Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the seventeenth vol*xiv Preface*

ume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

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

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrylonitrile (interim reports 19b, 21a, and 22), carbon tetrachloride (interim reports 13, 14, 18, and 22), cyanogen (interim report 19a), epichlorohydrin (interim reports 15, 19a, 20a, and 21a), ethylene chlorohydrin (interim reports 20a and 21a), toluene (interim reports 12, 18, and 22), trimethylacetyl chloride (interim reports 20a and 21a), hydrogen bromide (interim reports 16, 18, and 22), and boron tribromide (interim reports 19a and 22): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its re

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

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

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

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

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

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

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

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

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

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

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

In November 1995, the National Advisory Committee (NAC)[3] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

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

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

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared sixteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014). This report is the seventeenth volume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

3

Cyanogen[4]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

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

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

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

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

SUMMARY

Cyanogen is a colorless gas with a pungent, penetrating, almond-like odor (ACGIH 2001). It is generally prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper (II) sulfate or chloride. It may also be prepared from hydrocyanic acid by using copper oxide or from hydrocyanic acid and nitrogen dioxide. It is used as a gas for welding and cutting heat-resistant metals, as a rocket and missile propellant, and as a fumigant (HSDB 2009).

The hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as the AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If AEGL-1 values were derived on the basis of the cyanogen data, the no-observed-effect level for irritation in humans exposed to cyanogen for 6 min would be 8 ppm. Ocular and nasal irritation was reported at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be used because the study was conducted in humans. Thus, the threshold for irritation would be 2.7 ppm. Time scaling of this threshold would not be appropriate, because the critical effects (ocular and nasal irritation) are a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However,

because human data on exposures of durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective of both irritation and potential systemic cyanide effects.

In the absence of appropriate chemical-specific data to derive AEGL-2 values for cyanogen, the AEGL-3 values were divided by 3 to estimate the AEGL-2 values. That approach is justified by the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960).

Experimental concentrations causing no deaths in rats (McNerney and Schrenk 1960) were used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. Specifically, the concentration associated with 0% mortality after 10 min of exposure was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper. That approach estimated that no deaths would occur following a 10-min exposure at 1,530 ppm. The 30-min exposure at 500 ppm was used as the point-of-departure for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was used as the point-of-departure for the 1-h AEGL-3 value. An intraspecies uncertainty factor of 3 was applied and was considered sufficient due to the steep concentration-response curve evidenced in the mortality data from McNerney and Schrenk (1960), which implies limited intraindividual variability. An interspecies uncertainty factor of 3 was also applied. Although a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, and 4.3 ppm for 4 and 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects Lewis et al.
[1984].) Therefore, the total uncertainty factor was 10.

The 4- and 8-h AEGL-3 values were derived by applying a modifying factor of 2 to the 1-h AEGL-3 value. That approach was used because time scaling using the equation $C^n \times t = k$, with a default value of n = 1, and yielded possible 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months,

experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.

AEGL values for cyanogen are presented in Table 3-1.

1. INTRODUCTION

Cyanogen is a colorless gas with a pungent, penetrating, almond-like odor (ACGIH 2001). It is generally prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper (II) sulfate or chloride. It may also be prepared from hydrocyanic acid by using copper oxide or from hydrocyanic acid and nitrogen dioxide. It is used as a gas for welding and cutting heat-resistant metals, as a rocket and missile propellant, and as a fumigant (HSDB 2009).

Selected chemical and physical properties of cyanogen are presented in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data on cyanogen were not found.

2.2. Nonlethal Toxicity

An odor threshold of 235 ppm (500 mg/m^3) and an irritating concentration of 15 ppm (32 mg/m^3) for cyanogen were reported by Ruth (1986).

TABLE 3-1 AEGL Values for Cyanogen

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)	AEGL-1 values for cyanide were adopted (NRC 2002).
AEGL-2 (disabling)	50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)	One-third the AEGL-3 values.
AEGL-3 (lethal)	150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)	Concentrations causing no lethality in rats (McNerney and Schrenk 1960)

TABLE 3-2 Chemical and Physical Data for Cyanogen

Parameter	Value	Reference
Synonyms	Carbon nitride; cyanogene; dicyan; dicyanogen; ethanedinitrile; nitroloacetonitrile; oxalic acid dinitrile; oxalonitrile; oxalyl cyanide	HSDB 2009
CAS registry no.	460-19-5	HSDB 2009
Chemical formula	C_2N_2	HSDB 2009
Molecular weight	52.03	HSDB 2009
Physical state	Colorless gas	HSDB 2009
Melting point	-27.83°C	HSDB 2009
Boiling point	-21.1°C	HSDB 2009
Density/Specific gravity	0.9537 g/m^3 at -21°C	HSDB 2009
Solubility in water	450 cc/100 mL at 20°C	HSDB 2009
Relative vapor density	1.8 (air = 1)	HSDB 2009
Vapor pressure	4,300 mm Hg at 25°C	HSDB 2009
Explosive limits	Upper: 42.6%; lower: 6.6%, by volume in air	IPCS 2012
Conversion factors in air	1 ppm = 2.1 mg/m^3 1 mg/m^3 = 0.47 ppm	NIOSH 2011

