TROPODEGRADABLE AND OTHER ENVIRONMENTALLY ACCEPTABLE FLAME EXTINGUISHANTS NGP ELEMENTS: 4D/14/1 AND 4B/6/23

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ABSTRACT

In work sponsored by the National Institute of Standards and Technology and the Next-Generation Fire Suppression Technology Program, our current research effort is directed toward the continued study of known promising as well as several new chemical families with potential as 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 a systematic evaluation and prioritization of a broad range of chemical families for further study [1]. This survey resulted in several chemical families being classified as “High Priority” for future research efforts. Additional chemical families were identified as worthy of “Further Study” or “Quick Look” investigation.

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. As preliminary screening methods, water-octanol partition coefficients and in vitro tissue methods offer hope of meeting near-term needs for screening compounds. These methods would not, however, be expected to supplant the formal dog exposure-based cardiac sensitization test; instead, these methods could be an aid in the preselection of compounds; serving to highlight and advance very promising candidates to consideration for the formal cardiac sensitization test.

This NIST-funded project continues the study of tropodegradable candidates and also expands the search to the study of the promising chemical families identified in NIST Technical Note 1443. The project is in the initial phase of work to select, acquire, and test promising candidates from a wide variety of chemical families.

INTRODUCTION

The research review conducted [1] covered 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 chemical families prioritized into “High Priority”, “Further Study”, and “Quick Look” categories are listed

in Table 1. Compounds in the "Quick Look" category represent those that have not as yet been studied but appear to be promising based on chemical, toxicological, and physical data.

Table 1. Summary of NGP Analysis of Chemical Families.

Chemical Family	Recommendation		
	High Priority	**Further Study**	**Quick Look**
Iodine-containing alkanes		X	
Iodine-containing alkenes		X	
Bromine-containing alkenes	X		
Iodine-containing ethers			X
Bromine-containing ethers		X	
Bromine-containing alcohols			X
Fluorine-containing aldehydes and ketones		X	
Nitriles			X
Fluoro- and bromofluoroamines	X		
Bromofluorosulfides			
Sulfoxides			X
Phosphorus-containing Acids and Esters	X		X
Phosphonitriles		X	
Phosphorus halides		X	
Copper-containing Compounds			X
Manganese-containing Compounds	X		
Iron-containing compounds		X	
Tin-containing compounds	X		

The research plan is initially focused on the compound families identified as "High Priority". Some candidate compounds from the "Further Study" chemical families will also be acquired during this period should resources permit. The primary families targeted for acquisition during this project's initial year are the bromofluoro-alkenes, bromofluoro-ethers, bromofluoro-amines, hydrofluoroalkyl-amines, phosphorus acids and esters, and manganese compounds.

SELECTION OF COMPOUNDS

Compounds from the following chemical families are being sought. The actual numbers of compounds finally acquired will be a direct function of cost and availability. The potential sources for acquisition of these compounds include universities and institutes in the US, Japan, and FSU as well as commercial sources.

- Bromofluoroalkenes - Prior research has demonstrated that members of this family of compounds are environmentally acceptable and toxicological testing thus far has been

generally favorable. Compounds tested approach Halon 1301 in extinguishment performance but are considerably higher in boiling point. The primary challenge for future work in this chemical family is the identification of candidate compounds with cardiac sensitization LOAEL values approximating those of Halon 1301. To date selection of compounds for additional acquisition and testing has been hampered by a lack of a cardiac sensitization screening tool. Candidate methods being considered for use in future compound selection and cardiac sensitization screening will be described more fully later in this paper.

