PBPK Modeling of CF_3I Releases from F15 Engine Nacelles

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Efforts to replace ozone-depleting substances (ODS) have necessitated the quantitative toxicological evaluation of Halon replacement chemicals. Volatile organic compounds with halogen substituents have been regulated on the basis of cardiac sensitization tests conducted in dogs (U.S. EPA, 1994). Dogs, the usual test species, are challenged simultaneously with epinephrine and the test chemical of interest, during which time cardiac electrical activity is monitored for cardiac arrhythmias. The test is repeated using several different concentrations of the test chemical in order to establish a No Observable Adverse Effect Level (NOAEL) and a Lowest Observable Adverse Effect Level (NOAEL). The NOAEL and LOAEL in dogs have been applied directly by federal regulators to establish allowable exposure.

The task of determining appropriate allowable human exposure limits for Halon replacement chemicals requires consideration of both the exposure concentration and the duration of the exposure. Recent efforts supported by the EPA have focused on development of scientific approaches for establishing safe egress times for people occupying an area where Halon replacement chemicals are discharged. This approach involves the use of a physiologically based pharmacokinetic (PBPK) model which describes the uptake, distribution, metabolism, and elimination of the chemical by the human body.

A case report of an accidental inhalation of Halon illustrates the utility of the modeling approach. During an Israeli military exercise a small electrical fire was accidentally ignited in an armored vehicle and was extinguished by using two 1.36 kg cans of Halon 1211 (Lerman et al., 1991). The gunner, who was seated at the vehicle turret, escaped immediately and was symptomless within 60 seconds. Upon physical examination findings were unremarkable. The vehicle driver was in a more inward compartment which was isolated by closed hatches. He was not able to exit and after several minutes was removed unconscious, pulseless, and not breathing a few minutes after the fire was extinguished. Upon taking an EKG 40 minutes later, ventricular fibrillation was evident which did not respond to DC cardioversion. He was pronounced dead 2 hours later.

A reenactment was performed in an identical vehicle to determine the exposure to Halon 1211 received by the two men. Two cylinders **of** 1.36 kg Halon 1211 were released in the vehicle and concentrations were measured at the driver's compartment and the

turret. The published exposure profiles are shown in Figure 1. Both the driver and gunner potentially received exposures above the LOAEL for Halon 1211 (1.0%, 10000 ppm).

The PBPK model was used to generate five-minute simulations of exposure to Halon 1211 under rest and work conditions to determine the arterial blood concentrations associated with exposure to the cardiac sensitization LOAEL of 1.0% (Figure 2). Rationale for this approach was presented by Vinegar and Jepson (1996). These concentrations were 22.2 and 21.3 mg/L for rest and work conditions, respectively. The simulated arterial blood profile for the driver is shown in Figure 3 and assuming at least 2 to 3 minutes for removing him from the driver's compartment, his blood concentration greatly exceeded the LOAEL arterial blood concentrations reaching levels as high as 180 mg/L. The simulated blood profile for the gunner (Figure 8) also exceeded the LOAEL blood concentrations reaching levels of 80 mg/L after 1 minute of exposure. However, the gunner had a margin of 17 seconds for exiting the vehicle before his blood level would have reached the LOAEL blood concentration. Thus, in this particular case study, the correlation between exposures, blood concentrations, cardiac sensitization LOAEL and outcome for the two individuals was consistent with modeling predictions.

