

TOXICITY DATA COMPARISON OF CF₃I WITH CURRENTLY USED FIRE-EXTINGUISHING AGENTS AND REFRIGERANTS OF INTEREST TO THE MILITARY

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INTRODUCTION

In accordance with the US EPA's Significant New Alternatives Policy (SNAP) Program, information is required on both acute (single exposure) and chronic (long-term repeated exposure) toxicity to identify and assess human health hazard. Identification of hazard is one of the first steps to be taken in EPA's risk assessment process and, in many cases, results of hazard identification studies are the only data available to develop exposure guideline levels. To identify potential areas of toxicological concern, specialized tests are carried out in laboratory animals, primarily the rodent. Data obtained from mammalian toxicity tests form the basis for identifying and assessing human health hazard. It is common to compare the toxicity data profile of a newly selected chemical substitute to the toxicity data profiles of currently used agents that the substitute is intended to replace. This type of comparison provides a point of reference for understanding the potential health hazard of a newly selected chemical substitute and oftentimes helps to resolve the ambiguity associated with some toxicity findings.

Trifluoroiodomethane (CF₃I) is currently approved by the US EPA as a firefighting agent in normally unoccupied areas under SNAP. The use of CF₃I in a number of military and non-military applications is being evaluated, but issues surrounding the toxicity of CF₃I remain subject to clarification. The purpose of this paper is to compare the toxicity data profile of trifluoroiodomethane (CF₃I) to the toxicity data profiles of currently used (or previously used) fire extinguishing agents and refrigerants of interest to the military. Chemicals selected for toxicity data comparisons were Halons 1211, 1301, 1011, 1202, and 2402, and refrigerants CFC-11 and CFC-12. Except for Halon 2402, the chemicals selected for comparison with CF₃I are halogenated methanes (Table I).

METHODS

Toxicity data were reviewed from summary documents prepared for each chemical or for a group of similar chemicals (see Selected Readings). On occasion, individual journal articles or technical reports cited in the summary documents were reviewed to clarify toxicity data.

RESULTS

Acute Toxicity

Rat LC₅₀ data for two exposure durations (15 min and 4 hr) were obtained (Table 2). Halon 1301 and CFC-12 produced no mortality at exposure concentrations greater than 80% (v/v). Halon 1211 and CF₃I had 15-min LC₅₀ values in the 20-30% range. CFC-11, Halon 1202, and Halon

TABLE 1. CHEMICAL NAME, STRUCTURE, CAS NO., AND SELECT PHYSICAL PROPERTIES.

Common Name	Chemical Name	Structure	Molecular Weight	CAS No.	Boiling Point (°C)	Density/ Specific Gravity
Halon 1211	Bromochlorodifluoromethane	CBrClF ₂	165.4	353-59-3	-3	1.83
Halon 1301	Bromotrifluoromethane	CBrF ₃	148.9	75-63-8	-58	1.54
Halon 1011	Bromochloromethane	CH ₂ BrCl	129.4	74-97-5	67	1.93
Halon 1202	Dibromodifluoromethane	CBr ₂ F ₂	209.8	75-61-6	24	2.29
Halon 2402	1,2-Dibromo-1,1,2,2-tetrafluoroethane	CBrF ₂ CBBrF ₂	259.8	124-73-2	47	2.16
CFC-11	Trichlorofluoromethane	CCl ₃ F	137.4	75-69-4	-24	1.49
CFC-12	Dichlorodifluoromethane	CCl ₂ F ₂	120.9	75-71-8	-2x	1.29
CF ₃ I	Trifluoroiodomethane	CF ₃ I	195.9	2314-97-8	-22	2.10

TABLE 2. ACUTE TOXICITY—LC₅₀ DATA (RAT).

