the AEGL-3 value, is approximately 20 times lower than the NIOSH short-term exposure limit (STEL) and the ACGIH STEL values, which are based on pulmonary toxicity observed in short-term exposure studies. The NIOSH IDLH value is approximately 20 times higher than the 30-min AEGL-3 value. The AEGL-3 values are approximately 6-times lower than the occupational standards of the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. The threshold limit value for ketene is based on the reasoning that 1 ppm was tolerated for several weeks and up to 6 months without apparent injury in several animal species (Treon et al. 1949). A concentration of 5 ppm was considered the lowest concentration that produced a clinically-relevant physiologic response. A summary of currently available standards and guidelines is presented in Table 6-12.

8.3. Data Quality and Research Needs

The available database on ketene is of poor quality. No human data are available. Animal studies mainly deal with very short exposures (10-20 min). The one study dealing with longer exposures (Treon et al. 1949) did not report actual concentrations of ketene. Data clearly addressing AEGL-1 and AEGL-2 effects are lacking and no appropriate acute toxicity study or odor detection information was available.

TABLE 6-12 Standards and Guidelines for Ketene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm 0.050 mg/m^3)
AEGL-3	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)
IDLH (NIOSH)[a]	–	5 ppm (9 mg/m^3)	–	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	0.5 ppm (0.86 mg/m^3)
PEL-TWA (OSHA)[c]	–	–	–	–	0.5 ppm (0.9 mg/m^3)
REL-TWA (NIOSH)[d]	–	–	–	–	0.5 ppm (0.9 mg/m^3)
TLV-STEL (ACGIH)[e]	1.5 ppm (2.6 mg/m^3) (15 mins)	–	–	–	–
REL-STEL (NIOSH)[f]	1.5 ppm (3 mg/m^3) (15 mins)	–	–	–	–
MAC (The Netherlands)[g]	–	–	–	–	0.5 ppm (0.9 mg/m^3)

[a]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.

[b]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.

[c]PEL-TWA (permissible exposure limit - time-weighted average, Occupational Safety and Health Administration [(29 CFR 1910.1000) [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 8 h/day, 40 h/week.

[d]REL-TWA (recommended exposure limit - time-weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA.

[e]TLV-STEL (threshold limit value-short-term exposure limit, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA and up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[f]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health [NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.

[g]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR KETENE

Derivation of AEGL-1 Values

Due to the uncertainty of whether the lowest concentration of ketene tested of 1 ppm (Treon et al. 1949) would result in effects that exceed the definition of AEGL-1 effects, derivation of AEGL-1 values is not recommended for ketene. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

Toxicity end point:	3-fold reduction of AEGL-3 values
10-min AEGL-2:	0.24 ppm ÷ 3 = 0.080 ppm (0.14 mg/m^3)
30-min AEGL-2:	0.24 ppm ÷ 3 = 0.080 ppm (0.14 mg/m^3)
1-h AEGL-2:	0.19 ppm ÷ 3 = 0.063 ppm (0.11 mg/m^3)
4-h AEGL-2:	0.12 ppm ÷ 3 = 0.040 ppm (0.069 mg/m^3)
8-h AEGL-2:	0.088 ppm ÷ 3 = 0.029 ppm (0.050 mg/m^3)

Derivation of AEGL-3 for Ketene

Key study:	Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to air-borne ketene. J. Ind. Hyg. Toxicol. 31(4):209-219.
Toxicity end point:	No mortality in mice exposed to ketene at 1 ppm for 7 h.
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); time scaling not performed for the 10-min AEGL-3 value, because of the uncertainty in extrapolating a 7-h point of departure to a 10-min value.

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	$(1 \text{ ppm})^3 \times 7 \text{ h} = 7 \text{ ppm-h}$ $(1 \text{ ppm})^1 \times 7 \text{ h} = 7 \text{ ppm-h}$
10-min AEGL-3:	0.24 ppm (0.41 mg/m^3) (equal to 30-min value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 7 \text{ ppm-h}$ $C = 2.4 \text{ ppm}$ $2.4 \text{ ppm} \div 10 = 0.24 \text{ ppm}$ (0.41 mg/m^3)
1-h AEGL-3:	$C^3 \times 1 \text{ hr} = 7 \text{ ppm-h}$ $C = 1.9 \text{ ppm}$ $1.9 \text{ ppm} \div 10 = 0.19 \text{ ppm}$ (0.33 mg/m^3)
4-h AEGL-3:	$C^3 \times 4 \text{ h} = 7 \text{ ppm-h}$ $C = 1.2 \text{ ppm}$ $1.2 \text{ ppm} \div 10 = 0.12 \text{ ppm}$ (0.21 mg/m^3)
8-h AEGL-3:	$C \times 8 \text{ h} = 7 \text{ ppm-h}$ $C = 0.875 \text{ ppm}$ $0.875 \div 10 = 0.088 \text{ ppm}$ (0.15 mg/m^3)

APPENDIX B

ACUTE GUIDELINE LEVELS FOR KETENE

Derivation Summary

AEGL-1 VALUES

AELG-1 values for ketene are not recommended because of insufficient data. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)

Data adequacy: Data consistent with the definition of AEGL-2 values were not available. The AEGL-2 values for ketene were based on a 3-fold reduction of the AEGL-3 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

Key reference: Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to airborne ketene. J. Ind. Hyg. Toxicol. 31(4): 209-219.

Test species/Strain/Number: Mouse, strain and sex not specified, 10/ group

Exposure route/Concentrations/Durations: Inhalation, 1 ppm for 7 h/day for 14 days

End point/Concentration/Rationale: No deaths were observed after the first day of exposure; 1/10 mice died 3 days after the tenth exposure.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, mouse is the most susceptible animal species for ketene
Intraspecies: 3, mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations. An intraspecies uncertainty factor of 3 was used to derive AEGL-2 and AEGL-3 values for phosgene (NRC 2002).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

(Continued)

AEGL-3 VALUES Continued

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). Time scaling was not performed for the 10-min AEGL-3 value, because of the uncertainty in extrapolating a 7-h point of departure to a 10-min value. The 10-min AEGL-3 value of 0.24 ppm is supported by the study of Treon et al. (1949), which reported no deaths in mice (0/10) after exposure to ketene at 25 ppm for 10 min.

Data adequacy: The database on ketene is poor. Only four studies were available on the acute toxicity of ketene in laboratory animals; these studies are old and sometimes lack sufficient details. No human data on ketene were available. Although Treon et al. (1949) reported only nominal concentrations of ketene, the results of the study are generally in agreement with other studies. Therefore, the study by Treon et al. (1949) provides an appropriate point of departure for deriving AEGL-3 values because it used ketene of high purity (98-99%), involved dynamic exposure conditions, involved longer exposure durations (up to 7 h), and tested a wide concentration range of ketene.

APPENDIX C

CATEGORY PLOT FOR KETENE

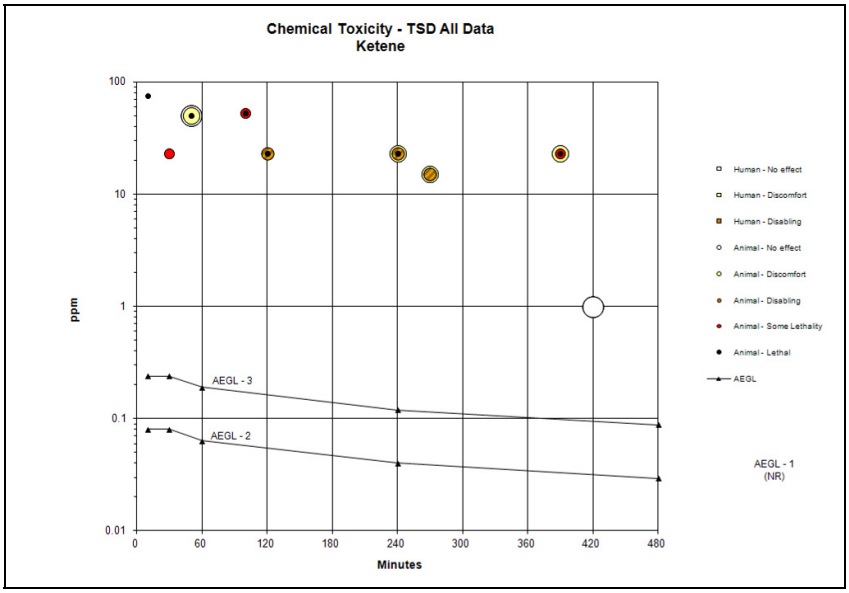

FIGURE C-1 Category plot of toxicity data and AEGL values for ketene.

TABLE C-1 Data Used in Category Plot for Ketene

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-2				0.08	10	AEGL	
AEGL-2				0.08	30	AEGL	
AEGL-2				0.063	60	AEGL	
AEGL-2				0.040	240	AEGL	
AEGL-2				0.029	480	AEGL	
AEGL-3				0.24	10	AEGL	
AEGL-3				0.24	30	AEGL	
AEGL-3				0.19	60	AEGL	
AEGL-3				0.12	240	AEGL	
AEGL-3				0.088	480	AEGL	
Treon et al. 1949	Mouse		1	75	10	3	Mortality (10/10)
Treon et al. 1949	Mouse		1	23	30	SL	Mortality (7/10)
Treon et al. 1949	Rabbit		1	50	50	0	
Treon et al. 1949	Rat		1	50	50	0	
Treon et al. 1949	Guinea pig		1	50	50	1	
Treon et al. 1949	Mouse		1	50	50	3	Mortality (10/10)
Treon et al. 1949	Guinea pig		1	53	100	3	Mortality (2/2)
Treon et al. 1949	Rat		1	53	100	3	Mortality (2/2)
Treon et al. 1949	Mouse		1	53	100	3	Mortality (10/10)
Treon et al. 1949	Rabbit		1	53	100	SL	Mortality (3/4)
Treon et al. 1949	Guinea pig		1	23	120	2	
Treon et al. 1949	Mouse		1	23	120	3	Mortality (10/10)
Treon et al. 1949	Cat		1	23	240	1	

Treon et al. 1949	Monkey	1	23	240	2	Adverse clinical effects, ocular irritation, coughing, lethargy
Treon et al. 1949	Guinea pig	1	23	240	3	Mortality (2/2)
Treon et al. 1949	Mouse	1	23	240	3	Mortality (10/10)
Treon et al. 1949	Rabbit	1	15	270	1	
Treon et al. 1949	Mouse	1	15	270	2	
Treon et al. 1949	Rat	1	15	270	2	
Treon et al. 1949	Cat	1	23	390	1	
Treon et al. 1949	Rat	1	23	390	3	Mortality (2/2)
Treon et al. 1949	Rabbit	1	23	390	SL	Mortality (1/4)
Treon et al. 1949	Cat	1	1	420	0	
Treon et al. 1949	Cat	1	1	420	0	
Treon et al. 1949	Monkey	1	1	420	0	
Treon et al. 1949	Mouse	1	23	30	SL	Mortality (7/10)
Treon et al. 1949	Rabbit	1	50	50	0	
Treon et al. 1949	Rat	1	50	50	0	
Treon et al. 1949	Guinea pig	1	50	50	1	
Treon et al. 1949	Mouse	1	50	50	3	Mortality (10/10)
Treon et al. 1949	Guinea pig	1	53	100	3	Mortality (2/2)
Treon et al. 1949	Rat	1	53	100	3	Mortality (2/2)
Treon et al. 1949	Mouse	1	53	100	3	Mortality (10/10)
Treon et al. 1949	Rabbit	1	53	100	SL	Mortality (3/4)
Treon et al. 1949	Guinea pig	1	23	120	2	
Treon et al. 1949	Mouse	1	23	120	3	Mortality (10/10)
Treon et al. 1949	Cat	1	23	240	1	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Treon et al. 1949	Monkey		1	23	240	2	Adverse clinical effects, ocular irritation, coughing, lethargy
Treon et al. 1949	Guinea pig		1	23	240	3	Mortality (2/2)
Treon et al. 1949	Mouse		1	23	240	3	Mortality (10/10)
Treon et al. 1949	Rabbit		1	15	270	1	
Treon et al. 1949	Mouse		1	15	270	2	
Treon et al. 1949	Rat		1	15	270	2	
Treon et al. 1949	Cat		1	23	390	1	
Treon et al. 1949	Rat		1	23	390	3	Mortality (2/2)
Treon et al. 1949	Rabbit		1	23	390	SL	Mortality (1/4)
Treon et al. 1949	Cat		1	1	420	0	
Treon et al. 1949	Cat		1	1	420	0	
Treon et al. 1949	Monkey		1	1	420	0	

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

7

Tear Gas (CS)[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), Lisa Ingerman (SRC, Inc.), Chemical Manager Glenn Leach (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (US Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Tear gas is a white crystalline powder with a pepper-like odor. It was first synthesized by Corson and Stoughton in 1928 and is, thus, abbreviated as CS (Corson and Stoughton 1928; US Army Chemical School 2005). CS was developed in the 1950s as a replacement for the chemical incapacitant, 1-chloroacetophenone (CN), because CS was a much more potent irritant than CN, but was significantly less toxic (WHO 1970; Colgrave and Creasey 1975; Hu et al. 1989). It was adopted for use by the military, and was widely used in the Vietnam War (WHO 1970; Hu et al. 1989). It is currently used as an incapacitating agent both by military and law enforcement personnel (HSDB 2005). Upshall (1973) reported that an aerosol concentration of CS at 4 mg/m^3 will disperse the majority of rioters within 1 min, and at 10 mg/m^3 will deter trained troops. With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, generally within 30 min after exposure (Ballantyne 1977). CS may be manufactured through carbonyl condensation by combining *o*-chlorobenzaldehyde and malononitrile (HSDB 2005). Recent production data on CS were not found.

Human studies did not identify a no-effect level for CS or effects of CS that would be consistent with the definition of AEGL-1. The severity of the effects observed at the lowest tested concentrations in humans (ocular stinging and watering, and nasal, throat, and mouth irritation) exceeded those defined by AEGL-1. Therefore, AEGL-1 values for CS are not recommended. AEGL-2

values were based on human exposure to CS at an average concentration of 0.75 mg/m^3 for 60 min (Beswick et al. 1972). All five subjects tolerated the exposure, but reported ocular stinging and watering, increased salivation, cough, and face stinging. Some subjects also reported throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects). An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. Furthermore, the responses of volunteers with jaundice, hepatitis, or peptic ulcer or who were 50-60 years old were similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate CS at 14-73 mg/m^3 and the recovery time in volunteers with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity were similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963). An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. A modifying factor of 3 was also used because the effects observed at 0.75 mg/m^3 were considered AEGL-2 effects. Time scaling was not performed because irritation is a function of direct contact with CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).

AEGL-3 values were based on calculated lethality thresholds for CS at each exposure duration. Rat data from the studies by McNamara et al. (1969), Ballantyne and Callaway (1972), and Ballantyne and Swanston (1978) were used calculate LC_{01} (lethal concentrations, 1% lethality) values for CS. Calculations were performed using the probit analysis-based dose-response program of ten Berge (2006). 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). An empirical value for n of 0.70 was determined on the basis of the rat data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values, which were derived from robust human data. A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences, because clinical signs are likely caused by a direct chemical effect on the tissues and this type of portal-of-entry effect is unlikely to vary greatly between species. Furthermore, calculated LCt_{50} values for different species were all well within a factor of 2 of each other (88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice) (Ballantyne and Swanston 1978). An uncertainty factor of 3 was used to account for intraindividual variability because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. As noted above in support of the AEGL-2 values, a factor of 3 is also supported by the results of studies by Punte et al. (1963) and Gutentag et al. (1960) in subjects with pre-existing conditions.

AEGL values for CS are presented in Table 7-1.

TABLE 7-1 AEGL Values for Tear Gas

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)	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	Ocular, nasal, and throat irritation in humans (Beswick et al. 1972)
AEGL-3 (lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3	Threshold for lethality (LC_{01}) in rats (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. The severity of effects observed at the lowest tested concentrations exceeded those defined by AEGL-1.

1. INTRODUCTION

CS is a white crystalline powder with a pepper-like odor. It was first synthesized by Corson and Stoughton in 1928 (thus, the abbreviation CS) (Corson and Stoughton 1928; US Army Chemical School 2005). It was developed in the 1950s as a replacement for the chemical incapacitant, 1-chloroacetophenone (CN), because CS was a much more potent irritant than CN, but was significantly less toxic (WHO 1970; Colgrave and Creasey 1975; Hu et al. 1989). CS was adopted for use by the military, and was widely used during the Vietnam War (WHO 1970; Hu et al. 1989; Smith and Greaves 2002). It is currently used as an incapacitating agent by military and law enforcement personnel (HSDB 2005). It is reported that an aerosol concentration of 4 mg/m^3 will disperse the majority of rioters within 1 min, and 10 mg/m^3 will deter trained troops (Upshall 1973). With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, usually within 30 min after exposure (Ballantyne 1977).

Because CS is stable when heated and has a low vapor pressure, it requires a means of dispersement (Blain 2003). Different forms of dispersement include the combination of CS with a pyrotechnic compound in a grenade or canister, generating a smoke or fog, and dispersement of a fine powder as an aerosol (WHO 1970; Smith and Greaves 2002). CS1 is a micronized powder formulation of CS containing 5% silica gel for dissemination by an explosive burst or dusting apparatus, and CS2 is the same as CS1 except that the CS1 is microencapsulated with silicone to improve its weather resistance and flow properties (WHO 1970).

