Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 5

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

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, other federal and state governments, the chemical indus-

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

try, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 185 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 Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the fifth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for chlorine dioxide, chlorine trifluoride, cyclohexylamine, ethylenediamine, hydrofluoroether-7100 (HFE-7100), and tetranitromethane for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Sidney Green, Jr., Howard University; Loren Koller, Independent Consultant; Ramesh Gupta, Murray State University; Harihara Mehendale, University of Louisana at Monroe; and Deepak Bhalla, Wayne State University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario, 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 committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory), Aida Neel (project associate),

and Radiah Rose (senior editorial assistant). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

William E. Halperin, *Chair*
Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 5

Introduction

This report is the fifth 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 (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma, or heart disease.

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

In November 1995, 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 9.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public, including susceptible subpopulations 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/m3 [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 non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, pregnant women, 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 Emer-

gency 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 risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points, including reproductive (in both genders), developmental, neurotoxic, respiratory, and other organ-related effects, are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 ($1 \times 10\text{-}4$), 1 in 100,000 ($1 \times 10\text{-}5$), and 1 in 1,000,000 ($1 \times 10\text{-}6$) 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, 2001). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

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

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

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

Thus far, the committee has prepared four reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2000, 2002, 2003, 2004). This report is the fifth volume in that series. AEGL documents for chlorine dioxide, chlorine trifluoride, cyclohexylamine, ethylenediamine, hydrofluoroether (HFE 7100), and tetranitromethane are published as an appendix to this report. The committee 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 (NRC 1993, NRC 2001).

AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

5

HFE-7100:
Methyl Nonafluorobutyl Ether (40%)
(CAS Reg. No. 163702-07-6)
plus
Methyl Nonafluoroisobutyl Ether (60%)
(CAS Reg. No. 163702-08-7)[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrofluoroether-7100 (HFE-7100) is a mixture of methyl nonafluorobutyl and nonafluoroisobutyl ethers in ratios of 30-50 and 50-70%, respectively. This mixture has been developed as a replacement for presently used chlorofluorocarbons and other ozone-depleting chemicals. It is used in industrial situations as a cleaning agent, lubricant carrier, drying

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

agent, specialty solvent, and heat transfer medium. It is a volatile liquid with a slight ethereal odor. No information on production was located.

Except for a single monitoring study conducted by 3M Company and reported by AIHA (1999) in which exposures were noted to be below 50 ppm, no information was located on human exposure. Animal data using the rat as the model addressed anesthetic properties, acute oral, dermal, and inhalation toxicity; neurotoxicity, and genotoxicity. A study with the beagle dog addressed cardiac sensitization. HFE-7100 is of low acute oral and inhalation toxicity. It does not have anesthetic properties, is not neurotoxic or genotoxic, and is not a cardiac sensitizer. In developmental studies with the rat, the fetal effect of an increase in supernumerary ribs was observed only in conjunction with slight maternal toxicity. No information useful for time scaling across the AEGL exposure durations was available.

The AEGL-1 value is based on a subchronic study with the rat (Coombs et al. 1996a). In this study, groups of 20 male and female rats were exposed to concentrations up to 15,159 ppm for 6 h/day, 5 days/week for 13 weeks. This concentration was not neurotoxic. Reversible increases in weight of the liver, kidney, and spleen were observed, and these were considered a natural adaptation to chemical treatment. An interspecies uncertainty factor of 1 was applied because the concentration was basically a NOAEL, the exposures were repeated, and uptake is greater in the rodent than in primates (based on the higher respiratory rate and cardiac output of rodents compared with primates). Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied. A modifying factor of 2 was applied because human data are very limited and because some of the key studies used limited numbers of animals. The resultant value is 2,500 ppm. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. The presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Furthermore, the repeated number of the exposures in the key study supports the use of the same value across all time points. Therefore, the 2,500 ppm concentration is applicable for all AEGL-1 time points.

The AEGL-2 value is based on a 5-min no-adverse-effect exposure prior to a cardiac sensitization test with beagles (Kenny et al. 1996) and is supported by a 4-week repeat exposure study with the rat (Coombs et

al. 1996b). Six male beagles exposed to 48,900 ppm for 5 min prior to a cardiac sensitization test showed no response to exposure. Although the beagles did exhibit clinical signs following a challenge dose of epinephrine, there was no cardiac sensitization. The beagles fully recovered and were used in subsequent tests. One of two beagles exposed to the next highest concentration, 89,300 ppm for 5 min (prior to the cardiac sensitization test), became slightly agitated and exhibited tremors and stiff limbs. This response might impair the ability to escape. Therefore, according to the definition of the AEGL-2 in the Standing Operating Procedures for developing AEGLs (NRC 2001), the 48,900 ppm was considered a NOAEL. In a second study, groups of 10 male and female rats were exposed to concentrations up to 30,000 ppm for 6 h/day, 5 days/week for 4 weeks (Coombs et al. 1996b). At 30,000 ppm, the majority of rats exhibited reversible centrilobular hepatocyte hypertrophy which is a normal adaptive response to chemical treatment.

Although of short duration, the 5-min study with beagles, supported by the 4-week repeat study with rats, was used to derive the AEGL-2. Beagles were considerably more sensitive to the effects of HFE-7100 than rats. Both beagles and rats have higher respiratory rates and cardiac output than humans, resulting in greater chemical uptake. Therefore, an interspecies uncertainty factor of 1 was applied. Studies with rats, including neurotoxicity and developmental studies, failed to identify significant toxicological end points. HFE-7100 was not a cardiac sensitizer; therefore, heart patients should not be at added risk. An intraspecies uncertainty factor of 3 was considered sufficient to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resulting value is 8,200 ppm. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Furthermore, the presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. The repeat nature of the rat study also supports the use of a single value across the AEGL exposure durations. Therefore, the 8,200 ppm concentration is applicable for all AEGL-2 time points.

The AEGL-3 value is based on the same study with beagles (Kenny et al. 1996) and is supported by an acute inhalation study with the rat (3M Company 1995). One of two beagles inhaling 89,300 ppm for 5 min became slightly agitated, and showed clinical signs of tremors and stiffness of the limbs. The second beagle, administered a challenge dose

of adrenaline during a second 5-min exposure exhibited severe clinical signs including whole-body tremors. Although the 89,300 ppm exposure for 5 min was a clear NOAEL for death, the challenge dose of epinephrine to the second dog (during continuing exposure) with the resulting severe clinical signs is applicable to an emergency situation and can be considered life-threatening in susceptible individuals. However, in a 4-h study with rats inhaling 100,000 ppm, clinical signs were slight, consisting of slightly lowered respiration and sluggishness in one of three rats (3M Company 1995). Convulsions leading to death occurred only in rats inhaling 214,000 ppm for 40 min or more (Eger 1998).

