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
Guideline Levels

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Committee on Toxicology

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 (1×10^{-4}), 1 in

100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

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

The AEGL draft reports are initially prepared by ad hoc AEGL Development Teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Subcommittee on Acute Exposure Guideline Levels for final evaluation.

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

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

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

concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendix

3

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

Acute Exposure Guideline Levels

SUMMARY

Hydrofluorocarbon-134a or 1,1,1,2-Tetrafluoroethane (HFC-134a) has been developed as a replacement for fully halogenated chlorofluorocarbons because, compared with chlorofluorocarbons, its residence time in the atmosphere is shorter and its ozone depleting potential is insignificant. HFC-134a

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

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

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

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

The AEGL-1 concentration was based on a 1-hour (h) no-effect concentration of 8,000 parts per million (ppm) in healthy human subjects (Emmen et al. 2000). This concentration was without effects on pulmonary function, respiratory parameters, the eyes (irritation), or the cardiovascular system. Because this concentration is considerably below that causing any adverse effect in animal studies, an intraspecies uncertainty factor (UF) of 1 was applied. The intraspecies UF of 1 is supported by the absence of adverse effects in therapy tests with patients with severe chronic obstructive pulmonary disease and adult and pediatric asthmatics who were tested with metered-dose inhalers containing HFC-134a as the propellant. Because blood concentrations in this study approached equilibrium following 55 minutes (min) of exposure and effects are determined by blood concentrations, the value of 8,000 ppm was made equivalent across all time periods. The AEGL-1 of 8,000 ppm is supported by the absence of adverse effects in experimental animals that inhaled considerably higher concentrations. No adverse effects were observed in rats exposed at 81,000 ppm for 4 h (Silber and Kennedy 1979) or in rats exposed repeatedly at 50,000 or 100,000 ppm for 6 h/day (d). Adjustment of the

81,000 ppm value by interspecies and intraspecies UFs of 3 each, for a total of 10, results in essentially the same concentration (8,100 ppm) as the AEGL-1 based on human data.

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

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

Values are summarized in Table 3-1.

1. INTRODUCTION

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

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

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

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

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

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

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

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

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

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

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

2.2. Nonlethal Toxicity

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

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

TABLE 3-2 Chemical and Physical Data

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

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

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

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

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

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

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

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

2.3. Neurotoxicity

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

2.4. Developmental and Reproductive Toxicity

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

2.5. Genotoxicity

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

2.6. Carcinogenicity

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

2.7. Summary

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

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

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

3.2. Nonlethal Toxicity

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

3.2.1. Nonhuman Primates

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

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

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

3.2.2. Dogs

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

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

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

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

3.2.3. Rats

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

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

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

TABLE 3-4 Acute Sublethal Effects in Laboratory Animals

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

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

3.2.4. Mice

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

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

3.3. Neurotoxicity

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

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

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

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

3.4. Developmental and Reproductive Toxicity

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

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

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

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

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

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

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

In the perinatal and postnatal part of the study, groups of 41 female rats were administered concentrations of 1,800, 9,900, or 64,400 ppm of HFC-134a (99.3% pure) for 1 h daily during days 17 to 20 of pregnancy and days 1 to 21 postpartum (Alexander et al. 1996). Females were allowed to deliver and rear their young. Selected F_1 animals were mated; these animals were sacrificed on day 20 of pregnancy, and the uterine contents were examined. There were no clinical signs or effects on body weights (F_0), corpora lutea, implants, numbers of live born pups, gender ratio, litter weights, fetal body weights, or development and survival of the F_1 generation. There was a statistically significant delay in the occurrence of pinnae detachment, eye opening, and startle response in the F_1 generation, whose dams inhaled 64,400 ppm. There were no visceral or skeletal abnormalities in the F_1 or F_2 generations.

3.5. Cardiac Sensitization

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

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

TABLE 3-5 Cardiac Sensitization in Dogs Administered Exogenous Epinephrine[a]

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

[a]Animals were administered intravenous epinephrine at 8 µg/kg (Mullin and Hartgrove 1979) or individualized doses of 2, 4, or 8 µg/kg (Hardy et al. 1991).
[b]Animals were administered epinephrine 5 min into the 10-min exposure.
[c]A marked response is considered an effect; number of animals affected per number of animals tested in parenthesis.

