

PBPK Modeling of Canine Inhalation Exposures to Halogenated Hydrocarbons

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Human exposure guidelines for halogenated hydrocarbons (halons) and halon replacement chemicals have been established using dose-response data obtained from canine cardiac sensitization studies. In order to provide a tool for decision makers and regulators tasked with setting guidelines for egress from exposure to halon replacement chemicals, a quantitative approach, using a physiologically based pharmacokinetic model, was established that allowed exposures to be assessed in terms of the chemical concentrations in blood during the exposure. This model, which includes a respiratory tract compartment containing a dead-space region, a pulmonary exchange area, and a breath-by-breath description of respiratory tract uptake, allows successful simulation of exhaled breath concentrations of humans during the first minute of exposure to the anesthetics halothane, isoflurane, and desflurane. In the current study, the human model was modified with canine parameters and validated with data obtained from dog studies with halothane, isoflurane, desflurane, and CFC-11. With consideration of appropriate values for ventilation and cardiac output, the model successfully simulated data collected under a variety of exposure scenarios. The canine model can be used for simulating blood concentrations associated with the potential for cardiac sensitization. These target blood concentrations can then be used with the human model for establishing safe human exposure duration. Development of the canine model stresses the need for appropriate data collection for model validation.

Key Words: PBPK model; canine; halogenated hydrocarbons; halothane; isoflurane; desflurane; CFC-11.

Replacement of ozone-depleting substances (ODS) has required quantitative toxicological evaluation of halon replacement chemicals. Historically, these volatile halogenated organic compounds have been regulated on the basis of cardiac sensitization tests conducted in dogs (U.S.EPA, 1994). The dogs are challenged simultaneously with epinephrine and the test chemical of interest, while cardiac electrical activity is monitored for cardiac arrhythmia. The test is conducted at increasing concentrations of the test chemical in order to determine a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL).

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Determining suitable permissible human exposure limits for halon replacement chemicals necessitates attention to both the level and duration of exposure. A procedure employing physiologically based pharmacokinetic (PBPK) modeling to establish egress times for humans in a halon replacement chemical environment was proposed by Vinegar and Jepsan (1996). Implementation of the procedure required modification of the respiratory tract (RT) compartment description commonly used in PBPK models (Vinegar et al., 1998). Usually, the PBPK RT compartment uses a steady-state approximation that results in an initial, unrealistically high arterial blood concentration. The steady-state approximation is suitable for describing inhalation exposures lasting from minutes to hours but is not able to describe the first second to minute of an exposure. Using the model with the modified RT, Vinegar et al. (2000) described a procedure for setting safe acute exposure limits for halon replacement chemicals. They linked the cardiac sensitization endpoint, after 5 min of exposure to the LOAEL concentration, to the associated arterial concentration. This arterial concentration measured in dogs was then used as the target concentration for simulated human exposures. For a given exposure concentration, the time until a human reached the target arterial concentration was considered safe from the potential for cardiac sensitization. However, pharmacokinetic studies in dogs are expensive. If a canine PBPK model could be used to predict the arterial concentration, the major experimental cost would be for the determination of partition coefficients.

The purpose of this study was to modify and validate an existing PBPK model for use with dogs. The model was originally developed to predict blood and exhaled breath chemical concentrations in humans during inhalation exposures of less than 5 minutes duration and includes a breath-by-breath description of inhalation in humans (Vinegar et al., 2000). Several data sets were found in the literature, containing pharmacokinetic data in dogs that were exposed by inhalation to the volatile anesthetics halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), isoflurane (2-chloro-2-[difluoromethoxy]-1,1,1-trifluoroethane), and desflurane (2-fluoro-2-[difluoromethoxy]-1,1,1-trifluoroethane) and to the chlorofluorocarbon CFC-11 (trichlorofluoromethane). An additional data set was found where CFC-11 was administered by intravenous injection.