Seven human subjects (four men and 3 women; ages 21-65 years) were exposed to cyanogen at 8 or 16 ppm in three separate tests (McNerney and Schrenk 1960). The tests were performed in a 1,185-ft^3 sealed room. The cyanogen gas contained less than 0.5% contaminants such as nitrogen, chlorine, and cyanogen chloride. Cyanogen concentrations were obtained by measuring the required volume of gas over mercury in a graduated, gas sampling tube and introducing it into the exposure space by displacement of the mercury. In the first test, four men and three women were exposed to cyanogen at 8 ppm for 6 min; none of the subjects detected an odor, and no ocular or nasal irritation was reported by the subjects. In the second test, three men and two women were exposed at 16 ppm for 6 min; none of the subjects detected an odor, all subjects reported ocular irritation, and four subjects reported nasal irritation (the subject who did not experiencing nasal irritation had mild cold symptoms). In the third test, four men and three women were exposed to cyanogen at 16 ppm for 8 min; none of the subjects detected an odor, and all subjects reported ocular and nasal irritation. During the 16-ppm tests, ocular irritation was noted immediately when the desired test concentration was attained. Ocular irritation was perceived simultaneously with or slightly before the occurrence of nasal irritation. Both ocular and nasal

irritation seemed to be transitory as signs persisted for several minutes following cessation of exposure. (There is a discrepancy in the description of the number of subjects for the first and second tests the report. The text suggests that the first test included five subjects and the second test included seven subjects; however, the data table indicates that the first test had seven subjects and the second test had five subjects. It was assumed that the data table correctly lists the number of subjects in each test. In either case, the study results are unaffected.] Results are summarized in Table 3-3.

In an additional test (McNerney and Schrenk 1960), three men and one woman attempted to detect the odor of cyanogen drawn from a sampling tube connected to a chamber where concentrations of 50, 100, and 250 ppm were produced; none of the subjects detected any odor.

2.3. Case Reports

No case reports on cyanogen were found.

2.4. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of cyanogen in humans were not available.

2.5. Genotoxicity

No information regarding the genotoxicity of cyanogen in humans was available.

2.6. Carcinogenicity

No information regarding the carcinogenicity of cyanogen in humans was available.

2.7. Summary

Cyanogen inhalation data in humans are sparse. Cyanogen causes immediate ocular and nasal irritation at 16 ppm, but no irritation was noted at 8 ppm. No developmental toxicity, reproductive toxicity, genotoxicity, or carcinogenicity data were available.

TABLE 3-3 Effects of Acute Cyanogen Exposure in Humans[a]

		Number per Group Experiencing Effects		
Concentration	Duration	Odor	Ocular Irritation	Nasal Irritation
8 ppm	6 min	0/7	0/7	0/7
16 ppm	6 min	0/5	5/5	4/5[b]
16 ppm	8 min	0/7	7/7	7/7

[a] Adapted from McNerney and Schrenk 1960.
[b] The subject without irritation had mild cold symptoms.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of six male albino rats were exposed to a total of six different concentrations of cyanogen for six different durations (McNerney and Schrenk, 1960). The tests were performed in a 2-ft^3 galvanized metal exposure chamber. A plexiglass door, bolted to the chamber, sealed the unit and allowed for observation of the rats during exposure. The cyanogen gas used contained less than 0.5% contaminants such as nitrogen, chlorine, and cyanogen chloride. Cyanogen concentrations were obtained by measuring the required volume of gas over mercury in a graduated, gas sampling tube and introducing it into the exposure space by displacement of the mercury. Experimental parameters and mortality incidence are summarized in Table 3-4. Observations during exposure included (in chronologic order) blinking, rubbing of forepaws over eyes and nose, huddling together with inactivity, slow gasping, tearing, yellow fluid from the nose and mouth, restlessness and "panic-type" movements, accentuated and poorly coordinated movements, bright pink coloration of the skin, labored breathing, deep and frequent gasping, tremors, sluggishness, prostration, shallow breathing, and death. All deaths occurred during or shortly after exposure except in the group exposed at 250 ppm for 120 min; two rats died during exposure, one died 7 h after exposure and exhibited signs of central nervous system damage starting at cessation of exposure through death, and one died 7 days after exposure and did not show any clinical signs. None of the rats showed any treatment-related gross lesions at necropsy.

TABLE 3-4 Mortality in Male Albino Rats after Acute Exposure to Cyanogen[a]

Concentration (ppm)	Duration (min)	Mortality Incidence
4,000	7.5	3/6
4,000	15	6/6
2,000	7.5	0/6

2,000	15	6/6
1,000	15	0/6
1,000	30	6/6
500	30	0/6
500	45	6/6
400	45	0/6
400	60	6/6
250	60	0/6
250	120	4/6 *a*

Adapted from McNerney and Schrenk 1960.