In controlled studies investigating the toxicologic properties of CS aerosol, CS was disseminated as a 2-10% solution in methylene chloride or acetone by means of a pneumatic atomizing nozzle assembly (Gutentag et al. 1960; Owens and Punte 1963; Punte et al. 1963) or by thermal dispersion by spraying the molten chemical (Gutentag et al. 1960; Punte et al. 1962, 1963).

CS may be manufactured through carbonyl condensation by combining *o*-chlorobenzaldehyde and malononitrile (HSDB 2005). Recent production data of CS were not available.

Hydrolysis of CS produces malononitrile and *o*-chlorobenzaldehyde (NTP 1990). Hydrolysis of CS is relatively rapid, with a half-life of about 15 min at a pH 7, but CS reacts faster with an alkaline solution, having a half-life of about 1 min at a pH of 9 (Blain 2003).

CS has a vapor pressure of 3.4×10^{-5} mm Hg; thus, at concentrations greater than 0.35 mg/m^3, it will exist in vapor and aerosol forms. CS in the vapor phase will be degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 110 h. CS in the particulate phase will be removed by wet and dry deposition.

The chemical and physical properties of CS are presented in Table 7-2.

TABLE 7-2 Chemical and Physical Properties of Tear Gas

Parameter	Value	Reference
Common name	Tear gas	
Synonyms	CS; *o*-chlorobenzylidenemalonitrile; 2-chlorobenzalmalononitrile; (2-chloro-phenyl)methylene) propanenitrile; 2-chlorobmn; beta, beta-dicyano-o-chlorostyrene	HSDB 2005; O'Neil et al. 2006
CAS registry no.	2698-41-1	O'Neil et al. 2006
Chemical formula	$C_{10}H_5ClN_2$	O'Neil et al. 2006
Molecular weight	188.6	O'Neil et al. 2006
Physical state	White crystalline solid	O'Neil et al. 2006
Melting point	95-96°C	ACGIH 1991
Boiling point	310-315°C	US Army Chemical School 2005
Density (solid)	Bulk: 0.24-0.26 g/mL; crystal: 1.04 g/mL	US Army Chemical School 2005
Solubility in water (g/L)	Sparingly soluble; 2.0×10^{-4} M	ACGIH 1991; O'Neil et al. 2006
Vapor density (air =1)	6.5	US Army Chemical School 2005
Vapor pressure	3.4×10^{-5} mm Hg at 20°C	US Army Chemical School 2005
Henry's Law Constant	1.0×10^{-8} atm-m^3/mol	HSDB 2005
Volatility	0.71 mg/m^3 at 25°C	US Army Chemical School 2005
Stability/reactivity	Combustible material; may burn but does not ignite readily	US Army Chemical School 2005
Conversion factors	1 ppm = 7.71 mg/m^3 1 mg/m^3 = 0.13 ppm	Calculated

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human acute lethality data on CS were found.

2.2. Nonlethal Acute Toxicity

2.2.1. Experimental Studies

In a review article, Blain (2003) reported a TC_{50} (concentration that caused a perceptible effect on 50% of the population exposed for 1 min) of 0.004 mg/m^3 for ocular irritation and 0.023 mg/m^3 for airway irritation. An ICT_{50} (concentration intolerable to 50% of the population exposed for 1 min) was also reported. No further details were presented.

A group of male volunteers was exposed to CS aerosol with a mass median diameter (MMD) of 0.9 microns (94 ± 15 mg/m^3; 4% larger than 10 microns) or up to 60 microns (85 ± 16 mg/m^3; 4% smaller than 20 microns) to assess differences in ocular and respiratory responses to different particle sizes of CS (Owens and Punte 1963). Six volunteers who had the best ability to tolerate CS were chosen from a group of approximately 50. Subjects wore tightly fitted goggles and a nose and mouth respirator designed to protect against particle sizes less than one micron, and were exposed individually in a wind tunnel with a constant air speed of 5 mph. The exposure protocol was designed to restrict exposure to either the small or large particles to the eyes, to the respiratory system, or to both the eyes and respiratory system. The wind tunnel was elevated to a height of 5 feet, and a rubber-lined port was installed in the bottom of the duct enabling the subject to insert his head into the airstream of the tunnel and remove it quickly after the exposure. CS was disseminated from a 2% solution in methylene chloride by means of a pneumatic atomizing nozzle assembly. CS concentrations were determined from air samples collected using filter paper placed on air sampling probes located around the head area (one on top and one on each side at eye level), followed by extraction with ethanol and measurement with ultraviolet spectrophotometry. A modified cascade impactor was used to measure the CS aerosol containing the small particles, while the larger particles were sized microscopically, measuring and counting the various particles in the pre-ground material before dissemination. Tolerance time was defined as the time at which a subject could no longer remain in the atmosphere containing the compound and left the exposure chamber, and recovery time was defined as the time after the exposure when the subjects were able to sort and arrange a series of 24 playing cards from which the corner numbers were removed. Control values were determined before each test. The results indicate that small particles are more effective in rapidly producing ocular irritation (see Table 7-3). The onset of ocular response is hypothesized to be faster with small particles because

TABLE 7-3 Tolerance and Recovery Time in Humans Exposed to Tear Gas Particles (1-60 microns)

	Subjects Tolerating 60-sec Exposure (%)		Recovery Time (sec)	
Exposure	Small Particles[a]	Large Particles[b]	Small Particles[a]	Large Particles[b]
Eyes	40	100	91	280
Respiratory system	0	67	51	9[c]
Eyes and respiratory system	16	85	52	188

[a]Measured concentration of 94 ± 15 mg/m^3.
[b]Measured concentration of 85 ± 16 mg/m^3.
[c]4/6 subjects were able to perform task immediately after exposure.
Source: Adapted from Owens and Punte 1963.

of they are more soluble than larger particles in ocular fluid. Once begun, however, the irritation process would continue for a longer period with the large particles compared with the small particles. Respiratory effects were more severe with small particles (no volunteers could withstand exposure for more than 30 seconds [sec]) and required more time for recovery than the large particles. The difference in response is due to the ability of smaller-sized particles to penetrate more deeply into the respiratory tract. When both the eyes and the respiratory system were exposed to CS, the respiratory response predominated with exposure to the small particles, whereas the ocular response predominated with exposure to the large particles.

A group of 4-6 volunteers was exposed to CS aerosol in a wind tunnel (8 × 8 × 8 feet; fixed wind speed of 5 mph) (Gutentag et al. 1960; Punte et al. 1963). Volunteers were both military and civilian personnel. Each volunteer's medical history was recorded, and each was given pre-exposure and post-exposure physical examinations. Volunteers were classified as "normal" or were placed in one of four special categories: those with hypertension (diastolic pressure of 80-110 mm Hg or normal blood pressure reading with a history of hypertension; pre-exposure tests included electrocardiogram, chest X-ray, liver function, and urinalysis); those with hay fever, drug sensitivity, or bronchial asthma (volunteers with asthma had normal chest X-ray before exposure); those with a history of jaundice, hepatitis, or peptic ulcers without gastrointestinal bleeding; and those that were 50-60 years of age. Subjects classified as normal were further categorized into untrained men with or without protective masks or trained men with or without protective masks. The trained men had previous exposure to CS, whereas the untrained men did not. CS was dispersed as a 10% solution in acetone or methylene dichloride with a spray nozzle (MMD 3.0 or 1.0 micron, respectively) or by thermal dispersion (spraying the molten chemical; MMD 0.5 micron). Airborne samples of the aerosol were collected at various points in the wind tunnel. Particle size was characterized using a 6-stage modified cascade impactor, and exposure concentrations were measured using ultraviolet spectrophotometry. The subjects did not report any noticeable difference in symptoms from the different dispersion methods.

Groups of 3-6 untrained men without masks were exposed to CS in acetone, and tolerance times were recorded. Times ranged from 53 to >120 sec at 5 mg/m^3, 19-43 sec at 12 mg/m^3, and up to 5 sec at 442 mg/m^3. When groups of 1-7 trained men were exposed, tolerance times ranged from 37 to >120 sec at 4 mg/m^3, 18-41 sec at 10 mg/m^3, and up to 12-25 sec at 141 mg/m^3. To compare the effects of hyperventilation on symptoms, untrained subjects ran for approximately 100 yards before exposure. Exercising subjects could not tolerate CS as well as normally breathing subjects; groups of three subjects exposed at 10, 13, or 39 mg/m^3 could tolerate CS for up to 13, 13, and 9 sec, respectively. While ocular irritation was minimal, chest symptoms were more pronounced and recovery time was slightly prolonged (by 1-2 min). The reactions of subjects with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of normal subjects. Subjects with a history of drug allergies or sensitivities, hay fever, or asthma also tolerated exposure to CS at concentrations comparable to those tolerated by normal subjects, but the group with preexisting conditions had a higher percentage of individuals with more severe chest symptoms, with many of them laying prostrate on the ground for several minutes. However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups. When subjects were exposed to CS at temperatures ranging from 0-95°F, tolerance to the chemical was slightly reduced at the high temperature of 95°F. Whether the decrease in tolerance was an actual effect of the exposure, the uncomfortable climate, or a combination of both was unclear. An increase in skin-burning symptoms with increased temperature was attributed to an increase in perspiration.

As part of the study described above, the potential for developing tolerance to CS was investigated by exposing a group of four subjects to CS at 1.5 mg/m^3 for 90 min in a 20,000-L chamber (Punte et al. 1963). No data were provided about the monitoring of the CS aerosol. During exposure, subjects were allowed to smoke, read, and play cards. Only one subject reported nasal irritation (after 2 min), three subjects reported headaches (after 45, 50, and 83 min), and all four subjects reported ocular irritation (after 20, 24, 70, and 75 min). In the second part of the experiment, the four subjects were exposed to CS at 1.5 mg/m^3 for 40 min, and then additional CS aerosol was added to the chamber to achieve an airborne concentration of 11 mg/m^3 in about 10 min. Although the subjects had not been told of the increase in concentration, they all left within 2 min due to respiratory irritation. The exposure concentration was estimated to be 4.3-6.7 mg/m^3 when the subjects left the chamber. In the third part of the experiment, the subjects were exposed to CS at 6 mg/m^3, which was attained over 10 min. Symptoms reported by the subjects included nasal and throat irritation, chest burning, sneezing, ocular irritation and lacrimation, headache, and dermal irritation. Three of the four subjects reported that the exposure was unbearable after 18, 20, and 29 min, with chest symptoms being the reason the subjects left the chamber. The remaining subject was able to tolerate the agent, and the exposure was terminated after 40 min. The investigators attempted to enter the chamber without the benefit of the gradual increase in exposure concentration,

and were unable to remain in the chamber. In the fourth experiment, a concentration of 6.6 mg/m^3 was attained over 30 min. The usual signs and symptoms of CS exposure developed, but to a lesser degree. One of the subjects had to leave after 2 min because of a violent cough, but he returned to the exposure chamber after his cough had ceased upon exposure to fresh air. He remained in the exposure chamber for the duration of the 60-min exposure.

To assess the potential effect of CS exposure on ventilation, cardiac frequency, and breathing pattern, a group of 11 healthy soldier volunteers was exposed to CS aerosol (particle diameter of 1 micron) at a concentration that was progressively increased from 0.2 mg/m^3 to 1.3 mg/m^3 (Cotes et al. 1972; Cole et al. 1977). The exposure duration was not specified, but appeared to be approximately 80 min. CS aerosol was produced by saturating the exposure chamber the evening before the exposure, followed by flushing with air to remove all of the gas except that adsorbed onto the walls and equipment. During exposure, pyrotechnic generators were ignited to progressively raise the concentration of CS throughout the exposure session. Subjects wore woolen or denim battle dress covered with cotton coveralls, boots, and gaiters. Electrocardiogram electrodes were applied to the chest, and subjects wore a full respirator into the chamber. For the commencement of exposure, each subject removed his own respirator. During each exposure, each subject completed two 8-min periods of exercise, which consisted of cycling at 20W up to 120W. During exercise, the subjects breathed through an oral-nasal mask and three-way valve box. Inspiration was from the chamber and expiration was through a 6-L capacity mixing bottle into a low resistance gas meter. Cardiac frequency was measured by electrocardiograph, while a thermister in the valve box recorded respiratory frequency. A control exposure including exercise was conducted the day before and the day after exposure to CS. A major difference between the control and CS exposures was that ventilation was continued throughout the control session but not the CS-exposure session; therefore, the temperature was much higher during the CS-exposure sessions than the control session (~24° vs. 20.5°C for controls).

All subjects experienced intense discomfort, including cough, lacrimation, and substernal pain, when first exposed to the CS aerosol. Discomfort was severe enough that two subjects withdrew (one before and one after the first period of exercise), and two additional subjects were unable to complete the first period of exercise due to coughing. Coughing coincided with ignition of the CS generators. The discomfort disappeared with continuing exposure. Although cardiac frequency increased during exposure to CS compared with control air, the difference was eliminated when the cardiac frequency was corrected for the increased ambient temperature (corrected to the arbitrary temperature of 20°C). The ventilation minute volume was reduced from exposure to CS compared with controls. The reduction appeared to be due to a decrease in respiratory frequency. The exposure was repeated using 17 volunteers (Cole et al. 1975, 1977). Exposure conditions were the same with the following exceptions: the CS candles were ignited between and not during periods of exercise, CS concentrations were slightly higher (0.92-2.15 mg/m^3), and the subjects were seen on five con-

secutive half-day sessions (the first, third, and fifth sessions were for control observations and the other two sessions were allocated one each for exposure to ammonia and to CS [the order of exposure changed between the different weeks of the study]). Results were generally the same as those observed in the first study. The only difference was that the reduction in the ventilation minute volume was the result of a diminution in tidal volume and occurred despite an increase in respiratory frequency.

To investigate the potential for developing tolerance to CS, 35 healthy male volunteers were exposed for 60 min to increasing concentrations of CS aerosol (Beswick et al. 1972). Exposures were conducted in a 100-m^3 chamber. The chamber was generally saturated an hour before the exposure, followed by air being blown through the chamber to remove the CS not absorbed on the walls and equipment. A number of parameters were assessed before and after exposure, including chest radiograph results, hematology and clinical-chemistry analysis, and respiratory-function tests to assess peak flow, tidal volume, and vital capacity. A total of 10 exposure trials were conducted, with no volunteers exposed more than once. Exposure concentrations were kept relatively constant in the first three trials: 0.53-0.86 mg/m^3 in trial 1 (three subjects), 0.71-0.78 mg/m^3 in trial 2 (five subjects), and 0.31-0.74 mg/m^3 in trial 3 (six subjects). For the seven remaining trials, exposure concentrations were increased by a factor of 2, 3, or 4 during the exposure period: 0.8-1.4 mg/m^3 in trial 4 (five subjects), 0.84-2.3 mg/m^3 in trial 5 (four subjects), 0.7-2 mg/m^3 in trial 6 (four subjects), 0.63-2.3 mg/m^3 in trial 7 (two subjects), 0.57-2.1 mg/m^3 in trial 8 (two subjects); 0.42-1.8 mg/m^3 in trial 9 (two subjects), and 0.45-1.7 mg/m^3 in trial 10 (two subjects). Chamber concentrations were measured at 10-min intervals. Volunteers entered the chamber wearing full respirators and protective coveralls. CS was generated and allowed to mix for 3 min before removal of the respirator. Symptoms from all volunteers were reported during individual interviews after exposure. The results of the 10 trials were consolidated into five groups: group I included trial 2 (five subjects), group II included trials 1 and 3 (nine subjects), group III included trial 4 (five subjects), group IV included trials 5 and 6 (eight subjects), and group V included trials 7, 8, 9, and 10 (eight subjects). One of the six subjects in trial 3 left the exposure chamber after 8 min of exposure with complaints of severe stinging of the eyes, throat irritation, cough and dyspnea, salivation, and nausea, and one subject in group IV left after 55 min due to vomiting. All other subjects remained in the chamber for the entire 60-min exposure period. A summary of the symptoms of the exposed individuals is presented in Table 7-4. The predominant symptoms included excess production of mucus and saliva (34/34 subjects), ocular irritation (stinging in 32/34 subjects and lacrimation in 32/34 subjects), runny nose (28/34 subjects), and face stinging (32/34 subjects). Symptoms generally resolved within 10 min of leaving the chamber. Nausea was reported by 11/34 subjects and two vomited, which appeared to follow swallowing of large amounts of saliva. The development of tolerance was assessed in two of the trials (group IV in Table 7-4); in these trials, half of the subjects removed the respirator at the start of the exposure (with the CS concen-

tration increasing with time), while the remaining subjects did not remove their respirators until the last 5 min of exposure. The subjects that were exposed to CS throughout the entire exposure period were able to withstand the entire 60-min exposure (concentrations increasing from 0.84 to 2.30 mg/m^3 and 0.70 to 2.00 mg/m^3) except for the one individual that had to leave the chamber at 55 min because of vomiting. Of the subjects that removed their respirators for the last 5 min of exposure, only one of eight subjects could remain in the chamber for more than 1 min; five left within 30 sec of removing their respirators. No exposure-related changes were observed in hematology or clinical chemistry parameters. Decreases in heart rate after exposure ceased were ascribed to the sense of relief each volunteer felt at the end of an uncomfortable experience, and the increase in systolic blood pressure observed in individuals when exposure commenced was due to the abrupt onset of discomfort; continued exposure resulted in normal blood pressure readings. No abnormalities were noted in measurements of respiratory function, but the investigator noted that the sample size was small and, thus, may not be representative. It was concluded that the main effects of CS are due to local irritation of exposed nerve endings, and systemic changes noted are due to stress.

