Development Of Quantitative Structure-Property Relationships For Screening Of Tropodegradable Halocarbons

Lawrence R Grzyll and Dwight D. Back
Mainstream Engineering Corporation
Rockledge, Florida 32955

Juan A. Vitali
Applied Research Associates, Inc.
Tyndall AFB, Florida 32403

Giovanni Linscheer
Department of Civil Engineering
University of Florida
Gainesville, Florida 32611

INTRODUCTION

This paper describes the development of quantitative structure-property relationships (QSPRs) for screening the key fire suppression agent properties of tropodegradable halocarbon agents, which included halogenated alcohols, halogenated alkenes and alkynes, halogenated amines, halogenated aromatics, halogenated carbonyls (carboxylic acids, esters, aldehydes, and ketones), halogenated ethers, hydrobromocarbons (HBCs), and hydrofluorocarbons (HFCs). The goal was to develop an accurate screening technique that would allow consideration of a large set of compounds from these families with unmeasured or unknown properties. The techniques of computational chemistry were applied to develop QSPRs that correlated structural features of these compounds to selected fire suppression agent properties. Once developed, the QSPRs were then used to predict the key properties of a large set of potential fire suppression agents from these families with previously unmeasured properties. Compounds with promising properties were then selected for synthesis and experimental evaluation.

DISCUSSION OF QSPRs

The computational chemistry system used to develop the QSPRs was ADAPT, which was installed on a Sun SPARC II workstation. The approach used by ADAPT begins with the assumption that there is a relationship between chemical structure and the property of interest. The steps are:

1. Select a list of key properties of interest and a study set of compounds from the families being considered with measured property data. These compounds, and their properties, are used for QSPR development. Another set of compounds, with unknown property data, are also selected and their properties are predicted by the QSPRs.

2. Draw the molecular structures of the compounds with molecular drawing software.

3. Generate computational-chemistry-based molecular descriptors for the compounds in the study set. Approximately 150 descriptors can be generated that are based on topological, electronic, or physicochemical features of the molecule. Topological descriptors encode information based on connectivity of the molecule, such as molecular shape, connected paths, molecular size and branching, number and types of atoms, bonds, rings, lone pairs, etc., and structural symmetry. Electronic descriptors encode the electronic features of molecules from two contributions: sigma charges, based on charge transfer due to atomic orbital eletronegativity differences; and pi charges, from simple molecular orbital calculations on each conjugated pi system in the structure. Physicochemical descriptors include properties such as molecular polarizability and molar refraction that can be estimated using computational chemistry methods. Finally, substructure-based descriptors were generated that were counts of any definable atomic or functional group on the molecule, such as the carboxylic acid functional group, the ether functional group, the amine functional group, etc.

4. Perform descriptor reduction analysis using statistical techniques to develop a smaller set of unique, independent descriptors for use in QSPR development. This analysis identifies and eliminates descriptors with identical values, or those descriptors that correlate highly with one another. The result of this analysis is a set of unique descriptors for QSPR development.

5. Develop a series of QSPRs using multiple regression or other statistical techniques that correlate the properties of interest to the molecular descriptors. Selection of the best models is based on the R^2 of the model, the F-statistic of the model (a measure of the statistical significance of the model), the standard deviation of the model, the T-statistic for each variable in the model (a measure of the statistical significance of each variable), and the ratio of compounds with measured data to model variables (this ratio should be greater than 5).

6. Investigate the QSPRs for internal consistency and statistical significance by identifying and eliminating outlier data points based residual statistical parameters. New QSPRs are then developed. The best QSPR for the property of interest is then selected.

7. Generate the necessary descriptors (those used by the QSPRs) for the compounds with unknown properties.

8. Use the QSPRs to predict the properties of the compounds with unknown properties.

QSPR DEVELOPMENT

Seven properties were selected for screening and QSPR development: fire suppression effectiveness, tropospheric lifetime, ozone depletion potential (ODP). global warming potential (GWP), normal boiling point, inhalation toxicity, and cardiac sensitization toxicity.

