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A Simplified Kinetic Model for Predicting Arterial Blood Concentrations for Humans Exposed to Gaseous Halocarbon Fire Extinguishing Agents

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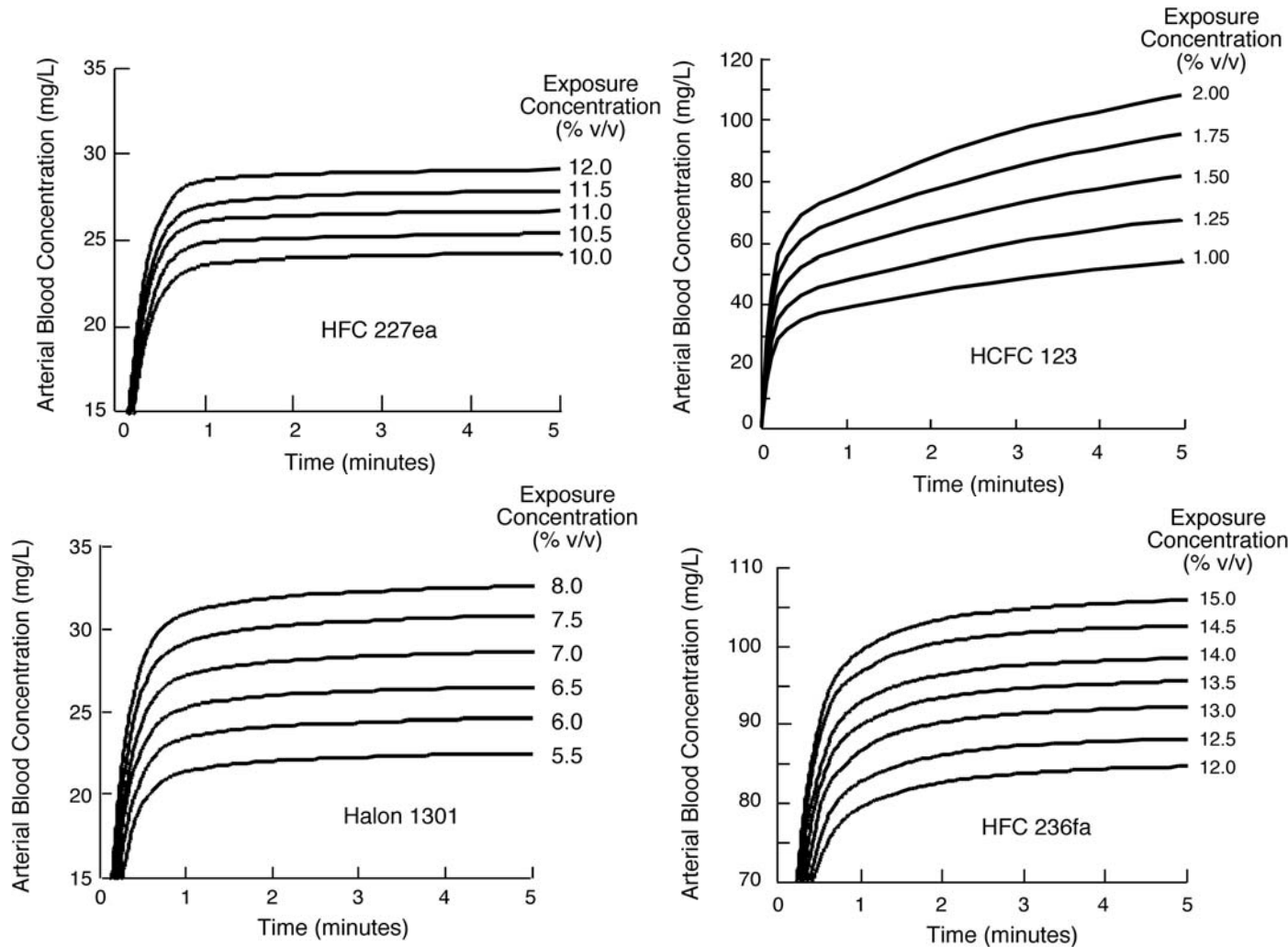
Goal

Provide an economical methodology for calculating safe human exposure limits for time-varying concentrations of gaseous halocarbon fire extinguishing agents when only PBPK-derived human blood concentration histories for constant exposure concentrations are available.

Outline

- Develop a simplified kinetic model to predict the blood concentration history for human inhalation of time varying concentrations of halocarbon fire extinguishing agents.
- Calibrate the simplified kinetic model using published PBPK-derived arterial concentration histories for constant concentration exposure to several fire extinguishing agents.
- Use calibrated kinetic model to predict human arterial blood concentration histories for time varying exposures.

Arterial Blood Concentrations Obtained from PBPK Modeling of Simulated Human Exposure to Constant Halocarbon Concentrations

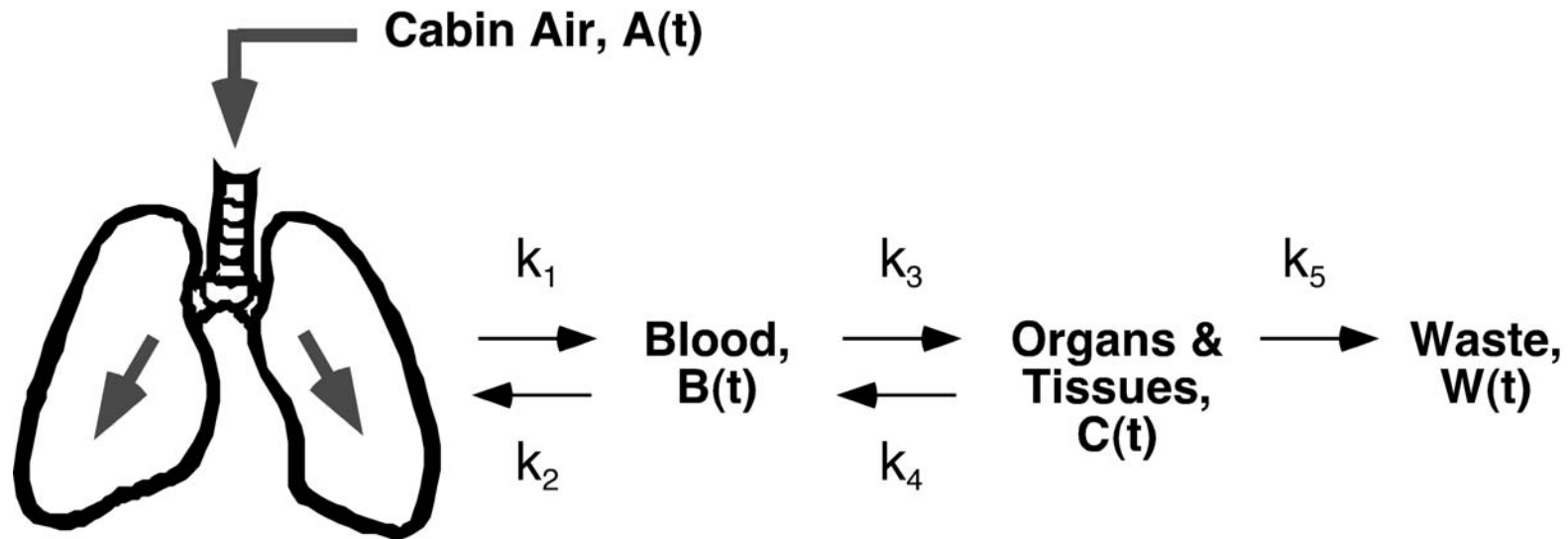


A Simplified Kinetic Model for Predicting Blood Concentrations of Humans Exposed to Gaseous Halocarbon Fire Extinguishing Agents



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Kinetic Model of Halocarbon Transport in Humans



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

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

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Kinetic Model of Halocarbon Transport in Humans

- 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:

$$P_{BA} = \frac{B(\infty)}{A_0} = \frac{k_1}{k_2}$$

$$P_{CA} \equiv \frac{C(\infty)}{A_0} \approx \frac{C(\infty)}{B(\infty)} \frac{B(\infty)}{A_0} = \frac{k_3}{k_4} P_{BA}$$

Kinetic Model Solution for Ventilated Compartment

Gas Concentration History:

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

Arterial Blood Concentration History:

$$B(t) = A_0 \left\{ \alpha \left(e^{-t/\tau} - e^{-k_{23}t} \right) + \beta \left(e^{-t/\tau} - e^{-k_4t} \right) \left(1 - e^{-k_{23}t} \right) \right\}$$

