Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 7

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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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 U.S. Department of Defense (DOD), the U.S. Department of Energy (DOE), the U.S. Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 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 seventh volume in the series

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

Acute Exposure Guideline Levels for Selected Airborne Chemicals. It reviews the AEGLs for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol for scientific accuracy, completeness, and consistency with the NRC guideline reports.

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

Two 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 two of the committtee's interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for monochloroacetic acid and phenol (*Thirteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2005) and acetone cyanohydrin and carbon disulfide (*Fourteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2006): Deepak K. Bhalla (Wayne State University), David W. Gaylor (Gaylor and Associates, LLC), and Sam Kacew (University of Ottawa).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were 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 the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowl-

edges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, senior program officer for toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (editorial projects manager), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

This report is the seventh 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 in experimental animals. 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 , 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 by the federal government 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:

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

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

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 types 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 are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are 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 NRC 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 for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared six reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b). This report is the seventh volume in that series. AEGL documents for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol are each published as an appendix in this report. The NRC 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

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Acetone Cyanohydrin[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). AEGL-1, AEGL-2, and AEGL-3, as appropriate, will be developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. The recommended exposure levels are considered applicable to the general population, including infants and children and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Peter Griem (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) and Chemical Managers Larry Gephart and Ernest V. Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). 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 guideline reports (NRC 1993, 2001).

predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) 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/m³) 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 levels that could produce mild and progressively increasing 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 AEGLs represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free hydrogen cyanide (HCN). The major use of acetone cyanohydrin is in the production of methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics. and synthetic resins, as well as in the manufacture of insecticides, pharmaceuticals, fragrances, and perfumes. Acetone cyanohydrin decomposes spontaneously in the presence of water to acetone and HCN.

Fatalities and life-threatening occupational intoxication have been described after accidental inhalation, skin contact, and ingestion. Initial symptoms after mild exposure to acetone cyanohydrin range from cardiac palpitation, headache, weakness, dizziness, nausea, and vomiting to nose, eye, throat, and skin irritation. Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All the pharmacologic actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase also known as ferrocytochrome c oxygen oxidoreductase. Cessation of electron transport across the inner mitochondrial membrane results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

Four studies exposed rats repeatedly to acetone cyanohydrin at about 10, 30, and 60 ppm for 6 h/day (d), 5 d/week (wk) for a total of 4 weeks (Monsanto

1986a; using groups of 10 male and 10 female rats), 10 weeks (Monsanto 1982b; using groups of 15 male rats) and 14 weeks (Monsanto 1986b; using groups of 15 male and 15 female rats) or for 6 h/d for 21 days (Monsanto 1982c; using groups of 15 female rats). Death was observed at 60 ppm after the first exposure in three animals of the Monsanto (1986a) study but not in subsequent exposures or in the other studies conducted under similar protocols. Preceding death, respiratory distress, prostration, convulsions, and tremors were obvious. In all studies, exposure at 60 and 30 ppm caused signs of irritation (red nasal discharge, clear nasal discharge, perioral wetness, and encrustations) during the first and subsequent weeks of exposure. At 10 ppm, red nasal discharge was not observed in one study (Monsanto 1986a); its incidence was not increased compared with the concurrent control group in two studies (Monsanto 1982b,c), but it was increased compared with the control group in the fourth study (Monsanto 1986b). No other signs of intoxication were reported in these four studies.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure at 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks, which did not result in red nasal discharge [Monsanto 1986a]) using a total uncertainty factor of 10.

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 milligrams per liter [mg/L]). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and acetone cyanohydrin concentrations in air. Since no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature, no level of distinct odor awareness (LOA) was derived.

The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats using a total uncertainty factor of 10 (derivation basis would be exposure at 29.9 ppm for 6 h/d, 5 d/wk for 4 weeks, which caused signs of irritation, while the next higher concentration produced respiratory distress, prostration, convulsions and tremors, Monsanto [1986a]).

The derivation of AEGL-3 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of

acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by the close similarity of acetone cyanohydrin and HCN regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm; the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto's (1986a) report of death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm); no additional deaths were found in the 19 subsequent exposures. The derived values are listed in Table 1-1 below.

1. INTRODUCTION

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free HCN (ACGIH 1996). The major use of acetone cyanohydrin is in the preparation of -methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics, and synthetic resins as well as an intermediate in the manufacture of insecticides, pharmaceuticals, fragrances, and perfumes (OECD 1997). About 0.5-1 million metric tons of acetone cyanohydrin is produced worldwide annually (IUCLID 2000) principally by reaction of HCN with acetone. Chemical and physical properties of acetone cyanohydrin are listed in Table 1-2.

TABLE 1-1 Summary of AEGL Values for Acetone Cyanohydrin[a,b]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)	Application of AEGL-1 values for HCN (NRC 2002)
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)	Application of AEGL-2 values for HCN (NRC 2002)
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)	Application of AEGL-3 values for HCN (NRC 2002)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.
[b]Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

TABLE 1-2 Chemical and Physical Data for Acetone Cyanohydrin

Parameter	Data	Reference
Molecular formula	$(CH_3)_2C(OH)CN$	IUCLID 2000
Molecular weight	85,1	E.I. du Pont de Nemours and Co. 1998
CAS Registry Number	75-86-5	IUCLID 2000
Physical state	Liquid	E.I. du Pont de Nemours and Co. 1998
Color	Colorless	E.I. du Pont de Nemours and Co. 1998
	Colorless to yellowish	ACGIH 1996
Synonyms	2-Propanone cyanohydrin; 2-cyano-2-propanol; 2-cyano-2-hydroxypropane; hydroxyisobutyronitrile; 2-methyl-lactonitrile; 2-hydroxy-2-methyl-propionitrile; Acetoncyanhydrin	IUCLID 2000
Vapor pressure	1.07 hPa at 20°C	IUCLID 2000
	0.8 mm Hg at 20°C	E.I. du Pont de Nemours and Co. 1998
	1 mm Hg at 25°C	E.I. du Pont de Nemours and Co. 1998
	1.6 hPa at 40°C	Grybat et al. 2003
	12.5 hPa at 72°C	Grybat et al. 2003
Density	0.932 g/cm^3 at 19°C	IUCLID 2000
	0.9267 g/cm^3 at 25°C	IUCLID 2000
Melting point	−19°C to −20°C	IUCLID 2000
Boiling point	81°C at 30.7 hPa	IUCLID 2000
	82°C at 23 mm Hg	E.I. du Pont de Nemours and Co. 1998
	95°C at 1013 hPa (decomposition to acetone and HCN)	IUCLID 1996
Solubility	Very soluble in water, alcohol and ether	E.I. du Pont de Nemours and Co. 1998
Odor	Characteristic bitter almond odor of free HCN	ACGIH 1996
Explosive limits in air	2.2 % (LEL) to 12 % (UEL)	IUCLID 2000
Conversion factors	1 ppm = 3.5 mg/m³	E.I. du Pont de Nemours and Co. 1998
	1 mg/m³ = 0.28 ppm	

Since the elimination reaction of HCN from acetone cyanohydrin is an endothermic reaction, the decomposition of acetone cyanohydrin is accelerated by heat. At temperatures of 120°C or higher, acetone cyanohydrin decomposes with

the evolution of HCN (IUCLID 2000). Rather than acting as mere diluents, water and ethanol (especially in the presence of amines) exert specific dissociative effects on acetone cyanohydrin (Stewart and Fontana 1940). The very rapid breakdown of acetone cyanohydrin with moisture would present some challenges in any accidental spill or release. Because acetone cyanohydrin breaks down so readily to HCN and the toxicity is due to HCN, both materials are present in a mixture and the ratio of the two could be rapidly changing. Therefore, both materials would need to be tracked to give an indication of the risk.

