SETTING ACUTE EXPOSURE LIMITS FOR THE HALOTRON® BrX (2-BROMO-3,3,3-TRIFLUOROPROPENE) CLEAN AGENT ONBOARD AIRCRAFT USING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

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Physiologically based pharmacokinetic (PBPK) modeling for 2-bromo-3,3,3-trifluoropropene (2-BTP or BTP), trade named 'Halotron BrX', has been performed using an Environmental Protection Agency (EPA) approved model that was developed for halon alternatives used in fire suppression. The results provided are based on constant concentrations (NOAEL, LOAEL, and 5-min PBPK allowable) and variable air exchange rates in accordance with Federal Aviation Administration (FAA) methods for evaluating exposures onboard aircraft. Handheld extinguishers containing 3.75 Lb. net weight of Halotron BrX have undergone UL and FAA testing in order to replace the standard commercial aviation extinguishers that contain 2.5 Lb of halon 1211. The modeling performed in this report provides safe use guidance for the use of the 3.75 Lb Halotron BrX extinguisher onboard aircraft as well as general information that will be applicable to other sizes that may be commercialized.

Exposures to elevated levels of halon 1211, halon 1301, or their replacements may cause cardiac sensitization that can lead to arrhythmia. In order to establish appropriate guidelines to avoid this, a Physiologically Based Pharmacokinetic (PBPK) model has been developed for humans to estimate arterial blood concentrations in acute timeframes. The PBPK model was first developed for clean fire extinguishing agents that are utilized for total flooding applications (Vinegar et al. 2000; Vinegar and Jepson 2000). Clean agent total flooding systems are designed to distribute agent as evenly throughout a room as possible to achieve a specific design concentration of agent in order to extinguish a fire within the room. With this in mind, the PBPK model was initially developed to understand which airborne concentration levels would be considered safe based on predicted blood concentrations when personnel were inside of the room during a total flooding system discharge. The PBPK model includes a Monte Carlo method to account for the variability within the population. The results of the model are believed to create conservative guidelines for exposure to halons and their replacements.

Federal Aviation Administration (FAA) Advisory Circular 20-42D, *Hand Fire Extinguishers for use in Aircraft*, was the first effort to apply the PBPK model to streaming agents, which are defined as any agent exiting a single nozzle with the intent to provide a stream of agent onto a localized fire area. Handheld fire extinguishers, wheeled fire extinguishers, and Aircraft Rescue Fire Fighting (ARFF) systems using a handline embody the primary streaming application configurations. There are several reasons that the PBPK model is not typically applied to streaming agents, and include: 1) that the extinguisher may not be fully discharged, 2) operators of portable extinguishers are typically able to walk away from the fire zone, 3) discharge nozzles for streaming applications are not designed to vaporize agent completely as this limits

the throw range, and 4) halocarbon agent vapors are several times denser than air and quickly stratify (i.e., vapors will fall quickly to floor level). While it is possible to utilize the PBPK model to evaluate clean agents used for streaming applications, it is important to evaluate assumptions used to determination airborne agent concentrations.

In handheld extinguisher applications in which a room may be considered a confined space, defined as a room that has little ventilation and is difficult to exit, a common assumption is that the concentration of agent becomes uniformly distributed (or perfectly mixed) throughout the room. Per UL 2129, clean agent extinguishers listed by Underwriters Laboratories (UL) will contain the statement "Do not use in confined spaces less than 'X' cubic feet per extinguisher." In these confined spaces, UL's acceptable exposure level is based on a calculation using: 2) the complete and instantaneous discharge of a single extinguisher, 2) the Lowest Observable Adverse Effect Level (LOAEL) concentration for the agent based on a cardiac sensitization study, 3) neat agent only (i.e., exposure to the agent alone in the absence of any fire; agent decomposition products and smoke and combustion products are not considered), 4) an ambient temperature equal to the maximum operating temperature for the extinguisher [120°F (49°C)], and 5) an ambient pressure of 1 atm.

A similar confined space calculation has been performed in the past for halons as used onboard aircraft (Eklund 1983). The 1983 Eklund report assumed perfect mixing, referred to as 'perfect stirring', of the halons throughout the cabin when an extinguisher is discharged. This perfect stirrer assumption was evaluated for both non-ventilated and ventilated scenarios. For perfect stirring with ventilation, the initial concentration of agent drops in accordance with the cabin ventilation rate, following an exponential decay rate where each air exchange reduces the concentration by 63 percent. Whether a halon exposure was acceptable in this 1983 report was based on an acceptable maximum dose for each halon. For halon 1211, this dose was set at 4 percent-minutes. An exposure of 4 percent for 1 minute was assumed to be the same as an exposure of 1 percent for 4 minutes. With a LOAEL of 1% for halon 1211, it is unlikely that either of these scenarios would be acceptable when using the PBPK modeling method, although the latter exposure would be more acceptable than the former. PBPK modeling has shown that high agent concentrations can rapidly be absorbed into the bloodstream while lower agent concentrations may equalize to a bloodstream level that can be tolerated for longer periods of time. Typically, the longest exposure time considered in a PBPK model is 5 minutes as the second phase of the cardiac sensitization test is 5 minutes in length and it is within this portion of the test that typically a response occurs. From a fire protection industry perspective, it is envisioned that individuals exposed to a discharge of agent would be able to move to safer areas within 5 minutes. Even onboard aircraft, standard airplane procedures require relocation of passengers to allow access to the fire source and allow safe firefighting (FAA AC 120-80), which is helpful in limiting exposure.

FAA Advisory Circular 20-42D provides exposure guidelines based on PBPK modeling for halon 1211 and its replacements that are approved for use onboard aircraft. Advisory Circular 20-42D, Section 4(b)(3) states "*Actual concentrations encountered by occupants may be significantly lower than would be encountered if there was perfect mixing depending on agent stratification, air distribution, air flow, and geometry of a particular aircraft/aircraft compartment and may be adjusted accordingly*." Section 4(b)(4) indicates that the FAA will release a report that will further address agent stratification/localization. That report was published as DOT/FAA/TC-14/50, March 2015, which found benefit in stratification to lower airborne concentrations and provides methodology on how to determine stratification multiplication factors for aircraft. Multiplication factors that are developed may be applied to the values in Table 3 below. Measured airborne concentration test data from existing reports documenting effective air exchange rates are also summarized in Colton and Nay 2005. The findings from that report indicated that halon 1211

discharge concentrations tended to follow an effective air exchange rate, in minutes per air exchange, 72 to 76% less than the perfect stirrer air exchange rate.

In the absence of available agent stratification/localization guidance, Advisory Circular 20-42D provides exposure guidance based on a calculation using: 1) a perfect stirrer assumption, 2) the complete and instantaneous discharge of a single extinguisher, 3) neat agent only (i.e., exposure to the agent alone in the absence of any fire; agent decomposition products and smoke and combustion products not included), 4) a cabin temperature of 70°F (21°C), and 5) a pressure altitude based on in-flight pressurization conditions. Using these assumptions, the standard 2.5 Lb halon 1211 extinguisher was determined to not to be safe onboard general aviation aircraft sizes, where it has a long history of safe use. By applying an additional correction to the perfect stirrer model for agent stratification/localization, halon 1211 again becomes safe for general aviation. This more realistic scenario is useful to understand the safe use of halon 1211 and to evaluate halon 1211 alternatives.

METHODS

Target Arterial Concentrations of Chemical in Blood

The acceptable arterial concentration for an agent is measured at 5 minutes in dogs exposed to the agent at the Lowest Observable Adverse Effect Level (LOAEL) determined by a cardiac sensitization test. This arterial concentration as measured in dogs serves as the target/acceptable arterial concentration for modeling of acceptable exposures for humans. Out of a group of dogs exposed to each chemical, the lowest steady state measured 5-minute value was taken as the target arterial concentration for use in modeling human exposure. The Huntingdon Life Sciences 1998 and Vinegar et al. 2000 reports were reviewed to ensure consistency of selection methodology of the target arterial concentration with the various agents that have been modeled in the past. The selection methodology for halon 1301 was not reviewed as it was not apparent where the values were referenced from; Vinegar et al. 2000 states that halon 1301 values are contained in Huntingdon Life Sciences 1998, but *in fact* halon 1301 is not contained in that study. The arterial blood concentrations for individual animals in the Huntingdon Life Sciences 1998 report was reviewed against the values used in the Vinegar et al. 2000 report for HFC-236fa, HFC-227ea, HFC-125 and CF_3I.

The LOAEL for Halotron BrX is 1.0% (2002 Huntingdon Life Sciences). The acceptable/target arterial blood concentration for Halotron BrX is 30.6 mg/L (Huntingdon Life Sciences 2013).

Physiologically Based Pharmacokinetic Model

The human PBPK model used in this work is described in the Vinegar et al. 2000 and Vinegar and Jepson 2000 reports and is the methodology approved by the EPA for halon alternatives. Vinegar et al. 2000 states that the PBPK model used for the fire extinguishing industry "differs from the more traditional PBPK model in that it includes a respiratory-tract compartment containing a deadspace region and a pulmonary exchange area. It was used successfully to simulate the pharmacokinetics of halothane, isoflurane, and desflurane, which are structurally similar to many of the chemicals being considered as halon replacements. The pulmonary exchange area has its own airspace, tissue, and capillary subregions."

Tissue volumes, blood flows, and ventilation rates for humans are shown in Table 1.

Partition Coefficients

The primary driver for the PBPK model is the blood:air partition coefficient and due to its importance, measurements with human blood were used to determine this value. The tissue:air partitions coefficients are based on rat data, which is standard and has been used for other agents (Vinegar et al. 2000). The human and rat partition coefficients used for Halotron BrX as inputs to the PBPK model were measured by Battelle, Pacific Northwest Division (2013 Battelle) and are shown in Table 2.

Monte Carlo Simulations

In order to consider the variability in a population, Monte Carlo simulations were run with 10,000 iterations. Each model run sampled randomly from the designated distribution for each of the model parameters (Tables 1 and 2). Monte Carlo simulations were performed using acslX simulation software (AEgis Technologies), version 3.0.2.1, operating under 64-bit Windows 7 Enterprise (Microsoft Corp.), on a Dell Precision M4500.

Table 1. Parameter Distributions for the Monte Carlo Analysis

Parameters		Means	CV	Upper Bound	Lower Bound	Distribution
Plasma flows (fraction of cardiac output)						
QPC	Alveolar ventilation (L/h/kg)	17.4	0.8			Lognormal
QCC Cardiac output (L/h/kg) = QPC						
QFC	Fat	0.029	0.30	0.042	0.016	Normal
QGC	Gut	0.219	0.33	0.364	0.075	Normal
QLC	Liver	0.089	0.32	0.147	0.030	Normal
QSC	Slowly perfused tissues	0.202	0.30	0.384	0.020	Normal
QRC Richly perfused tissues = 1.0 – QSC – QLC – QFC – QGC						
Tissue volumes (fraction of body weight)						
BW	Body weight (kg)	70	0.26	97.3	42.7	Normal
VFC	Fat	0.215	0.24	0.409	0.022	Normal
VGC	Gut	0.022	0.15	0.035	0.0088	Normal
VLC	Liver	0.027	0.25	0.043	0.011	Normal
VRC	Richly perfused tissues	0.041	0.30	0.066	0.016	Normal
VSC Slowly perfused tissues = 0.88 – VFC – VGC – VLC – VRC						

Table 2. Partition Coefficient (lognormal distribution) Input Values

Parameters	(geometric mean ± geometric standard deviation)			
PB	blood/air	0.21^{H}	±	1.86
PF	fat/air	15.74^{R}	±	1.07
PL	liver/air	3.43^{R}	±	1.15
PR	richly perfused tissues/air	3.43^{R}	±	1.15
PS	slowly perfused tissues/air	1.80^{R}	±	2.60

Note. Superscripts: H, human; R, rat.

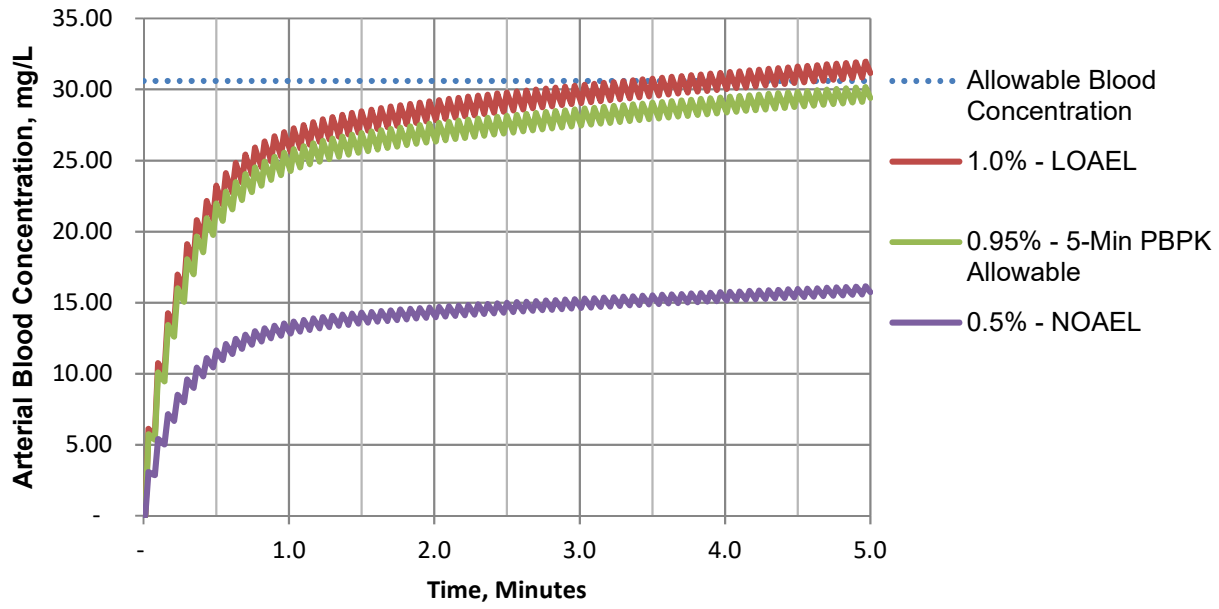
MODEL RESULTS

Constant Concentrations

PBPK model simulations using a constant airborne agent concentration are shown in Figure 1. Each plot in Figure 1 represents the mean arterial blood concentration plus normally distributed two standard deviations for a 10,000-iteration Monte Carlo simulation. The mean arterial concentration plus two standard deviations accounts for 97.5% of the population. This is to say that in 97.5% of the population, if exposed to the agent concentration shown in Figure 1, some individuals in that population would have arterial blood concentrations that would just reach the target arterial concentration at the time the model simulation reaches the target.

As depicted in Figure 1, the maximum allowable 5-minute exposure level for Halotron BrX has been determined to be 0.95% vol/vol.

Figure 1. PBPK 'Mean+2SD' Plots For Constant Concentration



Ventilated Concentrations

The FAA method is described in DOT/FAA/AR-08/3, *Guidelines for Safe Use of Gaseous Halocarbon Extinguishing Agents in Aircraft*, and determines uptake and removal constants from available PBPK modeling. The FAA method of simulating the PBPK model was not used to create the acceptable concentrations for the ventilation curves for Halotron BrX, instead actual PBPK model runs utilizing the Monte Carlo method (10,000 iterations) were conducted using perfect stirrer ventilation curves, as described in Eklund 1983, and increasing the initial agent concentration until modeled arterial blood levels met the target arterial concentration of 30.6 mg/L. Figure 2 provides examples of the perfect stirrer concentration decay curves with varying air exchange rates.

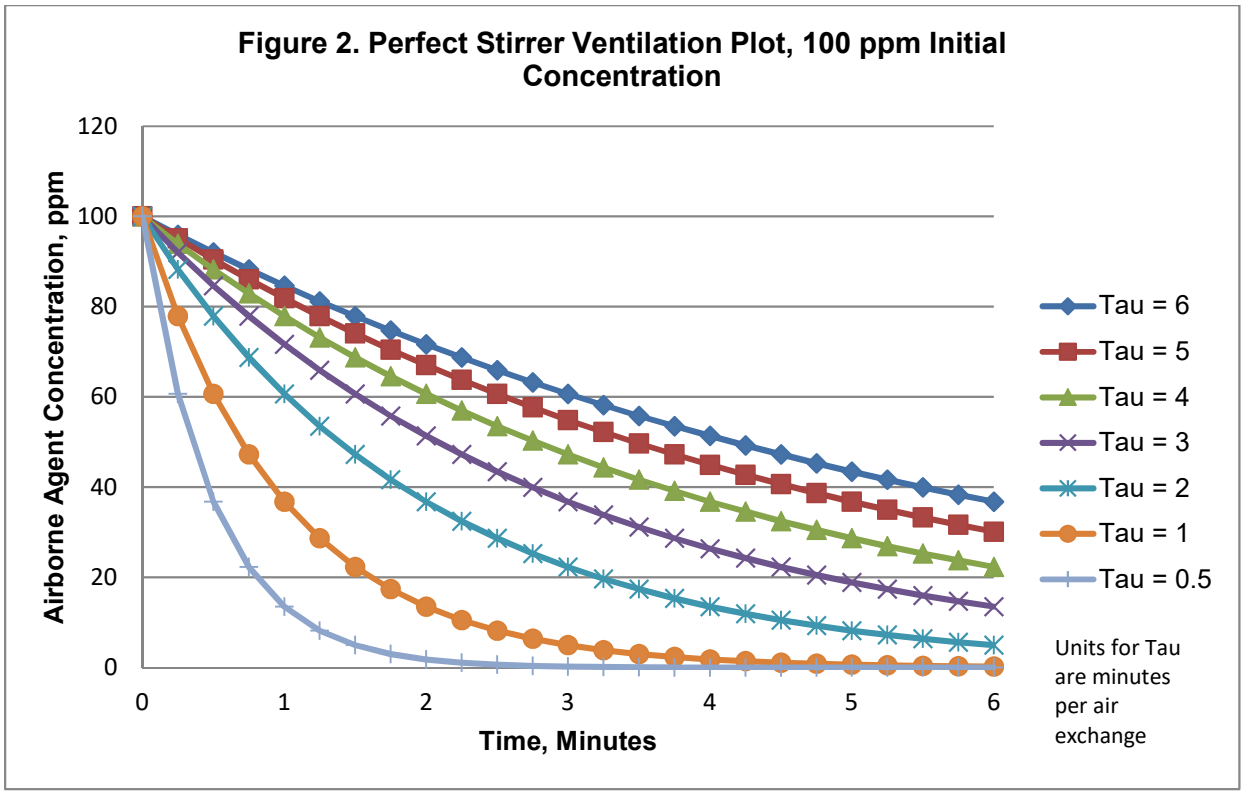


Figure 3 depicts the PBPK model results for acceptable Halotron BrX concentrations at various effective air exchange rates (tau). Table 3 translates these results into maximum safe agent weight per volume for various aircraft ventilation rates, with calculations based on Equation 18 in AC20-42D. The specific volume of the vapor was calculated using the critical pressure and temperature values measured (Ihmels et al. 2017) and the Redlich-Kwong equation of state (Hicks et al. 2012). Table 4a and 4b provides the PBPK model results in a format that matches that used by the FAA in AC20-42D. Table 5 provides the minimum compartment volumes based on a 3.75 Lb net agent weight Halotron BrX extinguisher.

In addition to the multiplication factors provided in Table 4b for ventilated aircraft cabins, the DOT/FAA/AR-08/3 report contains a multiplication factor based on assuming one may move away from a discharge in an unventilated cabin to a fresh air location within 30 seconds. The multiplication factor for this is based on the target arterial blood concentration divided by the PBPK-derived blood concentration at 30 seconds when modeling a constant concentration at the agent's 5-minute PBPK allowable concentration. At a constant concentration of 0.95%, the 5-minute PBPK allowable concentration, the arterial blood concentration is 21.96 mg/l at 30 seconds. Dividing the target arterial blood concentration of 30.6 mg/l by this results in a multiplication factor of 1.39.

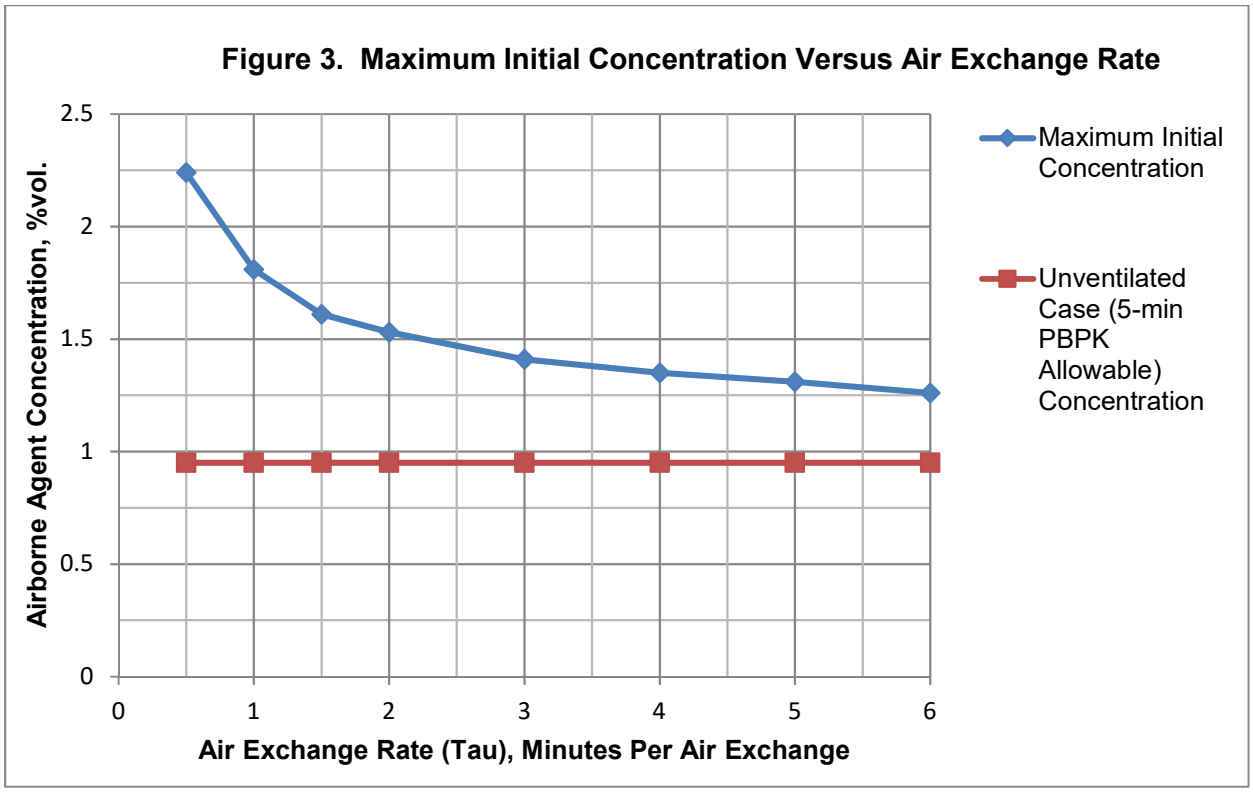


Table 3. PBPK Modeling Results for Onboard Aircraft [1,2]

Effective Ventilation Rate, Tau (minutes per air exchange)	Acceptable Initial Concentration, %vol.	Pressurized Aircraft, Maximum Allowable lb/ft^3	Unpressurized Aircraft at 12,500 ft, Maximum Allowable lb/ft^3	Unpressurized Aircraft at 14,000 ft, Maximum Allowable lb/ft^3	Unpressurized Aircraft at 18,000 ft, Maximum Allowable lb/ft^3	Unpressurized Aircraft at 25,000 ft, Maximum Allowable lb/ft^3
0.5	2.24	0.00799	0.00670	0.00632	0.00537	0.00399
1	1.81	0.00642	0.00539	0.00508	0.00432	0.00321
1.5	1.61	0.00570	0.00479	0.00451	0.00383	0.00285
2	1.53	0.00542	0.00454	0.00428	0.00364	0.00270
3	1.41	0.00498	0.00418	0.00394	0.00335	0.00249
4	1.35	0.00477	0.00400	0.00377	0.00321	0.00238
5	1.31	0.00463	0.00388	0.00366	0.00311	0.00231
6	1.26	0.00445	0.00373	0.00352	0.00299	0.00222
unventilated	0.95	0.00334	0.00281	0.00264	0.00225	0.00167

1. Conditions for Pressurized aircraft are 70°F and 8,000 ft
2. Conditions for unpressurized Aircraft are 70°F and altitude as listed in this table

Table 4a. PBPK Modeling Results In FAA Data Format – Maximum Safe W/V (lbs/ft^3) [1,2,3]

Sea Level (For Info Only)	Pressurized Aircraft (8k ft. CPA)	Unpressurized Aircraft			
		12.5k ft.	14k ft.	18k ft.	25k ft.
0.00436	0.00324	0.00272	0.00256	0.00218	0.00162

1. Conditions for Pressurized aircraft are 70°F and 8,000 ft.
2. Conditions for unpressurized Aircraft are 70°F and an altitude as listed in this table.
3. For unventilated compartments where egress can be performed within 30 seconds, a multiplication factor of 1.39 may be applied to the values in this table.

Table 4b. PBPK Modeling Results In FAA Data Format – Multiplication Factors[1,2]

Effective Ventilation Rate, Tau (minutes per air exchange)	0.5	1	1.5	2	3	4	5	6	>6
Multiplication Factors ($MF_{ventilated}$) for Ventilated Compartments	2.39	1.92	1.71	1.62	1.49	1.43	1.38	1.33	1.00

1. Multiplication factors may be applied to the Maximum Safe W/V in Table 4a, resulting in higher safe-use concentrations in ventilated compartments where the air change time is known.
2. Multiplication factors are derived from dividing the ventilated maximum allowable lb/ft^3 by that for unventilated condition in Table 3.

Table 5. Minimum Cabin Volume Requirements for 3.75 Lb Halotron BrX Extinguisher Onboard Aircraft [1,2,3]

Effective Ventilation Rate, Tau (minutes per air exchange)	Pressurized Aircraft, Minimum Volume Required, ft^3	Unpressurized Aircraft at 12,500 ft, Minimum Volume Required, ft^3	Unpressurized Aircraft at 14,000 ft, Minimum Volume Required, ft^3	Unpressurized Aircraft, at 18,000 ft, Minimum Volume Required, ft^3	Unpressurized Aircraft at 25,000 ft, Minimum Volume Required, ft^3
0.5	470	560	594	699	940
1	584	696	738	869	1169
1.5	658	784	831	979	1317
2	692	825	876	1031	1387
3	752	897	951	1120	1506
4	786	937	994	1170	1574
5	811	966	1025	1206	1623
6	843	1005	1066	1255	1688
unventilated	1122	1337	1419	1669	2246

1. Conditions for Pressurized aircraft are 70°F and 8,000 ft
2. Conditions for unpressurized Aircraft are 70°F and altitude as listed in this table
3. This chart is based on an Amerex prototype extinguisher which was tested at UL and successfully passed the fire performance tests required by AC 20-42D. This prototype extinguisher has a net agent weight of 3.75 lb. of Halotron BrX and would replace a UL 5B:C rated halon 1211 extinguisher for onboard aircraft use. This chart assumes that the entire extinguisher is discharged under perfect stirrer assumptions. Future Halotron BrX extinguishers for this application might vary in net agent weight.

CONCLUSION

This report presents PBPK modeling for the Halotron BrX clean agent under exposures of both constant concentration and variable concentration, using the perfect stirrer assumption with and without the benefit of ventilation. The method used to develop this data is based on EPA accepted models and FAA advisory material and reports. The 5-minute allowable concentration was determined to be 0.95%, just slightly lower than the 1.0% LOAEL for the agent. When applying this data to handheld fire extinguisher applications, perfect stirrer assumptions may result in overestimations of nose level concentrations for individuals seated or standing within the protected volume, whether it is within an office building or aircraft cabin. The FAA has released additional guidance for developing stratification and localization multiplication factors which take into account the higher relative vapor density of halon replacements as compared to the cabin air density, resulting in lower airborne concentrations at or above seated nose level than predicted by the perfect stirrer assumption. The methodology provided in DOT/FAA/TC-14/50, *Stratification and Localization of Halon 1211 Discharged in Occupied Aircraft Compartments,* may be used to create stratification and localization multiplication factors for specific aircraft and applied to the data within this report to provide more accurate exposure scenarios.

REFERENCES

Battelle 2013, *Determination of Tissue to Air Partition Coefficients for 2-bromo-3,3,3-trifluoropropene (Halotron BrX)*, Battelle, Pacific Northwest Division, Project Number 64197, April 2013, Final Report.

Colton, Bradford A. and Nay, Angela, 2005, *Evaluation of Calculation Methodologies for the Safe Use of Clean Agents Onboard Aircraft*, 2005 Halon Options Technical Working Conference proceedings.

Eklund, Thor I., 1983, *Analysis of Dissipation of Gaseous Extinguisher Agents in Ventilated Compartments*. DOT/FAA/CT-83/1. May 1983. Final Report.

FAA Advisory Circular 20-42D, *Hand Fire Extinguishers for use in Aircraft.* Federal Aviation Administration. 14 Jan 2011.

FAA Advisory Circular 120-80, *In-Flight Fires.* Federal Aviation Administration. 8 Jan 2004.

Huntingdon 1998. *HFC 236fa, HFC 227ea, HFC 125 and CF3I. An Inhalation Study to Investigate the Blood Levels of Inhaled Halocarbons in the Beagle Dog*. Prepared by Huntingdon Life Sciences Ltd, England. Huntingdon Report IFP 001/984370. Submitted under subcontract to ICF Incorporated, Washington DC, under U.S. EPA contract 68-D5-0147, work assignment 2-09.

Huntingdon 2002. *Agent 873, An Inhalation Study to Investigate The Cardiac Sensitisation in The Beagle Dog.* Prepared by Huntingdon Life Sciences Ltd, England. Huntingdon. Study AAS 001/014630. 16 Sept 2002.

Hicks, Tyler, and Nicholas Chopey. 2012. *Handbook of Chemical Engineering Calculations*, Fourth Edition. McGraw Hill Professional.

Huntingdon 2013. *2-bromo-3,3,3-trifluoropropene: Measurement of Arterial Blood Levels Following Inhalation Administration to Beagle Dogs.* Prepared by Huntingdon Life Sciences Ltd, England. Study WAG0016, 4 September 2013.

Ihmels, Christion et al. *Experimental Critical Data and Freezing Point for Halotron BrX (BTP) (2-bromo-3,3,3-trifluoropropene)*. LTP (Laboratory for Thermophysical Properties) GmbH, Report for American Pacific Corporation. October 6, 2017.

Speitel, Louise C. and Richard E. Lyon. *Guidelines for Safe Use of Gaseous Halocarbon Extinguishing Agents in Aircraft.* Federal Aviation Administration. DOT/FAA/AR-08/3. August 2009. Final Report.

Speitel, Louise C. *Stratification and Localization of Halon 1211 Discharged in Occupied Aircraft Compartments.* Federal Aviation Administration. DOT/FAA/TC-14/50. March 2015. Final Report.

UL 2129. *Halocarbon Clean Agent Fire Extinguishers. Underwriters Laboratories Inc.* Second Edition. February 28, 2005.

Vinegar, A., Jepson, G.W., Cisneros, M., Rubenstein, R., and Brock, W.J., 2000, *Setting Safe Acute Exposure Limits for Halon Replacement Chemicals Using Physiologically Based Pharmacokinetic Modeling*, Inhalation Toxicology 12, 751-763.

Vinegar, A., and Jepson, G., 2000, *Toxicological Assessment of Human Health Consequences Associated with Inhalation of Halon Replacement Chemicals; Section I: Physiologically- based Modeling of Halon Replacements for Human Safety Evaluations*, Final Report to the Strategic Environmental Research and Development Program, Air Force Research Laboratory, Wright Patterson Air Force Base, OH.