Inhalation Toxicology, 2010; 22(12-14): 1151-1161

informa
healthcare

ORIGINAL ARTICLE

A kinetic model for human blood concentrations of gaseous halocarbon fire-extinguishing agents

Richard E. Lyon, and Louise C. Speitel

Airport and Aircraft Safety R&D Division, Federal Aviation Administration, William J. Hughes Technical Center, Atlantic City International Airport, NJ

Abstract

A simple kinetic model for calculating the blood concentration history of humans exposed to time-varying concentrations of gaseous, halocarbon fire-extinguishing agents is described. The kinetic model was developed to extend experimental physiologically based pharmacokinetic (PBPK) models for arterial blood concentration of halocarbons, obtained from constant concentration exposure of dogs to time-varying exposure conditions for humans. In the present work, the simplified kinetic model was calibrated using published PBPK-derived arterial concentration histories for constant concentration exposure to several common fire-extinguishing agents. The calibrated kinetic model was then used to predict the blood concentration histories of humans exposed to time-varying concentrations of these fire-extinguishing agents in ventilated compartments and the results were compared with PBPK-derived data for the agents. It was found that the properly calibrated kinetic model predicts human arterial blood concentration histories for time-varying exposures as well as the PBPK models. Consequently, the kinetic model represents an economical methodology for calculating safe human exposure limits for time-varying concentrations of gaseous halocarbon fire-extinguishing agents when only PBPK-derived human arterial blood concentration histories for constant exposure conditions are available.

Keywords: *Cardiac arrhythmia; cardiac sensitization; physiologically based pharmacokinetic modeling; target arterial blood concentration; HALON; halocarbon fire extinguishing agents; ventilation benefit; safe human concentration*

Introduction

The Federal Aviation Administration (FAA) is issuing updated guidance for safe use of fire-extinguishing agents (FAA, 1984) that are being introduced to replace bromochlorodifluoromethane (Halon 1211) in aircraft, which is being phased out in response to restrictions on the production of ozone-depleting, halogen-containing hydrocarbon (halocarbon) fire-extinguishing agents under the Clean Air Act Amendment of 1990, which was implemented in response to the Montreal Protocol, signed September 16, 1987, as amended (Code of Federal Regulations, 1987). The need for environmentally safe fire extinguishers and the availability of approved (Tabscott and Speitel, 2002; Webster, 2002) handheld extinguishers containing hydrochlorofluorocarbons (HCFC) 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123), 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea), and 1,1,1,3,3,3-heptafluoropropane (HFC-236fa) required new guidance material.

Halocarbon-extinguishing agents are gaseous compounds under normal aircraft operating conditions. They are relatively nontoxic at recommended use concentrations (Tabscott and Speitel, 2002). In comparison, the combustion products of fires, such as carbon monoxide (CO) and hydrogen cyanide, cause hypoxia, manifesting as light-headedness and dizziness at low concentrations and more serious effects at higher concentrations (Speitel, 1995). A quick effective extinguishment of an onboard fire will prevent buildup of combustion products and maintain a safe cabin environment.

However, even for brief exposures, halocarbons can induce cardiac arrhythmia at high concentrations in the bloodstream (Vinegar et al., 1998, 2000; Tabscott and Speitel, 2002; National Fire Protection Association, 2008) and can induce anesthetic effects for prolonged exposures as they accumulate in the organs and tissues. In the context of the present discussion, a brief or short-term exposure is defined as <5 min and the blood concentrations of interest

Address for Correspondence: Richard E. Lyon, Ph.D., Manager, Fire Research Program, FAA Fire Safety Branch AJP-6320, William J. Hughes Technical Center, Atlantic City International Airport, NJ 08405. E-mail: Richard.E.Lyon@faa.gov

(Received 16 September 2010; accepted 03 October 2010)

ISSN 0895-8378 print/ISSN 1091-7691 online © 2010 Informa Healthcare USA, Inc.
DOI: 10.3109/08958378.2010.529623

for halocarbons are the no observable adverse effect level (NOAEL) and the lowest observable adverse effect level (LOAEL). The NOAEL is the highest concentration of the gaseous halocarbon in the air of the test environment at which none of the test animals exhibits any adverse physiological or toxicological effects. The LOAEL is the lowest concentration of the halocarbon in the test environment at which adverse physiological or toxicological effects are first detected. Consequently, the LOAEL represents a higher concentration of halocarbon in the air than the NOAEL. These limits are determined from gas concentration effect test data for beagle dogs exposed to various constant concentrations of halocarbon for 5 min combined with intravenous epinephrine at concentrations well above physiological levels. These exposure limits are conservative because the level of injected epinephrine reaching the dogs' hearts is estimated to be 150 to 1825 times greater than the levels circulating in normally stressed dogs (Vinegar et al., 1998, 2000). In these constant concentration tests, exposure limits are not based on a particular time (dose) (Eklund, 1983). They are based on the minimum halocarbon concentration in the bloodstream at which cardiac arrhythmias occur in the dogs (Reinhardt et al., 1971; Mullin et al., 1979; Kenny et al., 1998; Vinegar et al., 1998, 1999, 2000; Vinegar, 2001; Horrell et al., 2007; Colton et al., 2008).

Based on the similarity between humans and dogs with respect to pharmacology, exposures to these agents up to 5 min at or below the NOAEL have been determined to be safe for humans by the United States Environmental Protection Agency (EPA), which allows the application of the dog-derived NOAEL for halocarbons directly to humans without application of a dog-to-human adjustment because of the conservative nature of the canine cardiac sensitization test (Vinegar et al., 1998, 2000; Tabscott and Speitel, 2002; National Fire Protection Association, 2008). Anesthetic effects have not been observed for dogs exposed to the NOAEL and LOAEL concentrations of the halocarbons in the short-duration tests. However, halocarbons are known to have anesthetic effects in dogs after prolonged exposures; therefore, human exposure should be limited to 5 min (Jepson, 2008).

Each halocarbon agent has a target arterial blood concentration at which cardiac sensitization occurs for a group of dogs exposed to the LOAEL concentration for 5 min. This target arterial concentration has been shown to be the same for the dog and human (Vinegar et al., 1998) and provides the link for predicting safe 5-min human exposure concentrations. Halocarbon gas concentrations exceeding the NOAEL can be safely used if physiologically based pharmacokinetic (PBPK) modeling is used to show that human blood concentrations of halocarbon remain below the target arterial concentration (Vinegar et al., 2000). Table 1 lists the NOAEL, LOAEL, maximum safe 5-min human exposure concentration, and the target arterial concentration for the halocarbons. The target arterial blood concentration listed in Table 1 is based on the lowest measured 5-min value observed for a group of dogs (minimum, 3) exposed to each halocarbon.

Pharmacokinetics is the study of the time course of drug and metabolite levels in different fluids, tissues, and organs within the body. PBPK modeling has been used to describe the uptake, distribution, metabolism, and elimination of inhaled halocarbons in the human body and is a quantitative approach to determine human arterial blood concentrations histories (Vinegar et al., 1998, 1999, 2000; Vinegar, 2001; Colton et al., 2008).

Arterial concentration histories of halocarbon in the bloodstream of humans exposed to constant or varying concentrations of gaseous halocarbons for up to 5 min has been simulated using PBPK modeling (Vinegar et al., 1998, 1999, 2000; Vinegar, 2001; Colton et al., 2008). Physiological components in the model are the liver, fat, lung, gut, and slowly and rapidly perfused tissues (Vinegar et al., 1998, 2000; Colton et al., 2008).

The PBPK model for the present application includes a respiratory compartment containing a dead-space region and a pulmonary exchange area and a breath-by-breath description of respiratory tract uptake (Vinegar et al., 1998) to accurately simulate pharmacokinetic data in the

Table 1. No observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), maximum safe 5-min human exposure concentrations, and target arterial concentration for selected halocarbons.