3.1.2. Mice

Lethality was reported in mice exposed to cyanogen at 2,600 ppm for 12 min or 15,000 ppm for 1 min. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.3. Cats

Lethality was reported in cats exposed to cyanogen at 100 ppm for 2-3 h, at 200 ppm for 0.5 h, or 2,000 ppm for 13 min. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.4. Rabbits

Lethality was reported in rabbits exposed to cyanogen at 300 ppm for 3.5 h or 400 ppm for 1.8 h. However, lethality data were not provided and no additional details were available (Flury and Zernik 1931, as cited in Kopras 2012).

3.1.5. Summary of Animal Lethality Data

Well-described animal lethality data are restricted to studies in rats. On the basis of signs of toxicity, cyanogen is similar to other cyanides. Signs of irritation are followed by central nervous system effects and eventually death.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of 30 male Charles River albino rats were exposed to cyanogen at 0, 11, or 25 ppm for 6 h/day, 5 days/week for up to 6 months, in 4.8-m^3 stainless steel and glass chambers (Lewis et al. 1984). Chambers had pyramidal top and

bottom sections to obtain uniform dispersion of the test atmosphere. Cyanogen (99% pure) was introduced into the chamber from a compressed gas cylinder through a pressure regulator, metering valve, and flow meter. Breathing zone samples were taken two to six times per exposure period and analyzed by gas chromatography. Six rats per exposure group were killed after 2 days, 5 days, 1 month, 3 months, or 6 months of exposure. Serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were measured. Gross necropsies were performed, and lung tissue samples were collected for analysis of moisture content. Mean exposure concentrations of cyanogen over the 6-month period were 11.2 ppm (± 1.5 ppm) and 25.3 ppm (± 3.3 ppm). At the end of the 6-month exposure period, the mean body weights of rats in the control, 11 ppm, and 25 ppm groups were 543 g, 589 g, and 470 g, respectively. The decrease in the 25-ppm group compared with controls was statistically significant ($p < 0.05$). Mean values for serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were unaffected by treatment. There were no treatment-related effects noted at necropsy.

3.2.2. Mice

It was reported that mice exposed to cyanogen at 235 ppm for 15 min "recovered". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.3. Rabbits

It was reported that rabbits exposed to cyanogen at 100 ppm for 4 h had "practically no effect" and rabbits exposed at 200 ppm for 4 h had "slight symptoms". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.4. Cats

It was reported that cats exposed to cyanogen at 50 ppm for 4 h had "severe symptoms but recovered". No additional details were available (Flury and Zernik, 1931, as cited in Kopras 2012).

3.2.5. Monkeys

Groups of five male rhesus monkeys were exposed to cyanogen at 0, 11, or 25 ppm for 6 h/day, 5 days/week for up to 6 months in 4.8-m^3 stainless steel and glass chambers (Lewis et al. 1984). Chambers had pyramidal top and bottom sections to help attain uniform dispersion of the test atmosphere. Cyanogen (99% pure) was introduced into the chamber from a compressed gas cylinder through a pressure regulator, metering valve, and flow meter. Breathing zone samples were

taken two to six times per exposure period and analyzed by gas chromatography. Behavioral tests involving lever pressing activity on a variable interval schedule of reinforcement were conducted daily after exposure and for 4 weeks following the end of the exposure period. Electrocardiograms were performed prior to exposure and immediately following the last exposure. Serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were measured throughout the course of exposure. Gross necropsies were performed, and lung tissue samples were collected for analysis of moisture content. Mean exposure concentrations over the 6-month period were 11.2 ppm (± 1.5 ppm) and 25.3 ppm (± 3.3 ppm).

Behavioral testing suggested an increase in response rate in all three groups during the exposure period compared with the baseline measurements. Mean increases were 20%, 14%, and 145% ($p = 0.06$) for the control, 11 ppm, and 25 ppm groups, respectively. The increase in the 25-ppm group was considered "marginal" and transitory, as the response rate returned to normal before the end of the study (Data were presented in averaged intervals such that no assessment of behavioral effects after a day of exposure was possible.) There were no treatment-related effects on electrocardiograms. Mean values for serum T_3 and T_4, hematocrit values, and hemoglobin concentrations were unaffected by treatment. Total lung moisture content was lower in both the 11-ppm and 25ppm groups compared with controls; however, because the effect was not significant ($p > 0.3$) and was not noted in the rats (see Section 3.2.1), the investigators found the effect to be of questionable toxicologic significance. There were no other treatment-related effects noted at necropsy.

3.2.6. Summary of Nonlethal Toxicity in Animals

Nonlethal acute inhalation toxicity data are sparse. Repeated-exposure experiments in both rats and monkeys suggest that exposure to cyanogen at 11 ppm for up to 6 months yielded no adverse treatment-related effects. Decreased body weight was noted in rats and marginal-transitory behavioral effects were noted in monkeys exposed to cyanogen at 25 ppm for up to 6 months.

3.3. Developmental and Reproductive Effects

No developmental or reproductive toxicity data in animals were found.

3.4. Genotoxicity

No genotoxicity data on cyanogen were found.

3.5. Carcinogenicity

No carcinogenicity data on cyanogen were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Definitive metabolism and disposition data for cyanogen in humans or animals were not available. Cyanogen is reportedly converted in the body partly to hydrogen cyanide and partly to cyanic acid (Flury and Zernik, 1931, as cited in Kopras 2012). It reportedly hydrolyzes to yield one mole of hydrogen cyanide and one mole of cyanate (McNerney and Schrenk 1960). Clinical signs noted in cyanogen-exposed animals are similar to those noted in hydrogen cyanideexposed animals.