Common Name	15 min LC ₅₀ (ppm)	4 hr LC ₅₀ (ppm)	Comments
Halon 1211	200,000	31-131,000	—
Halon 1301	>800,000	>800,000	—
Halon 1011	-22-32,000	-10,000 (concentration x time extrapolation)	5000 ppm x 7 hr = no deaths
Halon 1202	110,000	-30,000 ppm	4 hr exposure results: 20,000 = 0% deaths; 40,000 = 100% deaths
Halon 2402	120,000	55,000	—
CFC-11	130-150,000	26,200	—
CFC-12	>800,000	>800,000	—
CF ₃ I	270,000	~160,000	4 hr exposure results: 128,000 = 0% deaths; 200,000 = 100% deaths

2402 had 15-min LC₅₀ values in the 11-15% range, and Halon 1011 has a 15-min LC₅₀ value below 10%. The pattern of potency was similar for the 4-hr LC₅₀ data.

Cardiac Sensitization

Table 3 lists cardiac sensitization No Observable Adverse Effect Levels (NOAEL) and Lowest Observable Adverse Effect Levels (LOAEL) for the chemicals investigated in this literature search. NOAELs/LOAELs were listed if the chemical had been tested in the standard 5 min exposure study using epinephrine-challenged dogs, similar to the experimental design of Reinhardt et al. [1]. Further, the lowest concentration causing a positive response in a single dog was the criteria for listing a LOAEL. LOAELs were used for chemical comparison of cardiac sensitization toxicity. Halon 1301 and CFC-12 have LOAELs in the 5.0-7.5% range. Although Halons 1211 and 1011 have LOAELs in the 0.7-1.0% range, the value for Halon 1011 is not directly

TABLE 3. CARDIAC SENSITIZATION NOAELS AND LOAELS (CANINE)

Common Name	NOAEL (5 min-ppm)	LOAEL (5 min-ppm)	Comments
Halon 1211	5000	10,000	EC ₅₀ = 19,000 ppm
Halon 1301	50,000	75,000	EC ₅₀ = 200,000 ppm
Halon 1011	Not available	7000	Dogs were anesthetized with a-chloralose.
Halon 1202	Not available	Not available	EC ₅₀ = 8000 ppm
Halon 2402	Not available	1000	EC ₅₀ = 2500 ppm
CFC-11	3200	3500	EC ₅₀ = 9000 ppm
CFC-12	40,000	50,000	EC ₅₀ = 77,000 ppm
CF ₃ I	2000	4000	

EC₅₀ = Calculated concentration that represents an effect in 50% of animals in the study group.

comparable, because dogs were anesthetized in this study. Anesthesia appears to raise the cardiac sensitization threshold. since the effect levels for Halons 1301 and 1211 are 8.0% and 1.4%, respectively, in anesthetized dogs. Chemicals with LOAELs in the 0.1-0.4% range were Halon 2402, CFC-11, and CF₃I. Since the EC₅₀ for Halon 1202 is 0.8% (unable to obtain individual animal data), the LOAEL would likely fall in the same range as Halon 2402, CFC-11, and CF₃I.

Genotoxicity

Halon 1211, Halon 1011, and CF₃I were positive (mutation observed in at least one strain) in the Ames bacterial test system (Table 4). CFC-11, CFC-12, and Halons 1301 and 2402 were negative. Four of the eight chemicals were tested for mutagenicity in an in vitro mammalian cell assay. They were Halon 1211, CFC-11, CFC-12, and CF₃I. All were negative. Halon 1211 and CF₃I were tested in the in vivo mouse micronucleus test. At 5%, Halon 1211 did not produce micronuclei, but CF₃I did. At 2.5%, CF₃I was negative in the mouse micronuclei assay.

TABLE 4. GENOTOXICITY DATA.

