Modeling Cardiac Sensitization Potential of Humans Exposed to Halon 1301 or Halon 1211 aboard Aircraft

ALLEN VINEGAR, M.S., PH.D.

VINEGAR A. *Modeling cardiac sensitization potential of humans exposed to Halon 1301 or Halon 1211 aboard aircraft.* Aviat Space Environ Med 2001; 72928–36.

Background: Halon 1301 and Halon 1211 are being replaced because they contribute to the depletion of ozone. Many of the potential candidate chemicals for replacing them are, like them, halogenated hydrocarbons. These chemicals have the potential to cause cardiac sensitization at high enough exposure concentrations. ***Methods:*** A physiologically based pharmacokinetic model, which mathematically describes the uptake, distribution, metabolism, and elimination of chemicals, was used to relate exposure to these chemicals with arterial blood concentrations resulting from the exposure. This information was then used to evaluate the potential for the occurrence of a cardiac-sensitizing event. The model was used to analyze the exposures to Halon 1301 and Halon 1211 in three aircraft (Navy E-2B, Cessna-421B, and Cessna-210C). Results: Halon 1301 exposures were shown to be safe, but Halon 1211 resulted in arterial concentrations in exposed individuals that reached levels that could potentially cause cardiac sensitization. ***Conclusions:*** Use of the model for evaluating the risk from exposure to Halon 1301 and Halon 1211 is a moot point since both chemicals are being replaced. However, demonstration of the validity of the approach provides a tool for the evaluation of the health safety of replacement candidates. The National Fire Protection Association has approved use of this model for assessing times for safe egress from situations where agents are used to flood an area to extinguish a fire.

Keywords: cardiac sensitization, halon, physiologically based pharmacokinetic model, fire extinguishant.

HALONS, USED AS FIRE extinguishants, have been banned from production because of international concern for the depletion of stratospheric ozone. Only existing stocks are available for essential application use in aircraft fire and explosion suppression systems. Constantly changing political pressure puts these stocks at risk for elimination, increasing the need to make halon alternatives available for aircraft use. Most chemicals being considered as replacements for Halon 1301 and 1211 are halogenated hydrocarbons which, as a class, are regulated by the U.S. Environmental Protection Agency *(6)*.

Cardiac sensitization is the acute toxic endpoint of concern. Dogs are monitored continually for electrocardiographic changes indicative of the appearance of a burst of multifocal ventricular ectopic activity or ventricular fibrillation. They are given an epinephrine challenge after 5 min of exposure to the test chemical. The test is performed at several chemical concentrations to determine a no observable adverse effect level (NOAEL) and a lowest observable adverse effect level (LOAEL). The LOAEL and NOAEL values are used directly for establishing human exposure limits because of the sensitive nature of the test *(6)*.

Recently, a mathematical tool was developed which allows the quantitative evaluation of short-term exposure to halogenated hydrocarbons (10). This tool is a physiologically based pharmacokinetic (PBPK) model, which can relate chemical exposure to concentrations in the body. It has been proposed that the model be used to relate external exposure of halon replacement chemicals to arterial blood concentration. Arterial blood concentration can then be compared with a target arterial blood concentration associated with cardiac sensitization. The methodology for doing this has been proposed **(7)** and described in detail (8). The National Fire Protection Association **(3)** has approved use of this model for assessing times for safe egress from situations where agents are used to flood an area to extinguish a fire.

The PBPK model can be used both retrospectively to evaluate previous actual exposure scenarios and prospectively to evaluate potential exposure scenarios. An example of a retrospective evaluation was given in Vinegar et al. (10) where they evaluated an accidental exposure to Halon 1211 that had occurred in an Israeli Army battle tank during a military exercise (2). In this instance, model predictions were consistent with the outcome where the gunner, having only brief exposure, successfully escaped without incident but the driver, with prolonged exposure, reached levels adequate for cardiac sensitization. The driver, in fact, was observed to be in ventricular fibrillation, never regained consciousness and died as a result of the incident. A prospective application of the model was demonstrated by Vinegar et al. (9). In order to evaluate the potential hazard to ground crews of an accidental release of CF_3I

From ManTech Environmental Technology, Inc. at Wright-Patterson AFB, OH.

This manuscript was received for review in July 2000. It was revised in March 2001. It was accepted for publication in April 2001.

Address reprint requests to: Allen Vinegar, Ph.D., P.O. Box 1398, Placitas, NM 87043; tokens@myranch.com