- Bromofluoro-ethers: While limited cup-burner studies have demonstrated effective fire suppression performance, only a few of these compounds have actually been prepared and tested. Bromomethyl trifluoromethyl ether, $CH_2Br\text{-}O\text{-}CF_3$, (39-41º C) and bromomethyl difluoromethyl ether, $CH_2Br\text{-}O\text{-}CF_2H$, (70º C) have both been previously reported. Their cup-burner extinguishment values were 3.2 and 3.6 vol. %, respectively. While their boiling points are considerably higher than that desired, fluorination of the CH2Br group may drop the boiling points further toward a more acceptable range (25º to 35º C). The additional fluorination may not improve cup-burner performance appreciably.
- Bromofluoro-amines: Several bromofluoro-amines have been previously reported. $N(CF_3)_2(CHFCF_2Br)$ (boiling pt. 72º C), $N(CF_3)_2(CF_2CFHBr)$ (boiling pt. 72º C), and $N(CF_3)_2(CH_2CF_2Br)$ (boiling pt. 80º C) all have cup-burner extinguishment values of 2.4%. The principle drawback to the otherwise effective flame suppressants compounds tested are their high boiling points. Lowering the boiling point by changes in the degree of fluorination and/or use of substituted methyl substituents is a real possibility. Replacing several of the fluorines in $N(CF_3)_3$, boiling point -10º C, with hydrogens and a bromine might yield a compound of acceptably short atmospheric lifetime and low boiling point. Table 2 provides a brief listing of possible candidate bromofluoroamines.

Table 2. Possible Bromofluoroamine Candidates

Formula	Boiling point, °C (°F)
(CHF_2)(CH2F)NCBrH2	NA
$(CF_3)_2NCBrH_2$	NA
$(CF_3)_2NCBrF_2$	40.6
$(CF_3)_2NCF_2CBrF_2$	59.5 to 60.5
$(CHF_2)_2NCBrF_2$	NA

- **Fluoroalkyl-amines** - Testing of perfluorinated alkyl amines, have yielded cup-burner values as low as 3.4% for compounds with boiling points in the low 20º to 22º C range. Perfluorinated alkyl amines (e.g., $N(CF_3)_3$, boiling point -10º C) are not under consideration, as they will have unacceptably high atmospheric lifetimes.

Fluoroalkylamines in general are expected to exhibit low toxicity, and further acquisition and cup burner testing targeting additional low molecular weight fluorinated amines are planned. The unsaturated perfluorinated amine $(CF_3)_2NCF=CF_2$ may well be tropodegradable due to its double bond and is under consideration as a candidate for acquisition and testing.

Table 3. Possible Hydrofluoro and Fluoroamine Candidates

Formula	Boiling point, °C
$(CF_3)_2NCF=CF_2$	13.7
$N(CH_2F)(CF_3)_2$	NA
$(CF_3)_2NCF_2CHF_2$	32.0
$N(CHF_2)_3$	NA

- **Phosphorus Acids and Esters** - These compounds were the subject of a recent NGP project just concluded [2]. The experimental determinations of compound flame extinguishment indicated cup-burner extinguishments, in general of over 3% with one significant exception. One of the compounds Bis(trifluoromethyl) 2,2,2-trifluoroethoxy Phosphine, $P(OCH_2CF_3)(CF3)_2$ yielded a cup-burner extinguishment of 1.8%. The air reactivity of the compound suggests that it may not long survive in the air stream and that the actual active flame extinguishing species is its air oxidation product. This possibility is under study and may result in the identification of additional phosphorus compounds for study. A thorough review of future research directions investigating the fire suppression potential of this group of compounds is presented in a companion paper [2].
- **Manganese compounds** - Methylcyclopentadienyl manganese tricarbonyl (MMT) is a fuel additive that Ethyl Corporation and/or Albemarl (a spin-off of Ethyl) have developed. As fuel additives may have fire extinguishment effectiveness, we had thought, at one time, of looking into this. It may be that MMT is too flammable for use and that fluorinated derivatives are needed. Among the fluorinated compounds identified [3] are —pentacarbonyl(pentafluoroethyl)manganese(I), pentacarbonyl[tetrafluoro-1-(trifluoromethyl)ethyl]manganese(I), pentacarbonyl(trifluoromethyl)manganese(I), and pentacarbonyl(heptafluoropropyl)manganese(I). While it is recognized, of course, that carbonyl derivatives are likely to have toxicity problems, these materials could provide starting points for additional concepts. Several of these compounds will be acquired and their cup-burner flame extinguishment performance evaluated.