Three groups of volunteers were exposed to CS aerosol at various concentrations to investigate potential effects on visual acuity (Rengstorff 1969). The first group was composed of 10 male volunteers exposed to CS2 aerosol (CS treated with Cab-o-Sil® 5 and hexamethyldisilaxane) at concentrations of 0.1 to 1.7 mg/m^3. The exposure was conducted in a wind tunnel suspended 4.5 feet above the floor; the volunteer sat on a chair at the end of the wind tunnel and put his head through a rubber aperture in the tunnel until he could no longer tolerate the exposure or for a maximum of 10 min. A powder dispenser disseminated specific concentrations of CS2 (MMD of 0.8 microns) into the air at a wind speed of 4.5 mph. An Orthorater was used to measure the binocular far and near visual acuity of the subjects before and after exposure. The second and third groups were exposed to CS aerosol in a circular steel chamber. CS aerosol (MMD of 0.9 micron) in a methylene dichloride solution was disseminated using a thermal generator, and introduced into the chamber as a uniform cloud. Subjects wore protective masks for the first 5 min in the chamber, and then removed their masks for the commencement of exposure. The second group was composed of 34 volunteers, and an Orthorater was again used to measure the binocular far and near visual acuity before and after exposure. A summary of the amount of time volunteers from this group could tolerate exposure to CS is presented in Table 7-5. The third exposure involved 22 volunteers who had a baseline visual acuity of 20/20 and who could remain in the exposure chamber for 10 min. Binocular acuity was measured using a Snellen visual acuity projector before, during, and a few minutes after exposure. The Snellen chart contained a row of 20/30, 20/25, and 20/20 letters. No exposure-related changes in visual acuity were noted except those due to the inability of some subjects to keep their eyes open because of intense ocular irritation. Visual acuity returned to normal in all subjects several minutes after exposure to CS ended.

TABLE 7-4 Symptoms of Volunteers Exposed to Tear Gas for 60 Minutes

	Exposure Group (nominal-fold increase in concentration during exposure)						
Symptoms	I (steady)	II (× 2)	III (× 2)	IV (× 3)	V (× 4)	Total	Observations
Number exposed	5[a]	8[b]	5[c]	8[d]	8[e]	34	–
Eyes:							
Stinging	5	8	4	7	8	32	No connection between severity and concentration, but duration of symptoms may be less with steady concentration.
Watering	5	8	5	7	7	32	
Nose:							
Stinging	3	4	1	6	4	18	Effects diminished in subjects exposed at steady concentrations or at concentrations that were doubled during the exposure duration.
Running	3	7	3	8	7	28	
Peppery feeling	2	4	2	4	5	17	
Blocked	1	3	2	3	2	11	
Mouth							
Irritation	2	4	–	6	3	15	Copious saliva production; subjects spitting appeared to be vomiting.
Salivation	5	8	5	8	8	34	
Throat:							
Irritation	4	5	3	6	5	23	–
Dry	–	1	–	6	1	8	
Chest:							
Burning	2	2	–	3	1	8	More severe effects appeared to be due to deep breaths taken after holding breath; coughing was sporadic.
Tight	1	3	2	2	3	11	
Dyspnea	–	2	2	2	3	9	
Cough	5	2	4	3	4	18	

Nausea	2	3	1	3	2	11	–
Vomiting (during exposure)	–	–	–	1	1	2	Likely due to swallowing large quantity of saliva. Subject in Group V vomited within first 5 min and left chamber, but returned for duration of exposure. Subject in Group IV vomited after 55 min.
Face stinging	5	7	5	7	8	32	Effects appeared to be of shorter duration in subjects exposed at steady concentrations. Stinging most unpleasant in shaved regions.
Headache	2	1	2	1	–	6	Persisted in 3 subjects throughout exposure; three cases reported post-exposure. Appeared to be due to irritation of the frontal sinuses.

[a]Five subjects exposed at 0.71-0.78 mg/m^3.
[b]Three subjects exposed at 0.56-0.86 mg/m^3, and five subjects exposed at 0.31-0.74 mg/m^3 (one subject excluded because he left the exposure chamber after 8 min).
[c]Five subjects exposed at 0.8-1.4 mg/m^3.
[d]Four subjects exposed at 0.84-2.3 mg/m^3, and four exposed at 0.7-2.0 mg/m^3. To assess the development of tolerance, four subjects removed respirators at start of exposure, while the other four removed respirators 5-min before the end of exposure; the subjects that removed respirators at beginning of exposure were able to withstand the entire 60-min exposure, except for one individual that had to leave the chamber after 55 min because of vomiting. Of the subjects that removed their respirators during the last 5 min of exposure, only one of eight could remain in the chamber for more than 1 min and five left within 30 sec of removing their respirators.
[e]Two subjects exposed at 0.63-2.3 mg/m^3, two exposed at 0.57-2.1 mg/m^3, two exposed at 0.42-1.8 mg/m^3, and two exposed at 0.45-1.7 mg/m^3.
Source: Adapted from Beswick et al. 1972.

TABLE 7-5 Tolerance of Humans Subjects Exposed to Tear Gas for Up to 10 Minutes in Study Evaluating Visual Acuity

Concentration (mg/m^3)	Number of Subjects	Exposure Duration (sec)
0.4	1	135
	1	420
	1	435
	4	600
0.6	1	30
	2	35
	1	38
	1	40
	1	65
	1	68
	1	102
	1	105
	1	135
	7	600
0.9	6	600
1.0	1	35
	1	40
	1	45
	1	50

Source: Adapted from Rengstorff 1969.

To assess the effect of CS exposure on respiration, a group of six volunteers (four with previous exposure to CS) were exposed to various concentrations of CS (3 micron) in a wind tunnel while a portable breathing device monitored respiration (Craig et al. 1960). Subjects remained in the tunnel until the exposure became intolerable (see Table 7-6). Notable coughing was observed in subjects exposed at 15 mg/m^3 for 61 sec or at 150 mg/m^3 for 12 sec. On the basis of the recordings made during exposure, it was concluded that although the breathing pattern of the volunteers was disrupted, adequate ventilation was maintained. Therefore, the incapacitation of CS is attributed to the unpleasant sensations of exposure rather than to any degree of respiratory failure.

A group of 38 US Marines was exposed to a cloud of CS dispersed by a thermal canister as part of a training exercise to test the ability and speed of the trainees in donning their gas masks (Thomas et al. 2002). The exposure occurred after 6 days of strenuous training with minimal sleep and reduced food consumption, and was followed by a 1.5-mile run. Temperature and relative humidity at the time of exposure were approximately 24°C and 91%, respectively. Clinical signs and symptoms began to develop 36-84 h post-exposure during and

TABLE 7-6 Tolerance of Human Subjects Exposed to Tear Gas in Study Evaluating Respiratory Effects

Concentration (mg/m^3)	Exposure Duration (sec)
5	110 +
12	24
15	61 +
64	15 +
80	12
150	12 +

+ Previous exposure to CS.
Source: Craig et al. 1960.

after periods of strenuous exercise (one subject became symptomatic after a 1,000-meter pool swim at 36 h post-exposure; seven became symptomatic after a second swim consisting of a 1,000-meter open ocean swim 60 h post-exposure; and one became symptomatic after a third swimming event consisting of a 1,500-meter open ocean swim 84 h post-exposure). A total of nine subjects were affected, with four requiring admission into intensive care. Effects of exposure included dyspnea upon exertion, hemopytosis (ranging from frank blood to blood-tinged sputum), cough, rales, reduced arterial blood gas (range of 60-68), and infiltrates visible on chest radiograph. Signs and symptoms resolved by 72 h, and lung function before and after exercise challenge returned to normal within 1 week post-exposure. When the exposure in this study was recreated (without test subjects) and air sampling was performed, CS concentrations were found to range from less than quantifiable to approximately 17 mg/m^3.

McDonald and Mahon (2002) proposed that the pulmonary symptoms in the Marines described in the study by Thomas et al. (2002) were not the result of CS exposure, but were rather the result of water aspiration or swimming-induced pulmonary edema (SIPE). Their conclusions were based on the observations that all subjects became symptomatic immediately after swimming, that there was a rapid resolution of symptoms, and that there was no evidence of airway dysfunction. Delayed pulmonary effects of CS exposure are unusual, and there were no other reports of such symptoms even though approximately 200,000 Marines have been exposed to CS since 1996 under similar field conditions.

2.2.2. Case Reports

The effects of exposure to CS are generally of an acute nature. However, reactive airways dysfunction syndrome was reported in two individuals exposed to CS. One case involved a healthy 21-year-old female exposed to CS smoke at a nightclub for 5-10 min (Hu and Christiani 1992). She exhibited the typical signs and symptoms of CS exposure, including tightness and burning in her chest and coughing. Results of a physical examination and chest radiography were normal,

and she was released from the hospital. She continued to experience coughing and shortness of breath, and had reduced measurements of forced expiratory volume in 1 sec (68% of predicted) and forced vital capacity (78%) 4 weeks after exposure. Cough and shortness of breath were still present at the 2-year follow-up exam, and were made worse by exertion, cold air, and some environmental pollutants. The second case report involved exposure to a riot-control agent containing 1% CS and 1% oleo resin capsicum (Roth and Franzblau 1996). A healthy 53-year-old male was exposed for at least 30 sec, and immediately experienced symptoms of mucous membrane irritation, cough, and chest tightness. Wheezing and shortness of breath continued for months after exposure, and were severe enough to require hospitalization. Pulmonary function test results indicated reversible and fixed obstructive pulmonary disease. Effects of exposure to the capsicum cannot be excluded.

A 4-month-old infant exposed to CS for 2-3 h developed pneumonitis and persistent leukocytosis (Park and Giammona 1972). The infant was exposed when a CS canister was fired into a house to subdue an adult. Upon hospitalization, the infant had copious nasal and oral secretions and was sneezing and coughing. A chest X-ray demonstrated that the lungs were clear, but laboratory testing revealed leukocytosis. The infant developed severe respiratory distress by the second day of hospitalization, with pulmonary infiltrates evident on X-ray by day 7. Pulmonary infiltration began to decrease on day 15, and the lungs were clear on day 17. White blood cell counts were elevated throughout hospitalization, and finally decreased when the infant was discharged from the hospital.

CS is a common riot-control agent in Britain; consequently, typical symptoms following exposure to CS have been described following its use in confined spaces, such as a night club (Breakell and Bodiwala 1998) or bus (Karagama et al. 2003), use by police on individuals for self-defense (Euripidou et al. 2004), or under conditions of large-scale riot control (Himsworth 1969; Anderson et al. 1996). Symptoms of exposure included but were not limited to ocular irritation, lacrimation, blurred vision, burning sensations sometimes accompanied by first degree burns, cough, headache, shortness of breath, chest pain, sore throat, retching, vomiting, and salivation (Himsworth 1969; Anderson et al. 1996; Breakell and Bodiwala 1998; Karagama et al. 2003; Euripidou et al. 2004). In general, the symptoms resolved rapidly; however, there were reports of effects lasting longer that that predicted. The hand-held spray canisters used by police contain CS dissolved in methyl isobutyl ketone, an industrial solvent and denaturant (Gray 2000; Euripiou et al. 2004). It has, therefore, been proposed that the ketone combined with the CS may result in longer lasting adverse effects than CS preparations without the solvent.

2.3. Developmental and Reproductive Toxicity

The National Teratology Information Service collected outcome data on 30 pregnant women who were exposed to CS gas: 12 women during the first

trimester, 11 during the second trimester, and seven during the third trimester (McElhatton et al. 2004). Acute maternal toxicity (transient symptoms of ear, nasal, and throat irritation) was reported by 50, 82, and 57% of the exposed women, respectively. Pregnancy outcome was not adversely affected by exposure to CS. Birth weight was within the normal range except for one female baby weighing less than 2,500 g. One infant had a congenital anomaly (hypospadia), and this anomaly has a background incidence of 1 in 1,000 live born male infants. No concentration or duration exposure parameters were described.

2.4. Genotoxicity

No data on the genotoxicity of CS in humans were found.

2.5. Summary

CS is a potent irritant, with symptoms of exposure including lacrimation, blepharospasm, erythema of the eyelids, chest tightness, coughing, nasal irritation and discharge, salivation, throat irritation, nausea, vomiting (from swallowing excess saliva), and cutaneous irritation (ranging from stinging to contact irritation or allergic dermatitis). Upshall (1973) reported that an aerosol concentration of CS at 4 mg/m^3 will disperse the majority of rioters within 1 min, and 10 mg/m^3 will deter trained troops. With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, generally within 30 min after exposure (Ballantyne 1977).

Data on human tolerance to CS are summarized in Table 7-7. Many studies investigated the amount of time that elapsed before subjects could no longer remain in an atmosphere containing CS. Gutentag et al. (1960) and Punte et al. (1963) reported tolerances of 5 sec at 442 mg/m^3, 12-25 sec at 141 mg/m^3, 9 sec at 39 mg/m^3, and more than 90 min at 1.5 mg/m^3. Tolerance to low concentrations of CS could be increased when exposure concentration was increased over time (Punte et al. 1963; Beswick et al. 1972). A study investigating the differences in respiratory and ocular responses to different particles sizes of CS found that small particles are more effective than larger particles in producing ocular and respiratory irritation. Recovery time for ocular irritation took longer for large particles, because the onset of irritation was delayed due to the lower solubility of large particles. Recovery time for respiratory irritation took longer for small particles, because the smaller sized particles penetrated further into the respiratory tract (Owens and Punte 1963).

Pregnancy outcomes were not affected in a prospective case study of 30 pregnant women who were exposed to CS gas and experienced transient symptoms of ear, nasal, and throat irritation (McElhatton et al. 2004). No other reproductive or developmental toxicity data of CS in humans were available. No human data on the toxicity of repeated exposures to CS or on the genotoxicity or carcinogenicity of CS were found.

TABLE 7-7 Summary of Selected Human Toxicity Data on Tear Gas

Concentration (mg/m^3)	Tolerance Duration[a]	Notes	Reference
94[b]	<60 sec	6 subjects chosen for ability to tolerate CS.	Owens and Punte 1963
85[c]	<60 sec		
5	53 to ≥120 sec	Untrained subjects; maximum exposure duration of 2 min.	Punte et al. 1963;
12	19-43 sec		Gutentag et al. 1960
442	5 sec		
4	37 to ≥120 sec	Trained subjects (previous exposure to CS); maximum exposure	Punte et al. 1963;
10	18-41 sec	duration of 2 min.	Gutentag et al. 1960
141	12-25 sec		
10	13 sec	Untrained subjects; exercised before exposure.	Punte et al. 1963;
13	13 sec		Gutentag et al. 1960
39	9 sec		
0.4	135-600 sec[d]	4/7 tolerated 10 min.	Rengstorff 1969
0.6	30-600 sec[d]	7/17 tolerated 10 min.	
0.9	600 sec[d]	6/6 tolerated 10 min.	
1	35-50 sec		
6 (attained over 10 min)	18 min	1 subject	Punte et al. 1963
	20 min	1 subject	
	29 min	1 subject	
0.75 (average)[e]	60 min[f]	5 subjects; all remained in chamber for duration of exposure; ocular, nasal, mouth, and throat irritation, nausea, chest discomfort, headache, and stinging of the face.	Beswick et al. 1972
0.56-0.86	8 min	9 subjects; concentration increased during exposure;	
0.31-0.74	60 min[f]	1 subject in 0.31–0.74-mg/m^3 group left after 8 min because of irritation; 8 subjects tolerated 60-min exposure with same signs as 0.75-mg/m^3 group.	

0.8-1.4	60 min[f]	5 subjects; all tolerated exposure with same signs as 0.75-mg/m^3 group.	
0.84-2.3 0.7-2.0 0.63-2.3 0.57-2.1 0.42-1.8 0.45-1.7	60 min[f]	16 subjects; 1 subject vomited after 5 min, left chamber but returned for duration of exposure; 1 subject vomited after 55 min; 14 subjects tolerated 60-min exposure with same signs as 0.75-mg/m^3 group.	
1.5	90 min[g]	4 subjects; 1 developed nasal irritation (at 2 min); 3 developed headache (at 45, 50, and 83 min); 4 had ocular irritation (at 20, 24, 70, and 75 min)	Punte et al. 1963

[a]Time at which the subject could no longer tolerate exposure.
[b]Mass median diameter of 0.9 microns.
[c]Mass median diameter of 60 microns.
[d]Exposure was for a maximum of 10 min.
[e]Average concentration calculated using the six interval concentrations.
[f]Exposure was for a maximum of 60 min.
[g]Exposure was for a maximum of 90 min.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

Groups of eight immature male and female *Macaca mulatta* monkeys (3-4 kg) were exposed to a cloud of CS dispersed via an M7A3 CS grenade in a 20,000-L chamber at an average CS concentration of 900 mg/m^3 for 3 min, 1,700 mg/m^3 for 5 min, 2,850 mg/m^3 for 10 min, or 2,500 mg/m^3 for 32 min (Striker et al. 1967). The report stated that the cloud was sampled and measured at various times, but details were not provided. A group of eight monkeys served as controls; they were treated similarly to the exposed monkeys except they were not put into an exposure chamber. Monkeys were observed frequently for clinical signs during the first 72 h after exposure. Chest radiographs were taken before exposure and after 2, 6, or 12 h or 1, 3, 7, or 30 days post-exposure. Monkeys were killed after 12 h or after 3, 7, or 30 days. Clinical signs in monkeys exposed to CS at 900 mg/m^3 for 3 min or at 1,700 mg/m^3 for 5 min included blinking and a "fright reaction" observed immediately after removal from the exposure chamber, which disappeared within a few minutes after the monkeys were moved to fresh air. Monkeys exposed at 2,850 mg/m^3 for 10 min exhibited frequent blinking, labored respiration, coughing, oral and nasal discharge, occasional vomiting, and decreased activity and response to external stimuli. One monkey also had copious ocular discharge. Clinical signs were most severe at 12 h and were generally resolved within 72 h. Clinical signs in monkeys exposed to CS at 2,500 mg/m^3 for 30 min were severe and included prostration, dyspnea, copious oral and nasal discharge, and scleral congestion after removal from the exposure chamber. Five monkeys died; four died 3-12 h after exposure and one died on day 4. Dyspnea was most severe at 12 h, while oral and nasal discharge and effects on the eyes were most severe at 24 h. Radiographic findings were present only in this group; infiltrates appeared 3 h after exposure, were most severe after 24 h, and cleared after 3 days.