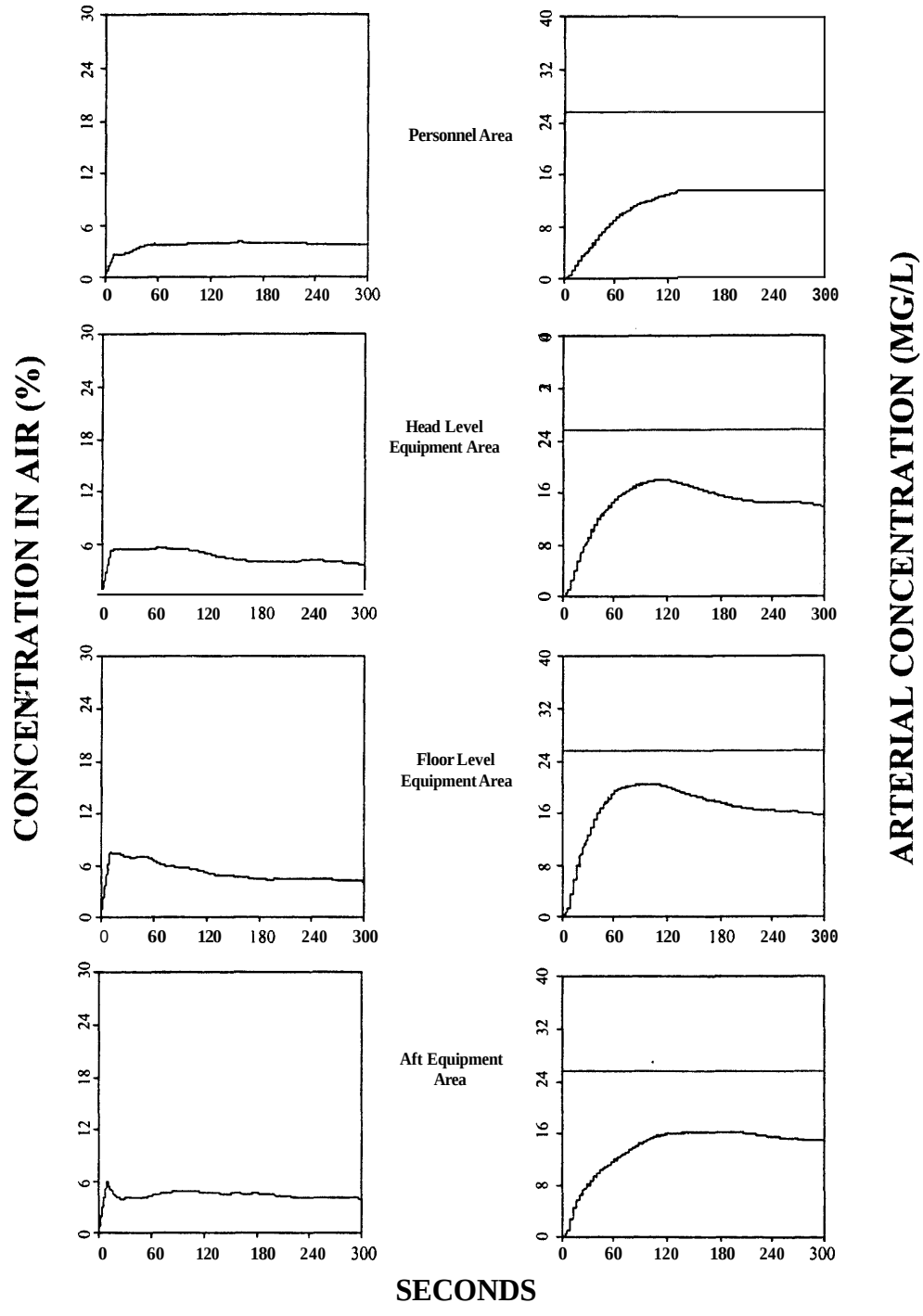

Fig. 1. Halon 1301 - **Ground Test (equipment cooling System** ON) **for Navy E-2b. Concentrations of Halon** 1301 **measured at four locations are shown in the left-hand column. Simulated arterial concentrations for each of the four locations are shown in the right-hand column. The straight line shown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

a discharge test was conducted on **an** F-15 jet to record CF_3I concentration time histories at various locations near the aircraft. These exposure data were used with the PBPK model to simulate the potential blood levels of workers at various locations around the aircraft during the release. The blood levels were compared with the target arterial blood concentration associated with cardiac sensitization. Results showed that at some locations the target was not reached but at the open nacelle the blood concentrations could potentially reach double the target. This information was put in perspective with a further retrospective simulation of individuals who had actually inhaled CF_3I **and** whose blood concentrations were simulated and estimated to be 100 times the target. These individuals experienced no apparent effect of their exposures, thus indicating the intended conservative nature of the cardiac sensitization test. Further prospective application of the model was demonstrated in Vinegar et al. (8). Here a method was demonstrated for establishing safe duration for exposure to potential halon replacements at different flood**ing** concentrations.

An issue of health concern is that of the intentional use of fire extinguishers in aircraft cabins with passengers aboard. No data were available for **any** of the potential halon replacements. However, there have