TABLE 1
Chemical-Specific Model Parameters and Values

Parameter	Chemical			
	Halothane	Isoflurane	Desflurane	CFC-11
Molecular wt @/mol	197.39	184.5	168.0	137.36
V _{maxc} , max metabolic rate (mg/h/kg)	7.4 ^a	0.74 ^b	.0074 ^c	0.0
K _m , affinity constant (mg/l)	0.1 ^a	0.1 ^b	0.1 ^c	0.0
Blood:air partition coefficient	3.51 ^d	1.3 ^e	0.42 ^f	1.5 ^g
Liver:air partition coefficient	6.64 ^d	4.2 ^e	0.588 ^f	1.64 ^h
Gut:air partition coefficient	4.23 ^d	3.8 ^e	0.362 ^f	1.22 ⁱ
Fat:air partition coefficient	155.0 ^d	75.0 ^e	12.6 ^f	45.6 ^g
Rapidly perfused:air partition coefficient	6.64 ^d	4.2 ^e	0.588 ^f	1.64 ^h
Slowly perfused:air partition coefficient	5.45 ^d	3.4 ^e	0.966 ^f	0.81 ⁱ

Williams *et al.*, 1996.

^bHoladay *et al.*, 1975

^cSutton *et al.*, 1991.

^dSteward *et al.*, 1975.

Thomas, 1975.

^eEger, 1990.

^fChang and Chiou, 1976.

These data were used to validate the use of the modified model for the dog. We discuss the importance of data quality and appropriateness of parameter values.

MATERIALS AND METHODS

Data used for model development and validation come from several sources. Azar *et al.* (1973) performed inhalation exposures of dogs to CFC-11. Chiou and Niazi (1973) administered CFC-11 by intravenous injection. Isoflurane inhalation exposures were administered by Thomas (1975), Frei *et al.* (1988), and Wilhelm (personal communication). The latter 2 investigations also presented data for desflurane and halothane. Hughes *et al.* (1980) presented additional halothane data. Further details of the exposures follow.

Azar *et al.* (1973) exposed awake male beagles (11–14 kg) to CFC-11 via a facemask. Arterial and venous concentrations were presented from 10-min exposures to 0.1%, 0.5%, and 1.0%.

Chiou and Niazi (1973) gave a 3-min intravenous infusion of 28 mg of CFC-11 dissolved in 36 ml normal saline to a 45-kg mongrel dog. Venous concentrations were presented over a 4-h period.

Thomas (1975) exposed anesthetized, artificially ventilated beagles to isoflurane through a tracheal cannula. The cannula was connected to a room breathing valve in a closed loop system that contained a CO₂ scrubber and an inflow of O₂. Data presented for an 8.5-kg male and a 7.0-kg female dog included total ventilation, respiratory rate, inhaled concentration, exhaled concentration, and arterial concentration.

Frei *et al.* (1988) exposed anesthetized, artificially ventilated mongrel dogs (24–39 kg) separately to isoflurane and halothane through a tracheal cannula. The anesthetics were delivered using a feedback-controlled delivery system that maintained a constant end alveolar concentration of agent. Breathing rate was maintained at 12 breaths per min with tidal volume being varied to maintain arterial carbon dioxide at 40 mm Hg. Data presented included inspired and end-expired concentration, arterial and mixed venous concentration, and cardiac output.

Hughes *et al.* (1980) exposed anesthetized, artificially ventilated greyhounds (20–30 kg) to halothane through a tracheal cannula. Data presented included arterial concentration and cardiac output.

Wilhelm (personal communication) exposed anesthetized, artificially venti-

lated male beagles (12.8 kg mean weight) for 4 h, separately, to 1766 isoflurane and 8.94% desflurane through a tracheal cannula. Exhaled concentration data were presented.

A breath-by-breath PBPK model (Vinegar *et al.*, 1998) that was used to simulate short-term (0 to 5 min) human inhalation exposure to various halogenated hydrocarbons was modified to include appropriate parameter values for dogs. The respiratory tract description differs from usual PBPK models in that it accounts explicitly for dead space (upper respiratory tract and tracheo-bronchial region) and pulmonary region volumes, inhalation-exhalation, the time delay for air and gases to travel through the dead-space volume and the pulmonary region, the absorption of the inhaled gas by pulmonary region tissues, and the exchange of the gas with blood. These enhancements allowed the successful simulation of the first several breaths of exposure, which was not possible with the traditional PBPK description of lung uptake.

Partition coefficients were obtained from the literature and are listed with citations in Table 1. The metabolic constants for halothane were taken from Williams *et al.* (1996). V_{maxc} (maximum metabolic rate) for isoflurane was set to one hundredth and for desflurane to one thousandth of that for halothane (Holaday, 1977; Holaday *et al.*, 1975; Sutton *et al.*, 1991).