Acetone cyanohydrin in air can be specifically determined using solid sorbent sampling (samples should be stored water-free and frozen to avoid decomposition), elution with a water-free solvent (ethylacetate), and gas chromatographic analysis (Glaser and O'Connor 1985; NIOSH 1985). Methods for total cyanide determination involving sampling in alkaline solutions or infrared spectroscopy also are available (Singh et al. 1986). Electrochemical detectors for HCN and Draeger tubes for HCN will not detect acetone cyanohydrin. However, these devices can be used to detect HCN that will form rapidly in a case of acetone cyanohydrin release because of its decomposition to acetone and HCN.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although deaths have occurred from exposures to acetone cyanohydrin, specific exposure concentrations and exposure periods have not been reported (Sunderman and Kincaid 1953; NIOSH 1978; DECOS 1995; ACGIH 1996). Fatalities and life-threatening poisonings with clonic-tonic convulsions in workers have been described after inhalation (Krefft 1955) and skin contact (Sunderman and Kincaid 1953; Thiess and Hey 1969) as well as after accidental ingestion (Sunderman and Kincaid 1953). Following mild exposure to acetone cyanohydrin, patients presented with cardiac palpitation; headache; weakness; dizziness; nausea; vomiting; and nose, eye, throat, and skin irritation (Ballantyne and Marrs 1987; DECOS 1995).

2.2. Nonlethal Toxicity

No relevant studies documenting nonlethal effects in humans after a single inhalation exposure to acetone cyanohydrin were located in the available literature. Cases of intoxication in workers after dermal contact with acetone cyanohydrin have been reported (Lang and Stintzy 1960; Zeller et al. 1969).

Sunderman and Kincaid (1953) described at least three pumpers who lost consciousness during the packing operation of acetone cyanohydrin. The men recovered after they had been revived on exposure to fresh air and cleaning their hands. No permanent injury apparently occurred following these exposures. It had been noted that the pumpers usually had their hands covered with grease.

When the employees had covered their hands, the effects of acetone cyanohydrin were minimal, suggesting dermal penetration of acetone cyanohydrin as the principal route of exposure in these cases. The symptoms following mild exposure to acetone cyanohydrin were predominantly cardiac palpitation, headache, nausea, and vomiting. No details about the exposure conditions were reported.

Oral exposure to acetone cyanohydrin may occur as a consequence of its liberation from linamarin, a cyanogenic glycoside found in cassava and other plant foodstuffs (Conn 1979). Linamarin is the common name given to a molecule composed of glucose and acetone cyanohydrin. Since toxic effects of linamarin usually become evident only after long-term, low-dose exposure, toxicity data for linamarin are not considered relevant to AEGL development and thus are not presented here.

Shkodich (1966) reported that according to a majority of people smelling and tasting acetone-cyanohydrin-containing water, the sensory threshold of smell for this substance is at a concentration of 0.06 mg/L and that of aftertaste is 0.48 mg/L. No experimental details were reported.

2.3. Developmental and Reproductive Toxicity

No studies documenting potential developmental or reproductive toxicity of acetone cyanohydrin exposure in humans were located in the available literature.

2.4. Genotoxicity

No studies documenting the genotoxic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.5. Carcinogenicity

No studies documenting the carcinogenic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.6. Summary

Deaths associated with inhaled acetone cyanohydrin have occurred, but exposure concentrations are unknown. Likewise, airborne exposure concentrations for those who survived the initial acute intoxication were not provided, but in each instance, there was ample opportunity for skin absorption. No information on developmental or reproductive effects, genotoxicity, or carcinogenicity was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data are available for the rat; only one study reporting lethality in mice was located. The lethality data are summarized in Table 1-3.

3.1.1. Rats

Smyth et al. (1962) exposed groups of six albino rats to acetone cyanohydrin vapors that were produced by passing a 2.5-L/min-air-stream through a fritted glass disc immersed in 50 mL of acetone cyanohydrin. Doses were logarithmically distributed, differing by a factor of two (doses were not stated explicitly). The observation period was 14 d. After exposure for 4 h, two of six rats were killed at 62.5 ppm and six of six rats were killed at 125 ppm. The maximum time rats could be exposed to saturated vapor (about 1,300 ppm) without producing any deaths was 5 min. No other signs of toxicity were reported.

Izmerov et al. (1982) reported an LC_{40} (concentration that is lethal for 40% of test organisms) of 185 mg/m³ (51.8 ppm) for 2 h in rats (no details reported).

Sunderman and Kincaid (1953) using saturated vapors of commercially available acetone cyanohydrin reported that six of six rats died after 1.5 min. When the free HCN contained in the acetone cyanohydrin was removed by precipitation with silver nitrate before exposure, the authors found that collapse occurred after an average time of 4 min and 50 % mortality after 10 min (the exact number of animals not stated).

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 20 exposure days (28 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN) four times daily. For the total exposure period, mean analytic concentrations (± standard deviation [SD]) were determined as 9.2 ± 0.9, 29.9 ± 1.2, and 59.6 ± 1.4 ppm, respectively. In the highest exposure group, respiratory distress, tremors or convulsions or both, foaming at the mouth, and prostration were observed in four males following the first exposure. Three of the four animals died. No deaths occurred in the 29.9-ppm group (see section 3.2.4 for nonlethal effects). In three other studies conducted under similar protocols, no deaths were observed at 60 ppm for 6 h/d (Monsanto 1982b,c, 1986b) (see sections 3.2.1 and 3.3.1). The authors suggested that the differences between the 28-d study and the 14-week study (Monsanto 1986b) were possibly due to the very steep dose-response for acetone

TABLE 1-3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	Saturated vapor (about 1,300 ppm)	1.5 min (time to death)	6/6 animals died during exposure period; using commercially available acetone cyanohydrin	Sunderman and Kincaid 1953
Rat	Saturated vapor (about 1,300 ppm)	10 min (time to death)	6/6 animals died during exposure period; using commercial acetone cyanohydrin with free HCN removed	Sunderman and Kincaid 1953
Rat	125	4 h	6/6 animals died	Smyth et al. 1962
Rat	62.5	4 h	2/6 animals died	Smyth et al. 1962
Rat	59.6	6 h/d, 5 d/wk, 4 wk	3/20 animals died (deaths occurred after first exposure during which exposure to an elevated concentration may have occurred)	Monsanto 1986a
Rat	58.6	6 h/d, 7 d/wk, 21 d	No deaths in 24 animals	Monsanto 1982c
Rat	57.7	6 h/d, 5 d/wk, 14 wk	No deaths in 30 animals	Monsanto 1986b
Rat	57.2	6 h/d, 5 d/w, 48 d	No deaths in 15 animals	Monsanto 1982b
Rat	51.8	2 h	LC_{40}	Izmerov et al. 1982
Mouse	574	2 h	LC_{50}	Gabor et al. 1962
Mouse	19.6	2 h	LC_{30}	Izmerov et al. 1982

cyanohydrin or to the normal variation in experimental animals of the same strain. Evaluation of the nominal and analytic concentrations revealed that the animals in the 60-ppm group may have been exposed to a slightly higher concentration during the second half of the first day: the nominal concentration of 64.8 ppm for the first day was the highest of all days (mean for the other 19 exposure days was 60.4 ± 1.8 ppm), likewise, the last two analytic concentrations measured during the first day (55.5, 60.5, 63.5, and 63.5 ppm; mean 60.8 ± 3.8) were greater than those measured on all subsequent exposure days (the highest individual value for exposure days 2-20 was 61.5 ppm; mean for exposure days 2-20 was 59.5 ± 1.4 ppm).