Fire Suppression Effectiveness

The flame extinguishing concentration (FEC) using the cup burner apparatus was selected as a measure of fire suppression effectiveness. Experimental data for 31 tropodegradable halocarbons, largely ethers and HFCs, was collected from various sources (Refs. 1-7). The FEC QSPR correlated the logarithm of the FEC to three ADAPT descriptors. There were 27

observations used for QSPR development and three outlier compounds identified that were eliminated from further consideration (two alkenes and one hydrofluorocarbon). Table 1 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics.

TABLE 1- SUMMARY OF FEC QSPR

$$\log_{10} FEC = 1.30315 - 0.27519*V1 + 0.0392576*NLP\ 0.786641*V5P$$

$R^2 = 0.824$ F-statistic = 37.478 standard deviation = 0.0682

VI - 1st order valence molecular connectivity (T-statistic = -9.650)

NLP - number of lone pairs of electrons (T-statistic = 3.631)

V5P - 5th order valence path molecular connectivity (T-statistic = 5.791)

Family	Number of Data Points	Percentage of Total	Family	Number of Data Points	Percentage of Total
Alcohols	0	0 %	Ethers	8	29.6 %
Alkenes	3	11.1 %	Unsaturated Ethers	0	0 %
Amines	0	0 %	Hydrobromocarbons	3	11.1 %
Aromatics	2	7.4 %	Hydrofluorocarbons	10	37.1 %
Carbonyls	1	3.7 %	Polyethers	0	0 %

Tropospheric Lifetime and Hydroxyl Radical Reaction Rate Constant

The tropospheric lifetime of a compound was calculated from the inverse ratio of its reaction rate constant with hydroxyl radicals in the atmosphere (k_{OH}) to the k_{OH} of 1,1,1-trichloroethane (Reference 8). This inverse ratio is then multiplied by the tropospheric lifetime of 1,1,1-trichloroethane. This calculation methodology does not account for other mechanisms that can further reduce the lifetime of a molecule in the atmosphere, such as photolysis, rainout, reaction with atmospheric ozone, **or** other mechanisms. Thus, the calculated values for tropospheric lifetime are conservatively high. The following equation was used:

$$t_{trop} = t_{CCl_3CH_3} \frac{[k_{OH}]_{CCl_3CH_3}}{[k_{OH}]_{agent}}$$

where: t_{trop} = tropospheric lifetime of compound (years)
$t_{CCl3CH3}$ = tropospheric lifetime of CCl_3CH_3
k_{OH} = hydroxyl radical reaction rate constant (cm^3/molecule-sec)

The k_{OH} data used on this effort were obtained from the NIST Chemical Kinetics Database (Reference 9), which contained data for 83 tropodegradable halocarbons. The k_{OH} QSPR correlated the logarithm of k_{OH} to three ADAPT descriptors. There were 71 observations used for QSPR development and 12 outlier compounds identified that were eliminated from

further consideration (five alkenes, one aromatic, and six carbonyls). Table 2 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics. The k_{OH} QSPR was developed largely from alkene, aromatic, carbonyl, ether, hydrobromocarbon, and hydrofluorocarbon data; little data was available for alcohols, amines, unsaturated ethers, or polyethers.

TABLE 2 - SUMMARY OF k_{OH} QSPR

$$\log_{10} k_{OH} = -13.1571 - 3.2640*NFPH + 1.2011*NDB + 0.3886*KAPA5$$

$R^2 = 0.917$ F-statistic = 255.48 standard deviation = 0.3618

NFPH - number of fluorine atoms/potential halogen sites (T-statistic = -20.13)

NDB - number of double bonds (T-statistic = 11.24)

KAPA5 - Kappa 5 index (T-statistic = 9.427)

Family	Number of Data Points	Percentage of Total	Family	Number of Data Points	Percentage of Total
Alcohols	3	4.2 %	Ethers	10	14.1 %
Alkenes	11	15.5 %	Unsaturated Ethers	0	0 %
Amines	0	0 %	Hydrobromocarbons	14	19.7 %
Aromatics	10	14.1 %	Hydrofluorocarbons	17	23.9 %
Carbonyls	6	8.5 %	Polyethers	0	0 %

