ENVIRONMENTALLY ACCEPTABLE FLAME EXTINGUISHANTS
NGP ELEMENT: 4D/6/23

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INTRODUCTION

In work sponsored by the National Institute of Standards and Technology and the Next-Generation Fire Suppression Technology Program, this research effort is directed toward the continued study of promising sources of Halon 1301 replacement compounds for aircraft applications. This effort continues the study of tropodegradable alkenes and ethers as well as efforts to identify screening methods for cardiac sensitization.

NIST Technical Note 1443, "Alternative Fire Suppressant Chemicals: A Research Review with Recommendations", provided the basis for this project through its systematic evaluation and prioritization of a broad range of chemical families for further study [1]. This research review surveyed five major chemical family types and individually evaluated fifty subgroups of compounds. While many of the chemical family subgroups were culled from further consideration, several were identified for continued research. The promising chemical families, prioritized into “High Priority”, “Further Study”, and “Quick Look” categories, are listed in Table 1. Chemical families in the “Quick Look” category generally represent those that have not as yet been studied but appear to be promising based on chemical, toxicological, and physical data.

The research review identified goals for evaluating and identifying chemical families that merit further research and, of those, the ones that are the most promising for aircraft applications.

- 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 5 % (at thermal equilibrium) exists at -40 °C, the minimal design temperature for aircraft suppression system performance. This boiling point is about 25 to possibly 35 ºC.

Highly effective agents that might require a smaller concentration for suppression increase the boiling point cut-off proportionately. Engine heating of the interior engine nacelle surfaces

along with the feasibility of warming the agent storage container are considerations in setting boiling point limits. Agents dispensed as a mist/powder or in particular by a solid propellant gas generator (SPGG), whose high temperatures and gas flow rates ensure complete volatilization and dispersion, could have considerably higher limiting boiling points.

Table 1.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	

Identifying a compound whose cardiac sensitization properties approximate the LOAEL and NOAEL values of Halon 1301 is a fundamental progammatic goal; therefore, refinement in the methods employed in the estimation and ranking of a compound's cardiac sensitization properties continue to be of great interest and are an ongoing effort.

DOWN-SELECT OF CHEMICAL FAMILIES

Of the fourteen general chemical families identified as worthy of additional testing and study six were identified for priority investigation based on their likely application in either volatile agent application or as enhanced flame suppressing additives in solid propellant gas generator designs. The bromofluoroalkenes, bromofluoroethers, bromofluoroamines, fluoroamines, fluoronitriles, and bromofluoronitrile chemical families as well as a very limited number of compounds from the fluoroalkylphosphorus chemical family have potential as volatile agents,

Table 2. The brominated and phosphorus containing compounds are expected to have the best fire suppression efficiency. The non brominated fluoroamines may overall be low in toxicity. Compounds based on the metals manganese, copper, and tin are all expected to have high boiling points and as such are only likely to be of use in solid propellant gas generator extinguishers as additives to increase flame suppression efficiency.

Table 2. Current down select of chemical families

Chemical Family	Bromofluoro alkenes	Bromofluoro ethers	Bromofluoroamines & Fluoroamines
Examples	$CBrF=CHCHF_2$ $CFBr=CFCFH_2$ $CHBr=CFCHF_2$ $CF_2=CHCFBrH$ $CFH=CFCFBrH$ $CF_2=CFCBrH2$ $CFH=CBrCF_2H$ $CF_2=CBrCFH_2$ $CF_2=CFCFHBr$ $CFBr=CFCF_2H$ $CF_2=CBrCF_2H$ CF_3CN CF_2BrCN $CF_3CFBrCN$ CF_2BrCF_2CN	$CF_2Br\text{-}O\text{-}CH_2F$ $CHFBr\text{-}O\text{-}CHF_2$ $CF_2Br\text{-}O\text{-}CHF_2$ $CHFBr\text{-}O\text{-}CF_3$ $CF_2=CFI$ $CF_2=CHI$ $CFH=CFI$ $CFH=CHI$ $CH_2=CFI$	$(CF_3)_2NCFHBr$ $(CF_3)(CF_2H)NCF_2Br$ $(CF_3)(CF_2H)NCFHBr$ $(CF_2H)(CF_2H)NCF_2Br$ $(CFH_2)(CF_3)NCF_2Br$ $(CF_2H)(CF_2H)N(CFHBr)$ $(CFH_2)(CF_3)N(CFHBr)$ $(CF_3)(CF_2H)N(CH_2Br)$ $(CH_3)(CF_3)N(CF_2Br)$ $P(OCFH_2)(CF_3)_2$ $P(OCHF_2)(CF_3)$ $O=P(CF_3)_2(CF_2H)$ $O=P(CF_3)(CF_2H)_2$ $O=P(CF_2H)_3$ $O=P(CFH_2)_3$

Following further review of the chemical family recommendations and with input on aircraft application requirements an abbreviated list of compounds was selected, Table 3. To this listing the chemical family of bromofluoropropene oxides (oxiranes) was added. The three carbon bromofluoro-propene oxides may well have low boiling points and may well be environmentally acceptable.