The PBPK model was used to generate five-minute simulations of exposure to CF_3I to determine the arterial blood concentrations associated with exposure to the cardiac sensitization LOAEL of 0.4% (Fig. 4a). The model was then used to simulate blood concentrations of maintenance personnel in the vicinity of an F15 engine nacelle if there were an accidental release of a bottle of CF_3I. Exposure and measurement details are provided by the poster presentation manned by Mark Kay of McDonnell Douglas Aircraft. The figures (4b-g) show exposure profiles at several points and the simulation of arterial blood concentration of an individual standing at each point. The worst case scenario of a person having his head inside the nacelle when the CF_3I is accidentally released results in the LOAEL blood concentration of about 18 mg/L being attained before the completion of the first inhalation. As a point of comparison, five-minute simulation of exposure to Halon 1301 results in the concentration profile shown in Figure 4h. Assuming that the exposures measured were of Halon 1301 then a person with his head inside the nacelle at the time of release would attain arterial blood concentrations shown in Figure 4i. The peak blood concentrations under this worst case scenario would result in blood concentrations of only about a tenth of the LOAEL blood concentration of about 26 mg/L. What remains to be done is to chart a path of egress and generate a concentration profile along the path of egress and **use** that profile to simulate the blood concentrations that might be attained by a person egressing from the point of CF_3I release.

ACKNOWLEDGMENTS

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Lerman, ***Y.,*** Winkler, E., Tirosh, M. **S.,** Danon, **Y.,** and Almog, S. (1991). Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). ***Human & Exper. Toxicol.*** 10,125-128.

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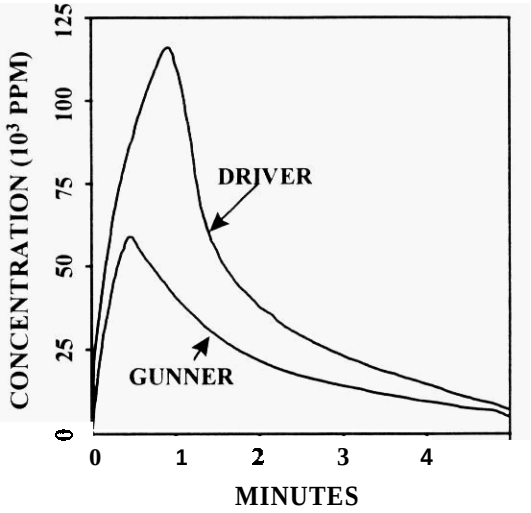


Figure 1. Concentration profiles of Halon 1211 in the driver's compartment and gunner's turret of an Israeli armored vehicle.

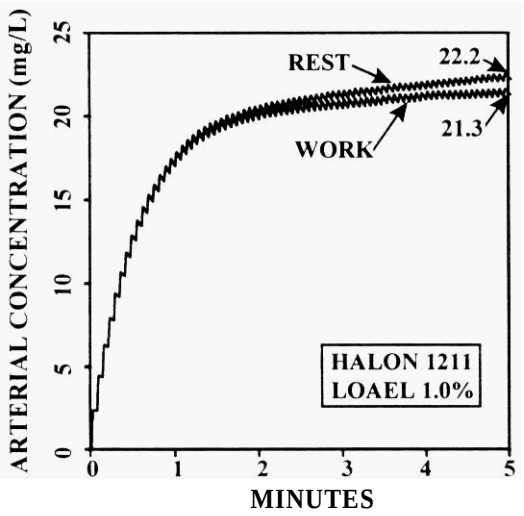


Figure 2. Simulated arterial blood concentration during 5-minute exposure of a human to Halon 1211 at 1.0% (LOAEL).