4.2. Mechanism of Toxicity

The mechanism of toxicity of cyanogen is reportedly similar to that of hydrogen cyanide (Kopras 2012). Hydrogen cyanide is a systemic poison that acts on the central nervous system. It interrupts cellular respiration by inhibiting cytochrome oxidase, thus blocking electron transfer to oxygen (Rieders 1971). Tissue oxygen concentrations rise, resulting in increased tissue oxygen tension and a decreased unloading for oxyhemoglobin. As a consequence, oxidative metabolism may slow to a point where it cannot meet metabolic demands. That is particularly critical in the brainstem nuclei where lack of an energy source results in central respiratory arrest and death. Cyanide can inhibit many other enzymes, particularly those that contain iron or copper, but cytochrome oxidase appears to be the most sensitive enzyme (Rieders 1971). Cyanide also stimulates the chemoreceptors of the carotid and aortic bodies to produce a brief period of hyperpnea. Cardiac irregularities may occur, but death is due to respiratory arrest. Brain lesions have been associated with exposure of animals to hydrogen cyanide at high concentrations (NRC 2002).

4.3. Structure-Activity Relationships

Cyanogen is structurally similar to cyanide and other nitriles. At relatively low concentrations, cyanogen appears to be much more irritating than hydrogen cyanide. In human subjects exposed to cyanogen at 16 ppm for 6 or 8 min, ocular irritation was noted immediately. The ocular irritation was perceived simultaneously with or slightly before the occurrence of nasal irritation (McNerney and Schrenk 1960). In contrast, although signs of systemic cyanide poisoning (headache, vertigo, weakness, and numbness) were noted in humans occupationally exposed to hydrogen cyanide at concentrations of 5-75 ppm, no irritation was reported (NRC 2002).

Qualitatively, clinical signs in animals exposed to cyanogen are consistent with clinical signs associated with cyanide exposure. However, rat data suggest

that cyanogen is less acutely toxic than hydrogen cyanide by a factor of 10 (McNerney and Schrenk 1960; ACGIH 2001). Analysis of available rat data suggests that this assumption may be true for very short exposure durations (up to approximately 15 min), but not for longer durations (30 min to 1 h). The 5min rat LC_{50} values for hydrogen cyanide range from approximately 400-500 ppm (NRC 2002), and three of six rats died when exposed to cyanogen at 4,000 ppm for 7.5 min (McNerney and Schrenk 1960). A 15-min rat LC_{50} value for hydrogen cyanide of 196 ppm was reported (NRC 2002), and no deaths occurred in six rats exposed to cyanogen at 1,000 ppm and six of six rats died when exposed to cyanogen at 2,000 ppm for 15 min (McNerney and Schrenk 1960). For 30-min exposures, rat LC_{50} values for hydrogen cyanide were 150-200 ppm (NRC 2002), and none of six rats exposed to cyanogen died when exposed at 500 ppm and six of six rats died when exposed at 1,000 ppm (McNerney and Schrenk, 1960). Finally, for 60-min exposures, rat LC_{50} values for hydrogen cyanide were 120-140 ppm (NRC 2002), and none of six rats died when exposed to cyanogen at 250 ppm and six of six died when exposed at 400 ppm (McNerney and Schrenk 1960) (see Table 3-5).

4.4. Species Variability

Data are insufficient to determine species variability for cyanogen.

4.5. Temporal Extrapolation

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). Because the data on cyanogen were insufficient for deriving an empirical value for n, temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

TABLE 3-5 Comparison of Toxicity Data on Hydrogen Cyanide and Cyanogen in Rats

Concentration (ppm)	Duration (min)	Hydrogen Cyanide End Point	Cyanogen End Point
400-500	5	LC_{50}	–
4,000	7.5	LC_{50}	Mortality: 3/6
196	15	LC_{50}	–
1,000	15	LC_{50}	Mortality: 0/6
2,000	15	LC_{50}	Mortality: 6/6

150-200	30	LC_{50}	–
500	30	LC_{50}	Mortality: 0/6
1,000	30	LC_{50}	Mortality: 6/6
120-140	60	LC_{50}	–
250	60	LC_{50}	Mortality: 0/6
400	60	LC_{50}	Mortality: 6/6

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Immediate ocular and nasal irritation was found in humans exposed to cyanogen at 16 ppm for 6 or 8 min. Irritation persisted for several minutes following cessation of exposure. No irritation was noted in humans exposed at 8 ppm for 6 min (McNerney and Schrenk 1960).

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to derivation of AEGL-1 values for cyanogen were available.

5.3. Derivation of AEGL-1 Values

The hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If that study were used to derive AEGL-1 values, the no-observed-effect level for irritation in humans would be 8 ppm for 6 min. Ocular and nasal irritation was reported at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. This would yield a threshold for irritation of 2.7 ppm. An intraspecies factor would not be applied because the critical study was performed on humans. Time scaling would not be appropriate, because the critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because of the lack of human data on exposures to cyanogen for durations longer than 8 min and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values were adopted as the AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective of both irritation and potential systemic cyanide effects. The AEGL-1 values for cyanogen are presented in Table

3-6. Appendix D includes a summary of how the AEGL values for hydrogen cyanide were determined, provides a comparison of the AEGL values for hydrogen cyanide and cyanogen.