3.1.2. Mice

Gabor et al. (1962) exposed albino mice to different acetone cyanohydrin concentrations (0.5-3 mg/L [40-840 ppm]) for 2 h. Deaths were reported as 0 of 10 mice at 140 ppm, 0 of 10 at 280 ppm, 8 of 10 at 420 ppm, 18 of 44 at 560 ppm, 4 of 10 at 700 ppm, and 10 of 10 at 840 ppm. The authors found a 50% narcosis level at 1.65 mg/L (462 ppm) and calculated a LC_{50} of 2.05 mg/L (574 ppm). The mouse strain, analytic methods, and post-exposure observation period were not reported.

Izmerov et al. (1982) reported an LC_{30} of 70 mg/m³ (19.6 ppm) for 2 h in mice (no details were reported).

3.2. Nonlethal Toxicity

No studies were located that evaluated nonlethal consequences of acetone cyanohydrin after a single inhalation exposure. Studies using repeated inhalation exposure reported signs of irritation, such as red nasal discharge and perioral wetness. These data are summarized in Table 1-4.

3.2.1. Rats

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to mean acetone cyanohydrin concentrations of 9.2 ± 0.9, 29.9 ± 1.2, and 59.6 ± 1.4 ppm, respectively, for 6 h/d, 5 d/wk for 20 exposure days (28 days in total) (see section 3.1.1). Three of 20 animals that inhaled 59.6 ppm died after the first exposure. The three animals that died and another animal that survived showed respiratory distress, prostration, tremors and/or convulsions (observed in three of the four animals), and foaming of the mouth (observed in two of the four animals). During the first week of exposure, red nasal discharge was reported in 0 of 20 control animals, 0 of 20 animals in the 10-ppm group, 4 of 20 animals in the 30-ppm group, and 2 of 20 animals in the 60-ppm group (the authors reported incidences of irritation only for whole weeks, but not for single days). Reduced ($p > 0.05$) body weight was found in the high-exposure group. No gross or microscopic lesions attributable to acetone cyanohydrin exposure were observed. Total serum protein was reduced in male rats at all exposure concentrations but only statistically significant in the mid- and high-exposure groups.

Monsanto (1986b) conducted exposures of 15 female and 15 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 14 weeks. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran

TABLE 1-4 Summary of Nonlethal Signs of Acetone Cyanohydrin Exposure in Laboratory Animals

Species	Target [analytic] concentration (ppm)	Exposure Time	Effect	Reference
Rat	60 [57.2]	6 h/d, 5 d/wk, 48 d	Red nasal discharge in 14/15 animals vs. 10/15 in controls and perioral wetness/red stain in 8/15 animals vs. 2/15 in controls during first 10-d period; 15 males tested	Monsanto 1982b
Rat	60 [58.6]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 12/24 animals vs. 6/24 controls; 24 females tested	Monsanto 1982c
Rat	60 [59.6]	6 h/d, 5 d/wk,4 wk	Respiratory distress, prostration, tremors and/or convulsions in 4/20, red nasal discharge in 2/20 animals vs. 0/20 in controls during week 1; 3/20 males died after first day; 10 females and 10 males tested	Monsanto 1986a
Rat	60 [57.7]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 20/30 animals vs. 6/30 in controls and clear nasal discharge in 2/30 animals vs. 0/30 in controls during week 1; no deaths occurred; 15 females and 15 males tested	Monsanto 1986b
Rat	30 [28.5]	6 h/d, 5 d/wk, 48 d	Red nasal discharge in 12/15 animals vs. 10/15 in controls and perioral wetness/red stain in 4/15 animals vs. 2/15 in controls during first 10-d period; 15 males tested	Monsanto 1982b
Rat	30 [30.4]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 10/24 animals vs. 6/24 controls; 24 females tested	Monsanto 1982c
Rat	30 [29.9]	6 h/d, 5 d/wk, 4 wk	Red nasal discharge in 4/20 animals vs. 0/20 in controls during week 1; 10 females and 10 males tested	Monsanto 1986a
Rat	30 [28.6]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 18/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto 1986b
Rat	10 [10.0]	6 h/d, 5 d/wk, 48 d	Red nasal discharge during week 1 in 10/15 animals vs. 10/15 in controls; 15 males tested	Monsanto 1982b

(Continued)

TABLE 1-4 Continued

Species	Target [analytic] concentration (ppm)	Exposure Time	Effect	Reference
Rat	10 [10.7]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 9/24 animals vs. 6/24 in controls; 24 females tested	Monsanto 1982c
Rat	10 [9.2]	6 h/d, 5 d/wk, 4 wk	No signs of irritation; 10 females and 10 males tested	Monsanto 1986a
Rat	10 [10.1]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 17/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto 1986b

infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.1 ± 0.9, 28.6 ± 1.8, and 57.7 ± 2.9 ppm, respectively. No deaths were observed. During the first week of treatment, bloodlike discharge about the nose was observed in 6 of 30 control animals, 17 of 30 animals in the 10-ppm group, 18 of 30 animals in the 30 ppm group, and 20 of 30 animals in the 60-ppm group; clear nasal discharge was reported in 0 of 30, 3 of 30, 3 of 30, and 2 of 30 animals, respectively (the authors reported incidences of irritation only for whole weeks, but not for single days). No exposure related signs of toxicity or changes in hematologic or clinical chemistry parameters were observed. No effect on body weight was found. No gross or microscopic lesions attributable to acetone cyanohydrin were observed.

Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 48 exposure days (69 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.0 ± 1.0, 28.5 ± 1.9, and 57.2 ± 3.0 ppm, respectively. For the period of exposure days 1-10, red nasal discharge was observed in 10 of 15 concurrent control animals and in 10 of 15, 12 of 15, and 14 of 15 animals that inhaled 10, 30, or 60 ppm, respectively; perioral wetness and red stain was observed in 2 of 15, 2 of 15, 4 of 15, and 8 of 15 animals, respectively. (The authors did not report the incidence of signs of irritation for single days.)

Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 7 d/wk for 21 d. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.7 ± 0.4, 30.4 ± 2.1, and 58.6 ± 2.3 ppm, respectively. During the first week of exposure, red nasal discharge or encrustations were observed in 6 of 24 animals of the control group and in 9 of 24, 10 of 24, and 12 of 24 animals exposed to 10, 30, and 60 ppm, respectively. (The authors reported incidences of irritation for whole weeks only but not for single days.)

3.3. Developmental and Reproductive Toxicity

3.3.1. Rats

No studies documenting potential developmental or reproductive toxicity

of acetone cyanohydrin after a single inhalation exposure were located in the available literature.

In fertility studies, Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin concentrations (±SD) of 0, 10.0 ± 1.0, 28.5 ± 1.9, or 57.2 ± 3.0 ppm for 6 h/d, 5 d/wk for 48 exposure days (69 days in total) (see section 3.2.1 for details and signs of irritation). After the treatment period, each male was mated consecutively with three untreated females. There were no adverse effects of inhaled acetone cyanohydrin in males as indicated by mortality, mean body weights (the high-exposure group showed a lower mean body weight, which was not significantly different from that of the concurrent control group), clinical observations and necropsy (males were killed about 3 weeks after the end of the exposure period). The number of live implants and pre- and post-implantation losses were comparable for females mated with untreated or treated males. The authors concluded that exposure to acetone cyanohydrin at 60 ppm failed to demonstrate any potential for reproductive toxicity in male rats.