Agent	NOAEL[a] (% v/v)	LOAEL[a] (% v/v)	Maximum safe 5-min human exposure concentration (% v/v)	Maximum safe 5-min human exposure concentration (mg/L)	A_{safe} (% v/v)	Target arterial concentration, B_{safe} (mg/L)
HCFC-123	1.0	2.0	1.28[b,c]	78.9	1.28	69.9[b,c]
HFC-227ea	9.0	10.5	10.84[d,e]	787	10.84	26.3[d-f]
HFC-236fa	10.0	15.0	12.75[d,e]	831	12.75	90.4[d-f]
Halon 1211	0.5	1.0	N/A	N/A	0.5 (35.7 mg/L)	11.1
					1.0 (71.3 mg/L)	22.2[d,g]
Halon 1301	5.0	7.5	6.25[d,e]	391	6.25	25.7[d,e,h]

[a]Tabscott and Speitel (2002).
[b]Speitel and Lyon (2009) adjusted Colton et al. (2008) data basing target concentration on the lowest rather than the second lowest arterial concentration for a group of dogs exposed to HCFC-123.
[c]Horrell et al. (2007).
[d]Speitel and Lyon (2009).
[e]Vinegar et al. (2000).
[f]Kenny et al. (1998).
[g]Vinegar et al. (1998).
[h]Mullin et al. (1979).

0- to 1-min range and Monte Carlo simulations with 1000 iterations to account for ±2 standard deviations (±2σ) of the simulated human population. Monte Carlo simulations of blood concentration in the PBPK model at the +2σ level represent a blood concentration that accounts for 95% of the expected human population. Vinegar et al. (1998) demonstrated the ability of the breath-by-breath model to simulate the exhaled breath concentrations of volunteers who were exposed to three anesthetics (halothane, isofluorane, and desflurane) and to distinguish between lethal and nonlethal conditions for individuals who were accidentally exposed to Halon 1211 using gas concentrations measured in a recreated event.

The arterial blood concentration history in the PBPK modeling simulation for a 5-min exposure of a human to a constant Halon 1211 concentration in air at the indicated level is shown in Figure 1 (Vinegar et al., 1998). The PBPK data for Halon 1211 in Figure 1 do not meet the same criteria as the PBPK modeling data of the other agents in this article, as the data were originally meant to be illustrative of the PBPK methodology and were computed without Monte Carlo simulations and without reference to experimental partition coefficients. More conservative PBPK modeling with Monte Carlo +2σ arterial blood concentration history simulations for a 5-min human exposure to a constant halocarbon concentration in air at the indicated level are shown in Figures 2 through 4 for Halon 1301, HFC-227ea, and HFC-236fa (Vinegar et al., 2000) and in Figure 5 for HCFC-123 (Speitel and Lyon, 2009) using data from Colton (Colton et al., 2008) with an adjusted target arterial concentration based on the lowest (rather than the second lowest) arterial concentration as was used in Colton et al. (2008). The agent HCFC-123 was used to represent Halocarbon Blend B since it is the most toxic component of that blend (Colton et al., 2008) and the predominant component. Figures 1–4 show that the arterial blood concentration of Halon 1211, Halon 1301, HFC-227ea, and HFC-236fa approaches an asymptotic (equilibrium) value at about 5 min, which is proportional to the exposure concentration. In contrast, the arterial blood concentration of HCFC-123, shown in Figure 5, increases continually throughout the exposure. For exposure times greater than a couple of minutes, the arterial blood concentration of HCFC-123 increases at a rate that is roughly proportional to the exposure concentration. These features of the halocarbon blood concentration history must be represented by any model that is used to determine the safety of halocarbon-extinguishing agents in aircraft cabins.

Performing PBPK analyses and Monte Carlo simulations are complicated and expensive procedures, requiring a great deal of chemical and physiological data as input to

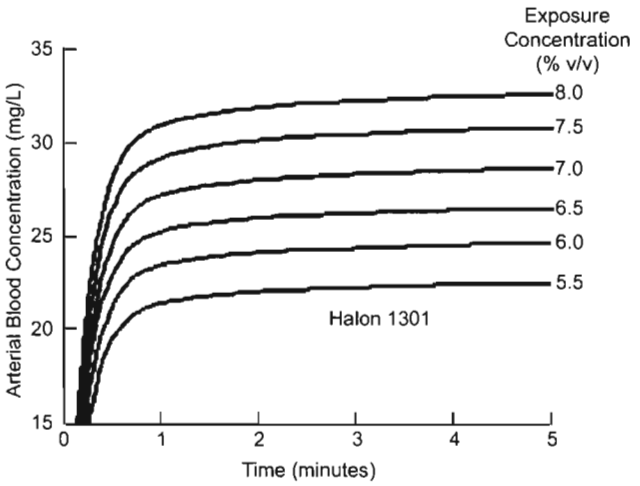

Figure 2. Monte Carlo simulations of physiologically based pharmacokinetic (PBPK) model-derived arterial blood concentration histories for 5-min human exposures to constant Halon 1301 concentrations of 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0% v/v (Vinegar et al., 2000).

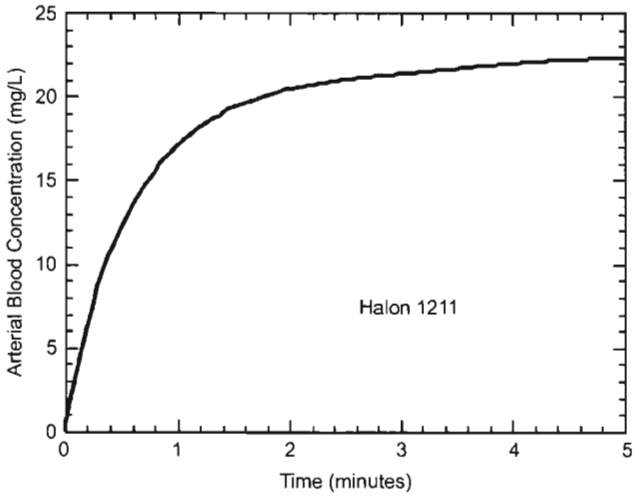

Figure 1. Simulation of physiologically based pharmacokinetic (PBPK) model-derived arterial blood concentration history for a 5-min human exposure to a constant lowest observable adverse effect level (Loael) Halon 1211 concentration of 1.0% v/v (Vinegar et al., 1998).

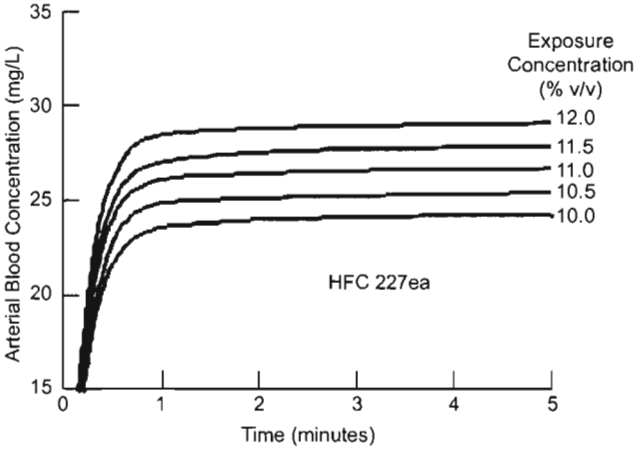

Figure 3. Monte Carlo simulations of physiologically based pharmacokinetic (PBPK) model-derived arterial blood concentration histories for 5-min human exposures to constant Hfc-227ea concentrations of 10.0, 10.5, 11.0, 11.5, and 12.0% v/v (Vinegar et al., 2000).

existing models. Very few toxicologists have experience with the specific PBPK models developed for the inhalation of halocarbons used for fire suppression, and some of those have or will retire with this information, as was the case in our situation. The objectives of this work were to develop a simplified kinetic model for the transport of halocarbons in the human body that uses existing, peer-reviewed PBPK-derived human arterial blood history curves for various agents at constant gas concentration to calculate the blood concentration history for a time-varying halocarbon concentration of these agents in air following the discharge of a fire extinguisher in an aircraft cabin. The validated kinetic model, in combination with a toxicity criterion based on the simulated arterial blood concentration reaching the target arterial blood concentration of a particular halocarbon, provides the technical basis for FAA guidance on the safe use of handheld fire extinguishers in aircraft.

