Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 2

Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

ISBN: 0-309-56773-4, 292 pages, 6x9, (2002)

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VOLUME 2

Subcommittee on Acute Exposure Guideline Levels
Committee on Toxicology
Board on Environmental Studies and Toxicology
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

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This project was supported by Contract Nos. DAMD17-89-C-9086 and DAMD17-99-C-9049 between the National Academy of Sciences and the U.S. Army. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-08511-X

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. The people 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. 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, along with 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.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances —consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other

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

federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 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 the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the second volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals.* It reviews the appropriateness of the AEGLs for five chemicals for their scientific validity, completeness, and consistency with the NRC guideline reports.

This report has been reviewed in draft form by individuals chosen 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 this report: Leonard Chiazze, Jr., of Georgetown University; Sidney Green of Howard University; Sam Kacew of the University of Ottawa; and Ralph Kodell of the National Center for Toxicological Research.

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 the report before its release. The review of this report was overseen by Robert A.Goyer, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report 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 subcommittee gratefully acknowledges the valuable assistance provided by the following persons: Roger Garrett, Paul Tobin, Ernest Falke, and Letty Tahan (all from EPA); George Rusch (Honeywell, Inc.); William Bress (Vermont Department of Health); George Rogers (University of Louisville); Po Yung Lu, Cheryl Bast, and Sylvia Talmage (all from Oak Ridge National Laboratory). Aida Neel was the project assistant. Kelly Clark edited the report. We are grateful to James J.Reisa, director of the Board on Environ

mental Studies and Toxicology (BEST), for his helpful comments. The subcommittee particularly acknowledges Kulbir Bakshi, project director for the subcommittee, for bringing the report to completion. Finally, we would like to thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

Daniel Krewski, *Chair*
Subcommittee on Acute Exposure
Guideline Levels
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Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals Volume 2

Introduction

This report is the second 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, and what steps to take in case of 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 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" (IDLH) values developed by the National Institute for Occupational Safety

and Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), 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 h, and only once in a lifetime for the general population, which includes infants, children, the elderly, and persons with diseases, such as asthma, heart disease, or lung 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 Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). 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 l995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] 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,

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The roster of NAC is shown on page 8.

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 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 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 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NAC guidelines report *Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances* (NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on a chemical. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data from 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, the data from the most sensitive animal species are used to set AEGLs. Uncertainty factors are commonly used when animal data are used to estimate minimal risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverseeffect 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 sexes), developmental, neurotoxic, respiratory, and other organ-related effects—are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, theoretical 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; NRC in press). The NRC assigned this project to the COT Subcommittee on Acute Exposure Guideline Levels. The subcommittee has expertise in toxicology, epidemiology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

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 Subcommittee on Acute Exposure Guideline Levels for final evaluation.

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

Because of the enormous amount of data presented in the AEGL reports, the NRC subcommittee cannot verify all the data used by NAC. The NRC subcommittee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

This report is the second volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals.* AEGL reports for aniline, arsine, monomethylhydrazine, and dimethylhydrazine were reviewed in the first volume. AEGL documents for five chemicals—phosgene, propylene glycol dinitrate, 1,1,1,2-tetrafluoroethane, 1,1-dichloro-1-fluoroethane, and hydrogen cyanide—are published as an appendix to this report. The subcommittee

concludes that the AEGLs developed in those documents 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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Appendix

1

Phosgene[1]

Acute Exposure Guideline Levels

SUMMARY

Phosgene is a colorless gas at ambient temperature and pressure. Its odor has been described as similar to new-mown hay. Phosgene is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal. The production of dyestuffs, isocyanates, carbonic acid esters (polycarbonates), acid chlorides, insecticides, and pharmaceutical chemicals requires phosgene. Manufacture of phosgene is approximately 1 million tons per year (y) in the United States, and more than 10,000 workers are involved in its manufacture and use. Manufacture of phosgene in the United States is

[1]This document was prepared by AEGL Development Team member Cheryl Bast of Oak Ridge National Laboratory and Bill Bress (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

almost entirely captive—it is used in the manufacture of other chemicals within a plant boundary. Only one company sells phosgene on the U.S. merchant market.

Inhalation is the most important route of exposure for phosgene. Because of phosgene's mild upper respiratory, eye, and skin irritancy and mildly pleasant odor, an exposed victim may not actively seek an avenue of escape before lower respiratory damage has occurred (Currie et al. 1987a; Lipsett et al. 1994). Pulmonary edema is the cause of death after a clinical latency period of ≤24 hours (h) (Franch and Hatch 1986).

Appropriate data were not available for deriving AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 parts per million (ppm), a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤24 h.

AEGL-2 values were based on chemical pneumonia in rats (exposure at 2 ppm for 90 min) (Gross et al. 1965). An uncertainty factor (UF) of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly among individuals. Therefore, the total UF is 10. The 1.5-h value was then scaled to the 30-min and 1-, 4-, and 8-h AEGL exposure periods using $C^n \times t = k$, where n=1 (Haber's law), because Haber's law has been shown to be valid for phosgene within certain limits. Haber's law was originally derived from phosgene data (Haber 1924). The 30-min value is also adopted as the 10-min value, because extrapolation would yield a 10-min AEGL-2 value approaching concentrations that produce alveolar edema in rats; Diller et al. (1985) observed alveolar pulmonary edema in rats exposed to phosgene at 5 ppm for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min AEGL-2 value of 0.5 ppm.

The 30-min and 1-, 4-, and 8-h AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 30-min exposure (15 ppm) (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and

because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals. Therefore, the total UF is 10. The value was then scaled to the 1-, 4-, and 8-h AEGL periods using $C^n \times t = k$, where n=1 (Haber's Law), because Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber 1924). The 10-min AEGL-3 value was based on the highest concentration causing no mortality in the rat or mouse (36 ppm) after a 10-min exposure (Zwart et al. 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed for lethal and nonlethal end points after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and causing irritation) is not expected to vary greatly between individuals (total UF, 10).

The calculated values are listed in Table 1–1.

1. INTRODUCTION

Phosgene is a colorless gas at ambient temperature and pressure. Its odor has been described as similar to new-mown hay (Leonardos et al. 1968). This mild odor and the weak acute irritant properties, however, provide little warning of its presence (Lipsett et al. 1994). The odor threshold has been established between 0.5 and 1.5 ppm (2.06 and 6.18 mg/m^3) (Lipsett et al. 1994).

Phosgene is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal. Manufacture of phosgene is approximately 1 million tons per year (y) in the United States, and more than 10,000 workers are involved in its manufacture and use (Currie et al. 1987a). Manufacture of phosgene in the United States is almost entirely captive (more than 99% is used in the manufacture of other chemicals within a plant boundary). Only one company sells phosgene on the U.S. merchant market. Over 80% of the phosgene used in the United States is involved in the manufacture of polyisocyanates in the polyurethane industry. The polycarbonate industry accounts for approximately 10% of phosgene used, and the remaining 10% is used in the production of aliphatic diisocyanates, monoisocyanates, chloroformates, agrochemicals, and intermediates for dyestuffs and pharmaceuticals. Phosgene can also be used in metal recovery operations (platinum, uranium, plutonium, and niobium) and has been used for manufacturing aluminum chloride, beryllium chloride, and boron trichloride. It has been pat

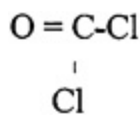
ented as a stabilizer for liquid SO_2. In addition, many pesticides have been produced by reaction of a thiol or dithiol with phosgene to produce thiol chloroformates (Kirk-Othmer 1991).

TABLE 1–1 Summary of Proposed AEGL Values for Phosgene (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)	Chemical pneumonia rats (Gross et al. 1965)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)	Highest concentration causing no mortality in the rat after a 30-min or 10-min exposure (Zwart et al. 1990)

Inhalation is the most important route of exposure for phosgene. Because of phosgene's mild upper respiratory, eye, and skin irritancy and mildly pleasant odor, an exposed victim may not actively seek an avenue of escape before lower respiratory damage has occurred (Currie et al. 1987a; Lipsett et al. 1994). Pulmonary edema is the cause of death after a clinical latency period of ≤24 h (Franch and Hatch 1986).

The chemical structure is depicted below, and the physicochemical properties of phosgene are presented in Table 1–2.



2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Diller and Zante (1982) performed an extensive literature review concerning human phosgene exposure, and found that a great majority of data were

anecdotal or rough estimates and, thus, did not contain reliable exposure concentrations and/or durations. Information synthesized from this review is presented in Table 1–3. Based on observations during World War I, the 2 min LC_{50} value for humans was estimated to be 790 ppm (Chasis 1944).

TABLE 1–2 Physical and Chemical Data

Parameter	Data	Reference
Synonyms	Carbonyl chloride, carbon oxychloride, carbonic dichloride, chloroformyl chloride	Lipsett et al. 1994; EPA 1986
Chemical formula	$COCL_2$	Lipsett et al. 1994
Molecular weight	98.92	Lipsett et al. 1994
CAS registry no.	75–44–5	Lipsett et al. 1994
Physical state	Gas	Lipsett et al. 1994
Vapor pressure	1215 mm Hg at 20°C	EPA 1986
Vapor density	3.4 (air=1)	Lipsett et al. 1994
Specific gravity	1.381 g/l at 20°C	ACGIH 2000
Melting/boiling/ flash point	−128°C/8.2°C/not applicable	Lipsett et al. 1994; NIOSH 1994
Solubility	Decomposes in water and alcohol; soluble in organic solvents	EPA 1986
Conversion factors in air	1 ppm=4.11 mg/m^3 1 mg/m^3=0.24 ppm	Lipsett et al. 1994
Incompatibility	Alkalis, ammonia, alcohols, copper	NIOSH 1997

Many case reports describe symptomology and postmortem results from human phosgene poisonings; however, exposure concentrations were not reported. Six men were occupationally exposed to phosgene when a pipe ruptured (Stavrakis 1971). A 24-y-old who had received the heaviest exposure arrived at the emergency room minutes after the accident. Upon admission, the patient was symptom-free; however, he was treated with methenamine intravenously and admitted for a 24-h observation. During this time, he remained symptom free and was discharged with no evidence of phosgene injury. The other five patients arrived at the emergency room between 6 and

12 h after the accident, presenting with various degrees of phosgene intoxication. One 31-y-old who had been exposed "in almost the same degree as the previous patient" rapidly developed pulmonary edema. He also exhibited extreme hemoconcentration and leukocytosis. He did not respond to methenamine treatment and died 3.5 h after admission. The other four exposed workers were hospitalized for various periods of time and recovered satisfactorily.

TABLE 1–3 Effect of Phosgene Exposure in Healthy Humans

Effect[a]	Cumulative Phosgene Exposure
LCT_1	~300 ppm·min
LCT_{50}	~500 ppm·min
LCT_{100}	~1,300 ppm·min

[a]Lethal concentration × time product.
Source: Diller and Zante 1982.

A 23-y-old man (healthy nonsmoker) was exposed to phosgene at an estimated concentration of at least 5–10 ppm for 5 to 10 seconds (s) (Bradley and Unger 1982). He began coughing upon exposure to phosgene and experienced dyspnea and chest tightness within 30 min. Four hours after exposure, he was hospitalized with hypotension, tachycardia, tachypnea, cyanosis, and pulmonary edema. The patient was intubated and administered dopamine and methylprednisolone. From the second to the sixth day of hospitalization, he developed mediastinal and subcutaneous emphysema, bilateral pneumohydrothoraces, elevated white blood cell counts, fever, and hemiparesis on the right side. Death occurred after the patient developed ventricular fibrillation.

Misra et al. (1985) described another accidental occupational phosgene poisoning case. A 30-y-old male was exposed to phosgene at an undetermined concentration and immediately began coughing and experienced a sense of suffocation and burning eyes. After removal to fresh air and administration of oxygen, he felt better. However, approximately 7.5 h after the exposure, he was rushed to the emergency room with difficulty breathing. Despite oxygen administration and antibiotic therapy, his condition deteriorated. He died approximately 18 h after exposure. An autopsy showed pulmonary edema and bronchiolar necrosis, both of which were more severe in the lower lobes of the lungs than in the upper lobes.

Hegler (1928) reported the effects of a phosgene accident that occurred in Hamburg, Germany, on May 20,1928. Eleven metric tons of "pure phosgene"

were released from a storage tank on a warm, dry, slightly windy day. Within a few hours, people as far as six miles from the release site began reporting to hospitals. Three hundred people reported to hospitals within a few days of the accident. Effects ranged from mild or moderate illness to death; ten people were reported to have died. In general, exposed persons exhibited symptoms consistent with other reported phosgene poisonings (headache, dizziness, nausea and vomiting, irritant cough, and sickening-sweet taste, followed by a latency period and then pulmonary symptoms). Autopsies on six of the fatalities showed pulmonary effects in all cases. Fatty degeneration of the kidneys, liver, and heart were observed in a few cases and were thought to be secondary to the pulmonary damage. In an atypical case, damage in the gray matter of the brain and spinal cord, hyperemia, and signs of bleeding in the white matter were observed at autopsy. That patient died 11.5 days (d) postexposure from a blood clot lodged in the lung. It was uncertain if the extrapulmonary effects were due to phosgene exposure.

2.2. Nonlethal Toxicity

NIOSH (1976) performed two studies to determine the odor threshold of phosgene. In the first, 56 military personnel were exposed to phosgene at increasing concentrations until all subjects could detect odor. The lowest detectable concentration was 0.4 ppm. Thirty-nine percent of subjects could detect odor at 1.2 ppm, and 50% of subjects detected odor at 1.5 ppm. In the other study, four subjects identified 1.0 ppm as the lowest concentration at which the distinctive “new-mown hay” odor of phosgene could be detected.

In their literature review, Diller and Zante (1982) also identified nonlethal effects from phosgene exposure (lethal effects are described in Section 2.1). Nonlethal information synthesized from this review is presented in Table 1–4. From the above data and from animal data for “initial lung damage,” Diller and Zante (1982) synthesized information for nonlethal effects of phosgene in humans (Table 1–5).

2.2.1. Case Reports

A 30-y-old male was occupationally exposed to phosgene at an unknown concentration (Stavrakis 1971). After a short episode of coughing, he returned to work and completed the final 3 h of his shift. Approximately 4 h post-

exposure, he presented at the emergency room with severe dyspnea, restlessness, chest pain, and persistent, productive cough. Chest x-rays confirmed acute pulmonary edema. He was treated and discharged free of symptoms 5 d after the phosgene exposure.

TABLE 1–4 Acute Irritative Effects of Phosgene Exposure in Humans

Effect	Phosgene Concentration
Throat irritation	3.1 ppm
Ocular irritation	4.0 ppm
Cough	4.8 ppm
Severe eye and airway irritation	10 ppm

Source: Diller and Zante 1982

An investigator was exposed to phosgene at an undetermined concentration during an experiment (Delephine 1922). He entered the phosgene chamber "at frequent intervals" over a period of 45 min to take instrument readings. At first, he experienced only laryngeal and conjunctival irritation, but as the phosgene concentration increased, he was forced to hold his breath and not stay in the room for more than 1 min. Toward the end of the experiment, some phosgene escaped from the chamber. At this time, the investigator and a colleague experienced a violent cough and began to run away. During their escape, both men had to stop frequently due to the violent nature of their coughs. After exiting the contaminated area, both individuals continued to cough for approximately 20 min. They then improved for 3 or 4 h, after which they experienced a choking sensation that lasted approximately 24 h. Marked lassitude lasted for an additional few days, after which recovery appeared to be complete.

Everett and Overholt (1968) discussed a 40-y-old male who received a "massive" phosgene exposure. His initial symptoms included coughing and burning of the eyes, which subsided within 5 min. He was asymptomatic for the next 2 h, after which a hacking cough began. Three hours after exposure, mild dyspnea was present, and 6 h postexposure, severe dyspnea and moist rales were observed. He was admitted to an intensive care unit 8 h postexposure and presented with anxiety, agitation, cyanosis, thirst, constant cough, and severe pulmonary edema. By the fifth day in the hospital, he was asymptomatic, and by the seventh day, pulmonary function and chest x-ray were normal. A 2-y follow-up was unremarkable.

TABLE 1–5 Effect of Phosgene Exposure in Humans

Effect	Phosgene Exposure
Odor perception	>0.4 ppm
Odor recognition	>1.5 ppm
Ocular, nasal, throat, and bronchiolar irritation	>3 ppm
Initial lung damage	>30 ppm·min
Clinical pulmonary edema	>150 ppm·min

Source: Diller and Zante 1982.

Regan (1985) described a phosgene release from a toluene diisocyanate plant. Fifteen employees were exposed to phosgene at an undetermined concentration, resulting in the hospitalization of four workers. Two of the four were released after an overnight observation. The other two were in more serious condition. One of them, a 31-y-old male, had pulmonary edema, rales in both lungs, and left chest pain 8 h postexposure. He was treated with oxygen, bronchodilators, steroids, and antibiotics and returned to work 6 d after the accident. His follow-up was unremarkable. The second man, a 47-y-old smoker, presented with dyspnea, bilateral rales, and pulmonary edema 11 h postexposure. He was also treated with oxygen, bronchodialators, steroids, and antibiotics but continued to deteriorate. He remained critical for 3 d with low right-side heart pressure, low arterial pressure, hemoconcentration, and leukocytosis. He was asymptomatic by 12 d postexposure. He had mild pulmonary obstruction four weeks after the accident; however, it is unclear if that was a result of phosgene exposure or of his smoking.

Longer-term effects from acute phosgene exposure have also been described. Galdston et al. (1947a) described the late effects of phosgene poisoning in six workers (two male, four female; ages 31–50). After an acute, accidental, occupational exposure to phosgene all of these workers experienced the typical effects of acute phosgene exposure. Chronic clinical findings present from 1 to 24 months (mo) postexposure included rapid, shallow breathing and changes in pulmonary function. However, no correlation was observed between the magnitude of phosgene exposure or the severity of acute effects and the severity of chronic symptoms. Galdston et al. (1947a) attributed the severity of chronic symptoms to the subjects' psychological state. Smoking habits were not reported, and long-term follow-up was not performed.

Galdston et al. (1947b) also examined five males (ages 24–50) who had repeated occupational exposure to phosgene in "small amounts" during the course of 1.5 to 3.5 y. The subjects were examined with regard to pulmonary function and cardiac status. The subjects exhibited transitory effects such as cough, shortness of breath on exertion, and pain or tightness of the chest. These symptoms abated upon removal from phosgene exposure for several weeks. Results suggested that although symptoms of chronic exposure to low concentrations of phosgene are generally not as disabling as those from acute exposure, emphysema may develop after chronic exposure. Also, pulmonary function effects are more severe after chronic low-level exposure than after recovery from a serious acute exposure.

Diller et al. (1979) examined 12 originally healthy workers 3 to 9 y after intoxication with phosgene (ten workers), nitric oxide (one worker), or treflon smoke (one worker). Six of the 12 individuals complained of pulmonary symptoms for 3 y postexposure, and three of the 12 showed slight to severe lung function effects. The severity of lung function decrement correlated more closely with smoking habits than with the severity of chemical intoxication. Diller et al. (1979) concluded that originally healthy survivors of phosgene intoxication recover fairly well over a period of years. However, individuals with preexisting chronic bronchitis may suffer significant chronic deterioration of lung function after acute phosgene intoxication, as an additional observation over 25 y showed. The individual, a light smoker who had mild chronic bronchitis since childhood, was exposed to phosgene and smoke at age 35. He developed severe pulmonary edema and was hospitalized for 7 weeks (wk) following the exposure. During the months following the exposure, his general condition worsened and the bronchitis became more severe. After 2 y, pulmonary function (forced expiratory volume [FEV] and vital capacity [VC]) was decreased to 70% of normal. Ten years postexposure, he developed pulmonary emphysema, and VC and FEV were decreased to 50% of normal.

Herzog and Pletscher (1955) observed squamous metaplasia of the ciliated bronchial epithelium in two patients exposed to undetermined concentrations of phosgene. The metaplasia was observed 3 mo or 3 y postexposure, respectively.

In a phosgene processing factory, phosgene concentrations were measured over an 8-mo period with a device capable of detecting phosgene at 0–0.5 ppm (Henschler 1971). Positive values, of relatively short duration, were recorded on only 32 of 240 d:22 d, 0.05 ppm; 6 d, between 0.06 and 0.1 ppm; 3 d, between 0.1 and 0.5 ppm; 1 d, 0.5 ppm (of short duration). For longer time

periods, elevated concentrations were measured on three occasions: twice for 3 h, between 0.015 and 0.035 ppm, and once for 1.5 h, 0.35 ppm. The above described conditions produced no intoxication or adverse effects on lung function.

In another factory, use of a phosgene indicator badge revealed an average of 34 phosgene exposures per year during the period from 1978 to 1988 (Kaerkes 1992). The workforce contained approximately 200 individuals ranging in age from <20 to 60 y. Exposure concentrations ranged from <50 to 300 ppm·min. Below 50 ppm·min, no signs or symptoms of phosgene toxicity were observed in 75 of 88 individuals; however, three cases of temporary pulmonary edema were observed.

In another report, Sandall (1922) examined 83 British soldiers 3 y after phosgene exposure. Shortness of breath upon exertion (70%), cough with expectoration (54%), tight feeling in chest (25%), sporadic giddiness (14%), and nausea (12%) were the most frequently reported complaints. No physical lung abnormalities were noted in 53% of the men.

2.2.2. Epidemiologic Studies

Polednak (1980) studied a uranium processing plant where phosgene was produced as a by-product of a chemical process in which UO_3 was combined with CCl_4 to produce UCl_4. Leaks and system failures resulted in the accidental release of phosgene into work areas. Although extensive monitoring data were not available, it was determined that the average exposure was below the detection limit of monitoring instruments used at that time. However, there were three to five episodes daily when concentrations exceeded the 1 ppm exposure limit recognized as the occupational standard of the time.

Approximately 30 y after exposure, there were no significant increases in mortality from overall cancer or cancers at specific anatomical sites, in diseases of the respiratory system, or in overall mortality noted in this cohort. However, the exposure period covered by the study was short, the exposed groups were small, and the exposure levels were not well documented. Consequently, evidence presented in this study is inadequate to assess the carcinogenicity of phosgene.

Polednak and Hollis (1985) reported a follow-up of the study discussed above. The study update reported the mortality experience of individuals through the end of 1978 and included 694 routinely exposed white male chemical workers, 97 acutely exposed chemical workers, and 9,280 controls.

Vital status ascertainment for the routinely exposed group and the controls was approximately 90% complete using Social Security Administration (SSA) records. For the acutely exposed group, SSA records as well as state death indexes were used to ascertain vital status, which was approximately 92% complete. Five individuals in the routinely exposed group, nine in the acutely exposed group, and 72 controls were lost to follow-up.

Approximately 35 y after exposure to phosgene, no increase in overall mortality or mortality from cancer or respiratory disease was noted in this cohort.

NIOSH (1976) compared the medical records of 326 workers exposed to phosgene with those of 6,288 unexposed workers from the same plant. Personal air sample measurements at this plant (20-min samples) showed phosgene concentrations ranging from undetectable to 0.02 ppm, and there was a 15 sample average of 0.003 ppm. Fixed-position air samples (20-min or 2-h collection) ranged from undectable to 0.13 ppm in 51 of 56 samples, and >0.14 ppm in 5 of 56 samples. There were no differences in pulmonary function or deaths attributable to respiratory disease between the exposed and control populations.

2.3. Developmental and Reproductive Toxicity

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

2.4. Genotoxicity

Genotoxic studies regarding acute human exposure to phosgene were not available.

2.5. Carcinogenicity

Polednak (1980) and Polednak and Hollis (1985) examined a cohort of chemical workers exposed to phosgene at chronic low levels as well as daily exposures above 1 ppm. Approximately 35 y after exposure to phosgene, no increase in overall mortality or mortality from cancer or respiratory disease

was noted. These studies are described in detail in Section 2.2.2 (Epidemiologic Studies).

2.6. Summary

Although there is a paucity of acute human data containing known exposure concentrations and times, reports of human phosgene poisonings present a relatively consistent set of clinical effects and sequelae. After acute phosgene exposure, brief (≤20 min) ocular and throat irritation, cough, nausea and vomiting, and dizziness are experienced, followed by a period (≤24 h) of apparent well-being. After this clinical latency phase, cough accompanied by expectoration, a sensation of pain or tightness of the chest, shortness of breath, and a choking sensation are experienced. Clinical findings may include hemoconcentration, leukocytosis, rales, and pulmonary edema. After recovery, rapid shallow breathing, shortness of breath on exertion, and a sense of decreased physical fitness may persist for months. Pulmonary emphysema may occur with repeated exposure to phosgene. Epidemiology studies have shown no increase in cancer in workers exposed to phosgene compared with controls. No information concerning reproductive and developmental toxicity or genotoxicity was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Mouse

Zwart et al. (1990) exposed groups of five male and five female Swiss mice to phosgene at varying concentrations for 5, 10, 30, or 60 min. The test atmosphere was monitored at both the inlet and outlet of the glass exposure chambers by gas chromatography and infrared analysis. Ten-minute LC_{50} values were 77 and 61 ppm for males and females, respectively. Thirty-minute LC_{50} values were 18 and 11 ppm for males and females, respectively, and 60-min LC_{50} values were determined to be 9 and 5 ppm for males and females, respectively.

Cameron et al. (1942) exposed 20 mice to phosgene at an average concentration of 0.86 ppm for 5 h. Twelve mice were dead the next morning. Sev

eral other acute lethality studies of phosgene in mice have been reported. However, these studies do not contain experimental details such as strain or gender of mouse, number of animals exposed, or analytical methodology. These values, in addition to those of Zwart et al. (1990), are presented in Table 1–6.

3.1.2. Rats

Zwart et al. (1990) exposed groups of five male and five female Wistar rats to phosgene at varying concentrations for 5, 10, 30, or 60 min. The test atmosphere was monitored at both the inlet and outlet of the glass exposure chambers by gas chromatography and infrared analysis. The 10-min LC_{50} value was 80 ppm, and the 30- and 60-min LC_{50} values were 20 and 12 ppm, respectively.

A total of 118 male Wistar rats were exposed to phosgene at 0.5 to 4.0 ppm for 5 min to 8 h (Rinehart 1962; Rinehart and Hatch 1964). The exposures were varied to give CT products between 12 and 360 ppm-min and were carried out in 1,700-L wooden exposure chambers operating at a constant ventilation rate of 1,000 L/min. The chamber surfaces were lacquered, and thus, potential loss of phosgene by reaction with the wooden surface was minimized. This system provided for air "turnover" every 2 min and a 99% equilibrium time of 8 min. Air samples were taken frequently during exposures, and adjustments were made when necessary to maintain constant phosgene concentrations. An $L(CT)_0$ of 180 ppm·min, a 75-min LC_{50} of 4 ppm, and a 125-min LC_{100} of 4 ppm were determined. The authors concluded that different combinations of concentration and time exposure giving equal products of C × T constitute equally effective doses.

Several other acute lethality studies of phosgene in rats have been reported. However, as is the case with the mice, these studies do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These studies are summarized in Table 1–7.

Box and Cullumbine (1947b) investigated phosgene-induced lethality in rats after the rats had experienced an exposure to phosgene at a nonlethal concentration. Rats were divided into two groups (12 per group). Half of each group was exposed to 19.2 ppm phosgene for 10 min and the other half served as a control group. Five days later, the preexposed and control rats were exposed to phosgene at 55.2, 60, 75.6, and 105.6 ppm for 10 min. The rats were then observed for the next 48 h for deaths. The pretreated rats had a reduced percentage of mortality (33%) compared with the control animals

(74%). Thus, partial protection from phosgene-induced lethality was obtained by the phosgene pretreatment.

TABLE 1–6 Acute Lethality of Phosgene in Mice

Time (min)	LC_{50} (ppm)	Reference
1	850	Chasis 1944
1	3,300	Moor and Gates 1946
5	33	Kawai 1973
10	77 (male); 61 (female)	Zwart et al. 1990
15	15	Cameron and Foss 1941
30	18 (male); 11 (female)	Zwart et al. 1990
30	5.1	Kawai 1973
60	9 (male); 5 (female)	Zwart et al. 1990

3.1.3. Guinea Pigs

The few acute lethality studies of phosgene in guinea pigs do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These less-than-adequate studies are summarized in Table 1–8.

3.1.4. Rabbits

As was the case with guinea pigs, the few acute lethality studies of phosgene in rabbits do not contain experimental details such as strain or gender, number of animals exposed, or analytical methodology. These less than adequate studies are summarized in Table 1–9.

3.1.5. Cats

Wirth (1936) reported no deaths in cats exposed to phosgene at 1.8 ppm for 470 min. A 1-min LC_{50} of 1,482 ppm was reported by Moor and Gates (1946), and a 15-min LC_{50} of 80 ppm was reported by Underhill (1920). No

TABLE 1–7 Acute Lethality of Phosgene in Rats

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	NR	10	35	LC_{20}	Shils 1943
NR	NR	10	60	LC_{40}	Shils 1943
NR	NR	1	1,625	LC_{50}	Chasis 1944
NR	44/NR	10	38–75	LC_{50}	Box and Cullumbine 1947a
NR	NR	12	30	LC_{50}	Chasis 1944
NR	NR	15	35	LC_{50}	Cameron and Foss 1941
NR	NR	20	15	LC_{50}	Kimmerle and Diller 1977
Wistar	40/NR	30	10–15	LC_{75}	Henschler and Laux 1960
NR	NR	20	25	LC_{50}	Rothlin 1941
NR	NR	12	85	LC_{60}	Shils 1943
NR	NR	10	40	LC_{70}	Kimmerle and Diller 1977
NR	32/NR	10	39–103	LC_{75}	Box and Cullumbine 1947a
Wistar	40/NR	20	25	LC_{50}	Henschler and Laux 1960
NR	NR	3	220	LC_{100}	Winternitz et al. 1920
NR	12/NR	10	147	LC_{100}	Box and Cullumbine 1947a
NR	10/NR	13	73	LC_{100}	Schultz 1945

details, such as number, gender, strain of cat, or methodology, were provided in any of these studies.

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	NR	20	37	LC_{100}	Rothlin 1941
NR	NR	30	22	LC_{100}	Winternitz et al. 1920

NR, not reported.

3.1.6. Dogs

Meek and Eyster (1920) exposed eight mongrel dogs (gender not specified) to phosgene at 80–100 ppm for 30 min. All eight died within 24 h postexposure. Pulmonary edema with some evidence of cardiac effects was observed at necropsy.

Additional dog lethality information is presented in Table 1–10.

3.1.7. Goats

Karel and Weston (1947) reported a 10-min LC_{50} of 250 ppm for a group of 30 female and 1 male goat, and Underhill (1920) reported a 15-min LC_{50} of 180 ppm for a group of 61 goats. All goats died when exposed to phosgene at 8,750 ppm for 1 min (Tobias 1945), 500 ppm for 3 min, or 110 ppm for 30 min (Winternitz et al. 1920). No further experimental details were available.

3.1.8. Sheep

A 10-min LC_{50} value of 333 ppm was determined from exposing groups of two Dorset crossbred wethers to phosgene at concentrations of 135, 240, 427, or 758 ppm for 10 min, followed by a 24-h observation period (Keeler et al. 1990b). Animals that died displayed a mixture of stringy mucous and frothy white material from the proximal trachea to the smaller bronchioles that

filled the alveoli, perivascular spaces, and interlobular septa. Sheep that survived the 24-h postexposure period were noted to have airways with scant amounts of mucus and frothy white material and mild to moderate alveolar edema.

TABLE 1–8 Acute Lethality of Phosgene in Guinea Pigs

Exposure Time (min)	Concentration (ppm)	End Point	Reference
1	672	LC_{50}	Chasis, 1944
15	32	LC_{50}	Underhill, 1920
30	18	LC_{50}	Chasis, 1944
30	141	LC_{50}	Moor and Gates, 1946
9	85	LC_{99}	Coman et al., 1947
3	220	LC_{100}	Winternitz et al., 1920
30	20	LC_{100}	Winternitz et al., 1920
20	77	LC_{100}	Ong, 1972

3.1.9. Nonhuman Primates

Chasis (1944) reported a 1-min LC_{50} of 240 ppm for a group of monkeys. The strain, gender, and number of animals were not reported. A 1-min LC_{50} of 500 ppm was reported for 19 male and 18 female Rhesus monkeys (Weston and Karel 1947). Moor and Gates (1946) found that all monkeys died when exposed to phosgene at a concentration of 1,087 ppm for 1 min. No other experimental details were available for either study.

3.2. Nonlethal Toxicity

3.2.1. Mice

Hatch et al. (1986) exposed Swiss albino mice (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h in an 11.3 ft^3 Rochester-type

chamber. The phosgene was mixed with filtered room air before the metering orifice of the chamber and introduced into the chamber airstream. The chamber airstream had a flow rate of 1 chamber volume per minute, and the chamber air was sampled every 10 min. Phosgene concentrations were first determined by gas chromatography, and an infrared analyzer was used for a second check. Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar aveolar lavage fluid protein (LFP), an indicator of pulmonary edema. The LFP findings were 292±18, 302±21, 941±105, 1,302 ±149, or 2,168±167 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a statistically significantly ($p<0.05$) altered protein concentration was 0.2 ppm.

TABLE 1–9 Acute Lethality of Phosgene in Rabbits

Exposure Time (min)	Concentration (ppm)	End Point	Reference
30	17	LC_{40}	Frosolono 1977
1	3,200	LC_{50}	Moor and Gates 1946
15	187	LC_{50}	Underhill 1920
20	110	LC_{50}	Cameron and Courtice 1946
20	20	LC_{50}	Laquer and Magnus 1921
30	100–135	LC_{70}	Halpern et al. 1950
30	93	LC_{75}	Frosolono 1976
30	82	LC_{90}	Shils 1943
35	151	LC_{99}	Coman et al. 1947
15	220	LC_{100}	Winternitz et al. 1920
30	110	LC_{100}	Winternitz et al. 1920

In another study, Illing et al. (1988) exposed groups of 37–39 female CD-1 mice to phosgene at 0.1 to 0.5 ppm for 4 h. Animals were exposed in stainless steel exposure chambers. Phosgene concentrations were monitored primarily by gas chromatography and double checked by infrared analysis. There was a significant ($p<0.05$) increase in pentobarbital-induced sleeping time in mice exposed at 0.15 to 0.5 ppm compared with air controls. No significant differences were observed in cytochrome P450 levels, body weights, or liver weights between phosgene-exposed mice and air controls.

TABLE 1–10 Acute Lethality of Phosgene in Dogs

Strain	Number/ Gender	Exposure Time (min)	Concentration (ppm)	End Point	Reference
NR	12/NR	10	110	LC_{25}	Cameron and Courtice 1946
NR	NR	1	2,100	LC_{50}	Chasis 1944
NR	NR	10	45	LC_{50}	Kimmerle and Diller 1977
NR	24/NR	15	60–70	LC_{50}	Underhill 1920
NR	NR	20	502	LC_{50}	Chasis 1944
NR	6/NR	30	100–175	LC_{50}	Patt et al. 1946
NR	NR	30	78	LC_{55}	Postel and Swift 1945
Mongrel	18/NR	3	745–880	LC_{70}	Coman et al. 1947
NR	94/NR	20	135	LC_{70}	Freeman et al. 1945
NR	42/NR	30	98	LC_{70}	Postel and Swift 1945
Mongrel	15/M,F	30	124	LC_{90}	Schultz 1945
Mongrel	32/NR	10	39–103	LC_{75}	Box and Collumbine 1947
Mongrel	NR	3	734	LC_{99}	Coman et al. 1947
Mongrel	NR	30	90	LC_{99}	Coman et al. 1947

NR, not reported.

Box and Cullumbine (1947b) exposed a group of 37 mice to phosgene at 144 ppm for an unspecified period of time. Subgroups of four or five of these

mice were sacrificed on postexposure days 1, 2, 3, 4, 5, 7, 10, or 14. A histopathological examination was performed on the lungs of these animals. Varying degrees of edema, patches of leucocytic infiltration, and bronchial and bronchiolitic epithelia being lifted by edema were observed on postexposure day 1. More severe edema and collapsed lungs with leukocytic infiltration were observed on postexposure days 2–5. The lungs of the remaining mice were essentially normal by postexposure days 10 through 14.

3.2.2. Rats

A total of 118 male Wistar rats were exposed to phosgene at 0.5 to 4.0 ppm for 5 min to 8 h (Rinehart 1962; Rinehart and Hatch 1964). The exposures were varied to give CT products between 12 and 360 ppm·min and were carried out in 1,700-L wooden exposure chambers operating at a constant ventilation rate of 1,000 L/min. The chamber surfaces were lacquered, and thus, potential loss of phosgene by reaction with the wooden surface was minimized. This system provided for air "turnover" every 2 min and a 99% equilibrium time of 8 min. Air samples were taken frequently during exposures, and adjustments were made when necessary to maintain constant phosgene concentrations. In addition to the lethality data presented in Section 3.1.2, several conclusions were also drawn concerning nonlethal end points. First, the CT product appears to be a valid way to express pulmonary irritation due to phosgene exposure. This is based on the finding of equal degrees of respiratory response, as measured by reduction in pulmonary gas exchange capacity, from exposures to various combinations of C and T that yield the same CT product. Second, there is no decrease in pulmonary performance from exposures less than CT=30 ppm·min, but above this level, gas exchange capacity decreases directly with a *log* increase in CT. Finally, for low level exposures (below CT=100), the major site of action is the respiratory bronchioles, although above this level, the alveoli are involved.

In a later publication of the above experiment (Gross et al. 1965), pulmonary pathology from the phosgene-exposed rats was described. Exposure to phosgene at high concentrations (2 ppm for 90 min) produced chemical pneumonia, and exposure at lower concentrations produced "chronic pneumonitis." The degree of pneumonitis produced by phosgene was rated as slight, moderate, or severe. Slight pneumonitis was defined as mural thickening of respiratory bronchioles with involvement of adjacent alveoli. Moderate pneumonitis was defined as alveolar involvement in a peribronchiolar zone that extends no

more than one-third of the distance to the next bronchiole. Severe pneumonitis was defined as mural thickening of the respiratory bronchioles accompanied by obliteration of adjoining alveoli and air spaces containing desquamated alveolar cells. The lowest 1-h phosgene concentration producing moderate pneumonitis was 0.8 ppm. The same effect occurred with 1-h exposures to phosgene at 0.9, 2.5, or 3 ppm. This occurred in two of three rats, the third rat displaying slight pneumonitis.

Hatch et al. (1986) exposed Sprague-Dawley rats (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar aveolar lavage fluid protein (LFP). The LFP findings were 340 ±38, 258±18, 506±54, 1,642±116, or 2,471±125 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p<0.05$) increased protein concentration was 0.2 ppm.

Male Sprague-Dawley rats were exposed to phosgene at 0, 0.125, 0.25, 0.5, or 1 ppm for 4 h and sacrificed on day 0, 1, 2, or 3 postexposure (Currie et al. 1987a). Animals were exposed in 0.32 m^3 Rochester-type inhalation chambers. The air flow was 0.32 m^3/min, and the gas mixture passed downward through stainless steel wire cages holding the animals and was exhausted at the bottom through a water scrubber. Temperature in the chambers was 23.0±3.4°C, and humidity was 60±10% during exposures. The chambers were monitored by both infrared analysis and gas chromatography continuously during exposure, and even phosgene distribution was assured by sampling from various areas of the exposure chamber. Measured phosgene concentrations were within 2% to 6% of target concentrations. Exposure-related changes were observed in body weights, wet lung weights, LFP concentrations, and total cell count and differential cell count in lavage fluid. Body weights were decreased immediately after exposure through day 2 for the 0.5-and 1-ppm exposure groups. Wet lung weights were increased in the 0.5 ppm exposure group on postexposure days 1, 2, and 3 and in the 1-ppm exposure group immediately after exposure and on postexposure days 1, 2, and 3. The relative wet-lung-to-body-weight ratios were increased immediately after exposure and on days 1, 2, and 3 in the 0.5- and 1-ppm exposure groups. LFP concentrations were increased in the 0.25-ppm exposure group on day 1 and in the 0.5- and 1-ppm exposure groups immediately after exposure and on days 1, 2, and 3. Total cell counts in lavage fluid were elevated in the 1-ppm exposure group on days 2 and 3. Percentage of polymorphonuclear leukocytes

were increased in the 0.25-ppm exposure group on days 1 and 2 and in the 0.5-and 1-ppm exposure groups on days 1, 2, and 3. The LFP and cellular parameters had their peak effect on day 1 postexposure and had begun a return to control values by day 3 postexposure, suggesting that the pulmonary damage was reversible or rapidly repairable.

In another study, Currie et al. (1987b) exposed male Sprague-Dawley rats to phosgene at 0, 0.05, 0.125, 0.25, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Currie et al. (1987a). Animals were sacrificed immediately after exposure and at days 1, 2, and 3 postexposure. The ATP concentrations in lungs were significantly ($p<0.05$) decreased immediately after exposure at all exposure concentrations. The 1-ppm exposure group also had decreased ATP concentrations on day 1 and increased ATP concentrations on days 2 and 3. All other exposure groups had ATP concentrations similar to control values on days 1, 2, and 3. LFP concentrations were only measured immediately after exposure and were linearly increased at 0.25, 0.5, and 1 ppm.

Frosolono and Pawlowski (1977) exposed anesthetized male CFE Carworth rats to phosgene at 0, 100, 200, or 430 ppm for approximately 10 min. Animals were exposed in a 364-L glass and stainless-steel chamber, and phosgene concentrations were estimated with a phosgene detector tube. The authors stated that "the analytical method for the determination of phosgene concentrations is not highly precise…and concentrations given should be considered putative or nominal." Groups of six to eight rats per concentration were sacrificed 0, 30, 60, or 90 min after exposure. No percentage change of lung water (used as a measure of pulmonary edema) was observed in rats exposed to phosgene at 100 or 200 ppm and sacrificed 0 and 30 min after exposure. However, 60 min postexposure, the 100-ppm exposure group had a 6.7% increase in lung water and the 200-ppm exposure group had an 8.7% increase in lung water. Cytochrome C oxidase activities (specific and total) from the lungs were decreased, ranging from 30.1% to 79.8% after rats were exposed at 100 ppm and sacrificed 0, 30, and 60 min after exposure. After exposure at 200 ppm, relative serum lactic dehydrogenase (LDH) activities were increased from 1- to 3-fold over the postexposure time of 0 to 90 min. An exposure at 430 ppm resulted in decreased lung LDH activities (specific and total) ranging from 3.3% to 70.8% in the organelle fractions (homogenate and soluble). The authors suggested that the decreased LDH activities were indicative of cellular damage resulting in increased serum LDH activities.

In a different report, Pawlowski and Frosolono (1977) describe pulmonary ultrastructural alterations in male CFE Carworth rats exposed to phosgene in

a manner essentially identical to that described in Frosolono and Pawlowski (1977). Immediately after exposure, animals exposed to phosgene at 100 ppm exhibited vesiculation of ciliated and Clara cell cytoplasm in the bronchiolar epithelium, and interstitial edema was observed 30 min postexposure. In animals exposed to phosgene at 200 ppm, interstitial edema was observed immediately after exposure, and focal Type I cell discontinuities and interstitial and intracellular edema were present 30 min postexposure. At 48 min postexposure to phosgene at 200 ppm, interstitial cellular edema with general septal thickening and involvement of Type II cells was observed. At 430 ppm, cytoplasmic sequestration figures were observed in Type II cells 60 min postexposure.

In another study, lavage protein concentrations and histopathological assessments of the lungs were determined in male Wistar rats (10–15 per group) exposed to phosgene at 0, 0.1, 0.15, 1, 2.5, or 5 ppm for 10, 20, 50, 60, 250, 330, or 500 min (Diller et al. 1985). The exposure concentrations and durations were paired to provide different exposure scenarios corresponding to ≤50 ppm·min. A special 7-L plexiglass chamber was constructed to achieve reliable exposures at low concentrations of phosgene. Air exchange was 8-fold per minute, and consistency of phosgene concentration throughout the chamber was confirmed by a movable suction probe. Long-term mean phosgene concentrations were measured by collection of the gas samples in a glass bubbler and subsequent titration. Consistency throughout exposure was determined by a galvanometric analyzer, and concentration was checked using detector paper. Animals were sacrificed either 24 or 48 h after the phosgene exposure. A phosgene concentration at 50 ppm·min (5 ppm for 10 min) was required to produce alveolar edema. A concentration of 50 ppm·min was also required to produce an increase in LFP, and widening of pulmonary interstices was observed at 25 ppm·min. No phosgene threshold was observed for the latter two parameters down to 0.1 ppm, indicating that the CT=k relationship is valid for these two parameters. However, under the conditions of this study, Haber's rule appears to be valid for pulmonary edema only down to 5 ppm.

Franch and Hatch (1986) exposed male Sprague-Dawley rats to phosgene at either 1 ppm for 4 h with the sacrifices occurring immediately after exposure and on recovery period days 1, 2, 7, or 14 or 1 ppm for 7 h with the sacrifices occurring hourly during the exposure period. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were 0.98±0.03 ppm for the 4-h exposure regimen and 1.03±0.02 ppm for the 7-h exposure regimen. Body weights of rats exposed at 1 ppm for 4 h were significantly ($p \leq 0.01$) decreased to 13% below controls on day 1 postexposure. Body weights in

creased toward control values, achieving 3% below controls on day 14. Food consumption was also decreased compared with controls but was less than 10% below normal by day 4. Lung weights of exposed animals were 60% greater than controls immediately after exposure and remained elevated through day 7 postexposure. Lung nonprotein sulfhydryl (NPSH) content was similar in control and exposed rats on day 1, had increased to 80% above controls on day 2, and decreased back to control levels by day 7. Glucose-6-phosphate dehydrogenase (G6PD) activity was increased 40% in exposed animals compared with controls from days 1 through 14. Sequential examination every hour during a 7-h exposure revealed lung weights increasing 4 h into the exposure, reaching a maximum elevation of 60% above controls at 6 h. Both the NPSH levels and G6PD activities were decreased in this exposure regimen.

Frosolono and Currie (1985) investigated the effect of phosgene on the pulmonary surfactant-system (PSS) in groups of six to 14 rats exposed to phosgene at 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). The actual chamber concentration was 1.0±0.06 ppm. Animals were sacrificed immediately after exposure, or on postexposure days 1, 2, or 3. Pulmonary edema was present immediately after exposure and persisted through day 3. Phosphatidylinositol levels were significantly ($p<0.05$) decreased compared with controls immediately after exposure only. Phosphatidylserine and phosphatidylethanolamine levels were significantly increased compared with controls on days 1, 2, and 3 postexposure. Phosphatidylcholine levels were increased at all time points compared with controls.

Jaskot et al. (1989) exposed groups of male Sprague-Dawley rats (16 per group) to phosgene at 0 or 0.5 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). The actual chamber concentration was 0.54±0.05 ppm. The rats were sacrificed immediately or 24 h postexposure. Phosgene-exposed rats showed no changes in angiotensin-converting enzyme (ACE) activity in lavage fluid or serum compared with controls. Whole-lung ACE activity was significantly increased immediately after exposure and 24 h postexposure, with increases of 55% and 44% above controls, respectively. Phosgene-exposed rats also had increased ACE activity in lavage cell pellets, with increases of 50% and 54% above controls at 0 and 24 h, respectively.

Assessment of pulmonary immunocompetence was determined by exposing male Fischer 344 rats to phosgene at 0.1, 0.5, or 1 ppm for 4 h and measuring pulmonary natural killer cell activity on day 1, 2, 4, or 7 postexposure (Burleson and Keyes 1989). The animals were exposed in a Rochester cham

her; temperature and humidity were maintained at 23.3±1.7°C and 60±10%, respectively. The chamber atmosphere was continuously monitored during exposures by both gas chromatography and infrared analysis. The actual chamber concentrations were 0.97, 0.49, and 0.10 ppm for the 1-, 0.5-, or 0.1-ppm groups, respectively. The pulmonary natural killer activities in the rats exposed at 1 ppm were significantly (p<0.05) decreased on days 1, 2, and 4. A decrease (p<0.05) in natural killer cell activity was also observed in the 0.5-ppm group. No effect was noted in the 0.1-ppm group.

Another immunological assessment, pulmonary cytotoxic T-lymphocyte (CTL) activity, was examined in male Fischer 344 rats exposed to phosgene at 0 or 1 ppm for 4 h. Animals were exposed in a Rochester exposure chamber, and the exposure atmosphere was monitored by gas chromatography and infrared analysis. The actual exposure concentration was 1.0±0.04 ppm. Twenty-four hours after phosgene exposure, subsets of both the control and phosgene-treated rats were infected with influenza virus. The remaining control and phosgene-exposed rats were sham infected with uninfected lung homogenate. Animals were sacrificed on day 2, 5, 7, 10, 15, or 20 postinfection (Ehrlich et al. 1989).

A significant suppression of CTL activity was noted in phosgene-exposed, influenza-infected rats compared with air-controls, air-infected, and phosgenetreated sham-infected animals. This effect was observed only on day 10 postinfection; however, this is a time when peak activity is normally detected in control rats. Body weights were significantly decreased (p<0.05) in phosgene-exposed, infected and uninfected rats on day 2 postinfection and in phosgene-exposed, infected animals at day 5. Lung weights were significantly increased (p<0.05) in phosgene-exposed, infected and uninfected rats on days 2 and 5 postinfection compared with air-infected and air-uninfected controls.

3.2.3. Guinea Pigs

Cameron et al. (1942) exposed ten guinea pigs to phosgene at an average concentration of 0.86 ppm for 5 h. All survived an apparent 24-h postexposure period.

Hatch et al. (1986) exposed Hartley guinea pigs (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters are similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchi

olar alveolar lavage fluid protein (LFP). The LFP findings were 305±19, 228 ±47, 407 ±75, 524±47, or 1,212±149 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly (p<0.05) altered protein concentration was 0.5 ppm.

In another study, Hartley guinea pigs (five per group) were exposed to phosgene at 0, 0.25, or 0.5 ppm for 4 h (Slade et al. 1989). The exposure chamber and atmosphere generation and measurement systems were similar to those used by Hatch et al. (1986). The LFP concentrations were measured 16 to 18 h after exposure. These investigators found that the LFP concentrations were elevated by 90% in animals exposed to phosgene at 0.25 ppm and 250% in animals exposed at 0.5 ppm, when compared with controls.

3.2.4. Hamsters

Hatch et al. (1986) exposed Syrian Golden hamsters (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar alveolar lavage fluid protein (LFP). The LFP findings were 319 ±6, 347±14, 520±63, 1,289±92, or 3,035±111 (units not provided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly (p<0.05) altered protein concentration was 0.2 ppm.

3.2.5. Rabbits

Cameron et al. (1942) exposed ten rabbits to phosgene at an average concentration of 0.86 ppm for 5 h. All survived an apparent 24-h postexposure period.

Hatch et al. (1986) exposed New Zealand white rabbits (eight per group) to phosgene at 0, 0.1, 0.2, 0.5, or 1 ppm for 4 h. The exposure system and parameters were similar to those described in Section 3.2.1 (Hatch et al. 1986). Actual chamber concentrations were within 2% to 6% of target concentrations. Eighteen to 20 h postexposure, the lungs were lavaged and analyzed for bronchiolar alveolar lavage fluid protein (LFP). The LFP findings were 292±11, 309±20, 346±26, 517±68, and 855±71 (units not pro

vided) for 0, 0.1, 0.2, 0.5, or 1 ppm, respectively. The lowest exposure concentration producing a significantly ($p<0.05$) altered protein concentration was 0.5 ppm.

3.2.6. Dogs

Coman et al. (1947) exposed adult mongrel dogs to phosgene at 108–197 ppm for 30 min and sacrificed the animals 0.63 to 8.58 h after exposure or exposed the dogs to phosgene at 71–80 ppm for 3 min and sacrificed the animals 0.13 to 5.32 h after exposure. Mild to severe emphysema was observed in all dogs, severity generally correlating to exposure concentration and time. Swelling and sloughing of the bronchiolar mucosa were then observed and were usually confined to bronchioles proximal to the respiratory bronchioles. Transient bronchiolar constriction, followed by dilatation of the bronchioles, was also observed. Congestion of the lung and alveolar edema usually followed in the lower exposure concentrations at the 30-min exposure time with the lung congestion preceding alveolar edema in the higher exposure concentrations at the 3-min exposure time. Lung-to-body weight ratios increased as both exposure concentration and/or sacrifice time after exposure increased.