CUP-BURNER TESTING

Cup-burner testing will utilize the same cup-burner design employed in prior projects, Figure 1. Due to the limited amount of compound to be prepared (5 to 10 grams), the cup-burner methodology employed will provide an upper bound extinguishment concentration which is expected to be slightly higher than the actual minimum extinguishment concentration.

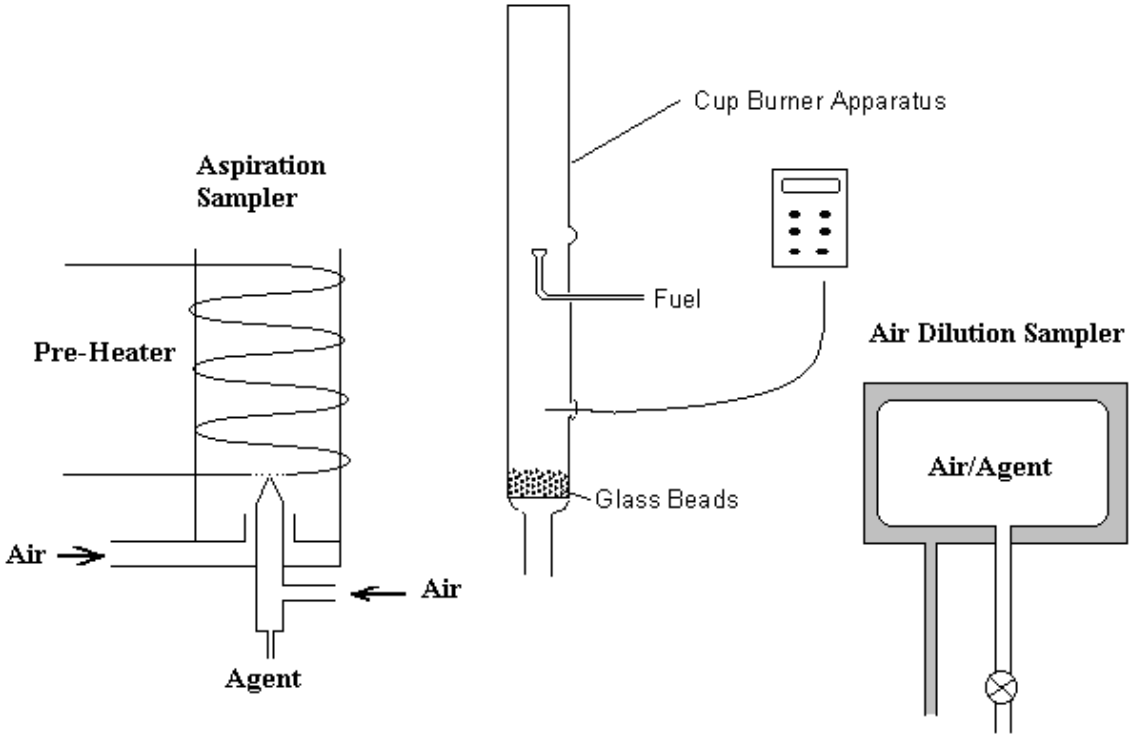

Figure 1. Cup-Burner and sample introduction equipment

TROPODEGRADABLE BROMOFLUOROCARBONS AND CARDIAC SENSITIZATION PRESCREENING

Past research firmly established the potential of tropodegradable bromocarbons as fire suppressants and resulted in preliminary lists of tropodegradable compounds ranked according to estimated toxicity and environmental acceptability [4, 5, 6, 7].

In the case of the bromofluoro alkenes, where cup-burner testing and limited toxicity testing have resulted in the identification of 2-bromo-3,3,3-trifluoropropene as a potential replacement for Halon 1201, there are many additional compounds that have yet to be tested, Table 4.

Toxicity testing is of greatest concern for occupied space extinguishment agents. Exposure of aircraft maintenance workers, under normal operating circumstances, as well as accidental discharge incidents, is a concern. Methods for estimation of toxicity or low cost screening methodologies are very limited. Cardiac sensitization, a property of a wide number of compounds [8], is not well modeled at present; individual compound tests involve extremely expensive animal testing protocols. To aid in the final selection of compounds for animal testing screening, a test method will need to be developed and validated.