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

Kinetic Model Solution for Unventilated Compartment

Arterial Blood Concentration History:

$$B(t) = A_0 \left(1 - e^{-k_{23}t}\right) \left(\alpha + \beta(1 - e^{-k_4t})\right)$$

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

If halocarbon transport between the tissues and bloodstream is negligible compared to the air-blood process,

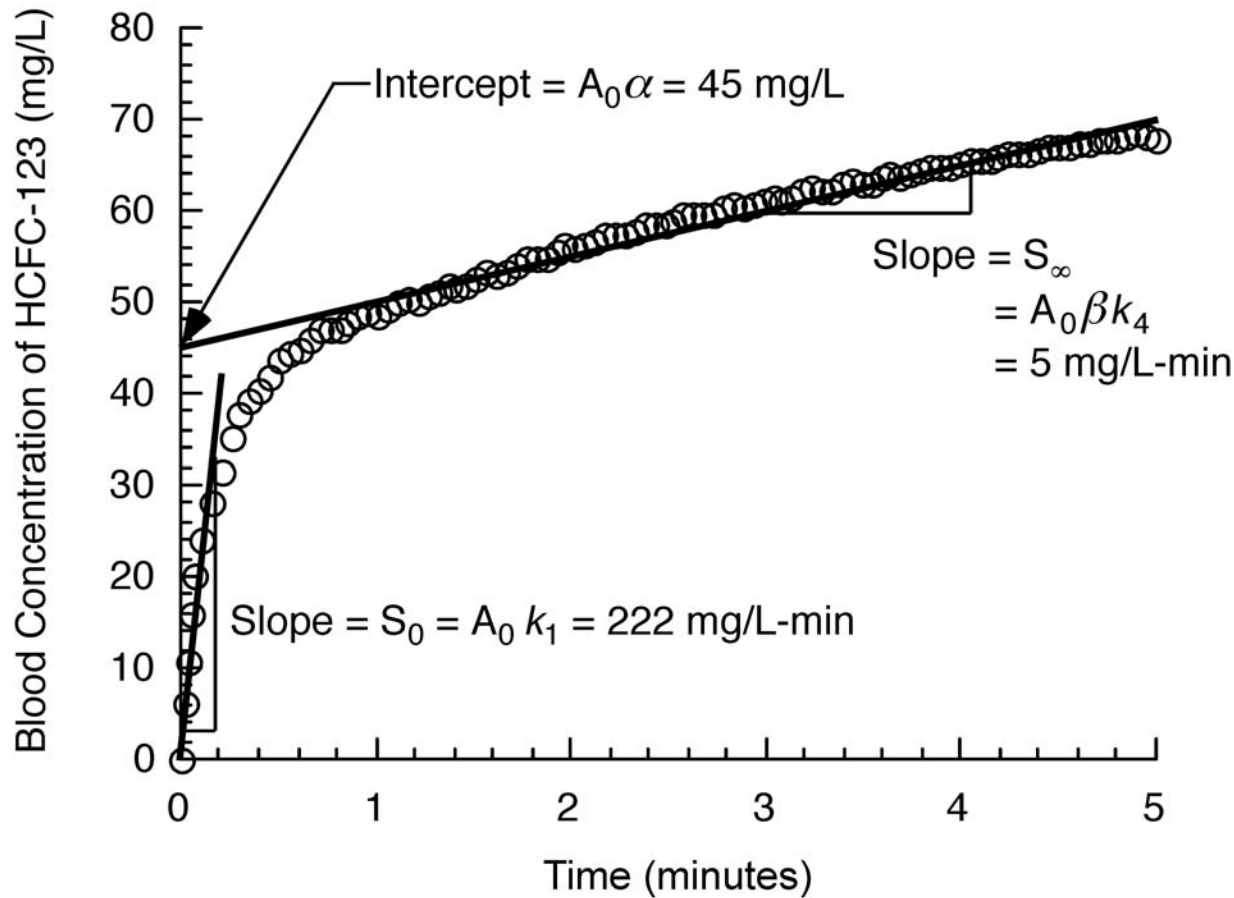
$k_3 = k_4 = 0$, $\beta = 0$, and above equation simplifies to:

$$B(t) = A_0 \alpha \left(1 - e^{-k_2t}\right) = A_0 \frac{k_1}{k_2} \left(1 - e^{-k_2t}\right)$$

Graphical Procedure Used as a First Estimate of Four Parameters

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

Unventilated Compartment
Solution for small k_4



4 Parameters:

$$\alpha = \frac{I}{A_0} \quad k_{23} = \frac{S_0}{I}$$

$$k_4 = \sqrt{\frac{S_\infty S_0}{A_0 I P_{CA}}}$$

$$\beta = \sqrt{\frac{I S_\infty P_{CA}}{A_0 S_0}}$$

$$P_{CA} \equiv \frac{C(\infty)}{A_0} \approx \frac{k_3}{k_4} P_{BA}$$

$$A_0 = 79 \text{ mg/L (1.28\%v/v)}$$

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Determination of Rate Constants

- 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} using the relationships:
 - $k_1 = \alpha k_{23}$,
 - $k_3 = \langle k_3 \rangle = \text{average of } \beta k_{23} / P_{BA} \text{ and } k_{23} - \langle k_2 \rangle$;
 - $k_2 = \langle k_2 \rangle = \text{average of } k_1 / P_{BA} \text{ and } k_{23} - \langle k_3 \rangle \text{ for each agent.}$
- *The rate constants are iterated in the formulae (ventilated compartments) until a best fit is obtained by inspection for a constant concentration of the halocarbon in air, A_0 .*

Rate Constants for Kinetic Model of Halocarbon Uptake

	Source							
	Partition Coefficient	Fitted Parameter				Calculated From Fitted Parameters		
		α	β	k_{23} (min ⁻¹)	k_4 (min ⁻¹)	k_3 (min ⁻¹)	k_2 (min ⁻¹)	k_1 (min ⁻¹)
Agent	P _{BA}							
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

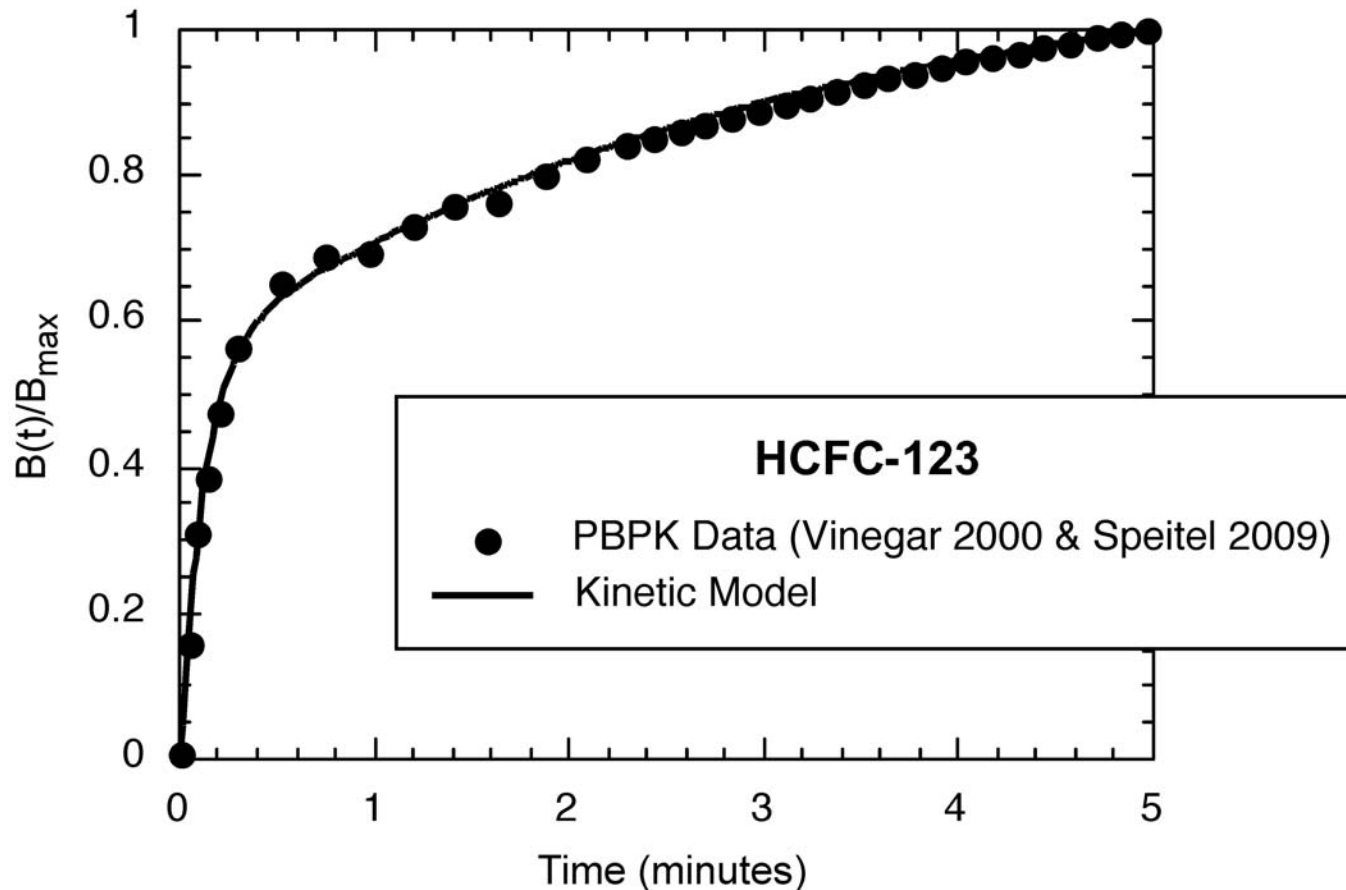
* $P_{BA} = k_1 / \langle k_1 / P_{BA} \rangle$, where $\langle k_1 / P_{BA} \rangle = 4.2 \pm 0.6 \text{ min}^{-1}$ is the average k_1 / P_{BA} for the other 4 halocarbons