In fertility studies, Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10.7 ± 0.4, 30.4 ± 2.1, and 58.6 ± 2.3 ppm for 6 h/d, 7 d/wk for 21 days (see section 3.2.1 for details and signs of irritation). There was no indication of a treatment-related adverse effect on body weight during exposure or during gestation. After cessation of exposure, the females were mated with untreated males. At examination on gestational days 13-15, fertility of mated females was comparable between the treated groups and the control group for mating efficiency, pregnancy rates, number of live implants, and pre- and post-implantation losses. The authors concluded that repeated inhalation of acetone cyanohydrin at 60 ppm failed to demonstrate any adverse effects on fertility of female rats.

Monsanto (1982a, 1983) treated groups of 25 pregnant Sprague-Dawley rats by gavage to 0, 1, 3, or 10 mg of acetone cyanohydrin per kilogram (kg) per day on days 6-15 of gestation. No deaths were observed. Maternal toxicity was evident by slight reductions in body-weight gain in the mid- and high-dose groups. Statistically significant differences between the high-dose group and controls were observed for the reduction of the number of corpora lutea per dam and the number of implantations per dam. Numbers of viable fetuses per dam, post-implantation losses per dam (nonviable fetuses, early and late resorptions), mean fetal body weight, and fetal sex distribution for all dose groups were comparable with controls. The incidence of malformations and developmental variations for all fetuses of treated animals were comparable with the concurrent control group fetuses.

3.4. Genotoxicity

In tests using different *Salmonella* strains, acetone cyanohydrin failed to yield a reproducible positive response. No mutagenic activity was observed in

vitro using the Chinese hamster ovary (CHO) gene mutation assay. No significant increases in the frequency of chromosome aberrations were observed in bone marrow cells of Sprague-Dawley rats (24 rats/sex/group) taken 6, 12, 24, or 48 h after administration of acetone cyanohydrin at 0, 1.5, 5, or 15 mg/kg by gavage (IUCLID 2000; E.I. du Pont de Nemours and Co. 1998).

3.5. Carcinogenicity

No information regarding the carcinogenic potential of acetone cyanohydrin exposure was located in the available literature. Genotoxicity studies with cyanide salts were generally negative, and no cancers were induced in rats in a 2-y feeding study with HCN (NRC 2002).

3.6. Summary

Inhalation data were available mainly for the rat. During exposure of rats, death was observed at saturated concentration (about 1,300 ppm) after 1.5 or 10 min (Sunderman and Kincaid 1953) or 5 min (Smyth et al. 1962). Other studies (failing to provide experimental details) reported death of two of six rats after 4 h at 62.5 ppm (Smyth et al. 1962), an LC_{40} of 51.8 ppm in rats, an LC_{30} of 19.6 ppm in mice (Izmerov et al., 1982), and an LC_{50} of 574 ppm for 2 h in mice (Gabor et al. 1962). In a series of studies exposing rats repeatedly at about 60 ppm for 6 h/d, deaths in 3 of 20, 0 of 20, 0 of 24, and 0 of 15 animals were observed (Monsanto 1982b,c, 1986a,b). Preceding death, respiratory distress, prostration, convulsions, and tremors were observed after the first exposure at 60 ppm (Monsanto 1986a). In the other three studies, exposure at 60 ppm and, in all studies, exposure at 30 ppm caused red nasal discharge and encrustations during the first week of exposure. At 10 ppm, the incidence of red nasal discharge was significantly increased in one of the four Monsanto studies.

4. SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism, and Disposition

Upon release into moist air, acetone cyanohydrin decomposes to yield HCN and acetone. This process is accelerated by heat and catalyzed by the presence of water. In dilute aqueous solutions, acetone cyanohydrin will fully decompose. The half-life for decomposition is pH dependent and was calculated for a 0.1% solution as 57 min at pH 4.9, 28 min at pH 6.3, and 8 min at pH 6.8 (ICI 1993). From the rate constant for decomposition at pH 7 and 26°C of 4.47 h^{-1}, a half-life of 9 min was calculated (Ellington et al. 1987).

In the humid air and the moist mucosa of the respiratory tract, acetone cyanohydrin decomposes to yield its molar equivalent in HCN and acetone. This

reaction is a result of the physical chemistry of acetone cyanohydrin (Stewart and Fontana 1940), and it is not known to be enzyme-catalyzed in animals or humans (Kaplita and Smith 1986; DECOS 1995).

Acetone cyanohydrin is miscible with water and is taken up by the moist respiratory passages. The pulmonary retention of acetone cyanohydrin has not been reported, but it is probably in the range for HCN (about 58%; ATSDR 1997), acrylonitrile (about 50%; ATSDR 1990), and acetone (70-80%; ATSDR 1994). Cyanide concentrations in liver and brain of CD-1 mice were similar after a single intraperitoneal injection of an equimolar dose of acetone cyanohydrin or sodium cyanide. After injection of acetone cyanohydrin at 9 mg/kg, 108.0 ± 27.5 and 30.0 ± 4.6 mmol/kg were found in liver and brain, respectively. After a single injection of a single dose of sodium cyanide at 4.8 mg/kg, cyanide concentrations in liver and brain were 87.8 ± 31.2 mmol/kg and 24.9 ± 4.8 mmol/kg, respectively (Willhite and Smith 1981).

With regard to the metabolism of cyanide, it is important to distinguish between low-dose cyanide metabolism, which occurs under circumstances in which cyanide is present in physiologic concentrations, and high-dose cyanide disposition, in which amounts of cyanide are far in excess of those present under normal physiologic conditions. Low-dose cyanide metabolism involves incorporation via vitamin B_{12}-dependent enzymes of cyanide into the C_1-metabolite pool from which it can be eliminated as carbon dioxide. Under physiologic conditions, the normal capacity of rhodanese to handle cyanide is not overwhelmed, and circulating cyanide remains in metabolic equilibrium with the C_1-metabolic pool (DECOS 1995; ATSDR 1997).

At high doses of cyanide, the metabolic pathway via the C_1-metabolite pool becomes quickly saturated, and detoxification involving enzymatic thiocyanate formation occurs. The enzyme rhodanese (E.C. 2.8.1.1) catalyzes the transfer of a sulfane sulfur atom from sulfur donors, such as thiosulfate, to cyanide, which acts as a sulfur acceptor, thus forming thiocyanate (DECOS 1995; ATSDR 1997). The activity of rhodanese is variable between species and tissues but is high in liver and kidney in most species (Ballantyne and Marrs 1987). The quantitative contribution to thiocyanate formation of beta-mercaptopyruvate-cyanide sulfurtransferase (E.C. 2.8.1.2), which is found in blood, liver, and kidney and catalyzes the transfer of a sulfur atom from 2-mercaptopyruvate to cyanide forming pyruvate and thiocyanate, is not known (DECOS 1995). The half-life time for the conversion of cyanide to thiocyanate from a nonlethal dose in humans is between 20 and 60 min (ATSDR 1997).

A minor pathway for cyanide detoxification is the formation of 2-aminothiazoline-4-carboxylic acid from cyanide and cystine. This reaction occurs spontaneously both in vitro and in vivo and is not enzyme-dependent. The reaction product has been identified in urine of experimental animals and in humans exposed to high concentrations of cyanide (Wilson 1987; Wood and Cooley 1956).