The phenomenon of cardiac sensitization refers to the ability of certain un-substituted and halogenated hydrocarbons to make the mammalian heart abnormally reactive to epinephrine, resulting in cardiac arrhythmias and, potentially, sudden heart failure. The mechanisms underlying the interaction of halogenated hydrocarbons and cardiac muscle resulting in cardiac arrhythmia are unknown.

Dose-response data obtained from animal (dog) testing is the accepted method for determination of cardiac sensitization No Observable Adverse Effect Level (NOAEL) and Lowest Observable Adverse Effect Level (LOAEL) values. For reference, Halon 1301 LOAEL and NOAEL values are 7.4 and 4.5 vol.% respectively. The LOAEL value, in concert with situational risk models and evacuation time estimates, determines the mandated maximum acceptable air concentration for human exposure in fire suppression events. It is widely accepted that LOAEL data obtained from the dog exposure based cardiac sensitization testing are conservative and, in fact, deaths due to human exposure to halons are rare.

Currently, halon replacement researchers are unable to evaluate and rank the cardiac sensitization potential of the large number of compounds being studied as possible halon replacements. This is due in part to the high cost of traditional dog exposure protocol test procedures and lack of usable models. This expense of standard dog exposure tests ($75,000. - not including the chemical) for determining a single compound's cardiac sensitization potential is effectively a major impediment to progress.

Quantitative Structure-Activity Relationships (QSAR) computational methods have been previously considered for estimating a chemical's cardiac sensitization potential. The development of a QSAR-based method, due to the lack of sufficient applicable dog exposure cardiac sensitization data with which to develop correlations capable of providing reliable estimates of unknown substances, is not viewed as a viable approach.. Under more recent consideration are in vitro toxicity methods.

A cardiac sensitization screen based on an in vitro method would involve the development of an experimental protocol capable of yielding an experimental ranking of known compounds that mirrors their LOAEL values. Even a general "best to worst" ranking capability applicable to the many halon replacement candidate compounds would provide a major step forward for the halon replacement research effort.

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 vol.%) and Halon 1211 (LOAEL 1.0 vol.%) or trifluoromethyl iodide (LOAEL 0.4 vol.%) 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 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.

In addition to the potential application of in vitro toxicity testing methods, there is a strong possibility of near term use of water-octanol or water-membrane partition coefficient methods as a method of establishing a relative ranking of compounds providing, perhaps, at least tentative ranking of cardiac sensitization potential as reflected in LOAEL values. This possibility offers hope of providing indicators of cardiac sensitization LOAEL values applicable to the preliminary compound selection of compounds required by halon replacement researchers. Ultimately all compounds would still require formal dog exposure based cardiac sensitization testing.

The status of in vitro toxicity options and partition coefficient approaches and applicability to the ranking of candidate compounds are discussed below.

