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Environmentally Acceptable Fire Extinguishants

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NIST

National Institute of Standards and Technology
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Prepared for
*U.S. Department of Commerce
Building and Fire Research Laboratory
National Institute of Standards and Technology
Gaithersburg, MD 20899-8664*

By

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PREFACE

This Final Project Report was prepared by Chemical Development Studies, Inc., Albuquerque, New Mexico, for the Department of Defense, Strategic Environmental Research and Development Program (SERDP), and was funded as part of the National Institute of Standards and Technology (NIST) Fire Research Grants Program. The NIST Grant Number was 60NANB3D1001. This is Project Element 4B/6/2345 under the Next Generation Fire Suppression Technology Program (NGP).

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LIST OF ABBREVIATIONS

ALC	approximate lethal concentration
AD ₅₀	dose that is anesthetic to 50 % of an animal test population
CAS	Chemical Abstracts Service (American Chemical Society)
DoD	Department of Defense
DTIC	Defense Technical Information Center
EPA	U.S. Environmental Protection Agency
FEC	flame extinguishment concentration
GWP	Global Warming Potential
GCMS	gas chromatography mass spectroscopy
HCFC	hydrochlorofluorocarbon
HFC	hydrofluorocarbon
HFE	hydrofluoroether
K _{OW}	water octanol partition coefficient
LC	liquid chromatography
LC _{LO}	lowest concentration causing death
LC ₅₀	concentration required to cause death in 50 percent of an animal test population
LD ₅₀	dose required to cause death in 50 percent of an animal test population
LOAEL	Lowest Observable Adverse Effect Level
NGP	Next Generation Fire Suppression Technology Program
NOAEL	No Observed Adverse Effect Level
ODP	Ozone Depletion Potential
PFC	perfluorocarbon
QSAR	Quantitative Structure-Activity Relationship
QSPR	Quantitative Structure-Property Relationship
RP-HPLC	Reverse Phase High Pressure Liquid Chromatography
SERDP	Strategic Environmental Research and Development Program
SNAP	Significant New Alternatives Policy

LIST OF UNITS AND SYMBOLS

g	gram
kg	kilogram
mL	milliliter
s	second
T	temperature
•	denotes a free radical, e.g., •OH, the hydroxyl free radical

SECTION I. PROJECT SUMMARY

A. BACKGROUND

1. The Challenge

The Montreal Protocol was adopted in 1987 and amended in 1990, 1992, and 1995. With the planned phase-out of production of halon 1211 (CF₂ClBr) and halon 1301 (CF₃Br) in the United States at the end of 1993, organized efforts to identify replacements were initiated by a broad range of governmental and non-governmental groups. These efforts, culminating in the Next Generation Fire Suppression Technology Program (NGP), have resulted in new fire extinguishment technologies, a clearer view of the chemical options available, better understanding of the dynamics of fire suppression under some of the more adverse conditions encountered in aircraft and subzero conditions, and greatly broadened the array of tools available for future developments in the area of fire suppression.

The NGP began in 1997. The program built on several efforts that occurred in the years prior to the NGP. These efforts contributed a broad range of test methods for evaluating halon replacement candidates and included investigations into several of what have turned out to be the more promising chemical families.

Changes in thinking of those involved in identifying new compounds occurred frequently in the early 1990s. These changes included realization that instead of a single drop-in replacement being identified for halon 1301 (as well as halon 1211), the world of fire suppression applications was going to see a broad range of proposed solutions. Criteria for environmental acceptability were tightened, risk-based toxicity limits and tests were identified. Situational toxicological constraints underwent considerable evolution. Some chemical options considered for halon replacement (e.g., the perfluorocarbons), though at first embraced, were later discarded as understanding of environmental impact issues developed.

The replacement of halon 1301 presented some very unique challenges. Halon 1301 is unique as a brominated fluorocarbon. Its -58 °C boiling point is the lowest for the bromofluoroalkanes chemical family, and its toxicity quite low. It is an excellent fire suppressant and explosion inertant. It has great dimensionality (space filling), tolerance to less than optimal discharge technique, and excellent chemical stability and low toxicity. Functionally, it is the standard by which all suggested alternative candidates have been judged. Comparison of halon 1301 (65 year atmospheric lifetime) to CF₂HBr (halon 1201, FM-100, atmospheric lifetime of 9 yr, boiling point of -15 °C) is typical of the undesirable tradeoffs encountered in developing a new fire suppressant. While adding hydrogen and reducing the degree of fluorination helps achieve the desirable effect of a shorter atmospheric lifetime, this change also unfortunately greatly increases boiling point, which directly impacts dimensionality and low temperature performance, notwithstanding other adverse performance changes that also are noted.

With the emphasis on dramatic reductions in both stratospheric ozone depletion effects and atmospheric global warming potentials, one research focus has been on identifying short

atmospheric lifetime molecules. Short atmospheric compounds incorporate structural components that are reactive with atmospheric constituents of the atmosphere or are photochemically reactive, as summarized in Table 1.

Table 1. Tropospheric Removal Mechanisms.

Primary Removal Mechanism	Example Families
Photodegradation	Iodides, Carbonyls, Bromides
Reaction with Hydroxyl	Alkenes, Aromatics, Hydrogen-Containing Amines, Hydrogen-containing Ethers, Carbonyls
Physical Removal	Ketones, Alcohols, Esters
Reaction with Tropospheric Ozone	Alkenes

This report describes NGP efforts to identify liquid or gaseous chemically active agent replacements for halon 1301. Other NGP projects addressed alternative approaches to halon replacement and fire suppression technology development with potential for employing compounds with chemical suppression properties and higher boiling points used as additives or incorporation in solid propellant gas generator extinguishers.

It is useful to identify organizations contributing to prior halon replacement efforts as well as the objective or goal(s) of their specific efforts, key observations, chemicals of interest and in some cases conclusions offered. While this review begins somewhat arbitrarily with work done after 1990, it should not be assumed that there were not efforts predating this point. Several governmental organizations had ongoing halon replacement efforts prior to 1990. The products of these efforts found their way into the many studies reported in symposia and professional journals in the 1990s.

The U.S. Department of Defense's (DoD) unique needs in the areas of fire extinguishment and explosion suppression and issues related to weapon system vulnerability and survivability catalyzed the considerable research effort prior to 1990 and much of the work done since. DoD services, including the Air Force, Navy, Army, and Marines, funded research programs which, while focused on their weapon systems and critical applications, provided broadly applicable results. The National Institute of Standards and Technology (NIST) Building and Fire Research Laboratory (BFRL)'s preliminary analysis of chemical families broke new ground serving to broaden what had been limited options to include new chemical families.

2. Prior Examinations of Chemicals

The history of halon replacement development strongly reflects concurrent progress in fire science and basic environmental and atmospheric research areas. The compounds and approaches taken in the process of developing acceptable halon replacements have the appearance of a sequential process of research-based discovery, environmental selection criteria revision followed by rejection of developed alternatives, and a resumption of applied research.

Several programs contributed to halon replacement and fire suppression technology development and helped to set the stage for the development work performed under the NGP on new chemicals. These programs are very briefly described in the following paragraphs.

1. NIST: Under U.S. Air Force sponsorship, NIST published Technical Note 1279 in August 1990.¹ Table 2 presents the chemical family recommendations resulting from this early analysis.

Table 2. NIST List of Recommended Chemical Families (1990).

Chemical Family Recommendation	Justification for Further Consideration - Environmental Advantage and Flame Suppression Estimates
Halogenated ketones, anhydrides, esters	Carbonyl red shift contributes to photolysis
Unsaturated halocarbons	Reactivity of alkenes to atmospheric OH
Halogenated ethers and related compounds	Absorption red shift due to C-O-C linkage aides in photolysis
Halons containing iodine	Iodinated halogenated compounds more photochemically reactive and a higher fire suppression efficiency
Sulfur halides	Desirable attributes - Low toxicity, possible significant fire suppression properties
Phosphorus containing compounds	Established fire suppression properties (expected free radical trap mechanism) needs a more volatile or gaseous compound
Silicon and germanium compounds	Silicon in particular (possibly germanium) expected flame suppression effectiveness and short atmospheric lifetime
Metallic compounds	Established flame suppression properties, likely alternative compounds of great interest
Inert gases	Physical suppressant options

2. DoD Technology Development Plan (TDP): The TDP was initiated to identify commercially available alternatives for fire extinguishment in occupied spaces and included alternative chemicals for extinguishment of slow-growth fires in occupied compartments of helicopters, fixed-wing aircraft, ships, maritime craft, ground armored vehicles, aircraft cargo bays, aircraft simulators, and mission-critical facilities as well as identifying alternative fire extinguishing agents for unmanned areas. It also addressed the identification of explosion suppression agents and techniques for application in manned and unmanned spaces.

3. Halon Options Technical Working Conferences (HOTWC): The HOTWCs began in the spring of 1991. The conferences continued through 2006 as a forum for presentation of research

related to halon replacements, and as such routinely covered topics ranging from new agents and fire suppression equipment to atmospheric science and chemical and suppression by-product toxicology. As early as the first of the conferences, there were papers presented describing the synthesis of compounds which to the present are topics of great current interest.²

4. Advanced Agent Working Group (AAWG): On August 23, 1994, representatives of the North Slope Oil Producing and Transmission Companies met with members of the “CF₃I Working Group.” The AAWG was formed in the course of this meeting, with participating representatives of most DoD services, NIST, EPA, several fire suppression industry representatives, private consultants, and the New Mexico Engineering Research Institute (NMERI). Table 3 presents the range of compounds considered by the AAWG.

5. Earlier NGP Effort. Prior candidate agent testing and toxicological and cardiac sensitization performance studies had only identified one potentially environmentally and toxicologically acceptable brominated compound of approximate equivalence to halon 1211.³ This continued search for acceptable compounds greatly expanded the number and types of chemical families tested.

Earlier efforts to identify new fire suppression technologies and agents for application to the demanding circumstances faced by aircraft designers and operators has yet to yield a potential candidate compound equivalent to halon 1301. The simplicity of the halon 1301 structure, CF₃Br, and the need to employ chemical features that instill short atmospheric lifetime essentially dictate that all potential halon alternative brominated compounds will have higher boiling points than that of halon 1301, -58 °C.

Options to develop a fire suppressant that is as effective as halon 1301 are limited. Nevertheless, reducing the weight penalty, enhancing fire suppression performance, and increased assurance that fires are reliably extinguished make it essential that all options to the identification and development of chemically active agent be evaluated.

A review of the state of knowledge of the fitness of a wide variety of chemical families to perform as acceptable fire suppressants, presented in NIST Technical Note 1443, describes a “down-selected” listing of prioritized chemical families that are known to or expected to have potential to act as chemical mechanism based fire suppressants.⁴ The review focused on fire-suppression effectiveness, toxicity, materials compatibility, colligative properties, and environmental impact. For each family, there is an evaluation of worthiness of further examination. This review lead to the current project whose goal is to further investigate the identified families based in part on the prioritization developed.

Table 3. AAWG Preliminary List of Compounds.

Formula	Name	CAS No., Notes
Alkenes		
CH ₂ =CHCF ₂ Br	3-bromo-3,3-difluoropropene	420-90-6, commercial
CF ₂ BrCH=CHCF ₃	<i>cis</i> - and <i>trans</i> -1-bromo-1,1,4,4,4-pentafluoro-2-butene	
CF ₂ BrCF ₂ CH=CH ₂	4-bromo-3,3,4,4-tetrafluorobutene	18599-22-9, commercial
CF ₂ BrC(CF ₃)=CH ₂	3-bromo-3,3-difluoro-2-(trifluoromethyl)propene	
Alcohols		
CF ₂ BrCH ₂ OH	2-bromo-2,2-difluoroethanol	420-94-0
CF ₃ CFBrCH ₂ OH	2-bromo-2,3,3,3-tetrafluoropropanol	94083-41-7
CF ₂ BrCF ₂ CH ₂ OH	3-bromo-2,2,3,3-tetrafluoropropanol	
CF ₃ CHOHCH ₂ Br	3-bromo-1,1,1-trifluoro-2-propanol	Prepared
Ethers		
CF ₂ H-O-CFHBr	(bromofluoromethyl)(difluoromethyl)ether	no CAS Number
CF ₂ Br-O-CH ₃	(bromodifluoromethyl)(methyl)ether	
CF ₂ BrCH ₂ -O-CF ₃	(2-bromo-2,2-difluoroethyl)(trifluoromethyl)ether	
CF ₂ BrCF ₂ -O-CH ₃	(2-bromo-1,1,2,2-tetrafluoroethyl)(methyl)ether	13749-39-8
-CH ₂ CF ₂ CBrFCH ₂ -O-	3-bromo-2,2,3-trifluorooxolane	
Amines		
(CBrF ₂)(CHF ₂) ₂ N	bis(difluoromethyl)(bromodifluoromethyl)amine	no CAS Number
(CBrF ₂)(CF ₃)(CH ₃)N	(bromodifluoromethyl)(trifluoromethyl)(methyl)amine	no CAS Number
(CF ₃) ₂ (CH ₂ CBrF ₂)N	bis(trifluoromethyl)(2-bromo-2,2-difluoroethyl)amine	
(CBrF ₂)(CF ₃) ₂ N	bis(trifluoromethyl)(bromodifluoromethyl)amine	
Carbonyl Compounds		
CBrF ₂ CH ₂ C(O)H	3-bromo-3,3-difluoropropanal	
CH ₃ C(O)CH ₂ CF ₂ Br	4-bromo-4,4-difluoro-2-butanone	
CBrF ₂ CH ₂ C(O)OCH ₃	methyl 3-bromo-3,3-difluoropropionate	99953-33-0
CBrF ₂ CH ₂ C(O)OCF ₃	trifluoromethyl 3-bromo-3,3-difluoropropionate	
Aromatics		
C ₆ F ₅ Br	Bromopentafluorobenzene	344-04-7, commercial
C ₆ F ₅ CBrF ₂	(bromodifluoromethyl)pentafluorobenzene	35523-39-8
C ₆ BrF ₄ CF ₃	bromoheptafluorotoluene 2-bromoheptafluorotoluene 3-bromoheptafluorotoluene 4-bromoheptafluorotoluene	113601-46-0 66820-64-2 5360-80-5 17823-46-0

Attributes of the desired halon 1301 replacement candidate have been identified as:

- Fire suppression and reignition quenching efficiency comparable to halon 1301 and higher than the hydrofluorocarbons (HFCs);
- Atmospheric lifetime short, on the order of a month, to keep ozone depletion, global warming, and any future adverse contributions to a minimum;
- Toxic potency of agent and combustion byproducts sufficiently low that brief exposure to an extinguishing concentration does not result in an unrecoverable injury;
- No serious interaction of the agent or its byproducts with contacted aircraft materials;
- Availability of compatible storage container components; and
- Boiling point sufficiently high that a suppressing volume fraction of 0.05 (at thermal equilibrium) exists at -40 °C, the minimal design temperature for aircraft suppression system performance. This boiling point is about 25 °C. Highly effective agents that might require a lower concentration for suppression loosen this boiling point criterion proportionately. Agents dispensed as a mist/powder or by a solid propellant gas generator (SPGG), whose high temperatures and gas flows ensure complete volatilization and dispersion, could have considerably higher limiting boiling points.

The authors of NIST Technical Note 1443 reviewed all available data covering a broad list of chemical families. Table 4 is their listing of families worthy of continued research effort or, in the case of new unstudied families, limited compound acquisition and testing.

Table 4. NIST Technical Note 1443 - Prioritized Listing.

Chemical Family	Recommendation		
	High Priority	Further Study	Quick Look
Iodinated alkanes & alkenes		X	
Brominated alkenes	X		
Iodinated ethers			X
Brominated ethers		X	
Brominated alcohols			X
Fluorinated aldehydes & ketones		X	
Nitriles			X
Fluoroamines & bromofluoroamines	X		
Sulfoxides			X
Phosphorus- acids and esters	X		
Phosphonitriles & phosphorus halides		X	
Copper-containing compounds			X
Manganese or tin compounds	X		
Iron-containing compounds		X	

Compounds that had been well studied as fire suppressants as well as compounds with known or suspected high toxicity, high boiling points, and/or expected poor fire suppression

performance were placed in the “No Further Study” category (Table 5). The current project did not further investigate these families, but did extend the listing in Table 4 to additional chemical families with the potential to act as bromine carriers and having short atmospheric lifetime.

Table 5. NIST Technical Note 1443 – Category - “No Further Study.”

Chemical Family	Major Disqualifying Finding		
	Well Studied	Drawback: Toxicity, Colligative Property or Other	Effectiveness Lacking or Expected to Equal HFCs
Brominated, Chlorinated, Fluorinated alkanes	X		
Chlorinated alkenes		X	X
Fluorinated alkenes			X
Alkynes			X
Iodinated ethers		X	
Chlorinated ethers			X
Fluoroethers	X		
Iodinated alcohols		X	
Chlorinated alcohols		X	
Fluorinated alcohols		X	X
Iodinated or brominated aldehydes & ketones		X	
Chlorinated aldehydes & ketones		X	X
Brominated, chlorinated, fluorinated aromatics		X	
Nitro Compounds		X	X
Nitrates, nitrites, nitroso compounds		X	
Hexavalent sulfur		X	X
Difluorosulfur Compounds		X	
Phosphines		X	
Pentacoordinate Phosphorus		X	
Alkali metal compounds	X		
Compounds of Alkaline Earths	X		
Boron and aluminum compounds			X
Antimony or Titanium-containing Compounds		X	
Silicon or Germanium-containing Compounds		X	

3. Chemical Volatility Limit Estimation and Chemical Options

A major factor in application of any fire suppressant is its ability to disperse under the existing ambient conditions of temperature and pressure. To effect flame extinguishment the flame extinguishing concentration must be achieved and held for a period sufficient to preclude an immediate relight in the volume being protected. Boiling point and vapor pressure are key physical properties affecting dispersion.

A physical chemistry based estimate⁵ of the maximum boiling point that a compound may have and still achieve the necessary air concentration under a range of ambient temperature conditions provides some guidance to compound selection, Table 6. While the results of this analysis are helpful they do not account for droplet size/evaporation rate effects, droplet heating rate due to absorption of flame radiation, or nozzle design changes which may enable the use of higher boiling chemicals. As can be seen from this table highly effective extinguishants, requiring lower design concentrations, allow use of higher boiling compounds.

Table 6. Estimates of Maximum Boiling Points for Fire Suppression.

Conc.	Ambient Temperature, °C											
	%	-60	-50	-40	-30	-20	-10	0	10	20	30	40
1	33	47	61	76	90	105	119	133	148	162	176	191
2	19	33	46	60	74	87	101	115	128	142	156	169
3	11	24	37	51	64	77	91	104	117	130	144	157
4	5	18	31	44	57	70	83	96	109	122	135	148
5	0	13	26	39	52	65	77	90	103	116	129	142
10	-14	-1	11	23	35	47	59	72	84	96	108	120
15	-22	-10	2	14	25	37	49	61	73	84	96	108
20	-28	-16	-5	7	19	30	42	53	65	76	88	99

Example: 4 % by volume in air at -20 °C may be achieved by agents boiling at 57 °C or lower.

Boiling Point Trends – Compound Selections Options

As the focus is on low boiling compounds, and the candidates are all small molecules from the alkene and ether families, it is useful to compile data enabling estimation of the likely results of compound selection and acquisition efforts. Keeping a focus on the physical limits to boiling point will bring direction to not only the options available, but will bring necessary attention to needed areas of development that may be required to provide adequate low temperature dispersion of chemicals.

Initially, a query was made in the NMERI CGET Compound Options Database (CCOD) to determine all double-bonded compounds with boiling point data. All records containing boiling points at pressures other than about 101 kPa (760 torr) were discarded. This left 53 compounds, some of them containing oxygen and three of them having boiling points estimated by other authors. As seen in Figure 1, higher molecular weight generally resulted in higher boiling point (as expected), but data scatter was large. The process was repeated, breaking the data set into chemicals with (Figure 2) and without (Figure 3) hydrogen. Although the data scatter was still large, it was reduced from that of the full set.

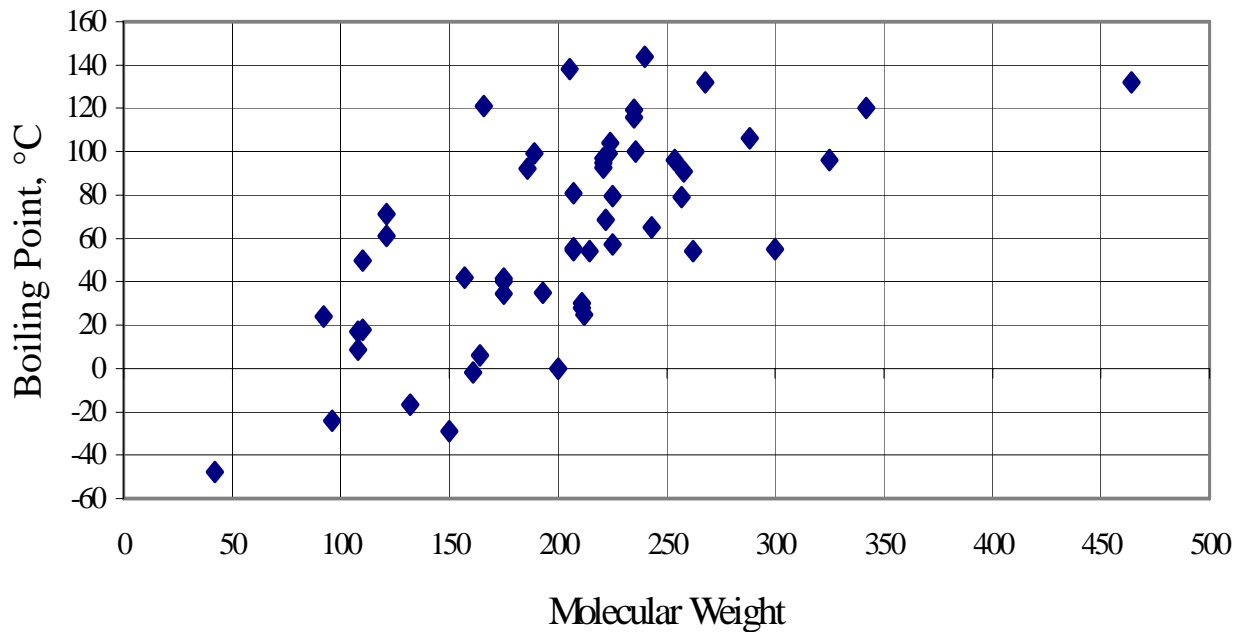


Figure 1. Boiling Point as a Function of Molecular Weight (g) for All Alkenes.

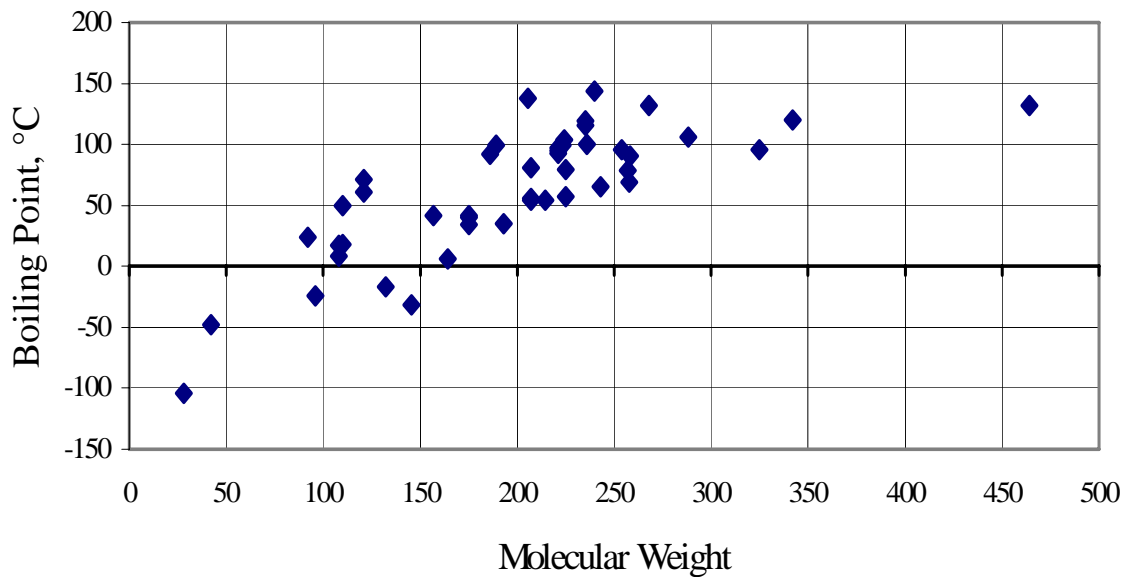


Figure 2. Boiling Point as a Function of Molecular Weight (g) for Alkenes containing Hydrogen.

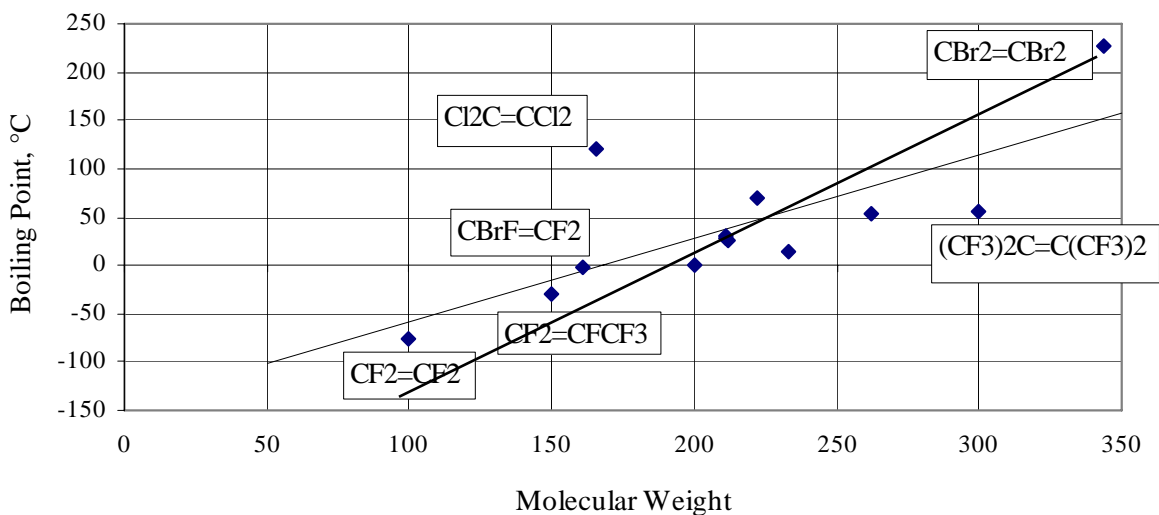


Figure 3. Boiling Point as a Function of Molecular Weight (g) for All Alkenes not Containing Hydrogen.

a) Classification by Halogens Contained

The foregoing analyses indicate that an examination of each chemical series by type of halogen is essential. This is of particular importance for the bromine-containing compounds, which are of greatest interest. Data for brominated and fluorinated compounds were plotted separately. Figure 4 through Figure 6 show data for bromine-containing compounds, most of which are fluorinated. Of particular interest is Figure 6, which shows data only for bromofluoroalkenes and hydrobromofluoroalkenes from which three estimated values have been removed. Despite the large scatter, there is a (somewhat poor) linear trend in Figure 6. Figure 7 gives some data for totally fluorinated alkenes.