Acetone is oxidized in the liver by cytochrome P450 2E1 to acetol. Acetol in turn can be used for gluconeogenesis, that is, biosynthesis of glucose, either

via further oxidation to methylglyoxal in the liver or extrahepatically via reduction to L-1,2-propanediol, which can return to the liver where it is oxidized to L-lactaldehyde and further to L-lactate, which is then incorporated into glucose. Alternatively, L-1,2-propanediol can be degraded to acetate and formate in the liver (Casazza et al. 1984; Kosugi et al. 1986).

Data regarding the excretion of acetone cyanohydrin per se are not available. The cyanide metabolic products thiocyanate, cyanocobalamin, and 2-aminothiazole-4-carboxylic acid are excreted into urine. HCN and carbon dioxide are expired (DECOS 1995; ATSDR 1997).

4.2. Mechanism of Toxicity

Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All of the pharmacologic actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase, also known as ferrocytochrome c–oxygen oxidoreductase. This enzyme is also known as cytochrome aa3, and it is the terminal oxidase in aerobic metabolism of all animals, plants, yeasts, and some bacteria. This enzyme is a heme-copper lipoprotein, and cytochromes a and a3 are combined in the same large oligomeric protein molecule. Mammalian cytochrome c oxidase contains two molecules of heme A and two copper atoms. This helical protein also contains 820 amino acids. The integrity of the disulfide groups to maintain the 30% helix structure is essential to the oxidase mechanism. Cessation of the mitochondrial electron transport results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

The interaction of cytochrome c oxidase with cytochrome c was reviewed by Lemberg (1969). The reaction proceeds by first-order kinetics with respect to the concentration of cytochrome c (Smith et al. 1979). Once absorbed, cyanide complexes with many metal ions and interferes with the activities of at least 39 heme zinc, copper, and disulfide enzymes (e.g., catalase and peroxidase) whose activities depend on either metals as cofactors or prosthetic groups (Dixon and Webb 1964). Cyanide also binds to nonhematin metal containing enzymes, like tyrosinase, ascorbic acid oxidase, xanthine oxidase, amino acid oxidase, formic dehydrogenase, and various phosphates. The cyanide concentration required for cytochrome c oxidase inhibition is 26 orders of magnitude less than that required for inhibition of these other enzymes. Thus, it is the critical position of cytochrome c oxidase in aerobic metabolism that makes its inhibition felt earliest, so the effects of HCN on other enzyme systems have scant chance to appear (Rieders 1971). The oxidase-HCN (not CN) (Stannard and Horecker 1948; Gibson and Greenwood 1963) complex is dissociable (Swinyard 1975).

Willhite and Smith (1981) measured the inhibition of the oxidation of purified bovine cardiac cytochrome c in vitro by a number of nitriles. In the presence of potassium cyanide (KCN) or acetone cyanohydrin, the reaction was inhibited in a concentration-dependent fashion. The addition of acetone cyano-

hydrin inhibited the reaction in a manner kinetically similar to the addition of KCN. Since the inhibitory effects of KCN and acetone cyanohydrin were observed at pH 6.0 and the pKa of HCN is 9.2, the data indicate that the inhibitory species is the undissociated acid HCN, as suggested previously (Stannard and Horecker 1948; Gibson and Greenwood 1963).

4.3. Structure-Activity Relationships

Willhite and Smith (1981) demonstrated that the behavior of acetone cyanohydrin parallels that of its molar equivalent of cyanide in vivo. For example, the intraperitoneal LD_{50} (lethal dose with 50% lethality) in mice for acetone cyanohydrin (equivalent to 2.65 mg of cyanide ion per kilogram) is similar to that of sodium cyanide at 2.54 mg of cyanide ion per kilogram; mean time-to-death was 5 min for both compounds. Pretreatment with sodium nitrite or thiosulfate (standard cyanide antidotes) protected mice against lethal doses of acetone cyanohydrin and HCN. The authors also studied the acute toxicity in mice for a series of seven aliphatic nitriles (acetonitrile, propionitrile, acrylonitrile, *n*-butyronitrile, malononitrile, succinonitrile, and acetone cyanohydrin) and sodium cyanide. Only the latter two compounds produced death within 5 min. All other nitriles produced death at widely varying intervals from a few minutes to many hours. Pretreatment with the liver toxicant carbon tetrachloride protected mice against death from all nitriles, except acetone cyanohydrin, suggesting that all nitriles examined (except for acetone cyanohydrin) possess little if any acute toxicity in the absence of normal hepatic function and that these nitriles (except acetone cyanohydrin) underwent hepatic metabolism to release cyanide, accounting for their acute toxicity. In contrast, acetone cyanohydrin did not require metabolic activation and released its cyanide moiety spontaneously in vivo.

Johannsen and Levinskas (1986) undertook a structure-activity comparison of acetone cyanohydrin, lactonitrile, four mononitriles (acetonitrile, propionitrile, *n*-butyronitrile, and acrylonitrile) and two dinitriles (succinonitrile and adiponitrile). The authors observed that with regard to oral and dermal LD_{50}, as well as repeated administration, acetone cyanohydrin was the most potent compound tested. For other nitriles, the time to onset of signs of toxicity in rats was between 50 and 300 min after exposure, and for acetone cyanohydrin ,a rapid onset of signs (within 5 min) before death was found. The authors concluded that the signs of acetone cyanohydrin toxicity resembled those seen after exposure to sodium cyanide.

4.4. Other Relevant Information

4.4.1. Effects of Cyanides and Acetone in Humans

Since acetone cyanohydrin exerts toxicity through rapid release of cyanide, it is appropriate to take into consideration relevant studies describing ef-

fects in humans after exposure to cyanide (summarized in NRC 2002). Several studies reporting effects after repeated occupational exposure to cyanides are available; however, accurate empirical exposure data usually were not reported.

Bonsall (1984) described the case of a worker who was exposed to HCN during inspecting a tank containing a thin layer of hydrazodiisobutyronitrile. The tank had been washed with water, which resulted in hydrolysis of the nitrile into HCN and acetone. The man collapsed after 3 min, was fitted with a breathing apparatus after another 3 min and removed from the tank after 13 min. At this time, the worker was unconscious with imperceptible breathing and dilated pupils and was covered with chemical residue. Immediately after the accident, a concentration of HCN of about 500 mg/m³ (450 ppm) was measured. The victim was administered sodium thiosulfate and was discharged from the hospital 2 weeks later without apparent sequelae.

El Ghawabi et al. (1975), compared the symptoms of 36 workers exposed to HCN in three electropating factories in Egypt with a control group; employment ranged between 5 and 17 years. None of the workers in either the exposed or control groups were smokers. Cyanide exposure resulted from a plating bath that contained copper cyanide, sodium cyanide, and sodium carbonate. Concentrations of cyanide in the breathing zone of the workers ranged from 4.2 to 12.4 ppm (means in the three factories: 6, 8, and 10 ppm). Fifteen-minute air samples were collected in sodium hydroxide and analyzed colorimetrically. Symptoms reported most frequently by exposed workers compared with the referent control group were, in descending order of frequency: headache, weakness, and changes in taste and smell. Lacrimation, vomiting, abdominal colic, precordial pain, salivation, and nervous instability were less common. The authors made no attempt to correlate the incidences of these symptoms with concentrations. Although there were no clinical manifestations of hypothyroidism or hyperthyroidism, 20 of the workers had thyroid enlargement to a mild or moderate degree; this condition was accompanied by higher ^{131}I uptake compared with the referent controls. Exposed workers also had significantly higher blood hemoglobin, lymphocyte cell counts, cyanmethemoglobin, and urinary thiocyanate levels than controls. Urinary thiocyanate levels were correlated with cyanide concentration in workplace air. Two workers in the factory with a mean exposure of 10 ppm suffered psychotic episodes; recovery occurred within 36 to 48 h. Although the sample size was small, the study used well-matched controls and included a biologic index of exposure (urinary thiocyanate). The NRC Subcommittee on Spacecraft Maximum Allowable Concentrations, in evaluating the El Ghawabi et al. (1975) data, concluded that "8 ppm would likely produce no more than mild CNS effects (e.g., mild headache), which would be acceptable for 1-h exposures" of healthy adults (NRC 2000).