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

3.6. Genotoxicity

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

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

3.7. Subchronic and Chronic Toxicity and Carcinogenicity

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

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

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

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

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

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

3.8. Summary

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

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

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

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

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

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

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition Considerations

4.1.1. Deposition and Elimination

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

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

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

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

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

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

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

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

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

4.1.2. Metabolism

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

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

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

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

4.2. Mechanism of Toxicity

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

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

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

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

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

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

4.3. Structure-Activity Relationships

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

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

4.4. Other Relevant Information

4.4.1. Species Differences

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

4.4.2. Susceptible Populations

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

4.4.3. Concentration–Exposure Duration Relationship

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

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

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

5. DATA ANALYSIS FOR AEGL-1

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

5.1. Summary of Human Data Relevant to AEGL-1

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

5.2. Summary of Animal Data Relevant to AEGL-1

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

5.3. Derivation of AEGL-1

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

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

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

6. DATA ANALYSIS FOR AEGL-2

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

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

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

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

6.3. Derivation of AEGL-2

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

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

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

bons can develop cardiac arrhythmias. A no-effect concentration of HFC-134a at 40,000 ppm under conditions of exogenous epinephrine was identified as the basis for AEGL-2 values. Because the dog heart is considered an appropriate model for the human heart, an interspecies UF of 1 was applied. Because this is a conservative test, an intraspecies UF of 3 was applied to protect potentially susceptible individuals. Blood concentrations were close to equilibrium within 55 min during human exposures, and concentrations of halocarbons that do not produce a positive response in the short-term cardiac sensitization test do not produce the response when exposures are continued for 6 h, so the value of 13,000 ppm (13,300 ppm rounded to two significant figures) was assigned to all AEGL-2 time periods (Table 3-7).

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

7. DATA ANALYSIS FOR AEGL-3

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

7.1. Summary of Human Data Relevant to AEGL-3

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

7.2. Summary of Animal Data Relevant to AEGL-3

Humans exposed to high concentrations of some halogenated hydrocar-

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

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

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

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

7.3. Derivation of AEGL-3

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

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

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

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End points

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

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

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

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

The AEGL values are summarized in Table 3-9.

8.2. Comparison with Other Standards and Guidelines

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

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

8.3. Data Adequacy and Research Needs

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

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

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

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

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Appendix

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

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

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

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

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

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

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

Uncertainty factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applicable, human subjects used.
Intraspecies: 1 - this no-effect concentration for eight healthy individuals was far below concentrations causing effects in animals. At this low exposure concentration there was no indication of differences in sensitivity among the subjects. This uncertainty factor is supported by the lack of effects in COPD and adult and pediatric asthmatic patients treated with metered-dose inhalers containing HFC-134a as a propellant.

Modifying factor: Not applicable.

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

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

(Continued)

AEGL-1 *Continued*
concentrations were approaching equilibrium after 55 min of exposure. Therefore, susceptibility to effects are predicted to remain the same as exposure time increases beyond 1 h.
Data adequacy: The key study was well designed and conducted and documented a lack of effects on heart and lung parameters as well as clinical chemistry. Pharmacokinetic data were also collected. The compound was without adverse effects when tested as a component of metered-dose inhalers on patients with COPD. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. The values are supported by a study with rats in which no effects were observed during a 4-h exposure to 81,000 ppm. Adjustment of the 81,000 ppm concentration by an interspecies and intraspecies uncertainty factors of 3 each, for a total of 10, results in essentially the same value (8,100 ppm) as that from the human study.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm

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

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

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

Effects:

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

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

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

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1- The cardiac sensitization model with the dog heart is considered a good model for humans.
Intraspecies: 3 - The test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

(Continued)

AEGL-2 *Continued*
Modifying factor: Not applicable.
Animal to human dosimetric adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.
Time scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15-55 min of exposure, and exposure duration did not influence the concentration at which the effect occurred.
Data adequacy: The key study was well conducted and documented. Supporting data include both human and animal studies. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures. No effects other than narcosis occurred in rats and mice exposed at 200,000 ppm for various periods of time. Adjustment by a total UF of 10 results in a higher value (20,000 ppm) than from the cardiac sensitization test with dogs.

AEGL-3				
10 min	30 min	1 h	4 h	8 h
27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm

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

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

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

Effects:

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

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

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

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - the cardiac sensitization model with the dog heart is considered a good model for humans.
Intraspecies: 3 - the test is optimized; there is a built in safety factor because of the greater-than-physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

(Continued)

AEGL-3 *Continued*
Modifying factor: Not applicable.
Animal to human dosimetric adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.
Time scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15-55 min of exposure, and exposure duration did not influence the concentration at which the effect occurred.
Data adequacy: The study was well conducted and documented. Supporting data include both human and animal studies. Animal studies covered acute, subchronic, and chronic exposure durations and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures. No deaths occurred in several species of animals exposed for various periods of time to concentrations less than those requiring supplemental oxygen (approximately 700,000 ppm).