The more conservative NOAEL for lethality in the study with beagles was used to develop AEGL-3 values. Beagles were considerably more sensitive to the effects of HFE-7100 than rats. Both beagles and rats have higher respiratory rates and cardiac output than humans, resulting in greater chemical uptake. Therefore, an interspecies uncertainty factor of 1 was applied. Studies with rats, including neurotoxicity and developmental studies, failed to identify significant toxicological end points. HFE-7100 was not a cardiac sensitizer; therefore, heart patients should not be at added risk. An intraspecies uncertainty factor of 3 was considered sufficient to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. Time scaling may not be relevant for anesthetics and halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Therefore, the resulting 15,000 ppm concentration is applicable for all AEGL-3 time points. The 89,300 ppm concentration may be a conservative estimate of the threshold for lethality as rats survived a 4-h exposure to 100,000 ppm (3M Company 1995) and the dose-response curve for convulsions and death (ED_{50} of 214,000 ppm) is predicted to be steep (Eger 1998).

The calculated values are listed in the Table 5-1.

1. INTRODUCTION

HFE-7100 is composed of a combination of methyl nonafluorobutyl and nonafluoroisobutyl ethers in ratios of 30-50 and 50-70%, respectively. Animal toxicity tests were generally performed using a 40:60

TABLE 5-1 Summary of AEGL Values for HFE-7100

Classification	10 min	30 min	1 h	4 h	8 h	End point (Reference)
AEGL–1 (Nondisabling)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	Reversible organ weight changes, repeated exposures, rat (Coombs et al. 1996a)
AEGL–2 (Disabling)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	NOAEL for clinical signs, dog (Kenny et al. 1996); NOAEL for clinical signs-repeat exposures, rat (Coombs et al. 1996b)
AEGL–3 (Lethal)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	Severe clinical signs, dog (Kenney et al. 1996); no deaths, rat (3M Company 1995)

mixture of the *n*-butyl and isobutyl isomers (AIHA 1999). HFE-7100 has been developed as a replacement for chlorofluorocarbons, hydrochlorofluorocarbons, hydrofluorocarbons and perfluorocarbons for use as a cleaning and rinsing agent, lubricant carrier, drying agent, specialty solvent, and heat transfer medium (AIHA 1999). The Environmental Environmental Protection (EPA) has listed 3M HFE-7100 as an acceptable substitute for ozone depleting substances in specific solvent cleaning and aerosol industry applications under its Significant New Alternatives Program. No information on the manufacturing process or production was located.

HFE-7100 is a highly volatile liquid with a slight ethereal odor. No information on the odor threshold was located. Chemical and physical data are listed in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. General Toxicity

No data on human toxicity were located. Air monitoring conducted by the 3M Company (1997) and reported by AIHA (1999) indicates that concentrations are generally less than 50 ppm near vapor degreasers where HFE-7100 was being used as a solvent. No adverse health effects were reported from workers engaged in this process.

2.2. Neurotoxicity

No information was located on neurotoxicity of HFE-7100 to humans.

2.3. Developmental/Reproductive Toxicity

No information was located on the developmental or reproductive toxicity of HFE-7100 to humans.

2.4. Genotoxicity

No information was located on the genotoxicity of HFE-7100 to humans.

2.5. Carcinogenicity

No information was located on the carcinogenicity of HFE-7100 to humans.

TABLE 5-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Methyl nonafluorobutyl ether: 1-methoxy-1,1,2,2,3,3,4,4,4-nonafluorobutane; 1-methoxyperfluorobutane; 1,1,1,2,2,3,3,4,4-nonafluoro-4-methoxybutane Methyl nonafluoroisobutyl ether: 1-methoxy-2-trifluoromethyl-1,1,2,3,3,3-hexafluoropropane; 1-methoxyperfluoroisobutane; 2-(difluoromethoxymethyl)-1,1,1,2,3,3,3-heptafluoropropane	3M Company 2000
Chemical formula	$C_5H_3F_9O$ Methyl nonafluorobutyl ether: CF_3-CF_2-CF_2-CF_2-O-CH_3 (31.0%) Methyl nonafluoroisobutyl ether: $(CF_3)_2$-CF-CF_2-O-CH_3 (68.7%)	AIHA 1999; Coombs et al. 1996b
Molecular weight	250	AIHA 1999
CAS Reg. No.	Methyl nonafluorobutyl ether: 163702-07-6 Methyl nonafluoroisobutyl ether: 163702-08-7	3M Company

(Continued)

TABLE 5-2 Continued

Parameter	Value	Reference
Physical state	Clear, colorless liquid	3M Company 2000
Solubility in water	<12 ppm	3M Company 2000
Oil/gas partition coefficient	9.66	Eger et al. 1999
Saline/gas partition coefficient	0.0050	Eger et al. 1999
Vapor pressure	202 mm Hg at 25°C 0.26 atmospheres	3M Company 2000 Eger et al. 1999
Saturated vapor pressure	2.24×10^5 ppm at 20°C	3M Company 2000
Vapor density (air = 1)	8.6	3M Company 2000
Flammable Limits LEL UEL	 None None	3M Company 2000
Specific gravity	1.5 g/mL	3M Company 2000
Melting point	−135°C	3M Company 2000
Boiling point	61°C	3M Company 2000
Conversion factors	1 ppm = 10.22 mg/m^3 1 mg/m^3 = 0.0978 ppm	AIHA 1999

2.6. Summary

HFE-7100 is a newly developed ether with a slight ethereal odor that is intended for use as a cleaning agent and speciality solvent. No information was located on toxicity, developmental or reproductive effects, genotoxicity, or carcinogenicity in humans. The only monitoring report indicates that workplace exposures were less than 50 ppm.

3. ANIMAL TOXICITY DATA

Orally, HFE-7100 is practically non-toxic. A dose of 5 g to 5 male and 5 female adult Sprague-Dawley rats produced no clinical signs (one animal exhibited soft stool on the day of treatment) and had no effect on mortality, morbidity, body weight, or gross pathology after 14 days (Hazleton Wisconsin, Inc. 1995a). Repeated (28-day) oral doses of 0, 8, 40, 200, or 1,000 mg/kg to male and female Sprague-Dawley rats produced irregular respiration and salivation at the high dose, but no deaths (Mitsubishi Chemical Safety Institute 1996a). Increased liver and thymus weights accompanied by cellular hypertrophy and increased blood albumin were observed, primarily in the 1,000 mg/kg/group. These effects were reversible during a 14-day recovery period. When tested on the skin or eyes of New Zealand white rabbits, HFE-7100 was minimally irritating to the skin (score of 0.7 out of 8 at the 4-h observation) and practically non-irritating to the eye (score or 2.0 out of 110 at the 1-h observation and 0 out of 110 at the 24-h observation) (Hazleton Wisconsin, Inc. 1995b; 1995c). HFE-7100 was not a dermal sensitizer when tested on the skin of guinea pigs (Hazleton Wisconsin, Inc. 1996a). When applied to the skin of rabbits for 5 days, absorption was minimal (Corning Hazleton 1996a).