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Comparison of the Kinetic Model to PBPK Data for Simulated Exposures to HCFC-123



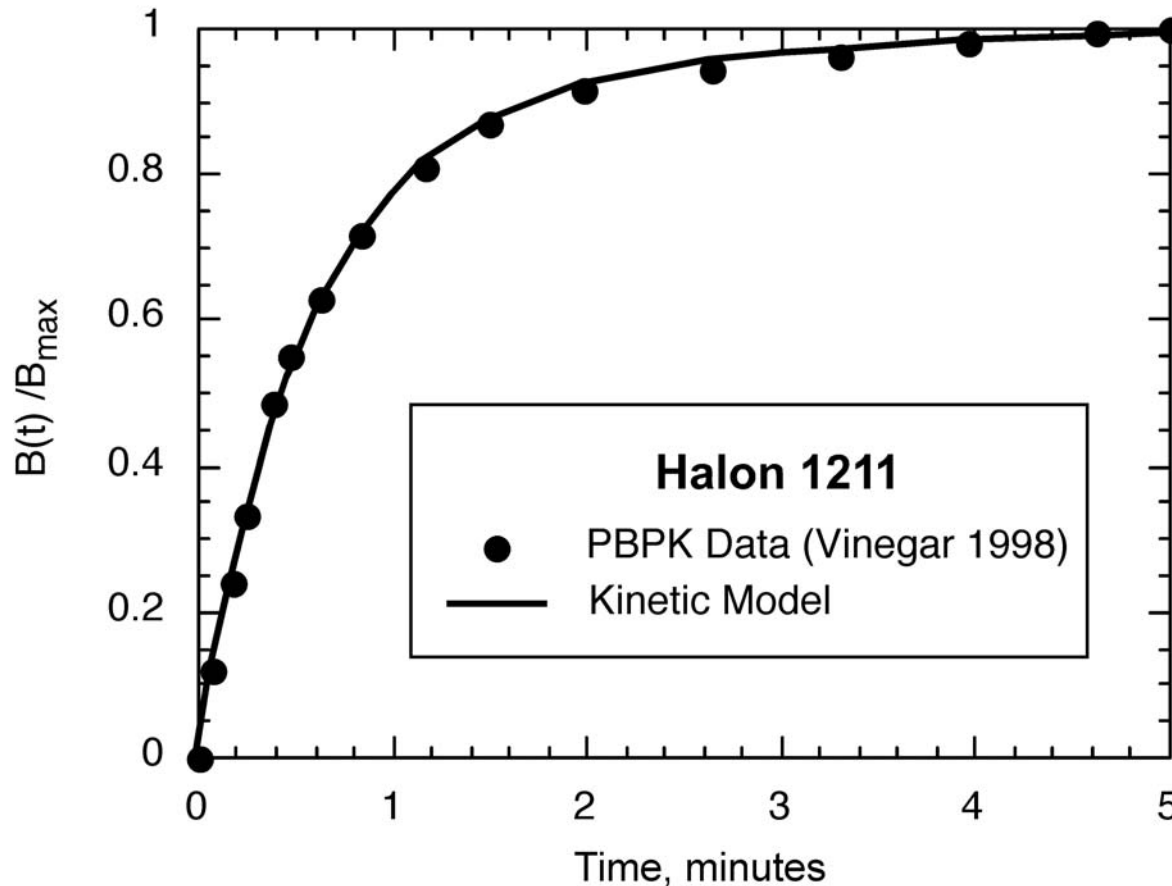
$A_0 = 1.28\% \text{ v/v (79 mg/L)}$

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Comparison of the Kinetic Model to PBPK Data for Simulated Exposures to Halon 1211



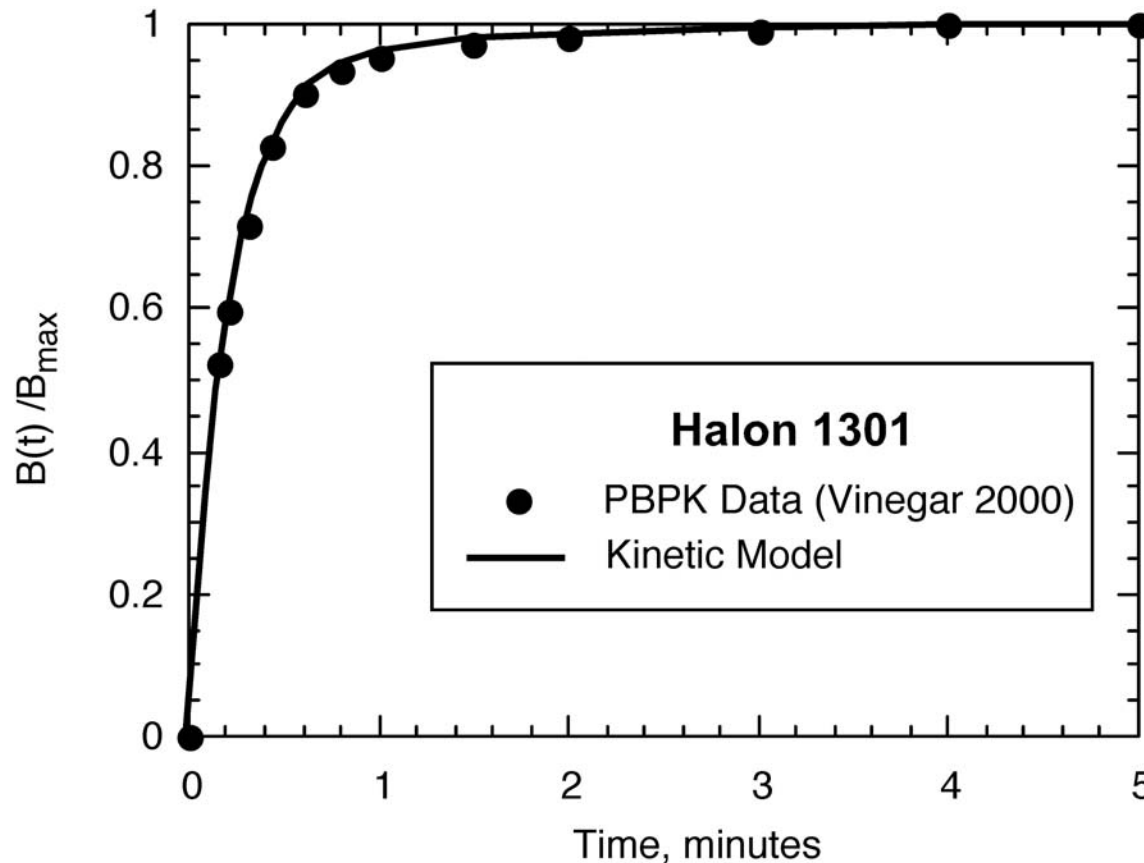
$A_0 = 1\% \text{ v/v (72 mg/L)}$

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Comparison of the Kinetic Model to PBPK Data for Simulated Exposures to Halon 1301