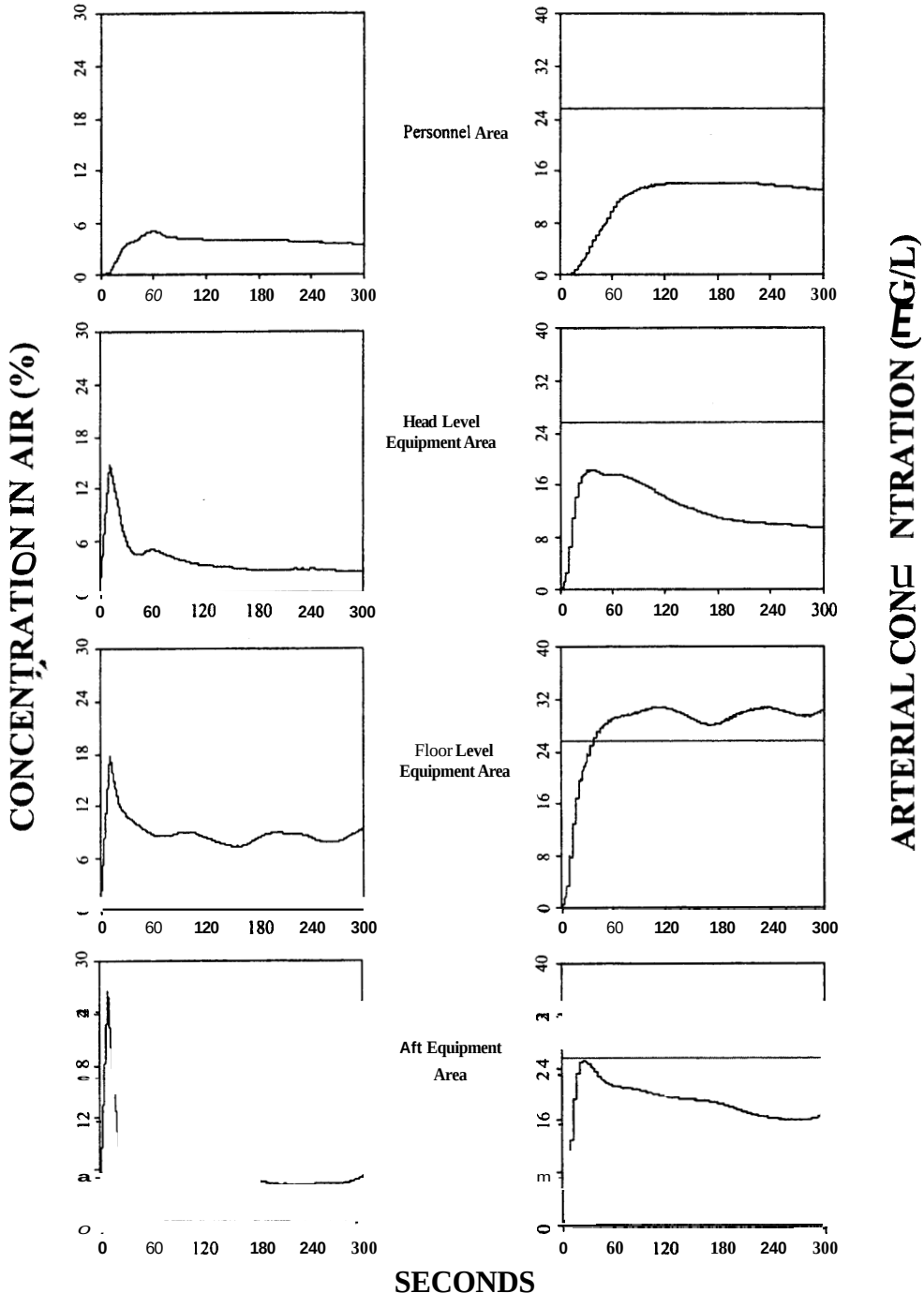

Fig. 2. Halon 1301 - Flight Test (Nozzle Jets Mixing Agent) for Navy E-2B. Concentrations of Halon 1301 measured at four locations are shown in the left-hand column. Simulated arterial concentrations for each of the four locations are shown in the right-hand column. The straight line shown at 25.7 mg · L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

been several published reports on measurements taken in aircraft cabins during the release of Halon 1301 and Halon 1211. These data were used with the PBPK model to see if any of the described scenarios could put passengers or crew at potential risk for cardiac sensitization. Results of these simulations are reported herein.

METHODS

Three publications were found that presented data on releases of Halon 1211 and/or Halon 1301 in aircraft. The first study **(5)** used a fleet configured Navy E-2B "Hawkeye" airplane. Concentrations of Halon 1301 were measured at head level in areas occupied by flight crewmembers, and in airplane locations where fire hazard potential posed the greatest threat. Halon 1301 was monitored using a Statham Laboratories Model GA-2A gas recorder and accessories.

The second study **(1)** used a Cessna Model C-421B, a small pressurized aircraft. Halon 1211 and Halon **1301** were measured using factory field modified Beckman Model 865 infrared gas analyzers. Measurements were made at three locations:

1. Test area –Actual fire extinguisher discharge location.
2. Knee area –20 in above the floor at the area of discharge. Discharge area for pilot's and copilot's