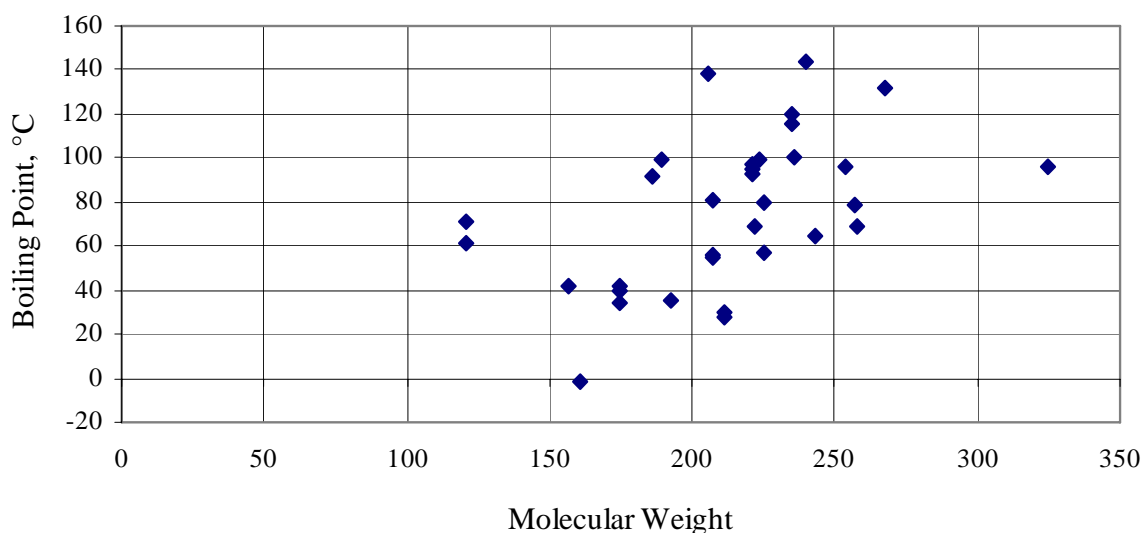


Figure 4. Boiling Point (°C) as a Function of Molecular Weight (g) for All Bromine-containing Alkenes

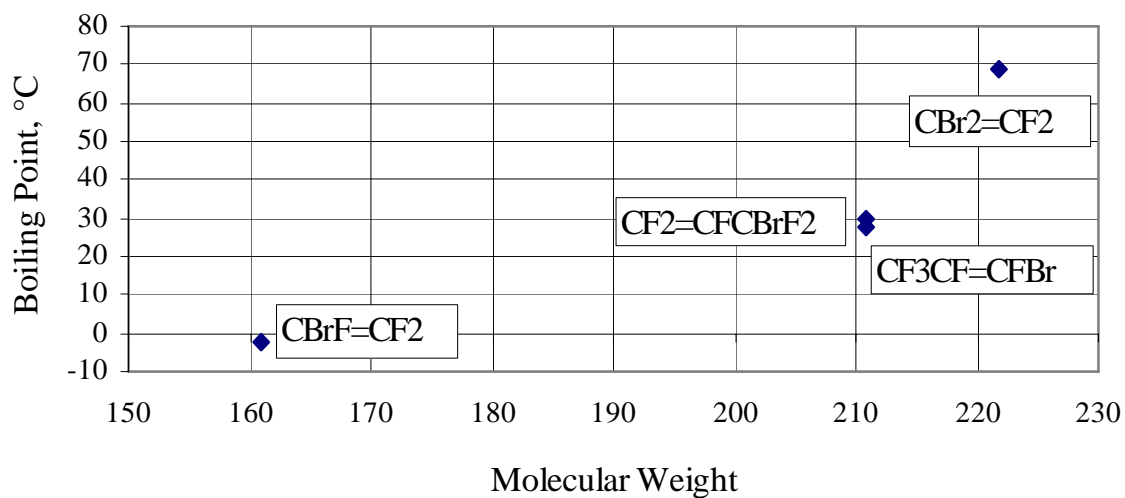


Figure 5. Boiling Point as a Function of Molecular Weight (g) for Bromine-containing Alkenes without Hydrogen

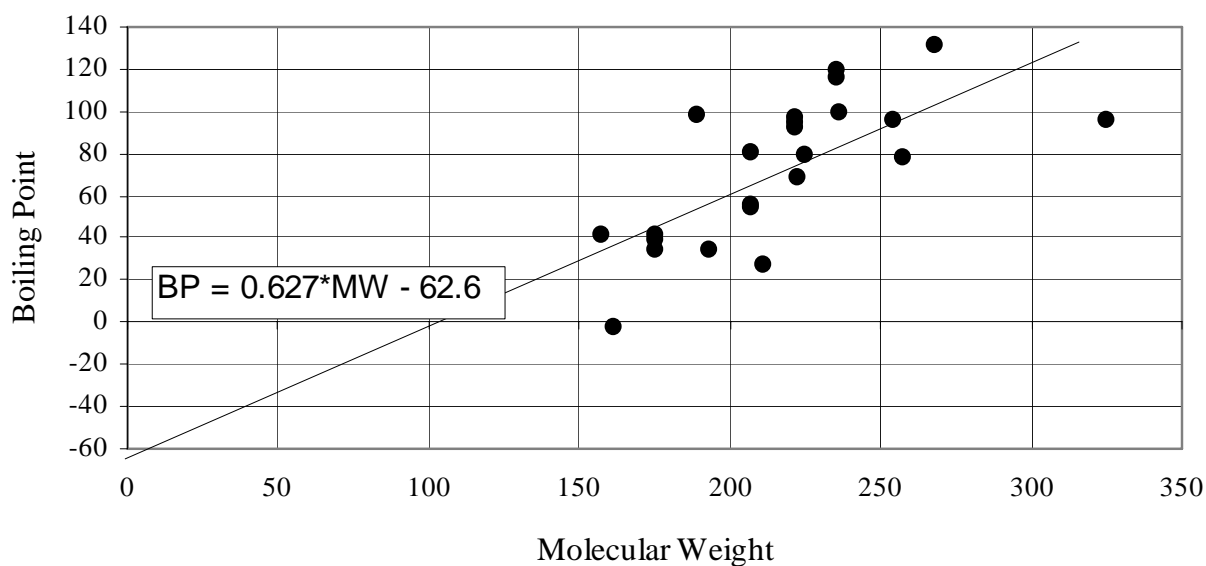


Figure 6. Boiling Point (°C) as a Function of Molecular Weight (g) for Bromofluoroalkenes and Hydrobromofluoroalkenes

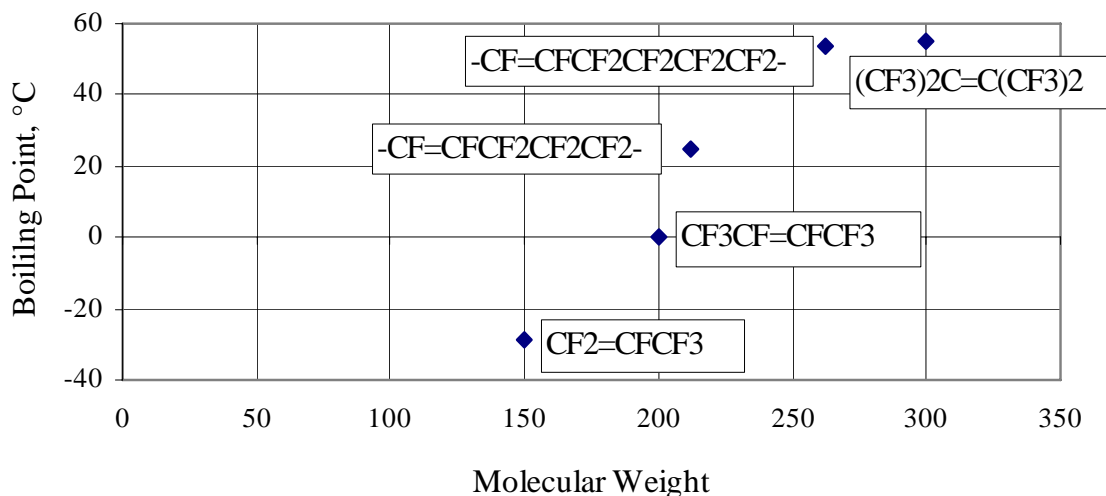


Figure 7. Boiling Point as a Function of Molecular Weight (g) for Totally Fluorinated Alkenes

b) Classification by Chain Length

A more fundamental approach, based on carbon chain length is revealing. Only molecules containing carbon, hydrogen, and specific halogens were plotted for ethenes, propenes, butenes, and a few pentenes (for which only a limited amount of data was available). Data were taken primarily from the Handbook of Chemistry and Physics.⁵⁹

c) Ethenes

The plots for brominated and chlorinated ethenes (none of which are fluorinated) show little scatter (Figure 8 and Figure 9); more scatter was found in the fluoroethene data (Figure 10).

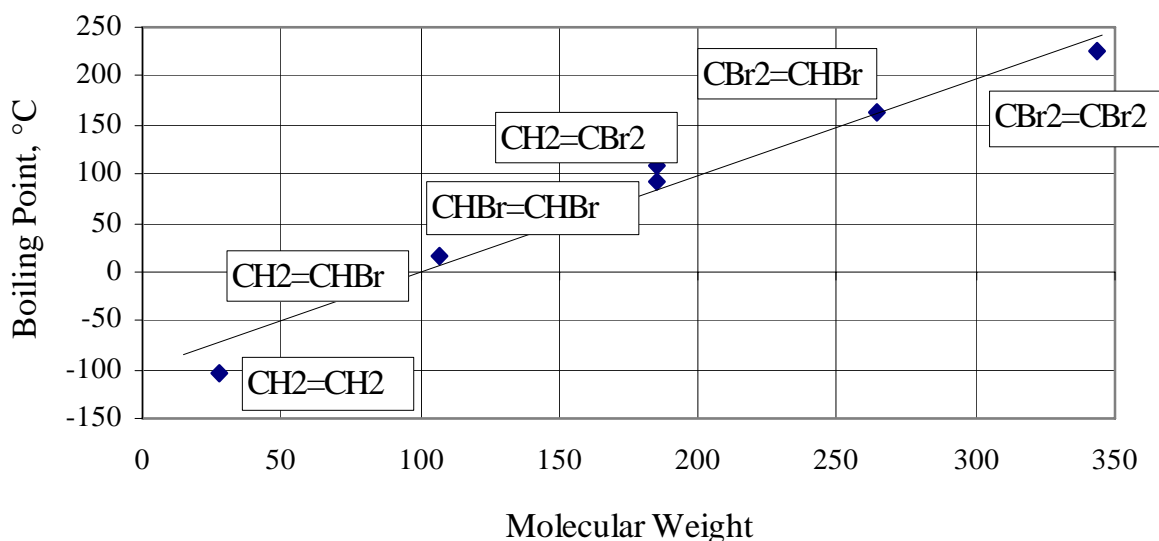


Figure 8. Boiling Point as a Function of Molecular Weight (g) for Bromine- and/or Hydrogen-containing Ethenes.

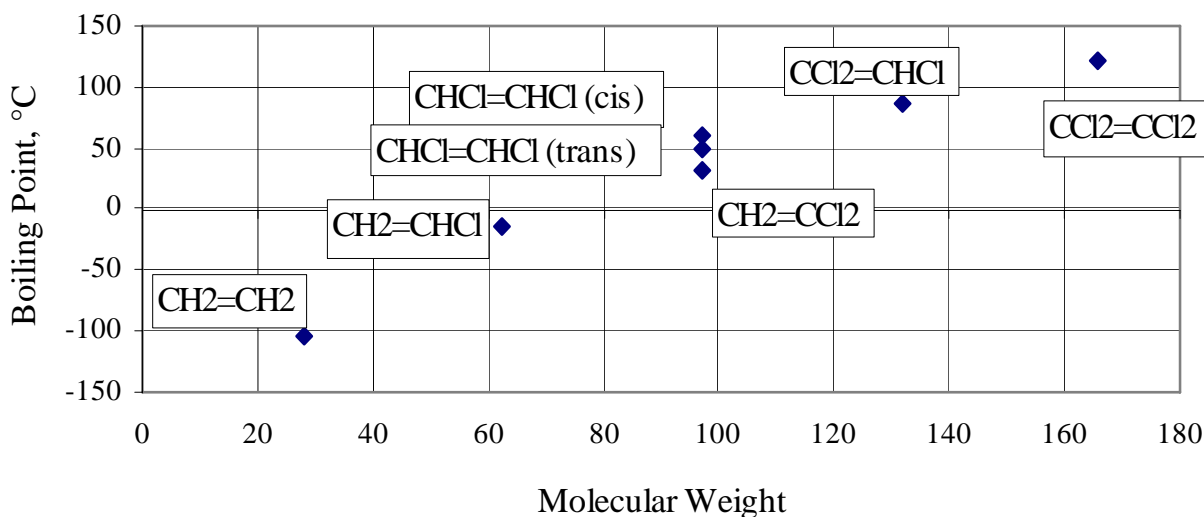


Figure 9. Boiling Point as a Function of Molecular Weight (g) for Chlorine- and/or Hydrogen-containing Ethenes

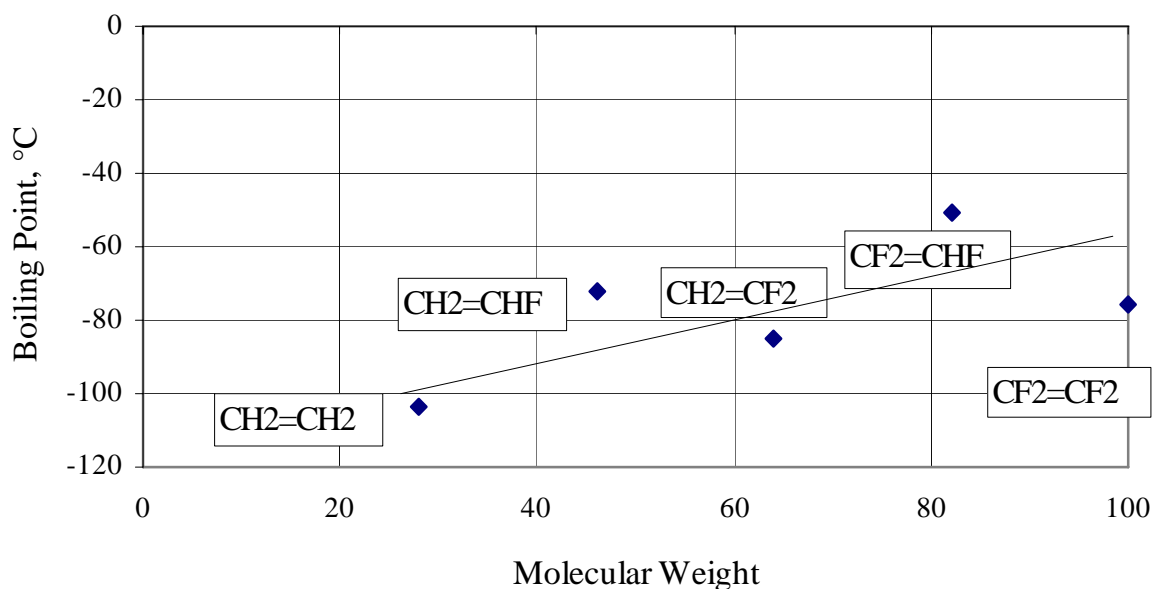


Figure 10. Boiling Point as a Function of Molecular Weight (g) for Fluorine- and/or Hydrogen-containing Ethenes

d) Propenes

The boiling point vs. molecular weight plot for all propenes in the CCOD indicated a trend of increasing boiling point with increased molecular weight, but with significant data scatter (Figure 11). Plots of brominated and chlorinated propenes (with only the bromine or chlorine atoms) (Figures 12 and 13) were smooth curves, but, like the ethenes, no smooth curve could be drawn for the fluorinated propenes (Figure 14).

The two C₃H₅F isomers indicated dramatically different boiling points: -24 °C for CH₂=CFCH₃, and -3 °C for CH₂=CHCH₂F. Seven isomers of dichloroethene (C₃H₄Cl₂) have

boiling points ranging from 76.5 °C to 112 °C, with steric isomers having differences of up to 16 °C. Three isomers of bromopropene (C_3H_5Br) range in value from 48.8 °C to 70.1 °C.

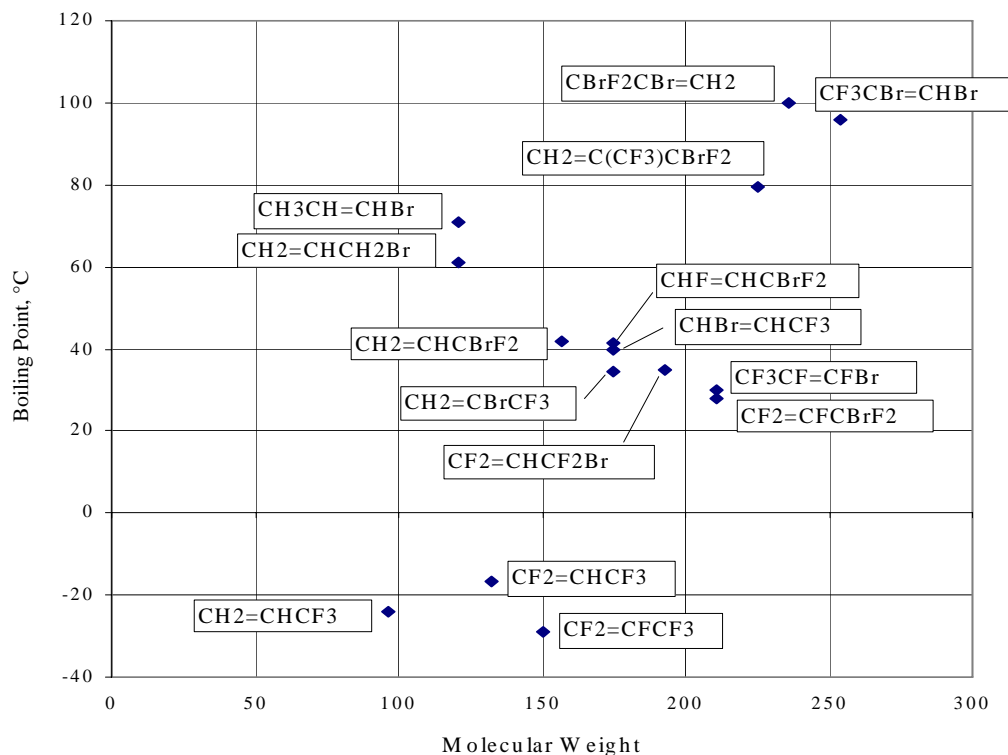


Figure 11. Boiling Point as a Function of Molecular Weight (g) for Bromine-, Hydrogen-, and/or Fluorine-containing Propenes

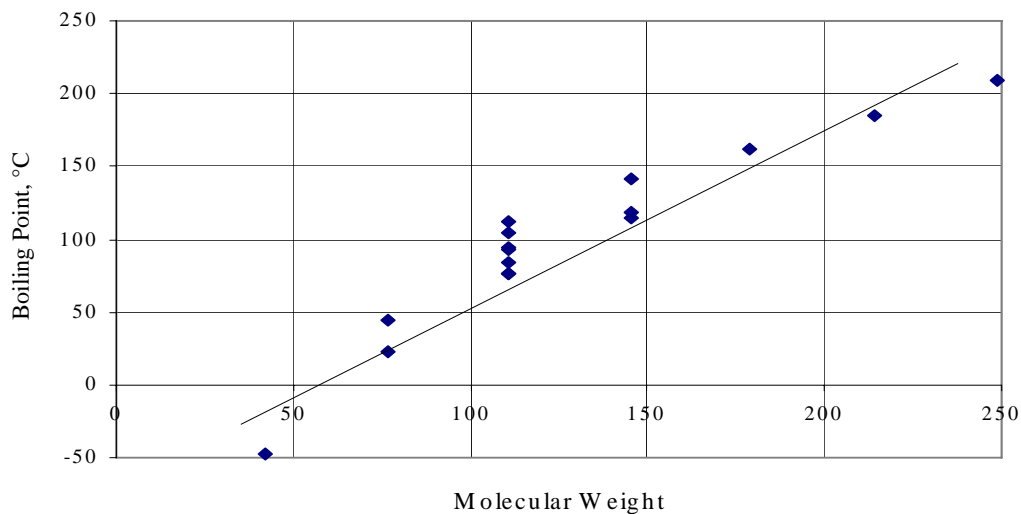


Figure 12. Boiling Point as a Function of Molecular Weight for Chlorine-, and/or Hydrogen-containing Propenes

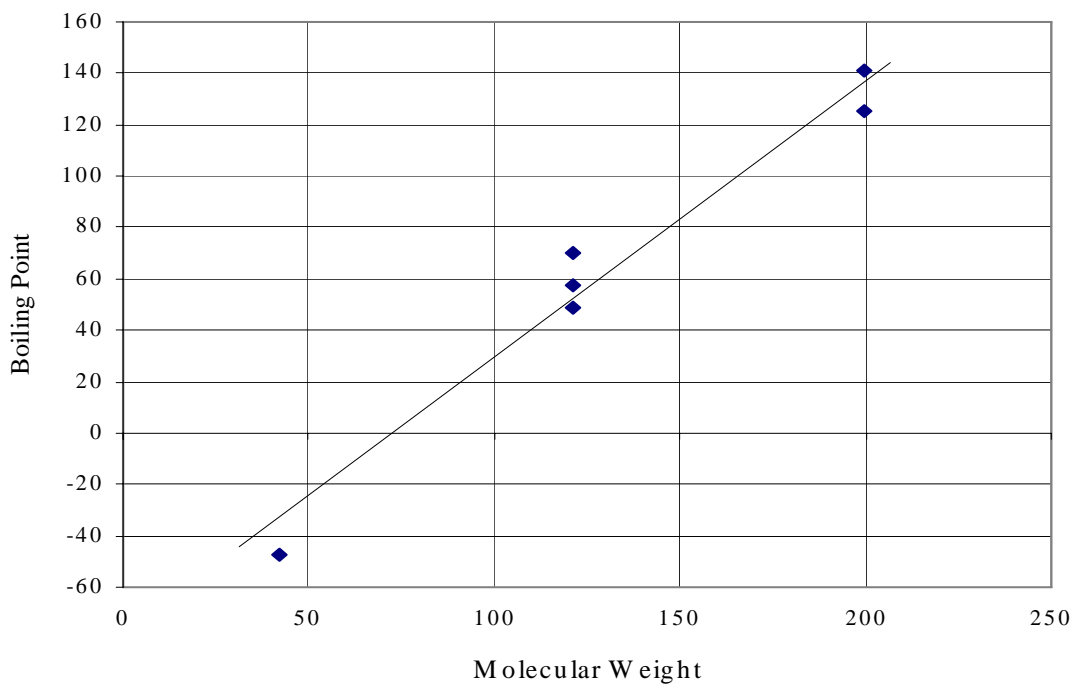


Figure 13. Boiling Point as a Function of Molecular Weight for Bromine-, and/or Hydrogen-containing Propenes

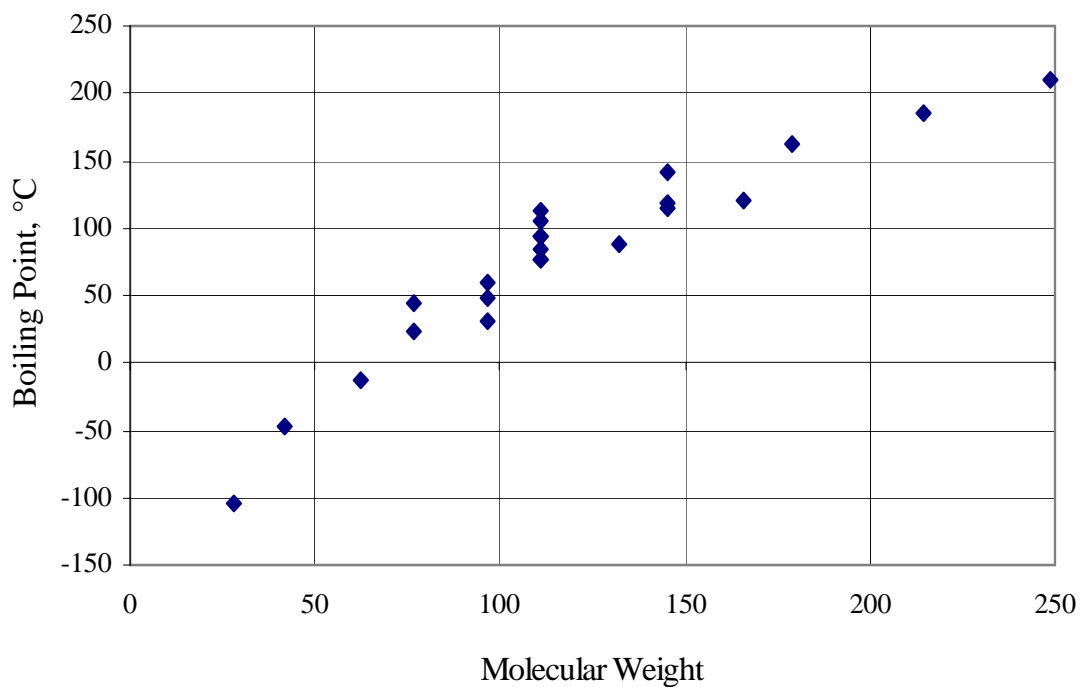


Figure 14. Boiling Point as a Function of Molecular Weight for Chlorine-, and/or Hydrogen-containing Ethenes and Propenes

A strong trend was found with mixed fluorinated and chlorinated compounds. A strikingly linear relationship exists between the boiling point and molecular weight of the ethenes (Figure 25) as chlorine atoms replace fluorine atoms. This linear relationship also holds for the propenes and butenes.

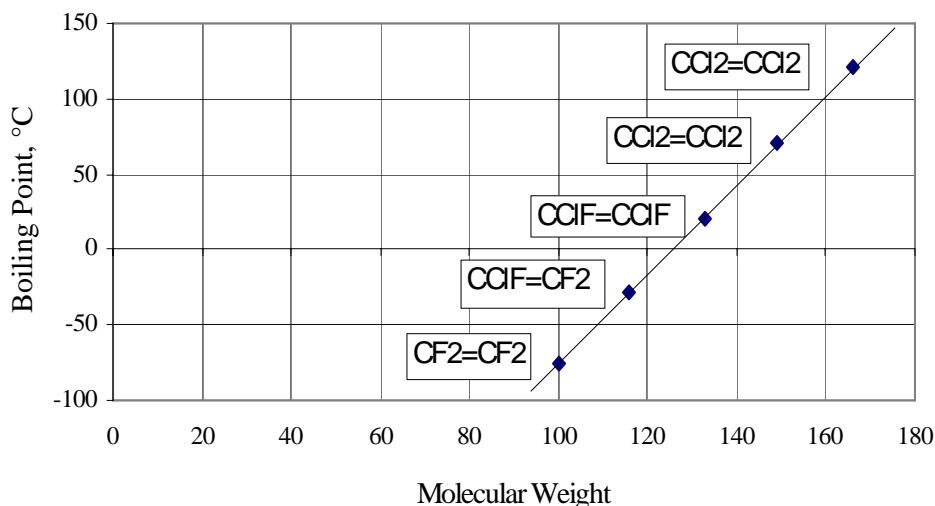


Figure 15. Boiling Point as a Function of Molecular Weight for Mixed Chlorinated and Fluorinated Ethenes

It has been shown that, especially for brominated and chlorinated alkenes, boiling point can be related to molecular weight; increasing the molecular weight increases the boiling point. There is one major exception. Fluorination generally decreases the boiling point, all other things being equal. For fluorinated alkenes, the excessive data scatter indicates only a general trend of increased boiling points with increased molecular weight (subject to the effect of fluorination noted above), but with significant data scatter. For brominated and chlorinated alkenes, there is much less data scatter.

Structural isomers of the chemicals can have different boiling points, sometimes with rather large temperature differences. Any analyses are complicated by the fact that double-bonded molecules such as alkenes have *cis* and *trans* isomers, which may also have boiling point temperature differences, although not as pronounced as for structural isomers. A full analysis of the impact of isomerism on boiling points must be reserved for a more detailed study.

4. Early Toxicity Assessments (Testing, Estimation, and Modeling Efforts)

Toxicological quantitative structure-activity relationships (QSARs) rely on the establishment of a statistically significant mathematical relationship between chemical toxicity and a particular chemical, structural or physical property of a group of similar compounds in order to be used to predict the toxicity of untested chemicals. Further, the predictive accuracy of values and trends is greatest only for compounds in the same group or very similar groups.

QSAR models also included proprietary models for halon property estimation which attempted the estimation of cardiac sensitization LOAEL values.⁶

QSAR modeling of 25 brominated compounds were performed by the U.S. Army Center for Health Promotion and Preventative Medicine (CHPPM) and the British Ministry of Defence (MOD) DERA. U.S. Army CHPPM employed TOPKAT to model QSAR toxicity predictions of acute LD₅₀, LC₅₀, eye sensitization and chronic LOAEL, mutagenicity, DPT, and carcinogenicity.⁷

DEREK (Deductive Estimation of Risk from Existing Knowledge version 15.1)⁸, a rule-based software system designed for qualitative prediction of the potential hazards of a chemical based on known structure-activity relationships, was also employed to evaluate the toxicity of the same list of compounds however the program does not estimate cardiac sensitization.⁹ Four endpoints were evaluated: carcinogenicity, mutagenicity, sensitization (presumably respiratory) and skin sensitization. DEREK identifies structures within a molecule that confer a particular type of biological (toxicity) effect. The main applications of the “rule-based” approach employed by DEREK are in the prediction of mutagenicity (Mut), carcinogenicity and skin irritation (Sk Irr) or sensitization and to a lesser extent reproductive and neurotoxicity. In addition, the “rules” incorporated into model skin sensitization (where the program has a tendency to predict false positives) as well as respiratory sensitization, irritation and corrosivity. Acute toxicity is generally of the highest concern for halons. Unfortunately acute toxicity is not specifically addressed by the program nor is cardiac sensitization.

As these estimation methods are totally dependant on the existence of a “training set” of data for similar chemical structures and chemical functional groups in order to establish the correlations and weightings needed to be predictive the almost complete lack of appropriate training data proved fatal to the approach. The approach was not pursued beyond these initial attempts.

General Chemical Toxicity Trends

Some general toxicity trends for alkanes, based on non-quantitative structure activity relationships (SARs), were identified from comprehensive reviews of the toxicity literature.¹⁰ This work identified trends, which are shown below in rows, with the compound formula followed by ln(LC₅₀) values in mice for 30 min exposures. General trends relating the number of fluorine or hydrogen atoms needed to impart favorable toxicity were not identified. This study indicated that location of substituents appeared to play a more important role than number of fluorine or hydrogen atoms.