Table 3. Principal chemical families of interest

Chemical Family – Focus List
Brominated alkenes
Brominated ethers
Nitriles – fluorinated and brominated
Fluoroamines & bromofluoroamines
Bromofluoropropene oxides (oxiranes)

Acquired compounds will have their cup-burner flame suppression performance determined. Synthesis evaluation and compound sourcing is ongoing and several compounds are either on order and being synthesized or in the process of being quoted. The boiling points of some targeted bromine containing compounds are predicted to be in the 0 °C to 10 ºC range; representing some of the lowest boiling brominated compounds yet tested.

Chemicals are being acquired for the following families;

- Fluoronitiriles and bromofluoronitriles. Trifluoroacetonitrile (CF_3CN) has a boiling point of -64 ºC. Its fire suppression is expected to reflect a non-chemical extinguishment mechanism. On the other hand bromodifluoroacetonitrile (CF_2BrCN), boiling point 3 ºC, and may have a suppression efficiency comparable to halon 1301. The atmospheric

lifetimes of all the nitriles are expected to be limited by hydrolysis of the CN group and rainout. These compounds are being acquired for cup-burner testing.

- Bromofluoropropene oxides (oxiranes) are a newly identified chemical family. Their atmospheric lifetimes are expected to be short, but this needs to be confirmed. Cup burner values for the monobrominated compounds should be similar to the bromofluoropropenes. Boiling points for these compounds are estimated to be between 0 °C and 10 ºC. Their synthesis has been studied and 2-bromo-1,2-perfluoropropene oxide is being acquired for cup-burner testing.
- Bromofluoropropenes: The atmospheric lifetimes of these compounds should be low since the double bond is reactive in the troposphere. Log K_{OW} values were calculated, using several available modeling methods, for the 35 possible penta-, tetra- and trifluorinated bromofluoropropenes. Overall, the calculated log K_{OW} values ranged from 1.4 to 2.5. Using experimental K_{OW} values of 1.84 for Halon 1301 and 2.3 for Halothane (CF3CHBrCl) as guides, a list of compounds whose low calculated values predicted a possibly equivalent or higher LOAEL was prepared and promising compounds selected for acquisition. Of particular interest are the bromotetrafluoropropenes listed as these compounds are generally of lower boiling point and may well have higher LOAEL values.
- Bromofluoroethers: These compounds are expected to have relatively low toxicity and good flame extinguishment properties but unless they prove sufficiently polar they will require some degree of hydrogenation to minimize ODP impact. Two of the simplest brominated ethers are $CBrH_2$-O-CF_3 (39 ºC) and $CBrF_2$-O-CF_3, (boiling point estimated between -30 °C and -8 °C). The tetrafluorinated C_2 bromoethers CBrHF-O-CF_3 (bromofluoromethyl trifluoromethyl ether) and $CBrF_2$-O-CHF_2 (bromodifluoromethyl difluoromethyl ether) are predicted to boil in the range 5 °C to 15 ºC and are being sought for testing. Bromodifluoromethyl trifluoromethyl ether is also being sought.
- Bromofluoroamines: There a number of derivatives of tris-trifluoromethyl amine being sought.

SELECTION CRITERIA

Selection criteria focus on obtaining compounds predicted to be effective extinguishants with acceptable boiling points and toxicity.

Boiling point and ambient pressure criteria

The ability to affect a flame extinguishing atmosphere in the fire zone or in the volume being protected is essential. A physical chemistry based estimate [2] of the maximum boiling point a compound may have and still achieve the extinguishment concentration provides some guidance to compound selection, Table 4.

Table 4. Estimates of Maximum Boiling Points for Fire Suppression at 760 mmHg

Conc.	Ambient Temperature, °C									
%	**-60**	**-50**	**-40**	**-30**	**-20**	**-10**	**0**	**10**	**20**	**30**
1	33	47	61	76	90	105	119	133	148	162
2	19	33	46	60	74	87	101	115	128	142
3	11	24	37	51	64	77	91	104	117	130
4	5	18	31	44	57	70	83	96	109	122
5	0	13	26	39	52	65	77	90	103	116

Example: A 4 vol.% air concentration at -20°C may be achieved by agents boiling at 57°C or less.

For aircraft in-flight as well as non sea level fire suppression applications the effects of lower atmospheric pressure contribute favorably to agent vaporization, Figure 1.