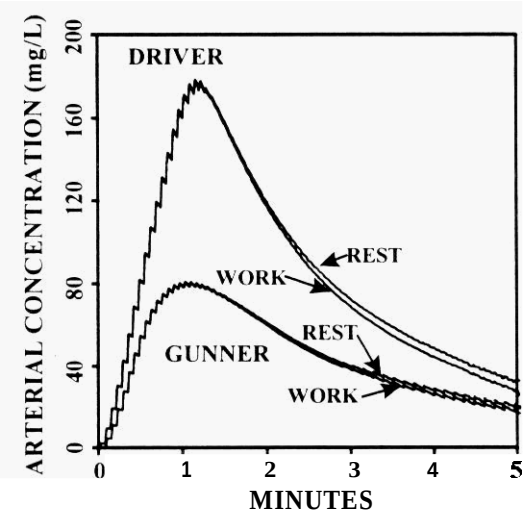
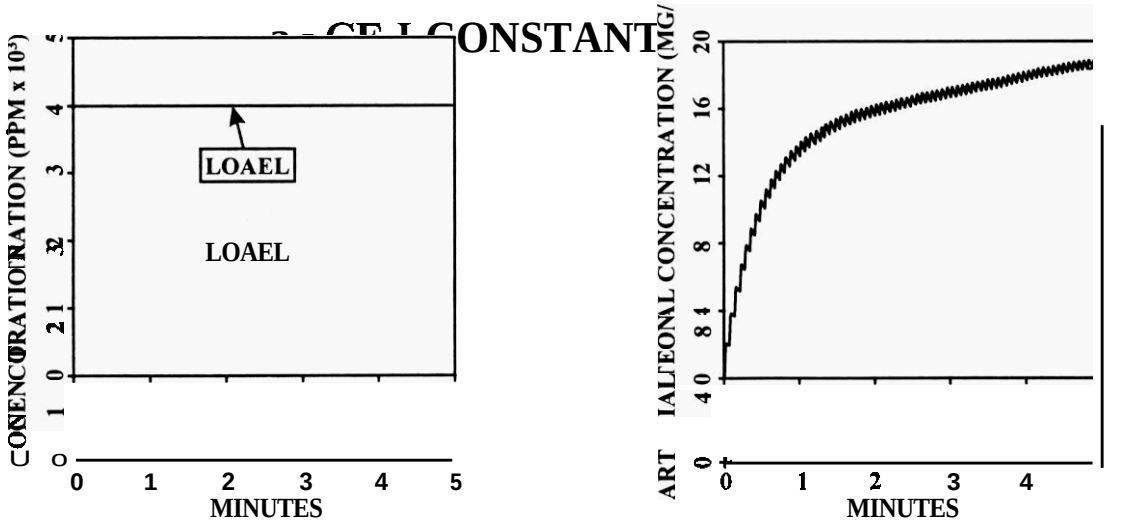
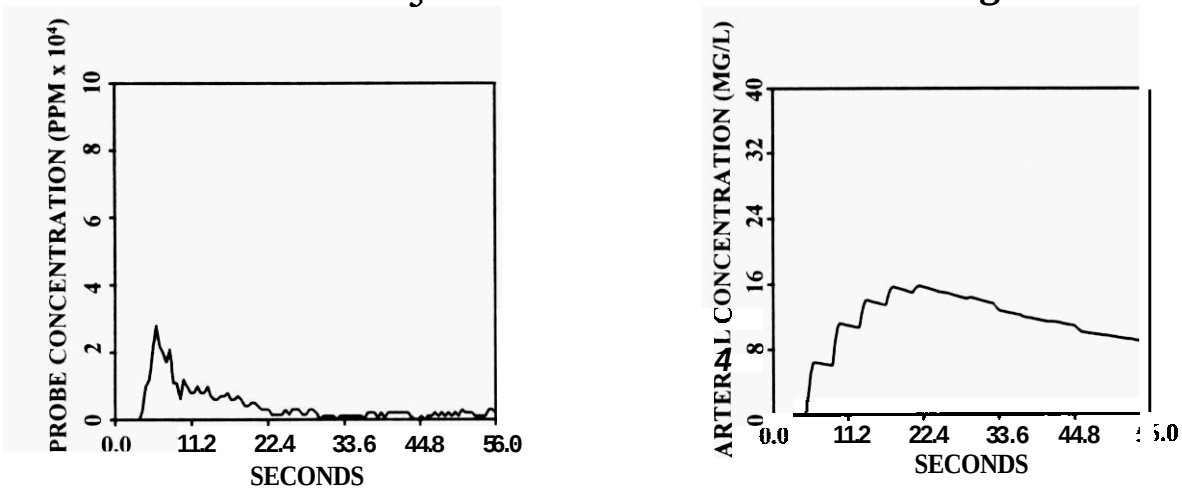