Common Name	In Vitro Bacteria (Ames)	In Vitro Mammalian cells	In Vivo Micronucleus (mouse)
Halon 1211	Positive (1/5 strains)	Negative	50,000 ppm NOAEL (6hr/day x 1 day)
Halon 1301	Negative	Not available	Not available
Halon 1011	Positive (weak - TA1535 strain)	Not available	Not available
Halon 1202	Not available	Not available	Not available
Halon 2402	Negative	Not available	Not available
CFC-11	Negative	Negative	Not available
CFC-12	Negative	Negative	Not available
CF ₃ I	Positive (4/5 strains)	Negative	15,000 ppm NOAEL 50,000 ppm LOAEL (6 hr/day x 3 days)

Short-Term Repeated Exposure Toxicity

Short-term (approximately two to three weeks in duration) general toxicity studies have been carried out in rats on seven of the eight chemicals (Table 5). Halon 1301 and CFC-12 had NOAELs in the 10-50% range. CFC-11 and CF₃I had NOAELs in the 2.5-3% range (LOAELs were 5-6%). Halons 1211 and 2402 had NOAELs of 0.33-1.25% and LOAELs of 1-2.5%. However, the daily exposure for these halon studies was 3.5-6 hr/day compared to 2 hr/day for the CFC-11 and CF₃I studies. A shorter daily exposure regimen in these studies may have produced slightly higher NOAELs and LOAELs. Halon 1202 produced mortality at a concentration of approximately 2.2%

TABLE 5. SHORT-TERM REPEATED EXPOSURE TOXICITY DATA (RAT).

Common Name	Exposure Duration	NOAEL or LOAEL
Halon 1211	6 hr/day x 15 days	10,000ppm LOAEL 3300 ppm NOAEL
Halon 1301	2 hr/day x 15 days	500,000ppm NOAEL
Halon 1011	Not available	Not available
Halon 1202	6 hr/day x few days	-22,000 ppm => 50% mortality
Halon 2402	3.5 hr/day x 20 days	25,000 ppm LOAEL 12,500 ppm NOAEL
CFC-11	1 hr (x2)/day x 15 days	50,000 ppm LOAEL 25,000 ppm NOAEL
CFC-12	3.5 hr/day x 20 days	100,000ppm NOAEL
CF ₃ I	2 hr/day x 14 days	60,000 ppm LOAEL 30,000 ppm NOAEL

90-Day Repeated Exposure Toxicity

Table 6 lists the NOAEL/LOAEL and target organ of concern for those chemicals that were evaluated for general toxicity following a 90-day (13-week) exposure regimen. NOAELs of 1-2.3% were observed for Halon 1301 and CFC-12. CFC-11 had a NOAEL of 0.1%. NOAELs of 90 days were not established for Halons 1011 and Halon 1202, but in exposure studies of several months' duration, the NOAEL for Halon 1202 was 350 ppm, and the LOAEL for Halon 1011 was 500 ppm (Table 6). For CF₃I, the LOAEL in a 90-day study was 2%. Repeated exposure toxicity data were not available for Halons 1211 and 2402. The target organs of concern for toxicity for most chemicals were the central nervous system (anesthesia or depression), the respiratory tract, and/or the liver. The target organ of concern for the iodine-containing chemical (CF₃I) was the thyroid gland. Life-time exposure studies in rats have been conducted with CFC-11 by the oral route and with CFC-12 by the inhalation route. Neither chemical was tumorigenic.

Developmental and Reproductive Toxicity

Developmental toxicity studies have been carried out in rats on four of the eight chemicals: reproductive toxicity studies were performed on three of the eight chemicals (Table 7). The developmental toxicity study with CFC-11 and CFC-12 used a 10:90 (CFC-11:CFC-12) mixture