Anatomic volumes and physiological parameters used in the model are shown in Table 2. Ventilation parameters were scaled to body weight, except where actual values were provided.

All simulations were performed using ACSL Tox V1.1 (Pharsight Corp., Mountain View, CA) on a Pentium III PC with a 550-MHz CPU. Adequacy of model fit was judged by visual inspection of simulation and data.

RESULTS

Azar *et al.*, 1973. Arterial and venous concentrations during 10-min exposure and 20-min postexposure to 0.1%, 0.5%, and 1.0% CFC-11 appear in Figure 1. The data are well simulated by the model both during and postexposure, except at 0.1% where data are slightly underpredicted.

Chiou and Niazi, 1973. The model does a reasonable job of simulating venous concentration after an intravenous injection.

TABLE 2
Physiological Parameters for Dog

Parameter	
Tissue volumes (% body weight)	
Slow	54.8
Rapid	4.1
Liver	3.3
Gut	3.7
Fat	15.0
Tissue blood flows (% cardiac output)	
Slow	27.7
Rapid	32.9
Liver	4.6
Gut	25.1
Fat	9.7
Scaled parameters (body weight ^{0.75})	
Alveolar ventilation rate (l/h/kg)	8.0-33.4
Cardiac output (l/h/kg)	9.3-34.4

Note: Tissue volume and blood flow parameter values based on Brown *et al.* (1997). Scaled parameter values taken from the simulation data sources in this paper.

tion of 28 mg of CFC-11 (Fig. 2). The model tends to overpredict venous concentration from 0.4 to 0.8 h and underpredict from 1.8 to 3.5 h.

Thomas, 1975. Arterial and alveolar concentrations are well simulated under changing inspired concentrations of isoflurane for dog 1 (Fig. 3). However, arterial concentration is consistently overpredicted for dog 2, even with good model fit for alveolar concentrations.

Frei et al., 1988. Simulations are shown for arterial, venous, and alveolar concentrations during and after exposure to halothane and isoflurane (Fig. 4). Overlapping simulations are shown that differ from 100 min to the end of the exposure. During this time period, the upper curve is a result of alveolar ventilation being set equal to cardiac output, while the lower curve results from alveolar ventilation being set equal to 1/2 of cardiac output (see Discussion section for explanation).

Hughes et al., 1980. Simulation of arterial concentration is shown during half-hourly, 0.5% stepped increases in inhaled concentration up to 2.0% (Fig. 5). Data shown at the end of each half hour are generally well represented by the model, although somewhat overpredicted at 2.0%.

Wilhelm (personal communication). Alveolar concentrations for desflurane and isoflurane are shown during and after exposure (Fig. 6). Desflurane and isoflurane data are generally well predicted both during and after exposure.

DISCUSSION

Using ventilation and inspired concentration, actually measured during the course of an inhalation exposure, has been demonstrated to lead to successful simulation of pharmacoki-

netic data collected during the study. Exhaled breath concentrations of rats exposed to chloropentafluorobenzene were successfully simulated when measured minute ventilation was incorporated into the model (Vinegar *et al.*, 1990). Similarly, exhaled concentrations of humans exposed to anesthetics were successfully simulated on a breath-by-breath basis when ventilation and inspired concentration were incorporated into the model (Vinegar *et al.*, 1998).

The data used to validate the breath-by-breath dog model were collected under varying protocols, which resulted in variability in ventilation and cardiac output. The degree of reporting of the values of these parameters also varied amongst the papers. Dogs inhaled CFC-11 while awake and spontaneously breathing (Azar *et al.*, 1973), and were given intravenous infusion while awake and spontaneously breathing (Chiou and Niazi, 1973). Exposure to the anesthetics isoflurane (Thomas, 1975), isoflurane and desflurane (Wilhelm, personal communication), isoflurane and halothane (Frei *et al.*, 1988), and halothane (Hughes *et al.*, 1980) was accomplished using mechanical ventilation.

Hughes *et al.* (1980) showed that cardiac output decreases by over 50% during the course of stepped increases in inhaled halothane concentration. Cardiac output decreased from a control level of 0.155 l/min/kg to 0.125, 0.122, 0.084, and 0.066 at 0.5, 1.0, 1.5, and 2.0% halothane, respectively.