Figure **3.** Simulated arterial blood concentration during 5-minute exposure of a human to Halon 1211 at concentrations measured in the driver's compartment and in the turret (gunner's position) of the Israeli armored vehicle.



b - CF_3I - Ground level under left wing



c - CF_3I - Ground level under nacelle

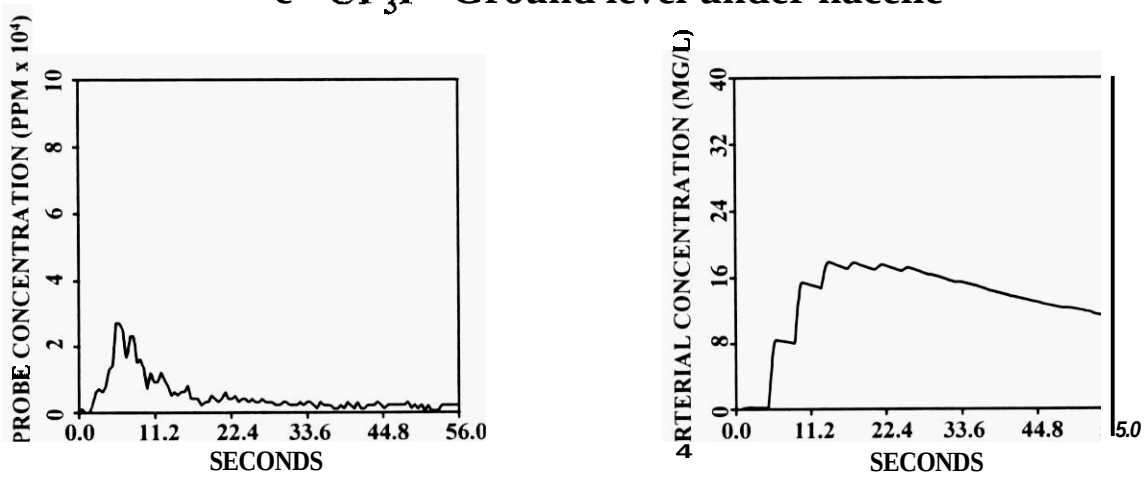


Figure 4. Exposure concentration profiles with corresponding simulated human arterial blood concentrations.