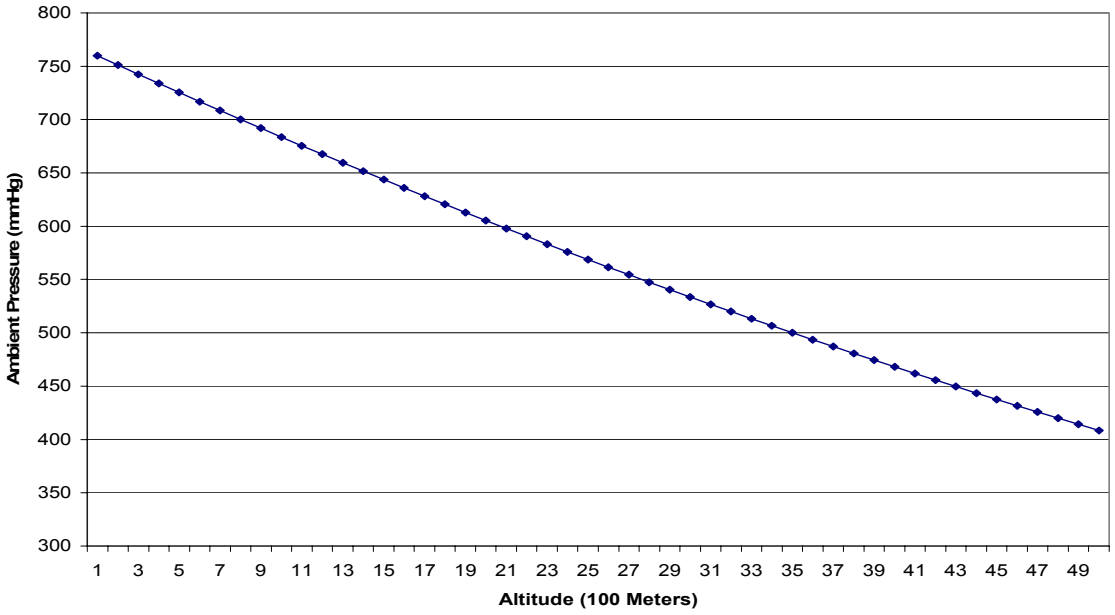

Figure 1. Ambient pressure at altitude

While the lower atmospheric pressure at higher altitude is accompanied by markedly cooler air temperatures lower air pressure also depresses the boiling points of chemicals, Figure 2, which may help higher boiling compounds achieve sufficient volatility to function as fire suppressants and also avoid condensation on cold aircraft surfaces. Figure 2 depicts the effect of altitude on the sea level boiling point 32 ºC of a compound. Assuming a heat of vaporization of 23 Kj/mole the estimated boiling point at an altitude of 5,000 meters is only 12 ºC.

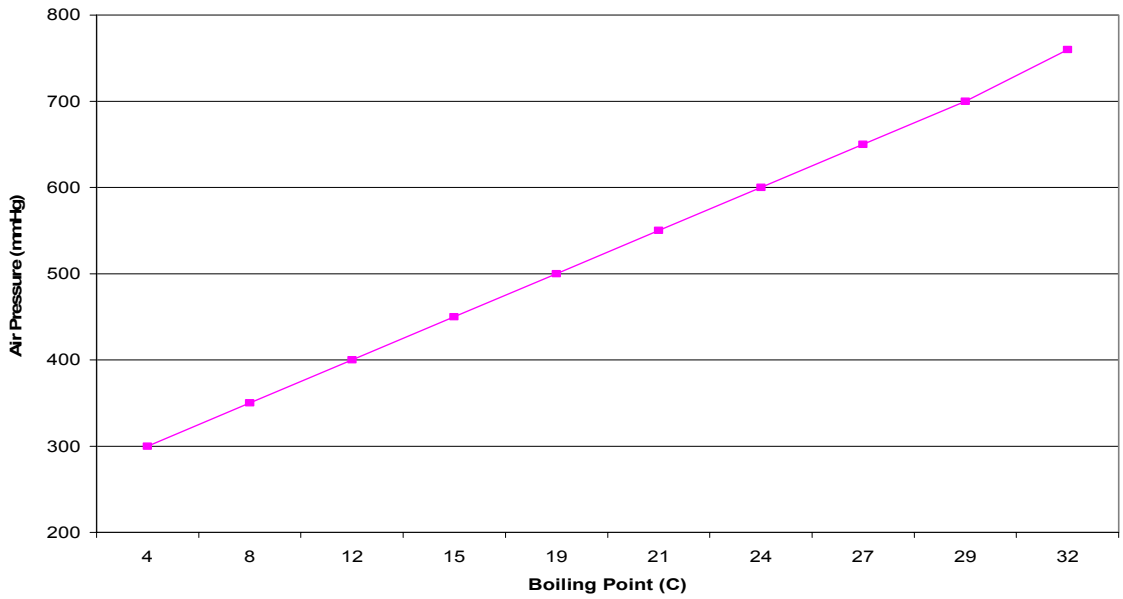

Figure 2. Boiling point estimate at low pressure

Toxicity estimates - Cardiac sensitization

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, and inhalation toxicity assessments.

If initial testing is successful, a compound advances in consideration to testing that, in part, determines an agents uses in occupied and non-occupied application areas. The principal test here is the determination of a compounds ability to cause cardiac sensitization (cardiac arrhythmia) under conditions of an epinephrine challenge. In real life exposure situations these premature ventricular contractions (PVC's) can cause immediate death. The cost of the standard dog exposure test to determine a compound's cardiac sensitization LOAEL is approximately $100 k. Cardiac arrhythmia is recognized as the primary (but not only) toxic effect of the halogenated compounds that dominates the search for halon alternatives.

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, Table 5, that just happens to cause cardiac arrhythmia when sufficient chemical is absorbed into heart nerve and muscle cells membranes [3]. Halothane, CF3CHClBr, is amongst the compounds listed and Clark and Tinston's determined EC50 level of 2.0 vol.% is similar to that of the structurally and compositionally and structurally similar halon 1211, CF2BrCl, whose LOAEL is 1.0 vol. %.