Blanc et al. (1985) surveyed and examined 36 former employees of a silver reclaiming facility to determine acute and potential residual adverse health effects resulting from occupational HCN exposure. The study was prompted by a worker fatality from acute cyanide poisoning. The workers had been chronically exposed to airborne cyanide at time-weighted-average (TWA) concentra-

tions (taken 24 h after the plant had closed down) of at least 15 ppm. The most frequent symptoms included headache, dizziness, nausea or vomiting, and a bitter or almond taste, eye irritation, loss of appetite, epistaxis, fatigue, and rash. The most prevalent symptoms (headache, dizziness, nausea or vomiting, and a bitter or almond taste) were consistent with cyanide poisoning. A concentration-response relationship corresponding to high- and low-exposure jobs was demonstrated, but exact breathing zone concentrations were not quantified. Some symptoms exhibiting a dose-response trend occurring 7 or more months after exposure had ceased. Mild abnormalities of vitamin B_{12}, folate, and thyroid function were detected, and those results suggested cyanide and/or thiocyanide involvement. The NRC (2000) pointed out that the 24-h TWA of 15 ppm was measured 1 day after the plant had ceased operation, suggesting that these workers may have been exposed to cyanide at more than 15 ppm.

Leeser et al. (1990) reported a cross-sectional study of the health of cyanide-salt production workers. Sixty-three cyanide production workers employed for 1 to 40 years were compared with 100 referent workers from a diphenyl oxide plant. Workers were examined before and after a block of six 8-h shifts. All workers had full medical examinations, routine clinical chemistry tests, and blood samples taken for measurement of blood cyanide and carboxyhemoglobin. In addition, circulating levels of vitamin B_{12} and thyroxin (T4) were measured. Atmospheric cyanide was monitored with static monitors, Draeger pump tests, and personal monitoring. For the personal monitoring, air was drawn through bubblers that contained sodium hydroxide. Cyanide collected in the sodium hydroxide solution was measured using an anion-selective ion electrode. All results (34 samples) were between 0.01 and 3.6 mg/m³ (0.01 and 3.3 ppm). Geometric mean values for eight job categories ranged between 0.03 and 1.05 mg/m³ (0.03 and 0.96 ppm). Values for only one job category (eight personal samples) averaged 0.96 ppm. Results of routine Draeger pump tests (area samples) were between 1 and 3 ppm (measurement method not stated). This increased exposure was reflected in an increase in mean blood cyanide level in the workers following a block of six 8-h shifts, and there was an increase of 5.83 µmol during the 6-ppm exposure compared with a decrease of 0.46 µmol across the shift block in the spring. Static monitors on all floors, set to trigger alarms at 10 ppm, failed to sound during the study. Circulating cyanide concentrations in exposed workers, though low, were generally higher than in control workers, and the highest levels were measured in cyanide-exposed nonsmokers compared with the nonsmoking control group (cyanide-exposed nonsmokers, 3.32 µmol; controls, 1.14 µmol; $p < 0.001$). For ex-smokers, the difference was smaller (cyanide exposed, 2.16 µmol; controls, 1.46 µmol), and for current smokers, the blood cyanide level was higher in the control group (2.94 µmol for cyanide workers who smoked; 3.14 µmol for controls who smoked). The percentage of workers reporting shortness of breath and lack of energy was higher in cyanide workers than in the diphenyl oxide plant workers. These differences were partially explained by the greater number of cyanide workers who were shift workers. Slightly higher hemoglobin values and lymphocyte counts in the cyanide

workers were not dose-related. Results of clinical and physical examinations and evaluation of medical histories failed to reveal any exposure-related health problems.

Compared with cyanide, the acute toxicity of acetone is low (ATSDR 1994). This fact is reflected in comparatively high values for the TLV (Threshold Limit Value) (ACGIH 1997) of 500 ppm for 8 h with a 750-ppm STEL (short-term exposure limit), the IDLH (immediately dangerous to life and health concentrations) of 2,500 ppm (NIOSH 1996), and the EEGL (emergency exposure guidance levels) of 1,000 ppm for 24 h and 8,500 ppm for 1 h (NRC 1984). Acetone and its metabolic products (Casazza et al. 1984; Kosugi et al. 1986; Gentry et al. 2003) contribute only insignificantly to the toxicity of acetone cyanohydrin.

4.4.2. Lethality of HCN in Animals

Only one study was located that evaluated lethality of HCN in rats for an exposure time comparable to that of the 6-h studies of Monsanto (1982b,c, 1986a,b) using acetone cyanohydrin.

Five male and five female Sprague-Dawley Crl:CD rats were exposed to HCN at 68 ppm in a stainless steel chamber for 6 h/d for 3 days (Blank 1983). HCN was generated by passing nitrogen over the liquid contained in a 500-mL flask. The concentration in the cage was measured with an infrared analyzer. During the exposures, hypoactivity and quick shallow breathing were observed in all animals. During the first day, three males exhibited anoxia and hypoxia followed by convulsions (one male). One male rat died during the exposure, a second male died during the post-exposure observation period, and a third male was found dead prior to the second day of exposure. Two additional males and all five females exhibited breathing difficulties following the first exposure. No additional mortality was observed following the second and third days of exposure; body weights by the third day were below pre-exposure weights. Necropsy of the three dead males revealed cyanosis of the extremities, moderate-to-severe hemorrhage of the lung, lung edema, tracheal edema, blanched appearance of the liver, singular occurrences of blood engorgement of the heart and surrounding vessels, chromorhinorrhea, urine-filled bladder, and gaseous distension of the gastrointestinal tract. Survivors were sacrificed following the last exposure. Of the seven survivors, three females developed slight-to-moderate pulmonary hemorrhage.

4.4.3. Species Variability

Because of the lack of sufficient data, the potential interspecies variability for acute inhalation toxicity of acetone cyanohydrin cannot be assessed directly. However, data on acute lethality after oral administration (Table 1-5) indicate that lethal doses are similar for different species.

TABLE 1-5 Summary of Oral LD_{50} Data for Acetone Cyanohydrin

Species	LD_{50} (mg/kg)	Reference
Rat	17	Smyth et al. 1962
Rat	13.3	Shkodich 1966
Rat	17.8	Marhold 1972
Mouse	14	Marhold 1972
Mouse	15	Hamblin 1953, personal commun., as cited in Sunderman and Kincaid 1953
Mouse	2.9	Shkodich 1966
Guinea pig	9	Shkodich 1966
Rabbit	13.5	Shkodich 1966

Likewise, nearly identical LD_{50} values have been found in rats and mice after parenteral application: An LD_{50} value of 8.7 mg/kg (95% confidence interval [CI], 8-9 mg/kg) (mean time to death, 5 ± 1 min) was found after intraperitoneal injection in CD-1 male mice (Willhite and Smith 1981), and one of 8.5 mg/kg was found after subcutaneous injection in male albino rats (Magos 1962).