- Toxicity increases in the order F < Cl < Br.
CHF₂CH₂Cl, 2.00 CHF₂CH₂Br, 1.52
CF₃CHFCl, 3.8 CF₃CHCl₂, 2.00 CF₃CHBrCl, 0.18
- For haloethanes, H adjacent to a -CF₃ group increases toxicity, therefore, CF₂XCHF_X is preferred over CF₃CHX₂. (The Xs can be identical or dissimilar halogens and follow the same trend as outlined above.)

CF ₂ ClCHFCl, 2.20	CF ₃ CHCl ₂ , 2.00	
CF ₂ BrCHFBr, 0.45	CF ₃ CHBr ₂ , 0.18	
CF ₂ ClCHFBr, 1.42	CF ₂ BrCHFCl, 1.22	CF ₃ CHBrCl, 1.10

- For halopropanes, the -CH₃ group reduces toxicity (at least when opposite a -CF₃ group); therefore CF₃CXRCH₃ is preferred over CF₃CRHCH₂X, where R can be either a halogen or H.

CF ₃ CCl ₂ CH ₃ , 2.30	CF ₃ CH ₂ CHCl ₂ , 0.88	CF ₃ CHClCH ₂ Cl, 0.79
CF ₃ CHBrCH ₃ , 2.03	CF ₃ CH ₂ CH ₂ Br, 1.50	

- For halopropanes, -CH₂- groups are favored over -CF₂- groups.

CHF ₂ CH ₂ CClF ₂ , 3.00	CHF ₂ CF ₂ CH ₂ Cl, 1.62
CF ₂ ClCH ₂ CH ₃ , 2.77	CH ₂ ClCF ₂ CH ₃ , 2.13

To decrease the toxicity, it is essential that carbon atoms alpha to the carbonyl group contain no halogen atoms. Carbonyl compounds exhibit a range of toxicities depending on whether the carbonyl group is in an aldehyde, ketone, carboxylic acid, or ester.

Collaborative Toxicity Studies of Tropodegradable Bromofluoroalkenes

Extremely promising inhalation exposure acute toxicity testing at 5 volume %, Table 7, of eight bromofluoroalkenes demonstrated no adverse effects in the five of the tested compounds.¹¹ The surprisingly good results from this round of initial testing provided impetus for a greatly expanded program of testing for selected bromofluoroalkenes. Members of the AAWG provided the funding for this effort.

Early compound toxicity efforts were greatly aided by research in anesthesiology. Only a limited number of anesthesia-related test results on halogenated alkenes have been reported.¹² Where provided, the concentrations used in these exposures were high. In some cases the exposure observations provided useful guidance and in one case gave strong support to the further study of a number of brominated fluoroalkenes structurally related to 2-bromo-3,3,3-trifluoropropene, CH₂=CBrCF₃. This compound was reported to be an excellent anesthetic with a rapid, uneventful recovery following exposure.¹³ As the concentrations used are unknown, it is difficult to determine the potency of this chemical as an anesthetic; however, that no adverse effects were observed indicates that this material may have a low toxicity. Studies of 3-chloro-3,3-difluoropropene, CF₂ClCH=CH₂, as an anesthetic in dogs show cardiac arrhythmia with ventricular extra systole, blood pressure decrease, and tremor. The related compound 3-bromo-3,3-difluoropropene, CF₂BrCH=CH₂, proved extremely toxic in inhalation exposure testing.¹¹

Overall the reported live animal toxicity testing performed in the course of anesthesia research provided the useful guidance in evaluation candidate compound acute inhalation toxicities and aided early efforts to down-select and target compounds for further synthesis and

testing. Efforts to identify suitable anesthesia agents confronted challenges similar to those of interest to the halon replacement community. One of these is cardiac sensitization.

Table 7. Acute Inhalation Toxicity of Tropodegradable Bromofluoroalkenes.

Compound	Formula	Deaths ^a during (post) Exposure
1-Bromo-3,3,3-trifluoropropene	CF ₃ CH=CHBr	0
2-Bromo-3,3,3-trifluoropropene	CF ₃ CBr=CH ₂	0
4-Bromo-3,3,4,4-tetrafluorobutene	CF ₂ BrCF ₂ CH=CH ₂	0
2-Bromo-3,3,4,4,4-pentafluorobutene	CF ₃ CF ₂ CBr=CH ₂	0
2-Bromo-3,3,4,4,5,5,5-heptafluoropentene	CF ₃ CF ₂ CF ₂ CBr=CH ₂	0 (1)
3-Bromo-3,3-difluoropropene	CH ₂ =CHCBrF ₂	7
2-Bromo-3-trifluoromethoxy-3,4,4,4-tetrafluorobutene	CH ₂ =CBr(OCF ₃)CFCF ₃	10
2-Bromo-3-trifluoromethyl-3,4,4,4-tetrafluorobutene	CH ₂ =CBrCFC(CF ₃) ₂	10

a 10 rats and a 30 min exposure at 5 volume % agent air concentrations

The Ames Mutagenicity test results¹⁴ on the more promising compounds selected based on boiling point were equally reassuring, Table 8, as were the results of the chromosomal aberration tests, Table 9.¹⁵

Table 8. Ames Mutagenicity Test Results.

Compound	Formula	Ames Test Result
2-Bromo-3,3,3-trifluoropropene	CF ₃ CBr=CH ₂	Negative
4-Bromo-3,3,4,4-tetrafluorobutene	CF ₂ BrCF ₂ CH=CH ₂	Negative
2-Bromo-3,3,4,4,4-pentafluorobutene	CF ₃ CF ₂ CBr=CH ₂	Negative

Table 9. Chromosomal Aberration Test Results.

Compound	Formula	Test Result
2-Bromo-3,3,3-trifluoropropene	CF ₃ CBr=CH ₂	Negative
4-Bromo-3,3,4,4-tetrafluorobutene	CF ₂ BrCF ₂ CH=CH ₂	Negative

Inhalation toxicity and other acute exposure toxic reactions must be fully examined. Fire suppressing events expose by-standers and firefighters briefly to the suppressant chemical. This type of exposure is categorized as an acute event. While chronic exposure is a serious

consideration, initial studies of toxicity are, for the most part, focused on acute effects and toxicity. Typical initial screens are the Ames test, mouse micronucleus test, inhalation toxicity assessments, and cardiotoxicity tests.

Cardiac sensitization is a property that has been associated with both halogenated and non-halogenated compounds. It has surfaced as a consideration in the development of solvents, halons, and propellants for medical inhalers, it is observed as a cause of cardiac arrest in substance abuse by inhalation of solvents used in spray paints, lubricants, glues and hairsprays and it is associated with some pharmaceuticals and frequently associated with volatile surgical anesthesia agents. Known cardiac sensitizing or arrhythmogenic compounds are represented by a wide range of chemical families including alkanes, alkenes, ethers, fluorocarbons, iodocarbons, and bromocarbons.

The cardiac sensitization test presented in Table 10 represents the only two such test attempted on bromofluoropropenes.^{16,17} While the 1 % LOAEL value observed for 2-bromo-3,3,3-trifluoropropene is disappointingly low and the compound not useable as a halon 1301 replacement, the compound may well be able to serve as a halon 1211 replacement, usable in unoccupied areas. Testing of 1-bromo-3,3,3-trifluoropropene was terminated due to severe adverse effects, including tremor.

Table 10. Cardiac Sensitization Testing of Bromofluoropropenes.

Compound	Formula	NOAEL	LOAEL
2-Bromo-3,3,3-trifluoropropene	CF ₃ CBr=CH ₂	0.5 % vol. %	1.0 vol. %
1-Bromo-3,3,3-trifluoropropene	CHBr=CHCF ₃	a	A

a Determination aborted due to adverse effects on dogs

While the limited toxicity data are promising, additional fluorination of these molecules is desirable to reduce boiling points. It is unclear where the optimum in degree and pattern of fluorination and site of bromination lies. Given the many additional compounds that have yet to be tested hope that at least one will have acceptable cardiac sensitization and other toxicity properties to be acceptable for use in occupied areas does not seem entirely unreasonable.

Cardiac Arrhythmia - Chemical Sensitization of the Heart to Epinephrine

Determining cardiac sensitization LOAEL and NOAEL concentrations entails measurement of cardiotoxic effects in animals made sensitive by the administration of epinephrine at dose levels just below the concentration at which epinephrine alone would cause cardiotoxicity. In the experimental animal the administered epinephrine levels are approximately 10 times greater than the concentration a human would be likely to secrete under stress, and therefore LOAEL and NOAEL values are conservative even in high-stress situations, with the result being an overall increased margin of safety.

The mechanism of cardiac sensitization is not understood, making design of a screening method difficult. Some researchers have concluded that cardiac sensitization is a direct result of

a physical-chemical interaction of the sensitizing agent with heart cell membrane structures.¹⁸ This mechanistic hypothesis is derived from the observation that a critical blood concentration of agent is needed to elicit a cardiac sensitization response and the effects are immediately reversible, if they are not sufficiently severe to cause death, when the sensitizing agent is removed. Below that critical concentration, the effect does not occur.

Cardiac sensitization LOAEL and NOAEL values of potential halon replacements are essential to compound selection and reducing risk for occupied space extinguishment agents. The cost of performing the test is currently in the range of \$100,000, and as a result the test is performed only rarely. Screening methods were sought in order to aid in the selection of compounds with a higher probability of have acceptable LOAEL and NOAEL values when actually tested. A wide variety of approaches to estimating and/or understanding the mechanism were reviewed in the course of the overall halon replacement effort.

Any estimation method enabling a ranking of compounds would greatly facilitate compound acquisition efforts. Methods would have to be able to distinguish between compounds whose LOAEL values differ by 1 volume % to 2 volume % in order to be of much use in final compound selection.

Cardiac Sensitization – Search for Trends

Cardiac sensitization is the sudden onset of cardiac arrhythmias caused by a chemical sensitization of the heart to epinephrine (adrenaline). Cardiac sensitization is a problem that has been associated with halogenated and non-halogenated compounds. It has surfaced as a consideration in the development of propellants for medical inhalers, it is observed as a cause of cardiac arrest in substance abuse by inhalation of solvents used in spray paints and hairsprays and it is seen in some pharmaceuticals and some surgical anesthesia agents. Cardiac sensitization is a particularly important concern in firefighting because under the stress of the fire event, higher levels of epinephrine are secreted by the body, increasing the possibility of sensitization. CFCs (which are closely related to the halons), a number of compounds currently under study as halon replacements, and many of the commercialized halon replacements, are cardiotoxins.¹⁹ These gases enter the arterial blood and cause arrhythmic cardiac rhythm resulting in a compromised blood pumping action.

The determination of a compounds ability to cause cardiac sensitization (cardiac arrhythmia) under conditions of an epinephrine challenge is used to assess cardiotoxicity. This test is performed on dogs and the approach is not without its critics. It is widely accepted that LOAEL data obtained from the dog exposure based cardiac sensitization testing are very conservative and, perhaps as a direct result, deaths due to human exposure to halons are extremely rare. The dog cardiac sensitization exposure based standard seems to be achieving exactly what it was designed to achieve – ensuring a wide margin of safety to a broad spectrum of end users.

A wide range of chemically diverse compounds are known to induce cardiac arrhythmia. This situation has led to the hypothesis that the mechanism involved is not a chemical (reactivity based) toxicity but instead a generalized physical property effect that just happens to cause

cardiac arrhythmia when sufficient chemical is absorbed into heart nerve and muscle cells membranes.²⁰

Past clinical research on anesthesia agents may provide guidance.^{21,22} Clinical observations reported in medical research literature suggest a possible link between a compounds oil/water partitioning and its tendency to initiate premature ventricular contractions (PVCs) under normal surgical anesthesia. The mechanism of cardiac sensitization is not understood, making design of a screening method difficult. Some researchers have concluded that cardiac sensitization is a direct result of a physical-chemical interaction of the sensitizing agent with heart cell membrane structures.²³ This mechanistic hypothesis is derived from the observation that a critical blood concentration of agent is needed to elicit a cardiac sensitization response and the effects are immediately reversible, if they are not sufficiently severe to cause death, when the sensitizing agent is removed. Below that critical concentration, the effect does not occur.

An estimation method, enabling a ranking of compounds, leading to the identification of the most promising (highest LOAEL) candidates and the identification of molecular features associated with both the extremes of LOAEL performance would greatly facilitate a focused compound acquisition effort. Such a method would have to be able to distinguish between compounds whose LOAEL values differ by 1 volume % to 2 volume % in order to be of much use in final compound selection.

The fluorocarbons and hydrofluorocarbons listed in Table 11 demonstrate a wide range of LOAEL values.

Table 11. Fluoro/hydrofluorocarbon Cardiac Sensitization Values.

#	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₃ CF ₂ CF ₂ CF ₃	40	>40
2	CF ₃ CF ₂ CF ₃	30	>30
3	CF ₃ CHFCHF ₂	2.5	3.5
4	CF ₃ CHFCF ₃	9	10.5
5	CF ₃ CH ₂ CF ₃	10	15
6	CH ₂ F ₂	20	25
7	CHF ₃	30	>50
8	CH ₂ FCF ₃	4	8
9	CH ₃ CF ₃	4	8
10	CHF ₂ CF ₃	7.5	10
11	CH ₃ CF ₂ H	5	15

Limited hydrofluoropropane data (Compounds 3 through 6) as well as hydrofluoroethane data (Compounds 8 through 11) in Table 11 demonstrate no correlation between degree of

fluorination and LOAEL value, but do suggest that fluorine (or conversely, hydrogen) position may be a strong factor in determining cardiac sensitization effects in these HFCs.

The iodofluorocarbons, bromofluorocarbons, and bromochlorofluorocarbons listed in Table 12 reflect increasing LOAEL values where bromine is replaced by iodine. Chlorofluorocarbon cardiac sensitization data,

Table 13, provide no indication of relationship between degree of fluorination, chlorination or hydrogenation and LOAEL values.

Table 12. Halogenated Fluorocarbon Cardiac Sensitization Values.

	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₃ I	0.2	0.4
2	CF ₃ Br	5.0	7.5
3	CF ₂ HBr	2	3.9
4	CF ₂ Br ₂	-	-
5	CF ₂ BrCl	0.5	1.0
6	CF ₂ BrCF ₂ Br	-	0.1
7	CBrClFCBrF ₂		0.5
8	CF ₃ CF ₂ CF ₂ I	-	0.1

Table 13. Chlorofluorocarbon Cardiac Sensitization Values.

	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₂ CIH	2.5	5
2	CF ₂ Cl ₂	2.5	5
3	CFCl ₃	-	0.5
4	CH ₂ =CCIH	2.5	5
5	CCl ₃ CH ₃	0.25	0.5
6	CF ₂ ClCH ₃	2.5	5
7	CFCl ₂ CH ₃	-	0.5
8	CF ₃ CF ₂ Cl	-	15
9	CF ₃ CCl ₂ H	1	2
10	CFCl ₂ CH ₃	-	1
11	CF ₂ ClCF ₂ Cl	-	2.5
12	CClF ₂ CFCl ₂	0.25	0.5
13	CF ₂ ClCF ₂ CFHCl	-	2.0

The highly fluorinated compound, CF₃CF₂Cl, is notable for its unusually high LOAEL of 15 volume % most values range from a low of 0.5 volume % to a nominal high of 5 volume %.

Cardiac Sensitization – Chemical Attributes and Structural Predictors

Skaggs et al, performed an extensive review of toxicity prediction and screening approaches, identifying chemical attributes employed in the development of QSARs, predictors of relationships between biological activity and chemical properties.²⁴ These can be classified as property descriptors and topological descriptors (steric and structural). Table 14 through Table 19 List and provide physical attributes for selected descriptors.

Table 14. QSAR - Hydrophobicity Measures.

Hydrophobicity Measure
Octanol-water partition coefficient, KOW
RM coefficient from reverse-phase chromatography
Solubility in water
Solubility in parachor

Table 15. QSAR - General Physical Properties.

Physical Property
Melting point
Boiling point
Vapor pressure
Dissociation constant
Activation energy
Heat of reaction
Reduction potential

Table 16. QSAR - Electronic Parameters.

Electronic Parameter
Hammett Constant, σ
Taft Polar Substituent Constant, σ^*
Ionization potential
Dielectric constant
Dipole moment
Hydrogen bonding

Table 17. QSAR - Steric Parameters.

Steric Descriptors
Molecular volume
Molecular weight
Molecular surface area
Molar refractivity
Substructure shape
Taft Steric Substituent Constant
Verloop STERIMOL constants

Table 18. QSAR - Quantum Mechanical Parameters.

Quantum Chemical
Molecular Orbit indices
Electron density
π -Bond reactivity
Electron polarizability

Table 19. QSAR - Structural Descriptors.

Structural Descriptors
Atom and bond fragments
Substructures
Substructure environment
Number of atoms in group
Number of rings (in polycyclics)
Molecular connectivity

Skaggs et al. reported that the key to using any of these techniques is to determine a family of chemicals for which biological indices (for example, LD₅₀), as well as physical/chemical properties, molecular structure, or both, are known. In actual QSAR modeling these sets of data are referred to as “training sets.” By the use of statistical techniques such as multiple regression analysis (MRA), a relationship between the biological indices and property/molecular structure is determined based on the “training set” data. The better or more extensive the training set the more the predictions are apt to be accurate.²⁵

Hydrophobicity is a measure of water insolubility. Neutral, unreactive chemicals exhibit a strong relationship between the hydrophobicity of the compound and its LC₅₀. Hydrophobicity is equated to the octanol-water partition coefficient (K_{OW}) and reflects the ability of a chemical to cross a biological membrane and correlates with toxicity because diffusion through cell walls allows chemicals to influence internal cellular processes and biochemistry. Both the Hammett Constant and the Taft Polar Substituent Constants are measures of substituent polarity. Steric properties relate to molecular structure and affect the binding of molecules to biological sites.

Molecular connectivity descriptors describe the number of atoms in a compound and their formally-bonded and spatial relationships. Molecular Connectivity Indices (MCI) associate numerical values with structure of the molecule. Many properties are directly related to the number and connections of atoms in molecules.²⁶ Linear Solvation Energy Relationship (LSER) analysis is based on the correlation of diverse chemical properties, including toxicity and solvent-solute interactions. The analysis is based on four molecular parameters: intrinsic molecular volume, polarity, and two measures of ability to hydrogen bond as an acceptor or

donor. While this measure provides the most accurate QSARs covering the widest range of chemical classes, the parameters are available on only a small amount of chemicals.²⁷

Molecular connectivity QSARs require that indices based on structure be determined, and generally the amount of data needed is less than that for quantitative property-activity relationships (QPAR). In both cases, sufficient toxicity data must be available with which to develop correlations capable of providing toxicity estimates of unknown substances. These data are not available in the required abundance to perform highly reliable assessments across a broad range of compounds.

Some general (but not universal) toxicity criteria shown in Table 20 have been used to provide a relative toxicity ranking for the candidate compounds and compound groups (alkenes, ethers, cyclics, etc.).*

Cardiac Sensitization - In vitro Screening Method Development

To be of greatest use to the halon replacement community, an in vitro-based test protocol capable of differentiating between halon 1301 (LOAEL 7.5 volume %) and halon 1211 (LOAEL 1.0 volume %) or trifluoromethyl iodide (LOAEL 0.4 volume %) is the desired goal. This is due in part to the need to identify compounds whose fire suppression design air concentrations are expected to be in the range of 3 volume % to 4 volume % and whose LOAEL values are likely to be only 2 volume % or 3 volume % higher.

The development of an in vitro cardiac sensitization screening method requires the development and validation of a system that retains the essential components of the process of cardiac sensitization. Identified requirements²³ for an in vitro system include a cardiomyocyte system that:

1. exhibits synchronized and spontaneous contraction,
2. is responsive to exogenous epinephrine,
3. exhibits sensitivity to known cardiac sensitizers, and
4. allows exposure of sensitizing agents to system in a controlled atmosphere.

To this list must be added the ability to accurately rank compounds whose LOAELs differ by as little as a few percent. As early as the 1960s, cardiac myocytes were used to study the mechanistic aspects of cardiac metabolism and function.²³

* Allen Vinegar, ManTech Environmental Technology Inc., Dayton, Ohio, personal correspondence to Robert E. Tapscott, New Mexico Engineering Research Institute, The University of New Mexico, Albuquerque, New Mexico, May 1997.

Table 20. General Toxicity and Cardiac Sensitization Rules.

Toxicity Ranking Criteria
Aromatics are more toxic than aliphatics.
Asymmetric molecules are more toxic than symmetric.
Straight (carbon) chains are more toxic than branched.
Ethers are more toxic than alkanes.
Short chain ethers are more toxic than long chain ethers.
Vinyl ethers are more toxic than saturated ethers.
Polyoxyethers are more toxic than mono ethers.
Cardiac Sensitization Ranking Criteria
Halogen presence is more potent than hydrogen.
Bromine presence is more potent than fluorine presence.
Iodine presence is more potent than bromine presence.

In vitro Cardiac Cell Preparation Options

Isolated ventricular myocytes have been isolated or cultured while retaining their spontaneous electrical activity,²⁸ cultured neonatal rat heart cell cultures have been used to investigate the effects of quinidine on cardiac cell function,²⁹ where sodium flux measurements and myocyte contraction rates demonstrated that quinidine reduced the spontaneous beating rate of the cells. In some preparations, contractility or “beating” can also be maintained.

Types of *in vitro* cardiac systems are shown in Table 21. Most of these studies, however, were not performed to assess effects of certain drugs on cardiac function, and others were performed to determine specifics of cardiac function itself.

Skaggs et al. concluded that despite the variety of *in vitro* systems available to assess the cardiac toxicity of certain agents, any model selected would have to be characterized with respect to the expression and response of adrenergic receptors and the ion fluxes (sodium and calcium) before cardiac sensitization validation studies could be initiated.²³

Table 21. In vitro Cardiac Cell Systems.

Model	Life stage	Species	Reference
Myocardial cells	Fetal	Human	[30]
Cardiomyocytes	Neonatal	Rat	[31]
Ventricular Cardiomyocytes	Neonatal	Rat	[32]
Ventricular Cardiomyocytes	Neonatal	Dog	[33]
Cardiomyocytes	Adult	Rat	[34]
Cardiomyocytes	Adult	Rabbit	[35]
Cardiomyocytes	Adult	Dog	[36]
Cardiomyocytes	Adult	Feline	[37]
Ventricular Cardiomyocytes	Adult	Guinea Pig	[38]
Ventricular Cardiomyocytes	Adult	Rat	[39]

Flame Extinguishment Performance Testing – Cup Burner Test Method

Because samples acquired in the course of these efforts covered a range of boiling points, two sample introduction methods were developed and employed. Samples were handled either as gases or liquids and their vapor partial volumes either determined (for liquids) based on the ideal gas law with corrections for barometric pressure and ambient temperature or based on measured volumetric flows in the case of gaseous samples. In some cases only a limited amount of a compound could be obtained. In these cases extinguishment test results are indicated as establishing upper bound extinguishment values. Both methods for testing of liquids and gases are briefly described. For the most part all cup burner testing evaluated the extinguishment of n-heptane flames by candidate chemical agents and reported data in units of volume %. Schematics of liquid and gaseous sample introduction methods are illustrated in Figure 17.

Cup burner configuration for liquid samples. The cup burner configuration for samples that are liquid at room temperature and pressure employed a syringe pump. A sample's liquid density is measured. The cooled sample is discharged by the syringe pump at a known rate and nebulized using an ICP nebulizer, Figure 16. The dispersed mist is carried by a make-up air flow into a heated glass column and fully evaporated. The resulting air agent mixture enters the cup burner at a temperature between 40 °C and 50 °C. Cooling the syringe and chemical depresses vaporization and the tendency to form bubbles within the syringe and connecting tubing. Under these conditions, reliable rates of sample introduction can be achieved. Barometric pressure measurements are employed in calculation of agent air concentrations.

Cup Burner configuration for volatile (gaseous) samples. The cup burner configuration for volatile samples takes advantage of the compounds ready vaporization to fill a Tedlar sample bag, Figure 17. The bag is contained within a pressure chamber and upon introduction of a known flow of air into the chamber an equivalent flow of the vaporized pure chemical is achieved into the cup burner base. Cup burner dilution air flows were established and monitored

using mass flow meters. Barometric pressure measurements are employed as needed to calculate effective air concentrations.

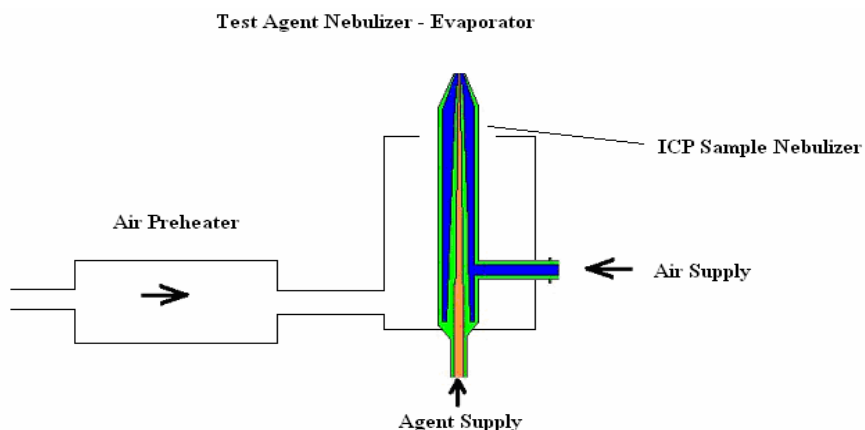


Figure 16. Sample Nebulizer and Air Pre-heater.

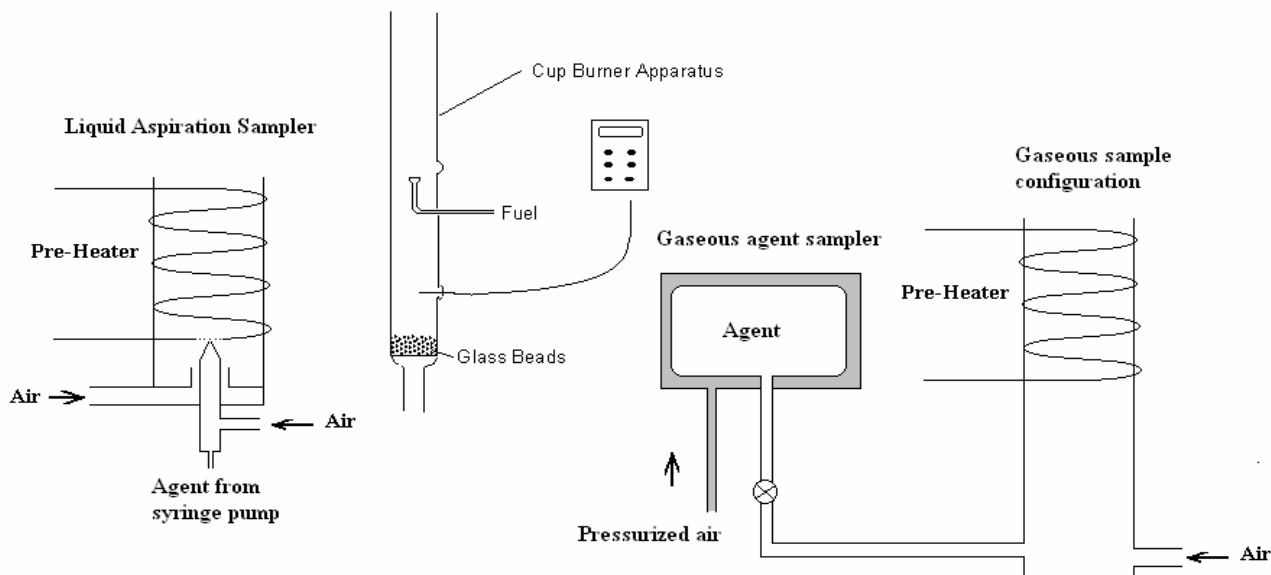


Figure 17. Cup Burner with Liquid Sample Nebulizer and Gaseous Sample Injection.

Decision Trees for Evaluation of Candidate Compounds

A decision tree for compound testing, evaluation, and possible acceptability has been developed. The overall decision tree procedure evaluates in turn (1) atmospheric release, (2) hydrolysis, (3) physical removal, (4) photolysis, (5) reaction with hydroxyl free radicals, (6) reaction with tropospheric ozone, (7) other reactions, (8) stratospheric ozone removal, and (9) global warming, allowing decision points at each stage, Figure 18. A detailed decision tree is shown in Figure 19 where t_{max} is the maximum allowable atmospheric lifetime and t_{hyd} , t_{phys} , t_{phot} ,

t_{OH} , and t_{O_3} are tropospheric lifetimes for hydrolysis, physical removal, photolysis, reaction with $\bullet OH$, and reaction with tropospheric ozone.

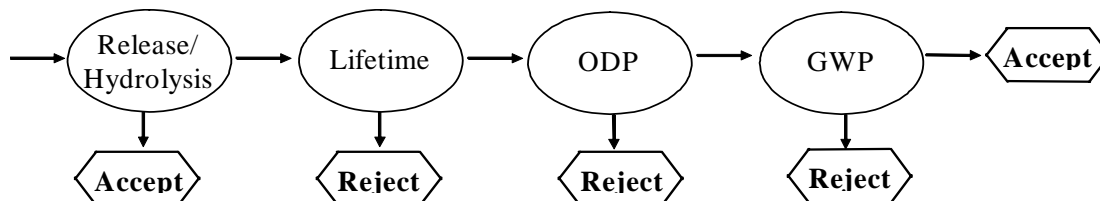


Figure 18. Abbreviated Decision Tree.