Ahlgren *et al.* (1978) exposed dogs to 1.5% halothane for either 30 or 120 min. Six dogs with average weight of 18 kg had a reduction in cardiac output from 2833 to 1630 ml/min after a 30-min exposure to 1.5% halothane. A second group of 7 dogs with average weight of 15 kg showed cardiac output dropping from 1827 to 1490 ml/min after 120 min of exposure. The 42% drop in cardiac output compared with control level, after a 30-min exposure, was comparable to the 45% drop in cardiac output seen by Hughes *et al.* (1980), also after 30 min of 1.5% halothane exposure.

Dogs exposed to desflurane while spontaneously breathing showed cardiac outputs of 128, 115, and 96 ml/kg/min and respiratory rates of 37, 47, and 22 at end tidal exposures of 10.3, 12.9, and 15.6%, respectively (Clarke *et al.*, 1996).

Measurements of respiration rate and tidal volume were made in spontaneously breathing dogs exposed for 40 min, via tracheal intubation, to 1.352 halothane or 1.95% isoflurane (Hellebrekers, 1986). They had previously been exposed to up to 4.54 of each agent by face mask in order to anesthetize them for the tracheal intubation. Respiratory rates increased for both agents during the 40-min period, although the rates for halothane were generally nearly twice those for isoflurane. Larger changes were seen in tidal volume, which initially dropped for 5 min, leveled off, and then started to increase at 30 min with values approaching control levels at 40 min. Halothane produced greater decreases in tidal volume than did isoflurane.

In light of the variability of ventilation and cardiac output during the exposures described, it is useful to consider the

