Fermilab

Particle Physics Division
Mechanical Department Engineering Note

Number: MD-ENG-80 Date: 25 May 2005

Project Internal Reference:

Project: COUPP and NuMI / MINOS

Title: ODH Analysis for Minos Near Detector Access Tunnel due to the CF3I in the COUPP Bubble chamber

Author(s): Dave Pushka

Reviewer(s): 5-25-05

Key Words: ODH Analysis, COUPP Bubble Chamber, CF3I, Iodotrifluoromethane

Abstract Summary: Analysis of the effects of the complete and instantaneous loss of the complete contents (1.3 liters) of CF3I (Iodotrifluoromethane) from the COUPP bubble chamber, which is located in the MINOS Near Detector Access tunnel. Assumes this liquid vaporizes immediately. Result is that this space remains ODH classification 0.

Applicable Codes: FESHM 5064

Complete Loss of 1.3 liters of CF3I Contents at the base of the MINOS Shaft:

The small COUPP bubble chamber contains 1.3 liters of liquid CF3I
This volume will be in the MINOS near detector access tunnel (not in the fire escape egress passage).
The volume in the area of the MINOS access tunnel is not less than : 15000 cubit feet
based on a tunnel diameter of 15 feet, tunnel height of 10 feet and tunnel lenght of 100 feet. Actual length of the tunnel is longer than 100 feet, height is higher than 10 feet, and width is greater than 15

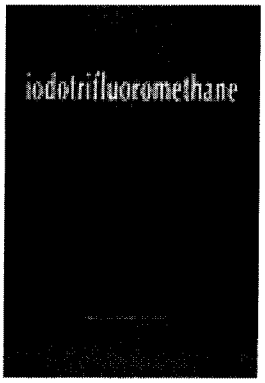
Liquid density of the CF3I is 2096 kg/m3 at 20 C
Vapor density is 8.051 kg / m3 at 25 C

1.3 liters of liquid * 1m3/1000 liters * 2096 kg / m3 gives a mass of CF3I of : 2.7248 kg
2.7248 kg of cF3I at a vapor density of 8.051 kg/m3 gives a volumn of CF3I vapor of: 0.338442 m3
0.338442 m3 of vapor * 35.31 ft3 per meter3 give a volume of: 11.9504 cubic feet of vapor

Calculating the fraction O2 concentration if this Cf3I vaporizes in the space gives:

Concentration, O2 %= 20.98328

This does not cause an ODH condition since the oxygen concentration remains above 18%
One does not need to go any further and consider the probability if this failure occuring since even if the bottle was breached, the oxygen concentration stays above 18%



Iodotrifluoromethane: Toxicity Review

Subcommittee on Iodotrifluoromethane, Committee on Toxicology, National Research Council

ISBN: 0-309-09307-4, 112 pages, 6 x 9, (2004)

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iodotrifluoromethane

TOXICITY REVIEW

Subcommittee on Iodotrifluoromethane

Committee on Toxicology

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This project was supported by Contract No. DAMD17-99-C-9049 between the National Academy of Sciences and the U.S. Army. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-09307-4 (Book)
International Standard Book Number 0-309-54550-1 (PDF)

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Preface

Chlorofluorobromines (halons) have been used in a variety of applications, including fire suppression. The U.S. Army uses halons as fire suppressants in several aircraft and ground vehicles. However, these substances have been associated with stratospheric ozone-layer depletion and, as required by international agreements, are being replaced. Iodotrifluoromethane (CF_3I) is one compound under consideration by the U.S. Army (and others) as a halon replacement.

The U. S. Army Center for Health Promotion and Preventive Medicine at Aberdeen Proving Ground, Maryland, prepared a toxicity review of CF_3I in 1999 and updated it in 2002. The Office of the Surgeon General of the Army asked the Committee on Toxicology (COT) of the National Research Council to conduct an independent evaluation of the Army's toxicity review for CF_3I. In response to the Army's request, the Research Council formed the Subcommittee on Iodotrifluoromethane, which prepared this report.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the Research Council'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 of 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 for their review of this report: Kerry Dearfield, U.S. Environmental Protection Agency, Washington, DC; Paul Foster, National Institute of Environmental Health Sciences, Research Triangle Park, NC; Donald E. Gardner, Inhalation Toxicology Associates, Raleigh, NC; Michael Gargas, The Sapphire Group, Beavercreek, OH; Murray Mittleman, Beth Israel Deaconess Medical Center, Boston, MA; James F. O'Bryon, The O'Bryon Group, Bel Air, MD; Carol Rice, University of Cincinnati, OH; and Henry J. Trochimowicz, Delaware Toxicology Associates, Inc., Newark, DE. Although the reviewers listed above have provided many constructive comments and

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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 Roger O. McClellan, consultant, Albuquerque, NM. Appointed by the Research Council, he 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 author committee and the institution.

The subcommittee also gratefully acknowledges the following for making presentations or providing information: Glenn Leach, U.S. Army; Leslie Chaney, Therimmune Research Corporation; Gary Jepson, Dupont Company; Charles Reinhardt, consultant; Samuel Dudley, Emory University; Reva Rubenstein, consultant; and Juan Vitali, Georgia Tech Research Institute.

The subcommittee is grateful for the assistance of the Research Council staff in preparing this report: Roberta Wedge, project director and program director for risk assessment; James Reisa, director of the Board on Environmental Studies and Toxicology; Kulbir Bakshi, program director for toxicology; Jennifer Saunders, research associate; Jennifer Roberts, research associate; Mirsada Karalic-Loncarevic, research associate; Norman Grossblatt, senior editor, Ruth E. Crossgrove, senior editor; Lucy Fusco, senior project assistant; and Jordan Crago, senior project assistant.

Finally, I thank the members of the subcommittee for their dedicated efforts throughout the development of this report.

Samuel Kacew, PhD
Chair, Subcommittee on
Iodotrifluoromethane

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
CAA	Clean Air Act
CF_3I	iodotrifluoromethane, trifluoroiodomethane, trifluoromethyl iodide, trifluoroiodide, FIC-1311
CFC	chlorofluorocarbon
COF_2	carbonyl fluoride
COT	Committee on Toxicology
ECG	electrocardiograph
EPA	U.S. Environmental Protection Agency
FVF	fatal ventricular fibrillation
HCFC	hydrochlorofluorocarbon
HF	hydrogen fluoride
HFC	hydrofluorocarbon
HI	hydrogen iodide
LC_{50}	lethal concentration, 50% of exposed population
LOAEL	lowest-observed-adverse-effect level
NFPA	National Fire Protection Association
NOAEL	no-observed-adverse-effect level
OSHA	U.S. Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic model
ppm	parts per million
SNAP	EPA Significant New Alternatives Policy
RBC	red blood cell
rT_3	reverse triiodothyronine
STEL	short-term exposure limit
T_3	triiodothyronine
T_4	thyroxine
TLV	Threshold Limit Value
TSH	thyroid-stimulating hormone
TWA	time-weighted average
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
WBC	white blood cell

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Iodotrifluoromethane: Toxicity Review

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Summary

Many halogenated hydrocarbons and other compounds are stratospheric ozone depleters, and the Montreal Protocol on Substances That Deplete the Ozone Layer proposed a ban on them in 1987. In response, the U.S. chemical industry ceased their production and has been phasing out their use ever since. Among the chemicals that were scheduled to be phased out were the chlorofluorobromines (halons). The U.S. military uses halons for fire suppression and extinguishment in electronic equipment, crew compartments in such combat vehicles as aircraft and armored vehicles, machinery spaces in military ships, and high-bay rooms in flight simulators. The U.S. Army is actively engaged in identifying effective, efficient, and safe substitutes for halons in those applications. Among the contenders as a replacement is iodotrifluoromethane (CF_3I).

CF_3I is an odorless, colorless gas with slight solubility in water. It was approved as a substitute for Halon 1301, a common fire extinguisher in total flooding systems under the U.S. Environmental Protection Agency (EPA) Significant New Alternatives Policy (SNAP), in 1997. However, EPA stipulated that any personnel that could possibly be in an area of exposure to CF_3I should be able to escape within 30 seconds (sec), that the employer ensure that no unprotected employees enter the area during CF_3I discharge and that the use of CF_3I be in accordance with the safety guidelines in the latest edition of the National Fire Protection Association (NFPA) standard. The *2001 Standard on Clean Agent Fire Extinguishing Systems* states that a human may be safely exposed to CF_3I at concentrations above the no-observed-adverse-effect level (NOAEL) of 0.2% (2,000 parts per million [ppm]) up to 0.3% (3,000 ppm) for as long as 5 minutes (min). Brief exposure at concentrations above 3,000 ppm is permissible in occupied and

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unoccupied spaces (where exposure might occur as a result of an accidental release), but the time for "safe" exposure decreases. NFPA used a NOAEL of 2,000 ppm and a lowest-observed-adverse-effect level (LOAEL) of 4,000 ppm derived from experiments in dogs for a pharmacokinetic model on which it based its determinations of the toxicity of CF_3I.

In May 1999, the U. S. Army Center for Health Promotion and Preventive Medicine at Aberdeen Proving Ground, Maryland, prepared a report that reviewed the toxicity of CF_3I, which it updated in 2002. Those reports did not accept the NFPA *2001 Standard* "safe" exposure limit of 2,000 ppm for CF_3I but instead indicated that any use at a design concentration greater than 2,000 ppm must conform to the EPA SNAP guidelines as published in 1995. The Office of the Surgeon General of the U.S. Army then requested that the National Research Council Committee on Toxicology (COT) independently review the Army's assessment and evaluate the scientific basis of its recommended exposure limit.

THE CHARGE TO THE SUBCOMMITTEE

In response to the Army's request, the National Research Council formed the Subcommittee on Iodotrifluoromethane under COT. Members were chosen for their expertise in toxicology, pharmacology, occupational health, chemistry, biostatistics, physiologically based pharmacokinetic modeling, and risk assessment. The subcommittee was asked to review the toxicologic, toxicokinetic, and related data on CF_3I and to evaluate the scientific basis of the Army's recommended exposure limit of 2,000 ppm in air. It was also asked to identify relevant database deficiencies and to make recommendations for future research need.

THE SUBCOMMITTEE'S APPROACH

To meet its charge, the subcommittee held two public sessions; reviewed materials submitted by the Army and others, including the Army's 1999 and 2002 toxicity review of CF_3I; and assessed current literature relevant to the toxicity of CF_3I, such as the NFPA *Standard 2001*. The subcommittee also conducted a literature search to identify any new materials published since the Army's 2002 report.

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THE SUBCOMMITTEE'S FINDINGS AND RECOMMENDATIONS

General Toxicity

The subcommittee found that the acute toxicity (continuous exposure for less than 24 hours [h]) of CF_3I is low; adverse effects are seen in rats at concentrations of 10.0% (100,000 ppm) or greater in inhalation studies. For subacute exposures (repeated exposures for less than 1 month), changes in some thyroid measures were seen in rats at 2.0% (20,000 ppm), hematologic effects and decreased body weights were seen at 4.0% (40,000 ppm) at 4 weeks. For subchronic exposures (repeat exposure for more than 1 month but less than 3 months), hematologic effects were seen at 2.0%, at 13 weeks.

On the basis of those results at high concentrations, the subcommittee found no need for further acute, subacute, or subchronic testing of CF_3I.

Genotoxicity

The subcommittee found that the conclusions reached by the Army on most of the genotoxicity data are scientifically appropriate. However, one reproductive study with a micronuclei-induction component had a weakness. Although it had negative results for micronuclei induction, the highest concentration (2.0% or 20,000 ppm) used in this negative study was below the lowest concentrations used in earlier micronuclei-induction studies (5.0% and 4.0% for mouse and rat, respectively), which had positive results. The ratio of polychromatic erythrocytes to normochromatic erythrocytes was the same in all concentration groups, including the control group; that suggests that the concentrations could have been higher. The subcommittee finds that the negative study should not be viewed as having as much weight as the other micronucleus studies. Five gene-mutation assays also had equivocal results: two were weakly positive for gene mutations, two strongly positive for gene mutations, and one negative for gene mutations and chromosomal aberrations.

Given the varied genotoxicity results, the subcommittee suggests that it would be prudent to verify the micronucleus results in a mouse or rat bone marrow chromosomal-aberration study that focuses on structural aberrations, as opposed to micronuclei induction. This recommendation

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is based on the positive results in two species (rat and mouse) in previous micronucleus assays and the potential for chronic exposure to CF_3I.

Carcinogenicity

No published studies on the carcinogenicity of CF_3I in animals were found by the Army in its toxicity review or by the subcommittee. However, studies suggest that CF_3I may be a mutagen, so it may also be a carcinogen.

On the basis of the positive genotoxicity findings, the subcommittee recommends that short-term testing for carcinogenicity be conducted. Studies of in vitro cellular transformation, as in the Syrian hamster embryo cell-culture assay, and transgenic animals should be considered. The subcommittee finds that if any of the recommended short-term carcinogenicity tests are positive, the Army must consider whether, given its proposed use and exposure scenarios, a 2-year, in vivo, inhalation bioassay for carcinogenicity should be conducted.

Reproductive Toxicity

The subcommittee and the Army found only one reproductive-toxicity study of CF_3I. It was negative for all reproductive indexes, and the subcommittee concurs with the Army's conclusion that CF_3I is not likely to have reproductive toxicity in the rat. However, in a subchronic inhalation study with rats via nose-only exposure, degeneration of the testes and a relative decrease in testicular weight were seen in the highest-exposure group. Review of the literature suggests that those effects may be due to heat stress associated with nose-only exposure. The subcommittee concluded that the effects seen in the subchronic study were most likely due to heat stress, not to CF_3I exposure.

In light of the negative findings in the reproductive-toxicity study, the subcommittee does not recommend further testing of CF_3I for reproductive or developmental effects.

Cardiac Sensitization

Primary among the toxic effects associated with halogenated hydrocarbons, such as CF_3I, is cardiac sensitization. Cardiac sensitization is

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typically manifest as an arrhythmia followed by ventricular fibrillation that may result in death. In the cardiac-sensitization protocol, dogs receive a dose of epinephrine, are exposed to the test chemical, and shortly thereafter receive a challenge dose of epinephrine while continuing to inhale the test chemical. Changes in a dog's electrocardiogram are taken as evidence of cardiac sensitization. Not all halocarbons induce cardiac sensitization; effects of those which do induce it depend on the blood concentrations of both epinephrine and halocarbon. That elevated endogenous concentrations of epinephrine, such as those achieved through exercise or by fright, can also result in fatal cardiac arrhythmia is of particular concern for human exposure. Halocarbon concentrations required to induce cardiac sensitization with endogenous epinephrine are 2-20 times higher than those required with exogenous epinephrine. Thus, the typical cardiac-sensitization protocol that uses exogenous epinephrine yields a conservative measure of toxicity. In addition, the subcommittee recognizes the lack of studies of cardiac response to CF_3I with endogenous epinephrine stimulation and suggests that such studies be conducted in the future. Although one study shows that dogs exposed to CF_3I at up to 2.5% with administration of exogenous epinephrine do not develop cardiac arrhythmias, additional studies of exposures to CF_3I with endogenous epinephrine may provide useful information.

Inhalation studies of CF_3I with exogenous epinephrine indicated that cardiac sensitization occurred in dogs at 0.4% (4,000 ppm)—the LOAEL, or greater; the NOAEL was 0.2% (2,000 ppm). The subcommittee concluded that the dog cardiac-sensitization studies that used exogenous epinephrine are appropriate for estimating the NOAEL in humans without any additional uncertainty factors to account for dog-to-human extrapolation or for endogenous epinephrine in humans, because of the high exogenous concentrations of epinephrine used in the studies. *The subcommittee suggests, however, that further research could be conducted to investigate the mechanisms of induction of cardiac arrhythmia in dogs.* Critical to the determination of the LOAEL for halocarbons is a measure of the blood concentration of the compound. Blood concentrations of halocarbons typically reach a steady state after about 5 min of exposure and do not increase substantially with longer exposures. The subcommittee concluded that cardiac sensitization is correlated with the peak blood concentration of the halocarbon before an epinephrine challenge. Prolonged exposure to an airborne concentration of halocarbon that does not achieve this peak blood concentration does not appear to increase the risk of cardiac sensitization.

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Physiologically Based Pharmacokinetic Modeling

Physiologically based pharmacokinetic (PBPK) models can provide an estimate of the internal concentration of a chemical at a target tissue, such as blood, on the basis of exposure concentrations. For cardiac-sensitizing agents, such as some halocarbons, the model must account for short exposure periods—0-5 min—with airborne concentrations at the NOAEL or LOAEL.

The subcommittee finds that the use of a validated, EPA-approved PBPK model is a reasonable scientifically based approach to determine safe egress times for exposure to CF_3I. The PBPK model depends on the determination of the critical blood concentration that would result in a cardiac event in epinephrine-challenged dogs, typically resulting from exposure to the LOAEL. Use of arterial CF_3I concentrations measured in dogs in the absence of exogenous or elevated endogenous epinephrine is a reasonable approach to estimate the critical arterial blood concentration. The NOAEL and LOAEL for CF_3I as determined with the dog cardiac-sensitization model are 0.2% and 0.4%, respectively. According to the PBPK model, people could be safely exposed to 0.4% for about 51 sec before the critical CF_3I blood concentration for cardiac sensitization is achieved. Furthermore, people could be exposed to concentrations as high as 0.3% 5 min or more without achieving the critical blood concentration. The Army's decision to use an exposure limit of 0.2% (2,000 ppm) in normally unoccupied areas is a conservative policy decision to protect military personnel from health effects of CF_3I exposure in undefined Army applications.

Human-Exposure Scenarios

The two Army toxicity reviews provide few specific exposure data on CF_3I. Two studies were performed: one to assess exposures that might result from the use of CF_3I in hand-held fire extinguishers, and one to assess exposures resulting from the intentional release of CF_3I from Air Force F-15 aircraft engine nacelles which encase the engine compressor, combustor, and turbine. There is also some anecdotal information on the inhalation of CF_3I by two salesmen.

Of primary concern to the subcommittee is the decomposition of CF_3I to highly toxic substances, such as hydrogen fluoride, hydrogen iodide, and carbonyl fluoride. *The subcommittee recommends that the Army collect and evaluate information on types of exposure (such as acute, chronic, and*

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intermittent) and exposure concentrations to CF_3I and its decomposition products in Army uses and that such information be considered in its assessment of the adverse health effects of CF_3I.

CF_3I has been approved for use in unoccupied spaces by Germany and Australia. No exposure or toxicity data were found on such use. *Because the proposed military applications of CF_3I might result in high concentrations in the event of an accidental discharge, particularly when used in Air Force F-15 aircraft, the subcommittee recommends that personnel who might be potentially exposed be trained in standard operating procedures and the use of appropriate personal protective equipment. The subcommittee concurs with NFPA that uses of CF_3I that may involve acute exposures should be restricted to normally unoccupied areas.* The Army is encouraged to monitor international exposure and toxicity data on CF_3I as they become available.

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1

Introduction

Several halocarbons—chlorofluorocarbons (CFCs), halons (chlorofluorobromines), carbon tetrachloride, and methyl chloroform—have been found to deplete the stratospheric ozone layer and thus to allow greater than normal amounts of harmful ultraviolet radiation to reach the earth. Such an increase in ultraviolet radiation could have devastating health consequences. The U.S. Environmental Protection Agency (EPA) estimated that by 2075 there could be over 150 million new cases of skin cancer in the United States alone that could be attributed to increased ultraviolet radiation (52 Fed. Reg. 47492 [1987]). In addition, an increase in ultraviolet radiation can increase the incidence of eye cataracts and cause a general weakening of the immune system. Concerns about ozone-depleting substances led to the adoption of the Montreal Protocol on Substances That Deplete the Ozone Layer,[1] and this internationally accepted agreement (signed by the United States on September 16, 1987) has led to bans on the production and use of halons and CFCs.

The U.S. Army has used Halon 1301 as a fire extinguishant in a number of rotary-aircraft engines (for example, Apache, Kiowa, Comanche, Chinook, Black Hawk, and Cobra) and in ground-vehicle engines and personnel compartments (including armored personnel carriers, interim armored vehicles, Crusader, medium tactical vehicles, Abrams, and Bradley) (Vitali 2003). Halon 1301 is a colorless, odorless, inert gas that is low in toxicity, and it has been particularly effective in protecting

[1]Information on the Montreal Protocol may be found at http://www.unep.org/ozone/pdfs/Montreal- Protocol2000.pdf.

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essential electronic equipment, crew compartments in combat vehicles, machinery spaces in military ships, and high bay rooms for flight simulators (Wickham 2002). The Army has begun a search to identify Halon 1301 replacements, such as hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs). In 1994, the United States under the Clean Air Act (CAA) banned the production and import of ozone-depleting substances, including halons (Halon 1211, 1301, and 2402). Those halons are being replaced with HFCs, HCFCs, and other chemicals. Before the use of these halon replacements by the Army, they must be reviewed to ascertain their ozone-depleting potential, as well as their efficacy, toxicity, flammability, and exposure potential. Iodotrifluoromethane (trifluoroiodomethane, trifluoromethyl iodide, trifluoroiodide, FIC-1311, CF_3I; Chemical Abstract, Service number 2314-97-8) is one of several candidate compounds under consideration by the Army (and others) as a replacement for Halon 1301.