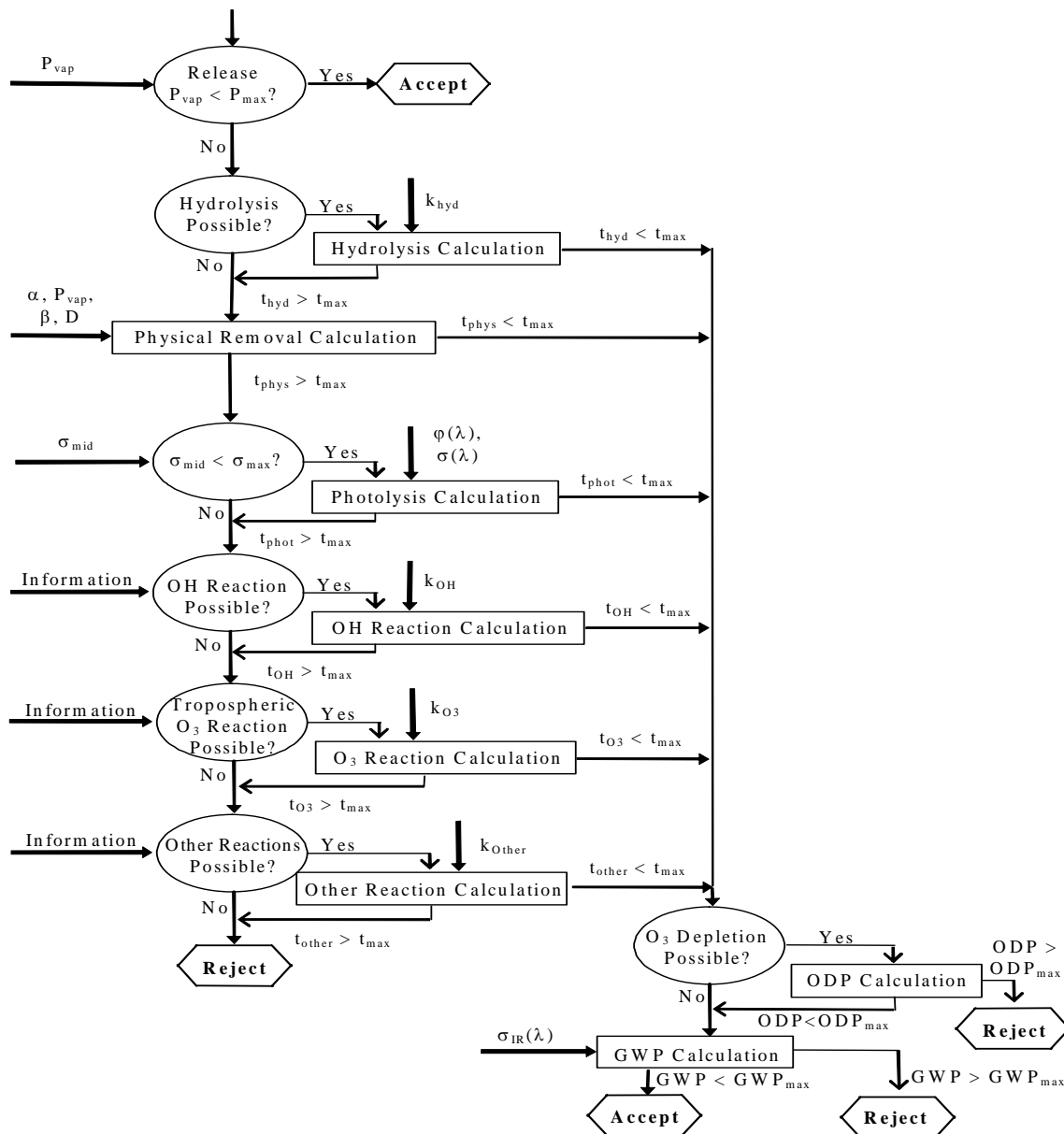


Figure 19. Decision Tree for Global Environmental Impact Screening.

The maximum allowable atmospheric lifetime is first established. The vapor pressure (P_{vap}) must be sufficient to permit release. Hydrolysis is then accessed from k_{hyd} , the hydrolysis rate constant. Lifetimes for various physical removal processes can be estimated - for rainout,

using α , the solubility coefficient; for aerosol scavenging, using P_{vap} , the vapor pressure (at 298 K); and for absorption (solution) into oceans, using β , the (ocean) water solubility of a gas in moles/m³-atm (essentially, a Henry's law constant), and D , the molecular diffusivity of a gas in water in m²/year.⁴⁰

One can estimate the possibility for photolysis from σ_{mid} , the absorption cross section at the tropospheric window midpoint for solar radiation, and σ_{max} , the maximum allowable value for this cross section. One must collect chemical information on the material of interest to determine whether reaction with •OH, O₃, or other species is possible. If reactions are possible, the lifetimes (t_{OH} , t_{O_3} , t_{other}) due to such reactions can be estimated from kinetic rate constants (k_{OH} , k_{O_3} , k_{other}) using a global averaging approximation. The final step, if needed, is to estimate the ODP and GWP (from $\sigma_{\text{IR}}(\lambda)$, the IR absorption cross section as a function of wavelength, λ) and compare the numbers obtained with ODP_{max} , and GWP_{max} , the maximum allowable values for these variables.

NGP – New Chemical Families Initial Screening

Screening of new chemicals screening for total flooding capability and performance is a critical feature of halon 1301. Its combined dimensionality and effectiveness are still unsurpassed. This situation is not expected to change for the simple reason that halon 1301 or CF₃Br is as simple a bromine-carrying compound as is possible amongst the brominated fluoroalkanes. Any larger molecule incorporating features imparting sufficient tropospheric reactivity will very likely have a higher boiling point with relatively diminished dimensionality at low application temperatures.

NGP projects whose goals were identification of new chemical extinguishants as possible replacements for halon 1301 began with general evaluations of chemical families but also built on earlier research and testing efforts that had already identified promising chemical families. These projects are listed in Table 22. Survey studies were followed by increasingly focused projects. A final extremely comprehensive review of chemical families was conducted later in the program. This review greatly extended the range of earlier surveys and helped identify many additional chemical families.

As physical property, toxicity, environmental impact, and extinguishment requirements of a candidate halon replacement became more defined and as options for employing agents (liquids, gases, or as flame extinguishing enhancements to new technologies, such as the solid propellant gas generator designs) a much more comprehensive analysis of chemical families was undertaken to list chemical families with either a demonstrated or suspected potential to act as a replacement flame extinguishant.

Table 22. NGP New Chemicals Projects.

NGP Project Title	Project Type	Chemical Families Investigated
Identification and Proof Testing of New Total Flooding Agents - Toxicity and Global Environmental Assessment	Survey of selected chemicals and development of selection methods and property estimation techniques	Alkyl Phosphorus, Silicon, Fluoro Amines, and Fluoro Ethers
Main Group Compounds as Extinguishants	Survey of compounds containing members of the main group elements	Periodic Table of the Elements—Groups IA, IIA, IIIB, IVB, VB, VIB, VIIB, and VIIIB
Tropodegradable bromocarbon extinguishants	Focused study of compounds and identification of cardiac sensitization screening methods	Bromofluoro alkenes, ethers, alkylamines,
Tropodegradable bromocarbon extinguishants-II, Task II	Focused study of compounds and identification of cardiac sensitization screening methods	Bromofluoro alkenes, ethers, alkylamines
Fluoroalkyl phosphorus compounds	Focused acquisition and evaluation of compounds	Fluoroalkyl Phosphorus
Environmentally Acceptable Extinguishants	Focused study of compounds and identification of cardiac sensitization screening methods	Broad coverage - Emphasis on low boiling points

This very broadly scoped review and analysis was summarized in NIST Technical Note 1443.⁴¹ The goal of this review was to identify chemical families still in need of scrutiny as potential flame suppressants and halon replacements, to list those chemical families for which sufficient knowledge exists to select the best candidates and finally to identify those families unlikely to contain useable alternative aircraft fire suppression and explosion inertion.

Other chemical families exhibited toxicities that were clearly outside all reasonable limits. In some cases the chemical families colligative properties rendered the likelihood of dispersion remote or there was simply no reason to suspect that the chemical family possessed chemical flame extinguishment properties that were significant that would justify the cost and effort involved in further consideration.

B. PROJECT TASKS AND OBJECTIVES

The search for alternative fire suppressants for halon 1301, was broad in scope. To ensure that the optimal chemicals were identified a comprehensive search and assessment of a broad array of chemical families and elements was performed. This survey began with an assessment of available literature information on physical properties, toxicity, and, if possible,

flame suppression. In some cases, representative compounds were obtained and flame suppression tests run.

- a) Employing the results of a broad review of chemical families compounds estimated to be acceptable were acquired for cup burner testing.
- b) Employing the results of prior reviews of cardiac sensitization estimation a further effort to identify and evaluate potential testing methods was made.
- c) Involvement in efforts to further the evaluation and possible development of an *in vitro* methods applicable to the low cost assessment of the cardiac sensitization potential (or relative performance) of a candidate halon replacement were continued

C. TECHNICAL PROBLEMS

Two historical barriers continue to impede progress. The selection of promising compounds requires methods of estimating physical properties and toxicity as well as refined estimates of the limits to these parameters in the fire suppression applications of greatest interest. The limited number of compounds for which toxicity end points have been determined obviates the determination of toxicity predictions based either on computational methods. Lastly, sources of the chemicals of interest must be identified. Synthetic methods all require starting materials and refined methods in order to be assured of success and often starting materials are either not available or too costly to be employed in this work.

Cardiac sensitization screening methods are nonexistent. This, coupled with the very limited number of related compounds for which the required dog exposure studies have been performed, stands as probably the greatest single impediment to progress.

D. GENERAL METHODOLOGY

The methodology employed was to use the best available information to aid in both the selection of promising chemical families as well as the selection of candidate compounds from those chemical families. The initial selection of compounds was not limited to those readily available or those for which existing synthetic methods exist. The chemical families identified are generally expected to act as carriers for bromine (or iodine) which is a known chemically active fire suppressing atom.

Identification of a particular chemical family as being promising was often based in some cases on unproven estimates of potential short atmospheric lifetimes in order to avoid overlooking any potential compounds.

Based on this assessment, screening methods for acute inhalation toxicity and cardiac sensitization potential were the two immediate needs. Cardiac sensitization data are particularly rare for the compounds of interest and very costly and difficult to obtain. Modeling approaches for cardiac sensitization are still in their infancy. General trends relating structure and composition to cardiac sensitization potential are incomplete and predictions tenuous. Unproven

screening methods based on physical properties of molecules appear to come the closest to being of reliable use and are all that is currently available. Employing both the limited trend data and estimates of physical properties that “may” be indicators of cardiac sensitization potential a number of chemical from the alkene and ether chemical families were selected. Application of these two selection approaches to all other chemical families is impossible as no data exists upon which to base a trend and it is also expected that differences in chemical functionality will have an unpredictable effect on the tendency of a compound to initiate an arrhythmic cardiac beat.

While all chemicals identified as being of interest are indicated in the text of this report, only a very few are off-the-shelf or catalogue items. While in some cases suppliers were able and willing to develop synthetic methods, at their own expense, that were expected to have such a high probability of success that quotes for delivery of small samples could be made, this was more frequently not the case. As a general rule, most chemical targeted for acquisition required synthetic method development, and where this was attempted it was generally but not always successful.

The cup burner method chosen of necessity employed small quantities of chemical often in the range of 5 g to 10 g. Extinguishment data that could be accumulated for each compound are limited as a result. It is expected that most if not all the values for flame extinguishment concentration reported here be considered upper bound values.

E. TECHNICAL RESULTS

The properties assessment performed provided a comprehensive list of prioritized chemical families for study. From these families a wide range of compounds was identified, and some were eventually acquired in research chemical quantities. These chemicals were evaluated using a cup burner with results that generally confirmed the predictions of fire suppression effectiveness. Those compounds not yet acquired are plentiful and should cardiac sensitization screening become a reality, identification of optimal compounds is possible.

F. IMPORTANT FINDINGS AND CONCLUSIONS

The potential of bromofluoroalkenes, bromofluoroethers and to a lesser extent bromofluoroimines, bromofluoronitriles and n-brominated imines and amines to act as possible halon 1301 replacements in unoccupied, low temperature aircraft applications is worthy of further assessment. The initial expectation that environmentally acceptable compounds containing chemically active bromine represented the best hope for the identification of suitable halon replacement appears firmly supported at this point. That boiling points of likely candidates will generally lie well above 20 °C is also a certainty. Efforts to enhance the dispersion of such compounds for application in low temperature aircraft environments characteristic are likely essential.

Screening methods for estimation of a chemicals tendency to cause cardiac arrhythmia may be possible if a relationship between cardiac sensitization LOAEL values and water/octanol values determined by HPLC-MS or GCMS methods is found. The work needed to evaluate this

relationship has not been done. Water/octanol values determined by the shake-flask method are not sufficiently accurate or reproducible for this evaluation.

G. SIGNIFICANT HARDWARE DEVELOPMENTS

This project did not involve any significant development of experimental hardware.

H. SPECIAL COMMENTS

One low cost and seemingly inexpensive, relatively uncomplicated test with the potential to rank the arrhythmogenic properties of the compounds of interest as halon replacements has been identified. This potential screening approach, if validated, would be a tremendous help and cost savings for future efforts to identify compounds with LOAEL values comparable to halon 1301. The method could possibly at a minimum provide means of obtaining a general ranking of cardiac sensitization effects by compounds.

I. IMPLICATIONS FOR FURTHER RESEARCH

Past projects have resulted in the identification and acquisition of a number of tropodegradable bromofluoroalkenes and bromofluoroamines with expected low atmospheric lifetimes and demonstrated flame extinguishment performance. The need for a reliable means of estimating cardiac sensitization is essential to down-selecting a final list of compounds for continued evaluation, scale-up study, and manufacturability evaluations. It is recommended that future work incorporate a study of the relationship between $\text{Log}(K_{ow})$ and HPLC and GCMS chromatographic retention-times. Comparison of compounds with known LOAEL values with experimentally derived LOAEL values is promising. This approach is potentially low in cost and quickly performed. It would greatly aid the continued acquisition of these interesting compounds, with an emphasis on those with low boiling points, in quantities sufficient to allow flame extinguishment performance characterization.

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SECTION III. DETAILED PROJECT DESCRIPTION

A. HALON REPLACEMENT CHEMICAL FAMILY REVIEWS

Employing NIST Technical Note 1443 as guidance, chemical families that were likely to represent low boiling candidate compounds were selected for study.⁴¹ Additional chemical families were included based on structural or functional similarities to known flame extinguishing compounds where examination indicated the possible tropodegradability. For each chemical family, available fire suppression performance, available environmental acceptability, available toxicity, and physical properties are briefly presented.

Halons 1301 and 1211 are unique chemicals. Their chemical structures are both based on a single carbon atom. Early developers of fire suppressing volatile agents, through variations in fluorine bromine and, in the case of halon 1211, addition of chlorine, were able to create non-flammable, highly effective fire suppressants. Of these two mainstays of volatile fire suppressants, developed halon 1301 is unique in having an extremely low boiling point and overall very favorable toxicity.

With the focus on aircraft application and with severe limits to boiling point as a criterion to chemical selection in place, the results of this extensive review and chemical testing has yielded a limited list of candidate chemical families.

1. Bromofluoroalkenes - High Priority Chemical Family

Bromofluoroalkenes have received and continue to receive attention as possible halon replacements. The range of alkenes studied includes the ethenes, propenes, butanes, isobutenes, and pentenes. The bromofluoroalkenes present a wide range of chemical structures. The degree of fluorine substitution greatly affects boiling point and extinguishment performance. It is unclear where the optimum in degree and pattern of fluorination and site of bromination lies. In view of these extremely promising results current research focused on the many additional compounds that have yet to be tested, Table 23.

a) Cup burner and boiling point performance

Past research has demonstrated that tropodegradable bromofluoropropenes have cup burner flame extinguishment performance ranging from a low of 2.6 volume % to 4.5 volume %.

b) Atmospheric lifetime and GWP and ODP impact

Short atmospheric lifetimes of tropodegradable compounds result from one or more of the following: (1) reaction with tropospheric hydroxyl free radicals; (2) photolysis; (3) reaction with tropospheric ozone; and (4) physical removal (rain-out).⁴²

Table 23. Bromofluoropropenes

Formula	Chemical Name
CF ₂ =CBrCF ₃	2-bromo-1,1,3,3,3-pentafluoropropene
CFBr=CFCF ₃	1-bromo-1,2,3,3,3-pentafluoropropene, (E) (Z)
CF ₂ =CHCF ₂ Br	3-bromo-1,1,3,3-tetrafluoropropene
CFH=CBrCF ₃	2-bromo-1,3,3,3-tetrafluoropropene, (E) (Z)
CHBr=CFCF ₃	1-bromo-2,3,3,3-tetrafluoropropene, (E) (Z)
CH ₂ =CBrCF ₃	2-bromo-3,3,3-trifluoropropene
CFH=CHCBrF ₂	3-bromo-1,3,3-trifluoropropene, (E) (Z)
CHBr=CHCF ₃	2-bromo-3,3,3-trifluoropropene, (E) (Z)
CFBr=CFCF ₂ H	1-bromo-1,2,3,3-tetrafluoropropene, (E) (Z)
CFBr=CHCF ₃	1-bromo-1,3,3,3-tetrafluoropropene, (E) (Z)
CHF=CFCF ₂ Br	3-bromo-1,2,3,3-tetrafluoropropene, (E) (Z)
CF ₂ =CBrCF ₂ H	2-bromo-1,1,3,3-tetrafluoropropene
CF ₂ =CBrCFH ₂	2-bromo-1,1,3-trifluoropropene
CFH=CBrCF ₂ H	2-bromo-1,3,3-trifluoropropene, (E) (Z)
CF ₂ =CFCBrH ₂	3-bromo-1,1,2-trifluoropropene
CFH=CFCBrH	3-bromo-1,2,3-trifluoropropene, (E) (Z)
CF ₂ =CHCBrH	3-bromo-1,1,3-trifluoropropene
CH ₂ =CFCF ₂ Br	3-bromo-2,3,3-trifluoropropene
CF ₂ =CFCF ₂ Br	3-bromo-1,1,2,3,3-pentafluoropropene
CHBr=CFCFH ₂	1-bromo-2,3,3-trifluoropropene, (E) (Z)
CFBr=CFCFH ₂	1-bromo-1,2,3-trifluoropropene, (E) (Z)
CBrF=CHCHF ₂	1-bromo-1,3,3-trifluoropropene, (E) (Z)
CHBr=CHCHF ₂	1-bromo-3,3-difluoropropene, (E) (Z)
CFBr=CHCHF ₂	1-bromo-1,3-difluoropropene, (E) (Z)
CHBr=CFCFH ₂	1-bromo-2,3-difluoropropene, (E) (Z)
CF ₂ =CFCFHB	3-bromo-1,1,2,3-tetrafluoropropene
CHBr=CHCHF ₂	1-bromo-3,3-difluoropropene, (E) (Z)
CFBr=CHCHF ₂	1-bromo-1,3-difluoropropene, (E) (Z)
CHBr=CFCFH ₂	1-bromo-2,3-difluoropropene, (E) (Z)
CH ₂ =CHCF ₂ Br	3-bromo-3,3-difluoropropene
CFBr=CFCH ₃	1-bromo-1,2-difluoropropene, (E) (Z)
CH ₂ =CFCFHB	3-bromo-2,3-difluoropropene
CF ₂ =CHCH ₂ Br	3-bromo-1,1-difluoropropene
CFH=CHCFHB	3-bromo-1,3-difluoropropene, (E) (Z)
CHF=CFCH ₂ Br	3-bromo-1,2-difluoropropene, (E) (Z)
CF ₂ =CBrCH ₃	2-bromo-1,1-difluoropropene
CHF=CBrCFH ₂	2-bromo-1,3-difluoropropene, (E) (Z)
CH ₂ =CBrCF ₂ H	2-bromo-3,3-difluoropropene

The parentheses indicate *cis* (Z) and *trans* (E) isomers.

Atmospheric lifetimes of some alkenes have been estimated to be on the order of a week based on atmospheric OH radical reactions. The bromofluoroalkene, 2-bromo-3,3,3-

trifluoropropene has been estimated to have atmospheric lifetimes of as low as 4 days.⁴³ Compounds with extremely low atmospheric lifetimes have proportionally less impact on global atmospheric warming and as they do not survive long enough to reach the stratosphere they also have little impact on stratospheric ozone depletion.

c) Toxicity studies on tropodegradable bromofluoropropenes

Extremely promising inhalation exposure acute toxicity testing of several alkenes demonstrated no adverse effects by the tested compounds.⁴⁴

While the limited toxicity data are promising, additional fluorination of these molecules is desirable to reduce boiling points. Unfortunately increased fluorination (of double bonded carbons in particular) may significantly, and possibly adversely, affect observed cup burner values and toxicity. Overall, the bromofluoroalkenes have been promising, though their boiling points may well limit their application in fire suppression at the lowest temperatures.

2. Phosphorus Acids and Esters - High Priority Chemical Families

The fire suppression performance of a number of phosphates and phosphonates has been previously reported.^{45,46} The estimated extinguishment concentrations were not determined using a cup burner, but instead were determined using a screening method based on Flame Ionization Detector response to each agent (Table 24). The gas chromatograph flame ionization detector (FID) technique method utilized allows estimation of the hydrogen flame extinguishment performance of a compound; however, FID extinguishment values and cup burner extinguishment values are not equivalent.

The data presented in Table 24 indicate that in general the non-fluorinated phosphates and phosphonates are likely to be excellent extinguishants. Principal drawbacks to these compounds are their high boiling points and their flammability.

A recent NGP-sponsored project, titled Fluoroalkyl Phosphorus Compounds attempted to overcome these drawbacks.⁴⁷ Incorporation of highly fluorinated alkyl substituents in the structures of these phosphonate and phosphate structures was expected to yield a reduction in boiling point and inherent flammability (

Table 25). The following discussion from that final report is presented here for the convenience of the reader.

The breakdown products of compounds $P(OCH_3)(CF_3)_2$ and $P(OCH_2CF_3)(CF_3)_2$ in air are predicted to be oxidation products containing $P=O$ and P-O-fluoro-alkane groups. These types of compounds should be pursued, as the extinguishing performance of $P(OCH_2CF_3)(CF_3)_2$ is a remarkable 1.8 volume %.

The observed air instability and markedly lower cup burner extinguishment of some P^{+3} phosphonates suggests that a strategy utilizing the heat and pressure of a solid propellant gas generator to disperse the compound could result in an effective agent/dispersal method.

Table 24. DERA Extinguishment Testing of Phosphorus Acids/Esters.

Compound	Structure	FID Extinguishment conc. (volume %)
Trimethyl phosphate	$O=P(OCH_3)_3$	0.6 to 2.8
Dimethyl methylphosphonate	$O=P(OCH_3)_2CH_3$	0.7
Diethyl methylphosphonate	$O=P(OC_2H_5)CH_3$	0.9
Dimethyltrifluoroethyl phosphate	$O=P(OCH_3)_2OCH_2CF_3$	0.7
Diethyltrifluoroethyl phosphate	$O=P(OC_2H_5)_2OCH_2CF_3$	0.7
Diethylpentafluoropropyl phosphate	$O=P(OC_2H_5)_2OCH_2CF_2CF_3$	0.7
Diethylhexafluoroisopropyl phosphate	$O=P(OC_2H_5)_2OCH(CF_3)_2$	0.7
Diethylheptafluorobutyl phosphate	$O=P(OC_2H_5)_2OCH_2CF_2CF_2CF_3$	0.6
Diethyloctafluoropentyl phosphate	$O=P(OCH_2H_5)_2OCH_2CF_2CF_2CF_2CF_2H$	1.1
Bis(2,2,2-trifluoroethyl)-2,2,3,3,3-pentafluoropropyl phosphate	$O=P(OCH_2CF_3)_2OCH_2CF_2CF_3$	0.7
Tris(2,2,2-trifluoroethyl) phosphate	$O=P(OCH_2CF_3)_3$	0.8
Tris(2,2,3,3,3-pentafluoro-1-propyl) phosphate	$O=P(OCH_2CF_2CF_3)_3$	1.0
Tris(2,2,3,3,4,4,4-heptafluoro-1-butyl) phosphate	$O=P(OCH_2CF_2CF_2CF_3)_3$	1.8

Table 25. Fluoroalkyl Phosphorus Compound Flame Extinguishment Results.

Compound – Formula (Boiling Point)	Cup Burner Extinguishment	Observations on Exposure of Test Agent to Air
Tris(trifluoromethyl) Phosphonate, $O=P(CF_3)_3$, (32 °C)	No flame lift-off or extinguishment @ 5 volume %	No white fumes, does not ignite cloth
Bis(trifluoromethyl)methoxy Phosphite, $P(OCH_3)(CF_3)_2$, (55 °C)	Not tested	White fumes, ignites spontaneously
Tris(2,2,2-trifluoroethoxy) Phosphite, $P(OCH_2CF_3)_3$, (≈ 130 °C)	3.1 volume%	No fumes, no ignition
Bis(trifluoromethyl) trifluoromethoxy Phosphate, $O=P(OCH_3)(CF_3)_2$, (42 °C)	4.6 volume %	Some fumes, no ignition
Bis(2,2,2-trifluoroethoxy) trifluoromethyl Phosphite, $P(OCH_2CF_3)_2CF_3$, (111 °C)	3.0 volume %	Some fumes, no ignition
Bis(trifluoromethyl) 2,2,2-trifluoroethoxy Phosphite, $P(OCH_2CF_3)(CF_3)_2$, (25 °C @ 7 kPa)	1.8 volume %	Ignites cloth, no spontaneous ignition, fumes strongly
Bis(trifluoromethyl) 2,2,2-trifluoroethoxy Phosphonate, $O=P(OCH_2CF_3)(CF_3)_2$, (≈ 130 °C)	Flame lift-off, no extinguishment @ 5 volume %	No white fumes, does not ignite cloth
Tris(trifluoromethoxy) Phosphonate, $O=P(OCF_3)_3$, (52 °C)	Synthesis unsuccessful	----

Phosphonates P(V), having only -CF₃ groups are possibly too stable to react in a flame. When compound 1, tris(trifluoromethyl) phosphonate O=P(CF₃)₃, was tested at 5 volume %, no evidence of flame lift-off was observable. Compound 4, a phosphonate, showed lift-off and flame extinguishment well below 5 volume %. Compound 7, also a phosphonate, showed lift-off, but no flame extinguishment, at 5 volume %. Limited data (compounds 1, 4, and 7) also suggest that phosphonates may need sufficient hydrogen atoms in their structures to enable compound breakdown in the flame zone in order to become chemically active as combustion suppressants.

Only tris(trifluoromethyl) phosphonate, O=P(CF₃)₃ approached the desired boiling point range. In the trade-off between higher degrees of fluorination to reduce the boiling point and moderate hydrogenation for efficient fire suppression, there may be limited further promise in this family of compounds. This conclusion must be tempered by the observed low cup burner test value (1.8 volume %) of bis(trifluoromethyl) 2,2,2-trifluoroethoxy phosphite, P(OCH₂CF₃)(CF₃)₂ and the tentative conclusion that it is likely that air reaction is converting it to a very efficient flame suppressant. It cannot, however, be concluded at this point that the air oxidation produces a complete conversion to a single compound or that the reaction is complete by the time the products enter the flame zone.

The more volatile phosphine P (III) compounds with -CF₃ groups tend to be spontaneously flammable, while those with fluoroethoxy groups were relatively stable (e.g., compound 3). While the higher boiling compounds clearly are not of practical value by themselves for aircraft application, they could be incorporated in solid propellant gas generation devices where adequate heat is available to fully vaporize, disperse, and possibly initiate the thermal breakdown of the compound (Table 26).

Table 26. Estimated Low Temperature Limits.

Compound, Formula	Boiling Point (°C) and Cup Burner Extinguishment Value (volume %)	Estimated Lowest Temperature at Which Extinguishing Concentration is Achievable (°C)
Bis(trifluoromethyl)methoxy Phosphine, P(OCH ₃)(CF ₃) ₂	55, NA	-38
Tris(2,2,2-trifluoroethoxy) Phosphite, P(OCH ₂ CF ₃) ₃	130, 3.1	30
Bis(trifluoromethyl) trifluoromethoxy Phosphonate, O=P(OCH ₃)(CF ₃) ₂	42, 4.6	-32
Bis(2,2,2-trifluoroethoxy) trifluoromethyl Phosphine, P(OCH ₂ CF ₃) ₂ CF ₃	111, 3.0	15
Bis(trifluoromethyl) 2,2,2-trifluoroethoxy Phosphine, P(OCH ₂ CF ₃)(CF ₃) ₂	≈100, 1.8	≈5

The possibility that some of these compounds, e.g., (bis(trifluoromethyl) 2,2,2-trifluoroethoxy phosphite, $P(OCH_2CF_3)(CF_3)_2$), decompose on air exposure to yield highly effective flame extinguishants is tantalizing, and the opportunity to implement such compounds with gas generating dispersion aids may well be worth investigation. Compounds with higher volatility (higher fluorine content) tend toward spontaneous flammability.