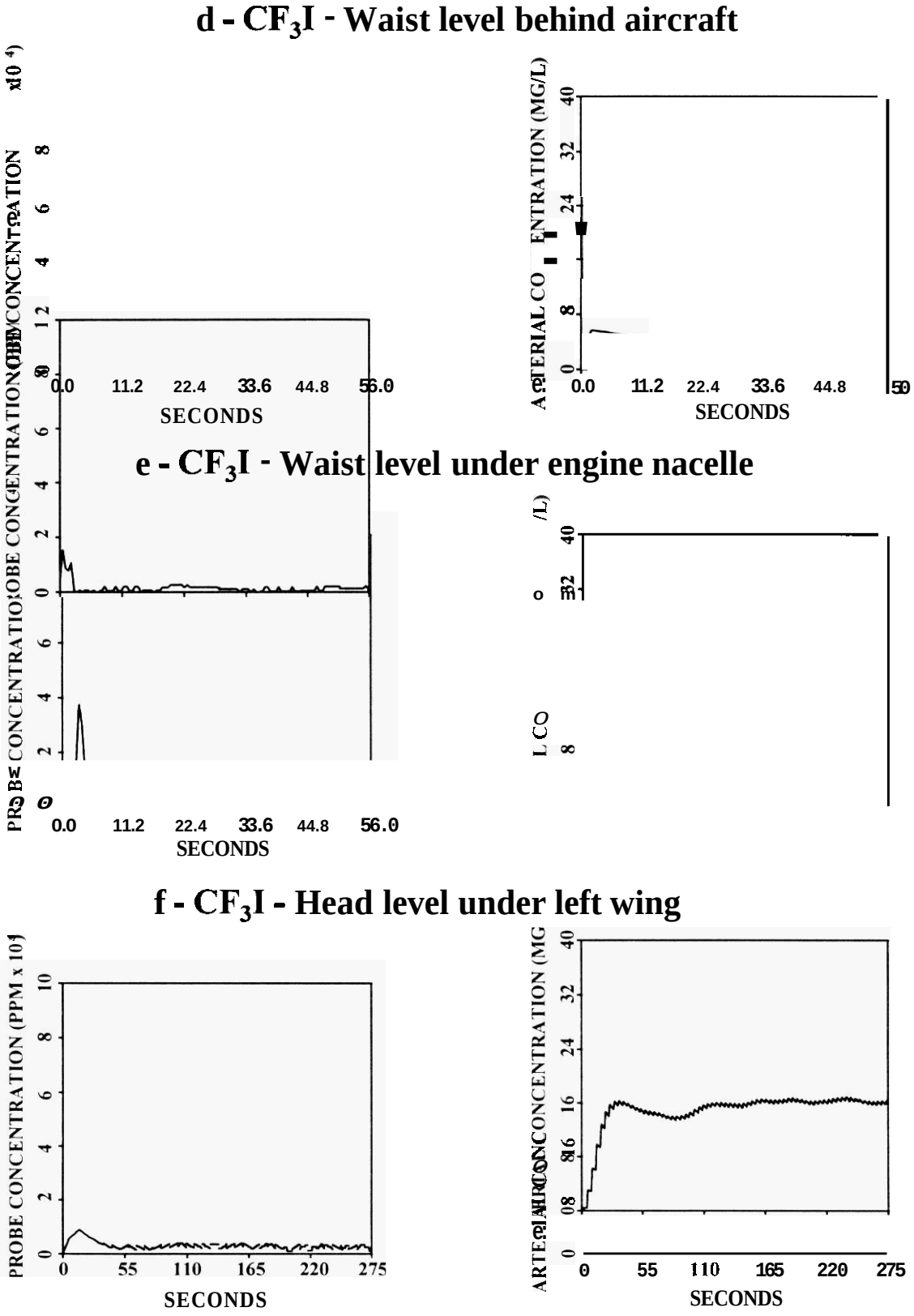
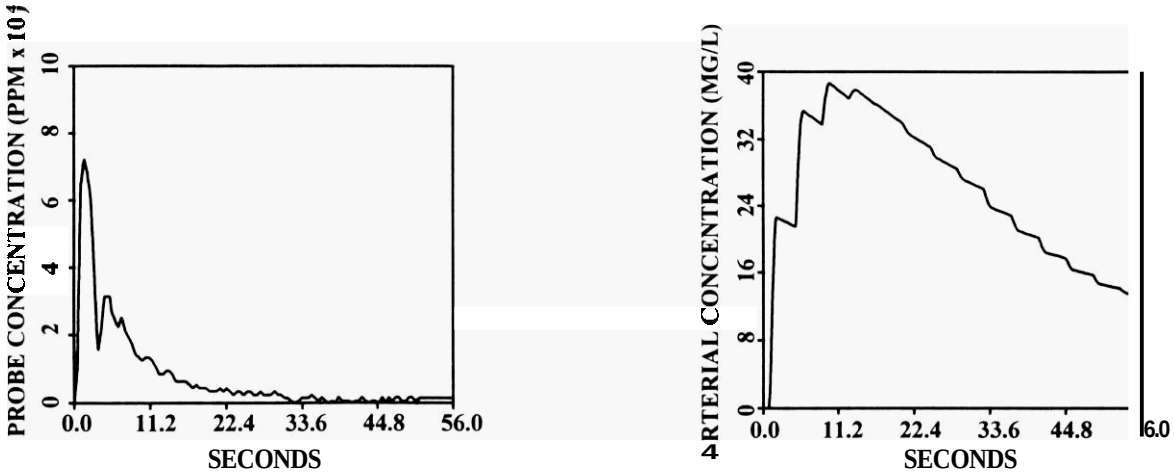
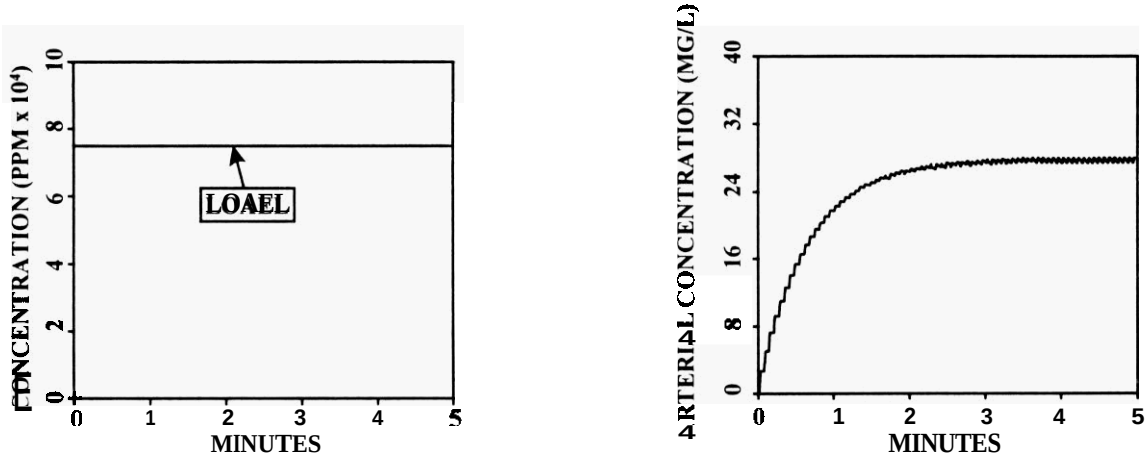