ODP

ODP data for 31 compounds was obtained from various sources (Refs. 8, 10-12). Twenty-nine of the 31 data points were outside of the tropodegradable halocarbon families considered on this effort (i.e. halogenated alkanes). By definition, compounds with no chlorine, bromine, or iodine were assigned an ODP of zero. Literature agrees with this, stating that HFCs have ODPs ranging from $4x10^{-4}$ or less (Reference 13). The ODP QSPR correlated the logarithm of ODP to four ADAPT descriptors. Table 3 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics. There were 27 observations used for QSPR development and four outlier compounds identified that were eliminated from further consideration.

GWP

GWP data for 26 compounds was obtained from various sources (Refs. 8, 10-12, 14). Ten of the 26 data points were outside of the tropodegradable halocarbon families considered on this effort (hydrochlorocarbons and hydrochlorofluorocarbons). The GWP QSPR correlated the logarithm of GWP to four ADAPT descriptors. Table 4 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics. There were 23 observations used for QSPR development and three outlier compounds identified that were eliminated from further consideration (one HFC, one hydrochlorofluorocarbon, and one ether).

TABLE 3 - SUMMARY OF ODP QSPR

log_{10} *ODP = -0.1977 + 2.5596*S4C + 0.5493*S6C - 1.0490*NC + 0.7832*NBR*

$R^2 = 0.901$ F-statistic = 49.97 standard deviation = 0.2871

S4C, S6C - 4th and 6th order simple cluster molecular connectivity (T-statistics = 7.285, 5.072)

NC - number of carbon atoms (T-statistic = -8.791)

NBR - number of bromine atoms (T-statistic = 7.237)

Family	# of Data Points	% of Total	Family	# of Data Points	% of Total
chlorocarbons	1	3.7 %	hydrobromofluorocarbons	2	7.4 %
hydrochlorocarbons	2	7.4 %	bromochlorofluorocarbons	1	3.7 %
chlorofluorocarbons	8	29.6 %	hydrobromochlorofluorocarbons	1	3.7 %
hydrobromocarbons	1	3.7 %	hydrochlorofluorocarbons	9	33.3 %
bromofluorocarbons	2	7.4 %			

TABLE 4 - SUMMARY OF GWP QSPR

log_{10} *GWP = 1.0493 - 0.1329*KAPA3 + 1.6242*S4C + 3.6193*NFPH - 0.5985*S5C*

$R^2 = 0.902$ F-statistic = 41.4 standard deviation = 0.290

S4C, S5C - 4th and 5th order simple cluster molecular connectivity (T-statistics = 5.005, -7.81)

NFPH - number of fluorine atoms/potential halogen sites (T-statistic = 11.51)

KAPA3 - Kappa-3 index (T-statistic = -4.076)

Family	Number of Data Points	Percentage of Total
hydrochlorocarbons	3	13.0 %
hydrofluorocarbons	12	52.2 %
ethers	2	8.7 %
hydrochlorofluorocarbons	6	26.1 %

Normal Boiling Point

Normal boiling point data for 187 tropodegradable halocarbons was obtained from various sources (Refs. 5-7, 15-22). The normal boiling point QSPR correlated the normal boiling point (K) to three ADAPT descriptors. There were 164 observations used for QSPR development and 17 outlier compounds identified that were eliminated from consideration (four alcohols, five alkenes, seven carbonyls, and one hydrofluorocarbon). The QSPR was developed largely from alkenes, aromatics, ethers, HBCs, HFCs, and carbonyls. There was less data available for alcohols, amines, unsaturated ethers, and polyethers. Table 5 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics.