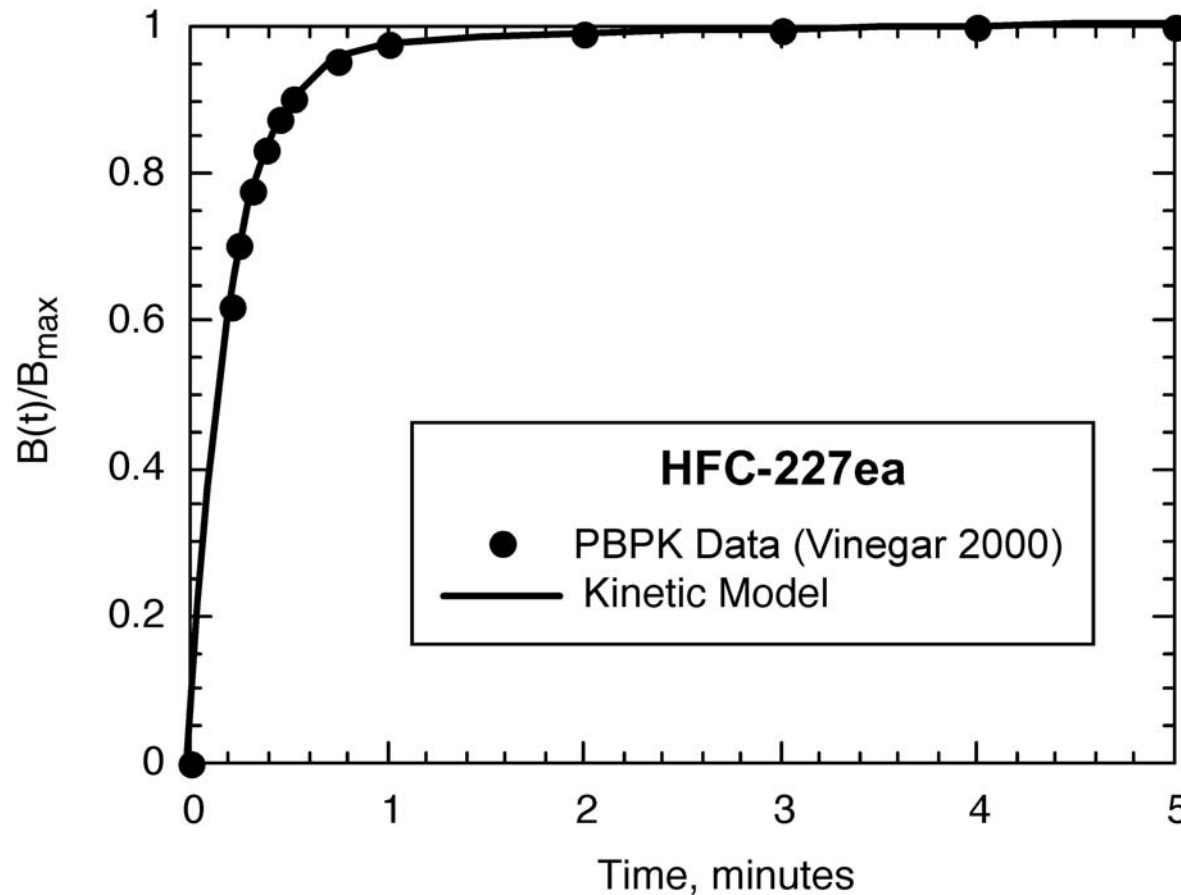
$A_0 = 7.0\% \text{ v/v (439 mg/L)}$

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Comparison of the Kinetic Model to PBPK Data for Simulated Exposures to HFC-227ea



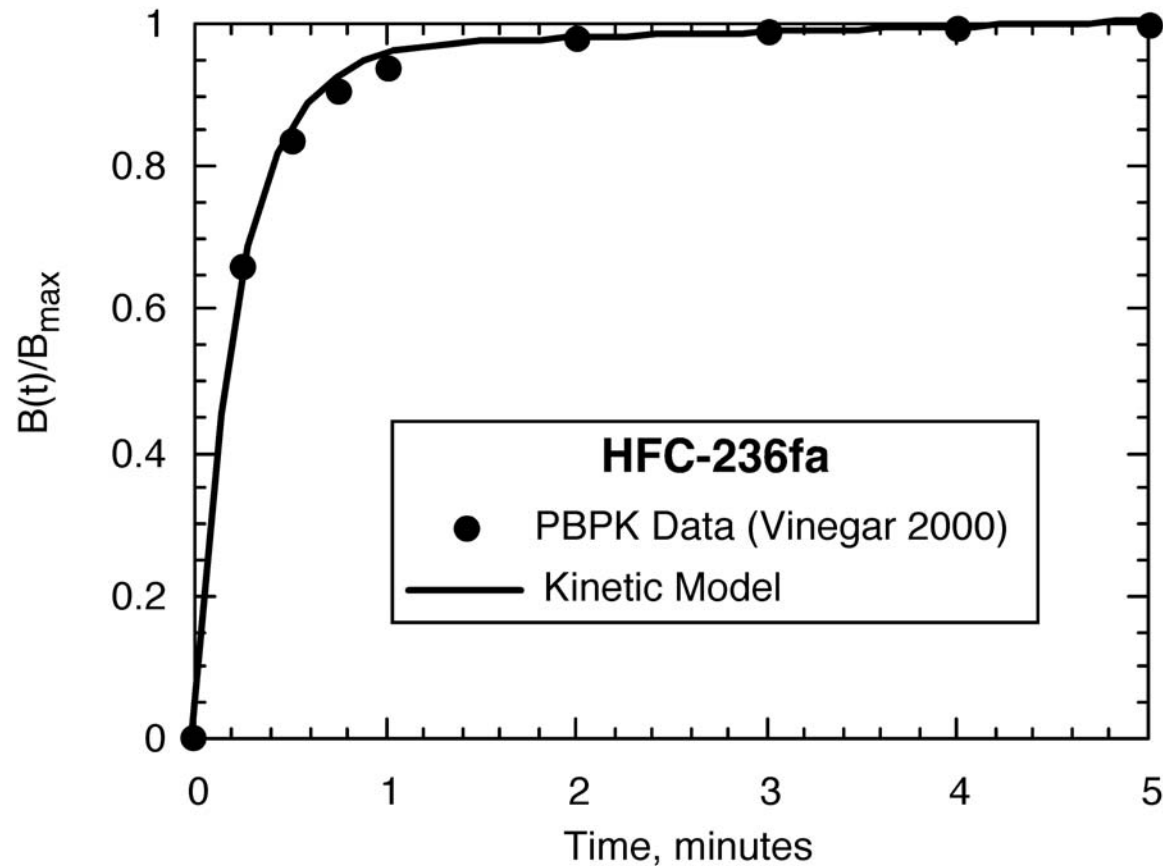
$A_0 = 10\% \text{ v/v (726 mg/L)}$

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Comparison of the Kinetic Model to PBPK Data for Simulated Exposures to HFC-236fa