TABLE 6. 90-DAY REPEATED EXPOSURE TOXICITY DATA (RAT),

Common Name	NOAEL or LOAEL	Target Organ of Concern for Toxicity	Comments
Halon 1211	Not available	—	—
Halon 1301	23,000 ppm NOAEL	Respiratory tract	18-week study
Halon 1011	1000 ppm: no deaths	Respiratory tract; liver; CNS (anesthesia)	500 ppm x several mo. = LOAEL
Halon 1202	Not available	Respiratory tract; liver; CNS (anesthesia)	350 ppm x 7 mo. = NOAEL
Halon 2402	Not available	—	—
CFC-11	1000 ppm (24 hr/day) NOAEL	Cardiotoxicity; CNS (depression)	18-mo. oral study was negative, but NCI considered study was inadequate
CFC-12	10,000 ppm NOAEL	CNS (depression)	5000 ppm NOAEL in chronic bioassay
CF ₃ I	20,000 ppm LOAEL	Thyroid gland	—

CNS = central nervous system

TABLE 7. DEVELOPMENTAL OR REPRODUCTIVE TOXICITY DATA (RAT).

Common Name	NOAEL or LOAEL (Developmental)	NOAEL or LOAEL (Reproductive)
Halon 1211	50,000 ppm NOAEL	25,000 ppm NOAEL
Halon 1301	49,505 ppm NOAEL	Not available
Halon 1011	Not available	Not available
Halon 1202	Not available	Not available
Halon 2402	Not available	Not available
CFC-11	200,000 ppm NOAEL CFC-11/	Not available for CFC-11
CFC-12	CFC-12 (10:90) mixture	Negative via oral route for CFC-12
CF ₃ I	Not available	2000 ppm NOAEL

of the two chemicals at an animal exposure concentration of 20%. The developmental toxicity NOAEL for the CFC-11/CFC-12 mixture was 20%. Halon 1211 and Halon 1301 had NOAELs in the range of 5%. In an orally administered study, CFC-12 was not a reproductive toxicant. The NOAELs for reproductive toxicity were 2.5% and 0.2% for Halon 1211 and CF₃I, respectively. These were the highest concentrations tested in the reproductive studies.

Acute Exposure — Human Studies

Controlled exposure clinical studies have been conducted with five of the eight chemicals (Table 8). In general, pharmacologic responses are elicited for brief exposure periods at high concentrations. These responses include dizziness, vertigo, variations in heart rate or blood pressure, and alterations in psychomotor test scores. For exposure periods of 30-60 min in duration, a concentration of 1000 ppm was a NOAEL for all chemicals tested. The 1000 ppm NOAEL can be extended to several hours of exposure for CFCs 11 and 12.

TABLE 8. ACUTE EXPOSURE STUDIES — HUMAN.

Common Name	Effects Observed	No Effects Observed	Additional Observations
Halon 1211	Brief (<60 sec) exposures at 40-50,000 ppm caused vertigo and paresthesia	Pharmacologic responses (blood pressure: ventricular premature beats) only at 1000ppm (several minutes)	—
Halon 1301	Brief (3 min) exposures at 40,000 ppm causes dizziness and drowsiness	Brief (3 min) exposures at ≤30,000 ppm or 1000 ppm x 30 min produced no responses	—
Halon 1011	Not available	Not available	—
Halon 1202	Not available	Not available	—
Halon 2402	500 ppm x 1 hr causes alterations in EEG-VER test: 1000ppm x 1 hr produced dizziness	1000 ppm x 30 min or 250 ppm x 4 hr produced no reproducible effects	—
CFC-11	Brief (15-60 sec) exposures at 1700ppm causes variations in heart rate	1000ppm x 8 hr produced no responses	1000ppm x 8 hr/day x 18 days produced no responses
CFC-12	10,000ppm x 2.5 hr produced reduction in psychomotor test scores	1000ppm x 8 hr produced no responses	—
CF ₃ I	Not available	Not available	—