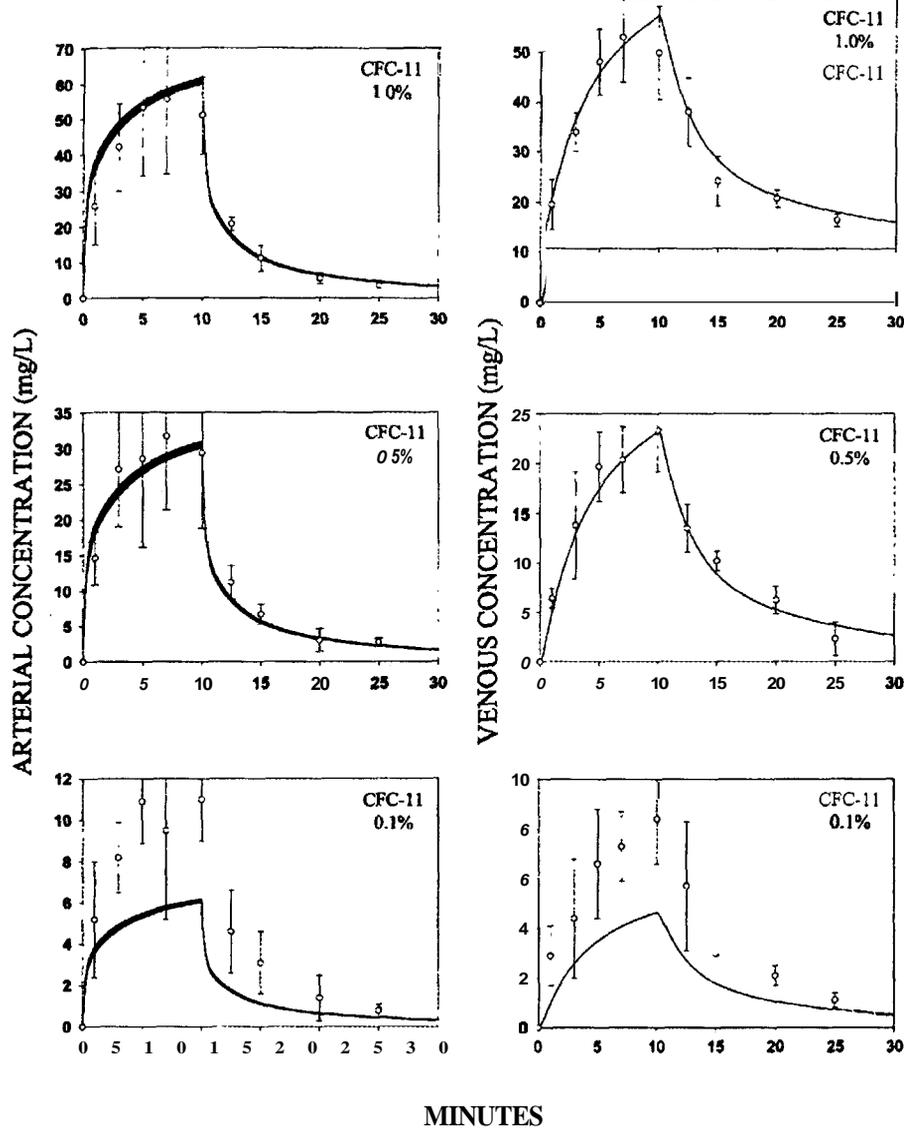


FIG. 1. Arterial and venous concentrations during and after inhalation exposure ($n = 4-5$) to 1.0, 0.5, and 0.1% CFC-11 (Azar *et al.*, 1973). Continuous lines represent simulations. Actual data are plotted with bars representing one standard deviation above and below the mean.

difference in the behavior of the model, comparing default values for ventilation and cardiac output with values that take into account the changes that might result from the exposure. Of the data sets used, the most complete is that of Frei *et al.* (1988) (Fig. 4). Measurements of inspired, end-expired, arterial, and mixed venous concentrations were made and reported for 160 min of exposure and 50 min of washout of the anesthetics halothane and isoflurane. Cardiac output was also measured and reported over the same time period. Ventilation was maintained at 12 breaths per min. but tidal volume was varied to maintain constant arterial PaCO₂. Periods of hyperventilation and hypercirculation were induced during the course of the experiment. The data provided in this study were useful for probing the effects of ventilation, perfusion, and ventilation: perfusion ratio (VPR) on the ability of the model to simulate a given data set. Since cardiac output data were available, the

actual cardiac output was used in the model and ventilation was calculated based on the VPR. The actual arterial, venous, and alveolar concentrations do not show significant change during the course of the exposure, because the anesthetic was administered with a feedback-controlled delivery system. However, initial simulations of arterial, venous, and alveolar concentration all show a sharp rise at around 100 min, which is when hypercirculation was induced with epinephrine. These simulations were performed initially with the assumption that the VPR was 1 throughout the experiment. However, the induced hypercirculation does not necessarily result in a corresponding change in ventilation. Epinephrine has a profound effect on cardiac output but also results in increased ventilation. The increased ventilation would lead to reduced pCO₂ and according to the protocol, would have resulted in the tidal volume delivered by the ventilator being reduced to allow a return to

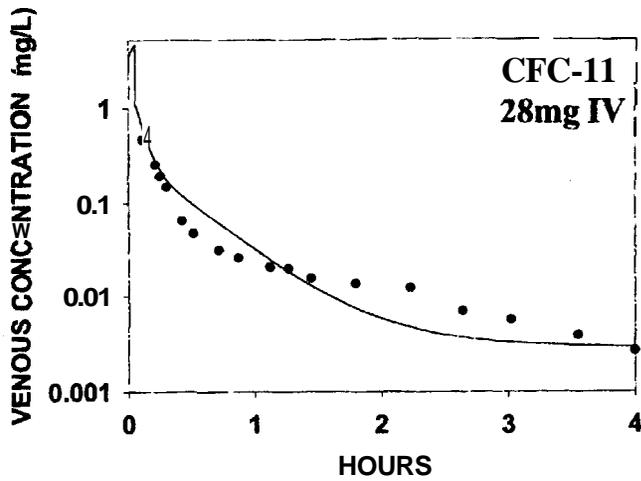


FIG. 2 Venous concentration following intravenous injection of 28 mg of CFC-11 to a 45 kg dog (Chiou and Niazi, 1973). Continuous line represents the simulation. Actual data are shown as individual points.

normal pCO_2 levels. Setting the VPR to 0.5 during the period of hypercirculation resulted in the simulations more closely predicting the actual data (see Fig. 4, lower curves). Ventilation was measured at times of sample taking for analysis, but the data were not reported. Ventilation and cardiac output are major contributors to the model's ability to simulate actual data, but another contributing factor may be the concomitant changes in the distribution of cardiac output as a result of anesthetic exposure and of other manipulations, such as the

intentional induction of hypercirculation reported in this study Ahlgren *et al.* (1978) presented data demonstrating effects of halothane exposure on the distribution of cardiac output. Significant changes were seen in flows to some organs. Data were presented for 30 and 60 min of exposure to 1.5% halothane. Unfortunately, there are not enough data to incorporate into the model.