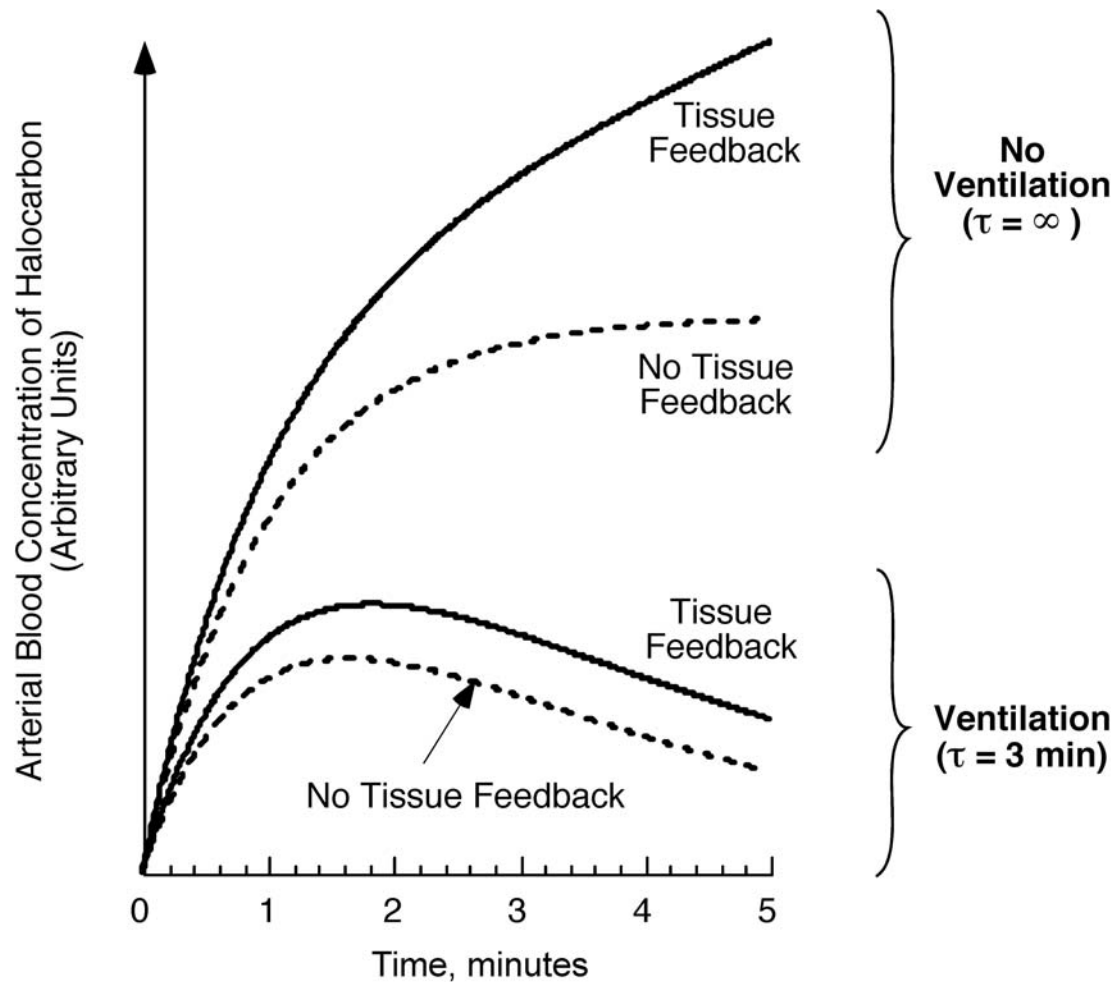
$A_0 = 15\% \text{ v/v (979 mg/L)}$

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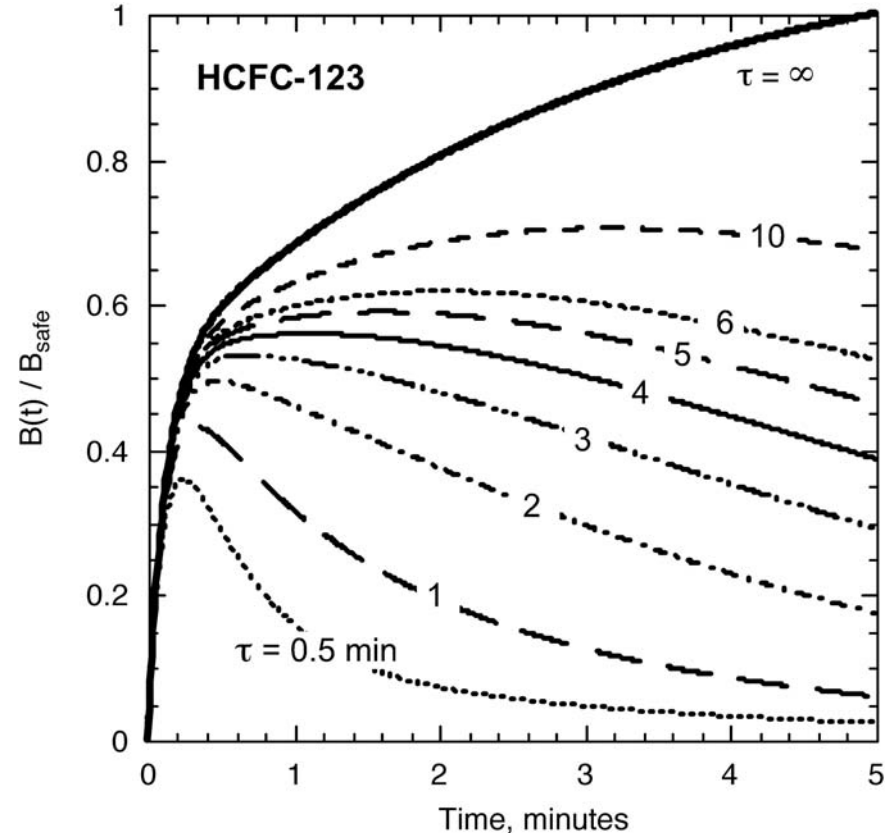
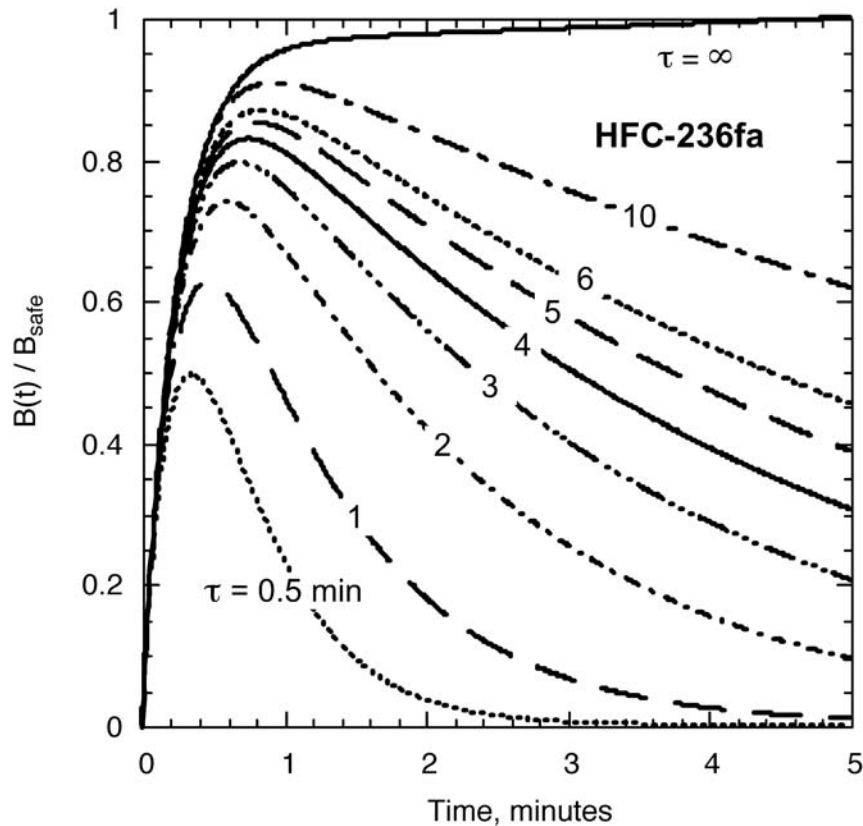
Arterial Blood Concentrations Histories for Halocarbon in Ventilated and Unventilated Cabins With and Without Tissue Feedback to the Blood



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Ratio of the Arterial Blood Concentration to the Target Value B_{Safe} for Simulated Human Exposures to A_{Safe} in a Ventilated Cabin