For HCN, LC_{50} values for various species differ by a factor of 2-3 (ATSDR 1997), and an interspecies extrapolation factor of 2 was used for derivation of AEGL-3 and -2 values for HCN (NRC 2002).

4.4.4. Intraspecies Variability

People at potentially increased risk for toxic effects caused by exposure to acetone cyanohydrin include those with chronic exposure to cyanide (e.g., heavy smokers) or cyanogenic glycosides from edible plants (e.g., cassava or lima beans) and those with an inadequate detoxification of cyanide (reviewed in NRC 2002). The latter condition can result from inadequate dietary intake of vitamin B_{12} and/or sulfur-containing amino acids as well as from inborn metabolic errors, such as the genetic component responsible for Leber's hereditary optic atrophy, which is possibly associated with a reduction in rhodanese activity, dominantly inherited optic atrophy, and recessively inherited optic atrophy (DECOS 1995). However, for a single acute exposure to high acetone cyanohydrin concentrations, the interindividual differences are probably not great because the decomposition of acetone cyanohydrin to cyanide is not dependent on metabolism and the cyanide detoxification pathway becomes quickly saturated at higher exposure concentrations. Due to conservatism of the cytochrome c oxidase during evolution, interindividual differences in the affinity of cyanide binding to its target receptor are unlikely to occur.

For HCN, an intraspecies extrapolation factor of 3 has been used for derivation of AEGL-3 and -2 values for HCN (NRC 2002).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 mg/L). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and cyanohydrin concentrations in air. Human data on irritation effects of acetone cyanohydrin are lacking.

Since the effects of acetone cyanohydrin are due to the release of cyanide after its rapid decomposition, data on exposure of humans to cyanide are relevant. In humans occupationally exposed to cyanide, no adverse effects have been found after exposure to a geometric mean cyanide concentration of 1 ppm (Leeser et al. 1990). At concentrations of 6-10 ppm, there were increased complaints of mild headache after repeated occupational exposure (El Ghawabi et al. 1975).

5.2. Animal Data Relevant to AEGL-1

During the first week of repeated 10-ppm 6-h exposure studies in rats, there was no sign of red nasal discharge in one study (Monsanto 1986a). The incidence of nasal discharge was not increased compared with concurrent control groups in two studies (Monsanto 1982b,c), but it was increased compared with the control group in a fourth study (Monsanto 1986b). No other adverse effects were reported in these four studies.

5.3. Derivation of AEGL-1

Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4 of 20 animals at 29.9 ppm and in 2 of 20 animals at 59.6 ppm, but not in control animals and in animals exposed to 9.2 ppm, during the first week of repeated 6-h/d exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that end point was present or not. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor end point on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin, it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathologic findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air, or upper respiratory tract infections.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats. The derivation basis would be an exposure at 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks, which did not result in red nasal discharge (Monsanto 1986a). Using the default time scaling procedure and a total uncertainty factor of 10, AEGL-1 values of 2.1, 2.1, 1.7, 1.1, and 0.69 ppm would be derived for the 10- and 30-min and 1-, 4-, and 8-h periods, respectively.

The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for HCN (NRC 2002). The values are listed in Table 1-6.

Because no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature (see section 5.1), no level of distinct odor awareness (LOA) was derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human exposure data relevant for the derivation of AEGL-2 values are lacking. Because the effects of acetone cyanohydrin are caused by the release of cyanide after rapid decomposition of acetone cyanohydrin, data on exposure of humans to cyanide are relevant. Chronic occupational exposure to cyanide concentrations of about 6-10 ppm produced mild CNS effects (mild headache) (El Ghawabi et al. 1975); more distinct symptoms were reported for occupational exposures of 15 ppm and higher (Blanc et al. 1985).

6.2. Animal Data Relevant to AEGL-2

Four studies using repeated 6-h inhalation exposures of rats, performed

TABLE 1-6 AEGL-1 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

according to good laboratory practice, reported signs of irritation at an exposure concentration of about 30 ppm (Monsanto 1982b,c, 1986a,b), such as red nasal discharge and encrustations and perioral wetness and red stain. Red nasal discharge was also observed at about 10 ppm in two of the four studies. At higher concentrations of about 60 ppm in one study (Monsanto 1986a), respiratory distress, prostration, and tremors and/or convulsions were observed after the first exposure in 4 of 20 animals, and of these, three animals died. No studies showing irreversible, nonlethal effects in animals were available in the literature.

6.3. Derivation of AEGL-2

The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This conclusion is supported by very similar AEGL-2 values that would be derived on the basis of chemical-specific data: in the Monsanto (1986a) study, repeated exposures to 29.9 ppm acetone cyanohydrin for 6 h/d, 5 d/wk for 4 weeks resulted in irritation, but not in respiratory distress, which was observed in 4of 20 animals during the first exposure at 60 ppm. Using the default time-scaling procedure and a total uncertainty factor of 10, AEGL-2 values of 6.8, 6.8, 5.4, 3.4, and 2.5 ppm would be derived for the 10- and 30-min and 1-, 4-, and 8-h periods, respectively.

The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for HCN (NRC 2002). The values are listed in Table 1-7.

TABLE 1-7 AEGL-2 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human exposure data relevant for the derivation of AEGL-3 values are not available.

7.2. Animal Data Relevant to AEGL-3

Reliable LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice are not available. Single-exposures killed two of six rats that inhaled 62.5 ppm for 4 h (Smyth et al. 1962). The LC_{40} was 51.8 ppm for 2 h in rats, and the LC_{30} was 19.6 ppm for 2 h in mice (Izmerov et al. 1982); however, due to the small number of animals in the study by Smyth et al. (1962), the lack of information on the rodent strain and the number of animals used in the study by Izmerov et al. (1982), and the failure of both studies to report experimental details, a thorough evaluation of these data is not possible.

The study by Sunderman and Kincaid (1953) used saturated acetone cyanohydrin vapor that led to death within 1.5 or 10 min. Likewise, Smyth et al. (1962) reported death of rats after 5 min of exposure to saturated vapor concentrations.

Four studies, performed according to good laboratory practice, exposed rats repeatedly to acetone cyanohydrin at about 60 ppm for 6 h/d (Monsanto 1982b,c, 1986a,b). Lethal effects were reported in only one of the studies (Monsanto 1986a): 3 of 10 males died after the first exposure, none of 10 female rats died, and no further deaths of males were observed in subsequent exposures. No deaths occurred in the other studies that used 15 males and 15 females (Monsanto 1986b), 24 females (Monsanto 1982c), or 15 males (Monsanto 1982b).

In the HCN study by Blank (1983), 3 of 10 rats died after the first exposure to at 68 ppm for 6 h.

7.3. Derivation of AEGL-3

The derivation of AEGL-3 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This conclusion is supported by very similar observations of lethal effects in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm, and the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (as

discussed in section 3.1.1, the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), and no additional deaths were found in the 19 subsequent exposures.

The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for HCN (NRC 2002). The values are listed in Table 1-8.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 1-9. They were derived using the following key studies and methods.

The derivation of AEGL values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the local and systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

All inhalation data are summarized in Figure 1-1. The data were classified into severity categories chosen to fit into definitions of the AEGL health effects.