Occupational Exposure Standards

Tables 9 and 10 lists short-term exposure limits (STEL) and 8 hr time-weighted average (TWA) threshold limit values (TLV), respectively, for chemicals that have occupational exposure standards set by professional committees, institutes, or government agencies. In general, standards recommended by American Conference of Governmental Industrial Hygienists (ACGIH) are conservative (i.e., lowest values), but are the same or similar in value to those recommended by other countries or US government agencies. Note that most ACGIH STELs have been expired due to lack of pertinent data, and because other committees or agencies are considering the establishment of acute or short-term exposure guideline levels for select hazardous substances. Halon 1301, CFC-11, and CFC-12 have Short-Term Exposure Limits (STEL) in the range of 1000 to 1250 ppm. Halons 1011 and 1202 are about an order of magnitude lower. The 8 hr TWA TLV for Halon 1301, CFC-11, and CFC-12 is 1000 ppm. Halon 1011, Halon 1202, and CF₃I have (or are recommended) 8-hr TWA values around 100 to 200 ppm.

DISCUSSION

The purpose of this paper is to compare the toxicity data profile of CF₃I to the toxicity data profiles of currently used (or previously used) fire extinguishing agents and refrigerants of

TABLE 9. OCCUPATIONAL EXPOSURE STANDARDS (STELS/CEILING VALUES).

Common Name	ACGIH (ppm)	Other Countries (ppm)
Halon 1211	Not available	—
Halon 1301	1200 (1976-85)	1200 (United Kingdom) 2000 (Federal Republic of Germany)
Halon 1011	250 (1976-89)	250 (United Kingdom) 400 (Federal Republic of Germany)
Halon 1202	150 (1976-85)	150 (United Kingdom) 200 (Federal Republic of Germany)
Halon 2402	Not available	—
CFC-11	1000	750 (Sweden) 1250 (United Kingdom) 2000 (Federal Republic of Germany)
CFC-12	1250 (1976-85)	750 (Sweden) 1250 (United Kingdom) 2000 (Federal Republic of Germany)
CF ₃ I	Not available	2000 (Environmental Protection Agency [USA] recommended)

interest to the military. The toxicity data profiles for chemicals discussed in this paper were divided subjectively into two or three relative toxicity categories for each biological endpoint evaluated (Table 11). This effort allows one to compare the toxicity profiles of the eight chemicals among each other. In conclusion, the toxicity data profile of CF₃I fits within the range of toxicity data profiles of currently used fire extinguishants and refrigerants.

TABLE 10. OCCUPATIONAL EXPOSURE STANDARDS (8 HR TWA).

Common Name	ACGIH Threshold Limit Value	Other Institutes (Permissible/Recommended/Acceptable Exposure Limits) (ppm)
Halon 1211	Not available	—
Halon 1301	1000	1000 (US Department of Labor, Occupational Safety and Health Administration [OSHA]) 1000 (US National Institute for Occupational Safety and Health [NIOSH])
Halon 1011	200	200 (OSHA) 200 (NIOSH)
Halon 1202	100	100 (OSHA) 100 (NIOSH)
Halon 2402	Not available	—
CFC-11	1000 (1950-81)	1000 (OSHA) 1000 (NJOSH)
CFC-12	1000	1000 (OSHA) 1000 (NIOSH)
CF ₃ I	Not available	150 (US EPA recommended)

TABLE 11. COMPARISON OF TOXICITY PROFILES.

Biological Endpoint	Relatively Low Toxicity	Relatively Intermediate Toxicity	Relatively High Toxicity
Acute Toxicity (LC ₅₀)	Halon 1301, CFC-12	Halon 1211, CF ₃ I, CFC-11, Halon 1202, Halon 2402	Halon 1011
Cardiac Sensitization (LOAEL)	Halon 1301, CFC-12	Halon 1211	Halon 2402, CFC-11, CF ₃ I
Genotoxicity	Halon 1301, Halon 1211, Halon 1011, Halon 2402, CFC-11, CFC-12	CF ₃ I	—
Short-term Repeated Exposure Toxicity	Halon 1301, CFC-12	CFC-11, CF ₃ I, Halon 1211, Halon 2402	Halon 1202
90-Day Repeated Exposure Toxicity	Halon 1301, CFC-12	Halon 1202, CFC-11, CF ₃ I	Halon 1011
Developmental and Reproductive Toxicity	Halon 1211, Halon 1301, CFC-11/ CFC-12 mixture	CF ₃ I	—
Acute Effects—Human	CFC-11, CFC-12	Halon 1211, Halon 1301, Halon 2402	—
Occupational STEL	Halon 1301, CFC-11, CFC-12, CF ₃ I	Halon 1011, Halon 1202	—
Occupational 8 Hr TLV	Halon 1301, CFC-11, CFC-12	Halon 1011, Halon 1202, CF ₃ I	—