Although Wilhelm (personal communication) measured inspired and expired (end tidal and mixed) agent concentrations, respiratory rate, and tidal volume on a breath-by-breath basis, the only data provided were the expired concentrations at selected time points and the target inhaled concentration. However, the volume of anesthetic administered was also provided. This was used to set the ventilatory parameters for the model. Fixing the frequency at 12 breaths per minute, a tidal volume of 185 ml provided simulated inspired volumes for isoflurane and desflurane of 9377 and 47,632 ml, respectively. The respective measured, inspired volumes were 9388 and 47,661 ml. Using the ventilatory parameters determined in this way resulted in the simulations of alveolar concentration shown in Figure 6.

Hughes *et al.* (1980) exposed dogs to stepped increases in halothane concentration and measured cardiac output at the end of each half-hour exposure period. Cardiac output data were used in the model so that values for cardiac output were interpolated for times between the half-hour measurement points. The simulation uses the measured cardiac output as input in the model, and ventilation is derived based on a VPR of 1 (Fig. 5).

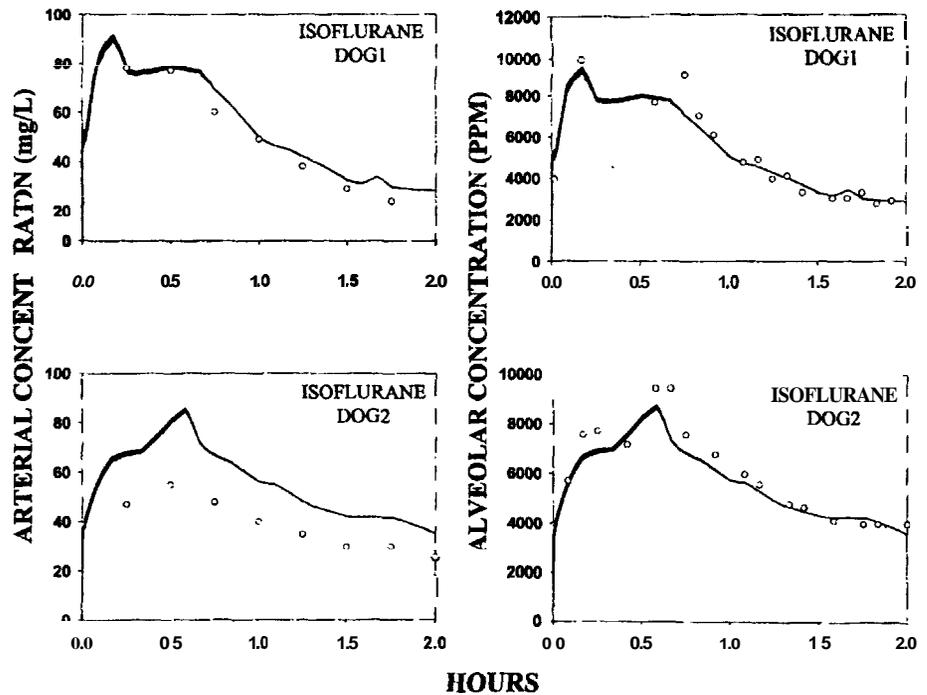


FIG. 3. Arterial and alveolar concentrations during a varying concentration inhalation exposure of isoflurane to 2 individual dogs (Thomas, 1975). Continuous lines represent simulations. Actual data are shown as individual points.