3.1. Acute Lethality

The convulsive and anesthetic properties of HFE-7100 were studied using four adult male Sprague-Dawley rats (Eger 1998). The rats were placed in individual tubes within a larger flow-through chamber. Chamber atmospheres were monitored by gas chromatography. Chamber atmospheres were increased in steps beginning with 25-50% of the predicted minimum alveolar anesthetic concentration (MAC; calculated by

dividing two atm by the oil/gas partition coefficient) and continuing until the animals exhibited clonic convulsions. Animals were observed for 20 min at each concentration. HFE-7100 was not anesthetic, as defined by movement in response to a painful stimulus, at any partial pressure applied, up to 0.24-0.26 atm, the vapor pressure, nor did it decrease the requirement for anesthesia for a known anesthetic when given concurrently with that anesthetic. With increasing partial pressures, the rats became increasingly excited and at slightly more than 0.2 atm, 3 of 4 exhibited convulsions. The convulsive ED_{50} was 0.214 atm (214,000±1,000 ppm). Convulsions were associated with an increase in body temperature. The three rats that exhibited convulsions subsequently died. No exposure durations were provided, but the stepwise increments in concentration leading up to the convulsive concentration would indicate an exposure of at least 40 min.

3.2. Nonlethal Toxicity

3.2.1. Dogs

During cardiac sensitization studies, six beagles were exposed to 0, 10,000, 18,800, or 48,900 ppm for 5 min before administration of exogenous epinephrine. Two beagles were successfully exposed to 89,300 ppm for 5 min. No clinical signs were described at the lower concentrations. During the 5-min exposure to 89,300 ppm, one beagle became slightly agitated and exhibited signs of tremors and stiff limbs. Signs were not described in the second dog prior to administration of a challenge dose of epinephrine.

3.2.2. Rats

The remaining studies used the rat as the test species. Only one study with acute exposure was located. Additional studies with repeated and subchronic exposures are included in the following discussion.

Three male Sprague-Dawley rats were exposed in a 40 L flow-through chamber at a nominal concentration of 100,000 ppm which was regularly monitored (3M Company 1995). Oxygen concentration was maintained near 20%. The exposure period was 4 h. The animals were active near the start of exposure, although one animal appeared slightly

sluggish approximately 30 min into the exposure. At 3 h into the exposure, respirations ranged from 60-80/min which was described as slightly depressed. All animals survived the exposure and recovery period (undefined). Therefore, the 4-h LC_{50} is greater than 100,000 ppm. No further details were provided in this unpublished memo.

Groups of 5 male and 5 female Crl:CD BR Sprague-Dawley rats were exposed to 0 (air) or targeted concentrations of 1,500, 3,000, 9,500, or 30,000 ppm for 6 h/day, 5 days/week, for 4 weeks (Coombs et al. 1996b). Measured concentrations, analyzed by gas chromatography, were 1,489, 2,935, 9,283, and 28,881 ppm, respectively. The study generally followed EPA guidelines for subchronic studies in that body weight was monitored, blood was collected to monitor effects on hematology and clinical chemistry, and urine was collected for urinalysis. Following exposure, major organs were weighed and tissues were examined microscopically. There were no treatment-related clinical signs during the exposures and there were no toxicologically significant effects on body weight, food consumption, hematology parameters, or gross pathology. A liver weight increase in male rats in the 28,881 ppm group was accompanied by centrilobular hepatocyte hypertrophy in 3 of 5 males. Hepatocyte hypertrophy was observed in 4 of 5 females in the 28,881 group although liver weight was not affected. Hepatocyte hypertrophy was also observed in 1 of 5 males and 2 of 5 females in the 9,283 ppm group. Hepatocyte hypertrophy was generally scored as minimal. Focal necrosis was not observed. Changes in clinical chemistry parameters involved increased serum glucose and decreased serum cholesterol in males in the 28,881 ppm group. Palmitoyl CoA oxidase activity was non-significantly increased in male rats in the 28,881 ppm group. Urinary protein was increased in males in the 9,283 and 28,881 ppm groups, and urinary fluoride was increased in rats of both sexes in all but the 1,489 ppm group.

Groups of 10 young male and 10 young female Sprague-Dawley rats were exposed to target concentrations of 1,500, 4,500, 7,500, or 15,000 ppm for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1996a). Mean analyzed concentrations were 1,502, 4,550, 7,533, and 15,159 ppm, respectively. Isomer ratios by weight were stated as being 68.7% methyl nonafluoroisobutyl ether and 31.0% methyl nonafluorobutyl ether. The study generally followed EPA guidelines for subchronic studies in that clinical signs and body weight were monitored, blood was collected for hematology and clinical chemistry measurements, and urine was collected for urinalysis. Following exposure, a necropsy was per-

formed, major organs were weighed, and tissues and organs were examined microscopically. There were no treatment-related clinical signs or effects on body weight, food consumption, or hematology, clinical chemistry, or urine parameters (with the exception of a dose-related increase in urinary fluoride excretion). Liver, spleen, and kidney weights were minimally, but statistically significantly increased in males receiving 15,159 ppm. This effect was not evident in female rats. Microscopically, minimal to moderate centrilobular hepatocyte hypertrophy was observed in males (9/10) and females (6/10) that were exposed to 15,159 ppm. There were no increases in serum enzyme activities including alkaline phosphatase, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, gamma-glutamyl transferase, or creatinine phosphokinase, and focal necrosis of the liver was not observed. There were no treatment-related microscopic liver changes in the lower dose groups. Palmitoyl CoA activity was increased in male rats in the 15,159 ppm group, and there was evidence that HFE-7100 acted as a peroxisome proliferator in male rats, also at 15,159 ppm. There were no histological correlates for the minimal increases in kidney and spleen weights. In light of the lack of effect on relevant clinical chemistry and hematology parameters and histopathology, the increased organ weights are considered an adaptive response to chemical treatment.

3.3. Neurotoxicity

A functional observational battery (FOB) of tests (a neurobehavioral screening) composed of the following observations and tests were taken or administered in the 28-day and 13-week studies: observations of posture, salivation, vocalizing, tremors, grooming activity, arousal, rearing counts, bolus and urine count, and gait; reactions to approach, touch, noise, tail pinch, light (pupillary reaction); righting reflex; forelimb and hindlimb grip strength; footsplay; body temperature; and body weight. A FOB was administered to groups of five male and five female Sprague-Dawley rats following exposure to measured concentrations of 0, 1,489, 2,935, 9,283, or 28,881 ppm for 6 h/day, 5 days/week for 28 days (Coombs et al. 1996b). Compared with preexposure observations and results, there were no treatment-related clinical signs and no effects on behavior following these exposures.

A functional observational battery was also administered pretest and during weeks 4, 8, and 12 during exposure of groups of 10 male and

10 female Sprague-Dawley rats to measured concentrations of 1,502, 4,550, 7,533, or 15,159 ppm for 6 h/day, 5 days/week, for 13 weeks (Coombs et al. 1996a). There were no effects of treatment on activity, rearing, grip strength, hind limb splay, body temperature, or body weight. During weeks 8 and 12 there were slightly increased incidences of vocalizations in male rats in the 15,159 ppm group compared with the controls (controls, 0/10; 15,159 ppm, 4/10 [week 8] and 3/10 [week 12]). Soft stools were also observed in two males in this group during week 8. Hair loss was greater in females in the 15,159 ppm group during week 12 (7/10) than in the control group (2/10). According to the authors, these observations do not indicate a neurotoxic effect.

3.4. Cardiac Sensitization

Kenny et al. (1996) evaluated the cardiotoxicity of HFE-7100 in six male beagles according to the method of Reinhardt (1971). The dogs were restrained and the test material was administered via a face mask. Electrocardiograms were recorded during the exposures. Epinephrine (adrenaline) doses were individualized to each dog so that the response to epinephrine alone produced a clear but minimal effect on the electrocardiogram, ideally a few ectopic beats. Dogs were categorized as weak to strong responders depending on the dose of epinephrine (1-12 μg/kg) that elicited a baseline response. The 17-min exposure procedure consisted of exposure to air for 2 min followed by an epinephrine challenge, a 5-min recovery period, and a 10-min exposure to the test material (beginning at 7 min) with administration of a second epinephrine challenge at 5 min into the exposure, i.e., the epinephrine challenge was administered at 12 min followed by a 5-min observation period. A positive cardiac sensitization test was characterized by a burst of multifocal ventricular ectopic activity or ventricular fibrillation during exposure to HFE-7100. Each of the dogs was exposed to 0 (air only), 10,000, 18,800, or 48,900 ppm with at least a day of rest between exposures. Only one dog was successfully exposed and tested at 89,300 ppm as clinical signs were severe following the second challenge dose of epinephrine. None of the exposures produced cardiac effects in any of the dogs. However, concentration-related signs of exposure in response to the second challenge dose of epinephrine were observed, particularly at the 48,900 and 89,300 ppm concentrations (Table 5-3).

TABLE 5-3 Response of Dogs during a Cardiac Sensitization Test[a,b,c]

Concentration (ppm)	Response
10,000	Struggling and slight salivation (1 dog) negative for cardiac sensitization (6 dogs)
18,800	Licked lips when mask removed (3 dogs) salivation (2 dogs) forelimbs cold to touch (1 dog) negative for cardiac sensitization (6 dogs)
48,900	Agitation, restlessness (6 dogs) head and body tremors, arched back, rigid body (4 dogs) ears and neck cold to touch (1 dog) negative for cardiac sensitization (6 dogs)
89,300	Restlessness, forepaws and ears cold to touch, tremors, agitation, arched back, excessive salivation; cardiac sensitization not measured due to struggling (1 dog); additional dogs not tested

[a]Dogs received individualized epinephrine doses of 1-12 µg/kg.
[b]Six dogs tested at each concentration except at 89,300 ppm.
[c]Data from Kenny et al. 1996.

The cardiac sensitization test involves only a 10-min exposure because exposure duration is not relevant to eliciting an effect. 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).

3.5. Developmental/Reproductive Toxicity

In a range-finding study, groups of 10 time-mated Crl:CD BR VAF Plus Sprague-Dawley female rats were exposed to nominal concentrations of 0, 3,000, 9,500, or 30,000 ppm for 6 h/day on days 6-19 of gestation (Huntingdon Life Sciences 1996a). A reduction in body weight gain was observed in the 30,000 ppm group during the first 2 days of treatment. A recovery was apparent beginning on day 8 when body weight gain was similar to that of the controls. On day 20, dams were sacrificed, litter values were determined, and fetuses were examined for gross abnormalities. There were no treatment-related effects on the litters or on gross appearance of the fetuses. No histopathologic examinations

were conducted. This study was used to set exposure concentrations for further studies.

In a second study, groups of 25 pregnant Crl:CD BR VAF Plus (Sprague-Dawley) rats were exposed whole-body to 0 (air), 4,500, 7,500, or 15,000 ppm for 6 h/day, on days 6 through 19 of pregnancy (Huntingdon Life Sciences 1996b). Measured concentrations were 4,629, 7,538, and 15,076 ppm, respectively. Dams were monitored for clinical signs, body weight, and food and water consumption. On day 20 of pregnancy, dams were sacrificed and examined. The ovaries were checked for corpora lutea and the uteri were weighed and examined for number and distribution of young and number and distribution of embryofetal deaths, both early and late; individual fetuses were sexed and weighed. Half of the fetuses of each litter were examined for visceral malformations and half were examined for skeletal malformations. In addition to malformations, anomalies (minor frequently detected differences) and variants (alternative structures that regularly occur in a population) were scored.

In dams in the high-dose group there was a slight and gradual reduction in mean body weight compared with the control group. Final mean body weight and body weight gain in the high-dose group were lower than the mean control weight by 2 and 5%, respectively. Food consumption was also slightly reduced in the high-dose dams. These effects were not present in the lower dose groups. Live young were produced by 24, 24, 22, and 24 dams in the control, low, mid, and high-dose groups, respectively. The total number of fetuses in the control through high-dose groups were 281, 307, 268, and 291, respectively. There were no differences among the groups in pre-implantation losses, implantation rate, or incidence and distribution of embryofetal deaths. Total litter weights were similar, but the mean fetal weight was slightly lower (by 4%) in the high-dose group compared with the control group. This effect was attributed to the increased litter size in the high-dose group. There were no dose or treatment-related visceral or skeletal malformations. Incomplete ossification of the skeleton was higher in the control group fetuses (both by litter and number of fetuses) than in any treatment group. This effect resulted in a higher incidence of skeletal anomalies in the control group than in the treated groups. The incidence of lumbar ribs, a commonly observed skeletal variant, was higher in the high-dose group than in the control group. The percent of fetuses with 14 ribs in the control through high-dose groups were 10.5, 13.5, 17.6, and 22.5. Litter incidences for 14 ribs in the control through dose group were 7/24, 12/24, 12/22, and 13/24, respectively. An associated finding in the high-dose

group was two fetuses in two litters with one extra thoracolumbar vertebra. In the 7,538 ppm group, a single fetus was observed with a complete lumbar rib. Visceral anomalies included dilated renal pelvis/ureter in the high-dose group (seven fetuses in five litters and none in the control group). Dilated renal pelvis/ureter is a common finding in control fetuses and is considered an anomaly rather than a malformation. The study authors note the possible effect of non-specific maternal stress on the formation of supernumerary lumbar ribs in rats. According to the authors the increased incidences of supernumerary ribs in test animals is equivocal.

The relationship of exposure concentration to the presence of supernumerary ribs was further studied by exposing pregnant rats to a higher concentration. Groups of 25 time-mated Crl:CD BR VAF Plus Sprague-Dawley female rats were exposed to nominal concentrations of 0 or 30,000 ppm on days 6-19 of gestation (Huntingdon Life Sciences 1998). At 30,000 ppm, dams exhibited a reduction in weight gain between days 10 and 12 of pregnancy compared with the control group, but recovery occurred by day 20. The number of supernumerary ribs was increased in fetuses in the 30,000 ppm group (25.8%) compared with the control group (15.1%). No other anomalies were observed.

3.6. Genotoxicity

Three mutagenicity/genotoxicity studies were located. HFE-7100 was not mutagenic to several strains of *Salmonella typhimurium* in a test conducted with and without metabolic activation (Mitsubishi Chemical Safety Institute 1996b). HFE-7100 tested negative in a chromosomal aberration assay in cultured Chinese hamster lung cells (Mitsubishi Chemical Safety Institute 1996c). In vivo, HFE-7100 was negative in a mouse micronucleus assay at dose levels up to 5,000 mg/kg (Huntingdon Life Sciences 1996c).

3.7. Chronic Toxicity/Carcinogenicity

No chronic toxicity or carcinogenicity studies with HFE-7100 were located. No tumors or biochemical changes indicative of carcinogenicity were apparent in a subchronic study with rats (Coombs et al. 1996a).

3.8. Summary

The animal inhalation data involving HFE-7100 are summarized in Table 5-4. Only at concentrations high enough to involve some oxygen deprivation are toxic effects observed. In a study with rats, the EC_{50} for convulsions was 214,000 ppm and 3 of 4 rats died following the exposure (Eger 1998). However, no rats died following a 4-h exposure to 100,000 ppm (3M Company 1995). Prior to administration of the challenge dose of epinephrine in a cardiac sensitization test, no clinical signs were described in dogs inhaling concentrations up to 48,900 ppm for 5 min. Signs of tremors and stiff limbs were observed in one of two dogs inhaling 89,300 ppm for 5 min. Following the second challenge dose of epinephrine during a cardiac sensitization test, one dog exposed to 89,300 ppm for at least 5 min exhibited severe clinical signs including restlessness, cold extremities, limb rigidity, head and whole-body tremors, head shaking, arched back, agitation, and salivation (Kenny et al. 1996). Tests for cardiac sensitization with dogs were negative.

Following repeat exposures to concentrations up to 30,000 ppm and subchronic exposures to concentrations up to 15,159 ppm, HFE-7100 had no effect on neurobehavioral parameters in rats (Coombs et al. 1996a; 1996b). These repeated dose studies resulted in reversible organ weight changes, primarily an increase in liver weight, and were accompanied by hepatocyte hypertrophy. These effects are considered an adaptative response to chemical exposure and are not considered adverse (the reversibility of both the hepatocyte hypertrophy and associated liver weight increase in rats was shown in the oral study by Mitsubishi Chemical Safety Institute 1996a). HFE-7100 was not teratogenic in a series of studies in which dams were administered concentrations of approximately 5,000 to 30,000 ppm during gestation days 6 to 19 (Huntingdon Life Sciences 1996a; 1996b; 1998).

Data on developmental toxicity were limited to studies with the rat. The data indicated that concentrations up to 30,000 ppm were slightly stressful to pregnant dams as indicated by slightly lower weight gain. The primary finding in fetuses was supernumerary ribs. Although incidences were increased in the treated group when both fetuses and litters were considered, there was no clear dose-response, especially considering the more than 6-fold difference in concentrations between the low and high concentrations. There was no indication of treatment-related growth retardation which is usually observed as delayed ossifica-

TABLE 5-4 Summary of Animal Toxicity Data for HFE-7100

Concentration (ppm)	Exposure Duration	Species (number)	Effect	Reference
214,000 ± 1,000	—	Rat (4)	Convulsions, death (3 of 4 rats); not anesthetic	Eger 1998; Eger et al. 1999
100,000	4 h	Rat (3)	No deaths; few signs	3M Company 1995
89,300	5 min	Dog (1)	Slightly agitated, tremors, stiff limbs (1 dog tested)[a]	Kenny et al. 1996
48,900 18,800 10,000	5 min 5 min 5 min	Dog (6) Dog (6) Dog (6)	No signs described No signs described No signs described	
30,000 15,056 7,538 4,629	Gestation days 6-19, 6 h/day	Rat (groups of 25)	Slight stress of dams at two higher Concentrations; no visceral or skeletal malformations	Huntingdon Life Sciences 1996b; 1998
28,881 9,283 2,935 1,489	4 weeks: 6 h/day, 5 days/week	Rat (groups of 10)	No clinical signs at any exposure; minimal, reversible hepatocellular hypertrophy in some animals at two higher exposures; no toxicologically significant	Coombs et al. 1996b

			effects; not neurotoxic	
15,159 7,533 4,550 1,502	13 weeks: 6 h/day, 5 days/week	Rat (groups of 20)	No clinical signs at any exposure; no toxicologically significant effects; reversible hepatocyte hypertrophy at high concentration; not neurotoxic	Coombs et al. 1996a

[a]The described signs were observed prior to administration of the second challenge dose of epinephrine.

tion and reduced body weight. Thus, the increased incidence of supernumerary ribs in the treated rats is of questionable biological significance. It should be noted that the historical control data on Sprague Dawley rats shows mean fetal and litter incidences of bilateral supernumerary ribs of 1% (maximum, 16%) and 5% (maximum, 55%), respectively (Charles River Laboratories 1996). From this study there was no indication that the fetus is more sensitive to HFE-7100 than the dam as fetal effects were observed only in conjunction with slight maternal toxicity.

Mutagenicity and genotoxicity assays with HFE-7100 were negative. No chronic studies or studies addressing carcinogenicity were located. Orally, HFE-7100 is considered practically nontoxic (LD_{50} > 5 g/kg).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Groups of 4 male and 4 female rabbits were administered single intravenous injections of 0, 1, 2, 5, or 10 mg/kg HFE-7100 in DMSO (Corning Hazleton, Inc. 1996b). Blood samples were collected prior to exposure, at 4, 8, 12, 24, and 48 h post-exposure, and on days 8 and 16 post-exposure. Heptafluorobutyric acid was detected in the serum from 4 to 48 h post-exposure, indicating cleavage of the ether group. No quantitative data were provided.

Increased urinary inorganic fluoride in Sprague-Dawley rats treated subchronically with HFE-7100 at concentrations of 0, 1,500, 4,500, 7,500, and 15,000 ppm (Coombs et al. 1996a) indicates that additional biotransformation of the parent molecule(s) takes place with release of free inorganic fluoride and its subsequent elimination by the kidneys. Urinary fluoride concentrations during week 13 of the study were 1.5, 5.1, 12.8, 21.5, and 39.8 µg/mL for males in the control through high-dose group and 1.5, 3.3, 9.6, 13.5, and 22.5 µg/mL for females in the control through high-dose group. Using a polynomial regression model (r^2 = 0.82), the AIHA (1999) calculated that an HFE-7100 concentration of 2,400 ppm corresponded to a urinary fluoride level of 5 mg/L. As noted by AIHA (1999), this compares well with the ACGIH (2002) end of shift biological exposure index for urinary fluoride of 12 mg/L.

4.2. Mechanism of Toxicity

No information on the mechanism of toxicity was located. HFE-7100 did not have anesthetic properties up to its known vapor pressure (Eger 1998). HFE-7100 is not an anesthetic but a "nonimmobilizer" (see Section 4.3). Nonimmobilizers may produce clonic convulsions by two interrelated mechanisms: one correlates with lipophilicity (nonpolarity), implying an action in a nonpolar phase, and the second correlates with an action on the neurotransmitter GABA (γ-aminobutyric acid), perhaps by modifying the action of GABA on $GABA_A$ receptors. Anesthetics generally have an affinity for both polar and nonpolar phases, whereas, HFE-7100 has a low affinity for the polar phase.

4.3. Structure Activity Relationships

HFE-7100 is a hydrofluoroether. Fluorine forms the strongest single bond to carbon encountered in organic chemistry. The "per"fluoroethers or highly fluorinated ethers are poorly water soluble.

The convulsive property of volatile polyhalogenated compounds generally correlates with lipophilicity. Of 42 volatile compounds studied in rats, the convulsive ED_{50} of 80% of the compounds (including HFE-7100) correlated with lipophilicity ($r^2 = 0.99$). The oil/gas partition coefficient for HFE-7100 of 9.66 is low for an anesthetic, predicting an anesthetizing concentration of perhaps 10-20% of an atmosphere (22,400-44,800 ppm). However, HFE-7100 is not an anesthetic compound but a "nonimmobilizer." Nonimmobilizers are perfluorinated compounds that deviate from the Meyer-Overton hypothesis, i.e., their MAC × oil/gas partition coefficients exceed those of conventional inhaled anesthetics of 1.8 atm. Nonimmobilizers are compounds whose lipophilicity predicts an anesthetic effect but have no such effect, either when given alone or when added to a known anesthetic. The butanes will be taken up, but primarily in nonpolar phases. They will be eliminated very rapidly, with one pass through the lungs. This elimination is orders of magnitude more rapid than the elimination of a typical ether such as diethyl ether (Eger 2002; see also Koblin et al. 1994).

Similar to HFE-7100, the hydrofluorocarbon, 1,1,1,2-tetrafluoroethane (HFC-134a) and the hydrochlorofluorocarbon 1,1-dichloro-1-fluoroethane (HCFC-141b) are low in toxicity (NRC 2002). These chemicals also rapidly reach equilibrium in the blood. However, in con-

trast to HFE-7100, both of these chemicals exhibit anesthetic properties. Although HFE-7100 is an ether, the perfluoro group limits its solubility in biological fluids. Storage in adipose tissue is expected to be minimal based on its poor solubility in biological fluids and the elimination of the heptafluorobutyric acid metabolite within 48 h of an intravenous dose (Corning Hazleton, Inc. 1996b).

4.4. Other Relevant Information

4.4.1. Species Variability

Few data on different species were available. Based on clinical signs observed during exposure to high concentrations, 89,300-100,000 ppm, the dog appears to be more susceptible to HFE-7100 toxicity than the rat (Kenny et al. 1996; 3M Company 1995).

4.4.2. Susceptible Populations

No information on susceptible populations was located. In studies of a hydrofluorocarbon (HFC-134a) and a hydrochlorofluorocarbon (HCFC-141b), asthmatics were not identified as a susceptible population; HFC-134a is inert and has been used as a carrier in inhalers for asthmatic individuals. HFE-7100 also appears to be practically nontoxic. It is not a cardiac sensitizer. Therefore, neither asthmatics nor individuals with heart problems would be a particularly susceptible population. In the developmental studies with the rat, the pregnant dams and fetuses represent potentially susceptible populations. There were no adverse effects on either population.

4.4.3. Concentration-Exposure Duration Relationship

No information on the concentration-exposure relationship for a single end point was located. When considering the cardiac sensitization test with beagles, the National Research Council (Bakshi 1998) states that, “Because blood concentrations of halogenated hydrocarbons are not likely to increase when exposure time is increased beyond 5-10 min, the NOAEL identified for cardiac sensitization following a 10-min exposure

can be used without time extrapolation to set a 1-h EEGL." The rapid attainment of equilibrium in the blood reasonably holds true for halogenated hydrocarbons that are not cardiac sensitizers.

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues were apparent.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No information on toxicity to humans was located.

5.2. Summary of Animal Data Relevant to AEGL-1

HFE-7100 is of low toxicity to rats and dogs. No acute studies with end points relevant to deriving AEGL-1 values were located. In the absence of acute studies, the 13-week repeated dose study with the rat (Coombs et al. 1996a) can be considered for development of AEGL-1 values. In this study, rats were exposed to concentrations up to 15,159 ppm for 6 h/day, 5 days/week for 13 weeks. Increased but reversible organ weight changes were attributed to the repeated nature of the exposures and are not predicted to occur following a single exposure. Except for hepatocyte hypertrophy, which is reversible, there were no histological correlates. There were no neurotoxic signs. The 15,159 ppm concentration in this repeated dose study can be considered a no-observed-effect-level (NOAEL) according to the definition of the AEGL-1, i.e., transient, asymptomatic effects.

5.3. Derivation of AEGL-1

The repeated exposure of the rat to 15,159 ppm (Coombs et al. 1996a) was used as the basis for development of AEGL-1 values. Because the concentration was basically a NOAEL, the exposures were repeated, and initial uptake would be more rapid in rodents than in pri-

mates (based on the higher respiratory rate and cardiac output of rodents compared with primates, equilibrium would be reached more rapidly in rodents), an interspecies uncertainty factor of 1 was applied. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resultant value is 2,500 ppm. Time scaling may not be relevant for anesthetics and halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased (NRC 1996). The presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Furthermore, the repeated nature of the exposures in the key study support the use of the same value across all time points. Therefore, the 2,500 ppm concentration is applicable for all AEGL-1 time points. Values appear in Table 5-5.

It should be noted that if the NOAEL for tremors in dogs (see AEGL-2 derivation below) were used as the basis for the AEGL-1 with application of interspecies and intraspecies uncertainty factors of 3 each and a modifying factor of 2, the same AEGL-1 value, 2,500 ppm, would be derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No information on toxicity to humans was located.

6.2. Summary of Animal Data Relevant to AEGL-2

Several studies can be considered appropriate for derivation of AEGL-2 values. In the first study, six beagles were exposed to 48,900

TABLE 5-5 AEGL-1 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)	2,500 ppm (25,550 mg/m^3)

ppm for 10 min. No clinical signs were described during the 5-min exposure prior to the second challenge dose of epinephrine. Clinical signs were observed during the second 5 min (of the 10-min exposure) following a challenge dose of epinephrine (Kenny et al. 1996). Therefore, 48,900 ppm for 5 min was a NOAEL for clinical signs in the absence of exogenous epinephrine. HFE-7100 was not a cardiac sensitizer at this concentration or at the higher concentration of 89,300 ppm.

A study with the rat used repeated exposures (Coombs et al. 1996b). Exposure to the highest concentration, 30,000 ppm for 4 weeks, resulted in only hepatocyte hypertrophy, a reversible effect when exposure is discontinued. This concentration was not neurotoxic as functional observational battery observations were negative. In a developmental study, exposure of pregnant rats to 30,000 ppm did not result in severe adverse effects to either the dams or fetuses.

6.3. Derivation of AEGL-2

The exposure of beagles to 48,900 ppm was chosen as the basis for the AEGL-2. No clinical signs were described during the 5-min exposure prior to the challenge dose of epinephrine. The NOAEL of 48,900 ppm was chosen as the basis for the AEGL-2 because at the next highest exposure, 89,300 ppm, the severe clinical signs of agitation, tremors, and stiff limbs might impair the ability to escape. An interspecies uncertainty factor of 1 was applied to the 48,900 ppm for several reasons: when considering clinical signs, the dog was shown to be more sensitive than the rat, and the respiration rate of dogs and rodents is greater than that of humans, resulting in greater uptake. Although exposures were at a lower concentration, the no-effect concentrations of 30,000 ppm in well-conducted repeat exposure and developmental studies support the interspecies uncertainty factor of 1. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Furthermore, the chemical is poorly soluble in biological fluids. Therefore, an intraspecies uncertainty factor of 3 was applied to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. The resulting value is 8,200 ppm.

Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do

not greatly increase as exposure duration is increased (NRC 1996). Furthermore, the presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Therefore, the 8,200 ppm concentration is applicable for all AEGL-2 time points. The use of the same value across all exposure durations is supported by the study in which rats were exposed to concentrations up to 30,000 ppm for 6 h/day, 5 days/week for four weeks. These rats exhibited reversible liver hypertrophy which is attributed to the repeated nature of the exposures (Coombs et al. 1996b). The use of repeated exposures in this study supports using a single value across the AEGL-2 timepoints. Values appear in Table 5-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were located.

7.2. Summary of Animal Data Relevant to AEGL-3

In a study with rats, the EC_{50} for convulsions was 214,000 ppm and 3 of 4 rats died following the exposure (Eger 1998). However, no rats died following a 4-h exposure to 100,000 ppm (3M Company 1995). Prior to the second challenge dose of epinephrine during a cardiac sensitization test, one of two dogs exposed to 89,300 ppm exhibited severe clinical signs including agitation, tremors, and stiff limbs (Kenny et al. 1996). The second dog survived the second challenge dose of epinephrine but exhibited extremely severe clinical signs.

TABLE 5-6 AEGL-2 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)	8,200 ppm (84,000 mg/m^3)

7.3. Derivation of AEGL-3

Taken together, the animal data indicate that the threshold for lethality in both the rat and dog lies above 89,300 ppm. Because the data are insufficient for calculating the exact threshold for lethality in either species, the 5-min exposure of the dog to 89,000 ppm was used as the basis for the AEGL-2 values. Although the tremors in dogs are rapidly reversible and do not cause lasting effects, they may have a severe effect on populations such as patients with heart disease. An interspecies uncertainty factor of 1 was applied to the 48,900 ppm for several reasons: when considering clinical signs, the dog was shown to be more sensitive than the rat, and the respiration rate of dogs and rodents is greater than that of humans, resulting in greater uptake. Studies addressing neurotoxicity and cardiac sensitization and studies with pregnant rats failed to identify significant toxicological end points. Therefore, an intraspecies uncertainty factor of 3 was applied to protect potentially susceptible individuals. Because human data are very limited and because some of the key studies used limited numbers of animals, a modifying factor of 2 was applied. Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals rapidly reach equilibrium and do not greatly increase as exposure duration is increased. Therefore, the resulting 15,000 ppm concentration is applicable for all AEGL-3 time points. The 89,300 ppm concentration may be a conservative estimate of the threshold for lethality as rats survived a 4-h exposure to 100,000 ppm (3M Company 1995). Application of the same uncertainty and modifying factors to the 100,000 ppm concentration results in a slightly higher value, 17,000 ppm. Values appear in Table 5-7.

The 15,000 ppm concentration is supported by the repeated exposure of pregnant rats to 30,000 ppm (Huntingdon Life Sciences 1998). No adverse effects other than a transient lower weight gain were observed in dams exposed from days 6 through 19 of gestation. Pregnant rats represent a susceptible animal population. Furthermore, humans have a much lower respiratory rate and cardiac output than rodents.

TABLE 5-7 AEGL-3 Values for HFE-7100

10 min	30 min	1 h	4 h	8 h
15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)	15,000 ppm (150,000 mg/m^3)

These are the two primary determinants of systemic uptake of volatile chemicals. Therefore, at similar concentrations, rodents will absorb substantially more of a chemical than primates.

The use of the 5-min value for all time periods is supported by fact that the exposures were repeated in the study with the rat above, a conservative approach to developing AEGL values was used, and there were no deaths in rats exposed to 100,000 ppm for 4 h (3M Company 1995). The only observed adverse effect in the latter study was mild—a slightly lower respiratory rate.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values and their relationship to each other are summarized in Table 5-8.

8.2. Comparison with Other Standards and Guidelines

HFE-7100 is a newly developed chemical and only a Workplace Environmental Exposure Level (WEEL) has been developed. The WEEL for an 8-h workday is 750 ppm (AIHA 1999). The WEEL was based on the NOEL of 7,500 ppm in the 90-day toxicity study with rats (Coombs et al. 1996a).

8.3. Data Adequacy and Research Needs

Human data are lacking. Recent animal studies were well conducted and addressed multiple end points; however several of the key studies used limited numbers of animals.

TABLE 5-8 Summary of AEGL Values (ppm)

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	2,500	2,500	2,500	2,500	2,500

AEGL-2 (Disabling)	8,200	8,200	8,200	8,200	8,200
AEGL-3 (Lethal)	15,000	15,000	15,000	15,000	15,000

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APPENDIX A

ACUTE EXPOSURE GUIDELINE LEVELS FOR HFE-7100 (CAS Reg. No. 163702-07-6 and 163702-08-7)

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
2,500 ppm	2,500 ppm	2,500 ppm	2,500 ppm	2,500 ppm

Key Reference: Coombs, D.W., C.K. Shepherd, M. Bannerman, C.J. Hardy, D. Cook, M. Hall and G.F. Healy. 1996a. T-6334: 13 Week repeat dose inhalation toxicity study in rats. MIN 196/961181, Huntingdon Life Sciences, Huntingdon, Cambridgeshire, England.

Test Species/Strain/Number: Rats/Sprague-Dawley/20 males and 20 females.

Exposure Route/Concentrations/Durations: Inhalation: 1,502, 4,550, 7,533, 15,159 ppm, 6 h/day, 5 days/week for 13 weeks.

Effects:
1,502, 4,550, 7,533 ppm - no effects
15,159 ppm - reversible liver weight increase, minimal organ weight changes.

End point/Concentration/Rationale: Reversible organ weight changes/15,159 ppm/no adverse effect with repeated exposures (changes attributed to repeat exposures).

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, uptake would be similar in primates and rodents, although based on higher respiratory rates and cardiac output, equilibrium would be reached more rapidly in rodents than primates.
Intraspecies: 3, no significant toxicological end points identified; poor solubility in biological fluids.

Modifying Factor: 2, limited data on humans; limited number of animals in several studies.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: Repeated nature of the exposures allows use of a single value across all timepoints.

Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies, but minimal human data and limited number of animals in several studies.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
8,200 ppm	8,200 ppm	8,200 ppm	8,200 ppm	8,200 ppm

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited, Huntingdon, Cambridgeshire, England.
Support: Coombs, D.W., C.K. Shepherd, M. Bannerman, C.J., Hardy, D. Crook, M. Hall, E.W. Hughes, and C. Gopinath. 1996b. T-6334: 28-Day repeat dose inhalation toxicity study in rats. MIN 181/952688, Huntingdon Life Sciences, Huntingdon, Cambridgeshire, England.

Test Species/Strain/Number: Dog/beagle/6 (Kenny et al. 1996).
Rat/Sprague-Dawley/10 (Coombs et al. 1996b).

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,000, 48,900, and 89,300 ppm/5 min prior to cardiac sensitization test (Kenny et al. 1996).
Inhalation/0, 1,500, 3,000, 9,500, or 30,000 ppm for 6 h/d, 5 d/wk, for 4 wk (Coombs et al. 1996b).

Effects:
Kenny et al. 1996:
10,000 ppm: no effects
18,800 ppm: minimal effects
48,900 ppm: no clinical signs prior to administration of epinephrine; signs of stress following second dose of epinephrine (restlessness, trembling, limb rigidity).
89,300 ppm: severe signs of stress (salivation, tremors, limb rigidity)
All dogs recovered; not a cardiac sensitizer when concurrently injected with epinephrine.
Coombs et al. 1996b:
No clinical signs at any concentration.

End point/Concentration/Rationale: No signs of stress in dogs; not a cardiac sensitizer, 48,900 ppm

(Continued)

AEGL-2 VALUES Continued

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, both beagles and rats have higher respiratory rates and cardiac output than humans.
Intraspecies: 3, no significant toxicological end points identified in other studies; poor solubility in biological fluids for all species.

Modifying Factor: 2, limited data on humans, limited number of animals in several studies.

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: Not applied; low solubility of test compound in blood, rapidly reaches equilibrium; cardiac response does not change when chemical is administered for hours.

Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies. Limited human data; limited number of animals in some key studies.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
15,000 ppm	15,000 ppm	15,000 ppm	15,000 ppm	15,000 ppm

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited, Huntingdon, Cambridgeshire, England.
Support: 3M Company. 1995. Acute inhalation toxicity for HFE-7100 in the rat. Unpublished memo, 3M Company, Toxicology Services, 3M Center, St. Paul, MN.

Test Species/Strain/Number: Dog/beagle/6 (only 1 of 2 dogs observed 89,300 ppm) (Kenny et al. 1996).
Rat/Sprague-Dawley/3 (3M Company 1995).

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,800, 48,900, and 89,300 ppm/5 min (Kenny et al. 1996).
Inhalation/100,000 ppm/4 h (3M Company 1995).

Effects:
Kenny et al. 1996.
10,000 ppm: no clinical signs.
18,800 ppm: no clinical signs.
48,900 ppm: no clinical signs prior to administration of epinephrine
89,300 ppm: severe clinical signs.

3M Company 1995. 100,000 ppm for 4 h: no deaths.
End point/Concentration/Rationale: Severe clinical signs/89,300 ppm/considered lethal threshold due to severity of signs. Supported by no deaths in rats at 100,000 ppm (3M Company 1995).
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1—respiratory rate and cardiac output higher in beagles and rats than in humans. Intraspecies: 3—no significant toxicological end points identified in other studies; poor solubility in biological fluids for all species.
Modifying Factor: 2—limited data on humans; limited number of animals in several studies.
Animal to Human Dosimetric Adjustment: Not applied.
Time Scaling: Not applied; low solubility of test compound in blood, rapidly reaches equilibrium; cardiac response does not change when chemical is administered for hours.
Data Adequacy: Well conducted repeat dose, subchronic, developmental/reproductive, neurotoxicity, and cardiac sensitization studies. Limited human studies; limited number of animals in this and several support studies. The 89,300 ppm may be a conservative estimate of a lethal concentration as no rats died after a 4-h exposure to 100,000 ppm.