In another study, adult mongrel dogs were exposed to phosgene for 30 min at concentrations that fluctuated between 24 and 40 ppm (Clay and Rossing 1964). The experimental design was as follows: (1) two dogs served as controls, (2) seven dogs were exposed one or two times and sacrificed 1 or 2 d after the last exposure, (3) seven dogs were exposed four to 10 times and sacrificed from 1 to 7 d after the last exposure, (4) five dogs were exposed 15 to 25 times and sacrificed immediately or from 1 to 14 d after the last exposure, and (5) four dogs were exposed 30 to 40 times and sacrificed immediately or from 1 to 12 wk after the last exposure. For all animals exposed one or two times, acute bronchiolitis or peribronchiolitis developed. Pulmonary emphysema was produced in dogs receiving more than two exposures.

3.2.7. Sheep

Groups often unanesthetized, adult sheep were exposed to phosgene at 0 or 767 ppm for 10 min (Assaad et al. 1990). Blood samples were collected

immediately before the exposure and 15, 30, 60, 120, 180, or 240 min after the exposure; also, plasma prostacyclin and thromboxane metabolites (6-keto-$PGFl_a$ and TXB_2) concentrations were measured. Levels of both metabolites were significantly ($p<0.05$) increased in the exposed animals compared with pre-exposure baseline values and air-control values. The 6-keto-$PGFl_a$ returned to control values by 180 min, whereas the TXB_2 did not. The authors concluded that (1) acute lung injury occurred immediately following exposure even though pulmonary edema and symptoms of pulmonary toxicity developed 4 to 8 h after exposure, (2) phosgene may induce pulmonary edema by injuring cell membranes, and (3) arachidonic acid metabolites may be useful as early, nonspecific markers for phosgene-induced lung injury.

In a subsequent study (Assaad et al. 1991), ten unanesthetized, adult sheep were exposed to phosgene at 0 or 767 ppm for 10 min and were sacrificed 4 h after exposure. Gross examination of the lungs revealed congestion and edema, and the light microscopic evaluation demonstrated alveolar and interstitial edema, fibrin and neutrophil exudation in the air spaces, and increased alveolar macrophages. The electron microscopic examination revealed that Type I pneumocytes had intracellular swelling, necrosis, and denuding of basement membrane with the preservation of the tight junctions. Type II pneumocytes showed loss of lamellar bodies, cytoplasmic swelling, and damage to the endoplasmic reticulum. Endothelial cells showed increased density and vesicular activity, cytoplasmic swelling, and displacement of the basement membrane.

Five Dorset-crossbred wether sheep underwent surgery in order to provide simultaneous information concerning phosgene exposure and pulmonary vascular and interstitial fluid dynamics (Keeler et al. 1990a). The efferent duct of the caudal mediastinal lymph node was cannulated to monitor pulmonary lymph flow. Additionally, a carotid atrial catheter, a pulmonary artery catheter, and a left atrial catheter were implanted to monitor systemic and pulmonary hemodynamics. After a 5- to 7-d recovery period, the sheep were exposed to phosgene at 480–600 ppm for 10 min. The control pulmonary lymph flow rate was 10.3±2.2 g/h, and the exposed sheep values were 19.5 ±6.0, 21.5±6.0, 22.5±6.0, 24.0±5.9, 26.5±5.3, 26.9±6.0, or 27.3±5.8 g/h for 1, 1.5, 2, 2.5, 3, 3.5, or 4 h postexposure, respectively. There was a small increase in mean pulmonary micro vascular pressure but no change in the ratio of lymph-to-plasma protein concentration. Sheep were sacrificed 4 h after exposure. Histopathological evaluations of the lungs revealed diffuse, moderate alveolar and interlobular edema.

3.2.8. Goats

Cameron et al. (1942) exposed two goats to an average phosgene concentration of 0.86 ppm for 5 h. Both survived an apparent 24-h postexposure period.

3.2.9. Cats

Cameron et al. (1942) exposed two cats to an average phosgene concentration of 0.86 ppm for 5 h. One cat became "very ill" with considerable labored breathing, but both survived an apparent 24-h postexposure period.

3.2.10. Monkeys

Cameron et al. (1942) exposed two monkeys to an average phosgene concentration of 0.86 ppm for 5 h. One of the monkeys became "very ill" with considerable labored breathing, but both survived an apparent 24-h postexposure period.

3.3. Developmental and Reproductive Toxicity

Developmental and reproductive toxicity studies regarding animal exposure to phosgene were not available.

3.4. Genotoxicity

Genotoxic studies regarding animal exposure to phosgene were not available. However, the two highly reactive chlorines of phosgene suggest that it could act on DNA in a similar manner to that of bifunctional alkylating agents (Shah et al. 1979).

3.5. Carcinogenicity

A study by Selgrade et al. (1989) showed that exposure to phosgene at very low levels enhances the susceptibility of mice to lung tumor formation.

Female C57BL/6 mice were exposed for 4 h to phosgene at 0.01 (N=13), 0.025 (N=28), or 0.05 ppm (N=35) and injected intravenously with syngeneic B16 melanoma cells on the following day. Controls were injected with tumor cells and exposed to air. The lungs were removed 2–3 wk after tumor cell injection and the tumors were counted. Compared with controls, there was a statistically significant ($p<0.05$) increase in the number of B16 melanoma tumors in the lungs of mice treated with phosgene at 0.025 or 0.05 ppm. The number of tumors per lung were 105, 110, or 185 in mice treated with 0.01, 0.025, or 0.05 ppm, respectively, compared with 90, 75, or 100 in the respective control groups. Exposure to 0.025 ppm was considered the lowest-observed-effect level. Extending the exposure time from 4 to 8 h did not alter the susceptibility to B16 tumors at 0.01 ppm.

In other experiments using a higher concentration, mice were exposed by inhalation to phosgene at 0.5 ppm for 4 h and injected intravenously with melanoma tumor cells on the following day or injected with tumors and then exposed at 0.5 ppm for 4 h/d for 4 consecutive days. There was a significant increase ($p<0.05$) in the number of lung tumors in the group exposed to phosgene prior to inoculation (96 tumors per lung compared with 38 tumors per lung for controls). Although the number of tumors in mice exposed to phosgene on 4 consecutive days beginning immediately after tumor injection was higher than in controls (65 tumors per lung compared with 48 tumors per lung for controls), the difference was not statistically significant. These experiments showed that exposure following tumor injection had little effect on tumor susceptibility compared with phosgene exposure prior to tumor injection.

3.6. Summary

Animal lethality studies are abundant; however, the studies are of varying quality and many are incompletely reported. Thus, the utility of the lethality studies must be considered on a case by case basis. Even though there are limitations concerning these studies, there appears to be little species variability between rats, mice, and guinea pigs, and the CT=k relationship appears to be generally valid. (Although at very high or very low concentrations or at exposure times so short that the animal can hold its breath, the CT=k relationship may not hold.)

Many nonlethal acute inhalation studies exist and are of generally good quality. These studies also suggest that there are few differences between species after acute exposure to phosgene and that the type and sequence of

effects are similar in humans and experimental animals. Many of the nonlethal toxicity studies describe biochemical changes in lung fluid, whose pathogenesis is likely due to acylation (see Section 4.2). Selected biochemical and other nonlethal effects are summarized in Table 1–11.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Following inhalation exposure, a small portion of phosgene hydrolyzes to hydrochloric acid (HCl) and carbon dioxide (CO_2) in the mucous coating of the upper respiratory tract (Diller 1985), but in the moist atmosphere of the terminal spaces of the lungs, more extensive hydrolysis is thought to occur (Beard 1982). Although phosgene is only slightly soluble in water, once in solution it rapidly hydrolyzes to HCl and CO_2. However, phosgene reacts even faster with other functional groups, such as amino, hydrazino, and sulfhydryl groups (Jaskot et al. 1991; Diller 1985).

4.2. Mechanism of Toxicity

The toxicity of phosgene is due to both acylation and hydrolysis. The acylation is most important and results from the reaction of phosgene with nucleophiles such as amino, hydroxyl, and sulfhydryl groups of macromolecules. The acylation causes lipid and protein denaturation, irreversible membrane changes, and disruption of enzymatic function. Phosgene depletes lung glutathione, and glutathione reductase and superoxide dismutase increase as a result of the lung's response to injury. Cellular glycolysis and oxygen uptake are decreased following exposure to phosgene, and there is a decrease of intracellular ATP and cyclic AMP associated with increased permeability of pulmonary vessels and pulmonary edema. Phosgene exposure also causes increased lipid peroxidation and increased leukotriene synthesis but no change in cyclooxygenase metabolism (TEMIS 1997).

The hydrogen chloride formed by the hydrolysis of phosgene causes initial irritation to the eyes, nasopharynx, and respiratory tract. However, because of phosgene's poor water solubility, a minimal amount of hydrogen chloride is formed (TEMIS 1997).

TABLE 1–11 Summary of Selected Nonlethal Effects of Phosgene

Phosgene Concentration (ppm)	Exposure Time (h)	Species	Effect	Reference
0.05	4	Rat	Decreased ATP	Currie et al. 1987b
0.1	1	Rat	No edema; no histopathology	Diller et al. 1985
0.1	4	Rat	Lung histopathology	Diller et al. 1985
0.1	4	Rat	No decrease in PNKC activity	Burleson and Keyes 1989
0.1	4	Rat	No increase in LFP levels	Hatch et al. 1986
0.1	4	Rat	Decreased ATP; no changes in LFP level	Currie et al. 1987b
0.1	4	Mouse	No changes in LFP levels	Hatch et al. 1986
0.1	4	Hamster	No changes in LFP levels	Hatch et al. 1986
0.125	4	Rat	No changes in LFP levels; no lung weight change	Currie et al. 1987a
0.2	4	Rat	Increased levels of LFP	Currie et al. 1987b
0.2	4	Mouse	Increased levels of LFP	Hatch et al. 1986
0.2	4	Guinea Pig	No changes in LFP levels	Hatch et al. 1986
0.2	4	Rabbit	No changes in LFP levels	Hatch et al. 1986
0.2	4	Hamster	Increased levels of LFP	Hatch et al. 1986
0.25	4	Rat	Increased levels of LFP and PMN; no lung weight change	Currie et al. 1987a

Phosgene Concentration (ppm)	Exposure Time (h)	Species	Effect	Reference
0.25	4	Guinea Pig	Increased levels of LFP	Slade et al., 1989
0.5	4	Rat	Decreased body weight; increased lung weight; increased levels of LFP	Currie et al. 1987a
0.5	4	Guinea Pig	Increased levels of LFP	Hatch et al. 1986
0.5	4	Rabbit	Increased levels of LFP	Hatch et al. 1986
0.5	4	Rat	Decreased PNKC activity	Burleson and Keyes 1989
0.5	4	Rat	Increased ACE activity	Jaskot et al., 1989
1	4	Rat	Increased lung weight (14 d); decreased body weight; increased G6PD activity and NPSH content	Franch and Hatch 1986
1	4	Rat	Decreased PNKC activity	Burleson and Keyes 1989
1	4	Rat	Increased lung weight; decreased body weight; suppressed cytotoxic T-lymphocytes	Ehrlich et al. 1989

4.3. Structure-Activity Relationships

Phosgene is a reactive intermediate of both chloroform and carbon tetrachloride metabolism. Chloroform is metabolized by oxidative dehydrochlorination of its carbon-hydrogen bond to form the highly unstable trichloro-methanol (Cl_3COH), which is then spontaneously converted to phosgene. This reaction is catalyzed by cytochrome P-450 and occurs in both the liver and kidneys. The evidence for phosgene formation from chloroform was the isolation of 2-oxothioazolidine-4-carboxylic acid from the microsomal incubation of chloroform in the presence of cysteine. This compound is the expected product of the reaction of phosgene with cysteine (Pohl et al. 1977; Mansuy et al. 1977). The electrophilic phosgene further reacts with water to yield CO_2 and Cl^- (major end products of chloroform metabolism), but significant amounts of phosgene bind covalently with proteins and lipids or conjugate with cysteine or glutathione (GSH) (EPA 1985).

Covalent binding of phosgene with cellular macromolecules has been proposed as a mechanism of chloroform-induced hepatic and renal toxicity (Pohl et al. 1980a,b), and it is generally accepted that the carcinogenic activity of chloroform resides in its highly reactive intermediate metabolites such as phosgene. Irreversible binding of reactive chloroform metabolites to cellular macromolecules support several theoretical concepts as a mechanism for its carcinogenicity (EPA 1985).

Covalent macromolecular binding of phosgene may be prevented to some extent by endogenous GSH (Sipes et al. 1977). Phosgene reacts with two molecules of GSH to form diglutathionyl dithiocarbonate (GSCOSG), a compound identified as a metabolite of chloroform in rat liver microsomes and mouse kidney homogenates incubated with chloroform in the presence of GSH (Pohl et al. 1981; Branchflower et al. 1984). In mouse kidney homogenates, GSCOSG was shown to be further metabolized by kidney α-glutamyl transpeptidase to *N*-(2-oxothiazolidine-4-carbonyl)-glycine, which in turn is hydrolyzed, possibly in the presence of cysteinyl glycinase, to 2-oxothiazolidine-4-carboxylic acid (Branchflower et al. 1984).

The metabolism of carbon tetrachloride proceeds via cytochrome P-450-dependent dehalogenation (Sipes et al. 1977). The first step involves cleavage of one carbon-chlorine bond to yield Cl^- and a trichloromethyl free radical, which is then oxidized to the unstable intermediate trichloromethanol, the precursor of phosgene. Hydrolytic dechlorination of phosgene yields CO_2 and HCl (Shah et al. 1979). Although there are similarities in the metabolism of chloroform and carbon tetrachloride, metabolic activation of chloroform produces primarily phosgene, whereas the level of phosgene production from

carbon tetrachloride appears to be small. Pohl et al. (1981) compared the amount of phosgene (as diglutathionyl dithiocarbamate) produced by the aerobic metabolism of carbon tetrachloride and the amount produced from chloroform by liver microsomes from phenobarbital-treated rats. The results indicate that phosgene production from carbon tetrachloride is only 4% of that produced from chloroform. The reactive metabolites of both chloroform and carbon tetrachloride covalently bind to proteins and lipids but bind only minimally to DNA and nucleic acids. The failure of the reactive species (e.g. phosgene, trichloromethyl free radical, and other metabolites) to significantly bind to DNA has been ascribed to their short half-lives and to their lack of nuclear penetration (EPA 1985).

Given to intact rats, ^{14}C-phosgene labeled liver proteins and to a smaller extent lipids (Reynolds 1967). The pattern of labeling was different from that of ^{14}C-carbon tetrachloride and was similar to that of ^{14}C-chloroform. It was also shown that ^{36}Cl-carbon tetrachloride radioactivity was stably incorporated into liver lipid and protein, pointing to the trichloromethyl radical rather than phosgene as the reactive form of carbon tetrachloride. Cessi et al. (1966) reported that phosgene labeled the terminal amino groups of polypeptides in a manner similar to in vivo protein labeling produced by carbon tetrachloride. However, after inhalation, phosgene reacts completely with lavage fluid, lung tissue, and lung capillary blood so that it is unlikely that phosgene will reach tissue beyond the lung (Diller 1974).

4.4. Other Relevant Information

4.4.1. Haber's Law and Time Scaling

The concept of a "death product" was introduced by Haber to explain the relationship between the extent of exposure to phosgene and death (Haber 1924). According to "Haber's law," the biological effect of phosgene is directly proportional to the exposure, expressed as the product of the atmospheric concentration (C) and the time of exposure (T), or CT=k, where k can be death, pulmonary edema, or other biological effects of phosgene exposure (EPA 1986). Haber's law has subsequently been shown by other investigators to be valid for both nonlethal and lethal effects within certain limits.

For example, Rinehart (1962) and Rinehart and Hatch (1964) showed that the CT product appears to be a valid way to express pulmonary irritation due to phosgene exposure in rats. This is based on the finding of equal degrees of respiratory response, as measured by reduction in pulmonary gas exchange

capacity, from exposures to various combinations of C and T that yield the same CT product.

Rat and mouse lethality data from the well-conducted study of Zwart et al. (1990) also suggest that Haber's law is valid for phosgene. The study by ten Berge et al. (1986) has shown that the concentration-exposure-time relationship for many irritant and systemically acting vapors and gasses can be described by the relationship $C^n \times t = k$. When the 10- to 60-min rat LC_{50} data are utilized in a linear regression analysis a value of the exponent, n, of 0.93 is obtained. The mouse 10- to 60-min lethality data yield a value of 1.3 for n.

Thus, the fact that these empirically derived values for the exponent n approximate 1 is further support that Haber's law is valid for phosgene.

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data were relevant for establishing AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

No animal data were relevant for establishing AEGL-1 values.

5.3. Derivation of AEGL-1

Appropriate data were not available for derivation of AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤24 h.

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were relevant to establishing the AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Chemical pneumonia was observed in rats exposed to phosgene at 2.0 ppm for 90 min (Gross et al. 1965). Biochemical markers of phosgene exposure, such as increased LFP, were observed in mice, rats, guinea pigs, hamsters, and rabbits exposed at up to 1 ppm for 4 h (Hatch et al. 1986; Diller et al. 1985). Other effects defined by AEGL-2 included "very ill" monkeys with labored breathing (Cameron et al. 1942) and acute bronchiolitis or peribronchiolitis in dogs (Clay and Rossing 1964). However, a lack of experimental details in the monkey and dog studies renders them inappropriate for AEGL derivation.

6.3. Derivation of AEGL-2

The chemical pneumonia observed in rats exposed to phosgene at 2 ppm for 90 min (Gross et al. 1965) will be used as the basis for deriving AEGL-2 values. This end point was chosen because at a C × t product of 180 ppm·min, approximately 60% of rats exhibited chemical pneumonia. Whereas, at C ×t products ≤180 ppm·min, only 15% of exposed rats showed pneumonia or chemical pneumonitis. An uncertainty factor (UF) of 3 will be applied for interspecies extrapolation because little species variability is observed in lethal and nonlethal end points after exposure to phosgene. A UF of 3 will also be applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. Thus, the total UF is 10. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t=k$, where the n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Haber's law ($C \times t=k$; n=1) has been shown to be valid for phosgene within certain limits and will be used for scaling of the AEGL values for phosgene for the 30-min and 1-, 4-, and 8-h time points. The 30-min value is also adopted as the 10-min value, because extrapolation would yield a 10-min AEGL-2 value close to concentrations producing alveolar edema in rats. The AEGL-2 values for phosgene are presented in Table 1–12, and the calculations for these AEGL-2 values are presented in Appendix A.

These AEGL-2 values are supported by the nonlethal toxicity studies of Franch and Hatch (1986) and Ehrlich et al. (1989). In both of these studies, rats exposed to phosgene at 1 ppm for 4 h developed severe pulmonary edema and body-weight loss. If this exposure regimen and a total UF of 10 are uti

lized to calculate AEGL-2 values, similar supporting values of 0.8, 0.4, 0.1, and 0.05 ppm are obtained for the 30-min and 1-, 4-, and 8-h time points, respectively. The 10-min value is supported by the fact that Diller et al. (1985) observed alveolar pulmonary edema in rats exposed at 5 ppm for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min value of 0.5 ppm.

TABLE 1–12 Proposed AEGL-2 Values for Phosgene (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were relevant to establishing the AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Many lethality data exist for a variety of species (mouse, rat, guinea pig, rabbit, cat, dog, goat, sheep, and monkeys). However, in most cases, experimental parameters are poorly described, and the quality of the data is questionable for AEGL derivation. The mouse and rat LC_{50} studies of Zwart et al. (1990) are the exception and are appropriate for AEGL-3 derivation.

7.3. Derivation of AEGL-3

The highest concentration causing no mortality in the rat after a 30-min exposure is 15 ppm (Zwart et al. 1990). This value will be used as the basis for deriving 30-min and 1-, 4-, and 8-h AEGL-3 values. The highest concentration causing no mortality in the rat and mouse after a 10-min exposure is 36 ppm (Zwart et al. 1990); this value will be used as the basis for the 10-min AEGL-3 value. A UF of 3 will be applied for interspecies extrapolation

because little species variability is observed both in lethal and nonlethal end points after exposure to phosgene. A UF of 3 will also be applied to account for sensitive human subpopulations due to the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. Thus, the total UF is 10. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Haber's law ($C \times t = k$; $n=1$) has been shown to be valid for phosgene within certain limits and will be used for scaling of the AEGL values for phosgene across time for the 1-, 4-, and 8-h values. The AEGL-3 values for phosgene are presented in Table 1–13 (above), and the calculations for these AEGL-3 values are presented in Appendix A.

TABLE 1–13 Proposed AEGL-3 Values for Phosgene (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 1–14. Data were insufficient for deriving

TABLE 1–14 Summary of Proposed AEGL Values for Phosgene (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)

AEGL-1 values. Chemical pneumonia in rats was used as the basis for AEGL-2, and the highest concentration causing no mortality in the rat after a 10- or 30-min exposure (and mice, 10-min value only) was used for AEGL-3.

8.2. Comparison with Other Standards and Guidelines

Table 1–15 provides existing standards and guidelines for phosgene.

TABLE 1–15 Extant Standards and Guidelines for Phosgene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NA	NA	NA	NA	NA
AEGL-2	0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm
AEGL-3	3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm
ERPG-l[a]			NA		
ERPG-2[a]			0.2 ppm		
ERPG-3[a]			1 ppm		
EEGL (NRC)[b]			0.2 ppm		0.02 ppm (24-h)
NIOSH IDLH[c]	2 ppm				
NIOSH STEL[d]	0.2 ppm (15-min ceilling)				
NIOSH REL[d]					0.1 ppm (10-h)
OSHA PEL-TWA[e]					0.1 ppm
ACGIH TLV[f]					0.1 ppm
MAK (Germany)[g]					0.02 ppm
MAC (Netherlands)[h]					0.02 ppm

[a]ERPG (emergency response planning guidelines) (AIHA 2000) The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for phosgene is not derived. The ERPG-2 is the maximum airborne concen-tration below which it is believed nearly all individuals could be exposed for up to onehour without experiencing or developing irreversible or other serious health effects orsymptoms that could impair an individual's ability to take protection action. TheERPG-2 for phosgene is based on pulmonary pathology and function studies sugges-tion that concentrations exceeding 0.2 ppm may produce serious pulmonary effects insome individuals. The ERPG-3 is the maximum airborne concentration below whichit is believed nearly all individuals could be exposed for up to one hour without expe-riencing or developing life-threatening health effects. The ERPG-3 for phosgene isbased on acute animal inhalation data indicating that concentrations exceeding 1 ppmfor 1 h may by expected to produce pulmonary edema and possible mortality in aheterogeneous human population. As of 2000, the ERPG values for phosgene areunder ballot consideration and review.

[b]EEGL (emergency exposure guidance levels) (NRC 1985) The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury. The EEGL for phosgene is based on the "most relevant animal exposure studies (Gross et al. 1965; Rinehart and Hatch 1964)" and studies suggesting that animals do not tolerate phosgene at 0.2 ppm administered 5 h/d for 5 d (Cameron and Foss 1941; Cameron et al. 1942).

[c]IDLH (immediately dangerous to life and health) (NIOSH 1997) represents the maximum concentration from which one could escape within 30 min without any escapeimpairing symptoms or any irreversible health effects. The IDLH for phosgene is based on acute inhalation toxicity data in humans (Diller 1978).

[d]NIOSH REL-STEL (recommended exposure limit-short-term exposure, limit) (NIOSH 1997) is analogous to the ACGIH TLV-TWA.

[e]OSHA PEL-TWA (permissible exposure limit-time-weighted average) (OSHA 1994) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/w.

[f]ACGIH TLV-TWA (Threshold Limit Value-time-weighted average) (ACGIH 2000) 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.

[g]MAK (Maximale Argeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is analogous to the ACGIH-TLV-TWA.

[h]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is analogous to the ACGIH TLV-TWA.

8.3. Data Adequacy and Research Needs

No reliable, quantitative human data exist. Human data are limited to descriptive effects from accidental exposure and are thus inappropriate for derivation of AEGL values. There is, however, a plethora of acute inhalation data in many experimental species. The database is sufficient to have good confidence in AEGL-2 and AEGL-3 values.

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Appendixes

APPENDIX A DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Data were insufficient for derivation of AEGL-1 values for phosgene.

Derivation of AEGL-2

Key study:	Gross et al. (1965)
Toxicity end point:	Chemical pneumonia in rats
Scaling:	C×t=k
	(2 ppm)×1.5 h=3 ppm·h
Uncertainty factors:	3 for interspecies variability
	3 for intraspecies variability
10-min AEGL-2:	0.6 ppm (30-min value adopted as the 10-min value)
30-min AEGL-2:	C×0.5 hr=3 ppm·h
	C=6 ppm
	30-min AEGL-2=6 ppm/10=0.6 ppm
1-h AEGL-2:	C×1 h=3 ppm·h
	C=3 ppm
	1-h AEGL-2=3 ppm/10=0.3 ppm
4-h AEGL-2:	C×4 h=3 ppm·h
	C=0.75 ppm
	4-h AEGL-2=0.75 ppm/10=0.075 ppm
8-h AEGL-2:	C×8 h=3 ppm·h
	C=0.375 ppm

8-h AEGL-2=0.375 ppm/10=0.038 ppm

Derivation of AEGL-3

Key study:	Zwart et al. (1990)
Toxicity end point:	The highest concentration causing no mortality in the rat or mouse after a 10-min exposure (10-min). The highest concentration causing no mortality in the rat after a 30-min exposure (30-min, 1-, 4-, and 8-h).
Scaling (30-min, 1-, 4-, and 8-h):	C×t=k (15 ppm)×0.5 h=7.5 ppm·h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability
10-min AEGL-3:	10-min AEGL-3=36 ppm/10=3.6 ppm
30-min AEGL-3:	C×0.5 h=7.5 ppm·h C=15 ppm 30-min AEGL-3=15 ppm/10=1.5 ppm
1-h AEGL-3:	C×1 h=7.5 ppm·h C=7.5 ppm 1-h AEGL-3=7.5 ppm/10=0.75 ppm
4-hr AEGL-3:	C×4 h=7.5 ppm·h C=1.875 ppm 4-h AEGL-3=1.875 ppm/10=0.19 ppm
8-h AEGL-3:	C×8 h=7.5 ppm·h C=0.94 ppm 8-h AEGL-3=0.94 ppm/10=0.094 ppm

APPENDIX B DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR PHOSGENE (CAS No. 75–44–5)

AEGL-1

10 min	30 min	1 h	4 h	8 h
NA	NA	NA	NA	NA

Key reference: NA
Test species/Strain/Number: NA
Exposure route/Concentrations/Durations: NA
Effects: NA
End point/Concentration/Rationale: NA
Uncertainty factors/Rationale: NA
Modifying factor: NA
Animal to human dosimetric adjustment: NA
Time scaling: NA
Confidence and Support for AEGL values: Data were insufficient for derivation of AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤24 h.

AEGL-2

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm

Key reference: Gross, P., Rinehart, W.E., and Hatch, T. 1965. Chronic pneumonitis caused by phosgene. Arch. Environ. Health. 10: 768–775.

Test species/Strain/Number: Wistar rats/118 males

Exposure route/Concentrations/Durations: Rats/Inhalation: 0.5 to 4.0 ppm for 5 min to 8 h to give C×T products between 12 and 360 ppm·min (2 ppm for 1.5 h was determinant for AEGL-2)

Effects: 2 ppm for 1.5 h: chemical pneumonia; 0.9 ppm for 1 h: "chronic pneumonitis"

End point/Concentration/Rationale: Rats/2 ppm for 1.5 h/chemical pneumonia

Uncertainty factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3—little species variability is observed with both lethal and nonlethal end points in many studies after exposure to phosgene

Intraspecies: 3—due to the steep concentration-response curve and effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals.

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$ where n=1. Haber's Law (C×t=k) has been shown to be valid for phosgene within certain limits (EPA 1986). Haber's Law was originally derived from phosgene data (Haber 1924). Reported 1.5 h data point used for AEGL-2 derivation. AEGL values for the 30-min and 1-, 4-, and 8-h exposure periods were based on extrapolation from the 1.5 h value. The 30-min value is also adopted as the 10-min value because Diller et al. (1985) observed alveolar pulmonary edema in rats exposed to 5 ppm phosgene for 10 min. Applying a total UF of 10 to this data point yields a supporting 10-min value of 0.5 ppm.

Data adequacy: The database is rich. The calculated AEGL-2 values are supported by rat studies where exposure of rats to 1 ppm phosgene for 4 h resulted in severe pulmonary edema and body weight loss. (Franch and Hatch 1986; Erlich et al. 1989). Use of these data (and application of a total UF of 10) results in supporting AEGL-2 values of 0.8, 0.4, 0.1, and 0.05 ppm for the 30 min, 1 h, 4 h, and 8 h time points, respectively. The 10-min value is supported by Diller et al. (1985) as described above in the time scaling section.

AEGL-3

10 min	30 min	1 h	4 h	8 h
3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm

Reference: Zwart, A. et al. 1990. Determination of concentration-time-mortality relationships to replace LC50 values. Inhalation Toxicol. 2: 105–117.

Test species/Strain/Sex/Number: Wistar rats/5 males and 5 females

Exposure route/Concentrations/Durations: Rats/Inhalation: 12, 15, 16, 17, or 24 ppm for 30 min (the highest concentration causing no mortality in the rat after a 30-min exposure of 15 ppm was determinant for AEGL-3)

Effects:	*Concentration*	*Mortality*
	12 ppm	0/10
	15 ppm	0/10
	16 ppm	1/10
	17 ppm	5/10
	24 ppm	9/10

End point/Concentration/Rationale: The highest concentration causing no mortality in the rat after a 30-min exposure 30-min experimental no-effect-level for death (15 ppm) was used as a threshold for death in rats for the 30-min, 1-, 4-, and 8-h values. The highest concentration causing no mortality in the rat after a 10-min exposure (36 ppm) was utilized for the 10-min value.

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3—little species variability is observed with both lethal and nonlethal end points in many studies after exposure to phosgene

Intraspecies: 3—due to the steep concentration-response curve and effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals .

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$ where n=1. Haber's Law ($C \times t = k$) has been shown to be valid for phosgene within certain limits (EPA 1986). Haber's Law was originally derived from phosgene data (Haber 1924). Reported 30-min data point used to determine the 30-min AEGL value. AEGL-3 values for 1-, 4-, and 8-h were based on extrapolation from the 30 min value. The 10-min value was based on a reported 10-min data point.

Data adequacy: The AEGL-3 values are based on a well-conducted study in rats and the database is rich.

2

Propylene Glycol Dinitrate[1,2]

Acute Exposure Guideline Levels

SUMMARY

Otto Fuel II, a liquid propellant used exclusively by the U.S. Navy in torpedoes and other weapon systems, is a mixture of three synthetic compounds: 1,2-propylene glycol dinitrate (PGDN) (a nitrate ester explosive), dibutyl sebacate (a desensitizer), and 2-nitrodiphenylamine (a stabilizer). The

[1]Also appropriate for Otto Fuel II (CAS Reg. No. 106602–80–60).

[2]This document was prepared by the AEGL Development Team comprising Sylvia Talmage (Oak Ridge National Laboratory) and members of the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances including William Bress (Chemical Manager) and Robert Snyder, William Pepelko, and Kenneth Still (Chemical Reviewers). The NAC reviewed and revised the document and AEGL values as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

primary component and the one responsible for the toxicity of Otto Fuel II is PGDN, a volatile liquid with a disagreeable odor. Because PGDN is the primary and most toxic component of Otto Fuel II and because only PGDN is relatively volatile compared with the other components, AEGLs have been derived in terms of PGDN with the notation that the values are appropriate for Otto Fuel II.

PGDN is a systemic toxicant with effects on the cardiovascular and central nervous systems. Its vasodilatory action results in headaches during human exposures. Dizziness, loss of balance, nasal congestion, eye irritation, palpitations, and chest pains have also been reported. Methemoglobinemia has been reported at the high concentrations used in studies with animals. The air-odor threshold in healthy subjects is 0.2 parts per million (ppm), but warning properties are poor inasmuch as olfactory fatigue sets in after as little as 5 minutes (min) (Stewart et al. 1974). Within 24 hours (h) of exposure, PGDN is rapidly and completely metabolized in vivo and eliminated primarily in the urine as inorganic nitrate.

Few data were available that met the definitions of AEGL end points. One inhalation study with 20 human subjects described headaches and slight loss of balance at exposure concentrations of 0.1 to 1.5 ppm for exposure durations of up to 8 h (Stewart et al. 1974). Acute exposure of monkeys for 6 h at concentrations ranging between 70 and 100 ppm resulted in severe signs of toxicity including convulsions but no deaths (Jones et al. 1972). In the same study, exposure of rats at a higher concentration, 189 ppm for 4 h, resulted in no toxic signs. Examination of the relationship between exposure duration and concentration for both mild and severe headaches in humans over periods of 1 to 8 h determined that the relationship is $C^1 \times t = k$.

The AEGL-1 values were based on concentrations at 0.5 ppm and 0.1 ppm, which were the thresholds for mild headaches in healthy individuals at exposure durations of 1 and 6 h, respectively (Stewart et al. 1974). This effect can be considered the threshold for mild discomfort (only one subject was affected at each exposure), which falls within the definition of an AEGL-1. The 0.5-ppm concentration was used to derive the 30-min and 1-h AEGL-1 values, and the 0.1-ppm concentration was used for the 4- and 8-h values. Because the time and concentration values were based on the most susceptible subject, these concentrations were adjusted by an uncertainty factor (UF) of 3 to account for potential differences in human sensitivity and scaled to the appropriate time periods using the $C^1 \times t = k$ relationship. A UF of 3 was considered sufficient as no susceptible populations were identified (the headache effect is the same as that experienced by patients medicated with nitro

glycerin for angina, and the calculated concentrations of nitrite arising from inhaled PGDN are far below those inducing methemoglobinemia in infants), and the vasodilatory effects of PGDN, responsible for the headaches, are not expected to vary greatly among individuals. The UF of 3 is supported by the steep dose-response curve for induction of headaches in the key study. (The threshold concentration and the concentration that induced headaches in approximately half of the individuals differed by a factor of 2.) The 10-min AEGL-1 value was set equal to the 30-min value.

The AEGL-2 values were based on a 0.5-ppm concentration, which caused severe headaches accompanied by dizziness in one subject and slight loss of equilibrium in two subjects in one of several sensitive equilibrium tests after 6 h of exposure (Stewart et al. 1974). This concentration-exposure duration was considered the threshold for impaired inability to escape as defined by the AEGL-2. The 0.5-ppm concentration was adjusted by an intraspecies UF of 3 to protect susceptible individuals and scaled across time for the 30-min and 1-, 4-, and 8-h time periods using the $C^1 \times t = k$ relationship, as was done for the AEGL-1 derivation. The UF of 3 is supported by the less than 2-fold difference among individuals for the induction of narcosis by central nervous system depressants and by the steep dose-response curve for the induction of headaches in the key study: namely, a 2-fold difference in the threshold concentration and the concentration that induced headaches in the majority of tested individuals. Because of the long exposure duration of 6 h for the chosen end point, time scaling was not performed for the 10-min AEGL-2. The 10-min AEGL-2 was set equal to the 30-min value.

The AEGL-3 values were based on the 6-h exposure of squirrel monkeys at concentrations that ranged between 70 and 100 ppm. This exposure resulted in vomiting, pallor, cold extremities, semiconscousness, and clonic convulsions; these signs disappeared upon removal from the exposure chamber (Jones et al. 1972). Because a range of concentrations were encountered during the 6-h exposure, the lower concentration, 70 ppm, was selected as the basis for the AEGL-3. This value may be conservative as rats showed no effects during a 4-h exposure at 189 ppm (Jones et al. 1972). The 70-ppm concentration was adjusted by a total UF of 10. An interspecies UF of 3 was chosen because the monkey is an appropriate model for extrapolation to humans: Both the monkey and human subjects showed changes in electrical activity of the brain at similar PGDN concentrations. An intraspecies UF of 3 was considered sufficient for differences in the threshold for convulsions, which are also attributable to central nervous depression. Because the end point for the AEGL-3 values (convulsions and lethality) is different than the

end point for AEGL-1 and AEGL-2 (headache), and no data on the relationship between concentration and exposure duration are available for the end point of convulsions, the more conservative values of n=3 and n=1 were used to scale from 6 h to the shorter (30-min and 1- and 4-h) and longer time periods, respectively. The 10-min AEGL-3 was set equal to the 30-min AEGL-3. The values are supported by the results of additional studies with squirrel monkeys and dogs by Jones et al. (1972). Monkeys and dogs exposed continuously at approximately 15 ppm for 90 days (d) showed no overt clinical signs; systemic toxicity consisted of biochemical and/or non-life-threatening histological changes in the liver, spleen, and kidneys.

The values appear in Table 2–1.

1. INTRODUCTION

Otto Fuel II is a liquid propellant used exclusively by the U.S. Navy in MK-46 and MK-48 torpedoes and other weapon systems (Rivera 1974; Gaworski et al. 1985). It is a mixture of three synthetic compounds. The primary component is the explosive, 1,2-propylene glycol dinitrate (PGDN) (approximately 75%); dibutyl sebacate (23%) is added as a desensitizer, and because pure PGDN is unstable, 2-nitrodiphenylamine (2%) is added as a stabilizer (ATSDR 1995). PGDN, a nitrated ester, is a volatile liquid with a disagreeable odor. Its primary use is as a propellant in Otto Fuel II (Forman 1988). No information on production was located. Wiltshire Chemical Company in Gardena, California, was the only identified producer (ATSDR 1995).

Neither Otto Fuel II nor its components are highly acutely toxic, as indicated by oral toxicity data. The oral LD_{50} for Otto Fuel II in male HA/ICR mice was 1.6 mL/kg (2.24 g/kg) (Litton Bionetics 1979). For PGDN, oral LD_{50} values for the rat ranged from 0.25–1.19 g/kg (Clark and Litchfield 1969; Jones et al. 1972; Andersen and Mehl 1979). About 10% of topically applied PGDN is absorbed through the skin (Clark and Litchfield 1967). Dibutyl sebacate, a food flavoring agent and plasticizer, has a very low acute oral toxicity; the oral no-effect level for lethality was 16 g/kg in the rat (Bisesi 1994). The low vapor pressure of 3 mm Hg at 180°C severely limits its risk as an inhalation hazard. ATSDR (1995) reported an oral LD_{50} value for 2-nitrodiphenylamine in rats of 6.15 g/kg. In addition to its use in Otto Fuel II, 2-nitrodiphenylamine is an orange-colored solvent dye (Sudan yellow 1339) with a low vapor pressure of 1×10^{-5} mm Hg at 25°C (Baughman and Perenich 1988; ATSDR 1995).

TABLE 2–1 Summary of AEGL Values for PGDN (Otto Fuel II) (ppm [mg/m3])

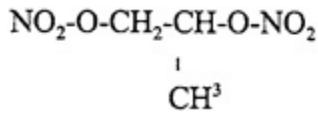
Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (Nondisabling)	0.33 (2.3)	0.33 (2.3)	0.17 (1.1)	0.05 (0.34)	0.03 (0.17)	Mild headaches in humans (Stewart et al. 1974)
AEGL-2 (Disabling)	2.0 (14)	2.0 (14)	1.0 (6.8)	0.25 (1.7)	0.13 (0.8)	Severe headaches and slight unbalance in humans (Stewart et al. 1974)
AEGL-3 (Lethal)	16 (114)	16 (114)	13 (93)	8.0 (57)	5.3 (38)	Convulsions in monkeys (Jones et al. 1972)

[a]The distinctive odor of PGDN will be noticeable to most individuals at the 0.33 and 0.17 ppm concentrations.

The vapor pressures of the three components of Otto Fuel II differ considerably. During vapor generation studies with Otto Fuel II, PGDN was the only component vaporized into inhalation exposure chambers in sufficient quantity to allow direct analysis (Stewart et al. 1974; MacEwen and Vernot 1982). In light of the low toxicity of dibutyl sebacate and 2-nitrodiphenylamine and the fact that they do not vaporize to a detectable extent at test compound generation temperatures up to 45°C, the toxicity of Otto Fuel II has been evaluated in terms of PGDN. Chemical and physical data for PGDN are listed in Table 2–2.

At low concentrations, PGDN has been reported to cause cardiovascular, irritant, and central nervous system effects including headaches, nasal congestion, eye irritation, and dizziness in humans (Stewart et al. 1974; Hovath et al. 1981). In animal studies that used higher concentrations, methemo-globinemia occurred (Jones et al. 1972). The acute and subchronic effects of PGDN were studied in monkeys, dogs, rats, and guinea pigs. Several studies with humans as well as with monkeys and rats addressed neurotoxicity. The air-odor threshold in healthy subjects is 0.2 ppm, but warning properties are poor inasmuch as olfactory fatigue sets in after as little as 5 min (Stewart et al. 1974).

TABLE 2–2 Chemical and Physical Data[a]

Parameter	Value	Reference
Synonyms (PGDN)	1,2-Propylene glycol dinitrate; propylene glycol dinitrate; 1,2-propanediol, dinitrate; propylene dinitrate; isopropylene nitrate; methynitroglycol	ATSDR 1995
Chemical formula	$C_3H_6N_2O_6$	Gingell et al. 1994
Structure		ATSDR 1995
Molecular weight	166	Gingell et al. 1994
CAS registry number	6423–43–4 (PGDN) 106602–80–6 (Otto Fuel II)	ATSDR 1995
Physical state	Liquid	ATSDR 1995
Color	Colorless (PGDN) red-orange (Otto Fuel II)	ACGIH 1991 Gaworski et al. 1985
Solubility in water	1.3 g/L	ACGIH 1991
Vapor pressure (25°C)	0.087 mm Hg	Gaworski et al. 1985
Vapor density (air=1)	No data	
Liquid density (water=1)	1.4	Gingell et al. 1994
Melting point	No data	
Boiling point	92°C Decomposes above 121°C	Gingell et al. 1994 Gaworski et al. 1985
Odor	Disagreeable (PGDN) Distinctive (Otto Fuel II)	ACGIH 1991 Gaworski et al. 1985
Conversion factors	1 ppm=7.14mg/m^3 1 mg/m^3=0.14 ppm	ATSDR 1995

[a]Data are for propylene glycol dinitrate (PGDN) unless specified otherwise.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although sudden deaths due to circulatory failure have been reported among workers exposed chronically to nitrated esters such as nitroglycerin and ethylene glycol dinitrate (Carmichael and Lieben 1963), no deaths attributable to cardiovascular effects were reported for U.S. Navy personnel involved in torpedo maintenance work (Horvath et al. 1981; Forman et al. 1987). The sudden deaths for workers in the explosives industry were attributed to a compensatory vasospasm that may produce coronary insufficiency upon withdrawal from nitrate ester exposure.

2.2. Nonlethal Toxicity

2.2.1. Occupational Exposures

Horvath et al. (1981) evaluated the neurophysiologic effects of acute and chronic exposure to PGDN of 87 workers employed in U.S. Navy torpedo facilities. Prior to the evaluation, the subjects reported subjective symptoms of frequent or occasional headaches (65% of respondents), nasal congestion (31%), eye irritation (26%), and dizziness (13%). Palpitations, dyspnea, chest pain, and loss of balance were reported by small percentages of workers. For the chronic exposure, evaluation of the workers included both quantitative oculomotor functions (saccades or synchronized eye tracking movements) and ataxia tests; comparison was made with a control group consisting of 21 nonexposed personnel from the same facilities. Results of the tests indicated no evidence of chronic neurotoxicity in either the study population or a subgroup of 28 workers with the longest exposure to PGDN.

In the same study (Horvath et al. 1981), acute effects were evaluated in a subgroup of 29 workers by comparing test values before and after a torpedo maintenance procedure, or "turnaround." The maintenance procedures lasted 30–60 min. During this time, PGDN concentrations, as indicated by approximately 400 grab samples (instantaneous atmospheric samples) taken in the work area, ranged from 0.00 to 0.22 ppm (average value of 0.06 ppm; 88% were $\leq$0.1 ppm, 50% were $\leq$0.05 ppm, and only one sample was above the ACGIH TLV-Ceiling value of 0.2 ppm, which was in effect at that time).

There were no decrements in the three ataxia tests (although the mean score in one test was increased), but mean saccade velocity was statistically significantly decreased (by 37.3 degrees per second [s]), and mean saccade delay time was statistically significantly increased (by 6.4 milliseconds). There were no changes in saccade accuracy or (eye) smooth pursuit index. The changes in the saccade test parameters did not correlate with peak PGDN levels measured during the turnaround procedure. The workers involved in the turnaround did not complain of headache or nasal congestion, although one individual involved in a spill developed a headache.

Forman et al. (1987) (see also Helmkamp et al. [1984] for preliminary study) evaluated cardiac morbidity among U.S. Navy "torpedoman's mates," a group potentially exposed to PGDN while engaged in torpedo maintenance work. Cardiovascular events in this group were compared with both a nonexposed group of torpedomen and a nonexposed group in the job category "fire control technician". The torpedoman's mate group consisted of 1,352 men, with an average yearly population of 822; hospitalization records were available for 1970 through 1979. The nonexposed-torpedomen control group consisted of 14,336 individuals over the 10-y period with a yearly average of 4,906. The fire control technician control group consisted of 29,129 individuals with a yearly average of 11,198. Measured concentrations of PGDN included those of the Horvath et al. (1981) study and current surveys in which 8-h time-weighted averages were below 0.05 ppm. Cardiac incidences considered were myocardial infarction, angina pectoris, and cardiac arrhythmia. Age-adjusted incidence rates and relative risk were calculated for each group. There were higher incidences of hospitalizations for myocardial infarctions and angina pectoris but not cardiac arrhythmias in the torpedoman's mates than in either control group. Relative risk was significant for myocardial infarction and angina pectoris when compared with the torpedoman control group (2.6 and 3.8, respectively; $p<0.05$) but not when compared with the fire control technicians. When incidences of myocardial infarction and angina pectoris were combined, relative risk was significant when compared with both the unexposed torpedoman and fire control technician control groups (2.6 and 2.9, respectively; $p<0.05$). Deaths attributable to cardiovascular events occurred in the control groups but not in the torpedoman's mate group. The authors discuss biases in the study, including the healthy worker syndrome and the small number of actual hospitalizations. For example, only four hospitalizations for myocardial infarction and two hospitalizations for angina pectoris occurred in the torpedoman's mates group over the 10-y period.

2.2.2. Experimental Studies

Stewart et al. (1974) exposed human volunteers to PGDN in a controlled environment chamber. "Each group underwent a training program in the chamber. The experiments were conducted in a double-blind mode. However, in those experiments in which the odor of PGDN was detectable, both the subjects and the research staff were aware that exposure to PGDN was occurring, although the magnitude of the exposure was not disclosed to them." Exposure concentrations were 0.0 (control), 0.03, 0.1, 0.2 (range, 0.21–0.26), 0.35 (range, 0.33–0.37), 0.5, or 1.5 (1.2 and 1.5) ppm, and exposures lasted from 1 to 8 h. The exposures at 0.2 ppm were repeated on a daily basis for 5 d. Selected exposure concentrations, exposure durations, and the number of subjects tested are summarized in Table 2–3. Seventeen healthy male subjects (ages 22–25), usually in groups of three, participated in the exposures. In addition, one of the exposures (to 0.5 ppm) included two male members of the research staff, ages 45 and 51, and a 24-y-old female for a total of 20 subjects.

PGDN was generated from a sample of Otto Fuel II by blowing air across a Pyrex reservoir of the compound to the return air duct of the air conditioner. Eighty percent of the air was recirculated. The concentration of PGDN in the air was monitored continuously by an infrared spectrophotometer and by a gas chromatograph fitted with an electron capture detector. The vaporized Otto Fuel II was 99% pure PGDN as measured by infrared analysis.

Testing of the subjects consisted of both subjective evaluations and physiological and central nervous system responses observed under medical supervision. The lowest concentration at which odor was detected was 0.2 ppm (four of nine subjects), but the ability to detect the odor disappeared within 5 min. Subjective symptoms consisted of headache and eye irritation. At 0.1 ppm, two of the subjects experienced mild headache (Table 2–3). One of these subjects had developed headache during each of the control exposures and during the exposure at 0.03 ppm. The other subject developed headache after 6 h, and the headache continued for several hours postexposure.

Of the nine subjects exposed at 0.21–0.26 ppm (18 exposures; all nine subjects took part in the 8-h exposures, and three of the nine were exposed for 8 h on two separate occasions), seven developed headaches of varying intensity. The headaches were mild in intensity for two of three subjects during the 2-h exposure. During the twelve 8-h exposures, there were five incidences of mild headache and six incidences of severe headache. The number of subjects in each category of headache could not be ascertained from the data. The

TABLE 2–3 Human Responses to PGDN

	0.0 ppm	0.03 ppm			0.1 ppm			0.21–0.26 ppm			0.35 ppm			0.5 ppm			1.5 ppm	
	1–8 h	1 h	4 h	8 h	1 h	4 h	8 h	1 h	2 h	8 h	1 h	2 h	8 h	1 h	2 h	7.3 h	1 h	3.2 h
Number of subjects	2–6[a]	2	3	3	2	3	3	3	3	9[b]	3	3	3	3	3	3	2	6
Number detecting odor	0	0	0	0	0	0	0	2	3	2	1	2	2	1	1	2	2	6
Number developing mild headache	1	0	1[c]	0	0	1[c]	1	0	2	5	0	3	1	1	2	0	0	0
Number developing severe headache	0	0	0	0	0	0	0	0	0	6	0	0	2	0	1	3	2	6
Number developing eye irritation	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	2	6

[a]Groups of eight and nine male subjects participated in a series of 4-h training sessions and all 17 male subjects, in groups of two to six, participated in a series of control exposures lasting from 1 to 8 h.

[b]Nine subjects participated in 12 exposures; numbers in column immediately below refer to incidences per 12 exposures rather than individuals.

[c]This individual developed a mild headache during each of the control exposures.

Source: Modified from Stewart et al. (1974).

visual evoked response (VER), a complex waveform representing the summed electrical activity of many neurons, was minimally altered in the majority of subjects but with no consistent pattern of response. No decrements in test performance or alterations in monitored physiological parameters occurred at this concentration. Subjects repeatedly exposed to this concentration developed tolerance to the induction of headache, but the alteration in visual evoked response morphology appeared cumulative.

At 0.35 ppm, all three subjects exposed for 2 h developed mild headaches, and one of three subjects exposed for 8 h developed a mild headache. Two of three subjects exposed for 8 h developed severe headaches. One subject also developed slight eye irritation, which persisted throughout the 2 h exposure. Four of the nine subjects detected the odor of the compound, which they described as mild at this concentration; however, the odor was not detectable after 5 min of exposure. The morphology of the visual evoked response, while variable, was altered, particularly in three subjects exposed for 8 h. The exposure produced an increase in the peak-to-peak amplitude of the 3–4–5 wave complex. The authors interpreted the VER changes as consistent with the VER changes produced by central nervous system depression.

Groups of three subjects were exposed at 0.5 ppm for time periods of 1, 2, or 7.3 h. Seven of the nine subjects developed headaches during these exposures, beginning with a mild headache after 1 h of exposure (Table 2–3). After exposure for 6.25 h, balance became impaired in two of three subjects (heel-to-toe test with eyes closed), and at 7.3 h, all three subjects had abnormal modified Romberg tests (postural stability with the eyes closed) as well as abnormal heel-to-toe tests with their eyes closed. One subject was unable to perform a normal heel-to-toe test with his eyes open. The authors compared the equilibrium disturbance with ethanol intoxication, which produced a blood alcohol concentration in the 100–150 mg/100 mL range. These three subjects also had a mean elevation of diastolic blood pressure of 12 mm Hg, which was not accompanied by alterations in pulse or cardiac rhythm. Headaches became increasingly severe and throbbing for all three subjects during exposure, and one of the three subjects reported dizziness and nausea after 6 h of exposure. Three members of the research staff, two males and one female, were exposed at this concentration for a period of 1.25 h and all developed a mild headache. These latter three exposures appear to be in addition to that of the nine subjects described above.

All eight subjects exposed at 1.5 ppm reported eye irritation (without conjunctivitis or excessive lacrimation) after 40 min of exposure. All of the subjects developed severe headaches, three after 30 min of exposure and the remaining five after 40–90 min of exposure. Headaches became so severe that

exposure was terminated after 3.2 h. Headaches persisted for 1 to 7.5 h after exposure. These subjects showed a dramatic alteration in the VER with an increased amplitude in the peak-to-peak voltage of one of the wave complexes. There was a shift to control values after 160–180 min of exposure, but VER were altered for 48 h after exposure.