Several directions for further work in this area present themselves. While the testing reported here exposed real limitations to phosphorus compounds as fire suppressants, it also provided, as initially hoped, a basis for more focused research of promising compound structural areas.

Given the observation of dramatically lower extinguishment concentration demonstrated for (bis(trifluoromethyl) 2,2,2-trifluoroethoxy phosphite, $P(OCH_2CF_3)(CF_3)_2$) and the possible lower extinguishment for the untested tris(trifluoromethyl) phosphonate, $O=P(CF_3)_3$, several compounds may demonstrate cup burner extinguishments of 1 volume % or lower. If achievable, such low cup burner values would have the effect of raising the estimated boiling point limit to 61 °C for agent application under -40 °C ambient conditions. This could open up several new opportunities for use of very highly effective extinguishants (Table 6) if the time were available to for the chemical to achieve its equilibrium vapor pressure.

The current compounds of interest are summarized in Table 27. Further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families.

Table 27. Fluorophosphorus Compounds of Interest

Phosphorus III Compounds	Phosphorus V Compounds
$P(OCH_3)(CFH_2)_2$	$O=P(CHF_2)_3$
$P(OCH_3)(CHF_2)_2$	$O=P(CHF_2)(CF_3)_2$
$P(OCF_3)(CF_3)_2$	$O=P(CF_3)(CHF_2)_2$
$P(OCF_3)_3$	$O=P(CFH_2)(CF_3)_2$
$P(CF_3)_3$	$O=P(CF_3)(CFH_2)_2$
$P(CH_3)(CF_3)_2$	$O=P(CF_3)_3$
$P(OCHF_2)(CF_3)_2$	$O=P(CF_3)_2(CF_2)$
$P(OCFH_2)(CF_3)_2$	

3. Fluoroamines - High Priority Chemical Family

Fluoroamines (and bromofluoroamines) are undoubtedly the most promising of the nitrogen-containing compounds as potential halon replacements. There is evidence that some could have low atmospheric lifetime, low toxicity, and good fire extinguishment capability.

Table 28. Fluoroamine Boiling Points.

Compound	Boiling Point (°C)
$N(CF_3)_3$	-10
$N(CF_3)_2CF=CF_2$	13.7
$N(CF_3)_2CH_3$	11 to 12
$N(CF_3)_2CF_2CF_3$	20.5
$N(CF_3)_2CF_2CHF_2$	32.0
$N(CF_3)_2CH_2CH_3$	33 to 34
$N(CF_3)_2CH_2CH_3$	33.3
$N(CF_3)_2CH_2CF_3$	38
$N(CF_3)(CF_2CF_3)_2$	46
$N(CF_3)_2CH_2CF_2H$	50 to 52
$N(CF_2CF_3)_3$	70.3

Amines are derivatives of ammonia (NH_3) and have the general formula $NRR'R''$, where at least one of the nitrogen substituents is an alkyl group. The others can be hydrogen atoms. Due to toxicity concerns, the only compounds of interest are amines containing three alkyl groups. Moreover, to decrease toxicity and corrosivity (by decreasing polarity) and to decrease flammability, the alkyl groups should be at least partially fluorinated.

Research from the National Industrial Research Institute of Nagoya has focused on fluoroalkylamines, with an emphasis on perfluoroalkyl derivatives, as fire suppressants.⁴⁸ All of their fluoroalkylamines inhibited flame propagation less efficiently than CF_3Br , but more efficiently than HFC-227ea.

A thorough assessment of the atmospheric impact of fluorinated amines and of bromofluoroamines (based on estimations and calculations) has been presented.⁴⁹ For example, the compound $(CBrF_2)(CF_3)NCH_3$ is estimated to have an atmospheric lifetime of 10 days and an ODP of 0.006 relative to CFC-11.⁴⁹

Testing of $N(CF_3)_3$ as well as non-perfluorinated $N(CF_{(3-x)}H_x)_3$ derivatives are targeted. In addition, the amine $N(CF_3)_2CF=CF_2$ is expected to have a lower atmospheric lifetime due to the presence of its $-CF=CF_2$ group, making this compound of especially strong interest for acquisition and testing (Table 29). Further consideration of these compounds was suspended pending the results of acquisition and testing of the more promising brominated chemical families.

Table 29. Fluoroamines of Interest

Compound	
$N(CF_3)_2CF_2H$	$N(CF_2H)_2(CFH_2)$
$N(CF_3)_2CFH_2$	$N(CF_3)(CF_2H)(CH_3)$
$N(CF_2H)_2CF_3$	$N(CF_2H)(CFH_2)(CFH_2)$
$N(CF_2H)_3$	$N(CF_3)(CFH_2)(CH_3)$
$N(CF_3)_2CH_3$	$N(CF_2H)(CF_2H)(CH_3)$
$N(CF_3)(CF_2H)(CFH_2)$	$N(CF_3)_3$
$N(CF_3)(CFH_2)_2$	$N(CF_3)_2(CF=CF_2)$

4. Brominated Fluoroamines - High Priority Chemical Family

Bromofluoroamines (and fluoroamines) are undoubtedly the most promising of the nitrogen-containing compounds as potential halon replacements. There is evidence that some could have low atmospheric lifetime, low toxicity, and good fire extinguishment capability. Boiling points of bromofluoroamines range down to as low as 40.6 °C (Table 30). Cup burner extinguishment studies of a very limited number of compounds have demonstrated excellent extinguishment performance (Table 31).

Table 30. Bromofluoroamine Boiling Points.

Formula	Boiling Point, °C
$(CF_3)_2NCBrF_2$	40.6
$(CF_3)_2NCF_2CBrF_2$	59.5
$N(CF_3)_2(CHFCF_2Br)$	72
$N(CF_3)_2(CH_2CF_2Br)$	80

Table 31. Tropodegradable Bromofluoroamines.

Compound, Formula	Boiling Point (°C)	Cup Burner (volume %)
Bis(trifluoromethyl)-2-bromo-1,2,2-trifluoroethyl amine, $N(CF_3)_2(CHFCF_2Br)$	72	2.4*
Bis(trifluoromethyl)-2-bromo-1,1,2-trifluoroethyl amine, $N(CF_3)_2(CF_2CFHBr)$	72	
Bis(trifluoromethyl)-2-bromo-2-fluoroethylamine, $N(CF_3)_2(CH_2CF_2Br)$	80	2.4

* Results of a 60/40 blend of $N(CF_3)_2(CHFCF_2Br)$ and $N(CF_3)_2(CF_2CFHBr)$

In order to achieve a lower atmospheric lifetime fluorination of the alkyl substituents can not be complete. With this restriction in mind several bromofluoroamines compounds are of interest and were sought (Table 32).

Table 32. Bromofluoroamines of Interest.

Compound	
N(CFH ₂)(CF ₂ H)(CFHBr)	N(CF ₃) ₂ CFHBr
N(CH ₃)(CF ₃)(CFHBr)	N(CF ₃)(CF ₂ H)CF ₂ Br
N(CH ₂ F)(CF ₃)(CH ₂ Br)	N(CF ₃)(CF ₂ H)CFHBr
N(CF ₂ H)(CF ₂ H)(CH ₂ Br)	N(CF ₂ H)(CF ₂ H)CF ₂ Br
N(CFH ₂)(CF ₂ H)(CH ₂ Br)	N(CFH ₂)(CF ₃)CF ₂ Br
N(CFH ₂)(CFH ₂)(CFHBr)	N(CF ₂ H)(CF ₂ H)(CFHBr)
N(CH ₃)(CFH ₂)(CF ₂ Br)	N(CFH ₂)(CF ₃)(CFHBr)
N(CH ₃)(CF ₂ H)(CFHBr)	N(CF ₃)(CF ₂ H)(CH ₂ Br)
N(CF ₂ H)(CF ₂ H)(CFHBr)	N(CH ₃)(CF ₃)(CF ₂ Br)
N(CFH ₂)(CFH ₂)(CFHBr)	N(CH ₃)(CF ₂ H)(CF ₂ Br)
N(CFH ₂)(CFH ₂)(CF ₂ Br)	

5. Manganese and Tin Compounds - High Priority Chemical Family

There are practically no data on fire suppression properties of manganese-containing compounds. Manganese acetylacetonate is a very effective inhibitor based on data obtained from an ethanol/air counter-flow burner experiments. It was found to be more effective than iron pentacarbonyl on a molar basis.⁵⁰ Methylcyclopentadienyl manganese tricarbonyl (MMT) is well known as an antiknock fuel additive.

The fire suppression efficiency of tin-containing compounds is expected to be high. The ratio of effectiveness of SnCl₄ relative to CF₃Br is 5.7, based on flame speed measurements in hydrogen/air and hexane/air flames.^{51,52} The fire suppression efficiencies of the following tin-containing compounds have been investigated: SnCl₂, SnCl₄, Sn(CH₃)₄. Further consideration of these compounds was suspended pending the results of acquisition and testing of the more promising brominated chemical families.

Table 33. Tin Compounds.

Compound	Boiling Point (°C)
Sn(CH ₃) ₄	78

6. Bromofluoropropene Oxides - High Priority Chemical Family

No studies of the flame extinguishment properties of brominated fluoropropene oxides have been reported. These compounds are expected to be stable under storage and may decompose readily in the flame front to liberate the chemical fire suppressing bromine atom. Their atmospheric lifetimes are expected to be short, but this needs to be confirmed.

Cup burner values for these monobrominated compounds should be similar to halon 1301, with specific values possibly reflecting the location of the bromine in the molecule. Boiling points for the bromoperfluoropropene oxides (oxiranes) are estimated to be between 0 °C and 10 °C. They can potentially be synthesized in a single step from existing bromofluoropropenes by a partial oxidation of the alkene bond. $\text{CF}_2(\text{O})\text{CFCF}_2\text{Br}$ (3-bromo-1,2-perfluoropropene oxide), $\text{CF}_2(\text{O})\text{CBrCF}_3$ (2-bromo-1,2-perfluoropropene oxide), and $\text{CFBr}(\text{O})\text{CFCF}_3$ (1-bromo-1,2-perfluoropropene oxide) were successfully sourced.

7. Iodinated Alkanes - Medium Priority Chemical Family

Iodides are efficient fire suppressants with low atmospheric lifetimes (Table 34).

Table 34. Flame Extinguishment Comparison Data.

Formula	Cup Burner Flame Extinguishment, volume %
CF_3Br	2.9
CF_3I	3.0
$\text{C}_2\text{F}_5\text{I}$	2.1
$\text{C}_3\text{F}_7\text{I}$	3.0
$\text{C}_4\text{F}_9\text{I}$	2.8
$\text{C}_6\text{F}_{13}\text{I}$	2.5
$\text{C}_8\text{F}_{17}\text{I}$	1.9
$\text{C}_4\text{F}_8\text{I}_2$	2.1

While boiling points of some iodoalkanes are low enough to make them of interest as possible fire suppressant for aircraft applications (Table 35), further consideration of these compounds was suspended pending the results of acquisition and testing of the more promising brominated chemical families.

Table 35. Iodoalkane Boiling Points.

Formula	Boiling Point (°C)
CF ₃ I	-22.5
CHF ₂ I	21.6
CH ₂ FI	53.5
CH ₃ I	42.5
C ₂ F ₅ I	12
CF ₃ CH ₂ I	55
CHF ₂ CF ₂ I	39.4
C ₃ F ₇ I	41.2
C ₄ F ₉ I	67

Previously the only iodoalkane known to have a sufficiently low toxicity and acceptable properties to be applied to fire protection needs was CF₃I. Because this compound's LOAEL is 0.5 volume %, it is unacceptable for use in normally occupied areas.

While CF₃I has been well studied as a possible fire suppressant, little effort has been applied to other compounds in this family. Again, further consideration of these compounds was suspended pending the results of acquisition and testing of the more promising brominated chemical families.

8. Iodinated Alkenes - Medium Priority Chemical Family

These compounds have been completely unstudied as fire suppressants. To the best of our knowledge, no extinguishment studies have been carried out on any iodoalkene. The effect of the double bond on extinguishment is uncertain; however, it is possible that some highly halogenated, lower molecular weight alkenes are flammable.⁵³

The potential compounds of interest (Table 36) are expected to possibly have stability and toxicity problems and therefore further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families.

Table 36. Iodinated Alkenes of Interest.

Compounds	
CF ₂ =CFI	CFH=CHI
CF ₂ =CHI	CH ₂ =CFI
CFH=CFI	

9. Brominated Ethers - Medium Priority Chemical Family

Only two studies of fire suppression by of hydrobromofluoroethers (HBFEs) have been carried out. $\text{CH}_2=\text{CBr}(\text{OCF}_3)\text{CF}_2\text{CF}_3$, which is unsaturated, has a cup burner extinguishment concentration of 3.8 volume %.³⁵ $\text{CH}_3\text{-O-CF}_2\text{CHBrF}$ has been estimated to have a heptane cup burner flame extinguishment value of 4.2 volume %.³⁶

Cup burner performance and boiling points for $\text{CH}_2\text{Br-O-CF}_3$, (3.2 volume %, 39 °C to 41 °C) and bromomethyl difluoromethyl ether, $\text{CH}_2\text{Br-O-CF}_2\text{H}$, (3.6 volume %, 70 °C) are promising (Table 37). Substituting additional fluorine for a hydrogen on $\text{CH}_2\text{Br-O-CF}_3$ may yield a compound (two structural isomer are possible) with a boiling point in the vicinity of 20 °C to 30 °C, suggesting that additional fluorination is worth a try. Ethers may well have superior long term materials stability with respect to the alkenes.

Table 37. Brominated Fluoroether Flame Extinguishment Data.

Compound	Formula	Boiling Point (°C)	Cup Burner Flame Extinguishment
Bromomethyl trifluoromethyl ether	$\text{CH}_2\text{Br-O-CF}_3$	39 – 41	3.2 volume %
Bromomethyl difluoromethyl ether	$\text{CH}_2\text{Br-O-CF}_2\text{H}$	70	3.6 volume %

The boiling points for brominated fluoro-ethers are generally higher than desirable (Table 38). This has led to a focused effort to study the C_2 bromofluoroethers.

Table 38. Brominated Fluoroether Boiling Points.

Formula	HBFE (or HFE) Boiling Point (°C)
$\text{CH}_3\text{-O-CF}=\text{CBrF}$	67
$\text{CH}_3\text{-O-CF}=\text{CBrF}$	59
$\text{CH}_3\text{CH}_2\text{-O-CF}_2\text{CH}_2\text{Br}$	70
$\text{CF}_3\text{-O-CH}_2\text{CH}_2\text{Br}$	78.5
$\text{CH}_2\text{BrCH}=\text{CFCH}_2\text{-O-CH}_3$	74
$\text{CH}_3\text{CH}_2\text{CH}_2\text{-O-CF}_2\text{CHFBr}$	75.2
$\text{CHF}_2\text{-O-CF}_2\text{CHBrF}$	73
$\text{CH}_3\text{CH}_2\text{-O-CF}_2\text{CHBr}_2$	65
$\text{CH}_3\text{CH}_2\text{CH}_2\text{-O-CF}_2\text{CHBr}_2$	72.2

Based on available data there are several brominated fluoro-ethers whose extinguishment and boiling points may be suitable, **TABLE 39**. Synthetic approaches to some of these compounds have been reported and suppliers were sought.⁵⁴

Table 39. Brominated Fluoroethers of Interest.

Compound	
CF ₂ Br-O-CH ₂ F	CHBr-O-CF ₃
CHBr-O-CHF ₂	CF ₂ Br-O-CF ₃
CF ₂ Br-O-CHF ₂	

10. Fluorinated Aldehydes and Ketones - Medium Priority Chemical Families

Fire suppression data are almost completely unknown for fluorinated carbonyl compounds. A major exception, however, is dodecafluoro-2-methylpentan-3-one, CF₃CF₂C(O)CF(CF₃)₂, which has a propane cup burner heptane extinguishment value of 3.5 volume %.⁷³ This can be compared with values of 3.6 volume % for halon 1211 and 4.3 volume % for halon 1301 with the same fuel.⁷³ Unfortunately, data for n-heptane extinguishment with this perfluorinated ketone have not been reported. Hexafluoroacetone, CF₃COCF₃, has a cup burner extinguishment value of over 6 volume %.

In the absence of the recent results reported for CF₃CF₂C(O)CF(CF₃)₂, there was little to recommend the fluorinated ketones as extinguishants. This is still true for the aldehydes; however, at least some of the fully fluorinated ketones may have acceptable environmental and toxicity characteristics. Little is known about the fire extinguishing capabilities although studies are under way.

These two families are not under consideration, as they lack a chemical fire suppression feature. Further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families

11. Phosphorus Halides and Phosphonitriles - Medium Priority Chemical Families

There are some enticing flame data on phosphorus halides (Table 40). Thus, despite the expected or known high toxicity and corrosivity of these compounds, it would be valuable to verify the flame suppression data. Further, it would be useful to examine the possibly more stable, totally fluorinated compounds, PF₃ and O=PF₃. Boiling points for some phosphorus halides are encouraging (Table 41).

Table 40. Phosphorus Halide Cup Burner Flame Extinguishment.

Compound	Efficiency Relative to Halon 1301
PCl ₃	6.7 to 6.9
PBr ₃	4.6 to 6.9
O=PCl ₃	5.2
S=PCl ₃	8
S=PBr ₃	6.7 to 6.9

Table 41. Phosphorus Halide Boiling Points.

Compound	Boiling Point (°C)
PF ₃	16.5
PF ₂ Br	23.9
PCl ₃	30.5
PBr ₃	38.8
O=PF ₃	-39.7
O=PF ₂ Br	30 to 32
O=PCl ₃	34.4

Attractively low cup burner flame extinguishment concentrations have been found for several phosphonitriles (Table 42).¹⁰⁴ The first of these compounds was even more efficient at extinguishing an opposed flow diffusion flame.³ A number of polyfluoroalkoxy-substituted compounds (e.g., P₃N₃(OCH₂CF₃)₆) have shown very good extinguishments characteristics,¹¹¹ although their boiling points are far too high for consideration as halon 1301 alternatives

Table 42. Phosphonitrile Flame Extinguishment.

Compound	Cup Burner Extinguishment Value (volume %)
P ₃ N ₃ F ₆	1.08 ± 0.07
P ₃ N ₃ ClF ₅	0.91 ± 0.02
P ₃ N ₃ Cl ₂ F ₄	0.96 ± 0.08

Further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families

12. Iron Compounds - Medium Priority Chemical Family

These compounds contain Fe bound to inorganic or organic ligands.

The flame inhibition efficiency of iron-containing compounds is high. The coefficient of effectiveness of iron pentacarbonyl and ferrocene relative to CF_3Br is 50 to 100 based on flame speed measurements in methane/air and hexane/air flames.^{51,55,56} Measured extinction concentrations for iron pentacarbonyl are 1.7 volume % (ethanol flame⁵⁷) and 0.23 volume % (methane flame).⁵⁸

The list of iron containing compounds for which flame suppression and/or extinction data exist include: iron pentacarbonyl, ferrocene, and iron acetylacetonate, $(\text{K}_4\text{Fe}(\text{CN})_6 \cdot 3\text{H}_2\text{O})$, $\text{K}_4\text{Fe}(\text{CN})_6$, $\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}] \cdot 2\text{H}_2\text{O}$, $\text{Na}_4\text{Fe}(\text{CN})_6 \cdot 10\text{H}_2\text{O}$, $\text{Fe}(\text{CF}_3\text{-CO-CH=CO-CF}_3)_3$.

The high flame inhibition effectiveness of these compounds has already been established, but no fires have been suppressed by an iron-containing compound. There is also the issue of their effective delivery to the fire, which is being addressed in other NGP projects. Further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families

13. Iodine Containing Ethers - Low Priority Chemical Family

Nothing is known about the effectiveness of the iodinated derivatives. There is no reason to believe that the suppression capabilities will significantly differ from those of the fluoroiodoalkanes, the hydrofluoroiodoalkanes, or the equivalent brominated compounds.

The lightest iodine-containing ether, iodomethyl methyl ether (iodomethoxymethane) has a relatively high boiling point of 122 °C at 101 kPa (1 atm).⁵⁹ It is expected that due to the higher molecular weight (all compounds must contain at least two carbon atoms and an oxygen atom) and the presence of iodine, compounds will have properties that are less than suitable for total flood application. Further consideration of these compounds was suspended pending the results of acquisition and testing of more promising chemical families.

14. Bromofluoro-Alcohols - Low Priority Chemical Family

Boiling points of the brominated fluoro-alcohols are higher than is desirable for a total flooding agent and even possibly too high for use in streaming agent applications (Table 43).

Table 43. Bromofluoro Alcohol Boiling Points.

Compound	Boiling Point (°C)
$\text{CBrF}_2\text{CH}_2\text{OH}$	67
$\text{CF}_3\text{CHOHCH}_2\text{Br}$	124
$\text{CHBrFCH}(\text{OH})\text{CF}_3$	124
$\text{CHFBrCF}_2\text{CH}_2\text{OH}$	149
$\text{CF}_3\text{CBrFCH}_2\text{OH}$	97
$\text{CF}_3\text{CHBrCH}_2\text{OH}$	108
$\text{CF}_3\text{CH}(\text{OH})\text{CHBrCH}_3$	66
$\text{CF}_3\text{CBrFCH}(\text{CH}_3)\text{OH}$	112
$\text{CF}_3\text{CBrFC}(\text{CH}_3)_2\text{OH}$	128
$\text{CF}_3\text{CH}(\text{OH})\text{CHBrCH}_2\text{CH}_3$	94
$\text{CF}_3\text{CH}(\text{OH})\text{CBr}(\text{CH}_3)\text{CH}_3$	68
$\text{CF}_3\text{CBrClC}(\text{CH}_3)_2\text{OH}$	137
$\text{CF}_3\text{CBr}_2\text{C}(\text{CH}_3)_2\text{OH}$	152
$\text{CF}_3\text{CHOHCHBr}_2$	156
$\text{CBr}_2\text{FCH}_2\text{OH}$	85

$\text{CF}_3\text{CHOHCH}_2\text{Br}$ is reported to have an n-heptane cup burner extinguishment value of 4.1 volume %⁶⁰, and it is also reportedly to extinguish the H_2/CH_4 flame in a GC/FID at 3 volume %.⁴⁶ A cup burner value of 4.87 volume %, is reported for the dibromo compound, $\text{CF}_3\text{CHOHCHBr}_2$.⁶¹ Further consideration of these compounds was dropped in favor of acquisition and testing of more promising chemical families.

15. Fluorinated and Brominated Nitriles - Low Priority Chemical Family

There is no evidence or reason to believe that the nitrile group itself possesses an intrinsic (chemical) fire suppression capability. Nonhalogenated nitriles are known or are expected to be flammable. Fluorination may well reduce flammability and these compounds would act mainly as physical suppressants. The addition of bromine or iodine would impart a chemical flame inhibition property to nitriles.

A cursory examination of the possibility for inherent fire suppression capability of the nitrile group is being pursued and two compounds have been targeted for acquisition. The low boiling points of both compounds are unique, Table 44. CF_3CN is potentially the lowest boiling possibly tropodegradable compound yet identified, and CF_2BrCN is the lowest boiling brominated potentially tropodegradable compound yet identified. A positive fire suppression test result in either case will stimulate a closer look at this family though toxicity is a concern.

Table 44. Low Boiling Fluorinated and Brominated Nitriles.

Compound	Formula	Boiling Point
Trifluoroacetonitrile	CF ₃ CN	-67C
Bromodifluoroacetonitrile	CF ₂ BrCN	3

16. Copper Compounds - Low Priority Chemical Family

The existing data on the fire suppression efficiency of these compounds is contradictory. CuO was found to be ineffective for suppression of a methane flame¹²⁸ and was characterized as a thermal inhibitor.¹²⁴ Cuprous chloride (CuCl), however, was found to be an effective inhibitor in methane flames. The inhibition effectiveness of CuCl relative to CF₃Br is 4 to 12 based on flame speed measurements in methane/air flames.¹¹⁶ It is reported that copper acetate monohydrate, copper carbonate, Cu₂O, CuO, CuCl, and CuCl₂ are all ineffective at suppressing the ignition of methane/air flames.¹²⁸ Further consideration of these compounds was dropped in favor of acquisition and testing of more promising chemical families

17. Sulfoxides - Low Priority Chemical Family

Since the nonhalogenated compounds are generally flammable, and only the highly halogenated compounds are of interest. No fire suppression tests have been conducted on these, and there is no evidence indicating that the -S- group itself possesses an intrinsic chemical fire suppression capability. A sulfur dioxide cycle has been proposed to inhibit combustion by removal of hydrogen atoms.¹⁰¹ Added bromine or iodine would impart chemical flame suppression effectiveness.

The sulfides suffer from several drawbacks: no distinctive fire suppression efficiency and potential toxicity, reactivity, and materials compatibility problems. However, the possibility that atmospheric lifetimes could be very short for brominated compounds makes a screening study of the smaller bromo-fluorosulfides desirable.

Table 45. Sulfoxide Boiling Points.

Compound	Boiling Point (°C)
CH ₃ -S-CH ₃	37.5
CF ₃ -S-CF ₃	-22
CF ₃ -S-C ₂ F ₅	6.3
CF ₃ -S-C ₃ F ₇	38.6

B. DOWN-SELECTION OF CHEMICAL FAMILIES FOR STUDY

Past research has identified chemical families with the potential to satisfy environmental concerns regarding ODP and GWP criteria while also satisfying the need for a chemically active fire suppressant mechanism.³ Very limited toxicity testing has significantly advanced the candidacy of the tropodegradable bromofluoroalkenes. This testing has also served to highlight one of the most serious challenges facing continued progress in the halon replacement effort.

These families are all further reviewed in this section with respect to the general boiling point limits expected to define applicability to aircraft fire suppression. Additional brominated chemical families were also identified as having low boiling points and possibly shorter atmospheric lifetimes. The combined list of chemical families (Table 46) served as the focus of compound acquisition and extinguishment testing.

Table 46. Potentially Low Boiling Chemical Families.

Chemical Family
Bromofluoro propenes and ethenes
Bromofluoro dimethyl ethers or methyl ethyl ethers
Bromofluoromethylamines and n-Bromofluoromethylamines
Bromofluoroimines
Bromofluoropropene oxides (oxiranes)
Bromofluoro acetonitriles

C. SELECTED CHEMICAL FAMILIES COMPOUND ACQUISITION

With the results of past evaluations as a guide selection of chemicals from the previously identified families of greatest interest (listed below) was initiated. The search for chemicals and efforts to acquire and characterize extinguishment performance in each case is described for each of the listed chemical families.

The low temperature conditions experienced by aircraft whether located in extreme climates or in flight at altitude greatly impact selection of chemical agents and their methods of discharge. While some estimates of fire suppression application needs are as low as -60 °C more recent analysis seem to suggest that application temperatures in the -20 °C range could be more representative of actual aircraft fire suppression application needs.

Regardless of the chemical family under consideration, low boiling points are most easily achieved by keeping molecular weight to a minimum (while avoiding flammability of the compound). These goals are somewhat in opposition as non-flammability can only be achieved through sufficient, usually 50 %, substitution of fluorine atoms for hydrogen atoms in the molecular structure. Too much fluorination in a molecule, while generally but not always imparting a lower boiling point and decreased flammability, can result in increased atmospheric lifetimes. This is an issue that affects ethers in particular.

1. Brominated Fluoroalkenes

Brominated fluoroalkenes are of great interest. Of the compounds previously acquired, extinguishment and toxicity results are for the most part promising. With the focus on the lowest boiling alkenes, the direction of compound acquisition and testing focuses primarily on tetrafluorinated and pentafluorinated bromopropenes and some selected bromofluoroethenes (Table 47).

Table 47. Bromofluoropropenes and Bromofluoroethenes.

Compound Name	Formula	Boiling Point (°C)
1-Bromo-1,2,3,3,3-pentafluoropropene	$\text{CBrF}=\text{CF}-\text{CF}_3$	27 to 28
2-Bromo-1,1,3,3,3-pentafluoropropene	$\text{CF}_2=\text{CBr}-\text{CF}_3$	25 to 26
3-Bromo-1,1,2,3,3-pentafluoropropene	$\text{CF}_2=\text{CF}-\text{CBrF}_2$	--
1-Bromo-1,3,3,3-tetrafluoropropene	$\text{CBrF}=\text{CH}-\text{CF}_3$	--
1-Bromo-2,3,3,3-tetrafluoropropene	$\text{CBrH}=\text{CF}-\text{CF}_3$	32 to 34
2-Bromo-1,3,3,3-tetrafluoropropene	$\text{CHF}=\text{CBr}-\text{CF}_3$	29 to 31
3-Bromo-1,1,3,3-tetrafluoropropene	$\text{CF}_2=\text{CH}-\text{CBrF}_2$	32 to 33
2-Bromo-1,1,3,3-tetrafluoropropene	$\text{CF}_2=\text{CBrCF}_2\text{H}$	--
1-Bromo-1,2,3,3-tetrafluoropropene	$\text{CFBr}=\text{CFCF}_2\text{H}$	--
3-Bromo-1,1,2,3-tetrafluoropropene	$\text{CF}_2=\text{CFCFHBr}$	--
1-Bromo-1,2,2-trifluoroethene	$\text{CF}_2=\text{CFBr}$	
1-Bromo-1,2-difluoroethene	$\text{CFH}=\text{CFBr}$	20 to 24 (est.)