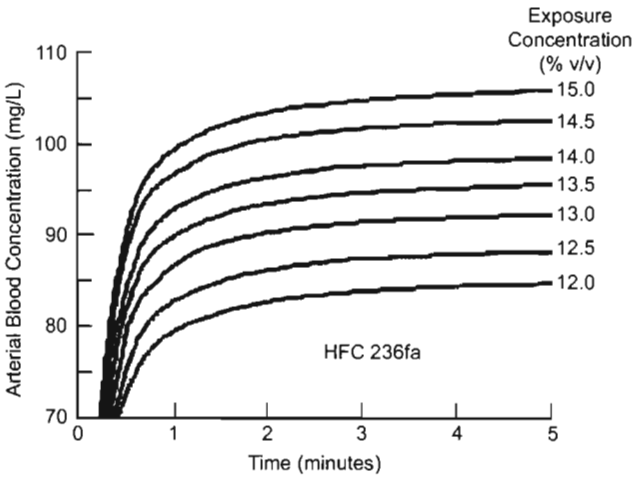

Figure 4. Monte Carlo simulations of physiologically based pharmacokinetic (PBPK) model-derived arterial blood concentration histories for 5-min human exposures to constant Hfc-236fa concentrations of 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, and 15.0% v/v (Vinegar et al., 2000).

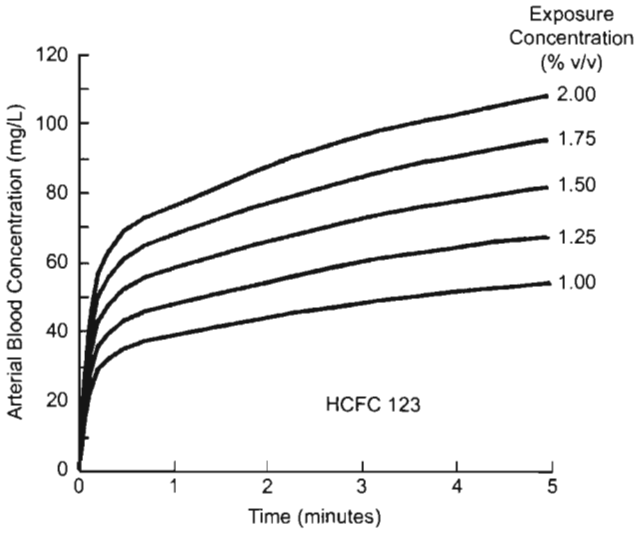

Figure 5. Monte Carlo simulations of physiologically based pharmacokinetic (PBPK) model-derived arterial blood concentration histories for 5-min human exposures to constant Hcfc-123 concentrations of 1.0, 1.25, 1.5, 1.75, and 2.0% v/v (Colton et al., 2008 adjusted by Speitel and Lyon, 2009).

Approach

Our kinetic model for the transport of halocarbon in the bloodstream is shown in Figure 6. In this kinetic model, halocarbon is transported between cabin air in the lungs and the bloodstream, and between the bloodstream and the organs and tissues with characteristic rate constants k_i. Halocarbon is finally eliminated as waste from the organs and tissues.

In the kinetic model for halocarbon transport (Figure 6), the halocarbon in the cabin air enters the lungs and is transported from the lungs to the bloodstream with rate constant k_1 and the reverse process (i.e. respiration) occurs with rate constant k_2. Halocarbon in the bloodstream is transported to the organs and tissues with a single rate constant k_3 and the reverse process (i.e. from the organs and tissues to the bloodstream) proceeds with rate constant k_4. Halocarbon is metabolized in, or eliminated from, the organs and tissues as waste with rate constant k_5. The kinetic model of Figure 6 differs from the PBPK kinetic model by lumping the individual halocarbon exchange reactions between the organs and tissues and blood (see Table 2) into a single transport reaction.

In the kinetic scheme of Figure 6, the instantaneous concentrations of halocarbon in the cabin air, bloodstream, organs and tissues, and waste are A, B, C, and W, respectively. If the equilibrium concentrations of halocarbon in the blood and organs and tissues are $B(\infty)$ and $C(\infty)$, respectively, for a constant concentration of halocarbon in the air $A(t)=A_0$, the partition coefficients for the halocarbon between blood and air (P_{BA}) and between the tissues and air (P_{CA}) are:

$$P_{BA} = \frac{B(\infty)}{A_0} = \frac{k_1}{k_2};$$
$$P_{CA} \equiv \frac{C(\infty)}{A_0} \approx \frac{C(\infty)}{B(\infty)} \frac{B(\infty)}{A_0} = \frac{k_3}{k_4} P_{BA} \quad (1)$$

The individual partition coefficients between the organs and tissues and the gaseous halocarbons in the air are shown in Table 2 (Vinegar et al., 2000; Colton et al., 2008). These

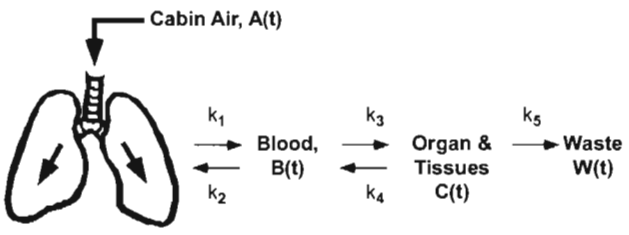

Figure 6. Kinetic model of halocarbon transport in humans.

Table 2. Partition coefficients (log normal distribution) for halocarbons in blood, organs, and tissues (geometric mean ± geometric standard deviation).

	Parameter	HCFC-123[a]	HFC-227ea[b]	HFC-236fa[b]	Halon 1211	Halon 1301[b]
P_{BA}	Blood/air	1.16 ± 1.01	0.033 ± 1.033	0.106 ± 1.053	N/A	0.062 ± 1.057
P_{CA}	Fat/air	70 ± 1	0.347 ± 1.541	0.678 ± 1.104	N/A	0.771 ± 1.164
	Liver/air	3.3 ± 1.1	0.031 ± 1.965	0.106 ± 1.075	N/A	0.145 ± 1.085
	Richly perfused tissues/air	3.3 ± 1.1	0.031 ± 1.965	0.106 ± 1.075	N/A	0.145 ± 1.085
	Slowly perfused tissues/air	2.1 ± 1.1	0.021 ± 5.889	0.091 ± 1.067	N/A	0.159 ± 1.498

[a]Colton et al. (2008).
[b]Vinegar et al. (2000).

partition coefficients are used in the PBPK model to derive the rate constants for the separate transport processes. In the present kinetic model, the individual partition coefficients are lumped together into a single value P_{CA} that represents some average of the global transport process between the blood and the organs and tissues.

According to Figure 6, the rate of accumulation of halocarbon in the arterial blood is the difference between the rate that halocarbon enters the bloodstream by absorption from the lungs and tissues and the rate at which halocarbon leaves the bloodstream by respiration through the lungs and by absorption into the organs and tissues. In Figure 6, the concentration of halocarbon in the cabin air $A(t)$, blood $B(t)$, organs and tissues $C(t)$, and waste $W(t)$ are in units of mg/L, and all of the rate constants have units of reciprocal minutes (min^{-1}).