Pathologic examination of the monkeys 12 h after exposure to CS at 900 or 1,700 mg/m^3 revealed mild pulmonary congestion, bronchorrhea, emphysema, and atelectasis (Striker et al. 1967). These effects disappeared in the monkeys examined on day 3, but recurred in monkeys examined on days 7 and 30. Pathologic lesions were more severe and developed earlier in monkeys exposed at 2,850 mg/m^3 for 10 min. Pulmonary edema and congestion and bronchorrhea were found at 12 h, and progressed to purulent bronchitis and bronchopneumonia at day 3. After 1 week, acute pleuritis and interstitial pneumonitis were seen, and mucosal lesions and bronchopneumonia were resolving. Lesions were still present after 4 weeks, and included emphysema, atelectasis, and focal interstitial pneumonitis. Pathologic findings in monkeys that died after exposed to CS at 2,500 mg/m^3 for 30 min included severe pulmonary edema and congestion. The three surviving monkeys were killed on days 3, 7, or 30. The monkey killed on

day 3 days had considerable edema, but congestion was less prominent. Examination of the monkey killed on day 7 revealed emphysema involving all lobes and bronchiolitis, but most of the edema had cleared. The monkey killed on day 30 had small shrunken lungs, purulent mucoid material filling many small bronchioles, and distinct bronchiolitis.

McNamara et al. (1969) exposed groups of four monkeys (strain and sex not specified) to seven different CS concentration-duration combinations. No further experimental details were available. Mortality data from this study are summarized in Table 7-8.

3.1.2. Rats

Groups of 10 rats were exposed to an aerosol of CS for 25-90 min (Punte et al. 1962). Animals were exposed in a dynamic inhalation chamber containing individual cages on racks. Aerosol was generated by passing dry nitrogen through an aspirator. Molten CS was maintained in a side-armed flask in an oil bath at 140-150°C. The aerosol was easily generated and liquid droplets recrystalized before entering the exposure chamber. Chamber concentrations were measured by drawing chamber air through filter paper for subsequent analysis by spectrophotometry. Samples for particle-size determinations were collected by a Cascade impactor, and MMD was derived by use of stage calibrations based on the density of the compound; the particle size was about 1.5 microns (MMD). Observations for clinical signs were made during and after exposure. Surviving animals were maintained for 14 days, and then killed and examined histopathologically. Immediately after exposure began, the animals became excitable and hyperactive, and lacrimation and salivation occurred within 30 sec. Lethargy and dyspnea occurred after approximately 5-15 min. Dyspnea persisted for approximately an hour after exposure ceased, and all other signs subsided about 5 min after the rats were removed from the chamber. Histopathologic examinations revealed an increase in the number of Goblet cells in the respiratory tract and conjunctiva, necrosis in the respiratory and gastrointestinal tracts only if particles had impacted the surface, and an occasional animal with pulmonary edema and hemorrhage in the adrenal glands. The calculated LCT_{50} was 32,500 mg-min/m^3.

An unpublished report by McNamara et al. (1969) appears to provide data additional to those that were published by Punte et al. (1962). Specific study details are not provided in the unpublished report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results from tests with additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by different methods. As discussed above, Punte et al. (1962) reported mortality data for rats, but the values were reported only in terms of mg-min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in the unpublished study by McNamara et al. (1969) and are presented in Table 7-8.

TABLE 7-8 Mortality Data from Studies by McNamara et al. (1969) in Different Species Exposed to Tear Gas

Species	Concentration (mg/m^3)	Duration (min)	Mortality	Time to Death (days)[a]
Rats[b]	560	25	1/10	1(1)
	543	35	2/10	1(2)
	489	45	3/10	2(1), 3(1), 4(1)
	454	55	5/10	1(3), 3(2)
	500	60	2/10	1(2)
	500	80	6/10	1(1), 2(2), 6(3)
	500	90	8/10	1(1), 3(2), 7(2), 11(3)
Mice[b]	1,200	10	0/20	–
	1,100	20	7/20	7(1), 8(3), 9(3)
	900	30	2/20	7(2)
	800	40	5/20	5(2), 9(3)
	740	50	5/20	5(1), 6(3), 7(1)
	683	60	14/20	5(4), 8(5), 9(4), 13(1)
Guinea pigs[b]	400	5	1/10	7(1)
	400	10	2/10	7(1), 8(1)
	400	15	4/10	1(2), 6(2)
	500	20	3/10	1(1), 6(1), 7(1)
	400	25	7/10	2(5), 7(1), 8(1)
	400	30	7/10	1(4), 5(1). 7(1), 9(1)
	425	40	8/10	1(7), 3(1)
Rabbits[b]	500	30	1/4	6(1)
	250	40	0/4	–
	267	45	0/4	–
	250	80	3/4	1(1), 2(1), 7(1)
	333	90	4/4	1(1), 2(1), 3(1), 8(1)
Dogs[c]	833	20	0/4	–
	649	30	1/4	12(1)
	508	36	2/4	5(1), 10(1)
	899	40	2/4	1(1), 2(1)
	520	45	2/4	1(1), 4(1)
	612	45	2/4	1(2)
	797	60	3/4	1(2), 3(1)
	909	60	2/4	1(2)
Monkeys[c]	469	24	1/4	5(1)
	673	30	2/4	1(2)
	381	45	2/4	1(2)
	612	45	1/4	1(1)
	699	60	1/4	1(1)
	941	60	3/4	1(3)
	1,057	60	2/4	1(2)

[a]Number in parenthesis indicates number of deaths on that day.
[b]Source of CS was the same for rats, mice, guinea pigs, and rabbits.
[c]Source of CS was the same for dogs and monkeys, except CS used in the monkey studies had a mass-median diameter of 2.0-3.2 microns (ultraviolet analysis was conducted at 260 nanometers).
Source: Adapted from McNamara et al. 1969.

Groups of 18 male albino SPF rats were exposed to pyrotechnically-generated CS smoke in a 10-m^3 chamber (Colgrave and Creasey 1975). The rats were exposed to at 5,871 ± 476 mg/m^3 for 15 min, at 6,030 ± 590 mg/m^3 for 10 min, or at 6,800 ± 1,166 mg/m^3 for 5 min (averages and standard deviations were calculated on the basis of the values reported by the investigators as 6,000, 6,000, and 6,400 mg/m^3, respectively). CS was released from four CS cartridges, each containing CS (12.5 g), potassium chlorate (16 g), lactose (15 g), and kaolin (7.5 g). The cloud of CS in the exposure chamber was sampled at approximately 1-min intervals for the 10- and 15-min exposures and at 30-sec intervals during the 5-min exposure. The analytic method used to measure CS concentrations was not described. Survivors were killed at times ranging from 15 min to 2 days post-exposure. All animals were necropsied, and selected tissues were analyzed by both light and electron microscopy. Nonexposed controls were used to establish the typical macroscopic and microscopic appearance of the tissues of the particular strain used. Mortality occurred in four rats exposed at 5,871 mg/m^3 for 15 min (death occurred with 24 h), and in two rats exposed at 6,030 mg/m^3 for 10 min (death occurred within 24 or 36 h). All animals exposed at 6,800 mg/m^3 survived until the study terminated after 2 days. Animals that died after exposure to CS for 15 min developed marked pulmonary congestion with scattered alveolar hemorrhages and patchy edema. Survivors developed less marked pulmonary congestion and only occasional areas of edema and hemorrhaging. Rats that died after exposure to CS for 10 min also developed pulmonary congestion, but the severity was much less than that seen with the 15-min exposures. Hemorrhages and edema were occasionally seen in the lungs of survivors. Examination of rats exposed to CS for 5 min revealed mild pulmonary congestion with occasional hemorrhage up to 6 h post-exposure. Rats killed between 12 h and 2 days post-exposure had no pulmonary findings except for one rat with moderate and extensive pulmonary congestion. Electron microscopic examination of the lungs from all exposed rats revealed changes in the epithelium and interstitium, with accumulation of fluid between the membrane layers and collagen-containing areas of the septum. Degenerative changes of the epithelium and endothelium led to rupture or dissolution of the capillary wall. The investigators stated that the changes were similar in all exposed rats, with the changes varying only in the degree of severity. Damage was evident as early as 15 min after exposure, and became more severe after 30 and 60 min.

Ballantyne and Callaway (1972) exposed groups of male and female Wistar-derived SPF rats to pyrotechnically-generated CS smoke at concentrations of 750 mg/m^3 for 30 min, 480 mg/m^3 for 1 h, or 150 mg/m^3 for 2 h in a 10-m^3 exposure chamber. A group of control animals was also maintained, but no description of the treatment of the controls was provided to determine whether they were exposed under similar conditions to clean air. The grenades used for the exposure contained CS (2 g), potassium chlorate (2.4 g), lactose (2.4 g), and kaolin (1.2 g). Although the report stated that the concentration of CS in the exposure chamber was sampled at the start of the exposure and at 6-min intervals up to and including 57 min, no information was provided about the analytic

technique. Groups of animals were killed after 1, 10, and 28 or 29 days. Some of the animals exposed at 480 or 150 mg/m^3 were retained for up to 32 months to evaluate potential lasting toxicity and pathology (Marrs et al. 1983a). Animals that died or were moribund after 1 month and those killed after 32 months were subjected to gross necropsy, and the heart, lungs, small intestine, liver, pancreas, spleen, kidneys, brain, gonads, and pituitary and adrenal glands were removed and processed for histologic examination.

All animals exposed for 30 min at 750 mg/m^3 survived to the scheduled necropsy, and histopathologic changes were found only on post-exposure day 1 (see Table 7-9). One rat had congestion of alveolar capillaries and a few scattered alveolar hemorrhages, while another rat had a few minute foci of renal tubular necrosis at the inner cortex. No pathologic changes were found in rats at post-exposure day 10 or 28. Exposure to CS at 480 mg/m^3 for 1 h resulted in the mortality of some rats (see Table 7-9), with the majority of the deaths occurring on post-exposure days 1 and 2. Pathologic changes in animals surviving exposure at 480 mg/m^3 were generally confined to post-exposure day 1; lesions were limited to minimal pulmonary congestion and hepatic congestion in one rat, minimal pulmonary hemorrhage and hepatic necrosis in another rat, and mild pulmonary congestion in a third rat. Two rats had mild pulmonary edema. A few rats killed after 10 days had healed lesions, as evidenced by binucleate liver cells around centrilobular veins and immature epithelium in some renal tubules. No abnormal pathologic changes were noted at day 29. Histopathologic findings in rats that died were much more severe and included renal changes (mild-to-moderate necrosis of the cortex, moderate-to-severe necrosis of the medulla, and some mild congestion), pulmonary changes (mild-to-severe congestion, mild hemorrhage, and some mild edema), and hepatic changes (glycogen depletion in all rats and a few cases of mild congestion and mild-to-moderate necrosis).

Exposure to CS at 150 mg/m^3 for 2 h resulted in no mortality. Pathologic examination of the animals revealed lesions only on day 1 post-exposure. Lesions were confined to female animals; one rat had a few scattered alveolar hemorrhages, one had acute mucoid enteritis, and one had pneumonic consolidation of the upper right lung lobe.

Exposure to CS at 480 mg/m^3 for 1 h or at 150 mg/m^3 for 2 h did not affect the lifespan of rats, and no statistically significant increases were found in non-neoplastic lesions in the exposed groups compared with controls (Marrs et al. 1983a). Common non-neoplastic lesions in male and female rats included changes in the lungs (engorgement, congestion, inflammatory changes, and pulmonary edema) and pyelonephritis of the kidneys. Liver congestion was also a common finding. No exposure-related neoplastic lesions were evident in male rats. Female rats in the 150-mg/m^3 group exhibited an increased incidence of pituitary tumors; incidence was 26% in the control group, 29% in the group exposed to CS at 480 mg/m^3 for 1 h, and 47% in the group exposed at 150 mg/m^3 for 2 h. The increases were not statistically significant.

TABLE 7-9 Summary of Acute Toxicity Data from Studies by Ballantyne and Callaway (1972) in Hamsters and Mice Exposed to Tear Gas

						Day 1		Day 10		Day 25 or 29	
						No. killed	No. w/ lesions	No. killed	No. w/ lesions	No. killed	No. w/ lesions
750	30	Hamster	Male	24	0	8	3	8	0	8	0
		Rat	Male	24	0	8	2	8	0	8	0
480	60	Hamster	Male	47	16 (34%)	8	4	2	0	9	0
			Female	59	15 (25%)	7	6	3	0	8	0
		Rat	Male	60	6 (10%)	6	2	2	0	8	0
			Female	60	3 (3%)	7	1	2	0	8	0
150	120	Hamster	Male	58	2 (3%)	8	0	6	0	6	0
			Female	62	0	8	3	10	0	8	0
		Rat	Male	60	0	8	0	8	0	8	0
			Female	60	0	8	2	8	1	8	0

Source: Adapted from Ballantyne and Callaway 1972.

In another experiment, Ballantyne and Callaway (1972) exposed groups of 10 rats for 5 to 20 min to CS at an approximate concentration of 4,000 mg/m^3, followed by a 14-day observation period. An anti-riot grenade containing approximately 50 g of CS was ignited in a 10-m^3 static chamber and allowed to burn to completion. All animals that died and the survivors killed at the end of the 14-day observation period were subjected to gross and histologic examinations. Clinical signs during exposure could not be recorded because the aerosol generated in the chamber resulted in a complete lack of visibility. Upon removal from the chamber, animals exhibited signs of increased buccal and nasal secretions and dyspnea, particularly at the longer exposure durations. Mortality data are summarized in Table 7-10. No animals died during exposure. Necropsy revealed pulmonary edema and congestion, often with multiple, variable sized areas of hemorrhage, and mucus in the trachea and major bronchi. Histopathologic examination of these animals revealed severe congestion of the alveolar capillaries and intrapulmonary veins and alveolar hemorrhage. Mucus was seen in some bronchi and bronchioles, and occasional areas of collapse and hemorrhage were seen distal to a completely occluded bronchiole. Moderate-to-marked pulmonary edema was also observed in several animals. No evidence of acute inflammatory cell infiltrate was observed in any of the lungs examined, suggesting that the CS aerosol produced direct injury to the pulmonary capillary endothelium. Circulatory failure evidenced as congestion of the liver, kidneys, and spleen and dilation of the right ventricle was present in most of the animals that died. Animals that survived to day 14 days did not have any residual pathologic changes at necropsy.

Groups of 20 or 21 male Porton-Wistar rats were exposed by whole body inhalation to various concentrations of CS aerosol for 10-60 min (see Table 7-11) (Ballantyne and Swanston 1978). Animals were exposed in a 1-m^3 dynamic flow chamber. The aerosol was generated by filling a Collision spray with molten CS (heated to 150°C) and passing pure nitrogen into the air stream. The resultant aerosol was fed into the diluting air stream. The chamber atmosphere was sampled for 1 min at 5-min intervals by aspirating air through glass fiber discs held in double cone filters. A bubbler containing hydrochloric acid in ethanol was connected in line to the glass filter to act as an additional trap. The contents of the bubbler were used to elute CS from the filter discs, and the concentration of CS in the resultant extract was measured by absorption spectrophotometry and compared with a prepared standard. Signs of toxicity included increased nasal and buccal secretions and increased rates of respiration when removed from the chamber; effects disappeared within approximately 1 h post-exposure. No animals died during exposure; deaths generally occurred within the first 2 days following exposure. A summary of mortality data is presented in Table 7-11. Necropsy findings in animals dying within 48 h included pulmonary congestion and edema (with some animals also having multiple variable sized hemorrhages) and congestion of the trachea. Moderate amounts of mucus were also seen in the trachea. Histopathologic examination of the lungs from these animals revealed moderate-to-marked congestion, inter- and intra-alveolar hem-

orrhaging, and excess secretions in the bronchioles and intrapulmonary bronchi. Examination of animals dying after 48 h revealed similar findings, as well as evidence of early bronchopneumonia. Congestion of the liver, kidneys, spleen, and small intestines were also frequently seen in animals dying from exposure. No abnormal findings were found in animals surviving the 14-day observation period.

3.1.3. Mice

Groups of 20 mice were exposed to an aerosol of CS for 10-60 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for the corresponding study in rats (see Section 3.1.2). The calculated LCT_{50} was 43,500 mg-min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that were published in this study. Specific study details are not provided in the unpublished report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results from tests with additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by different methods. Punte et al. (1962) reported mortality data for mice, but the values were reported only in terms of mg-min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in the unpublished study by McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of 10 mice for 5-20 min to CS at an approximate concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings were similar to those described in the corresponding study in rats (see Section 3.1.2). Mortality data are summarized in Table 7-10.