CFCs and halon substitutes have been the subjects of scientific inquiry and scrutiny by numerous organizations, such as EPA, the National Fire Protection Association (NFPA), and the U.S. Occupational Safety and Health Administration (OSHA). EPA, under Section 612 of the CAA, is required to "evaluate substitutes for ozone-depleting substances in an effort to reduce risk to human health and the environment." The EPA Significant New Alternatives Policy (SNAP) was established to conduct the evaluations of these substitutes and to generate a list of acceptable substitutes for major industrial use sectors. The SNAP-use sectors include refrigeration and air conditioning; foam blowing; solvent cleaning; fire suppression and explosion protection; sterilants; aerosols; adhesives, coatings, and inks; and tobacco-fluffing agents. EPA defines "substitute" as "any chemical, product substitute, or alternative manufacturing process, existing or new, intended for use as a replacement for a Class I or Class II substance."[2]

In 1995, EPA published a final rule under the SNAP program to accept CF_3I as a substitute for Halon 1301 in "normally unoccupied areas only" (60 Fed. Reg. 31092 [1995]). The rule stated that any employee who could possibly be in the area must be able to escape within 30 seconds (sec),

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[2]Class I substances include CFCs, halons, carbon tetrachloride, methyl chloroform, methyl bromide, and hydrobromofluorocarbon. Class II (hydrochlorofluorocarbon) substances are those with any substitute that the EPA administrator determines may present adverse effects to human health or the environment where the administrator has identified an alternative that (1) reduces the overall risk to human health and the environment, and (2) is currently or potentially available (40 Code of Federal Regulations 82.172).

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and the employer must ensure that no unprotected employees enter the area during agent discharge. In 1997, EPA published a final rule accepting CF_3I as a substitute for another halocarbon, Halon 1211, used for fire suppression in nonresidential applications only (61 Fed. Reg. 25585 [1997]). EPA prohibits consumer residential applications of CF_3I. The SNAP program now recommends that use of CF_3I be in accordance with the safety guidelines in the latest edition of the NFPA *2001 Standard on Clean Agent Fire Extinguishing Systems* (67 Fed. Reg. 4185 [2002]).

The *2001 Standard* (NFPA 2000) is a guidance document that contains minimal requirements for total-flooding clean fire-extinguishing systems. It states that a human may be exposed to concentrations of CF_3I above the no-observed-adverse-effect level (NOAEL) of 2,000 parts per million (ppm) up to 3,000 ppm for as long as 5 minutes (min). At concentrations above 3,000 ppm, exposure to the chemical is permissible in both occupied and unoccupied spaces, but the time of "safe" exposure decreases. In determining the time for human exposure to various chemicals, NFPA has required that an agent "must first have been evaluated in a manner equivalent to the process used by the U.S. Environmental Protection Agency's SNAP Program" (NFPA 2000). NFPA evaluated data derived from EPA-approved and peer-reviewed physiologically based pharmacokinetic (PBPK) models. In the case of CF_3I, EPA and NFPA based their reviews on a NOAEL of 2,000 ppm and a lowest-observed-adverse-effect level (LOAEL) of 4,000 ppm in dogs.

OSHA has also set general guidelines for the use of halocarbon substitutes. These state that "where egress from a normally occupied area takes longer than 30 seconds but less than one minute, the employer shall not use the agent in a concentration greater than its cardiotoxic LOAEL" (29 CFR 1910 Subpart L).

The Army does not have a stated policy regarding ozone-depleting substances. Army Regulation 40-5: Preventive Medicine (1990) addresses the health and safety issues related to the use of the substances. The U.S. Army Center for Health Promotion and Preventive Medicine at Aberdeen Proving Ground, Maryland, reviewed the toxicity of CF_3I, in May 1999 (McCain and Macko 1999) and updated the review in 2002 (Chaney 2002) and proposed an exposure limit of 2,000 ppm for CF_3I.

THE SUBCOMMITTEE'S CHARGE

The Office of the Surgeon General of the U.S. Army requested that the National Research Council Committee on Toxicology (COT) form a sub-

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committee to review the toxicologic, toxicokinetic, and related data on CF_3I and to evaluate the scientific basis of the Army's proposed CF_3I exposure limit of 2,000 ppm. At the Army's request, the Research Council convened the Subcommittee on Iodotrifluoromethane under COT. Members of the subcommittee were selected for their expertise in toxicology, pharmacology, occupational health, chemistry, biostatistics, PBPK modeling, and risk assessment. In addition to evaluating the Army's toxicity review, the subcommittee was asked to identify relevant database deficiencies and to make recommendations for future research.

ORGANIZATION OF REPORT

The body of this report is organized in five chapters. Chapter 2 presents an overview of the physical and chemical properties and efficacy section of the Army's toxicity review of CF_3I. Chapter 3 comments on the health-effects data on acute, subacute, subchronic, reproductive and developmental toxicity, carcinogenicity, and genotoxicity of CF_3I. Chapter 4 reviews available data on cardiac sensitization. Chapter 5 presents an overview of the use of a PBPK model in understanding the modes of action of CF_3I. Finally, Chapter 6 critiques the available human exposure information, including those in the Army's toxicity review.

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2

Physical and Chemical Properties And Efficacy

PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of iodotrifluoromethane (CF_3I) are presented in the Army's updated toxicity review (Chaney 2002). The table of physical properties of CF_3I from that report is included here (Table 2-1); the entire update is included as Appendix B. The review briefly discusses the degradation of CF_3I in air and during a fire and states that no attempt was made by the Army to determine the toxicity of any CF_3I degradation products.

The update's presentation of the physical and chemical properties of CF_3I is well written and concise. However, the subcommittee found three points that merit some clarification:

- The update states on page 6, lines 9-10, in the section "Regulatory Information" that "cardiac sensitization has been demonstrated at relatively low concentrations. . . ." The Army should specify that the statement refers to dogs.
- On the same page, the Army should also indicate quantitatively what is meant by "relatively low concentrations."
- The Army should have added vapor density to the list of physical and chemical properties as halocarbons are usually much heavier than air and can accumulate in "dead spaces" such as tanks. This information has been added to Table 2-1.

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TABLE 2-1 Physical Properties of CF_3I

Physical or Chemical Property	Value or Description
Chemical Abstracts Service no. (CAS)	2314-97-8
European Chemical no. (EC)	219-014-5
Molecular weight	195.91
Physical state at 20°C	Gas
Melting point	-110°C (-166°F)
Boiling point at 1 atm	-22.5°C (-8.5°F)
Liquid density at -32.5°C	2.36 g/mL
Liquid density at 25°C	g/mL
Odor threshold	Odorless
Solubility in water	Slight
Vapor pressure at 25°C	78.4 psia
Pressure-temperature curve	log psia = 5.7411-1146.82/T/K
Critical pressure	586 psia (estimated)
Critical temperature	122°C (estimated)
Critical volume	225 cm^3/mole (estimated)
Heat of formation	-141 kcal/mole
Heat of vaporization	5.26 kcal/mole
Electron affinity	150 ± 20 kJ/mole
Refractive index (liquid) at -42°C	1.379
Dipole moment	1.68 debye
Vapor heat capacity	16.9 cal/mole-K
C-I bond disassociation energy	54 kcal/mole
Vapor density (air = 1)	6.9[a]

[a]Data from PTCL 2003.
Abbreviations: g/mL, gram per milliliter; cm^3/mol, cubic meter per mole; kcal/mole, kilocalorie per mole; kJ/mole, kilojoule per mole; cal/mole-K, calorie per mole - Kelvin; psia, pounds per square inch absolute.
Source: Adapted from Moore et al. 1994 (see Appendix B).

EFFICACY

The "Efficacy" section of the update indicates that the minimal design concentration—that is, the minimal amount of a chemical required to extinguish an *n*-heptane fire—of CF_3I, 3.2 vol%, is slightly lower than that

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of Halon 1301, 3.3 vol%. One point in the efficacy section (see Appendix B) should be clarified: The phrase "will be slightly lower" does not have biologic meaning. The term "slightly" should be quantified and the actual amounts given.

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3

Health Effects: Toxicity Studies

The Army's toxicity review of iodotrifluoromethane (CF_3I) (McCain and Macko 1999) and its update (Chaney 2002) covered health-effects data on the acute, subacute, subchronic,[1] reproductive and developmental toxicity, and on genotoxicity and carcinogenicity. In this chapter, the subcommittee reviews the toxicity data on CF_3I and indicates whether it agrees with the Army's identification of relevant studies and its interpretation of the data. Chapter 4 deals with the cardiac-sensitization potential of CF_3I, and Chapter 5, with the Army's consideration of a physiologically based pharmacokinetic model to determine concentration and effects.

ANIMAL STUDIES

Acute Exposure

In an acute inhalation study, groups of 30 young adult male Fischer 344 rats were given a single 4-h nose-only exposure to CF_3I at 0.0%, 0.5%, or 1.0% (0, 5,000, or 10,000 ppm). Ten rats in each exposure group were sacrificed immediately after exposure and on days 3 and 14 after exposure (Kinkead et al. 1994; Dodd et al. 1997). No deaths or clinical signs of toxicity were observed immediately after exposure or during the 3- or 14-

[1]As used by the subcommittee, acute means continuous exposure for up to 24 h, subacute means repeated exposures for at least 1 month; and subchronic means repeated exposures for at least 1 month but no longer than 3 months. In the evaluation of the toxicity of CF_3I, rats are the preferred animal model for acute, subacute, and subchronic tests (Dodd et al. 2000).

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day observation period, and there were no biologically significant effects on body weight. Although there were some statistically significant variations in hematologic and clinical-chemistry measures examined, including thyroxine (T_4) and T_4-binding globulin, all were within historical and biologic limits and were considered unrelated to treatment.

Groups of five male and five female Sprague-Dawley rats were given a single whole-body inhalation exposure to CF_3I at 0.0%, 10.0%, 12.8%, 20.0%, or 32.0% (0, 100,000, 128,000, 200,000, or 320,000 ppm) for up to 4 h (Ledbetter 1994). All rats exposed to 32.0% test material died within 20 min of the start of exposure. However, hydrogen fluoride at 7 ppm had contaminated the test gas, and that necessitated the installation of a potassium hydroxide scrubber for the later 20.0% exposure. All male and female rats exposed to 20.0% CF_3I died within 20 min of the start of exposure. A new sample of test material was used for the 10.0% and 12.8% exposures. Within 30 min of the start of exposure, all male and female rats exposed to 10.0% CF_3I became unconscious or semiconscious, and they had limb twitching for the remainder of exposure. After cessation of exposure, the rats awakened after about 3 min. Male and female rats exposed to 12.8% CF_3I appeared to enter a deep sleep and remained there until the end of exposure. All male and female rats exposed to 10.0% or 12.8% CF_3I survived the 2-wk observation period, and no other clinical signs of toxicity were noted. At necropsy, the rats exposed to 32.0% test material had dark red and puffy lungs that were consistent with hydrogen fluoride exposure. Rats exposed at 20.0% had puffy lungs that were much less red than the 32.0% animals. The lungs of two male rats exposed to 12.8% CF_3I had slight redness or red foci, but no other treatment-related effects were noted in the remaining rats. Given the animal responses seen at 12.8%, the responses seen at 20.0% and 32.0% may have been indicative of CF_3I toxicity with little contribution from HF.

Ledbetter (1994) also conducted a nose-only 15-min exposure to 24.2% or 28.8% CF_3I with groups of five male and five female Sprague-Dawley rats. All the female rats and two male rats died during exposure to 28.8% CF_3I; no female rats and one male rat died during exposure to 24.2% CF_3I. All surviving rats were shaky when removed from the exposure chamber, but they recovered within minutes. On the basis of the results, the authors calculated a 15-min CF_3I LC_{50} (the concentration of a substance that is estimated to be lethal to 50% of the test animals) of 27.4%. Typically, three concentrations are used for the determination of LC_{50}. However, the authors reasoned, and the subcommittee concurs, that the steepness of the LC_{50} curve between the two exposure concentrations made it unnecessary

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to sacrifice additional test animals for the small amount of information that would be gained.

The acute exposure studies discussed by the Army in its review of the toxicity of CF_3I and discussed above are summarized by the subcommittee in Table 3-1. The subcommittee finds that the Army's interpretation of the acute toxicity studies of CF_3I was appropriate, and no further acute toxicity testing is recommended.

The Army's review of CF_3I also considered overall toxicity. Ledbetter (1994) reported that for acute exposures in rats, the 15-min LC_{50} was 27.4% (274,000 ppm). That is about 100 times higher than the exposure that causes cardiac arrhythmias in dogs (see Chapter 4). Therefore, the subcommittee finds that noncardiac acute-toxicity end points would not pose a problem at projected exposures of 0.2% for up to 5 min and 0.4% for less than 1 min.

Subacute and Subchronic Exposure

In a 2-wk range-finding study, groups of five male Fischer 344 rats were exposed to 0.0%, 3.0%, 6.0%, or 12.0% CF_3I nose-only for 2 h/day, 5 days/wk (see Table 3-2) (Dodd et al. 1997; Kinkead et al. 1995). Rats in the 6.0% and 12.0% exposure groups were lethargic after treatment, but, none died during the study. The body weight of male rats exposed to 12.0%

TABLE 3-1 Summary of Acute Rat Inhalation Exposure Studies

Animal	CF_3I Exposure	Results	Reference
30 male Fischer 344 rats	Single 4-h, nose only; 0.0%, 0.5%, or 1.0%	No deaths during the 3- or 14-day observation period; slight decreases in thyroxine and thyroxine-binding globulin	Kinkead et al. 1994; Dodd et al. 1997
5 male and 5 female Sprague-Dawley rats	Single 4-h, whole body, 0.0%, 10.0%, 12.0%, or 20.0%	at 20.0%, death; at 10.0% and 12.0%, narcosis, no deaths	Ledbetter 1994
5 male and 5 female Sprague-Dawley rats	15-min, nose only; 24.2%or 28.8%	$LC_{50,}$ 27.4%	Ledbetter 1994

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TABLE 3-2 Summary of Subacute and Subchronic Rat Inhalation Exposure Studies

Animal	CF_3I Exposure	Results	Reference
5 male Fischer 344 rats	2-wk, 5-day/wk, 2-h/day, nose only; 0.0%, 3.0%, 6.0% or 12.0%	No deaths; at 6.0% and 12.0%, WBC count decreased 20%	Kinkead et al. 1995; Dodd et al. 1997
15 male and 15 female Fischer 344 rats	13-wk, 5-day/wk, 2-h/day, whole body; 0.0%, 2.0%, 4.0%, or 8.0%	8 deaths, not attributed to treatment; at 4.0% or 8.0%, dose-related increase found for micronucleated RBCs in male and female rats at 4 wk, T_3 decreased up to 50% in male and female rats at 4 or 13 wk; at 8.0%, rhinitis in male and female rats at 4 wk but not at 13 wk; 8.0%, necrosis of nasal turbinates in male rats (56%) and female rats (40%); 8.0%, mild increase in thyroid follicular colloid in male and female rats at 13 wk	Dodd et al. 1997

CF_3I was statistically decreased on study days 7 and 14, and the body weight of male rats exposed to 6.0%, on study day 14. In addition, the white-blood-cell (WBC) count of rats in the 6.0% and 12.0% exposure groups was decreased by about 20%, whereas the serum thyroglobulin and reverse triiodothyronine (rT_3) levels were statistically increased but still within acceptable biologic limits. No treatment-related effects were found on histologic examination of the thyroid or parathyroid glands.

Dodd et al. (1997) exposed groups of 15 male and 15 female Fischer 344 rats to 0.0%, 2.0%, 4.0%, or 8.0% CF_3I for 2 h/day, 5 days/wk for up to 13 wk (see Table 3-2). Five male and five female rats in each group were sacrificed after 30 days of treatment, and the remainder after 13 wk of exposure. Six male rats in the 2.0% group died after the ninth exposure, and one died following the 13th exposure. One male rat in the 8.0% exposure group died after the 10th exposure. All deaths were attributed to the animal-restraint system, not to treatment. During exposure, all rats in the 8.0% group were highly active, the 4.0% group was moderately active, and the 2.0% group was slightly active compared with the control rats. The body weights of male and female rats in the 8.0% group decreased slightly during the first 3 wk of treatment and did not return to their initial weight

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until after day 28 of the study. Body weights of rats in the 4.0% exposure group were also statistically ($p < 0.01$) decreased relative to controls from study day 14 to the end. No significant treatment-related effects were found on the body weight of male and female rats exposed to 2.0% CF_3I.

After 4 wk of exposure, the mean hemoglobin, red-blood-cell (RBC) count, and lymphocyte percentage were statistically ($p < 0.01$) decreased by 6-23% in male rats exposed to 8.0% CF_3I. By 13 wk of treatment, those measures returned to normal (Dodd et al. 1997). A dose-related increase in micronucleated RBCs was found in male and female rats exposed to 4.0% or 8.0% CF_3I for 4 wk, and in male and female rats exposed to CF_3I at higher than 2.0% for 13 wk. In addition, the ratio of polychromatic to normochromatic RBCs was decreased in a dose-related manner in male and female rats exposed to 4.0% or 8.0% CF_3I for 4 or 13 wk.

No biologically significant treatment-related effects were found in clinical-chemistry measures investigated (Dodd et al. 1997). However, the triiodothyronine (T_3) of male and female rats exposed to 8.0% CF_3I was decreased by up to 50% after 4 or 13 wk of treatment, and dose-related biologically significant decreases in T_3 were found in male and female rats exposed to 2.0% or 4.0%. With the decrease in T_3 in those groups, thyroid-stimulating hormone (TSH) was increased by up to a factor of 2 in a dose-related manner in male and female rats exposed for 4 or 13 wk to 2.0%, 4.0%, or 8.0% CF_3I. In addition, rT_3 was increased in a dose-related manner after 4 or 13 wk of exposure in all CF_3I groups, although no biologically significant effects in T_4 were found.

On necropsy, a mild increase in thyroid follicular colloid was found in all CF_3I groups, although no biologically significant effects were found in the absolute or relative organ weights after 4 or 13 wk of treatment. Treatment-related microscopic effects, such as rhinitis, were found after 4 wk of treatment in male and female rats exposed to CF_3I at greater than 4.0% but not after 13 wk of exposure.

The subcommittee finds that all subacute and subchronic studies summarized in Table 3-2 and reviewed in the Army's 2002 update appear to be appropriate, and no further testing is recommended.

Genotoxicity

The Army's 1999 review of the toxicity of CF_3I evaluated several genotoxicity studies (McCain and Macko 1999). The *Salmonella typhimurium* histidine reversion (Ames) assay was conducted with CF_3I at 1,060, 2,775, 10,586, 23,230, and 85,908 ppm (0.11%, 0.28%, 1.1%, 2.3%, and

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8.6%) (Mitchell 1995a). For the mouse lymphoma forward-mutation assay with L5178-Y cells, five concentrations of CF_3I, from 8.0% to 51.0%, were tested (Mitchell 1995c) with and without metabolic activation with S-9. In the in vivo mouse bone-marrow RBC micronucleus test, mice were exposed to CF_3I at 2.5%, 5.0%, or 7.5% (Mitchell 1995b).

The Army concluded that two of the five strains of *Salmonella* (TA 1537 and TA 98) tested with and without S-9 metabolic activation were weakly positive for inducing frame-shift and base-pair mutations, two (TA 1535 and TA 100) were strongly positive, and in the micronucleus test the two highest concentrations were positive for structural chromosomal aberrations in both sexes. The mouse lymphoma assay was negative for gene mutations. All in vitro studies were conducted in exposure chambers in which the agent was in direct contact with the media of the cells, so solubility in all likelihood was not an issue. CF_3I was also positive in both sexes in a micronucleus study conducted in male and female Fischer 344 rats after 4 or 13 wk of exposure via inhalation (nose only) to 2.0%, 4.0%, or 8.0% CF_3I vapor for 2 h/day, 5 days/wk. The two highest concentrations were positive at the end of 4 wk, and all concentrations were positive after 13 wk of exposure (Kinkead et al. 1996; Dodd et al. 1997).

In the Army's 2002 update (Chaney 2002), the only new genotoxicity study reviewed was that of Dodd et al. (1998, 1999). It was a micronucleus study conducted as a component of a reproductive investigation in male and female Sprague-Dawley rats. Animals were exposed in whole-body inhalation chambers to 0.2%, 0.7%, and 2.0% CF_3I for 7 or 12 wk. Dodd et al. and the Army concluded that CF_3I did not induce an increase in the number of micronuclei in rats of either sex. Table 3-3 summarizes the available genotoxicity data on CF_3I.

The conclusions reached by the Army regarding most of the genotoxicity data seem appropriate. However, the subcommittee finds that the Dodd et al. study (1998, 1999) cited in the 2002 update with regard to the micronucleus test, although negative, has a weakness. Specifically, the doses used in the study were below those used in earlier studies; for example, the highest dose used by Dodd et al. was 2.0%. The highest doses used in the two previous studies, in which positive results were found, were 7.5% and 8.0% in the mouse and rat, respectively. It is also notable that in the Dodd et al. study the ratio of polychromatic to normochromatic RBCs was the same in all groups, including controls. That indicates that the dose used by Dodd et al. could have been higher. The subcommittee finds that the Dodd et al. study should not be viewed as having equal weight with the other micronucleus studies.