According to the kinetic scheme of halocarbon transport (Figure 6), the rate of change of arterial blood concentration of halocarbon with time t is

$$\frac{dB}{dt} = k_1 A - k_2 B - k_3 B + k_4 C \tag{2}$$

To solve Equation 2, an expression must be found for C in terms of A or B. The rate of change of halocarbon concentration in the organs and tissues from Figure 6 is

$$\frac{dC}{dt} = k_3 B - k_4 C - k_5 C \tag{3}$$

The rate of elimination of halocarbon from the organs and tissues to waste is negligible in the time scale of interest (5 min), so for practical purposes, $k_5 = 0$. If the blood and air are in rapid equilibrium such that $B(t) = P_{BA} A(t)$, Equation 3 can be solved for C using an integrating factor:

$$C(t) = \int_0^t k_3 B(x) e^{-k_4 (t-x)} dx = k_3 P_{BA} \int_0^t A(x) e^{-k_4 (t-x)} dx \tag{4}$$

Substituting Equation 4 into Equation 2 and separating terms, with $k_{23} = k_2 + k_3$

$$\frac{dB}{dt} + k_{23} B = k_1 A + k_3 k_4 P_{BA} \int_0^t A(x) e^{-k_4 (t-x)} dx \tag{5}$$

Equation 5 can be solved for the halocarbon blood concentration history $B(t)$ for an arbitrary, time-varying concentration of halocarbon in the air $A(t)$.

$$B(t) = k_1 \int_0^t A(x) e^{-k_{23}(t-x)} dx + k_3 k_4 P_{BA} \int_0^t \left(\int_0^t A(x) e^{-k_4 (t-x)} dx \right) e^{-k_{23}(t-y)} dy \tag{6}$$

Equation 6 is the general solution of the kinetic scheme of Figure 6. Two results are of particular interest.

Ventilated compartment: instantaneous discharge of halocarbon at $t = 0$

For a time-varying concentration of halocarbon in a constantly ventilated compartment, such as an aircraft cabin, a particular solution of Equation 6 is obtained as follows. If V is the cabin volume, V^* is the volumetric dilution rate of cabin air with fresh air, and $\tau = V/V^*$ is the characteristic time for cabin air exchange, the concentration of halocarbon at time t is the solution of

$$-\frac{dA}{dt} = \frac{A}{\tau} \tag{7}$$

Assume that an instantaneous discharge of a fire extinguisher(s) at $t = 0$ produces a uniform initial concentration A_0. Separating terms and integrating Equation 7 for an initial condition, $A(0) = A_0$ at $t = 0$

$$A(t) = A_0 e^{-t/\tau} \tag{8}$$

Equation 8 describes a halocarbon air concentration history that decreases exponentially with time due to dilution of the cabin air with fresh air. Substituting Equation 8 for $A(t)$ into Equation 6 gives the concentration of halocarbon in the bloodstream at time t for a ventilated cabin experiencing an instantaneous discharge of halocarbon-extinguishing agent at $t = 0$.

$$B(t) = k_1 A_0 \int_0^t e^{-k_{23} t + (k_{23} - 1/\tau) x} dx + A_0 k_3 k_4 P_{BA} \int_0^t \left(\int_0^t e^{-k_4 t + (k_4 - 1/\tau) x} dx \right) e^{-k_{23}(t-y)} dy \tag{9}$$

Equation 9 is explicit in time and can be solved exactly for $B(t)$

$$B(t) = A_0\left\{\alpha\left(e^{-t/\tau} - e^{-k_{23}t}\right) + \beta\left(e^{-t/\tau} - e^{-k_4 t}\right)\left(1 - e^{-k_{23}t}\right)\right\} \quad (10)$$

The constants in Equation 10 are

$$\alpha = \frac{k_1}{k_{23} - 1/\tau};\ \beta = \frac{k_3 k_4 P_{BA}}{(k_4 - 1/\tau)k_{23}} \quad (11)$$

Unventilated compartment: instantaneous discharge of halocarbon at $t = 0$

An unventilated compartment is a compartment in which the air-exchange rate is 0, or the time constant for air exchange is infinite, $\tau = \infty$, so that the concentration of halocarbon is static (constant). For this condition, the constants (Equation 11) reduce to $\alpha = k_1/k_{23}$ and $\beta = k_3 P_{BA}/k_{23}$. Equation 11 then becomes

$$B(t) = A_0\left(1 - e^{-k_{23}t}\right)\left(\alpha + \beta\left(1 - e^{-k_4 t}\right)\right) \quad (12)$$

Equation 12 requires four parameters—α, k_{23}, k_4, and β—that can be determined from the initial slope of the concentration history and the slope and intercept at long times, as will be described. According to Equation 12, the equilibrium of concentration of halocarbon in the arterial blood at $t = \infty$ is $B(\infty) = A_0(\alpha + \beta) = (k_1 + k_3 P_{BA})/k_{23}$ from which $P_{BA} = B(\infty)/A_0 = k_1/k_2$, as per Equation 1.

If halocarbon transport between the tissues and the bloodstream is negligible compared with the air-blood processes, $k_3 = k_4 = 0$, $\beta = 0$, and Equation 12 simplifies to

$$B(t) = A_0\alpha\left(1 - e^{-k_2 t}\right) = A_0\frac{k_1}{k_2}\left(1 - e^{-k_2 t}\right) \quad (13)$$

Again, the ratio of the equilibrium concentration of halocarbon in the arterial blood to the concentration in air is $B(\infty)/A_0 = k_1/k_2 = P_{BA}$, as per Equation 1. The qualitative behavior of the kinetic model for ventilated and unventilated compartments in which transport of halocarbon between the organs and tissues to the bloodstream is allowed (Equations 10 and 12) or disallowed (Equation 13) is shown in Figure 7. The arterial blood concentration histories in Figure 7 were evaluated for unit values of k_1, k_2, k_{23}, and A_0, and for $\beta = 1/2$, $k_4 = 1/10$ (feedback from organs and tissues) or $\beta = 0$ (no feedback), and for $\tau = 3$ min (ventilation) or $\tau = \infty$ (no ventilation).

Methods

The kinetic model was fit to PBPK-derived human arterial blood concentrations of the halocarbons in Figures 1–5 using a commercial spread sheet program (KaleidaGraph, Synergy Software, Reading, PA) and personal computer (Apple iMac). Values of α, k_{23}, β, and k_4 were obtained by inspection of the fit of Equation 12 to discreet PBPK values abstracted from published graphical data by digitization. The absolute relative deviation of the arterial blood concentrations of the kinetic model y_{kin} from the PBPK-derived data y_{PBPK} for each of the data points used for the fits in Figures 8–12 is defined:

Absolute relative deviation ≡

$$\frac{\frac{1}{n}\sum|y_{kin} - y_{PBPK}|}{\frac{1}{n}\sum y_{PBPK}} = \frac{\sum|y_{kin} - y_{PBPK}|}{\sum y_{PBPK}}$$

The kinetic parameters determined in this way were used in Equation 10 to calculate the arterial blood concentration history $B(t)$ for a human in an aircraft cabin in which halocarbon-extinguishing agents are discharged, producing an instantaneous and uniform initial concentration A_0 that

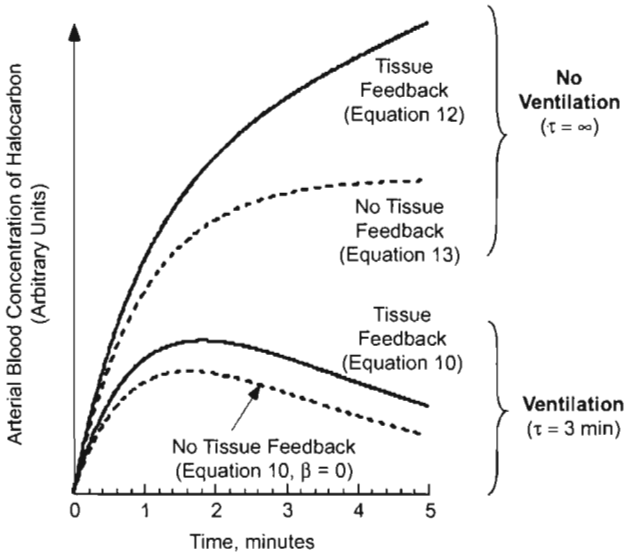

Figure 7. Arterial blood concentration histories for halocarbon in ventilated and unventilated cabins with and without tissue feedback to the blood.