Table 4. Additional Bromofluoro-Alkenes

Compound Formula	Compound Name	CAS Number
$CHBr=CHCF_2H$	1-Bromo-3,3-difluoropropene	691-46-3
$CHBr=CFCFH_2$	1-Bromo-2,3-difluoropropene	
$CFBr=CHCFH_2$	1-Bromo-1,3-difluoropropene	
$CFBr=CFCH_3$	1-Bromo-1,2-difluoropropene	
$CH_2=CBrCF_2H$	2-Bromo-3,3-difluoropropene	
$CHF=CBrCFH_2$	2-Bromo-1,3-difluoropropene	
$CF_2=CBrCH_3$	2-Bromo-1,1-difluoropropene	51326-64-8
$CH_2=CFCFHBr$	3-Bromo-2,3-difluoropropene	
$CF_2=CHCH_2Br$	3-Bromo-1,1-difluoropropene	60917-29-5
CFH=CHCFHBr	3-Bromo-1,3-difluoropropene	
$CFH=CFCH_2Br$	3-Bromo-1,2-difluoropropene	
CFH=CFCFBrH	3-Bromo-1,2,3- trifluoropropene	
$CH_2=CFCF_2Br$	3-Bromo-3,3,2-trifluoropropene	178676-13-6
CF2=CFCBrH2	3-Bromo-2,1,1-trifluoropropene	
CFH=CHCBrF2	3-Bromo-3,3,1-trifluoropropene	
CHBr=CHCF3	1-Bromo-3,3,3- trifluoropropene	
CHBr=CFCF2H	1-Bromo-3,3,2- trifluoropropene	
CBrF=CHCHF2	1-Bromo-1,3,3- trifluoropropene	
$CFBr=CFCH_2F$	1-Bromo-1,2,3- trifluoropropene	
$CHBr=CFCHF_2$	1-Bromo-2,3,3- trifluoropropene	
CH2=CBrCF3	2-Bromo-3,3,3- trifluoropropene	
CF2=CBrCFH2	2-Bromo-1,1,3- trifluoropropene	
$CFH=CBrCF_2H$	2-Bromo-1,3,3- trifluoropropene	25602-04-4, 25602-05-5

IN VITRO TOXICITY TESTING METHODS

In vitro toxicity testing methods have been identified as having the great future potential to guide a down-select to the "best" candidate compounds for further consideration and formal cardiac sensitization testing. Unfortunately, in vitro methods for this application are at an embryonic stage of development. Potential projects will require considerable effort to evaluate and select cell strains, determine the conditions of exposure, select observational methods, and identify those physical and physiological factors to be monitored.

Fortunately, there appears to be strong current interest on the part of pharmaceutical companies in developing an in vitro screening test for cardiac sensitization to identify problematic chemical compounds earlier in the drug development process. This is an active area of interest and an in vitro method for evaluating the arrhythmia inducing potential of volatile halocarbons may well be identified at some future point.

No in vitro method exists for evaluating the cardiac sensitization properties of compounds. Attempts are currently being made to obtain funding for the development of an in vitro method based on cardiomyocytes. The goal of this proposal is development of micro-scale in vitro testing systems, based on human or animal cardiomyocytes, with long-term viability of the cells. Cardiomyocyte-based systems are expected to outperform in vitro Purkinje fiber systems and unorganized cell cultures because cardiac cells will be the actual target of drug toxicity; endpoints from an in vitro test will be directly relatable to the abnormal clinical ECG patterns that define drug-induced arrhythmia

Such in vitro testing systems could play an important role in evaluating a large number of compounds with potential to affect the electrophysiology of the myocardium in man.

WATER – OCTANOL PARTITION COEFFICIENTS

In the near term, water-octanol partition coefficients may well offer the means to prescreen chemicals for their cardiac arrythmogenic properties. Water-octanol partition coefficients are recognized as correlating with biological activity [9]. 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[10].

In fact, a wide range of compounds, including halogenated and unhalogenated alkanes, alkenes, and ethers, are known to induce cardiac arrhythmia. This situation has led some to speculate 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, or adsorbed onto, heart nerve and muscle cells and cell membranes [8].

Recent research has shown, using differential scanning calorimetry, that the inhalation anesthetic agent halothane ($CF_3CHClBr$) destabilizes some proteins in aqueous solution with respect to thermal unfolding, presumably due to halothane binding to the native folded state [11]. 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 ^{o}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.

Octanol-water partition coefficients are used in QSAR analysis and rational drug design as a measure of molecular hydrophobicity. Hydrophobicity is a key factor in drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of a compound, and toxicity. In addition, LogKOW values are key parameters in studies of the environmental fate of chemicals.

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).

PARTITION COEFFICIENT DETERMINATION BY RP-HPLC

Reverse phase high pressure liquid chromatography (RP-HPLC) is widely utilized for this determination. RP- HPLC employing compounds for which KOW values are known and accepted is used to develop relationships between measured chromatographic retention times and known partition coefficients. This method requires only mg's of compound. 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 COEFFICIENT CALCULATION

Partition coefficients may be calculated (Molinspiration Cheminformatics website http://www.molinspiration.com and Syracuse Research Corporation http://esc.syrres.com). Generally, Log(KOW) values are calculated as a sum of the fragment-based contributions and correction factors.
The calculated Log(KOW) values for a brief series of halogenated (brominated or iodinated) short chain fluorocarbons are listed, Table 5. While this data is by itself not all that convincing it does suggest a tentative relationship between the tendency of a compound to be hydrophobic and observed cardiac sensitization test results. There are doubtless other factors that influence the activity of a compound (possible size, shape, reactivity), and it is also possible that additional toxicological mechanisms are involved in certain types of cardiac arrhythmia.

Table 5. Calculated Log(Kow) Comparison Of Bromofluoro-Carbons

Compound	Log KOW * (calculated)	Log KOW (literature)	LOAEL, vol. %
CF3Br (Halon 1301)	1.833	1.86	7.4
CHBrF2 (FM-100)	1.849	NA	3.9
CH2=CBrCF3	2.141	NA	1.0
CF2ClBr (Halon 1211)	2.175	2.1	1.0
CF3I	2.219	NA	0.4

*Molinspiration Cheminformatics algorithm

Water-octanol partition coefficients were calculated for the difluorinated bromo-propenes using the Molinspiration Cheminformatics and Syracuse Research Corporation molecular fragment contribution-based methods, Figure 2. The plotted data points (the lines delineate points calculated by a particular method) are roughly comparable. Interestingly, the highest Log(KOW) value calculated for this series is for CH_2=$CHCF_2Br$, which proved highly toxic in inhalation toxicity tests.