TABLE 3-6 AEGL-1 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values for cyanogen were found.

6.2. Animal Data Relevant to AEGL-2

No animal data relevant to derivation of AEGL-2 values for cyanogen were found.

6.3. Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data, the AEGL-2 values were derived by dividing the AEGL-3 values for cyanogen by 3. That approach is justified by the steep concentration-response curve for cyanogen (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960). The AEGL-2 values for cyanogen are presented in Table 3-7.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values for cyanogen were found.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats exposed to a total of six concentrations of cyanogen for six exposure durations (McNerney and Schrenk 1960). Durations were 7.5-120 min and concentrations of cyanogen were 2504,000 ppm. Mortality incidences ranged from 0 to 100%, depending on concentration-duration pairings. The experimental parameters are summarized in Table 3-4. No death occurred in rats exposed to cyanogen at 2,000 ppm for 7.5 min, 1,000 ppm for 15 min, 500 ppm for 30 min, or 250 ppm for 60 min.

TABLE 3-7 AEGL-2 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm 9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)

7.3. Derivation of AEGL-3 Values

The experimental concentrations causing no deaths in rats (McNerney and Schrenk 1960) were used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. Specifically, the concentration associated with 0% mortality after 10 min of exposure was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper. That approach estimated that no deaths would occur following a 10-min exposure at 1,530 ppm. A point-of-departure of 1,530 ppm is supported by time scaling the empirical data for the 7.5-min exposure (no deaths at 2,000 ppm) to 10 min using the equation $C^n \times t = k$, with n = 1 (default value when extrapolating to longer durations), which results in a point-of-departure of 1,500 ppm. The 30-min exposure at 500 ppm was the point-of-departure for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was the point-ofdeparture for the 1-h AEGL-3 value. An intraspecies uncertainty factor of 3 was applied and was considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min) (McNerney and Schrenk 1960), which implies limited intraindividual variability. An interspecies uncertainty factor of 3 was also be applied. Although a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, and 4.3 ppm for 4 and 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced

transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984].) Therefore, a total uncertainty factor of 10 was used.

The 4- and 8-h AEGL-3 values were determined by applying a modifying factor of 2 to the 1-h AEGL-3 value. That approach was used instead because time scaling using the equation $C^n \times t = k$, with a default value of n = 1, yielded possible 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm. The AEGL-3 values for cyanogen are presented in Table 3-8, and their derivation is presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for cyanogen are presented in Table 3-9. AEGL-1 values for cyanogen were set equal to those established for hydrogen cyanide. AEGL-2 values were derived by dividing the AEGL-3 values by 3, and the AEGL-3 values are based on experimental concentrations of cyanogen causing no mortality in rats.

8.2. Other Standards and Guidelines

Other standards and guidelines for cyanogen are presented in Table 3-10.

TABLE 3-8 AEGL-3 Values for Cyanogen

10 min	30 min	1 h	4 h	8 h
150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

TABLE 3-9 AEGL Values for Cyanogen

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)

AEGL-2 (disabling)	50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)
AEGL-3 (lethal)	150 ppm (320 mg/m^3)	50 ppm (100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

TABLE 3-10 Standards and Guidelines for Cyanogen

	Exposure Duration				
Guideline	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	50 ppm	17 ppm	8.3 ppm	4.3 ppm	4.3 ppm
AEGL-3	150 ppm	50 ppm	25 ppm	13 ppm	13 ppm
TLV-TWA (ACGIH)[a]	–	–	–	–	10 ppm
REL-TWA (NIOSH)[b]	–	–	–	–	10 ppm
MAK (Germany)[c]	–	–	–	–	5 ppm

[a] TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The value was determined by analogy to cyanide, to prevent irritation and systemic effects. [b] REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health (NIOSH 2011) is defined as the time-weighted average concentration for up to a 10-h workday during a 40-h workweek.

[c] MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (DFG 2007) is defined analogous to the ACGIH TLV-TWA. Skin notation.

8.3. Data Adequacy and Research Needs

Human and animal data on cyanogen are sparse. Acute exposure studies in animals other than rats would be helpful.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CYANOGEN

Derivation of AEGL-1 Values

The AEGL-1 values for hydrogen cyanide were adopted as AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). The no-observed effect level for irritation in humans was 8 ppm for 6 min. Ocular and nasal irritation was noted at the next highest concentration tested (16 ppm). If that study were used as the basis for deriving AEGL-1 values for cyanogen, the point-of-departure would be 8 ppm. An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be applied because the study was conducted in humans. Thus, the threshold for irritation would be 2.7 ppm. Time scaling of that concentration would not be appropriate, because the critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because human data on exposures to cyanogen for durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective for both irritation and potential systemic cyanide effects.