It is interesting to note the relative consistency of the Relative Saturation Values in the right-hand column of Table 5 and in view of the wide range of compounds listed to consider the possibility that if a chemical mechanism was the determining factor in cardiac sensitization, the Relative Saturation for Cardiac Sensitization values would be expected to be far less consistent and instead would exhibit a much wider range of values. The fact that these values are so

consistent suggests that the predominant cardiac sensitization mechanism is the same for all of the compounds and compound types listed and is physical in nature.

Table 5. Clark and Tinston data on cardiac sensitization in dogs [3].

Compound	Vol. % at EC_{50}	Partial pres at EC_{50} mmHg	Vapor pressure at 37C, mm Hg	Relative Saturation for Cardiac Sensitization
$CFCl_2CFCl_2$	0.12	2.0	99	0.02
CCl_4	0.5	4.0	190	0.02
CH_3CCl_3	0.75	6.0	210	0.03
CCl_2FCF_2Cl	1.0	8.0	524	0.02
$CFCl_3$	1.25	10	524	0.02
$CF_3CHClBr$	2.0	15.0	1186	0.01
CH_2Cl_2	2.4	18	480	0.03
$CHFCl_2$	2.5	19	661	0.03
CH_2=$CHCl$	5	38	2052	0.01
CF_2Cl_2	8	61	4218	0.01
CF_2ClCF_2Cl	10	76	6764	0.01
$CH_3CH_2CH_3$	20	153	2310	0.03
CF_3Br	20	153	9538	0.01
CF_3Cl	80	610	15276	0.01

The "physical effect" conclusions of Clark and Tinston are consistent with recent research that has also shown, using differential scanning calorimetry, that the inhalation anesthetic agent halothane ($CF_3CHClBr$) decreases some cell membrane protein thermal unfolding temperatures [4]. The authors of this study reported that low, millimolar, concentrations of halothane produce significant destabilization of proteins [4]. Investigation of the effects of volatile anesthesia agent on voltage gated ion channels is also provides evidence for their inhibition of voltage-gated ion channels and to a greater extent on ligand-gated ion channels [5]. 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".

Existing limited cardiac sensitization data for halogenated and non-halogenated volatile hydrocarbons provide few trends. The data compiled,

Table 6, include non-halogenated compounds whose LOAEL values are considerably higher than those of halons.

Table 6. Hydrocarbon, fluorocarbon and hyrofluorocarbon cardiac sensitization values

Chemical formula	NOAEL (vol. %)	LOAEL (vol. %)
CH3OCH3	10	20
CH3CH2CH3	5	10
CH2=CHCH3	-	15
CF3CF2CF2CF3	40	>40
CF3CF2CF3	30	>30
CF3CHFCHF2	2.5	3.5
CF3CHFCF3	9	10.5
CF3CH2CF3	10	15
CH2F2	20	25
CHF3	30	>50
CH2FCF3	4	8
CH3CF3	4	8
CHF2CF3	7.5	10
CH3CF2H	5	15
CF2ClH	2.5	5
CF2Cl2	2.5	5
CFCl3		0.5
CH2=CClH	2.5	5
CCl3CH3	0.25	0.5
CF2ClCH3	2.5	5
CFCl2CH3		0.5
CF3CF2Cl	-	15
CF3CCl2H	1	2
CFCl2CH3	-	1
CF2ClCF2Cl	-	2.5
CClF2CFCl2	0.25	0.5
CF2ClCF2CFHCl		2.0

The fluorocarbons and hydrofluorocarbons listed,

Table 6, demonstrate a wide range of LOAEL values. Degree of fluorination or total lack of fluorination appears to not be a determining factor in the LOAEL value. Limited data for partially fluorinated methane compounds demonstrate a relatively low tendency to induce cardiac sensitization. Limited hydrofluoropropane data fail to demonstrate increasing LOAEL values with increasing fluorination. Limited hydrofluoropropane data as well as hydrofluoroethane data 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.

Iodofluorocarbons, bromofluorocarbons, and bromochlorofluorocarbons listed in Table 7 reflect increasing LOAEL values where bromine is replaced by iodine. While the impact of iodine on cardiac sensitization LOAEL values might, based on the relative LOAEL's of CF3Br and CF3I, be interpreted as high similarly low 0.1% LOAEL performances of CF3CF3CF2I and CF2BrCF2Br seem to suggest a more subtle mechanism.

Table 7. Bromo, chloro and iodofluorocarbon cardiac sensitization values

Chemical formula	NOAEL (vol. %)	LOAEL (vol. %)
CF_3I	0.2	0.4
CF_3Br	5.0	7.5
CF_2HBr	2	3.9
CF_2Br_2	-	-
CF_2BrCl	0.5	1.0
CF_2BrCF_2Br	-	0.1
CBrClFCBrF2		0.5
$CF_3CF_2CF_2I$	-	0.1

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 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.

Medical research in the areas of anesthesiology and cardiac arrhythmia does report links between a compounds physical properties and cardiac arrhythmia in clinical settings [6]. A primary difference of course being that the clinical setting reflect surgical anesthesia of humans with no epinephrine challenge while the cardiac sensitization test involves 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 lower bound to ensure that chemicals employed in commercial settings do not put people in any danger of PVC induced sudden cardiac arrest. Clinical data presented by medical researchers seems to provide a reasonable basis for their observation that a relatively basic physical property, water/oil

partitioning, and cardiac arrhythmia may be linked [6]. This relationship could well form the basis for a QSAR type of an approach to compound screening for cardiac sensitization.

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 or mild CNS depression can also be observed in humans using performance decrement studies. Structure-activity relationships have been developed for predicting anesthetic effects [7].

The study of anesthesia is an active area of research with considerable published data on the influence of various compounds on human systems [6]. 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 [8, 9]. 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.

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 [5,10] and clinical observations of the tendency of volatile anesthetics to induce cardiac arrhythmia or PVC's [11]. These are summarized in a listing of the more common volatile anesthesia agents is presented in Table 8. These data demonstrate a correlation between the tendency of a compound to induce PVC's and the Log(KOW) of the anesthesia agent. Halothane is notable for its greater tendency to induce PVC's as compared to the other anesthesia agents listed.

The search for a screening method that would provide an easy, low cost, method of guiding compound selection within a family of chemicals has thus far been unsuccessful. Past clinical research on anesthesia agents may provide guidance [12,11]. Clinical observations reported in medical research literature suggest a possible link between a compounds oil/water partitioning and its tendency to initiate PVC's under normal surgical anesthesia, Table 8.

Table 8. Anesthesia Compounds – Partitioning and Arrhythmia Properties

Property	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Formula	$CF_3CHBrCl$	CF_3-O-CF_2CHFCl	CF_3-O-$CHCl$-CF_3	CHF_2-O-CHF-CF_3	CH_2F-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 PVC's 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.

Halothane ($CF_3CBrClH$) is very prone to causing premature ventricular contractions (PVC's). The alternative anesthetics listed above have progressively lower tendencies to induce PVC's and also progressively lower oil-water distribution ratios when compared to halothane. This correlation is worth further study and at least preliminary examination as a means of guiding the selection of halon replacement candidate compounds.

Intriguingly, the Meyer-Overton hypothesis predicts that the potency of conventional inhaled anesthetics correlates inversely with lipophilicity: minimum alveolar anesthetic concentration and the olive oil/gas partition coefficient [13].

Though limited in potential this approach may offer a near term means of screening and ranking the current candidate halon replacement candidates propensity to induce cardiac arrhythmia. There are similarities between the compounds used in anesthesia, representing a variety of fluorinated, chlorinated, and brominated agents from the alkane and ether families, and the families of current interest as halon replacement,

CARDIAC SENSITIZATION SCREENING OPTIONS

Two options for screening compounds for the purpose of identifying the most promising compounds for testing have been identified. Both of these approaches are in their infancy and need varying degrees of work in order to be of use. In both cases though, progress is hindered by the lack of cardiac sensitization test data for similar compounds - bromofluoroalkenes or ethers for instance. QSAR method development relies on a training set of data. The training set would link compounds, with known cardiac sensitization values and similar to those under consideration, to one or more attributes or physical properties in order to develop a predictive model.

In vitro cardiac sensitization screening

While the potential for developing an *in vitro* cardiac sensitization toxicity screen appears to be good it is likely to be a longer term research effort. In contrast, the development of a method based on one or more physical attributes of the compounds under consideration offers some promise.

To be of greatest use to the halon replacement community, an *in vitro*-based test protocol (or a QSAR method) capable of at least differentiating between Halon 1301 (LOAEL 7.5 vol. %) and Halon 1211 (LOAEL 1.0 vol. %) or trifluoromethyliodide (LOAEL 0.4 vol. %) is a basic 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 to 4 vol.% and whose LOAEL values are likely to be only two or three % higher. These tight air concentration constraints mandate the development of a protocol and test apparatus capable of closely controlling chemical exposure levels and durations. Future models would have to be able to distinguish between compounds

whose LOAEL values differ by 1 to 2 vol. % in order to be of much use in final compound selection.

Structure property relationships as cardiac sensitization models

Hydrophobic hydrophilic partition coefficients have previously been identified as a possible property for inclusion in a QSPR approach [14] means of assessing oil/water partitioning properties are typically measured experimentally by shake flask or RP-HPLC methods. Of these two methods, the RP-HPLC based determination has the greater potential to yield a correctly ordered relative assessment of compound chromatographic retention times and therefore Log(KOW) values.

Existing methods for calculating Log(KOW) values generally lack both experimentally determined values needed to yield models capable of yielding accurate estimates for similar compounds.

Anecdotal reports, presumably referring to shake flask based (water/octanol) KOW determinations, suggest no relationship between partition coefficients and cardiac sensitization exists. This conclusion seems at odds with the clinical anesthetic discussed earlier, Table 8. Given the shake flask experimental accuracy requirement of 0.3 Log units [15] it is not surprising that no relationship was identified. Without a more precise Log(KOW) experimental method evaluating the link between compounds with known LOAEL values and their experimental Log(KOW) values is likely to be inconclusive.

Calculated Log(KOW) estimates, Table 9, for an incomplete list of the tri and tetra fluorinated bromopropenes do not reflect the *cis* and *trans* structural isomerism of alkenes.

Table 9. Representative calculated Log(KOW) estimates for bromofluoropropenes

Compound	Estimation Method					Average*
	KOWWIN	CLogP	XLogP	A Log P	IA Log P	
CF2=CBrCF3	2.46	2.41	1.90	2.10	2.88	2.32
CFBr=CFCF3	2.46	2.41	1.90	2.10	2.89	2.32
CF2=CBrCF2H	1.85	1.75	1.85	1.93	2.65	1.88
CFH=CBrCF3	2.41	2.16	2.11	2.14	2.86	2.24
CFBr=CFCF2H	1.85	1.75	1.85	1.87	2.62	1.86
CFBr=CHCF3	2.41	2.16	2.11	2.15	2.52	2.24
CHBr=CFCF3	2.41	2.16	2.11	2.17	2.61	2.25
CHF=CFCF2Br	2.47	1.93	1.95	2.15	2.82	2.19
CF2=CFCFHBr	1.92	1.64	1.69	1.79	2.72	1.80
CF2=CHCF2Br	2.47	1.69	1.95	2.25	2.51	2.22
CF2=CBrCFH2	1.99	1.60	1.71	2.03	2.23	1.91
CFH=CBrCF2H	1.80	1.50	2.06	1.91	1.89	1.87
CHBr=CHCF3	2.35	1.90	2.33	2.38	2.00	2.23
CH2=CBrCF3	2.49	2.5	1.86	2.16	2.78	2.38

* Average – not including high and low values

When compared to experimental Log(KOW) data for Halon 1301 and halothane the bromotrifluoropropenes and bromotetrafluoropropenes reveal one aspect in common. In both cases the modeling programs, on the average, rank compounds with a terminal CF3 higher (more hydrophobic) than compounds with a terminal -CFHBr, -CF_2H, or -CFH_2 group, Figures 2 and 3.

The lower range of compound estimated Log(KOW) values in both cases are consistently similar to that of Halon 1301's experimental value while the higher range of Log(KOW) values are consistently in the range of halothane – a known cardiac sensitizer in clinical settings, Figures 2 and 3.

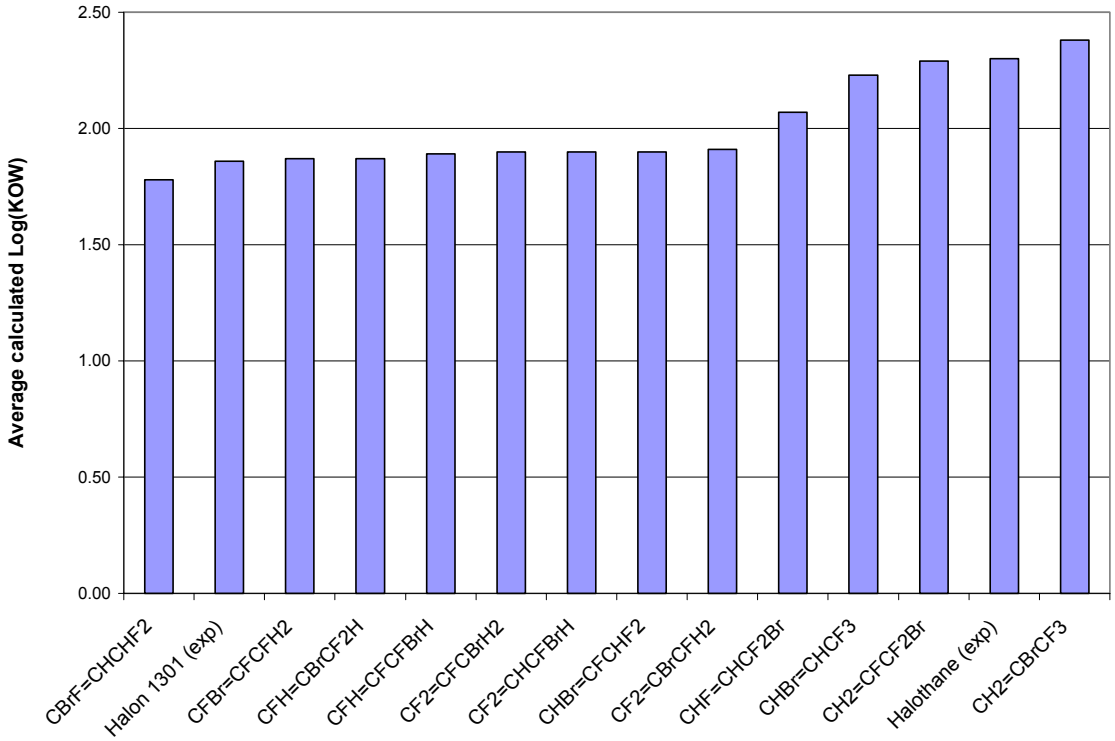

Figure 3. Calculated Log(KOW) values for bromo-trifluoropropenes

The available cardiac sensitization LOAEL results demonstrating a LOAEL of 1.0 vol % for CH2=CBrCF3, Clark and Tinstons observed 2.0 vol. % cardiac sensitization level for Halothane, the failure to observe PVC's at 1.5 vol % in the dogs exposed to CHBr=CHCF3 in the recent AAWG sponsored study of this compound, and the 7.5 vol. % LOAEL of halon 1301 and the calculated Log(KOW) values seem to correlate relatively well and indicates that there are several trifluorinated bromopropenes whose cardiac sensitization properties are worthy of further investigation.

While there are no tetrafluorinated bromopropenes for which LOAEL values have been determined to aid in the comparison of known LOAEL to calculated Log(KOW) the calculated Log(KOW) data and relative performance of halon 1301 and halothane in Figure 4 suggests that there are several tetrafluorinated bromopropenes worthy of acquisition and testing.

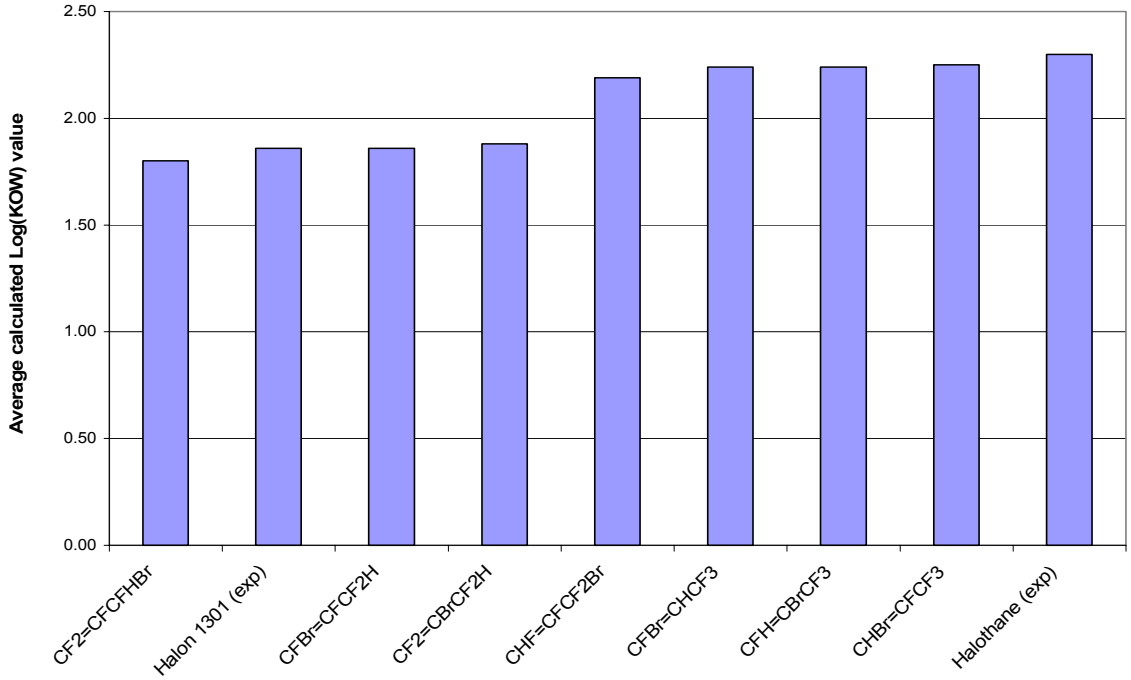

Figure 4. Calculated Log(KOW) values for bromo-tetrafluoropropenes

Near term screening approach to screening compounds for testing

High Pressure Liquid Chromatography (HPLC) employing reverse-phase C_{18} stationary phase chromatography columns and gradient elution programming has the potential to quickly, accurately and relatively inexpensively provide the high resolution (0.05 Log (KOW) units) determinations needed to further investigate relationships between compounds LOAEL values and water/octanol partitioning property. Derivatives of this method are applied to model blood-brain, blood-air, blood-tissue and other chemical uptake interfaces. This approach typically allows several compounds to be simultaneously injected along with standards (internal references of known Log(KOW)) enabling the comparative and reliable determination of experimental Log(KOW) values for a number unknown compounds as illustrated in Figure 5. Accuracy and reproducibility for this method are much higher than protocols based on the shake flask method [15]. Using an HPLC based method, the Log(KOW) of many compounds of interest as Halon 1301 replacements could be easily employed to generate a LOAEL prediction and identify the most promising halon replacement candidate(s).

Several commercial pharmaceutical testing laboratories, where this testing is commonly done, have been identified and a preliminary estimate of laboratory cost is considerably less than $7,000. In addition, once experimental Log(KOW) values have been determined by RP-HPLC for available compound these values could be input into online models, incorporated in the models predictive "training sets", with the result that additional un-synthesized compounds calculated Log(KOW) could be more accurately estimated.

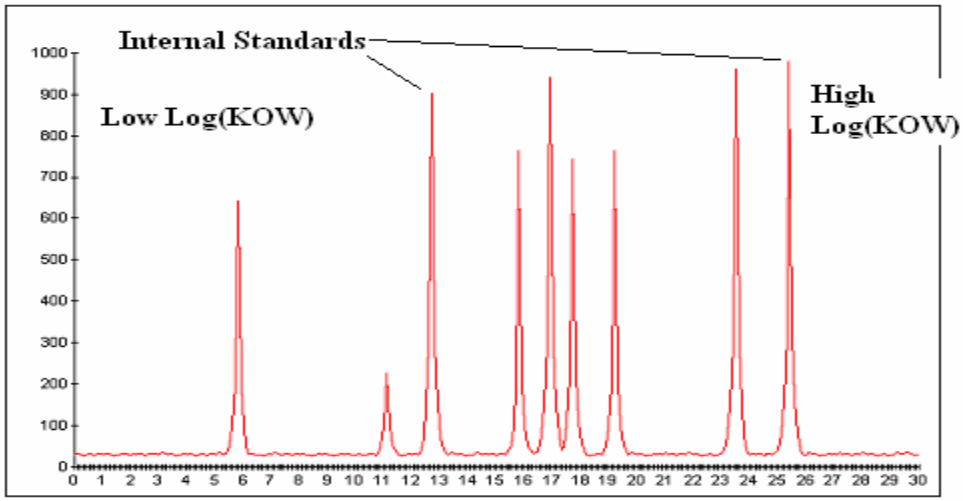

Figure 5. Illustration of RP-HPLC characterization of chromatographic retention times for use in estimating Log(KOW) values (x-axis is time).[16]

These more accurate estimates could greatly enhance future compound selection.

Summary

Future progress in the study of the chemical families discussed here is expected to soon yield a clearly identified set of options. Cardiac sensitization screens are still needed and the study of potential relationships of hydrophobicity and lipophilicity may provide a reliable, time and resource saving approach to selection of the optimum compounds from the many bromofluropropene, bromofluoroether, and bromofluoroamine candidates.

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REFERENCES

1 Tapscott, R.E., Sheinson, R.S., Babushok, V., Nyden, M.R., Gann, R.G., "Alternative Fire Suppressant Chemicals: A Research Review with Recommendations," NIST Technical Note 1443, National institute of Standards and Technology, Gaithersburg MD, December 2001.

2 Brabson, G.D., Garcia, M.M., Heinonen, E.W., Juarez, G., "Main Group Compounds as Extinguishants", Final Report May 2001, NMERI 98/8/33380.

3 Clark, D.G., Tinston, D.J., "Correlation of the Cardiac Sensitizing Potential of Halogenated Hydrocarbons With Their Physicochemical Properties", British Journal of Pharmacology, Vol.49, 355-357, 1973.

4 Tanner, Liebman & Eckenhoff, Toxicology Letters 100-101:387-391, 1998.

5 Hemmings, H. C., and Hopkins, P. M., "*Foundations of Anesthesia Basic and Clinical Science*", Chapter 22 Mechanisms of Anesthesia, 2000, Harcourt

6 Hemmings, H. C., and Hopkins, P. M., "*Foundations of Anesthesia Basic and Clinical Science*", 2000, Harcourt.

7 Larsen, E. R., "Fluorine Compounds in Anesthesiology," in *Fluorine Chemistry Reviews*, P. Tarrant, editor, Marcel Dekker, New York, pp. 1-44, 1969.

8 Hemmings, H. C., and Hopkins, P. M., "*Foundations of Anesthesia Basic and Clinical Science*", Chapter 5 Molecular Physiology, 2000, Harcourt

9 Hemmings, H. C., and Hopkins, P. M., "*Foundations of Anesthesia Basic and Clinical Science*", Chapter 8 Pharmacokinetics of Inhalation Anesthetics, 2000, Harcourt.

10 Hemmings, H. C., and Hopkins, P. M., "*Foundations of Anesthesia Basic and Clinical Science*", Chapter 24 - Inhalational Anesthetic Agents, 2000, Harcourt

11 www.virtual-anaesthesia-textbook.com/vat/volatile.htm . A tutorial website with a wide variety of anesthesia agents clinical human exposure and cardiac effects information as well as further reference citations.

12 Hemmings, H. Jr., and Hopkins, P., Foundations of Anesthesia - Basic and Clinical Sciences, Chapters 24 and 41, Harcourt Publishers Ltd., 2000.

13 Eger EI; Ionescu P; Laster MJ; Gong D; Hudlicky T; Kendig JJ; Harris RA; Trudell JR; Pohorille A., "Minimum alveolar anesthetic concentration of fluorinated alkanols in rats: relevance to theories of narcosis,"Anesthesia and Analgesia, 1999 Apr, 88(4):867-76.

14 Skaggs, S. R., Tapscott, R. E., Heinonen, E.W., Advanced Agent Program: Toxicological Screening Methods," NMERI 95/48/31882, Wright Laboratories (WL/FIVCF), Tyndall Air Force Base, Florida, December 1996.

15 EPA – Product Properties Test Guidelines, OPPTS 830.7550, Partition Coefficient (n-Octanol/Water), Shake Flask Method, Prevention, Pesticides and Toxic Substances (7101), EPA 712–C–96–038, August 1996

16 The reader is directed to the following internet site for additional examples and discussion of the application of RP-HPLC to comparison of compound retention times www.limathon.com/