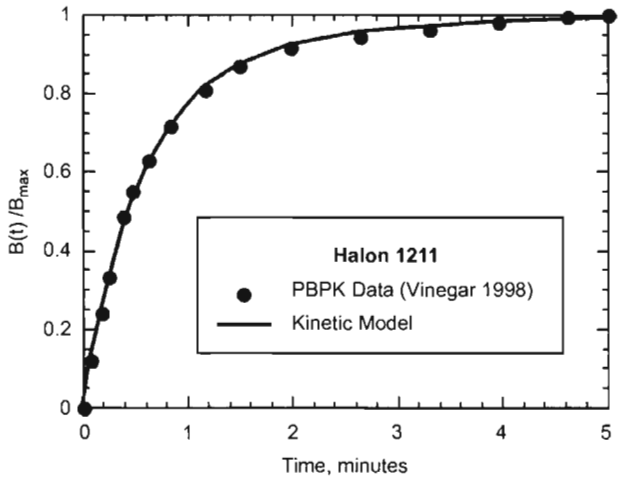

Figure 8. Comparison of kinetic model to PBPK data for human arterial blood concentration history of Halon 1211 for simulated exposure to $A_0 = 1\%$ v/v (72 mg/L). The absolute relative deviation is 1.6%.

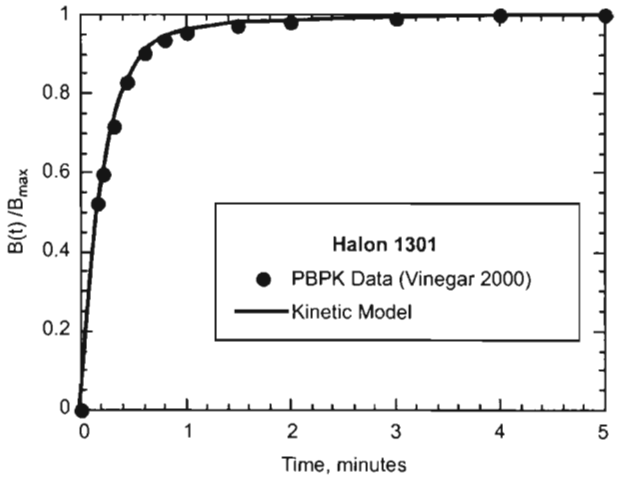

Figure 9. Comparison of kinetic model to PBPK data for human arterial blood concentration history of Halon 1301 for simulated exposure to $A_0 = 7.0\%$ v/v (439 mg/L). The absolute relative deviation is 1.0%.

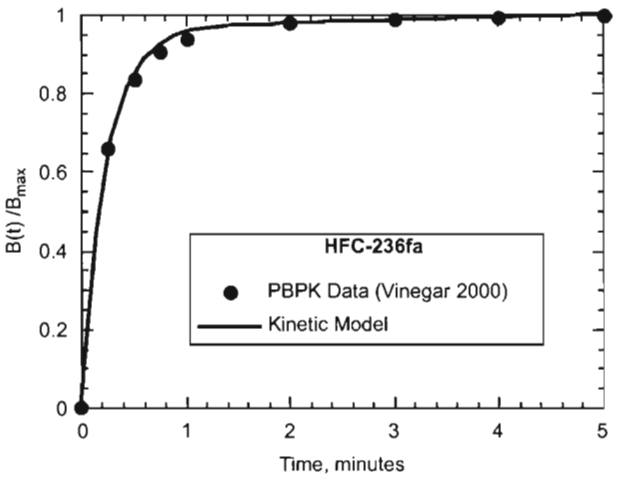

Figure 11. Comparison of kinetic model to PBPK data for human arterial blood concentration history of HFC-236fa for simulated exposure to $A_0 = 15\%$ v/v (979 mg/L). The absolute relative deviation is 1.2%.

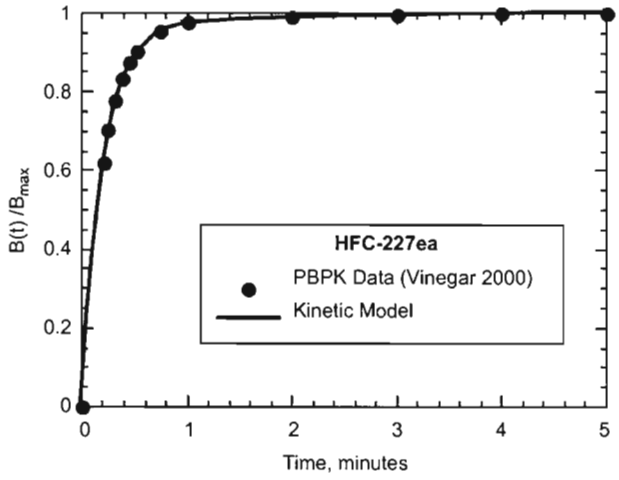

Figure 10. Comparison of kinetic model to PBPK data for human arterial blood concentration history of HFC-227ea for simulated exposure to $A_0 = 10\%$ v/v (726 mg/L). The absolute relative deviation is 1.2%.

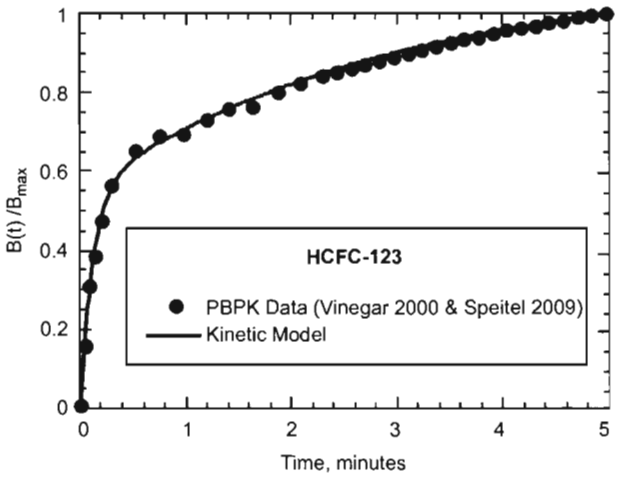

Figure 12. Comparison of kinetic model to PBPK data for human arterial blood concentration history of HCFC-123 for simulated exposure to $A_0 = 1.28\%$ v/v (79 mg/L). The absolute relative deviation is 3.1%.

decays with time according to a simple dilution curve (i.e. Equation 8). The kinetic parameters for Halon 1211 were also used in Equation 6 to calculate the arterial blood concentration histories $B(t)$ for two occupants of a small military vehicle (a tank) subjected to a measured time-varying concentration of Halon 1211 (Vinegar et al., 1998). The Halon 1211 concentration history and the associated PBPK predictions $B(t)$ of Vinegar et al. (1998) were obtained by digitizing the graphical data. The derived kinetic parameters for HCFC-123 were used to calculate the maximum arterial blood concentration $B(t_{max}) = B_{max}$ of that agent discharged into a perfectly mixed, constantly ventilated aircraft cabin at various cabin air-exchange times. The normalized results B_{max}/B_{safe} were compared with PBPK-derived values for the same conditions (Colton et al., 2008) and the same target arterial blood concentration B_{safe} (Speitel and Lyon, 2009).

Results and discussion

Calibration of the kinetic model for fire-extinguishing agents

The full kinetic model includes tissue exchange of halocarbon between the bloodstream and the tissues (Equations 6, 10, and 12) and requires four parameters. If the concentration of halocarbon in the arterial blood is measured (or modeled using PBPK) for a closed compartment ($\tau = \infty$) having a constant concentration of the halocarbon in the air, A_0, Equation 12 applies, and the four parameters that need to be determined are α, k_{23}, k_4, and β. These parameters can be determined from the measured or simulated (PBPK) blood concentration history using a robust curve-fitting computer program with initial estimates for the parameters determined by a graphical procedure. The

graphical procedure used as a first estimate of the four model parameters is based on the approximation that, for small k_4, Equation 12 reduces to

$$B(t) \approx A_0\left(1-e^{-k_{23}t}\right)\left(\alpha+\beta k_4 t\right) \tag{14}$$

The initial slope $S(0)=S_0$ of a plot of $B(t)$ versus time is $S_0=A_0k_1$ according to Equations 12–14. The intercept and slope at long times are $I=A_0\alpha=(S_0/k_{23})$ and $S_\infty=A_0\beta k_4$, respectively. From these relationships and a numerical value for P_{CA} (from Table 2), the four independent parameters needed to describe the blood concentration history in any situation are obtained from the initial slope of the concentration history (S_0) and the slope (S_∞) and intercept (I) at long times:

$$\alpha=\frac{I}{A_0} \quad k_{23}=\frac{S_0}{I} \quad k_4=\sqrt{\frac{S_\infty S_0}{A_0 I P_{CA}}} \quad \beta=\sqrt{\frac{I S_\infty P_{CA}}{A_0 S_0}} \tag{15}$$

Figure 13 illustrates the graphical procedure used to obtain the first estimate of these parameters for HCFC-123 from the blood concentration history at a constant exposure concentration in air, $A_0=79$ mg/L (1.28% v/v).