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

Derivation of AEGL-2 Values

AEGL-2 values for cyanogen were derived by taking one-third of the respective AEGL-3 values (see below), because there were no data on cyanogen consistent with an AEGL-2 end point. That approach is justified by the steep concentrationresponse relationship (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]).

10-min AEGL-2:	150 ppm ÷ 3 = 50 ppm
30-min AEGL-2:	50 ppm ÷ 3 = 17 ppm
1-h AEGL-2:	25 ppm ÷ 3 = 8.3 ppm
4-h AEGL-2:	13 ppm ÷ 3 = 4.3 ppm
8-h AEGL-2:	13 ppm ÷ 3 = 4.3 ppm

Derivation of AEGL-3 Values

Key study:	McNerney, J.M., and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 2(21):121-124.
Toxicity end point:	Concentrations of cyanogen causing no deaths in rats is 1,530 ppm for 10 min (extrapolated from Figure 1 of paper by McNerney and Schrenk [1960]); 500 ppm for 30 min; and 250 ppm for 1 h.
Time scaling:	None
Uncertainty factors:	3 for interspecies differences; a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen. However, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL-3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, 4.3 ppm for 4 h, and 4.3 ppm for 8 h. Humans exposed at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed to cyanogen at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984].)
	3 for intraspecies variability; considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats

exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]), which implies limited intraindividual variability.

Modifying factor: 2; applied to the 1-h AEGL-3 value to derive the 4- and 8-h AEGL-3 values. That approach was used because time scaling using the equation $C^n \times t = k$, with n = 1, would yield 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.

Calculations:

10-min AEGL-3: 1,530 ppm ÷ 10 = 150 ppm

30-min AEGL-3: 500 ppm ÷ 10 = 50 ppm

1-h AEGL-3: 250 ppm ÷ 10 = 25 ppm

4-h AEGL-3: 25 ppm ÷ 2 = 13 ppm

8-h AEGL-3: 25 ppm ÷ 2 = 13 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CYANOGEN

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
2.5 ppm (5.2 mg/m^3)	2.5 ppm (5.2 mg/m^3)	2.0 ppm (4.2 mg/m^3)	1.3 ppm (2.7 mg/m^3)	1.0 ppm (2.1 mg/m^3)

Data adequacy: The AEGL-1 values for hydrogen cyanide (NRC 2002) were adopted as the AEGL-1 values for cyanogen. That approach is supported by cyanogen irritation in humans (McNerney and Schrenk 1960). If AEGL-1 values were derived from the cyanogen data, the no-observed effect level for irritation in humans would be 8 ppm for 6 min. Ocular and nasal irritation was noted at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 would be applied because contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 would be applied because the study was conducted in humans. Thus, the threshold for irritation would have been 2.7 ppm. Time scaling of that concentration would not be appropriate, because the critical effects (ocular and nasal irritation) are a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC 2001). However, because human data on exposures to cyanogen for durations longer than 8 min are lacking and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values (NRC 2002) were adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are, thus, protective for both irritation and potential systemic cyanide effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
50 ppm (100 mg/m^3)	17 ppm (36 mg/m^3)	8.3 ppm (17 mg/m^3)	4.3 ppm (9.0 mg/m^3)	4.3 ppm (9.0 mg/m^3)

Data adequacy: The data on cyanogen were inadequate for deriving AEGL-2 values, so the values were estimated by taking one-third of the AEGL-3 values. That approach is supported by steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min (McNerney and Schrenk1960).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
150 ppm (320 mg/m^3)	50 ppm 100 mg/m^3)	25 ppm (53 mg/m^3)	13 ppm (27 mg/m^3)	13 ppm (27 mg/m^3)

Reference: McNerney, J.M. and H.H. Schrenk. 1960. The acute toxicity of cyanogen. Am. Ind. Hyg. Assoc. J. 2(21):121-124.

Test species/Strain/Sex/Number: Rat; albino; male; 6/group

Exposure route/Concentrations/Durations: Inhalation, 250-4,000 ppm for 7.5-120 min.

Effects: Lethality

Concentration (ppm)	Duration (min)	Mortality

4,000	7.5	3/6
4,000	15	6/6
2,000	7.5	0/6
2,000	15	6/6
1,000	15	0/6
1,000	30	6/6
500	30	0/6
500	45	6/6
400	45	0/6
400	60	6/6
250	60	0/6
250	120	4/6

End point/Concentration/Rationale: Experimental concentrations causing no deaths in rats used as points-of-departure for the 10-min, 30-min, and 1-h AEGL-3 values. The 10-min point-of-departure of 1,530 ppm was extrapolated from Figure 1 in the McNerney and Schrenk (1960) paper, the 30-min exposure at 500 ppm was the point-ofdeparture for the 30-min AEGL-3 value, and the 1-h exposure at 250 ppm was the pointof-departure for the 1-h AEGL-3 value.