TABLE 5 - SUMMARY OF NORMAL BOILING POINT QSPR

Tboil (K) = 130.6062 + 19.7344*MPOL - 211.1438*QNEG - 82.5252*S4C

$R^2 = 0.927$ F-statistic = 699.7 standard deviation = 17.34

MPOL - molecular polarizability (T-statistic = 45.38)

QNEG - charge on most negative atom in molecule (T-statistic = -10.65)

S4C - 4th order simple cluster molecular connectivity (T-statistic = -18.03)

Family	Number of Data Points	Percentage of Total	Family	Number of Data Points	Percentage of Total
Alcohols	3	1.8 %	Ethers	30	18.0 %
Alkenes	52	31.1 %	Unsaturated Ethers	1	0.6 %
Amines	6	3.6 %	Hydrobromocarbons	16	9.6 %
Aromatics	18	10.8 %	Hydrofluorocarbons	19	11.4 %
Carbonyls	15	9.0 %	Polyethers	7	4.2 %

Inhalation Toxicity

Inhalation toxicity data was obtained for numerous tropodegradable halocarbons from various sources (Refs. 5-7, 15-19, 23-24). Data for both rats and mice, with endpoints of LC_{50} and LC, were obtained, with durations ranging from 10 minutes to 24 hours.

Attempts were made to separately correlate the mouse and rat LC,, data to both molecular descriptors and exposure duration. Unsatisfactory models were obtained using the rat LC_{50} data. Two QSPRs were developed for the mouse LC_{50} data; one for families containing oxygen atoms (alcohols, carbonyls, and ethers) and one for families with no oxygen atoms (alkenes, amines, aromatics, hydrobromocarbons, and hydrofluorocarbons).

The QSPR for oxygenated compounds correlated the logarithm of the product of LC,, and duration to eight ADAPT descriptors. There were 43 observations and five outlier compounds eliminated from the study (one alcohol, two carbonyls, and two ethers). Table ***6*** provides a summary of the data used to develop the QSPR by family and also lists the statistics of the QSPR. There were no unsaturated ethers used to develop the QSPR.

The QSPR for families with no oxygen atoms correlated the logarithm of LC_{50} to five ADAPT descriptors and the logarithm of exposure duration. There were 38 observations and three outlier compounds eliminated from the study (two alkenes and one aromatic). Table **7** provides a summary of the data used to develop the QSPRs by family and also lists the QSPR models and their statistics.

TABLE 6 - SUMMARY OF MOUSE LC_{50} QSPR FOR OXYGENATED FAMILIES

$$\log_{10}(LC_{50}*duration) = 2.1956 + 6.8665*NFPH + 7.0566*NCPH + 3.91748*RALK + 4.1857*REST - 0.989786*KAPA2 + 0.39866*KAPA3 + 4.81205*V5P - 1.2063*V4PC$$

$R^2 = 0.850$ F-statistic = 23.99 standard deviation = 0.5737

duration = exposure duration (hrs.)

NFPH = number of fluorine atoms/potential halogen sites (T-statistic = 9.389)

NCPH = number of chlorine atoms/potential halogen sites (T-statistic = 4.131)

RALK = number of C=C groups/total number of carbon atoms (T-statistic = 3.315)

REST = number of ester carbon atoms/total number of carbon atoms (T-statistic = 4.201)

KAPA2 = kappa-2 index (T-statistic = 8.710)

KAPA3 = kappa-3 index (T-statistic = 5.503)

V5P = 5th order valence path molecular connectivity (T-statistic = 3.909)

V4PC = 4th order valence path-cluster molecular connectivity (T-statistic = 2.971)

Family	Number of Data Points	Percentage of Total	Family	Number of Data Points	Percentage of Total
Alcohols	5	11.6 %	Ethers	10	23.3 %
Carbonyls	28	65.1 %			

TABLE 7 - SUMMARY OF MOUSE LC_{50} QSPR FOR NON-OXYGENATED FAMILIES

$$\log_{10} LC_{50} = 5.47618 - 3.48023*NFPH + 0.66948*NC + 1.18777*V2 - 0.298067*MREF + 534.274/bp(K) - 0.860115\log_{10}(duration)$$

$R^2 = 0.841$ F-statistic = 27.399 standard deviation = 0.5739

NFPH = number of fluorine atoms/potential halogen sites (T-statistic = -4.449)