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TABLE 3-3 Summary of Genotoxicity Studies

Organism	End Point	Dose, %	Results	Reference
Salmonella typhimurium TA-1537 with/ without activation	Gene mutations	0.11, 0.28, 1.1, 2.3, 8.6	Weakly positive	Mitchell 1995a
Salmonella typhimurium TA-98 with/without activation	Gene mutations	0.11, 0.28, 1.1, 2.3, 8.6	Weakly positive	Mitchell 1995a
Salmonella typhimurium TA-1535 with/ without activation	Gene mutations	0.11, 0.28, 1.1, 2.3, 8.6	Strongly positive	Mitchell 1995a
Salmonella typhimurium TA-100 with/ without activation	Gene mutations	0.11, 0.28, 1.1, 2.3, 8.6	Strongly positive	Mitchell 1995a
Mouse lymphoma L5178-Y	Gene mutations and chromosomal aberrations	8.0, 17.7, 30.6, 42.6, 45.4, 49.7, 51.8	Negative	Mitchell 1995c
Mouse (male and female)	Micronuclei	2.5, 5.0, 7.4	Positive in male and female	Mitchell 1995b
Fischer 344 rat (male and female)	Micronuclei	2.0, 4.0, 8.0	Positive in male and female	Kinkead et al. 1996
Sprague-Dawley rat (male and female)	Micronuclei	0.2, 0.7, 2.0	Negative in male and female	Dodd et al. 1998, 1999

The differences in the data on the micronucleus tests, although possibly explained by dose, are of concern and cannot be dismissed. The micronucleus test detects chromosomal aberrations. The mouse lymphoma assay can detect both gene and chromosomal aberrations, but this study was negative for CF_3I. Given the varied genotoxicity results, the subcommittee suggests that it would be prudent to verify the micronucleus results in a mouse or rat bone marrow chromosomal-aberration study. We offer this

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recommendation because positive results have been found in two species in previous micronucleus assays, and there is a potential for chronic but intermittent exposure to CF_3I. Chronic exposure to a mutagen or clastogen may facilitate carcinogenesis. The bone marrow chromosomal-aberration study would focus on structural aberrations as opposed to micronuclei. If such a study demonstrates positive results, it would be appropriate to conclude that CF_3I is a clastogen.

Carcinogenicity

No published studies of the carcinogenicity of CF_3I in animals were found by the Army for its toxicity reviews or by the subcommittee. In its 2002 update review of CF_3I, the Army cited a study by Koski et al. (1997) that used free-radical modeling as a predictor of carcinogenicity; CF_3I was determined to be a potent toxicant and an expected carcinogen. The information from the Ames assays and the micronucleus tests suggests that CF_3I is a potential mutagen and clastogen in humans. The subcommittee's concern with respect to mutagenicity is that chemicals that exhibit such activity may be determined to be carcinogenic. Therefore, the subcommittee recommends short-term testing for carcinogenicity. Studies of in vitro cellular transformation, such as the Syrian hamster embryo cell culture (LeBoeuf et al. 1999), and possibly transgenic-animal studies in one or more of three models—P53+/- hemizygous knockout mouse (Pritchard et al. 2003), Tg.AC (Pritchard et al. 2003), or rasH2 (Pritchard et al. 2003)—should be considered. The subcommittee finds that if any of the recommended short-term carcinogenicity tests are positive, the Army must consider whether, given its proposed use and exposure scenarios, a 2-year, in vivo, inhalation bioassay for carcinogenicity should be conducted.

Reproductive and Developmental Toxicity

Only one reproductive study was identified by the subcommittee in its review of the available literature. This study was reviewed by the Army in its 1999 and 2002 reports. The study, "Reproductive Toxicity Screen of Trifluoroiodomethane in Sprague-Dawley Rats," was conducted by Dodd et al. (1998). Male and female rats were exposed in whole-body inhalation chamber to CF_3I at 0.2%, 0.7%, or 2.0%. Index of effects on fertility, pregnancy, lactation, and pup development were evaluated, and there were no indications of adverse effects for any of the reproductive or developmen-

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tal indices. The Army's conclusion that CF_3I is not a reproductive toxicant in Sprague-Dawley rats seems appropriate.

There is evidence from another study that CF_3I may adversely affect the testes. In a subchronic (13-wk) inhalation study, Fischer 344 rats were exposed nose-only to 0.0%, 2.0%, 4.0%, or 8.0% CF_3I (Dodd et al. 1997). The authors noted mild atrophy and degeneration of the testes and a relative decrease in testicular weight at 8.0% in male rats at 13-wk. The study used higher doses than, and a different rat strain from, the reproductive-toxicity study. The animals were not mated in the former study (Dodd et al. 1997), so there was no opportunity to determine the possible influence of the testicular effects on reproduction. The authors stated that CF_3I appeared to produce an indirect effect on the testes, although they did not suggest a mechanism by which they thought the alterations occurred. They did note that they believed the exposure design was partly responsible—that is, heat stress associated with nose only exposure in the treated animals. In the Dodd et al. (1998) reproductive study, no macro or micro adverse testicular effects were reported in the 16 male rats.

Support for heat stress as the basis for atrophy and degeneration of the testes is provided by two 28-day subacute studies of HFC-143a (Malley 1993), in which animals were exposed nose only at 2,000, 10,000, or 39,000 ppm or whole body at concentrations of 2,000, 10,000, or 40,000 ppm. Those exposed nose only had morphologic changes in the testes and decreased body weight. Elevated temperatures occurred during the exposure period. In the animals exposed whole body, there were no significant differences in body weight, testicular weight, or evidence of testicular changes. In another study (Malley 1993), rats were exposed whole body to 2,000, 10,000, or 40,000 ppm of HCF-143a five times per week for 90 days. No evidence of testicular atrophy or degeneration was found under these conditions. Because there is evidence that testicular changes can be associated with heat stress from nose-only inhalation exposure (Lee et al. 1993; Malley 1993; Rothenberg et al. 2000), the subcommittee concludes that the effects seen in the study by Dodd et al. (1997) were most likely due to heat stress and not CF_3I exposure.

A search of the published literature by the subcommittee failed to identify any other reproductive or developmental toxicity studies for CF_3I. Therefore, given the lack of reproductive or development toxicity from exposure to CF_3I and the availability of developmental toxicity studies conducted for several other halocarbons that failed to demonstrate any adverse effects, no additional testing of CF_3I for reproductive or developmental effects is recommended by the subcommittee.

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HUMAN STUDIES

No published human studies of the toxicity of CF_3I were found by the Army or by the subcommittee. There is minimal human experience with CF_3I (see Chapters 4 and 6), but no human health studies were identified.

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4

Cardiac Sensitization

In this chapter, the subcommittee presents background information on the development of cardiac sensitization as a toxic end point, the various cardiac-sensitization methods that may be used for determining the toxicity of halocarbons, and the pharmacokinetics of cardiac sensitization.

DEVELOPMENT OF CARDIAC-SENSITIZATION STUDIES

The identification of cardiac sensitization as a potential adverse reaction to an airborne chemical goes back almost 100 years. Cats lightly anesthetized with chloroform were unexpectedly sensitive to injected epinephrine (Levy and Lewis 1911). When the animals inhaled chloroform at 0.5% or 2.0% in air and then received a bolus intravenous injection of epinephrine (total dose, up to 65 micrograms [μg]), they had a "heterogenetic" electrocardiograph (ECG) pattern, that is, short pauses in heartbeat followed by tachycardia. Continued administration of chloroform ultimately resulted in ventricular fibrillation. Later studies showed that the variations in cardiac sensitivity depended on the duration and degree of anesthesia (Levy 1913). Light anesthesia with chloroform produced more cardiotoxic effects than deeper surgical anesthesia, possibly because of a decrease in central nervous system impulses to the heart. Levy found a number of published cases in which humans had been overcome by chloroform and medical treatment had consisted of injecting epinephrine (to stimulate the cardiovascular system). In many cases, the patients died after exhibiting tachycardia followed by ventricular fibrillation. The increased sensitivity of the heart to epinephrine brought about by exposure to a specific organic chemical was referred to as cardiac sensitization.

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In 1937, Meek et al. (1937) refined the experimental protocol of Levy and used dogs as the experimental animal. They also demonstrated an increased sensitivity of the heart to hydrocarbons (cyclopropane) when inhalation was accompanied by intravenous injections of epinephrine. On the basis of those studies, the potential hazard associated with administering hydrocarbon anesthetic agents followed by epinephrine became clearly recognized.

As a result of those and later studies on the ability of anesthetic agents to produce cardiac arrhythmia in the presence of exogenous epinephrine, it became evident that hydrocarbons, both halogenated and nonhalogenated, alone or in combination with injected epinephrine could sensitize the myocardium to produce cardiac arrhythmia. The hydrocarbon concentrations required to produce such sensitization ranged from 0.5% to 90% in air.

Although cardiac arrhythmia presents a risk to anesthetized patients, it was not until the 1960s, when chlorofluorocarbons (CFCs) began to be used as aerosol propellants in consumer products, that cardiac sensitization received more toxicologic consideration. CFC propellants were sniffed to reach light anesthesia, that is, to get "high"; and there were 65 reported deaths from such abuse (Bass 1970; Reinhardt et al. 1971). Such deaths occurred during or shortly after inhalation of high concentrations of the aerosols and were generally accompanied by physical or other stress. The deaths were thought to be due to ventricular fibrillation resulting from cardiac sensitization caused by the combination of inhalation of high concentrations of aerosol propellants and high blood concentrations of endogenous epinephrine produced by excitement. At autopsy, there were no unusual pathologic findings, and no anatomic changes were seen in the heart, brain, or other organs. Cardiac sensitization as the cause of death was typically based on circumstantial evidence at the scene—the position of the body and empty aerosol cans and a lack of autopsy findings that might otherwise be responsible for the death.

Such abuse was of concern to the CFC manufacturers, who began to develop a toxicologic method that could determine the cardiac-sensitization potential of the chemicals. Reinhardt et al. (1971) and Clark and Tinston (1973) worked on identifying an appropriate animal model and determining appropriate doses of exogenous epinephrine to simulate circulating blood epinephrine.

As CFCs have been phased out over the last 2 decades in compliance with the Montreal Protocol, the search for effective alternatives has focused on using cardiac sensitization as a mechanism for ranking the human health risk posed by the alternative chemicals. In some applications, the exposures are very brief, lasting several seconds to a few minutes.

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METHODS FOR STUDYING CARDIAC SENSITIZATION

Cardiac sensitization can be studied using exogenously administered (injected) epinephrine or by induction of high concentrations of epinephrine with external stimuli. This section briefly describes the differences between the study methods and discusses the results that may be obtained with each.

Exogenous-Epinephrine Studies

In response to reported deaths in humans, apparently associated with sniffing of aerosol propellants, Reinhardt et al. (1973) developed a systematic screening approach for determining the cardiac-sensitization potential of unsubstituted and halogenated hydrocarbons. The fixed-epinephrine-dose protocol has been modified recently, to what is referred to as the epinephrine-titration protocol, to account for individual test-animal variation in sensitivity to epinephrine. The protocols differ in the dose of epinephrine used and the procedure for its administration. Each method affects the risk assessments associated with human exposures.

Fixed-Epinephrine-Dose Protocol

Table 4-1 lists the steps (and their durations) of the cardiac-sensitization screening method of Reinhardt et al. (1971). A conscious male beagle is fitted with a flow-through mask and exposed to various concentrations of the test chemical in air. The animal is given an intravenous epinephrine injection before exposure and a second injection during exposure. Its ECG

TABLE 4-1 General Protocol for Cardiac Sensitization in Dogs

Time, min	Activity
0	Start; control (air) administration
2	Administer epinephrine intravenously
5	
7	Begin test-chemical administration
10	
12	Administer epinephrine challenge dose intravenously
15	
17	Stop test-chemical administration

Source: Adapted from Reinhardt et al. 1971.

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response is continuously monitored. The dog breathes air alone for the first 7 min of the experiment. A control intravenous injection of epinephrine (8 μg per kilogram [kg]) in 1 milliliter (mL) of saline is administered at 2 min into the experiment over a 9-sec interval, and exposure to air continues for an additional 5 min. Each dog serves as it own control. If the dog shows a cardiac arrhythmia in response to the control injection of epinephrine, he is not used for that chemical concentration, although he may be used for another concentration. Thus, any response that is seen in response to exposure to the test chemical occurs at a dose of epinephrine which does not otherwise cause cardiac sensitization. For 7-17 min, the dog inhales a given concentration of the chemical-air mixture. After 5 min of exposure to the chemical-air mixture (12 min into the study), a challenge injection of epinephrine (8 μg/kg) is given. If the concentration of the chemical produces cardiac sensitization, an arrhythmia (potentially life-threatening) would be seen on the ECG. After the 10-min exposure to the chemical, the study is stopped (17-min point into the protocol).

The dose of epinephrine used to challenge the animal and the exposure duration are important variables in inducing cardiac sensitization. High doses of epinephrine produce ventricular fibrillation, so cardiac-sensitization tests must use smaller doses. Reinhardt et al. (1971) used an epinephrine dose of 8 μg/kg, which resulted in a dose rate of about 50 μg/kg per minute. That was inherently conservative in as much as the dose rate of epinephrine was about 10 times the dose calculated to occur in humans during times of stress (5 μg/kg per minute) (Price et al. 1958; Mullin et al. 1972).

Reinhardt et al. (1971) investigated the length of exposure to dichlorodifluoromethane (CFC-12) required to induce cardiac sensitization. Groups of seven dogs received an epinephrine injection at 2 min and then 10 min later inhaled CFC-12 at 7.0% or 13.5% for 30 sec. None of the dogs at the lower concentration and two of seven dogs at the higher concentration exhibited cardiac sensitization, including one case of cardiac arrest. In Reinhardt's standard 17-min protocol (1971), exposure to 2.5% CFC-12 for 5 min produced no cardiac sensitization, whereas exposure to 5.0% CFC-12 resulted in cardiac sensitization in five of 12 dogs. The absence of cardiac sensitization in dogs exposed to CFC-12 at 2.45-2.58% for 30 min or even 60 min before epinephrine challenge suggests that the threshold for cardiac sensitization may be independent of length of exposure (Reinhardt et al. 1971). The 5-min threshold for cardiac sensitization was demonstrated in later experiments (Reinhardt et al. 1971); 5-min exposures to CFC-113 at 0.5% (5,000 ppm) resulted in serious arrhythmias in 10 of 29 dogs, but none at 0.25% (2,500 ppm), and only one of 12 dogs exposed at 0.25% (2,500 ppm) for 6 h before epinephrine challenge developed an arrhythmia.

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The results of the screening studies (Reinhardt et al. 1971) with various hydrocarbons showed that cardiac sensitization occurred generally at concentrations of 5-20%, although CFC-11 and CFC-113 induced arrhythmias at concentrations as low as 0.5%. Those screening studies, although not intended for quantitative risk assessments, can be used to rank fluorocarbons with regard to their cardiac-sensitization potential. CFC-11 is considered to be a "strong sensitizer"; CFC-12, which produced arrhythmias at 5.0% (2.5-7.5%), a "moderate sensitizer"; and CFC-115, which required concentrations of 15.0% or more to produce arrhythmias, a "weak sensitizer." Since the Reinhardt et al. studies, nearly 100 halocarbons and hydrocarbons have been tested, and most have shown cardiac-sensitization potential with the dog model. Iodotrifluoromethane (CF_3I), which produces arrhythmia at 0.4% in the dog (see next section), would rank as a strong sensitizer according to the above criteria.

The results seen with CF_3I and other selected fluorocarbons have been reviewed by Brock et al. (2003). The studies that they reviewed strongly indicate that arrhythmias that occur after epinephrine challenge result from exposure to the test chemical and are potentially life-threatening. No serious arrhythmia followed any control epinephrine injection or followed a challenge injection in several control experiments that used air alone.

Epinephrine-Titration Protocol

With the recognition that CFCs were stratospheric ozone depleters, efforts increased to identify alternative chemicals. Prominent among the possible alternatives were hydrochlorofluorocarbons (HCFCs) and hydrofluorocarbons (HFC). Cardiac-sensitization studies of those compounds were undertaken, in large part, under the coordination of the international industry consortium Program for Alternative Fluorocarbon Toxicity Testing (PAFT). The protocol used for the studies was based on that of Reinhardt et al. (1971). However, instead of using the same dose of epinephrine in all dogs, the dose of epinephrine was titrated for each animal to help to control for individual dog variation in response to cardiac sensitizers (Brock et al. 2003). Each dog received an epinephrine dose that ranged from 1 to 12 μg/kg while exposed to air to determine the minimal arrhythmic dose. If an arrhythmia was observed, the dose was decreased; if no arrhythmia was observed, the dose was increased up to a maximum dose of 12 μg/kg. Once the minimal arrhythmic dose of epinephrine was established, it would be used when the dog was exposed to the test chemical in accordance with the Reinhardt et al. protocol.

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The advantage of using a titrated epinephrine dose is that it allows for individual animal sensitivities. Although Reinhardt et al. (1971) determined that a dose of 8 μg/kg injected over 9 sec tended to be optimal in the fixed-epinephrine-dose protocol, Hardy et al. (1994) found that titration of the dose for each dog with epinephrine at doses of 2-12 μg/kg was more sensitive for detecting cardiac sensitization. In addition, there is less chance of choosing an epinephrine dose for an animal that might itself induce arrhythmia or, conversely, might not induce any change in heartbeat when the chemical being evaluated is a sensitizer at that level. However, differences in the epinephrine dose make it difficult to compare results of the two protocols. The epinephrine titration protocol might be expected to yield a different no-observed adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) for a test chemical than would be found with the fixed-epinephrine protocol. That has been the case with a few chemicals, such as HCFC-141b: in one study, the cardiac-sensitization LOAEL with the epinephrine-titration method was 9,000 ppm (epinephrine at 10 μg/kg), but in another study with the Reinhardt et al. fixed-epinephrine dose protocol (8 μg/kg), the LOAEL was 5,000 ppm. In a third study of HCFC-141b also with the titration method, the LOAEL was 20,000 ppm (epinephrine at 10 μg/kg) (Brock et al. 2003). The concentration of CFC-11 required to induce cardiac sensitization in dogs ranged from 5,000 ppm in a fixed-epinephrine-dose study to about 10,000 ppm in a later epinephrine-titration protocol, although the reason for the variability is unclear. The selection of a LOAEL or NOAEL for a risk assessment based on those experiments is equally uncertain.

In the first titration study, the lowest concentration tested was 9,000 ppm; it caused arrhythmia in one of four dogs. However, in the second titration study conducted in the same laboratory, the NOAEL was 10,000 ppm and the LOAEL was 20,000 ppm, the next highest concentration tested. Given that none of four dogs responded at 10,000 ppm in the first study (Brock et al. 1995) and only one of two at 9,000 ppm, these results are all consistent with a threshold near 10,000 ppm.

Using the Reinhardt protocol with a titrated epinephrine dose, the potential for iodotrifluoromethane (CF_3I) to induce cardiac sensitization in the dog was evaluated (Kenny et al. 1995; Dodd and Vinegar 1998). The study involved male beagles exposed at 0.1% (6 dogs), 0.2% (5 dogs), 0.4% (5 dogs), and 1.0% (1 dog) (1,000, 2,000, 4,000, and 10,000 ppm) CF_3I with epinephrine doses of 1-8 μg/kg (see Table 4-2). Exposures at 0.1% and 0.2% did not result in any response, regardless of the epinephrine dose. One dog that received 0.1% CF_3I (epinephrine at 8 μg/kg) had no response; but when it was exposed to 1.0% CF_3I, fatal ventricular fibrillation (FVF)

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TABLE 4-2 Cardiac-Sensitization Responses to CF_3I

Dog	Epinephrine Dose, μg/kg	CF_3I Concentration			
		0.1%	0.2%	0.4%	1.0%
1	8	Neg[a]	—	—	FVF
2	8	Neg	Neg	FVF	—
3	8	Neg	Neg	—	—
4	1	Neg	Neg	—	—
5	4	Neg	Neg	—	—
6	1	Neg	Neg	—	—

[a]Neg, no response; —, not tested; FVF, fatal ventricular fibrillation.
Source: Kenny et al. 1995.

occurred. A second dog showed no effect at 0.1% or 0.2% but had FVF at 0.4% (epinephrine at 8 μg/kg), so no additional exposures were conducted. No blood concentrations of CF_3I were measured in any dog. On the basis of these responses in dogs, the NOAEL for the 5-min exposure (before epinephrine challenge) to CF_3I was therefore considered to be 0.2% (2,000 ppm), and the threshold for response 0.4% (4,000 ppm).

Endogenous-Epinephrine Studies

As noted earlier, the doses of exogenous epinephrine used in the fixed-epinephrine protocol of Reinhardt et al. (1971) are about 10 times the physiological concentrations that might occur in humans under stress conditions (Mullin et al. 1972). To determine whether halogenated hydrocarbons would induce sensitization without the administration of exogenous epinephrine, "endogenous-epinephrine" studies were conducted in dogs by Reinhardt et al. (1971) and Mullin et al. (1972). Reinhardt et al. (1971) exposed beagles to a mixture of 80.0% fluorocarbon and 20.0% oxygen for 30 sec while frightening the animals with a loud noise. In contrast with the exogenous-epinephrine studies, no other substances were given to the animals; the frightened dogs were expected to release endogenous epinephrine. Results from Reinhardt et al. (1971) are shown in Table 4-3.