Uncertainty factors/Rationale: Total uncertainty factor was 10.
Interspecies: 3, a factor of 10 might normally be applied because there are insufficient data to define species sensitivity to cyanogen. However, application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base. (AEGL3 values derived with a total uncertainty factor of 30 would be 50 ppm for 10 min, 17 ppm for 30 min, 8.3 ppm for 1 h, 4.3 ppm for 4 h, and 4.3 ppm for 8 h. Humans exposed to cyanogen at 8 ppm for 6 min experienced no irritation; those exposed at 16 ppm for 6 min experienced transient ocular and nasal irritation [McNerney and Schrenk 1960]. Rats and monkeys repeatedly exposed at 11 ppm for 6 h/day, 5 days/week for up to 6 months, experienced no treatment-related adverse effects. Rats repeatedly exposed at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed showed only marginal behavioral effects [Lewis et al. 1984]).
Intraspecies: 3, considered sufficient due to the steep concentration-response curve (0% mortality in rats exposed at 1,000 ppm for 15 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 500 ppm for 30 min and 100% mortality at 1,000 ppm for 30 min; 0% mortality in rats exposed at 400 ppm for 45 min and 100% mortality at 500 ppm for 45 min; 0% mortality in rats exposed at 250 ppm for 60 min and 100% mortality at 400 ppm for 60 min [McNerney and Schrenk 1960]), which implies limited intraindividual variability.

Modifying factor: 2, applied to the 1-h AEGL-3 value to derive the 4- and 8-h AEGL-3 values. That approach was used because time scaling using the equation $C^n \times t = k$, with n = 1, would yield 4- and 8-h AEGL-3 values of 6.3 and 3.2 ppm, respectively. Those values are inconsistent with the repeated-exposure data in both monkeys and rats (Lewis et al. 1984). Rats repeatedly exposed to cyanogen at 25 ppm for 6 h/day, 5 days/week for up to 6 months, experienced only decreased body weight, and monkeys similarly exposed

showed only marginal behavioral effects. No effects were noted in either species similarly exposed at 11 ppm.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Performed to determine the 10-min point-of-departure from a 7.5-min exposure at 2,000 ppm. Time scaling was performed using the equation $C^n \times t = k$ equation, with n = 1 (default value when extrapolating to longer durations) to derive a value protective of human health (NRC 2001).

Data adequacy: Sparse data set. Support from repeated-exposure studies.

APPENDIX C

CATEGORY PLOT FOR CYANOGEN

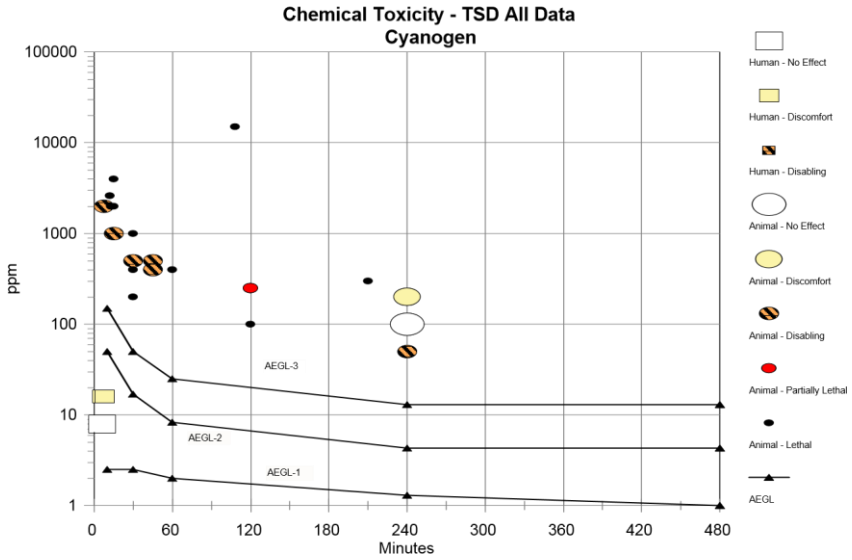

FIGURE C-1 Category plot of toxicity data and AEGL values for cyanogen.

TABLE C-1 Data Used in the Category Plot for Cyanogen

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				2.5	10	AEGL	
AEGL-1				2.5	30	AEGL	
AEGL-1				2.0	60	AEGL	
AEGL-1				1.3	240	AEGL	
AEGL-1				1.0	480	AEGL	
AEGL-2				50	10	AEGL	
AEGL-2				17	30	AEGL	
AEGL-2				8.3	60	AEGL	
AEGL-2				4.3	240	AEGL	
AEGL-2				4.3	480	AEGL	
AEGL-3				150	10	AEGL	
AEGL-3				50	30	AEGL	
AEGL-3				25	60	AEGL	
AEGL-3				13	240	AEGL	
AEGL-3				13	480	AEGL	
	Rat		1	4,000	7.5	PL	
	Rat		1	4,000	15	3	
	Rat		1	2,000	7.5	2	
	Rat		1	2,000	15	3	
	Rat		1	1,000	15	2	

	Rat		1	1,000	30	3	
	Rat		1	500	30	2	
	Rat		1	500	45	2	

Rat	1	400	45	2	
Rat	1	400	60	3	
Rat	1	250	120	PL	
Mouse	1	2,600	12	3	Assumes all dead/worst case scenario.
Mouse	1	15,000	108	3	Assumes all dead/worst case scenario.
Cat	1	300	210	3	Assumes all dead/worst case scenario.
Cat	1	400	30	3	Assumes all dead/worst case scenario.
Rabbit	1	100	120	3	Assumes all dead/worst case scenario.
Rabbit	1	200	30	3	Assumes all dead/worst case scenario.
Rabbit	1	2,000	13	3	Assumes all dead/worst case scenario.
Rabbit	1	100	240	0	Questionable data point.
Rabbit	1	200	240	1	Questionable data point.
Cat	1	50	240	2	Questionable data point.
Human	1	8	6	0	
Human	1	16	6	1	
Human	1	16	8	1	

Categories: 0 = no effect, 1 = discomfort, 2 = disabling, PL = partial lethality, 3 = lethal.