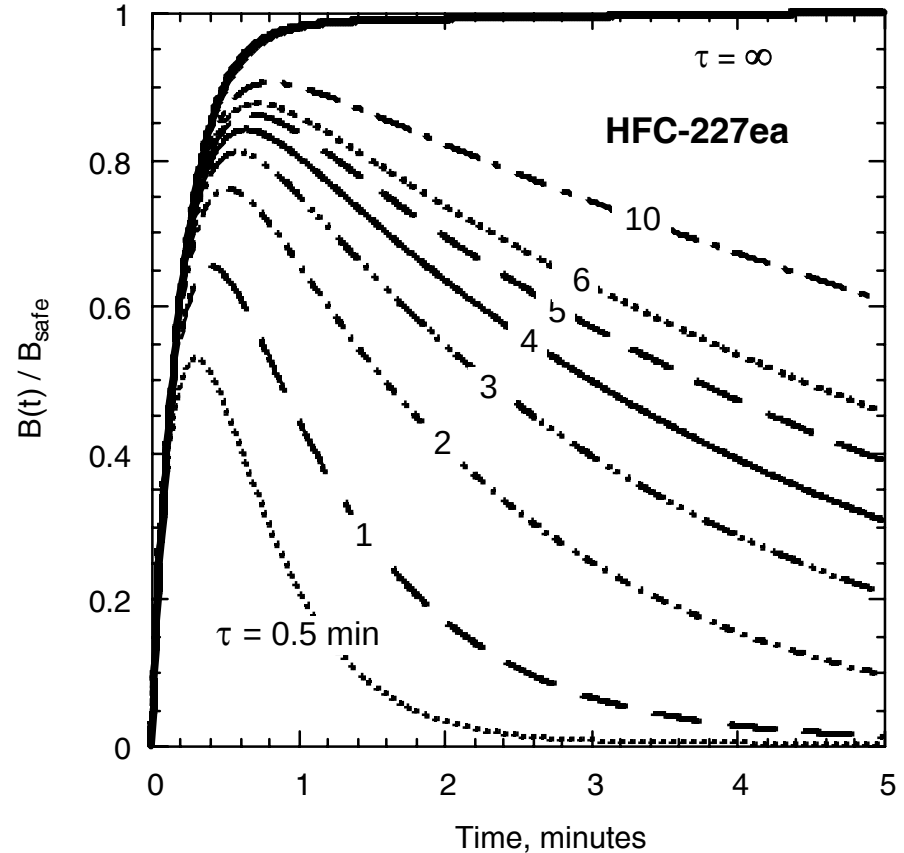
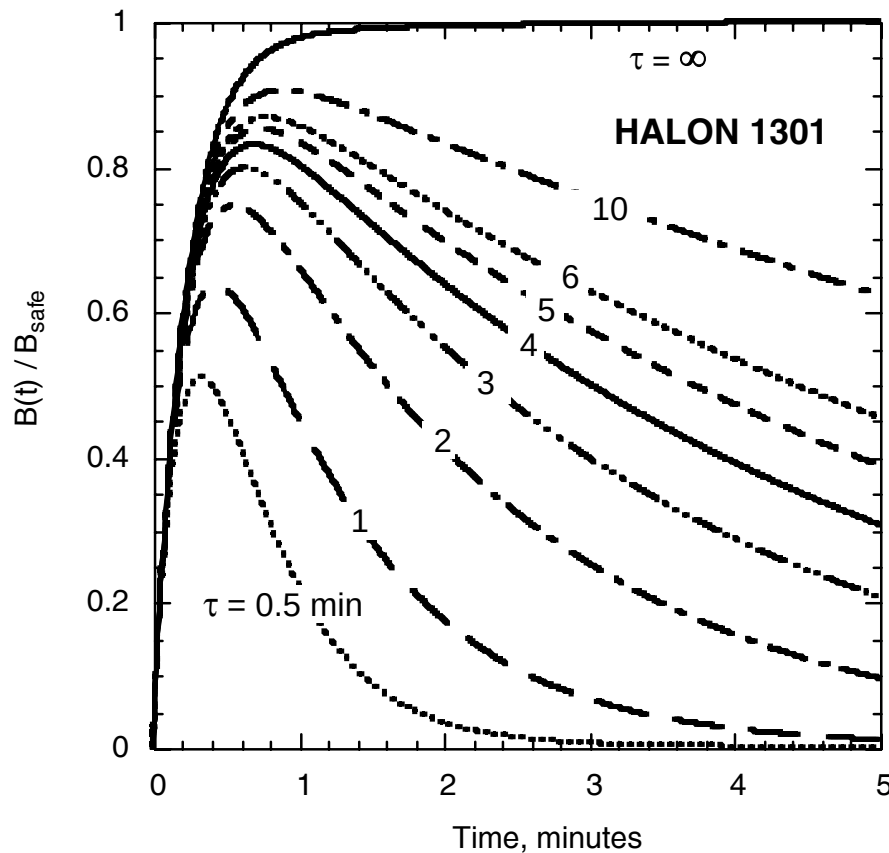
The inverse of $B(t)/B_{\text{safe}}$ at its maximum point is the ventilation benefit

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Ratio of the Arterial Blood Concentration to the Target Value B_{Safe} for Simulated Human Exposures to A_{Safe} in a Ventilated Cabin



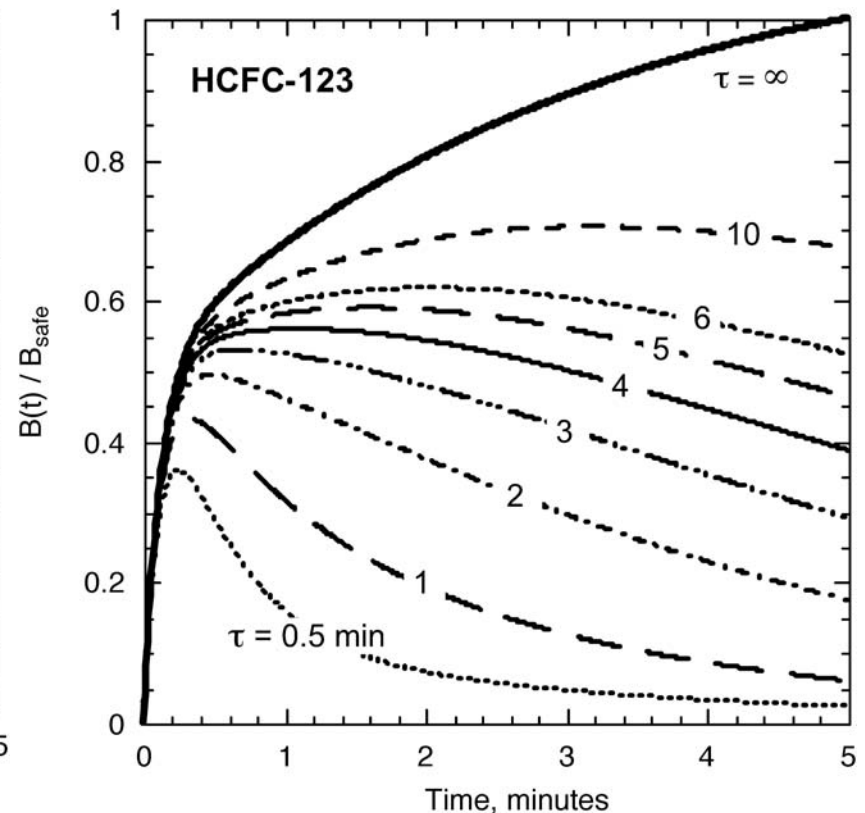
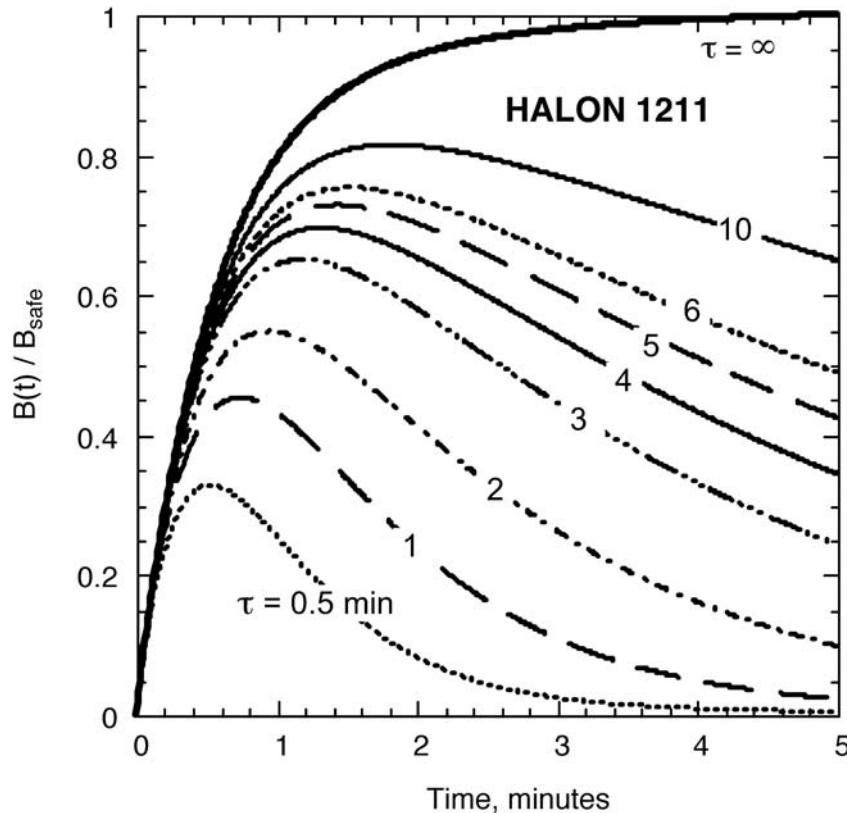
The inverse of $B(t)/B_{\text{Safe}}$ at its maximum point is the ventilation benefit