TABLE 1-8 AEGL-3 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

TABLE 1-9 Summary of AEGL Values for Acetone Cyanohydrin[a,b]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.
[b]Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

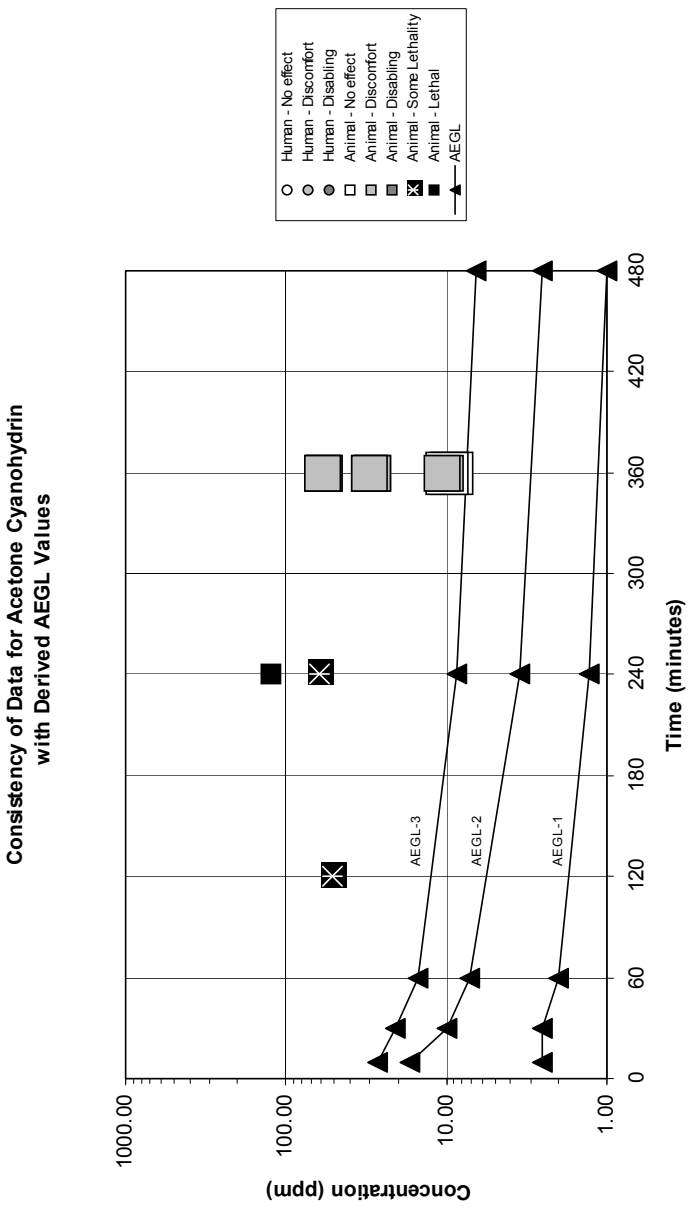

FIGURE 1-1 Categorical representation of acetone cyanohydrin inhalation data.

The category severity definitions are "no effect," "discomfort," "disabling," "lethal," "some lethality" (at an experimental concentration in which some of the animals died and some did not, this label refers to the animals that did not die), and "AEGL." Note that the AEGL values are designated as triangles without an indication to their level. AEGL-3 values are higher than the AEGL-2 values, and the AEGL-2 values are higher than the AEGL-1 values.

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 1-10.

8.3. Data Adequacy and Research Needs

Definitive exposure-response data for acetone cyanohydrin in humans are not available. Data from earlier animal studies were often compromised by uncertain quantitation of exposure atmospheres, small numbers of animals, and poor data presentation. Four more recent repeated inhalation exposure studies in rats sponsored by Monsanto Company utilized accurate and reliable methods for characterizing concentrations. However, repeat exposure studies were considered of limited relevance for the derivation of AEGL values.

TABLE 1-10 Extant Standards and Guidelines for Acetone Cyanohydrin

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
AEGL-2	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm
WEEL (AIHA)[a]	5 ppm for 15 min				2 ppm
TLV ceiling (ACGIH)[b]	4.7 ppm as cyanide				
REL ceiling (NIOSH)[c]	1 ppm				

[a]AHIA WEEL (American Industrial Hygiene Association, workplace environmental exposure level) (AIHA1999) represent workplace exposure concentrations to which, it is estimated, nearly all employees could be repeatedly exposed without adverse effects. WEELs are expressed as time-weighted-average values for different time periods.
[b]ACGIH TLV ceiling (American Conference of Governmental Industrial Hygienists, Threshold Limit Value) (ACGIH 1996) is defined as a 15-min TWA exposure concentration, which should not be exceeded at any time during the workday. Because acetone cyanohydrin behaves qualitatively and quantitatively both in vitro and in vivo exactly as does its molar equivalent in free cyanide, the TLV for acetone cyanohydrin is assigned to be identical to that for free HCN.
[c]NIOSH REL ceiling (National Institute of Occupational Safety and Health, recommended exposure limits) (NIOSH 1978)is defined analogous to the ACGIH TLV ceiling. NIOSH based the value on the assumption that acetone cyanohydrin was approximately 18.3 times as toxic as acetonitrile by inhalation.

With regard to toxic effects, the similarity between acetone cyanohydrin and HCN concerning both the mechanism of toxic effects and dose-response relationships was considered high enough to apply the AEGL-1, AEGL-2, and AEGL-3 values derived for HCN to acetone cyanohydrin on a part per million basis. In contrast to HCN, appropriate studies are not available for acetone cyanohydrin in exposed workers for the derivation of AEGL-1 or in well-performed inhalation exposure studies evaluating neurotoxic or lethal effects for the derivation of AEGL-2 and AEGL-3 values. However, the available results of studies in rats are in good agreement with HCN studies. LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice would strengthen the derived AEGL-3 values.

It Because of the steep dose-response relationship, concentrations of AEGL-2 and AEGL-3 values differ only by a factor of 1.6 to 2.6, which could cause problems in regulatory applications of AEGL values especially when it is considered that uncertainties of measurements and dispersion (plume) calculations can be in the same order of magnitude or even higher.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR ACETONE CYANOHYDRIN

AEGL-1 VALUES[a]

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Reference: The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: National Academy Press,.

Test Species/Strain/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4/20 animals at 29.9 ppm and in 2/20 animals at 59.6 ppm, but not in control animals and in animals exposed at 9.2 ppm during the first week of repeated 6-h/d exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto (1982b,c, 1986b) studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that end point was present. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor end point on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin, it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathologic findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals but also by stress, dry air, or upper respiratory tract infections.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Time Scaling: Not applicable.

(Continued)

AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Data Quality and Support for AEGLs: Similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be an exposure of 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks that did not result in red nasal discharge [Monsanto 1986a]) using a total uncertainty factor of 10.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

AEGL-2 VALUES[a]

10 min	30 min	1 h	4 h	8 h
17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm

Reference: The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. National Academy Press, Washington, DC.

Test Species/Strain/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Quality and Support for AEGLs: Very similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be an exposure of 29.9 ppm for 6 h/d, 5 d/wk for 4 weeks that caused red nasal discharge as a sign of irritation, and the next higher concentration produced respiratory distress, prostration, convulsions, and tremors [Monsanto 1986a]) using a total uncertainty factor of 10.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

AEGL-3 VALUES[a]

10 min	30 min	1 h	4 h	8 h
27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

Reference: The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. National Academy Press, Washington, DC.

Test Species/Strain/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: The derivation of AEGL-3 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Quality and Support for the AEGLs: Support comes from the close similarity of acetone cyanohydrin and HCN regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm, but the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), and no additional deaths were found in the 19 subsequent exposures.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.