Table 4-3 highlights the importance of increased epinephrine, whether exogenous or endogenous, in cardiac sensitization. It also shows that the concentration of epinephrine did not substantially change the number of dogs that had cardiac arrhythmias. For example, when dogs were exposed to 80.0% HCFC-142b, it was apparent that noise was a contributing factor:

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TABLE 4-3 Cardiac Sensitization with Endogenous[a] or Exogenous Epinephrine

Compound with Noise or Epinephrine	No. Dogs Exposed	No. Marked Responses	Exposure Without Epinephrine, ppm	LOAEL, ppm[b]
CFC-11 + noise	12	2	800,000	
CFC-11 + epinephrine	12	1	—	5,000
CFC-114 + noise	12	1	800,000	—
CFC-114 + epinephrine	12	1	—	25,000
CFC-12 + epinephrine or noise	12	0	—	50,000
HCFC-142b + epinephrine	6	0	—	25,000 (NOAEL)
HCFC-142b + epinephrine	12	5	—	50,000
HCFC 142b + noise	12	5	800,000	—
HCFC-142b (no noise)	12	1	—	800,000
Noise only	6	0	—	—

[a]Dogs were exposed to 80.0% compound (20.0% O_2) for 30 sec while being frightened with loud noise.
[b]LOAEL determined in screening studies with intravenous exogenous epinephrine.
Source: Adapted from Reinhardt et al. 1971.

five of 12 dogs exhibited cardiac sensitization compared with one of 12 dogs that received the chemical only. No cardiac sensitization was observed with noise alone during air exposures. Thus, without the stimulation of the epinephrine, the threshold increased 32-fold; with the noise, the threshold was 16 times as high as with the chemical alone.

In an effort to determine whether cardiac sensitization would occur without administration of exogenous epinephrine, Mullin et al. (1972) exposed beagles to various concentrations of CFCs while they ran on a treadmill. Exercise has been found to increase circulating epinephrine in dogs by a factor of 5 after 15 min at 500 ft/min (Ohukuzi 1966).

Animals were exposed to increasing concentrations of CFC-11, CFC-12, or CFC-114. If the test compound at a specific concentration were a sensitizing agent, an arrhythmia such as multiple ventricular beats, would be seen on the electrocardiogram. Results from the study are shown in Table 4-4.

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TABLE 4-4 Treadmill Studies of Cardiac Sensitization

Compound	Exposure Concentration, ppm	No. Dogs Exposed	No. Marked Responses	LOAEL,[a] ppm	LOAEL,[b] ppm
CFC-11	5,000	8	0	5,000	10,000
	7,500	8	0		
	10,000	7	0		
CFC-114	25,000	6	0	25,000	50,000
	50,000	7	1		
	100,000	7	1		
CFC-12	50,000	6	0	50,000	100,000
	75,000	6	0		
	100,000	6	1		

[a]LOAEL determined in screening studies with intravenous epinephrine.
[b]LOAEL based on endogenous epinephrine studies.
Source: Adapted from Mullin et al. 1972.

The inhaled concentrations of CFCs required to induce cardiac sensitization in exercising dogs were 2-4 times as high as those needed for animals receiving intravenous exogenous epinephrine. The study demonstrated that the LOAEL of a compound may depend on the circulating epinephrine concentrations. Brock et al. (2003) stated the following:

> The importance of experiments involving endogenous adrenaline production is three-fold. First, these experiments confirmed the validity of the standard 5-minute screening study using injected epinephrine as a valid ranking tool. Secondly, these data (especially the 'fright' studies) provide more evidence that the phenomenon of cardiac sensitization is most likely the mechanism of death in aerosol 'sniffing' episodes. Finally, these data indicate that the cardiac-sensitization protocol is a conservative measure of toxicity relative to the circulating blood levels of epinephrine following intravenous injection.

No studies of CF_3I with endogenous epinephrine were found in the publicly available literature.

BLOOD AND TISSUE PHARMACOKINETICS

The goal of the studies described above was to identify the lowest concentration of halocarbons or other agents that would induce cardiac

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sensitization on the basis of a dose-response relationship. That information was used to rank the halocarbons in terms of cardiac-sensitization potency. To help to establish the dose-response relationship, investigators (Azar et al. 1973; Trochimowicz et al. 1974) attempted to correlate the concentration of the test chemical in air that would induce cardiac sensitization with the arterial and venous blood concentrations of the chemical at the time of sensitization.

One approach to estimating the blood concentrations of these chemicals after inhalation exposure is physiologically based pharmacokinetic (PBPK) modeling. This technique permits estimates of body burden that are correlated with the magnitude and duration of exposure. The use of PBPK models to estimate arterial blood concentrations rather than using the airborne exposure concentration as the measure of dose is discussed in Chapter 5.

Mullin et al. (1979) showed that blood concentrations of Halon 1301 increase rapidly during the first 5 min of inhalation exposure and reach equilibrium after about 20 min (Figure 4-1). At 5 min of exposure at 5.0%, the arterial concentration was 10.7 μg/mL. By 20 min, arterial concentration had increased to 19.9 μg/mL, and it stayed there for the remainder of the hour-long exposure. At 7.5% and 10.0%, the arterial concentrations at 5 min were 30.9 and 40.0 μg/mL, and at 20 min were 30.9 and 35.4 μg/mL, respectively. Although the arterial concentrations values increased between 5 and 20 min with exposure to 5.0%, the venous concentrations were constant (10.3 and 11.3 μg/mL, respectively). Overall, the similarity of these values at each exposure concentration suggests that equilibrium between blood and air is reached rapidly. At the end of the 60-min exposure period, blood concentrations dropped rapidly in the first 5 min and then decreased more slowly (Azar et al. 1973; Mullin et al. 1979). Other CFCs, such as CFC-12 and CFC-113, have shown a similar pharmacokinetic pattern of uptake and elimination (Azar et al. 1973; Trochimowicz et al. 1974; Mullin et al. 1979).

Table 4-5 shows the cardiac-sensitization results and mean arterial and venous concentrations of various halocarbons at the 5-min sampling time according to the Reinhardt et al. protocol. Although the inspired concentrations of halocarbons required to produce cardiac sensitization ranged from 0.5% to 15.0%, the arterial and venous concentrations at 5 min were similar for the various types of halocarbons. That is, two-carbon halocarbons (CFC-113, CFC-114, and CFC-115) tended to result in lower blood concentrations at induction of cardiac sensitization than did one-carbon halocarbons (CFC-11 and CFC-12). The difference may be related to the water solubility of the halocarbon.

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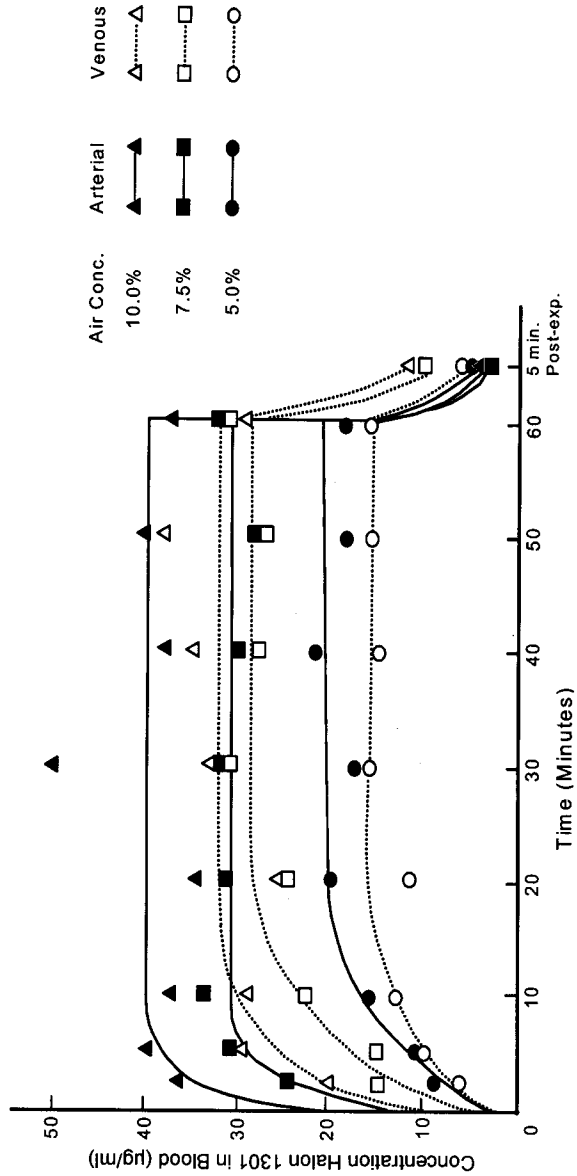

FIGURE 4-1 Arterial and venous dog blood concentrations of Halon 1301 versus time. Source: Mullin et al. 1979. Reprinted with permission; copyright 1979, American Industrial Hygiene Association.

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TABLE 4-5 Blood Concentrations of Halocarbons Associated with Cardiac Sensitization

Compound	Exposure Concentration, ppm	No. Dogs Sensitized/ Exposed	5-Min Blood Concentration, μg/mL	
			Arterial	Venous
Halon 1301	50,000	0/62	10.7	10.3
	75,000[a]	1/18	30.9	14.8
	100,000	7/69	40.0	29.8
CFC-11	1,000	0/12	10.9	6.6
	5,000[a]	1/12	28.6	19.7
	10,000	5/12	53.2	37.2
CFC12	1,000	ND	1.0	0.9
	25,000	0/12	ND	ND
	50,000[a]	5/12	35.3	22.8
	100,000	ND	46.3	39.8
CFC-113	1,000	ND	2.6	1.5
	2,500	0/12	ND	ND
	5,000[a]	10/29	12.5	4.9
	10,000	3/4	18.0	12.1
CFC-114	1,000	ND	0.4	0.3
	25,000[a]	1/12	13.8	7.2
	50,000	7/12	23.6	10.0
CFC-115	100,000	ND	2.8	1.9
	150,000[a]	1/13	5.8	3.9
	250,000	4/12	11.4	5.9

[a]LOAEL based on Reinhardt et al. 1971.
Abbreviation: ND, not determined.
Sources: Azar et al. 1973; Trochimowicz et al. 1974; Mullin et al. 1979.

In addition to solubility, the blood:air partition coefficient also influences the uptake and elimination of halocarbons in the body. For example, short-chain CFC-12 is only slightly soluble in blood. It is readily absorbed from the lungs into the bloodstream, where it rapidly equilibrates with blood as a function of the blood:air partition coefficient and essentially reaches steady state within minutes (Azar et al.1973). As shown in Figure 4-1 for Halon 1301, blood concentrations rapidly decrease once exposure ends. The observed increase in blood concentrations for these and other halocarbons clearly indicates a multiplicative relationship between concentration and length of exposure: steady-state blood concentrations occur within about 5 min of exposure.

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Longer exposures do not substantially change the plateau blood concentrations of most halocarbons. That was demonstrated by Beck et al. (1973), who showed that dogs exposed to Halon 1211 at 8.0%, 5.0%, or 2.0% for 1, 2, or 5 min, respectively, had blood concentrations of 21-24 μg/mL when cardiac sensitization was induced. They found that cardiac sensitization was independent of whether the blood concentration was achieved rapidly by exposure at high concentrations or more slowly at lower concentrations. As noted earlier, Reinhardt et al. (1971) found that cardiac sensitization occurred with a 5-min exposure to 5.0%, but not 2.5% CFC-12. Furthermore, longer exposures—up to an hour—at 2.5% still produced no cardiac arrhythmias. Induction of cardiac sensitization appears to correlate with the peak blood concentration of the halocarbon before epinephrine challenge.

Determining peak blood concentrations requires knowledge of the arterial and venous concentrations of the test chemical. As shown in Figure 4-1, arterial blood concentrations of halocarbons are greater than venous concentrations during exposure, but this reverses when exposure ceases. That suggests that halocarbons are taken up by body tissues (Azar et al. 1973). In another series of experiments with CFC-11 and CFC-12 (Trochimowicz et al. 1974), dogs were exposed to various concentrations for 5 min and then immediately sacrificed, and halocarbon concentrations were measured in about 10 tissues. Although they are not detailed here, tissue concentrations of halocarbon were directly correlated with the blood and inhaled concentrations associated with cardiac sensitization. In addition, there was no evidence of retention of halocarbon in tissues after acute inhalation. Together, those studies suggest that steady-state blood concentrations of the halocarbons are reached within about 5 min of exposure, at least in the dog, and the peak blood concentrations depend on the exposure concentrations. It is the peak blood concentration that is related to the induction of cardiac sensitization. Prolonged exposure to an airborne concentration of halocarbon that does not achieve the critical blood concentration does not appear to increase the risk of cardiac sensitization.

VALIDITY OF THE CARDIAC-SENSITIZATION PROTOCOL

The mechanism for cardiac sensitization in humans is unknown, but results of cardiac-sensitization studies with epinephrine using the method of Reinhardt et al. (1971) may be used to establish human exposure limits for halocarbons. For over 30 years, when exposures to halocarbons have been maintained below the NOAEL defined by the studies, there have been

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no reported deaths. When exposures exceeded the NOAEL, however, as may occur in such confined spaces as military tanks, airplane wings, large degreasers, or large leaking refrigeration units, incidents of cardiac problems, some fatal, have been reported (NIOSH 1989). Furthermore, cardiac sensitization can be demonstrated in animals exposed to halocarbons with noise, shock, or exercise as the only stimulus for epinephrine (endogenous epinephrine), albeit at halocarbon concentrations greater than those which produce cardiac arrhythmias in the presence of exogenous epinephrine (Reinhardt et al. 1971; Mullin et al. 1972).

Cardiac-sensitization potential may also be evaluated from studies that do not employ an epinephrine challenge. In these studies, induction of cardiac arrhythmia typically does not occur or it occurs at much higher exposure concentrations than with epinephrine challenge studies (Reinhardt et al. 1971). A study conducted at Huntingdon Life Sciences (2000) to determine the arterial and venous blood concentrations of CF_3I in dogs during and after 10-min nose-only exposures confirmed this reduced cardiac-sensitization potential. Six male beagles were exposed to CF_3I at 0.3% or 0.4%, five dogs were exposed to 0.5% or 2.5%, and one dog was exposed to 5.0%. Blood samples were taken during exposure and for 1 h after exposure for use in the development of a PBPK model (see Chapter 6). Except for the lack of exogenous epinephrine administration, the protocol used was that of Reinhardt et al. No cardiac sensitization was seen at any CF_3I concentration even though the exposures at 2.5% were 6.25 times higher than the concentration that induced a cardiac arrhythmia when the dogs were given an injection of epinephrine. The exposure to 5.0%, the highest concentration tested, was stopped after 4 minutes due to excessive adverse clinical signs. Even at this concentration, coupled with the observations of severe stress, the only cardiac sign reported was marked tachycardia in the one dog tested. Adverse clinical signs seen during exposure at 0.3% CF_3I included agitation (3/6 dogs), deep breathing (1/6 dogs), and vomiting 1 h after exposure (1/6 dogs). At 0.4% CF_3I, only one dog exhibited deep breathing during exposure and another dog vomited 48 min after exposure ceased. At 0.5%, no adverse clinical signs were observed during or after exposure in the five dogs; at 2.5%, adverse clinical signs during exposure included rigid legs (3/5 dogs), arched back (2/5), excessive swallowing (2/5), shallow breathing (1/5), and moderate salivation (1/5).

For an experimental evaluation, studies with multiple or different catecholamines could provide insight into the mechanism of action of halocarbon-induced cardiac sensitization. The subcommittee notes that the same cardiac-sensitization protocol is used for developing hazard informa-

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tion for traditional risk assessments and PBPK-modeled risk assessments. The difference is that the "modeled" risk assessment goes one step further than a traditional risk assessment and predicts the time that it will take to achieve the maximal "safe" blood concentration at different exposure concentrations (see Chapter 5).

In spite of the considerable dataset available from cardiac-sensitization tests with halocarbons, critical questions remain. Are cardiac-sensitization studies conducted in beagles satisfactory for predicting the potential of a halocarbon or halocarbon substitute to produce arrhythmia in humans? If so, do the tests reliably predict the concentration at which humans will develop an arrhythmia?

Answering those two questions touches a number of issues. It is well known that halocarbons may be antiarrhythmic at some concentrations and proarrhythmic at others (Muir et al. 1959; Purchase 1966). It has also been suggested that halocarbons increase the likelihood that stress will produce arrhythmias in humans and that the arrhythmias result from sensitization of the heart to epinephrine; that is, the arrhythmias are merely an exaggeration of the proarrhythmic effects of epinephrine. One important concern is that in humans under stress, norepinephrine, epinephrine, and dopamine—all potentially proarrhythmic catecholamines—increase in the order norepinephrine >>> epinephrine > dopamine. It is unlikely that the pathogenesis of a ventricular arrhythmia precipitated by the interactions of a halocarbon with epinephrine may mimic production of arrhythmias by halocarbons and stress in humans, in as much as epinephrine is only one of the catecholamines produced in humans by stress. The issue could be addressed by studies conducted in dogs exposed to increasing concentrations of halocarbons and given a mixture of all catecholamines at concentrations that mimic those observed in humans under stress.

The mechanism of sudden death in humans exposed to halocarbons is not known. Sudden death may be caused by ventricular fibrillation, asystole hypotension, respiratory arrest, acute heart failure (rarely), or a combination thereof. It is dangerous to presume that all sudden deaths result from ventricular fibrillation even if fibrillation can be produced in combination with halocarbons in dogs. If the mechanism of death is not fibrillation, studies conducted on dogs exposed to both epinephrine and halocarbons, although perhaps interesting, are not relevant to human deaths.

It is well known that ventricular arrhythmias may be produced by the actions of various compounds on the heart, on the brain (particularly the area postrema), or both. The knowledge of a mechanism of action may be extremely important in understanding hazardous concentrations. For example, if the mechanism involves increased automaticity of Purkinje or

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"M" fibers, blockade of the delayed rectifier currents of ventricular depolarizations, increased temporal dispersion of repolarization, altered Ca^{++}-calmodulin interaction, or altered balance in parasympathetic and sympathetic efferent activity, then different conclusions can be drawn about how to identify impending arrhythmia and how it might be prevented. This issue could be addressed with a comprehensive panel of in vitro studies (for example, patch clamp, Purkinje fiber, Langendorff) and in vivo studies (for example, close exposures of the brain and heart at relatively low concentrations and intravenous exposures).

Although cardiac sensitization is a well-documented adverse effect of exposure to halocarbons, research on the mechanism by which it occurs is not extensive and has focused primarily on prediction of cardiac-sensitization potential on the basis of development of an arrhythmia. Among the various cardiac end points studied, a change in heart rate appears to be the best indicator of a prearrhythmogenic event (E. Kimmel, Wright-Patterson Air Force Base, personal commun., 2001). A shift in cardiac conductance and destruction of the sinus node was also seen by Hashimoto and Hashimoto (1972), although the halocarbon-epinephrine-induced arrhythmia could be corrected by increasing the heart rate with electric stimulation. Intraventricular pressure increases will also produce ventricular arrhythmia (Reynolds 1983). Thus, halogenated hydrocarbons in combination with epinephrine can result in disrupted heart rhythm. Possible mechanisms of cardiac sensitization are discussed in Box 4-1.

The sensitivity and specificity of the beagle cardiac-sensitization test for predicting arrhythmogenicity or magnitude of exposure in humans are unknown, and this lack of knowledge can be attributed to the difficulty in ascertaining whether death due to halocarbon exposure necessarily results from true sensitization to epinephrine. The lack of information makes it important to understand the mechanism of sensitization. For example, if patch-clamp studies show that halocarbons or halocarbons with catecholamines alter conductance over the delayed rectifier currents, animal surrogates that might possess polymorphisms similar to those of humans should be used.

If an arrhythmia in the presence of a halocarbon and a concentration of epinephrine that by itself does not produce an arrhythmia is a positive signal in the dog and it is presumed that the halocarbon concentration at which the arrhythmia just occurs is the LOAEL, the test might appear to have great sensitivity if the result occurs with all halocarbons known to produce arrhythmia at that concentration. However, it will still be unknown whether that concentration will produce an arrhythmia in humans. Thus, some halocarbons and some concentrations may be indicted incorrectly as

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BOX 4-1 Possible Mechanisms of Cardiac Sensitization

The mechanisms whereby some halocarbons sensitize the myocardium to the action of epinephrine is not well understood. One mechanism, "cardiac sensitization," has been proposed for the interaction of halocarbons with catecholamines to produce ventricular arrhythmias. Dudley (2003) proposed that abnormal calcium cycling from the sarcoplasmic reticulum is the prime factor in cardiac sensitization. That is based on the observation that the initial ventricular premature depolarization results from a delayed after-depolarization, and it is thought that delayed after-depolarizations—as occur with ouabain toxicity—depend on abnormal calcium cycling. Abnormal calcium cycling between cytosol and sarcoplasmic reticulum depends on the balance between calcium exit from the sarcoplasmic reticulum over ryanodine channels and calcium entry into the sarcoplasmic reticulum through channels activated by energy from sarcoplasmic-endoplasmic reticulum calcium-ATPase (SERCA2a) via phosphorylation of phospholamban. Sympathetic activity—manifested by increased concentration of sympathetic neurohormones (norepinephrine, epinephrine, and dopamine)—is known to activate protein kinase A, which phosphorylates and activates ryanodine channels, renders them "leaky" to calcium (predominantly in diastole), and increases their sensitivity to calcium release from the sarcoplasmic reticulum. Increased sympathetic activity—and putatively halocarbons—may activate protein kinase A, which hyperphosphorylates the ryanodine receptor and results in depletion of the important regulatory protein FKBP12.6. Thus, one explanation of cardiac sensitization may be synergism between halocarbons and sympathetic activity on calcium kinetics; and an avenue to prevent cardiac sensitization—for example, with beta adrenergic blockade—may be to minimize the synergism at the ryanodine receptors, possibly by preventing hyperphosphorylation or depletion of FKBP12.6.

cardiac sensitizers, and it will still be unknown whether halocarbons or particular halocarbon concentrations that are arrhythmogenic in the dog are also arrhythmogenic in humans.

As discussed previously in this chapter, it is known that CFC-11 and CFC-113 produce cardiac arrhythmias in dogs at 5,000 ppm and in humans at estimated concentrations of over 20,000 ppm without the use of exogenous epinephrine. HCFC-22, HCFC-141b, and Halon 1301 have been shown to cause death in humans, which has been attributed to cardiac arrhythmia. Several other halocarbons have been shown to react with the dog model, but overexposures in humans have not been reported.

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Nevertheless, it is almost impossible to determine the sensitivity and specificity of a cardiac-sensitization test without knowing how many halocarbons (and at which concentrations) produce arrhythmias in both humans and the test animal (sensitivity) and how many halocarbons and concentrations that do not produce arrhythmias in humans also do not produce them in the test animal (specificity). It is impossible to answer the question whether the cardiac-sensitization test identifies halocarbons and their concentrations that might produce arrhythmias in humans unless the above issues are addressed. Box 4-2 identifies some considerations that should be included in refining cardiac-sensitization testing.

No uncertainty factors are necessary for extrapolation from dogs to humans, because the doses of exogenous epinephrine achieve plasma concentrations that are 10 times greater than those achieved during physiologic stress, such as exercise or loud noise. Therefore, the dog cardiac-sensitization test procedures are likely to be conservative enough to account for any uncertainty in dog-to-human extrapolation.

It is reasonable to conclude that the NOAEL for CF_3I in humans for a 5-min exposure is 0.2% if epinephrine mimics the conditions of stress in humans, sudden death from halocarbons is caused by ventricular fibrillation, and all halocarbons identified as arrhythmogenic in the epinephrine-challenged dog are potentially arrhythmogenic in humans and halocarbons that do not produce arrhythmias in dogs also do not produce them in humans.

CONCLUSIONS

Numerous reports on laboratory animals and humans indicate that cardiac sensitization can occur as a result of exposure to halocarbons and that most halocarbons with fluorine substitution are capable of sensitizing the heart to epinephrine. That endogenous concentrations of epinephrine, such as those achieved through exercise or by frightening an animal, can result in fatal cardiac arrhythmia is of particular concern for human exposures.

The studies reviewed in this chapter generally were conducted to rank halocarbons with regard to their cardiac-sensitization potential. The subcommittee cautions that the studies were not conducted with the goal of quantitative risk assessment of the compounds, and it notes that the results of the studies are nonetheless often used for PBPK modeling. The doses used in some of the procedures increase severalfold, and this makes it difficult to determine a precise NOAEL or LOAEL from a particular study.

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BOX 4-2 Proposed Method to Further Explore Cardiac Sensitization

Cardiac sensitization refers to the increased likelihood of ventricular arrhythmias—sometimes leading to death—caused by exposure to halocarbons. Cardiac sensitization has been explored by challenging animals, which have been exposed to graded doses of halocarbons, with incremental concentrations of epinephrine and comparing the arrhythmic dose of epinephrine required to produce ventricular ectopia during halocarbon exposure with that required before exposure. There are no strong data to support the extrapolation of this method performed on laboratory animals to humans, and the stress profile of arrhythmogenic catecholamines includes a balance among epinephrine, norepinephrine, and dopamine. There is no way of dealing with extrapolation without testing for the sensitivity and specificity of the method, but it is feasible to simulate a more physiologic catecholamine stress profile that might mimic more closely that observed in humans.[1] The following is one possible scheme for exploring cardiac sensitization with dogs as surrogates for humans.

Select dogs of varied sizes, ages, and sexes[2] that might correspond to the humans at risk.[3] Train dogs to stand quietly with a catheter in a peripheral vein for infusion of catecholamines and a head bubble for exposure to various concentrations of halocarbons. Challenge the dogs with continuous intravenous infusions[4] of increasing doses of epinephrine, norepinephrine, and permutations of epinephrine and norepinephrine[5] to determine the arrhythmogenic threshold of each. There may be a number of thresholds (such as, first premature ventricular depolarization, first monomorphic paroxysmal ventricular tachycardia, sustained monomorphic ventricular tachycardia, sustained pleomorphic ventricular tachycardia, and ventricular fibrillation).[6] Determine the arrhythmic dose of catecholamines for each concentration of each halocarbon, to rank halocarbons according to potential to sensitize to ventricular arrhythmia. Another variation might be to expose dogs to any of the various pharmacologic agents that might be used recreationally (such as, cannibis, amphetamine, or cocaine) or medically (such as, beta blockers, ACE inhibitors, calcium-channel blockers,[7] or drugs for erectile dysfunction) to mimic more closely the spectrum of humans at risk of halocarbon exposure.

Suggesting these studies is not intended to imply that studies already conducted exposing beagles to increasing concentrations of epinephrine by bolus injections might not possess high sensitivity and specificity for predicting cardiac sensitization in humans. Rather, it is a supplement to consider factors (such as, polymorphisms, catecholamine profiles of stress, concomitant diseases, and concomitant pharmacologic interventions) that might confound results already published. Any or all of these proposed studies must be done carefully in a laboratory with good-laboratory-practice methods and experience in inhalation toxicology.

(Continued)

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BOX 4-2 *Continued*

[1]Although the stress profile of catecholamines in humans varies with the stressor and its magnitude.
[2]Because of polymorphisms in specific ion channels or other receptors for catecholamines or halocarbons, using a greater variety of dogs would reduce the risk of making an error, because genetically "pure" dogs might or might not have the arrhythmic profile (see papers by George Billman on dog classification according to sensitivity to arrhythmia).
[3]It might be helpful to use dogs with iatrogenic diseases (such as, left ventricular hypertrophy produced by aortic banding or myocardial ischemia produced by ameroid constrictors) to mimic more closely humans with those disorders who might be exposed to halocarbons.
[4]It may be more reproducible to expose dogs by constant infusion rather than by administration of boluses.
[5]For example, concentrations of epinephrine/norepinephrine of 1:1, 1:2, and 2:1.
[6]There is evidence that one halocarbon produces serious ventricular arrhythmias but not fibrillation, whereas another produces fibrillation but none to few ventricular premature depolarizations.
[7]Calcium-channel blockers might be appropriate because it is possible that sensitization involves ryanodine receptors in the sarcoplasmic reticulum.

Furthermore, various protocols have been used to assess cardiac sensitization with differing times between exposure onset and epinephrine challenge. As noted by Brock et al. (2003), "the key factor for inducing sensitization has been the arterial blood concentration of the agent at the time of epinephrine challenge. Therefore, understanding the pharmacokinetics of the agent helps interpret results of these studies within the context of risk assessment. It also allows better interpretation of potential exposure scenarios and the likelihood of cardiac-sensitizing concentrations being reached by individuals under various exposure conditions."

Is the dog model, with injections of epinephrine, an appropriate model of human cardiac-sensitization potential? The model was developed by Reinhardt et al. (1971) after Bass (1970) and others reported on deaths resulting from deep breathing of aerosol propellants. Other catecholamines may be responsible, either in part or completely, for the development of cardiac arrhythmias in humans after overexposure to halocarbons, but in the dog model, administration of exogenous epinephrine gives rise to a cardiac response (ventricular premature depolarizations) that would be seen only at much higher concentrations of a hydrocarbon without the injection (Reinhardt et al. 1971; Brock et al. 2003). The most difficult assumption that one must make is that the dose, determined as a measured blood

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concentration that does not produce an arrhythmia in the dog, will also not cause one in a human. As has been shown in studies with HCFC-142b and CFC-113 (NRC 1996), administration of epinephrine results in a highly sensitive model; this supports the assumption.

ARMY CONCERNS

Although they were not included in the statement of work for the subcommittee, the Army posed several questions with regard to the cardiac-sensitization potential of CF_3I, and the subcommittee strove to address them. What follows is the first question and the subcommittee's response. The other questions are discussed at the end of Chapter 5.

Is the information from cardiac-sensitization tests in dogs appropriate for developing safe exposure levels in humans? If these studies are valid to serve as a basis for human exposure levels, should the data be extrapolated to humans directly without using uncertainty factors? The subcommittee found that although it is difficult to ascertain absolutely that cardiac-sensitization studies in the dog are appropriate for developing safe exposures for humans, a substantial body of evidence nevertheless indicates that many halocarbons that produce cardiac arrhythmias in the dog also cause them in humans. No uncertainty factors are necessary for extrapolation from dogs to humans, because the doses of exogenous epinephrine achieve plasma concentrations that are 10 times greater than those achieved during physiologic stress. Therefore, the dog cardiac-sensitization test procedures are conservative enough to account for any uncertainty in dog-to-human extrapolations.

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5

Physiologically Based Pharmacokinetic Modeling

The discussion of cardiac sensitization in Chapter 4 highlights the need to predict the blood concentration of an agent and the duration of exposure needed to achieve a critical blood concentration. A tool that allows the investigation of those pharmacokinetic factors is the physiologically based pharmacokinetic (PBPK) model. Such models allow one to examine the relationship between external exposure scenarios and internal concentrations in a target tissue, for example, blood. PBPK models incorporate a mathematical description of the uptake, distribution, metabolism, and elimination of chemicals by the body. PBPK models have provided toxicologists with an advantage with respect to understanding the modes of action of chemicals. A number of investigators have used them for various cancer and noncancer end points (Andersen 1981; Conolly and Andersen 1991) as the regulatory agencies, such as the U.S. Environmental Protection Agency (EPA), pursue quantitative risk assessment in public policy. This chapter discusses the application of a PBPK model to estimate blood concentrations of halocarbons after exposure to them at various concentrations.

PBPK MODELING OF EXPOSURE TO FIRE SUPPRESSANTS

Modeling of airborne exposure to cardiac sensitizing agents requires that accounting for short-term (up to 5 min) events. Such a model has been described by Vinegar and colleagues (1998). It includes a respiratory-tract compartment containing a dead space and a pulmonary-exchange volume. The pulmonary-exchange volume contains air space, tissue, and capillary

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subregions. Respiratory-tract uptake is described on a breath-by-breath basis that allows successful simulation of exhaled-breath concentration of agent during the first minute of exposure.

The model was used to simulate exposure of two persons who were trapped in an armored personnel carrier in Israel after the release of a fire extinguishing agent, Halon 1211; one of them died (Vinegar et al. 1998). The investigators re-enacted the release in an identical vehicle. They measured the Halon 1211 concentrations in various portions of the vehicle and found very high concentrations—exceeding 50,000 ppm—within 1 min of the release. Later, they used the PBPK model to simulate the arterial blood concentration at the lowest-observed-adverse-effect level (LOAEL) of Halon 1211 (1.0% or 10,000 ppm). The cardiac-sensitization LOAEL was determined with the Reinhardt et al. (1971) protocol described in Chapter 4. With this PBPK simulation, the authors reported that within 5 min, the arterial blood concentration of Halon 1211 would be about 22 mg/L, which is the critical blood concentration for inducing cardiac sensitization as determined in the dog. At 1 min, the blood concentration would be about 15 mg/L. The investigators then simulated the blood concentrations at the airborne concentrations encountered in the vehicle. In this simulation, the survivor's arterial concentration at 1 min approached 80 mg/L, at about 20 sec it was closer to 20 mg/L. Hence, this person was able to survive the incident because escape from the vehicle was presumably very quick. For the other person, however, the arterial blood concentration rose very rapidly in the first few seconds to about 30 mg/L, which exceeded the critical blood concentration; at 1 min, the arterial blood concentration was about 170 mg/L. The person died from the exposure because his escape was impaired either because of the physical environment or because of nervous system effects (central nervous system depression) of Halon 1211. The cause of death was judged to be due to cardiac sensitization. The authors suggested that the simulation under actual exposure conditions was consistent with the model predictions when compared with the simulation conducted at the cardiac-sensitization LOAEL.

The validated PBPK model can be used to assess exposure to cardiac-sensitizing agents in a number of ways. Each method, however, depends on the determination of the critical blood concentration, typically the peak (steady-state) blood concentration resulting from exposure to the LOAEL. Such data are not often available from dog studies and less often available on humans, the target population. The most direct way to obtain them is to perform a pharmacokinetic study with arterial blood samples taken at various times during exposure. Because the exposure of interest is the threshold concentration or LOAEL, the pharmacokinetic study in dogs

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should be performed at this concentration but without epinephrine challenge. An alternative is to use a PBPK model to simulate the blood concentrations in humans subjected to the critical airborne exposure level, that is, the cardiac-sensitization LOAEL. Data on the arterial and venous blood concentrations in dogs during the first 5 min of exposure (and beyond) to iodotrifluoromethane (CF_3I) are available (Huntingdon Life Sciences 2000) and have been used in the PBPK model to simulate blood concentrations in humans during exposure to CF_3I (Vinegar et al. 2000). This approach is detailed later in this chapter. A limitation to this approach is that the lack of human data makes it difficult to validate the model for predicting human blood concentrations. For ethical reasons it is unlikely that human data will ever be available. Use of a PBPK model to simulate human blood concentrations based on dog and rodent data is a scientifically based approach to assess human health risk from exposure to CF_3I and other compounds for which human data are unavailable.

With the target arterial concentration determined either experimentally or by simulation, various exposure scenarios can be examined. Vinegar and Jepson (1996) and Vinegar et al. (2000) have proposed using PBPK models for estimating egress times after the release of fire-suppression agents. This model has been extensively reviewed as an approach to developing guidelines for safe exposure to halocarbon fire-extinguishing agents (ISO 2004). Vinegar et al. (2000) have suggested that if one can determine the critical arterial blood concentration at the 5-min cardiac-sensitization LOAEL, egress times can be estimated from the shape of the blood concentration-time curve and thus from the time before cardiotoxic blood concentrations are reached. For this PBPK model, the investigators used experimentally determined human blood:air partition coefficients, which lent confidence to uptake values of the compound in humans. They also used human anatomic and physiologic parameters. However, other tissue:air partition coefficients included in the model were usually determined in rats, not humans. Biochemical parameters included in the model were scaled[1] from rodent data to humans because rodent data were usually the only data available. With those parameters, the investigators constructed a model of time versus arterial blood concentration from various airborne concentrations, most notably the cardiac-sensitization no-observed-adverse-effect level (NOAEL) or LOAEL. Monte Carlo methods

[1]In the paper by Vinegar et al. (2000), the authors used a 0.75 exponential scaling factor to convert rodent metabolic parameters to humans. That is common practice in risk assessment, but it represents an added variable and assumption to the model.

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were used to account for exposure population variability in physiological and biochemical parameters, which control blood concentration.

Vinegar et al. (2000) published results of PBPK modeling that simulated human arterial blood concentrations during the first 5 min of exposure to fire-suppression agents. Halon 1301, CF_3I, and the four halofluorocarbons (HFCs) HFC-125, HFC 134a, HFC-227ea, and HFC-236fa were examined. The authors used target arterial concentrations based on the lowest measured 5-min value observed in dogs exposed to the agent of interest at the LOAEL and cited data published in a Huntingdon Life Sciences study (2000). Critical arterial blood concentrations are shown in Table 5-1 for Halon 1301, CF_3I, HFC-125, HFC-227ea, and HFC-236fa (Vinegar et al. 2000). They used the PBPK model to simulate arterial blood concentrations for various exposure scenarios. A central objective of the modeling was to determine, at efficacious fire-suppressant concentrations, how long a person could safely be exposed, that is, for what duration the blood concentration would remain below the critical blood concentration as determined in dog cardiac-sensitization studies. For each agent, simulations were run at increasing exposure concentrations to determine the concentrations that would be considered safe for 5 min and at higher concentrations to determine the duration of safe exposure before the critical blood concentration was reached.

The results of the studies are summarized in Table 5-1. On the basis of measured dog arterial blood concentrations, results of model simulations for Halon 1301 indicated that at the LOAEL (7.5%), humans could be safely exposed for only 0.42 min (25.2 sec) before their blood concentrations reached the critical point measured in dogs. Similarly, for HFC-236fa, humans could be safely exposed at the LOAEL (15.0%) for 0.49 min (29.4 sec). For HFC-125, humans could be safely exposed at the LOAEL (10.0%) indefinitely, at up to 11.5% for 5 min, and at higher concentrations for shorter periods. For HFC-227ea, humans could be safely exposed at the LOAEL (10.5%) for 5 min and at higher concentrations for shorter periods. For CF_3I, humans could be safely exposed at the LOAEL (0.4%) for 0.85 min (51 sec), at 0.35% for 4.30 min, and up to 0.3% for 5 min or more; the NOAEL of CF_3I is 0.2% (Vinegar et al. 2000). Confidence in this PBPK model may increase if experimental data were available for human tissue partition coefficients of the halocarbons. However, Monte Carlo simulations included lognormal distributions of values for each tissue partition coefficient with upper and lower limits of two geometric standard deviations. Therefore, experimental determination of human tissue partition coefficients would probably not change the model predictions as determined with rodent tissue partition coefficients.

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TABLE 5-1 Simulated Egress Times for Exposure to Fire-Suppression Agents

Fire-Suppression Agent	Critical Blood Concentration,[a] mg/L	Cardiac-Sensitization Exposure LOAEL,[b] %	Simulated Egress Time at Exposure LOAEL,[c] min	Highest Simulated "Safe" 30-sec Exposure Concentration[c]
Halon 1301	25.7	7.5	0.42	7.0% (0.59 min)
CF_3I	12.9	0.40	0.85	0.40% (0.85 min)
HFC-125	47.8	10	>5	13.5% (0.50 min)
HFC-227ea	26.3	10.5	5	11.5% (0.60 min)
HFC-236fa	90.37	15	0.49	14.5% (0.55 min)

[a]Based on arterial blood concentrations in dogs exposed to the cardiac-sensitization LOAEL.
[b]Based on cardiac-sensitization studies in dogs.
[c]"Safe" human egress times, based on lowest measured 5-min arterial blood concentration in exposed dogs.
Source: Vinegar et al. 2000.

MODEL SIMULATIONS TO DETERMINE SAFE EXPOSURES

The Army reviewed the toxicity of CF_3I in 1999 (McCain and Macko 1999) and updated its review in 2002 (Chaney 2002) (see Appendix B). At the time of the 1999 review, CF_3I was accepted as a substitute for Halon 1301 in normally unoccupied areas under the EPA Significant New Alternatives Policy (SNAP). On the basis of SNAP, any employee that could possibly be in the area must be able to escape within 30 sec, and employers were required to ensure that no unprotected employees entered the area during agent discharge. The Army concluded in 1999 that a potential hazard for cardiac sensitization was associated with acute exposure to CF_3I at over 0.2% (2,000 ppm), the reported NOAEL based on cardiac sensitization in the dog model. It further concluded that the available data indicated that toxicity of CF_3I precludes its use in many Army systems without further evaluation. The Army noted in its 2002 update that EPA had rescinded use conditions imposed under the SNAP program that limited human exposure to halocarbon and inert-gas agents used in the fire-suppression and explosion-protection industry, including CF_3I. In April 2002, the EPA SNAP program recommended that use of CF_3I and several other halocarbons be in accordance with the safety guidelines in the latest edition of the National Fire Protection Association (NFPA) *2001 Standard on Clean Agent Fire-Extinguishing Systems* (NFPA 2000).

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According to NFPA *2001 Standard*, on the basis of PBPK modeling it would be considered safe for a human to be exposed to CF_3I above the NOAEL (0.2%) and up to 0.3% for as long as 5 min. At concentrations above 0.3%, "safe" exposure time decreases, but exposure is still allowed. The EPA-approved PBPK model simulates how long it will take the human arterial concentration to reach the critical point (as determined in the dog cardiac-sensitization test) during human inhalation of any particular concentration of a halocarbon. As long as the simulated human arterial concentration remains below the critical point, the exposure is considered safe. Inhaled halocarbon concentrations that produce human arterial concentrations equal to or greater than the critical concentration are considered unsafe because they represent inhaled concentrations that potentially yield arterial concentrations at which cardiac sensitization occur in dogs. The PBPK model predicts that at concentrations of up to 0.4% a human could be exposed for up to 30 sec without exceeding the critical arterial concentration. The Army concluded that because of the acute toxicity of CF_3I at concentrations over 0.2%, it could not endorse the NFPA *2001 Standard* recommendations for "safe" exposure to CF_3I in as much as the recommendations were determined by using PBPK modeling based on a LOAEL (0.4%) for cardiac sensitization in the dog that resulted in death of the animal.

In the NFPA standard (NFPA 2000), egress times have historically reflected knowledge of the NOAEL and LOAEL with recognition that cardiac sensitization to fluorocarbons will occur within 5 min. Establishing egress times by using PBPK modeling predictions based on the human blood:air partition coefficients in combination with Monte Carlo simulations to account for sensitive individuals in the population adds a level of quantification to the risk assessment for the safe use of fire-suppression agents. In the design of cardiac-sensitization studies, an airborne concentration is selected for administration on the basis of the test compound's structural relationship with other compounds, the known acute toxicity of the compound in question, and the physical and chemical properties of the material. Furthermore, because this protocol was established to rank compounds according to cardiac-sensitization potency, there was no attempt to study incremental increases in airborne concentrations. For example, CFC-12 is known to induce cardiac sensitization at 5.0% in five of 12 dogs, and this concentration has been recognized as the LOAEL of CFC-12. No responses were observed in 12 dogs at 2.5%, this is the NOAEL of CFC-12. On the basis of the incidence at 5.0%, one would reasonably estimate that a true LOAEL could be lower. Therefore, assigning a LOAEL to such a

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compound and using it as a point of departure in a risk assessment may not be appropriate. Using the NOAEL, although possibly conservative, offers a more reliable starting point.

In spite of that limitation, the use of PBPK models does have merit for quantifying acceptable exposure magnitudes relative to egress times. However, it is imperative that the input parameters in the model be known with confidence, for example, LOAEL and partition coefficients. Most important, the model should be accurately validated for each compound under investigation before it is used to recommend exposure-egress time relationships. During cardiac-sensitization testing, collection of blood to determine concentrations of the compound over time, particularly at shorter intervals, such as, less than 5 min, will yield the most robust data. Alternatively, if the model has been validated with data for similar compounds, that information and the blood:air partition coefficient may be used. In the absence of such data, the NOAEL would be the conservative determinant for establishing egress time for fire-suppression. A validated PBPK model does exist for determining arterial blood concentrations of CF_3I and other halon replacements during short-term exposure, and arterial concentrations of CF_3I in dogs during the first 5 min of exposure in the absence of an epinephrine challenge are also available. It is unlikely that blood concentrations of CF_3I would be substantially different in the presence of an exogenous epinephrine challenge of 8 μg/kg using the cardiac-sensitization protocol. Because the circulating blood concentrations of epinephrine are low under normal physiologic conditions, intravenous administration of epinephrine at 8 μg/kg would not markedly elevate the existing amounts of endogenous epinephrine. Use of arterial CF_3I concentrations measured in dogs in the absence of exogenous epinephrine is a reasonable approach to estimate the critical arterial blood concentration that would result in a cardiac event in epinephrine-challenged dogs. The dog cardiac-sensitization model was developed to rank potency of halocarbons, not as a risk-assessment tool; however, the resulting data are available and are useful in a PBPK model. PBPK models have been evaluated for many chemicals starting with publications by Andersen (1981). What is unique about this application is that the dose is calculated as a function of time over fairly short periods—1-5 min. This approach has also been studied extensively (Vinegar and Jepson 1996; Vinegar et al. 1998, 1999, 2000). Thus, the subcommittee finds that the use of a validated PBPK model is a reasonable scientifically based approach to determining safe egress times for exposure to CF_3I.

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ARMY CONCERNS

Although they were not part of the statement of work of the subcommittee, the Army posed several questions with regard to the cardiac-sensitization potential of CF_3I. The subcommittee addressed the first in Chapter 4. The others and the subcommittee's responses follow here.

> *Historically, the cardiac-sensitization dog studies were designed to identify cardiac-sensitization potential, not to quantify risks. Please comment on the use of these data in PBPK modeling to estimate blood concentrations, which pose a threat to human health.*

The subcommittee finds that although the dog cardiac-sensitization model was developed to rank the potency of halons and not as a risk assessment tool; nevertheless, these data are available and cannot be ignored and are appropriate for use in a PBPK model. PBPK models have been evaluated for many chemicals. What is unique about this PBPK application is that the dose is calculated as a function of time over fairly short time periods, that is, 1-5 min. This approach has also been studied extensively for a variety of halons and halon substitutes, including CF_3I.

> *According to the NFPA 2001 Standard, based on PBPK modeling, it would be considered safe for a human to be exposed to levels of CF_3I above the NOAEL and up to 0.3% (3,000 ppm) for as long as 5 minutes. At concentrations above 0.3% (3,000 ppm), the time for "safe" exposure decreases, but exposure is still allowed. [The Army] feels that, given the severe toxic effect (death) that was observed in the dog model at the LOAEL of 0.4% (4,000 ppm), and considering that in many Army applications there is still significant potential for human exposure in unoccupied areas, a conservative approach is justified in defining "safe" exposure levels for military applications of CF_3I.*
>
> *[The Army's] current recommendations are in agreement with previous EPA SNAP guidelines for CF_3I, but [the Army is] not comfortable adopting the NFPA 2001 recommendations, based on PBPK modeling data for this particular agent because of the severe toxic effect (death) that was observed in the dog model at the LOAEL of 0.4%. Based on the available information, is this position reasonable?*

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The subcommittee finds that the use of a validated, EPA-approved PBPK model is a reasonable scientifically based approach to determining safe egress times for exposure to CF_3I. The NOAEL and LOAEL for CF_3I as determined with the dog cardiac-sensitization model are 0.2% and 0.4%, respectively. According to the PBPK model, people could be safely exposed at 0.4% for about 51 sec before the critical blood CF_3I concentration for cardiac sensitization is reached. Furthermore, people could be exposed to concentrations as high as 0.3% for more than 5 min without reaching the critical blood concentration. The Army's decision to use an exposure limit of 0.2% (2,000 ppm) in normally unoccupied areas is a conservative policy decision to protect military personnel from health effects of CF_3I exposure in (undefined) Army applications.

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Human Exposure

Two documents from the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) (McCain and Macko 1999; Chaney 2002) provide basic information on potential scenarios of U.S. Army exposure to iodotrifluoromethane (CF_3I). However, few specific exposure data were available for or included in the two reviews. Two experimental studies, one assessing exposure to CF_3I in handheld extinguishers (Skaggs and Cecil 1995, as cited in Chaney 2002) and one assessing exposure from intentional release of CF_3I in Air Force F-15 aircraft engine nacelles (Vinegar et al. 1999), are discussed in detail. They also discuss anecdotal evidence from two people who inhaled CF_3I during sales demonstrations (Vinegar et al. 1999). Lack of realistic exposure data on CF_3I (or even a potential exposure surrogate, Halon 1301) and on potential decomposition products collected in situations and conditions of interest to the U.S. Army makes it difficult to evaluate the conclusions reached in the 2002 update (Chaney 2002).

This chapter discusses specific issues related to exposure that should be considered in the Army's review.

CF_3I AND ITS DECOMPOSITION PRODUCTS

Since the United States signed the 1987 Montreal Protocol on Substances That Deplete the Ozone Layer, which restricted the use of halon fire suppressants and banned production of many of them after 1993, U.S. military and firefighting agencies have been seeking so-called drop-in replacements for the widely used Halons 1211 and 1301 (CF_2BrI and CF_3Br, respectively). Of special interest as a replacement for Halon 1301 has been CF_3I, which is chemically similar to but replaces its bromine atom

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with an iodine atom. CF_3I has similar fire-suppression potential (Tapscott 1999; Chaney 2002) but much lower ozone-depletion potential—0.008-0.01 compared with 12 for Halon 1301 (Solomon et al. 1994; Connell et al. 1996; Bannister et al. 2003). The cited inerting[1] concentration of CF_3I is 6.5% (NFPA 2000). CF_3I breaks down in the presence of sunlight and degrades rapidly at temperatures above 100°C, producing hazardous by-products that include hydrogen fluoride (HF), hydrogen iodide (HI), and carbonyl fluoride (COF_2) (McCain and Macko 1999). Exposure to those decomposition products should be considered in the assessment of health effects of use of CF_3I. Orion Safety Industries (2000) has discussed one of the decomposition products, HF, and suggests that concentrations of HF produced by degradation of CF_3I are similar to those produced by degradation of Halon 1301.

USES OF CF_3I

The 1999 Army review of CF_3I concludes that it should not be used "in many Army systems without further evaluation" (McCain and Macko 1999). The 2002 update (Chaney 2002) concludes that CF_3I can be used in normally unoccupied areas only and that "any employee that could possibly be in the area must be able to escape within 30 sec, and the employer must ensure that no unprotected employees enter the area during agent discharge." Those conclusions are based on the U.S. Environmental Protection Agency (EPA) Significant New Alternatives Policy guidelines (60 Fed. Reg. 31092 [1995]).

A presentation on potential military uses of CF_3I was given to the present National Research Council subcommittee by J. Vitali, of Georgia Tech Research Institute (Vitali 2003). The presentation also discussed approved uses in countries other than the United States. Suggested potential uses include many Army systems that now use Halon 1301, such as

1. Fire suppression in helicopter engines.
2. Ground vehicle engine compartments, for example, armored personnel carriers.

Halon 1301 can be used in occupied and unoccupied spaces; however,

[1]An inerting gas usually refers to a gaseous mixture containing little or no oxygen and mainly consisting of non-reactive gases or gases having a high threshold before they react. Nitrogen, argon, and carbon dioxide are common examples.

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CF_3I can be used only in normally unoccupied spaces. Weapon systems and facilities in which Halon 1301 fire suppression might be required include

1. Unoccupied spaces, such as Air Force F-16 aircraft engines, auxiliary power units, dry bays, and fuel tanks.
2. Occupied spaces, such as personnel compartments.
3. Command and control facilities, generally considered to be occupied, including computer rooms, base operations, flight lines, hangars, depots, and testing facilities.

Halon 1301 is now used in rotary aircraft engines (Apache, Kiowa, Comanche, Chinook, Black Hawk, and Cobra) and in ground vehicles and personnel compartments (armored personnel carriers, interim armored vehicles, medium tactical vehicles, and Abrams and Bradley tanks).

In rotary-engine fire-suppression systems, CF_3I would not be expected to enter the personnel compartment. For inerting of Air Force F-16 fuel tanks, occupant exposure would not be expected to occur. The primary potential exposure would be of service and maintenance personnel.

CF_3I has been approved for use in unoccupied areas in two other countries. In June 1996, the German Hygiene Institut des Ruhrgebiets recommended CF_3I use in unoccupied areas of military vehicles and aerospace engine compartments. Australia has approved use of CF_3I as a total flooding agent in unoccupied spaces, such as aircraft-engine compartments and auxiliary power units, and in unoccupied engine and power compartments on a variety of military and nonmilitary vehicles, including its Sea Sprite helicopters. Commercial-aircraft test systems and a railroad diesel power car have been installed with CF_3I. Australia also has approved use of CF_3I as an explosion suppressor in grain silos, gluten-formulation facilities, and starch-processing plants. CF_3I may be used as a streaming agent in portable and wheeled fire-fighting units for high-risk fires, such as in aircraft engines and refueling fires (Vitali 2003). So far, with limited CF_3I use, no accidental discharges have occurred, according to Australian officials (O.E. Aberle, Australian Government Department of Defense, personal commun., December 4, 2003).

Thus, many uses of Halon 1301 represent potential uses of CF_3I. The Army review update (Chaney 2002) recommends use in normally unoccupied areas only. Most likely uses of CF_3I are as a fire suppressor or a streaming agent for handheld fire extinguishers, a flooding agent for tanks and military aircraft (for example, in F-15 aircraft-engine nacelles) and for electronic equipment, and an inerting agent in Air Force F-16 aircraft-engine wing fuel tanks (McCain and Macko 1999; Rupnik et al. 2002).

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No commercial uses of CF_3I, other than fire suppression have been identified in the published literature. However, there may be fire-suppression uses that are not covered in the Army update (Chaney 2002). To assess exposure fully, the subcommittee recommends that the Army review all potential use scenarios, not just those in normally unoccupied areas. USACHPPM should more clearly define specific situations in which CF_3I is likely to be used. Refining such exposure scenarios would allow more accurate assessment of potential exposure, particularly during maintenance and accidental releases. Measured levels of CF_3I can be dangerously high (up to 70,000 ppm) in cases of accidental discharge when it is used as a flooding agent for fires in Air Force F-15 engine nacelles (Vinegar et al. 1999). The subcommittee recommends that personnel potentially exposed in similar situations be properly trained and use appropriate personal protective equipment. Furthermore, the subcommittee recommends that release technologies be studied so that the potential for accidental release in normally unoccupied spaces, such as aircraft engine nacelles, can be minimized.

RECOMMENDED STANDARDS FOR CF_3I AND ITS DECOMPOSITION PRODUCTS

The Army update (Chaney 2002) discusses and reviews exposure standards for CF_3I but does not discuss exposure standards for potential decomposition products. For completeness, exposure standards for CF_3I and its decomposition products are discussed below. The subcommittee recommends that additional information on types of exposure (such as, acute, chronic, intermittent) and exposure concentrations for CF_3I and its decomposition products in various Army uses be collected and evaluated. Without such information, assessment of the safety of CF_3I as a Halon 1301 replacement in Army applications cannot be complete. When specific exposure data for CF_3I or its decomposition products are lacking, the subcommittee finds that it may be possible to use, with adjustments for physical and chemical properties, exposure data on Halon 1301.

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In 1994, EPA approved CF_3I as a substitute for Halon 1301 but only for normally unoccupied areas, owing primarily to concerns about cardiac sensitization. Specifically, approved systems using CF_3I were required to be designed up to the no-observed-adverse-effect level (NOAEL) (0.2%

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vol/vol) where egress could not be accomplished within 1 min, up to the lowest-observed-adverse-effect level (LOAEL) (0.4% vol/vol) where egress could occur within 30 sec to 1 min, and above the LOAEL where egress could occur in less than 30 sec (EPA 1994). In 1997, EPA approved CF_3I as a replacement for Halon 1211 in nonresidential applications only.

However, both those restrictions on the use of CF_3I were withdrawn by EPA in April 2002 because they were considered redundant with respect to the National Fire Protection Association (NFPA) *2001 Standard on Clean Agent Fire Extinguishing Systems* (NFPA 2000). The standard allows CF_3I to be used for systems in normally occupied areas up to the NOAEL (0.2% vol/vol) for any period, although unnecessary exposures to CF_3I and decomposition products "shall be avoided." For both normally occupied and unoccupied areas, exposures may exceed either the NOAEL (0.2% vol/vol) or the LOAEL (0.4% vol/vol) or both, according to durations based on physiologically based pharmacokinetic (PBPK) model studies (Vinegar et al. 2000). Specifically, up to 5 min of exposure is allowed for CF_3I concentrations of 0.2-0.3% vol/vol—that is, above the NOAEL—and decreasing times are allowed as concentrations increase above this level and may even exceed the LOAEL if escape can occur within 30 sec (see Table 6-1). The NFPA standards are designed for the protection of firefighting personnel in emergency-response and cleanup operations.

Hydrogen Fluoride

The American Conference of Government Industrial Hygienists (ACGIH) has set a ceiling limit for exposure to HF of 3 ppm, and the Occupational Safety and Health Administration (OSHA) permissible exposure limit is 3 ppm for an 8-h exposure time-weighted average (TWA) (Table Z-2) (29 CFR § 1910.1000). However, NFPA considers those standards "not relevant" for fire-extinguishing use, although they "may need to be considered" for cleanup operations (NFPA 2000). NFPA considers the recommendations of the American Industrial Hygiene Association Emergency Response Planning Guidelines to be more appropriate for firefighting situations: for 1-h exposures, mitigating steps such as respiratory protection should be taken above 20 ppm, and 50 ppm is the maximal nonlethal exposure for nearly everyone, except those who are "susceptible persons" (NFPA 2000); for 10-min exposures, the corresponding recommendations are 50 and 170 ppm, respectively. The NFPA document also notes that at about 100 ppm, escape-impairing effects may develop, and at

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TABLE 6-1 Time for Safe Human Exposure at Stated Concentrations of CF_3I

Concentration (% vol/vol)	Concentration (ppm)	Exposure Time (min)
0.2[a]	2,000	5.00
0.25	2,500	5.00
0.30	3,000	5.00
0.35	3,500	4.30
0.40[b]	4,000	0.85
0.45	4,500	0.49
0.5	5,000	0.35

[a]NOAEL.
[b]LOAEL.
Source: NFPA 2004. Reprinted with permission, copyright 2004, National Fire Protection Association, Quincy, MA. This material is not the complete and official position of the NFPA on the referenced subject, which is represented only by the standard in its entirety.

100-200 ppm, humans convert from nose breathing to mouth breathing, greatly increasing the possibilities of lower respiratory system damage and death (Dalby 1996). EPA has developed a 10-min acute exposure guideline level (AEGL-2) for HF of 95 ppm (NRC 2004).

Hydrogen Iodide

HI is colorless and, because of its great affinity for water, highly corrosive to skin, eyes, and mucous membranes. It has a relatively low OSHA ceiling limit of 0.1 ppm as iodine (29 CFR § 1910.1000). There is also an ACGIH emergency short-term exposure limit (STEL) of 0.1 ppm as a ceiling value for iodine, but none specifically for HI.

Carbonyl Fluoride

COF_2 is highly toxic and unstable, and it does not have an OSHA standard. The ACGIH standards are 2 ppm for the TLV and 5 ppm for the STEL (ACGIH 2003).

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EXPOSURE TO CF_3I AND ITS DECOMPOSITION PRODUCTS

Three potential exposure scenarios have been identified by the subcommittee:

- Exposures to CF_3I during manufacture, transfer and filling of tanks, and tank leakage in transfer and storage.
- Exposures to CF_3I and its decomposition products due to streaming with handheld fire extinguishers (2.5-13 lb fire extinguishers) or due to accidental discharge from firefighting equipment during training, maintenance, repair, or overhaul (Skaggs 1995, as cited in Chaney 2002).
- Exposures to CF_3I and its decomposition products due to accidental discharge of high-volume firefighting systems, such as those in airplane engine nacelles or tanks or of CF_3I storage cylinders, could result in exposures to greater than 70,000 ppm at head level (Vinegar et al. 1999).

Anecdotally, several instances of salespersons intentionally breathing in CF_3I gas have been reported (Vinegar et al. 1999). The third scenario is of greatest concern because it could result in exposures exceeding the NOAEL and LOAEL and be life threatening. Exposures resulting from the first two scenarios are also of concern but are less likely to be immediately dangerous to life and health.

Human-Exposure Reports

The Army reviews (McCain and Macko 1999; Chaney 2002) contain several reports related to human exposure to CF_3I or its decomposition products. They are reviewed below with comments by the subcommittee on other data sources and data gaps.

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There do not appear to be any human-exposure or health-effects studies in the published scientific literature related to low-level exposures, either chronic or acute, to CF_3I.

Several studies to examine the extent and effects of CF_3I exposures have been undertaken to assess its potential as a drop-in replacement for

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Halon 1301 or 1211. Most of the studies have been sponsored by the Department of Defense or EPA. One series of studies was undertaken in the early 1990s to determine exposures of firefighters during simulated streaming operations with handheld fire extinguishers (Skaggs 1995, as cited in Chaney 2002). Three room sizes were studied—from 900 to 5,100 cubic feet (ft^3)—and discharges varied from 2.5 to 13 lb of CF_3I. The 1-ft target was placed on or at various heights above the floor. In all cases, the firefighter stood 8 ft from the target. The peak concentrations of CF_3I varied from 1.0% to 3.0% and were all above the NOAEL (0.2%) and LOAEL (0.4%). More important, the average concentrations over the first 30 min varied from 1,040 ppm (0.1%), which is below the NOAEL, to 4,678 ppm (0.5%), which is above the LOAEL. Both the NOAEL and the LOAEL are related to cardiac sensitization, so most of those exposure scenarios represent situations immediately dangerous to life and health and would require self-contained breathing apparatus respiratory protection for the firefighters at all times.

To assess the potentially very high exposure of personnel who might be affected by accidental discharges of CF_3I from an aircraft engine nacelle during ground maintenance and repair operations, a series of CF_3I discharges were carried out on a grounded F-15 jet. The CF_3I exposures were measured with three test instruments whose sensitivities covered a broad range of possible CF_3I exposure. Sensors were at various potential ground-personnel work locations. The lowest peak CF_3I concentration (0.9%) occurred at head level behind the left wing with the nacelle doors open, the highest (7.0%) at head level under the nacelle. In two of the six instances illustrated, the concentrations peaked and returned to low levels within 5-10 sec, but in the other four, the concentrations remained above the NOAEL and LOAEL for 30-275 sec. The average concentrations of CF_3I were not quoted (Vinegar et al. 1999).

However, the authors attempted to assess the arterial blood concentrations of CF_3I with a PBPK model to estimate the exposure that affected the heart on the basis of the observed CF_3I measurements. The concentrations were compared with the estimated blood concentrations 5 min after steady-state ambient exposure at the LOAEL. Some of the strengths and limitations of that approach were discussed in Chapter 5. According to this relatively sophisticated model, the estimated blood concentration due to ambient air exposure near the head under the open nacelle was about twice the LOAEL-based concentration for cardiac sensitization. None of the other scenarios exceeded the LOAEL-based concentration of 19 mg/L, but the estimated blood concentrations in three of the six scenarios were about

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16 mg/L—relatively close to the danger value for a model in which a number of key parameter values had to be extrapolated from values in rats (Vinegar et al. 1999, 2000).

Reports have circulated for many years about two CF_3I salesmen who are alleged to have inhaled CF_3I from a balloon 15-17 times, as part of their sales presentations, without reported ill effects. Vinegar et al. (1999) estimated that the average volume inhaled was 1.25 L of CF_3I during each presentation, resulting in a PBPK-based estimate of a peak blood concentration of about 2,000 mg/L, more than 100 times the LOAEL-based level of 19 mg/L. However, no clinical measurements were made of the two men after their demonstrations, so their survival attests to the absence of fatal arrhythmias, not necessarily to nonfatal sensitization incidents—the two men were 35 and 38 years old, ages at which many people are in peak health. Rupnik et al. (2002) has criticized the estimates for ignoring the possibility of tolerance after repeated trials. Those issues suggest that reliance on the data are of little use in setting exposure limits.

A fundamental difficulty in using CF_3I as a Halon 1301 replacement is that its inerting concentration to extinguish fires is 6.5%, whereas its LOAEL is 0.4%. Thus, its inerting concentration is 16 times as great as its LOAEL, and its use as a flooding agent for fire suppression is inappropriate except for unoccupied areas and poses potentially grave risks to firefighters should the concentration of CF_3I be greater than the LOAEL, should exposure exceed 30 sec, or should personal protective equipment not be worn. The subcommittee recommends that uses of CF_3I that may involve acute exposures should be restricted to normally unoccupied areas.

Hydrogen Fluoride, Hydrogen Iodide, and Carbonyl Fluoride

None of the exposure studies examined contained any reports of experimental measurements of any of these three chemicals, nor were the estimates of the possible exposure to them expected from various CF_3I discharges. Although it is understandable that studies related to cardiac sensitization, which can be fatal, have attracted the greatest initial research interest, HF, for example, is highly toxic and can lead to death, as NFPA *2001 Standard* notes (NFPA 2000). Before the safety of CF_3I as a Halon 1301 replacement can be properly assessed, the subcommittee suggests that studies of possible exposure to its potential degradation products—HF, HI, and COF_2—be carried out or that reliable estimates of exposures to these chemicals be made to ensure that their presence is not of health consequence.

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Human-Exposure Limits

The NOAEL and LOAEL of CF_3I as determined with the dog cardiac-sensitization model are 0.2% and 0.4%, respectively. On the basis of the PBPK model, people could be safely exposed at 0.4% for about 51 sec before the critical CF_3I blood concentration for cardiac sensitization is reached. Furthermore, people could be exposed at up to 0.3% for more than 5 min without reaching the critical blood concentration. In addition, the subcommittee recommends that personnel potentially subjected to short-term high exposures (maintenance and service personnel) be trained and use personal protective equipment deemed appropriate by industrial hygienists and described in NFPA *2001 Standard* (NFPA 2000). An exposure limit of 2,000 ppm may not be appropriate for other scenarios, however, including those that may involve chronic, low-level exposure or repeated exposure at moderate or high concentrations. For uses and exposures other than those specific to the Army (McCain and Macko 1999; Chaney 2002), the subcommittee recommends that separate exposure assessments be made. It also suggests that the Army monitor for international exposure and toxicity data. Exposure data from Australia and Germany may be available in the future, as CF_3I is approved for some uses in those countries.

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Appendix A

Biographical Information on Subcommittee on Iodotrifluoromethane

SAMUEL KACEW (*Chair*) is professor of pharmacology at the University of Ottawa and scientist at the Institute of Population Health Risk Assessment at the University of Ottawa, from which he received his PhD in pharmacology. Dr. Kacew's research interests are in general toxicology, and he has expertise in pediatric toxicology, breast-milk contaminants, and children's health issues. He has worked in kidney, liver, and lung toxicity with a variety of chemicals. He is a fellow of the Academy of Toxicological Sciences and is the editor-in-chief of the *Journal of Toxicology and Environmental Health*. Dr. Kacew served as a member of the National Research Council Committee on Toxicology and on several of its subcommittees, including the Subcommittee on Risk Assessment of Flame-Retardant Chemicals and the Subcommittee on Jet Propulsion Fuel-8.

H. TIM BORGES is research staff member in the Toxicology and Risk Analysis Section at Oak Ridge National Laboratory. Dr. Borges's research interests include the study of acute and chronic inhalation and oral toxicity, metabolism of industrial chemicals and pesticides, and the link between cancer and immunosuppression. He is a diplomate of the American Board of Toxicology and certified as a medical technologist by the American Society of Clinical Pathologists. Dr. Borges received his PhD in Toxicology from the University of Kentucky.

KELLY DIX is a scientist in the Toxicology Division of the Lovelace Respiratory Research Institute. Dr. Dix's research focuses on the metabolism, pharmacokinetics, and toxicity of pharmaceuticals, natural products, and industrial and environmental chemicals. She is a diplomate of the

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American Board of Toxicology. She received her PhD in toxicology from North Carolina State University.

MARCIE FRANCIS is a senior research scientist for Battelle and focuses on environmental and occupational exposure and risk for the Statistics and Data Analysis Division. She was recently the senior director of science policy with the Chlorine Chemistry Council. Dr. Francis has expertise in occupational and environmental exposure assessment, epidemiology, biostatistics, and risk assessment. She holds a PhD in environmental health sciences from the University of California, Berkeley, and she is a certified industrial hygienist.

SIDNEY GREEN, Jr., is graduate professor of pharmacology at Howard University College of Medicine. Dr. Green's research interests include tissue culture, alternatives to using animals in toxicology, and mutagenic assay systems for genetic toxicology. He has served on the editorial boards of several scientific journals, and he is a fellow of the Academy of Toxicological Sciences. Dr. Green is a member of the National Research Council Committee on Toxicology and has served on several other National Research Council panels, including the Subcommittee on Acute Exposure Guideline Levels and the Subcommittee on the Toxicity of Diisopropyl Methylphosphonate. He received his PhD in biomedical pharmacology from Howard University.

ROBERT HAMLIN is professor in the Department of Veterinary Biosciences at Ohio State University. Dr. Hamlin's research focuses on pulmonary mechanics, cardiac function, comparative electrocardiology, and models of heart failure and responses to vasoactive chemicals. He is a diplomate of the American College of Veterinary Internal Medicine. Dr. Hamlin received his PhD and DVM from Ohio State University.

DAVID KOTELCHUCK is associate professor in the Urban Public Health Program and director of the Center for Occupational and Environmental Health at the Hunter College School of Health Sciences. He is also deputy director of the New York/New Jersey NIOSH Education and Research Center. Dr. Kotelchuck works with community-based organizations, schools, libraries, labor unions, private employers, and municipal and state agencies to improve community and workplace health. He is a certified industrial hygienist and received his PhD in physics from Cornell University and his MPH from Harvard University.

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GEORGE RUSCH is the director of the Department of Toxicology and Risk Assessment for Honeywell Corporation (AlliedSignal Inc.). He is also adjunct professor in the Department of Pharmacology and Toxicology at Rutgers University and chair of the National Advisory Committee for Acute Exposure Guideline Development. Dr. Rusch's research interests in inhalation toxicology include the chemical causes of lung cancer, the toxicity of fluorinated substitutes for chlorofluorocarbons, cardiac sensitization, and risk assessment. He previously served on the National Research Council Committee on Toxicology. Dr. Rusch is certified in general toxicology by the American Board of Toxicology and is a fellow of the Academy of Toxicological Sciences. He received his PhD in organic chemistry from Adelphi University.

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Appendix B

Toxicity Review for Iodotrifluoromethane (CF_3I): 2002 Update

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EXECUTIVE SUMMARY

PURPOSE: In 1987, 23 countries, including the United States, signed an agreement that would reduce the production of ozone depleting substances (ODS). Amendments to this agreement, called the "Montreal Protocol on Substances that Deplete the Ozone Layer," placed controls on the production and consumption of ozone depleting materials, including the fire suppressants Halon 1211 and Halon 1301. These compounds are effective and have acceptable risk when used correctly, but have been identified as ozone depleting substances. The restrictions set forth in the Montreal Protocol forced a search for suitable replacements for Halon 1211 and Halon 1301, which are effective, safe, and environmentally acceptable. A number of candidate replacement agents for Halon 1301 that have been tested for efficacy and safety are currently in use. Iodotrifluoromethane (CF_3I) (a.k.a. iodotrifluoromethane, trifluoroiodomethane, trifluoromethyl iodide) is another candidate replacement agent currently being considered.

The USACHPPM has been supporting the search for a non-ozone depleting fire extinguishing agent to replace Halon 1301. A request for a Toxicology Profile for CF_3I was submitted by the Army Acquisition

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Pollution Prevention Support Office of the Army Materiel Command in 1993. Since no toxicity data for CF_3I were available at that time, a battery of tests were recommended to characterize toxicity. In 1999, CHPPM published a Toxicity Review of CF_3I that presented a critical discussion of much of the new data. In this 2002 update, the current status of CF_3I is considered, particularly in regard to defining exposure levels that would be considered acceptable for military use of the agent.

CONCLUSIONS: Overall, the toxicity of CF_3I is relatively low. Available data indicate a potential health hazard exists in the area of cardiac sensitization following acute inhalation exposure to concentrations of CF_3I greater than 0.2%. The effect of CF_3I on mutagenicity and reproductive parameters is equivocal and may warrant further investigation. Human exposure to CF_3I could occur during the manufacturing, transportation, storage, or packaging processes. Accidental releases are also potential sources of exposure in the military setting.

USACHPPM will not endorse the NFPA Standard 2001 (2000) recommendations for "safe" exposure limits to CF_3I because these levels were determined using PBPK modeling data based on a LOAEL (0.4%) for cardiac sensitization in the dog that resulted in death of the animal.

RECOMMENDATIONS: Any proposed use of CF_3I in army systems at design concentrations greater than 0.2% must conform to EPA Significant New Alternatives Policy (SNAP) guidelines which accept CF_3I as a substitute for Halon 1301 in normally unoccupied areas only (Federal Register, 1995). Based on this ruling, any employee that could possibly be in the area must be able to escape within 30 seconds, and the employer must ensure that no unprotected employees enter the area during agent discharge.

INTRODUCTION

General

In 1987, 23 countries, including the United States, signed an agreement that would reduce the production of ozone depleting substances (ODS). Amendments to this agreement, called the "Montreal Protocol on Substances that Deplete the Ozone Layer", placed controls on the production and consumption of ozone depleting materials, including the fire suppressants Halon 1211 and Halon 1301. These compounds are effective and have acceptable risk when used correctly, but have been identified as

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ozone depleting substances. The restrictions set forth in the Montreal Protocol forced a search for suitable replacements for Halon 1211 and Halon 1301, which are effective, safe, and environmentally acceptable. A number of candidate replacement agents for Halon 1301 that have been tested for efficacy and safety are currently in use. Iodotrifluoromethane (CF_3I) (a.k.a. iodotrifluoromethane, trifluoroiodomethane, trifluoromethyl iodide) is another candidate replacement agent currently being considered.

The USACHPPM has been supporting the search for a non-ozone depleting fire extinguishing agent to replace Halon 1301. A request for a Toxicology Profile for CF_3I was submitted by the Army Acquisition Pollution Prevention Support Office of the Army Materiel Command in 1993. Since no toxicity data for CF_3I were available at that time, a battery of tests were recommended to characterize toxicity. In 1999, CHPPM published a Toxicity Review of CF_3I that presented a critical discussion of much of the new data (McCain and Macko, 1999). In this 2002 update, the current status of CF_3I is considered, particularly in regard to defining exposure levels that would be considered acceptable for military use of the agent.

Physical Properties of CF_3I

The physical properties of CF_3I are summarized in Table B-1. CF_3I is a gas at room temperature with a relatively high boiling point of −2.5°C, a melting point of −110°C, and a vapor pressure of 78.4 psia. CF_3I also has a C-I dissociation energy of 54 kcal/mol, indicative of a compound that can readily disassociate (Moore et al, 1994; NFPA, 1996). Exposure to CF_3I in the workplace is most likely to occur through inhalation.

There is evidence that CF_3I photolyzes in the presence of sunlight and common fluorescent lights, resulting in an atmospheric half-life of 1.15 days. Potential degradation products following release in a well-lighted area would include low concentrations of highly toxic carbonyl fluoride (COF_2), and hydrogen fluoride (HF) (Nyden, 1995). These compounds would be produced to a greater degree during fire suppression, but CF_3I would be expected to produce less HF than other candidate Halon replacement agents like HFC-125, HFC-227ea, or FC-218 (Gann, 1995).

Long-term stability testing indicates that CF_3I would degrade more rapidly in the presence of moisture, copper, and at temperatures above 100°C (Harris, 1995). Yamamoto et al. (1997) indicated that fluorinated compounds containing iodine or bromine atoms decomposed easier than perfluoridated compounds. It is unknown how product degradation will

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TABLE B-1 Physical Properties of CF_3I

Physical or Chemical Property	Value or Property
Chemical Abstracts Service No. (CAS)	2314-97-8
Molecular Weight	195.91
Physical State @ 20°C	Gas
Melting Point	-110°C (-166°F)
Boiling Point @ 1 atm pressure	-22.5°C (-8.5°F)
Liquid Density @ -32.5°C	2.36 g/ml
Liquid Density @ 25°C	2.096 g/ml
Odor Threshold	Odorless
Solubility in Water	Slightly
Vapor Pressure	78.4 psia @ 25°C
Pressure Temperature Curve	log P (psia)= 5.7411-1146.82/T(K)
Critical Pressure	586 psia (estimated)
Critical Temperature	122°C (estimated)
Critical Volume	225 cm^3/mol (estimated)
Heat of Formation	-141 kcal/mol
Heat of Vaporization	5.26 kcal/mol
Electron Affinity	150 ± 20 kJ/mol
Refractive Index (liquid) @ -42°C	1.379
Dipole Moment	1.68 debye
Vapor Heat Capacity	16.9 cal/mol-K
C-I Bond Disassociation Energy	54 kcal/mol

Source: Adapted from Moore et al. 1994.

affect toxicity. No attempt to identify or evaluate the toxicity of degradation products has been performed.

Regulatory Information

The proposed design concentration for CF_3I use in most systems exceeds the lowest observed adverse effect (LOAEL) for cardiac sensitization of 0.4%. The EPA published a final rule under its Significant New Alternatives Policy (SNAP) program to accept CF_3I as a substitute for Halon 1301 in normally unoccupied areas only (Federal Register, 1995). Based on this ruling, any employee that could possibly be in the area must be able to escape within 30 seconds, and the employer must ensure that no unprotected employees enter the area during agent discharge.

The EPA also published a final rule accepting CF_3I as a substitute for

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Halon 1211 in nonresidential applications only (Federal Register, 1997). Because cardiac sensitization has been demonstrated at relatively low concentrations of CF_3I, the EPA prohibits use of this agent in consumer residential applications where the possibility exists of incorrect use by untrained individuals.

As of April 1, 2002, EPA removed restrictions previously imposed on the use of certain halon alternatives under the SNAP program. EPA rescinded use conditions imposed under SNAP that limit human exposure to halocarbon and inert gas agents used in the fire suppression and explosion protection industry. EPA considers these use conditions to be redundant with the safety standards outlined in the NFPA 2001 Standard. Currently, the EPA SNAP program recommends that use of CF_3I and several other halocarbon agents should be in accordance with the safety guidelines in the latest edition of NFPA Standard 2001 (Federal Register, 2002).

The NFPA 2001 Standard on Clean Agent Fire Extinguishing Systems (1996; 2000) is a guidance document prepared by the Technical Committee on Halon Alternative Protection Options to address the need for information regarding the design, installation, maintenance, and operation of systems using clean agent fire extinguishants. In the most recent edition (2000), NFPA endorses the use of physiologically-based pharmacokinetic (PBPK) modeling procedures to recommend "safe" exposure limits.

According to the NFPA 2001 Standard (2000), Section 1-6.1.2.1 (c) states, "In spaces that are not normally occupied and protected by a halocarbon system designed to concentrations above the LOAEL..., and where personnel could possibly be exposed, means shall be provided to limit exposure times using Tables 1-6.1.2.1(b) through 1-6.1.2.1(e)." The relevant table for CF_3I (see Table B-2 adapted from Table 1-6.1.2.1(e)) describes human exposure times that would be considered "safe" for exposure to increasing concentrations of CF_3I, based on estimates derived from PBPK modeling and LOAEL values established during cardiac sensitization testing in a dog model:

Based on the NFPA 2001 (2000) guidelines, it would be considered safe for a human to be exposed to levels of CF_3I above the NOAEL (0.2%) and up to 0.3% for as long as 5 minutes. At concentrations greater than 0.3%, the time for "safe" exposure decreases, but exposure is still allowed.

The Army does not have a separate policy regarding ozone-depleting substances. Health and safety issues are addressed in Army Regulation 40-5 (AR 40-5: Preventive Medicine) (1990). One of the Preventive Medicine functional areas of AR 40-5 is the Health Hazard Assessment Program (AR 40-10: Health Hazard Assessment Program in Support of the Army Materiel

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TABLE B-2 Time for Safe Human Exposure at Stated Concentrations for FIC-1311 [CF_3I]

FIC-1311 [CF_3I] Concentration		
% v/v	ppm	Human Exposure Time (minutes)
0.2	2000	5.00
0.25	2500	5.00
0.3	3000	5.00
0.35	3500	4.30
0.4	4000	0.85
0.45	4500	0.49
0.5	5000	0.35

Notes: (1) Data derived from the EPA-approved and peer-reviewed PBPK model or its equivalent; (2) Based on LOAEL of 0.4 percent in dogs.
Source: NFPA 2004. Reprinted with permission, copyright 2004, National Fire Protection Association, Quincy, MA. This material is not the complete and official position of the NFPA on the referenced subject, which is represented only by the standard in its entirety.

Acquisition Process) (1991). The primary objective of this regulation is to identify and eliminate or control health hazards associated with the life cycle management of weapons, equipment, clothing, training devices, and materiel systems. One objective of this program is to preserve and protect the health of the individual soldier and other personnel. Another objective is to reduce the health hazards due to potential environmental contamination associated with the use of Army systems. This objective is protective of the stratospheric ozone and complies with all federal regulations and guidelines. The Army is in the process of revising both AR 40-5 and AR 40-10.

The USACHPPM considers all available standards and guidelines when evaluating agents proposed for use in an Army system. In the interest of its primary responsibility, to protect US Army personnel from exposure to potentially hazardous substances, USACHPPM has traditionally adopted a conservative approach when evaluating and approving such agents.

Efficacy

The minimum design concentration for a gaseous agent is determined by the ISO Cup Burner Test. The concentration of Halon 1301 necessary to extinguish a n-heptane fire by this test method is 3.3 vol%. The "best value" for CF_3I as determined by the National Fire Protection Association

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(NFPA) Cup Burner Data Task Group is 3.2 vol% (Tapscott, 1999). Therefore, for n-heptane, the design concentration for CF_3I will be slightly lower than that for Halon 1301 regardless of the applied safety factor. The NFPA 2001 Standard (1996) requires a minimum 20% safety factor above the cup burner values with a minimum design concentration of 5.0% for Halon 1301. This safety margin was chosen as a requirement for extinguishment of Class A fires. According to Meyer (1997), the extinguishing concentration of CF_3I is almost half of the concentration needed by any other gaseous agent under consideration. In a turbulent spray burner test, CF_3I required the lowest mass fraction at extinction of any compound tested (Hamins, 1997).

HEALTH EFFECTS

General

The U.S. Army Environmental Hygiene Agency prepared a toxicity profile for CF_3I in 1993 (Haight and Macko, 1993). The profile indicated that no toxicity data were available for CF_3I and recommended that a number of toxicity tests be conducted in order to fully evaluate its safety. These suggestions included a skin and eye irritation test, acute and 14-day inhalation studies, genotoxicity testing, cardiac sensitization testing, and a full evaluation of combustion, pyrolysis and decomposition products. Comprehensive tests, such as reproductive and developmental toxicity and subchronic inhalation, were also suggested if projected use scenarios indicated a need. Many of these tests have since been conducted and data were incorporated into the comprehensive review of CF_3I released in 1999 by McCain and Macko. A summary of the toxicity studies performed for CF_3I is provided in Table B-3, and a brief overview of the results is provided below.

Toxicity Testing

1. 15-Minute Acute Exposure. Several acute inhalation studies have been conducted using CF_3I. Ledbetter (1993) exposed 5 male and 5 female Sprague-Dawley rats to CF_3I vapor in a nose-only inhalation chamber for 15 minutes. The intended target concentration was 60,000 ppm (6.0%). Due to an error in the wavelength setting for the infrared monitoring system, the actual measured concentration during exposure was 127,289 ± 5,574, nearly

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TABLE B-3 Summary of Toxicology Studies Performed on CF_3I

Date	Investigator	Type of Study	Test System	Exposure Concentrations
1993	Ledbetter	Acute Inhalation: 15-min, nose-only	Rat (Sprague-Dawley)	12.7%
1994	Ledbetter	Acute Inhalation: 4-hr, whole-body 15-min, nose-only	Rat (Sprague-Dawley)	4-hr: 10, 12.8, 20, 32% 15-min: 24, 28.8%
1994	Kinkead et al.*	Acute Inhalation: 4-hr, nose-only	Rat (Fischer-344)	0.0%, 0.5%, 1.0%
1995 a,b,c	Mitchell**	Genetic Screening: Ames Assay	*Salmonella typhimurium*	Ames: 0.1060, 0.2775, 1.0586, 2.3230, 8.5908%
		In Vivo Mouse Micronucleus	Mouse (Swiss Webster)	Mouse Micronucleus: 2.5, 5.0, 7.5%
		Mouse Lymphoma	L5178Y/$tk^{+/-}$ cells	Mouse Lymphoma: 8.0, 17.7, 30.6, 42.6, 45.4, 49.7, 51.8%
1995	Kenny et al.	Acute Inhalation: Cardiac Sensitization	Dog	0.1, 0.2, 0.4, 1.0%
1995	Kinkead et al.*	Inhalation: Repeated exposure, 14-day range-finder	Rat (Fischer-344)	0.0, 3.0, 6.0, 12.0% 2 hr/day, 5 days/wk
1996	Kinkead et al.*	Subchronic Inhalation: 13 wk, nose-only	Rat (Fischer-344)	0.0, 2.0, 4.0, 8.0% 2 hr/day, 5 days/wk
1998	Dodd et al.	Reproductive: 14-wk, whole-body	Rat (Sprague-Dawley)	0.0, 0.2, 0.7, 2.0%

*Also reported by Dodd et al., 1997a.
**Also reported by Dodd et al., 1997b.

twice the targeted dose. No deaths were reported during the study. Immediately following exposure, severe salivation was noted for all exposed rats, and 2 males exhibited audible respiration (rales). All clinical signs resolved within 1 hour after exposure was discontinued. No other clinical signs or changes in body weight were reported during the 14-day post-exposure observation period. No gross abnormalities were reported at necropsy.