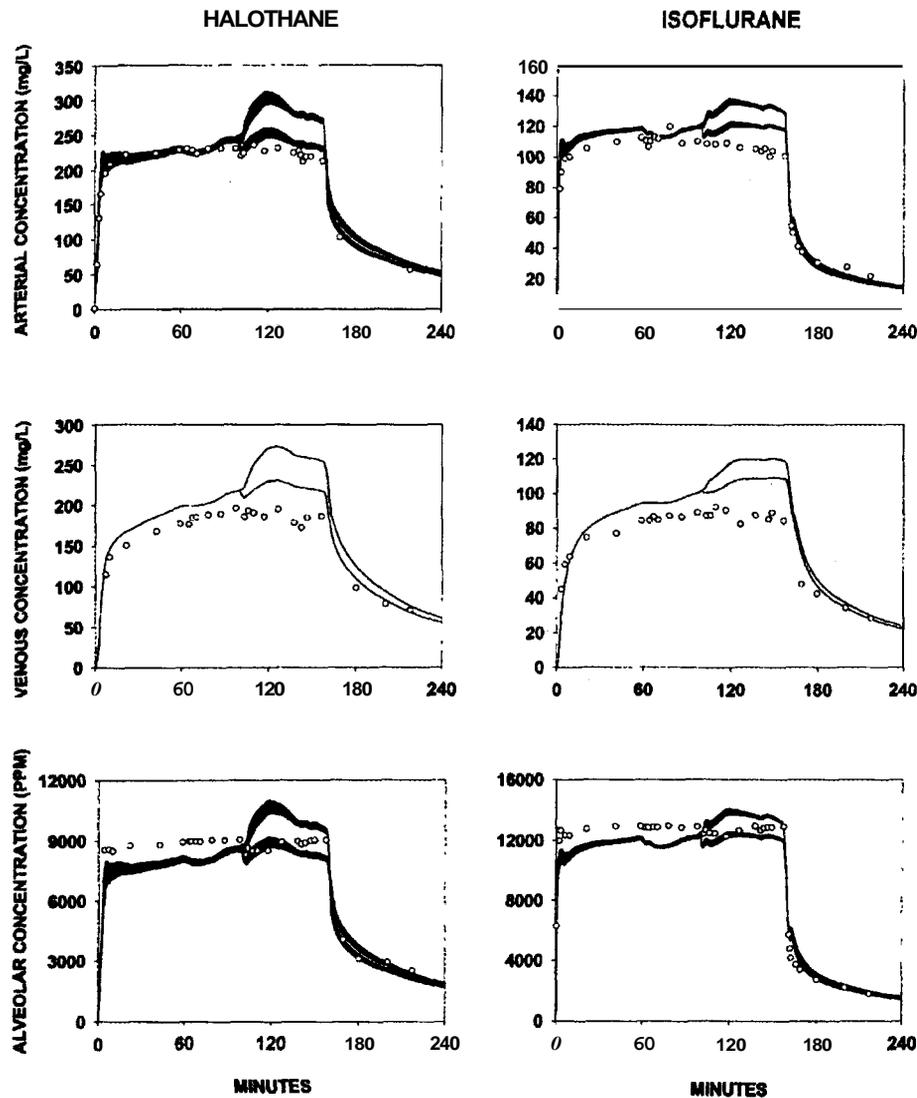


FIG. 4. Arterial, venous, and alveolar concentrations during and after inhalation exposure to halothane and isoflurane (Ezei *et al.*, 1988). Continuous lines represent simulations. See text for explanation of simulation lines. Actual data (average of 6 dogs) are shown as individual points.

Development of a PBPK model is an iterative process involving model formulation, collection of pharmacokinetic data to test the model's structure, and often reformulation to account for any shortcoming of the model in simulating the collected data. Ideally, data collection should occur in conjunction with model development, with the modeler having considerable oversight on the quality and quantity of data collected. Often, the data requirements may go beyond pharmacokinetic samples but may include key physiological variables such as ventilation and cardiac output. There are times when it is necessary to develop and validate a model with data that already exist in the literature. This was the case in this study, where the model was already validated for use in humans but its use in dogs required obtaining results of published pharmacokinetic studies. At first glance, this might not appear to be a bad thing. After all, one now has the opportunity to pick

from a variety of studies, choose several, and demonstrate the successful simulation of the pharmacokinetic data presented. However, as a modeler, one quickly learns that not all data sets are created equal. Alas, experiments and data resulting from them are obtained to suit the requirements of the original author and not those of the modeler, who may come along later and want to borrow the data for model validation purposes. When, there are a number of papers to pick from, they generally fall into two broad categories: those from which the data, when modeled, are at least in general agreement with model prediction and those from which the data and model are in hopeless disagreement. Focus will remain on the first category where general agreement occurs between model and data. Then focus must turn to the details of the experiment. Were the animals awake or anesthetized? If awake, were they active (excited) or resting? If they were anesthetized, were they

artificially ventilated or allowed to breathe spontaneously? If artificially ventilated, what were the frequency and tidal volume settings of the ventilator? In actuality, in any one of these instances, frequency and tidal volume are important parameter values for the model. In many studies involving anesthetics, the respiratory frequency is often set (and reported in the paper) but tidal volume is varied (and not reported in the paper) to maintain $p\text{CO}_2$ within acceptable physiological limits. Published studies with anesthetics often report in the methods that ventilation and inspired and expired anesthetic concentrations were measured on a breath-by-breath basis. Data such as these would of course be ideal for validation of a breath-by-breath PBPK model. However, these measurements are generally not the focus of the study and hence do not appear in the paper. One is then forced to make use of bits and pieces from various papers to determine what the range of acceptable values of ventilation and cardiac output could be under circumstances of the described experiment. Model predictions that may have been off by 30% or more often come into line with the data when appropriate adjustments are made to ventilation and cardiac output.