None of the exposures produced changes in clinical chemistry values (blood count, blood nitrate, blood urea nitrogen, serum enzymes, and serum electrolytes or urinalysis and nitrate and nitrite urinary excretion), spontaneous electrical activity of the cortex of the brain (detected by EEG), pulse rate and sinus rhythm, or pulmonary function. Visual and auditory acuity, exercise EKG, and time estimation tests did not differ from control values for any of the exposures. Only one of several cognitive tests was affected by exposure and the change occurred only in the four subjects exposed at 1.5 ppm. The test was taken during the time the subjects were experiencing severe headaches.

2.3. Neurotoxicity

Torpedo maintenance workers exposed to PGDN at concentrations of 0– 0.22 ppm (average of approximately 0.06 ppm) for 30–60 min exhibited significantly altered responses in some oculomotor performance tests but no statistically significant decrement in balance (see Section 2.2.1 for further details) (Horvath et al. 1981). The oculomotor function changes observed in workers after acute exposures to Otto Fuel II were not observed in chronically exposed workers. Eight-hour time-weighted average (TWA) concentrations during chronic exposures Were below 0.05 ppm (Forman et al. 1987).

Human volunteers exposed to PGDN at various concentrations of also exhibited central nervous system effects (Stewart et al. 1974). At 0.35 ppm, the VER was altered, particularly at 8 h. This effect became more pronounced at 0.5 ppm and 1.5 ppm, after 45–90 min at the latter concentration. After 6.25 h of exposure at 0.5 ppm, two subjects had abnormal heel-to-toe balance tests with their eyes closed, and after 8 h, all three subjects had abnormal modified Romberg tests as well as abnormal heel-to-toe tests with eyes closed. At this time, one subject was unable to perform the heel-to-toe test with open eyes.

2.4. Developmental and Reproductive Effects

The Naval Health Research Center investigated pregnancy outcomes of

women engaged in torpedo repair work and compared their spontaneous abortion rate with three other groups: unexposed female torpedomen munitions workers, hospital corpsmen, and other uniformed U.S. Navy enlisted females (NHRC 1986). During the years of the study, 1980–1983, there were no spontaneous abortions among the five PGDN-exposed pregnant women.

2.5. Genotoxicity

No studies were located regarding genotoxic effects in humans exposed to PGDN or Otto Fuel II

2.6. Carcinogenicity

No studies were located regarding Carcinogenicity in humans exposed to PGDN or Otto Fuel II.

2.7. Summary

No deaths attributable to exposure to Otto Fuel II or its primary component, PGDN, were reported in the available literature, but relative risk for combined myocardial infarction and angina pectoris among torpedomen chronically exposed at unknown concentrations of Otto Fuel II and PGDN were significantly elevated compared with control groups (Forman et al. 1987). The number of subjects hospitalized with these cardiovascular events was small. Symptoms described during occupational exposures included headaches, nasal congestion, eye irritation, and dizziness (Horvath et al. 1981). Acute exposures to an average concentration of approximately 0.06 ppm resulted in no effects on motor coordination and only subtle changes in eye movements. There were no spontaneous abortions among five PGDN-exposed female U.S. Navy personnel. No information on genotoxicity or Carcinogenicity in humans was located.

PGDN has effects on the cardiovascular and central nervous systems. Exposure of healthy, primarily male subjects to PGDN at a concentration of 0.03 ppm for 8 h was without adverse effects. A mild headache was present in one of three subjects after exposure at 0.1 ppm for 6 h. Adverse effects became more severe at higher concentrations and shorter exposure durations: 0.2 ppm for 8 h produced severe headache in six of 12 exposures; 0.35 ppm for 8 h produced severe headache in two of three subjects and disturbance of

the VER in three of three subjects; 0.5 ppm resulted in severe headache in one of three subjects after 2 h and produced impairment of balance after 6.25 h and ataxia at 7.3 h; 1.5 ppm for 3.2 h produced throbbing and painful headaches in six of six subjects accompanied by some abnormal cognitive and coordination tests. Nonincapacitating eye irritation was also reported during the exposures at 1.5 ppm

Based on the Stewart et al. (1974) study, the threshold for odor detection in healthy adults is 0.2 ppm, and the threshold for eye irritation is 1.5 ppm, although one of three subjects developed eye irritation during a 2-h exposure at 0.35 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

No acute studies involving lethality and the exposure durations relevant to AEGL derivations were located. Jones et al. (1972) reported deaths in preliminary, range-finding studies in which single animals were exposed to PGDN. Because pure PGDN is chemically unstable, a physiologically and chemically inert stabilizer of low volatility was added. Exposure concentrations are based on the PGDN concentration of the mixture. One rabbit that was exposed to PGDN mist at a mean concentration of 240 mg/m^3 (34 ppm) for 23 h/d died on day 4. The rabbit became cyanotic on day 4 and died with a methemoglobin value of 32.8%. A squirrel monkey exposed at 415 mg/m^3 (approximately 60 ppm) for 23 h/d died on day 3 and had a methemoglobin level of 40.2%. In a continuous inhalation study by the same authors (Jones et al. 1972), one of nine squirrel monkeys exposed at 236 mg/m^3 (33 ppm) died on day 31 of exposure. Adult filarial parasites in the abdominal cavities of a majority of the monkeys were the only gross abnormality observed at autopsy. No further details on the deaths were available. However, these and other authors (Clark and Litchfield 1969; Andersen and Mehl 1973) attribute deaths to methemoglobinemia and the resulting anoxia. Rats treated with lethal doses of PGDN (either oral or subcutaneous) were ataxic and lethargic with signs of methemoglobinemia and respiratory depression (Clark and Litchfield 1969). Death consistent with anoxia occurred up to 48 h after administration.

TABLE 2–4 Summary of Acute Sublethal Effects in Animals

Species	Concentration	Exposure Duration	Effect	Reference
Monkey	70–100 ppm	6 h	Vomiting, pallor, cold extremities, semiconscousness, clonic convulsions	Jones et al. 1972
Rat	189 ppm	4 h	No toxic signs	Jones et al. 1972

3.2. Nonlethal Toxicity

Acute studies are summarized in Table 2–4. These studies and effects following longer-term exposures are described in the following text.

3.2.1. Nonhuman Primates

In a range-finding study prior to a continuous inhalation study, squirrel monkeys (number not specified) exposed at 500–700 mg/m^3 (70–100 ppm) PGDN for 6 h developed vomiting, pallor, cold extremities, semiconsciousness and clonic convulsions (Jones et al. 1972). These signs disappeared within 30–45 min after removal from the exposure chambers. In a follow-up study by the same authors (Jones et al. 1972), groups of three male squirrel monkeys were exposed to PGDN at concentrations of 67, 108, or 236 mg/m^3 (approximately 10, 15, or 33 ppm) continuously, 24 h/d, for 90 d. Groups of three monkeys served as control groups for each exposure. PGDN was generated from heated flasks over which pre-dried air was drawn into a dilution air stream upstream of the exposure chambers. The chamber air was sampled and monitored by a modified diphenylamine color analysis for nitrates; the concentrations were similar to nominal inputs determined gravimetrically. Hematology parameters were measured prior to and after exposure; methemoglobin was measured weekly during the exposure to 33 ppm. Although one monkey died on day 31 of exposure at 33 ppm (possibly complicated by a parasitic infection; see Section 3.1), these animals did not show signs of intoxication during the exposures, and body weight gains of surviving

animals were normal. Fatty infiltration was present in the liver of monkeys exposed at 10 ppm. Heavy iron-positive deposits consistent with mononuclear cell infiltrates and focal necrosis were present in the liver, spleen, and kidney sections of monkeys exposed at 33 ppm. Monkeys exposed at 15 and 33 ppm also had elevated serum urea nitrogen levels and decreased serum alkaline phosphatase activity. In monkeys exposed at 33 ppm, methemoglobin levels increased to 17% by day 14, declining by day 42 to approximate control levels.

3.2.2. Dogs

Groups of two male beagle dogs were exposed to PGDN at concentrations of 67, 108, or 236 mg/m^3 (approximately 10, 15, or 33 ppm) continuously, 24 h/d, for 90 d (Jones et al. 1972). Six dogs (two per exposure) served as control groups. PGDN was generated as in the study with monkeys. All dogs gained weight at a normal rate, but hemoglobin and hematocrit were decreased by 63% and 37% in the two dogs in the 33-ppm exposure group. Livers showed dose-related changes, including hemosiderin deposits in the 10-ppm group, hemosiderin deposits and fatty changes in the 15-ppm group, and heavy hemosiderin deposits accompanied by focal necrosis in the 33-ppm group. The 33-ppm exposure group also had iron-positive deposits in the spleen and kidneys. The methemoglobin level reached 23% on day 14 of exposure at 33 ppm and declined thereafter but did not return to control values.

3.2.3. Rats

Six rats (strain unidentified) were exposed for 4 h to a mist of PGDN at a concentration of 1,350 mg/m^3 (189 ppm) (Jones et al. 1972). No toxic signs were noted during the exposure or within the 14 d postexposure period. The mean methemoglobin level immediately postexposure was 23.5%. In repeated inhalation studies by the same authors, eight male Sprague-Dawley derived rats were exposed at a concentration of 65 mg/m^3 (approximately 10 ppm) for 7 h/d, 5 d/week (wk), for a total of 30 exposures. No mortalities or clinical signs of intoxication were observed. All rats gained weight at a normal rate, hematology values remained normal, and histopathological examinations of major organs failed to reveal any effects.

Jones et al. (1972) also exposed 15 Sprague-Dawley-derived rats of both genders to PGDN at concentrations of approximately 10, 15, or 33 ppm con

tinuously, 24 h/d, for 90 d. An additional group of 15 rats served as a control group and were treated the same as the exposed groups except for the addition of PGDN to the exposure chamber. Fatty deposits were observed in the livers of rats exposed at 10 ppm, and female rats exposed at 33 ppm showed focal necrosis of the liver and acute tubular necrosis of the kidneys. Male rats appeared normal. Methemoglobin levels of two rats exposed at 33 ppm were elevated to 12.8% by day 14 but decreased with continued exposure.

3.2.4. Guinea pigs

Groups of 15 Hartley-derived guinea pigs were exposed to PGDN at concentrations of approximately 10, 15, or 33 ppm continuously, 24 h/d, for 90 d (Jones et al. 1972). A concurrent control group of 15 animals was placed in an exposure chamber without the addition of PGDN. Fatty deposits were observed in the livers of guinea pigs exposed at 10 ppm. Guinea pigs exposed at 15 ppm consistently showed foci of pulmonary hemorrhage, and vacuolar changes occurred in the liver of all guinea pigs exposed at 33 ppm.

3.3. Neurotoxicity

Two male rhesus monkeys trained in free operant avoidance tests were exposed to PGDN at concentrations of 2–33 ppm and observed for successful completion of the avoidance test and VER (Mattsson et al. 1981). The avoidance test involved response to a red light by operating a lever within 10 s of the light cue in order to avoid an electrical shock. For the VER, the A-B-C complex, comparable to the 3–4–5 complex in the Stewart et al. (1974) study, was measured in response to flashes from a strobe light. The monkeys were tested individually, each at several concentrations, which were separated by a 1-wk interval. One monkey was exposed at 2 ppm three times and also at 7 and 20 ppm. The other monkey was exposed at 3, 10, and 33 ppm. Exposure durations were 4 h. Halothane at one-tenth of the concentration that produces anesthesia in monkeys served as a reference depressant. Free operant behavior was not affected by any PGDN concentration, but the VER was statistically significantly altered by exposure to PGDN ($p<0.05$). The C wave increased 20% in amplitude at 2 ppm and decreased 25% at higher concentrations; there were no changes in amplitude of the A and B waves or in the latency of the waveforms. No changes occurred in one of three trials at 2 ppm and in the trial at 10 ppm. During the course of the training, the au

thors found that the C wave could be increased or decreased by 30% to 40% by changes in the environment or a change in the tension of the operant response lever tension, and therefore the authors suggested that the changes observed during the exposures might have been caused by the irritating or distracting properties of the vapor. Halothane produced significant increases in the A, B, and C waves and slowed the latency of the B and C waves but did not change free operant avoidance behavior.

In longer-term exposures, two rhesus monkeys were exposed to PGDN vapors for 125 d at concentrations that were increased in increments from 0.3 to 4.2 ppm (Mattsson et al. 1981). Two monkeys served as controls. Daily testing involving either the cued or free operant avoidance tests showed no effects on either type of avoidance performance, and there was no disruption of the ability to discriminate between the two avoidance schedules.

Three male squirrel monkeys previously trained to perform visual discrimination or visual acuity threshold tests were exposed continuously for 90 d to PGDN at a concentration of 262 mg/m^3 (approximately 37 ppm) (Jones et al. 1972). The animals were removed from the exposure chambers for a 2-h period once a week for the respective behavior tests. A fourth trained monkey exposed to filtered room air under the same conditions served as the control. The only sign during exposure was mydriasis (excessive dilatation of the pupil of the eye), which increased from slight to moderate. There were no changes in avoidance behavior in the monkeys as determined by the visual tests.

Groups of 13–14 anesthetized male Sprague-Dawley rats that had previously been trained on the accelerod, a test of motor performance, were injected with saline (control) or 5 or 10 μL of PGDN (0.01 or 0.02 μL/kg; approximately 0.007 or 0.014 μg/kg) directly into the cisterna magna of the brain (Bogo et al. 1987). Motor performance was tested 12 min after injection, hourly for 6 h, and at 24 h in rats that had not been grossly traumatized by the injection procedure. Compared with the control group, no change in motor performance was observed in rats injected with 5 μL of PGDN. A significant decrease in motor performance was observed during the first 2 h in rats injected with 10 μL. The authors suggest that this study confirms the observations of PGDN-induced changes in human motor performance.

3.4. Developmental and Reproductive Effects

Groups of 28 or 47 (high-dose) pregnant Crl:CD BR rats were treated dermally with neat Otto Fuel II at doses of 0, 400, 2,000, or 4,000 mg/kg/d beginning on day 5 of pregnancy (Cooper et al. 1993). On day 20 of preg

nancy the dams were euthanized and the total number of fetuses, corpora lutea, implantation sites, and resorption sites were recorded. Fetuses were examined for grossly visible abnormalities. Half of the fetuses were examined for soft tissue abnormalities, and half of the fetuses were examined for skeletal deformities. The highest dose was toxic, resulting in a maternal mortality of 53% and significantly lower body weights of surviving dams and fetuses; fetal resorptions per dam were increased and viable fetuses and fetuses per dam were significantly decreased in this group (all, $p<0.05$). Dams receiving 4 g/kg/d displayed a moderate erythema of the skin in the area exposed to the fuel. Body weights of dams and fetuses were also significantly reduced in the group receiving 2 g/kg/d. No other parameters were affected in the 2 g/kg/d groups, and none of the measured parameters were altered in the 400 mg/kg/d group. There was no evidence of terata erythema at any concentration.

In the same study (Cooper et al. 1993), pregnant New Zealand white rabbits were dermally treated with neat Otto Fuel II at a rate of 0, 100, 316, or 1 g/kg/d on days 6–18 of pregnancy. Although body weights of dams treated with 1 g/kg/d lagged behind the other groups on days 20 and 25 of pregnancy, no differences were present at sacrifice on day 28 of pregnancy. The number of corpora lutea, implantation sites, and resorption sites and fetal body weights did not differ significantly between treated and control groups. There was no evidence of terata. Marked erythema of the skin in the area of application was observed in the group treated with 1 g/kg/d.

Dibutyl sebacate was tested for reproductive toxicity in a dietary study with Sprague-Dawley rats: 6.25% (approximately 5.6 g/kg/d) in the diet for 10 wk prior to breeding (Smith 1953). No effect on fertility, litter size, or pup survival was found. However, pups from treated dams weighed less than pups from the control group.

3.5. Genotoxicity

The genotoxicity of Otto Fuel II was evaluated in a series of assays conducted by Litton Bionetics (1979). Otto Fuel II was not mutagenic in microbial assays involving five strains of *Salmonella typhimurium* or in *Saccharomyces cerevisiae* D4, with or without exogenous metabolic activation. The test compound was active in inducing mutations at the TK locus in L5178Y mouse lymphoma cells at concentrations that were clearly cytotoxic. Otto Fuel II failed to induce sister chromatid exchanges in the same cell line, either with or without metabolic activation. In the mouse bone marrow cytogenetic analysis, the test compound was administered acutely and

subchronically (five doses). Chromosomal aberrations were not elevated compared with the control values, but the presence of ring chromosomes suggested weak activity. Otto Fuel II was not active in the dominant lethal assay with mice.

3.6. Chronic Toxicity and Carcinogenicity

Fischer 344 rats and C57BL/6 mice were exposed to vaporized Otto Fuel II at concentrations of 0, 1.4, or 240 mg/m^3 (0 and approximately 0.20 or 34 ppm) for 6 h/d, 5 d/wk for 1 y, and purebred beagle dogs were exposed at 0 or 0.20 ppm for 6 h/d, 5 d/wk for 14 months (mo) (MacEwen and Vernot 1982; Gaworski et al. 1985). For both rats and mice, groups of 100 males and 100 females were exposed at the 0- and 34-ppm concentrations and 75 animals per gender were studied at the 0.20-ppm concentration. For dogs, the exposure groups consisted of three males and three females. Separate generation systems were used for the exposures, but atmospheres were generated in a similar manner by heating the fuel and passing the vapor into the exposure chambers with a controlled air sweep. The lower concentration was monitored with an infrared analyzer; the higher concentration was monitored with a gas chromatograph. Ten male and ten female rodents from each exposure group were sacrificed at 1 y after initiation of exposures. The remaining rodents were held for 1 y postexposure. The dogs exposed at 0.20 ppm were exposed for an additional 60 d for a total of 14 mo, at which time they were necropsied. During the study, animals were weighed and monitored for hematology and clinical chemistry changes. Gross and histological examinations of all lesions and major tissues and organs were performed.

For rats, differences in the examined parameters among exposure groups were minor and generally did not reflect a dose-response relationship. Only very slight pulmonary inflammatory changes were present in the treated groups compared with the control group. Bone tumors, three osteosarcomas (male rats, one in the 0.2-ppm group and two in the 34-ppm group) and one osteoma (female rat, 0.2-ppm group) were observed in the treated rats, whereas none were observed in the concurrent control groups. These are rare tumors and could be indicative of a tumorigenic response; however, the lack of a dose-response relationship, particularly with the large differences in treatment concentrations, suggests that the tumors were not treatment related.

No remarkable changes or lesions were present in treated mice at either the end of exposure or at terminal sacrifice compared with the control groups.

In fact, lesions such as ulcerative dermatitis were generally more prevalent in the control mice than in the treated mice.

Although dogs exposed to an atmosphere containing 0.20 ppm of Otto Fuel II had slightly decreased hematocrit and hemoglobin values and increased methemoglobin levels (<5%) and liver weights relative to body weight compared with controls, there were no overt signs of toxicity and no increased incidences of tumors. As noted, these parameters were either not affected or affected to a lesser degree in mice and rats.

In a chronic toxicity study, groups of 20 male and female Sprague-Dawley rats were administered a diet containing 6.25% dibutyl sebacate (Smith 1953). The dose ranged between 2.5 and 7.2 g/kg/d over the course of the study. This concentration did not affect growth or survival. No gross or histopathological changes attributable to treatment were observed.

3.7. Summary

No data on lethality following acute exposures of ≤1 day were available. Squirrel monkeys exposed to PGDN at concentrations of 70–100 ppm for 6 h exhibited vomiting, pallor, cold extremities, semiconsciousness, and clonic convulsions. Rats exposed at 189 ppm for 4 h exhibited no overt signs of intoxication, although the mean methemoglobin level was increased to 23.5% (Jones et al. 1972).

In neurotoxicity studies with PGDN, 4-h exposures of rhesus monkeys at 2–33 ppm (Mattsson et al. 1981) and continuous exposures of squirrel monkeys at 37 ppm (Jones et al. 1972) did not change trained avoidance behavior, although the VER was significantly altered (increase in the C-wave amplitude) in the rhesus monkeys exposed at 2 ppm for 4 h. Increases in the same wave were observed in humans exposed at 0.35 to 1.5 ppm (Stewart et al. 1974). The VER changes are subclinical disruptions of the extraocular motor system and are not functionally significant. The VER changes were very minimal and were not reflected in the cognitive abilities of humans exposed at 1.5 ppm for 3 h. The cued avoidance and free operant avoidance of monkeys exposed at 2–33 ppm for 6 h were unchanged.

When applied dermally to rats and rabbits, PGDN was not teratogenic and showed no evidence as a reproductive and developmental toxicant at doses that were less than maternally toxic (Cooper et al. 1993). In rats, lower fetal weights reflected the lower body weights of surviving dams.

In a battery of mutagenicity and genotoxicity studies, PGDN tested negative except in L5178Y mouse lymphoma cells where it induced mutations at

concentrations that were cytotoxic (Litton Bionetics 1979). There were no clear treatment-related increases in tumors in rats or mice exposed to vaporized Otto Fuel II at concentrations of 0, 0.20, or 34 ppm for 1 y or in beagle dogs exposed at 0.20 ppm for 14 mo (MacEwen and Vernot 1982; Gaworski et al. 1985).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Absorption of PGDN during inhalation occurs in humans, as evidenced by symptoms of headache and changes in blood pressure. During exposures of human subjects at 1.5 ppm for 3.2 h, the circulating concentration was less than 5 ppb (the analytical limit of detection). After 1 h of exposure at 1.5 ppm, the expired breath of the subjects contained 20–35 ppb; no PGDN was detected in the breath 15 min after exposure (Stewart et al. 1974). Dermal absorption also occurs, as evidenced by deaths of rabbits with elevated methemoglobin and urinary nitrogen levels following repeated applications of 4 g/kg (Jones et al. 1972). About 10% of topically applied PGDN is absorbed through the intact skin of rats, as indicated by blood pressure changes relative to subcutaneous injections (Clark and Litchfield 1969).

Plasma levels of PGDN of rhesus monkeys could not be detected during inhalation exposures at concentrations ≤0.8 ppm (Mattsson et al. 1981). Plasma PGDN was approximately 35 μg/mL during 20 d of exposure at 1.6 ppm and 170 μg/mL during 14 d of exposure at 4.2 ppm. Plasma PGDN was not detectable within 24 h of termination of exposure.

Metabolism of PGDN is rapid and follows first order kinetics (Kylin et al. 1964). Metabolism occurs in the liver and within the erythrocyte, resulting in mononitrates and inorganic nitrate; the latter is eliminated in the urine. Clark and Litchfield (1969) studied the metabolism of PGDN in Alderley Park rats in vitro and in vivo following a subcutaneous injection of 65 mg/kg. Blood PGDN, the mononitrates, and blood inorganic nitrite and nitrate were measured at various times after incubation or administration. In vitro metabolism took place in the erythrocytes yielding primarily propylene glycol 2-mononitrate and inorganic nitrate by 3 h; the remainder was propylene glycol 1-mononitrate and unmetabolized PGDN. Fifty percent of the 50 μg/mL dose was metabolized in the first hour and 50% of the remainder in the next hour.

Following subcutaneous injection, circulating PGDN peaked within 1 h and then declined to an undetectable level by 8–12 h postinjection. The 2-

mononitrate was the predominant isomer in blood and the time course of metabolism was similar to that of the in vitro experiment. The major metabolite in urine was inorganic nitrate, accounting for 56% of the administered dose. Parent PGDN and nitrite were almost undetectable in urine. Excretion was complete at 24 h. The following metabolic scheme was proposed: reduction of a nitrate group to yield an unstable organic nitrite-nitrate intermediate followed by hydrolysis to yield the mononitrate and inorganic nitrite. The inorganic nitrite in the blood is oxidized to inorganic nitrate, which is excreted in the urine.

4.2. Mechanisms of Toxicity

PGDN has effects on both the cardiovascular and central nervous systems. The most commonly encountered symptom of exposure to PGDN is headache due to vasodilation of cerebral blood vessels. Nitrate and nitrite esters are vasodilators, resulting in rapid lowering of systolic and, to a lesser extent, diastolic blood pressure with a compensatory tachycardia. Administration of nitrites produces dilation of meningeal blood vessels (via relaxation of vascular smooth muscle), which is the basis for the transient pulsating headache (Nickerson 1975). Headache of presumed vascular origin is a frequent complaint following therapeutic doses of the structurally similar nitrate triester nitroglycerin for the treatment of angina. Vasodilation of the dural arteries is the probable cause of headaches and nasal congestion experienced by torpedo maintenance workers in the study of Horvath et al. (1981).

Vasodilation is attributable to nitric oxide (NO), which is produced either directly from the nitroester or liberated by decomposition of NO intermediates (Feelisch and Noack 1987). Either glutathione in cells of vascular tissue or sulfhydryl groups of proteins in these tissues may be responsible for converting nitrates to NO. Nitric oxide activates guanylyl cyclase, which increases intracellular levels of cyclic guanosine 3'5'-monophosphate and thereby produces vasodilation (Kelly and Smith 1996; Robertson and Robertson 1996).

To study the effect of PGDN on cerebral blood flow, Godin et al. (1995) injected male Sprague-Dawley rats (through a jugular vein cannula) with PGDN at 0.1 to 30 mg/kg and measured cerebral blood flow with a fiberoptic laser-Doppler flow probe in contact with the brain. Following a small initial drop in cerebral perfusion that lasted 1 min, blood flow rapidly increased and reached a maximum 2 min after injection. The increase in perfusion was correlated with dose, but due to the small number of animals and individual variability, a clear dose-response relationship was not obtained.

Peripheral vasodilation can precipitate a fall in blood pressure. Intravenous injection of male Fischer 344 rats with PGDN at 0.1 to 30 mg/kg produced a dose-related fall in systolic blood pressure within 1 min (Godin et al. 1995). No drop in blood pressure in rats was observed over a 30–45 min period during exposure to an atmosphere of saturated PGDN vapor (82–90 ppm) generated from Otto Fuel II (Godin et al. 1993).

An effect on blood pressure was shown in the study by Clark and Litchfield (1969) in which subcutaneous injections of PGDN to anesthetized rats at 5, 10, 20, 40, 80, or 160 mg/kg resulted in a dose-related fall in mean arterial blood pressure (measured in the cannulized femoral artery) within 30 min with recovery over the next 12 h. The maximum drop in blood pressure correlated with the maximum concentration of PGDN in the blood. However, a drop in blood pressure did not occur in human volunteers who inhaled 0.5 ppm PGDN for 7.3 h. Rather, a mean elevation of diastolic blood pressure of 12 mm Hg was associated with severe and throbbing headaches (Stewart et al. 1974). A drop in blood pressure and decreasing stroke volume can result in brain ischemia, causing the dizziness and weakness reported by one subject after exposure at 0.5 ppm for 6 h in the Stewart et al. (1974) study as well as in occupationally exposed workers (Horvath et al. 1981).

The sudden deaths of workers in the explosives industry have been attributed to a series of cardiovascular events that occur after repeated occupational exposures (Carmichael and Lieben 1963). Acute exposures result in a depression of both the systolic and diastolic blood pressure. Continued exposure to low concentrations of nitrate esters produces a progressive rise in the diastolic blood pressure from the previously depressed level without a comparable rise in the systolic blood pressure. This narrowing of the pulse pressure combined with an increased diastolic pressure and high pulse rate, which occurs following cessation of exposure, may contribute to acute myocardial ischemia.

High doses of PGDN are associated with increased circulating methemoglobin. Methemoglobin and blood nitrate levels were not increased in human subjects exposed at concentrations up to 1.5 ppm for 3.2 h (Stewart et al. 1974). Subcutaneous injection of rats with PGDN at 0, 25, 50, 100, 200, or 400 mg/kg resulted in a dose-related methemoglobinemia with values ranging from <10% at ≤50 mg/kg to approximately 85% at 400 mg/kg (Clark and Litchfield 1969). At the LD_{50} (approximately 500 mg/kg) in rats, almost complete conversion of hemoglobin to methemoglobin was achieved. Maximal methemoglobin levels were reached 2–3 h after injection. Methemoglobin reached peak levels of approximately 20% during the second week of continuous inhalation exposure of dogs and monkeys to 33 ppm (Jones et al. 1972).

PGDN also acts as a central nervous system depressant in humans. The changes in the VER, disturbances in postural balance (Stewart et al. 1974), and changes in oculomotor performance (Horvath et al. 1981) are consistent with central nervous system depression. The concentrations in these studies did not greatly influence cognitive functions. Similarly, higher concentrations had little or no effect on monkeys trained in avoidance tests (Jones et al. 1971; Mattsson et al. 1981). The mechanism of central nervous system depression induced by PGDN exposure is poorly understood but may be the same as that of volatile anesthetics. The difference in susceptibility of individuals to central nervous system depressants such as volatile anesthetics varies by no more than 2-fold as indicated by the minimum alveolar concentration (MAC), the concentration that produces immobility in 50% of patients (Kennedy and Longnecker 1996; Marshall and Longnecker 1996).

4.3. Structure-Activity Relationships

As noted under Mechanisms of Toxicity (Section 4.2), nitrate and nitrite esters are vasodilators with resulting hypotension (Nickerson 1975). Therapeutic doses of nitroglycerin for relief of angina are associated with headaches of vascular origin. Both PGDN and the structurally related ethylene glycol dinitrate produce headaches in humans and methemoglobinemia and hypotension in rats (Andersen and Mehl 1979).

4.4. Other Relevant Information

4.4.1. Species Differences

The erythrocytes of several species show different susceptibilities to PGDN-induced methemoglobin formation (Wyman et al. 1985). Blood was collected from Fischer 344 rats, Hartley guinea pigs, beagle dogs, and humans, and PGDN-induced methemoglobin was determined in whole-cell preparations, hemolysates, and partially purified hemoglobin solutions. A comparison of the net rate of methemoglobin formation in erythrocytes and stroma-free hemolysates over a 4-h period revealed that dogs showed the highest rate, followed by the guinea pig; the guinea pig was greater than the rat, and the rat was greater than the human. In enzyme-free hemoglobin preparations, the rate of methemoglobin formation was essentially in the same order, with dog greater than guinea pig, guinea pig greater than rat, and rat equal to human.

Activities of the erythrocyte enzymes methemoglobin reductase, glutathione-S-transferase, catalase, superoxide dismutase, glutathione peroxidase, 6-phosphogluconate dehydrogenase, and glucose-6-phosphate dehydrogenase failed to correlate with methemoglobin formation. The primary determinant of methemoglobin formation appeared to be the structure of each species' hemoglobin molecule.

Methemoglobin formation during chronic inhalation exposures at 33 ppm indicated that dogs and monkeys are more susceptible to PGDN-induced methemoglobinemia than rats and guinea pigs (Jones et al. 1972). Slightly higher methemoglobin levels were present in the dog than in the monkey. During a 1-y exposure of rats and dogs, similar low levels of methemoglobin were induced in dogs exposed at 0.2 ppm and rats exposed at 33 ppm (Gaworski et al. 1985).

Acute subcutaneous LD_{50} values in the rat, mouse, and cat were 463–524, 1,208, and 200–300 mg/kg, respectively, indicating that by this route of administration the cat is approximately twice as sensitive as the rat, which in turn is approximately twice as sensitive as the mouse (Clark and Litchfield 1969).

4.4.2. Susceptible Populations

A review of the literature on PGDN did not reveal human populations that are unusually susceptible to this chemical. The elderly, especially those with heart disease, may be susceptible to the vasodilatory effects of PGDN. However, similar nitrate esters are used to treat heart patients with angina, and those patients may have developed a tolerance to induction of headaches. Older persons with arteriosclerosis or cardiac disease may have a limited ability to constrict blood vessels or to increase cardiac output in response to the vasodilatation action of PGDN and, therefore, may have a greater degree of hypotension than other individuals (ATSDR 1995). Compensatory vasospasm following withdrawal from nitrate ester exposure has been described in chronic exposures but not following an acute exposure. Although methemoglobinemia occurred in laboratory animals at high concentrations, an in vitro study showed that the hemoglobin of humans is less susceptible to PGDN-induced methemoglobin formation than the hemoglobin of laboratory animals. The exposure levels of PGDN in the occupational and human experimental studies did not result in methemoglobinemia.

There is probably a wide variation in the susceptibility of individuals in the population to the induction of headache from various stimuli. However, in the case of individuals exposed to PGDN in the study by Stewart et al.

(1974), the difference in concentration that induced mild headache in the most susceptible individual (0.1 ppm for 8 h) and the concentration that induced headaches in approximately half of the tested individuals (0.21–0.26 ppm for 8 h) was small, indicating little individual variation with this direct-acting chemical. At the 1.5-ppm concentration, induction of severe headaches in all individuals was rapid; the range of times was between 30 and 90 min.

Infants are more susceptible to methemoglobin-generating chemicals than adults as they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor [electron donor] for methemoglobin reductase) and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992). NADH lacks full activity until infants are 4 mo of age. Because infants are more susceptible than adults to methemoglobin formation from nitrites and nitrates, there may be some concern that nitrite and nitrate released from inhaled PGDN may form methemoglobin in infants. Following calculation of the AEGL values (Appendix A), the amounts of nitrogen (N) released from exposure to PGDN at the 8-h AEGL concentrations were calculated and compared with EPA's (1999) oral reference dose (RfD) for infants (Appendix B). EPA's RfD for nitratenitrogen (NO_3^-) was based on a clinical study in newborn infants that showed that ingestion of 6.4 mg/d (1.6 mg/kg/d for a 4 kg infant) of nitrate-nitrogen failed to increase circulating methemoglobin. Although nitrate to nitrite conversion occurs in the achlorhydric neonatal gut, the assumption was made that systemic bioavailability in the infant is equivalent following ingestion and inhalation. The amount of nitrate-nitrogen taken up by an infant at the 8-h AEGL-3 is 4.8 mg. The calculation shows that at the AEGL-3 the amount taken up by inhalation is below the RfD if the absorbed N were to be released as nitrate. Because there were no data for nitrite-nitrogen (NO_2^-), EPA applied a modifying factor of 10 to derive a RfD for nitrite-nitrogen. Metabolism studies with PGDN show that released nitrite-nitrate is rapidly converted to nitrate, and nitrite was almost undetectable in the urine. Therefore, it is unlikely that methemoglobin induced from nitrite from PGDN would approach lethal levels at AEGL-3.

4.4.3. Concentration-Exposure Duration Relationship

Data from the study by Stewart et al. (1974) suggest that the relationship between exposure concentration and exposure duration for end points of both mild and severe headaches is approximately linear (i.e., mild headaches induced by 6, 2, 2, and 1 h at exposure concentrations of 0.1, 0.2, 0.3, and 0.5

ppm, respectively, and severe headaches induced at 8, 8, 2, and 1 h at exposure concentrations of 0.2, 0.3, 0.5, and 1.5 ppm, respectively). The concentration × time product is approximately 0.5 for mild headaches and approximately 1.6 for severe headaches. The linear relationship is consistent with an n value of 1 in the relationship between concentration and time, $C^n \times t = k$. No data were available to calculate the relationship between concentration and time for other end points.

4.4.4. Concurrent Exposures

PGDN may be absorbed percutaneously. A comparison of blood pressure changes in anesthetized rats administered PGDN by the subcutaneous and dermal routes suggests that at least 10% of a cutaneous dose penetrates the skin within 30 min (Clark and Litchfield 1969). When PGDN doses of 5 to 450 mg/kg (1.2 to 108 mg/animal) were applied to a 1-cm^2 area of the shaved intact dorsal skin of anesthetized male Fischer 344 rats, the percent absorbed, as measured in the excised skin 30–45 min later, ranged from 75% at the 5 mg/kg dose to 20% at the 450 mg/kg dose (Godin et al. 1993). The relationship between the applied dose and the percent absorption was not linear over the range of applied doses.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Occupational exposures and the study with human volunteers indicate that exposures at low concentrations cause headaches and signs of central nervous system depression. No headaches were reported and no equilibrium disturbances were measured during occupational exposures of healthy workers to Otto Fuel II (measured as PGDN) at concentrations ≤0.22 ppm (average of approximately 0.06 ppm) for periods of 30–60 min, although subtle changes in eye movements were recorded (Horvath et al. 1981). In a study with healthy but previously unexposed male volunteers, the threshold for odor detection was 0.2 ppm (Stewart et al. 1974). Mild headaches were reported in one of three subjects after a 6-h exposure at 0.1 ppm, in two of three subjects after a 2-h exposure at 0.2 ppm, and in one of three subjects after a 1-h exposure at 0.5 ppm. Severe headaches occurred after an 8-h exposure at 0.2

(six of 12 exposures) and 0.35 ppm and after a 2-h exposure at 0.5 ppm (one of three subjects).

5.2. Summary of Animal Data Relevant to AEGL-1

Few data on acute exposures with effects that meet the definition of an AEGL-1 were located. No clinical signs of intoxication were observed in rats exposed to PGDN at a concentration of 189 ppm for 4 h when the methemoglobin level was 23.5% (Jones et al. 1972). Repeated exposures of rats at 10 ppm resulted in no toxic signs, changes in hematology parameters, or organ lesions (Jones et al. 1972).

5.3. Derivation of AEGL-1

The study by Stewart et al. (1974) with human volunteers is relevant to the derivation of AEGL-1 values. Within the definition of an AEGL-1, both healthy and susceptible individuals could experience mild discomfort. A mild headache can be considered mild discomfort and the threshold concentration-time at which one or more subjects first developed a mild headache was used to derive the AEGL-1 values. No subjects (other than the one that developed a headache during the control sessions) developed headaches during an 8-h exposure at 0.03 ppm. The highest concentrations and exposure durations that did not result in headache and the lowest concentrations and exposure durations that resulted in mild headaches are as follows:

No headache	*Mild headaches*
0.03 ppm for 8 h	0.1 ppm after 6 h
0.1 ppm for 3–4 h	0.2 ppm (0.21–0.26) for 2 h
0.2 ppm for 1 h	0.35 ppm for ≥2 h
0.35 ppm for 1 h	0.5 ppm for 1 h

The subjects were primarily healthy young males. Because no susceptible populations were identified (angina patients are not considered at additional risk and the absorbed dose at these concentrations is far below that inducing methemoglobinemia), an intraspecies uncertainty factor (UF) of 3 was used. The intraspecies UF of 3 is supported by the steep dose-response curve for the induction of headaches: namely, a 2-fold difference in the threshold concentra-

tion of PGDN and the concentration that induces headache in the majority of healthy individuals.

TABLE 2–5 AEGL-1 Values for PGDN (Otto Fuel II) (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
0.33 (2.3)	0.33 (2.3)	0.17 (1.1)	0.05 (0.3)	0.03 (0.17)

The data from Stewart et al. (1974) provide appropriate concentrations and exposure times to derive AEGL-1 values. The starting points are 1 h at 0.5 ppm and 6 h at 0.1 ppm. Using a value of n=1 in the concentration-time scaling equation of $C^n \times t = k$, the 30-min value was calculated from the 1-h value of 0.5 ppm (k=0.167 ppm·h) and the 4- and 8-h values were calculated from the 6-h value of 0.1 ppm (k=0.2 ppm·h). The 10-min AEGL-1 was set equal to the 30-min value. Calculations are in Appendix A, and the resulting values are listed in Table 2–5.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Occupational and controlled human volunteer studies indicate that exposures at low concentrations of PGDN cause headaches and central nervous system depression. No headaches were reported and no equilibrium problems were recorded during occupational exposures of healthy workers to Otto Fuel II (measured as PGDN) at concentrations ≤0.22 ppm (average of approximately 0.06 ppm) for periods of 30–60 min, although subtle changes in eye movements were recorded (Horvath et al. 1981). In a study with healthy but previously unexposed male volunteers, mild headaches were reported after a 6-h exposure at 0.1 ppm and after a 2-h exposure at 0.21–0.26 ppm (Stewart et al. 1974). Severe headaches occurred after an 8-h exposure at 0.21–0.26 and 0.35 ppm, after a 2-h exposure at 0.5 ppm, and after a 1-h exposure at 1.5 ppm. The VER was altered after 45–90 min of exposure at 0.5 ppm. Changes in VER are not considered an adverse effect in the absence of a sensory effect or motor impairment. One subject reported dizziness and nausea after 6 h of exposure at 0.5 ppm. A slight loss of equilibrium in one of several neurobehavioral tests (heel-to-toe test with eyes closed) first occurred after 6.25 h of exposure at 0.5 ppm; loss of balance increased with increasing exposure

time, becoming more severe after 8 h of exposure. There were no reported changes in cognitive tests at this concentration.

6.2. Summary of Animal Data Relevant to AEGL-2

Few data on acute exposures with effects that meet the definition of an AEGL-2 were located. No clinical signs of intoxication were observed in rats exposed to PGDN at 189 ppm for 4 h. The methemoglobin level was 23.5% (Jones et al. 1972). Exposure of monkeys to PGDN at a concentration of 33 ppm for 4 h failed to affect performance in an operant avoidance behavioral test but altered the VER (Mattsson et al. 1981).

6.3. Derivation of AEGL-2

The study by Stewart et al. (1974) with human volunteers exposed to PGDN is relevant to derivation of AEGL-2 values. Within the definition of an AEGL-2, both healthy and susceptible individuals could experience notable but nondisabling effects The alteration in VER as well as the decrease in saccade velocity observed in the occupational exposures are subclinical disruptions of the extraocular motor system and are not functionally significant. Although the slight loss of balance observed at 6.25 h of exposure at 0.5 ppm would not cause irreversible or other serious, long-lasting effects or impair the ability to escape, it could be considered a threshold for inability to escape. After exposure at 1.5 ppm, severe, throbbing headaches became incapacitating, and the exposure was terminated after 3.2 h. Eye irritation at this concentration was without conjunctivitis or excessive lacrimation.

The severe headache accompanied by slight loss of equilibrium in one of several sensitive equilibrium tests after a 6.25-h (rounded down to 6 h) exposure at 0.5 ppm was considered the threshold for inability to escape and was used to derive the AEGL-2 values. A UF of 3 was used to adjust the value as no susceptible populations were identified and the threshold for narcosis for most anesthetics does not differ among individuals by more than a factor of 2 (Kennedy and Longnecker 1996; Marshall and Longnecker 1996). The intraspecies UF of 3 is supported by the steep dose-response curve for the induction of headaches: namely, a 2-fold difference in the threshold concentration of PGDN and the concentration that induces headache in the majority of healthy individuals (Stewart et al. 1974). The 6-h 0.5-ppm concentration was

adjusted by a UF of 3 and scaled to the 30-min and 1-, 4-, and 8-h time periods using $C^n \times t = k$ where n=1 (based on the concentration and time data for headaches) and k=1 ppm·h. Because of the long exposure duration of the key study, the 10-min value was set equal to the 30-min value. Calculations are in Appendix A, and the values are listed in Table 2–6.

TABLE 2–6 AEGL-2 Values for PGDN (Otto Fuel II) (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
2.0 (43)	2.0 (43)	1.0 (6.8)	0.25 (1.7)	0.13 (0.8)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to the definition of an AEGL-3 were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Few data on acute exposure with effects that meet the definition of an AEGL-3 were located. As noted for the AEGL-2 above, no overt signs of intoxication were observed in rats exposed to PGDN at a concentration of 189 ppm for 4 h. The methemoglobin level was 23.5% (Jones et al. 1972), which may be manifest as clinical cyanosis but does not produce hypoxia (Seger 1992). Exposure of an unspecified number of monkeys to PGDN at concentrations of 70–100 ppm for 6 h resulted in semiconsciousness and clonic convulsions. These signs resolved within 30–45 min after removal from exposure (Jones et al. 1972). No gross or histopathological effects were observed in the brain, spinal cord, or nerves of monkeys and dogs continuously exposed at 33 ppm for 90 d (Jones et al. 1972) or in the organs and tissues of rats and mice repeatedly exposed at 33 ppm for 1 y (MacEwen and Vernot 1982; Gaworski et al. 1985). With the exception of the death of one of nine monkeys on day 31 of exposure, this repeated daily inhalation at 33 ppm had no effect on survival. Continuous exposure of dogs and guinea pigs at 33 ppm for 90 d also had no effect on survival (Jones et al. 1972).

7.3. Derivation of AEGL-3

Two animal studies conducted with high exposure concentrations are suitable for deriving the AEGL-3 values. No deaths and no toxic signs were observed in rats exposed to a PGDN mist at 189 ppm for 4 h and no deaths occurred in monkeys exposed at ≥70 ppm (70–100 ppm) for 6 h (Jones et al. 1972). Although no deaths occurred, the severe signs during exposure of monkeys at ≥70 ppm for 6 h can be considered the threshold for lethality. These signs are consistent with central nervous system depression and/or cardiovascular effects and suggest that the monkey is more susceptible to inhaled PGDN than the rat. The study with monkeys was chosen as the basis for the AEGL-3 because the monkey is more susceptible than the rat and the respiratory tract of the monkey is more similar to the human respiratory tract than that of the rat. The magnitude of interspecies difference in susceptibility to PGDN is unknown, but the mechanism of action is similar for all mammals, and the difference between monkeys and humans would not be great (both monkeys and humans showed changes in VER at similar concentrations). Because the most susceptible test species was chosen, the 70-ppm concentration was adjusted by an interspecies UF of 3. For extreme central nervous system depression leading to convulsions, an intraspecies UF of 3 was considered sufficient (concentrations of anesthetics causing narcosis in infants and adults generally do not differ by more than a factor of 2 [Kennedy and Longnecker 1996; Marshall and Longnecker 1996]). The intraspecies UF of 3 is supported by the steep dose-response curve for the induction of headaches; namely, a 2-fold difference in the threshold concentration of PGDN and the concentration that induces headache in the majority of healthy individuals (Stewart et al. 1974). The result is adjustment by a total UF of 10. Because an n value of 1 is relevant to the end point of headaches and the end point for the AEGL-3 is convulsions, the more conservative n values of 1 and 3, with k values of 2,058 ppm·h and 42 ppm·h, were used to time-scale from the 6-h exposure duration to the longer and shorter time periods, respectively. The 10-min AEGL-3 was set equal to the 30-min value. Calculations are in Appendix A, and the resulting values are listed in Table 2–7.

These values are supported by the results of subchronic studies with squirrel monkeys and dogs (Jones et al. 1972). Monkeys and dogs exposed continuously at approximately 15 ppm for 90 d showed no overt clinical signs; systemic toxicity consisted of biochemical and/or non-life-threatening histological changes in the liver, spleen, and kidneys.

TABLE 2–7 AEGL-3 Values for PGDN (Otto Fuel II) (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
16 (114)	16 (114)	13 (93)	8.0 (57)	5.3 (38)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End points

The AEGL values and toxicity end points are summarized in Table 2–8.

8.2. Comparisons with Other Standards and Guidelines

PGDN has limited uses and only workplace standards have been developed. Both the ACGIH TLV-TWA and NIOSH REL TWA are 0.05 ppm. The recommended ACGIH TLV-TWA is based on the study of Stewart et al. (1974) in which volunteers exposed at 0.5 ppm for 6 to 8 h showed a marked impairment of their performance on simple behavioral tests, and volunteers exposed at 0.2 ppm or greater showed a disruption of the visual evoked response and headache. The 8-h TWA value of 0.05 ppm derived by ACGIH and NIOSH for healthy workers is identical to the 4-h AEGL-1 and is slightly greater than the 8-h AEGL-1 of 0.03 ppm.

TABLE 2–8 Summary of AEGL Values (ppm [mg/m3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.33 (2.3)	0.33 (2.3)	0.17 (1.1)	0.05 (0.3)	0.03 (0.17)
AEGL-2 (Disabling)	2.0 (14)	2.0 (14)	1.0 (6.8)	0.25 (1.7)	0.13 (0.8)
AEGL-3 (Lethal)	16 (114)	16 (114)	13 (93)	8.0 (57)	5.3 (38)

8.3. Data Adequacy and Research Needs

Data from human exposures were used to derive the AEGL-1 and AEGL-2 values. The study on which the AEGL-1 and AEGL-2 were based was well designed, conducted, and documented and used 20 volunteers. In addition, supporting data were available. Occupational data were available to support the margin of safety associated with the AEGL-1 values; developmental toxicity data were available from both occupational exposures and experimental animal studies; specific neurotoxicity tests were performed with both human and animal subjects; and a battery of genotoxicity and chronic toxicity bioassays were reported. Moreover, the mechanism of action for the headache associated with nitrate esters is well understood from medical applications.

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Appendixes

APPENDIX A DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	Stewart et al. 1974
Toxicity end point:	Mild headache (threshold); 1 h at 0.5 ppm and 6 h at 0.1 ppm
Scaling:	$C^1 \times t = k$ based on concentrations and exposure durations for the end points of mild and severe headache in the key study.
Uncertainty factor:	3; no unusually susceptible populations were identified and the end point was a threshold effect. More severe headaches are known to occur in some patients medicated with other nitrate esters and the threshold for vasodilatation in the key study did not vary greatly among individuals.
Calculations:	$C \times t = k$ 30-min and 1-h AEGL-1: $(0.5 \text{ ppm}/3) \times 1 \text{ h} = 0.167 \text{ ppm·h}$ 4- and 8-h AEGL-1: $(0.1 \text{ ppm}/3) \times 6 \text{ h} = 0.2 \text{ ppm·h}$
10-min AEGL-1:	Set equal to the 30-min value
30-min AEGL-1:	$C \times t = k$ $C \times 1/2 \text{ h} = 0.167 \text{ ppm·h}$ $C = 0.33 \text{ ppm}$
1-h AEGL-1:	$0.5 \text{ ppm}/3 = 0.17 \text{ ppm}$
4-h AEGL-1:	$C \times t = k$ $C \times 4 \text{ h} = 0.2 \text{ ppm·h}$ $C = 0.05 \text{ ppm}$

8-h AEGL-1:	C×t=k C×8 h=0.2 ppm·h C=0.03 ppm

Derivation of AEGL-2

Key study:	Stewart et al. 1974
Toxicity end point:	Severe headache and threshold for central nervous system effects after 6-h exposure at 0.5 ppm
Scaling:	$C^1 \times t=k$ based on concentrations and exposure durations for the end points of mild and severe headache in the key study
Uncertainty factor:	3; severe headaches are known to occur in angina patients medicated with nitroglycerin and the threshold for vasodilatation does not vary greatly among individuals. The effect was also a threshold effect for central nervous systems depression (no change in cognitive abilities; slight imbalance in one of several sensitive motor tests). Individual variation in susceptibility to central nervous system depressants such as anesthetics varies no more than 2-fold.
Calculations:	C×t=k (0.5 ppm/3)×6 h=1 ppm·h
10-min AEGL-2:	Set equal to the 30-min value
30-min AEGL-2:	C×t=k C×1/2 hour=1 ppm·h C=2 ppm
1-h AEGL-2:	C×t=k C×1 h=1 ppm·h C=1 ppm

4-h AEGL-2:	C×t=k
	C×4 h=1 ppm·h
	C=0.25 ppm
8-h AEGL-2:	C×t=k
	C×8 h=1 ppm·h
	C=0.13 ppm

Derivation of AEGL-3

Key study:	Jones et al. 1972
Toxicity end point:	Severe effects (vomiting, pallor, cold extremities, semiconscousness, and clonic convulsions) in monkeys exposed at 70–100 ppm for 6 h; no effects in rats exposed at 189 ppm for 4 h
Scaling:	Default values of n=3 for shorter exposure durations and n=1 for longer exposure durations
Uncertainty factors:	Interspecies: 3—The monkey was more susceptible than the rat; the lowest concentration in a range was chosen (70 ppm); humans and monkeys showed changes in the visual evoked response at similar concentrations; the monkey is a good model for the human. The concentration inducing central nervous system depression does not vary greatly among mammalian species. Intraspecies: 3—Individual variation in susceptibility to central nervous system depressants such as anesthetics varies no more than 2-fold.
Calculations:	30-min and 1- and 4-h exposure durations: $C^3 \times t = k$ $(70 \text{ ppm}/10)^3 \times 6 \text{ h} = 2{,}058 \text{ ppm·h}$ 8-h exposure duration: C×t=k

	(70 ppm/10)×6 h=42 ppm·h
10-min AEGL-3:	Set equal to the 30-min value
30-min AEGL-3:	$C^3 \times t = k$
	$C^3 \times 1/2$ h=2,058 ppm·h
	C=16 ppm
1-h AEGL-3:	$C^3 \times t = k$
	$C^3 \times 1$ h=2,058 ppm·h
	C=13 ppm
4-h AEGL-3:	$C^3 \times t = k$
	$C^3 \times 4$ h=2,058 ppm·h
	C=8.0 ppm
8-h AEGL-3:	C×t=k
	C×8 h=42 ppm·h
	C=5.3 ppm

APPENDIX B Potential Methemoglobin Formation in Infants

Calculation of N released from exposure to PGDN at the 8-h AEGL concentrations:
Assumptions:

- a breathing rate in infants of 4.5 m^3/day (U.S. EPA Exposure Factors Handbook)
- 100% of the PGDN that enters the lung is absorbed into the circulatory system
- 1 molecule of N per molecule of PGDN (M.W.=14/166) (the 2-mononitrate is the predominant metabolite in the blood)

4.5 m^3×8 h/24 h×0.17 mg/m^3=0.26×14/166=0.02 mg

4.5 m^3×8 h/24 h×0.8 mg/m^3=0.12×14/166=0.10 mg

4.5 m^3×8 h/24 h×38 mg/m^3=57×14/166=4.8 mg

EPA's reference dose for nitrate-nitrogen (NO_3^-) is based on a clinical study in newborn infants. That study showed that ingestion of 6.4 mg/d of nitratenitrogen did not cause an increase in the circulating methemoglobin in infants. The NOEL of 6.4 mg/d for methemoglobin formation in infants is higher than the amount of nitrogen released from PGDN even assuming complete systemic bioavailability upon inhalation and complete in vivo conversion of PGDN to NO_3^- during exposure to the 8-h AEGL-3.