These chemical families of bromofluoropropenes represent a wide range of structural possibilities and variations of physical properties. The tetrafluorinated and pentafluorinated bromopropenes alone represent 17 unique compounds, some of which are *cis* (Z) and *trans* (E) isomers of one another (Table 48).

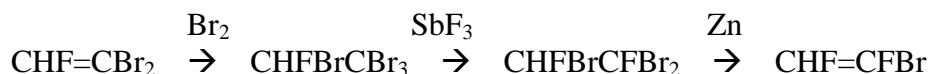
Table 48. Tetra- and Pentafluorinated Bromopropenes.

Formula	Chemical Name
CF ₂ =CBrCF ₃	2-bromo-1,1,3,3,3-pentafluoropropene
CFBr=CFCF ₃	1-bromo-1,2,3,3,3-pentafluoropropene, (E) (Z)
CF ₂ =CFCF ₂ Br	3-bromo-1,1,2,3,3-pentafluoropropene
CF ₂ =CHCF ₂ Br	3-bromo-1,1,3,3-tetrafluoropropene
CFH=CBrCF ₃	2-bromo-1,3,3,3-tetrafluoropropene, (E) (Z)
CHBr=CFCF ₃	1-bromo-2,3,3,3-tetrafluoropropene, (E) (Z)
CFBr=CFCF ₂ H	1-bromo-1,2,3,3-tetrafluoropropene, (E) (Z)
CFBr=CHCF ₃	1-bromo-1,3,3,3-tetrafluoropropene, (E) (Z)
CHF=CFCF ₂ Br	3-bromo-1,2,3,3-tetrafluoropropene, (E) (Z)
CF ₂ =CFCFHBr	3-bromo-1,1,2,3-tetrafluoropropene
CF ₂ =CBrCF ₂ H	2-bromo-1,1,3,3-tetrafluoropropene

Identifying brominated fluoroalkenes boiling well under 30 °C requires consideration of ethene-based candidates. In some ethenes (e.g., CF₂=CBr), a high degree of fluorination results in flammability on exposure to air, so the outcome of this approach was not promising. In fact, only one ethene remained as a possible candidate for consideration under this project. Reported nonflammability of 1-chloro-1,2-difluoroethene directed attention to the acquisition of this compound's brominated analogue: 1-bromo-1,2-difluoroethene.

a) Preparation of 1-Bromo-1,2-Difluoroethylene

A review of approaches to this compound yielded positive results. The published literature route was determined to represent the best method of preparing 1-bromo-1,2-difluoroethylene and the compound was successfully prepared. The literature approach⁶² is outlined as follows:



This process has two major drawbacks. Firstly, it involves the use of highly corrosive, toxic and difficult to handle antimony trifluoride. Secondly, the starting material, CHF=CBr₂, is not commercially available and a synthesis for it had to be developed. In theory there are other potential ways to make bromo-1,2-difluoroethylene, but experience indicated that this combination of reactions represented the best practical chance of success.

The cup burner extinguishment performance of 1-bromo-1,2-difluoroethene is not remarkable. Interestingly, the compound 1-bromo-2,2-difluoroethene, CHBr=CF₂, which is a structural isomer, is flammable. While 1-bromo-1,2-difluoroethene cup burner extinguishment performance of 8.4 volume % is outside the desired range for continued consideration, these

results did demonstrate the effects of structural isomerism on flammability in these very small molecules. While 1-bromo-1,2-difluoroethene serves as a bromine carrier, this was clearly not sufficient to assure an acceptable cup burner value.

Table 49. Low Boiling Bromofluoroalkene Cup Burner Values.

Compound	Boiling Point (°C)	Cup Burner Extinguishment (volume %)
1-Bromo-pentafluoropropene	27	3.1
2-Bromo-pentafluoropropene	25	3.5
3-Bromo-1,1,3,3-tetrafluoropropene	33	3.3
2-Bromo-1,3,3,3-tetrafluoropropene	29	3.5
2-Bromo-1,1,3,3-tetrafluoropropene	29	3.3
1-Bromo-2,3,3,3-tetrafluoropropene	30 (est.)	3.3
2-Bromo-3,3,3-trifluoropropene	32 to 34	3.1
1-Bromo-1,2-difluoroethene	20 to 24 (est.)	8.4

Trifluorinated, tetrafluorinated and pentafluorinated bromopropenes all are good extinguishants with no indications of flammability. A further down-select of the bromofluoropropenes would require atmospheric lifetime and toxicity testing. Bromofluoropropene boiling points significantly lower than 25 °C are extremely unlikely. If adequate means are found to disperse these compounds they may yet prove useful in some aircraft applications.

2. Bromofluoro Ethers

Prior work had concluded that the bromofluoroethers would likely be effective flame suppressants and that their environmental performance, as measured by atmospheric lifetime, possibly acceptable. Toxicity estimates were also favorable. The focus on low boiling compounds focused consideration on bromofluorodimethyl ethers and a few bromofluoromethyl ethyl ethers. Compounds having at least a one-to-one ratio of fluorine to hydrogen again provides some assurance of probable nonflammability.

With variation in site of bromination and fluorinating, a large number of structural isomers are possible even with this very limited range of ethers. The number of compounds was reduced through a selection process which focused on the most symmetrically substituted compounds (lower expected boiling point) and those compounds expected to be the least polar based on calculated octanol-water partition coefficients. This latter criterion is generally expected to select the least toxic compounds. Even with such limiting selection criteria, the

resources available to prepare compounds were sufficient to allow only a few compounds to be prepared.

With compound selection criteria based on an upper limit cut-off of 30 °C for the boiling point of a compound to be considered, the number of brominated fluoroethers becomes very limited, and unfortunately those of greatest interest, the bromofluorodimethyl ethers, are not readily synthesizable due for the most part to a lack of starting materials.

Synthesis of the brominated dimethyl ethers was first presented at the 1991 HOTWC.² Further clarification and elaboration from the author of this report enabled the successful synthesis of bromodifluoromethyl difluoromethyl ether, CF₂Br-O-CF₂H.* This information indicated that as elemental bromine will not substitute into these ethers in good yields without decomposition, the more reactive interhalogen compound, bromine chloride, should be employed. In this method, equimolar amounts of chlorine and bromine form bromine chloride on short pre-irradiation of the halogen mixture prior to introduction of the fluorinated ether. A small excess of bromine suppresses virtually any chlorination, but too large an excess of bromine significantly slows the rate of reaction. Stepwise bromination of the dihydride fluoroether, HCF₂-O-CF₂H is observed under these conditions. Additional synthetic information provided valuable insight and enabled the successful synthesis of adequate amounts of CF₂Br-O-CF₂H for very limited extinguishment testing. That information included:

1. Employ a high pressure Hg lamp. The high pressure lamp gives a pressure broadened spectrum unlike the older medium or low pressure lamps and therefore provides an increased rate of reaction. Medium and low pressure lamps do not sufficiently promote this reaction.

2. Eliminate all O₂ and H₂O from the bromine and chlorine reactants and the bisdifluoromethyl ether. Remove all oxygen (both O₂ and H₂O) from all glassware and photolysis equipment. These are extremely important steps, and failure of the reaction will result if they are not followed.

3. Adjust the Br₂/Cl₂ ratio such that Br₂ is in very slight excess to Cl₂. The amount of Br₂ employed is approximately stoichiometric to the halocarbon (fluoroether) being brominated. This method was reported to require only a couple of hours of photolysis. In the reaction, chlorine abstracts hydrogen, and bromine then adds to form the product. If too high a Br₂ to halocarbon ratio is employed, the reaction slows down due to light absorption. If too much chlorine is present, chlorination of the ether occurs instead of the desired bromination.

It was emphasized that the reaction is tricky and several attempts will likely be needed to optimize the synthetic conditions. With recycling of unreacted reactants, a high yield may well be achieved.

The cup burner extinguishment performance (Table 50), of the sample of approximately 6.5 volume % bromodifluoromethyl difluoromethyl ether was initially calculated as if the sample were 100 % pure. If the observed 3.7 volume % extinguishment value is corrected for the actual

* Personal communication of the authors with Dr. J. Adcock, University of Tennessee, June to July 2005.

65 % purity of the sample, an extinguishment value of 2.4 volume % is obtained. It is unlikely that the major impurity in this sample (bisdifluoromethyl ether) contributes significantly to extinguishment at its effective low concentration of 0.9 volume %. The remaining impurities in this sample included predominantly chlorinated analogues to the desired product. Based on these results, bromofluoromethyl trifluoromethyl ether (CFHBr-O-CF₃) would also be of interest. However, the fluoroether starting material (CFH₂-O-CF₃) is not available.

Bromofluoro ethers exhibit some of the lowest boiling points of any of the compounds tested. The toxicity of ethers is relatively low and the ether linkage has a relatively low biological and chemical reactivity. There are an abundant number of structural isomers, and boiling points as low as 20 °C to 24 °C appear to be possible. Limited atmospheric lifetime estimates⁶³ suggest the possibility of acceptable performance over a range of many of these compounds.

Table 50. Bromofluoro Ether Cup Burner Testing Summary.

Compound, Formula	Boiling Point (°C)	Cup Burner Extinguishment (volume %)
1-Bromo-1,2,2-trifluoroethyl trifluoromethyl ether, CF ₃ OCFBrCF ₂ H	42	< 4.5 ^c
2-Bromo-1,1,2-trifluoroethyl trifluoromethyl ether, CF ₃ OCHF ₂ CF ₂ Br	37	< 4.5 ^c
Bromomethyl trifluoromethyl ether, CH ₂ Br-O-CF ₃	39	3.2
Bromodifluoromethyl difluoromethyl ether, CF ₂ Br-O-CF ₂ H ^a	20 to 24 (est.)	3.7 (2.4) ^b

a Impure sample: 65 % bromodifluoromethyl difluoromethyl ether, 25 % bisdifluoromethyl ether, 10 % other ethers

b Estimated extinguishment value, based on 65 % purity

c Upper limit extinguishment value.

3. Bromofluoropropene Oxides

The propene oxides (or oxiranes) were expected to be low boiling compounds. As carriers of bromine there was potential for them to exhibit acceptable flame extinguishment properties as well. Testing indicates that perfluoropropene oxide has a cup burner value of 9.6 volume %.⁶⁴ Its toxicity is unknown. These compounds are expected to be stable under storage and may be readily attached by OH radicals. Their atmospheric lifetimes may well be short, but this suspicion is unconfirmed.

There are three possible bromine locations in the pentafluorinated propene oxide molecule. Further isomerism due to the formation of one or more optically isomeric carbons

results in further isomeric complexity. This complexity yields a total of eight unique compounds, as shown in Figure 20.

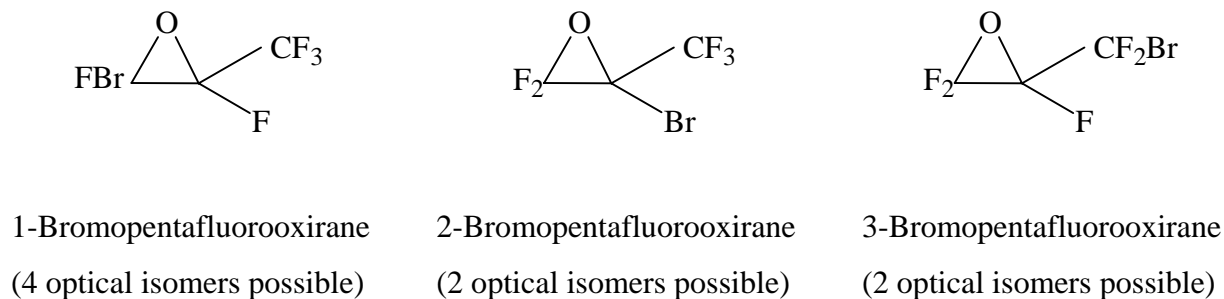


Figure 20. Structural and Optical Isomerism of Bromopentafluoropropene Oxide.

These compounds might also potentially be synthesized in a single step from existing bromofluoropropenes by a partial oxidation of the alkene bond. These compounds are expected to be stable under storage and may be readily attacked by OH radicals. Their atmospheric lifetimes may well be short, but this is unconfirmed.

Synthesis of 3-bromopentafluorooxirane has been reported. A brief survey of the literature also revealed that 30 volume % hydrogen peroxide in a basic medium had been used successfully in the epoxidation of fluorinated alkenes such as hexafluoropropene.⁶⁵

Of these only 3-bromopentafluorooxirane has been reported (USP 5,557,010), CAS# 181951-69-9. Examination of this patent reveals no experimental data for its production, although it does reference an earlier patent (USP 3,536,733), which describes reaction of oxygen with perfluoroallyl chloride at 160 °C and 2 MPa to give a 28 % yield of 3-chloropentafluorooxirane, again with no mention of addition to perfluoroallyl bromide.

The use of oxygen at high pressure is impractical for small-scale manufacture, so the supplier initiated a brief study into alternative methods for epoxidation of bromopentafluoropropenes that would be suitable for the manufacture of 10 g to 100 g of the corresponding oxiranes.

A brief survey of the literature also revealed that 30 volume % hydrogen peroxide in a basic medium had been used successfully in the epoxidation of fluorinated alkenes such as hexafluoropropene. (See, for example, *Angew. Chem. Int. Ed. Engl.* **24**, (1985) 161-179.)

CFBr(O)CFCF₃ (-bromo-1,2-perfluoropropene oxide) was eventually successfully synthesized and its flame extinguishment properties determined (Table 51). Given the unspectacular cup burner results, further investigation of the bromofluoropropene oxides was halted.

Table 51. Bromofluoropropene Oxide Cup Burner Testing Summary.

Compound	Boiling Point (°C)	Cup Burner Extinguishment (volume %)
2-Bromopentafluorooxirane	20 (est.)	4.9
1-Bromopentafluorooxirane	Unknown	Not Acquired
3-Bromopentafluorooxirane	Unknown	Not Acquired

4. Bromofluoro- and N-Bromofluoroamines, Imines and Nitriles

Bromofluoroamines have been studied previously. However, the boiling points of acquired compounds representing bromine and fluorine substituted dimethyl ethyl amines were well outside acceptable volatility limits. Bromofluoronitriles, as well as the related n-brominated amines, imines and nitriles were not considered as candidate fire suppressants until recently. This is in large measure due to a lack of availability of starting materials and facilities willing to attempt the chemistry.

Synthetic approaches to some of these nitrogen-containing compounds have been reported.^{66,67,68} Several compounds have very low boiling points and warrant further study and confirmation. The two compounds, n-bromobistrifluoromethylamine, ((CF₃)₂N-Br, boiling point 22 °C) and N-bromo-difluoromethanimine, (CF₂=NBr, boiling point 14 °C) have low boiling points near the screening limit, and bromodifluoroacetonitrile, (CF₂BrCN, boiling point 3 °C) is well below the boiling point criterion. These compounds may be toxic. However, as possibly environmentally acceptable compounds with boiling points lower than 30 °C are very rare, initial evaluation is warranted. The synthesis of the first two of these compounds, as well as other related bromofluoro- and n-brominated amines, imines, nitriles (Table 52) was attempted.

Attempts to source two compounds that, due to their low boiling points, are of particular interest have made significant progress. Published syntheses for (CF₃)₂NBr, boiling point 22 °C, and CF₂=NBr, boiling point 14.7 °C, indicated that preparation of these compounds is feasible in relatively high yield.^{69,70,71} Availability of the useful intermediate, perfluoro-2-azapropene, could provide access to a wide variety of possibly low boiling n-bromofluoroalkylamines and bromofluoroalkyl amines, imines, and nitriles.

The attempted preparation of N-bromodifluoromethanimine, CF₂=NBr, has been reported by Hennek and Thrasher.⁷² Their attempts involved the intermediate cyanogen fluoride, F-CN. They identified two literature methods. One involving the pyrolysis of cyanuric fluoride passed through either an impermeable graphite pipe held at 1300 °C to 1400 °C⁷³ or alternatively passing the compound through a platinum tube at 1100 °C,⁷⁴ and the second route to the compound involving the pyrolysis of a perfluoro alkylimine (Figure 21).⁷⁵ They chose the latter method as, according to the literature, it offered a high yield method of obtaining cyanogen fluoride and avoided the use of additional high-temperature equipment.

Also identified as a source of trace quantities of cyanogen fluoride is the pyrolysis of difluoromethyl azide (HCF_2N_3).⁷⁶ The method employs inexpensive starting materials but was not attempted because of the inherent danger associated with azides.

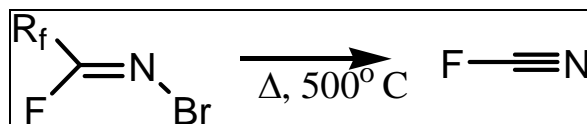


Figure 21. Formation of Cyanogen Fluoride.

Hennek and Thrasher described their attempts at preparation of the perfluoroalkylimines, $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ and $\text{C}_2\text{F}_5(\text{F})\text{C}=\text{NBr}$, as follows. The starting material for $\text{CF}_3(\text{F})\text{C}=\text{NBr}$, trifluoroacetonitrile (CF_3CN) was available in-house, but it was found that if left in a stainless steel lecture bottle at room temperature for extended periods of time, this compound will trimerize (Figure 22). However, if the trimer is passed through a 450 °C Pyrex tube, small quantities of the monomer can easily be separated via trap-to-trap distillation. Additional quantities of trifluoroacetonitrile were also purchased (SynQuest). It was also found that pentafluoropropionitrile, $\text{C}_2\text{F}_5\text{CN}$, polymerizes if stored for significant periods of time, but breaking that polymer was unsuccessful (450 °C and hotter through a Pyrex tube under vacuum). Hennek and Thrasher reported that pentafluoropropionitrile was also available from SynQuest Laboratories, Inc.

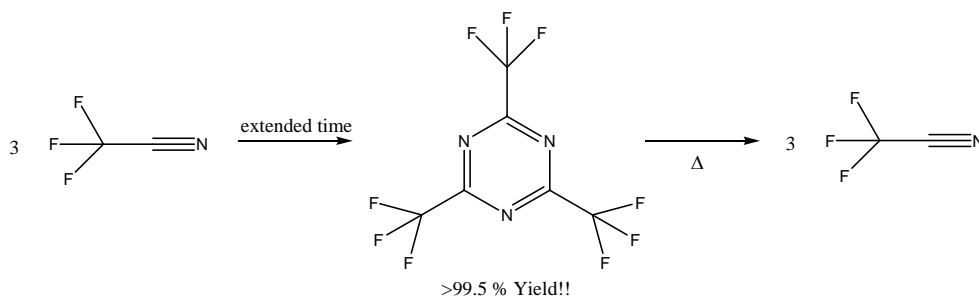


Figure 22. Formation of Trifluoroacetonitrile.

In a typical method for synthesis of the cyanogen fluoride precursor, N-bromo-2,2,2-trifluoro-ethanimidoyl fluoride ($\text{CF}_3(\text{F})\text{C}=\text{NBr}$), a 4 L Pyrex cylinder equipped with a Teflon stopcock was charged with finely ground, anhydrous cesium fluoride (15 g, 99 mmol). Bromine gas (14.4 g, 90 mmol) and trifluoroacetonitrile (2.85 g, 30 mmol) were then condensed into the cylinder, and the mixture was allowed to react in the absence of light at room temperature. By examination of the contents of the vapor space of the reactor by infrared spectroscopy, it was found that a rather long induction period existed before any significant reaction took place. This aforementioned induction period is believed to be the formation of $\text{CsF}\cdot\text{Br}_2$, thus “freeing” the active bromonium ion.⁷⁷ This induction period lasted anywhere from one day to five days, but could be shortened by first ensuring that the cesium fluoride was finely ground and then by allowing the bromine to first react with the cesium fluoride before adding the perfluoroalkyl nitrile. After the initial formation of product was observed, the reaction was allowed to continue

for several additional hours. Mechanical agitation, via rotating the flask, was also found to aid the progress of the reaction. The compound, N-bromo-2,2,2-trifluoro-ethanimidoyl fluoride, $\text{CF}_3(\text{F})\text{C}=\text{NBr}$, was found to decompose if stored in a stainless steel or Monel Hoke cylinder for more than short durations of time (hours); therefore, only pyrex cylinders were used.

The progress of the reaction described above was monitored by infrared spectroscopy (trifluoroacetonitrile $\text{C}=\text{N}$ stretching peak at 2273 cm^{-1} , $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ peak at 1705 cm^{-1}). Once the reaction was complete, the products were condensed into a stainless steel cylinder containing ethylene (2.8 g, 100 mmol), which was to react with any remaining bromine. (The physical properties of $\text{BrCH}_2\text{CH}_2\text{Br}$ render it more easily separated from $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ than bromine.) Finally, the product was separated via trap-to-trap fractionation; percent yields ranged from 65 mass % to 82 mass %%. It should be noted that, like many compounds with a nitrogen-bromine bond, N-bromo-2,2,2-trifluoro-ethanimidoyl fluoride is quite light sensitive (Figure 23). The same procedure was followed for the preparation of $\text{C}_2\text{F}_5(\text{F})\text{C}=\text{NBr}$.

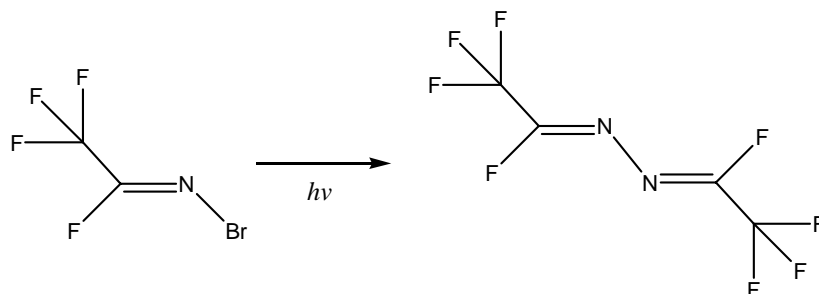


Figure 23. Photolysis of Nitrogen-Bromine Bond.

Once a significant quantity of N-bromo-2,2,2-trifluoro-ethanimidoyl fluoride was synthesized, efforts to pyrolyze it were made. In the published method, $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ passed through a pyrex tube heated at $400\text{ }^\circ\text{C}$ to $500\text{ }^\circ\text{C}$; however, no information was given with regard to flows or pressures used. Without this information, several small scaled experiments were carried out in which $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ was allowed to pass down an evacuated, pyrex bead-packed, 50 cm long tube held at $450\text{ }^\circ\text{C}$. Under these conditions, the contact time was insufficient for pyrolysis. In order to increase the contact time, several reactions were carried out at different pressures ranging from 1 kPa to 100 kPa, while the $\text{CF}_3(\text{F})\text{C}=\text{NBr}$ was introduced slowly via the use of a needle valve. Although this and several other variables were tested, all pyrolysis reactions failed to produce any cyanogen fluoride. After discussing this with a co-author of the cited literature, Dr. Brian A. O'Brien, a longer perfluorinated alkyl chain starting material, pentafluoropropionitrile, was tried. As with trifluoroacetonitrile, this compound was reacted with cesium fluoride and bromine to produce the N-brominated intermediate, which was pyrolyzed using the above methods. Very small quantities of cyanogen fluoride were generated (, as verified using IR spectroscopy), but it was found that most of the intermediate was converted back to pentafluoropropionitrile. Additional attempts at higher temperatures were employed using a 8 cm long, 2.5 cm i.d. Hastalloy C276 tube packed with Hastalloy Propack. For example, attempts to prepare FCN from the pyrolysis of $\text{C}_2\text{F}_5(\text{F})\text{C}=\text{NBr}$ were made from $500\text{ }^\circ\text{C}$ to $850\text{ }^\circ\text{C}$ in $50\text{ }^\circ\text{C}$ increments with no success. This synthesis approach was discontinued.

The attempted preparation of N-Bromo-1,1,1-trifluoro-N-(trifluoromethyl)-methanamine, $(\text{CF}_3)_2\text{NBr}$, was also investigated by Hennek Thrasher.⁷⁸ They report a synthetic scheme for, N-bromo-1,1,1-trifluoro-N-(trifluoromethyl)-methanamine, involving synthesis of perfluoro-2-azapropene, followed by fluorination with mercury(II) fluoride, and finally reaction with bromine (Figure 24).

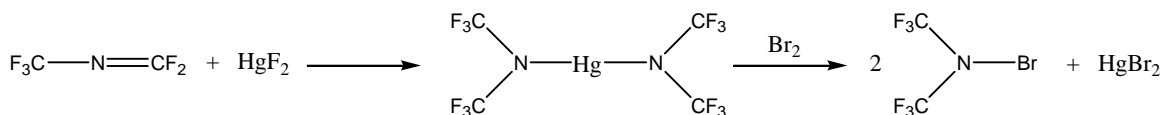


Figure 24. Synthetic Approach to N-Bromo-1,1,1-Trifluoro-N-(trifluoromethyl)-Methanamine.

They indicated that synthesis of perfluoro-2-azapropene is a key step and identified several reported approaches are illustrated in Figure 25,^{79,80,81,82,83,84,85,86} Each approach has advantages and disadvantages.

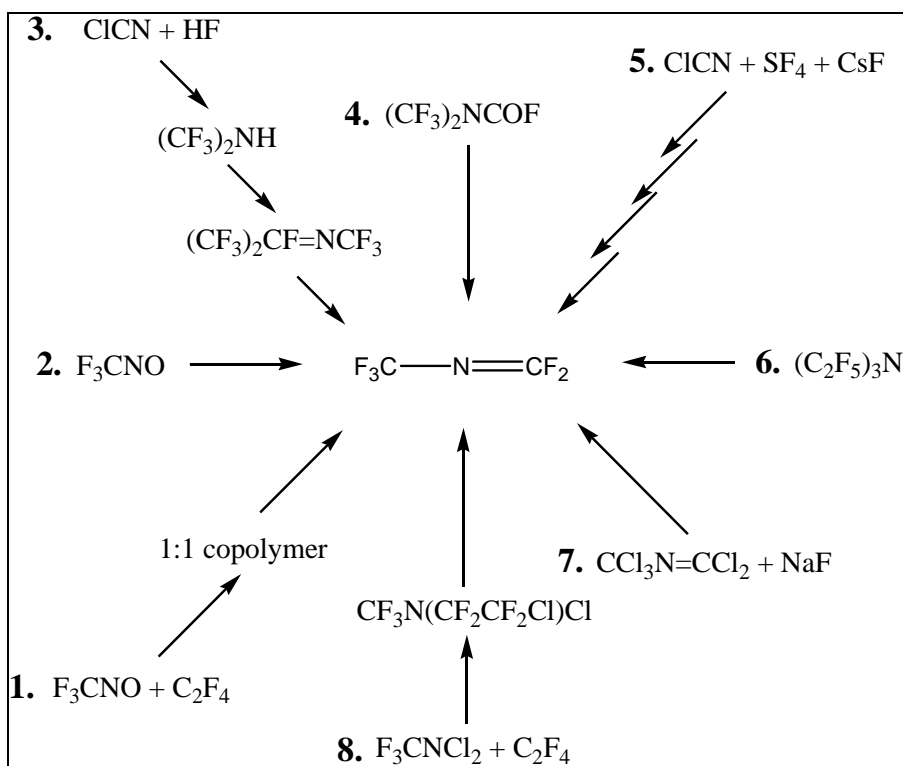


Figure 25. Synthetic Approaches to the Key Intermediate 2-Azapropene.

Method “1” of Figure 25 was chosen, as it does not require any special setup, reliance on high-energy compounds, or extensive purifications. Initially tetrafluoroethylene and trifluoronitrosomethane are condensed in equimolar amounts into a Hoke cylinder and reacted at

-30 °C, forming a polymer. The polymer can then either be pyrolyzed at 400 °C or photolyzed at 254 nm, forming perfluoro-2-azapropene and carbonyl difluoride.⁸⁷

Experimentally, they first prepared trifluoronitrosomethane (CF₃NO) employing as starting materials CF₃I (Matheson) and NO (SynQuest). Both were used as received. They describe a typical reaction as follows: nitric oxide (2.07 g, 69.0 mmol) and iodotrifluoromethane (6.05 g, 31.5 mmol) were condensed into a 16 L pyrex cylinder equipped with a Teflon stopcock, and the reaction vessel was placed into a super-blue light reactor for 24 hours. The reactor consists of 12 fluorescent bulbs (Phillips 40 W, 03RS), whose light output is centered at 420 nm. To accumulate enough material for purification, the products from five similar runs were combined. The products were first separated by trap-to-trap distillation (-78 °C and -196 °C), and afterwards the contents of the -196 °C trap were bubbled through water into a cold trap. A final trap-to-trap distillation was used separate any water from the product CF₃NO. The average yield was 31 mass %, and thus far 12 g of CF₃NO have been synthesized in this manner.