TABLE 7-10 Summary of Mortality Data from Studies by Ballantyne and Callaway (1972) in Different Species Exposed to Tear Gas

	Exposure Duration	Mortality (No. died/No. exposed)			
Concentration (mg/m^3)	(min)	Rat	Mouse	Guinea Pig	Rabbit
3,950	5	0/10	1/10	1/5	0/5
4,760	5	0/10	0/10	0/5	0/5
4,250	10	1/10	0/10	5/5	0/5
4,330	10	1/10	4/10	3/5	2/5
4,150	15	0/10	3/10	3/5	2/5
5,167	15	7/10	3/10	5/5	2/5
4,000	20	9/10	8/10	5/5	4/5
4,300	20	8/10	6/10	5/5	5/5

Source: Adapted from Ballantyne and Callaway 1972.

TABLE 7-11 Summary of Mortality Data from Studies by Ballantyne and Swanston (1978) in Different Species Exposed to Tear Gas

Species	Average Concentration (mg/m^3)	Duration (min)	Mortality (No died/No. exposed)	Mortality (%)	LCT_{50} ($mg\text{-}min/m^3$ ± 95% CI)
Rat (male)	1,802	10	0/20	0	88,480 (77,370-98,520)
	1,806	45	8/20	40	
	1,911	45	9/20	45	
	2,629	60	20/21	95	
	2,699	60	20/20	100	
Mouse (male)	1,432	15	1/40	3	
	2,753	20	17/40	43	50,010 (42,750-60,220)
	2,333	30	10/19	53	
	2,400	30	17/40	43	
	2,550	30	24/36	67	
Guinea pig (female)	2,326	10	2/20	10	67,200 (59,200-78,420)
	2,380	15	2/10	20	
	1,685	25	10/20	50	
	2,310	20	8/20	40	
	1,649	30	11/20	55	
	1,302	45	9/11	82	
	2,041	30	13/20	65	
	2,373	30	10/19	53	

Rabbit (female)	846	5	0/10	0	54,090 (42,630-70,400)
	836	10	0/10	0	
	1,434	10	0/10	0	
	1,802	10	1/5	20	
	2,188	15	2/10	20	
	2,380	15	3/8	38	
	1,407	30	4/10	40	
	1,653	30	2/10	20	
	1,309	45	4/5	80	
	2,118	45	9/10	90	
	2,133	60	7/8	88	
	3,066	60	8/9	89	

Source: Adapted from Ballantyne and Swanston 1978.

Groups of 19-40 male albino mice were exposed by whole body inhalation to various concentrations of CS aerosol for 15-30 min (see Table 7-11) (Ballantyne and Swanston 1978). The experimental protocol, clinical signs, and necropsy findings were similar to those described in the corresponding study in rats (see Section 3.1.2). Mortality data are summarized in Table 7-11.

3.1.4. Guinea Pigs

Groups of ten guinea pigs were exposed to an aerosol of CS for exposure durations of 5-40 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for rats in Section 3.1. 2. The calculated LCT_{50} is 8,300 mg min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that have been published. Specific study details are not provided in this report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results of additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by various methods. As described above, Punte et al. (1962) reported mortality data for guinea pigs, but the values were reported only in terms of mg min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of five guinea pigs for 5 to 20 min to an approximate CS concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings are similar to those described in the rat study (see Section 3.1.2). Mortality data are summarized in Table 7-10.

Groups of ten to twenty female Dunkin Hartley guinea pigs were exposed by whole body inhalation to various concentrations of CS aerosol for durations of 10 to 45 min (see Table 7-11) (Ballantyne and Swanston 1978). Experimental protocol, clinical signs, and necropsy findings are as described for the rat study in Section 3.1.2. Mortality data are summarized in Table 7-11.

3.1.5. Rabbits

Groups of four rabbits were exposed to an aerosol of CS for exposure durations of 30-90 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for rats in Section 3.1.2, except that hyperactivity, salivation, and lachrymation were not reported. The calculated LCT_{50} is 17,000 mg min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that have been published. Specific study details are not provided in this report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results of additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by various methods. As described above,

Punte et al. (1962) reported mortality data for guinea pigs, but the values were reported only in terms of mg min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of five rabbits for 5 to 20 min to an approximate CS concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings are similar to those described in the rat study (see Section 3.1.2). Mortality data are summarized in Table 7-10.

Groups of five to ten female New Zealand white rabbits were exposed by whole body inhalation to various concentrations of CS aerosol for durations of 5 to 60 min (see Table 7-11) (Ballantyne and Swanston 1978). Experimental protocol, clinical signs, and necropsy findings are as described for the rat study in Section 3.1.2. Mortality data are summarized in Table 7-11.

3.1.6. Hamsters

Ballantyne and Callaway (1972) exposed groups of male and female golden hamsters to pyrotechnically-generated CS smoke at concentrations of 750 mg/m^3 for 30 min, 480 mg/m^3 for 1 h, or 150 mg/m^3 for 2 h in a 10-m^3 exposure chamber. The experimental protocol is the same as that for the corresponding study in rats (see Section 3.1.2). All animals exposed for 30 min at 750 mg/m^3 survived to the scheduled necropsy, and histopathologic changes were observed only on post-exposure day 1 (see Table 7-11). Three hamsters had a few scattered alveolar hemorrhages, and one also had congestion of the alveolar capillaries. No pathologic changes were found at post-exposure day 10 or 28. Exposure at 480 mg/m^3 for 1 h killed some hamsters (see Table 7-11); the majority of the death occurred after 1-2 days. Pathologic changes in animals surviving exposure at 480 mg/m^3 were generally found only on post-exposure day 1. Eight hamsters had mild pulmonary congestion, and four of them also had mild pulmonary hemorrhage. One hamster with no lung lesions had mild renal congestion and necrosis in the medulla, and another had mild necrosis in the medulla. A few hamsters killed after 10 days had healed lesions, as evidenced by binucleate liver cells around centrilobular veins and immature epithelium in some renal tubules. No abnormal pathologic changes were found at day 29. Histopathologic findings in hamsters that died were generally similar to those in rats (see Section 3.1.2); however, the lesions were less severe in hamsters than in rats.

Exposure to CS at 150 mg/m^3 for 2 h resulted in the mortality of two male hamsters (after 12 or 16 days), and necropsy revealed bronchopneumonia. Pathologic examination of surviving animals revealed lesions only on day 1. Lesions were found only in female hamsters; one had a few scattered alveolar hemorrhages and two had a few scattered foci of acute renal tubular necrosis at the inner cortex.

Exposure to CS at 480 mg/m^3 for 1 h or at 150 mg/m^3 for 2 h did not affect the lifespan of the hamsters, and no statistically significant increases in non-neoplastic lesions were found in the exposed groups compared with controls (Marrs et al. 1983a). Common non-neoplastic lesions in male and female hamsters included changes in the lungs (engorgement, congestion, inflammatory changes, and pulmonary edema) and pyelonephritis of the kidneys. No exposure-related neoplastic lesions were evident in male or female hamsters.

3.1.7. Dogs

McNamara et al. (1969) exposed groups of four dogs (strain and sex not specified) to eight different CS concentration-duration combinations. No further experimental details were available. Mortality data are summarized in Table 7-8.

Following a 30-sec exposure to CS at 25 mg/m^3, one dog exhibited increased blood pressure, an altered respiratory pattern, tachycardia, and increased femoral artery blood flow (Cucinell et al. 1971). In another test, two dogs were exposed for 23 min to CS at 2,600 mg/m^3. One dog survived and the other dog died after 52 h. The investigators noted that dogs recover partially when exposed to a lethal dose of CS but then develop respiratory distress and die within 48-70 h.

3.2. Nonlethal Acute Toxicity

3.2.1. Mice

An RD_{50} (concentration that reduces the respiratory rate by 50%) for CS of 4.0 mg/m^3 (95% confidence interval: 3.3-5.2 mg/m^3) was reported for male Swiss-Webster mice (Kane et al. 1979).

3.2.2. Rabbits

To investigate whether CS exposure can cause diarrhea, four rabbits were exposed to thermally-generated pure CS in a 10-m^3 chamber (Ballantyne and Beswick 1972). The exposures involved the following: one rabbit each was exposed at 58 mg/m^3 for 30 min, 46 mg/m^3 for 20 min, 54 mg/m^3 for 12 min, or 17 mg/m^3 for 17 min. Animals were placed singly in cages with removable trays lined with several layers of filter paper arranged to collect stool samples. The number of stool pellets passed, their total weight, and their water content were recorded for several day before and after exposure. Exposure to CS did not result in an increased incidence of diarrhea.

Two rabbits were exposed in a static chamber to the entire contents of a 3-ounce unit containing 71.5 g of CS (Gaskins et al. 1972). The unit required 20 sec to fully dispense. Both rabbits became unconscious after approximately 2 min of exposure and were moved to fresh air. The rabbits regained their righting

reflex approximately 10-20 min after exposure and were almost completely recovered after 1 h (moderate ocular wetness was the only visible effect). Gross necropsy of the rabbits performed after 2 weeks did not reveal any abnormalities. Two other rabbits were exposed to 23.2 g of CS during dispersion of a CS unit requiring about 10 sec to completely discharge. The dispensed CS formed a cloud in the chamber. The rabbits tried to avoid the spray as it was dispensed, and then sat quietly with their eyes tightly closed for the remainder of the 5-min exposure. No abnormalities were observed in the eyes or skin of the rabbits.

3.3. Repeat-Dose Studies

3.3.1. Rats

Groups of five male and five female F344/N rats were exposed to CS2 at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6 h/day, 5 days/week for 2 weeks (NTP 1990). (CS2 contains 94% CS, 1% hexamethyldisilizane, and 5% Cab-o-Sil®). All rats exposed at 30 or 100 mg/m^3 died before the end of the study. Rats from all exposure groups exhibited adverse clinical signs, ranging from erythema and blepharospasm at the lower concentrations to dacryorrhea, mouth breathing, listlessness, and mouth breathing at the higher concentrations. Rats in the 1-mg/m^3 group gained more weight over the exposure period than controls, but at concentrations of 3 mg/m^3 and higher body weight was generally decreased.

Groups of 10 male and 10 female F344/N rats were exposed to CS2 at 0, 0.4, 0.75, 1.5, 3, or 6 mg/m^3 for 6 h/day, 5 days/week for 13 weeks (NTP 1990). One male rat exposed at 6 mg/m^3 died, and all others survived to study termination. Clinical signs of ocular irritation (partial or complete eyelid closure) were noted in all exposure groups, and rats exposed at 6 mg/m^3 developed erythema of the extremities that persisted overnight. Rats exposed to CS2 at 1.5 mg/m^3 or higher gained significantly less weight over the study period than controls; final mean body weight was 17-44% lower than that of controls for males and 10-24% lower for females. An approximate 46% reduction in thymus weight relative to body weight was noted in male and female rats exposed at 6 mg/m^3. Concentration-related histopathologic changes included focal erosion with regenerative hyperplasia and squamous metaplasia of the respiratory epithelium. Acute inflammation and hyperplasia of the respiratory epithelium were also found.

One group of 56 male rats was exposed to a mean CS concentration of 1,470 or 1,770 mg/m^3 for 5 min/day for 5 days and another group of 49 male rats was exposed at a mean concentration of 12.5 or 14.8 mg/m^3 for 80 min/day for 9 days to (Ballantyne and Callaway 1972). Exposures to the thermally-generated CS aerosol (MMD of 1-2 micrometers) were conducted in a 1-m^3 chamber, with chamber air sampled continuously throughout exposure at a rate of 1 L/min using a double cone filter. The samples were analyzed for CS content (details not provided). Groups of three to five survivors were killed after 1, 6,

and 24 h and 2, 3, 4, 5, 7, 10, 14, and 21 days, and gross and microscopic examinations were performed. All animals survived the 5-min exposures. Histopathologic examination revealed minimal congestion of the alveolar capillaries after 1 or 6 h in two of five rats and a few scattered alveolar hemorrhages after 2 days in one of four rats. Scattered patches of bronchopneumonia were found in one of five rats after 7 days, in one of three rats after 8 days, one of three rats after 10 days, and two of five rats after 18 days. Pathologic changes in control rats included scattered alveolar hemorrhages in two of 11 rats and subacute mucoid enteritis in one of 11 rats. Death occurred in five of the 49 rats exposed at 12.5 or 14.8 mg/m^3 for 80 min/day; one died after the seventh exposure, two after the eight exposure, and two died 5 days after the final exposure. Necropsy revealed widespread acute bronchopneumonia. Histopathologic examination of the surviving animals revealed lesions for up to 5 days after exposure and not thereafter.

3.3.2. Mice

Groups of five male and five female B6C3F$_1$ mice were exposed to CS2 at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6 h/day, 5 days/week for 2 weeks (NTP 1990). All mice exposed at 10 mg/m^3 and greater died before study termination. Mice from all exposure groups exhibited adverse clinical signs, ranging from erythema and blepharospasm at the lower concentrations to dacryorrhea, mouth breathing, listlessness, and mouth breathing at the higher concentrations. Mice exposed at 1 mg/m^3 gained more weight over the exposure period than controls, but generally lost body weight at exposure concentrations of 3 mg/m^3 and higher.

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to CS2 at 0, 0.4, 0.75, 1.5, 3, or 6 mg/m^3 for 6 h/day, 5 days/week for 13 weeks (NTP 1990). All mice exposed at 6 mg/m^3 died and one male and one female mouse from the 3-mg/m^3 group died during the second week of exposure. Closed or partially-closed eyes during exposure were observed in mice from all exposure groups through week 6, and in mice exposed at 3 mg/m^3 during weeks 12 and 13. Concentration-related decreases in body weight compared with controls were found in all exposure groups; final mean body weights of mice in the 3-mg/m^3 group were 13% lower for males and 9% lower for females. Exposure-related histopathologic changes were observed in mice exposed at 1.5 mg/m^3 and higher, and included focal inflammation and squamous metaplasia (primarily in the nasal turbinates) and inflammation of the vomeronasal organ.

3.3.3. Rats, Mice, Guinea Pigs, and Rabbits

Groups of five to 10 guinea pigs, five rabbits, 10 rats, and 10-20 mice were exposed to CS at approximate concentrations of 30-40 mg/m^3 for 5 h/day for 1-7 successive days (Ballantyne and Callaway 1972). An anti-riot grenade

containing 0.5 to 0.75 g of CS was ignited every 30 min in a 10-m^3 static chamber to maintain the nominal concentration. The investigators stated that concentrations were determined by continuous sampling throughout the exposure, but no details were provided. Animals were removed to fresh air following each exposure, and were maintained for a 14-day post-exposure period. All animals that died and the survivors killed at the end of the study were given gross and histologic examinations. A summary of the mortality data is presented in Table 7-12. The description of clinical signs was limited to a statement that rabbits and rats exhibited more rhinorrhea and lacrimation than did mice, whereas guinea pigs showed few clinical signs apart from occasional sneezing during the first hour of exposure. Necropsy of animals that died revealed moderate-to-marked congestion of the alveolar capillaries and intrapulmonary veins and inter- and intra-alveolar areas of hemorrhage; many of the animals that died also had congestion of the liver, kidneys, and small intestine. Moderate pulmonary edema was noted in a "few of the animals." No residual pathologic changes were found in animals that survived until the end of the study.

3.4. Developmental and Reproductive Toxicity

Groups of 22-24 pregnant Porton strain rats or 12 pregnant New Zealand white rabbits were exposed to CS aerosol for 5 min/day on gestation days 6-15 or 6-18, respectively (Upshall 1973). CS The aerosol had a particle size of 1-2 micrometers and was generated by melting pure crystalline CS at 120°C using a Collison spray. A preliminary study investigated exposure to CS at 0 or 20 mg/m^3, and was followed by a concentration-response study that evaluated CS at concentrations of 0, 6, 20, or 60 mg/m^3. Control rats were recaged and moved out of their normal environment during the test-group exposure, and control rabbits were exposed to a siliconized silica aerosol at 60 mg/m^3. Additional control groups of pregnant rats were exposed to a particulate aerosol (60 mg/m^3 of Neosil) or to water aerosol to evaluate the stress of aerosol exposure. Rats were killed on gestation day 21 and rabbits on gestation day 30. Cesarean sections were performed, and the fetuses were evaluated for skeletal or visceral abnormalities. In addition, the lungs, liver, kidneys, and adrenal glands from the rabbit dams in the concentration-response study were evaluated histologically. No definitive effects of treatment were noted. In the preliminary rat study, exposed animals exhibited a decrease in maternal weight gain compared with controls (-23%), but a clear concentration-response relationship was not observed in the main study (-23, -12, and 15% for the 6, 20, or 60 mg/m^3 groups, respectively). Fetal weight appeared to decrease with increasing concentration in the main rat study (3.3, 3.2, and 3.1 g, respectively, vs. 3.5 for controls), but the fetal weights were comparable those in other studies. No other statistically significant effects were observed. No exposure-related effects were found in exposed rabbits or their offspring. Although the exposure concentrations were sufficient to cause extreme irritation, clinical signs in exposed rats and rabbits were not reported.

TABLE 7-12 Summary of Mortality Data in Different Species Exposed to Tear Gas for 5 Hours per Day for Up to 7 Days

Species	Duration		Concentration (mg/m^3)	Mortality (No. died/No. exposed)
	Hours/Day	No. Days		
Guinea pig	5	1	44.7	0/5
		3	36.0	2/5
		4	34.2	3/10
		6	35.2	2/5
		7	43.7	10/10
Rabbit	5	3	36.0	1/5
		5	34.2	2/5
Rat	5	1	37.0	1/10
		3	36.0	9/10
		5	34.2	7/10
Mouse	5	1	40.0	0/10
		2	38.8	0/10
		3	36.0	1/10
		4	31.9	10/10
		5	56.4	16/20

Source: Ballantyne and Callaway 1972.