NC = number of carbon atoms (T-statistic 7.042)

V2 = 2nd order valence molecular connectivity (T-statistic = 3.540)

MREF = molar refraction (T-statistic = 5.949)

1/bp(K) = inverse boiling point in Kelvin (T-statistic = 2.983)

$\log_{10}(duration)$ = logarithm of duration in hours (T-statistic = 2.831)

Family	Number of Data Points	Percentage of Total	Family	Number of Data Points	Percentage of Total
Alkenes	22	57.9 %	Hydrobromocarbons	3	7.9 %
Aromatics	10	26.3 %	Hydrofluorocarbons	3	7.9 %

Cardiac Sensitization Toxicity

Cardiac sensitization toxicity data for 31 halogenated halocarbons was obtained from numerous sources (Refs. 25-40). Twenty-one of the 31 data points, were outside of the tropodegradable halocarbon families considered on this effort (hydrochlorocarbons and hydrochlorofluorocarbons). The cardiac sensitization QSPR correlated the logarithm of cardiac sensitization NOAEL (no observed adverse effect level) to four ADAPT descriptors. Table 8 provides a summary of the data used to develop the QSPR by family and also lists the QSPR model and its statistics. There were 30 observations used for QSPR development and one outlier compound identified that was eliminated from further consideration (one HFC).

TABLE 8 - SUMMARY OF CARDIAC SENSITIZATION NOAEL QSPR

$$\log_{10} CS\text{-}NOAEL = 1.31908 + 771.048/bp(K) + 0.49868*KAPA2 - 0.923602*SYMM - 4.1726*V6C$$

$R^2 = 0.921$ F-statistic = 73.32 standard deviation = 0.2031

bp(K) - normal boiling point in Kelvin (T-statistic = 10.54)

KAPA2 - Kappa-2 index (T-statistic =8.671)

SYMM - structural symmetry (T-statistic = -4.384)

V6C - 6th order valence cluster molecular connectivity (T-statistic = -4.245)

Family	Number of Data Points	Percentage of Total
hydrochlorocarbons	2	6.7%
perfluorocarbons	5	16.7 %
chlorofluorocarbons	5	16.7 %
hydrochlorofluorocarbons	4	13.3 %
bromofluorocarbons	1	3.3 %
bromochlorofluorocarbons	1	3.3 %
alkenes	2	6.7 ,%
hydrofluorocarbons	7	23.3 %
others (hydrocarbons and ethers)	3	10.0 %

COMPOUND SCREENING AND SELECTION

A database containing 493 compounds from the tropodegradable halocarbon families was assembled for screening purposes. Where experimental data for the key properties was available, it was used. In the absence of data; the QSPR prediction for that property was used. An initial screening/selection criteria was developed to select compounds for experimental work. The initial criteria developed was: 1) normal boiling $\leq$ 125°C, 2) FEC $\leq$ 6.0 %, 3) ODP $\leq$ 0.02, 4) GWP $\leq$ 4000, 5) tropospheric lifetime $\leq$ 1 year, 6) 2-hour mouse $LC_{50} \geq$ 5,000 ppm (0.5 %), and 7) cardiac NOAEL $\geq$ FEC.

Application of the criteria to the compounds in the database resulted in the selection **of** seven compounds: 1-bromodifluoromethoxy-2-trifluoromethyl-3,3,3-trifluoro-1-propene [$(CF_3)_2C$=CH-O-CF_2Br], 1-bromodifluoromethoxy-2-trifluoromethoxy- ethene [CF_3-O-CF=CF-O-CF_2Br], 3,3,3-trifluoro-2-trifluoromethyl-1-propene [CH_2=$C(CF_3)CF_3$], perfluorotoluene [c-C_6H_5-CF_3], 1-bromodifluoromethoxy-1,2,3,3,3-pentafluoro-1-propene [CF_3CF=CF-O-CF_2Br], 1-**bromodifluoromethoxy-2-trifluoromethyl-ethene** [CF_2Br-O-CH=$CHCF_3$], and (2,2,2-trifluoroethyl)(2-bromo-2,2-difluoroethyl) ether [CF_3CH_2-O-CH_2CF_2Br]. Table 9 lists the key properties of these compounds.