APPENDIX C DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS PROPYLENE GLYCOL DINITRATE (CAS No. 6423–43–4)

AEGL-1

10 min	30 min	1 h	4 h	8 h
0.33 ppm	0.33 ppm	0.17 ppm	0.05 ppm	0.03 ppm

Key reference: Stewart, R.D., J.E.Peterson, P.E.Newton, C.L.Hake, M.J. Hosko, A.J.Lebrun, and G.M.Lawton. 1974. Experimental human exposure to propylene glycol dinitrate. Toxicol. Appl. Pharmacol. 30:377–395.

Test species/Strain/Number: 20 human subjects

Exposure route/Concentrations/Durations: Inhalation; 0.0, 0.03, 0.1, 0.2, 0.35, 1.2, or 1.5 ppm for periods of 1 to 8 h. Subjective evaluations and physiological and central nervous system responses reported.

Effects:
No headache: 0.03 ppm for 8 h
0.1 ppm for 3–4 h
0.2 ppm for 1 h
0.35 ppm for 1 h

Mild headache:
0.1 ppm after 6 h
0.2 ppm (0.21–0.26 ppm) for 2 h
0.35 ppm for >2 h
0.5 ppm for 1 h

End point/Concentration/Rationale: Threshold for mild headache in 1 of 3 subjects after a 6-h exposure at 0.1 ppm and after a 1-h exposure at 0.5 ppm. The threshold for mild headache falls within the AEGL-1 definition of mild discomfort.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: Not applicable; human subjects tested.

Intraspecies: 3—no unusually susceptible populations were identified. Because the time and concentration values were based on a threshold, these concentrations were adjusted by an uncertainty factor of 3 to account for differences in human sensitivity. More severe headaches are often experienced by heart patients medicated with nitroglycerin for angina and these concentrations are far below those inducing methemoglobinemia in infants.

Modifying factor: Not applicable
Animal to human dosimetric adjustment: Not applicable; human data used.
Time scaling: $C^n \times t = k$ where n=1 (k=0.167 ppm·hour for the 30-min value and 0.2 ppm·h for the 4- and 8-h values). Data from the key study suggest that the relationship between exposure concentration and exposure duration for end points of both mild and severe headaches is approximately linear (i.e., mild headaches induced by 6, 2, 2, and 1 h at exposure concentrations of 0.1, 0.2, 0.3, and 0.5 ppm, respectively, and severe headaches induced at 8, 8, 2, and 1 h at exposure concentrations of 0.2, 0.3, 0.5, and 1.5 ppm, respectively). The concentration×time product is approximately 0.5 for mild headaches and approximately 1.6 for severe headaches. The linear relationship is consistent with an n value of 1 in the relationship between concentration and time, $C^n \times t = k$. The 1-h value was used to extrapolate to the shorter duration (30 min) and the 6-h value was used to extrapolate to the longer durations (4 and 8 h). The 10-min value was set equal to the 30-min value.
Data adequacy: The key study was well designed, conducted, and documented; used 20 human subjects; and utilized a range of concentrations and exposure durations. Occupational exposures support the 8-h AEGL value. The mechanism of headache induction (vasodilation) is well understood and occurs following therapeutic administration of nitrate esters to humans. Animal studies utilized several mammalian species and addressed metabolism, neurotoxicity, developmental and reproductive toxicity, and potential carcinogenicity.

AEGL-2

10 min	30 min	1 h	4 h	8 h
2.0 ppm	2.0 ppm	1.0 ppm	0.25 ppm	0.13 ppm

Key reference: Stewart, R.D., J.E.Peterson, P.E.Newton, C.L.Hake, M.J. Hosko, A.J.Lebrun, and G.M.Lawton. 1974. Experimental human exposure to propylene glycol dinitrate. Toxicol. Appl. Pharmacol. 30:377–395.

Test species/Strain/Sex/Number: 20 human subjects

Exposure route/Concentrations/Durations: Inhalation; 0.0, 0.03, 0.1, 0.2, 0.3, 0.35, 1.2, or 1.5 ppm for periods of 1 to 8 h. Subjective evaluations and physiological and central nervous system responses reported.

Effects: Severe headache:
0.21–0.26 ppm for 8 h
0.35 ppm for 8 h
0.5 ppm for 2 h
1.5 ppm for 1 h
Change in visual evoked response: 0.35 ppm for 8 h
Threshold for impairment of balance: 0.5 ppm for 6 h
Threshold for abnormal cognitive test: 1.5 ppm for 3.2 h

End point/Concentration/Rationale: A 6-h exposure at 0.5 ppm which resulted in severe headache and was the threshold for loss of equilibrium falls within the AEGL-2 definition of threshold for impaired ability to escape.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: Not applicable; human subjects tested.

Intraspecies: 3—no unusually susceptible populations were identified. The threshold for vasodilatation does not vary greatly among individuals. Furthermore, severe headaches are often experienced by heart patients medicated with nitroglycerin for angina and these concentrations are far below those inducing methemoglobinemia in infants. The threshold for anesthetic effects also does not differ greatly among individuals.

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Not applicable, human data used.

Time scaling: $C^n \times t = k$ where n=1 and k=1 ppm·h. Data from the key study suggest that the relationship between exposure concentration and exposure duration for end points of both mild and severe headaches is approximately linear (i.e., mild headaches induced by 6, 2, 2, and 1 h at exposure concentrations of 0.1, 0.2, 0.3, and 0.5 ppm, respectively, and severe headaches induced at 8, 8, 2, and 1 h at exposure concentrations of 0.2, 0.3, 0.5, and 1.5

ppm, respectively). The concentration × time product is approximately 0.5 for mild headaches and approximately 1.6 for severe headaches. The linear relationship is consistent with an n value of 1 in the relationship between concentration and time, $C^n \times t = k$. Because of the long exposure duration of the key study, the 10-min AEGL-2 was not time-scaled, but was set equal to the 30-min value.
Data adequacy: The key study was well designed, conducted and documented; used 20 human subjects; and utilized a range of concentrations and exposure durations. The mechanism of headache induction (vasodilation) is well understood and occurs following therapeutic administration of nitrate esters to humans. Animal studies utilized several mammalian species and addressed metabolism, neurotoxicity, developmental and reproductive toxicity, and potential carcinogenicity.

AEGL-3

10 min	30 min	1 min	4 min	8 min
16 ppm	16 ppm	13 ppm	8.0 ppm	5.3 ppm

Key reference: Jones, R.A., J.A.Strickland, and J.Siegel. 1972. Toxicity of propylene glycol 1,2-dinitrate in experimental animals. Toxicol. Appl. Pharmacol. 22:128–137.

Test species/Strain/Sex/Number: Squirrel monkeys (number and sex not stated)

Exposure route/Concentrations/Durations: Inhalation; 70–100 ppm for 6 h

Effects: Severe effects (vomiting, pallor, cold extremities, semiconsciousness, and clonic convulsions)

End point/Concentration/Rationale: The 6-h exposure at 70–100 ppm was a NOEL for lethality in monkeys

Uncertainty factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3—the monkey was more susceptible than the rat, the lowest concentration in a range was chosen, humans and monkeys showed changes in the visual evoked response at similar concentrations, and the monkey is a good model for the human.

Intraspecies: 3—the threshold for central nervous system effects (narcosis) does not vary greatly among individuals.

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Not applied.

Time scaling: Default values of n=3 and n=1 for shorter and longer time-scaling durations, respectively, with respective k value of 2,058 ppm·h and 42 ppm·h, because no data were available for time scaling the central nervous system end points of convulsions and narcosis. Because of the long exposure duration of the key study, the 10-min value was not time scaled but was set equal to the 30-min AEGL-3.

Data adequacy: Although the key study lacked details of methodology, the AEGL-3 values are supported by the additional observation of no adverse effects in rats exposed at a concentration of 189 ppm for 4 h (Jones et al. 1972). The AEGL-3 values are also supported by subchronic and chronic exposures of several animal species at concentrations up to 34 ppm with no life-threatening effects.

3

1,1,1,2-Tetrafluoroethane (HFC-134a)[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrofluorocarbon-134a or 1,1,1,2-Tetrafluoroethane (HFC-134a) has been developed as a replacement for fully halogenated chlorofluorocarbons because, compared with chlorofluorocarbons, its residence time in the atmo

[1]This document was prepared by the AEGL Development Team comprising Sylvia Talmage (Oak Ridge National Laboratory) and members of the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances, including George Rusch (Chemical Manager) and Robert Benson and Kenneth Still (Chemical Reviewers). The NAC reviewed and revised the document and AEGL values as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

sphere is shorter and its ozone depleting potential is insignificant. HFC-134a is used in refrigeration and air conditioning systems, as a blowing agent for polyurethane foams, and as a propellant for medical aerosols. Yearly production is estimated at 175,000 tons. HFC-134a is a colorless gas with a faint ethereal odor that may go unnoticed by most individuals.

HFC-134a has a very low acute inhalation toxicity. Both uptake and elimination are rapid, but uptake is low, and most of the compound is exhaled unchanged. Consequences of acute HFC-134a inhalation have been studied with human subjects and several animal species, including the monkey, dog, rat, and mouse. Considerable inhalation data from controlled studies with healthy human subjects as well as patients with respiratory diseases are available. Studies addressing repeated and chronic exposures, genotoxicity, carcinogenicity, neurotoxicity, and cardiac sensitization were also available. At high concentrations, halogenated hydrocarbons may produce cardiac arrhythmias; this end point was considered in development of AEGL values.

Adequate data were available for development of the three AEGL classifications. Inadequate data were available for determination of the relationship between concentration and time for a fixed effect. Based on the observations that (1) blood concentrations in humans rapidly approach equilibrium with negligible metabolism and tissue uptake and (2) the end point of cardiac sensitization is a blood-concentration related threshold phenomenon, the same concentration was used across all AEGL time periods for the respective AEGL classifications.

The AEGL-1 concentration was based on a 1-hour (h) no-effect concentration of 8,000 parts per million (ppm) in healthy human subjects (Emmen et al. 2000). This concentration was without effects on pulmonary function, respiratory parameters, the eyes (irritation), or the cardiovascular system. Because this concentration is considerably below that causing any adverse effect in animal studies, an intraspecies uncertainty factor (UF) of 1 was applied. The intraspecies UF of 1 is supported by the absence of adverse effects in therapy tests with patients with severe chronic obstructive pulmonary disease and adult and pediatric asthmatics who were tested with metered-dose inhalers containing HFC-134a as the propellant. Because blood concentrations in this study approached equilibrium following 55 minutes (min) of exposure and effects are determined by blood concentrations, the value of 8,000 ppm was made equivalent across all time periods. The AEGL-1 of 8,000 ppm is supported by the absence of adverse effects in experimental animals that inhaled considerably higher concentrations. No adverse effects were observed in rats exposed at 81,000 ppm for 4 h (Silber and Kennedy 1979) or in rats exposed

repeatedly at 50,000 or 100,000 ppm for 6 h/day (d). Adjustment of the 81,000 ppm value by interspecies and intraspecies UFs of 3 each, for a total of 10, results in essentially the same concentration (8,100 ppm) as the AEGL-1 based on human data.

The AEGL-2 concentration was based on the no-effect concentration of 40,000 ppm for cardiac sensitization in dogs (Hardy et al. 1991). The cardiac sensitization model with the dog is considered an appropriate model for humans. Because the dog heart is considered an appropriate model for the human heart, an interspecies UF of 1 was applied. Because the cardiac sensitization test is highly sensitive as the response to exogenous epinephrine is optimized, an intraspecies UF of 3 was applied to account for sensitive individuals. Cardiac sensitization is concentration-dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that peak circulating concentration is the determining factor in HFC-134a cardiac sensitization, and exposure duration is of lesser importance, the resulting value of 13,000 ppm was applied to all time periods.

The AEGL-3 concentration was based on a concentration of 80,000 ppm, which caused marked cardiac toxicity but no deaths in dogs (Hardy et al. 1991). The cardiac sensitization model with the dog is considered an appropriate model for humans; therefore, an interspecies UF of 1 was applied. Because the cardiac sensitization test is highly sensitive as the response to epinephrine is optimized, an intraspecies UF of 3 was applied to account for sensitive individuals. Cardiac sensitization is concentration-dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that peak circulating concentration is the determining factor in HFC-134a cardiac sensitization, and exposure duration is of lesser importance, the resulting value of 27,000 ppm was applied to all time periods.

Values are summarized in Table 3–1.

1. INTRODUCTION

Hydrofluorocarbons (HFCs) are replacing chlorofluorocarbons (CFCs) in industry because the substitution of hydrogen for halogen in methane and ethane reduces residence time in the stratosphere compared with completely halogenated compounds and therefore causes less depletion of ozone. The contribution of radicals formed by the atmospheric degradation of 1,1,1,2-tetrafluoroethane (HFC-134a) to ozone depletion is insignificant and its global

warming potential is much lower than that of CFCs (Ravishankara et al. 1994; ECETOC 1995).

TABLE 3–1 Summary of AEGL Values for HFC-134a (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	8000 (34,000)	8000 (34,000)	8000 (34,000)	8000 (34,000)	8000 (34,000)	No effects — humans (Emmen et al. 2000)
AEGL-2 (Disabling)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	No effect, cardiac sensitization — dogs[a] (Hardy et al. 1991)
AEGL-3 (Lethal)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	Marked effect, cardiac sensitization —dogs[a] (Hardy et al. 1991)

[a]Response to challenge dose of epinephrine (cardiac sensitization test).

HFC-134a has been developed as a replacement for fully halogenated chlorofluorocarbons and for partially halogenated hydrochlorofluorocarbons. Its primary use is in refrigeration and air conditioning systems in which it is used alone or as a component of blends. It has been used as a blowing agent for polyurethane foams and as a propellant for medical aerosols (ECETOC 1995; Harrison et al. 1996). On August 15, 1996, the U.S. Food and Drug Administration (FDA) approved the use of metered-dose inhalers containing HFC-134a as the propellant. These metered-dose inhalers are used in the treatment and prevention of bronchospasm in patients 12 years (y) of age and older with reversible obstructive airway disease (FDA 1996). As of June, 1999, the age of treatment with HFC-134a containing inhalants was lowered from 12 y to 4 y. The same dosage is recommended for children and adults.

HFC-134a is produced commercially by (1) the hydrofluorination of trichloroethylene via 1-chloro-1,1,1-trifluoroethane, (2) isomerization and hydrofluorination of 1,1,2-trichloro-1,2,2-trifluoroethane to 1,1-dichloro-1,2,2,2-tetrafluoroethane followed by hydrodechlorination, and (3) hydrofluorination of tetrachloroethylene to 1-chloro-1,2,2,2-tetrafluoroethane and subsequent hydrodechlorination to tetrafluoroethane (ECETOC 1994). It is manufactured by four companies in the United States and 13 companies worldwide. World production capacity was estimated at 175,000 tons/y in the

early 1990s (ECETOC 1995). Production is estimated to reach 300,000 tons/y by 2020.

HFC-134a is a nonflammable, colorless gas or liquified gas with a faint ethereal odor. The odor, characterized as weak and nonirritating (Shulman and Sadove 1967), may not be noticeable for most individuals and thus will not serve as a warning property. The vapor is heavier than air and can displace air in confined spaces (ECETOC 1995). Additional chemical and physical properties are listed in Table 3–2.

Experimental studies with human subjects and several mammalian species (monkey, dog, rat, mouse, and rabbit) were located. Animal studies addressed neurotoxicity, genotoxicity, carcinogenicity, and cardiac sensitization and were conducted over acute, subchronic, and chronic exposure durations.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although deaths from exposure to CFCs have occurred during refrigeration repair, its use as solvents, and its use and abuse as aerosol propellant (Aviado 1994), no data specific to HFCs were located.

2.2. Nonlethal Toxicity

Eight healthy human volunteers, four males and four females, ages 20–24, were exposed individually (whole body) to concentrations at 0 (air), 1,000, 2,000, 4,000, or 8,000 ppm for 1 h in a 13.6 m^3 room (Emmen and Hoogendijk 1998; Emmen et al. 2000).[2] Each subject was exposed at each concentration in a partially blind ascending order of concentration. With the exception of one 14-d interval, each exposure was separated by a period of 7 d. Chlorofluorocarbon-12 (CFC-12) was used as a reference compound. No mention was made of the ability of the test subjects to recognize the odor of either test chemical. Prior to and during exposures, blood pressure and cardiac rate and rhythm (EKG) were monitored. Pulmonary function, as indi

[2]The protocol was approved by the Medical Ethics Testing Committee of The Netherlands Organization. Subjects signed an informed consent form.

cated by peak expiratory flow, was measured before and after exposures. Blood samples were taken prior to, during, and after exposure. Clinical chemistry and hematology parameters were also recorded before and after exposure. The test chemical was vaporized and introduced into the air supply of the exposure chamber via a calibrated rotameter; the atmospheres were monitored with a gas monitor. Five samples were taken from each of six locations in the exposure chamber.

TABLE 3–2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	HFC-134a 1,1,1,2-tetrafluoroethane HFA-134a HCFC 134a R-134a	ECETOC 1995, HSDB 2000
Molecular formula	$C_2H_2F_4$	ECETOC 1995
Molecular weight	102.03	HSDB 2000
CAS registry number	811–97–2	HSDB 2000
Physical state	Gas or liquified gas	ECETOC 1995
Color	colorless	ECETOC 1995
Solubility in water	1 g/L	ECETOC 1995
Vapor pressure	4,730 mm Hg @25°C	HSDB 2000
Vapor density	3.52	ECETOC 1995
Melting point	−108°C	ECETOC 1995
Boiling point	−26°C	ECETOC 1995
Odor	Faint ethereal	ECETOC 1995
Conversion factors	1 ppm=4.25 mg/m^3 1 mg/m^3=0.24 ppm	ECETOC 1995

Atmospheres were within a few percent of nominal concentrations; the mean oxygen concentration was approximately 20.5%. No significant or consistent differences were found between air exposure and test chemical exposure for clinical observations, blood pressure, heart rate, peak expiratory flow, or EKG recordings. During blood sampling and blood pressure measurements, all subjects showed sinus arrhythmia before and after exposure.

A Mobitz type I heart block was present in one subject before, during, and after exposure. Medical personnel did not consider this a risk, and the informed subject completed the study without any evidence of adverse effect.

CFCs are used as propellants in metered-dose inhalers for the treatment of asthma. To that end, HFC-134a has been tested with human subjects using single or repeated inhalations. A number of studies are cited here as examples of direct inhalation from such devices (up to 90% of the aerosol from metereddose inhalers may consist of the propellant). In a 28-d, double-blind parallel study, two groups of eight healthy nonsmoking male subjects, ages 18–55, inhaled either HFC-134a propellant from a pressurized metered-dose inhaler (HFC 134a as propellant, ethanol as co-solvent, and oleic acid as surfactant) or chlorofluorocarbon propellants, CFC-11 or CFC-12 (Harrison et al., 1996). All subjects gave written informed consent. Subjects received either four inhalations four times per day for 14 d or eight inhalations four times per day for 14 d; after 14 d the subjects were given the alternate propellant. Subjects held their breath for 10 seconds (s) after each inhalation and waited 30 s between inhalations. Blood pressure, heart rate, and EKGs were recorded; pulmonary function tests were administered immediately before and 20 min after the first exposure on each day; blood was taken for clinical chemistry determinations at this time on various days. No clinically significant differences from baseline occurred in blood pressure, heart rate, EKGs, pulmonary functions, hematology, or serum chemistry. One subject had an elevated eosinophil count throughout the study. The most frequently reported subjective adverse effect was headache, reported by four subjects in each propellant group.

Twelve healthy subjects showed no adverse clinical or pulmonary function response to inhalation of HFC-134a (Donnell et al. 1995), but three subjects reported coughing or nausea and vomiting. Coughing occurred in one subject after dosing from an inhaler that contained HCF-134a but no bronchodilator medication, and the other events occurred prior to cumulative dosing and approximately 21 h after the previous dosing regime. The relationship of these events to HFC-134a exposures is unknown. When radiolabeled HFC-134a was delivered by metered dose inhalers to healthy subjects and patients with severe chronic obstructive pulmonary disease (COPD), there were no adverse effects in either group as monitored by vital signs, pulmonary function tests, EKG, and liver function. No symptoms or complaints of upper respiratory tract irritation were recorded (Ventresca 1995). In preclinical trials, there were no significant acute or long-term neurobehavioral effects from exposure to four to eight metered-dose inhalations, four to 16 times per day (Bennett 1991; Engle 1991; Graepel and Alexander 1991).

As part of an extensive toxicological assessment of HFC-134a, metereddose inhalers using HFC-134a as a propellant have been tested with adult and pediatric asthmatic patients (Woodcock 1995). In a single-dose, double-blind, placebo-controlled study, 20 adult patients (mean age, 27 y) with mild to moderate asthma were exposed to a therapeutic agent (salmeterol, a β_2 agonist) with currently used chlorofluorocarbons or HFC-134a as the propellant prior to challenge with methacholine, a bronchoconstricting agent (Smith et al. 1994). All subjects completed the study without significant side effects. The therapeutic agent was equally protective against methacholine challenge regardless of propellant. In a similar study with 24 male and female asthmatic patients (mean age, 37 y), the efficacy of salbutamol delivered with either HFC-134a or two currently used chlorofluorocarbons was tested (Taggart et al. 1994). The challenge agent was histamine. Again, there were no significant side effects. There was no difference in the level of protection of the therapeutic agent whether it was delivered with HFC-134a or the currently used chlorofluorocarbons. In a third study, which used pediatric asthmatic subjects (mean age, 10 y), salbutamol delivered by HFC-134a or the currently used CFCs was equally protective against histamine-induced bronchoconstriction (Woodcock 1995).

In a randomized, double-blind, placebo-controlled, multicenter trial of several hundred adult asthmatic patients requiring inhaled β-adrenergic bronchodilators for symptom control, metered-dose inhalers with HFC-134a had a safety profile similar to the currently marketed product formulated with a CFC (Tinkelman et al. 1998). Patients with other serious concomitant diseases were excluded from the study. The study lasted 12 weeks (wk). Although several adverse events, such as vomiting and tachycardia, were increased over those in patients receiving the drug with CFC propellant (7% vs. 2% in patients receiving the CFC propellant), overall incidences for adverse events did not differ among patients receiving the drug with either propellant or receiving HFC-134a without the drug.

2.3. Neurotoxicity

No signs of central or peripheral neurologic involvement were reported following inhalation exposure to HFC-134a (Donnell et al. 1995; Woodcock 1995; Harrison et al. 1996; Tinkelman et al. 1998).

2.4. Developmental and Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to HFC-134a.

2.5. Genotoxicity

No information on genotoxicity in humans was located. In vitro, a cytogenic assay with human lymphocytes was negative (Collins et al. 1995). Vapor concentrations ranged from 5% to 100% volume per volume (v/v), and the incubation period was 3 h in both the presence and absence of metabolic activation.

2.6. Carcinogenicity

No information on the carcinogenic potential of HFC-134a in humans was located.

2.7. Summary

In a study with human volunteers exposed at concentrations up to 8,000 ppm for 1 h, no adverse effects on pulmonary function, clinical chemistry, hematology parameters, or heart rate or rhythm were observed. When HFC134a was delivered directly to the respiratory tract with metered-dose inhalers, no adverse effects, as indicated by clinical signs, respiratory tract irritation, or heart rhythm, were reported. The occurrences of headache, coughing, or nausea in some of the subjects that tested metered-dose inhalers are difficult to interpret but were not limited to HFC-134a exposure. Healthy subjects, as well as patients with COPD and asthma, were included in the test protocols, and no differences between the response of these populations could be discerned. No information on developmental and reproductive effects or carcinogenicity in humans was located. A single in vitro genotoxicity test with human lymphocytes was negative.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data are summarized in Table 3–3. The only species tested in these studies was the rat. In the rat, a 15-min LC_{50} of >800,000 ppm and a 4-h LC_{50} of >500,000 ppm have been reported (Collins 1984; Alexander 1995). These high concentrations required oxygen supplementation (19% v/v) to prevent anoxia of the test animals. The 30-min LC_{50} was 750,000 ppm (Rissolo and Zapp 1967). In another study, groups of six rats were exposed at time-weighted average (TWA) concentrations of 81,100, 205,200, 359,300, 566,700, 646,700, or 652,700 ppm for 4 h (Silber and Kennedy 1979a). The lowest lethal concentration was 566,700 ppm, which resulted in the deaths of five of six rats during the exposure period. Two of six rats exposed at 652,700 ppm also died. No deaths were recorded following exposure to the three lower concentrations, and no adverse effects were reported at the concentration of 81,000 ppm. Signs observed during exposures in these studies included lethargy, rapid respiration, trembling, tearing, foaming at the nose, pallor, and weight loss in survivors during the first 24 h of the recovery period. Surviving rats appeared normal within 5 min after cessation of exposure, and no abnormalities were present in surviving rats necropsied 14 d postexposure.

3.2. Nonlethal Toxicity

Results of acute HFC-134a exposures are summarized in Table 3–4. Many of these studies are reviewed in Alexander and Libretto (1995).

3.2.1. Nonhuman Primates

Exposure at 500,000 ppm induced narcosis in rhesus monkeys within 1 min (Shulman and Sadove 1967). Respiratory depression accompanied by multiple premature ventricular contractions occurred when concentrations exceeded 60%. Blood pressure was said to be increased, but the actual data were not reported.

TABLE 3–3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	>800,000	15 min	LC_{50}	Collins 1984
Rat	750,000	30 min	LC_{50}	Rissolo and Zapp 1967
Rat	566,700	4 h	Lowest lethal concentration	Silber and Kennedy 1979a
Rat	>500,000	4 h	LC_{50}	Collins 1984

3.2.2. Dogs

Concentrations at 700,000 and 800,000 ppm for 3 to 5 h induced deep anesthesia in dogs, usually within 1 min (Shulman and Sadove 1967). Respirations remained spontaneous, and blood pressure remained normal. Light anesthesia was induced at concentrations of 500,000 to 600,000 ppm. Emergence time was usually less than 2 min.

The effect of HFC-134a on the histamine-induced bronchial constriction of anesthetized male beagle dogs was studied (Nogami-Itoh et al. 1997). Bronchial constriction in the dogs was induced by the intravenous administration of histamine. The β2-agonist, salbutamol, in metered-dose inhalers was used for treatment of the constriction. When HFC-134a was tested as the propellant for the salbutamol treatment (one to four puffs of 100 or 200 μg of the drug), there was no effect of the HFC-134a on the salbutamol treatment compared with other CFC propellants. HFC-134a added to the formulation had no influence on histamine-induced bronchoconstriction, blood pressure, or heart rate in the anesthetized dogs.

Alexander et al. (1995b) exposed a group of four male and four female beagles to a nominal 12% HFC-134a (120,000 ppm) by means of a face mask. The measured concentration was 118,278 ppm. Two control groups consisting of three males and three females each were used, an atmospheric-air control group and a group exposed to medical-grade air mixed with an additional 12% nitrogen to simulate the depleted oxygen level of the HFC-134a-exposed group. The HFC-134a was approximately 99.3% pure and was specially prepared to contain all likely related hydrocarbons that might be formed during production. The dogs were exposed for 1 h/d for 1 y in order to simulate

prolonged use of a metered-dose inhaler. Clinical signs, body weights, and food consumption were monitored throughout the study, as were effects on the eyes, heart (electrocardiographs), respiratory rate, and pulse rate. Blood was collected at several time points for evaluation of hematology and clinical chemistry parameters, and urine was collected for urinalysis. After 1 y, the animals were sacrificed, and a full necropsy was performed; organs were weighed, and tissues and organs were examined microscopically. One female died on day 263 of causes unrelated to exposure to HFC-134a. After the first few exposures, which resulted in some anxiety as reflected by higher respiratory rates, the animals tolerated the exposure system well. There were no treatment-related effects on any of the measured or observed parameters throughout the study.

3.2.3. Rats

At 280,000 ppm, there was a loss of righting reflex within 10 min (10-min EC_{50}) (Collins 1984). Rats exposed at 205,000 ppm were lethargic and developed tachypnea (Silber and Kennedy 1979a). At 359,300 ppm, trembling and tearing also occurred. No effect was observed after a similar exposure at 81,000 ppm. At 300,000 ppm, anesthesia of rats occurred in less than 2 min (Ritchie et al. 2001). During 15-min exposures at 40,000 to 140,000 ppm, there was no evidence of tearing, nasal discharge, or pulmonary congestion in these same rats, although shallow, rapid breathing and a rapid heart rate were observed after exercise on a motorized running wheel. No longer-term problems were identified during a 30-d observation period. These studies (Ritchie et al. 2001) are discussed further in Section 3.3.

Groups often male rats were exposed at concentrations of 0, 10,000, 50,000, or 100,000 ppm for 6 h/d, 5 d/wk for 2 wk (Silber and Kennedy 1979b). Five rats from each group were sacrificed at the end of the tenth exposure, and the remaining five rats per group were sacrificed after a 14-d recovery period. No treatment-related changes in weight gain, hematology parameters, blood chemistry, or organ weights were observed. Increased incidence of focal interstitial pneumonitis of the lung was the only adverse effect observed in the groups exposed at 50,000 and 100,000 ppm. The fluoride content of the urine was significantly increased in the treated rats.

In a similar study, groups of 16 male and 16 female rats were exposed at concentrations of 0, 1000, 10,000, or 50,000 ppm 6 h/d for 20 d of a 28-d period (Riley et al. 1979). No treatment-related effects were observed with

regard to body weight, clinical signs, hematology, blood chemistry, urine composition, or ophthalmoscopy. Changes in liver, kidney, and gonad weights of male rats in the group exposed at 50,000 ppm were noted with a significant increase in liver weight in the 10,000-ppm group also. In the absence of pathological changes in these organs, Riley et al. (1979) considered these changes physiological adaptations to treatment.

TABLE 3–4 Acute Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Monkey	500,000	1 min	Narcosis	Shulman and Sadove 1967
Dog	500,000	–	Light anesthesia	Shulman and Sadove 1967
	700,000	1 min	Deep anesthesia	
	750,000	3 h	Deep anesthesia with normal, rapid respiration, tachycardia, and stable ECG	
Rat	40,000–140,000	15 min	No tearing or nasal discharge	Ritchie et al. 2001
	300,000	<2 min	Narcosis	
Rat	280,000	10 min	Loss of righting reflex	Collins 1984
Rat	81,100	4 h	No effect	Silber and Kennedy 1979a
	205,200	4 h	Lethargy, rapid respiration	
	359,300	4 h	Lethargy, rapid respiration, trembling, tearing	
Mouse	270,000	–	EC_{50}: loss of righting reflex	Shulman and Sadove 1967
	500,000	<30 s	Narcosis	

3.2.4. Mice

The EC_{50} for anesthesia (measured by the loss of righting reflex) was

270,000 ppm (Shulman and Sadove 1967). At 500,000 ppm, induction time for narcosis was under 30 s, and emergence time at cessation of administration was 10 s or less. Shulman and Sadove (1967) concluded that these concentrations "appear(ed) to have no direct toxic effect."

3.3. Neurotoxicity

HFC-134a has anesthetic and narcotic action at high concentrations. As reported in Section 3.2, the 10-min EC_{50} for anesthesia in rats was 280,000 ppm (Collins 1984), and the EC_{50} in mice was 270,000 ppm (Shulman and Sadove 1967). A concentration of 30% induces narcosis in rats (Ritchie et al. 2001), and at a concentration of approximately 50%, narcosis develops in dogs, cats, and monkeys within a few seconds to minutes (Shulman and Sadove 1967). According to patent information, concentrations of at least 20% are required to induce anesthesia (Larsen 1966).

Ritchie et al. (2001) tested adult male Wistar rats on a motorized rotarod wheel during progressively increasing concentrations of HFC-134a at 0 to 470,000 ppm, with or without added oxygen, or in an operant chamber during 30-min exposures at 40,000, 60,000, 80,000, 100,000, or 140,000 ppm. Using the rotarod apparatus, 3–20 min exposures at 140,000 to 470,000 vapor induced neurobehavioral changes ranging from motor and equilibrium deficits to anesthesia with occasional convulsions. Although there was a progression of effects ranging from slight loss of equilibrium to loss of the righting reflex with increasing concentration, the authors did not correlate specific end points with specific concentrations. Maintaining the oxygen concentration at 21% in the test atmospheres, in contrast to allowing oxygen in the atmospheres to deplete to approximately 11%, did not lengthen the time to any of the end points. Convulsions were observed only in rats subjected to atmospheres in which the oxygen content was not augmented.

In the operant performance test (Ritchie et al. 2001), groups of four rats were exposed separately for four successive test sessions to each test concentration. Performance was measured by the number of food rewards earned in a specific time. The exposures to HFC-134a were for approximately 15 min and were either preceded or followed by a 15-min exposure to room air. Atmospheres were measured with infrared spectrometry. Compared with the air exposures, there were no significant differences in any performance measures during exposures at 40,000 to 100,000 ppm. At 140,000 ppm, food rewards earned were significantly reduced, although the error-to-reward ratios were significantly increased.

In a study with rats involving two generations, locomotor activity, tested with a rotarod apparatus, was not affected by repeated treatment of the dams or young at concentrations up to 64,400 ppm (Alexander et al. 1996). Alexander et al. (1995a) exposed rats at concentrations of 0, 2,500, 10,000, or 50,000 ppm for 1 h daily and mice to concentrations of 2,500, 15,000, or 75,000 ppm, also for 1 h daily, for 18 months (mo). The animals were examined on two consecutive days after 18 mo of exposure (immediately after exposure on one day and 30 min after treatment on the following day) for effects on the central and/or peripheral nervous system using the modified Irwin screen test. There were no changes in behavior attributable to HFC-134a treatment.

3.4. Developmental and Reproductive Toxicity

In a 28-d study conducted by Riley et al. (1979), 16 male rats were exposed to HFC-134a at 0, 1,000, 10,000, or 50,000 ppm 6 h/d, 5 d/wk. Rats exposed at 50,000 ppm exhibited decreased testicular weights. However, in a 13-wk study, no effects on testicular weight were evident (see Section 3.7) (Hext 1989; Collins et al. 1995). In the chronic study (see Section 3.7) (Collins et al. 1995), Leydig (interstitial) cell hyperplasia and benign Leydig cell tumors were reported following exposure at 50,000 ppm for 104 wk; no such effects were reported following exposure for 104 wk at 10,000 ppm. However, it should be noted that these findings are not relevant for humans because the rat is prone to developing these types of tumors spontaneously.

In a developmental toxicity study, Lu and Staples (1981) exposed pregnant CD rats to HFC-134a at 30,000, 100,000, or 300,000 ppm for 6 h/d from days 6 to 15 of gestation. Following exposure of dams at 300,000 ppm, there was a significant reduction in fetal weight and significant increases in several skeletal variations. At 300,000 ppm, signs of maternal toxicity included reduced food consumption, reduced body weight gain, lack of response to noise stimuli, severe tremors, and uncoordinated movements. Dams exposed at 100,000 ppm showed reduced response to noise stimuli and uncoordinated movements. No terata or evidence for developmental toxicity were observed following exposure of dams at 30,000 or 100,000 ppm.

Hodge et al. (1979) exposed groups of 29 or 30 pregnant Wistar-derived rats to HFC-134a at 0, 1,000, 10,000, or 50,000 ppm for 6 h/d on days 6 to 15 of gestation. Abnormal clinical signs were observed in the animals, but there was no effect on maternal body weights. At 50,000 ppm, there was no evidence of terata, but fetal body weight was significantly reduced, and skeletal

ossification was significantly delayed. There were no effects on any parameter at 10,000 ppm.

Groups of 28 pregnant New Zealand white rabbits were exposed at 0, 2,500, 10,000, or 40,000 ppm for 6 h/d on days 7 through 19 of pregnancy (Collins et al. 1995; Wickramaratne 1989a,b). Doe were weighed during the study and sacrificed on day 29 of gestation. For each group, number of corpora lutea, number of implantations and live fetuses per female, percentage of preimplantation and postimplantation loss, percentage of implantations that were early or late intrauterine deaths, gravid uterus weight, litter weight, mean fetal weight, gender ratio, and percentage of fetuses with major or minor skeletal or visceral defects were recorded. No clinical signs were observed in the treated doe. In the mid- and high-dose exposure groups, doe had reduced body weight gains compared with the control group; lower weight gains were partially associated with decreased food consumption. With the exception of a significantly increased incidence of unossified seventh-lumbar transverse process in fetuses in the 10,000- and 40,000-ppm groups, all other parameters were similar among control and treatment groups. This effect was also observed in the control group and was not considered treatment related. Therefore, there was no adverse developmental or teratogenic effect associated with exposure to HFC-134a.

Male and female AHA rats (of both Sprague-Dawley and Wistar origins) were exposed (nose only) at 0 (filtered air), 2,500, 10,000, or 50,000 ppm of HFC-134a (99.3% pure) for 1 h daily throughout gametogenesis, mating, pregnancy, and lactation (Alexander et al. 1996). The HFC-134a was formulated to contain all likely impurities. In the first part of the study, groups of 30 male and 30 female rats (F_0) were treated prior to mating (10 wk for males and 3 wk for females) and during mating. Treatment continued for males until sacrifice at week 18. Treatment continued for females until day 19 of pregnancy; 14 females were sacrificed on day 20, and the fetuses were examined. The remaining females were allowed to deliver litters with no treatment between days 20 and day 1 postpartum. On day 21 postpartum, the F_0 females were sacrificed and examined along with selected F_1 progeny. Selected F_1 rats were raised to maturity and mated. The survival and physical and functional development of the F_1 rats were assessed. Neurotoxicity (locomotor coordination, exploratory activity, and learning activity) was assessed between 4 and 9 wk of age. The survival and physical development of the resulting F_2 progeny were also assessed. There were no adverse effects on the fertility of the F_0 generation and no adverse effects on the maturation and development of the F_1 and F_2 generations. The only treatment-related effect was a slight reduction

in body weight gain of males of the F_0 generation in the 50,000-ppm group.

In the perinatal and postnatal part of the study, groups of 41 female rats were administered concentrations of 1,800, 9,900, or 64,400 ppm of HFC134a (99.3% pure) for 1 h daily during days 17 to 20 of pregnancy and days 1 to 21 postpartum (Alexander et al. 1996). Females were allowed to deliver and rear their young. Selected F_1 animals were mated; these animals were sacrificed on day 20 of pregnancy, and the uterine contents were examined. There were no clinical signs or effects on body weights (F_0), corpora lutea, implants, numbers of live born pups, gender ratio, litter weights, fetal body weights, or development and survival of the F_1 generation. There was a statistically significant delay in the occurrence of pinnae detachment, eye opening, and startle response in the F_1 generation, whose dams inhaled 64,400 ppm. There were no visceral or skeletal abnormalities in the F_1 or F_2 generations.

3.5. Cardiac Sensitization

Mullin and Hartgrove (1979) evaluated the cardiac sensitization potential of HFC-134a with male beagle dogs (Table 3–5; see Section 4.2, Mechanism of Toxicity). Nominal exposure concentrations were 50,000, 75,000, or 100,000 ppm. A fixed dose of epinephrine at 8 μg/kg was used pretest and as the challenge dose after 5 min of exposure to the test chemical. Exposure was continued for 5 min after the challenge. Cardiac rate and EKG were monitored throughout the experiment. No marked response was observed at 50,000 ppm. Two often dogs exhibited multiple ventricular beats during exposures at 75,000 ppm, and two of four dogs showed marked responses at 100,000 ppm; one dog developed multiple consecutive ventricular beats, and one dog was afflicted with ventricular fibrillation leading to cardiac arrest.

Hardy et al. (1991) exposed a group of six male beagles to concentrations at 40,000, 80,000, 160,000, or 320,000 ppm. Because the response to epinephrine alone varied among the dogs, the individual doses (2, 4, or 8 μg/kg) were adjusted to result in a few ectopic beats in the absence of the test chemical. Five or more multifocal ventricular ectopic beats or ventricular fibrillation were considered marked responses. Dogs that had a marked response at one concentration were not tested at higher concentrations. No cardiac sensitization occurred at 40,000 ppm. Two of six dogs responded at 80,000 ppm, and one of the remaining four dogs developed convulsions at 160,000 ppm. Two of the remaining three dogs developed marked responses at 320,000 ppm, and the third suffered convulsions. Blood samples were taken just before administration of the second dose of epinephrine; the lowest concentration

of HFC-134a that was associated with cardiac sensitization was 55 μg/mL. Because the administration of exogenous epinephrine results in an increase in circulating epinephrine concentration—up to ten times the physiological level in stressed animals (Chengelis 1997)—the results of the cardiac sensitization protocol are considered to represent a highly sensitive measurement.

TABLE 3–5 Cardiac Sensitization in Dogs Administered Exogenous Epinephrinea

Concentration (ppm)	Exposure Time[b]	Response[c]	Reference
50,000	10 min	No response (10/10)	Mullin and Hartgrove 1979
75,000	10 min	Marked response (2/10)	
100,000	10 min	Marked response (1/4); death (1/4)	
40,000	10 min	No response (6/6)	Hardy et al. 1991
80,000	10 min	Marked response (2/6)	
160,000	10 min	Convulsions (1/4)	
320,000	10 min	Marked response (2/3); convulsions (1/3)	

[a]Animals were administered intravenous epinephrine at 8 μg/kg (Mullin and Hartgrove 1979) or individualized doses of 2, 4, or 8 μg/kg (Hardy et al. 1991).

[b]Animals were administered epinephrine 5 min into the 10-min exposure.

[c]A marked response is considered an effect; number of animals affected per number of animals tested in parenthesis.

3.6. Genotoxicity

HFC-134a has been tested in a variety of mutagenicity and clastogenicity tests, both in vitro and in vivo. These studies are summarized in Collins et al. (1995), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (1995), and NRC's *Toxicity of Alternatives to Chlorofluoro-carbons: HFC-134a and HCFC-123* (NRC 1996) and include the following: bacterial mutation *(Salmonella typhimurium, Escherichia coli,* and *Saccharomyces cerevisiae)* with and without metabolic activation; chromosome aberrations (human lymphocytes, Chinese hamster lung cells, and inhalation study with the rat); micronucleus assay with the mouse (inhalation at test concentrations at 0, 50,000, or 150,000 ppm for 6 h or 500,000 ppm for 5 h); dominant lethal assay with the mouse (test concentrations at 0, 1,000,

10,000, or 50,000 ppm for 6 h/d for 5 d); and unscheduled DNA synthesis with the rat (test concentrations at 0, 10,000, 50,000, or 100,000 ppm for 6 h). All assays were negative.

3.7. Subchronic and Chronic Toxicity and Carcinogenicity

In a subchronic study, groups of 20 male and 20 female Wistar-derived rats (Alpk:APfSD) were exposed at 0, 2,000, 10,000, or 50,000 ppm for 6 h/d, 5 d/wk for 13 wk (Hext 1989; Collins et al. 1995). Atmospheres were generated by evaporating the test compound and metering it into the air flow supply of each exposure chamber. Samples were automatically collected and analyzed by a gas chromatograph equipped with a flame ionization detector. Half of the animals in each group were sacrificed at the end of the exposure period, and the remaining half were sacrificed after a 4-wk recovery period. Survival, clinical condition, growth, and a variety of hematological, clinical chemistry, and urinary parameters were monitored. During the exposures there were no treatment-related clinical signs. Statistically significant changes in a few urine, blood, and hematological parameters and in organ weights were neither consistent with repeated sampling nor dose related; there were no histological correlates.

In a similar study, groups of 85 male and 85 female rats were exposed to concentrations at 0, 2,500, 10,000, or 50,000 ppm for 6 h/d, 5 d/wk for 104 wk (Collins et al. 1995). Exposure conditions and analytical measurements were identical to procedures followed in the 13-wk study. Ten animals from each group were sacrificed at 52 wk. At 52 and 104 wk there were no effects on clinical condition, food consumption, growth, survival, hematology, clinical chemistry, or urinary parameters. Absolute liver weights of females were increased in the groups exposed at 2,500 and 50,000 ppm but not in the group exposed at 10,000 ppm. Males in groups that received 10,000 or 50,000 ppm for 104 wk had an increased incidence of enlarged testes (not statistically significant), and males in the group that received 50,000 ppm for 104 wk had a statistically significant increase in incidence of Leydig cell hyperplasia (40 vs. 27 in the concurrent control group) and Leydig cell adenomas (23 vs. 9 in the concurrent control group). There was no evidence of progression to malignancy. As discussed earlier, these tumors are not relevant to humans.

Groups of 60 male and 60 female Han-Ibm Wistar rats were exposed nose-only to vapor concentrations of production-grade HFC-134a at 2,500, 10,000, or 50,000 ppm for 1 h daily for 108 wk (Alexander et al. 1995a). The 1-h

treatments were used to more closely simulate daily treatments from metered-dose inhalers. There were no effects on survival, clinical signs, behavior (neurotoxicity), body weights, and hematology or on the type, incidence, site, or severity of gross or microscopic lesions or neoplasms. There was a dose-related increase in incidence and severity of "laryngitis" (not described) in female rats. In contrast to the study by Collins et al. (1995), there were no treatment related effects on Leydig cells. However, the dose was lower in this study. As discussed earlier, these tumors are not relevant to humans.

Groups of 60 male and 60 female B6C3F1 mice were exposed nose-only to vapor concentrations of production-grade HCF-134a at 2,500, 10,000, or 50,000 ppm for 1 h daily for 104 wk (Alexander et al. 1995a). The 1-h treatments were used to more closely simulate daily treatments from metered-dose inhalers. There were no effects on survival, clinical signs, behavior (neurotoxicity), body weights, hematology or on the type, incidence, site, or severity of gross or microscopic lesions or neoplasms.

In a 52-wk oral gavage study with Wistar-derived rats (36 males and 36 females per group), daily administration of 300 mg/kg, in corn oil, for 5 d/wk failed to increase the incidence of any type of tumor compared with corn-oil treated and untreated groups. Rats were sacrificed after 125 wk (Longstaff et al. 1984).

3.8. Summary

HFC-134a has very low acute inhalation toxicity. In rats, lethal concentrations during exposure periods of 15 min to 4 h ranged from >500,000 to >800,000 ppm (Collins 1984; Silber and Kennedy 1979a). Concentrations at 200,000 ppm and greater induce anesthetic-like effects (Larsen 1966). Monkeys, dogs, and mice recovered without adverse effects from anesthetic doses of 270,000 (mice) to 800,000 ppm (dogs), the latter exposures at up to 5 h (Shulman and Sadove 1967).

In a subchronic study, no significant toxicological effects were observed in rats following inhalation at 50,000 ppm (Collins et al. 1995). Likewise, in a chronic study with rats and exposures at 50,000 ppm, no adverse effects other than testicular hyperplasia and benign Leydig cell tumors were observed on microscopic examination (Collins et al. 1995). HFC-134a was not mutagenic or clastogenic in a variety of in vivo and in vitro genetic toxicity tests.

Results from developmental toxicity studies indicate that HFC-134a does not cause terata in rats or rabbits (Collins et al. 1995; Alexander et al. 1996).

Fetotoxicity was observed in rats when dams were exposed at 50,000 ppm (Hodge et al. 1979). Slight maternal toxicity in rabbits, as indicated by lower body weight gains compared with the control group, were noted at 10,000 and 50,000 ppm (Collins et al. 1995). There was a slight delay in physical development of F_1 rats following exposure of F_0 females at 64,400 ppm (Alexander et al. 1996).

HFC-134a is a weak cardiac sensitizer in the epinephrine challenge test in dogs. Epinephrine-induced cardiac arrhythmias were observed at a concentration of 75,000 ppm when doses of epinephrine were not individualized (Mullin and Hartgrove 1979) and at a concentration of 80,000 ppm when doses of epinephrine were individualized (Hardy et al. 1991). No evidence for cardiotoxicity was observed at $\leq$50,000 ppm.

Although there was an increased incidence of testicular Leydig cell adenomas in male rats administered 50,000 ppm for 104 wk (Collins et al. 1995), these tumors do not progress to malignancy (Boorman et al. 1990) and have little significance in humans (Cook et al. 1999). The lack of genotoxicity also supports the conclusion that there is no carcinogenic risk for humans.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition Considerations

4.1.1. Deposition and Elimination

Although absorption of fluorocarbons via inhalation is rapid, and maximal blood concentrations are reached in about 15 min, pulmonary uptake is low (Azar et al. 1973; Trochimowicz et al. 1974; Mullin et al. 1979). Negligible metabolism and tissue retention take place. Blood concentrations fall rapidly following cessation of exposure as the parent compound is exhaled unchanged. Rapid elimination is typical of poorly soluble materials with high vapor pressures and demonstrates a lack of potential to bioaccumulate (Emmen et al. 2000).

In a study designed to gather pharmacokinetic data, two healthy human volunteers were exposed to HFC-134a at 4,000 ppm delivered via a mouthpiece (Vinegar et al. 1997). The exposures were scheduled to last for 30 min. Blood samples were collected throughout the exposures. The exposures were abruptly terminated following an unexpected and uncontrollable rise in pulse rate in one subject and a drop in pulse rate and blood pressure and loss of consciousness in the second. This vasovagal response is sometimes observed

in individuals undergoing clinical investigations or donating blood. In the first subject, the blood concentration of HFC-134a reached 0.7 mg/L (0.7 μg/mL) at 10 min, and in the second subject, the blood concentration reached 1.29 mg/L (1.29 μg/mL). The study by Emmen and Hoogendijk (1998) was commissioned partially in response to the effects observed by Vinegar et al. (1997). It should be noted that four subjects in the study by Emmen and Hoogendijk (1998) nearly fainted during insertion of the indwelling cannula prior to exposure.

In a study with eight human subjects (Emmen and Hoogendijk 1998; Emmen et al. 2000) (Section 2.2), concentrations of the test chemical in blood were measured at 1, 3, 5, 15, 30, and 55 min during exposure and postexposure. The mean blood concentrations in males at 55 min following initiation of exposures to concentrations at 1,000, 2,000, 4,000, and 8,000 ppm were 1.02, 1.92, 3.79, and 7.22 μg/mL, respectively; respective concentrations for females were 1.02, 1.44, 3.06, and 5.92 μg/mL. Concentrations rose rapidly during the first 15 min of exposure and were within 75–100% of levels measured at 55 min. The elimination half-lives at the respective concentrations were at 10.24, 12.69, 12.26, and 9.77 min in males and 11.36, 14.01, 13.20, and 16.69 min in females.

Absorption of ^{18}F-radiolabeled HFC-134a delivered by metered-dose inhalers via a single breath to seven healthy male subjects was rapid, and maximum blood concentrations of approximately 1.1 and 1.3 μg/mL were attained within 30–60 s (Pike et al. 1995; Ventresca 1995). Elimination by ventilation was rapid and biphasic, and there was a half-life of elimination of 31 min. As measured by whole-body γ-counting, HFC-134a was uniformly distributed throughout the body. There was no evidence of metabolism, as disposition of radioactivity was independent of the position of the label. Retention in severe COPD patients was slightly longer than in healthy subjects and was attributed to their decreased ventilatory efficiency. The radioactivity recovered in urine was extremely low—0.006% in healthy subjects and 0.004% in COPD patients. In another study, uptake and elimination were similar in healthy subjects and subjects with mild asthma (Harrison 1996). The half-life in the blood was 5 min. In another study with metered-dose inhalers, blood levels of HFC-134a reached 717 ng/mL (0.72 μg/mL) and 1,381 ng/mL (1.38 μg/mL) 1 min after four and eight inhalations per day, respectively, for 28 d. Circulating concentrations of HFC-134a decreased to one-tenth of the original level by 18 min postexposure (Harrison et al. 1996).

