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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 there agents is cardiac *sensitization* An approach is described that 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_3I (trifluoroiodomethane), HFC-*125 *(pentafluoro-*ethane), *HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane),* and *HFC-236fa (1,*I, I, *3,3,3-hexafluoropropane)* Application of the modeling technique described here not only

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The *statements* and *opinions* expressed in this article are **those** of the authors and **do** not necessarily reflect the official policies of the U S. Environmental Protection Agency, unless this is clearly **specified.**

The animals used in this study were handled in accordance with the principles stated in the Guide for the Caie and Use of **Laboratory** Animals, prepared by the Committee on Care and Use of Laboratory Animafs of the Institute of Laboratory Animal Resources, National Research Council, DHHS, National Institute of Health Publication **86-23, 1985,** and the Animal Welfare Act of **1966,** a5 amended.

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makes use of the conservative cardiac sensitization ciidpoint, but also uses an understanding of the pharmacokinetics of the chemical agents to better establish standards for sdfe 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

Many, if not most, of the proposed replacements for Halon 1301 (bromotrifluoromethane) 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 et al., 1971; Mullin *et al.,* 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 lowest-observed-adverse-effect level (LOAEL) 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 5 min 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 5 min 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 & Paxman, 1992; Clewell & Jarnot, 1994; Cronin et al., 1995; Farrar et al., 1989, Hetrick et al., 1991; Portier & Kaplan, 1989; Simon, 1997; Spear et al., 1991; Thomas et al., 1996a, 1996b; Yang et al., 1995). However, none of these studies involved predicting short-term (0 to 5 min) effects. This article 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_3I (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 5 min 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 5-min 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_3I, 12.9 mg/L; HFC-125, 47.8 mg/L; HFC-227ea, 26.3 mg/L; and HFC-236fa, 90.3 mg/L (Huntingdon Life Sciences, 1998).

Physiologically Based Pharmacokinetic 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 deadspace region and a pulmonary exchange area. It was used successfully to simulate the pharmacokinetics of halothane, isoflurane, and desflurane, which are structurally similar to many of the chemicals being considered as halon replacements. The pulmonary exchange area has its own airspace, tissue, and capillary subregions. 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, and slowly perfused and rapidly perfused tissues. All model compartments arc 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 1.

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 ([body weight]$^{.75}$). 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, 1995b; Vinegar et al., 1995) and (2) metabolism has not demonstrated an effect on these short-term (5-min) simulations even

TABLE 1. Parameter distributions for Monte Carlo analysis

Parameters		Means	CV	Upper bound	Lower bound	Distribution
Plasma flows (fraction of cardiac output)						
QPC	Alveolar ventilation (L/h/kg)	174	0 8			Lognormal
QCC	Cardiac output (L/h/kg) = QPC					
QFC	Fat	0029	0.30	0 042	0.016	Normal
QCC	Gut	0219	0 33	0364	0 075	Normal
QLC	Liver	0 089	0.32	0.147	0 030	Normal
QSC	Slowly perfused tissues	0.202	030	0384	0.020	Normal
QRC	Richly perfused tissues = 1 0 – QSC – QLC – QFC – QGC					
Tissue volumes (fraction of body weight,						
BW	Body weight (kg)	70	026	97.3	42 7	Normal
VFC	Fat	0 215	024	0 409	0.022	Normal
VGC	Gut	0022	015	0035	00088	Normal
VLC	Liver	0027	025	0043	0 011	Normal
VKC	Richly perfused tissues	0041	030	0066	0 016	Normal
VSC	Slowly perfused tissues = 0.88 – VFC - VCC – VLC – VRC					

Note Mean values taken from Davis and Mapelson (1981) and Williams et al (1996). Coefficients of variation taken from Thomas et al (1996a)

when moderate levels are incorporated into the model. Metabolism for all chemicals was set to zero except for CF_3I, where the maximal velocity constant $V_{MAXC} = 0.375$ 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 (Egcr, 1987; Lerman et al., 1985, 1986) and appear in Table 2.

