# Acute Exposure Guideline Levels for Selected Airborne Chemicals

## Volume 2

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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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 federal

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

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 Environmental Studies and Toxicology (BEST), for his helpful comments. The sub-

committee 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
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# Contents

# 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 November1995, 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, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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[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.

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-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points—including reproductive (in both 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 ($1 \times 10^{-4}$), 1 in

100,000 ($1 \times 10^{-5}$), and 1 in 1,000,000 ($1 \times 10^{-6}$) 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

# 4

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

# Acute Exposure Guideline Levels


**SUMMARY**

Hydrochlorofluorocarbon-141b, or 1,1-dichloro-1-fluoroethane (HCFC-141b), 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/m$^3$])

| 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 may be noticeable to some individuals at the 1,000-ppm 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<br>1,1-dichloro-1-fluoroethane<br>Freon 141<br>CFC 141, 141b<br>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$^3$<br>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-141b 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; |
| female | 64,991 | 4 h | $LC_{50}$ | Brock et al. |
| combined | 61,647 | 4 h | $LC_{50}$ | 1995 |
| 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 | Vlachos 1988 |
| | 20,000 | 6 h | No clinical signs | |
| | 30,000 | 6 h | No clinical signs | |

*(Continued)*

**TABLE 4-4** *Continued*

| 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).

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.)

### 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 of ten 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 post-implantation 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 treatment-related 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 Sprague-Dawley 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 of ten 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 Sprague-Dawley (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-141b 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 trichloro-fluoromethane 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 within145 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/m$^3$])

| 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-

**TABLE 4-7** AEGL-2 Values for HCFC-141b [ppm ($mg/m^3$)]

| 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) |

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.

## 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

**TABLE 4-8** AEGL-3 Values for HCFC-141b [ppm ($mg/m^3$)]

| 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) |

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).

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-

**TABLE 4-9** Summary of AEGL Values (ppm [mg/m$^3$])

| | 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) |

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.

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.

*(Continued)*

| **AEGL-1** *Continued* |
| --- |
| 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

*(Continued)*

| **AEGL-2** *Continued* |
| --- |
| 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.

*(Continued)*

| **AEGL-3** *Continued* |
| --- |
| 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. |