In pregnant rats (Sprague-Dawley and Wistar strains) exposed nose-only at 2,500, 10,000, or 50,000 ppm for 1 h, maximum mean concentrations in the blood during exposure were 3.5, 13.9, and 84.7 μg/mL, respectively (Alexan

der et al. 1996). The elimination half-life was 6–7 min. Following exposure of both male and female rats for 1 h daily for 110 wk, blood concentrations in the 2,500-, 10,000-, and 50,000-ppm groups were 4.2–4.5, 16.5, and 62.3 μg/mL, respectively (Alexander et al. 1995a). In male and female Sprague-Dawley rats exposed to a 15% atmosphere for 1 h, the blood concentration approached equilibrium in 25 min (Finch et al. 1995). The half-life of elimination was <5 min.

With the exception of the first day of exposure, when the mean blood concentration was 549 μg/mL, 1 h daily exposures of beagles at 118,278 ppm resulted in mean blood concentrations between 125 and 254 μg/mL (Alexander et al. 1995b). Absorption was rapid and reached a plateau during the 1-h exposure. Elimination was also rapid, and there was a half-life of 7 min until a blood concentration of approximately 5% of the maximum was reached. The remainder of the compound was eliminated more slowly. There were no gender-related differences in blood concentrations.

In the 10-min cardiac sensitization study with dogs, exposures to concentrations at 40,000, 80,000, 160,000, and 320,000 ppm resulted in mean blood concentrations of HFC-134a at 28.7, 52.2, 79.7, and 154.6 μg/mL, respectively (Hardy et al. 1991).

4.1.2. Metabolism

The carbon-fluorine bond is relatively resistant to metabolism. In vitro studies with rabbit, rat, and human hepatic microsomes and rat hepatocytes (Olson and Surbrook 1991; Olson et al. 1990a, 1990b) identified the major route of metabolism of HFC-134a as oxidation by P-450 2E1 to 2,2,2,1-tetrafluoroethanol; elimination of hydrogen fluoride or fluoride ion yields 2,2,2-trifluoroacetaldehyde, which is further oxidized to trifluoroacetic acid.

Hepatic microsome preparations from 12 human subjects differed in the rate at which HFC-134a was metabolized. In a study that utilized microsomes from human subjects with relatively high P-450 2E1 levels, HFC-134a was metabolized at rates 5-fold to 10-fold greater than in microsomes of individuals with lower levels of this enzyme (Surbrook and Olson 1992).

Following delivery of 1,200 mg of HFC-134a by inhalation from metered-dose inhalers to four healthy adult male volunteers (16 actuations of 75 mg per inhalation; each inhalation within 30 s of the previous inhalation), the only fluorinated urinary component was trifluoroacetic acid. Urinary trifluoroacetic acid accounted for less than 0.0005% of the administered dose, indicating minimal metabolism (Monte et al. 1994).

Metabolism in the rat is qualitatively similar to that in humans. Four male and four female Wistar rats were exposed individually to ^{14}C-labeled HFC134a at 10,000 ppm for 1 h (Ellis et al. 1993). Atmospheres were monitored with a gas chromatograph. After exposure, urine and feces were collected at 6 h intervals up to 24 h and every 24 h for up to 5 d thereafter. Approximately 1% of the inhaled dose was recovered in urine, feces, and expired air; of that 1%, approximately two-thirds was exhaled within 1 h postexposure as unchanged HFC-134a. Exhaled CO_2 was the primary metabolite and accounted for approximately 0.22% and 0.27% of the inhaled dose in males and females, respectively. Excretion in the urine and feces occurred within 24 h and accounted for 0.09% and 0.04% of the inhaled dose, respectively. The only metabolite identified in urine was trifluoroacetic acid. At sacrifice, 5 d postexposure, radioactivity was uniformly distributed among tissues and accounted for 0.14–0.15% of the inhaled dose. The average total metabolized dose in male and female rats was 0.37% of the inhaled dose.

4.2. Mechanism of Toxicity

At high concentrations, HFC-134a has anesthetic and narcotic properties; cardiac sensitization may also occur. The biochemical mechanism(s) of action of these two effects is not well understood. The anesthetic effect was fully reversible.

Inhalation of certain hydrocarbons, including some anesthetics, can make the mammalian heart abnormally sensitive to epinephrine, resulting in ventricular arrhythmias, which in some cases can lead to sudden death (Reinhardt et al. 1971). The mechanism of action of cardiac sensitization is not completely understood but appears to involve a disturbance in the normal conduction of the electrical impulse through the heart, probably by producing a local disturbance in the electrical potential across cell membranes. The hydrocarbons themselves do not produce arrhythmia; the arrhythmia is the result of the potentiation of endogenous epinephrine (adrenalin) by the hydrocarbon.

Although other species have been tested, the dog is the species of choice for the mammalian cardiac sensitization model because the dog is a reliable cardiovascular model for humans, has a large heart size, and can be trained to calmly accept the experimental procedures (Aviado 1994; NRC 1996). The cardiac sensitization test was evaluated by NRC (1996) who recommended that the male beagle be used as the model in this test.

Testing for cardiac sensitization consists of establishing a background (control) response to an injection of epinephrine followed by a second injec

tion during exposure to the chemical of concern (Reinhardt et al. 1971). The dose of epinephrine chosen should be the maximum dose that does not cause a serious arrhythmia (NRC 1996). Because a second injection of epinephrine during air exposure often induces a mild cardiac response, Reinhardt et al. (1971) considered only "marked" responses to the second injection of epinephrine significant cardiac sensitization responses. Cardiac sensitization is defined as greater than five ectopic beats or ventricular fibrillation, as evident on the EKG, in response to epinephrine. Ventricular tachycardia alone is not considered a positive response. The response to injected epinephrine lasts less than 60 s. Concentrations of halocarbons that do not produce a positive response in this short-term test generally do not produce the response when exposures are continued for 6 h (Reinhardt et al. 1971; NRC 1996). This information indicates that cardiac sensitization is a concentration-related threshold effect. Furthermore, the exposure-concen-tration dependent level in the blood determines cardiac sensitization. The study by Hardy et al. (1991) indicated that, for dogs, this concentration is ≥55 μg/mL.

Although this test is useful for identifying compounds capable of cardiac sensitization, the capacity to establish an effect level is limited. The test is very conservative as the levels of epinephrine administered represent an approximate 10-fold excess over blood concentrations that would be achieved endogenously in dogs (Chengelis 1997) or humans (NRC 1996), even in highly stressful situations. According to Mullin et al. (1979), the epinephrine dosage of 8–10 μg/kg/9 s is equivalent to 50–70 μg/kg/min, whereas in times of stress, the human adrenal secretes 4–5 μg/kg/min. In earlier studies with dogs in which a loud noise was used to stimulate endogenous epinephrine release, arrhythmias occurred only at very high halocarbon concentrations (80% halocarbon compound and 20% oxygen) for 30 s (Reinhardt et al. 1971). In another study (Trochimowicz 1997), the cardiac sensitization response was induced in exercising dogs at halocarbon concentrations that were two to four times the concentrations that induced the response with the exogenous epinephrine.

4.3. Structure-Activity Relationships

The halogenated hydrocarbons are generally of low acute toxicity, but several are associated with anesthetic effects and cardiac sensitization. Cardiac sensitization to halogenated alkanes appears related to the number of chlorine or fluorine substitutions. Halogenated alkanes in which >75% of the

halogens consist of fluorine are of low cardiac sensitization potential compared with halogenated alkanes in which ≥50% of the halogen substitutions are chlorine (Hardy et al. 1994). However, halogenation is not necessary for cardiac sensitization to occur (Reinhardt et al. 1971). Compared with presently used chlorofluorocarbon propellants in metered-dose inhalers, HFC-134a is a much weaker cardiac sensitizer; it is two to ten times less potent (Azar et al. 1973; Alexander 1995).

4.4. Other Relevant Information

4.4.1. Species Differences

Few data were located. Lethality data were available for only one species, the rat. In studies that addressed sublethal effects, narcosis was induced at approximately the same concentration in the monkey, dog, rat, and mouse.

4.4.2. Susceptible Populations

1,1,1,2-Tetrafluoroethane has been tested in metered-dose inhalers for the treatment of respiratory diseases. Test subjects included adult and pediatric asthmatic patients as well as individuals with severe COPD. No adverse effects were reported (Smith et al. 1994; Taggart et al. 1994; Ventresca 1995; Woodcock 1995). Structurally related compounds, including 1,1,1-trichloroethane and trichlorofluoromethane, were also tested for cardiac sensitization in dogs with experimentally induced myocardial infarctions. In these experiments cardiac sensitization occurred at the same concentration as in healthy dogs (Trochimowicz et al. 1976). Thus, no sensitive or particularly susceptible populations can be identified for HFC-134a.

4.4.3. Concentration-Exposure Duration Relationship

Insufficient data were available to establish a concentration-exposure duration relationship for a single end point. LC_{50} values for the rat at 15 min and 4 h were several hundred thousand parts per million (Table 3–3).

Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals do not increase as exposure time increases

beyond 15 min. In the study with human volunteers exposed to HFC-134a (Emmen and Hoogendijk 1998), the relationship between exposure concentration and blood level was linear, and at all exposure concentrations (1,000, 2,000, 4,000, and 8,000 ppm), blood concentrations approached equilibrium at 55 min. Cardiac sensitization is considered a concentration threshold phenomenon.

5. DATA ANALYSIS FOR AEGL-1

The AEGL-1 refers to the concentration of an airborne substance at or below which the general population could be exposed without experiencing effects other than mild odor, taste, or slight or mild sensory irritation but above which persons might experience notable discomfort.

5.1. Summary of Human Data Relevant to AEGL-1

No adverse effects were reported in human volunteers exposed to concentrations at 1,000, 2,000, 4,000, or 8,000 ppm for 1 h (Emmen and Hoogendijk 1998). Concentrations of the parent compound in blood appeared to approach equilibrium in <55 min. Following direct inhalation from metered-dose inhalers, no effects were observed in either healthy subjects or pediatric or adult patients with asthma or severe COPD (Smith et al. 1994; Taggart et al. 1994; Ventresca 1995; Woodcock 1995).

5.2. Summary of Animal Data Relevant to AEGL-1

Animals were tested at much higher concentrations than those used in the human study. A concentration of HFC-134a at 40,000 ppm was a no-effect concentration in the cardiac sensitization test with dogs (Hardy et al. 1991). No adverse effects were observed in rats exposed at 81,000 ppm for 4 h (Silber and Kennedy 1979a). Repeated exposure of rats at 100,000 ppm for 6 h/d, 5 d/wk for 2 wk was without clinical signs (Silber and Kennedy 1979b); the interstitial pneumonia observed in the HFC-134a treated group was not observed in other studies with rats or rabbits. Concentrations <200,000 ppm were considered no-effect levels for anesthetic effects in several species (Larsen 1966; Shulman and Sadove 1967).

5.3. Derivation of AEGL-1

The study with human volunteers exposed at 8,000 ppm for 1 h is the basis for the AEGL-1 values. This concentration-exposure duration was a noeffect level for irritation and lung and heart parameters. Although the 1-h concentration at 8,000 ppm is a free-standing NOAEL, animal studies with several species indicate that this concentration is far below any effect level. Humans may differ in their sensitivity to halocarbons, but no clear intraspecies differences were evident at this low concentration or in the studies with asthma and COPD patients. Therefore, the 8,000 ppm concentration was adjusted by an intraspecies uncertainty factor (UF) of 1. The intraspecies UF of 1 is supported by the lack of reported effects in potentially susceptible populations tested with single or repeated exposures from metered-dose inhalers in which HFC-134a was used as the propellant. Potentially susceptible populations included patients with severe COPD (Ventresca 1995) and adult and pediatric asthma patients (Smith et al. 1994; Taggart et al. 1994; Woodcock 1995). Structurally similar compounds have been tested for cardiac sensitization in a dog heart model in which myocardial infarctions were experimentally induced. In this model, cardiac sensitization occurred at the same concentrations as in the undamaged heart.

Circulating concentrations of halocarbons do not increase greatly with time after 15 min of exposure (NRC 1996) and decline rapidly following cessation of exposure (Emmen and Hoogendijk 1998). The parent compound is present in blood; HFC-134a is poorly absorbed and poorly metabolized by body tissues and organs. Because the pharmacokinetic data for humans show that blood concentrations do not increase greatly with time after 55 min, no greater effects (regarding cardiac sensitization) should be experienced at longer exposure intervals. Therefore, the 1-h value of 8,000 ppm was assigned to all AEGL-1 exposure durations (Table 3–6).

The NOAEL value of 8,000 ppm is supported by results of animal studies. No adverse effects were observed in rats exposed at 81,100 ppm for 4 h (Silber and Kennedy 1979a). Adjustment by interspecies and intraspecies UFs of 3 and 3, for a total of 10, results in essentially the same concentration (8,100 ppm) as that based on the human study.

6. DATA ANALYSIS FOR AEGL-2

The AEGL-2 refers to the concentration above which the general popula

tion could experience irreversible or other serious, long-lasting effects or impaired ability to escape.

TABLE 3–6 AEGL-1 Values for HFC-134a (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
8,000 (34,000)	8,000 (34,000)	8,000 (34,000)	8,000 (34,000)	8,000 (34,000)

6.1. Summary of Human Data Relevant to AEGL-2

No human data that address the level of effects defined by the AEGL-2 were located.

6.2. Summary of Animal Data Relevant to AEGL-2

Humans exposed to some halogenated hydrocarbons at high concentrations may develop cardiac arrhythmias, which are potentially fatal. The cardiac sensitization test in dogs is an effective test for determining potential cardiac sensitization in humans. This effect is observed at concentrations well below those causing any acute toxic signs but only in the presence of greaterthan-physiological doses of exogenous epinephrine. In the cardiac sensitization tests with dogs conducted by Hardy et al. (1991), doses of epinephrine were adjusted for each dog to a point at which a mild response occurred in the absence of the test chemical. This individualized dose provides a more accurate physiological protocol than would delivery of a constant dose to each animal. In this study, a second exogenous dose of epinephrine during exposure to HFC-134a did not produce cardiac sensitization (more than the mild effect) at an exposure concentration of 40,000 ppm; cardiac sensitization (a marked response) was induced in two of six dogs at an exposure concentration of 80,000 ppm.

6.3. Derivation of AEGL-2

Although it is an optimized model, the end point of cardiac sensitization is relevant because humans exposed at high concentrations of some halocar

bons can develop cardiac arrhythmias. A no-effect concentration of HFC134a at 40,000 ppm under conditions of exogenous epinephrine was identified as the basis for AEGL-2 values. Because the dog heart is considered an appropriate model for the human heart, an interspecies UF of 1 was applied. Because this is a conservative test, an intraspecies UF of 3 was applied to protect potentially susceptible individuals. Blood concentrations were close to equilibrium within 55 min during human exposures, and concentrations of halocarbons that do not produce a positive response in the short-term cardiac sensitization test do not produce the response when exposures are continued for 6 h, so the value of 13,000 ppm (13,300 ppm rounded to two significant figures) was assigned to all AEGL-2 time periods (Table 3–7).

TABLE 3–7 AEGL-2 Values for HFC-134a (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)

The AEGL-2 value is supported by animal toxicity data, which produce a higher value. The threshold for narcosis for several animal species is approximately 200,000 ppm (Collins 1984; Silber and Kennedy 1979a). Adjustment by interspecies and intraspecies UFs of 3 each (for a total of 10) results in an AEGL-2 value of 20,000 ppm.

7. DATA ANALYSIS FOR AEGL-3

The AEGL-3 refers to the concentration above which death or life-threatening effects may occur.

7.1. Summary of Human Data Relevant to AEGL-3

No human data that address the level of effects defined by the AEGL-3 were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Humans exposed to high concentrations of some halogenated hydrocar

bons may develop heart arrhythmias, which are potentially fatal. The cardiac sensitization test in dogs is an effective test for identification of materials that have the potential to induce cardiac sensitization in humans. This effect is observed at concentrations well below those causing any acute signs of intoxication, but it occurs only in the presence of greater-than-physiological doses of exogenous epinephrine.

TABLE 3–8 AEGL-3 Values for HFC-134a (ppm [mg/m3])

10 min	30 min	1 min	4 min	8 h
27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)

In the cardiac sensitization study with dogs conducted by Hardy et al. (1991), doses of epinephrine were adjusted for each dog to a point at which a mild response occurred in the absence of the test chemical. This individualized dose provides a more accurate physiologic test than would delivery of a constant dose to each animal. In this study, a second exogenous dose of epinephrine during exposure to HFC-134a failed to produce cardiac sensitization (more than the mild effect) at an exposure concentration of 40,000 ppm; cardiac sensitization (a marked response) was induced in two of six dogs at 80,000 ppm. The nominal HFC-134a concentration that results in death could not be ascertained in this study as dogs were not tested at doses higher than those causing the marked response. Death occurred in the Mullin and Hartgrove (1979) study at a concentration of HFC-134a at 100,000 ppm, but doses of exogenous epinephrine were not individualized. (The highest dose of epinephrine [8 μg] was used for all dogs.)

7.3. Derivation of AEGL-3

Although it is an optimized model, the end point of cardiac sensitization is relevant as humans exposed at high concentrations of some halocarbons may develop cardiac arrhythmias. The concentration of 80,000 ppm along with intravenous epinephrine, which induced a marked cardiac response in the dog, was used as the basis for the AEGL-3 values. Because the dog heart is considered an appropriate model for the human heart, an interspecies UF of 1 was applied. Because the cardiac sensitization test is a conservative test, the 80,000 ppm concentration was adjusted by an intraspecies UF of 3 to protect potentially susceptible individuals. Blood concentrations were close to equi

librium within 55 min during human exposures, and concentrations of halocarbons that do not produce a positive response in the cardiac sensitization test do not produce the response when exposures are continued for 6 h, so the value of 27,000 ppm (26,600 ppm rounded to two significant figures) was assigned to all AEGL-3 time periods (Table 3–8).

The AEGL-3 value is supported by additional animal data, which result in a higher value. The highest nonlethal concentration for the rat was a 4-h exposure at 359,300 ppm (Silber and Kennedy 1979a). Adjustment by interspecies and intraspecies UFs of 3 each (for a total of 10) results in an AEGL-3 value of approximately 36,000 ppm. Developmental toxicity studies in which exposures were repeated for 9–13 d (Hodge et al. 1979; Lu and Staples 1981; Collins et al. 1995) also support this value (i.e., no effects following daily exposures to concentrations <30,000 ppm).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End points

AEGL values for various levels of effect were derived using the following methods. The AEGL-1 was based on a controlled 1-h inhalation no-effect level of 8,000 ppm in humans. Because effects occurred in animal studies only at considerably higher concentrations, an intraspecies UF of 1 was applied. Because blood concentrations achieved equilibrium approximately 55 min into the exposure and circulating HFC-134a concentrations determine the level of effect, the 8,000 ppm concentration was applied across all time periods.

The AEGL-2 was based on the threshold for cardiac sensitization using the dog model. Because this test is highly sensitive as the response to exogenous epinephrine is optimized, the 40,000 ppm concentration was adjusted by a single intraspecies UF of 3 to protect potentially susceptible individuals. An interspecies UF was not applied, because the dog is a reliable model for humans, and this is a highly sensitive test. Blood concentrations rapidly reach equilibrium, and the blood concentration determines the effect, so the 13,000 ppm value was used across all time periods.

The AEGL-3 was based on the lowest response that induced a marked cardiac effect in the cardiac sensitization test with the dog. This concentration of 80,000 ppm was adjusted by a single intraspecies UF of 3 to protect potentially susceptible individuals. An interspecies UF was not applied, because the

dog is a reliable model for humans, and this is a highly sensitive test. Blood concentrations rapidly reach equilibrium, and the blood concentration determines the level of effect, so the 27,000 ppm value was applied across all time periods.

The AEGL values are summarized in Table 3–9.

8.2. Comparison with Other Standards and Guidelines

HFC-134a is a relatively new chemical, and only the American Industrial Hygiene Association (AIHA 1991) has developed a workplace guideline. The AIHA Workplace Environmental Exposure Level (WEEL) of 1,000 ppm is an 8-h time-weighted average. The German MAK and Dutch MAC are also 1,000 ppm (German Research Association 1999; Ministry of Social Affairs and Employment 2000).

For establishment of a 1-h Emergency Exposure Guidance Level (EEGL), the NRC (1996; Bakshi et al. 1998) recommended application of a single interspecies UF of 10 to the cardiac sensitization observed in male beagle dogs (40,000 ppm) (Hardy et al. 1991) resulting in a value of 4,000 ppm. Because blood concentrations of several halocarbons rapidly reached equilibrium, the NRC subcommittee also extrapolated this 10-min test to the longer exposure duration of 1 h. The subcommittee proposed a 24-h EEGL of 1,000 ppm based on the NOAEL of 10,000 ppm for fetoxicity in the study by Hodge et al. (1979). The 10,000 ppm concentration was adjusted by a UF of 10 for interspecies variability. It should be noted that the controlled inhalation study with humans (Emmen and Hoogendijk 1998) was not available to the NRC.

8.3. Data Adequacy and Research Needs

The database for HFC-134a is extensive; it contains studies with both human subjects and animal models. Potentially sensitive populations, including patients with COPD and adult and pediatric asthmatic patients, were tested with direct inhalation of HFC-134a from metered-dose inhalers. The response of these groups was no different than that of healthy adults. The animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. The metabolism of HFC-134a is well understood, and the relationship of exposure con

centration to blood concentration (and effect) has been addressed in both humans and dogs. The data were sufficient to derive three levels of AEGLs for the five exposure durations.

TABLE 3–9 Summary of AEGL Values (ppm [mg/m3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	8000 (34,000)	8000 (34,000)	8000 (34,000)	8000 (34,000)	8000 (34,000)
AEGL-2 (Disabling)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)
AEGL-3 (Lethal)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)

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Appendix

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR 1,1,1,2-TETRAFLUOROETHANE (HCF-134a) (CAS No. 811–97–2)

AEGL-1

10 min	30 min	1 h	4 h	8 h
8,000 ppm	8,000 ppm	8,000 ppm	8,000 ppm	8,000 ppm

Key reference: Emmen, H.H., and E.M.G.Hoogendijk. 1998. Report on an ascending dose safety study comparing HFA-134a with CFC-12 and air, administered by whole-body exposure to healthy volunteers. MA-250B-82–306, TNO Report V98.754, The Netherlands Organization Nutrition and Food Research Institute, Zeist, The Netherlands.

Test species/Strain/Number: Eight healthy adult human subjects

Exposure route/Concentrations/Durations: Inhalation: 0, 1,000, 2,000, 4,000, 8,000 ppm for 1 h.

Effects: No effects on tested parameters of blood pressure, heart rate, electrocardiogram (EKG) rhythms, or lung peak expiratory flow.

End point/Concentration/Rationale: The highest no-effect concentration of 8,000 ppm for 1 h was used as the basis for the AEGL-1. This concentration is considerably below the threshold for effects in animal studies. For example, anesthetic effects occur at a concentration of approximately 200,000 ppm.

Uncertainty factors/Rationale:

Total uncertainty factor: 1

Interspecies: Not applicable, human subjects used.

Intraspecies: 1—this no-effect concentration for eight healthy individuals was far below concentrations causing effects in animals. At this low exposure concentration there was no indication of differences in sensitivity among the subjects. This uncertainty factor is supported by the lack of effects in COPD and adult and pediatric asthmatic patients treated with metered-dose inhalers containing HFC-134a as a propellant.

Modifying factor: Not applicable.

Animal to human dosimetric adjustment: Not applied, human subjects used.

Time scaling: Not applied. Effects such as cardiac sensitization have been correlated with blood concentrations. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15 min of exposure. The key study showed that at each exposure concentration, blood

concentrations were approaching equilibrium after 55 min of exposure. Therefore, susceptibility to effects are predicted to remain the same as exposure time increases beyond 1 h.

Data adequacy: The key study was well designed and conducted and documented a lack of effects on heart and lung parameters as well as clinical chemistry. Pharmacokinetic data were also collected. The compound was without adverse effects when tested as a component of metered-dose inhalers on patients with COPD. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. The values are supported by a study with rats in which no effects were observed during a 4-h exposure to 81,000 ppm. Adjustment of the 81,000 ppm concentration by an interspecies and intraspecies uncertainty factors of 3 each, for a total of 10, results in essentially the same value (8,100 ppm) as that from the human study.

AEGL-2

10 min	30 min	1 h	4 h	8 h
13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm

Key reference: Hardy, C.J., I.J.Sharman, and G.C.Clark. 1991. Assessment of cardiac sensitisation potential in dogs: comparison of HFA 134a and A12. Report No CTL/C/2521, Huntingdon Research Centre, Cambridgeshire, U.K.

Test species/Strain/Sex/Number: Male beagle dogs, six total.

Exposure route/Concentrations/Durations: Inhalation: 40,000, 80,000, 160,000, or 320,000 ppm for 10 min (the cardiac sensitization test is a 10-min exposure test). The test is based on the principle that halocarbons make the mammalian heart abnormally sensitive to epinephrine. Epinephrine is administered prior to and during test exposures at doses that are up to ten times higher than levels secreted by die human adrenal gland in time of stress. Doses of epinephrine were adjusted for each individual dog so that administration of epinephrine without the test chemical produced a threshold response.

Effects:

Concentration (ppm)	*Response*
40,000	No response
80,000	Marked response (2/6)
160,000	Convulsions (1/4)
320,000	Marked response (2/3); convulsions (1/3)

A marked response is considered an effect; number of dogs affected per number of dogs tested in parenthesis. Dogs that responded at one concentration were not tested at higher concentrations.

End point/Concentration/Rationale: The no-effect concentration of 40,000 ppm was chosen as the basis for the AEGL-2 because the next higher concentration of 80,000 ppm produced a serious effect.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1—The cardiac sensitization model with the dog heart is considered a good model for humans.

Intraspecies: 3—The test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

Modifying factor: Not applicable.
Animal to human dosimetric adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.
Time scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15–55 min of exposure, and exposure duration did not influence the concentration at which the effect occurred.
Data adequacy: The key study was well conducted and documented. Supporting data include both human and animal studies. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures. No effects other than narcosis occurred in rats and mice exposed at 200,000 ppm for various periods of time. Adjustment by a total UF of 10 results in a higher value (20,000 ppm) than from the cardiac sensitization test with dogs.

AEGL-3

10 min	30 min	1 h	4 h	8 h
27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm

Key reference: Hardy, C.J., I.J.Sharman, and G.C.Clark. 1991. Assessment of cardiac sensitisation potential in dogs: comparison of HFA 134a and A12. Report No CTL/C/2521, Huntingdon Research Centre, Cambridgeshire, U.K.

Test species/Stain/Sex/Number: Male beagle dogs, six total.

Exposure route/Concentrations/Durations: Inhalation: 40,000, 80,000, 160,000, or 320,000 ppm for 10 min (the cardiac sensitization test is a 10-min exposure test). The test is based on the principle that halocarbons make the mammalian heart abnormally sensitive to epinephrine. Epinephrine is administered prior to and during test exposures at doses that are up to ten times higher than levels secreted by the human adrenal gland in time of stress. Doses of epinephrine were adjusted for each individual dog so that administration of epinephrine without the test chemical produced a threshold response.

Effects:

Concentration (ppm)	*Response*
40,000	No response
80,000	Marked response (2/6)
160,000	Convulsions (1/4)
320,000	Market response (2/3); convulsions (1/3)

A marked response is considered an effect; number of dogs affected per number of dogs tested in parenthesis. Dogs that responded at one concentration were not tested at higher concentrations.

End point/Concentration/Rationale: The concentration at 80,000 ppm was chosen as the basis for the AEGL-3 because it produced a serious, life-threatening cardiac arrhythmia in two of six dogs. No dogs died at this or the two higher concentrations, although one of four dogs suffered convulsions at 160,000 ppm, and one of three dogs suffered convulsions at 320,000 ppm.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1—the cardiac sensitization model with the dog heart is considered a good model for humans.

Intraspecies: 3—the test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

Modifying factor: Not applicable.
Animal to human dosimetric adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.
Time scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15–55 min of exposure, and exposure duration did not influence the concentration at which the effect occurred.
Data adequacy: The study was well conducted and documented. Supporting data include both human and animal studies. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures. No deaths occurred in several species of animals exposed for various periods of time to concentrations less than those requiring supplemental oxygen (approximately 700,000 ppm).

4

1,1-Dichloro-1-fluoroethane (HCFC-141b)[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrochlorofluorocarbon-141b, or 1,1-dichloro-1-fluoroethane (HCFC141b), has been developed as a replacement for fully halogenated chlorofluorocarbons because its residence time in the atmosphere is shorter, and its ozone depleting potential is lower than that of presently used chlorofluoro

[1]This document was prepared by the AEGL Development Team comprising Sylvia Talmage (Oak Ridge National Laboratory) and members of the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances including George Rusch (Chemical Manager) and Robert Benson and Kenneth Still (Chemical Reviewers). 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) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes 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; NRC 2001).

carbons. HCFC-141b is used in the production of rigid polyurethane and polyisocyanurate or phenolic insulation foams for residential and commercial buildings. It may also be used as a solvent in electronic and other precision cleaning applications.

HCFC-141b is of low inhalation toxicity. Uptake and elimination are rapid, and most of the absorbed dose is excreted unchanged in the exhaled air. Its effects have been studied with human subjects and several animal species, including the monkey, dog, rat, mouse, and rabbit. In addition, studies addressing repeated and chronic exposures, genotoxicity, carcinogenicity, neurotoxicity, and cardiac sensitization were also available. At high concentrations, halogenated hydrocarbons may produce cardiac arrhythmias; this sensitive end point was considered in the development of AEGL values. The air odor threshold in healthy subjects is approximately 250 parts per million (ppm) (Utell et al. 1997). The ethereal odor is not unpleasant.

Adequate data were available for development of the three AEGL classifications. Inadequate data were available for determination of the relationship between concentration and exposure duration for a fixed effect. However, based on the rapidity with which blood concentrations in humans approached equilibrium, the similarity in lethality values in rats exposed for 4 or 6 hours (h), and the fact that the cardiac sensitization effect is based on a concentration threshold rather than exposure duration, a single AEGL value was used across all time periods for each AEGL classification. Some experimental exposure durations in both human and animal studies were generally long, 4 to 6 h, which lends confidence to using the same value for all exposure durations.

The AEGL-1 value was based on the observation that exercising healthy human subjects could tolerate exposure to concentrations of 500 or 1,000 ppm for 4 h with no adverse effects on lung function, respiratory symptoms, sensory irritation, or cardiac symptoms (Utell et al. 1997). The exercise, which tripled the subjects' minute ventilation, simulates an emergency situation and accelerates pulmonary uptake. Results of the exposure of two subjects for an additional 2 h to the 500-ppm concentration and the exposure of one subject to the 1,000-ppm concentration for an additional 2 h failed to elicit any clear alterations in neurobehavioral parameters. The 4- or 6-h 1,000-ppm concentration is a NOAEL in exercising individuals, there were no indications of response differences among tested subjects, and animal studies indicate that adverse effects occur only at considerably higher concentrations, so the 1,000-ppm value was adjusted by an uncertainty factor (UF) of 1. The intraspecies UF of 1 is supported by the lack of adverse effects in patients with severe

chronic obstructive pulmonary disease (COPD) or asthma who were treated with metered-dose inhalers containing chemically similar chlorofluorocarbon propellants. Because blood concentrations of HCFC-141b rapidly achieved a plateau and did not greatly increase after 55 minutes (min) of exposure, the value of 1,000 ppm was applied to all AEGL-1 time periods. An AEGL-1 of 1,000 ppm is supported by an acute animal study in which no adverse effects were observed in rats exposed at 11,000 ppm for 6 h (Brock et al. 1995). Adjustment of the 6-h 11,000-ppm concentration by interspecies and intraspecies UFs of 3 each, for a total UF of 10, results in essentially the same concentration (1,100 ppm) as that derived from the human data. Furthermore, selection of a subchronic NOAEL of 8,000 ppm in rats (Brock et al. 1995) results in a similar value given the differences in duration of exposure and selection of an appropriate UF.

The AEGL-2 value was based on the lowest concentration that caused cardiac sensitization in dogs administered exogenous epinephrine and exposed to HCFC-141b at concentrations of 2,600, 5,200, 10,000, or 21,600 ppm for 10 min (Mullin 1977). This value of 5,200 ppm is less than the lowest concentrations that caused death by cardiac arrest (10,000 to 20,000 ppm) (Hardy et al. 1989a). Because the dog heart is a good model for that of the human, an interspecies UF of 1 was applied. The cardiac sensitization test is highly sensitive as the response to exogenous epinephrine is optimized, so an intraspecies UF of 3 was applied. Cardiac sensitization is concentration dependent; duration of exposure does not influence the concentration at which this effect occurs. Because the peak circulating HCFC-141b concentration is the determining factor in cardiac sensitization, and exposure duration is of lesser import, the resulting value of 1,700 ppm was assigned to all time periods. The 1,700-ppm concentration is supported by animal studies in which no effects other than prenarcotic signs and/or narcosis were observed in rats and mice exposed at approximately 30,000 ppm for 4 or 6 h (Vlachos 1988; Hardy et al. 1989b; Brock et al. 1995). Adjustment of the 30,000 ppm concentration by interspecies and intraspecies UFs of 3 each, for a total UF of 10, results in a higher concentration (3,000 ppm) than that derived from the cardiac sensitization data.

The AEGL-3 value was based on a concentration of 9,000 ppm, the highest value that resulted in mild to marked cardiac responses but did not cause death in a cardiac-sensitization study with the dog (Hardy et al. 1989a). Because the dog heart is a reliable model for that of the human, an interspecies UF of 1 was applied. The cardiac sensitization test is highly sensitive as the response to exogenous epinephrine is optimized, so a single intraspecies UF of 3 was applied. Cardiac sensitization is concentration dependent; duration

of exposure does not influence the concentration at which this effect occurs. Because the peak circulating HCFC-141b concentration is the determining factor in cardiac sensitization, and exposure duration is of lesser import, the resulting value of 3,000 ppm was assigned to all time periods. The 3,000 ppm concentration is supported by animal studies in which no deaths occurred in rats exposed at 42,800 ppm for 6 h or 45,781 ppm for 4 h (Brock et al. 1995). Adjustment of the 45,781 ppm concentration by interspecies and intraspecies UFs of 3 each, for a total UF of 10, results in a higher concentration (4,600 ppm) than that derived from the cardiac sensitization data.

AEGL values are summarized in Table 4–1.

1. INTRODUCTION

Hydrochlorofluorocarbons (HCFCs) are replacing chlorofluorocarbons (CFCs) in industry because the substitution of hydrogen for halogen in methane and ethane reduces residence time in the stratosphere compared with completely halogenated compounds and causes less depletion of ozone (Aviado 1994). HCFC-141b has been developed as a replacement for CFCs (Brock et al. 1995). In particular, HCFC-141b is a replacement for CFC-11 (trichlorofluoromethane) and is used in the production of rigid polyurethane and polyisocyanurate or phenolic insulating foams (Millischer et al. 1995). These foams are used in insulation for commercial buildings, in insulation foam boards for residences, in residential wall insulation, or in foam fill for refrigerators. HCFC-141b may also be employed as a solvent replacement for CFC-113 in the removal of soldering flux from printed circuit boards, in precision cleaning of intricate parts, and, in combination with a surfactant, in the removal of trace water from intricate parts.

HCFC-141b is produced commercially by the hydrofluorination of 1,1,1-trichloroethane or 1,1-dichloroethylene (ECETOC 1994). It is manufactured by three companies in the United States. In 1992, total world production was 15,000 tons; production was expected to increase to 100,000 tons by 1994 and then be phased out by 2003 (ECETOC 1994).

HCFC-141b is a colorless, volatile liquid with a weak, ethereal odor. The vapor is heavier than air and can displace air in confined spaces. Additional chemical and physical properties are listed in Table 4–2. Experimental studies with human subjects and several mammalian species (monkey, dog, rat, mouse, and rabbit) were located. Animal studies addressed both acute and chronic exposure durations as well as neurotoxicity, genotoxicity, carcinogenicity, and cardiac sensitization.

TABLE 4–1 Summary OF AEGL Values for HCFC-141b (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (Nondisabling)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	No effect in humans (Utell et al. 1997)
AEGL-2 (Disabling)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	Threshold for cardiac arrhythmia in the dog[b] (Mullin 1977)
AEGL-3 (Lethal)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	Threshold for severe cardiac response in the dog[b] (Hardy et al. 1989a)

[a]The ethereal odor of HCFC-141b maybe noticeable to some individuals at the 1,000ppm concentration.
[b]Response to challenge dose of epinephrine (cardiac sensitization test).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Deaths from exposure to HCFCs have occurred during refrigeration repair and the use of HCFCs as solvents (Aviado 1994). Information on one fatality attributable to the use of HCFC-141b was located. A 40-year-old man was found dead inside a degreasing tank in which pure HCFC-141b was used as the degreasing solvent (Astier and Paraire 1997). The tank was free of liquid at the time. The worker wore no protective clothing. Postmortem examination revealed violaceous coloration and edema of the face. Concentrations of HCFC-141b in tissues and organs were as follows: blood, 14 mg/L; and liver and heart, 29 μg/g. Concentrations in the lungs and spleen were said to be less than those in the blood (no specific values given).

TABLE 4–2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	HCFC-141b 1,1-dichloro-1-fluoroethane Freon 141 CFC 141, 141b Refrigerant 141b	CHEMID 1998
Molecular formula	$C_2H_3Cl_2F$	HSDB 2000
Molecular weight	116.95	HSDB 2000
CAS registry number	1717–00–6	HSDB 2000
Physical state	Liquid	ECETOC 1994
Color	Colorless	ECETOC 1994
Solubility in water	Approximately 4 g/L	ECETOC 1994
Vapor pressure	412 mm Hg @25°C	HSDB 2000
Density, g/cm^3 at 20°C	1.24	ECETOC 1994
Melting point	−103.5°C	ECETOC 1994
Boiling point	32°C	ECETOC 1994
Odor	Weak ethereal	ECETOC 1994
Conversion factors	1 ppm=4.85 mg/m^3 1 mg/m^3=0.206 ppm	ECETOC 1994

2.2. Nonlethal Toxicity

The air odor threshold in healthy subjects is approximately 250 ppm (Utell et al. 1997). During a clinical study with exposures at 250, 500, or 1,000 ppm, subjects were asked to record their responses to any perceived odor. At 250, 500, and 1,000 ppm, one, two, and three of eight subjects, respectively, noticed the odor. A subject that responded at 250 and 500 ppm did not notice the odor at 1,000 ppm. In all cases, the odor was rated as mild, which was defined as noticeable but not annoying.

2.2.1. Occupational Exposures

According to information compiled by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (1994), typical 8-h

time-weighted average (TWA) values for different occupations in an HCFC-141b production plant ranged from 1 to 70 ppm. In a research laboratory in which machines using dichlorofluoroethane (isomer not described) as a solvent were operating, grab sample results ranged from 10 to 100 ppm; 8-h TWA values for technicians working in the machine room and a contiguous room were approximately 2 to 9 ppm.

2.2.2. Experimental Studies

Eight healthy volunteers (six males and two females, ages 22–30 years) were exposed to concentrations of HCFC-141b at 0 (purified air), 250, 500, or 1,000 ppm in a 43 m^3 chamber located at the University of Rochester Medical Center's Clinical Research Center (Utell et al. 1997).[2] Liquid HCFC-141b, 99.88% pure, was metered from a reservoir into a heat-regulated delivery tube where it was vaporized to 50 L/min of diluting air. The vapor was then mixed with 10 m^3/min air intake for the exposure chamber and delivered to the chamber through five ceiling defusers. The chamber concentration was monitored with an infrared analyzer calibrated with a gas chromatograph; the gas chromatograph was calibrated with known amounts of HCFC-141b through a closed-loop system.

Two volunteers were exposed at one time for an exposure time of 4 h; the exposure included three 20-min exercise periods. The exposure to air was randomized among the three concentrations, but exposure concentrations were in sequence from lowest to highest. Exposures were separated by at least 1 week (wk). Prior to the first exposure, the subjects underwent a pre-exposure screening, which consisted of a cardiac and respiratory history, physical examination, a baseline electrocardiogram (EKG), blood chemistries with complete blood count, and baseline spirometry. On the day of exposure, subjects filled out a questionnaire involving 17 subjective symptoms. In addition, the following clinical chemistries were obtained: liver function (total bilirubin, lactate dehydrogenase activity, aspartate aminotransferase activity, creatinine), blood parameters (urea nitrogen, total protein, albumin, electrolytes, glucose), complete blood count, spirometry (forced vital capacity [FVC], forced expiratory volume in 1 second [s] [FEV_1], and forced expira

[2]This study was reviewed and approved by the Research Subjects Review Board of the University of Rochester. Informed consent was obtained from all subjects.

tory flow rate at 25% and 75% capacity [$FEF_{25/75}$]), and EKG (rhythm strips). Blood and exhaled air were collected before exposure, after each exercise period, and immediately postexposure for HCFC-141b concentrations. Nasal lavage (to obtain inflammatory response information) was performed pre-exposure, immediately following exposure, and 24 h after each exposure. The exercise period consisted of 20 min on a bicycle ergometer at a rate sufficient to triple the subjects' minute ventilation; there were three 20-min exercise periods during each exposure. Two of the subjects were exposed for an additional 2 h during which time they underwent computerized neurobehavioral testing.

Exposure concentrations were within 3% of targeted concentrations. Clinical chemistry and hematology findings did not differ pre- and postexposure at any concentration. Baseline EKGs were normal and responded appropriately during exercise. There were no differences between air and HCFC-141b exposures. FEV_1 and FEV_1/FVC did not change significantly after exposure. Increases in FVC of 2.5% from baseline immediately after the 500 ppm exposure and 4.4% from baseline 24 h after the 1,000 ppm exposure are considered clinically insignificant. The number of polymorphonuclear neutrophils in nasal lavage fluid was greater pre-exposure than postexposure, which may have been a result of pre-exposure washout. There was no evidence of nasal inflammation. Subjective symptoms such as headache appeared unrelated to exposures. No symptoms consistent with respiratory affects were reported during exposures. Concentrations of metabolites in blood, urine, and expired air are discussed in Section 4.1 (Disposition and Metabolism Considerations). Results of neurobehavioral tests are discussed below.

2.3. Neurotoxicity

In the study with human volunteers (Section 2.2.2) (Utell et al. 1997), two of the subjects were exposed at 0 or 500 ppm for 6 h, and computerized neurobehavioral testing was performed during the last 2 h. One subject also completed neurobehavioral testing during the last 2 h of the 6-h exposure to 1,000 ppm. The neurobehavioral testing was composed of two parts. The first part was a work simulation test that involved simultaneous monitoring of memory, calculation, and visual and auditory activities; the second part involved response time during a cognitive test of arithmetic processing, procedural memory, memory of letter sequence, and visual-spatial processing.

In the first part, scores were generally higher (i.e., performance improved) for one subject at 500 ppm compared with 0 ppm, and there was a slightly higher value at 1,000 ppm compared with 500 ppm. Scores were generally lower for the other subject. Changes in scores were minimal for the response times during the cognitive tests. Subjective mood descriptions prior to and after the test indicated a "decreased activity level" but no changes related to fatigue, happiness, depression, anger, or fear.

2.4. Developmental and Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to HCFC-141b.

2.5. Genotoxicity

No information on genotoxicity in humans was located. In vitro, chromosome aberration assays were negative with human lymphocytes at vapor concentrations of 1.25% to 35% v/v; incubation times ranged from 3 to 24 h (Millischer et al. 1995).

2.6. Carcinogenicity

No information on carcinogenicity in humans was located.

2.7. Summary

A single study with eight human volunteers exposed at 0, 250, 500, or 1,000 ppm for 4 or 6 h addressed clinical chemistry and subjective symptoms as well as neurotoxicity, nasal inflammation, respiratory functions, and metabolism (Utell et al. 1997). There were no significant differences in respiratory and nonrespiratory symptoms and no changes in lung function or nasal lavage parameters before and after exposure. A battery of neurotoxicity tests, undertaken by two of the subjects, failed to show clear pre- and postexposure differences; however, there were too few subjects to make rigorous comparisons. No information on developmental and reproductive toxicity, chronic exposures, or carcinogenicity in humans was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data are summarized in Table 4–3.

3.1.1. Rats

Groups of five male and five female Sprague-Dawley rats were exposed (whole-body) to concentrations at 0 (air), 29,958, 45,781, 68,143, or 77,215 ppm for 4 h in a 115 L chamber (de Rooij 1989; Brock et al. 1995). Atmospheres were generated by heating the HCFC-141 b and diluting the vapor with clean air. The pressure of the supply generator provided a flow rate of 25 L/min. Several samples were collected during each exposure, and the concentrations were measured by gas chromatography and flame ionization. Animals were observed for 14 days (d), and clinical signs, body weights, and food and water consumption were recorded. Twenty-four hour urine samples were collected, and blood samples were collected 48 h postexposure. At death or termination of the study, lungs, liver, and kidneys were examined microscopically. Mortalities for males were 0/5, 0/5, 4/5, and 5/5 for the respective exposures; respective mortalities for females were 0/5, 0/5, 1/5, and 5/5 (time of death was not provided). Calculated LC_{50} values for male and female rats were 58,931 and 64,991 ppm, respectively; the combined LC_{50} was 61,647 ppm. Reduced motor activity, shallow breathing with rapid respiration, and anesthesia were observed at concentrations greater than 29,000 ppm. Above 50,000 ppm, tremors, incoordination, and convulsions were noted in some animals. Clinical signs and respiratory changes in survivors resolved by the next day. Lung-to-body weight ratios were increased in the highest dose group. No treatment-related microscopic changes were observed.

Groups of six male Chr-CD rats were exposed to concentrations at 31,700, 42,800, 50,200, 55,270, 72,400 or 95,950 ppm for 6 h in 20 L chambers (Brock et al. 1995). Atmospheres were generated as above with continuous monitoring by gas chromatography. Clinical signs and body weights were recorded during a 14-d observation period; no histological examinations were performed. Deaths were observed at concentrations at 50,200 ppm and above. Mortalities at the 31,700-, 42,800-, 50,200-, 55,270-, 72,400-, and 95,950-ppm concentrations were 0/6, 0/6, 1/6, 2/6, 6/6 and 6/6. The calculated LC_{50} was 56,700 ppm (time of death was not provided). Clinical signs were similar to those in the above study.

TABLE 4–3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat				de Rooij
male	58,931	4 h	LC_{50}	1989; Brock
female	64,991	4 h	LC_{50}	et al. 1995
combined	61,647	4 h	LC_{50}	
Rat (male)	56,700	6 h	LC_{50}	Brock et al. 1995
Mouse	100,000	30 min	LC_{50}	Davies et al. 1976
Mouse	80,000	30 min	60% mortality	Vlachos 1988

[a]Observed 14 d postexposure.

Sources: de Rooij 1989; Brock et al. 1995.

3.1.2. Mice

Davies et al. (1976) reported unpublished data on concentrations resulting in lethality and narcosis and found a 30-min LC_{50} of 100,000 ppm in Alderley Park mice. The time of death was not stated. In a second study, groups of five male and five female Crl:CD-1(ICR)BR mice were exposed to concentrations at 9,700, 20,000, 30,000, 40,000, or 80,000 ppm for 6 h during preliminary testing (Vlachos 1988). A concentration of 80,000 ppm resulted in 60% mortality (3/5 males and 3/5 females) within 30 min. According to de Rooij (1989), clinical signs were consistent with those of an anesthetic agent. The proximate cause of death was deep anesthesia.

3.2. Nonlethal Toxicity

Results of acute exposures are summarized in Table 4–4. These studies and studies involving longer-term exposures are discussed below.

3.2.1. Nonhuman Primates

During cardiac sensitization tests, cynomolgus monkeys were exposed at 0, 3,000 (one monkey), 5,000 (two monkeys), or 10,000 ppm (two monkeys)

TABLE 4–4 Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Monkey	3,000, 10,000	5 min	No cardiac effect	Hardy et al. 1989a
Dog	2,600, 5,200, 10,000, 21,600	5 min	No cardiac effect	Mullin 1977
Dog	9,000, 12,000, 13,000, 14,000, 15,000, 18,000, 19,000, 20,000	5 min	No cardiac effect	Hardy et al. 1989a
Rat	3,000, 6,000, and 11,000	6 h	No clinical signs; increase in serum phosphate, slight body weight loss	Brock et al. 1995
Rat	>30,000	—	Prenarcotic signs	Hardy et al. 1989b
Rat	2,000–30,000	3 h	No serum biochemical changes, decrease in liver glutathione at ≥8,000 ppm	Loizou et al. 1996
Rat	29,958	4 h	Shallow/rapid respiration, anesthesia	Brock et al. 1995
	42,800	6 h	No deaths	
Rat	45,781	6 h	No deaths	de Rooij 1989; Brock et al. 1995
Mouse	10,000	25 min	No effect on respiratory frequency	Janssen 1989
Mouse	9,700	6 h	No clinical signs	Vlachos1988
	20,000	6 h	No clinical signs	*(Continued)*
	30,000	6 h	No clinical signs	

for 5 min (Hardy et al. 1989a). The vapor was administered to each restrained animal via a face mask. All animals survived these exposures. (See Section 3.4 for discussion on cardiac sensitization.)

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
	34,000	6 h	Lethargy, tremors	
	41,000	6 h	Lethargy, tremors, hunched posture	
Mouse	64,000	30 min	Narcosis in 50% of mice	Davies et al. 1976

[a]Observed for 14 d postexposure (Brock et al. 1995).

3.2.2. Dogs

During cardiac sensitization tests, groups of two purebred male beagle dogs were exposed to concentrations at 0, 2,600, 5,200, 10,000, or 21,600 ppm (Mullin 1977) or concentrations of 9,000, 12,000, 13,000, 14,000, 15,000, 18,000, 19,000, or 20,000 ppm for 5 min (Hardy et al. 1989a). The vapor was administered to each restrained animal via a face mask. Prior to administration of intravenous epinephrine challenge, no evidence for cardiotoxicity was observed at these concentrations. (See Section 3.4 for discussion of cardiac sensitization tests.)

3.2.3. Rats

In acute studies similar to those described in Section 3.1.1, groups of five male and five female CPB-WU Wistar rats were given single nose-only exposures at 0, 3,000, 6,000, or 11,000 ppm for 6 h (Brock et al. 1995). Concentrations were monitored by infrared spectrometry. At sacrifice, lungs, liver, kidneys, and testes were weighed and examined microscopically. No clinical signs were observed during or after exposures. Slight body weight losses were present in all treated groups at day 1, but rats continued to gain weight during the 14-d postexposure period. The only change in clinical chemistry parame

ters was increased serum phosphate at all exposure concentrations. There were no treatment-related microscopic findings.

In the studies reviewed by Brock et al. (1995) and summarized in Section 3.1.1, no deaths occurred in male and female rats exposed at 29,958 or 45,781 ppm for 4 h or in male rats exposed at 31,730 or 42,800 ppm for 6 h. Shallow but rapid respiration and anesthesia were noted at concentrations above 29,000 ppm. A 25 min exposure at 10,000 ppm had no effect on respiratory frequency of male Wistar rats (Janssen 1989).

As part of a pharmacokinetic study, groups of four to six male Wistar rats were exposed singly to concentrations at 2,000, 4,000, 8,000, 20,000, or 30,000 ppm for 3 h in a closed, recirculated-atmosphere exposure chamber and sacrificed 2 h later (Loizou et al. 1996). No changes in serum activities of the enzymes sorbitol dehydrogenase, glutamate dehydrogenase, or lactate dehydrogenase, measured as indicators of tissue damage, were detected. Lung glutathione and liver glutathione disulfide were unchanged, but total liver glutathione was significantly decreased at 8,000 ppm and higher,

Prenarcotic signs were observed in rats inhaling concentrations >30,000 (Hardy et al. 1989b). No further details of this study were provided.

In a 2-wk study, ten male Chr-CD rats were exposed at 0 or 10,000 ppm (one-fifth of the 6-h lethal concentration of 50,000) for 6 h/d, 5 d/wk (Brock et al. 1995). Chamber concentrations were determined with a gas chromatography system. Animals were observed for clinical signs and weighed daily, and urinary and blood samples were collected for clinical chemistry and hematological evaluations. No adverse clinical signs or body weight changes were noted throughout the exposure or the 14-d recovery period. At termination of the exposures, a slightly higher erythrocyte count, slight increases in plasma bilirubin and urinary fluoride, and reduced mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were observed in the exposed group. These findings were not present at the conclusion of the recovery phase. No treatment-related pathological findings were reported; however, murine pneumonia incidence was higher in the treated group than in the controls at the end of the recovery phase.