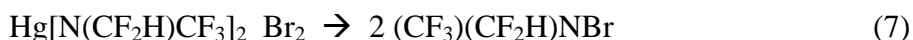
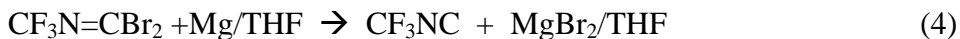
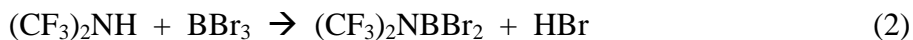
As stated above, in the synthesis of the CF₃NO/F₂C=CF₂ copolymer, equimolar amounts of CF₃NO and F₂C=CF₂ are condensed in into a Hoke cylinder and reacted at -30°C. Higher reaction temperatures favor formation of the cyclic compound, perfluoro-2-methyl-1,2-oxazetidine, c-CF₂CF₂(CF₃)NO. This compound can also be pyrolyzed, forming CF₃N=CF₂, but higher temperatures (600 °C) are necessary.

Two such small-scale (5 mmol) reactions between CF₃NO and CF₂=CF₂ have been carried out. The first reaction was done at -20 °C, and the resulting gases were of high molecular weight, believed to be perfluoro-2-methyl-1,2-oxazetidine. The second reaction was done at -35° C to -40 °C, resulting in some higher molecular weight polymer. Efforts to pyrolyze this polymer are being made.

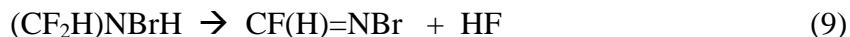
An extensive exploratory evaluation of possible approaches to the of Synthesis of (CF₃)(CF₂Br)NH, (CF₃)(CF₂H)NBr, (CF₂H)NBrH, and CF₃NBrF was prepared by Thrasher.⁸⁸ His analysis of approaches to (CF₃)(CF₂Br)NH was promising and based on a reference for the preparation of (CF₃)(CF₂Br)NH.⁸⁹ This compound was reportedly prepared by reacting HBr with CF₃N=CF₂ for 20 hours at 120 °C and 1 MPa. The product was obtain in 31 % mass yield and was found to have a boiling point of 87 °C and a density of 2.228 g/mL. Unfortunately, a typographical error exists in the Chemical Abstracts reference⁹⁰ in which the abstract states incorrectly that CF₃CF₂Br is the product; this cannot be correct as CF₃CF₂Br is known to have a boiling point of -21 °C. However, one would imagine that with further study, the percent yield of the reaction producing (CF₃)(CF₂Br)NH could be improved. This synthetic route, which seems to be the most reasonable, is dependent upon having a ready supply of or route to CF₃N=CF₂.

Thrasher also assessed the probability of Synthesis of (CF₃)(CF₂H)NBr and reported following a search of the literature, that the compound (CF₃)(CF₂H)NBr has never been prepared. He indicates that the synthesis is possible and envisions a route to compound (CF₃)(CF₂H)NBr going through CF₃N=CF₂, although considerably more synthetic steps will be required. Steps 2 and 3, shown immediately below, actually take place together, so one does not have to isolate the intermediate (CF₃)₂NBr₂. Furthermore, all of the first five (5) steps and the compound CF₃N=C(H)F are known.⁹¹ The final two steps, although unknown, have precedence

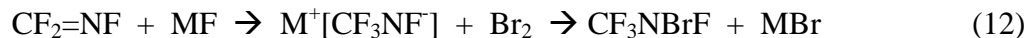
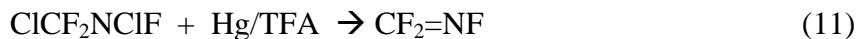
in the conversion of $\text{CF}_3\text{N}=\text{CF}_2$ to $(\text{CF}_3)_2\text{NBr}$ or $\text{SF}_5\text{N}=\text{CF}_2$ to $(\text{SF}_5)(\text{CF}_3)\text{NBr}$ or $\text{TeF}_5\text{N}=\text{CF}_2$ to $(\text{TeF}_5)(\text{CF}_3)\text{NBr}$, respectively via reaction first with HgF_2 followed by Br_2 .⁹²



Thrasher also assessed the probability of successful synthesis of $(\text{CF}_2\text{H})\text{NBrH}$, which is an unreported compound, as highly unlikely. He observed that although one can envision perhaps finding the proper conditions to hydrogenate the compound $\text{CF}_2=\text{NBr}$ to $(\text{CF}_2\text{H})\text{NBrH}$ (see equation 8 below), the precursor is not all that easy to prepare unless one can come up with a source of cyanogen fluoride, FCN . He added, that even if $(\text{CF}_2\text{H})\text{NBrH}$ could be prepared, it would probably lose HF well below room temperature, as shown in equation 9 below, as is the case for any primary amine containing an alpha-fluorine atom, e.g. the well-known instability of CF_3NH_2 .



Finally Thrasher has also assessed the probability of synthesis of CF_3NBrF . He found that the compound CF_3NBrF (boiling point, -2.8°C ; melting point, -90°C) is known in the literature (equations 10 through 12 below). It is prepared from the reaction of bromine, Br_2 , with the anion CF_3NF^- , which is prepared from the in-situ reaction of $\text{CF}_2=\text{NF}$ with fluoride, F^- .⁹³ Perfluoro(methanimine), $\text{CF}_2=\text{NF}$, is prepared via the dechlorination of ClCF_2NCIF with mercury in the presence of trifluoroacetic anhydride, (TFA, $[\text{CF}_3\text{C}(\text{O})]_2\text{O}$).⁹⁴ Finally, the precursor ClCF_2NCIF can be prepared by the reaction of cyanogens chloride, ClCN , with chlorine monofluoride, ClF , and fluorine, F_2 .⁹⁵ The synthetic scheme outlined in these references and equations 10 through 12 below seems to be the most rational for preparing additional samples of CF_3NBrF .



While none of the efforts to synthesize these interesting compounds were successfully concluded the fact that they had been made is assurance of eventual success. The difficulty of repeating reported syntheses is not uncommon and refinement of the methods described above

may yet provide these compounds for study as halon 1301 replacements such as those listed in Table 52.

Bromofluoro amines have been studied previously however the boiling points of acquired compounds representing bromine and fluorine substituted dimethyl ethyl amines were well outside acceptable volatility limits. These compounds may be unacceptably toxic, but that is as yet unconfirmed. As possibly environmentally acceptable compounds with boiling points lower than 30 °C are rare, interest in pursuing the synthesis of these two compounds as well as other related bromofluoro and n-brominated amines, imines, nitriles (Table 52) were attempted.

Table 52. Bromofluoro- and N-Bromofluoroalkyl Nitrogen Compounds.

Amine Sub-family	Examples
Bromofluoroamines	(CF ₃)(CF ₂ Br)NH, (CF ₂ Br)NH ₂
N-Bromofluoroamines	(CF ₃)(CF ₂ H)NBr, (CF ₃)(CF ₂ Br)NBr, (CF ₃) ₂ NBr, CF ₂ Br-NHBr, (CF ₂ H)NBrH

The related and readily available compounds bromodifluoroacetonitrile (CF₂BrCN), boiling point 3 °C) and trifluoroacetonitrile, ((CF₃CN), boiling point -64 °C) reported for trifluoroacetomitrile (CF₃CN) were also of interest due to their rather low boiling points and the opportunity they offered to enable evaluation of the effects of CN triple bonds on flame extinguishment.

Table 53. Cup Burner Extinguishment of Nitrogen-based Extinguishants.

Compound	Boiling Point, (°C)	Cup Burner Extinguishment (volume %)
N-Bromo-difluoromethanimine, CF ₂ =NBr	14	I
N-Bromobistrifluoromethylamine, (CF ₃) ₂ N-Br	22	I
Bromodifluoroacetonitrile, CF ₂ BrCN	3	< 4
Trifluoroacetonitrile, CF ₃ CN	-64	9

I: Compound synthesis incomplete

D. EVALUATION RESULTS FOR LOW BOILING CHEMICAL FAMILIES

Production of halon 1301 ended in January 1994, and the supply of halon 1301 for essential uses now is met entirely by banked reserves for fire protection in military and commercial aircraft. A true drop-in replacement, where all the properties of the replacement chemical are so similar to those of halon 1301 as to ensure compatibility with existing weapons platforms, was a goal of early replacement programs of research but has not materialized. Replacement of halon 1301 with minimal required modifications to the existing fire suppression system is essential for applications involving legacy military aircraft.

1. Chemical Family Down-selection Review and Considerations

The search for replacements for halon 1301 has been broad-based, with commercial sources offering several fluorocarbon products from different chemical families. Some efforts focused on finding high fire suppression efficiency agent while others sought replacement compounds that were free of any of the generally recognized disqualifying properties. As early research efforts progressed, some observations emerged which have aided and directed future efforts to develop fire suppressant chemicals:⁴¹

- For the remaining essential uses, satisfactory and affordable solutions were hard to identify and it became reasonable, necessary and essential to consider chemicals with some less-than-fully-desirable behavior - if the drawback(s) could be overcome.
- The list of attributes to be evaluated and factored into the fire suppression process and for a suppressant has evolved (i.e., atmospheric lifetime has been added, and cardiac sensitization toxicity criterion need not be as limiting as had previously been thought). By contrast, there had been little resolution as to an acceptable minimal contribution to ozone depletion and global warming.
- All new weapons systems are being designed free of ozone depleting substances, and the U.S. Army has committed to retrofitting its ground vehicles with alternate fire suppressants.

The NGP identified, developed, and utilized appropriate screening criteria to aid in the search for alternative suppressants and identify those chemical families most likely to provide acceptable replacements. Those criteria, as applied in the limited NGP research described in this report, were:⁴¹

- Fire suppression and efficiency comparable to halon 1301 and superior to the hydrofluorocarbons (HFCs).
- Atmospheric lifetime short, on the order of a month, to keep ozone depletion, global warming, and any future adverse contributions to a minimum.
- Toxic potency of agent and combustion byproducts sufficiently low that brief exposure to an extinguishing concentration does not result in an unrecoverable injury;
- No serious interaction of the agent or its byproducts with contacted aircraft materials;
- Availability of compatible storage container components;
- Boiling point sufficiently high that a suppressing volume fraction of 5 volume % (at thermal equilibrium) exists at -40 °C, the minimal design temperature for aircraft suppression system performance. This boiling point is about 25 °C. Consideration was given to agents that might require a smaller concentration for suppression; for example, this boiling point criterion rises to 35 °C for a 3 volume % suppression concentration. Even this is not an absolute criterion, since the engine heats the interior engine nacelle surfaces during flight and since

it is often feasible to warm the agent storage container. The boiling point can be as high as 75 °C if the suppression takes place in an environment at 22 °C. Of course, if the agent is dispensed as a mist/powder or via a solid propellant gas generator (SPGG), the concept of a limiting boiling point criterion is not applicable.

Early estimates of vapor pressure, Table 6, indicated that with a degree of atomization, some chemicals with boiling points up to approximately 35 °C might well be usable in fire suppression applications. Further enhancements to atomization and or consideration of altitude effects such as reductions in air pressure could also aid in vaporization and further increase the useable boiling point limit.

This estimate of upper boiling point limit and estimation methods for a number of other targeted attributes provides a starting point for compound selection. A boiling point maximum was not rigidly applied as a general selection criterion in the compound selection and testing program. Consideration including chemical heats of vaporization, agent storage bottle temperature, nozzle design, pressurization and new technologies and methods of producing atomized or misted agent discharges were as likely to result in significantly increased volatilization and effectively a higher upper boiling point limit.

Fundamentally, fire fighting agents first and foremost must extinguish the fire. Once a compound is determined to have an acceptable fire suppression performance, other considerations impact its continued candidacy as a replacement. Historically, water represents one of the earliest chemical agents employed in fire suppression. Fire extinguishment capability to protect structures and people to reduce the vulnerability of society to fire caused loss is a valued asset. From the basic use of water to extinguish fire (as reflected in the use of vats of stored water, the oldest of which were cast as early as ca. 1500 AD during the Ming Dynasty (**Figure 26**)) to the present, extinguishants and agent storage and delivery systems are tailored to the threat and the economics issues associated with structures and equipment impacted by the fire threat.

Water is still a broadly used firefighting agent and changes in application and dispersion method have enabled improvements in performance, new fire suppression uses, and improved safety, reduced vulnerability of protected facilities, vehicles, and personnel and improved overall survivability. For instance misting of water has enabled applications around electrically energized equipment and fuel fires as well as combination extinguishment systems. Additional examples of the continued application of misted water are contained in the annual HOTWC proceedings. The potential for agent distribution and application methods to greatly affect the performance and ultimately the usability of an agent as a fire suppressant should be kept in mind as we review and summarize the chemical families and individual chemicals studied under the NGP.



Figure 26. Fire Fighting Water Storage Ca. 1500 AD, Forbidden City, Beijing, China.⁹⁶

Early in the halon replacement effort chemicals that reacted with tropospheric components, such as hydroxyl radicals, or chemicals that are sensitive to photolysis or were inherently polar and subject to rainout were recognized as having the potential for short atmospheric lifetimes and therefore minimal ozone depletion potential and global warming impact.¹ These chemical families were recognized as prime areas of investigation. Such chemical families and chemicals are sometimes identified as being “tropodegradable,” and they offer a means to continue to incorporate the highly effective fire suppressing bromine atom in a new potentially environmentally acceptable extinguishant.

The NGP research effort into new chemicals has resulted in the characterization of the flame suppression properties of chemicals representative of several chemical families whose physical properties may eventually be determined to be consistent with a range of fire suppression applications including those encountered in extreme aircraft environments. Other less demanding fire suppression applications may also find use for some of these chemicals.

With the focus on aircraft application the limits of temperatures experienced in flight were a prime consideration and fire related agent discharge characteristics at these temperature of great interest. Dispersion testing of CF_3I at $-40\text{ }^\circ\text{C}$ was performed with results that were not reassuring. These tests indicated that even with its relatively low boiling point, CF_3I ($-22.5\text{ }^\circ\text{C}$) lacks sufficient volatilization under conditions of the testing to give assurance that a uniform extinguishment concentration would be obtained.

The dispersion testing result for CF_3I illustrates and validates earlier intuitive conclusions that agent boiling point is a key and critical criterion to chemical selection and will likely remain so especially under low temperatures ($-40\text{ }^\circ\text{C}$) and particularly where agent discharge is characterized by a need to introduce large quantities of chemical in extremely short time frames to achieve extinguishment concentrations under conditions of high air flow. The chemicals and

chemical families reviewed in the preceding sections of this report do not overcome this fundamental problem and as such fail at this point to demonstrably represent drop-in replacements for halon 1301 in overall aircraft applications. That said, some chemical families potentially do offer alternatives to halon 1301 and certainly to halon 1211. Other than limits due to toxicity and exposure risk issues, the limits of usage might in some cases be offset through use of agent dispersion aids.

An overall assessment of chemical family attribute suitability and individual chemical potential acceptability for use as fire extinguishants and in some cases as halon replacements is presented in Table 54. This table provides generalized information. For a more detailed review the reader is referred to the relevant report section.

Table 54. Chemical Families Assessment Summary.

Chemical Family (Example)	Overall Candidacy Assessment - Conclusions/Recommendations
Iodinated fluoroalkanes (CF ₃ I)	Chemical family of iodoalkanes possesses strong chemical suppression characteristics and unfortunately strong cardiac sensitization properties. Short atmospheric lifetimes and some with relatively low boiling points (CF ₃ I, -22.5 °C) have resulted in considerable interest.
Iodinated fluoroalkenes, (CF ₂ =CFI)	Of comparatively little interest as this chemical family is expected to have chemical stability problems.
Brominated fluoroalkenes (CH ₂ =CBr-CF ₃)	Many brominated fluoroethenes, propenes, butenes and some pentenes of which program allowed study of only a few examples. Effective fire suppression performance, acceptable acute inhalation toxicity in some cases, and demonstrated short atmospheric lifetimes. Inability to easily screen for cardiac sensitization a major hurdle to progress. Boiling points are generally higher than 25 °C for the bromofluoro propenes. Bromotetrafluoroalkenes may have the best mix of toxicity, flame suppression, and boiling point.
Iodinated fluoroethers (CH ₂ I-O-CF ₃)	Of comparatively little interest as this chemical family is expected to have high boiling points and the possible presence of iodine adjacent to ether oxygen may exacerbate chemical stability problems.
Brominated fluoroalcohols (HO-CH ₂ CBr-CF ₃)	Of comparatively little interest as this chemical family is characterized by high boiling points and the presence of bromine and hydroxyl groups exacerbate chemical stability problems.
Brominated fluoroethers CF ₂ Br-O-CF ₂ H	Demonstrated fire suppression effectiveness, lower boiling points, possible shorter atmospheric lifetimes if sufficient hydrogen's in structure. Toxicity may in some cases to be acceptable for some applications. Synthetic pathways ²

Chemical Family (Example)	Overall Candidacy Assessment - Conclusions/Recommendations
	converting fluoromethyl ethers to their brominated congeners provide ready approaches to other members of this family.
Fluorinated aldehydes/ketones, (CF ₃ CFHC(O)H, CHF ₃ -O-CF ₃)	Of comparatively little interest, as this chemical family is characterized by high boiling points. Fluorinated aldehydes and fluoro ketones are expected to have serious chemical stability problems.
Fluoronitriles (CF ₃ CN)	The only example of this family to be studied has a low boiling point (-64 °C) and a high cup burner value of 9 volume %. CN groups may degrade suppression effectiveness.
Fluoro- and bromofluoroamines ((CHF ₂) ₂ (CF ₂ Br)N, (CF ₃)(CF ₂ Br)NH, (CF ₂ H) ₂ (CF ₃)N)	Earlier testing of N(CF ₃) ₂ (CH ₂ CF ₂ Br), N(CF ₃) ₂ (CF ₂ CFHBr), and N(CF ₃) ₂ (CHF ₂ CF ₂ Br) demonstrated their excellent fire suppression capability. Attempts to synthesize lower boiling methyl analogues were unsuccessful. If this difficulty were to be overcome this chemical family could well present a very significant opportunity to identify additional candidate compounds. The unbrominated amines N(CF ₃) ₂ (C ₂ F ₅) and N(CF ₃) ₃ will have unacceptably long atmospheric lifetimes. Partial replacement of fluorine by hydrogen will help reduce the lifetimes; however, this is not likely to be sufficient to allow their use.
Bromo Fluoro Propene Oxides CF ₂ (O)CBrCF ₃	The only example of this family to be studied has a moderate boiling point and a disappointingly cup burner value of 4.9 volume %. Suppression effectiveness is not much improved over the HFCs.
Bromofluoronitriles CF ₂ BrCN	CF ₂ BrCN, boiling point 3 °C, whose cup burner extinguishment value of < 4 volume % is possibly a shorter atmospheric lifetime chemical. It is rumored to be quite toxic, but attempts to confirm this unpublished determination have been unsuccessful.
n-Bromofluoro amines / imines (CF ₃)(CF ₂ H)NBr, CF ₂ =NBr	Fluoroamines and bromofluoroamines are undoubtedly the most promising of the nitrogen-containing compounds as potential halon replacements. There is evidence that some could have low atmospheric lifetime, low toxicity, and good fire extinguishment capability. To the extent misting is practical for suppressing aircraft fires, this family is worth a further look. Incorporation in SPGG to enhance dispersion is a possible approach.
Phosphorus Acids and Esters ⁴¹ (P(OCF ₃) ₃ , O=PR(OCF ₃) ₂ , P(OH)(OCF ₃) ₂)	Phosphorus compounds are highly effective at suppressing some types of flames, yet poor at suppressing others. ⁴¹ Most work to date has emphasized alkyl phosphonates and related materials or phosphonitriles. Low volatility remains one of the major

Chemical Family (Example)	Overall Candidacy Assessment - Conclusions/Recommendations
	problems with phosphorus compounds as flame suppressants. Phosphorus compounds containing fluoroalkyl and hydrofluoroalkyl groups, however, are often nonflammable and have higher volatilities; they should be given high priority for additional study. To the extent misting is practical for suppressing aircraft fires, this family is worth a further look. Incorporation in SPGG to enhance effectiveness and dispersion is a possible approach.
Phosphonitriles ⁴¹ (P ₃ N ₃ F ₆ , P ₃ N ₃ ClF ₅ , P ₃ N ₃ Cl ₂ F ₄)	A number of phosphonitriles have been shown to be excellent extinguishants in laboratory and carefully controlled field conditions; however, the exceedingly low volatilities make it unlikely that these could be practical total flooding extinguishants unless delivered as mists. To the extent misting is practical for suppressing aircraft fires, this family is worth a further look. Potential incorporation in SPGG to enhance effectiveness and dispersion a possible approach.
Phosphorus halides ⁴¹ (PCl ₃ , PBr ₃ , O=PCl ₃)	Promising flame extinguishment data for phosphorus halides is demonstrated. Untested areas would include examination of the possibly more stable, totally fluorinated compounds, PF ₃ and O=PF ₃ . Published extinguishment data and extinguisher application in jet engine nacelle applications employing PBr ₃ and descriptions of dispersion methodology employed need further information for evaluation.
Bromofluorosulfides ⁴¹ (CBrF ₂ S(O)CF ₃)	It is predicted that bromination will be needed to prepare an acceptable extinguishant. ⁴¹ Brominated fluorosulfoxides are unavailable.
Sulfoxides ⁴¹ (CF ₃ S(O)CF ₃)	Insufficient information exists to make a truly informed judgment on the applicability of sulfoxides as fire suppressants. ⁴¹
Copper Compounds ⁴¹ (CuO, Cu ₂ O, CuCl ₂ , CuCl)	The fire suppression effectiveness of copper-containing compounds is open to question. ⁴¹ If fire suppression performance were demonstrated compound boiling points are likely to be high and stability (hydrolysis) may result in even higher boiling point compounds. Potential incorporation in SPGG to enhance effectiveness and dispersion a possible approach.
Manganese Compounds ⁴¹ MnBr ₂ , MnI ₂	There are few data on the fire suppression properties of these compounds, but what little there is points to a high degree of effectiveness. ⁴¹ Boiling points are high and stability (hydrolysis) may result in even higher boiling point compounds.

Chemical Family (Example)	Overall Candidacy Assessment - Conclusions/Recommendations
	Potential incorporation in SPGG to enhance effectiveness and dispersion a possible approach.
Iron compounds ⁴¹ Fe(CO) ₅ , Iron acetylacetonate	The high flame inhibition effectiveness of these compounds has been established, but no flames or fires have been suppressed by an iron-containing compound. ⁴¹ Boiling points are high and stability (hydrolysis) may result in even higher boiling point compounds. Effective delivery to the fire is addressed in other NGP projects. Potential incorporation in SPGG to enhance effectiveness and dispersion a possible approach.
Tin-containing compounds ⁴¹ SnCl ₂ , SnCl ₄ , Sn(CH ₃) ₄	Existing data suggest that tin based extinguishants would have a high fire suppression efficiency and low environmental impact. ⁴¹ Boiling points are high and stability (hydrolysis) may result in toxicity and or even higher boiling point compounds. Potential incorporation in SPGG to enhance effectiveness and dispersion a possible approach.

2. Chemical Family Options

No chemical studied thus far satisfactorily addresses aircraft applications, which demand a unique combination of high flame suppression efficiency, low boiling point, acceptably short atmospheric lifetime, and acceptable toxicity. Should any of these constraining attributes, particularly boiling point, be relaxed, it is likely that some chemical families options may well be applicable. New agent dispersion methods may facilitate use of chemicals whose boiling points are in the 25 °C to 35 °C range.

This extensive review and evaluation of chemical families and chemical testing has yielded a limited list of candidate chemical families that might be useable should boiling point limits be relaxed. Some of these chemical families, particularly the bromofluoroalkenes and bromofluoroethers may well include compounds with toxicity low enough to allow consideration for use in occupied areas. Chemical families such as the bromofluoronitriles, bromofluoroimines, and the n-brominated amines and imines should include relatively low boiling compounds whose applications will likely be restricted to unoccupied areas. Additional study and testing might also allow inclusion of selected fluoroalkyl phosphorus compounds in this listing however at this point no such justification exists.

Bromofluoroamines may eventually offer significant promise if sources of these compounds can be located. The toxicity of this class of compounds is expected to be low and there are numerous compounds that in theory might well be considered if available. Compounds such as N(CFH₂)₂(CF₂Br) could provide short atmospheric lifetimes and chemical suppression. The primary barrier to progress remains compound availability.

3. Limitation due to Low Boiling Point Criterion

Aircraft experience a wide range of environmental conditions, and fire suppression chemicals must disperse and vaporize in order to be effective in suppressing fire. This search for alternative agents has focused first on identifying chemical families either known to be environmentally acceptable or reasonably expected based on functional characteristics or expected reactivities to have short atmospheric lifetimes. Examination of the listed chemical families led to a dramatic narrowing of the possibilities. Meeting the low boiling requirement focused attention even further to a very few chemicals which boiled lower than 20 °C. Cup burner testing was required in order to confirm expected flame extinguishment and screen out any structural characteristics having adverse effects on flame extinguishment performance. This process of acquisition and testing has been reviewed in the prior sections of this report for the chemical families identified as most likely to yield low boiling chemically active flame suppressants. The listed chemical families and their representative chemicals clearly indicate the limited range of boiling points for each (Table 55).

Table 55. Chemical Family Boiling Point Options and Trends.

Compound/Formula	Boiling Point
Bromofluoro Alkenes with Boiling Points < ≈40 °C	
1-Bromo-3,3,3-trifluoropropene/CHBr=CH ₂ -CF ₃	40 °C
3-Bromo-1,3,3-trifluoropropene/CHF=CH ₂ -CBrF ₂	40 °C
3-Bromo-1,1,3,3-tetrafluoropropene/CF ₂ =CH ₂ -CBrF ₂	33 °C
2-Bromo-3,3,3-trifluoropropene/CH ₂ =CBrH-CF ₃	32 °C
1-Bromo-2,3,3,3-tetrafluoropropene/CHBr=CHF-CF ₃	32 °C
2-Bromo-1,1,3,3-tetrafluoropropene/CF ₂ =CBrH-CHF ₂	est. 30 °C
2-Bromo-1,3,3,3-tetrafluoropropene/CFH=CBrH-CF ₃	29 °C
1-Bromo-pentafluoropropene/CFBr=CF ₂ -CF ₃	27 °C
2-Bromo-pentafluoropropene/CFBr=CF ₂ -CF ₃	25 °C
3-Bromo-pentafluoropropene/CF ₂ =CF ₂ -CBrF ₂	26 °C
Bromofluoro Ethers with Boiling Points < ≈40 °C	
Bromomethyl trifluoromethyl ether/ CH ₂ Br-O-CF ₃	39 °C
2-Bromo-1,1,2-trifluoroethyl trifluoromethyl ether/CF ₃ OCHF ₂ CF ₂ Br	37 °C
Bromomethyl tetrafluoromethyl ether/ CHFBr-O-CHF ₂	est. 22 °C
Bromofluoro Amines/Nitriles/Imines with Boiling Points < ~40 °C	
Bromodifluoromethyl bistrifluoromethyl amine/(CF ₃) ₂ N(CBrF ₂)	40 °C
N-Bromo-bistrifluoromethyl amine/(CF ₃) ₂ NBr	22 °C
N-bromo-difluoromethanimine/ CF ₂ =NBr	14 °C
Bromodifluoroacetonitrile/CF ₂ BrCN	3 °C

Faced with a boiling point limit of approximately 20 °C, investigation of dispersion methods for application to aircraft fire suppression needs is an option to be investigated carefully. Not all chemicals of interest could be acquired. These additional compounds include ethers, n-bromofluoroamines and imines. Some of the more interesting compounds remaining untested include the brominated and n-brominated fluoroamines (CF₃)(CF₂Br)NH, (CF₃)(CF₂H)NBr, (CF₂H)NBrH, and (CF₂Br)NH₂. The synthesis of each of these compounds may be possible as synthetic methods have been identified.

4. Limitations due to Lack of a Cardiac Sensitization Screen

Cardiac sensitization ranking of the many bromofluoroalkenes requires at the very least development of a method of estimating relative ordering of a series of chemicals. The search for a method is covered in the next section. In order to maintain continuity of this presentation the results of this search and possible method for estimating a compounds LOAEL is described below.

As will be described further in the following section, cardiac sensitization LOAEL and a compound's octanol-water partition coefficient, K_{OW}, may be related. There is evidence that the higher the experimental Log(K_{OW}), the higher the potential to induce cardiac arrhythmia under conditions of epinephrine challenge. Estimation methods (Figure 27) indicate that some bromofluoropropenes (CFBr=CFCFH₂, CF₂=CFBrH₂, and CF₂=CBrCFH₂) may well have low Log(K_{OW}) values and therefore a lower tendency to cause cardiac arrhythmia.

Provide CAS RN or SMILES of a molecule and press the "submit" button

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Halothane

CAS RN	151-67-7	formula	C2HF3ClBr	MW	197.38
SMILES	FC(F)(F)C(Cl)Br				
logP [exp]	2.30	logS [exp]	-1.71 (3.85 g/l)		
ALOGPs	2.50 <+0.20>	ALOGpS	-1.73 (3.67 g/l) <-0.02>		
IA_logP	2.44 <+0.14>	IA_logS	-1.78 (3.28 g/l) <-0.07>		
CLOGP	2.27 <-0.03>	PhysProp reference			
KOWWIN	2.26 <-0.04>				
XLOGP	2.74 <+0.44>				

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Press calculated results to see details of calculations. Press underlined links to read about a particular method.