3.5. Genotoxicity

In general, CS was not mutagenic to *Salmonella typhimurium*. Mutations were not induced with or without the presence of S9 at CS concentrations of 12.5-800 µg/plate in strains TA97a, TA98, TA100, TA102, or TA104 (Meshram et al. 1992); of up to 1.5 mg/plate in strains TA98, TA100, TA1535, or TA1537 (Wild et al. 1983); ranging from 10 µg/plate to 2 mg/plate in strains TA98, TA1535, TA1537, or TA1538 (von Däniken et al. 1981); or at CS2 concentrations of 3.3-333 µg/plate in strains TA98, TA100, TA1535, or TA1537 (NTP 1990). Equivocal responses for CS and CS2 were reported in strain TA100 only without S9 (von Däniken et al. 1981; NTP 1990), and for CS2 in strain TA97 but only with 30% S9 (NTP 1990). Cytotoxicity from CS was observed starting at 200 µg/plate, but the presence of 30% S9 generally reduced the cytotoxicity.

Other in vitro genotoxicity testing was generally positive. CS induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells both with and without S9 at CS2 concentrations of 6 µg/mL and greater (NTP 1990). Trifluorothymidine resistance in mouse L5178Y lymphoma cells

was induced in the absence of S9 at a CS concentration of 2.5 µg/mL (McGregor et al. 1988; NTP 1990). V79 Chinese hamster cells exposed to CS in culture at 19, 38, or 75 µM for 3 h and evaluated 6 days later showed reduced survival (by about 20, 30, and 80%, respectively; estimated from a graph), and exhibited a concentration-related increase in the frequency of mutants resistant to 6-thioguanine (mutations induced approximately 4- to 5-fold above controls at the highest concentration) (Ziegler-Skylakakis et al. 1989). Exposure to CS also increased the frequency of micronuclei by approximately 2-fold at 19 µM and up to 18-fold at 75 µM (measured 24 h after exposure), but did not induce DNA-repair synthesis as assessed using the BrdUrd density-shift method. A concentration-dependent increase was observed in spindle cell disturbances, particularly C-metaphases (chromosomes completely scattered in cytoplasm and often highly contracted), when cells were exposed to CS at 5, 9, 19, or 38 µM for 3 h (Schmid and Bauchinger 1991). The C-mitotic effect was also reflected in the appearance of a metaphase block and the disappearance of other mitotic figures (prophases and ana-telophases). When a differential staining technique was applied to allow for visualization of the spindle apparatus and chromosomes, a concentration-dependent increase in the number of mitoses with abnormal spindles was again observed, particularly apolar mitoses (mitotic figures without any signs of polar spindle configurations) (Salassidis et al. 1991). Further investigation into the mechanism of CS-induced c-mitotic spindle damage found that exposure of cells to CS at 38 µM for 20 h or 3 h followed by 20 h of recovery resulted in an increase in the number of aneuploid cells and in the polyploid index (Schmid and Bauchinger 1991). The number of aneuploid cells and the polyploid index were increased to a much greater extent by exposure to the metabolite *o*-chlorobenzaldehyde than to CS, suggesting that this metabolite may play a role in the induction of spindle damage. A comparison of the effectiveness of various exposure conditions revealed that cells exposed to CS at concentrations of up to 38 µM for 20 h exhibited a concentration-dependent increase in the number of S-cells and the frequency of chromatid-type aberrations (single breaks, isolocus breaks and exchanges, and gaps). Exposure to CS for 3 h followed by a 20-h recovery period resulted in similar effects but was not as effective. No effects were observed when cells were incubated with the supernatant from the 3 h exposure (Bauchinger and Schmid 1992). The cell cycle time of the V79 cell line is approximately 8-10 h; therefore, the cells had time to run through one or two S-phases.

Genotoxicity testing in vivo was generally negative. CS did not bind to DNA in the liver or kidneys of rats injected intraperitoneally with radiolabeled CS at 13 mg/kg and evaluated 8 or 75 h after dosing, but did bind to nuclear proteins in these organs (von Däniken et al. 1981). CS did not cause an increase in sex-linked recessive mutations in germ cells of male *Drosophila* when administered in the feed at concentrations ranging from 5×10^{-4} M to 2.6×10^{-3} M for 3 days (Wild et al. 1983), and did not increase micronucleated polychromatic erythrocytes in the bone marrow of NMRI mice administered CS by intraperito-

neal injection at 19 or 38 mg/kg or by oral administration at 113 or 226 mg/kg (Wild et al. 1983). The oral dose of 226 mg/kg killed 10 of 13 exposed mice.

3.6. Chronic Toxicity and Carcinogenicity

Groups of 50 male and 50 female $B6C3F_1$ mice and 50 male and 50 female F344/N rats were exposed to CS2 at target concentrations of 0, 0.75, or 1.5 mg/m^3 (mice) or 0, 0.075, 0.25, or 0.75 mg/m^3 (rats) for 6 h/day, 5 days/week for 105 weeks (NTP 1990). Rats exposed at 0.75 mg/m^3 developed histopathologic changes in the respiratory and olfactory epithelium of the nasal passage and inflammation and proliferation of the periosteum of the turbinate bones. No neoplastic effects were present. Lesions seen in the nasal cavity of exposed mice included inflammation in the anterior middle portions of the nasal passage and focal hyperplasia and/or squamous metaplasia of the respiratory epithelium. No other adverse effects were noted. Female mice exhibited a statistically significant, exposure-related reduction in the incidences of hyperplasia and adenomas of the pituitary gland pars distalis (adenoma rates in the 0-, 0.75-, and 1.5-mg/m^3 groups were 16/47, 5/46, and 1/46, respectively). Lymphomas in female mice also occurred with a significant negative trend (21/50, 12/50, and 8/50, respectively).

Groups of 75 male SPF Porton strain mice, 50 male Porton Wistar-derived rats, and 50 Dunkin Hartley guinea pigs were exposed to CS at nominal concentrations of 0, 3, 30, or 300 mg/m^3 (MMD of 3-4 micrometers) for 1 h/day, 5 days/week for up to 55 exposures (11 weeks) in mice and up to 120 exposures (24 weeks) in rats and guinea pigs (Marrs et al. 1983b). Exposure at the high concentration resulted in excessive mortality in mice and guinea pigs within days of exposure; therefore, tests at the high concentration was discontinued after three exposures in mice and after five exposures in rats and guinea pigs (the number of deaths were not provided) (Marrs et al. 1983b). During the first month of the experiment, 17% of the mice and 46% of the guinea pigs in the high-concentration groups died. A significant trend ($p < 0.001$) was found in the incidence of early death in mice with concentration. The investigators also reported a significant trend ($p < 0.001$) in the incidence of early death with concentration in guinea pigs; however, most of the mortality in guinea pigs occurred during the first month. Post-mortem examination of 10 guinea pigs that died during exposure revealed acute alveolitis in seven of the animals, with mild alveolitis present in the other three. The cause of death in mice that died during exposure to CS could not be determined. The investigators reported that toxic signs were not usually observed, and that death occurred suddenly and without warning. No cause of death could be ascribed to animals that died during the observation period. CS exposure did not affect the growth of rats or guinea pigs, but did result in a concentration-related decrease in the growth of mice. No definitive, exposure-related histologic findings were observed in mice, rats, or guinea pigs at the end of the study. No exposure-related neoplasms were found.

3.7. Summary

Clinical signs in the acute and repeated-dose animal studies suggest that CS is highly irritating. The majority of the acute inhalation exposure data in animals focused primarily on lethality, and death was generally caused by pulmonary edema and congestion. Renal damage was also occasionally noted, but may have been secondary to anoxia. Results of genotoxicity tests were mixed. Results in gene mutations tests using *S. typhimurium* were generally negative, as were results of in vivo genotoxicity assays. CS induced trifluorothymidine resistance in mouse L5178/TK lymphoma cells in the absence of S9, and induced both sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of S9. No developmental toxicity was found in rats or rabbits, and there was no evidence of carcinogenicity in rats or mice.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

4.1.1. Absorption

One cat with a cannulated trachea was exposed to CS aerosol by an oral-nasal mask to assess absorption of CS by the upper respiratory tract (cannulation prevented access to the lower respiratory tract), while a second cat was exposed via a tracheal tube to assess absorption by the lower respiratory tract (Leadbeater 1973). Blood concentrations of CS and its metabolites after exposure to the upper and lower respiratory tract were about 30 and 80%, respectively, of those measured in intact cats.

4.1.2. Toxicokinetics

The half-lives of CS, 2-chlorobenzylmalonitrile, and 2-chlorobenzaldehyde were measured in cats and rabbits (Leadbeater 1973; Paradowski 1979). The chemicals were administered directly into the femoral artery via a cannula in cats and directly into the ear vein of rabbits. The half-lives of CS, 2-chlorobenzylmalonitrile, and 2-chlorobenzaldehyde in cats were 5.5, 9.5, and 4.5 sec, respectively, and in rabbits they ranged from 19-25, 38-55, and 38-41 sec, respectively. The in vitro half-lives of these chemicals in the blood of cats, humans and rats were also measured. In cat blood, the half-life was 5 sec for CS, 470 sec for 2-chlorobenzylmalonitrile, and 70 sec for 2-chlorobenzaldehyde. The respective half lives in humans were 5, 660, and 15 sec and in rats were 7, 30, and 15 sec (Leadbeater 1973). The in vitro half-life of CS in the blood of rabbits was approximately 60 sec; the investigators postulated that this half-life might be longer than

those of rats, cats, and humans because of the higher concentration of CS tested in rabbits (Paradowski 1979).

CS incubated with rat liver homogenate for 5 min (ethanol-buffer; pH 7.4; 37°C) resulted in a 59% decrease in the initial amount of glutathione, with 26% of the depletion occurring spontaneously (non-enzymatically) (Rietveld et al. 1986). Binding to glutathione in vivo was confirmed by enhanced urinary thioether excretion in rats following intraperitoneal administration of CS (Rietveld et al. 1983, 1986). The thioether was identified as 2-chlorobenzylmercapturic acid.

4.1.3. Metabolism

Metabolism of CS appears to be qualitatively similar in different species. In vivo, CS can be hydrolyzed to 2-chlorobenzaldehyde or malononitrile or can be reduced to 2-chlorobenzyl malononitrile (see Figure 7-1) (Leadbeater 1973; Paradowski 1979). 2-Chlorobenzaldehyde can then be either oxidized to 2-chlorobenzoic acid for subsequent glycine conjugation or reduced to 2-chlorobenzyl alcohol for ultimate excretion as 2-chlorobenzyl acetyl cysteine or 2-chlorobenzyl glucuronic acid. Malononitrile can break down to cyanide, and be excreted as thiocyanate. The reduction of CS to 2-chlorobenzyl malononitrile is a relatively minor pathway; 2-chlorobenzyl malononitrile can be conjugated with glycine or can be hydrolyzed to 2-chlorophenyl 2-cyanoproprionate.

Radiolabeled CS was administered intravenously to rats at 0.08, 0.8, and 80 μmol/kg (^{3}H-ring labeled), 0.8 and 80 μmol/kg (^{14}C-cyanide labeled), or 0.8 and 80 μmol/kg of (^{14}C=C side-chain labeled) (Brewster et al. 1987). Rats were also treated intragastrically with CS at 80, 106, and 159 μmol/kg (^{14}C-cyanide labeled). The major urinary metabolites recovered in rats up to 96 h after intravenous or intragastric administration of CS were 2-chlorohippuric acid (49% of dose), 2-chlorobenzyl glucuronic acid (10%), 2-chlorobenzyl cysteine (8%), and 2-chlorobenzoic acid (8%), and minor metabolites included 2-chlorophenyl acetyl glycine (3%), 2-chlorobenzyl alcohol (1.6%), and 2-chlorophenyl 2-cyano propionate (1.6) (see Figure 7-1).

In another investigation, urinary concentrations of cyanide and thiocyanate were measured over a 24-h period in untreated rats, in rats administered CS intravenously, or in rats exposed to the CS hydrolysis product malononitrile intraperitoneally or intragastrically (Brewster et al. 1987). Following CS and malononitrile administration, urinary cyanide concentrations remained at or below baseline levels, while thiocyanate concentrations generally increased with the CS or malononitrile dose. The percentage molar conversion from CS to thiocyanate was 21.5% at an intraperitoneal dose of 212 μmol/kg and 30% at an intragastric dose of 212 μmol/kg. In tests with malononitrile, the percentage was 60% or more at an intraperitoneal dose of 80 μmol/kg or intragastric dose of 212 μmol/kg.

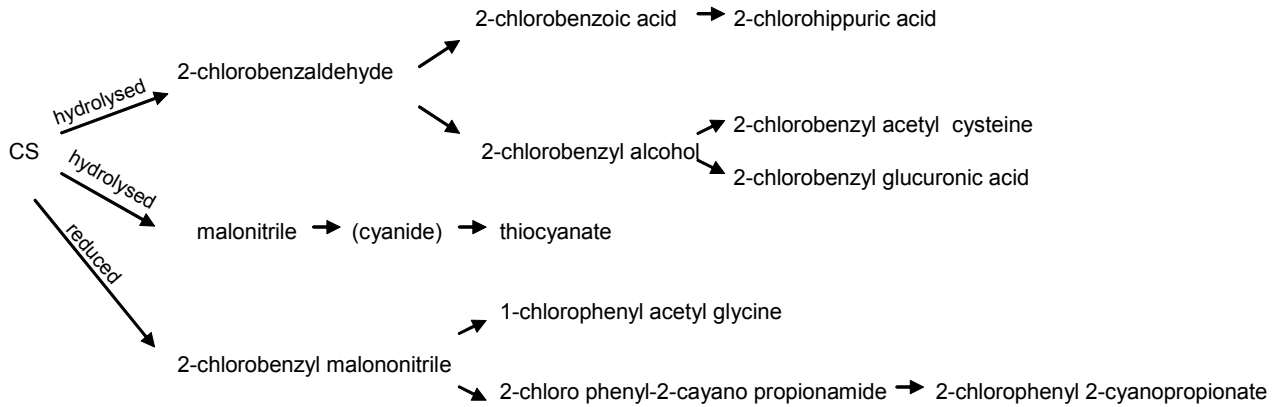

FIGURE 7-1 Predominant metabolic pathways of tear gas in rats proposed by Leadbeater (1973), Paradowsk (1979), and Rietveld et al. (1983).

Metabolism in rabbits is similar to that in rats. The predominant biotransformation pathway in the blood of rabbits administered high doses of CS by intravenous injection (0.5 LD_{50} to the LD_{50}) was hydrolysis of CS to 2-chlorobenzyaldehyde and malononitrile (~30-40%) (Paradowski 1979). A minor pathway involved reduction to 2-chlorobenzyl malononitrile (10%) The investigators indicated that the remaining 50-60% of the administered CS disappeared from the blood by other means; no other explanation was provided. The liver is involved in the metabolism of CS, as demonstrated by an increase in the half-lives of CS and its metabolites in the blood of rabbits when the liver was excluded from the circulation. More of the CS was accounted for after dosing, with approximately 75% of the CS hydrolyzed to 2-chlorobenzyaldehyde and 15% reduced to 2-chlorobenzyl malononitrile. When the kidneys were excluded from the circulation, no changes were observed in CS or metabolites in the blood.

Maximum blood concentrations of CS and its derivatives in cats were attained 30 min after intragastric administration at 40 mg/kg (Leadbeater 1973). After 90 min, blood concentrations of 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde were still elevated, can CS concentrations had returned to zero. When anesthetized cats were exposed for 60 min via oral-nasal masks to CS aerosol (75 or 750 mg/m^3 of pyrotechnically-generated CS aerosol, 750 mg/m^3 of pure CS aerosol from molten CS, or 62.5 mg/m^3 of CS aerosol generated from an aqueous suspension of micronized CS in acetic acid using a Collison sprayer), concentrations of CS and 2-chlorobenzylmalonitrile rapidly reached steady values, but concentrations of 2-chlorobenzaldehyde continued to increase. Comparison of the blood concentrations resulting from exposure to CS at 750 and 75 mg/m^3 showed that there was not a 10-fold decrease in the concentration of CS and its metabolites 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde; the concentrations were reduced by 4.5, 7.7, and 5.9, respectively. Exposure of cats to CS at 100 mg/m^3 for 5 min/day for 4 days, followed by exposure to CS at 75 or 750 mg/m^3, resulted in reduced blood concentrations of CS and its derivatives.

Rats receiving a single oral dose of CS at 50-500 mg/kg had lower blood concentrations of CS and its derivatives than cats (Leadbeater 1973). CS was only detected in high-dose group. Blood concentrations of 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde in rats and cats did not increase in a dose-related manner. Rats exposed by inhalation to CS aerosol at concentrations of 14-245 mg/m^3 for 5 min had measurable amounts of CS and 2-chlorobenzylmalonitrile in their blood immediately after exposure, but 2-chlorobenzaldehyde was detected only in rats exposed at concentrations greater than 100 mg/m^3.

Animal data suggest that CS should be absorbed by the human respiratory tract following inhalation exposure, and that metabolism of CS should proceed via a pathway similar to those found in laboratory animals. However, humans are not able to tolerate concentrations of CS as great as those tolerated by animals. Six healthy human males were exposed by inhalation to CS at 0.5-1.5 mg/m^3 over 90 min, and blood was drawn before and after exposure to measure CS and its derivatives (Leadbeater 1973). Two men left the chamber within 20

min. CS and 2-chlorobenzaldehyde were not detected in the blood of any of the volunteers, and only a trace of 2-chlorobenzylmalonitrile was detected in the blood of one man who remained in the chamber for the entire exposure.