In a 90-d study with a 4-wk interim sacrifice, groups of 15 male and 15 female Fischer 344 rats were exposed at 0, 2,000, 8,000, or 20,000 ppm for 6 h/d, 5 d/wk in a 4 m^3 stainless steel and glass chamber (Brock et al. 1995). Chamber concentrations were measured by infrared spectrometry. The animals were examined daily, and body weights and food consumption were measured weekly. Prior to sacrifice, blood and urine samples were collected. At the end of 4 wk, five rats per gender per group were sacrificed, and organs

were weighed and tissues samples taken for microscopic examination. The remainder of the rats continued to inhale HCFC-141b for a total 90-d period.

One female rat died of causes unrelated to exposure. At the end of 4 wk, reduced food consumption and body weight decreases of <10% were statistically significant for males in all treatment groups and females in the 20,000 ppm group. Increased chamber temperatures (due to the heat needed to generate the HCFC-141b vapor) in the higher exposure level groups appear to have been responsible for the reduced body weight. Rats in the high-dose group appeared to be less alert, moved more slowly than rats in the other groups, and appeared more responsive to touch (8,000- and 20,000-ppm groups). The following changes in clinical chemistry and hematology parameters were observed in males in the high-concentration and mid-concentration groups: an increase in serum triglycerides and decreases in activities of serum alanine and aspartate aminotransferases. Serum cholesterol was also decreased in the 20,000-ppm group. No compound-related organ weight changes or gross or microscopic pathology were found. After the 90-d exposure, increased serum cholesterol was observed in female rats exposed at 20,000 ppm, and decreased absolute organ weights and increased relative organ weights (brain, heart, kidneys, lung, liver) were observed in both genders exposed at 20,000 ppm for 90 d. The lack of significant findings at 8,000 ppm was indicative of a NOAEL.

In a study similar to that described above, groups of five male and five female Crl:CD(SD) rats were exposed at 1,500, 8,000, or 20,000 ppm for 4 wk with a 2-wk recovery period (Hino et al. 1992). Effects were similar to those observed in the above study, with the following additional observations: a shortened thromboplastin time (females, 8,000- and 20,000-ppm groups), increased MCV (females, 20,000-ppm group), decreased creatinine (females, 1,500- and 20,000-ppm groups), increased albumin and albumin: globulin (males, 20,000-ppm group), and an increased serum calcium concentration (males, 8,000-ppm group). There were no treatment-related gross or microscopic findings. (The study did not clearly state whether the observations were made at the end of the 4-wk exposure or after the 2-wk recovery period.)

3.2.4. Mice

To estimate a maximum tolerated concentration following a 6-h exposure, groups of five male and five female Crl:CD-1(ICR)BR mice were exposed at 9,700, 20,000, 30,000, 41,000, or 80,000 ppm (Vlachos 1988). The mice were observed for clinical signs during exposure and for 2–3 d postexposure. Mice

inhaling 9,700, 20,000, or 30,000 ppm for 6 h showed no clinical signs during or postexposure. Mice exposed at 41,000 ppm were lethargic and developed tremors, dark eyes, and hunched posture. Mice appeared to be narcotized within 15 min of exposure at 80,000 ppm.

Davies et al. (1976) reported a 30-min anesthetic effective concentration (EC_{50}) of 64,000 ppm for Alderley Park mice; no further details were provided.

3.3. Neurotoxicity

Groups often male and ten female Sprague-Dawley rats were exposed at 0, 1,500, 5,000, or 15,000 ppm for 6 h/d, 5 d/wk for 16 wk (Coombs et al. 1992). The following day and at 2 and 4 wk postexposure the animals were studied for neurobehavioral changes (behavior and motor activity, grip strength, pain response, corneal and pinna reflexes, and catalepsy). At weeks 17 and 21, whole-body perfusion fixation was performed on five males and five females from each group and the brain was weighed and the brain and nervous tissue were examined microscopically. No neurobehavioral changes, changes in brain weight, or histopathologic changes were observed in the treated groups.

In a review of studies under the Program for Alternative Fluorocarbon Toxicology II (PAFT), de Rooij (1989) stated that narcosis can be induced in mice after the following exposures: 80,000 in 15 min, 64,000 ppm in 30 min, and 41,000 after 6 h. Clear narcotic signs are observed in both rats and mice at concentrations >30,000 ppm. No further details were provided.

3.4. Developmental and Reproductive Toxicity

Groups of 25 time-mated SPF female rats (Crl:CD BR VAF/plus strain) were exposed at 0, 3,200, 8,000, or 20,000 ppm for 6 h/d on days 6 through 15 of gestation (Rusch et al. 1995). Atmospheres in the 0.7 m^3 stainless steel and glass chambers were analyzed by gas chromatography. Food and water consumption and body weights were monitored. At sacrifice on day 20, maternal organs were examined and uteri were scored for live fetuses, embryonic deaths, implants, corpora lutea, pre- and postimplantation losses, litter weight, and mean fetal weight. Half of the fetuses in each litter were examined for visceral abnormalities, and half were examined for skeletal abnormalities. In the 20,000-ppm exposure group there was a decreased number of live fetuses

per litter (9.7 vs. 11.6 in the control group; $p<0.05$), and that reduction was associated with increased incidences of early embryonic deaths and postimplantation losses. This concentration was also associated with a reduction in litter weight and mean fetal body weight. Associated with the weight decrease was a slight retardation of fetal ossification. There was no evidence for increased malformations in any of the treatment groups. No evidence for developmental toxicity was observed in the lower exposure groups. During exposure at 20,000 ppm, the dams showed a decreased response to noise (time of onset not defined). At this concentration, piloerection, half-closed eyes, hunched posture, diaphragmatic breathing, and increased salivation, observed during the exposures, resolved without sequelae within 30 min postexposure.

Groups of 16 time-mated New Zealand white rabbits were exposed to concentrations at 0, 1,400, 4,200, or 12,600 ppm for 6 h/d on days 7 through 19 of pregnancy (Rusch et al. 1995). Exposure conditions and protocol were similar to those in the rat study above. There was no evidence of treatmentrelated developmental toxicity. During exposures, partially closed eyes and tachypnea were observed in dams of the 4,200- and 12,800-ppm groups; occasional slow, irregular breathing patterns and prone postures were observed in the 12,800-ppm group. These signs were not present postexposure. There were no clinical signs observed in the 1,400-ppm exposure group.

A two-generation reproduction study was conducted with male and female rats (Crl:CD BR VAF/plus strain) with concentrations of HCFC-141b at 0, 2,000, 8,000, or 20,000 ppm for 6 h/d, 7 d/wk (Rusch et al. 1995). The F_0 generation of 32 males and 32 females was treated beginning at age 7 wk for a period of 70 d prior to mating. Exposure continued during the 20-d mating period and up to the presumed day 20 of pregnancy. At that time, exposure continued for males but females were housed in separate cages and allowed to deliver their young (F_{1A} generation) and establish lactation. At 5 d postpartum, females were again exposed during the day and returned to their breeding cages overnight. Females that did not deliver by day 20 of presumed pregnancy were re-exposed beginning 7 d after the presumed day 20 of pregnancy. Females that were identified as nonpregnant were exposed throughout the experiment. The F_0 generation females were mated a second time (with different males), producing an F_{1B} generation. Randomly selected offspring from the F_{1A} litter (28 males and 28 females) were exposed to HCFC-141b under the same conditions as their F_0 parents (females from 4 wk of age until day 20 of presumed pregnancy) and an F_2 generation was produced. For the F_0 generation, body weights, food and water consumption, mating performance, deaths, number of young born, litter loss, and rearing young to wean

ing were recorded. Litters of the F_0 and F_{1A} generations were evaluated at several time points with respect to rearing to weaning, litter size, total live pups, pup loss, litter weight, and mean pup weight.

The only treatment-related observation on reproduction was a decreased number of litters from the F_0 parents exposed at 20,000 ppm. This effect occurred after both matings. The percentages of females with litters in the 0-, 2,000-, 8,000-, and 20,000-ppm groups were 94%, 91%, 88%, and 70%, respectively, for the first mating; and 88%, 84%, 90%, and 66%, respectively, for the second mating. This finding was not present when the F_{1A} parents were mated to produce the F_2 pups. Litter size was similar for all groups following the first F_0 mating but was lower in the 20,000-ppm exposure group following the second mating (12.1 vs. 14.8 in the controls). The litter size was also smaller for this exposure group following the F_{1A} mating (11.5 vs. 13.4 for the controls). Survival and body weights of F_{1A} litters from the four exposure groups to day 4 were similar. Sexual maturation was slightly retarded in male pups, which may have been caused by the slightly lower body weight gain. Adults rats exposed at 20,000 ppm showed an increase in water consumption, slight increase in food consumption, and decrease in body weight. These factors were minimally present in the group administered 8,000 ppm and absent in the group inhaling 2,000 ppm.

3.5. Cardiac Sensitization

In an undated study, HCFC-141b was administered to male SpragueDawley rats at concentrations of 5,000, 10,000, or 20,000 ppm for 30 min (Eger, unpublished data). As exposure continued, bolus intravenous epinephrine, characterized as three times the dose that produced arrhythmias in the same rats anesthetized with halothane, was administered. The dose of epinephrine was defined as "a maximum of 12 μg/kg." For this study, three or more premature ventricular contractions was considered an arrhythmic response (Table 4–5). Marked arrhythmias occurred at all concentrations. The author further compared the concentrations of halothane and HCFC-141b that produced arrhythmias with administration of various doses of exogenous epinephrine. The nominal chamber concentration for HCFC-141b did not differ from that of halothane. Furthermore, the arrhythmias were characterized as relatively mild and within acceptable limits for surgical anesthesia in humans.

In a screening study, dogs were exposed at 2,600, 5,200, 10,000, or 21,600

ppm for 5 min followed by an intravenous challenge of epinephrine at 8 μg/kg (Mullin 1977). A concentration of HCFC-141b at 2,600 ppm was a no-effect level; sensitization was induced in one often dogs at 5,200 ppm, and at higher concentrations, deaths ensued.

In a second study, four male purebred beagle dogs were exposed to HCFC-141b at 9,000–20,000 ppm and wild-caught cynomolgus monkeys were exposed to HCFC-141b at 3,000, 5,000, or 10,000 ppm (Hardy et al. 1989a). Exposures were performed one at a time via a face mask while the animals were restrained. Each dog underwent exposure to several concentrations in a sequence designed to eliminate bias. Electrocardiograms (EKGs) were recorded during exposures. Following 2 min of exposure to air, 10 μg/kg of intravenous epinephrine at a rate of 0.001 mg/second was administered to establish a baseline response. The dose of epinephrine was selected to cause a noticeable effect on the EKG without causing cardiac arrhythmias or ectopic beats. The dose was not individualized for each dog. Five minutes later, the animals were exposed to HCFC-141b for 10 min. At 5 min into the exposure, the same dose of epinephrine was again administered.

In both monkeys and dogs, epinephrine alone induced the normal response of a transient increase in heart rate followed by a reflex slowing and irregularity of the heart rate, which persisted for 1–2 min. Following the second dose of epinephrine (during exposure to HCFC-141b), responses ranged from no response to death in one dog (Table 4–5). A marked response is considered a frank effect level (See Section 4.2). A marked response occurred in one of two monkeys at 5,000 ppm and one of two dogs at 9,000 ppm. The positive response in the dog at 9,000 ppm was the only such finding in nine trials over the concentration range of 9,000 to 13,000 ppm (trials at 10,000 ppm with two dogs were repeated several times with no response). Exposure of one dog at 20,000 ppm followed by the epinephrine challenge produced severe ventricular fibrillation and cardiac failure.

In a follow up to the Hardy et al. (1989a) study, six beagle dogs were exposed to concentrations of HCFC-141b at 10,000 or 20,000 ppm (Hardy 1994). At 10,000 ppm, no dogs responded to epinephrine challenge; five of six dogs exposed at 20,000 ppm also showed no response, and the sixth responded with multifocal ventricular ectopic activity followed by fatal ventricular fibrillation. Because the exogenous epinephrine dose used in these studies results in a circulating epinephrine concentration that is up to ten times the physiological level in stressed animals (Chengelis 1997), the results of the cardiac sensitization protocol are considered to represent a pharmacological bioassay.

TABLE 4-5 Cardiac Sensitization in Animals Exposed to HCFC-141b and Administered Exogenous Epinephrine

Species	Concentration (ppm)	Exposure Time[a]	Effect[b]	Reference
Rat	5,000	30 min	Marked arrhythmia (4/11)	Eger, no date
	10,000	30 min	Marked arrhythmia (13/15)	
	20,000	30 min	Marked arrhythmia (15/15)	
Monkey	3,000	10 min	No EKG effects (1/1)	Hardy et al. 1989a
	5,000	10 min	Marked cardiac response (1/2)	
	10,000	10 min	Marked cardiac response (2/2)	
Dog	2,600	10 min	No effect (10/10)	Mullin 1977
	5,200	10 min	Marked effect (1/10)	
	10,000	10 min	Death ((1/10)	
	21,600	10 min	Death (2/2)	
Dog	9,000	10 min	Marked cardiac response (1/2)	Hardy et al. 1989a
	10,000	10 min	No response (2/2)	
	12,000	10 min	No response (1/1)	
	13,000	10 min	No response (1/1)	
	14,000	10 min	Marked cardiac response (1/2)	
	15,000	10 min	Marked cardiac response (1/2)	
	18,000	10 min	Marked cardiac response (2/2)	
	19,000	10 min	Marked cardiac response (1/2)	
	20,000	10 min	Death (1/1)	
Dog	10,000	10 min	No response ((0/6)	Hardy 1994
	20,000	10 min	No response (5/6); death (1/6)	

[a]Rats were administered an intravenous dose of epinephrine of up to 12 μg/kg after 30 min of exposure to the test compound; monkeys and dogs were administered 8 μg/kg (Mullin 1977) or 10 μg/kg (Hardy et al. 1989a) 5 min into the 10-min exposures. Dogs were administered individualized doses of epinephrine of 2 to 12 μg/kg (Hardy 1994).

[b]A marked response is considered an effect; number of animals affected per number of animals tested in parenthesis.

3.6. Genotoxicity

The potential genotoxicity of HCFC-141b, in the vapor phase, was tested in a battery of tests with respect to both mutation and clastogenic end points (Millischer et al. 1995). Bacterial gene mutation assays with *Salmonella typhimurium* and *Escherichia coli* were negative in all strains with and without metabolic activation at concentrations up to 35%. In vitro, chromosomal aberration assays were positive with Chinese hamster ovary cells but negative with human lymphocytes. In other tests for chromosomal aberrations in Chinese hamster ovary cells, one study showed an increase in gaps but not aberrations when HCFC-141b was incorporated as the liquid into the culture medium (Wilmer and De Vogel 1988); the other study gave positive results using vapor concentrations up to 35% (Bootman and Hodson-Walker 1988). There was no evidence for clastogenicity in the mouse bone marrow micronucleus assay in which exposure was by inhalation at 34,000 ppm for 6 h (Millischer et al. 1995). Similar negative results were found in an earlier test with CD-1 mice that inhaled 2,000, 8,000, or 20,000 ppm for 6 h (Bootman et al. 1988a).

There was no increase in mutation frequency at the hypoxanthine-guanine phosphoribosyl transferase gene locus in the presence or absence of S9 (Bootman et al. 1988b), and results were negative in a DNA repair assay with *E. coli* (Hodson-Walker and May 1988).

3.7. Chronic Toxicity and Carcinogenicity

In a chronic inhalation study, groups of 80 male and 80 female SpragueDawley (Crl:CD[SD]BR) rats were exposed at 1,500, 5,000, or 15,000 ppm for 6 h/d, 5 d/wk for 104 wk (Millischer et al. 1995). Because of the lack of significant toxicity in the group inhaling 15,000 ppm, this concentration was increased to 20,000 ppm after 17 wk. Atmospheres were monitored regularly during the 6-h exposure using gas chromatography and flame ionization detection. Hematology and clinical chemistry analyses were performed at weeks 13, 26, 52, 78, and 104. Ten animals of each gender were sacrificed and autopsied after 52 wk. Two deaths each in the control and low-exposure groups and one in the high-exposure group were not considered treatment related.

No clinical signs were noted in any of the groups. Survival was similar among control and treated groups, and survival in the male treated groups was higher than in the control group. No exposure-related effects involving clini

cal signs, hematology, clinical chemistry, urinalysis, or organ weights were observed. Reduced food intake accompanied by reduced rates of body weight gain in both genders was evident during the first weeks of the study at an exposure concentration of 15,000 ppm. Although the rates of body weight gain were similar among groups thereafter, the final body weight in the 15,000-ppm group remained depressed. There were no treatment-related changes in the respiratory tract.

Macroscopic and microscopic examinations revealed testicular pathology. At study termination there were statistically significant increases in interstitial cell (Leydig cell) adenomas in the 5,000- and 20,000-ppm groups. As discussed earlier, these tumors are not relevant to humans. Incidences of testicular hyperplasia and seminiferous tubule atrophy were marginally increased. The incidence of adenomas in the 20,000-ppm group was lower than in the 5,000-ppm group, 17% and 20%, respectively, indicating a lack of dose-response.

3.8. Summary

HCFC-141b has a very low order of acute toxicity by inhalation. LC_{50} values for the rat and mouse were >50,000 ppm for time periods of 30 min to 6 h. A 6-h exposure at 41,000 ppm can induce narcosis in mice, and concentrations of >30,000 ppm caused prenarcotic signs in mice and rats. Lethargy, tremors, and body weight loss were observed in mice exposed at 34,000 ppm for 6 h. Exposure of rats to concentrations at 30,000 ppm for 3 h and 11,000 ppm for 6 h resulted in minor liver enzyme and serum biochemical changes, respectively.

In studies utilizing repeated exposures (6 h/d, 5 d/wk for up to 13 wk), exposure of male and female rats at 8,000 ppm (4 and 13 wk) and 10,000 ppm (2 wk) resulted in biochemical changes and an increased responsiveness to touch (8,000 ppm) but no clinical signs or clinical pathology. Repeated exposures at 20,000 ppm resulted in reduced alertness, nonsignificant reduction in food consumption and body weight gain, and nonsignificant biochemical changes but no macroscopic or microscopic effects on tissues or organs. Repeated exposures of male and female rats at concentrations up to 15,000 ppm for 16 wk failed to affect neurobehavioral parameters or produce histopathological changes in the brain.

Lifetime exposures of male and female rats to concentrations as high as 20,000 ppm produced no significant toxicity (Millischer et al. 1995). Chronic exposures resulted in only minimal effects on body weight and an increased

incidence of benign testicular interstitial cell tumors. These tumors occur commonly in the aging rat, although the incidences were greater than the range of historical control values. Interstitial cell (Leydig cell) adenomas in the rat rarely progress to malignancy (Boorman et al. 1990). The authors (Millischer et al. 1995) attributed these tumors at high exposure levels in aging rats to a change of the senile hormonal imbalance in geriatric rats. This species-specific occurrence would indicate little tumorigenic risk to human males. It should be noted that the NRC Subcommittee to Review Toxicity of Alternatives to Chlorofluorocar-bons did not consider an increase in Leydig cell tumors applicable to humans (Bakshi et al. 1998). Although results were mixed in standard assays for genotoxicity (with positive results for chromosomal aberrations only in Chinese hamster ovary cells), evaluation of the weight of evidence indicated that HCFC-141b showed no significant genotoxic activity. The primarily negative results in genotoxicity assays also support the conclusion of no carcinogenic risk for humans.

Increased postimplantation loss and reduced litter and fetal weights were associated with overt maternal toxicity in rats exposed at 20,000 ppm on days 6 through 16 of gestation. In rabbits, maternal toxicity was observed at 12,600 ppm. There was no evidence of congenital malformations in either species that could be attributed to HCFC-141b exposures.

Cardiac arrhythmias were induced in rats injected with exogenous epinephrine and exposed to HCFC-141 b at 5,000 ppm. However, the intravenous dose of epinephrine required was 3-fold that which induced arrhythmias in the same rats administered halothane, a common clinical anesthetic. Furthermore, the arrhythmias were characterized as mild. The threshold for cardiac sensitization for dogs was approximately 5,200 ppm. Deaths occurred in one study at 10,000 ppm and in another study at 20,000 ppm (with no deaths between concentrations of 9,000 and 19,000 ppm).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition Considerations

4.1.1. Deposition

Healthy male and female human subjects (ages 22–30 y) were exposed two at a time to HCFC-141b in a 45-m^3 chamber (see Section 2.2.1) (Utell et al. 1997). Concentrations were 0, 250, 500, or 1,000 ppm as measured by an

infrared analyzer. Mean expired concentrations while breathing 250, 500, or 1,000 ppm were 213.7, 407.2, and 837.9 ppm, respectively. These values yield mean depositions of 15.3%, 16.5%, and 16.6%, respectively. The percent deposition was similar during the three exercise periods. At 24 h postexposure, expired concentrations ranged from 0 to 5 ppm.

Blood measurements of HCFC-141b were made prior to exposure, after each exercise period (55, 145, and 225 min into exposure), and 24 h postexposure (Utell et al. 1997). Mean peak circulating concentrations occurred after 225 min (approximately 4 h) of exposure and were 0.90, 1.65, and 2.98 μg/g of blood, respectively, at the three nominal concentrations. The relationship between exposure concentration and blood level appeared linear and reached a plateau at the 250-ppm concentration by 145 min. For all exposure concentrations, the blood concentrations at 55 min were within 80% of the concentrations at 225 min. For volunteers that underwent neurobehavioral testing, circulating HCFC-141b concentrations after 6 h at 500 and 1,000 ppm were 1.56 and 3.33 μg/g, respectively. These values were similar to those at 4 h.

Gas uptake studies with rats showed that pulmonary absorption of HCFC-141b into the systemic circulation is a first-order process (Loizou and Anders 1993; Loizou et al. 1996).

4.1.2. Metabolism

In the Utell et al. (1997) study, urine samples were collected prior to exposure, at the end of exposure (0–4 h), and at 4–12 h and 12–24 h for measurement of metabolites (Tong et al. 1998). The major metabolite was 2,2-dichloro-2-fluoroethyl glucuronide. Excretion of the metabolite was dose-dependent with the highest amounts present in the 4–12 h urine samples. A small amount of dichlorofluoroacetic acid was present. HCFC-141b was not detected in blood 24 h after exposure.

Metabolism in rats was similar to that of humans, with formation of 2,2-dichloro-2-fluoroethanol followed by conjugation with glucuronic acid and excretion in the urine. Four to six male Fischer 344 rats were exposed individually by inhalation for 3 or 6 h in a 1.67 liter closed-chamber recirculating exposure system (Loizou and Anders 1993; Loizou et al. 1996). Concentrations at 1,000, 3,000, 5,000, 8,000, or 10,000 ppm for 6 h (first study) or 2,000, 4,000, 8,000, 20,000, or 30,000 ppm for 3 h (second study) were measured during the exposures by gas chromatography. Uptake was rapid during

an initial 100 min followed by a slow linear accumulation. The blood: air partition coefficient was 2.10. The relationship between exposure and excretion was linear over the exposure concentration range studied. The only urinary metabolite formed at concentrations <40,000 ppm was 2,2-dichloro-2-fluoroethanol (via cytochrome P-450 2E1), which was conjugated with glucuronic acid. At 40,000 ppm, a small amount of the alcohol was oxidized to 2,2-dichloro-2-fluoroacetic acid (Harris and Anders 1991; Loizou et al. 1996).

HCFC-141b is a poor substrate for cytochrome P-450 2E1, and the level of metabolism is low (Harris and Anders 1991). Pharmacokinetic data indicate that <6% of the inhaled dose was metabolized, and the rest was excreted unchanged (Loizou et al. 1996).

4.2. Mechanism of Toxicity

HCFC-141b at high concentrations has anesthetic and narcotic properties; cardiac sensitization may also occur. The biochemical mechanism(s) of action of these two effects is not well understood.

Inhalation of certain hydrocarbons, including some anesthetics, can make the mammalian heart abnormally sensitive to epinephrine, resulting in ventricular arrhythmias, which in some cases can lead to sudden death (Reinhardt et al. 1971). The mechanism of action of cardiac sensitization is not completely understood but appears to involve a disturbance in the normal conduction of the electrical impulse through the heart, probably by producing a local disturbance in the electrical potential across cell membranes. The hydrocarbons themselves do not produce arrhythmia; the arrhythmia is the result of the potentiation of endogenous epinephrine (adrenalin) by the hydrocarbon.

Although other species have been tested, the dog is the species of choice for the mammalian cardiac sensitization model as they serve as a reliable cardiovascular model for humans, possess a large heart size, and can be trained to calmly accept the experimental procedures (Aviado 1994; NRC 1996). The cardiac sensitization test has been evaluated by NRC (1996) who recommended that the male beagle be used as the model in this test.

Testing for cardiac sensitization consists of establishing a background (control) response to an injection of epinephrine followed by a second injection during exposure to the chemical of concern (Reinhardt et al. 1971). The dose of epinephrine chosen is the maximum dose that does not cause a serious arrhythmia (NRC 1996). Because a second injection of epinephrine during air exposure often induces a mild cardiac response, Reinhardt et al. (1971) con

sidered only "marked" responses to the second injection of epinephrine a significant cardiac sensitization response. Cardiac sensitization is defined as greater than five ectopic beats or ventricular fibrillation, as evidenced on the EKG, in response to epinephrine. Ventricular tachycardia alone is not considered a positive response. The response to injected epinephrine lasts less than 60 s. Concentrations of halocarbons that do not produce a positive response in this short-term test generally do not produce the response when exposures are continued for 6 h (Reinhardt et al. 1971; NRC 1996). This information indicates that cardiac sensitization is a concentration-related threshold effect.

Although this test is useful for identifying compounds capable of cardiac sensitization, the capacity to establish an effect level is limited. The test is very conservative as the levels of epinephrine administered represent an approximate 10-fold excess over blood concentrations that would be achieved endogenously in dogs (Chengelis 1997) or humans (NRC 1996), even in highly stressful situations. The dose of epinephrine is chosen to be just below the threshold for inducing a cardiac effect. In earlier studies with dogs in which a loud noise was used to stimulate endogenous epinephrine release, arrhythmias occurred only at very high concentrations of halocarbons (80% halocarbon compound and 20% oxygen) for 30 s (Reinhardt et al. 1971).

4.3. Structure-Activity Relationships

The halogenated hydrocarbons are generally of low acute toxicity, but several are associated with anesthetic effects and cardiac sensitization. Cardiac sensitization of halogenated alkanes appears related to the number of chlorine or fluorine substitutions. Halogenated alkanes in which >75% of the halogens consist of fluorine are of low cardiac sensitization potential compared with halogenated alkanes in which ≥50% of the halogen substitutions are chlorine (Hardy et al., 1994). However, halogenation is not necessary for cardiac sensitization to occur, as it has been reported to occur with hydrocarbons (Reinhardt et al. 1971).

4.4. Other Relevant Information

4.4.1. Species Variability

Concentrations <20,000 ppm appeared to be no-effect levels among the

dog, rat, and mouse. Induction of anesthesia occurred at approximately 30,000 ppm for both the rat and mouse.

4.4.2. Susceptible Populations

No information on potentially susceptible populations was located for HCFC-141b. A structurally related chemical, 1,1,1,2-tetrafluoroethane, has been tested in metered-dose inhalers for the treatment of asthma. Test subjects included adult and pediatric asthma patients as well as individuals with severe COPD. No adverse effects were reported (Smith et al. 1994; Taggart et al. 1994; Ventresca 1995; Woodcock 1995). The structurally related chemicals trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) are presently used in metered-dose inhalers for the treatment of asthma but are phased out under the Montreal Protocol of 1987 (Alexander 1995). Structurally related compounds including 1,1,1-trichloroethane and trichlorofluoromethane were also tested for cardiac sensitization in a dog model with experimentally induced myocardial infarction. In these experiments cardiac sensitization occurred under the same conditions as in healthy dogs (Trochimowicz et al. 1976).

4.4.3. Concentration-Exposure Duration Relationship

Insufficient data were available to establish a concentration-exposure duration relationship for a single end point. LC_{50} values for the male rat were similar at 4 and 6 h (58,931 and 56,700 ppm, respectively), indicating a plateau. Only one exposure duration involving lethality was available for the mouse, a mean 30-min LC_{50} of approximately 90,000 ppm.

Time scaling may not be applicable to halogenated hydrocarbons as blood concentrations of these chemicals do not increase as exposure time is increased beyond 5–10 min (Bakshi et al. 1998). In the Utell et al. (1997) study with human volunteers exposed to HCFC-141b, the relationship between exposure concentration and blood level was linear and reached equilibrium at 250 ppm within 145 min. Graphical representation of the exposure time-blood concentration indicated that at the higher concentrations, equilibrium was approached at 225 min, and at 55 min concentrations were within 80% of the 225 min concentration. Furthermore, the circulating HCFC-141b concentration, rather than duration of exposure, defines whether or not a cardiac response will occur.

5. DATA ANALYSIS FOR AEGL-1

The AEGL-1 refers to the concentration of an airborne substance below which the general population could be exposed without experiencing symptoms other than mild odor or taste or other slight or mild sensory irritation but above which persons might experience notable discomfort.

5.1. Summary of Human Data Relevant to AEGL-1

The study in which eight exercising subjects were exposed to concentrations at 250, 500, or 1,000 ppm for 4 h and one subject was exposed at these concentrations for 6 h (Utell et al. 1997) is relevant to the derivation of the AEGL-1. The absence of any measurable adverse effect indicates that these concentrations are below those defined by the AEGL-1. No symptoms, clinical signs, or respiratory effects were associated with these exposures. It should be noted that EKG tracings indicated that the heart responded in a normal manner for all exposures, even during exercise.

5.2. Summary of Animal Data Relevant to AEGL-1

In the studies that did not involve special procedures such as the cardiac sensitization test, exposures to concentrations up to 30,000 ppm for up to 6 h did not induce clinical signs in mice (Vlachos 1988). At 30,000 ppm and lower concentrations, only nonsignificant serum or liver biochemical changes occurred in rats that inhaled HCFC-141b for >3 h (Brock et al. 1995; Loizou et al. 1996).

5.3. Derivation of AEGL-1

In the Utell et al. (1997) study with exercising humans, the highest concentration tested, 1,000 ppm for 4 or 6 h, was a no-effect level. Although humans may differ in their sensitivity to halocarbon chemicals, no clear variations for this chemical were observed in the key study. The exercise period takes into consideration stress that humans might undergo under emergency conditions. Although the 1,000 ppm is a free-standing NOAEL, the animal studies indicate that this concentration is far below any adverse effect level.

Thus, the 4- or 6-h NOAEL of 1,000 ppm in exercising humans was se

lected as the basis for the AEGL-1. Because it is a no-effect level in exercising subjects and there were no indications of differences in responses among the subjects, an intraspecies uncertainty factor (UF) of 1 was applied. The intraspecies UF is supported by the lack of adverse effects in patients with respiratory diseases who use metered-dose inhalers containing structurally related chemicals as the major propellant. Because the pharmacokinetic data indicated that the blood concentration of humans exposed at 1,000 ppm does not greatly increase with time after 55 min and dog studies showed that the circulating concentration of HCFC-141b, rather than duration of exposure, is the defining factor for the cardiac response, the same value was adopted across all AEGL-1 time points (Table 4–6).

Studies with laboratory animals support an AEGL-1 of 1,000 ppm. Only nonsignificant liver and serum biochemical changes occurred in rats exposed at 30,000 ppm for 3 h or 11,000 ppm for 6 h (Table 4–4). Adjustment of the 6-h, 11,000-ppm concentration by interspecies and intraspecies UFs of 3 each, for a total of 10, results in essentially the same concentration (1,100 ppm) as that derived from the human data.

6. DATA ANALYSIS FOR AEGL-2

The AEGL-2 refers to the concentration above which the general population could experience irreversible or other serious, long-lasting effects or impaired ability to escape.

6.1. Summary of Human Data Relevant to AEGL-2

No human data that address the level of effects defined by the AEGL-2 were located.

6.2. Summary of Animal Data Relevant to AEGL-2

Humans exposed at high concentrations of some halogenated hydrocarbons can develop cardiac arrhythmias. The cardiac sensitization test in dogs is considered an effective determination of potential cardiac sensitization in humans. Cardiotoxicity was observed at concentrations well below those associated with any acute toxic signs but only in the presence of greater-than-physiological doses of exogenous epinephrine.

TABLE 4–6 AEGL-1 Values for HCFC-141b (ppm [mg/m3])

10 min	30 min	1 h	4 h	8 h
1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)

In a well-conducted study with dogs, the threshold for cardiac sensitization was 9,000–10,000 ppm (Hardy et al. 1989a), although 5,200 ppm was the threshold in an earlier study (Mullin 1977). Although neither author distinguished the level of effect at the threshold concentrations from the marked cardiac toxicity that occurred at higher concentrations, the 5,200-ppm concentration in the Mullin (1977) study was below that causing death in the dog (by a factor of 3, approximately) in the Hardy et al. (1989a) study. Furthermore, although cardiac sensitization occurred, the animal recovered from the event, and no cardiac sensitization occurred at the three next highest concentrations in the Hardy et al. (1989a) study.

6.3. Derivation of AEGL-2

Although it is an optimized model (injected epinephrine results in up to ten times the physiological level in stressed animals), the end point of cardiac sensitization is relevant to human exposures because humans exposed at high concentrations of some halocarbons can develop cardiac arrhythmias. The supersensitivity of the animal model might argue for application of no uncertainty factors (UFs). The 5,200-ppm concentration, which appears to be the threshold for cardiac sensitization in the dog, was chosen as the basis for the AEGL-2 values. Because the dog heart is a reliable model for that of the human, an interspecies UF of 1 was applied. Because this is a conservative test, an intraspecies UF of 3 was applied to account for potentially susceptible individuals. Blood concentrations were at equilibrium within approximately 55 min during human exposures, and concentrations of halocarbons that do not produce a positive response in this short-term test generally do not produce the response when exposures are continued for 6 h, so the value of 1,700 ppm was applied across all AEGL-2 time periods (Table 4–7).

The 1,700 ppm AEGL-2 is supported by studies in which no effects other than prenarcotic signs and/or narcosis were observed in rats and mice exposed at approximately 30,000 ppm for 4 or 6 h (Vlachos 1988; Hardy et al. 1989b; Brock et al. 1995). Adjustment of the 30,000 ppm concentration by inter

species and intraspecies UFs of 3 each, for a total of 10, results in a higher concentration (3,000 ppm) than that derived from the dog cardiac sensitization data.

TABLE 4–7 AEGL-2 Values for HCFC-141b [ppm (mg/m3)]

10 min	30 min	1 h	4 h	8 h
1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)

7. DATA ANALYSIS FOR AEGL-3

The AEGL-3 refers to the concentration above which death or life-threatening effects may occur.

7.1. Summary of Human Data Relevant to AEGL-3

No human data that address the level of effects defined by the AEGL-3 were located.

7.2. Summary of Animal Data Relevant to AEGL-3

The highest concentration that caused cardiac sensitization but no deaths in dogs given intravenous epinephrine was 9,000 ppm (Hardy et al. 1989a).

7.3. Derivation of AEGL-3

The 9,000-ppm concentration, which appears to be the threshold for death in the dog cardiac sensitization test, was chosen as the basis for the AEGL-3 values. Because the dog heart is a reliable model for that of the human, an interspecies UF of 1 was applied. This concentration was adjusted by an intraspecies UF of 3 to account for potentially susceptible individuals. Adjustment by an intraspecies UF of 3 was considered sufficient because the cardiac sensitization test is a conservative model. (The dose of epinephrine results in a level greater than physiological by up to a factor of 10.) Using the

same reasoning as for the AEGL-2 values above, the value of 3,000 ppm was applied to all AEGL-3 time periods (Table 4–8).

TABLE 4–8 AEGL-3 Values for HCFC-141b [ppm (mg/m3)]

10 min	30 min	1 h	4 h	8 h
3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)

The NOAELs for developmental effects in rats and rabbits exposed to HCFC-141b during pregnancy were 8,000 and 12,600 ppm, respectively (Rusch et al. 1995). There was no evidence of congenital malformation during these and higher exposures, and signs of developmental toxicity were attributed to concomitant overt maternal toxicity. A concentration of 8,000 ppm was also a NOAEL in the two-generation study with rats (Rusch et al. 1989), but the study protocol has the disadvantage of very long duration for application to acute exposure scenarios.

In lethality studies, the highest nonlethal concentrations were as follows: rat, 4 h, 45,781 ppm (Brock et al. 1995); rat, 6 h, 42,800 ppm (Brock et al. 1995); and mouse, 6 h, 41,000 ppm (Vlachos 1988). Using the highest NOAEL for death and UFs of 3 for interspecies variability and 3 for intraspecies variability, the AEGL-3, based on the threshold for lethality, would be approximately 4,600 ppm.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL-1 was based on a 4- or 6-h NOAEL of 1,000 ppm in exercising human volunteers. Because effects occurred in animal studies only at considerably higher concentrations, an intraspecies UF of 1 was applied. Because blood concentrations of HCFC-141b did not greatly increase after 55 min of exposure, the resulting value of 1,000 ppm was used for all time periods.

The AEGL-2 was based on the threshold for cardiac sensitization using the dog model. This concentration was 5,200 ppm. Because the cardiac sensitization test is highly sensitive as the response to epinephrine is optimized, a single intraspecies UF of 3 was applied. Cardiac sensitization is concentration dependent; duration of exposure failed to influence the circulating concentration at which this effect occurred. Because cardiac sensitization is concen

tration dependent, the resulting value of 1,700 ppm was assigned to all time periods.

The AEGL-3 was based on the highest concentration that did not cause death in the cardiac sensitization test with the dog. Because the cardiac sensitization test is optimized, this concentration of 9,000 ppm was adjusted by an intraspecies UF of 3 to protect potentially susceptible humans. Because cardiac sensitization is concentration dependent, the resulting value of 3,000 ppm was assigned to all time periods.

The AEGL values are summarized in Table 4–9.

8.2. Comparison with Other Standards and Guidelines

HCFC-141b is a relatively new chemical and only the American Industrial Hygiene Association (AIHA 1998) has developed workplace guidelines. The AIHA Workplace Environmental Exposure Level (WEEL) of 500 ppm is to be applied as an 8-h time-weighted average (TWA).

It should be noted that, for establishment of a 1-h Emergency Exposure Guidance Level (EEGL) for another halocarbon, the NRC (NRC 1996; Bakshi et al. 1998) recommended application of a single interspecies UF of 10 to the cardiac sensitization test with the dog. Because blood concentrations of several halocarbons rapidly reached equilibrium, the NRC also extrapolated this 10-min test to the longer time period of 1 h. Controlled human data were not available for many of the materials considered by the NRC, whereas human data are available for HCFC-141b.

8.3. Data Adequacy and Research Needs

The data base for HCFC-141b is extensive and contains studies with human subjects as well as several mammalian species. The study with human subjects was well conducted and addressed clinical symptoms, respiratory effects, cardiotoxicity, hematology and clinical chemistry effects, and pharmacokinetics. The study with humans established a no-effect level (AEGL-1) that may be conservative, because a lowest-observed-effect level was not attained. The AEGL-1 of 1,000 ppm is supported by the animal data, which show an absence of effects at concentrations that are higher by a factor of 10. Animal studies addressed both acute and chronic exposure durations as well as neurotoxicity, genotoxicity, carcinogenicity, and cardiac sensitiza

tion. Except for the short-term cardiac sensitization test, most of the study exposure durations were for relatively long periods of time, 4 and 6 h. Using the values derived from longer exposure durations for the shorter durations results in conservative values. Cardiac sensitization is a threshold effect and it is based on circulating HCFC-141b concentrations; exposure durations were not as relevant as nominal concentration. For this reason, the same AEGL value was applied across all time periods.

TABLE 4–9 Summary of AEGL Values (ppm [mg/m3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)
AEGL-2 (Disabling)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)
AEGL-3 (Lethal)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)

Because the cardiac sensitization studies use exogenous epinephrine that is greater than physiological levels under stress, the protocol utilized may be pharmacological rather than physiological cardiac sensitization, which would develop under emergency conditions. In one study (Trochimowicz 1997), the cardiac sensitization response was induced in exercising dogs at halocarbon concentrations that were two to four times the concentrations that induced the response with the exogenous epinephrine. Using this sensitive end point further increases confidence in the AEGL values. In addition, both key studies for the AEGL-2 and AEGL-3 used high doses of epinephrine that were not individualized to the animals. Although the key study for the AEGL-2 (Mullin 1977) lacked details of procedures, prior publications indicate that the authors have considerable experience in performing this test. Although the Mullin (1977) study reported the lowest dose that caused cardiac sensitization in the dog, more recent studies by Hardy et al. (1989a) and Hardy (1994) indicate that the threshold for HCFC-141b-induced cardiac sensitization may be as high as 9,000 ppm. The Hardy (1994) study has the advantage in that doses of epinephrine were individualized to each dog. The relative responses of the dog, monkey, and human heart to exogenous or endogenous epinephrine during exposure to halogenated hydrocarbons are unknown; however, the dog heart is considered a reliable model for that of the human.

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Appendix

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR 1,1-DICHLORO-1-FLUOROETHANE (HCFC-141b) (CAS No. 1717–00–6)

AEGL-1

10 min	30 min	1 h	4 h	8 h
1,000 ppm	1,000 ppm	1,000 ppm	1,000 ppm	1,000 ppm

Key reference: Utell, M.J., M.W.Anders, and P.E.Morrow. 1997. Clinical inhalation studies with HCFC-141b. Final report: December 4, 1997. MA-RR-97–2406, Departments of Medicine, Environmental Medicine, and Pharmacology and Physiology, University of Rochester Medical Center, Rochester, NY.

Test species/Strain/Number: Eight healthy human subjects

Exposure route/Concentrations/Durations: Inhalation: 0, 250, 500, 1,000 ppm for 4 h (eight subjects); two subjects were exposed at 500 ppm for 6 h; and 1 subject was exposed at 1,000 ppm for 6 h. Subjects exercised for three 20-min periods during each exposure.

Effects: No effects at any concentration for any subject.

End point/Concentration/Rationale: The highest tested concentration of 1,000 ppm for 4 or 6 h was used as the basis for the AEGL-1. This concentration was a NOAEL for irritation and cardiac, lung, and respiratory effects.

Uncertainty factors/Rationale:

Total uncertainty factor: 1

Interspecies: Not applicable; human subjects tested.

Intraspecies: 1—This no-effect concentration for eight healthy, exercising individuals was far below concentrations causing effects in animals. At this low concentration there was no indication of differences in sensitivity among the subjects. Studies with structurally related chemicals administered in metered-dose inhalers to patients with respiratory diseases show that these chemicals produce no adverse effects.

Modifying factor: Not applied.

Animal to human dosimetric adjustment: Not applicable; human data used.

Time scaling: Not applied; inadequate data. Based on the rapidity with which blood concentrations approached equilibrium in human subjects, the similarity of lethality values in rats exposed for 4 or 6 h, and the fact that cardiac sensitization, the most sensitive end point in studies with halocarbons, is a concentration-dependent threshold effect, the 6-h value was used for all exposure durations.

Data adequacy: The key study was well designed, conducted, and documented. Exercise takes into consideration some of the stress that humans might experience under emergency conditions. Animal studies addressed both acute and chronic exposure durations as well as neurotoxicity, genotoxicity, carcinogenicity, and cardiac sensitization. In animal studies, concentrations up to 11,000 ppm for up to 6 h did not produce adverse effects. Adjustment of the 11,000-ppm concentration by interspecies and intraspecies uncertainty factors of 3 each, for a total of 10, results in essentially the same concentration (1,100 ppm) as that derived from the human data.

AEGL-2

10 min	30 min	1 h	4 h	8 h
1,700 ppm	1,700 ppm	1,700 ppm	1,700 ppm	1,700 ppm

Key reference: Mullin, L.S. 1977. Cardiac sensitisation. Haskell Laboratory Report 957–77, E.I. du Pont de Nemours and Co., Newark, DE.

Test species/Strain/Sex/Number: male beagle dogs (1–2 per exposure group)

Exposure route/Concentrations/Durations: Inhalation: 2,600, 5,200, 10,000, and 21,600 ppm for 10 min (the cardiac sensitization test is a 10-min test); epinephrine dose at 8 μg/kg. The cardiac sensitization test is based on the observation that some halocarbons make the mammalian heart abnormally sensitive to epinephrine, resulting in ectopic beats and/or ventricular fibrillation, which may result in death. The dose of administered epinephrine results in blood levels that may be approximately ten times endogenous levels and is close to the threshold for inducing cardiac effects in the absence of the test chemical.

Effects: No cardiac effects at 2,600 ppm; cardiac response in 1/10 dogs at 5,200 ppm; death of 1/10 dogs at 10,000 ppm.

End point/Concentration/Rationale: The concentration of 5,200 ppm was chosen as the basis for the AEGL-2. This concentration is the threshold for cardiac sensitization in the dog.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1—The cardiac sensitization model with the dog heart is considered a good model for humans.

Intraspecies: 3—The test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there are no data indicating individual differences in sensitivity.

Modifying factor: Not applied.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: Not applied. The cardiac sensitization response is a concentration-dependent threshold effect; dogs exposed for longer durations to similar chemicals responded in a similar manner. Therefore, the same concentration was used for all exposure durations.

Data adequacy: Humans exposed to halocarbons may develop cardiac arrhythmias. The cardiac sensitization test with the dog is a good model because the test is highly sensitive (i.e., the exogenous dose of epinephrine is at much greater than physiological levels). The concentration of 1,700 ppm is far below

the highest 6-h non-narcotic concentration in mice (30,000 ppm). Adjustment of the 30,000-ppm concentration by interspecies and intraspecies uncertainty factors of 3 each, for a total of 10, would result in a higher concentration (3,000 ppm) than that based on cardiac sensitization. Additional animal studies addressed neurotoxicity, reproductive and developmental toxicity, and carcinogenicity.

AEGL-3

10 min	30 min	1 h	4 h	8 h
3,000 ppm	3,000 ppm	3,000 ppm	3,000 ppm	3,000 ppm

Key reference: Hardy, J.C., I.J.Sharman, and D.O.Chanter. 1989a. Assessment of cardiac sensitisation potential in dogs and monkeys. Comparison of I-141b and F11. PWT 86/89437, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

Test species/Strain/Sex/Number: male beagle dogs (1–2 per exposure group)

Exposure route/Concentrations/Durations:

Inhalation: 2,600, 5,200, 10,000, and 21,600 ppm; epinephrine dose at 8 μg/kg (Mullin 1977).

Inhalation: 9,000–20,000 ppm; epinephrine dose at 10 μg/kg (Hardy et al. 1989a).

The cardiac sensitization test is based on the observation that some halocarbons make the mammalian heart abnormally sensitive to epinephrine, resulting in ectopic beats and/or ventricular fibrillation, which may result in death. Effects are monitored with electrocardiograms (EKG). The dose of administered epinephrine results in blood levels that may be approximately ten times endogenous levels and is close to the threshold for inducing cardiac effects in the absence of the test chemical.

Effects: No cardiac effects at 2,600 ppm; cardiac response at ≥5,200 ppm (Mullin 1977).
Marked cardiac response at 9,000 ppm; death at 20,000 ppm (Hardy et al. 1989a).

End point/Concentration/Rationale: The concentration of 9,000 ppm was chosen as the basis for the AEGL-3 because it was the highest tested concentration that did not result in lethality in the cardiac sensitization test.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1—The cardiac sensitization model with the dog heart is considered a good model for humans.

Intraspecies: 3—The test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there are no data indicating individual differences in sensitivity.

Modifying factor: Not applied.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: Not applied. The cardiac sensitization response is a concentration-dependent threshold effect; dogs exposed to similar chemicals for longer durations responded in a similar manner. Therefore, the same concentration was used for all exposure durations. Data adequacy: Humans exposed to halocarbons may develop cardiac arrhythmias. The cardiac sensitization test with the dog is a good model because the test is highly sensitive (i.e., the exogenous dose of epinephrine is at much greater than physiological levels). The concentration of 3,000 ppm is far below the highest 4–6 h nonlethal concentration of 45,781 ppm in studies with laboratory animals. Adjustment of the 45,781 ppm concentration by interspecies and intraspecies uncertainty factors of 3 each, for a total of 10, results in a higher concentration (4,600 ppm) than that derived from the cardiac sensitization data. Using repeated exposures, 8,000 ppm was a NOAEL and 20,000 ppm was a LOAEL for developmental effects associated with maternal toxicity in rats. Additional studies addressed neurotoxicity and carcinogenicity.

5

Hydrogen Cyanide[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrogen cyanide (HCN) is a colorless, rapidly acting, highly poisonous gas or liquid that has an odor of bitter almonds. Most HCN is used as an intermediate at the site of production. Major uses include the manufacture of nylons, plastics, and fumigants. Exposures to HCN may occur in industrial situations as well as from cigarette smoke, combustion products, and naturally occurring cyanide compounds in foods. Sodium nitroprusside ($Na_2[Fe(CN)_5\ NO]\cdot 2H_2O$), which has been used as an antihypertensive in humans, breaks down into nonionized HCN.

[1]This document was prepared by the AEGL Development Team comprising Sylvia Talmage (Oak Ridge National Laboratory) and National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member George Rodgers (Chemical Manager). The NAC reviewed and revised the document and the AEGL values as necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

HCN is a systemic poison; toxicity is due to inhibition of cytochrome oxidase, which prevents cellular utilization of oxygen. Inhibition of the terminal step of electron transport in cells of the brain results in loss of consciousness, respiratory arrest, and ultimately, death. Stimulation of the chemoreceptors of the carotid and aortic bodies produces a brief period of hyperpnea; cardiac irregularities may also occur. The biochemical mechanisms of cyanide action are the same for all mammalian species. HCN is metabolized by the enzyme rhodanese which catalyzes the transfer of sulfur from thiosulfate to cyanide to yield the relatively nontoxic thiocyanate.

Human exposures with measured concentrations were limited to occupational reports. Symptoms of exposed workers ranged from no adverse health effects to mild discomfort to frank central nervous system effects. Repeated or chronic exposures have resulted in hypothyroidism. Inhalation studies resulting in sublethal effects, such as incapacitation, and changes in respiratory and cardiac parameters were described for the monkey, dog, rat, and mouse; lethality studies were available for the rat, mouse, and rabbit. Exposure durations ranged from a few seconds to 24 hours (h). Regression analyses of the exposure duration-concentration relationships for both incapacitation and lethality for the monkey determined that the relationship is $C^2 \times t = k$ and that the relationship for lethality based on rat data is $C^{2.6} \times t = k$.

The AEGL-1 is based on human monitoring studies in which the preponderance of data as a weight-of-evidence consideration indicates that an 8-h exposure to HCN at 1 parts per million (ppm) would be without adverse health effects for the general population. Although the exposures were of chronic duration (generally 8 h/day (d) for extended work periods) and the data are lacking in various aspects of specific exposure concentrations and well-documented exposure-related symptoms, it is human data which are most relevant in determining the AEGL-1 threshold of notable discomfort.

Chronic exposures (5–15 years [y]) in three electroplating plants to mean concentrations of 6, 8, and 10 ppm produced exposure-related symptoms including headache, weakness, and objectionable changes in taste and smell (El Ghawabi et al. 1975), but the authors failed to relate symptoms to air concentrations. Over half of the workers presented with enlarged thyroids (characteristically observed in cases of chronic cyanide exposure), which may have been responsible for certain symptoms. In evaluating the El Ghawabi et al. (1975) study, a National Research Council (NRC) subcommittee concluded that a 1-h exposure at 8 ppm would cause no more than mild headache in healthy adults (NRC 2000). Mild headache meets the definition of the AEGL-1. Chronic exposures of 63 healthy adult cyanide-production workers to

geometric mean concentrations of ≤1 ppm of HCN (range, 0.01–3.3 ppm; measured with personal samplers), with potential exposures at 6 ppm (as measured with area samples), for part of a year resulted in no exposure-related adverse health effects (Leeser et al. 1990). Finally, although health effects were not specifically addressed, workers in five apricot kernel processing plants were exposed to air concentrations of HCN at <1 to 17 ppm (Grabois 1954). The fact that engineering controls were recommended "where required" at a time when the maximum allowable concentration was 10 ppm suggests that no untoward effects were occurring at the lower concentrations. The National Institute for Occupational Safety and Health (NIOSH) concluded from the Grabois (1954) data that 5 ppm was a no-effect concentration in an occupational setting (NIOSH 1976). Additional monitoring studies indicated that workers were routinely exposed to HCN at 4 to 6 ppm (Hardy et al. 1950; Maehly and Swensson 1970). Humans may differ in their sensitivity to the effects of HCN, but no data regarding specific differences among individuals were located in the available literature (occupational monitoring studies and the clinical use of nitroprusside solutions to treat chronic hypertension). The detoxifying enzyme rhodanese is present in large amounts in all individuals, including newborns. Because no specific susceptible populations were described following chronic exposures or during use of nitroprusside solutions to treat chronic hypertension, the potential differences in susceptibility among humans are not expected to exceed 3-fold.