TABLE 9 - KEY PROPERTIES OF RECOMMENDED AGENTS

Compound	Boiling Point (C)	FEC (%)	ODP	GWP	Trop. Life (yrs.)	LC_{50} (ppm)	NOAEL (ppm)
$(CF_3)_2C$=CH-O-CF_2Br	86.9	3.4	0.007	2730	0.08	101,151	146,507
CF_3-O-CF=CF-O-CF_2Br	83.4	4.6	0.016	682	0.04	207,955	143,161
CH_2=$C(CF_3)CF_3$	-5.9	5.7	***0.000***	1686	0.60	9,519	117,966
c-C_6H_5-CF_3	***104.0***	5.5	***0.000***	335	1.14	6,114	69,764
CF_3CF=CF-O-CF_2Br	72.4	4.1	0.013	1334	0.14	183,008	68,427
CF_2Br-O-CH=$CHCF_3$	65.8	4.6	0.016	238	0.06	> 1.0e6	52,187
CF_3CH_2-O-CH_2CF_2Br	88.6	4.5	0.016	238	0.96	584,884	45,488

Values on boldface italic are measured data, all others are QSPR predictions.

This criteria could obviously be modified, resulting in other compounds being recommended. Synthesis and manufacturability of these compounds is currently being investigated. Laboratory evaluations of these compounds will take place once sufficient quantities have been synthesized.

CONCLUSIONS

The objective of this effort was to develop quantitative structure-property relationships (QSPRs) for screening the key fire suppression agent properties of tropodegradable halocarbon fire suppression agents with unmeasured properties. The properties selected for study were the cup burner FEC, tropospheric lifetime (calculated from k_{OH}), ODP, GWP, normal boiling point, inhalation toxicity (mouse LC_{50}), and cardiac sensitization NOAEL. QSPRs were developed for these properties with correlation coefficients (R^2) ranged from **0.824** to **0.927.** A database of **493** tropodegradable halocarbon compounds was assembled and the QSPRs were used to predict the unmeasured properties of these compounds. Application of an initial selection criteria resulted in the recommendation of seven compounds for synthesis and experimentation. Synthesis and manufacturability of the recommended compounds is underway.

The tropodegradable halocarbons appear to offer significant potential as a halon replacement. The computational chemistry approach used on this project enabled the consideration of a large set of compounds from the tropodegradable halocarbons. The QSPRs developed successfully predicted previously unmeasured properties of compounds from this group, providing a systematic technique to screen the 493 compounds considered. This screening process, in its current form or modified, allowed for a rational recommendation of compounds for experimental evaluation. This approach was demonstrated to be a cost effective way to evaluate compounds with unmeasured properties without experimental evaluation.

ACKNOWLEDGMENT

The authors gratefully acknowledge the U.S. Air Force Wright Laboratory (WL/FIVCF), Tyndall AFB, Florida, for their support of this effort. This effort was funded under Scientific Engineering Technical Assistance contract number F08635-93-C-0020, SETA Supplemental Support Group (SSG) Subtask 3.24, subcontract number S-5000.48

REFERENCES

1. Skaggs, S. R., Dierdorf, D. S., and Tapscott, R. E., "Update on Iodides as Fire Extinguishing Agents," ***Proceedings of the 1993 International CFC and Halon Alternatives Conference,*** 800-809, 1993.

2. Nimitz, J. and Lankford, L., "Fluoroiodocarbons as Halon Replacements," ***Proceedings of the 1993 International CFC and Halon Alternatives Conference,*** 810-19, 1993.

3. Adcock, J., "Fluorinated Ethers: A New Family of Halons," ***Proceedings of the 1991 International CFC and Halon Alternatives Conference,*** 642-51, 1991.