The model did a reasonable job of simulating data obtained from a variety of experimental protocols. It is apparent that the absolute and relative values of ventilation and cardiac output, both of which vary as a result of exposure to anaesthetic agents, are important contributors to the degree of success of a simulation. With an understanding of how these two parameters vary, Monte Carlo simulation techniques could then be used to predict canine blood concentrations during exposure to selected chemicals. These values would then be the target blood concentrations needed for the human risk assessment

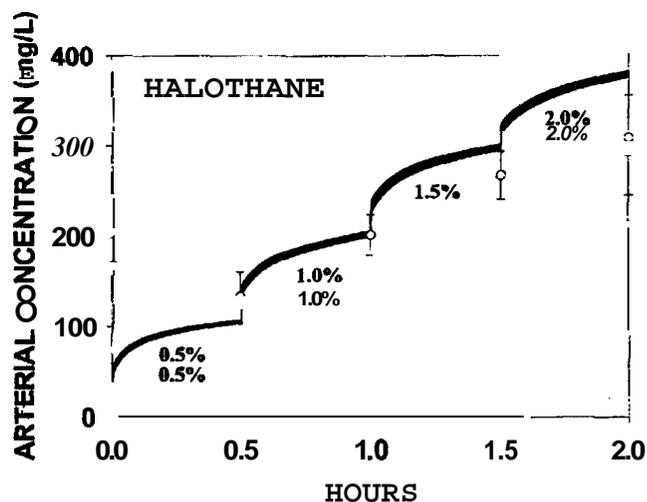


FIG. 5. Arterial Concentration during stepped increases in inhalation exposure to halothane (Hughes *et al.*, 1980). Continuous lines represent simulations. Actual data ($n = 6$) are plotted with bars representing one standard deviation each above and below the mean.

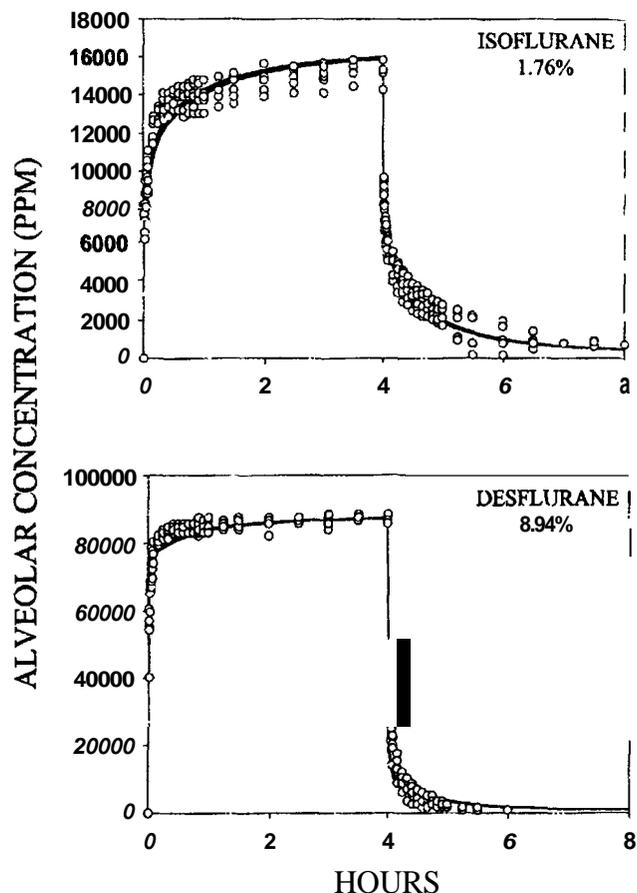


FIG. 6. Alveolar concentration during and after inhalation exposure to isoflurane and desflurane (Wilhelm, personal communication). Continuous lines represent simulations. Actual data ($n = 6$) are shown as individual points

process for determining safe exposure to Halon replacement chemicals (Vinegar *et al.*, 2000).

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