The 8-h AEGL-1 value was derived from a consideration of the dose-response data obtained from all of the monitoring studies cited and subsequently time-scaled to the shorter AEGL exposure durations. Although the exposures were of chronic duration in all studies, they represent the only viable human data available. Furthermore, because symptoms observed or reported at given concentrations for the multiple 8-h exposures of a typical work schedule should represent the greatest potential responses, the use of the data represents a conservative approach to AEGL derivation. All of the exposure durations reported exceed the AEGL exposure durations, so the longest, or 8-h, AEGL exposure duration was selected as the basis for AEGL development. Dividing the 8-h concentration of 5 ppm from the Grabois (1954), Hardy et al. (1950), or Maehly and Swensson (1970) studies by an intraspecies uncertainty factor (UF) of 3 or dividing the 1-h concentration of 8 ppm from the El Ghawabi et al. (1975) study by an intraspecies UF of 3 result in very similar AEGL-1 values. The resulting 8-h value of 1.7 ppm is also similar to the 8-h geometric mean value of 1 ppm in the Leeser et al. (1990) study that was derived without application of a UF. A UF should not be applied to the

Leeser et al. (1990) study, because it was the lowest no-observed-adverseeffect level (NOAEL). Using the 8-h value of 1 ppm as the basis for time scaling to shorter durations, the conservative relationship of $C^3 \times t = k$ was chosen for the derivations. The 10-minute (min) AEGL-1 was set equal to the 30-min value so as not to exceed the highest personal exposure concentration of 3.3 ppm in the well-conducted Leeser et al. (1990) study.

The AEGL-2 was based on an exposure of cynomolgus monkeys to a concentration of HCN at 60 ppm for 30 min, which resulted in a slight increase in the respiratory minute volume near the end of the exposure and a slight depressive effect on the central nervous system as evidenced by changes in electroencephalograms, also near the end of the exposure; there was no physiological response (Purser 1984). The mechanism of action of HCN is the same for all mammalian species, but the rapidity and intensity of the toxic effect is related to relative respiration rates as well as pharmacokinetic considerations. Based on relative respiration rates, the uptake of HCN by the monkey is more rapid than that of humans. The monkey is an appropriate model for extrapolation to humans because, compared with rodents, the respiratory systems of monkeys and humans are more similar in gross anatomy, the amount and distribution of types of respiratory epithelium, and airflow pattern. Because the monkey is an appropriate model for humans but is potentially more susceptible to the action of cyanide based on relative respiration rates, an interspecies UF of 2 was applied. Humans may differ in their sensitivity to HCN, but no data regarding specific differences among humans were located in the available literature. The detoxifying enzyme rhodanese is present in all individuals, including newborns. Therefore, an intraspecies UF of 3 was applied. The 30-min concentration of 60 ppm from the Purser (1984) study was divided by a combined interspecies and intraspecies UF of 6 and scaled across time for the AEGL-specified exposure periods using the relationship $C^2 \times t = k$. The safety of the 30-min and 1-h values of 10 and 7.1 ppm, respectively, is supported by monitoring studies in which chronic exposures to average concentrations of 8 to 10 ppm may have produced primarily reversible central nervous system effects such as headaches in some workers (El Ghawabi et al. 1975).

The rat provided the only data set for calculation of LC_{01} values for different time periods (E.I. du Pont de Nemours and Company 1981). The LC_{01} values were considered the threshold for lethality and were used as the basis for deriving AEGL-3 values. The mouse, rat, and rabbit were equally sensitive to the lethal effects of HCN, as determined by similar LC_{50} values for the same time periods (for example, 30-min LC_{50} values of 166, 177, and 189 ppm

for the mouse, rat, and rabbit, respectively). In an earlier study, times to death for several animal species showed that mice and rats may be slightly more sensitive to HCN than monkeys (and presumably humans). The differences in sensitivity were attributed, at least partially, to the more rapid respiratory rate of the rodent compared to body weight. Because LC_{50} values for several species were within a factor of 1.5 of each other and the respiration rate of rodents is higher than that of humans, resulting in more rapid uptake of HCN, an interspecies UF of 2 was applied. Humans may differ in their sensitivity to HCN, but no data regarding specific differences among humans were located in the available literature. The detoxifying enzyme rhodanese is present in all individuals, including newborns. Therefore, an intraspecies UF of 3 was applied to protect sensitive individuals. The 15- and 30-min and 1-h LC_{01} values (138, 127 and 88 ppm, respectively) were divided by a total UF of 6. The 15-min LC_{01} value was time scaled to 10 min to derive the 10-min AEGL-3; the 30-min LC_{01} was used for the 30-min AEGL-3 value; and the 60-min LC_{01} was used to calculate the 1-, 4-, and 8-h AEGL-3 concentrations. For the AEGL-3 values, scaling across time utilized empirical data (i.e., the lethal concentration-exposure duration relationship for the rat in the key study, $C^{2.6} \times t = k$). The safety of the 4- and 8-h AEGL-3 values of 8.6 and 6.6 ppm is supported by the lack of severe adverse effects in healthy workers chronically exposed to similar values during monitoring studies (Grabois 1954; El Ghawabi et al. 1975). The values appear in Table 5–1.

I. INTRODUCTION

Hydrogen cyanide (HCN) is a colorless, highly poisonous gas or liquid (below 26.7 °C) having an odor of bitter almonds (Hartung 1994; Pesce 1994). It is a weak acid. Exposures may occur in industrial situations as well as from cigarette smoke and combustion products and from naturally occurring cyanide compounds in foods. There is a potential for exposure when any acid is mixed with a cyanide salt. Intravenously administered sodium nitroprusside ($Na_2[Fe(CN)_5NO]\cdot 2H_2O$) has been used clinically to lower blood pressure (Schulz et al. 1982). Chemical and physical properties are listed in Table 5–2.

HCN is produced commercially by the reaction of ammonia, methane, and air over a platinum catalyst or from the reaction of ammonia and methane. HCN is also obtained as a by-product in the manufacture of acrylonitrile and may be generated during many other manufacturing processes (Pesce 1994). In 1999, there were 34 companies operating 47 HCN production facilities in

the United States, Western Europe, and Japan (CEH 2000). The estimated production capacity was 3.5 billion pounds. The demand for HCN is expected to increase by 2.8% per year through 2004.

TABLE 5–1 Summary Table of AEGL Values for Hydrogen Cyanide (ppm [mg/m3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (Nondisabling)	2.5 (2.8)	2.5 (2.8)	2.0 (2.2)	1.3 (1.4)	1.0 (1.1)	No adverse health effects—humans (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970; Leeser et al. 1990); mild central nervous system effects—humans (El Ghawabi et al. 1975)
AEGL-2 (Disabling)	17 (19)	10 (11)	7.1 (7.8)	3.5 (3.9)	2.5 (2.8)	Slight central nervous system depression—monkey (Purser 1984)
AEGL-3[b] (Lethal)	27 (30)	21 (23)	15 (17)	8.6 (9.7)	6.6 (7.3)	Lethality (LC_{01})—rat (E.I. du Pont de Nemours 1981)

[a]The bitter almond odor of HCN may be noticeable to some individuals at the AEGL-1.
[b]Values for different time points were based on separate experimental values closest to the time point of interest.

Most HCN is used at the production site (CEH 2000). HCN is widely used; according to Hartung (1994), the major uses are in the fumigation of ships, buildings, orchards, and various foods; the production of various resin monomers such as acrylates, methacrylates, and hexamethylenediamine; and the production of nitriles. HCN may also be generated during the use of cyanide salts in electroplating operations and mining. Pesce (1994) estimated the following usage percentages: adiponitrile for nylon, 41%; acetone cyanohydrin for acrylic plastics, 28%; sodium cyanide for gold recovery, 13%; cyanuric chloride for pesticides and other agricultural products, 9%; chelating agents such as EDTA, 4%; and methionine for animal feed, 2%. CEH (2000) lists the following three dominant products: acetone cyanohydrin (for methyl methacrylate), adiponitrile (for hexamethylenediamine), and sodium cyanide (used as a reagent).

The U.S. Department of Transportation subjects HCN to rigid packaging, labeling, and shipping regulations. HCN can be purchased in cylinders rang

ing from 300 mL to 75 kg. Tank car sizes are 24 and 46 tons. Since 1950, there have been no accidents during the bulk transportation of HCN (Pesce 1994). HCN is usually shipped as a water solution containing a stabilizer of 0.05% phosphoric acid (HSDB 2000).

2. HUMAN TOXICITY DATA

HCN is among the most rapidly acting of all known poisons. Absorption occurs by all routes; the mechanism of action is inhibition of cellular respiration. The respiratory, central nervous, and cardiovascular systems are the primary targets of an acute exposure. Information on human exposures was limited to exposures to high concentrations for short time intervals, poorly documented accidental exposures, and chronic occupational exposures.

TABLE 5–2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Formonitrile, hydrocyanic acid, prussic acid	ACGIH 1996
Molecular formula	HCN	Budavari et al. 1996
Structure	H−C`N	ATSDR 1997
Molecular weight	27.03	Budavari et al. 1996
CAS registry number	74–90–8	ACGIH 1996
Physical state	Gas or liquid	Budavari et al. 1996
Color	Colorless gas, bluish-white liquid	Budavari et al. 1996
Solubility in water	Miscible	Budavari et al. 1996
Vapor pressure	807 mm Hg at 27°C	Hartung 1994
Vapor density (air=1)	0.941	Budavari et al. 1996
Liquid density (water=1)	0.687	Budavari et al. 1996
Melting point	−13.4°C	Budavari et al. 1996
Boiling point	25.6°C	Budavari et al. 1996
Odor	Bitter almond	Ruth 1986
Conversion factors	1 ppm=1.10 mg/m^3 1 mg/m^3=0.91 ppm	ACGIH 1996

According to Hartung (1994), a few breaths at "high concentrations" may be followed by rapid collapse and cessation of respiration. If the exposure continues, unconsciousness is followed by death. At much lower concentrations, the earliest symptoms may be numbness, weakness, vertigo, some nausea, and rapid pulse. The respiratory rate increases initially and at later stages becomes slow and gasping. Chronic exposures have been related to thyroid enlargement. Cardiac effects include electrocardiogram changes (HSDB 2000). HCN is not considered a lacrimator (Weedon et al. 1940). Should individuals survive the acute phase of HCN intoxication, recovery can be uneventful and without permanent sequelae.

In addition to occupational exposures, humans are exposed to cyanide in their diets (from cyanide- and amygdalin-containing foods and fumigation residues) and through cigarette smoke, automobile exhaust, and fires (NIOSH 1976; HSDB 2000). Exposure from smoking is not trivial; each puff from an unfiltered cigarette, which contains 35 μg of HCN, momentarily exposes the lung to a concentration of approximately 46 ppm (Carson et al. 1981). Yamanaka et al. (1991) reported that mainstream cigarette smoke contains HCN at 40–70 ppm, and side-stream smoke contains less than 5 ppm.

The odor of HCN has been described as that of bitter almond. The ability to detect the odor varies widely and about 20% of the population is genetically unable to discern this characteristic odor (Snodgrass 1996). A review of literature on odor thresholds revealed that the odor threshold for HCN can range from 0.58 to 5 ppm (Amoore and Hautala 1983; Ruth 1986). An irritating concentration was not reported.

2.1. Acute Lethality

Although a great many deaths have occurred from accidental, intentional, or occupational exposures to HCN, in only a few cases are specific exposure concentrations known. In a review of human fatalities (ATSDR 1997), it was stated that exposure to airborne concentrations of HCN at 180 to 270 ppm were fatal, usually within several minutes, and a concentration of 135 ppm was fatal after 30 min. The average fatal concentration for humans was estimated at 546 ppm for 10 min. The latter data point is based on the work of McNamara (1976), who considered the resistance of man to HCN to be similar to that of the goat and monkey and four times that of the mouse. Fatal levels of HCN cause a brief period of central nervous system stimulation followed by depression, convulsions, coma with abolished deep reflexes and dilated pupils, and death. Several review sources, such as Dudley et al. (1942),

Hartung (1994), and ATSDR (1997), report human toxicity data that appear to be based largely on pre-1920 animal data.

2.2. Nonlethal Toxicity

Several studies of occupational exposures and one study with a human subject were located. In the occupational exposures (summarized in Table 5– 3), neurological symptoms consistent with cyanide intoxication were demonstrated, but the likelihood of concomitant exposure to other chemicals could not be ruled out. For example, cleaners and cutting oils, as well as sodium and copper cyanide, may be present in electroplating operations (ATSDR 1997). The experimental human study involved the exposure of a single subject and a dog to a high concentration for a short exposure period.

Adverse health consequences on systems other than the central nervous and respiratory systems have been documented during occupational and/or accidental exposures. Generally, these effects occurred following chronic exposures, but the cardiovascular and dermal effects could occur following acute exposures. For example, cardiovascular effects (palpitations, hypotension, and chest pain) (El Ghawabi et al. 1975; Blanc et al. 1985; Peden et al. 1986), hematological effects (increased or decreased hemoglobin) (El Ghawabi et al. 1975; Kumar et al. 1992), hepatic effects (increased serum alkaline phosphatase activity but not serum bilirubin) (Kumar et al. 1992), gastrointestinal effects (nausea and vomiting) (El Ghawabi et al. 1975), endocrine effects (thyroid enlargement) (Hardy et al. 1950; El Ghawabi et al. 1975; Blanc et al. 1985), and dermal effects (burns and rashes) (Blanc et al. 1985; Singh et al. 1989) have been observed. Authors of several studies, including Hardy et al. (1950), observed that some of the symptoms of chronic cyanide exposure are a result of thiocyanate-induced goiter. These authors noted that goiter has also been reported following thiocyanate therapy for hypertension.

El Ghawabi et al. (1975) compared the symptoms of 36 workers exposed to HCN in three electroplating factories in Egypt with a referent group; employment ranged between 5 and 15 y. 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 NaOH 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. Lachrimation, vomiting, abdominal colic, precordial pain, salivation, and nervous instability were less common. The authors made no attempt to correlate the incidences of these symptoms

TABLE 5–3 Occupational Exposures to Hydrogen Cyanide

Concentration (ppm)	Effect	Reference
Breathing zone: 0.7 Work area: 0.2	Undefined symptoms of HCN poisoning	Chandra et al. 1980
Geometric mean values of personal samples: 0.03–0.96 (range: 0.01–3.3) Area samples: up to 6	No clear exposure related symptoms or adverse health effects; employment for 1–40 y	Leeser et al. 1990
2–8 (average 5)	Monitoring study; no symptoms reported	Maehly and Swensson 1970
4–6	Monitoring study; no symptoms reported	Hardy et al. 1950
5–13	Headache, fatigue, weakness, tremor, pain, nausea; symptoms increased with years of employment of 0–15 y	Radojocic 1973
<1–17 in different work areas; <1–6.4, general workroom air	Health effects not reported; NIOSH (1976) considered 5 ppm a no-effect concentration	Grabois 1954
6, 8, 10 (mean concentrations) range, 4.2–12.4	Most frequent symptoms: headache, weakness, and changes in taste and smell; employment 5–15 y	El Ghawabi et al. 1975
Unknown; NRC (2000) suggests these exposures were >15	Headache, dizziness, nausea or vomiting, almond or bitter taste, eye irritation, loss of appetite	Blanc et al. 1985
25–75 for approximately 1 h	Numbness, weakness, vertigo, nausea, rapid pulse, and flushing of the face	Parmenter 1926

with concentrations. Although there were no clinical manifestations of hypoor hyperthyroidism, 20 of the workers had thyroid enlargement to a mild or moderate degree; this conditions was accompanied by higher ^{131}I uptake compared with the referent controls. Exposed workers also had significantly higher blood hemoglobin, lymphocyte cell counts, cyanmethemhemoglobin, 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 biological 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-hour exposures" of healthy adults (NRC 2000). ATSDR (1997) noted that exposure to cleaners and cutting oils may have contributed to the effects observed in this study.

Grabois (1954) surveyed HCN levels in five plants that processed apricot kernels in order to determine possible health hazards. The survey was performed by the Division of Industrial Hygiene of the New York State Department of Labor. Work area concentrations in the plants ranged from <1 to 17 ppm, and two areas in one of the plants had levels of 17.0 ppm (comminuting area) and 13.9 ppm (cooking area). The general workroom atmosphere in this plant averaged a 6.4 ppm concentration of HCN. Medical questionnaires were not given and the health status of the employees was not reported. However, recommendations were made for controlling HCN exposures "where required," presumably where concentrations were above the then maximum recommended concentration of 10 ppm. NIOSH (1976), in interpreting the Grabois (1954) data, stated that 5 ppm was a no-effect level, and higher concentrations were only rarely present.

Chandra et al. (1980) studied the effects of HCN exposure on 23 male workers engaged in electroplating and case hardening. The workers avoided cyanogenic foods such as cabbage and almonds for 48 h prior to blood and urine sampling. In spite of the low exposure levels—0.8 mg/m^3 (0.7 ppm) in the breathing zone and 0.2 mg/m^3 (0.2 ppm) in the general work area—the workers complained of typical symptoms of HCN poisoning (symptoms not stated); however, no objective measures of adverse health effects were reported. Higher blood and urine cyanide and thiocyanate were measured in exposed workers compared with a control group. Higher levels of blood and urine cyanide and thiocyanate were present in smokers than in nonsmokers in both the exposed and control groups.

Blanc et al. (1985) surveyed and examined 36 former employees of a silver reclaiming facility in order 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 exposed long-term to excessive concentrations of cyanide as the time-weighted average (TWA) taken 24 h after the plant had closed down was 15 ppm. The most frequently reported symptoms included headache, dizziness, nausea or vomiting, almond or bitter 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 acute cyanide poisoning. A concentration-response relationship corresponding to high- and low-exposure jobs was demonstrated, but exact breathing zone concentrations were unknown. Some symptoms exhibiting a dose-response trend occurring seven or more months after exposure had ceased. Mild abnormalities of vitamin B_{12}, folate, and thyroid function were detected and suggested long-term cyanide and thiocyanate involvement. The NRC (2000), in reviewing this study, pointed out that the 24-h TWA of 15 ppm was measured one day after the plant had closed down, suggesting that workers may have been exposed to cyanide at more than 15 ppm.

Hardy et al. (1950) observed increased urinary excretion of thiocyanate in a group of case-hardener workers (hot metals are dropped into baths of cyanide salts in order to harden the material). Two workers with unqualified exposures suffered persistent headaches, sweating, chest pains, dizziness, fatigue, weakness, mental confusion, disturbed motor function, nervousness, coughing, sneezing, cramping in the lower abdomen, auricular fibrillation, and thyroid enlargement. The authors indicated that $\leq$10 ppm should prevent cyanide toxicity in workers, and with adequate engineering controls, workers were routinely exposed at 4–6 ppm. No symptoms were surveyed or discussed for these routine exposures.

Radojicic (1973) reported fatigue, headache, weakness, tremor in the arms and legs, pain, and nausea in 28 electroplating workers and 15 foundry workers chronically exposed to cyanide. Employment duration ranged from 0 to 15 y. Area atmospheric concentrations ranged from 6 to 13 ppm in the electroplating facility (four measurements) and 5 to 8 ppm in the foundry (three measurements). In the electroplating facility, higher concentrations were measured over work vats, 10 to 13 ppm, than in the middle of the room where concentrations were 6 to 8 ppm. In both facilities, urinary thiocyanate levels of workers were higher after work than prior to work, were higher in smokers than in nonsmokers, and increased with the number of years of work. Urinary

thiocyanate concentrations were higher in smokers prior to a work day than in nonsmokers following a work shift. Symptoms were more pronounced in workers with the longer exposures.

Urinary and blood cyanide and thiocyanate were measured in a group of 140 workers consisting of exposed and nonexposed smokers and nonsmokers (Maehly and Swensson 1970). The HCN-exposed group consisted of 39 nonsmokers and 55 smokers. Area measurements, sampled with Draeger tubes at each work station, ranged from 1 to 10 ppm (average, 5 ppm). Blood and urinary cyanide and thiocyanate levels varied widely among the groups, and there was no clear relationship to occupational exposure at these concentrations; blood cyanide levels did not bear a relationship to exposure via smoking, but free thiocyanate levels in the urine tended to be higher in smokers than in nonsmokers. No worker symptoms were reported in this study.

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 y 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 thyroxine (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 which contained sodium hydroxide. Cyanide collected in the sodium hydroxide solution was measured using an anion-selective ion electrode. All results (a total of 34 samples) were between 0.01 and 3.6 mg/m^3 (0.01 and 3.3 ppm). Geometric mean values for eight job categories ranged between 0.03 and 1.05 mg/m^3 (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 (none were above 10 ppm). In addition, during the fall of the year, production problems in part of the plant caused the HCN level to increase to 6 ppm from the usual 1–3 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, did not sound during the study. Blood cyanide levels in exposed workers, though low, were generally higher than in control workers, and the highest levels were measured in cyanide-exposed nonsmokers com

pared 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 actually 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 symptoms such as 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.

A 20-year-old man employed in a photographic darkroom suffered attacks of numbness, weakness, vertigo, some nausea, rapid pulse, and flushing of the face after 1 h of work (Parmenter 1926). Two other workers were unaffected. Following improved ventilation in the room, cyanide was measured in several areas of the workroom, including over a sink into which ferrous sulphate and potassium cyanide were routinely disposed. Concentrations of cyanide at that time (with the improved ventilation) ranged from 25 to 75 ppm.

During inspection of a tank containing a thin layer of hydrazodiisobutyronitrile (HZDN), a worker collapsed after 3 min, was fitted with a breathing apparatus after another 3 min, and removed from the tank after 13 min, resulting in a 6-min exposure (Bonsall 1984). At that time the worker was unconscious with imperceptible breathing and dilated pupils. He was covered with chemical residue. The tank had previously been washed with water; HZDN decomposes with water to give HCN and acetone. No HCN was measured prior to entry into the tank, but immediately after the incident, levels of HCN of about 500 mg/m^3 (450 ppm) were measured. One hour after the exposure, the comatose individual was administered sodium thiosulfate, and following subsequent complications and treatment, he was discharged after 2 weeks (wk). No sequelae were apparent.

Barcroft (1931) described the controlled exposure of a 45-year-old, 70-kg man and a 12-kg dog to a concentration of HCN at 500–625 ppm in an airtight chamber. The human volunteer attempted to maintain the same level of activity as the dog. The dog became unsteady at 50 seconds (s), unconscious at 75 s, and convulsive at 90 s. One second later, the man walked out of the exposure chamber with no apparent effect. At 5 min after initiation of exposure, the man experienced a momentary feeling of nausea, and at 10 min from the

start, his ability to concentrate in "close conversation" was altered. The dog at first appeared to be dead but recovered without adverse signs by the next day. Barcroft (1931) cites two other studies in which fumigation workers were exposed to a concentration of HCN at 250 ppm for 2 min or 350 ppm for 1.5 min without dizziness.

2.3. Developmental and Reproductive Effects

No data concerning developmental or reproductive effects of HCN in humans were identified in the available literature.

2.4. Genotoxicity

No data concerning the genotoxicity of HCN in humans were identified in the available literature.

2.5. Carcinogenicity

No data concerning the carcinogenicity of HCN in humans were identified in the available literature.

2.6. Summary

A great many human fatalities associated with acute HCN exposure have occurred, but exposure concentrations are for the most part unknown. Acute exposures that failed to result in mortality were either to high concentrations for very short exposure durations (approximately 500 or 450 ppm for approximately 1.5 min or 6 min, respectively [Barcroft 1931; Bonsall 1984]) or to exposure concentrations and times that were estimated (>25 ppm for about 1 h [Parmenter 1926]). Monitoring studies indicate that workers were routinely exposed at ≤10 ppm (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970). Occupational HCN exposures at 1–10 ppm were acceptable at the time of these surveys as 10 ppm was the maximum acceptable concentration for workers. More effective exhaust ventilation was implemented "where re

quired," presumably where exposures were greater than 10 ppm, as in the Grabois (1954) study. The low exposures in the Leeser et al. (1990) study did not result in adverse health effects. Concentrations greater than 8–10 ppm may cause discomfort, and with long-term exposures, more serious symptoms can develop (El Ghawabi et al. 1975). The most common complaints in the monitoring study by El Ghawabi et al. (1975) were headache, weakness, and changes in taste and smell. Specific exposure levels for specific symptoms were not provided nor were concurrent exposures to other chemicals noted. Chronic exposure to low concentrations of HCN has been associated with hypothyroidism (development of goiter) (Hardy et al. 1950), and some symptoms associated with chronic exposures may be attributed to thyroid effects. It should be noted that in the study of Radojicic (1973) symptoms in workers increased with the number of years of work, and 20 of 36 workers in the study of El Ghawabi et al. (1975) had thyroid enlargement. No information on developmental and reproductive effects, genotoxicity, or carcinogenicity in humans was located.

3. ANIMAL TOXICITY DATA

NIOSH (1976) reviewed and summarized animal studies prior to 1976. Many of those studies are deficient in descriptions of exposure and analytical techniques as well as exposure concentrations and durations. Considerations of most of those pre-1976 studies are not reviewed here. Several of those earlier studies describe brain lesions in exposed animals. Histopathological examinations were performed in only a few of the studies conducted after 1976.

3.1. Acute Lethality

Acute inhalation lethality data for the rat, mouse, and rabbit for exposure times of 10 s to 12 h were located. A single inhalation study with the dog did not give an exposure duration. The data are summarized in Table 5–4. Data from studies with nonlethal concentrations are summarized in Table 5–5. Barcroft (1931) reported LC_{50} values and times to death for eight species of animals, the times to death at a constant concentration. Due to experimental design constraints, the LC_{50} values are not reported here, but relevant data are discussed in the section on relative species sensitivity (Section 4.4.1).

3.1.1. Dogs

Dudley et al. (1942) cites a brief exposure to 115 ppm as fatal to dogs. Ninety parts per million may be tolerated for "hours" with death occurring after exposure. Exposures at 30–65 ppm for an unspecified duration led to vomiting, convulsions, and possibly death. No details on the source of the data, exposure durations, or experimental protocols were provided.

3.1.2. Rats

Groups of ten Wistar rats (gender not stated) inhaled concentrations of 280, 357, 368, 497, 583, or 690 ppm for 5 min in a Rochester chamber (Higgins et al. 1972). The animals were observed for 7 days (d) following exposure. A cage containing the animals was rapidly lowered into a chamber into which HCN was continuously delivered; the cage was rapidly removed after 5 min. HCN concentrations were continuously monitored using specific ion electrodes. All deaths occurred during the exposure period or within 20 min after exposure. The 5-min LC_{50} was 503 ppm (95% confidence limit (CL), 403–626 ppm). Using the same protocol, the 5-min LC_{50} for five male Sprague-Dawley rats was 484 ppm (95% CL, 442–535 ppm) (Vernot et al. 1977). Protocol details of the Vernot et al. (1977) study were not provided.

Groups of ten male Crl:CD rats were exposed to HCN in polymethymethacrylate exposure chambers under flow-through conditions (E.I. du Pont de Nemours 1981). The chamber atmosphere was measured continuously by infrared spectrophotometry; measurements were validated by gas chromatography. The experiment was performed in duplicate with one set of animals exposed head-only to the test gas while the other set was allowed free movement inside the exposure chamber. Free-moving rats inhaled concentrations of 273 to 508 ppm for 5 min, 110 to 403 ppm for 15 min, 128 to 306 ppm for 30 min, or 76 to 222 ppm for 60 min. The postexposure observation period was 14 d, during which body weights were monitored.

For all exposure durations, deaths occurred during exposures or within 1 d postexposure. The LC_{50} values for the 5-, 15-, 30-, and 60-min exposure periods for the unrestrained rats were 369 ppm (95% CL, 350–395 ppm), 196 ppm (95% CL, 181–209 ppm), 173 ppm (95% CL, 163–188 ppm), and 139 ppm (95% CL, 120–155 ppm), respectively. Using probit analysis, the authors also calculated LC_{01} values for the 5-, 15-, 30-, and 60-min exposure durations of 283, 138, 127, and 88 ppm, respectively. The LC_{50} values were lower

TABLE 5–4 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Dog	115	Not given	Fatal	Dudley et al. 1942
Rat	3,438	10 s	LC_{50}	Ballantyne 1983
Rat	1,339	1 min	LC_{50}	Ballantyne 1983
Rat	1,000	1.4 min	LT_{50}[b]	Weedon et al. 1940
	250	8.7 min	LT_{50}	
	63	40 min	LT_{50}	
Rat	503	5 min	LC_{50}	Higgins et al. 1972;
	484	5 min	LC_{50}	Vernot et al. 1977
Rat	449	5 min	LC_{50}	Ballantyne 1983
Rat	283	5 min	LC_{01}	E.I. du Pont de
	369	5 min	LC_{50}	Nemours 1981
Rat	138	15 min	LC_{01}	E.I. du Pont de
	196	15 min	LC_{50}	Nemours 1981
Rat	200	30 min	LC_{50}	Kimmerle 1974
Rat	127	30 min	LC_{01}	E.I. du Pont de
	173	30 min	LC_{50}	Nemours 1981
Rat	157	30 min	LC_{50}	Ballantyne 1983
Rat	110[c]	30 min	LC_{50}	Levin et al. 1987
Rat	144	1 h	LC_{50}	Ballantyne 1983
Rat	88	1 h	LC_{01}	E.I. du Pont de
	139	1 h	LC_{50}	Nemours 1981
Rat	120	1 h	LC_{50}	Kimmerle 1974
Rat	68	6 h	Lethal to 3/10 animals	Blank 1983
Mouse	1,000	1.2 min	LT_{50}	Weedon et al. 1940
	250	5.1 min	LT_{50}	
	63	66 min	LT_{50}	
Mouse	323	5 min	LC_{50}	Higgins et al. 1972; Vernot et al. 1977
Mouse	166	30 min	LC_{50}	Matijak-Schaper andAlarie 1982

(higher toxicity) for restrained rats: 398, 163, 85, and 63 ppm for the respective exposure durations.

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Mouse	150	4 h	100% mortality	Pryor et al. 1975
Mouse	100	4 h	Lethal to 1/10 animals	Pryor et al. 1975
Mouse	100	12 h	100% mortality	Pryor et al. 1975
Rabbit	2,213	45 s	LC_{50}	Ballantyne 1983
Rabbit	372	5 min	LC_{50}	Ballantyne 1983
Rabbit	189	35 min	LC_{50}	Ballantyne 1983

[a]Postexposure observation periods were as follows: 7 d, Higgins et al. (1972); 10 d, Pryor et al. (1975); and 14 d, E.I. du Pont de Nemours (1981).
[b]Time to 50% mortality.
[c]Animals were restrained.

Ballantyne (1983) exposed groups of six to ten rats to various concentrations of HCN for 10 s to 60 min. Lethal values are reported in Table 5–4; no further details of the study were reported. Kimmerle (1974), in citing his own unpublished data, reports 30- and 60-min LC_{50} values for the rat of 200 and 120 ppm, respectively. No details of the exposures were given.

Groups of six male Fischer 344 rats were exposed to various concentrations of HCN (not given) for 30 min (Levin et al. 1987). The rats were placed in restrainers for head-only exposures. Exposure chamber atmospheres were analyzed every 3 min with a gas chromatograph equipped with a thermionic detector. Most deaths occurred during the exposures. The 30-min LC_{50}, calculated from deaths during the exposure period plus any deaths occurring up to 24 h postexposure, was 110 ppm with 95% CL of 97–127 ppm. It should be noted that LC_{50} values are lower for restrained animals than for unrestrained animals (E.I. du Pont de Nemours 1981).

Weedon et al. (1940) exposed groups of eight rats (strain not identified) to HCN at 1,000, 250, 63, or 16 ppm; times to 50% mortality (LT_{50}) were recorded. Times to 50% mortality at the respective concentrations were as follows: 1.4, 8.7, 40, and >960 min.

Five male and five female Sprague-Dawley Crl:CD rats inhaled HCN at 68 ppm in a stainless steel chamber for 6 h/d for 3 d (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 rapid, shallow breathing were observed in all animals. During the first day, three males exhibited anoxia or hypoxia, followed by convulsions in one male. One male died during the exposure, a second male died during the postexposure 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 examinations 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 exhibited slight-to-moderate hemorrhage of the lung.

3.1.3. Mice

Groups of 15 ICR mice (gender not stated) inhaled concentrations of 200, 283, 357, 368, 414, or 427 ppm for 5 min in a Rochester chamber (Higgins et al. 1972). The animals were observed for 7 d following exposure. Exposures were conducted in the same manner as for rats (Section 3.1.2). All deaths occurred during the exposure period or within 20 min after exposure. The 5-min LC_{50} was 323 ppm (95% CL, 276–377 ppm). The same data were reported in summary form by Vernot et al. (1977).

According to Matijak-Schaper and Alarie (1982), the 30-min LC_{50} of male Swiss-Webster mice inhaling HCN is 166 ppm. Mortality ratio for the mice (four per exposure group) were 0/4, 2/4, 3/4 and 4/4 for exposure to concentrations of HCN at 100, 150, 220, and 330 ppm, respectively. The recovery period was 10 min, during which the surviving mice appreciably recovered. The LC_{50} was the same for cannulated mice. At exposure concentrations of 500 and 750 ppm, the mean times to death were 12 min and 2 min, respectively.

Weedon et al. (1940) exposed groups of four mice (strain not identified) to HCN at 1,000, 250, 63, or 16 ppm and times to 50% mortality were re

corded. Times to 50% mortality at the respective concentrations were: 1.2, 5.1, 66, and >960 min.

Groups often Swiss-Webster mice (both genders) inhaled HCN at concentrations of 30 ppm for 24 h, 100 ppm for 4 or 12 h, or 150 ppm for 4 h in flow-through chambers (Pryor et al. 1975). The temperature was 30°C and the atmosphere contained 21% oxygen. HCN was detected and quantified with detector tubes. All ten mice survived the 24 h exposure at 30 ppm; the postexposure period was 10 d. One mouse died during exposure at 100 ppm for 4 h, and all mice died from exposure at 100 ppm for 12 h and 150 ppm for 4 h. Although not specifically stated for HCN, it was indicated that all mice in the study, including those exposed to other gases, showed evidence of congestion of the lungs and vascular system. The authors noted the difficulty in attaining targeted concentrations of HCN in the chambers due to absorption on chamber surfaces; that difficulty was overcome by removing individual animal partitions from the exposure chamber.

3.1.4. Rabbits

Ballantyne (1983) exposed groups of six to ten rabbits to various concentrations of HCN for 45 s to 35 min. Values are reported in Table 5–4; no further details of the study were reported.

3.2. Nonlethal Toxicity

Toxicity studies resulting in nonlethal effects are reported in Table 5–5. Acute exposure data were available for the monkey, rat, and mouse with exposure durations ranging from 5 min to 24 h. Limited data were available for the dog.

3.2.1. Nonhuman Primates

Four cynomolgus monkeys (gender not stated) were individually exposed via a face mask to a concentration at 60 ppm for 30 min (Purser 1984). Each animal was exposed on three occasions. The same animals were used for hypoxia and hypercapnia tests. HCN, supplied from a standard gas mixture, was diluted with air; the concentration was measured intermittently using

colorimetric tubes. Air flow into and out of the lungs was measured with a pneumotachograph connected to a differential gas pressure transducer. Several heart, blood, muscular, and central nervous system parameters were measured before, during, and after the exposures.

At 60 ppm, there was a slight depressive effect on the central nervous system, as evidenced by changes in brain wave activity at the end of the exposure periods (indicated in electroencephalograms [EEGs]), and the auditory cortical evoked potential (measured by electrodes on the surface of the auditory cortex) was reduced in amplitude during the late response. There was no physiological response to the EEG changes. There was a small increase in respiratory minute volume, but no adverse effects were observed on cardiovascular parameters or on neuromuscular conduction. The authors stated that concentrations of HCN below 60 ppm are unlikely to produce a significant impairment of escape capability.

In a follow-up study, four cynomolgus monkeys were individually exposed via a face mask to concentrations of HCN at 100 to 156 ppm for 30 min in order to measure time to incapacitation ("defined as a semiconscious state with loss of muscle tone") (Purser et al. 1984). HCN was produced by introducing air, oxygen, and a mixture of HCN in nitrogen directly into the mixing chamber in proportions needed to produce the required atmospheric concentration; concentrations were estimated by silver nitrate titration from samples taken in 0.1 M sodium hydroxide solution. Several physiological parameters were measured before, during, and after the exposures. Results of earlier tests (not described) had determined at what concentration early signs of a physiological response occurred.

Time to incapacitation for the 100, 102, 123, 147, and 156 ppm concentrations were 19, 16, 15, 8, and 8 min, respectively; the relationship between exposure and time to incapacitation was linear. During exposures, effects consisted of hyperventilation (within 30 s), loss of consciousness, and bradycardia with arrhythmias and T-wave abnormalities; recoveries were rapid after exposure. The animal inhaling 147 ppm stopped breathing after 27 min and required resuscitation. Two additional exposures were terminated prior to the end of the 30 min due to severe signs. Animals rapidly recovered and were active during the first 10 min after exposure even though blood cyanide remained at levels that initially caused incapacitation. Purser (1984) states that the hyperventilatory response followed by incapacitation occurs at ≥80 ppm, but neither paper (Purser 1984; Purser et al. 1984) provides the experimental data for the 80 ppm concentration. At 180 ppm, hyperventilation occured almost immediately, and at 90 ppm the response was delayed for 20 min.

TABLE 5–5 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Monkey	125	12 min	"Distinctly toxic"	Dudley et al. 1942
Monkey	100	19 min	Time to incapacitation;	Purser et al. 1984
	102	16 min	Time to incapacitation;	
	123	15 min	Time to incapacitation;	
	147	8 min	Time to incapacitation;	
	156	8 min	Time to incapacitation	
Monkey	60	30 min	Slight depressive effect—central nervous system	Purser 1984
Rat	283	5 min	No toxic signs	Higgins et al. 1972
Rat	273	5 min	No toxic signs	E.I. du Pont de Nemours 1981
Rat	200	12.5 min	Possible changes in blood enzymes attributed to cardiac effects	O'Flaherty and Thomas 1982
Rat	110	15 min	No toxic signs	E.I. du Pont de Nemours 1981
Rat	149	30 min	No toxic signs	E.I. du Pont de Nemours 1981
Rat	55	30 min	No toxic signs, changes in lung dynamics, lung phospholipids	Bhattacharya et al. 1984
Rat	76	60 min	No toxic signs	E.I. du Pont de Nemours 1981
Rat	16	16 h	No deaths, no toxic signs	Weedon et al. 1940
Mouse	200	5 min	No toxic signs	Higgins et al. 1972

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Mouse	63	30 min	Respiratory depression of 50%;	Matijak-Schaper and Alarie 1982
	100	30 min	No toxic signs	
Mouse	16	16 h	No toxic signs	Weedon et al. 1940
Mouse	30	24 h	Lung congestion	Pryor et al. 1975
mouse	123.5	5 min	Incapacitation, rotating cage;	Sakurai 1989
	74.4	10 min	Incapacitation, rotating cage;	
	50.0	20 min	Incapacitation, rotating cage;	
	41.7	30 min	Incapacitation, rotating cage	

[a]Animals in the Higgins et al. (1972) and E.I. du Pont de Nemours (1981) studies were observed for 7 and 14 days postexposure, respectively.

Although the primary mechanism of action of HCN is not respiratory irritation, the RD_{50}—the concentration that produces a 50% decrease in respiratory rate—was measured in rats (E.I. du Pont de Nemours 1981). Respiratory rates were measured in restrained rats during all exposure durations (5–60 min). The RD_{50} was approximately 125 ppm. Although the RD_{50} may be considered in setting standards for primary irritants (to protect against sensory irritation), it is of limited use in setting standards for highly toxic, systemically acting chemicals. The highest concentrations that did not result in deaths of rats (see section 3.1.2 for details) are also listed in Table 5–5.

Six male Wistar rats inhaled HCN at 55 ppm for 30 min (Bhattacharya et al. 1984). HCN was generated by reaction of KCN with sulfuric acid and circulated through the chamber at the rate of 1 L/min. The rats were fitted with a lung mechanics analyzer (Buxco Electronic Inc.), and changes in air flow, transthoracic pressure, tidal volume, compliance, resistance, respiratory rate, and minute volume were determined every 10 min. Animals were sacrificed immediately following the exposure, and lungs were excised and analyzed for phospholipids (surfactant).

The authors stated that the exposure was "well tolerated" for the 30-min duration (Bhattacharya et al. 1984). With the exception of airway resistance, all lung dynamic parameters were significantly changed at 30 min, with increases in air flow, transthoracic pressure, and tidal volume and decreases in compliance, respiratory rate (60–70% decrease), and minute volume. There was a significant decrease in phospholipids in the lungs, but the toxicological relevance of that finding to AEGL derivation is not clear.

Five repeated exposures of 200 ppm for 12.5 min every 4 d resulted in increased cardiac-specific creatine phosphokinase activity in the blood (pooled data measured at 2 h after the first, third, and fifth exposures) and ectopic heart beats during the first 2 min after injection of norepinephrine (after the fifth exposure) but failed to induce cardiac lesions (histopathologic examinations at 14 d postexposure) (O'Flaherty and Thomas 1982). The rats were restrained and anesthetized.

Weedon et al. (1940) exposed groups of eight rats to a concentration of HCN at 16 ppm for 16 h. No deaths occurred, and rats appeared normal during the exposure. At autopsy of two rats, the lungs of one rat showed "pseudotuber-culosis." All other organs in that rat and the other rat were normal.

3.2.4. Mice

Matijak-Schaper and Alarie (1982) measured the RD_{50} in four male Swiss-Webster mice. They pointed out that HCN is not primarily an irritant, and its mechanism of action is depression of the central respiratory center. The concentration that decreased the respiratory rate by 50% was 63 ppm (lower than the LC_{50} by a factor of 2.6). The exposure was for 30 min. Unconsciousness did not occur at this concentration (Alarie 1997). The RD_{50} for cannulated mice was 34 ppm, indicating that at least part of the respiratory decrease in noncannulated mice is due to sensory irritation. The breathing pattern of a mouse inhaling 80 ppm for 30 min was characterized as having "intermittent periods of sensory irritation…between segments of normal but slower breathing." Time to asphyxia (as determined by respiratory pattern) at 150 ppm was 11 min. Times to asphyxia were not given for lower concentrations; however, "below the RD_{50} of 63 ppm, there were occasional breaths that were characteristic of asphyxiation, but this was a very transient occurrence. Above the RD_{50}, asphyxiation was first seen intermittently between periods of normal breathing, but was continuous at concentrations that approached lethal levels (i.e., 100 ppm)." The highest concentration of HCN that did not result in death during a 30-min exposure of these mice (100 ppm) was also added to Table 5–5.

Weedon et al. (1940) exposed groups of four mice to HCN at 16 ppm for 16 h. No deaths occurred and mice appeared normal during the exposure. One mouse was autopsied; the organs were described as normal. Mice survived a 24-h exposure to 30 ppm (Pryor et al. 1975).

Sakurai (1989) measured incapacitation times for groups of eight female Jcl ICR mice inhaling various HCN concentrations. HCN was introduced into the exposure chamber from a pressurized tank; chamber concentrations were determined by a "gas detecting tube method." Animals were placed in rotating cages during the exposures, and incapacitation time was recorded by an electrical signal emitted from the rotating cage at every half rotation. Apnea times were assessed by visual observation. Lack of movement for 5 min was defined as the incapacitation time. The data were graphed, and incapacitation times and concentrations of 5 min, 123.5 ppm; 10 min, 74.4 ppm; 20 min, 50.0 ppm; and 30 min, 41.7 ppm were determined.

3.2.5. Rabbits

Exposure of 24 male Danish rabbits at 0.5 ppm HCN for 4 wk produced

no microscopically detectable changes in the lung parenchyma, pulmonary arteries, coronary arteries, or aorta (Hugod 1979).

3.3. Developmental and Reproductive Effects

No information regarding developmental and reproductive effects of HCN in animals via the inhalation route was located in the available literature. The teratogenic potential of inorganic cyanide was studied by infusing sodium cyanide to pregnant golden hamsters between gestation days 6 and 9 (Doherty et al. 1982). Anomalies were induced only at tested doses of 0.126 to 0.1295 mmol/kg/h because preliminary tests had shown that a dose of 0.125 mmol/kg/h did not produce anomalies, and a dose of 0.133 mmol/kg/h produced 100% resorptions. Maternal signs of toxicity were observed after 36 to 48 h, at which time the doses administered by infusion were 30 to 40 times the subcutaneous LD_{50}. This range of doses produced high incidences of congenital malformations and resorptions. The most common anomalies were neural tube defects including encephalocoele and exencephaly. Fetal crown-rump length was significantly reduced in the offspring of treated dams. Maternal toxicity did not correlate with the incidence of anomalies in the offspring. Simultaneous subcutaneous infusion of thiosulfate protected against the teratogenic effects of cyanide. Signs of cyanide poisoning appear if detoxification occurs at a slower rate than absorption (90% of an acute lethal dose of cyanide can be detoxified in an hour when given to guinea pigs by slow infusion). Because signs of maternal toxicity did not appear for 36 to 48 h, the authors suggested that the rate at which sulfur in the form of thiosulfate, cystine, or cysteine became available for cyanide detoxification was the critical step. In addition to sodium cyanide, aliphatic nitriles and cyanogenic glycosides have been demonstrated to be teratogenic to golden hamsters by the oral and inhalation routes (Willhite 1981, 1982; Willhite and Smith 1981; Willhite et al. 1981; Frakes et al. 1985, 1986a,b). The teratogenic activities were attributed to the cyanide released through metabolism of the parent compounds; in each case, developmental toxicity was observed only at doses also inducing signs of maternal cyanide intoxication.

3.4. Genotoxicity

No information regarding the genotoxicity of HCN in animals was located in the available literature. Studies that addressed genotoxicity from other

forms of cyanide were reviewed in ATSDR (1997). In those studies, cyanide in the form of potassium cyanide tested negative in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA10, TA97, and TA102; one study gave positive results with strain TA100. Sodium cyanide gave negative results in several strains of *S. typhimurium*. Potassium cyanide also tested negative in the DNA repair test in *Escherichia coli* and in an *in vivo* testicular DNA synthesis inhibition test with the mouse.

3.5. Chronic Toxicity and Carcinogenicity

No information regarding the carcinogenicity of HCN in animals via the inhalation route was located in the available literature. In a 2-y feeding study, ten male and ten female rats were administered food fumigated with HCN at each of two concentrations (Howard and Hanzal 1955). The average daily concentrations were 73 and 183 mg CN/kg diet. Based on food consumption, body weight, and concentrations at the beginning and end of each feed preparation period, estimated doses were 4.3 and 10.8 mg CN/kg body weight per day. There were no treatment-related effects on body weight and no clinical signs or histopathologic lesions attributable to cyanide ingestion. In a review of feeding studies by the U.S. Environmental Protection Agency (EPA) (1993), 10.8 mg/kg/d (11.2 mg/kg/d as HCN), in the study by Howard and Hanzal (1955), was identified as the highest NOAEL.

3.6. Summary

Lethality data were available for the rat, mouse, and rabbit for exposure periods of 10 s (rat) to 12 h (mouse). Five-minute LC_{50} values ranged from 323 ppm (mouse) to 503 ppm (rat). Thirty-minute LC_{50} values ranged from 166 ppm for the mouse to an average of 177 ppm for the rat. The average 1-h LC_{50} value for the rat was 134 ppm. The LC_{50} values tend to be similar for the mouse and rat, and the mouse was slightly more sensitive in accordance with its slightly smaller body size and higher relative respiratory rate. Sublethal effects were characterized by incapacitation (or loss of consciousness) and changes in respiratory or cardiac parameters. Exposures causing little to no effect were: monkey, 60 ppm for 30 min—slight changes in EEGs; rat, 200 ppm for 12.5 min—changes in cardiac-released blood enzymes; rat, 55 ppm for 30 min—changes in pulmonary parameters; and mouse, 63 ppm for 30

min—50% decrease in respiratory rate. No information on developmental and reproductive effects, genotoxicity, or carcinogenicity by the inhalation route 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.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

HCN is miscible with water and is taken up by the moist respiratory passages. Retention levels of HCN in the nose and lung of human subjects were measured by Landahl and Herrmann (1950) while the subjects inhaled 0.5 to 20 ppm. HCN was delivered to the nose via a mask; the sample was drawn through the nose and out of the mouth while the subject held his breath. Using this procedure, the percentage retained in the nasal passages ranged from 13% to 23%. The percentage retained by the lung when inhaling through the mouth (no mask) ranged from 39% to 77%. The average exposure time was 1 min.

HCN in the blood is almost completely contained in the red blood cells where it is bound to methemoglobin. Immediately after infusion of sodium nitroprusside into patients, 98.4% of the blood cyanide was found in the red blood cells (Vesey et al. 1976). At normal physiological levels of body methemoglobin (0.25% to 1% of the hemoglobin), a human adult can bind about 10 mg of HCN (Schulz 1984).

HCN is detoxified to thiocyanate (SCN^-) by the mitochondrial enzyme rhodanese; rhodanese catalyzes the transfer of sulfur from thiosulfate to cyanide to yield thiocyanate, which is relatively nontoxic (Smith 1996). The rate of detoxification of HCN in humans is about 1 μg/kg/min (Schulz 1984) or 4.2 mg/h, which, the author states, is considerably slower than in small rodents. This information resulted from reports of the therapeutic use of sodium nitroprusside to control hypertension. Rhodanese is present in the liver and skeletal muscle of mammalian species as well as in the nasal epithelium. The mitochondria of the nasal and olfactory mucosa of the rat contain nearly seven times as much rhodanese as the liver (Dahl 1989). The enzyme rhodanese is present to a large excess in the human body relative to its substrates (Schulz 1984). This enzyme demonstrates zero-order kinetics, and the limiting factor in the detoxification of HCN is thiosulphate. However, other sulfur-containing substrates, such as cystine and cysteine, can also serve as sulfur donors. Other enzymes, such as 3-mercapto-pyruvate sulfur transferase, can convert

cyanide to thiocyanate (ATSDR 1997; NRC 2000). Thiocyanate is eliminated in the urine.

Venous blood levels of cyanide reached a steady state (mean value, 200 μg/100 mL) within 10 min of exposure of cynomolgus monkeys at 100–156 ppm (Purser et al. 1984). The blood level stayed constant during the remainder of the 30-min exposure, during which time the animals lost consciousness; the blood level remained the same for 1 h after exposure, even though the monkeys recovered consciousness within 10 min. The mean concentration of whole blood cyanide in rabbits that died following inhalation exposure was 170 μg/100 mL; the mean plasma concentration was 48 μg/100 mL (Ballantyne 1983).

Plasma levels of cyanide in unexposed, healthy adults average 0 to 10.7 μg/100 mL (mean, 4.8 μg/100 mL) (Feldstein and Klendshoj 1954). Following mild exposures to cyanide, plasma levels return to this normal range within 4 to 8 h after cessation of exposure; the half-life for the conversion of cyanide to thiocyanate from a nonlethal dose in humans was between 20 min and 1 h.

Although Feldstein and Klendshoj (1954) reported plasma levels of cyanide, most data available are for whole blood. Average whole blood values for cyanide are as follows: nonsmokers, 1.6 μg/100 mL; smokers, 4.1 μg/100 mL; and nitroprusside therapy, 5 to 50 μg/100 mL (Tietz 1986). These data can be compared with the whole blood values measured in several studies, including the study of Aitken et al. (1977) in which patients were infused with nitroprusside solutions to induce hypotension during intracranial surgery (see Box 1–1). In the Chandra et al. (1980) study, blood cyanide levels of up to 220 μg/100 mL appear excessively high in light of the low measured exposures. Snodgrass (1996) states that blood cyanide greater than 20 μg/100 mL may be associated with acute signs of cyanide poisoning, and deaths occur after blood cyanide reaches 100 μg/100 mL. As noted by Aitken (1977), metabolic acidosis occurred in patients at blood cyanide levels of ≥90 μg/100 mL.