Press LogP or LogS LIBRARY to read how to improve your predictions.

Figure 27. Estimation of Partition Coefficients - Input of New KOW Values Improves Models.⁹⁷

Experimental determination of Log(K_{OW}) values (by RP-HPLC or GCMS methods) would allow incorporation of these new values and refinement of structure based calculation methods used in QSAR methods (Figure 27). The resulting improved calculations may well then be used to identify additional promising chemicals.

E. CARDIAC SENSITIZATION SCREENING OPTIONS

Cardiac sensitization is the sudden onset of cardiac arrhythmias caused by a chemical sensitization of the heart to epinephrine (adrenaline). Cardiac sensitization is a particularly important concern in firefighting because under the stress of the fire event, higher levels of epinephrine are secreted in the body, increasing the possibility of sensitization.⁹⁸

It is widely accepted that LOAEL data obtained from the dog exposure based cardiac sensitization testing are very conservative and, perhaps as a direct result, deaths due to human exposure to halons are extremely rare. The dog cardiac sensitization exposure based standard seems to be achieving exactly what it was designed to achieve – ensuring a wide margin of safety to a broad spectrum of end users.

Cardiac sensitization LOAEL and NOAEL concentrations entail measurement of cardiotoxic effects in animals made sensitive by the administration of epinephrine at dose levels just below the concentration at which epinephrine alone would cause cardiotoxicity. In the experimental animal, the administered epinephrine levels are approximately ten times greater than the concentration a human would be likely to secrete under stress. Therefore LOAEL and NOAEL values are conservative even in high-stress situations, with the result being an overall increased margin of safety.

The mechanism of cardiac sensitization is not understood, making design of a screening method difficult. Some researchers have concluded that cardiac sensitization is a direct result of a physical-chemical interaction of the sensitizing agent with heart cell membrane structures.⁹⁹ This mechanistic hypothesis is derived from the observation that a critical blood concentration of agent is needed to elicit a cardiac sensitization response, and the effects are immediately reversible, if they are not sufficiently severe to cause death, when the sensitizing agent is removed. Below that critical concentration, the effect does not occur.

Cardiac sensitization LOAEL and NOAEL values of potential halon replacements are essential to compound selection and reducing risk for occupied space extinguishment agents. The cost of performing the test is currently in the range of \$100,000, and as a result the test is performed only rarely. Screening methods were sought in order to aid in the selection of compounds with a higher probability of having acceptable LOAEL and NOAEL values when actually tested. A wide variety of approaches to estimating and or understanding the mechanism were reviewed in the course of the over all halon replacement effort.

Any estimation method enabling a ranking of compounds would greatly facilitate compound acquisition efforts. Methods would have to be able to distinguish between compounds whose LOAEL values differ by 1 volume % to 2 volume % in order to be of use in final compound selection.

1. Cardiac Sensitization – Search for Structural Predictors

Cardiac sensitization is a property that has been associated with halogenated and non-halogenated compounds. It has surfaced as a consideration in the development of propellants for medical inhalers, it is observed as a cause of cardiac arrest in substance abuse by inhalation of

solvents used in spray paints and hairsprays, and it is seen in some pharmaceuticals and some surgical anesthesia agents.

The fluorocarbons and hydrofluorocarbons listed in Table 56 demonstrate a wide range of LOAEL values. Limited data for partially fluorinated methane compounds (Table 56, Compounds 6 and 7) demonstrate a relatively low tendency to induce cardiac sensitization. Limited hydrofluoropropane data (Compounds 3 through 6) as well as hydrofluoroethane data (Compounds 8 through 11) demonstrate no correlation between degree of fluorination and LOAEL value but do suggest that fluorine (or conversely, hydrogen) position may be a strong factor in determining cardiac sensitization effects in these HFCs. The iodofluorocarbons, bromofluorocarbons, and bromochlorofluorocarbons listed in Table 57 reflect increasing LOAEL values where bromine is replaced by iodine.

Table 56. Fluoro- and Hydrofluorocarbon Cardiac Sensitization Values.

#	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₃ CF ₂ CF ₂ CF ₃	40	>40
2	CF ₃ CF ₂ CF ₃	30	>30
3	CF ₃ CHFCHF ₂	2.5	3.5
4	CF ₃ CHFCF ₃	9	10.5
5	CF ₃ CH ₂ CF ₃	10	15
6	CH ₂ F ₂	20	25
7	CHF ₃	30	>50
8	CH ₂ FCF ₃	4	8
9	CH ₃ CF ₃	4	8
10	CHF ₂ CF ₃	7.5	10
11	CH ₃ CF ₂ H	5	15

Table 57. Bromo-, Chloro- And Iodofluorocarbon Cardiac Sensitization Values.

#	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₃ I	0.2	0.4
2	CF ₃ Br	5.0	7.5
3	CF ₂ HBr	2	3.9
4	CF ₂ Br ₂	-	-
5	CF ₂ BrCl	0.5	1.0
6	CF ₂ BrCF ₂ Br	-	0.1
7	CBrClFCBrF ₂	-	0.5
8	CF ₃ CF ₂ CF ₂ I	-	0.1

CFCs (which are closely related to the halons), many compounds currently under study as halon replacements, and many of the commercialized halon replacements, are cardiotoxins.^{100,101} These gases enter the arterial blood and cause arrhythmic cardiac rhythm resulting in a compromised blood pumping action. The arrhythmia most damaging to blood pumping are premature ventricular contractions (PVCs) and ventricular tachycardia. Examination of chlorofluorocarbon cardiac sensitization data (Table 58) give little, if any, indication of relationships between degree of fluorination, chlorination, or hydrogenation and LOAEL values. While the highly fluorinated compound, CF₃CF₂Cl, is notable for its unusually high LOAEL of 15 volume %, most values range from a low of 0.5 volume % to a nominal high of 5 volume %.

Table 58. Chlorofluorocarbon Cardiac Sensitization Values.

#	Chemical Formula	NOAEL (volume %)	LOAEL (volume %)
1	CF ₂ ClH	2.5	5
2	CF ₂ Cl ₂	2.5	5
3	CFCl ₃	-	0.5
4	CH ₂ =CClH	2.5	5
5	CCl ₃ CH ₃	0.25	0.5
6	CF ₂ ClCH ₃	2.5	5
7	CFCl ₂ CH ₃	-	0.5
8	CF ₃ CF ₂ Cl	-	15
9	CF ₃ CCl ₂ H	1	2
10	CFCl ₂ CH ₃	-	1
11	CF ₂ ClCF ₂ Cl	-	2.5
12	CClF ₂ CFCl ₂	0.25	0.5
13	CF ₂ ClCF ₂ CFHCl	-	2.0

As an indication of the status of modeling, QSARs have developed for only a very few chemical families.¹⁰² Cell based or in vitro method requirements have been identified.¹⁰³

Toxicity prediction and screening approaches which involve chemical attributes typically employed in the development of QSARs have linked some predictors of relationships between biological activity and chemical properties.^{104,105} These can be classified as property descriptors and topological descriptors (steric and structural). A list of general toxicity and cardiac sensitization rules is presented in Table 59.

Table 59. Basic Cardiac Sensitization Rules.

Cardiac Sensitization Ranking Criteria
Halogen presence is more potent than hydrogen.
Bromine presence is more potent than fluorine presence.
Iodine presence is more potent than bromine presence.

Isolated ventricular myocytes¹⁰⁶ and neonatal cell cultures¹⁰⁷ have been used to investigate cardiac cell function. Cell cultures of several species have been used in *in vitro* studies of cardiac cells.^{108,109,110,111,112,113,114,115,116,117,118,119, 120}

A highly significant early study demonstrated a possible correlation between chemical induction of cardiac sensitization and physiochemical properties.¹²¹ These studies receive some support from experimental work demonstrating the effects of halothane (CF₃CHClBr) on cell membrane protein conformation energy thresholds.¹²² Environmental risk assessments employ chemical water octanol partition data as a model of lipid and cellular fluids chemical distribution as toxicity predictors.^{123,124}

Finally, medical anesthesiology research reports provide insight into possible nerve conduction and cardiac cellular level effects of anesthetics and by inference the fluorinated and brominated organic compounds of interest as halon replacements.^{125,126,127,128}

2. Clark and Tinston - Study of Chemically induced Arrhythmia

Recent cardiotoxicity research reflects interest in the use of fluorocarbons and chlorofluorocarbons in many industrial as well as medical applications. Though not conclusive, this research does provide some indication of possible cardiotoxicity predictors.

Clark and Tinston reported (1973) on the possible correlation of cardiac sensitizing potentials of halogenated and some non-halogenated chemicals with selected physiochemical properties.¹²⁹ Their report concluded that cardiac sensitization was an example of “physical toxicity” and that cardiac arrhythmia was a structurally non-specific reaction, occurring once the chemical “occupied a constant fraction of the critical biophase” based on data in Table 60. EC₅₀ data represent the air concentration of a chemical which induces the more serious arrhythmia such as multifocal ventricular ectopic beats or ventricular fibrillation in 50 % of test animals. The EC₅₀ values* vapor pressures at 37 °C for the series of compounds tested appear to increase in approximate unison.

* The EC₅₀ is the concentration of a substance in air that causes the designated effect in 50 % of the exposed population within a specified exposure time.

Table 60. Air Concentration Inducing Cardiac Sensitization in 50 % of Animals.

Compound	EC ₅₀ (volume %)	Partial Pressure at EC ₅₀ (mm Hg)	Vapor Pressure at 37 °C (mm Hg)	Relative Saturation for Cardiac Sensitization
CFCl ₂ CFCl ₂	0.12	2.0	99	0.02
CCl ₄	0.5	4.0	190	0.02
CH ₃ CCl ₃	0.75	6.0	210	0.03
CCl ₂ FCF ₂ Cl	1.0	8.0	524	0.02
CFCl ₃	1.25	10	1186	0.01
CF ₃ CHClBr	2.0	15.0	480	0.03
CH ₂ Cl ₂	2.4	18	661	0.03
CHFCl ₂	2.5	19	2052	0.01
CH ₂ =CHCl	5	38	4218	0.01
CF ₂ Cl ₂	8	61	6764	0.01
CF ₂ ClCF ₂ Cl	10.0	76	2310	0.03
CH ₃ CH ₂ CH ₃	20	153	9538	0.02
CF ₃ Br	20	153	15276	0.01
CF ₃ Cl	80	610	40698	0.02

3. Cell Membrane, Protein Folding and Biological Activity Effects

Recent research has also shown, using differential scanning calorimetry, that the inhalation anesthetic agent halothane (CF₃CHClBr) destabilizes some proteins in aqueous solution with respect to thermal unfolding, presumably due to halothane binding to the native folded state.¹³⁰ The authors of this study reported that low millimolar concentrations of halothane produce significant destabilization of proteins. They reported that at 14 mM halothane concentrations, unfolding temperatures were reduced by up to 8.8 °C in most proteins studied, and they concluded that destabilization of proteins by halothane can be attributed to mainly hydrophobic interactions of halothane with the proteins.

Water-octanol partition coefficients are recognized as correlating with biological activity.¹³¹ Partition coefficients are typically used to describe the relative concentrations of a compound in two adjacent media (air/water and/or water/octanol or water/membrane). Water-octanol partition coefficients are frequently employed in quantitative structure activity relationships (QSAR) in the early stages of developing environmental risk assessments.¹³² Partition coefficients have also been employed in the past in the assessment of chemical toxicity. While they are widely accepted by the pharmaceutical industry as valuable indicators of drug effectiveness, they are typically just part of the data used to predict a compound's overall toxic effect(s).

4. Relevant Anesthesiology and Cardiac Research

Of the medical research areas impacted by phenomenon of cardiac sensitization, surgical anesthesia agents and pharmaceutical development are two areas that stand out. Published work in these areas provides an opportunity to gain additional insight into the phenomenon of cardiac sensitization and possibly some guidance for the development of a screening method. While the literature is abundant in the general research areas of anesthesiology and cardiac electrophysiology and arrhythmia there was found, not surprisingly, no information or commercial laboratory services describing the approaches and methods employed by major pharmaceutical companies in their drug development research related to avoiding cardiac sensitizing or arrhythmia inducing drugs.

Anesthesia is the condition of loss of consciousness, usually coupled with the loss of response to pain and other stimuli. General anesthesia results from a depression of the central nervous system (CNS), which can be exerted by a wide range of chemicals. Anesthetic potency of chemicals is tested in animals by observing decreases in righting reflex (ability to stand up after being knocked over) or diminished response to foot or tail shock. The AD₅₀ is the calculated value corresponding to the concentration at which 50 % of the test animals experience anesthesia. In AD₅₀ experiments, anesthesia is defined as loss of the righting reflex or lack of response to shock. Anesthetic potency or mild CNS depression can also be observed in humans using performance decrement studies. Structure-activity relationships have been developed for predicting anesthetic effects.¹³³

The study of anesthesia is an active area of research with considerable published data on the influence of various compounds on human systems.¹³⁴ Published studies includes data on the relative tendencies of a wide range of current and former anesthesia agents to induce cardiac arrhythmia as well as comparison molecular property data, toxicity information and models for agent uptake to target tissues. Reviews covering cell membrane ion gate channel effects and the effects of molecular structure can be found in studies of pharmacokinetics and molecular physiology.^{135, 136} Data presented relate uptake of anesthesia agents and physical properties such as blood gas ratios (partitioning) of the anesthesia agent based on relative solubility in the two media.

Evidence for some of the effects of general (volatile) anesthetics on membranes and membrane ion channels are described in terms of protein binding mechanism.¹³⁷ However, this interpretation does not account for the lack of demonstrated differential anesthetic effects of the two stereoisomers (R and S) of isoflurane. The R and S stereoisomers of isoflurane would be predicted to bind quite differently to stereo specific protein sites yielding marked differences in the relative abilities of the R and S forms of isoflurane to induce anesthesia. Investigation of the effects of volatile anesthesia agent on voltage gated ion channels is also ongoing and provides evidence for their inhibition of voltage-gated ion channels and to a greater extent on ligand-gated ion channels.¹³⁷ These same researchers report that “we can summarize these findings with the generalization that volatile anesthetics have high-efficacy on ligand-gated ion channels, whereas they have relatively low potency and high efficacy effects on voltage-gated ion channels.” While these observations do not conclusively or perhaps significantly further the identification of one particular mode of interaction, relevant to the search for cardiac sensitization screening

methods, they do provide insight to both the status of current investigations into the interaction of volatile halocarbons and cell membranes.

Volatile anesthesia agents are not unlike halons in elemental composition. Anesthesia agents are represented by lower molecular weight brominated and chlorinated hydrofluoro alkanes and ethers. Some are chlorinated fluorocarbons. What may be more useful are studies of the minimum alveolar concentration (MAC) values determined for anesthesia agents^{137,138} and clinical observations of the tendency of volatile anesthetics to induce cardiac arrhythmia or PVCs.¹³⁹ These are summarized in a listing of the more common volatile anesthesia agents is presented in Table 61. These data demonstrate a correlation between the tendency of a compound to induce PVCs and the Log(K_{OW}) of the anesthesia agent. Halothane is notable for its greater tendency to induce PVCs as compared to the other anesthesia agents listed.

Table 61. Anesthesia Agents and Cardiac Arrhythmia.

Property	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Formula	CF ₃ CHBrCl	CF ₃ -O- CF ₂ CHFCI	CF ₃ -O- CHCl-CF ₃	CHF ₂ -O- CHF-CF ₃	CH ₂ F-O- CH(CF ₃) ₂
Blood-gas Ratio ^a	2.5	1.9	1.4	0.42	0.6
Oil-water Ratio ^b	220	120	170	19	55
Arrhythmia ^c	+++	+	+	~	~
MAC ^d	0.74 %	1.68 %	1.15 %	6.3 %	2.0 %

a Ratio - (blood anesthesia agent concentration)/(air concentration).

b The "oil" phase is commonly, but not exclusively, octanol.

c The symbols "+++", "+," and "~" reflect, in order, a decreasing tendency of the anesthetic to induce PVCs in human patients during anesthesia. "~" indicates only a slight tendency.

d Minimum Alveolar (air) Concentration (MAC) is a measure of the anesthetic potency of the compound, i.e., the air concentration where 50 % of patients don't have a motor response to a pain stimulus.

Medical research in the areas of anesthesiology and cardiac arrhythmia does report links between a compounds' physical properties and cardiac arrhythmia in clinical settings.¹³⁸ The difference of course being that the clinical setting reflect surgical anesthesia of humans and the cardiac sensitization test a dog's exposure to the chemical, at levels that are just below the level at which the compound alone causes arrhythmia, with epinephrine challenge. While the clinical setting seeks to avoid the chemical induction of arrhythmia in patients, dog exposure studies seek to determine an extreme upper bound well to ensure that chemicals employed in commercial settings do not put people in any danger of premature ventricular contractions (PVCs) induced sudden cardiac arrest. Clinical data presented by medical researchers provides some support for the suggestion that the physical property, water/oil partitioning, and cardiac arrhythmia are linked.¹³⁴ Anesthesia agent and chlorofluorocarbon effects on cardiac muscle studies in some cases provide some reason to consider a physiochemical mechanism.^{140, 141}

5. Hydrophobic/Hydrophilic Partition Coefficients

Octanol-water partition coefficients are used in QSAR analysis and rational drug design as a measure of molecular hydrophobicity and are key parameters in studies of the environmental fate of chemicals. This is because the degree of hydrophobicity of a compound is known to affect its drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of a compound, and toxicity.

Given the compositional and molecular similarities between anesthesia agents and many of the current halon replacement compounds of interest as well as the reports reviewed above linking a compounds hydrophobicity to toxicity, cardiac arrhythmia, protein interaction effects measures of hydrophobicity seem a clear strong choice for further evaluation and study as potential screening methods for cardiac sensitization. The possibility of a near term screening method based on the comparative hydrophobicities of the candidate compounds seems worthy of further investigation.

6. Hydrophobic Hydrophilic Partition Coefficients Calculation

Partition coefficients may be calculated.¹⁴² Generally, Log(KOW) values are calculated as a sum of the fragment-based contributions and correction factors. A major drawback to use of these calculations is that they do not recognize or differentiate between the cis and trans structural isomers of compounds, Figure 28 and Figure 29.



cis-1-bromo-3,3,3-trifluoropropene

trans-1-bromo-3,3,3-trifluoropropene

Figure 28. Cis and Trans Conformations of 1-Bromo-3,3,3-trifluoropropene.



cis-3-bromo-1,3,3-trifluoropropene

trans-3-bromo-1,3,3-trifluoropropene

Figure 29. Cis and Trans Conformations of 3-Bromo-1,3,3-trifluoropropene.

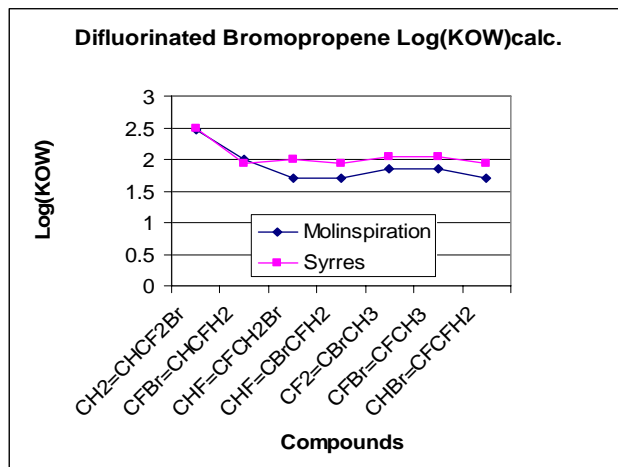


Figure 30. Comparison of Two Difluorobromopropene Log(K_{OW}) Calculation Methods.

Water-octanol partition coefficients have been calculated for the difluorinated bromopropenes using the Molinspiration Cheminformatics and Syracuse Research Corporation molecular fragment contribution-based methods and plotted in Figure 30. Interestingly, the highest Log(K_{OW}) value calculated for this series is for CH₂=CHCF₂Br, which proved highly toxic in inhalation toxicity tests. Water-octanol partition coefficients were also calculated for the trifluorinated bromopropenes using the Molinspiration Cheminformatics and Syracuse Research Corporation molecular fragment contribution based methods. The plotted data points (line connecting data points from same method calculation) are also roughly comparable (Figure 31).

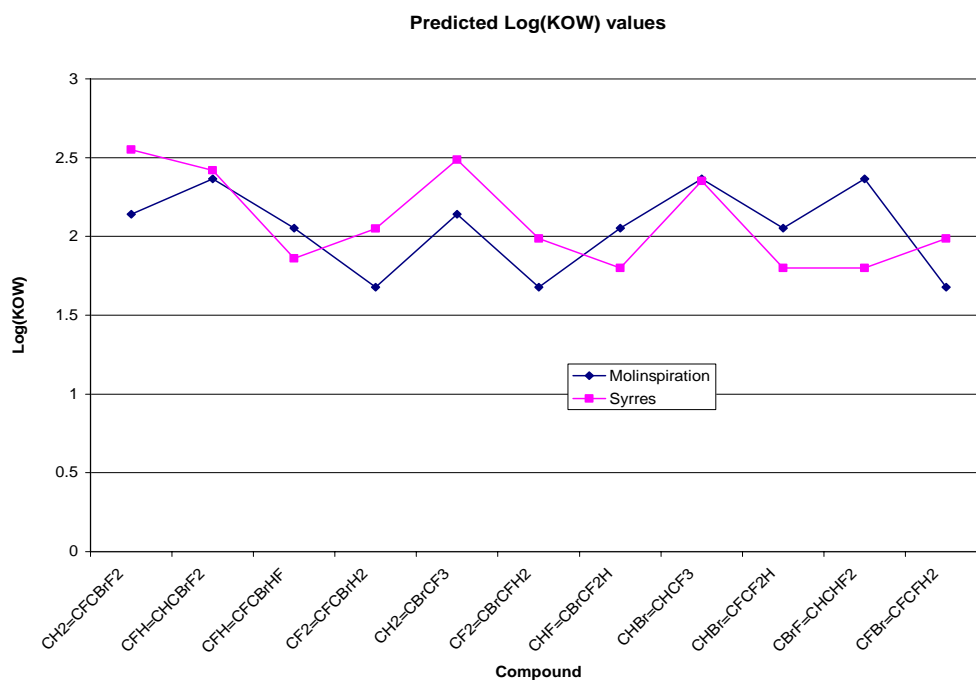


Figure 31. Comparison of Two Trifluorobromopropene Log(K_{OW}) Calculation Methods.

The calculated values presented in Figure 30 and Figure 31 point to the potential candidacy of several additional compounds from the difluorobromopropene and trifluorobromopropene subfamilies. RP-HPLC determination of these compounds Log(K_{OW}) values relative to 2-bromo-3,3,3-trifluoropropene would further aid in assessing their promise.

Log(K_{OW}) values have been calculated and compared to experimental cardiac sensitization LOAEL values for current fire suppressants (Table 62). The data seem to suggest at least a tentative correlation between a compounds hydrophobicity and cardiac sensitization LOAEL values.

Table 62. Calculated Log(K_{OW}) Comparison of Bromofluorocarbons.

Compound	Log K_{OW} ^a (calculated)	Log K_{OW} (literature)	LOAEL (volume %)
CF ₃ Br (Halon 1301)	1.833	1.86	7.4
CHBrF ₂ (FM-100)	1.849	NA	3.9
CH ₂ =CBrCF ₃	2.141	NA	1.0
CF ₂ ClBr (Halon 1211)	2.175	2.1	1.0
CF ₃ I	2.219	NA	0.4

a Molinspiration Cheminformatics algorithm

7. Cardiac Sensitization Screening Option

Cardiac arrhythmia induced by clinical anesthetics (Table 61) appear to follow a trend. A more precise Log(K_{OW}) experimental method applied to evaluating the link between compounds with known LOAEL values and their experimental Log(K_{OW}) values is desirable.

The suggested next step in the evaluation of the applicability of water-octanol partition coefficients was to determine experimental partition coefficients for halons 1211 and 1301 as well as several of the more promising bromofluoropropenes.

Reverse phase high pressure liquid chromatography (RP-HPLC) and gas chromatography-mass spectrometry (GC-MS) are both widely utilized for this type of determination. Each method employs compounds for which K_{OW} values are known and compares chromatographic retention time data for unknown compounds to that of the known compounds. K_{OW} values for unknowns are derived directly from this data. Both methods require only nanogram or milligram quantities of compound. Each method is potentially capable of resolving and ranking many compounds at once (Figure 32). The chromatographic method yields high precision data for retention time that are reproducible within 0.1 s on a consistent basis. This obviates many of the concerns over which calculation to employ, provides an easy means for identifying/modifying calculation methods that yield correct answers, and enables the use of the best calculation methods in the selection of additional promising compounds.

Partition coefficients are a measurement of lipophilicity, and substances having high negative partition coefficient values dissolve better in fats and oils than in water. This enhances their ability to enter lipid membranes in the body and enhances their potential for interaction with ion channel performance and cell membrane processes of absorption.

Chromatographic separation of candidate compounds

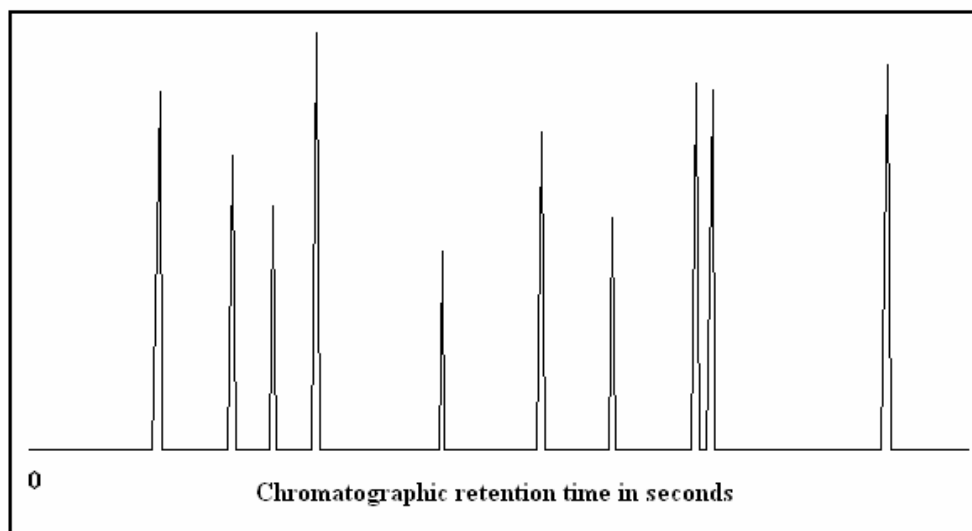


Figure 32. Illustration of RP-HPLC Characterization of Chromatographic Retention Times for Use in Estimating $\text{Log}(K_{\text{OW}})$ Values.

RP-HPLC-based determination appears to have potential to serve as a means of evaluating the relative tendencies of a series of compounds to induce arrhythmia. A chemical screening and ranking method with the potential for more immediate use in compound selection and testing based on hydrophobic hydrophilic partition coefficients is relatively easy to validate and, if confirmed, to then apply. The approach may provide a method for estimating cardiac sensitization for a series of compounds. The result could be a ranking of compounds, identification of compounds with expected higher LOAEL values and facilitation of compound acquisition.

SECTION IV. TECHNICAL PROBLEMS

The lack of cardiac sensitization data for the compound families of interest and the current status of knowledge concerning cardiac sensitization mechanisms preclude a definitive conclusion regarding any screening method. In spite of this situation the results of this survey of past work, medical literature and anesthesiology research do suggest a focus in the near term on $\text{Log}(K_{\text{OW}})$ as a means of ranking the cardiac sensitization properties of compounds.

SECTION V. RECOMMENDATIONS

This project builds on the previously developed lists of promising tropodegradable bromocarbon halon replacements. It is recommended that future studies further investigate the utility of employing $\text{Log}(K_{OW})$ values in estimates of cardiac sensitization and the ranking of compounds. Comparison of known compound $\text{Log}(K_{OW})$ values is problematic due to the lab to lab variation and the use of shake flask methods – not recommended for volatile compounds. The needed precision of 0.1 $\text{Log}(K_{OW})$ unit necessitates a restudy in which similar compounds whose LOAEL values are known have their $\text{Log}(K_{OW})$ determined under the same experimental protocol. Reverse Phase High Pressure Liquid Chromatography (RP-HPLC) characterization of compounds, whose LOAEL values are known has the potential to allow simultaneous determination of many new compounds and the proper ordering of partition estimates, is recommended.

SECTION VI. CONCLUSION

This research projects' goal was to confirm selection of chemical families' cup burner flame suppression properties and hopefully identify a near-term method for estimating the cardiac sensitization properties of the many bromofluoroalkenes and ethers of interest as potential halon replacements. The only near-term method found would in practice utilize the hydrophobicity measure $\text{Log}(K_{\text{OW}})$ based on the oil/water or octanol-water partitioning of a compound to develop a ranking of compounds. This ranking would identify compounds with expected higher LOAEL values and facilitate compound acquisition and further progress in the halon replacement research area. Reverse Phase High Pressure Liquid Chromatography (RP-HPLC) testing has the potential to definitively and relatively inexpensively settle the question of applicability of $\text{Log}(K_{\text{OW}})$ values as measures of cardiac sensitization.

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