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 1 and 2). Upper and lower bounds on normally distributed para-

TABLE 2. Partition tocfficrents (lognormal distribution) of Halon 1301 and selected ieplacement agents (geometric mean ± geometric standard deviation)

Parameters	Halon 1301	CF_3I	HFC-227ea	HFC-125	HFC-236fa
PB	$0.062^H \pm 1.057$	$0.410^H \pm 1.118$	$0.033^H \pm 1.033$	$0.074^H \pm 1.081$	$0.106^H \pm 1.053$
PF	$0.771^H \pm 1.164$	$9.014^R \pm 1.145$	$0.347^R \pm 1.541$	$0.533^R \pm 1.334$	$0.678^R \pm 1.104$
PL	$0.145^H \pm 1.085$	$0.192^R \pm 1.380$	$0.031^R \pm 1.965$	$0.062^R \pm 1.381$	$0.106^R \pm 1.075$
PR	$0.145^H \pm 1.085$	$0.192^R \pm 1.380$	$0.031^R \pm 1.965$	$0.062^R \pm 1.381$	$0.106^R \pm 1.075$
PS	$0.159^R \pm 1.498$	$0.239^R \pm 1.180$	$0.021^R \pm 5.889$	$0.070^R \pm 1.230$	$0.091^R \pm 1.067$

Note PH, blood/air, PF, fat/air; PL, liver/air; PR, richly perfused tissues/air; PS, slowly perfused tissues/air. Superscripts: H, human, R, rat

meters were set at the ±2 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., Kedmond, WA).

RESULTS

Results of the simulations are shown graphically for each chemical (Figures 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, that is, the lowest dog arterial concentration measured at 5 min of exposure to the LOAEL. At lower exposure concentrations the target arterial concentration is not reached in the 5-min 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 (Tables 3–7). **Exposure** concentration is presented in increments of 0.5% (0.05% for CF_3I), and the time in minutes (up to 5) that a human can safely be exposed to that concentration is indicated.

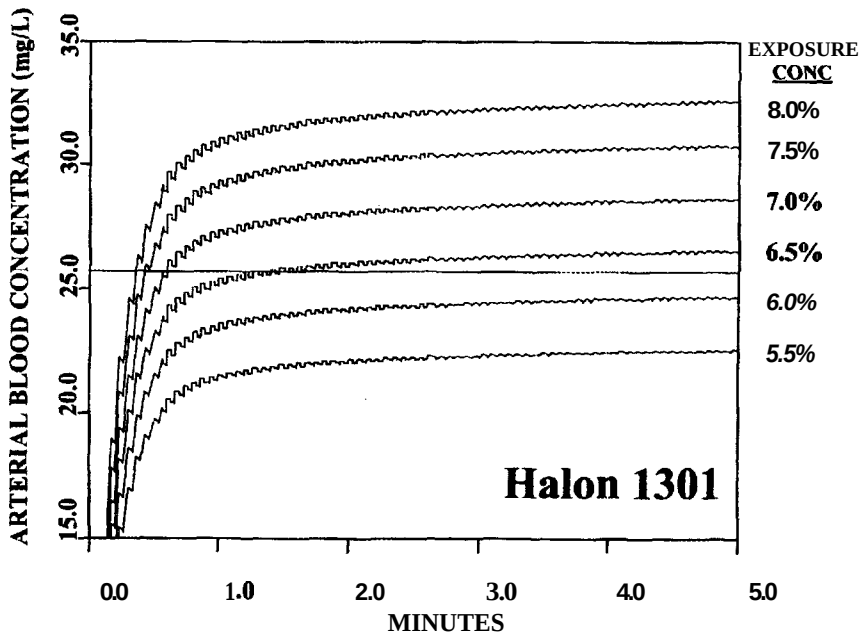

FIGURE 1. Monte Carlo simulations of arterial concentration of humans exposed to Halon 1301 for 5 min at concentrations of 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0%. The horizontal line at 25.7 mg/L represents the lowest arterial blood concentration measured at 5 min in a group of b dogs exposed to Halon 1301 at the cardiac sensitization LOAEL of 7.5%.

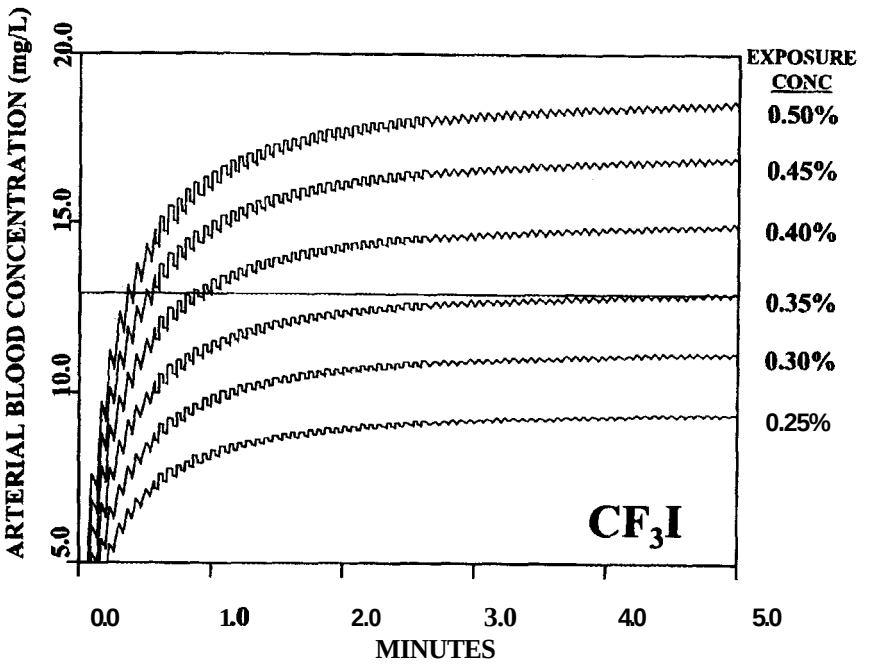

FIGURE 2. Monte Carlo simulations of arterial roncentration of humans exposed to CF_3I for 5 min *at* concentrations of 0.25, 0.30, 0.35, 0 40, 0 45, and 0 50% The horizontal line *at* 12 9 mg/L represents the lowest arterial blood concentration measured at 5 min in a group of 6 dogs exposed to CF_3I at the cardiac sensitization of LOAEl of *0* 4%.

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 1 min.
2. Up to LOAEL if egress can occur in 30 *s* to 1 min.
3. Above the LOAEl if egress can occur in less than 30 s 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 3–7 reveals interesting relationships between the cardiac sensitization LOAEL and time for safe human exposure. Exposure to HFC-125 can occur safely for at least 5 min 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 5 min at 10.5%, which actually is the LOAEL. How-

ever, the safe 5-min exposure for HFC-236fa occurs at 12.5%, which is 2.5% below the **LOAEL**; for CF_3I 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 5-min 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 **LOAFI.,** 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 5-min 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.

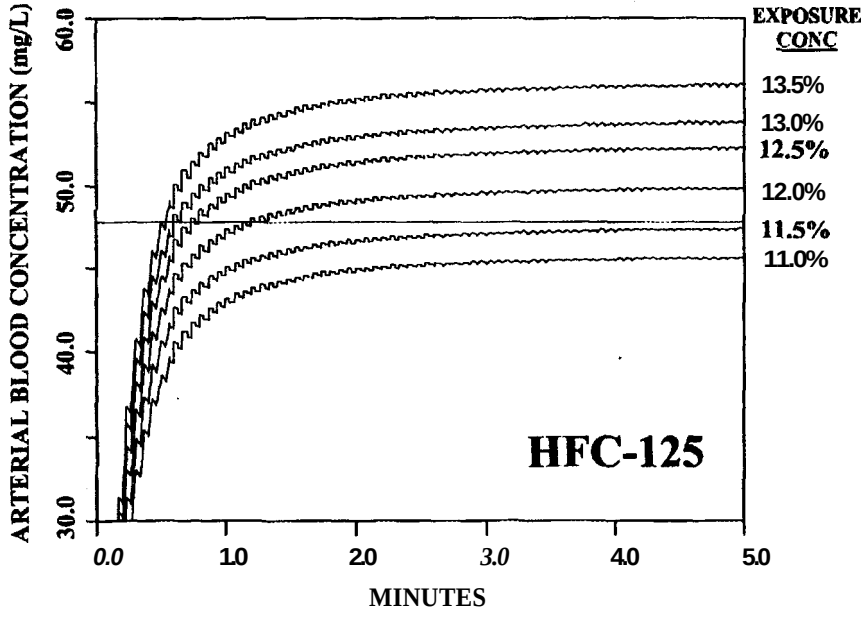

FIGURE 3. Monte Carlo simulations of arterial concentration of humans exposed to HFC-125 for 5 rnin at Concentrations of 11 0, 11.5, 12 0, 12.5, and 13 0, and 13.5% The horizontal line at 47.8 mg/L represents the lowest arterial blood concentration measured at 5 min in a group of 6 dogs exposed to HFC-125 at the cardiac Sensitization LOAEL of 10 0%

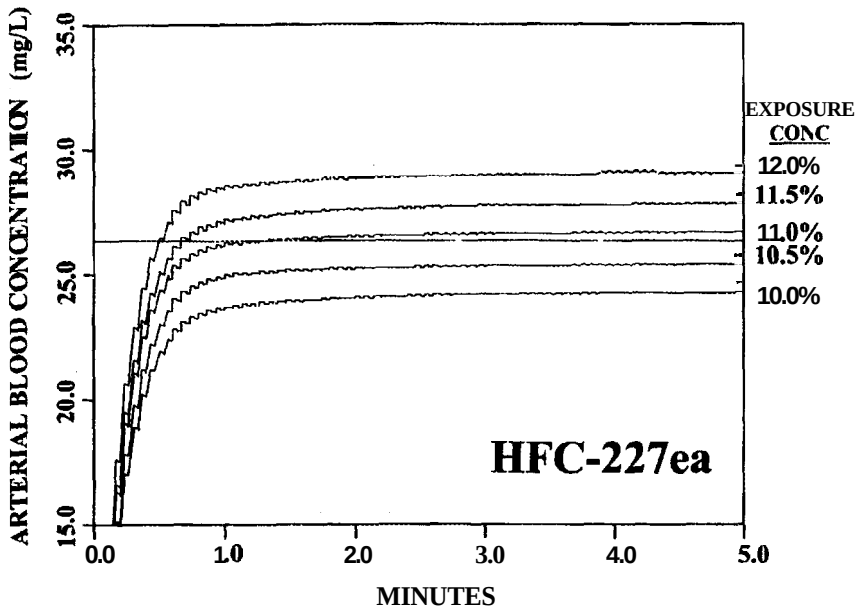

FIGURE 4. Monte Carlo simulations of arterial concentration of humans exposed to HFC-227ea for 5 min at concentrations of 10.0, 10.5, 11.0, 11.5, and 12.0%. The horizontal fine at 26.3 mg/L represents the lowest arterial blood concentration measured at 5 min in a group of 6 dogs exposed to HFC-227ea at the cardiac sensitization LOAEL of 10.5%

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 5 min of exposure. Therefore, the increased level of sensitivity is due to the concentration of chemical at the heart at 5 min. It is this level attained after 5 min 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; that is, 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

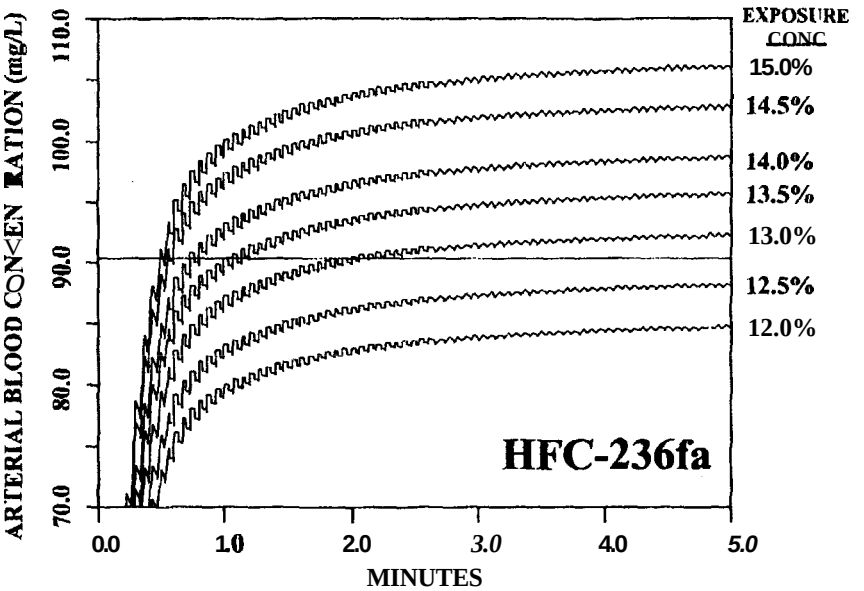

FIGURE 5. Monte Carlo simulations of arterial concentration of humans exposed to HFC-236fa for 5 min at concentrations of 12, 12.5, 13.0, 13.5, 14.0, 14.5, and 15.0%. The horizontal line at *90.37* mg/L represents the lowest arterial blood concentration measured at 5 min in a group of 6 dogs exposed to HFC-236fa at the cardiac sensitization LOAEL of 15.0%.

during a cardiac sensitization test ranges from 1.0 to 12.0 μg/kg body weight (Dodd & Vinegar, **1998).** Since **dogs** have a **total** blood volume *of* **about** 8.2% **of** 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 preceding calculation assumes that the

TABLE 3. Acceptable human exposure times at stated concentrations for Halon 1301

Halon 1301 concentration		
% v/v	ppm	Time (min)[a]
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*

[a]Based on the 5-min blood concentration of dogs exposed to Halon 1301 at the LOAEL of 7.5%.

TABLE 4. Acceptable human exposure limes at stated concentrations foi CF_3I

CF_3I Concentration		
% v/v	ppm	Time (min)[a]
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

[a]Based on the 5-min blood concentration of dogs exposed to CF_3I at the LOAEL of 0 4%

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 the preceding calculations indicate (60 to 730 µg/L or I50 to 1825 times the circulating levels). It is recognition of the conservative nature of the cardiac sensitization test that allows the U.S. Environmental Protection Agency (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

TABLE 5. Acceptable human exposure times at stated concentrations for HFC-125

HFC-125 concentration		
% v/v	ppm	Time (min)[a]
11.5	115,000	5.00
12 0	120,000	1.13
12.5	123,000	0 73
13.0	130,000	0 59
13 5	135,000	0.50

[a]Based on the 5-min blood concentration of dogs exposed tu HFC-125 at the LOAEL of 10 0%

TABLE 6. Acceptable human exposure times at stated concentrations for HFC-227ea

HFC-227ea concentration		
% v/v	ppm	Time (min)[a]
10 5	105,000	5 00
11 0	110,000	1 13
11.5	115,000	0.60
12 0	120,000	0.43

[a]Based on the 5-min blood concentration of dogs exposed to HFC-227ea at the LOAEL of 10 5%.

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 sensitizatian data and physiologically based modeling provides a quantitative approach, which can facilitate the selection and effective use of halon replacement candidates.

TABLE 7. Acceptable human exposure times at slated concentrations for HFC-236fa

HFC-236fa concentration		
% v/v	ppm	Time (min)[a]
12 5	125,000	5.00
13.0	130,000	1.93
13 5	135,000	0 99
14.0	140,000	0.7 3
14 5	145,000	0 55
15 0	150,000	0 49

[a]Based on the 5-min blood concentration of dogs exposed to HFC-236fa at the LOAEL of 15.0%.

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