Figure 4 (continued). Exposure concentration profiles with corresponding simulated human arterial blood concentrations.

g - CF_3I - Head level inside nacelle



h - HALON 1301 CONSTANT LOAEL EXPOSURE



i - HALON 1301 - Head level inside nacelle

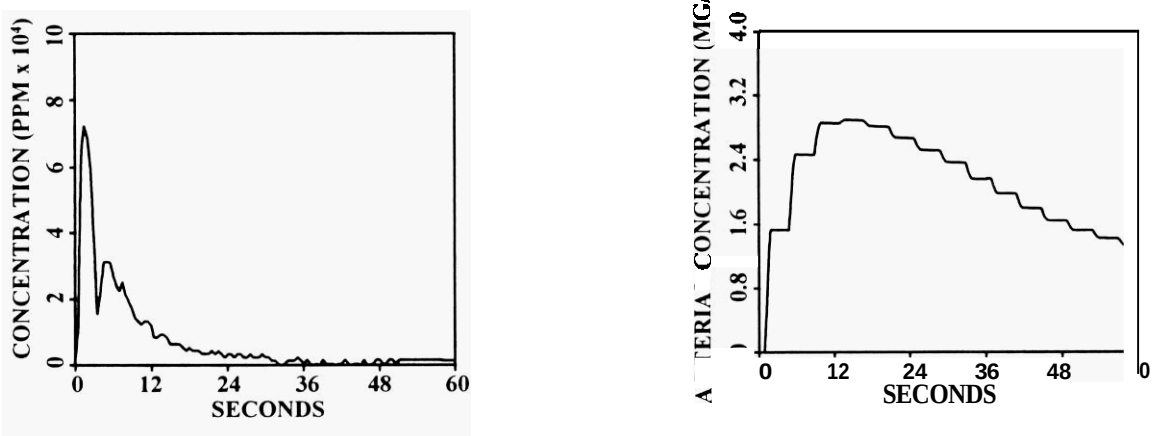


Figure 4 (continued). Exposure concentration profiles with corresponding simulated human arterial blood concentrations.