4. Moore, T. A., Moore, J. P., and Floden, J. R., "Technology Transfer for New Laboratory Apparatuses For Fire Suppression Testing of Halon Alternatives," presented at the 1990 International CFC and Halon Alternatives Conference, Baltimore, MD, 1990.

5. Grzyll, L. R., Back, D. D., Ramos, C., and Samad, N. A., "Development of a Rapid Screening Technique for Second-Generation Halon Alternatives," Final Report, submitted to the Advanced Research Projects Agency (ARPA), Department of Defense, August 1996.

6. Tapscott, R. E., Heinonen, E. W., Moore, T. A., Kaizerman, J. A., Lifke, J. L., and Weitz, C. A., "Advanced Streaming Agent Development," Technical Progress Report No. 5, submitted to Applied Research Associates, Inc., August 1996.

7. Tapscott, R. E., Heinonen, E. W., Moore, T. A., Kaizerman, J. A., Lifke, J. L., and Weitz, C. A., "Advanced Streaming Agent Development," Technical Progress Report No. 6, submitted to Applied Research Associates, Inc., September 1996.

8. ***Scientific Assessment of Ozone Depletion: 1991.*** World Meteorological Organization, Global Ozone Research and Monitoring Project - Report No. 25, 1991.

9. "NIST Chemical Kinetics Database, Version **6.01,** User's Guide," NIST Standard Reference Database **17,** National Institute of Standards and Technology, November **1994.**

10. Nimitz, J. S. and Skaggs, S. R., "Estimating Tropospheric Lifetimes and Ozone Depletion Potentials of One- and Two-Carbon Hydrfluorocarbons," ***Environ.*** *Sci.* ***Technol.,*** **26,739-44, 1992.**

11. Tapscott, R. E., Lee, M. E., Watson, J. D., Nimitz, J. S., and Rodriquez, M. L., "Next-Generation Training Agents Phase IV - Foundation for New Training Agent Development," **ESL-TR-87-03,** December **1989.**

12. ***Scientific Assessment of Ozone Depletion: 1994.*** World Meteorological Organization, Global Ozone Research and Monitoring Project - Report No. **37,1995.**

13. Ravishankara, A. R., Turnipseed, A. A., Jensen, N. R., Barone, S., Mills, M., Howard, C. J., and Solomon, S., "Do Hydrofluorocarbons Destroy Stratospheric Ozone?, ***Science,*** 263, 71-5, **1994.**

14. Houghton, J. T., Meria Filho, L. G., Callander, B. A., Harris, N., Kattenberg, A., and Maskell, K., Eds., ***Climate Change*** 1995. ***The Science of Climate Change,*** Cambridge University Press, **1996.**

15. Heinonen, E. W., Like, J. L., and Tapscott, R. E., "Advanced Streaming Agent Development, Volume IV: Tropodegradable Halocarbons," Final Report, prepared for WL/FIVCF and Applied Research Associates, Inc., May **1996.**

16. Tapscott, R. **E.,** Heinonen, E. W., Kaizerman, J. A., Lifke, J. L., and Weitz, C. A., "Advanced Streaming Agent Development," Technical Progress Report No. **3,** submitted to Applied Research Associates, Inc., June **1996.**

17. Tapscott, R. **E.,** Heinonen, E. W., Moore, T. A., Kaizerman, J. A., Lifke, J. L., and Weitz, C. A., "Advanced Streaming Agent Development," Technical Progress Report No. **4,** submitted to Applied Research Associates, Inc., July **1996.**

18. Tapscott, R. **E.,** Heinonen, E. W., Moore, T. A., Lifke, J. L., and Weitz, C. A., "Advanced Streaming Agent Development," Technical Progress Report No. **7,** submitted to Applied Research Associates, Inc., June **1996.**

19. Tapscott, R. E., Mather, J. D., Heinonen, E. W., Moore, T. A., and Lifke, J. L., "Tropodegradable Toxicity Assessment," Technical Progress Report #2, December **1996.**

20. ***Catalog and Handbook*** *of* ***Fine Chemicals,*** Aldrich Chemical Co., Milwaukee, WI, **1996.**