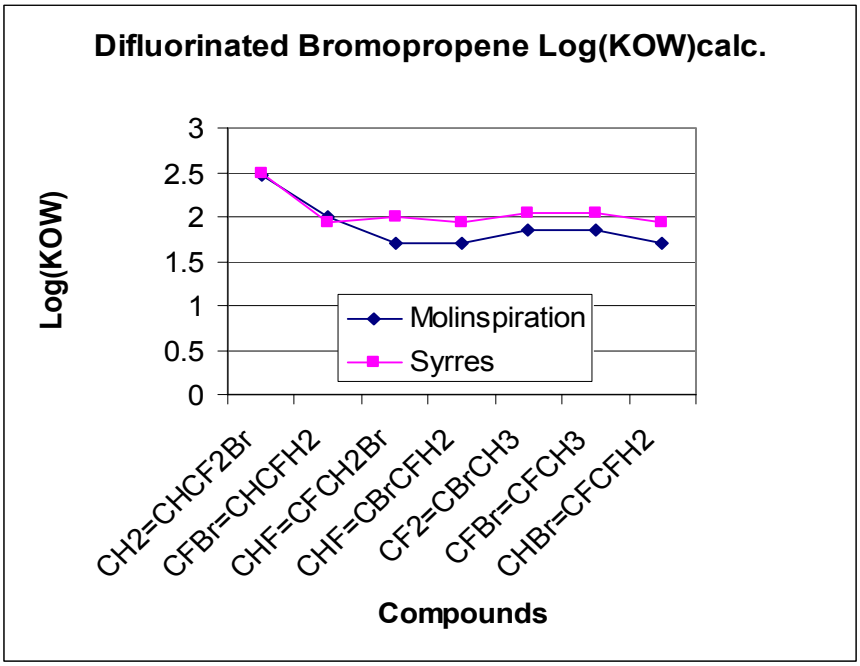

Figure 2. Comparison of two difluoro-bromopropene Log(KOW) calculation methods

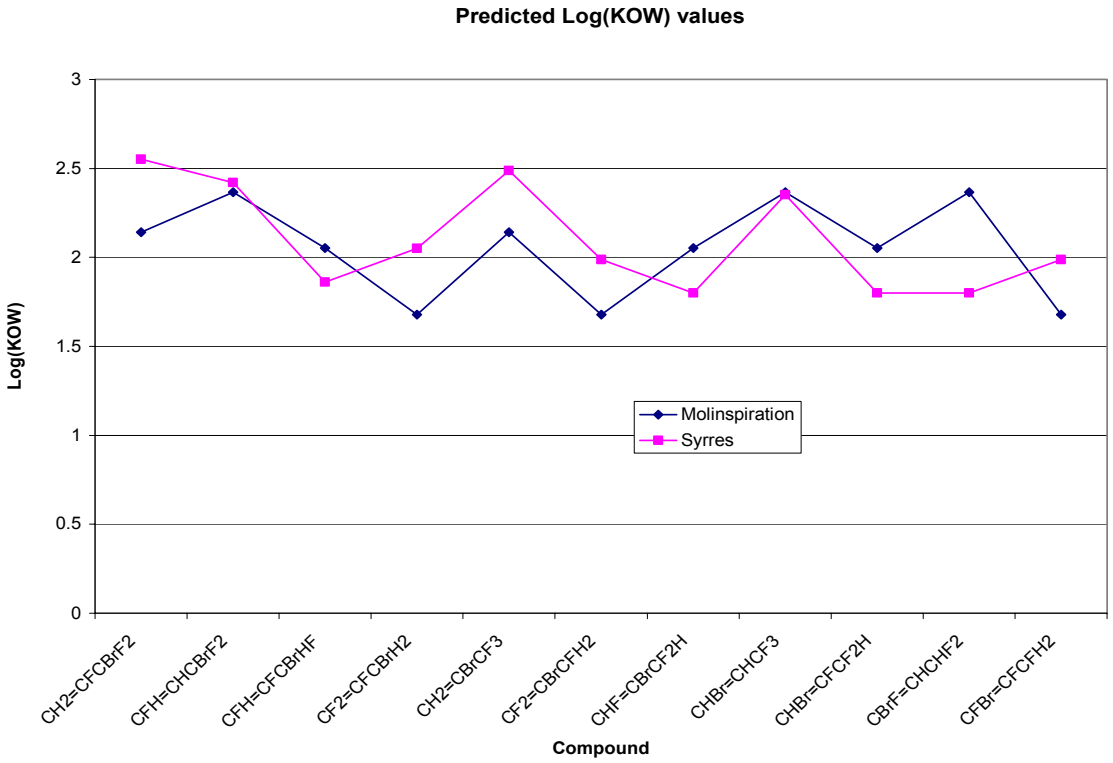

Figure 3. Comparison of two trifluoro-bromopropene Log(KOW) calculation methods

Water-octanol partition coefficients were also calculated for the trifluorinated bromopropenes using the Molinspiration Cheminformatics and Syracuse Research Corporation molecular fragment contribution based methods, Figure 3. The plotted data points (line connecting data points from same method calculation) are also roughly comparable.

The calculated values presented in Figures 2 and 3 point to the potential candidacy of several additional compounds from the difluorobromopropene and trifluorobromopropene subfamilies. Several of these compounds are currently being sought for RP-HPLC determination of their Log(KOW) values relative to 2-bromo-3,3,3-trifluoropropene.

SUMMARY

The next step in the evaluation of the applicability of water-octanol partition coefficients will be the experimental determination of partition coefficients for the known halons, bromopropenes, and selected additional bromofluoropropenes, and application of these results to the identification of additional compounds for acquisition and testing.

It is apparent that any additional information relating a chemical's composition and structure to its cardiac sensitization properties will enhance future compound selection and reduce the number of cardiac sensitization tests required. It seems apparent that eventual identification and application of validated in vitro based prescreening methods to rank compounds with respect to induction of cardiac arrhythmia could greatly facilitate subsequent decisions to fund formal cardiac sensitization testing.

The broad survey of promising chemical families conducted identified five “High Priority”, seven “Further Study”, and six “Quick Look” chemical families for investigation. While this project places its initial emphasis on the families of compounds past studies have shown to be most promising, compound acquisition and testing will include as many families as resources allow.

The broad scope of the project may reasonably be expected to give additional basis upon which the study of several new compound families may be advanced and also provide further guidance in, and direction to, the search for effective fire extinguishants amongst the known promising families, such as the bromofluoropropenes.

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