4.1.4. Distribution and Elimination

To evaluate the fate of CS, radiolabeled CS was administered intravenously (^{3}H-ring labeled, ^{14}C-cyanide labeled, or ^{14}C=C side-chain labeled) or intragastrically (^{14}C-cyanide labeled) to rats, and urine, feces, and CO_2 were collected for 96 h (Brewster et al. 1987). The majority of the administered dose was recovered in the urine (44.4 to 100%). Recovery in feces was 1.2-23.4%, and recovery in CO_2 was minimal at 0-2.1%. Comparison of recovery data for the three different radiolabels after intravenous administration showed that more radioactivity was recovered in the feces of rats administered the ^{14}C=C side-chain labeled CS (21-23%) than from rats administered the other two labels (4-8%).

Male mice were administered ^{14}CN-CS by intravenous injection, and were killed at selected intervals to evaluate distribution by autoradiography (Brewster et al. 1987). A significant amount of radioactivity was present in the gastrointestinal tract after 5 min. After 1 h, significant amounts of radioactivity were present in the gastrointestinal tract, urinary bladder, mouth, and esophagus, with lesser amounts in the blood, liver, and salivary glands. At 24 h, most of the residual radioactivity was present in the mouth, salivary glands, gastrointestinal tract, or urinary bladder.

4.2. Mechanism of Toxicity

CS is an SN_2 alkylating agent and, therefore, reacts directly with nucleophilic compounds (Cucinell et al. 1971). Consequently, sulfhydryl-containing enzymes and other biologic compounds are prime targets. Most notably, CS reacts rapidly with the disulfhydryl form of lipoic acid, a coenzyme in the pyruvate decarboxylase pathway. In in vitro studies, CS reacted readily with cysteine, N-acetyl L-cysteine, glutathione, dithiothreitol, and lipoic acid, and had first-order reaction constants of 0.33, 0.42, 0.85, 4.88, and 10.4, respectively. Incubation of rat liver homogenate with CS for 5 min (ethanol-buffer; pH 7.4; 37°C) resulted in a 59% decrease in the initial amount of glutathione, with 26% of the depletion occurring spontaneously (non-enzymatically) (Rietveld et al. 1986). Binding to glutathione in vivo was confirmed by enhanced urinary thioether excretion in rats after intraperitoneal administration of CS; the thioether was identified as 2-chlorobenzylmercapturic acid (Rietveld et al. 1983, 1986). In another study, rats administered CS intraperitoneally at a dose that was 120% of the LD_{50} became moribund approximately 30 min after injection (most likely

due to the relatively slow generation of cyanide from the malononitrile metabolite). The role of cyanide in CS-induced lethality is supported by the observation that administration of thiosulfate intraveneously reduced mortality by 65% compared with control rats (21/32 exposed rats survived vs. 1/11 control rats). Intravenous administration of CS at 8 mg/kg in dogs resulted in a rapid drop in the plasma sulfhydryl concentration, which returned to normal within approximately 3 h (Cucinell et al. 1971).

4.3. Other Relevant Information

4.3.1. Species Variability

CS is a potent acute irritant. Ocular and pulmonary toxicity results from direct contact with CS and its associated alkylating properties; therefore, the mechanism of action is not expected to vary greatly between species. Ballantyne and Swantson (1978) calculated LCT_{50} values of 88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice. These values are well within a factor of two of each other.

4.3.2. Susceptible Populations

CS is an irritant and the mechanism of toxicity is a direct contact effect; therefore, the mechanism of action is not expected to vary greatly between individuals. The reactions in people with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed at highly irritating concentration of CS for short durations (Gutentag et al. 1960; Punte et al. 1963). Subjects with a history of drug allergies or sensitivities, hay fever, or asthma also tolerated exposure to CS and were similar to normal subjects, but the group with pre-existing conditions had a higher percentage of individuals with more severe chest symptoms (many of them laying prostrate on the ground for several minutes). However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups.

4.3.3. Concentration-Exposure Duration Relationship

The concentration-exposure time 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). The value of n for CS was determined on the basis of acute lethality data from studies of rats, mice, rabbits, guinea pigs, dogs, and monkeys (see Table 7-13). The dose-response software of ten Berge (2006) was used in the analyses (see Appendix A for details).

TABLE 7-13 Values of the Exponent n for Tear Gas

Species	n value	95% Confidence Limits
Rat	0.704	0.543–0.865
Mouse	0.701	0.509–0.892
Rabbit	0.658	0.467–0.849
Guinea pig	0.559	0.018–1.099
Dog	0.356	-1.464–0.751
Monkey	0.187	-0.281–0.656

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Several studies describe irritation in humans cause by CS (see Table 7-7); however, the severity of the effects exceeds those defined by AEGL-1.

5.2. Animal Data Relevant to AEGL-1

No animal studies of CS were available for deriving AEGL-1 values.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Effects observed at the lowest tested concentrations exceeded the severity of those defined by AEGL-1. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Five subjects exposed to CS at 0.71-0.78 mg/m^3 (average concentration 0.75 mg/m^3, calculated from the six interval measurements) tolerated a 60 min exposure (Beswick et al. 1972). All subjects reported ocular stinging and watering, increased salivation, cough, and face stinging. Other effects reported by some of the subjects included throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects). Nausea was likely due to swallowing large amounts of saliva and the headaches were likely due to frontal sinus irritation (Beswick et al. 1972). In another study, four subjects exposed to CS at 1.5 mg/m^3 tolerated a 90 min exposure, but experienced clinical signs of irritation. One subject developed nasal irritation within 2 min, three subjects

developed headache (at 45, 50, and 83 min), and all four experienced ocular irritation (at 20, 24, 70, and 75 min) (Punte et al. 1963). When the CS concentration was gradually increased over the course of 60 min, most of the 30 subjects were able to tolerate exposure to concentrations ranging from 0.31 to 2.3 mg/m^3; one subject left at 5 min because of vomiting but returned for the duration of the exposure, another vomited at 55 min of exposure, and one subject left after 8 min because of irritation (Beswick et al. 1972). The two cases of vomiting were attributed to swallowing large amounts or saliva. Clinical signs noted during the 60 min exposure included ocular, nasal, mouth, and throat irritation, nausea, chest discomfort, headache, and stinging of the face.

6.2. Animal Data Relevant to AEGL-2

Blinking, mild pulmonary congestion, and emphysema were observed in monkeys exposed to CS at 900 mg/m^3 for 3 min or 1,700 mg/m^3 for 5 min. Monkeys exposed at 2,500 mg/m^3 for 32 min exhibited blinking, labored respiration, coughing, oral and nasal discharge, vomiting, decreased activity, pulmonary edema, and congestion (Striker et al. 1967). Mice exposed to CS at 40 mg/m^3 for 5 h had rhinorrhea and lacrimation, and guinea pigs exposed at 45 mg/m^3 for 5 h showed occasional sneezing during the first hour of exposure.

6.3. Derivation of AEGL-2 Value

AEGL-2 values are based on human exposure to CS at 0.75 mg/m^3 for 60 min (Beswick et al. 1972). All five subjects tolerated the exposure, but experienced ocular irritation, increased salivation, and coughing; some subjects also reported nasal, mouth, and throat irritation, nausea, and headache. An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. This factor is also supported by the finding that responses of volunteers with jaundice, hepatitis, or peptic ulcer or who were 50-60 years old were similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate CS at 14-73 mg/m^3 and the recovery time in volunteers with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity were similar to "normal" volunteers; although more severe chest symptoms were reported in the volunteers with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963). An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. A modifying factor of 3 was also used because the effects observed at 0.75 mg/m^3 were considered AEGL-2 effects (watering eyes could impair escape). Time scaling was not performed because ocular irritation is a function of direct contact with the CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001). AEGL-2 values for CS are presented in Table 7-14, and the calculations are in Appendix B.

TABLE 7-14 AEGL-2 Values for Tear Gas

10 min	30 min	1 h	4 h	8 h
0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3

These values are supported by the Punte et al. (1963) study in which four subjects tolerated a 90-min exposure at 1.5 mg/m^3 and reported ocular and nasal irritation and headache. The values are also supported by other experiments conducted by Beswick et al. (1972). When an additional 30 subjects were exposed for 60 min to CS at 0.31-2.3 mg/m^3, one subject left at 5 min because of vomiting, but returned for the duration of the exposure, and another vomited at 55 min of exposure. Both cases of vomiting were attributed to swallowing large amounts or saliva. One subject voluntarily left after 8 min because of irritation; this subject was exposed at 0.56-0.86 mg/m^3 (AEGL-2 values are below this range).

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human studies of CS were available for deriving AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats, mice, rabbits, guinea pigs, dogs, and monkeys exposed to varying concentrations of CS for varying durations (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978). Exposure durations ranged from 5 to 300 min and concentrations of CS ranged from 37 to 5,176 mg/m^3. Mortality incidences ranged from 0 to 100%, depending on concentration-duration pairings. The experimental parameters are summarized in Tables 7-8, 7-10, 7-11, and 7-12.

7.3. Derivation of AEGL-3 Values

Using the rat, mouse, rabbit, guinea pig, dog, and monkey data sets of McNamara et al. (1969), Ballantyne and Callaway (1972), and Ballantyne and Swanston (1978), the lethality threshold for CS at each AEGL-3 exposure duration was calculated using the probit analysis-based dose-response program of ten Berge (2006) (see Appendix A). The threshold for lethality was set at the LC_{01}. The rat, mouse, and rabbit data all yielded similar time-scaling values and AEGL-3 values (see Appendix A). Large variances in the dog and monkey data precluded calculation of 95% confidence intervals. The rat data set was used to

derive AEGL-3 values, because it yielded values that were the most consistent with the available human data. 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). An empirical value for n of 0.70 was determined on the basis of the rat data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values, which were derived from a rather robust human dataset. A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences, because clinical signs are likely caused by a direct chemical effect on the tissues and this type of portal-of-entry effect is unlikely to vary greatly between species. Furthermore, calculated LCt_{50} values for different species are all well within a factor of 2 of each other (88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice) (Ballantyne and Swanston 1978). An uncertainty factor of 3 was used to account for intraindividual variability because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. As noted above in support of the AEGL-2 values, a factor of 3 is also supported by the results of studies by Punte et al. (1963) and Gutentag et al. (1960) in subjects with pre-existing conditions. AEGL-3 values for CS are presented in Table 7-15, and calculations presented in Appendix B.

The AEGL-3 values are considered protective. No mortality was noted in rats, rabbits, or mice exposed to CS at 1,802, 1,434, or 4,250 mg/m^3 for 10 min, respectively (Ballantyne and Swanston 1978), suggesting that the 10-min AEGL-3 of 140 mg/m^3 is appropriate. Similarly, no deaths were observed in 10 mice or five guinea pigs exposed at 40 or 44.7 mg/m^3, respectively, for 5 h (Ballantyne and Callaway 1972). One of 10 rats died after exposure to CS at 37 mg/m^3 for 5 h (Ballantyne and Callaway 1972). These data support the 4-h AEGL-3 of 1.5 mg/m^3.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 were detected at the lowest concentrations tested.

AEGL-2 values are based on irritation in humans and AEGL-3 values are based on an estimated threshold for lethality in rats. AEGL values for tear gas are presented in Table 7-16.

TABLE 7-15 AEGL-3 Values for Tear Gas

10 min	30 min	1 h	4 h	8 h
140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

8.2. Other Standards and Guidelines

Standards and guidelines for CS are presented in Table 7-17. Differences between the emergency response planning guideline 3 (ERPG-3) and the 1-h AEGL-3 value and between the immediately dangerous to life or health and 30-min AEGL-2 values are due to differences in the point of departure and uncertainty factors. The ERPG-3 is based on a 1-h LC_{50} of 1,000 mg/m^3 and undisclosed uncertainty factors (AIHA 2008). The IDLH is based on a Department of Army safety guide, which reported that a 2-min exposure to CS at 2-10 mg/m^3 was considered intolerable by six of 15 people (NIOSH 1996).

TABLE 7-16 AEGL Values for Tear Gas

	Exposure Duration				
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)	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3
AEGL-3 (lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. The severity of effects observed at the lowest tested concentrations exceeded those defined by AEGL-1.

TABLE 7-17 Standards and Guidelines for Tear Gas

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3
AEGL-3	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3
ERPG-1 (AIHA)[a]			0.005 mg/m^3		
ERPG-2 (AIHA)[a]			0.1 mg/m^3		
ERPG-3 (AIHA)[a]			25 mg/m^3		
IDLH (NIOSH)[b]		2 mg/m^3			
PEL-TWA (OSHA)[c]					0.4 mg/m^3
REL-TWA (NIOSH)[d]					0.4 mg/m^3
TLV-STEL (ACGIH)[e]	0.005 ppm (0.4 mg/m^3)				
MAC (The Netherlands)[f]					0.4 mg/m^3

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 2008]).
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 CS is based on one of 10 individuals reporting a burning or itching sensation at 0.0004 mg/m^3 and a calculated EC_{50} of 0.004 mg/m^3.
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 CS is based on human irritation 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 tear gas is based on animal lethality data (ab approximate 1-h LC_{50}).
[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.
[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29CFR Part1910.1000 [1996]) 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 2011) is defined analogous to the OSHA PEL-TWA.
[e]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.
[f]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the OSHA PEL-TWA.

8.3. Data Adequacy and Research Needs

Inadequate data are available to derive AEGL-1 values for CS. Adequate human data are available for deriving AEGL-2 values, and animal data are available for deriving AEGL-3 values. Additional data providing information at exposures that produce minimal irritation would be useful for deriving AEGL-1 values.

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APPENDIX A

TIME-SCALING CALCULATIONS FOR TEAR GAS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant), has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent on the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific (and even a toxic end point-specific) exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent n in the equation $C^n \times t = k$ quantifies the relationship between exposure concentration and exposure duration. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of concentration vs. time yields a progressive decrease in the slope of the curve.

An n of 0.70 mg/m^3 for CS was obtained by analysis of lethality data in rats (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978) using the software of ten Berge (2006). This exposure-time relationship for lethality was considered appropriate for deriving AEGL-3 values. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values that were derived from robust human data.

TABLE A-1 Results of ten Berge Program (1% Lethality)

		LC_{01} Point Estimate, mg/m^3 (95% confidence limits)					
Species	Exponent *n*	10 min	30 min	1 h	4 h	8 h	Reference(s)
Rat	0.704 (0.543–0.865)	1,385 (477–2,500)	290 (97–496)	109 (32–196)	15 (3.1–35)	5.6 (-0.93–15)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Mouse	0.701 (0.509–0.892)	998 (208–1,899)	208 (36–404)	77 (11–166)	11 (-0.86–3.2)	4.0 (-0.23–15)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Rabbit	0.658 (0.467–0.849)	656 (227–1,136)	124 (28–249)	43 (7.0–103)	5.2 (0.40–19)	1.8 (0.094–8.6)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Guinea pig	0.559 (0.018–1.099)	3.65 (0–100)	0.51 (0–25)	0.15 (0–12)	0.012 (0–3.3)	0.0036 (0–1.8)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Dog	0.356 (-1.464–0.751)	349[a]	7,604[a]	53,150[a]	2,597,000[a]	18,150,000[a]	McNamara et al. 1969
Monkey	0.187 (-0.281–0.656)	26[a]	0.075[a]	0.0018[a]	0.0000011[a]	0.000000028[a]	McNamara et al. 1969; Striker et al. 1967
Monkey	2.123 (-21–25)	11[a]	6.6[a]	4.7[a]	2.5[a]	1.8[a]	McNamara et al. 1969

[a]Large variances precluded estimating 95% confidence limits.

TABLE A-2 Data in Rats Used in Log Probit Model
Date: 02 October 2008 Time: 09:11:09

Sequence No.	Concentration (mg/m^3)	Minutes	Exposed	Responded
1	560	25	10	1
2	543	35	10	2
3	489	45	10	3
4	454	55	10	5
5	500	60	10	2
6	500	80	10	6
7	500	90	10	8
8	750	30	8	0
9	150	120	8	0
10	3,950	5	10	0
11	4,760	5	10	0
12	4,250	10	10	1
13	4,330	10	10	1
14	4,150	15	10	0
15	5,176	15	10	7
16	4,000	20	10	9
17	4,300	20	10	8
18	1,802	10	20	0
19	1,806	45	20	8
20	1,911	45	20	9
21	2,629	60	21	20
22	2,699	60	20	20
23	37	300	10	1

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/m^3, ln-transformed
X2 = minutes, ln-transformed

ChiSquare = 50.11
Degrees of freedom = 20
Probability Model = 2.13E-04

Ln(Likelihood) = -47.54

B 0 = -9.6233E+00 Student t = -3.9484
B 1 = 1.1705E+00 Student t = 5.6748
B 2 = 1.6634E+00 Student t = 5.6382

Variance B 0 0 = 5.9402E+00
Covariance B 0 1 = -4.8485E-01
Covariance B 0 2 = -6.7032E-01
Variance B 1 1 = 4.2542E-02
Covariance B 1 2 = 4.9302E-02
Variance B 2 2 = 8.7045E-02

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.704
Lower limit (95% CL) = 0.543
Upper limit (95% CL) = 0.865

Estimation of conc mg/m^3 at response of 1%
Minutes = 10
Point estimate conc mg/m^3 = 1.385E+03 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 4.772E+02 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 2.500E+03 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 30
Point estimate conc mg/m^3 = 2.906E+02 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 9.659E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 4.963E+02 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 60
Point estimate conc mg/m^3 = 1.085E+02 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 3.223E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 1.958E+02 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 120
Point estimate conc mg/m^3 = 4.052E+01 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 1.021E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 8.137E+01 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 240
Point estimate conc mg/m^3 = 1.513E+01 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 3.122E+00 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 3.501E+01 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 480
Point estimate conc mg/m^3 = 5.649E+00 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 9.345E-01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 1.540E+01 for response of 1%

APPENDIX B

DERIVATION OF AEGL VALUES FOR TEAR GAS

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for CS because the effects observed at the lowest tested concentrations exceeded the severity of AEGL-1 effects.