It should be noted that HCN can be absorbed through the skin. For this reason, ACGIH (1996) and NIOSH (1997) guidelines carry a skin notation. Drinker (1931) cites the case of three men protected with gas masks in an atmosphere of 2% (20,000 ppm) HCN. After 8 or 10 min the men felt symptoms of marked dizziness, weakness, and throbbing pulse. They left the chamber just before collapse. For several hours after the exposure they experienced weakness, high pulse rate, and headache. They were incapacitated for several days, followed by complete recovery. Based on exposure to several cyanide salts, the dermal LD_{50} in rabbits was calculated to be 6.7 mg CN^-/kg (Ballantyne 1983).

4.2. Mechanism of Toxicity

HCN is a systemic poison that acts on the central nervous system. HCN interrupts cellular respiration by blocking electron transfer from cytochrome oxidase to oxygen. Tissue oxygen levels rise, resulting in increased tissue oxygen tension and decreased unloading for oxyhemoglobin. As a consequence, oxidative metabolism may slow to a point where it cannot meet metabolic demands. This 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. 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 (Hartung 1994; Smith 1996). Brain lesions have been associated with exposure of animals to high concentrations of HCN (ATSDR 1997).

Wexler et al. (1947) studied the effect of intravenously administered sodium cyanide on the electrocardiogram of 16 soldiers. A dose of 0.15 to 0.2 mg/kg (HCN at 0.06–0.11 mg/kg) was chosen based on the known inability of 0.11 mg/kg to stimulate respiration during medical tests (a dose of 0.11 mg of sodium cyanide per kilogram of body weight is used to determine arm-tocarotid blood circulation time). The electrocardiograms of 15 of the 16 men revealed a sinus pause (without auricular activity), which persisted for 0.88 to 4.2 s. The sinus pause immediately preceded or accompanied respiratory stimulation. The pause was followed by marked sinus irregularity, a slowing of the heart rate for a few seconds to 2 min, followed by a gradual acceleration to rates above the baseline level. Baseline heart rate and rhythm were generally restored within 3 min. There was a lesser effect on the sixteenth subject. According to AIHA (2000), this dose is equivalent to inhaling 10 ppm for 1 h.

4.3. Structure-Activity Relationships

No structure-activity relationships were applicable for establishing AEGLs for HCN. It has been observed that the signs of intoxication associated with excessive exposure to HCN and with certain aliphatic nitriles are similar. While the toxic concentrations of acrylonitrile are similar to HCN when compared on the basis of cyanide content (Dudley et al. 1942), the time course of aliphatic nitrile intoxication is different. The authors also observed

BOX 1–1 WHOLE BLOOD LEVELS OF CYANIDE IN MONITORING AND NITROPRUSSIDE THERAPY STUDIES

Leeser et al. (1990)

	Control Workers	*Cyanide Workers*
Nonsmoker	2.9 μg/100 mL	8.6 μg/100 mL
Ex-smoker	3.8 μg/100 mL	5.6 μg/100 mL
Current smoker	8.2 μg/100 mL	7.6 μg/100 mL

Chandra et al. (1980)

	Control Workers	*Cyanide Workers*
Nonsmoker	0.0–8.6 μg/100 mL (mean, 3.2)	2.0–36 μg/100 mL (mean, 18.3)
Smoker	0.0–9.4 μg/100 mL (mean, 4.8)	10.0–220 μg/100 mL (mean, 56)

Thiocyanate in blood	40 μg/100 mL in control nonsmokers 100 μg/100 mL in control smokers 420 μg/100 mL in cyanide-exposed nonsmokers 480 μg/100 mL in cyanide-exposed smokers

Maehly and Swensson (1970)

Found no relationship between exposure and blood cyanide levels

Blood CN—of control nonsmokers ranged from 3.5–10.1 μg/100 mL

Blood CN—of control smokers ranged from 2.0–13.0 μg/100 mL

Blood CN—of control and cyanide-exposed workers combined ranged from 2.0–15 μg/100 mL

(Separate data were not provided for cyanide workers)

Aitken et al. (1977)

Male and female patients, ages 13–66, presurgery mean: 2.7 μg/100 mL

Following infusion of sodium nitroprusside: 13–205 μg/100 mL

Metabolic acidosis at ≥90 μg/100 mL

Nitroprusside doses: 12–783 μg/kg (0.8–9.8 μg/kg/min over durations of 15 to 86 min)

that dogs are more susceptible to acrylonitrile than monkeys, but repeated exposures to acrylonitrile were more toxic to monkeys than to rats, guinea pigs, or rabbits.

4.4. Other Relevant Information

4.4.1. Species Differences

Lethal concentrations are relatively similar for various animal species and humans (Hartung 1994), with the monkey and goat being the least sensitive, according to Barcroft (1931). Barcroft (1931) reports relative species sensitivity as determined by time to death (in minutes) at a concentration of 1,000 mg/L (910 ppm): dog, 0.8; mouse, cat, and rabbit, 1.0; rat and guinea pig, 2.0; goat, 3.0; and monkey, 3.5. He reported that monkeys (two monkeys per exposure) were only beginning to show signs of unsteadiness when the dogs (two dogs per exposure) died. Also, Barcroft's study (1931) with one human subject and one dog tends to indicate that dogs are much more sensitive to the effects of HCN than humans. Barcroft notes that body size and respiration rate influence the rapidity of effect, small, rapidly respiring animals succumbing first, but he also notes that there are exceptions to the body size effect (i.e., the goat was much less sensitive than the dog). Bancroft's pre-1970 animal studies were not cited in Section 3.1 because time to death is not useful in determining exposure concentration-duration relationships but is useful for determining relative species sensitivity.

Relative to body weight, humans have a much lower respiratory rate and cardiac output than rodents. These are the two primary determinants of systemic uptake of volatile chemicals. Therefore, at similar nominal concentrations, rodents absorb substantially more cyanide than primates. From a pharmacokinetic view, lower hepatic rhodanese levels in primates will not be significant at high, acute HCN exposures. It should be noted that Barcroft's subject withstood a 1 min and 31 s exposure at approximately 500 to 625 ppm without immediate effects (Barcroft 1931), whereas mice suffer asphyxia during a 2 min exposure at 500 ppm (Matijak-Schaper and Alarie 1982). Compared with rodents, the respiratory tracts of humans and monkeys are more similar in gross anatomy, the amount and distribution of types of respiratory epithelium, and airflow patterns (Barrow 1986; Jones et al. 1996).

In the rat and mouse studies by Higgins et al. (1972) and the rat and rabbit studies by Ballantyne (1983), LC_{50} values differed by less than a factor of two

(1.5). All of the 30-min LC_{50} values summarized in Table 5–4 range from 157 to 200 ppm (rat, mouse, and rabbit and excluding the restrained rats in the study by Levin et al. [1987]). The 1-h LC_{50} values range from 120 ppm to 144 ppm (data for rat only). The LC_{30} for the rat at 6 h was 68 ppm. The LC_{30} and LC_{50} values are presented graphically in Figure 5–1. The concentrations for the rat are means for the respective time intervals. As can be seen in Figure 5–1, the concentration-time curve is steep, particularly at the shorter time intervals.

Species differences are recognized in the activity of rhodanese; sheep have relatively high levels of activity and dogs have relatively low levels (Aminlari and Gilanpour 1991). Himwich and Saunders (1948) assayed tissues from several animal species for their ability to produce thiocyanate from cyanide. Activity was generally highest in liver tissue. Rats had the highest levels, dogs had the lowest levels, and rhesus monkeys and rabbits had intermediate levels. Liver and kidney rhodanese activity was two to three times higher in rats and hamsters than in rabbits and female beagles (Drawbaugh and Marrs 1987). The authors point out that in acute exposures at high concentrations, the normal low levels of rhodanese present in tissues would not allow time for substantial detoxification, and other pharmacokinetic considerations may be important in the outcome of acute poisonings.

4.4.2. Susceptible Populations

According to ATSDR (1997), reasons that populations may be more susceptible to the effects of HCN include genetic makeup, age, health and nutritional status, and exposure to other substances. A number of dietary deficiencies, such as vitamin B_{12} deficiency, may predispose individuals to higher risk for cyanide-associated neuropathies. For example, in tropical areas where cassava is the primary dietary staple, women and children appeared to be more susceptible than adult males to the neurological effects of metabolically liberated cyanide (generated by gut flora from cyanogenic glycosides). These differential responses are observed after repeated ingestion of cyanogenic glycoside-containing foods (e.g., cassava), usually due to the shortage of other dietary staples, particularly those high in protein. No specific information was located on differences in toxicity, metabolism, and/or detoxification between adults and children or between healthy and nutritionally deficient humans following inhalation of HCN.

As noted in Section 4.4.1, the enzyme rhodanese is present to a large excess in the human body relative to its substrates, thus demonstrating zero

order kinetics (Schulz 1984). This enzyme is functional in newborns, although, in newborns, thiosulphate may be a limiting factor in cyanide detoxification (Schulz and Roth 1982).

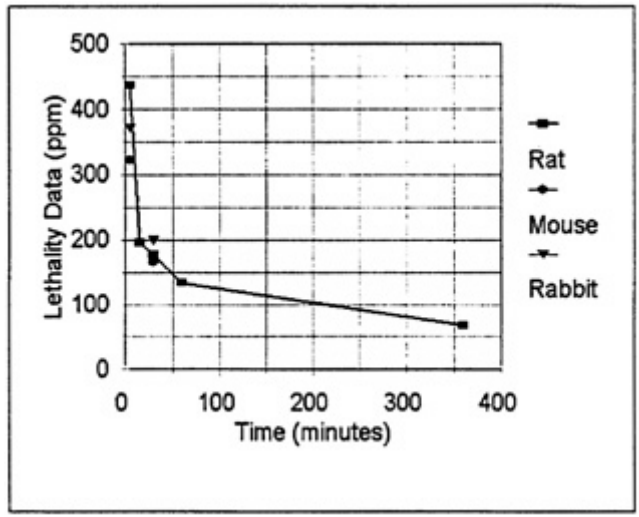

FIGURE 5–1 Lethality values for three species of animals. All values are LC_{50} values except the data point for the rat at 360 min, which is an LC_{30}.

Fitzgerald (1954) injected newborn mice (less than 12 h old) and adult mice subcutaneously with sodium cyanide (NaCN). The threshold for lethality was the same in newborn and adult male and female male mice, NaCN at 2 mg/kg. The dose-response curve for neonatal mice was much steeper than for adult mice, which resulted in a lower LC_{50} value. The LC_{50} for adult male mice was approximately 5 mg/kg; for female mice it was 3.5 to 3.7 mg/kg; and for neonatal mice it was between 2.0 and 2.5 mg/kg. On the basis of the threshold for lethality, newborn and adult mice were equally sensitive to HCN, but on the basis of LC_{50} values, newborn mice were approximately two to three times more sensitive than adult male mice.

Individuals with high blood pressure might be considered a susceptible population. Schulz et al. (1982) reported on the infusion of 70 patients, ages 17 to 78, with nitroprusside solutions to lower blood pressure. Administration of nitroprusside with or without thiosulfate continued for several hours to several days, apparently without adverse symptoms. Schulz (1984) states that at 150 to 250 μmol/L of "erythrocyte concentrate" headaches, palpitations, and hyperventilation occur. Unfortunately, blood cyanide levels were ex

pressed in terms of erythrocyte concentrate and could not be compared directly with the data in Section 4.1.

4.4.3. Concentration-Exposure Duration Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between concentration and exposure duration ($C^n \times t=k$) when a common end point is used (ten Berge et al. 1986). The end points for HCN are incapacitation and lethality. Regression analysis of the data of Sakurai (1989), using incapacitation concentrations for mice for the exposure durations of 5, 10, 20, and 30 min, results in a value for n of 1.6. Regression analysis of the incapacitation data of Purser et al. (1984) for monkeys for the time period of 8 to 19 min results in a value for n of 2.1 (Appendix A, Figure A-1). These studies were of relatively short duration.

Several lethality studies conducted over various exposure durations were available for calculation of concentration-exposure duration relationships. Using the animal lethality data of Barcroft (1931), ten Berge et al. (1986) calculated a mean value of 2.7 for n for six species of animals (range, 1.6 to 4.3). The value for the monkey was 1.9 and the value for the rat was 1.6. Using rat and mouse LC_{50} data sets and exposure times of 5 to 60 min, Hilado and Cumming (1978) calculated an n value of 2. These data indicate a mean n value of 2. Additional data sets were available for the calculation of n values in the present document. Regression analysis of the rat lethality data by E.I. du Pont de Nemours (1981) for exposure durations of 5, 15, 30, and 60 min results in an n value of 2.6 (Appendix A, Figure A-2), and regression analysis of the rat lethality data of Ballantyne (1983), for the exposure durations of 5, 30, and 60 min, results in an n value of 2.1 (data not graphed).

It should be noted that extrapolation of the rat 1-h LC_{50} value of 139 ppm of E.I. du Pont de Nemours (1981) to 6 h (using $C^{2.6} \times t=k$) results in a value of 70 ppm, which is similar to the rat LC_{30} value of Blank (1983), 68 ppm, illustrated in Figure 5–1. Similar results from two different studies support the n value of 2.6 for extrapolation across time in lethality studies with the rat.

4.4.4. Concurrent Exposure Issues

Because many materials release HCN when burned, the combined toxicity of HCN and smoke components—carbon monoxide, carbon dioxide, nitrogen dioxide—have been studied. Combination experiments with fire gases showed

that the effects of carbon monoxide and HCN are additive, and a combination of 5% carbon dioxide in HCN decreased the LC_{50} of HCN for rats (Levin et al. 1987). In 5-min exposures with rats and mice, Higgins et al. (1972) found no measurable interaction between carbon monoxide and HCN. These studies suggest a range of effects, including additive effects, for combinations of gases that may be formed during combustion.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The odor threshold, 0.58 ppm to 5.0 ppm (Amoore and Hautala 1983; Ruth 1986) is low compared with irritant or toxic concentrations. No acute exposures were located resulting in mild effects in humans. Three monitoring studies, involving no symptoms to mild symptoms during chronic occupational exposures of adult males, are relevant to development of AEGL-1 values. The symptoms and blood concentrations of cyanide in the monitoring study of Chandra et al. (1980) indicate that the workers may have been exposed at higher atmospheric concentrations than those reported.

Mean concentrations of cyanide in the breathing zone of workers (all nonsmokers) in an electroplating area of three factories were 6, 8, and 10 ppm (range, 4.2–12.4 ppm) (El Ghawabi et al. 1975). Employment ranged from 5 to 15 y. Complaints of headache, weakness, and changes in taste and smell were reported by approximately 80% of the workers; incidences were much higher than in a matched control group. Irritation of the throat, vomiting, and effort dyspnea were commonly reported, and lachrimation and precordial pain were reported relatively less frequently. Two workers in the factory with the highest exposures suffered from psychotic episodes during the survey. Twenty of the 36 workers had thyroid enlargement to a mild or moderate degree. Air cyanide concentrations and exposure durations were not linked to specific symptoms. Mean levels of thiocyanates in the urine correlated with air concentrations of cyanide. Although the sample size was small, 36 workers, the study used 20 well-matched controls and a biological index of exposure (urinary thiocyanate). An NRC subcommittee concluded from this study that 1-h exposures at 8 ppm might produce mild headache in healthy adults (NRC 2000).

The Leeser et al. (1990) study was a controlled study with comprehensive medical examinations. In this study, presumably healthy workers were exposed to geometric mean HCN concentrations up to 1 ppm (range, 0.01–3.3

ppm) determined by personal monitoring in the work areas. Concentrations in the atmosphere of the plant ranged up to 6 ppm during the fall of the year, as indicated by Draeger pump tests or static monitors. It is not clear that the geometric mean concentrations include the later, higher values, as ranges during the spring were reported to be up to only 3.3 ppm. Higher blood cyanide levels were correlated with the higher exposure levels in the fall of the year. The results of clinical histories and medical examinations showed no differences to only minor differences for a variety of parameters between the HCN workers and a matched control group.

Medical questionnaires were not given in the Grabois (1954) study. However, both NIOSH (1976) and ACGIH (1996) reviewed the study. NIOSH (1976) identified 5 ppm as a no-effect concentration using the data for the five plants presented by Grabois (1954). Similar exposures were reported in the studies of Hardy et al. (1950) and Maehly and Swensson (1970).

5.2. Animal Data Relevant to AEGL-1

Animal studies that addressed sensory irritation or mild effects were not clearly distinguishable from those that addressed more severe effects.

5.3. Derivation of AEGL-1

The AEGL-1 is based on monitoring studies in which the preponderance of data as a weight-of-evidence consideration indicates that an 8-h exposure to 1 ppm would be without adverse effects for the general population. El Ghawabi et al. (1975) reported symptoms such as headache, weakness, changes in taste and smell, irritation of the throat, vomiting, and effort dyspnea in three electroplating plants in which mean concentrations of HCN were 6, 8, and 10 ppm, but the authors failed to relate symptoms to air concentrations. It should be noted that 20 of the 36 workers in the El Ghawabi et al. (1975) study had thyroid enlargement, which is characteristically observed in cases of chronic cyanide exposure and may have been responsible for some of the symptoms. An NRC subcommittee, in evaluating the El Ghawabi et al. (1975) data, concluded that the average concentration of 8 ppm in the three plants would likely produce no more than mild headache, which would be acceptable for a 1-h exposure of healthy adults. In the monitoring study of Leeser et al. (1990), chronic exposure of 63 workers in a cyanide salt produc

tion plant to geometric mean concentrations up to approximately 1 ppm and possible excursions up to 6 ppm during part of the year produced no clear exposure-related symptoms. According to NIOSH (1976), chronic exposure of workers to 5 ppm while processing apricot kernels in the monitoring study of Grabois (1954) was without effect. Additional monitoring studies with mean exposures to 5 ppm failed to report adverse health effects (Hardy et al. 1950; Maehly and Swensson 1970). It is unlikely that the population of workers in these and additional monitoring studies represent only healthy individuals.

The AEGL-1 was derived from a consideration of the dose-response data, which were obtained from all of the monitoring studies and subsequently time scaled to the shorter exposure durations. Although the exposures were of chronic duration in the monitoring studies, they represent the best available human data. Symptoms observed during chronic exposures should represent the greatest potential response. An 8-h exposure duration was selected as the basis for AEGL development.

Mild headache is a symptom of exposure that meets the definition of an AEGL-1. Dividing the 8-h concentration of 5 ppm of the Grabois (1954), Hardy et al. (1950), or Maehly and Swensson (1970) study by an intraspecies uncertainty factor (UF) of 3 or dividing the 1-h concentration of 8 ppm of the El Ghawabi et al. (1975) study by an intraspecies UF of 3 results in very similar AEGL-1 values. The resulting 8-h value of 1.7 ppm is also similar to the 8-h no-effect concentration of 1 ppm in the Leeser et al. (1990) study, where no UF was applied. UFs are generally applied to the highest NOAELs or lowest LOAELs. A UF was not applied to the Leeser et al. (1990) study because it was the lowest NOAEL. No specific susceptible populations were identified during numerous occupational monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. Thus, potential differences in susceptibility among humans are not expected to exceed 3-fold. All individuals, including infants, possess large amounts of the cyanide detoxifying enzyme rhodanese (as well as other detoxifying enzymes) and normally have adequate amounts of sulfur-containing compounds.

The 8-h no-effect mean geometric concentration of 1 ppm (with excursions up to 6 ppm) from the Leeser et al. (1990) study was used as the basis for time scaling the AEGL-1 values. This study was chosen because it was well conducted: all workers had full medical examinations and routine blood tests, including measurements of blood cyanide and carboxyhemoglobin. Atmospheric HCN concentrations were monitored in the plant several times during the year. Because of the extrapolation from a long-term exposure, the

8-h value of 1 ppm was time scaled to the other exposure durations using the relationship $C^3 \times t = k$ where k=480 $ppm^3 \cdot min$. In order to stay below the highest measured concentration from personal samplers, at 3.3 ppm in the Leeser et al. (1990) study, the 10-min value was set equal to the 30-min value. Calculations are in Appendix B, and values appear in Table 5–6 below.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

As noted above for the AEGL-1, chronic occupational exposure of adult males to >10 ppm produced symptoms of headache, weakness, changes in taste and smell, irritation of the throat, vomiting, and effort dyspnea (El Ghawabi et al. 1975; NIOSH 1976; Blanc et al. 1985). For a few individuals, chronic exposures occasionally produced more serious adverse effects, such as fainting and psychotic episodes. There was no evidence that these symptoms occurred after one exposure. A concentration of ≥25 ppm for 1 h resulted in numbness, weakness, vertigo, nausea, rapid pulse, and flushing of the face (Parmenter 1926). Only one individual was involved, and neither the exposure duration nor the concentration were measured.

6.2. Animal Data Relevant to AEGL-2

Several animal studies listed in Table 5–5 describe effects at concentrations below those causing incapacitation or unconsciousness. These 30-min studies are as follows: monkey, 60 ppm (slight CNS effects) (Purser 1984); rat, 55 ppm (changes in lung dynamics and phospholipids) (Bhattacharya et al. 1984); and mouse, 63 ppm (respiratory depression of 50%) (Matijak-Schaper and Alarie 1982). From the description given by Matijak-Schaper and Alarie (1982), the concentration of 63 ppm for 30 min appears to be the

threshold for a breathing pattern characteristic of asphyxiation. The effects in these three studies are reversible and do not impair the ability to escape, but they can be considered close to the threshold for such effects. Incapacitation in monkeys occurs at higher concentrations (80–150 ppm) (Purser et al. 1984). The 24-h exposure of mice at 30 ppm (Pryor et al. 1975), resulting in lung congestion, is also relevant to the definition of AEGL-2. The data of Sakurai (1989), incapacitation in mice inhaling 41.7 ppm in rotating cages for 30 min, appear low compared with the other studies and were not considered.

TABLE 5–6 AEGL-1 Values for Hydrogen Cyanide

10 min	30 min	1 h	4 h	8 h
2.5 ppm (2.8 mg/m^3)	2.5 ppm (2.8 mg/m^3)	2.0 ppm (2.2 mg/m^3)	1.3 ppm (1.4 mg/m^3)	1.0 ppm (1.1 mg/m^3)

6.3. Derivation of AEGL-2

Because the human exposure concentrations are less reliable than the experimental animal data, the animal data were used in the derivation of the AEGL-2 values. The study chosen for the AEGL-2 derivation was the study by Purser (1984) with the monkey, because it was well conducted and used an appropriate species (compared with the rodent, the respiratory tracts of humans and monkey are more similar in anatomy, the amount and distribution of types of respiratory epithelia, and airflow pattern). This concentration was 60 ppm for 30 min. Although this end point (a slight depressive effect on the central nervous system as evidenced by a change in brain-wave activity near the end of the exposure) was a NOAEL for the definition of an AEGL-2, it was chosen because the next higher experimental concentration resulted in severe adverse effects of incapacitation, unconsciousness, and possibly death. The Barcroft (1931) lethality and incapacitation study has shown that the monkey is less sensitive to the respiratory and central nervous system effects of HCN than the rat and mouse (by factors of 1.75 and 3, respectively), and the adult human is less sensitive than the dog. The differences in sensitivity were based, at least partially, on the more rapid respiratory rates and greater cyanide uptake of rodents and the dog compared with humans and the monkey.

Because the respiratory tracts of humans and monkeys are more similar than those of humans and rodents, because uptake is more rapid in the monkey than in humans, and because both species have been shown to be relatively insensitive to the incapacitative and lethal effects of HCN (but at the same time, species susceptibilities to lethal effects do not differ by more than a factor of 1.5), an interspecies UF of 2 was applied. Human (adult) accidental and occupational exposures (El Ghawabi et al. 1975) indicate that there are individual differences in sensitivity to HCN, as evidenced by symptoms fol

lowing chronic exposures, but the magnitude of these differences does not appear to be great. These studies and the clinical use of nitroprusside solutions to control hypertension do not demonstrate a susceptible population. The detoxifying enzyme rhodanese is functional in all individuals, including newborns. Therefore, a UF of 3 was applied to account for potential differences in human susceptibility. For the concentration-exposure duration relationship, the mean value for n of 2.0 for the monkey was calculated from two data sets involving incapacitation (2.1) and lethality (1.9) (Section 4.4.3). The 30-min exposure value of 60 ppm was divided by a total UF of 6 and scaled across time using the $C^n \times t = k$, where n=2 and k=3,000 $ppm^2 \cdot min$. Values appear in Table 5–7 below, and calculations are in Appendix B.

The safety of the values is supported by the data of Grabois (1954), in which occupational exposures ranged up to 17 ppm, and two additional animal studies. The 30-min exposure of rats at 55 ppm (Bhattacharya et al. 1984), when divided by a total UF of 6 (2 for interspecies and 3 for intraspecies), results in a 30-min AEGL-2 of 9.2 ppm. The described effects of changes in lung dynamics and lung phospholipids are not irreversible or long-lasting. Mice experienced a decrease of 50% in respiratory rate when inhaling 63 ppm for 30 min but did not lose consciousness (Matijak-Schaper and Alarie 1982; Alarie 1997). Dividing by a total UF of 6 results in a 30-min AEGL-2 value of 11 ppm.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human studies of sufficient exposure duration with measured concentrations producing irreversible or life-threatening effects were located in the available literature. However, the data of Barcroft (1931), a 1.5-min exposure at 500–625 ppm, and Bonsall (1984), a 6-min exposure at approximately 450 ppm, with recovery from symptoms and effects, can be considered short-term upper limits for healthy adults.

TABLE 5–7 AEGL-2 Values for Hydrogen Cyanide

10 min	30 min	1 h	4 h	8 h
17 ppm (19 mg/m^3)	10 ppm (11 mg/m^3)	7.1 ppm (7.8 mg/m^3)	3.5 ppm (3.9 mg/m^3)	2.5 ppm (2.8 mg/m^3)

7.2. Animal Data Relevant to AEGL-3

LC_{01} values for four time periods were provided by E.I. du Pont de Nemours (1981) for the rat. They are as follows: 5 min, 283 ppm; 15 min, 138 ppm; 30 min, 127 ppm; and 60 min, 88 ppm. Ballantyne (1983) used several concentrations and exposure durations but did not provide the actual concentrations; therefore, an LC_{01} could not be calculated. Matijak-Schaper and Alarie (1982) reported no deaths in mice inhaling HCN at 100 ppm for 30 min. Mice inhaling HCN at 30 ppm for 24 h showed signs of lung congestion (Pryor et al. 1975).

7.3. Derivation of AEGL-3

The 15- and 30-min and 1-h LC_{01} values of 138, 127, and 88 ppm, respectively, provided by E.I. du Pont de Nemours (1981) for the rat were used to derive the AEGL-3 values. Lethal concentrations are very similar for various animal species (Table 5–4), and Barcroft (1931) has shown that man and the monkey are less sensitive to the effects of HCN than are the rat and dog, a conclusion based at least partially on relative respiratory rates. Relative to body weight, humans have a much lower respiratory rate and cardiac output than rodents. These are the primary determinants of systemic uptake of volatile chemicals. Thus, at similar exposure concentrations, rodents will absorb substantially more cyanide than primates. Lower rhodanese activity levels in primates will not be significant at high, acute HCN exposure levels. These factors might argue for use of an interspecies UF of 1. However, an interspecies UF was applied because of the high acute toxicity and rapid action of HCN. Because LC_{50} values among animal species differed by less than a factor of 2, an interspecies UF of 2 was applied. Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN, but the magnitude of these differences does not appear to be great. No specific data on susceptible populations were located in numerous published monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese, as well as other enzymes, is functional in all individuals, including newborns. Therefore, a UF of 3 was applied to protect susceptible individuals. The concentration-exposure duration relationship for this data set is $C^{2.6} \times t = k$ (Section 4.4.3); therefore, the value of 2.6 for n was applied. The 15- and 30-min and 1-h values were divided by a total UF of 6 and the 15-min and 1-h values were scaled across time using the $C^{2.6} \times t = k$ relationship (the 15-min

value for the 10-min AEGL-3 and the 1-h for the 4- and 8-h AEGL-3 values). Values appear in Table 5–8 and calculations are in Appendix B.

TABLE 5–8 AEGL-3 Values for Hydrogen Cyanide

10 min	30 min	1 h	4 h	8 h
27 ppm (30 mg/m^3)	21 ppm (23 mg/m^3)	15 ppm (17 mg/m^3)	8.6 ppm (9.7 mg/m^3)	6.6 ppm (7.3 mg/m^3)

The AEGL values are supported by the study of Pryor et al. (1975) with the mouse in which a 24-h exposure at 30 ppm induced pulmonary congestion but was not lethal. The 30 ppm concentration divided by a total UF of 6 and scaled across time from 24 h to 30 min using $C^{2.6}\times t=k$ results in a 30-min AEGL-2 of 22 ppm. The AEGL values are also supported by the study of Parmenter (1926) in which an individual potentially exposed at 25–75 ppm for part of a day had severe symptoms but recovered fully. Furthermore, Barcroft's subject withstood a 1.5-min exposure at 500–625 ppm (Barcroft 1931). Time scaling the AEGL-3 values to 1.5 min results in a concentration at 60 ppm, which is less than the actual exposure by a factor of approximately 10.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values and toxicity end points are summarized in Table 5–9.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 5–10. The Leeser et al. (1990) study was not available at the time many of these standards and guidelines were developed. The American Industrial Hygiene Association (AIHA 2000) did not derive an ERPG-1 value. The 1-h AEGL-2 and AEGL-3 values are slightly lower than the corresponding 1-h ERPG values. The ERPG-2 value was based on the Wexler et al. (1947) study in which sodium cyanide given intravenously to human volunteers at 0.11 mg/kg caused no deaths or serious injuries. The AIHA suggested that the intravenous dose approximates a 1-h exposure at 10 ppm. Because a

bolus dose of cyanide does not take into account metabolism over the 1-h exposure duration, a well-conducted animal study was chosen with an appropriate species, but inter- and intraspecies UFs were applied. The ERPG-3 was based on several animal studies, including Purser (1984), in which concentrations of 45 to 60 ppm resulted in only reversible effects. These studies, and several additional lethality studies, were also reviewed for the AEGL-3.

TABLE 5–9 Summary of AEGL Values (ppm [mg/m3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5	2.5	2.0	1.3	1.0
(Nondisabling)	(2.8)	(2.8)	(2.2)	(1.4)	(1.1)
AEGL-2	17	10	7.1	3.5	2.5
(Disabling)	(19)	(11)	(7.8)	(3.9)	(2.8)
AEGL-3	27	21	15	8.6	6.6
(Lethal)	(30)	(23)	(17)	(9.7)	(7.3)

The 1-h AEGL-2 (7.1 ppm) is close to the 1-h Spacecraft Maximum Allowable Concentration (SMAC) of 8 ppm (NRC 2000), and both groups considered available monitoring studies in their derivations. Although the SMAC definition is similar to the AEGL-1 definition, the SMAC applies to healthy adults, whereas the AEGL-2 applies to the general population; therefore, the AEGL-2 value is conservative in comparison with the SMAC. The NRC subcommittee on SMACs used the monitoring data of El Ghawabi et al. (1975) to develop the values. The subcommittee suggested that the average concentration of "8.0 ppm in the three plants would likely produce no more than mild CNS effects (e.g., mild headache), which would be acceptable for 1-hour exposures in a spacecraft." The subcommittee concluded that it was "likely that the more serious symptoms, such as vomiting, were the result of brief exposures to high HCN concentrations." Therefore, 8 ppm was identified as the 1-h allowable concentration of HCN. The 24-h SMAC is 4 ppm and the 7-d SMAC is 1 ppm.

The NIOSH immediately dangerous to life and health (IDLH) value (NIOSH 1994) is greater than the 30-min AEGL-3. NIOSH based their recommended exposure limit (REL) on the statement by Flury and Zernik (1931) that 45–54 ppm could be tolerated by man for 0.5 to 1 h without immediate or late effects. Although the Flury and Zernik (1931) data are based on animal studies, NIOSH did not apply a UF.

TABLE 5–10 Extant Standards and Guidelines for Hydrogen Cyanide

	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	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
ERPG-1 (AIHA)[a]			Not Applicable		
ERPG-2	10 ppm				
ERPG-3	25 ppm				
SMAC (NRC)[b]	8 ppm				
PEL-TWA (OSHA)[c]			10 ppm[†]		
REL-STEL (NIOSH)[d]			4.7 ppm[†]		
IDLH (NIOSH)[e]		50 ppm			
TLV-Ceiling (ACGIH)[f]			4.7 ppm[†],[‡]		
MAK (Germany)[g]			4.7 ppm[†]		
MAC (The Netherlands)[h]			10 ppm[†]		

[†]Skin notation.

[‡]Measured as CN.

[a]ERPG (emergency response planning guidelines) (AIHA 2000): The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for HCN is based on the Wexler et al. (1947) study. It is believed that the intravenous dose that caused no deaths or serious injuries is approximately equal to one that would be associated with 10 ppm for 1 h. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1-h without experiencing or developing life-threatening health effects. The ERPG-3 for HCN is based on several animal studies, including Purser (1984), in which exposures up to 60 ppm caused only reversible effects.

[b]SMACs (spacecraft maximum allowable concentrations) (NRC 2000) are intended to provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The 1-h SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[c]OSHA PEL-TWA (permissible exposure limits-time-weighted average) (NIOSH 1997) is analogous to the ACGIH-TLV-TWA but is for exposures of no more than 10 h/d, 40 h/wk. OSHA established a PEL of 4.7 ppm in 1989, but the U.S. Court of Appeals for the Eleventh Circuit vacated the PELs promulgated under the 1989 rulemaking. Therefore, the current OSHA PEL is 10 ppm (Federal Register 58 (124):35345, Wednesday, June 30, 1993).

[d]NIOSH REL-STEL (recommended exposure limit-short-term exposure limit) (NIOSH 2001) is analogous to the ACGIH TLV-TWA.

[e]IDLH (immediately dangerous to life and health) (NIOSH 2001) represents the maximum concentration from which one could escape within 30 min without any escapeimpairing symptoms or any irreversible health effects. The IDLH for HCN is based on a statement by Flury and Zernik (1931).

[f]ACGIH Ceiling (American Conference of Governmental Industrial Hygienists, Threshold Limit Value-ceiling) (ACGIH 1996; 2001) is the concentration that should not be exceeded during any part of the working exposure. Only a ceiling value has been established for HCN and cyanide salts. In 1993, the ceiling was reduced from 10 ppm to 4.7 ppm in order to protect against the irritation, headaches, and thyroid enlargement observed at 10 ppm in the El Ghawabi et al. (1975) study.

[g]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is analogous to the ACGIH-TLV-TWA.

[h]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is analogous to the ACGIH-TLV-TWA.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AIHA, American Industrial Hygiene Association; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Health and Safety Administration.

Both ACGIH (1996) and NIOSH (1999) based their ceiling and short-term exposure limits, respectively, on one of the studies used for development of the AEGL-1. The value for both agency limits of 4.7 ppm was based on symptoms described during chronic exposures of workers in several studies and specifically on El Ghawabi et al. (1975). In 1993, the ACGIH value was reduced from 10 ppm to minimize the potential for irritation to the respiratory

tract as well as potential acute and chronic effects of cyanide. The German and Dutch occupational exposure concentrations, analogous to the 8-h ACGIH time-weighted average (TWA), are 4.7 and 10 ppm, respectively. The German maximum workplace concentration (MAK) peak category or ceiling value is two times the MAK; this concentration is of a 5-min maximum duration and must not be exceeded at any time during the work shift.

8.3. Data Adequacy and Research Needs

The data base from animal studies is robust, but there are little definitive data on human exposure concentrations for short exposure durations and no definitive data on differences in susceptibilities among adults or between adults, infants, and children, other than well-understood ventilatory differences in the latter case. Gender and age-related differences in response to chronic cyanogenic glycoside consumption are difficult to interpret due to confounding, marked protein deficiencies in those populations that consume cassava as a major dietary staple (see Section 4.4.2). However, monitoring studies of presumably healthy adults that established no effect and/or minor discomfort concentrations to inhaled cyanide were available to set projected safe levels for the entire population by applying appropriate uncertainty factors (UFs). The metabolism and mechanism of action of cyanide are well understood and identical in all mammalian species. Data were available on concentrations involving lethal and sublethal effects for the monkey, dog, rat, mouse, and rabbit. Exposure durations included those ranging from a few seconds to 24 h. Where different mammalian species were tested in the same study, the results indicated that sensitivity to cyanide toxicity is similar among species, but slight differences may be related to body size, which in turn is related to respiration rate. Thus, establishing safe levels for humans based on small mammalian species adds confidence to the AEGL derivation. Animal studies with different toxicologic end points were available to establish concentration-exposure duration relationships. The extreme toxicity of HCN precludes certain types of tests, including long-term inhalation studies; therefore, genotoxicity, carcinogenicity and developmental and reproductive studies were performed with cyanide salts.

Several studies provided data on blood and urine concentrations of cyanide and thiocyanate following occupational exposures at low concentrations. These values are generally similar to those of smokers who have not been occupationally exposed to HCN. Whole-blood cyanide concentrations during

nitroprusside infusion also have been measured and related to symptoms. There are also data on nonlethal oral doses and metabolism rates in humans. Taken together, the data indicate that the HCN AEGL values may be conservative. However, data on infants, children, and the elderly, populations that may be more susceptible to HCN toxicity than healthy adults based on higher respiration rates and slower metabolism, among other factors, are lacking. Furthermore, occupational monitoring data were collected under normal working conditions; stress or physical exertion may be greater under emergency conditions. Because HCN is extremely toxic and the range of human susceptibility is not definitively known, the AEGL derivations make use of appropriate UFs.

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Appendixes

APPENDIX A TIME-SCALING CALCULATIONS FOR HYDROGEN CYANIDE

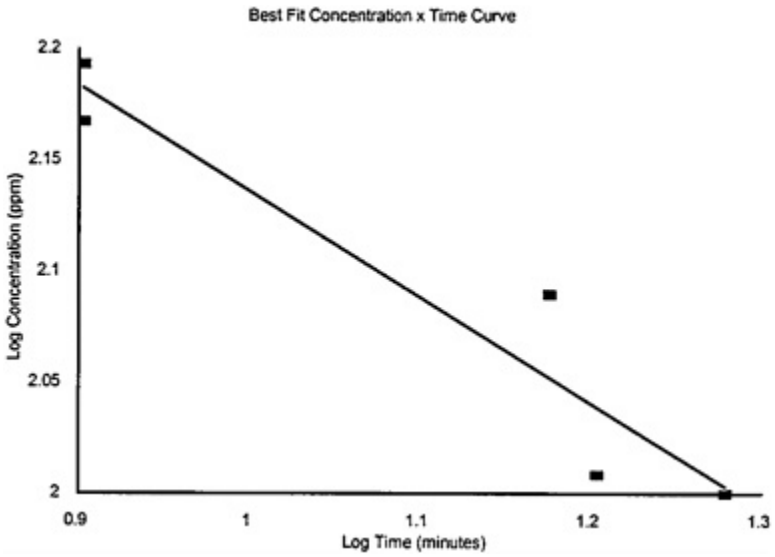

FIGURE A-1 Regression line for incapacitation in monkeys (data of Purser et al. [1984])

Data:			
Time (min)	Concentration (ppm)	*Log* time	*Log* concentration
19	100	1.2788	2.0000
16	102	1.2041	2.0086
15	123	1.1761	2.0899
8	147	0.9031	2.1673
8	156	0.9031	2.1931

Regression Output:	
Intercept	2.6131
Slope	−0.4769
R Squared	0.9142
Correlation	−0.9561
Degrees of Freedom	3
Observations	5
n=2.1	
k=301326	

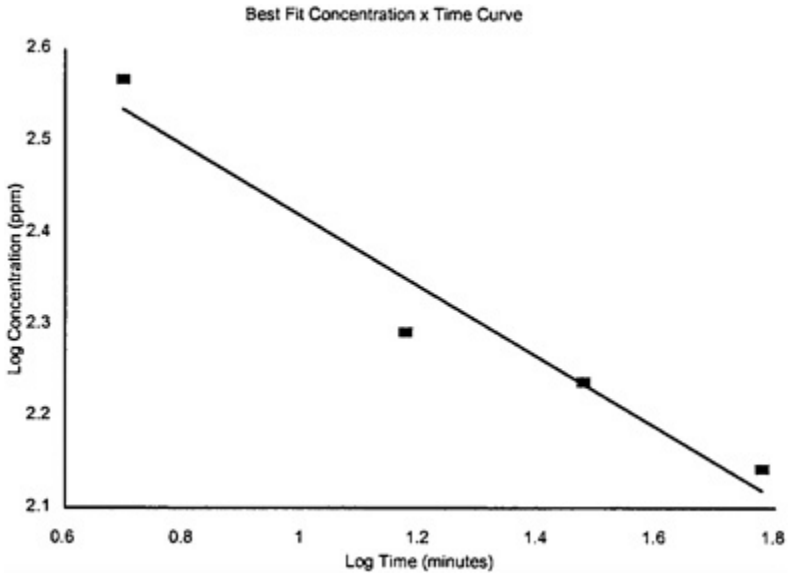

FIGURE A-2 Regression Line for LC_{50} values in rats (dta of E.I du Pont de Nemours [1981])

Data:			
Time (min)	Concentration (ppm)	*Log* time	*Log* concentration
5	369	0.6990	2.5670
15	196	1.1761	2.2923
30	173	1.4771	2.2380
60	139	1.7782	2.1430

Regression Output:	
Intercept	2.8044
Slope	−0.3854
R Squared	0.9490
Correlation	−0.9742
Degrees of Freedom	2
Observations	4
n=2.59	
k=1.9E+07	

APPENDIX B DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	Leeser et al. 1990
Supporting studies:	El Ghawabi et al. 1975; Hardy et al. 1950; Grabois 1954; Maehlyand Swensson 1970;
Toxicity end point:	No adverse effect in healthy adult humans occupationally exposed at geometric mean concentration of ≤1 (range 0.01–3.3 ppm, personal samplers [up to 6 ppm, area samples]) or 5 ppm; mild headache in adult humans occupationally exposed at 8 ppm. The exposure duration was considered to be 8 h.
Uncertainty factor:	An uncertainty factor was not applied to the Leeser et al. (1990) 1-ppm concentration because it is the lowest NOAEL. A factor of 3 for intraspecies differences was applied to the supporting studies because no susceptible populations were identified. The uncertainty factor was applied to the 8-h 5 ppm and 8 ppm concentrations, which resulted in concentrations close to the 8-h 1-ppm concentration in the Leeser et al. (1990) study.
Scaling:	$C^3 \times t = k$ (conservative time-scaling relationship, because the relationship between concentration and exposure duration for the headache effect is unknown). An 8-h 1 ppm concentration was used as the starting point for time scaling.
Calculations:	$(C^3/\text{uncertainty factors}) \times t = k$ $(1\ \text{ppm})^3 \times 480\ \text{min} = 480\ \text{ppm}^3 \cdot \text{min}$

10-min AEGL-1:	$(480\ ppm^3 \cdot min/10\ min)^{1/3}=3.6$ ppm Because 3.6 ppm is above the highest exposure concentration in the Leeser et al. (1990) study, as measured by personal monitors, the 10-min value was set equal to the 30-min value.
30-min AEGL-1:	$(480\ ppm^3 \cdot min/30\ min)^{1/3}=2.5$ ppm
1-h AEGL-1:	$(480\ ppm^3 \cdot min/60\ min)^{1/3}=2.0$ ppm
4-hour AEGL-1:	$(480\ ppm^3 \cdot min/240\ min)^{1/3}=1.3$ ppm
8-hour AEGL-1:	1.0 ppm

Derivation of AEGL-2

Key study:	Purser 1984
Toxicity end point:	Slight central nervous system depression in monkeys inhaling 60 ppm for 30 min.
Scaling:	$C^2 \times t=k$ (this document; based on regression analysis of incapacitation and lethality data for the monkey)
Uncertainty factors:	2 for interspecies 3 for intraspecies combined uncertainty factor of 6
Calculations:	$(C^2/\text{uncertainty factors}) \times t=k$ $(60\ ppm/6)^2 \times 30\ min=3{,}000\ ppm^2 \cdot min$
10-min AEGL-2:	$(3{,}000\ ppm^2 \cdot min/10\ min)^{1/2}=17$ ppm
30-min AEGL-2:	60 ppm/6=10 ppm
1-hour AEGL-2:	$(3{,}000\ ppm^2 \cdot min/60\ min)^{1/2}=7.1$ ppm

4-hour AEGL-2:	$(3{,}000\ ppm^2 \cdot min/240\ min)^{1/2}=3.5\ ppm$
8-hour AEGL-2:	$(3{,}000\ ppm^2 \cdot min/480\ min)^{1/2}=2.5\ ppm$

Derivation of AEGL-3

Key study:	E.I. du Pont de Nemours 1981
Toxicity end point:	15-min LC_{01} of 138 ppm in the rat 30-min LC_{01} of 127 ppm in the rat 1-h LC_{01} of 88 ppm in the rat LC_{01} derived by probit analysis
Scaling:	$C^{2.6} \times t=k$ (this document; based on the E.I. du Pont de Nemours [1981] rat data set)
Uncertainty factors:	2 for interspecies 3 for intraspecies combined uncertainty factor of 6
Calculations:	$(C^{2.6}/\text{uncertainty factors}) \times t=k$ $(138\ ppm/6)^{2.6} \times 15\ min=52{,}069.5\ ppm^{2.6} \cdot min$ $(127\ ppm/6)^{2.6} \times 30\ min=83{,}911\ ppm^{2.6} \cdot min$ $(88\ ppm/6)^{2.6} \times 60\ min=64{,}656.6\ ppm^{2.6} \cdot min$
10-min AEGL-3:	$(52{,}069.5\ ppm^{2.6} \cdot min/10\ min)^{1/2.6}=27\ ppm$
30-min AEGL-1:	$127\ ppm/6=21\ ppm$
1-h AEGL-1:	$88\ ppm/6=15\ ppm$
4-h AEGL-1:	$(64{,}656.6\ ppm^{2.6} \cdot min/240\ min)^{1/2.6}=8.6\ ppm$
8-h AEGL-1:	$(64{,}656.6\ ppm^{2.6} \cdot min/480\ min)^{1/2.6}=6.6\ ppm$

APPENDIX C DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR HYDROGEN CYANIDE (CAS No. 74–90–8)

AEGL-1

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, Maccles field, 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. Brit. J. Ind. Med. 32:215–219.
(2) Grabois, B. 1954. Monthly Review 33:33; Publication of the Division of Industrial Hygiene, New York Department of Labor, September 1954.
(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. 27:195–209.
(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 ≤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 y (El Ghawabi et al. 1975); Inhalation/5 ppm/unknown/(Grabois 1954; Maehly and Swensson 1970; Hardy et al. 1950).

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 (Grabois 1954; Maehly and Swensson 1970; Hardy et al. 1950).

End point/Concentration/Rationale: 1 ppm from the Leeser (1990) study; 8 ppm from the El Ghawabi et al. (1975) study; or 5 ppm from the Hardy et al. (1950), Grabois (1954), and Maehly and Swensson (1970) studies 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:	An uncertainty factor was not applied to the Leeser et al. (1990) 1 ppm concentration, as it is the lowest NOAEL. A factor of 3 was applied to the supporting studies as 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.

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 $ppm^3 \cdot min$) was applied when scaling to shorter exposure durations. The starting point for time scaling was an 8-h concentration at 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, supports 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.

AEGL-2

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

Key references: (1) Purser, D.A. 1984. A bioassay model for testing the incapacitating effects of exposure to combustion product atmospheres using cynomolgus monkeys. J. Fire Sciences 2:20–36.
(2) Purser, D.A., P.Grimshaw and K.R.Berrill. 1984. Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile. Arch. Environ. Health 39:393–400.

Test species/Strain/Sex/Number: Cynomolgus monkeys, 4 per exposure group (gender not stated)

Exposure route/Concentrations/Durations: Inhalation, 60, 100, 102, 123, 147, or 156 ppm for 30 min

Effects: (30-min exposures)

60 ppm	increased respiratory minute volume and slight changes in EEGs near end of exposure
100 ppm	incapacitation (semi-conscious state) in 19 min
102 ppm	incapacitation in 16 min
123 ppm	incapacitation in 15 min
147 ppm	incapacitation in 8 min
156 ppm	incapacitation in 8 min

End point/Concentration/Rationale: The 30-min exposure to 60 ppm, a NOAEL, was chosen because the next higher tested concentration, 100 ppm, resulted in incapacitation within the 30-min exposure period.

Uncertainty factors/Rationale:

Total uncertainty factor: 6

Interspecies:	2—The monkey is an appropriate model for humans, the small size and higher respiratory rate of the monkey may result in more rapid uptake and greater sensitivity than in humans.
Intraspecies:	3—No specific susceptible populations were identified during monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals, including newborns.

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Insufficient data.

Time scaling:	$C^n \times t = k$, where n=2 and k=3,000 $ppm^2 \cdot min$ on the basis of regression analysis of time-concentration relationships for both incapacitation times of 8 to 19 min and lethality data (3–60 min) for the monkey.

Data Adequacy: Although human data are limited to primarily occupational monitoring studies, the data base on animal studies is good. The test atmosphere in the key study was supplied via a face mask to the restrained test subjects; restrained animals have been shown to be more sensitive than unrestrained animals to inhaled toxicants. Relative species sensitivity to inhaled HCN may be related to breathing rate. Compared to rodents, the slower breathing rate of humans and monkeys may make them less sensitive to the effects of HCN.

The following two supporting studies were located:

1. A 30-min exposure of rats at 55 ppm resulted in changes in lung phospholipids and lung dynamics. Use of an uncertainty factor of 6 results in a 30-min AEGL-2 of 9.2 ppm, which is similar to the AEGL value.
2. Humans inhaling mean concentrations at 10 or 15 ppm in electroplating or silver-reclaiming factories for up to 15 y reported symptoms including headache, fatigue, effort dyspnea, and syncopes. There was no evidence that these symptoms occurred on the first day of employment.

AEGL-3

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

Key reference: E.I. du Pont de Nemours and Company 1981. Inhalation toxicity of common combustion gases. Haskell Laboratory Report No. 238–81. Haskell Laboratory, Newark, DE

Test species/Strain/Sex/Number: Crl:CD male rats, 10/exposure group

Exposure route/Concentrations/Durations:

Inhalation

273, 328, 340, 353, 441, 493, or 508 ppm for 5 min 110, 175, 188, 204, 230, 251, 283, or 403 ppm for 15 min 128, 149, 160, 183, 222, or 306 ppm for 30 min 76, 107, 154, 183, or 222 ppm for 60 min

Effects (LC_{01} values were calculated by Haskell Laboratory using probit analysis):

5-min LC_{01}: 283 ppm
15-min LC_{01}: 138 ppm
30-min LC_{01}: 127 ppm
60-min LC_{01}: 88 ppm

End point/Concentration/Rationale:

The LC_{01}, the threshold for lethality, was used as the basis for the derivation of the AEGL-3.

The 15-min LC_{01} was used to calculate the 10-min value; the 30-min LC_{01} was used for the 30-min value; and the 60-min LC_{01} was used to derive the 1-, 4-, and 8-h AEGL-3 values.

Uncertainty factors/Rationale:

Total uncertainty factor: 6

Interspecies: 2—LC_{50} values for the same exposure durations for several species (rat, mouse, and rabbit) were within a factor of approximately 1.5 of each other. Based on relative respiration rates, humans are expected to be less sensitive than rodents. The mechanism is the same for all species.

Intraspecies: 3—No specific susceptible populations were identified during monitoring studies or during the clinical use of nitroprusside solutions to control hypertension. The detoxifying enzyme rhodanese is present in all individuals, including newborns.

Modifying factor: Not applicable

Animal to human dosimetric adjustment: Insufficient data.

Time scaling:	$C^n \times t = k$ where n=2.6 was derived from empirical data and used in a regression analysis of time-concentration relationships for rat LC_{50} values conducted at time periods of 5, 15, 30, and 60 min in the key study. However, the 15-, 30-, and 60-min values were calculated directly from the empirical (LC_{01}) data. The k value of 52,069.5 $ppm^{2.6} \cdot min$, based on the 15-min LC_{01}, was used for the 10-min value and the k value of 64,656.6 $ppm^{2.6} \cdot min$, based on the 1-h LC_{01}, was used for the 4- and 8-h AEGL-3 values.

Data adequacy: The study was well conducted. The HCN concentrations were continuously monitored using infrared spectrophotometry and validated by gas chromatography.

One supporting study was located: exposure of rats to 30 ppm for 24 hours resulted in lung congestion but no deaths. Use of a total uncertainty factor of 6 and extrapolation across time to 30 minutes results in a 30-minute AEGL-3 of 22 ppm which is similar to the derived value of 21 ppm.