The rate constants k_1, k_2, k_3, and k_4 for halocarbons are obtained from the initial estimates for k_4, k_{23}, α, β and the P_{BA} in Table 2 using the relationships: $k_1=\alpha k_{23}$, $k_3=\langle k_3\rangle$ = average of $\beta k_{23}/P_{BA}$ and $k_{23}-\langle k_2\rangle$; $k_2=\langle k_2\rangle$ = average of k_1/P_{BA} and $k_{23}-\langle k_3\rangle$ for each agent. The rate constants are iterated in the formulae (Equations 10 and 11) until a best fit is obtained by inspection for a constant concentration of the halocarbon in air, A_0. The optimized values of the rate constants for each agent are listed in Table 3 in units of reciprocal minutes based on gas and blood concentrations of halocarbon expressed in units of mg/L. Figures 8–12 show the agreement and relative error between the kinetic model with the parameters in Table 3 and the PBPK-derived arterial blood concentrations, $B(t)$, divided by the maximum arterial blood concentration, B_{max}, at the end of the 5-min exposure to a constant concentration of the agents listed in Table 1.

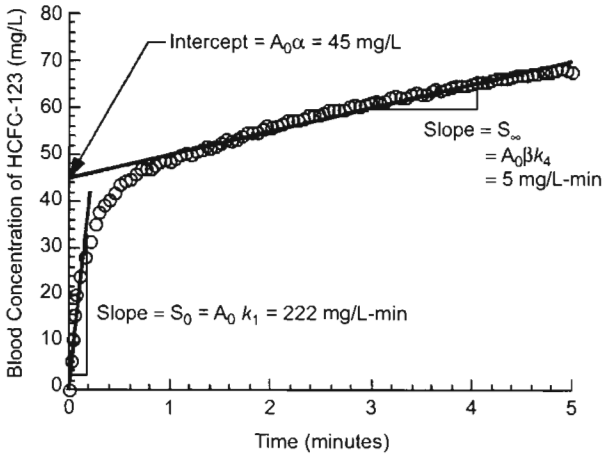

Figure 13. Graphical procedure used to determine rate constants for kinetic model from halocarbon blood concentration history.

Blood concentration histories of fire-extinguishing agents in ventilated compartments

For the blood concentration history described by Equation 10 or 12, the ratio of two blood concentrations, $B_1(t)$ and $B_2(t)$ at any time, t, is independent of the initial halocarbon concentration in air A_0 and is simply the ratio of the time-dependent terms $f_1(t,\tau_1)/f_2(t,\tau_2)$. If $f_2(t,\tau_2)=f_2(5,\infty)$ corresponds to the arterial blood concentration at 5 min in an unventilated compartment ($\tau=\infty$) containing halocarbon at the maximum safe-use concentration, A_{safe}, in Table 1, then $B_{max}=B_{safe}$, then the ratio of the arterial blood concentration at t,τ to the target arterial concentration B_{safe}, is

$$\frac{B(t,\tau)}{B(5,\infty)}=\frac{B(t,\tau)}{B_{safe}} =\frac{\alpha\left(e^{-t/\tau}-e^{-k_{23}t}\right)+\beta\left(e^{-t/\tau}-e^{-k_4 t}\right)\left(1-e^{-k_{23}t}\right)}{\alpha_\infty\left(1-e^{-5k_{23}}\right)+\beta_\infty\left(1-e^{-5k_4}\right)\left(1-e^{-5k_{23}}\right)} \tag{16}$$

where $\alpha_\infty=\alpha(\tau=\infty)$ and $\beta_{safe}=\beta(\tau=\infty)$. The inverse of Equation 16 at its maximum point is the ventilation benefit.

$$\textit{Ventilation benefit}=\frac{B_{safe}}{B(t,\tau)} =\frac{\alpha_\infty\left(1-e^{-5k_{23}}\right)+\beta_\infty\left(1-e^{-5k_4}\right)\left(1-e^{-5k_{23}}\right)}{\alpha\left(e^{-t/\tau}-e^{-k_{23}t}\right)+\beta\left(e^{-t/\tau}-e^{-k_4 t}\right)\left(1-e^{-k_{23}t}\right)} \tag{17}$$

Figures 14–18 show the ratio of the arterial blood concentration of halocarbon in a ventilated compartment at time t for various air-exchange times τ to the arterial blood concentration at 5 min in an unventilated compartment for an instantaneous discharge of the safe-use concentration (for

Table 3. Rate constants for kinetic model of halocarbon uptake and elimination.

	Source							
	Table 1	Fitted parameter				Calculated from fitted parameters		
Agent	P_{BA}	α	β	k_{23} (min^{-1})	k_4 (min^{-1})	k_3 (min^{-1})	k_2 (min^{-1})	k_1 (min^{-1})
Halon 1211	0.12*	0.26	0.050	1.9	0.50	0.6	1.3	0.49
Halon 1301	0.062	0.06	0.003	4.4	0.40	0.1	4.3	0.27
HFC-227ea	0.033	0.03	0.003	4.8	0.10	0.2	4.6	0.16
HFC-236fa	0.106	0.10	0.17	4.1	0.01	0.02	4.08	0.43
HCFC-123	1.16	0.48	0.48	8.5	0.33	4.2	4.3	4.08

*$P_{BA}=k_1/\langle k_1/P_{BA}\rangle$, where $\langle k_1/P_{BA}\rangle=4.2\pm0.6$ min^{-1} is the average k_1/P_{BA} for the other four halocarbons.

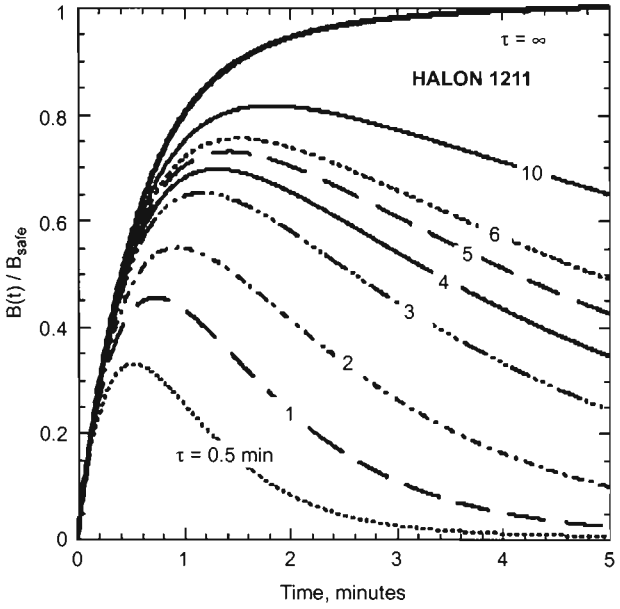

Figure 14. Ratio of the arterial blood concentration of Halon 1211 to the target value B_{safe} for simulated human exposures to A_{safe} in a ventilated cabin at the indicated air-exchange times.