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Ratio of the Arterial Blood Concentration to the Target Value B_{Safe} for Simulated Human Exposures to A_{Safe} in a Ventilated Cabin



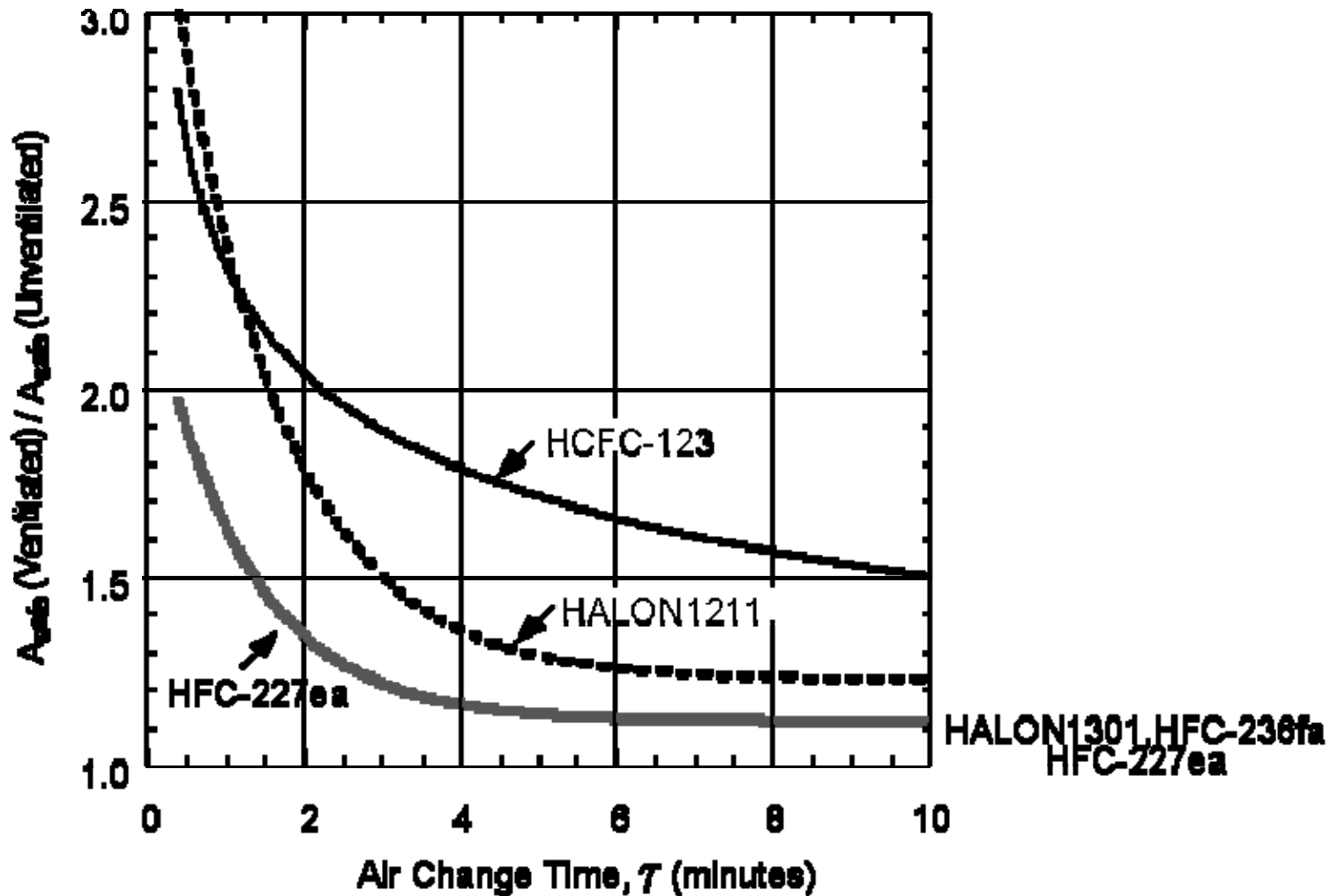
The inverse of $B(t)/B_{\text{Safe}}$ at its maximum point is the ventilation benefit

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Ventilation Benefit Versus Cabin Air Exchange Time for Different Agents Using Kinetic Model