REFERENCE

1. Reinhardt, C. F., Azar, A. Maxfield, M. E., Smith, P. E., Jr., and Mullin, L. S., "Cardiac Arrhythmias and Aerosol 'sniffing'," *Archives of Environmental Health* 22:265, 1971.

SELECTED READINGS

CF₃I

- Dodd et al., *Fundam. Appl. Toxicol.* 35: 64-77, 1997
 Dodd et al. *Inhal. Toxicol.* 9: 111-131, 1997
 Dodd and Vinegar, *Drug Chem. Toxicol.* 21: 137-149, 1998
 Dodd et al. *Inhal. Toxicol.* 11: in press, 1999

Ledbetter, A.D., Unpublished observations. ManTech Environment;¹ Technology, Inc., Final Reports (2), Project No. 6030-012, 1993, and Project No. 1530-001, 1994

CFC-11

- ACGIH *Documentation of TLV-TWA, Revised 1992*
 DuPont Haskell Laboratory Review, Unpublished, Updated October 24, 1988, 36 pages
 EPA Environmental Hazard Assessment of One and Two Carbon Fluorocarbons, Final Report, EPA-560/2-75-003, 1975

CFC-12

- ACGIH *Documentation of TLV-TWA, Revised 1991*

DuPont Haskell Laboratory Review, Unpublished, Updated February 19, 1992, 32 pages
EPA Environmental Hazard Assessment of One and Two Carbon Fluorocarbons. Final Report,
EPA-560/2-75-003, 1975

Halon 1011

ACGIH Documentation of TLV-TWA, Revised 1991

Engibous and Torkelson. Wright Air Development Division Technical Report 59-463, 1960

Van Stee, E.W., Aerospace Medical Research Laboratory Technical Report. AMRL-TR-74-143,
1974

Halon 1202

ACGIH Documentation of TLV-TWA, Revised 1991

DuPont Haskell Laboratory Review, Unpublished, Updated September 5, 1978, 6 pages

Engibous and Torkelson, Wright Air Development Division Technical Report 59-463, 1960

EPA Environmental Hazard Assessment of One and Two Carbon Fluorocarbons, Final Report.
EPA-560/2-75-003. 1975

Halon 1211

DuPont Haskell Laboratory Review, Unpublished, Updated May 30, 1993, 25 pages

EPA Environmental Hazard Assessment of One and Two Carbon Fluorocarbons. Final Report,
EPA-560/2-75-003, 1975

Van Stee, E.W., Aerospace Medical Research Laboratory Technical Report. AMRL-TR-74-143,
1974

Halon 1301

ACGIH Documentation of TLV-TWA, Revised 1992

DuPont Haskell Laboratory Review, Unpublished, Updated May 25, 1990, 30 pages

EPA Environmental Hazard Assessment of One and Two Carbon Fluorocarbons, Final Report,
EPA-560/2-75-003, 1975

Van Stee, E.W., Aerospace Medical Research Laboratory Technical Report, AMRL-TR-74-143,
1974

Halon 2402

International Organization for Standardization. Document Relevant to the Toxicity of Halon

2402 (Submitted by Italy), Document ISO/TC 21/SC 6/WG 3 – Halons and Carbon Dioxide,
Nov., 1980

DuPont Haskell Laboratory Review, Unpublished, Updated July 9, 1985, 11 pages.