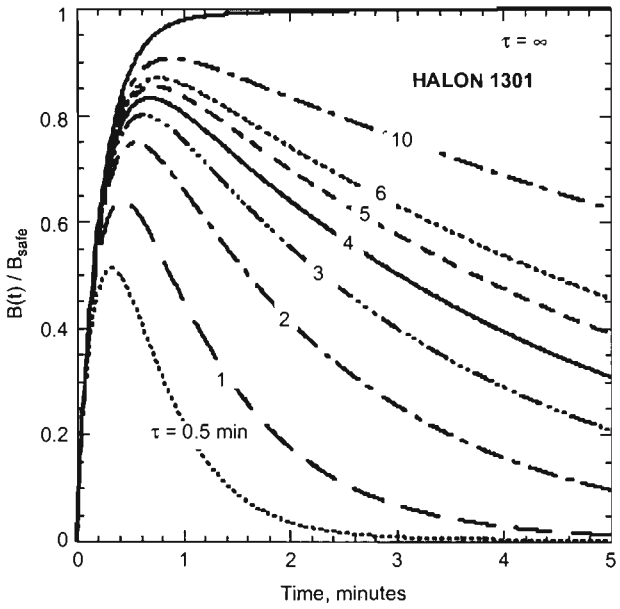

Figure 15. Ratio of the arterial blood concentration of Halon 1301 to the target value B_{safe} for simulated human exposures to A_{safe} in a ventilated cabin at the indicated air-exchange times.

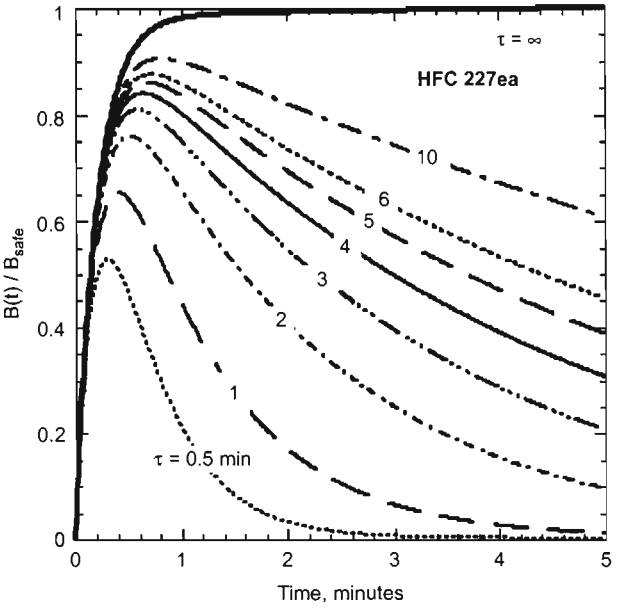

Figure 16. Ratio of the arterial blood concentration of HFC-227ea to the target value B_{safe} for simulated human exposures to A_{safe} in a ventilated cabin at the indicated air-exchange times.

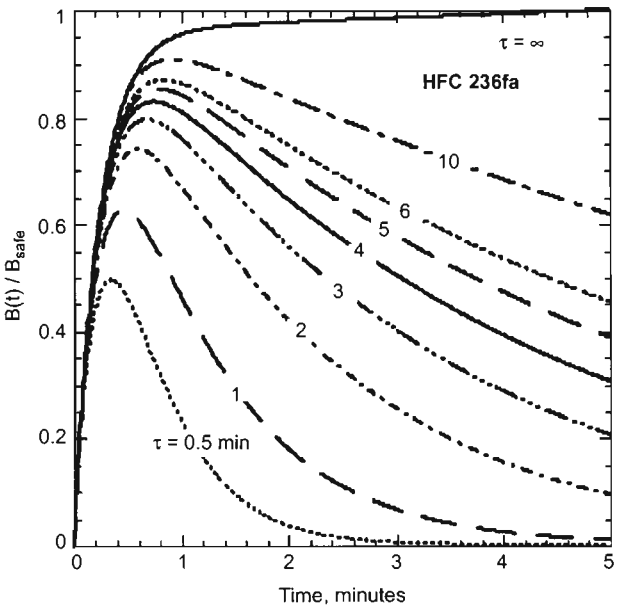

Figure 17. Ratio of the arterial blood concentration of HFC-236fa to the target value B_{safe} for simulated human exposures to A_{safe} in a ventilated cabin at the indicated air-exchange times.

unventilated aircraft) A_{safe}, as per Equation 16. For the special case when the initial concentration is the maximum safe 5-min human exposure concentration, A_{safe}, B_{max} is the target arterial concentration, B_{safe}.

The maximum values of $B(t)/B_{safe}$ in Figure 18 for HCFC-123 are plotted as B_{max}/B_{safe} in Figure 19 versus cabin air-exchange time. Also plotted in Figure 19 are B_{max}/B_{safe} values obtained from the arterial blood concentration histories computed with the PBPK model for HCFC-123 (Colton et al., 2008) adjusted to have the same B_{safe} values (Speitel and Lyon, 2009). It is seen that the maximum arterial blood concentration of HCFC-123 in a ventilated aircraft cabin, $B(t_{max}, \tau) = B_{max}(\tau)$, to the target arterial concentration B_{safe} is plotted in Figure 19 versus cabin air-exchange time for the kinetic model and the PBPK model (Colton et al., 2008) using the same B_{safe} values (Speitel and Lyon, 2009).

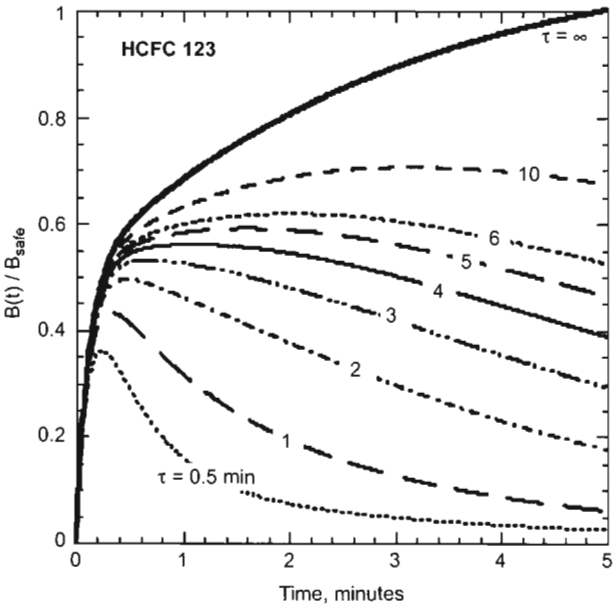

Figure 18. Ratio of the arterial blood concentration of HCFC-123 to the target value B_{safe} for simulated human exposures to A_{safe} in a ventilated cabin at the indicated air-exchange times.

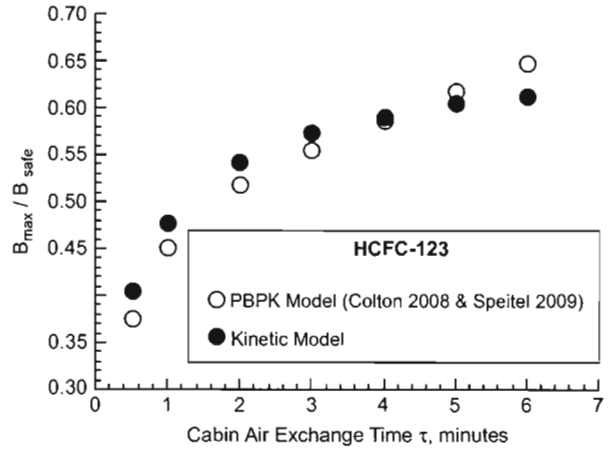

Figure 19. Ratio of the maximum arterial blood concentration B_{max}, to the target value B_{safe} for simulated exposure to HCFC-123 at A_{safe} in a ventilated cabin at the indicated air-exchange times for the kinetic model (black circles) and the physiologically based pharmacokinetic (PBPK) model (white circles) (Colton et al., 2008, and Speitel et. al., 2009). The absolute relative deviation is 4%.

The arterial blood concentration histories $B(t)$ calculated by the PBPK model for the measured air concentration histories $A(t)$ of Halon 1211 discharged in a small compartment are shown in Figures 20 and 21 (Vinegar et al., 1998) for two positions in the compartment at which Halon 1211 concentration measurements were made. Also shown in Figures 20 and 21 are the $B(t)$ calculated for the measured $A(t)$ using Equation 6 with the Halon 1211 kinetic parameters in Table 3. It is seen that the kinetic model reproduces the magnitudes and dynamics of the PBPK-derived arterial

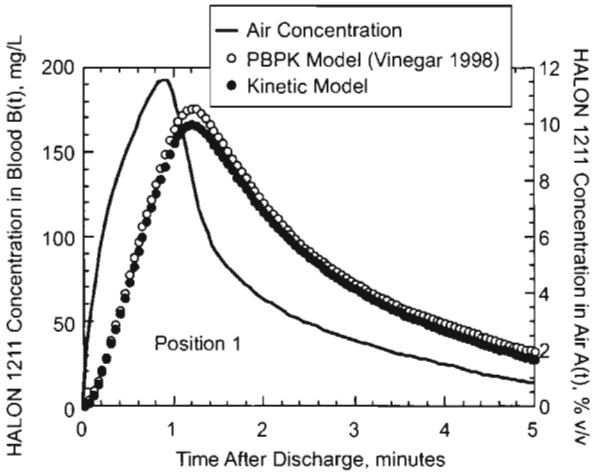

Figure 20. Comparison of the arterial blood concentration history at position 1 in a small compartment for the indicated time-varying concentration of Halon 1211 calculated by the kinetic model (black circles) and the physiologically based pharmacokinetic (PBPK) model (white circles) for Halon 1211 (Vinegar et al., 1998). The absolute relative deviation is 5.6%.

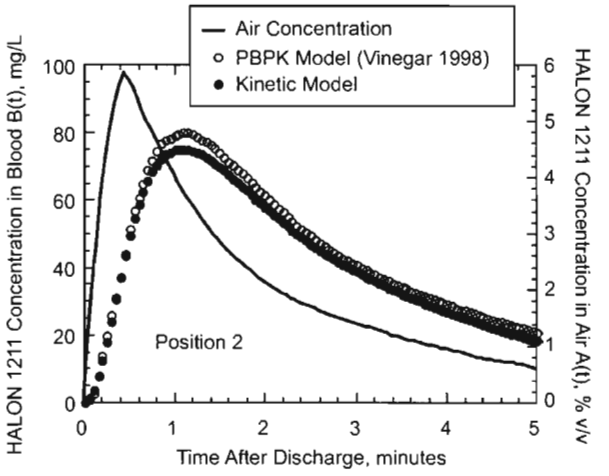

Figure 21. Comparison of the arterial blood concentration history at position 2 in a small compartment for the indicated time-varying concentration of Halon 1211 calculated by the kinetic model (black circles) and the physiologically based pharmacokinetic (PBPK) model (white circles) for Halon 1211 (Vinegar et al., 1998). The absolute relative deviation is 5.8%.

blood concentration histories to a high degree of accuracy, with an absolute relative error of <6%.

Conclusions

A phenomenological kinetic model for uptake and elimination of gaseous halocarbons was developed to describe the arterial blood concentration history of humans exposed to time-varying concentrations of fire-extinguishing agents. The kinetic model was calibrated using PBPK-derived data for constant concentration exposures to several common fire-

extinguishing agents. The calibrated kinetic model was able to predict the blood concentration histories of passengers in perfectly mixed, constantly ventilated aircraft cabins in which these agents are instantaneously discharged as well as the PBPK model for HCFC-123. The kinetic model also captured the magnitude and dynamics of the human arterial blood concentration history as well as the PBPK model for a time-varying Halon 1211 concentration in a small compartment. We therefore conclude that the kinetic model, properly calibrated with PBPK-derived human arterial blood concentration data for a constant exposure concentration, can be used to calculate safe exposure limits in compartments with time-varying concentrations of halocarbon fire-extinguishing agents.

Declaration of interest

Commercial equipment, instruments, materials, and companies may be identified in this article to adequately specify the experimental procedure. This in no way implies endorsement or recommendation by the Federal Aviation Administration.

References

Code of Federal Regulations. 1987. Title 40, Chapter 1—Environmental Protection Agency, Part 82, Protection of Stratospheric Ozone, Subpart G—Significant New Alternatives Policy Program, and Subpart H—Halon Emissions Reduction.

Colton B, Gargas M, Sweeney L. 2008. Setting Acute Exposure Limits for the Halotron 1 Clean Agent Onboard Aircraft Using Physiologically Based Pharmacokinetic Modeling, Private Communication, July 16, 2008.

Eklund TI. 1983. Analysis of Dissipation of Gaseous Extinguisher Agents in Ventilated Compartments, FAA report DOT/FAA/CT-83/1.

Federal Aviation Administration Advisory Circular AC 20-42C. March 1984. Hand Fire Extinguishers for Use in Aircraft.

Horrell PJ Hardy CJ Moore SA Mann P. 2007. Huntingdon Life Sciences Ltd., Halotron 1 Measurement of Blood Levels for Cardiac Sensitization Assessment Following Inhalation Administration to Beagle Dogs, Huntingdon, England, November 6, 2007.

Jepson G. August 2008. Senior Fluoroproducts Toxicologist and Manager of the Biochemical and Molecular Toxicology Haskell Laboratory for Health and Environmental Sciences at DuPont, Private Communication.

Kenny TJ Grierson KL Bannerman M Hardy CJ Gilkison IS. 1998. Huntingdon Life Science Ltd., HFC-236fa, HFC-227ea, HFC-125 and CF3I/ An Inhalation Study to Investigate the Blood Levels of Inhaled Halocarbons in the Beagle Dog, Huntingdon, England, Report 1FP 001/984370.

Mullin LS, Reinhardt CF, Hemingway RE. 1979. Cardiac arrhythmias and blood levels associated with inhalation of Halon 1301. Am Ind Hyg Assoc J 40:652-658.

National Fire Protection Agency. 2008. 2001: Standard on Clean Agent Fire-Extinguishing Systems, NFPA, 1 Batterymarch Park, Quincy, MA 02169-7471.

Reinhardt CF, Azar A, Maxfield ME, Smith PE Jr, Mullin LS. 1971. Cardiac arrhythmias and aerosol 'sniffing.' Arch Env Health 22:265-279.

Speitel LC. July 1995. Toxicity Assessment of Combustion Gases and Development of a Survival Model, FAA Report DOT/FAA/AR-95/5.

Speitel LC, Lyon RE. August 2009. Guidelines for Safe Use of Gaseous Halocarbon Extinguishing Agents in Aircraft, FAA Report DOT/FAA/AR-08/3.

Tabscott RE, Speitel LC, eds. February 2002. Options to the Use of Halons for Aircraft Fire Protection Systems—2002 Update, Task Group on Halon Options, International Halon Replacement Working Group, FAA report DOT/FAA/AR-99/63.

Vinegar A. 2001. Modeling cardiac sensitization potential of humans exposed to Halon 1301 or Halon 1211 aboard aircraft. Aviat Space Environ Med 72:928-936.

Vinegar A, Jepson GW, Cisneros M, Rubenstein R, Brock WJ. 2000. Setting safe acute exposure limits for Halon replacement chemicals using physiologically based pharmacokinetic modeling. Inhal Toxicol 12: 751-763.

Vinegar A, Jepson GW, Hammann SJ, Harper G, Dierdorf DS, Overton JH. 1999. Simulated blood levels of CF3I in personnel exposed during its release from an F-15 Jet Engine Nacelle and during intentional inhalation. AIHA J 60:403-408.

Vinegar A, Jepson GW, Overton JH. 1998. PBPK modeling of short-term (0-5 min) human inhalation exposures to halogenated hydrocarbons. Inhal Toxicol 10:411-429.

Webster H. August 2002. Development of a Minimum Performance Standard (MPS) for Hand-Held Fire Extinguishers as a Replacement for Halon 1211 on Civilian Transport Category Aircraft, FAA report DOT/FAA/AR-01/37.