Derivation of AEGL-2 Values

Key study:	Beswick, F.W., P. Holland, and K.H. Kemp. 1972. Acute effects of exposure to orthochlorobenzilidene malononitrile (CS) and the development of tolerance. Br. J. Ind. Med. 29(3):298-306.
Toxicity end point:	Human exposure to CS at an average concentration of 0.75 mg/m^3 for 60 min. All five subjects tolerated the exposure but reported ocular stinging and watering, increased salivation, coughing, and face stinging. Some subjects also reported throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects).
Time scaling:	None. Irritation is a function of direct contact with CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).
Uncertainty factors:	1 for interspecies differences 3 for intraspecies variability; contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. Value of 3 is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).
Modifying factor:	3, because effects observed at 0.75 mg/m^3 were AEGL-2 effects.

Calculations: $0.75 \text{ mg/m}^3 \div 9 = 0.083 \text{ mg/m}^3$ (applied to all AEGL durations)

Derivation of AEGL-3 Values

Key studies: McNamara, B.P., E.J. Owens, J.T. Weimer, T.A. Ballard, and F.J. Vocci. 1969. Toxicology of Riot Control Chemicals CS, CN, and DM. Edgewood Arsenal Technical Report EATR-4309. US Department of the Army, Edgewood Arsenal Medical Research Laboratory, Edgewood Arsenal, MD. November 1969.

Ballantyne, B., and S. Callaway. 1972. Inhalation toxicology and pathology of animals exposed to o chlorobenzylidene malononitrile. Med. Sci. Law 12(1):43-65.

Ballantyne, B., and D.W. Swanston. 1978. The comparative acute mammalian toxicity of 1-chloroacetophenone (CN) and 2-chlorobenzylidene malononitrile (CS). Arch. Toxicol. 40(2):75-95.

Toxicity end point: L_{01} for rats; calculated using probit analysis-based dose-response program of ten Berge (2006), see Appendix A.

	LC_{01} Point Estimate, mg/m^3 (95% confidence limits)				
Exponent *n*	10 min	30 min	1 h	4 h	8 h
0.704 (0.543-0.865)	1,385 (477–2,500)	290 (97–496)	109 (32–196)	15 (3.1–35)	5.6 (-0.93–15)

Time scaling: $C^n \times t = k$; n = 0.70 (based on rat lethality data). No time scaling was performed for the 8-h AEGL value, because time scaling yielded a value that was inconsistent with the AEGL-2 values that were derived from robust human data.

Uncertainty factors: 3 for interspecies differences. Effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is unlikely to vary greatly between species. Value is also supported by calculated LCT_{50} values of 88,480 mg min/m^3 for rats, 67,200 mg min/m^3 for guinea pigs, 54,090 mg min/m^3 for rabbits, and 50,010 mg min/m^3 for mice (Ballantyne and Swanston 1978); values all well within a factor of two of each other.

3 for intraspecies variability. Effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Calculations:

10-min AEGL-3:	1,385 $mg/m^3 \div 10 = 140$ mg/m^3
30-min AEGL-3:	290 $mg/m^3 \div 10 = 29$ mg/m^3
1-h AEGL-3:	109 $mg/m^3 \div 10 = 11$ mg/m^3
4-h AEGL-3:	15 $mg/m^3 \div 10 = 1.5$ mg/m^3
8-h AEGL-3:	Set equal to the 4-h AEGL-3 of 1.5 mg/m^3

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR TEAR GAS

Derivation Summary

AEGL-1 VALUES

AEGL-1 values are not recommended for CS because the effects observed at the lowest tested concentrations exceeded the severity of AEGL-1 effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.083 mg/m^3	0.083mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3

Key reference: Beswick, F.W., P. Holland, and K.H. Kemp. 1972. Acute effects of exposure to orthochlorobenzilidene malononitrile (CS) and the development of tolerance. Br. J. Ind. Med. 29(3):298-306.

Test species/Strain/Number: Humans, 5

Exposure route/Concentration/Duration: Inhalation, 0.71-0.78 mg/m^3 (average: 0.75 mg/m^3) for 60 min

Effects: Clinical signs of irritation. Ocular stinging and watering, increased salivation, cough, and face stinging was reported in all subjects. Additional signs of irritation included throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects).

End point/Concentration/Rationale: Ocular, nasal, mouth, and throat irritation, coughing, nausea, and headache at 0.75 mg/m^3 for 60 min.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because data were from human volunteers
Intraspecies: 3, contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer and those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate the exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Modifying factor: 3, because effects at 0.75 mg/m^3 were considered AEGL-2 effects.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applied. Irritation is a function of direct contact with the CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).

(Continued)

AEGL-2 VALUES Continued

Data adequacy: AEGL-2 values are supported by the data of Punte et al. (1963) and Beswick et al. (1972). Exposure of four subjects at 1.5 mg/m^3 for 90 min resulted in ocular and nasal irritation in all subjects and headache in 3 subjects (Punte et al. 1963). When a total of 30 subjects were exposed for 60 min to gradually increasing CS concentrations ranging from 0.31-2.3 mg/m^3, one subject left at 5 min because of vomiting but returned for the duration of the exposure, and another vomited at 55 min of exposure (vomiting in both cases attributed to swallowing large amounts or saliva). One subject voluntarily left the exposure after 8 min because of irritation; this subject was exposed in the range of 0.56-0.86 mg/m^3, and the AEGL-2 values are below this range.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

Key references:

McNamara, B.P., E.J. Owens, J.T. Weimer, T.A. Ballard, and F.J. Vocci. 1969. Toxicology of Riot Control Chemicals CS, CN, and DM. Edgewood Arsenal Technical Report EATR-4309. US Department of the Army, Edgewood Arsenal Medical Research Laboratory, Edgewood Arsenal, MD. November.

Ballantyne, B., and S. Callaway. 1972. Inhalation toxicology and pathology of animals exposed to o chlorobenzylidene malononitrile. Med. Sci. Law 12(1):43-65.

Ballantyne, B., and D.W. Swanston. 1978. The comparative acute mammalian toxicity of 1- chloroacetophenone (CN) and 2-chlorobenzylidene malononitrile (CS). Arch. Toxicol. 40(2):75-95.

Test species/Strain/Number: Rat, various strains; 8, 10, 20, or 21 per group

Exposure route/Concentration/Duration: Inhalation, 37-5,175 mg/m^3 for 5-300 min.

Effects: Lethality

End point/Concentration/Rationale: LC_{01} for rats calculated using probit-analysis dose-response program of ten Berge (2006).

	LC_{01} Point Estimate, mg/m^3				
Exponent *n*	10 min	30 min	1 h	4 h	8 h
0.704 (0.543-0.865)	1,385 (477-2,500)	290 (97-496)	109 (32-196)	15 (3.1-35)	5.6 (-0.93-15)

Uncertainty factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3, effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is unlikely to vary greatly between species. Value is also supported by calculated LCT_{50} values of 88,480 mg min/m^3 for rats, 67,200 mg min/m^3 for guinea pigs, 54,090 mg min/m^3 for rabbits, and 50,010 mg min/m^3 for mice (Ballantyne and Swanston 1978); values are all well within a factor of two of each other.

Intraspecies: 3, effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those

of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate the exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Modifying factor: None applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 0.70 based on rat lethality data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values that were derived from robust human data.

Data adequacy: The AEGL-3 values are considered protective. No mortality was noted in rats exposed to CS at 1,802 mg/m^3 for 10 min (Ballantyne and Swanston 1978), in rabbits at 1,434 mg/m^3 for 10 min (Ballantyne and Swanston 1978), or in mice and rabbits at 4,250 mg/m^3 for 10 min (Ballantyne and Callaway 1972). Dividing these concentrations by a total uncertainty factor of 10, yields values ranging from 140-425 mg/m^3, suggesting that the 10-min AEGL-3 is appropriate. No mortality was noted in guinea pigs exposed at 44.7 mg/m^3 for 5 h or in mice exposed at 40 mg/m^3 for 5 h (Ballantyne and Callaway 1972). Applying a total uncertainty factor of 10 to these concentrations yields a value of approximately 4.0 mg/m^3 for 5 h. One of ten rats died when exposed at 37 mg/m^3 for 5 h (Ballantyne and Callaway 1972). Dividing 37 mg/m^3 by 2 to obtain an approximate threshold for lethality, yields 18.5 mg/m^3; application of a total uncertainty factor of 10, yields a value of 1.9 mg/m^3 for 5 h. The values derived from the 5-h data show that the AEGL-3 values are protective.

APPENDIX D

CATEGORY PLOT FOR TEAR GAS

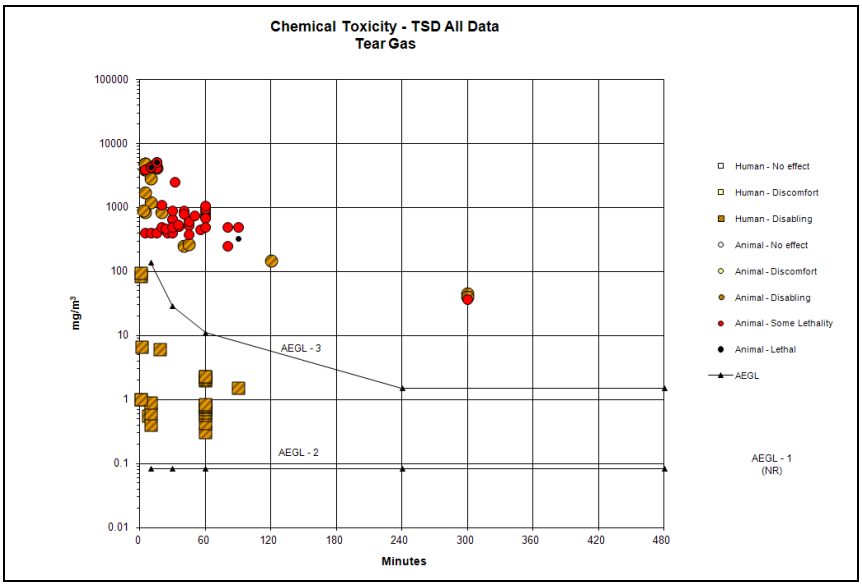

FIGURE D-1 Category plot of toxicity data and AEGL values for tear gas.

TABLE D-1 Data Used in the Category Plot for Tear Gas

Source	Species	Sex	No. Exposures	mg/m^3	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				0.083	10	AEGL	
AEGL-2				0.083	30	AEGL	
AEGL-2				0.083	60	AEGL	
AEGL-2				0.083	240	AEGL	
AEGL-2				0.083	480	AEGL	
AEGL-3				140	10	AEGL	
AEGL-3				29	30	AEGL	
AEGL-3				11	60	AEGL	
AEGL-3				1.5	240	AEGL	
AEGL-3				1.5	480	AEGL	
Ballantyne and Calloway 1972	Guinea pig		1	45	300	2	Sneezing
Ballantyne and Calloway 1972	Guinea pig		1	3,950	5	SL	Mortality: 1/5
Ballantyne and Calloway 1972	Guinea pig		1	4,150	15	SL	Mortality: 3/5
Ballantyne and Calloway 1972	Guinea pig		1	4,250	10	3	Mortality: 5/5
Ballantyne and Calloway 1972	Guinea pig		1	4,330	10	SL	Mortality: 3/5
Ballantyne and Calloway 1972	Guinea pig		1	4,760	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Guinea pig		1	5,167	15	3	Mortality: 5/5

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
Ballantyne and Calloway 1972	Mouse		1	40	300	2	Rhinorrhea and lacrimation
Ballantyne and Calloway 1972	Mouse		1	3,950	5	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Mouse		1	4,150	15	SL	Mortality: 3/10
Ballantyne and Calloway 1972	Mouse		1	4,250	10	2	Mortality: 0/10
Ballantyne and Calloway 1972	Mouse		1	4,330	10	SL	Mortality: 4/10
Ballantyne and Calloway 1972	Mouse		1	4,760	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Mouse		1	5,167	15	SL	Mortality: 3/10
Ballantyne and Calloway 1972	Rabbit		1	3,950	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	4,150	15	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rabbit		1	4,250	10	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	4,330	10	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rabbit		1	4,760	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	5,167	15	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rat		1	37	300	SL	Rhinorrhea, lacrimation, and mortality (1/10)
Ballantyne and Calloway 1972	Rat		1	150	120	2	Mortality: 0/8
Ballantyne and Calloway 1972	Rat		1	3,950	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	4,150	15	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	4,250	10	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Rat		1	4,330	10	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Rat		1	4,760	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	5,167	15	SL	Mortality: 7/10
Ballantyne and Swanston 1978	Rabbit	Female	1	846	5	2	Mortality: 0/10

Beswick et al. 1972	Human	1	0.31	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.42	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.56	8	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.57	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.63	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.7	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.78	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.8	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.84	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.1	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.3	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.3	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
McNamara et al. 1969	Dog	1	508	36	SL	Mortality: 2/4
McNamara et al. 1969	Dog	1	520	45	SL	Mortality: 2/4

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
McNamara et al. 1969	Dog		1	612	45	SL	Mortality: 2/4
McNamara et al. 1969	Dog		1	649	30	SL	Mortality: 1/4
McNamara et al. 1969	Dog		1	797	60	SL	Mortality: 3/4
McNamara et al. 1969	Dog		1	833	20	2	Mortality: 0/4
McNamara et al. 1969	Dog		1	899	40	SL	Mortality: 2/4
McNamara et al. 1969	Dog		1	909	60	SL	Mortality: 2/4
McNamara et al. 1969	Guinea pig		1	400	5	SL	Mortality: 1/10
McNamara et al. 1969	Guinea pig		1	400	10	SL	Mortality: 2/10
McNamara et al. 1969	Guinea pig		1	400	15	SL	Mortality: 4/10
McNamara et al. 1969	Guinea pig		1	400	25	SL	Mortality: 7/10
McNamara et al. 1969	Guinea pig		1	400	30	SL	Mortality: 7/10
McNamara et al. 1969	Guinea pig		1	500	20	SL	Mortality: 3/10
McNamara et al. 1969	Monkey		1	381	45	SL	Mortality: 2/4
McNamara et al. 1969	Monkey		1	469	24	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	612	45	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	673	30	SL	Mortality: 2/4
McNamara et al. 1969	Monkey		1	699	60	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	941	60	SL	Mortality: 3/4
McNamara et al. 1969	Monkey		1	1,057	60	SL	Mortality: 2/4
McNamara et al. 1969	Mouse		1	683	60	SL	Mortality: 14/20
McNamara et al. 1969	Mouse		1	740	50	SL	Mortality: 5/20
McNamara et al. 1969	Mouse		1	800	40	SL	Mortality: 5/20
McNamara et al. 1969	Mouse		1	900	30	SL	Mortality: 2/20

McNamara et al. 1969	Mouse	1	1,100	20	SL	Mortality: 7/20
McNamara et al. 1969	Mouse	1	1,200	10	2	Mortality: 0/20
McNamara et al. 1969	Rabbit	1	250	40	2	Mortality: 0/4
McNamara et al. 1969	Rabbit	1	250	80	SL	Mortality: 3/4
McNamara et al. 1969	Rabbit	1	267	45	2	Mortality: 0/4
McNamara et al. 1969	Rabbit	1	333	90	3	Mortality: 4/4
McNamara et al. 1969	Rabbit	1	500	30	SL	Mortality: 1/4
McNamara et al. 1969	Rat	1	454	55	SL	Mortality: 5/10
McNamara et al. 1969	Rat	1	500	60	SL	Mortality: 2/10
McNamara et al. 1969	Rat	1	500	80	SL	Mortality: 6/10
McNamara et al. 1969	Rat	1	500	90	SL	Mortality: 8/10
McNamara et al. 1969	Rat	1	543	35	SL	Mortality: 2/10
Owens and Punte 1963	Human	1	1.5	90	2	Nasal and ocular irritation, headache
Owens and Punte, 1963	Human	1	6	18	2	Intolerable irritation; escape possible
Owens and Punte 1963	Human	1	6.7	2	2	Intolerable irritation; escape possible
Owens and Punte 1963	Human	1	85	1	2	Intolerable airway and ocular irritation
Owens and Punte 1963	Human	1	94	1	2	Intolerable airway and ocular irritation
Rengsdorf 1969	Human	1	1	1	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.4	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.6	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.9	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	1	1	2	Intense ocular irritation
Striker et al. 1967	Monkey	1	900	3	2	Pulmonary congestion, emphysema

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
Striker et al. 1967	Monkey		1	1,700	5	2	Pulmonary congestion, emphysema
Striker et al. 1967	Monkey		1	2,500	32	SL	Severe irritation, pulmonary edema, emphysema, mortality (5/8)
Striker et al. 1967	Monkey		1	2,850	10	2	Pulmonary congestion, emphysema, ocular/respiratory irritation

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