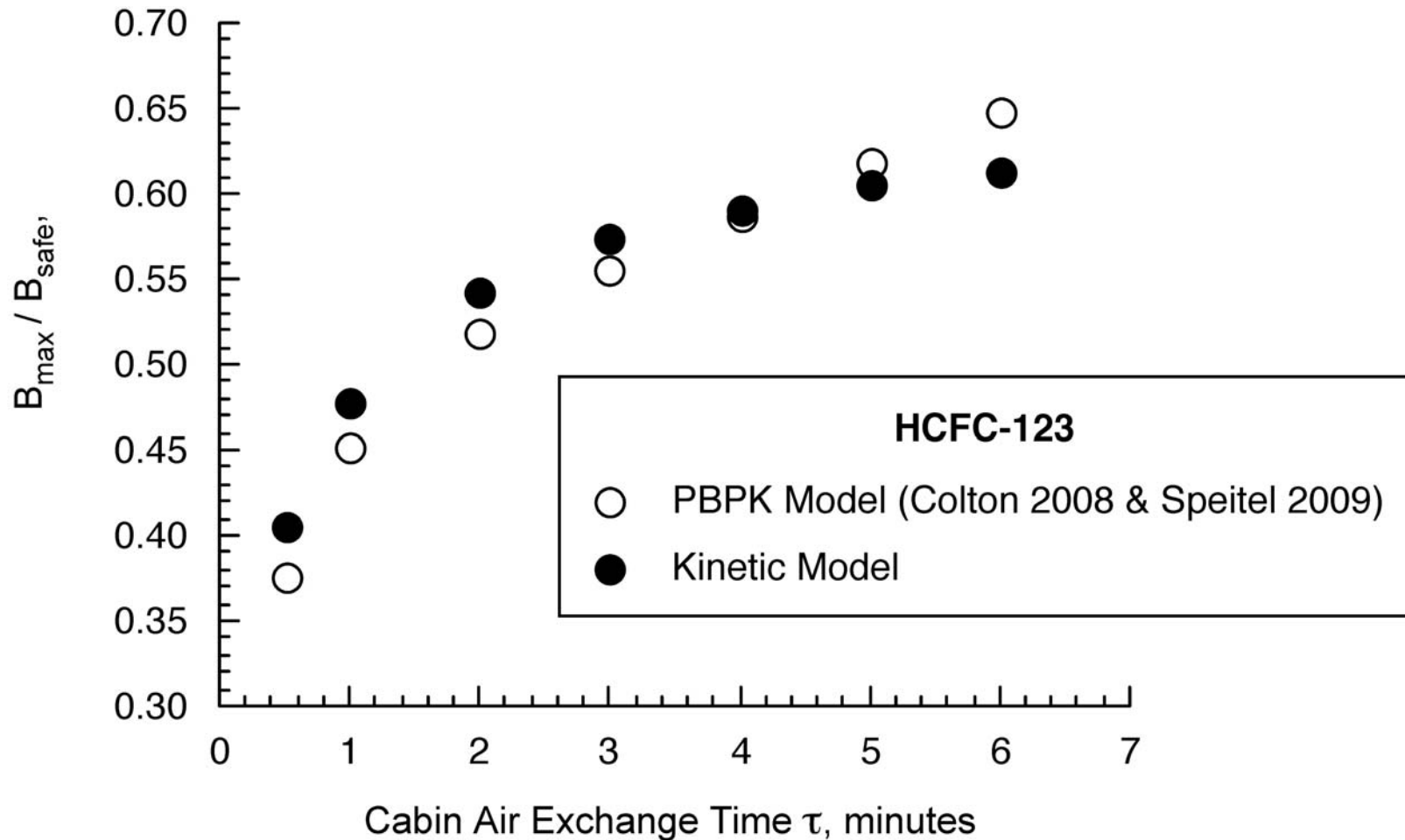


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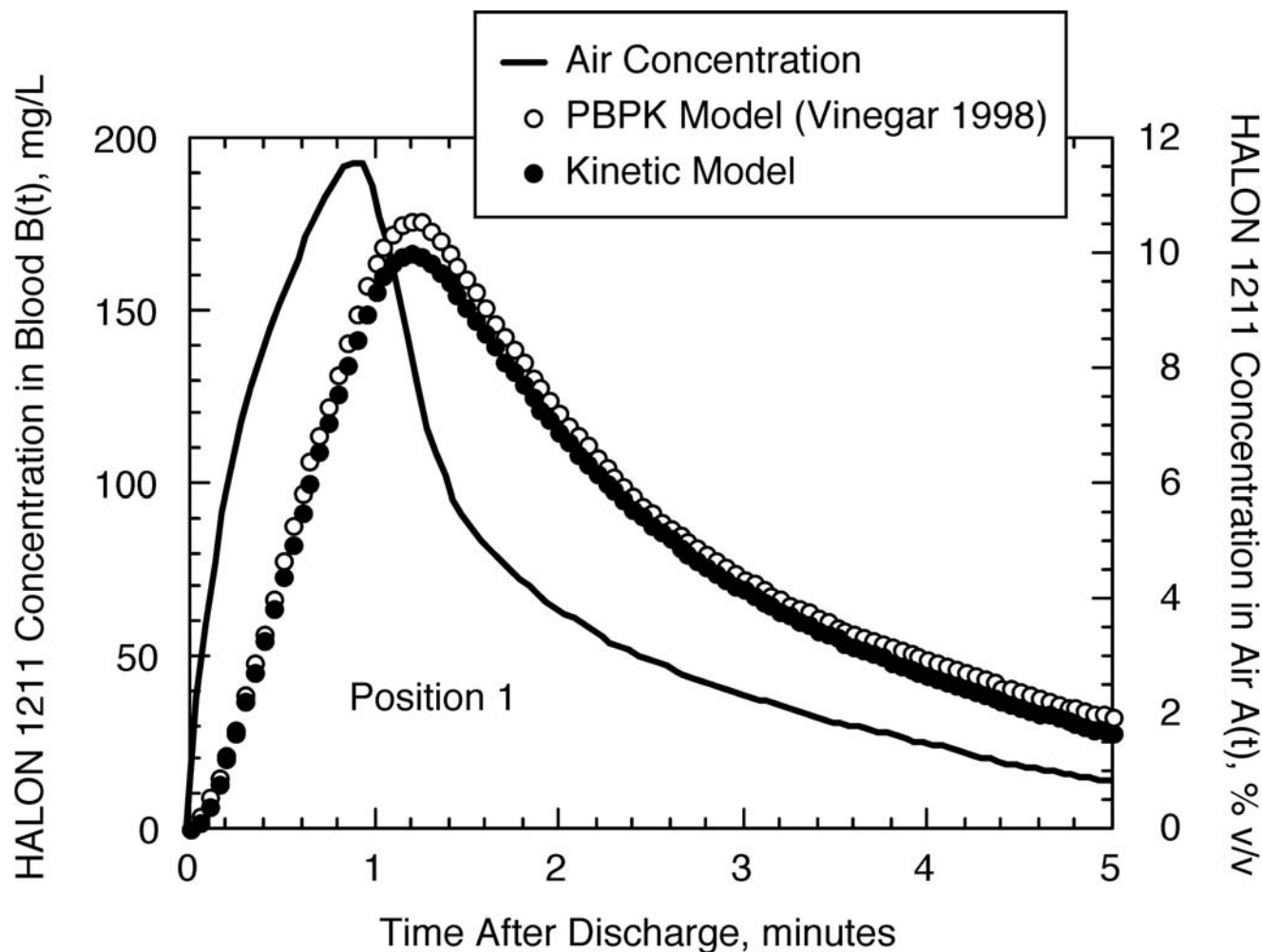


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Ratio of the Maximum Arterial Blood Concentration $B_{\max}$ to the Target Value B_{safe} for Simulated Human Exposures to A_{safe} in a Ventilated Cabin



Comparison of the Arterial Blood Concentration History at Position 1 in a Small Compartment for the Indicated Time-Varying Concentration of Halon 1211

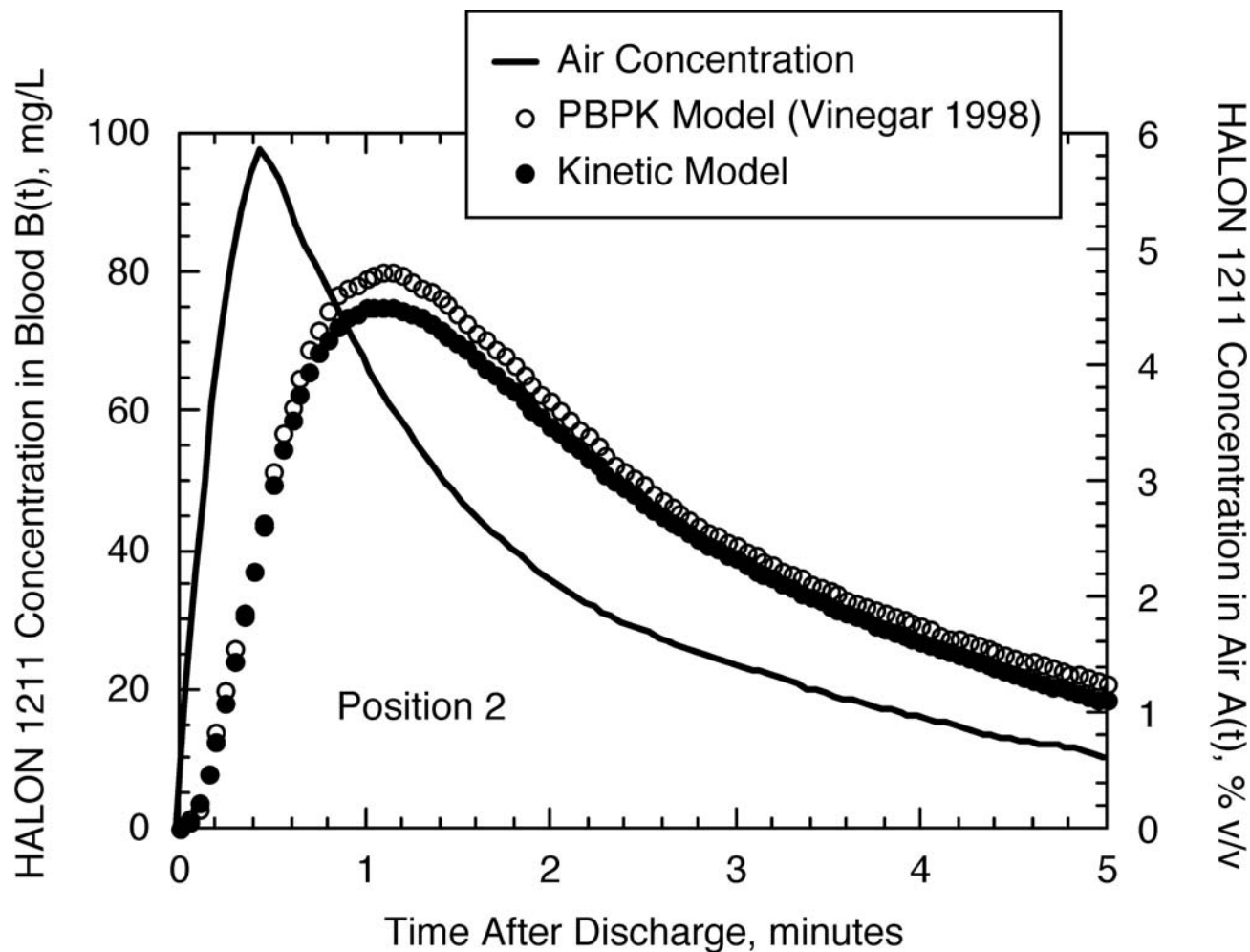


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Comparison of the Arterial Blood Concentration History at Position 2 in a Small Compartment for the Indicated Time-Varying Concentration of Halon 1211



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Conclusion

Properly calibrated kinetic model was found to predict human arterial blood concentration histories for time varying exposures as well as PBPK models.

Reference Report

FAA Report DOT/FAA/AR-08/3

Speitel, Louise C. and Lyon, Richard E., “Guidelines for Safe Use of Gaseous Halocarbon Extinguishing Agents in Aircraft”

See FAA Website: www.fire.tc.faa.gov

Reports

Author