APPENDIX D

DERIVATION OF HYDROGEN CYANIDE AEGL-1 VALUES AND COMPARISON OF HYDROGEN CYANIDE AND CYANOGEN AEGL VALUES

HYDROGEN CYANIDE AEGL-1 VALUES (NRC 2002)

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

Key reference: Leeser, J.E., J.A. Tomenson, and D.D. Bryson. 1990. A cross-sectional study of the health of cyanide salt production workers. Report No. OHS/R/2, ICI Central Toxicology Laboratory, Alderley Park, Cheshire, U.K.

Supporting references:

(1) El Ghawabi, S.H., M.A. Gaafar, A.A. El-Saharti, S.H. Ahmed, K.K. Malash, and R. Fares. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br. J. Ind. Med. 32(3):215-219.

(2) Grabois, B. 1954. Exposure to hydrogen cyanide in processing of apricot kernels. Monthly Review NY Department of Labor 33:33-36.

(3) Maehly, A.C., and A. Swensson. 1970. Cyanide and thiocyanate levels in blood and urine of workers with low-grade exposure to cyanide. Int. Arch. Arbeitsmed. 27(3):195–209.

(4) Hardy, H.L., W.M. Jeffries, M.M. Wasserman, and W.R. Waddell. 1950. Thiocyanate effect following industrial cyanide exposure - report of two cases. New Engl. J. Med. 242: 968-972.

Test species/Strain/Number:
Occupational exposures/63 employees, mean age 44.7 (Leeser et al. 1990)
Occupational exposures/36 workers (El Ghawabi et al. 1975)
Occupational exposures/five factories (Grabois, 1954)
Occupational exposures/94 workers (Maehly and Swensson, 1970) Occupational exposures/factories (Hardy et al. 1950)

Exposure route/Concentrations/Durations: Inhalation/geometric mean exposure of $\leq$1 ppm (range, 0.01-3.3 ppm; personal samplers), up to 6 ppm (area samples)/mean service years, 16.5 (Leeser et al. 1990); Inhalation/average exposure 8 ppm/5-15 years (El Ghawabi et al. 1975); Inhalation/5 ppm/unknown (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970).

Effects: No exposure related adverse symptoms or health effects (surveys and medical examinations taken in spring and fall of year) (Leeser et al. 1990); mild headache, other symptoms (El Ghawabi et al. 1975); no effects reported (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970).

End point/Concentration/Rationale: 8 ppm from the El Ghawabi et al. (1975) study; 5 ppm from the Hardy et al. (1950), Grabois (1954), and Maehly and Swensson (1970)

studies; or 1 ppm from the Leeser (1990) study, were considered no-adverse-effect to mild effect concentrations for an 8-h work day. The NRC adjusted the chronic 8 ppm value of El Ghawabi et al. (1975) to a 1-h exposure for healthy adults.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable
Intraspecies: 3, no specific susceptible populations were identified in monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals including newborns. Application of the uncertainty factor to the El Ghawabi et al. (1975; as adjusted by the NRC) and Grabois (1954) data results in a value close to the 8-h 1 ppm concentration in the Leeser et al. (1990) study. The uncertainty factor was not applied to the Leeser et al. (1990) 1 ppm concentration as it is the lowest no-observed-adverse-effect level.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Because of the long-term exposure duration of the key studies, the conservative time-scaling value of n = 3 (k = 480 ppm^3-min) was applied when scaling to shorter exposure durations. The starting point for time scaling was an 8-h concentration of 1 ppm.

Data adequacy: The preponderance of data from the key studies support an 8-h no effect concentration of 1 ppm. The Leeser et al. (1990) study encompassed subjective symptoms as well as extensive medical examinations. The occupational monitoring study of El Ghawabi et al. (1975) in which it is believed that workers inhaling a mean concentration of 8 ppm may suffer mild headaches support the safety of the derived values. The values are also supported by a NIOSH (1976) report in which 5 ppm was identified as a no-effect concentration in the Grabois et al. (1954) occupational study. Additional monitoring studies support the values.

COMPARISON OF AEGL VALUES FOR CYANOGEN AND HYDROGEN CYANIDE

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1					
Cyanogen	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
Hydrogen cyanide	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

AEGL-2					
Cyanogen	50 ppm	17 ppm	8.3 ppm	4.3 ppm	4.3 ppm
Hydrogen cyanide	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3					
Cyanogen	150 ppm	50 ppm	25 ppm	13 ppm	13 ppm
Hydrogen cyanide	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm