

**PHYSIOLOGICALLY BASED MODELING OF HALON REPLACEMENTS FOR HUMAN  
SAFETY EVALUATION**

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## GENERAL INTRODUCTION

This section of the final report contains several parts. The first part describes the necessary requirements for enabling one to conduct simulations for assessing safe exposure times. These requirements involve chemical specific data necessary for running the model and biological data collection for validating the model. The second part demonstrates the use of the model in setting acute exposure limits for Halon 1301 and four potential replacement candidates: CF<sub>3</sub>I, HFC-125, HFC-227ea, and HFC-236fa. This part has been submitted to the journal *Inhalation Toxicology* and has been accepted for publication. The third part makes use of published data on releases of Halon 1301 and Halon 1211 in aircraft. These data are used to demonstrate whether in the scenarios presented there would be any potential hazard for individuals being exposed under the stated conditions. This part will be submitted to the journal *Aviation, Space, and Environmental Medicine*. Finally, the fourth part presents a listing of the actual code for the physiologically based pharmacokinetic model used for simulating short-term exposures to halogenated hydrocarbons. This code, as it stands, is written to run with the Advanced Continuous Simulation Language package called ACSL-TOX. The distributor for this software is Pharsight Corporation, Mountain View, CA.

Requirements for Conducting Monte Carlo Simulations for Establishing  
Safe Exposure Times for Potential Halon Replacement Agents

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The procedures for determining safe exposure time involve using a physiologically based pharmacokinetic (PBPK) model to determine the arterial blood concentration associated with a potential human exposure to a chemical agent and comparing it with the arterial blood concentration attained by a dog exposed to that agent after five minutes of exposure at the lowest observable adverse effect level (LOAEL) for cardiac sensitization (Vinegar and Jepson, 1996; Vinegar et al., (in press)). In order to make these determinations for any chemical agent the following chemical specific information is needed: 1 - cardiac sensitization LOAEL determined in beagle dogs, 2 - arterial concentration measured after five minutes of exposure of beagles to the LOAEL concentration, 3 - partition coefficients of the chemical in blood, liver, fat, and muscle from rat, 4 - metabolic constants (determined from gas uptake studies using rats), 5 - partition coefficients of the chemical in human blood (partitions measured using human liver, fat, and muscle would be desirable but not necessary). A validated PBPK model capable of tracking ventilation on a breath-by-breath basis is needed for performing the simulations (Vinegar et al., 1998). The model must be capable of running under a system that allows the performance of Monte Carlo simulations.

#### 1 – Cardiac sensitization LOAEL determined in beagle dogs.

The standard for evaluating exposure to agents that might potentially evoke a cardiac sensitization response is the cardiac sensitization test performed in beagle dogs (Dodd and Vinegar, 1998). The results of this test are expressed in terms of the lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL). The LOAEL value is used as the target value for the PBPK assessment of safe exposure time. One of the problems is how far apart the LOAEL and NOAEL values are from each other. This is a function of the step size in concentration used for the cardiac sensitization test. The expense of the test often prevents a small increment from being used.

#### 2 – Arterial concentration measured after five minutes of exposure of beagles to the LOAEL concentration.

The arterial concentration attained by a beagle after five minutes of exposure is taken as the target with which to compare a human exposure simulation. Attaining this information requires that studies be done with beagles that have been cannulated for the sampling of arterial blood. At least six beagles should be exposed, without epinephrine challenge, at three exposure concentrations for 10 minutes at each exposure. The concentrations should be the LOAEL, approximately 25% above the LOAEL, and approximately 25% below the LOAEL. Blood samples should be taken at least at 1, 2, 5, 7, and 10 minutes. The five minute time point is most critical as it provides the target arterial concentration. Multiple sample points and exposure concentrations are necessary to check the reliability of the data obtained. The volatility and low biological tissue solubility of these chemicals produce challenges for accurate data collection and analysis. Prior to performing the exposures, tests should be done on the material to be used for arterial cannulation. The materials used in the manufacture of cannulas often absorb chemicals. A cannula that is inert with respect to one chemical may not be so for another. Furthermore, even if the solubility is low in the cannula, the tissue solubility may be in the same order of magnitude or lower. Therefore, as blood is drawn it may give up chemical to or take up chemical from the cannula depending on the concentration gradient. Sampling at multiple time points gives

information about expected pharmacokinetic behavior. If the data don't conform to expected behavior, the reliability of the five-minute point is called into question. Performing exposures at three concentrations also allows observation of expected relationships in blood concentration vs. time of sampling vs. exposure concentration. It is important that the laboratory performing these studies be aware of and know how to conduct experiments in light of these problems.

3 - Partition coefficients of the chemical in blood, liver, fat, and muscle from rat.

One of the basic chemical specific requirements for the PBPK model is solubility in tissues. Standard techniques have been published for determining solubility or partition coefficients of volatile chemicals (Gargas et al., 1989). However, this method depends upon a difference measurement as part of the methodology. Partition coefficients of chemicals of low solubility, such as many of the halon replacements candidates, can not be accurately measured by this method. Instead, a method using direct measurements such as the direct tonometry method described by Eger (1987) and Lerman et al. (1985 and 1986) must be used instead. A modification of this method is currently being addressed in our laboratory. The published method uses homogenized tissue. We find that non-uniform homogenization and sticking of tissue to glass with resulting loss results in variable data. Our modification uses whole tissue pieces.

4 - Metabolic constants (determined from gas uptake studies using rats).

The other chemical specific data needed for running a PBPK model are the metabolic constants. These are obtained using a gas uptake method as described by Gargas et al. (1986). Fortunately, most of the proposed halon replacements are relatively inert and have extremely low to no measurable metabolism. Furthermore, even with moderate metabolism, there is no noticeable effect on the outcome of short-term simulations required for modeling of cardiac sensitization.

5 - Partition coefficients of the chemical in human blood (partitions measured using human liver, fat, and muscle would be desirable but not necessary).

The most sensitive parameter for determination of the correct blood concentration is the blood partition coefficient. Therefore since the model is being used to simulate human exposures, human blood partition coefficients must be measured. For short term simulations the model is almost insensitive to differences in the other partitions. Since human blood partitions often differ by as much as two-fold from rat blood partitions it is necessary to make the human blood measurements. Other tissue partitions tend not to differ as much. However, if human tissue is available then the tissue partitions should be determined. Statements concerning methodology under 3 above, apply to this section also.

Model validation.

After obtaining partition coefficients and determining metabolic constants for a chemical it is necessary to collect data to demonstrate that the model is capable of simulating exposures to the chemical. Since the initial model is constructed using rat partition coefficients and rat metabolic constants, pharmacokinetic data should be collected from at least six rats that have been exposed by inhalation to the chemical. Typically, the exposure should be for an hour with an hour post-exposure for sampling during the off gassing of the chemical. Validation using only blood requires a minimum number of animals since blood can be serially sampled. However, validation for tissue concentrations requires serial sacrificing of animals during and after the exposure. The total number of animals would then be six times the number of time points sampled (minimally five during exposure and five post-exposure). Only seldom are there human data for a direct validation of the human model. For new agents the likelihood of obtaining human data is negligible.



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# SETTING SAFE ACUTE EXPOSURE LIMITS FOR HALON REPLACEMENT CHEMICALS USING PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING

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Most proposed replacements for Halon 1301 as a fire suppressant are halogenated hydrocarbons. The acute toxic endpoint of concern for these agents is cardiac sensitization. An approach is described which links the cardiac endpoint as assessed in dogs to a target arterial concentration in humans. Linkage was made using a physiologically based pharmacokinetic (PBPK) model. Monte Carlo simulations, which account for population variability, were used to establish safe exposure times at different exposure concentrations for Halon 1301 (bromotrifluoromethane), CF<sub>3</sub>I (trifluoroiodomethane), HFC-125 (pentafluoroethane), HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane), and HFC-236fa (1,1,1,3,3,3-hexafluoropropane). Application of the modeling technique herein described not only makes use of the conservative cardiac sensitization endpoint, but also uses an understanding of the pharmacokinetics of the chemical agents to better establish standards for safe exposure. The combined application of cardiac sensitization data and physiologically based modeling provides a quantitative approach, which can facilitate the selection and effective use of halon replacement candidates.

**Key Words:** Cardiac Sensitization, Halon Replacement Chemicals, Physiologically Based Pharmacokinetic Modeling, Safe Exposure Limits, Humans, Halon 1301, CF<sub>3</sub>I, HFC-125, HFC-227ea, HFC-236fa

## INTRODUCTION

Many, if not most, of the proposed replacements for Halon 1301 in fire suppression applications are halogenated hydrocarbons. As a group, acute exposure to the halogenated hydrocarbons has been associated with the ability to reversibly increase the sensitivity of the heart to epinephrine (Reinhardt, 1971; Mullin, 1979). Consequently cardiac sensitization has been of keen interest to regulatory authorities for setting guidelines for human exposure to these agents because the use of these agents involves potentially acute high concentration exposure. Vinegar and Jepson (1996) outlined a procedure for setting exposure limits for halon replacement chemicals using physiologically-based pharmacokinetic (PBPK) modeling to predict blood levels associated with the potential onset of a cardiac sensitization response. The approach outlined by Vinegar and Jepson links the laboratory data that are generated from a routine cardiac sensitization toxicity test in dogs to relevant events occurring for humans exposed to potential cardiac sensitizers. The LOAEL (lowest observed adverse effect level) for cardiac sensitization in beagle dogs is determined by inhalation exposure to the chemical of interest and challenging intravenously with epinephrine levels well above physiological levels. Therefore, the test is considered conservative and the resulting LOAEL is used without any correction factors. The epinephrine challenge is given five minutes into the exposure. That the effect is due to the peak concentration of chemical rather than area under the curve (AUC) has been established (Reinhardt et al., 1971). Thus, the arterial concentration at five minutes is the target arterial concentration or dose metric that is associated with the potential for cardiac sensitization. Different exposure concentration scenarios can then be modeled using the PBPK model. The time required for an arterial concentration to reach the LOAEL target arterial concentration could be considered the safe (i.e., protective) exposure duration.

Variability in human physiological parameters should be considered in determining safe exposure times. Others have used Monte Carlo simulations to describe the effect of interindividual variability on the output of PBPK models (Bois et al., 1991; Bois and Paxman, 1992; Clewell and Jarnot, 1994; Cronin et al., 1995; Farrar et al., 1989, Hetrick et al., 1991; Portier and Kaplan, 1989; Simon, 1997; Spear et al., 1991; Thomas et al., 1996a&b; Yang et al., 1995). However, none of these studies involved predicting short-term (0 to 5 min) effects. This paper describes the methods developed for determining short-term safe exposure times for halon replacement candidates using Monte Carlo simulations to account for variability and presents the results for Halon 1301 (bromotrifluoromethane) and four potential replacement chemicals CF<sub>3</sub>I (trifluoroiodomethane), HFC-125 (pentafluoroethane), HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane), and HFC-236fa (1,1,1,3,3,3-hexafluoropropane).

## METHODS

### *Target Arterial Concentrations of Chemical in Blood*

Arterial concentrations measured at five minutes in dogs exposed to the LOAEL concentration served as the target arterial concentrations for modeling a safe exposure for humans. Out of a group of dogs exposed to each chemical, the lowest measured five-minute value was taken as the target arterial concentration for use in modeling human exposure. The target arterial concentrations used were: Halon 1301, 25.7 mg/L; CF<sub>3</sub>I, 12.9 mg/L; HFC-125, 47.8 mg/L; HFC-227ea, 26.3 mg/L; and HFC-236fa, 90.3 mg/L (Huntingdon, 1998).

### *Physiologically Based Pharmacokinetic (PBPK) Model*

The human PBPK model used in this work was described by Vinegar et al. (1998) and differs from the more traditional PBPK model in that it includes a respiratory-tract compartment

containing a dead-space 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 air space, tissue, and capillary subregions. Respiration is described on a breath-by-breath basis. This more detailed lung description was necessary to successfully simulate pharmacokinetic data in the 0 to 1 min range as illustrated for halothane (Vinegar et al., 1998). Additional physiological compartments described in this model are liver, fat, lung, gut, slowly perfused and rapidly perfused tissues. All model compartments are perfusion limited and metabolism, if present, is assumed to occur in the liver. Tissue volumes, blood flows and ventilation rates for humans are shown in Table I.

#### *Chemical-Specific Model Parameters and Values*

Blood/air partitions were measured using human blood. In some cases human tissue partition coefficient data were available and in others only rodent data were available. Rodent metabolic rate constants were available for these chemicals, but none of them had human metabolism data. The assumption made for this work was that rat metabolism data can be extrapolated to humans using allometric scaling ( $[\text{body weight}]^{0.75}$ ). Variance from this assumption does not impact the work here because: (1) this group of chemicals shows as a general characteristic extremely slow metabolism (Creech et al., 1995a,b; Vinegar et al., 1995) and (2) metabolism has not demonstrated an effect on these short term (five minute) simulations even when moderate levels are incorporated into the model. Metabolism for all chemicals was set to zero except for  $\text{CF}_3\text{I}$  where the maximal velocity constant  $V_{\text{MAXC}} = 0.375$  for an allometrically scaled 1.0 kg animal and the Michaelis-Menten constant  $K_M = 0.1$ . Partition coefficients were determined using a

modification of a described tonometry method (Eger, 1987; Lerman et al., 1985; Lerman et al., 1986) and appear in Table II.

### *Monte Carlo Simulations*

In order to consider the variability in a population Monte Carlo simulations were run with 1000 iterations. Each iteration was sampled randomly from the designated distribution for each of the model constants (Tables I and II). Upper and lower bounds on normally distributed parameters were set at the  $\pm 3$  standard deviation levels. Monte Carlo simulations were performed using ACSL TOX simulation software (Pharsight Corp., Mountain View, CA) operating under Windows95 and WindowsNT (Microsoft Corp., Redmond, WA).

## RESULTS

Results of the simulations are shown graphically for each chemical (Figure 1-5). Each simulation line represents the mean arterial concentration plus two standard deviations for a 1000-iteration simulation of human exposure at a given concentration. The horizontal line represents the target arterial concentration, i.e., the lowest dog arterial concentration measured at five minutes exposure to the LOAEL. At lower exposure concentrations the target arterial concentration is not reached in the five-minute period. As exposure concentrations are increased the arterial concentrations begin to approach the target arterial concentration and do so sooner at higher exposure concentrations.

The same information is presented in tabular form (Table III-VII). Exposure concentration is presented in increments of 0.5% (0.05% for CF<sub>3</sub>I) and the time in minutes (up to 5) that a human can safely be exposed to that concentration is indicated.

## DISCUSSION

Currently, requirements for safe exposure design of Halon 1301 and potential replacement chemicals for use as total flooding agents in a fire-fighting scenario are specified as follows (U.S. EPA, 1994).

1. Design to NOAEL (cardiac sensitization in dog) where egress from an area cannot be accomplished within one minute
2. Up to LOAEL if egress can occur in 30 sec to 1 min
3. Above the LOAEL if egress can occur in less than 30 sec and area is normally unoccupied

These specifications do not take into consideration the pharmacokinetics of the agents and the relationship between the exposure concentration and the internal concentration actually associated with a cardiac event. Examination of Tables III-VII reveals interesting relationships between the cardiac sensitization LOAEL and time for safe human exposure. Exposure to HFC-125 can occur safely for at least five minutes at an exposure concentration of 11.5%, which is 1.5% above the LOAEL. Similarly, exposure to HFC-227ea can occur safely for at least five minutes at 10.5%, which actually is the LOAEL. However, the safe five minute exposure for HFC-236fa occurs at 12.5% which is 2.5% below the LOAEL, for CF<sub>3</sub>I occurs at 0.3% which is 0.1% below the LOAEL, and for Halon 1301 occurs at 5.5% which is 2.0% below the LOAEL.



Ultimately, the duration of safe exposure must be examined in relation to the concentration of agent needed to extinguish a fire. A comparison can be made between the concentration for safe five-minute exposure and the recommended design concentration of agent. HFC-125 with an 11.5% safe exposure concentration has a recommended design concentration of 10.0 to 11.0%. HFC-227ea with a 10.5% safe exposure concentration has a recommended design concentration of 7.0%. Thus, even though safe exposure to HFC-125 can occur above the LOAEL and to HFC-227ea only at the LOAEL, the difference between the safe exposure concentration and the recommended design concentration is only 0.5% for HFC-125 and 3.5% for HFC-227ea. Interestingly, Halon 1301 with a five-minute safe exposure concentration of 5.5%, 2.0% below the LOAEL, has a recommended design concentration of 5.0% which is only 0.5% below the safe exposure concentration. Halon 1301 has a long history of safe use, which points to the conservative nature of the cardiac sensitization endpoint, which ultimately determines the target arterial concentration, which in turn is used for determining safe exposure time.

The cardiac sensitization endpoint occurs as a result of the exposure of a chemical sensitizing the heart to an epinephrine challenge. The challenge is given to the dog after five minutes of exposure. Therefore, the increased level of sensitivity is due to the concentration of chemical at the heart at five minutes. It is this level attained after five minutes of exposure that is used as the target for simulations of human exposure to the chemical. Whenever the simulated human exposure indicates that the human arterial concentration approaches that of the target level the assumption is made that there can then be a potential for cardiac sensitization to occur in the exposed human.

In order to account for individual variability, Monte Carlo simulations were performed. The mean simulated arterial concentration plus two standard deviations, which is compared with the

target arterial concentration, accounts for 97.5% of the simulated population, i.e., in 97.5% of the population arterial concentration would reach the target arterial concentration at the time (or later) where the simulation reaches the target.

Furthermore, the target arterial concentration used for this assessment of safe exposure is determined in a conservative manner. Stressed exercising dogs reached a level of circulating epinephrine of about 0.4 µg/L (Buhler et al., 1978; Carriere et al., 1983; Keller-Wood et al., 1982; Young et al., 1985). The level of epinephrine used to challenge the dogs during a cardiac sensitization test ranges from 1.0 to 12.0 µg/kg body weight (Dodd and Vinegar, 1998). Since dogs have a total blood volume of about 8.2 percent body weight (Brown et al., 1997) the stated doses of epinephrine would result in concentrations of about 12 to 146 µg/L or 30 to 365 times the levels circulating under normal stressed physiological conditions. These are conservative estimates of the concentration that reaches the heart with an epinephrine challenge since the above calculation assumes that the epinephrine immediately dilutes throughout the whole blood volume. The actual dilution, between the site of injection into the cephalic vein and reaching the heart muscle through the coronary artery, takes place in about one fifth of the blood volume. This dilution is an estimate of the blood volume in the vasculature between the injection site and the arterial blood feeding the coronary arteries. It is an approximation using blood flow information from Leggett and Williams (1995) and Bischoff and Brown (1966). Concentrations reaching the heart through the coronary arteries would be five times higher than calculations above indicate (60 to 730 µg/L or 150 to 1825 times the circulating levels). It is recognition of the conservative nature of the cardiac sensitization test that allows the EPA to apply the LOAEL and NOAEL determined in the dog directly to humans without application of adjustment for a dog to human extrapolation.

The critical issue in applying any standard for safe exposure is the relationship between the effective concentration of agent necessary to extinguish a fire and the concentration that poses a potential threat for cardiac sensitization. Where the extinguishing concentration approaches the cardiac sensitization concentration the agent may still be approved for use as a fire extinguishant but only in areas that are normally unoccupied. For candidate agents where the extinguishing concentration is above the cardiac sensitization concentration there is reluctance by some to risk using the agent because of perceived potential for accidental exposure. An additional consideration is that many of these agents release halogen acids upon contact with heat. The toxicity of these acids is of concern. Levels of release can be reduced if the fire can be put out quickly, which can be done if higher concentrations of extinguishing agent are used.

Application of the modeling technique herein described not only makes use of the conservative cardiac sensitization endpoint, but also uses an understanding of the pharmacokinetics of the chemical agents to better establish standards for safe exposure. The combined application of cardiac sensitization data and physiologically based modeling provides a quantitative approach, which can facilitate the selection and effective use of halon replacement candidates.

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Table I - Parameter Distributions for Monte Carlo Analysis

<u>Parameters</u>		<u>Means</u> <sup>1</sup>	<u>CV</u> <sup>2</sup>	<u>Upper Bound</u>	<u>Lower Bound</u>	<u>Distribution</u>
Plasma Flows (fraction of cardiac output)						
QPC	Alveolar ventilation (L/hr/kg)	17.4	0.8			Lognormal
QCC	Cardiac output (L/hr/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					

<sup>1</sup>Mean values taken from Davis and Mapelson (1981) and Williams et al. (1996)

<sup>2</sup>Coefficients of variation taken from Thomas et al. (1996a)

Table II – Partition Coefficients (Lognormal Distribution) of Halon 1301 and Selected Replacement Agents (Geometric Mean ± Geometric Standard Deviation)

<u>Parameters</u>	<u>Halon 1301</u>	<u>CF<sub>3</sub>I</u>	<u>HFC-227ea</u>	<u>HFC-125</u>	<u>HFC-236fa</u>
PB <sup>1</sup>	0.062 <sup>H</sup> ± 1.057	0.410 <sup>H</sup> ± 1.118	0.033 <sup>H</sup> ± 1.033	0.074 <sup>H</sup> ± 1.081	0.106 <sup>H</sup> ± 1.053
PF <sup>2</sup>	0.771 <sup>H</sup> ± 1.164	9.014 <sup>R</sup> ± 1.145	0.347 <sup>R</sup> ± 1.541	0.533 <sup>R</sup> ± 1.334	0.678 <sup>R</sup> ± 1.104
PL <sup>3</sup>	0.145 <sup>H</sup> ± 1.085	0.192 <sup>R</sup> ± 1.380	0.031 <sup>R</sup> ± 1.965	0.062 <sup>R</sup> ± 1.381	0.106 <sup>R</sup> ± 1.075
PR <sup>4</sup>	0.145 <sup>H</sup> ± 1.085	0.192 <sup>R</sup> ± 1.380	0.031 <sup>R</sup> ± 1.965	0.062 <sup>R</sup> ± 1.381	0.106 <sup>R</sup> ± 1.075
PS <sup>5</sup>	0.159 <sup>R</sup> ± 1.498	0.239 <sup>R</sup> ± 1.180	0.021 <sup>R</sup> ± 5.889	0.070 <sup>R</sup> ± 1.230	0.091 <sup>R</sup> ± 1.067

<sup>1</sup>Blood/air

<sup>2</sup>Fat/air

<sup>3</sup>Liver/air

<sup>4</sup>Richly perfused tissues/air

<sup>5</sup>Slowly perfused tissues/air

<sup>H</sup>Human

<sup>R</sup>Rat

**Table III. Acceptable Human Exposure Times at Stated Concentrations for Halon 1301.**

Halon 1301 Concentration		Time (Minutes)*
% v/v	PPM	
6.0	60,000	5.00
6.5	65,000	1.33
7.0	70,000	0.59
7.5	75,000	0.42
8.0	80,000	0.35

\*Based on the 5-minute blood concentration of dogs exposed to Halon 1301 at the LOAEL of 7.5%

**Table IV. Acceptable Human Exposure Times at Stated Concentrations for CF<sub>3</sub>I**

CF <sub>3</sub> I concentration		Time (Minutes)*
% v/v	PPM	
0.30	3000	5.00
0.35	3500	4.30
0.40	4000	0.85
0.45	4500	0.49
0.50	5000	0.35

\*Based on the 5-minute blood concentration of dogs exposed to CF<sub>3</sub>I at the LOAEL of 0.4%

**Table V. Acceptable Human Exposure Times at Stated Concentrations for HFC-125.**

HFC-125 concentration		Time (Minutes)*
% v/v	PPM	
11.5	115,000	5.00
12.0	120,000	1.13
12.5	125,000	0.73
13.0	130,000	0.59
13.5	135,000	0.50

\*Based on the 5-minute blood concentration of dogs exposed to HFC-125 at the LOAEL of 10.0%

**Table VI. Acceptable Human Exposure Times at Stated Concentrations for HFC-227ea.**

<b>HFC-227ea concentration</b>		<b>Time (Minutes)*</b>
<b>% v/v</b>	<b>PPM</b>	
<b>10.5</b>	<b>105,000</b>	<b>5.00</b>
<b>11.0</b>	<b>110,000</b>	<b>1.13</b>
<b>11.5</b>	<b>115,000</b>	<b>0.60</b>
<b>12.0</b>	<b>120,000</b>	<b>0.49</b>

**\*Based on the 5-minute blood concentration of dogs exposed to HFC-227ea at the LOAEL of 10.5%**

**Table VII. Acceptable Human Exposure Times at Stated Concentrations for HFC-236fa.**

<i>HFC-236fa concentration</i>		<b>Time (Minutes)*</b>
<b>% v/v</b>	<b>PPM</b>	
<b>12.5</b>	<b>125,000</b>	<b>5.00</b>
<b>13.0</b>	<b>130,000</b>	<b>1.93</b>
<b>13.5</b>	<b>135,000</b>	<b>0.99</b>
<b>14.0</b>	<b>140,000</b>	<b>0.73</b>
<b>14.5</b>	<b>145,000</b>	<b>0.55</b>
<b>15.0</b>	<b>150,000</b>	<b>0.49</b>

**\*Based on the 5-minute blood concentration of dogs exposed to HFC-236fa at the LOAEL of 15.0%**

## Figure Legends

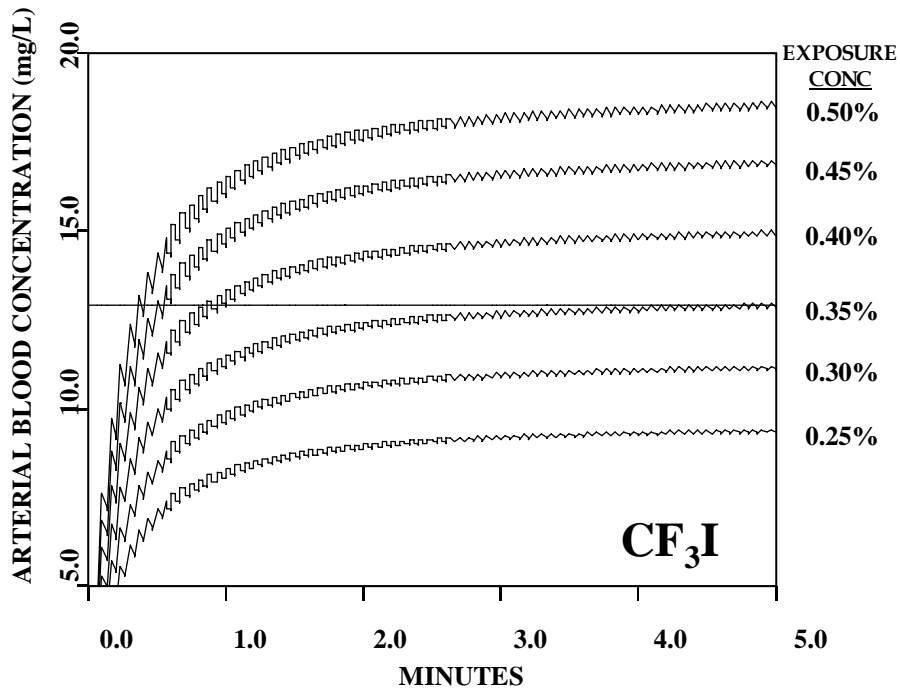
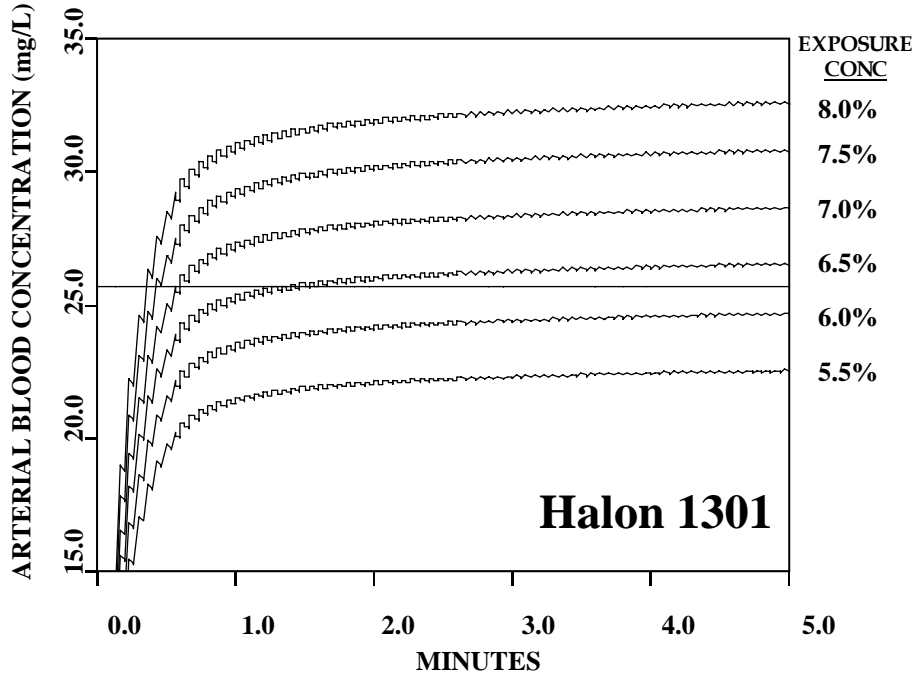
Figure 1 – Monte Carlo simulations of arterial concentration of humans exposed to Halon 1301 for five minutes at concentrations of 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0%. The horizontal line at 25.7 mg/L represents the lowest arterial blood concentration measured at five minutes in a group of six dogs exposed to Halon 1301 at the cardiac sensitization LOAEL of 7.5%.

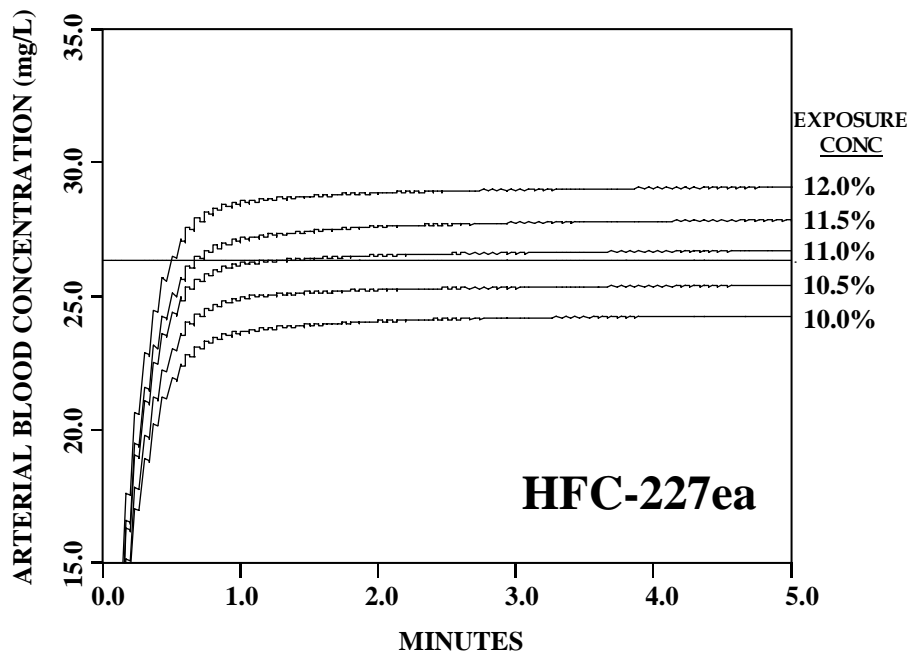
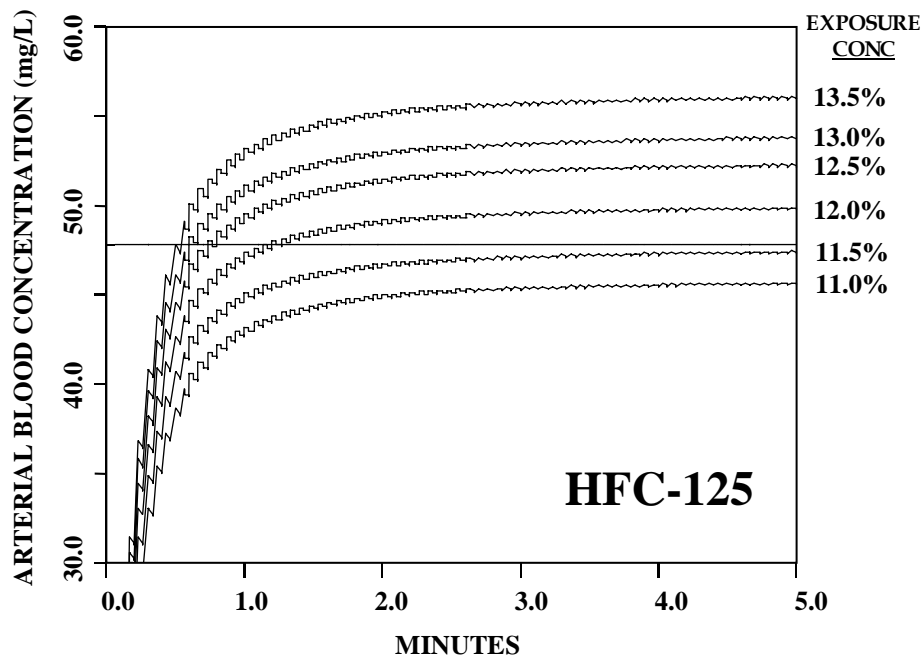
Figure 2 – Monte Carlo simulations of arterial concentration of humans exposed to CF<sub>3</sub>I for five minutes at concentrations of 0.25, 0.30, 0.35, 0.40, 0.45, and 0.50%. The horizontal line at 12.9 mg/L represents the lowest arterial blood concentration measured at five minutes in a group of six dogs exposed to CF<sub>3</sub>I at the cardiac sensitization of LOAEL of 0.4%.

Figure 3 – Monte Carlo simulations of arterial concentration of humans exposed to HFC-125 for five minutes at concentrations of 11.0, 11.5, 12.0, 12.5, and 13.0%. The horizontal line at 47.8 mg/L represents the lowest arterial blood concentration measured at five minutes in a group of six dogs exposed to HFC-125 at the cardiac sensitization LOAEL of 10.0%.

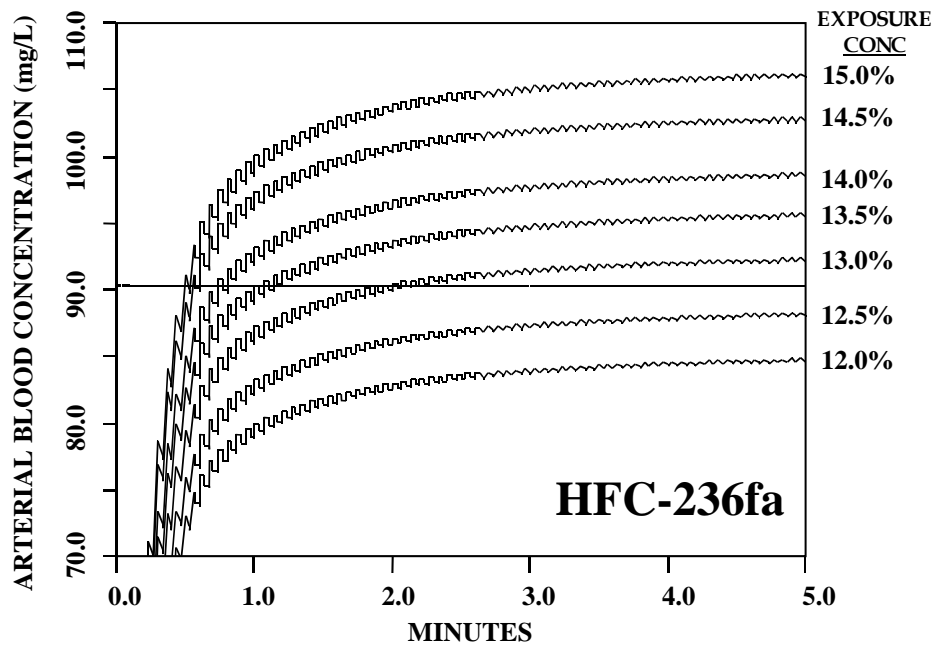
Figure 4 – Monte Carlo simulations of arterial concentration of humans exposed to HFC-227ea for five minutes at concentrations of 10.0, 10.5, 11.0, 11.5, 12.0%. The horizontal line at 26.3 mg/L represents the lowest arterial blood concentration measured at five minutes in a group of six dogs exposed to HFC-227ea at the cardiac sensitization LOAEL of 10.5%.

Figure 5 – Monte Carlo simulations of arterial concentration of humans exposed to HFC-236fa for five minutes at concentrations of 12.5, 13.0, 13.5, 14.0, 14.5, and 15.0%. The horizontal line at 90.37 mg/L represents the lowest arterial blood concentration measured at five minutes in a group of six dogs exposed to HFC-236fa at the cardiac sensitization LOAEL of 15.0%.









MODELING CARDIAC SENSITIZATION POTENTIAL OF  
HUMANS EXPOSED TO HALON 1301 OR HALON 1211  
ABOARD AIRCRAFT

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## Abstract

Halon 1301 and Halon 1211 are being replaced because they contribute to the depletion of ozone. Many of the potential candidate chemicals for replacing them are, like them, halogenated hydrocarbons. These chemicals have the potential to cause cardiac sensitization at high enough exposure concentrations. A physiologically based pharmacokinetic model, which mathematically describes the uptake, distribution, metabolism, and elimination of chemicals, was used to relate exposure to these chemicals with arterial blood concentrations resulting from the exposure. This information was then used to evaluate the potential for the occurrence of a cardiac-sensitizing event. The model was used to analyze the exposures to Halon 1301 and Halon 1211 in three aircraft. Halon 1301 exposures were shown to be safe but Halon 1211 resulted in arterial concentrations in exposed individuals that reached levels that could potentially cause cardiac sensitization. Use of the model for evaluating the risk from exposure to Halon 1301 and Halon 1211 is a moot point since both chemicals are being replaced. However, demonstration of the validity of the approach provides a tool for the evaluation of the health safety of replacement candidates.

Index Terms: cardiac sensitization, halon, physiologically based pharmacokinetic model, fire extinguishant

## Introduction

Halons, used as fire extinguishants, have been banned from production because of international concern for the depletion of stratospheric ozone. Only existing stocks are available for essential application use in aircraft fire and explosion suppression systems. Constantly changing political pressure puts these stocks at risk for elimination, increasing the need to make halon alternatives available for aircraft use. Most chemicals being considered as replacements for Halon 1301 and 1211 are halogenated hydrocarbons which, as a class, are regulated by the U.S. Environmental Protection Agency (1).

Cardiac sensitization is the acute toxic endpoint of concern. Dogs are monitored continually for electrocardiographic changes indicative of the appearance of a burst of multifocal ventricular ectopic activity or ventricular fibrillation. They are given an epinephrine challenge after 5 min of exposure to the test chemical. The test is performed at several chemical concentrations to determine a no observable adverse effect level (NOAEL) and a lowest observable adverse effect level (LOAEL). The LOAEL and NOAEL values are used directly for establishing human exposure limits because of the sensitive nature of the test (1).

Recently, a mathematical tool was developed which allows the quantitative evaluation of short-term exposure to halogenated hydrocarbons (2). This tool is a physiologically based pharmacokinetic (PBPK) model, which can relate chemical exposure to concentrations in the body. It has been proposed that the model be used to relate external exposure of halon replacement chemicals to arterial blood concentration. Arterial blood concentration can then be compared with a target arterial blood concentration associated with cardiac

sensitization. The methodology for doing this has been proposed (3) and described in detail (4).

The PBPK model can be used both retrospectively to evaluate previous actual exposure scenarios and prospectively to evaluate potential exposure scenarios. An example of a retrospective evaluation was given in Vinegar et al. (2) where they evaluated an accidental exposure to Halon 1211 that had occurred during an Israeli military exercise (5). In this instance, model predictions were consistent with the outcome where the gunner, having only brief exposure, successfully escaped without incident but the driver, with prolonged exposure, reached levels adequate for cardiac sensitization. The driver, in fact, was observed to be in ventricular fibrillation, never regained consciousness and died as a result of the incident. A prospective application of the model was demonstrated by Vinegar et al. (6). In order to evaluate the potential hazard to ground crews of an accidental release of  $CF_3I$  a discharge test was conducted on an F-15 jet to record  $CF_3I$  concentration time histories at various locations near the aircraft. These exposure data were used with the PBPK model to simulate the potential blood levels of workers at various locations around the aircraft during the release. The blood levels were compared to the target arterial blood concentration associated with cardiac sensitization. Results showed that at some locations the target was not reached but at the open nacelle the blood concentrations could potentially reach double the target. This information was put in perspective with a further retrospective simulation of individuals who had actually inhaled  $CF_3I$  and whose blood concentrations were simulated and estimated to be 100 times the target. These individuals experienced no apparent effect of their exposures. Further prospective application of the model was demonstrated in Vinegar et al. (4). Here

a method was demonstrated for establishing safe duration for exposure to potential halon replacements at different flooding concentrations.

An issue of health concern is that of the intentional use of fire extinguishers in aircraft cabins with passengers aboard. No data were available for any of the potential halon replacements. However, there have been several published reports on measurements taken in aircraft cabins during the release of Halon 1301 and Halon 1211. These data were used with the PBPK model to see if any of the described scenarios could put passengers or crew at potential risk for cardiac sensitization. Results of these simulations are reported herein.

#### Materials and Methods

Three publications were found that presented data on releases of Halon 1211 and/or Halon 1301 in aircraft. The first study (7) used a fleet configured Navy E-2B “Hawkeye” airplane. Concentrations of Halon 1301 were measured at head level in areas occupied by flight crewmembers, and in airplane locations where fire hazard potential posed the greatest threat. Halon 1301 was monitored using a Statham Laboratories Model GA-2A gas recorder and accessories.

The second study (8) used a Cessna Model C-421B, a small pressurized aircraft. Halon 1211 and Halon 1301 were measured using factory field modified Beckman Model 865 infrared gas analyzers. Measurements were made at three locations:

1. Test area – Actual fire extinguisher discharge location.

2. Knee area – 20 inches above the floor at the area of discharge. Discharge area for pilot's and copilot's seat tests was at knee level where the seat cushion meets the seat back.
  
3. Nose area – 37 inches above the floor at the area of discharge.

The last study (9) used a Cessna Model 210C, a small non-pressurized aircraft. Halon 1211 and Halon 1301 were measured using modified Beckman Model 865 infrared gas analyzers. Measurements were made at the point of release and at two other selected sites during each test.

In all three publications there are diagrams showing the specific locations monitored. The data were presented in graphic form. Results reaching the highest peak exposure concentrations were used from each paper. The data were digitized and converted to ASCII so that they could be used with the PBPK model. Exposure scenarios selected were used to simulate the arterial concentration using the model described by Vinegar et al. (2). Arterial concentrations were compared with target arterial concentrations for cardiac sensitization (4).

## Results

Representative results for the Navy E-2B are shown in Figures 1 and 2. A ground test is illustrated in Figure 1. Concentrations of Halon 1301 measured at four locations are shown in the left-hand column. Simulated arterial concentrations for each of the four

locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization. None of the simulated concentrations reached the target. An example of a flight test is shown in Figure 2. Under these conditions at floor level in the equipment area the concentrations of Halon 1301 in arterial blood exceeded the target concentration at about 40 seconds into the exposure and remained above the target for the duration of the measurements. Arterial concentration simulations remained below target at the other measured sites.

Results for representative releases aboard the Cessna C-421B are shown in Figures 3 to 6. Halon 1301 releases at the last vent before the left side door (Figure 3) or at the last vent on the right side of the cabin (Figure 4) resulted in simulated arterial concentrations well below the target concentration. Both releases of Halon 1211 resulted in simulated arterial concentrations that surpassed the target concentration of 21.0 mg/L (Figures 5 and 6). The target was exceeded at both sites of release. The release at the copilot's seat (Figure 5) had measurements at nose level, which exceeded the target after about 45 seconds of exposure. Release at the cabin side of grill under the copilot's seat resulted in simulated arterial concentration at the knee area exceeding the target after about 16 seconds and peaking at more than three times the target at about 26 seconds (Figure 6). However, nose area concentrations remained below the target.

Halon 1301 arterial concentrations remained below the target concentration for releases, in the Cessna 210C, directed to the copilot's door with overhead vents closed (Figure 7) and directed to fuel and hydraulic selector valves with overhead vents open (Figure 8).



Halon 1211 arterial concentrations exceeded the target level at all measured locations when the extinguisher was directed under the instrument panel on the pilot's side with overhead vents open (Figure 9) or closed (Figure 10).

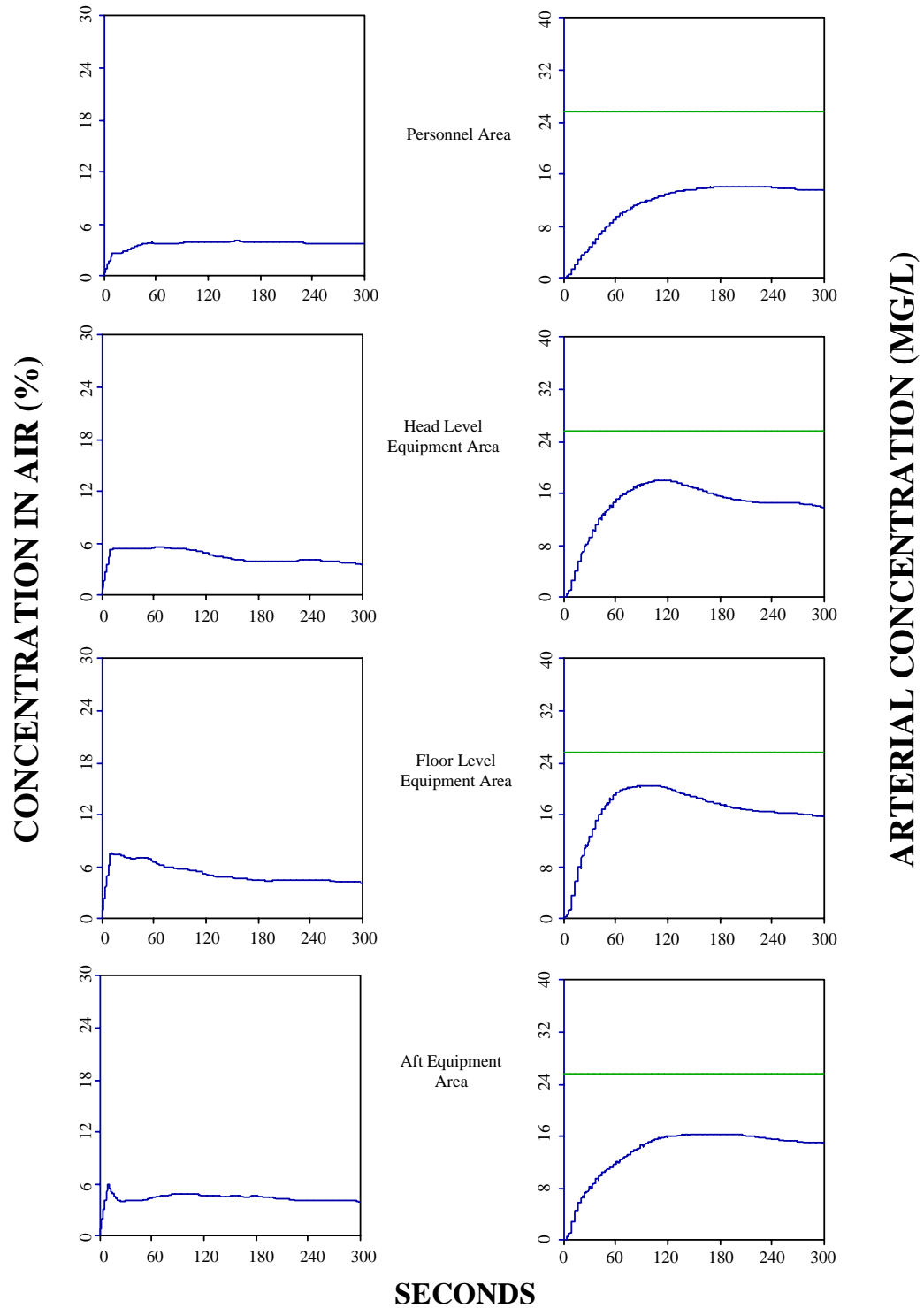


Figure 1 - Halon 1301 - Ground Test (equipment cooling System ON) for Navy E-2b. Concentrations of Halon 1301 measured at four locations are shown in the left hand column. Simulated arterial concentrations for each of the four locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

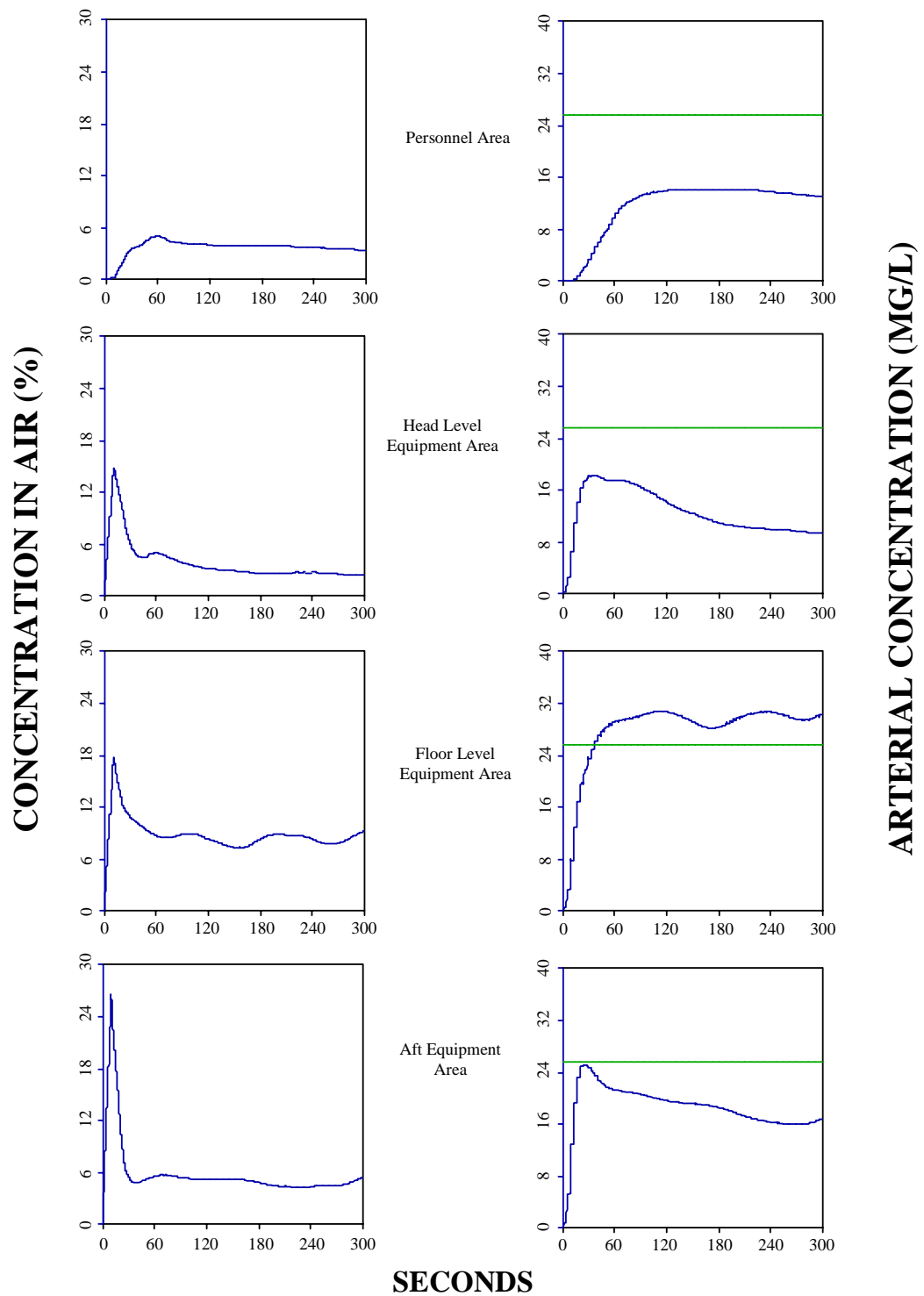


Figure 2 - Halon 1301 - Flight Test (Nozzle Jets Mixing Agent) for Navy E-2B. Concentrations of Halon 1301 measured at four locations are shown in the left hand column. Simulated arterial concentrations for each of the four locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

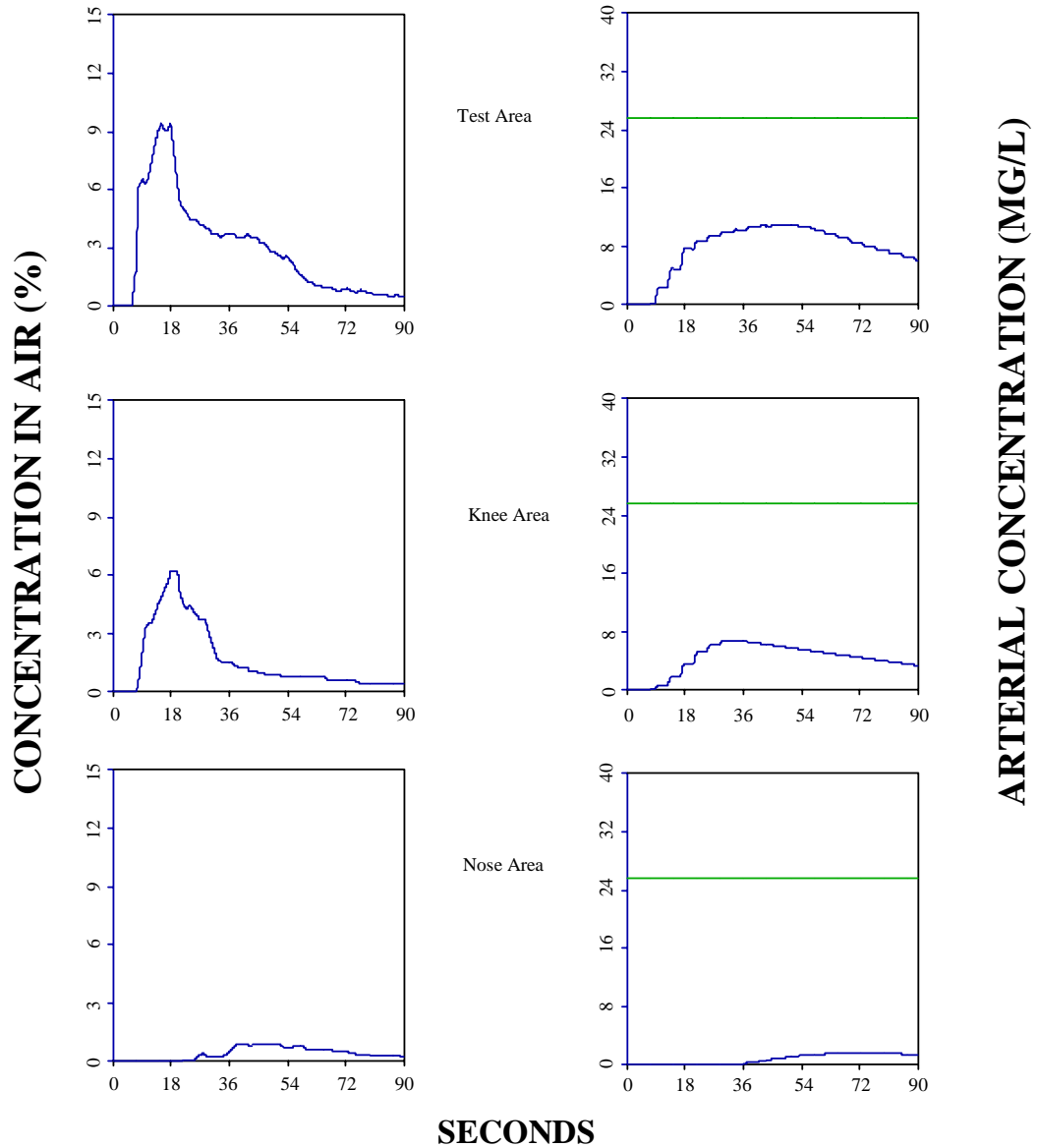


Figure 3 - Halon 1301 - Concentrations Cabin Area Last Vent Before Door Left Side for Cessna C-421B. Concentrations of Halon 1301 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

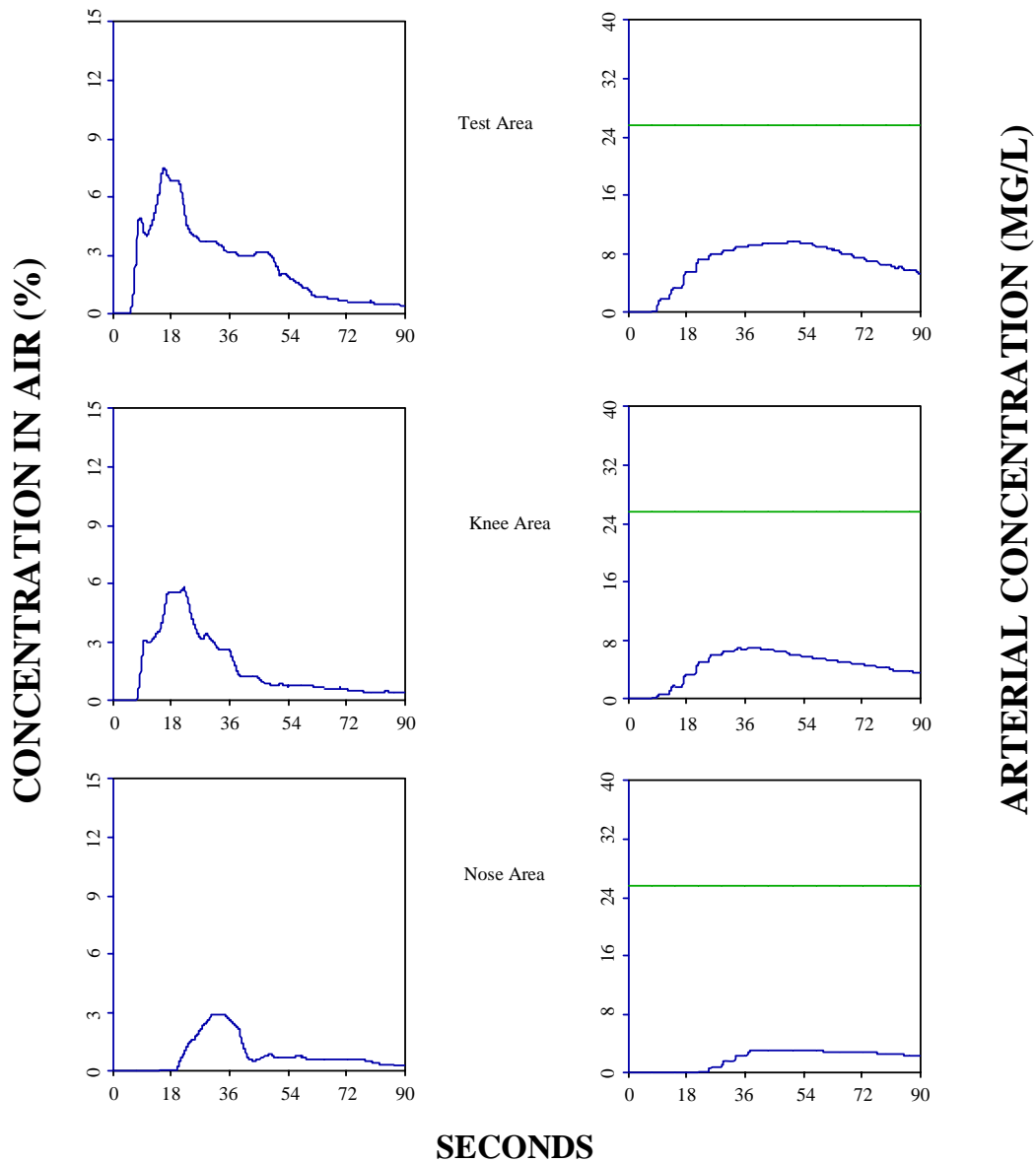


Figure 4 - Halon 1301 - Concentrations Cabin Area Last Vent Right Side for Cessna C-421B. Concentrations of Halon 1301 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

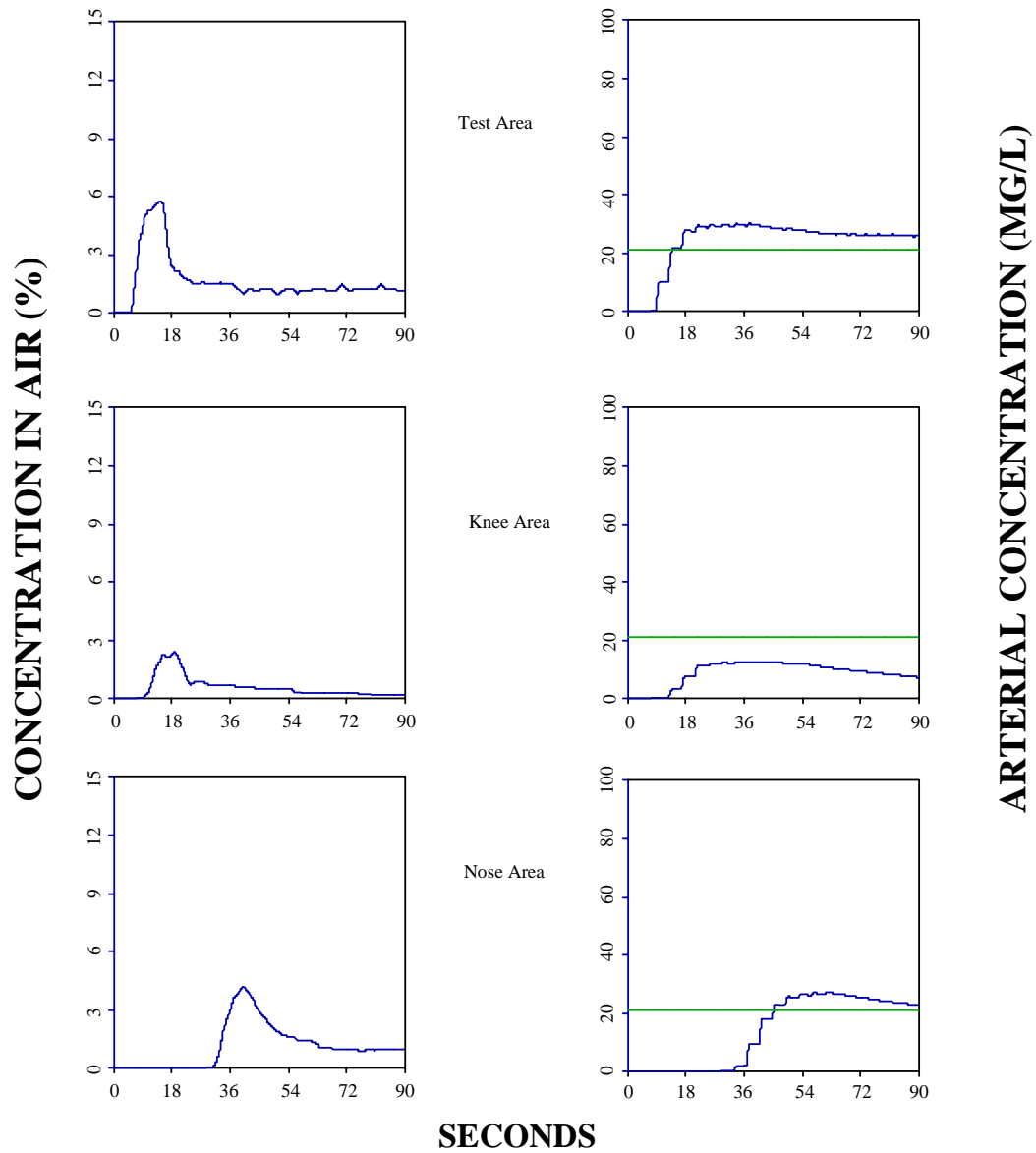


Figure 5 - Halon 1211 - Concentrations Copilot's Seat for Cessna C-421B. Concentrations of Halon 1211 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 21.0 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

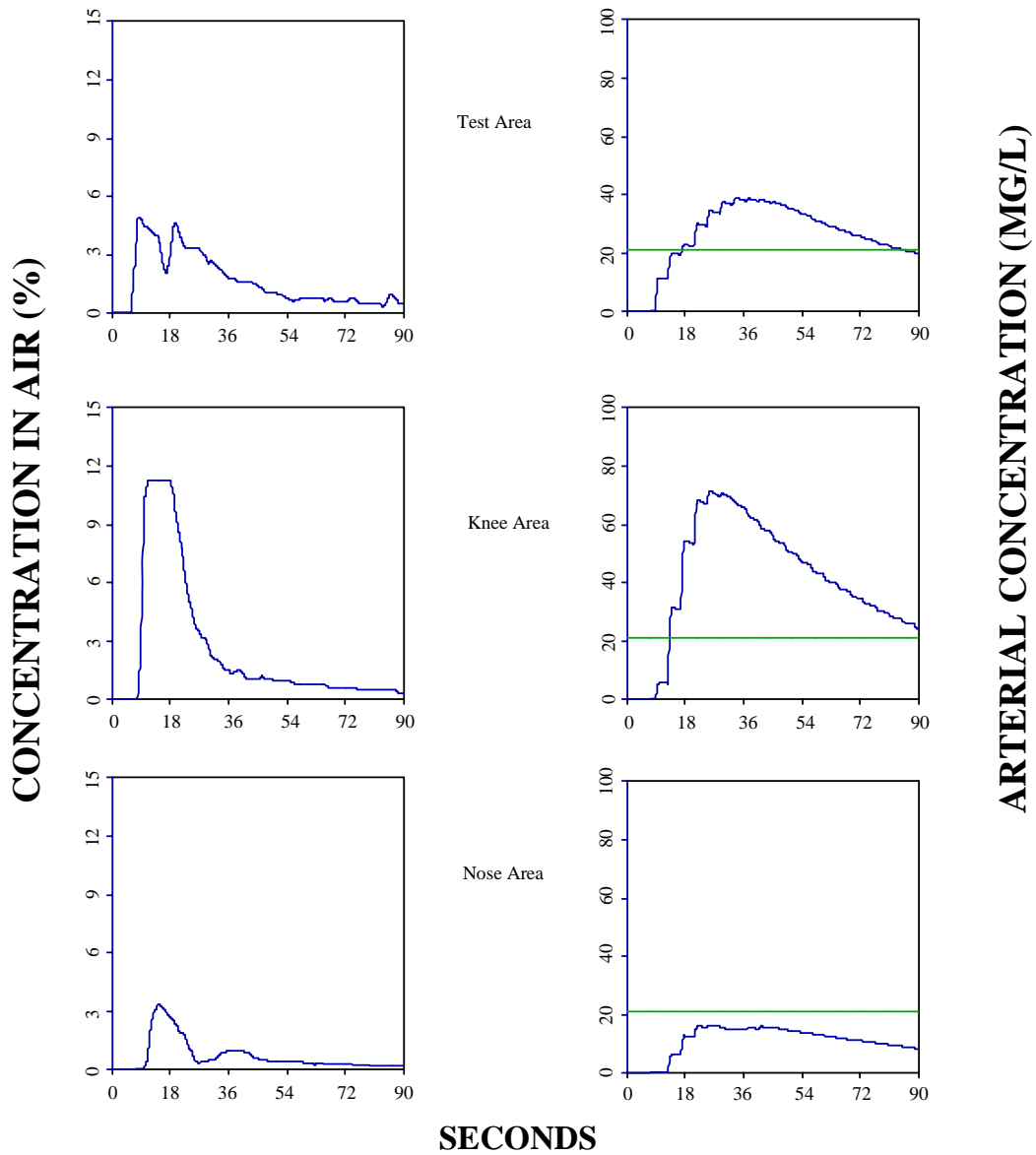


Figure 6 - Halon 1211 - Concentrations Cabin Side Of Grill Under Copilot's Seat for Cessna C-421B. Concentrations of Halon 1211 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 21.0 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

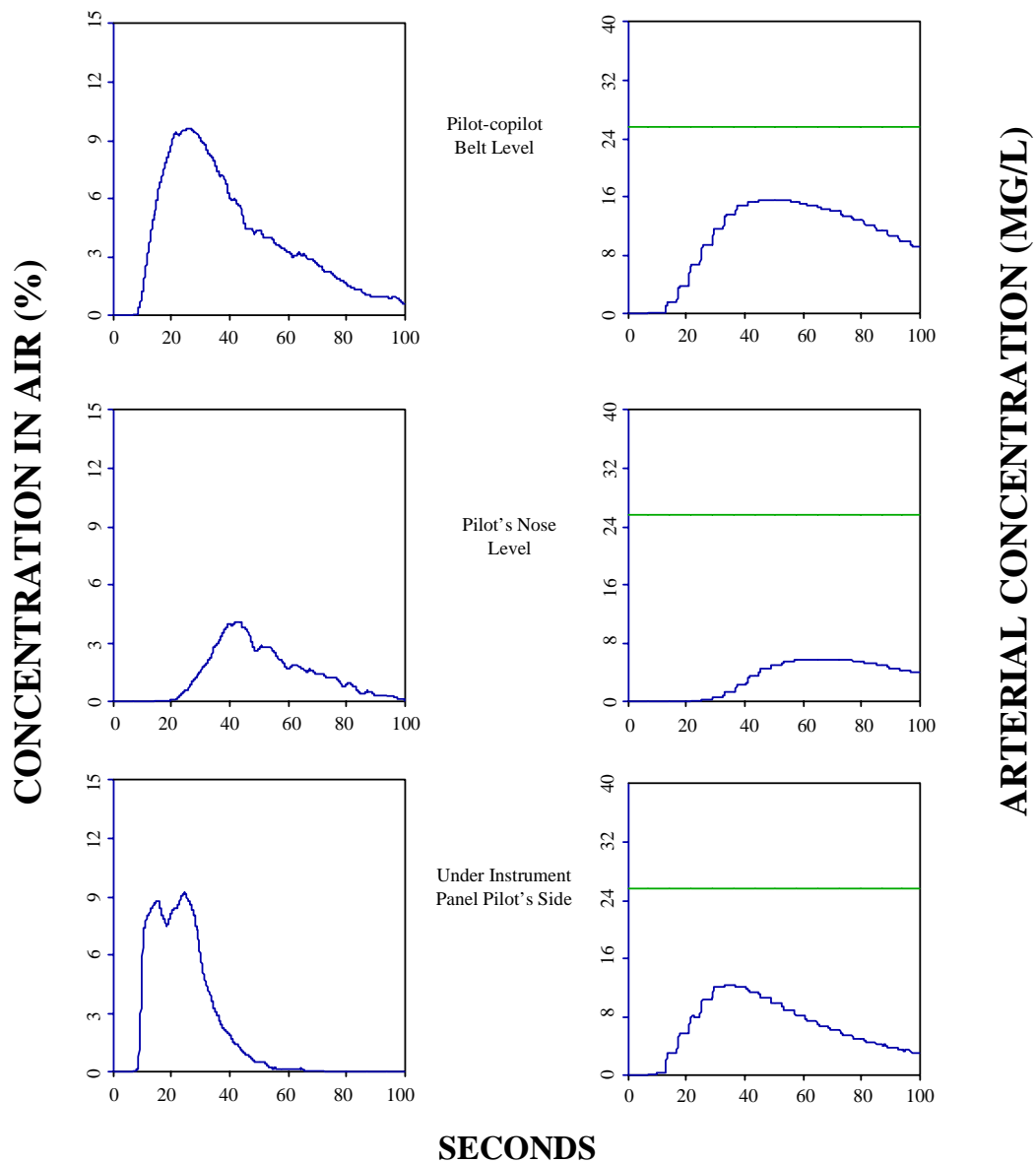


Figure 7 - Halon 1301 - 3-lb Extinguisher Directed To Copilot's Door - Overhead Vents Closed for Cessna 210C. Concentrations of Halon 1301 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.



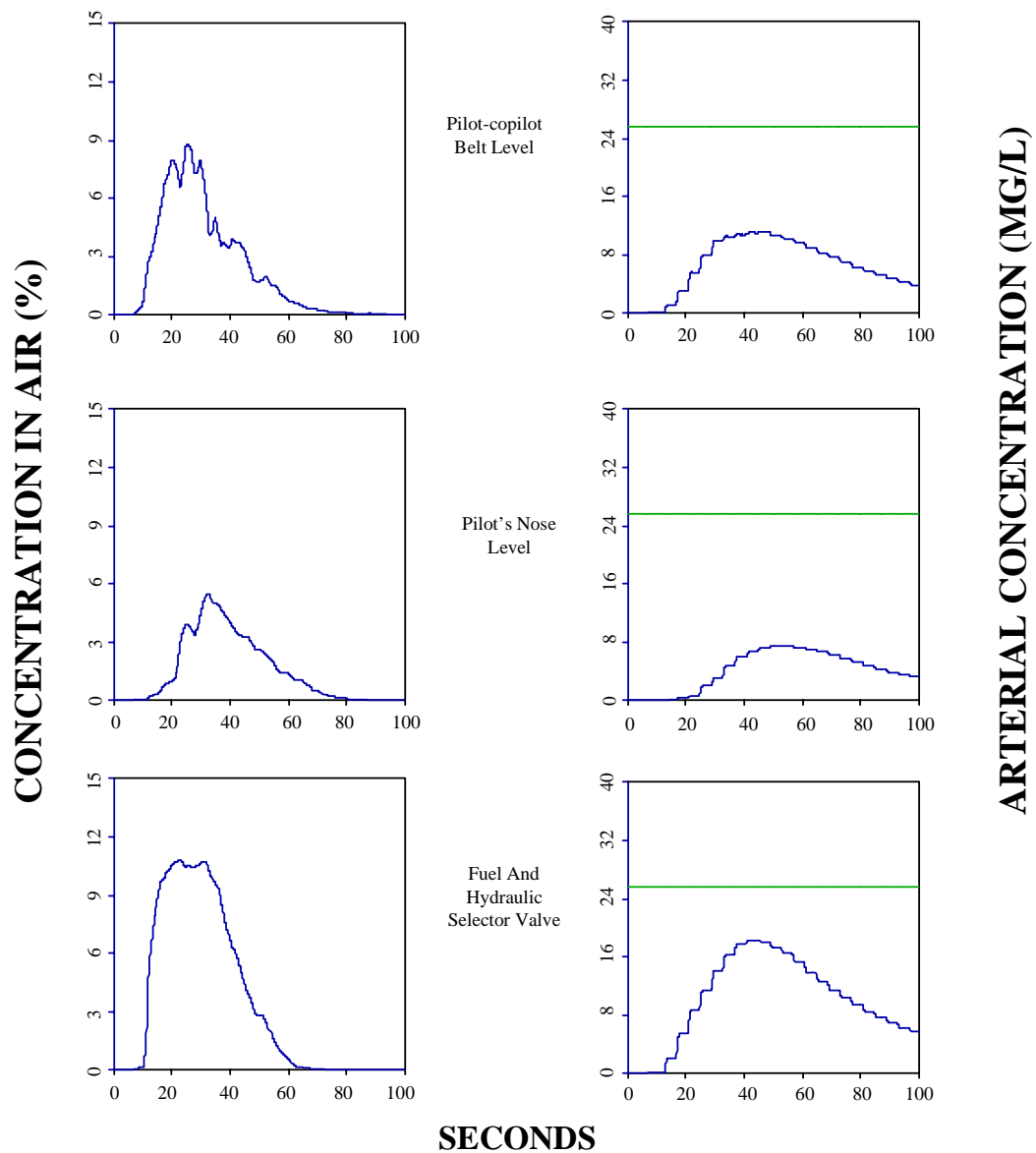


Figure 8 - Halon 1301 - 3-lb Extinguisher Directed To Fuel And Hydraulic Selector Valves - Overhead Vents Open for Cessna 210C. Concentrations of Halon 1301 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 25.7 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

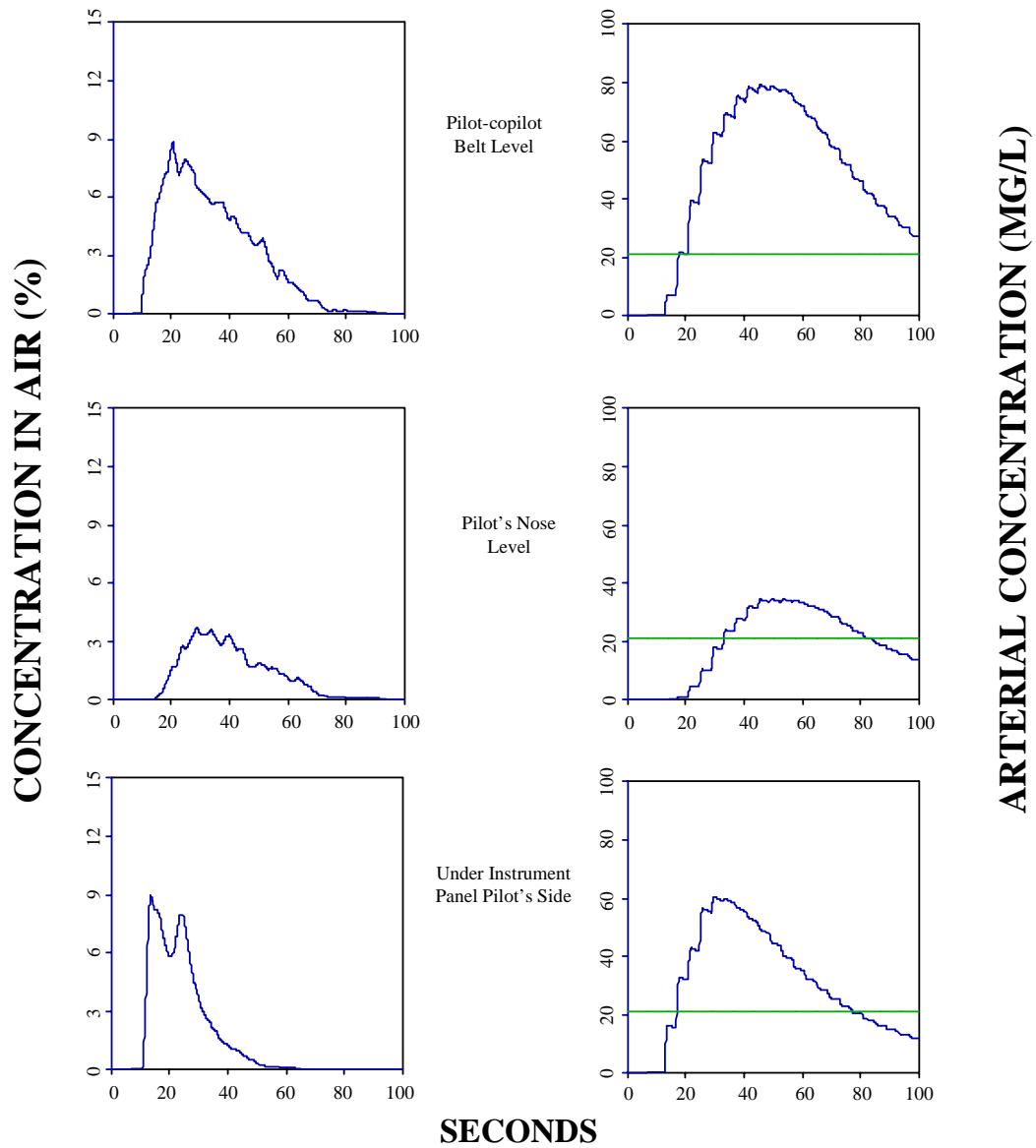


Figure 9 - Halon 1211 - 2.5-lb Extinguisher Directed Under Instrument Panel Pilot's Side - Overhead Vents Open for Cessna 210C. Concentrations of Halon 1211 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 21.0 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

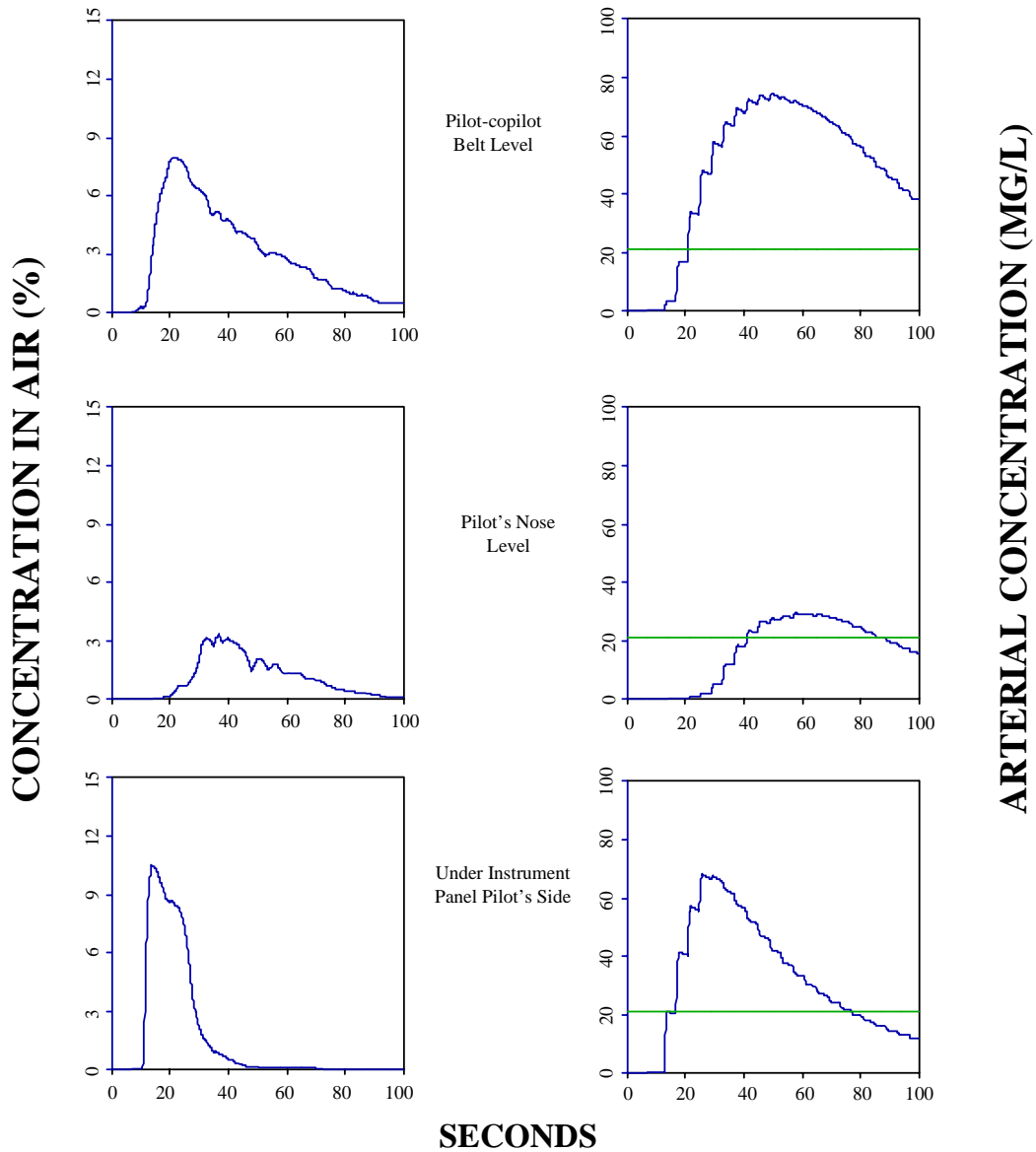


Figure 10 - Halon 1211 - 2.5-lb Extinguisher Directed Under Instrument Panel Pilot's Side - Overhead Vents Closed for Cessna 210C. Concentrations of Halon 1211 measured at three locations are shown in the left hand column. Simulated arterial concentrations for each of the three locations are shown in the right hand column. The straight line shown at 21.0 mg/L for each of the arterial simulations represents the target concentration for cardiac sensitization.

## Discussion

The use of Halon 1301 for several decades has occurred with an excellent safety record. Retrospective modeling of scenarios such as those illustrated above show that generally under normal use there has been little to no opportunity for the occurrence of exposure situations where individuals have been put at potential risk of having blood levels of Halon 1301 ever reach a target concentration that might predispose for the onset of a cardiac sensitization response. Halon 1211 when used as a streaming agent under open conditions likewise has posed little risk. However, when used under more confined situations the potential for cardiac sensitization exists. Several scenarios illustrated above showed situations where arterial concentrations of Halon 1211 exceeded the target associated with a potential for cardiac sensitization. The report of an incident by Lerman et al. (5) (see introduction) demonstrates that the risk is real if Halon 1211 is used under confined situations where the exposure concentration can get high enough to result in highly elevated blood concentrations.

The discussion with reference to Halons 1301 and 1211 is perhaps a moot point with both of them being replaced with other agents. However, the use of PBPK modeling to evaluate exposure scenarios with replacement agents should be considered. Prospective modeling of potential scenarios can forewarn against situations such as that reported by Lerman et al. (5).

## Acknowledgments

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# Physiologically Based Pharmacokinetic Model for Simulating Breath-By-Breath Inhalation

PROGRAM: PHYSIOLOGICAL PHARMACOKINETIC MODEL

!Ventilation described on a breath-by-breath basis

!-----

IAS=INTEG(RAS,0.) Amount slowly perfused tissue (mg)  
 !AR=INTEG(RAR,0.) Amount rapidly perfused tissue (mg)  
 !AF=INTEG(RAF,0.) Amount in fat (mg)  
 !AG=INTEG(RAG,0.) Amount in gut (mg)  
 !AM=INTEG(RAM,0.) Amount amount metabolized in liver (mg)  
 !AL=INTEG(RAL,0.) Amount in liver (mg)  
 !CVGDD=INTEG(RCVGDD,0.0) concentration (mg/L) in distal deadspace  
 !CVGDP=INTEG(RCVGDP,0.0) concentration (mg/L) in proximal deadspace  
 !AI=INTEG(RAI,0.) Amount inhaled (mg)  
 !AX=INTEG(RAX,0.) Amount exhaled (mg)  
 !AP=INTEG(RAP,0.0) AMOUNT IN PULMONARY REGION (mg)

!-----

INTEGER CTABLE, VTABLE, ICRP, BREATH, INHALE, VGDCAL, IGEVGD, IHALT \$'FLAGS'

TABLE VENTT,1,19/0.,.0016667,.0033333,.005,.0066667,.0083333,...  
 .0125,.0166667,.025,.0333333,.05,.0833333,.125,.1666667,...  
 .2083333,.25,.3333333,.4166667,.5,...  
 5.42,5.42,5.42,5.42,5.42,5.42,5.42,5.42,5.42,5.42,5.21,...  
 5.19,5.19,5.33,5.53,5.27,5.58,5.58/  
 TABLE CONCT,1,19/0.,.0016667,.0033333,.005,.0066667,.0083333,...  
 .0125,.0166667,.025,.0333333,.05,.0833333,.125,.1666667,...  
 .2083333,.25,.3333333,.4166667,.5,...  
 2025.,2025.,2025.,2025.,2025.,2025.,2025.,2025.,2025.,2025.,...  
 1996.,1966.,2000.,2035.,2014.,2051.,2056.,2034./

INITIAL

!\*\*Miscellaneous\*\*

LOGICAL GENDER, MALE  
 GENDER=.TRUE. \$ 'Male=.T., Female=.F.'  
 MALE = GENDER

!\*\*Timing commands\*\*

CONSTANT	TSTOPS	=300	!	LENGTH OF EXPERIMENT (SECS)
		TSTOP =TSTOPS/3600		
CONSTANT	TCHNG=40		!	Length of inhalation exposure (hr)
!**Physiological Parameters**				
CONSTANT	VGDCAL	=1	!	>=1: calculate VGD. <1: use input value of VGD
CONSTANT	CTABLE	=-1	!1	!Switch for using the table
CONSTANT	VTABLE	=-1	!1	!Switch for using the table,
CONSTANT	ICRP	=0	!	SWITCH FOR METHOD OF CALCULATING VT & F
CONSTANT	KAP	=0	!	PUL. REGION GAS PHASE RATE CONSTANT
CONSTANT	KS	=10000	!	Suppression rate constant (mg/hr)
CONSTANT	BW	=70	!	Body weight (kg) {or L where 1 L/kg}



CONSTANT	H	=1.8	!Height (m)
CONSTANT	A	=21	!Age (yr)
CONSTANT	QPC	=17.4	!L/(hr*kg)
	QP	=QPC*BW**0.74	!L/hr
	QPM	=QP/60	!L/min
	VENTLM	=QPM/0.70	!L/min=70% OF QPM
CONSTANT	QLC	=0.0885	!Proportion cardiac output to liver
CONSTANT	QGC	=0.2192	!Proportion cardiac output to gut
CONSTANT	QFC	=0.0288	!Proportion cardiac output to fat
CONSTANT	QSC	=0.2019	!Proportion cardiac output to slow
CONSTANT	QRC	=0.4616	!Proportion card output to rapid
	QRCC	=QRC	
CONSTANT	VLC	=0.027	!Liver volume (L/L BW)
CONSTANT	VGC	=0.022	!Gut volume (L/L BW)
CONSTANT	VFC	=0.215	!Body fat volume (L/L BW)
CONSTANT	VRC	=0.041	!Rapid volume (L/L BW)
CONSTANT	VSC	=0.575	!Slow volume (L/L BW)
! **Toxicant**			
CONSTANT	CONC	=105000	!Inhaled concentration (ppm)
CONSTANT	MW	=168.02	!Molecular weight (g/mol)
CONSTANT	VMAXC	=0.0	!Michaelis-Menten Vmax (mg/hr/kg BW)
CONSTANT	KM	=1	!Michaelis-Menten Km (mg/L)
CONSTANT	KFC	=0.	!First order metab. rate constant (1/hr/kg BW)
CONSTANT	PLA	=0.038	!Liver/air partition coefficient
CONSTANT	PGA	=0.056	!Gut/air partition coefficient
CONSTANT	PFA	=0.745	!Fat/air partition coefficient
CONSTANT	PSA	=0.074	!Slowly perfused tissues/air part. coefficient
CONSTANT	PRA	=0.038	!Richly perfused tissues/air part. coefficient
CONSTANT	PB	=0.033	!Blood/air partition coefficient
	PL	=PLA/PB	!Liver/blood partition coefficient
	PG	=PGA/PB	!Gut/blood partition coefficient
	PF	=PFA/PB	!Fat/blood partition coefficient
	PS	=PSA/PB	!Slowly perfused tissues/blood part. coefficient
	PR	=PRA/PB	!Richly perfused tissues/blood part. coefficient
CONSTANT	PI	=3.1415927	
!CONSTANT	VT	=0.5	!TIDAL VOLUME (L)
CONSTANT	F	=900	!BREATHING FREQUENCY /HR
CONSTANT	VGP	=3.	!PULMONARY REGION GAS VOLUME
CONSTANT	VDG	=0.2	!DEAD SPACE GAS VOLUME
CONSTANT	VPR	=1.	!VENTILATION PERFUSION RATIO
CONSTANT	VCAPP	=0.169	!VOL OF PUL CAPILLARIES
CONSTANT	VTP	=0.270	!VOL OF PUL TISS (AIR-BLOOD BARRIER)
! **Scaled and other derived parameters**			
FRC	=0.65*(2.34*H+.009*A-1.09)	IFUNCTIONAL RESIDUAL CAPACITY (L)	
IF(.NOT. MALE)	FRC=.65*(2.24*H+.001*A-1.00)		
IF(VGDCAL .LE. 0)	GOTO 20		
	VGD	=0.002*bw	!VGD from Lerou et al.(1991)'
20..CONTINUE			
	VGP	=FRC-VGD	
	VL	=VLC*BW	!Volume liver (L)

VG =VGC\*BW !Volume gut (L)  
 VF =VFC\*BW !Volume fat (L)  
 VR =VRC\*BW !Volume rapid (L)  
 VS =VSC\*BW !Volume slow (L)  
 VMAX =VMAXC\*BW\*\*0.75 !Vmax for toxicant (mg/hr)  
 KF =KFC/BW\*\*0.25 !First-order metabolism of toxicant (1/hr)

!\*\*VARIABLE INITIALIZATION\*\*

!\*\*Inhalation exposure\*\*

IF(CTABLE .GT. 0.5) ...  
 CONC=CONCT(T) !INHALED CONC DERIVED FROM  
 TABLE (PPM)  
 CIZONE =RSW((T.LT.TCHNG),1.,0.) !Exposure switch, 0 or 1  
 !CI =CONC\*MW/24450.\*CIZONE !Concentration inhaled (mg/L)  
 CI =RSW((T.LT.TCHNG),CONC\*MW/24450.,.0000000000000001)

!\*\*Activity\*\*

IF(VTABLE .GT. 0.5) ...  
 VENTLM=VENTT(T) !VENTILATION DERIVED FROM  
 TABLE (L/MIN)  
 VT =(VENTLM\*60.)/F !TIDAL VOLUME DERIVED FROM  
 VDOT & FREQ  
 IF( ICRP .LT. 0.5) GO TO 100  
 VT =3.050\*(1.0-EXP(-0.023\*VENTLM))+0.166  
 ! (L),VT EQ. FOR ADULT FROM HOFMANN ET

AL.(89);

F =VENTLM\*60/VT !BASE ON ICRP # 23(75).  
 !BREATHS/HR  
 100..CONTINUE

VTA =VT-VGD !MAX VOL OF FRESH AIR  
 PENETRATION INTO PUL REGION!  
 VDOTA=F\*VTA !ALVEOLAR VENTILATION (L/HR)  
 VDOT =VT\*F !TOTAL VENTILATION (L/HR)  
 QCI =VDOTA/VPR !CARDIAC OUTPUT=ALVEOLAR  
 VENTILATION/V:P RATIO  
 !IF(VPR .GT. 1E6) QCI =0.0 !SET VPR > 1E6 FOR NO BODY UPTAKE  
 QL =QLC\*QCI !Blood flow to liver (L/hr)  
 QG =QGC\*QCI !Blood flow to gut (L/hr)  
 QF =QFC\*QCI !Blood flow to fat (L/hr)  
 QS =QSC\*QCI !Blood flow to slow (L/hr)  
 QR =QRCC\*QCI !Blood flow to rapid (L/hr)  
 QC =QL+QG+QF+QS+QR

PERIOD =1.0/F  
 !MAXT(4) =PERIOD/(2\*NMAXT)  
 HALFP =PERIOD/2  
 OMEGA =2.\*PI\*F  
 CINT = PERIOD/(2\*NCIPHB)  
 CI =CONC\*MW/24450.

!CVGDD = 0.0 \$ !CVGDP = 0.0 \$ !CGP = 0.0  
 !HALF = 0 \$ !INHALE = 1 \$ !UPTAKE = 0  
 !AG=0 \$ !AF=0 \$ !AL=0 \$ !AS=0 \$ !AR=0 \$ !AD=0 \$ !AP=0  
 !AM=0 \$ !AX=0 \$ !AI=0 \$ !VOLEX=0 \$ !BREATH=0  
 !AI=0 \$ !AX=0 \$ !DOSEXL=0.0 \$ !DOSEPB=0.0 \$ !AMRPB=0.0

```

!IGEVD=0.0 $ !RATEI=0.0 $ !RATEX=0.0 $ !RATEP=0 $ !CXMIX=0
!AXL=0.0 $ !AXPB=0.0 $ !AMRPH=0 $ !AVGDD=0 $ !AVGDP=0 $ !CX=0
!CXALV=0 $ !CXON2=0 $ !DOSEX=0
massba=0 $ minute=0 $ rmasba=0 $ rmass=0 $ second=0
secxxx=0 $ tbody=0 $ ti=0 $ tmass=0 $ txxx=0
xx=0 $ xxx=0
SCHEDULE IN1 .AT. 0.0                                !NEW

END                                                    !End of initial
!-----
DYNAMIC

CONSTANT  NMAXT=1                                !MIN NO OF INTEG STEPS PER PERIOD
CONSTANT  NCIPHB      =1                        !# OF COMMUNICATION INTERVALS
PER HALF BREATH

ALGORITHM  IALG  =2
NSTEPS     NSTP  =1000000
MAXTERVAL  MAXT  =1.0E+33
MINTERVAL  MINT  =1.0E-33
CINTERVAL  CINT  =2.22E-5

DISCRETE IN1                                !PROCEDURAL
PROCEDURAL
  CALL LOGD(.TRUE.)
  XX = AI - AX                                !Total amount retained
  DOSEPB = XX - DOSEXL                        !Dose per breath
  DOSEXL = XX                                !Previous amount retained
  AXPB = AX - AXL                            !Amount exhaled per breath
  AXL = AX                                    !Previous amount exhaled

!Inhalation exposure**1

!***** Activity *****1
IF(VTABLE .GT. 0.5) ...
VENTLM=VENTT(T)                                !VENTILATION DERIVED FROM TABLE
(L/MIN)
          VT      =(VENTLM*60.)/F            !TIDAL VOLUME DERIVED FROM VDOT &
FREQ
IF( ICRP .LT. 0.5) GO TO 200
! 'VT EQ. FOR ADULT FROM HOFMANN ET AL.(89); BASE ON ICRP # 23(75).'
  VT = 3.050*(1.0 - EXP(-0.023*VENTLM)) + .166 $ '(L)'
          F      =VENTLM*60/VT              !BREATHS/HR
200..CONTINUE

          PERIOD      =1.0/F
          !!MAXT(4)   =PERIOD/(2*NMAXT)
          HALFP      =PERIOD/2
          OMEGA      =2.*PI*F
          CINT      =PERIOD/(2*NCIPHB)

          VDOTPI     =PI*VDOTE
(L/HR)                                !PI*TOTAL VENTILATION

```

```

          VTHALF      =VT/2.0

          BREATH      =BREATH+1
          IHALF      =IHALF+1
          TI         =HALFP*IHALF
                                !Counting breaths
                                !Counting half breaths
                                !Time at given half breath

SCHEDULE EX1 .AT. TI
inhale                                !Schedule exhale at end of

          XXX      =(1/OMEGA)*ACOS(1.-VGD/VTHALF) !Time within breath that inh
vol=ds
          TXXX     =T+XXX                                !Absol time at which inh
vol=dead space
          SECXXX   =TXXX*3600
SCHEDULE GEVGD .AT. TXXX
TXXX                                !Schedule integration restart at

          IGEVGD   =-1                                !Flag to change pulmonary rate
equation
          INHALE   =1                                !Inhale state
          CVGDP=CI                                !Proximal deadspace conc=inhaled conc
CALL RSTART(DEV1, 1.E-7)
CALL LOGD(.TRUE.)
END
END
                                !Integration restart
                                !END PROCEDURAL
                                !END DISCRETE IN1

```

```

DISCRETE GEVGD
PROCEDURAL
IGEVD = 1
CALL RSTART(DEV1, 1E-7)
CALL LOGD(.TRUE.)
END
END

```

```

DISCRETE EX1 $ PROCEDURAL
CALL LOGD(.TRUE.)
IHALF = IHALF + 1      '$Counting half breaths'
TI = HALFP*IHALF      '$Time at given half breath'
SCHEDULE IN1 .AT. TI  '$Schedule inhale at end of exhale'
INHALE = -1           '$Exhale state'
CVGDD = CGP           '$Distal deadspace conc = pulmonary conc'
CALL RSTART(DEV1, 1.E-7) '$Integration restart'
CALL LOGD(.TRUE.)
END
END
                                '$END PROCEDURAL'
                                '$END DISCRETE EX1'

```

```

***** DERIVATIVE *****
DERIVATIVE DEV1 $ PROCEDURAL $ *****

```

```

IF(CTABLE .GT. 0.5) ...
  CONC=CONCT(T) '$INHALED CONCENTRATION DERIVED FROM TABLE (PPM)'
  CIZONE=RSW((T.LT.TCHNG),1.,0.) '$ Exposure switch, 0 or 1'
  'CI=CONC*MW/24450.*CIZONE'      '$ Concentration inhaled (mg/L)'
  CI=RSW((T.LT.TCHNG),CONC*MW/24450.,.0000000000000001)

```

SINX=SIN(OMEGA\*T)  
 SINHX=SIN((OMEGA\*T)/2)  
 FLOW=VDOTPI\*ABS(SINX)  
 DELVOL=VTHALF\*(1.0-COS(OMEGA\*T))  
 VOLP=VGP+DELVOL

\*\*\*TOXICANT PHARMACOKINETICS\*\*\*

\*\*\*Toxicant in blood\*\*\*

CA=AP/(VOLP/PB+VTP\*PR+VCAPP)      \$ 'Arterial conc. (mg/L)'

ACA=INTEG (CA, 0.0)      !AUCCA OF CA

CTP=CA\*PR  
 CGP=CA/PB

\*\*\*Toxicant in slowly perfused tissues\*\*\*

CS=AS/VS      \$ 'Concentration (mg/L)'  
 CVS=CS/PS      \$ 'Concentration in venous outflow (mg/L)'  
 RAS=QS\*(CA-CVS)      \$ 'Rate of change (mg/hr)'  
 AS=INTEG(RAS,0.)      \$ 'Amount (mg)'

\*\*\*Toxicant in rapidly perfused tissues\*\*\*

CR=AR/VR      \$ 'Concentration (mg/L)'  
 CVR=CR/PR      \$ 'Concentration in venous outflow (mg/L)'  
 RAR=QR\*(CA-CVR)      \$ 'Rate of change (mg/hr)'  
 AR=INTEG(RAR,0.)      \$ 'Amount (mg)'

\*\*\*Toxicant in fat\*\*\*

CF=AF/VF      \$ 'Concentration (mg/L)'  
 CVF=CF/PF      \$ 'Concentration in venous outflow (mg/L)'  
 RAF=QF\*(CA-CVF)      \$ 'Rate of change (mg/hr)'  
 AF=INTEG(RAF,0.)      \$ 'Amount (mg)'

\*\*\*Toxicant in gut\*\*\*

CVG=AG/(VG\*PG)  
 CG=AG/VG  
 RAG=QG\*(CA-CVG)  
 AG=INTEG(RAG,0.)

\*\*\*Toxicant in liver\*\*\*

CL=AL/VL      \$ 'Concentration (mg/L)'  
 CVL=AL/(VL\*PL)      \$ 'Concentration in venous outflow (mg/L)'  
 RAM=(VMAX\*CVL)/(KM+CVL\*(1+CVL/KS))      \$ 'Rate (mg/hr)' \$ 'metabolism'  
 AM=INTEG(RAM,0.)      \$ 'Amount (mg)'  
 RAL=QL\*(CA-CVL)+QG\*(CVG-CVL)-RAM      \$ 'Rate of change (mg/hr)'  
 AL=INTEG(RAL,0.)      \$ 'Amount (mg)'  
 CV = 0.0  
 IF(QC .GT. 0.0) CV=(QF\*CVF+(QL+QG)\*CVL+QS\*CVS+QR\*CVR)/QC \$ ' (mg/L)'

VOLEX=VT-DELVOL

'BEGINDS'

IF(INHALE .LT. 1) GOTO EXHALE

'INHALE PHASE: SINX >= 0.0 '

```

CMOUTH=CI          $ 'Conc at mouth equals inhaled conc'
RAI=FLOW*CI       $ 'Rate of inhalation (mg/hr)'
RAX = 0.0         $ 'RATE OF EXHALATION'
'proximal compartment'
  VGDP = MIN(DELVOL,VGD)
  RATEI = FLOW/(VGDP + (1E-4)*VGD)
  RCVGDP = FLOW*(CI - CVGDP)/(VGDP+(1E-4)*VGD)
'distal compartment'
  VGDD = VGD - VGDP
  RCVGDD = 0.0

IF(IGEVGD .LT. 0.0) RATEP = FLOW*CVGDD
IF(IGEVGD .GT. 0.0) RATEP = FLOW*CVGDP

GOTO ENDDS

EXHALE..CONTINUE

RATEP=-FLOW*CGP
IF(VOLEX .LT. VGD) CMOUTH=CVGDP $'Conc at mouth equals DS conc'
IF(VOLEX .GE. VGD) CMOUTH=CVGDD  $'Conc at mouth equals PUL conc'
RAX=FLOW*CMOUTH          $ 'Rate of exhalation (mg/hr)'
RAI = 0.0                $ 'RATE OF INHALATION'
'distal compartment'
  VGDD= MIN(VOLEX, VGD)
  RATEX = FLOW/(VGDD + (1E-4)*VGD)
  RCVGDD=FLOW*(CGP-CVGDD)/(VGDD+(1E-4)*VGD)
'proximal compartment'
  VGDP = VGD - VGDD
  RCVGDP = 0.0

ENDDS..CONTINUE

CVGDD=INTEG(RCVGDD,0.0) $'concentration (mg/L) in distal deadspace'
CVGDP=INTEG(RCVGDP,0.0) $'concentration (mg/L) in proximal deadspace'

AI=INTEG(RAI,0.)        $ 'Amount inhaled (mg)'
AX=INTEG(RAX,0.)        $ 'Amount exhaled (mg)'

RAP=RATEP+QC*(CV-CA) - KAP*CGP $ 'TOTAL RATE OF CHANGE OF AMOUNT IN'
                                'PULMONARY REGION'
AP=INTEG(RAP,0.0) $ 'AMOUNT IN PULMONARY REGION'

END $ END $ 'END PROCEDURAL & End of derivative *****'

'**Toxicant mass balance**'
AVGDP = CVGDP*VGDP
AVGDD = CVGDD*VGDD      $ 'NEW !!!!!!!!!!!!!!!!!!!!!!!'
AD=AVGDD+AVGDP $ 'AMOUNT IN DEAD SPACE'
TMASS=AG+AF+AL+AS+AR+AD+AP+AM+AX $ 'Total dose (mg)'
DOSEX=AI-AX             $ 'Net amount absorbed (mg)'
TBODY=AG+AF+AL+AS+AR+AD+AP $ 'Total in tissues (mg)'
MASSBA=AI-TMASS

RMASS=AG+AF+AL+AS+AR+AD+AP+AM $ 'TOTAL RETAINED MASS (MG)'
RMASSBA=DOSEX-RMASS           $ 'MASS BALLANCE'
'AVERAGE MASS RETAINED PER BREATH:'

```

```
IF(BREATH .GT. 0) AMRPB = DOSEX/BREATH $'AVERAGE MASS RETAINED/BREATH'  
AMRPH = F*AMRPB $ 'AVERAGE MASS RETAINED/HOUR'  
IF(AI .GT. 0.0) UPTAKE = DOSEX/AI $ 'AVERAGE FRACTIONAL UPTAKE'
```

```
***Toxicant exhaled***
```

```
IF(BREATH .GT. 0.0) ...
```

```
CXMIX = (AXPB/VT)*24450/MW $ 'Mixed exhaled conc. (ppm)'
```

```
CX=CA/PB $ 'Exhaled alveolar conc. (mg/L)'
```

```
CXALV=CX*24450./MW $ 'Exhaled alveolar conc. (ppm)'
```

```
CONSTANT CXEND=5.39106
```

```
CXON2=RSW((T.LT.TCHNG),(CX/CI),CX/CXEND)
```

```
MINUTE=T*60
```

```
SECOND = 3600*T
```

```
***Condition for termination of run***
```

```
TERMT(T.GE.TSTOP)
```

```
'-----'
```

```
END $ 'End of dynamic'
```

```
'-----'
```

```
END $ 'End of program'
```

# APPENDIX: Setup File for Performing Monte- Carlo Simulation Using ACSL-Tox Software



```

% FILE: setup.m
% Defines functions for implmenting a Monte-Carlo simulation

% -----
% NORMAL - Returns a normally distributed random variable with
%      mean mu and standard deviation sigma.
% -----
function v=normal(mu, sigma)
    v = mu + sigma*randn(1,1) ;
end

% -----
% NORMBND - Returns a truncated normal distribution with
%      mean mu, standard deviation sigma, upper and
%      lower bound
% -----
function v=normbnd(mu, sigma, lower, upper)
    if(lower >= upper)
        v = NaN;
        return;
    end
    while ( 1 )
        v = normal(mu, sigma) ;
        if (v >= lower & v <= upper)
            break;
        end
    end
end

% -----
% LOGNORMAL - Returns a lognormally distributed random variable
%      with geometric mean mu and geometric standard deviation
%      sigma
% -----
function v=lognormal(mu, sigma)

    r1 = rand(1,1) ;    % uniform distribution
    r2 = rand(1,1) ;    % uniform distribution

    v = exp(log(mu) + log(sigma)*sin(pi()*2*r1)*sqrt(-2*log(r2))) ;
end

% -----
% PMINMAX - plot mean, min and max of a matrix
% -----
function pminmax(x,y)
    bar = mean(y)';
    maximum = max(y)';
    minimum = min(y)';
    curve = [minimum bar maximum];
    plot(x, curve);
end

% End of file

```

## APPENDIX:

Sample M File for Conducting Monte Carlo Simulation for Halon 1301. Must Be Used in Conjunction With The Setup File

```

% File: halon.m
% Date: 14 Aug 98
% This will run a Monte Carlo simulation

!! prepare minute, ca
!! set mw=148.91
!! set wesitg=.f.
!! set vmaxc=0, km=10000, kfc=0

sprintf('CINT=%g. Are you sure?', CINT)
pause

% Empty the bucket into which I will be saving output
caBucket=[];
caHist =[];

% Run it one hundred times
%figure
    for run=1:numRun
        run
    % Vary the body weight
    % Fraction of total body volume allocated to various compartments
    % Means from Dr. Vinegar
    % Coefficient of Variation from Thomas (Am. Ind. Hyg. Ass. J.)
    BW =normbnd(70,          9.1,          42.7,  97.3);
    VFC =normbnd(0.215,          0.0645,          0.0215, 0.4085);
    %FOR VGC CV IS ASSUMED TO BE =20%
    VGC =normbnd(0.022,          0.0044,          0.0088, 0.0352);
    VLC =normbnd(0.027,          0.0054,          0.0108, 0.0432);
    VRC =normbnd(0.041,          0.0082,          0.0164, 0.0656);

    VSC =0.88 - VFC - VGC - VLC - VRC;

    VGP =normal(3.0,          0.60);
    VGD =normal(0.2,          0.04);
    VTP =normal(0.270,          0.054);
    VCAPP =normal(0.169,          0.0338);
    %F =normal(900,          0.8);

    % Fraction of total blood volume going to various compartments
    % Means from Dr. Vinegar
    % Coefficient of Variation from Thomas (Am. Ind. Hyg. Ass. J.)
    QPC =lognormal(17.4,          0.8);
    QSC =normbnd(0.2019,          0.06057,          0.02019, 0.38361);
    QLC =normbnd(0.0885,          0.01947,          0.03009, 0.14691);
    QFC =normbnd(0.0288,          0.00432,          0.01584, 0.04176);
    QGC =normbnd(0.2192,          0.048224,          0.074528, 0.363872);

```

```
QRC =1.0 - QSC - QLC - QFC - QGC;
```

```
% Partition coefficients
```

```
PLA = lognormal(0.144594, 1.085094);
```

```
PGA = lognormal(0.150, 1.25);
```

```
PFA = lognormal(0.771412, 1.163943);
```

```
PSA = lognormal(0.159411, 1.497855);
```

```
PRA = lognormal(0.144594, 1.085094);
```

```
PB = lognormal(0.061841, 1.057053);
```

```
% Run the simulation
```

```
!! start
```

```
%plot (_minute, caBucket);
```

```
% Put the final in the bucket by appending it to the
```

```
% end.
```

```
caBucket= [ caBucket ; CA ] ;
```

```
% Put the history into the final column of this bigger
```

```
% bucket, caHist.
```

```
caHist = [ caHist _ca ];
```

```
end
```

```
% Finished
```

```
% figure
```

```
% hAxis=axes()
```

```
% set (hAxis, @xLim=[0 5])
```

```
% set (hAxis, @yLim=[0 40])
```

```
% xlabel ('MINUTE'), ylabel ('ARTERIAL CONC (MG/L)');
```

```
% title ('HALON1301 7.5% LOAEL');
```

```
%plot(_minute, caHist, 'k');
```

```
% Calculate the mean, standard deviation, max, and min of ca
```

```
meanHist=mean(caHist)';
```

```
maxHist=max(caHist)';
```

```
minHist=min(caHist)';
```

```
stdHist=std(caHist)';
```

```
ca2sg=[meanHist + 2*stdHist meanHist meanHist - 2*stdHist]
```

```
% Open a new plot window
```

```
% figure
```

```
% hAxis=axes()
```

```
% set (hAxis, @xLim=[0 5])
```

```
% set (hAxis, @yLim=[0 40])
```

```

%      xlabel ('MINUTE'), ylabel ('ARTERIAL CONC (MG/L)') ;
%      title ('HALON1301 7.5% LOAEL') ;
%plot(_minute, meanHist, 'k') ;
%h=line(_minute, maxHist) ;
%set(h,@color='k')
%h=line(_minute, minHist);
%set(h,@color='k');

% Open a new plot window
figure
    hAxis=axes()
    set (hAxis, @xLim=[0 5])
    set (hAxis, @yLim=[0 30])
    xlabel ('MINUTE'), ylabel ('ARTERIAL CONC (MG/L)') ;
    title ('HALON1301 7.5% LOAEL') ;
plot(_minute, ca2sg, 'k') ;

% Save the mean data into a Excel file
%mydata=[_minute meanHist ] ;
%save mydata @file=mydata.csv @format=ascii @separator=comma

% end of file

```