21. ***Research Chemicals Catalog,*** PCR Inc., Gainesville, FL, **1994.**

22. ***Fluorine Compounds Catalogue,*** Fluorochem, Ltd., UK, **1993.**

23. ***Registry of Toxic Effects*** *of* ***Chemical Substances Database,*** National Institute for Occupational Safety and Health, Cincinnati, OH, **1997.**

24. "CGET Chemical Options Database," Center for Global Environmental Technologies, New Mexico Engineering Research Institute, February **1997.**

25. *HARC News,* 4(1), March **1994.**

26. Pignato, J. A. and Pike, M. T., "Development of Perfluoroalkanes as Clean Extinguishing Agents. Toxicology Protocols," *Proceedings of the Halon Alternatives Technical Working Conference* 1993, 57-61, 1993.

27. Mullin, L. S., Reinhardt, C. F., and Hemingway, R. E., "Cardiac Arrhythmias and Blood Levels Associated With Inhalation of Halon 1301," *American Industrial Hygiene Association Journal,* 40, 653-8, 1979.

28. Clark, D. G. and Tinston, D. J., "Correlation of the Cardiac Sensitizing Potential of Halogenated Hydrocarbons With Their Physicochemical Properties," *British Journal of Pharmacology,* 49, 355-7, 1973.

29. McDougal, J. N., Dodd, D. E., and Skaggs, S. R., "Recommending Exposure Limits for Halon Replacements," *Proceedings of the Halon Alternatives Technical Working Conference 1993*, 63-73, 1993.

30. Beck, P. S., Clark, D. G., and Tinston, D. J., "The Pharmacologic Actions of Bromochlorodifluoromethane (BCF)," *Toxicology and Applied Pharmacology,* 24, 20-29, 1973.

31. Egle, J. L., Long, J. E., Simon, G. S., and Borzelleca, J. F., "An Evaluation of the Cardiac Sensitizing Potential of a Fabric Protector in Aerosol Form, Containing 1,1,1-Trichloroethane," *Toxicology and Applied Pharmacology,* 38,369-77,1976.

32. Trochimowicz, H. J., Azar, A., Terrill, J. B., and Mullin, L. S., "Blood Levels of Fluorocarbon Related to Cardiac Sensitization: Part II," *American Industrial Hygiene Association Journal,* 632-9, 1974.

33. Reinhardt, C. F., Mullin, L. S., and Maxfield, M. E., "Epinephrine-Induced Cardiac Arrhythmia Potential of Some Common Industrial Solvents," *Journal of Occupational Medicine,* 15(12), 953-5, 1973.

34. EPA/OPTS Public Files 84-900000050, 86-870001015, 86-870000987, 86-870000982, 86-890000885S, 86-920000850S, 87-8220404.

35. **Azar,** A., "Cardiovascular Effects of Fluorocarbon Exposure," *Proceedings of the Second Annual Conference on Environmental Toxicology,* 41-56, 1971.

36. "Toxicity Update on FE-13 and FE-25: Cardiac Sensitization Study Results," DuPont, 1992.

37. Personal communication from A. Vinegar of ManTech Environmental Technology, Inc. to D. Back of Mainstream, February 1995.

38. Tapscott, R. E., "Commercialized Halon Options," *1995 International CFC and Halon Alternatives Conference Proceedings,* 536-45, 1995.

39. Brock, W. J., Trochimowicz, H. J., Millischer, R-J., Farr, C., Kawano, T.. and Rusch, G. M., "Acute and Subchronic Toxicity of 1,1-Dichloro-1-Fluoroethane (HCFC-141b)," *Food and Chemical Toxicology,* 33(6), 483-90. 1995.

40. Brock, W. J., Trochimowicz, H. J.. Farr, C., Millischer, R-J., and Rusch, G. M., "Acute, Subchronic, and Developmental Toxicity and Genotoxicity of 1,1,1-Trifluoroethane (HFC-143a), *Fundamental and Applied Toxicology,* 31,200-9, 1996.