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In a separate study, 5 male and 5 female rats were exposed to CF_3I vapor in a nose-only inhalation chamber at concentrations of 28.8% or 24% for 15 minutes (Ledbetter, 1994). Following exposure to 28.8%, 5 females and 2 males died. Necropsy findings indicated red lungs in 2 males and 1 female. One male rat died following exposure to 24%. Two male rats had hemorrhagic foci in the lungs and one had red lungs. All other organs were normal. The median lethal concentration (LC_{50}) following 15-minute exposure to CF_3I was determined using only two exposure levels and was estimated to be 27.4%.

2. 4-Hour Acute Exposure. A 4-hour whole-body exposure study was conducted using CF_3I at concentrations of 32%, 20%, 12.8%, and 10% (Ledbetter, 1994). Five males and five females were exposed at each concentration. All rats exposed to 32% became unconscious and died within 20 minutes of exposure. Necropsy findings indicated that the lungs in this exposure group were dark red and puffy. It was determined that the gas for the 32% group was contaminated with hydrogen fluoride (HF). A second group of animals was exposed at 20% CF_3I with a KOH scrubber system in place to remove HF prior to entry of test material into the chamber. Again, all exposed rats became unconscious and died after approximately 20 minutes of exposure. Upon necropsy, lungs from this group were puffy but much less red. No HF was detected in the test atmosphere. Remaining exposures were conducted using new CF_3I test material containing no detectable HF. No deaths were observed in the 12.8% or 10% exposure groups, although all rats became unconscious to semi-unconscious after approximately 30 minutes of exposure. All animals regained consciousness immediately (within 1-3 minutes) after exposure was discontinued. No other clinical signs were noted and rats exhibited normal weight gain during the 14-day observation period. Upon necropsy, the lungs of 2 male rats exposed to12.8% CF_3I were red. All other organs appeared normal.

In another study, male Fisher 344 rats (30/group) were exposed to CF_3I in a nose-only chamber for 4 hours at 0.0%, 0.5%, or 1.0% (Kinkead et al., 1994). No deaths occurred during exposure. Ten animals per group were sacrificed either immediately, at 3 days, or at 14 days after exposure. Body weights, clinical pathology, including thyroxine and thyroxine binding globulin assays, and histopathology evaluations were performed. No biologically significant findings were noted during the 4-hour exposure or during the 14-day post-exposure observation period.

3. 14-Day Repeated Exposure. A two-week range-finding study was performed using CF_3I at concentrations of 0%, 3%, 6%, and 12% (Kinkead et al., 1995; Dodd et al., 1997a). Five male Fischer 344 rats were exposed (nose-only) at each concentration for 2 hours per day, five days per week

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(10 exposures). No deaths were reported. Lethargy and incoordination were observed in the 6% and 12% groups at the end of each daily exposure. A significant decrease in mean body weight gain was noted for rats in the 6% and 12% groups. There was also a 20% decrease in white blood cells of animals exposed in the two highest dosage groups (6% and 12%) and an 8% increase in serum albumin of animals exposed to 12% CF_3I. Elevated levels of serum thyroglobulin and reverse triiodothyronine (rT_3) were observed in all treatment groups. No changes in organ weights or gross lesions were observed. No histopathologic lesions were noted in the thyroid or parathyroid glands following examination of CF_3I exposed rats.

4. 13-Week Subchronic Exposure. A subchronic inhalation (90-day) study of CF_3I was performed in Fisher 344 rats (Kinkead et al., 1996; Dodd et al., 1997a). Fifteen males and females per group were exposed to 0%, 2%, 4%, or 8% CF_3I vapor for 2 hours/day, 5 days/week for 13 weeks in nose-only chambers. Clinical effects, body weights, hematology, bone marrow toxicity/mutagenicity (micronuclei induction), serum chemistry, organ weights, gross pathology and histopathology were evaluated. To investigate potential effects of CF_3I on thyroid function, morphometric image analysis and immunoradiometric assays for serum thyroid hormones were also performed. Five males and females per group were sacrificed after 30 days of exposure. Remaining animals were necropsied after 90 days. Six male rats in the 2% group died during the 9th exposure day, and one on the 13th exposure day. One male from the 8% group was also found dead following the 10th exposure. Remaining males from all study groups were placed into larger nose-only exposure tubes for the remainder of the study. All deaths were attributed to accidental death due to the restraint system. It is unknown if other measured parameters were affected by heat stress due to restraint. Mean body weights were significantly decreased for males and females in the 8% treatment group, and for males only in the 4% group. Hematological analysis showed a slight decrease in red blood cell count in male rats, and decreased total lymphocytes in both males and females in CF_3I treated groups. A statistically significant, dose-dependent increase was noted in micronucleated bone marrow polychromatic erythrocytes (PCE) in all rats exposed to CF_3I as well as a reduction in the PCE/NCE (normochromatic erythrocytes) ratio. Exposure to 8% CF_3I resulted in significant reductions in serum levels of calcium, alanine aminotransaminase (ALT), triglycerides (males only), and triiodothyronine (T_3), and increased levels of thyroglobulin, rT_3, thyroxine (T_4) and thyroid stimulating hormone (TSH). Similar changes in thyroglobulin, T_3, rT_3, T_4 and TSH were also found in males and females in the 4% and 2% groups. Organ to body weight ratios were significantly increased in the 8%

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treatment group for brain, liver and thyroid, and significantly decreased for thymus and testes. The decrease in relative weight for thymus and increase for thyroid were also found in the 4% and 2% treatment groups. Biologically significant changes in histopathology included rhinitis, which was noted in all rats exposed to CF_3I concentrations of 4% and 8% after 30 days, but not after 90 days of exposure. A mild increase in thyroid follicular colloid content was observed in all treatment groups. Testicular atrophy with loss of spermatogonia and spermatids, including aspermia, of male rats was observed after 30 days of exposure to 4% and 8% CF_3I. These lesions were also present but less severe after 90 days of exposure. The finding of testicular degeneration was considered equivocal due to the potential heat stress associated with the method of restraint.

5. Cardiac Sensitization Testing. Cardiac sensitization studies for CF_3I (Kenny et al., 1995) were performed using experimental procedures developed by Reinhardt et al. (1971, 1973). Beagle dogs were initially challenged by injecting adrenaline (epinephrine, 0.1 mg/kg/sec) to establish the response of each individual dog to adrenaline alone. The appearance of multifocal ventricular ectopic activity (MVEA), or ventricular fibrillation following exposure indicated a positive response. Dogs were then exposed to CF_3I for 5 minutes and challenged again with adrenaline. For this study, selected CF_3I concentrations were 0.1%, 0.2%, 0.4% and 1.0%. A single dog exposed to CF_3I at a concentration of 1.0% displayed a severe positive response (fatal ventricular fibrillation) and died. A second dog also died following exposure to 0.4% CF_3I. No other animals were tested at these concentrations. Dogs exposed to CF_3I concentrations of 0.1% and 0.2% displayed no dysrhythmia following epinephrine challenge. The lowest observed adverse effect level (LOAEL) for this CF_3I was 0.4% and the no observed adverse effect level (NOAEL) was 0.2%.

6. Genotoxicity Testing. Genetic toxicity testing completed for CF_3I incudes the *Salmonella typhimurium* histidine reversion assay (Ames Assay), the *in vivo* mouse bone marrow erythrocyte micronucleus test, and the mouse lymphoma forward mutation assay using L5178Y cells (Mitchell, 1995a; b; c; Dodd et al., 1997b).

The Ames assay used five tester strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, and TA100) at 5 dilutions of CF_3I. Desired concentrations of CF_3I were determined following a range finding study. Actual concentrations of CF_3I achieved for exposures were 1060, 2775, 10586, 23230 and 85908 ppm (0.11%, 0.28%, 1.1%, 2.3% and 8.6%). Assays were conducted using three plates per dose level, in the presence and absence of S-9 metabolic activation. Tester strain TA1538 was not affected by CF_3I. Strains TA1537 and TA98 displayed a weak positive

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response both with and without S-9 activation. Strong positive responses were displayed in strains TA100 and TA1535 with and without activation. The results indicate that CF_3I is mutagenic with and without activation, inducing frame-shift and base-pair mutations in *Salmonella typhimurium*.

For the *in vivo* mouse bone marrow micronucleus assay, Swiss Webster mice were exposed for 6 hours/day for 3 consecutive days to 2.5%, 5% or 7.5% concentrations of CF_3I. All animals survived and appeared normal during the study. Some treatment-related weight loss was observed in both male and female mice. Positive results were assessed according to criteria set forth by MacGregor, et al. (1988). The ratios of polychromatic erythrocytes (PCE) / 1000 erythrocytes of female mice were significantly decreased with increasing concentrations of CF_3I. This effect was also observed in male mice although one outlier prevented statistical significance. The ratio of micronucleated erythrocytes (MN)/1000 PCEs was significantly elevated in both genders for the 5.0% and 7.5% exposure groups. The results indicate that CF_3I can cause structural chromosomal aberrations *in vivo*. These data are supported by similar information obtained from Fisher 344 rats used in the 90-day inhalation study (Kinkead et al., 1996; Dodd et al., 1997a).

The forward mutation assay, using L5158Y/$tk^{+/-}$ mouse lymphoma cells (clone 3.7.2C) was conducted using 5 concentrations of CF_3I (8.0%, 17.7%, 30.6%, 42.6%, 45.4%, 49.7%, and 51.8%). Tests were performed with and without metabolic activation by S-9. Results indicated no evidence of CF_3I-induced mutations of L5158Y/$tk^{+/-}$ mouse lymphoma cells at any concentration tested.

Free radical modeling has indicated that CF_3I has the characteristics to be carcinogenic (Koski et al., 1997). The model was based on carbon tetrachloride, where it is thought that cellular damage is caused by free radicals produced when an electron is transferred from an enzyme to the carbon tetrachloride molecule. Vertical electron affinities were calculated for a series of halocarbons and suggested that CF_4 would be non-carcinogenic, CF_3Cl was equivocal, and CF_3Br and CF_3I were considered to be potent toxicants expected to be carcinogenic.

7. Reproductive Toxicity. Reproductive toxicity screening was performed in Sprague-Dawley rats by Dodd et al. (1998). These studies were designed to evaluate the effects of CF_3I on parental fertility, maternal pregnancy and lactation, and growth and development of offspring. Four groups of sixteen rats of each gender were exposed to concentrations of 0.0%, 0.2%, 0.7% and 2.0% CF_3I in a whole-body inhalation chamber. Animals were exposed for four weeks at 6 hours/day, 5 days/week prior to mating. During mating, gestation and lactation, rats were exposed for 6

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hours/day, 7 days/week. Females were not exposed from gestation day 21 through lactation day 4 to allow for early parturition. Pups were not exposed to CF_3I, and were separated from the dams for 6 hrs/day, 5 days/wk during lactation days 5 through 21. Following the mating period, half of the male rats (8) from each group were sacrificed at 7 weeks. The remaining adult animals (males and females) were sacrificed after 14 weeks. Evaluated endpoints included measurement of body weights, hematology and clinical chemistry, thyroid hormone levels, bone marrow micronuclei, gross necropsy, organ weights and histopathology. Pups were examined at birth for viability and physical abnormalities and were sacrificed at weaning on postnatal day 21 with gross necropsies performed. The results of the study indicated no biologically significant differences in measured body weights, clinical pathology (except for thyroid hormone levels), relative or absolute organ weights, histopathology, bone marrow micronuclei, PCE/NCE ratios, or reproductive endpoints between animals exposed to CF_3I and control animals.

At both 7 and 14 weeks, T_3 levels were reduced and serum TSH, rT_3 and T_4 levels were increased. The observed changes in thyroid hormone levels are similar to those reported previously by Kinkead et al. (1996) in the 13-week subchronic exposure study.

REPORTED EXPOSURE SCENARIOS

An exposure assessment of CF_3I in handheld fire extinguishers was conducted to determine the exposure of fire fighters during simulated streaming scenarios. Three different room sizes were used in the study (912 ft^3, 3822 ft^3, and 5133 ft^3). In each scenario, the firefighter stood 8 feet from a 1-foot target, and fully discharged the extinguisher. The firefighters discharged 2.5 lb., 5.0 lb., 9.0 lb., and 13 lb. fire extinguishers. Peak concentrations of CF_3I varied from approximately 10,000 ppm (1%) to 30,000 ppm (3%), depending on the height off of the floor, size of the room, and amount of CF_3I discharged. Average concentrations for the first 30 minutes varied from 1040 ppm (0.1%) to 4678 ppm (0.5%) (Skaggs, 1995).

Exposures from intentional release of CF_3I in an F-15 engine nacelle have been estimated (Vinegar et al., 1997; 1999). Portions of the data were obtained from air sampling conducted during a discharge test of an F-15A engine fire-suppression system at the Robbins Air Force Base, GA. The fire suppression bottle was filled with 6.6 pounds of CF_3I and charged with nitrogen at 600 psi. Air sampling for CF_3I concentrations was conducted using the Halonyzer, which provided accurate data for CF_3I concentrations

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above 10,000 ppm (1%) and the Triodide analyzer, which accurately measured concentrations below 10,000 ppm. Two Fourier Transform Infrared Spectroscopy (FTIR) analyzers were used to sample extremely low concentrations of CF_3I. The samplers were strategically placed in various locations around the aircraft. Three crew locations appropriate for maintenance activities were identified: 1) kneeling or standing near engine bay, 2) working in or under the engine bay, and 3) prone near the engine bay. Paths of and time to egress were determined for each crew location. Blood concentrations of CF_3I were estimated using PBPK modeling. The estimated blood concentration resulting from a 5-minute exposure to 4000 ppm (0.4%) CF_3I, the LOAEL for cardiac sensitization, was 19 mg/L. Estimated blood concentrations for potentially exposed crewmembers ranged between 6 and 40 mg/L. The highest estimated blood concentration of CF_3I was predicted for individuals who were at head level inside the open engine nacelle. Concentrations of CF_3I in this area were in excess of 70,000 ppm (7%), which resulted in an estimated blood concentration of 40 mg/L. This estimated blood concentration for the "head-at-the-engine" scenario was obtained following the first breath, and remained above the level of cardiac sensitization for more than 30 seconds. Levels of CF_3I under the left wing remained above 4000 ppm for more than five minutes.

An event where two salesmen inhaled CF_3I from balloons as part of their sales demonstration has also been described (Vinegar et al., 1999). The salesmen reportedly inhaled deep breaths of CF_3I on 15 to 17 different occasions without reporting adverse effects. The average volume inhaled was estimated to be 1.25 L, resulting in a simulated peak blood concentration of 2000 mg/L and after five minutes, 71 mg/L. It is not known whether cardiac arrhythmia occurred since the salesmen were not monitored.

COMMENTS

CF_3I and several other compounds have been screened as potential replacements for Halon 1301. The review of the available data indicates that adverse health effects could occur following exposure to CF_3I. Potential health hazards appear to exist in the area of cardiac sensitization and genotoxicity.

Since it is reasonable to expect that most exposures would be intermittent and of short duration, acute toxicity information is critical. The LC_{50} for CF_3I following 15-minute nose-only inhalation has been approximated at 27.4%. This approximation was determined using two concentrations (24% and 28.8%) for 15-minute exposures. Normally, at least three

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concentrations are used, and the animals are exposed for 4 to 6 hours. Due to the steep mortality curve, full determination of the LC_{50} for CF_3I was not completed (Ledbetter, 1994). The LD_{50} (or LC_{50}) is a somewhat imprecise value traditionally used to compare toxicity among chemicals. Lethality is only one of many parameters used to characterize acute toxicity. The slope of the dose-response curve, time to death, clinical signs, and pathological findings generally contribute more than the LC_{50} in the evaluation of acute toxicity.

Abnormal cardiac activity, resulting in death, occurred when a single dog was exposed to CF_3I at 1.0% in the presence of epinephrine. Another dog died after exposure to CF_3I at 0.4% in the presence of epinephrine. The cardiac sensitization testing procedure is based on methodology developed by Reinhardt et al. (1971). Although developed for use as a screening test, it has traditionally been accepted by EPA for use as a conservative tool in setting regulatory exposure guidelines to halocarbon agents. The dose of epinephrine used in most cardiac sensitization testing procedures is more than 10 times the level produced by humans, and testing is performed using only one animal at each dose level. Other potential replacement compounds that have been tested using this methodology resulted in only mild to moderate MVEA, and not death (Reinhardt et al., 1971; 1973; Mullin et al., 1972; Trochimowicz et al., 1974; 1976). Cardiac sensitization data, therefore, is paramount in considering the risk associated with the use of CF_3I. A potential health hazard is believed to exist in the area of cardiac sensitization following acute exposure to concentrations of CF_3I greater than 0.2% (NOAEL).

Since the dog model used to measure cardiac sensitization is a conservative assessment of human risk, PBPK modeling can also be used to simulate concentrations of halocarbon agents in human blood following different exposure scenarios that may cause cardiac effects. PBPK modeling is a mathematical description of the uptake and disposition of chemicals based on quantitative interrelationships among critical determinates of these processes (Anderson, 1991). The PBPK model developed to evaluate blood levels of halocarbon agents may be used in some cases to provide extrapolations essential for dose-response assessment of this class of chemicals.

PBPK modeling was used to simulate a blood level of CF_3I for a salesman reportedly inhaling CF_3I from a balloon without adverse effects. This level, 2000 mg/L, was two orders of magnitude greater than that predicted for a response in humans (19 mg/L) based on cardiac sensitization testing in dogs. However, the available information regarding actual human exposure to high levels of CF_3I is anecdotal, at best. In the most recent edition of NFPA Standard 2001 (2000), NFPA endorses the use of PBPK

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modeling procedures to recommend "safe" exposure limits to CF_3I. Given that the modeling data is based on the cardiac sensitization LOAEL (0.4%) in the dog that resulted in death of the animal, endorsement of this guideline and recommendation for use of this particular agent by the US military is unlikely.

Mutagenicity was demonstrated in two of the three screening techniques performed using CF_3I. The Ames Salmonella Reverse Mutation assay indicated that CF_3I was a potent mutagen. It induced both frameshift and base-pair mutations in *Salmonella typhimurium* tester strains with and without activation by mitochondrial S-9. Positive results were also obtained from the mouse bone marrow micronucleus assay, where elevated polychromatic erythrocyte (PCE) to erythrocyte ratios and micronuclei to PCE ratios were observed. These data are supported by similar information obtained from Fisher 344 rats used in the 90-day inhalation study (Kinkead et al., 1996; Dodd et al., 1997), but not by results from the 14-week reproductive toxicity studies performed in Sprague-Dawley rats (Dodd et al., 1998). Overall, the results indicate that CF_3I is capable of causing structural changes in the chromosomes *in vivo*. Positive results on these screens indicate that a potential for mutagenesis exists and that further testing is warranted. Furthermore, free radical modeling has indicated that CF_3I could potentially be carcinogenic (Koski et al., 1997). Examination of tissues taken from animals exposed to CF_3I in repeated-dose studies, however, has revealed no pre-neoplastic lesions. The ability of CF_3I to induce mutagenesis is considered to be equivocal and may warrant further investigation in additional developmental/reproductive toxicity and carcinogenicity testing.

Results of the 13-week subchronic nose-only inhalation study in Fischer-344 rats indicated a complete absence of sperm as well as a reduction in testicular weight and testicular atrophy in males from the two highest exposure groups (4% and 8%) (Kinkead et al., 1996; Dodd et al., 1997a). This finding was interpreted by the authors to be an effect of restraint resulting in heat stress, and not associated with CF_3I exposure. The fact that testicular changes were reduced at 90 days may support this hypothesis. However, the alterations were only seen in animals of the two highest dosage groups, not control animals. It is possible that CF_3I mediated reproductive effects observed in the Kinkead study may have been potentiated by heat stress. The pathology report indicated potential reproductive toxicity associated with exposure to CF_3I occurred at the high and medium dosage levels and recommended further investigation.

Reproductive toxicity was not demonstrated in a subsequent 14-week whole-body exposure study using male Sprague-Dawley rats (Dodd et al.,

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1998). The highest dosage level used was 2%, but the exposure time (6 hours/day) was 3 times greater than that of the Kinkead study (2 hours/day). Strain differences, as well as the different inhalation exposure delivery systems may have contributed to the equivocal findings between these two studies. Although long-term inhalation is not an anticipated exposure scenario for CF_3I, further studies could be performed to clarify reproductive toxicology issues.

Subacute and subchronic exposures to CF_3I resulted in significant changes in thyroid hormone levels (Kinkead et al., 1995; 1996; Dodd et al., 1998). While these effects could be related to exposure to CF_3I, they could also be a result of species differences, with the rat being more susceptible to perturbations in the pituitary-thyroid axis (Capen, 2001; McClain et al., 1988; 1999).

CONCLUSIONS

Overall, the toxicity of CF_3I is low. Available data indicates a potential health hazard exists in the area of cardiac sensitization following acute inhalation exposure to concentrations of CF_3I greater than 0.2%. The effect of CF_3I on mutagenicity and reproductive parameters is equivocal and may warrant further investigation. Human exposure to CF_3I could occur during the manufacturing, transportation, storage, or packaging processes. Accidental releases are also potential sources of exposure in the military setting.

USACHPPM will not endorse the NFPA Standard 2001 (2000) recommendations for "safe" exposure limits to CF_3I because these levels were determined using PBPK modeling data based on a LOAEL (0.4%) for cardiac sensitization in the dog that resulted in death of the animal.

Any proposed use of CF_3I in army systems at design concentrations greater than 0.2% must conform to EPA Significant New Alternatives Policy (SNAP) guidelines which accept CF_3I as a substitute for Halon 1301 in normally unoccupied areas only (Federal Register, 1995). Based on this ruling, any employee that could possibly be in the area must be able to escape within 30 seconds, and the employer must ensure that no unprotected employees enter the area during agent discharge.

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