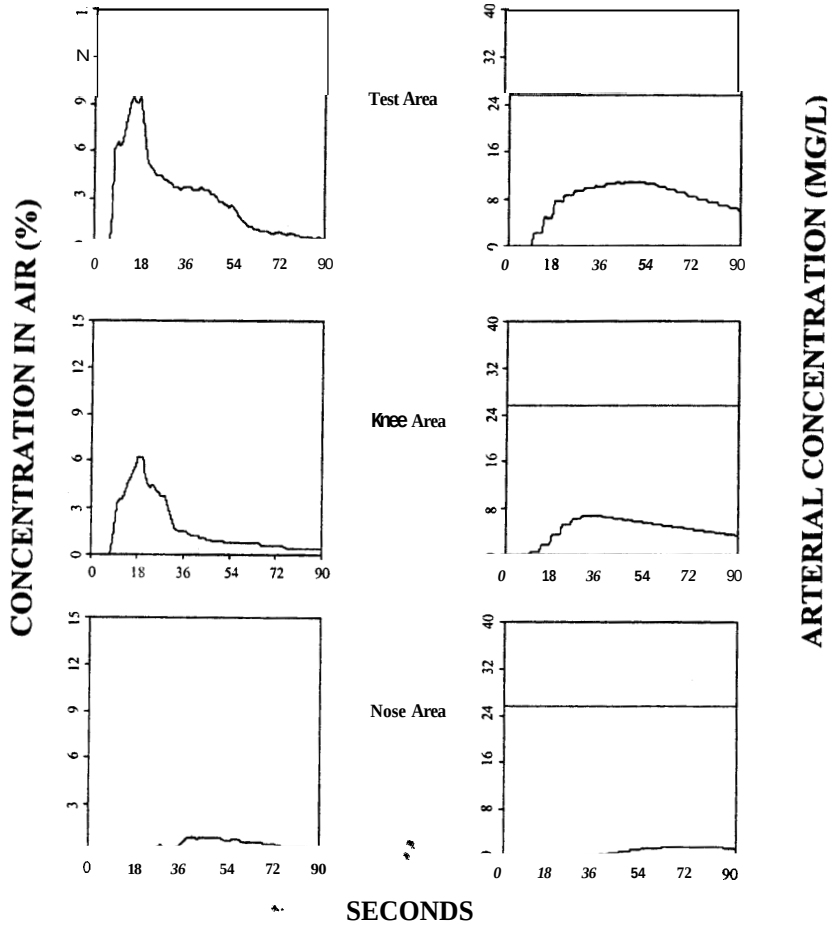

Fig. 3. Halon 1301 - Concentrations Cabin Area Last Vent Before Door Left Side for Cessna C-421B. Concentrations of Halon 1301 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 25.7 mg • L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

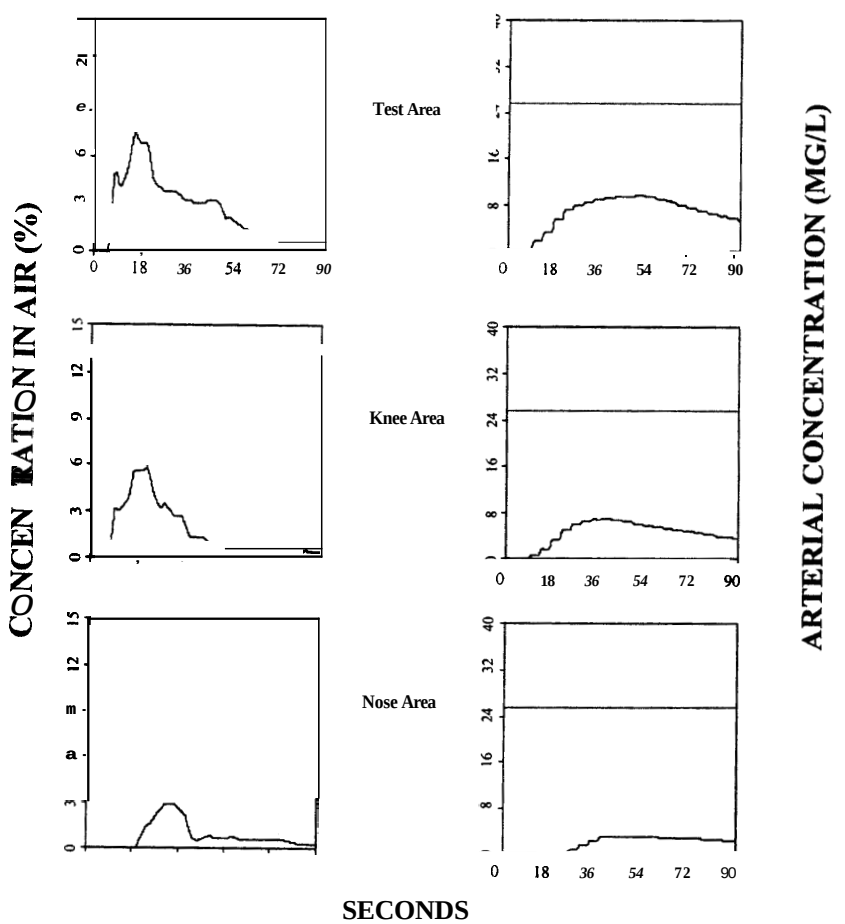

Fig. 4. Halon 1301 - Concentrations Cabin Area Last Vent Right Side for Cessna C-421B. Concentrations of Halon 1301 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 25.7 mg • L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

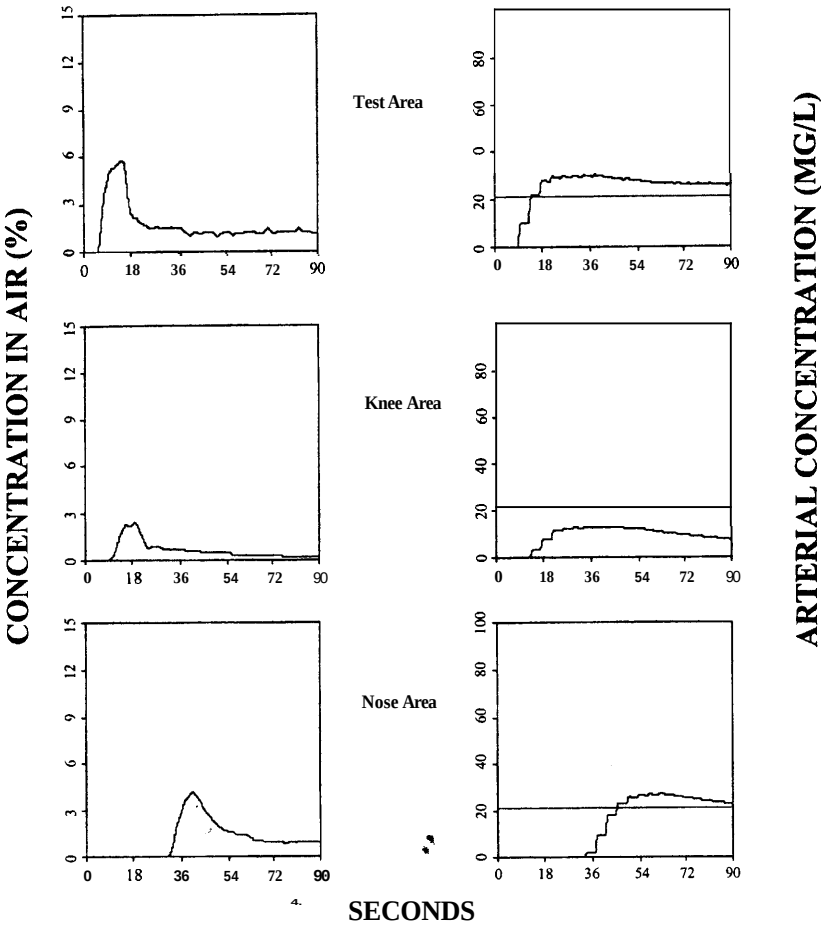

Fig. 5. Halon 1211 - Concentrations Copilot's Seat for Cessna C-4218. Concentrations of Halon 1211 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 21.0 mg·L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

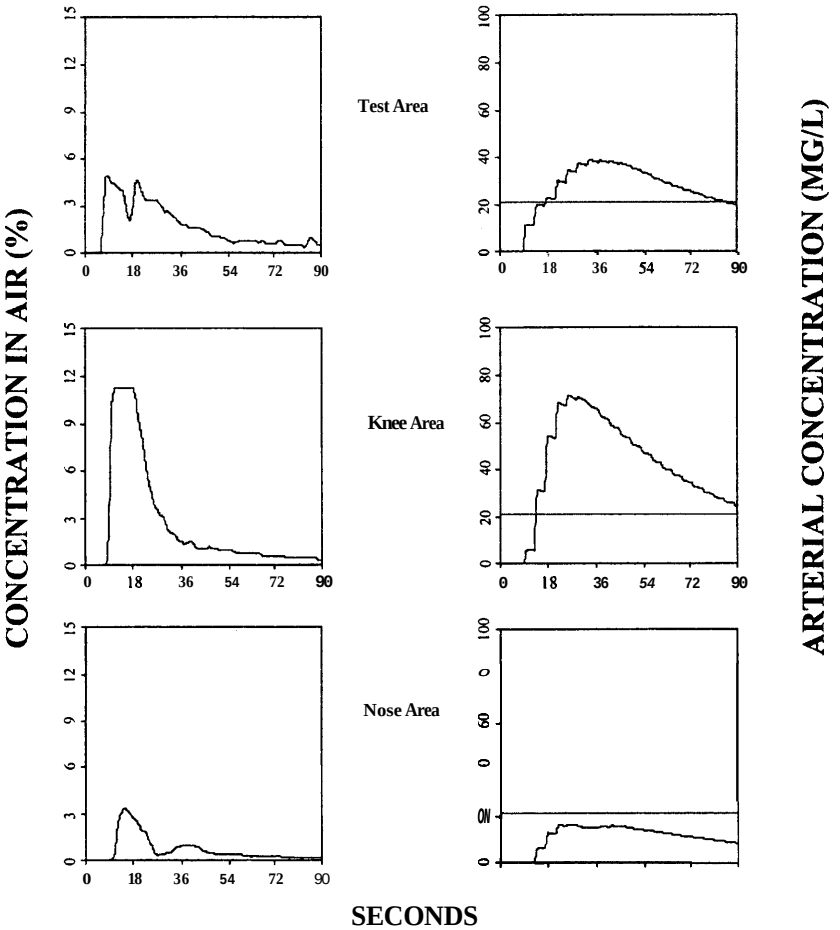

Fig. 6. Halon 1211 - Concentrations Cabin Side Of Grill Under Copilot's Seat for Cessna C-421B. Concentrations of Halon 1211 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 21.0 mg·L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

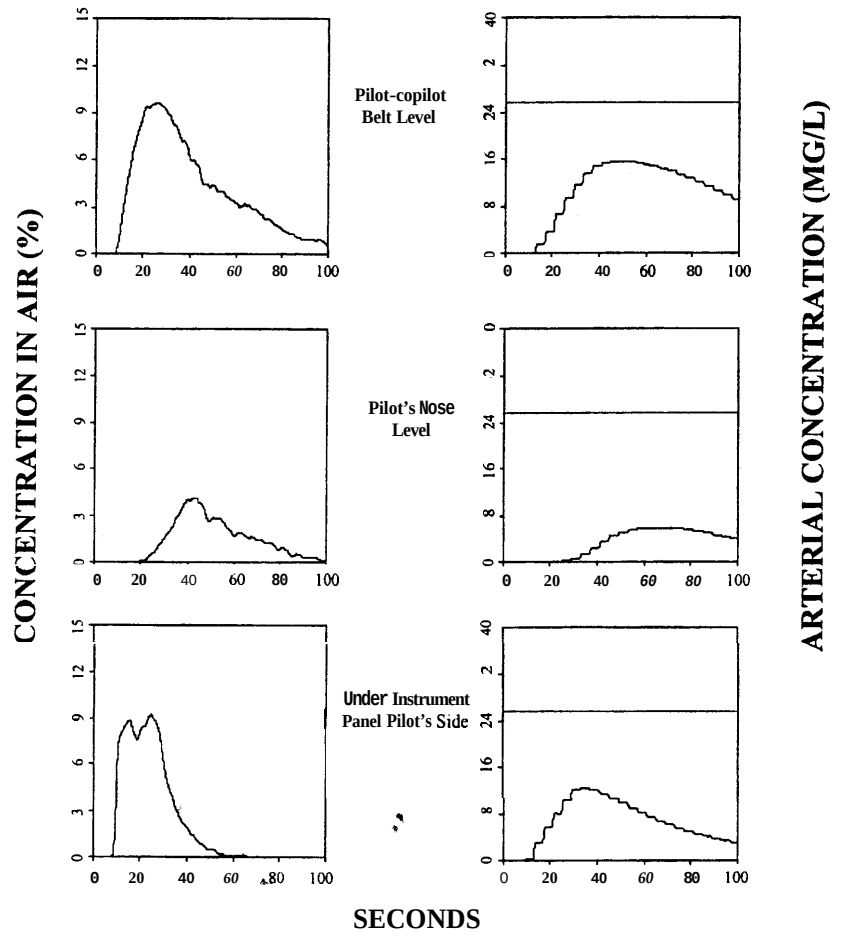

Fig. 7. Halon **1301–3-lb** Extinguisher Directed To Copilot's Door - Overhead Vents Closed for Cessna **21**OC. Concentrations of Halon 1301 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 25.7 $mg \cdot L^{-1}$ for each of the arterial simulations represents the target concentration for cardiac sensitization.

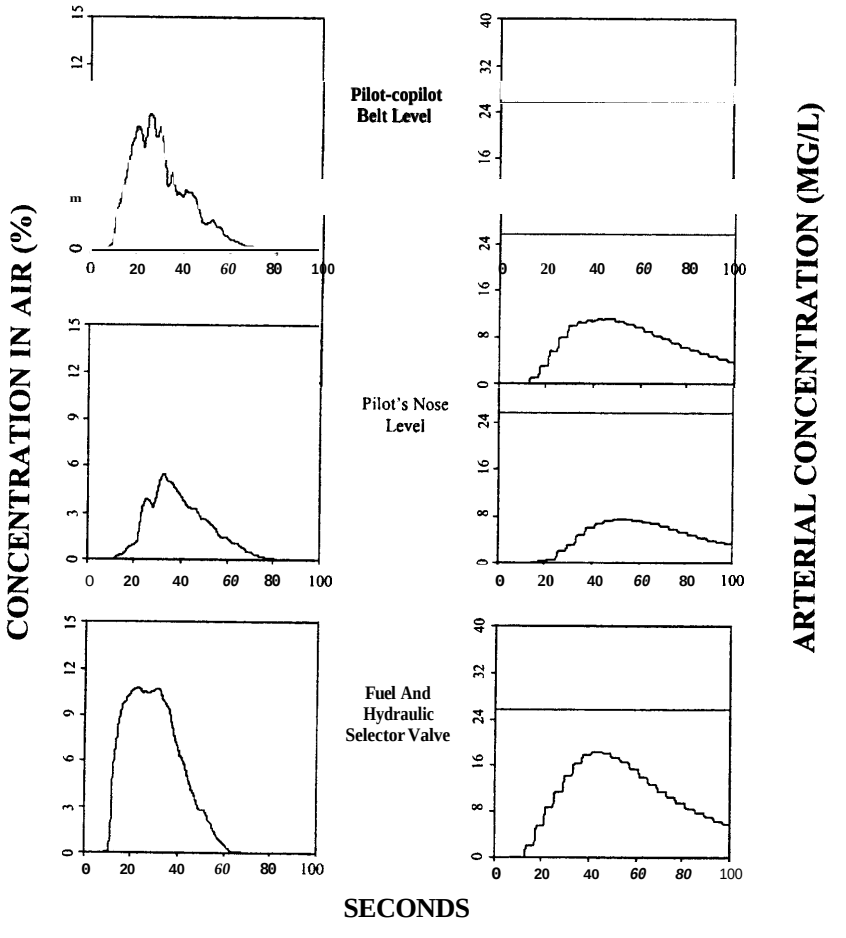

Fig. 8. Halon **1301–3-lb** Extinguisher Directed To Fuel And Hydraulic Selector Valves - Overhead Vents Open for Cessna 210C. Concentrations of Halon 1301 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 25.7 $mg \cdot L^{-1}$ for each of the arterial simulations represents the target concentration for cardiac sensitization.

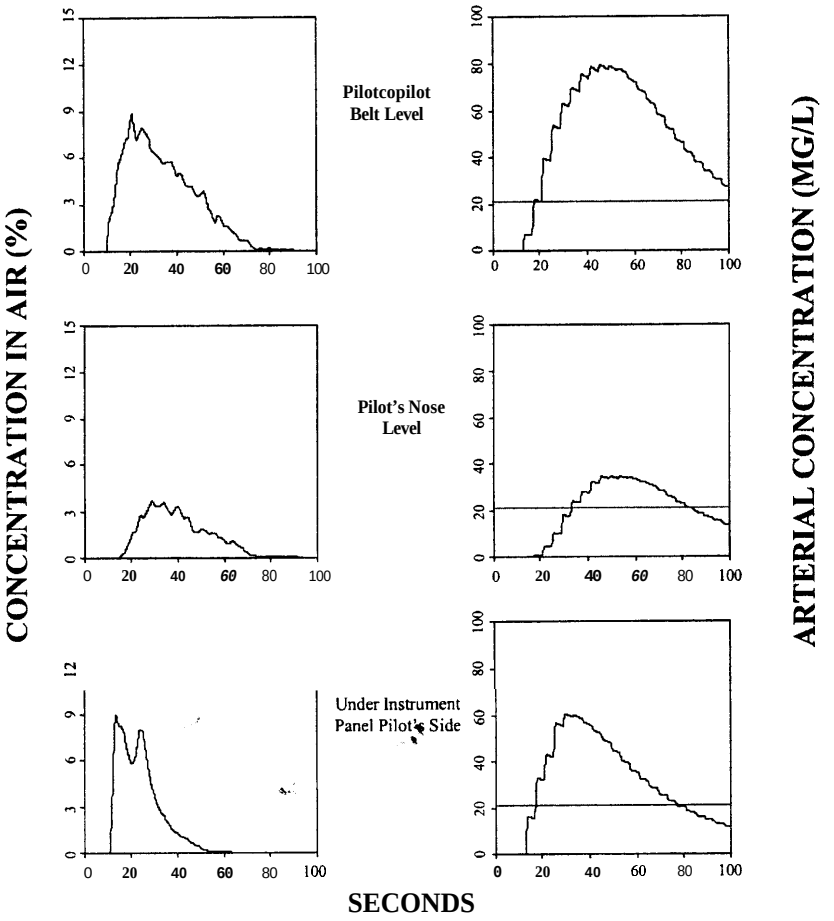

Fig. 9. Halon 1211–2.5-lb Extinguisher Directed Under Instrument Panel Pilot's Side - Overhead Vents Open for Cessna 210C. Concentrations of Halon 1211 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 21.0 mg · L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

seat tests was at knee level where the seat cushion meets the seat back.
3. Nose area –37 in above the floor at the area of discharge.

The last study (4) used a Cessna Model 210C, a small non-pressurized aircraft. Halon 1211 and Halon 1301 were measured using modified Beckman Model 865 infrared gas analyzers. Measurements were made at the point of release and at two other selected sites during each test.

In all three publications there are diagrams showing the specific locations monitored. The data were presented in graphic form. Results reaching the highest peak exposure concentrations were used from each paper. The data were digitized and converted to **ASCII** so that they could be used with the PBPK model. Exposure scenarios selected were used to simulate the arterial concentration using the model described by Vinegar et al. (10). Arterial concentrations were compared with target arterial concentrations for cardiac sensitization (8).

RESULTS

Representative results for the Navy E-2B are shown in **Figs. 1 and 2.** A ground test is illustrated in Fig. 1. Concentrations of Halon 1301 measured at four locations are shown in the left-hand column. Simulated arterial concentrations for each of the four locations are shown in the right-hand column. The straight line shown at 25.7 mg · L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization. None of the simulated concentrations reached the target. *An* example of a flight test is shown in Fig. 2. Under these conditions at floor level in the equipment area the concentrations of Halon 1301 in arterial blood exceeded the target concentration at about 40 s into the exposure and remained above the target for the duration of the measurements. Arterial concentration simulations remained below target at the other measured sites.

Results for representative releases aboard the Cessna C-421B are shown in **Figs. 3** to *6*. Halon 1301 releases at the last vent before the left side door (Fig. **3)** or at the last vent on the right side of the cabin **(Fig. 4)** resulted in simulated arterial concentrations well below the target concentration. Both releases of Halon 1211 resulted in simulated arterial concentrations that surpassed the target concentration of 21.0 mg · L^{-1} **(Figs. 5 and 6).** The target was exceeded at both sites of release. The release at the copilot's seat (Fig. 5) had measurements at nose level, which exceeded the target after about 45 s of exposure. Release at the cabin side of grill under the copilot's seat resulted in simulated arterial concentration at the knee area exceeding the target after about **16** s and peaking at more than three times the target at about **26** s (Fig. *6).* However, nose area concentrations remained below the target.

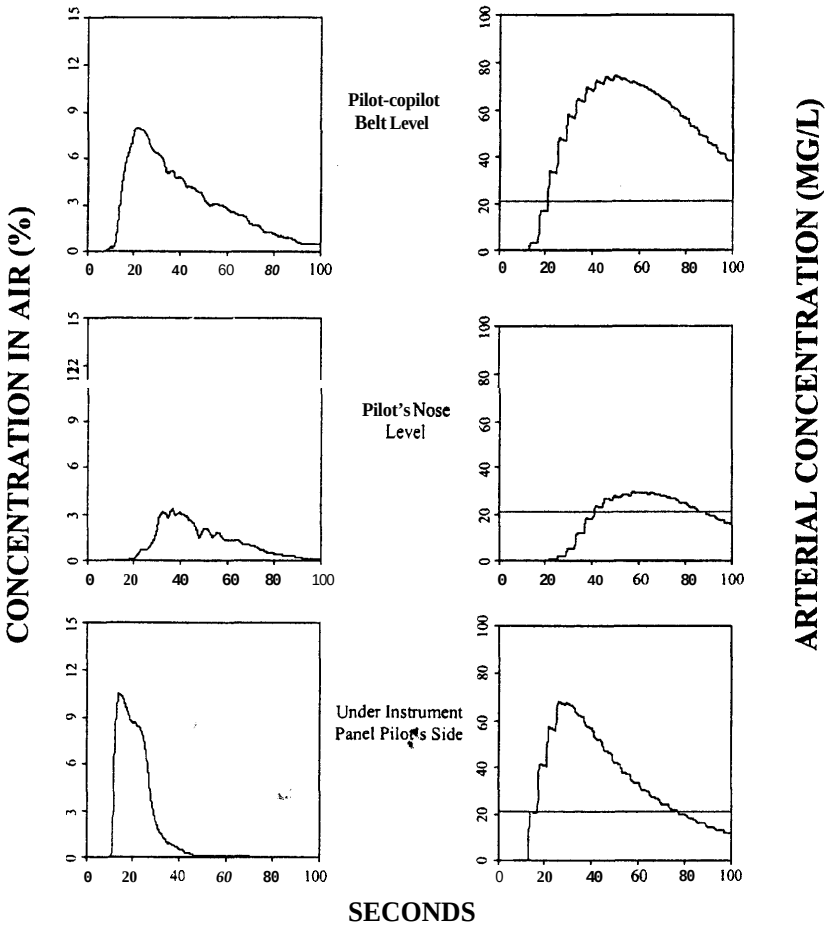

Fig. 10. Halon 1211–2.5-lb Extinguisher Directed Under Instrument Panel Pilot's Side - Overhead Vents Closed for Cessna 210C. Concentrations of Halon 1211 measured at three locations are shown in the left-hand column. Simulated arterial concentrations for each of the three locations are shown in the right-hand column. The straight line shown at 21.0 mg · L^{-1} for each of the arterial simulations represents the target concentration for cardiac sensitization.

Halon 1301 arterial concentrations remained below the target concentration for releases, in the Cessna 210C, directed to the copilot's door with overhead vents closed **(Fig. 7)** and directed to fuel and hydraulic selector valves with overhead vents open **(Fig. 8)**. Halon 1211 arterial concentrations exceeded the target level at all measured locations when the extinguisher was directed under the instrument panel on the pilot's side with overhead vents open **(Fig. 9)** or closed **(Fig. 10).**

DISCUSSION

The use of Halon 1301 for several decades has occurred with an excellent safety record. Retrospective modeling of scenarios such as those illustrated above show that generally under normal use there has been little to no opportunity for the occurrence of exposure situations where individuals have been put at potential risk of having blood levels of Halon 1301 ever reach a target concentration that might predispose for the onset of a cardiac sensitization response. Halon 1211, when used as a streaming agent under open conditions, likewise has posed little risk. However, when used under more confined situations the potential for cardiac sensitization exists. Several scenarios illustrated above showed situations where arterial concentrations of Halon 1211 exceeded the target associated with a potential for cardiac sensitization. The report of an incident involving exposure in an army battle tank by Lerman et al. (2) (see introduction) demonstrates that the risk is real if Halon 1211 is used under confined situations where the exposure concentration can get high enough to result in highly elevated blood concentrations.

The discussion with reference to Halons 1301 and 1211 is perhaps a moot point with both of them being replaced with other agents. However, the use of PBPK modeling to evaluate exposure scenarios with replacement agents should be considered. Prospective modeling of potential scenarios can forewarn against situations such as that reported by Lerman et al. **(2)** for army battle tanks.

ACKNOWLEDGMENTS

Support for this work was provided partially by the Department of Defense's Next Generation Fire Suppression Technology Program, funded by the DoD Strategic Environmental Research and Development Program (SERDP); through an Interagency Agreement between the U.S. EPA and the Department of the Air Force; and through Department of the Air Force Contract No. F41624-96-C-9010. The manuscript has been reviewed by the Office of Public Affairs and assigned the following journal article number, AFRL-HEST-WP-JA-2000-0001.

REFERENCES

1. Abramowitz A, Neese W, Slusher G. Smoke and extinguisher agent dissipation in a small pressurized fuselage. Washington, DC: US Dept. of Transportation, Federal Aviation Administration. DOT/FAA/CT-89/31; 1990.
2. Lerman Y, Winkler E, Tirosh MS, et al. Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). **Hum Exp Toxicol 1991; 10:125–8.**

3. National Fire Protection Association. NFPA 2001 standard for clean agent fire extinguishing systems. Quincy, MA. NFPA, 2000.
4. Slusher GR, Wright J, Demaree J. Halon extinguisher agent behavior in a ventilated small aircraft. Washington, DC: US Dept. of Transportation, Federal Aviation Administration DOT/FAA/CT-86/5; 1986.
5. Smith DG, Harris DJ. Human exposure to Halon 1301 ($CBrF_3$) during simulated aircraft cabin fires. Aerosp Med 1973; 44:198–201.
6. "SNAP Technical Background Document. Risk Screen on the Use of Substitutes for class I Ozone-Depletingsubstances, Fire Suppression and Explosion Protection (Halon Substitutes)," Federal Register 1994; 59:13044.
7. Vinegar A, Jepson GW. Cardiac sensitization thresholds of halon replacement chemicals predicted in humans by physiologically based pharmacokinetic modeling. Risk Anal 1996; 16:571–9.
8. Vinegar A, Jepson GW, Cisneros M, et al. Setting safe acute exposure limits for halon replacement chemicals using physiologically-based pharmacokinetic modeling. Inhal Toxicol 2000; 12751–63.
9. Vinegar A, Jepson GW, Hammann SJ, et al. Simulated blood levels of CF_3I in personnel exposed during its release from an F-15 jet engine nacelle and during intentional inhalation. Am Indust Hyg Assoc J 1999; 60:403–8.
10. Vinegar A, Jepson GW, Overton JH. PBPK modeling of short-term (0 to 5 min) human inhalation exposures to halogenated hydrocarbons. Inhal Toxicol 1998; 10:411–29.