PHARMACOKINETIC MODELING FOR DETERMINING EGRESS FROM EXPOSURE TO HALON REPLACEMENT CHEMICALS

Allen Vinegar and *Gary* W. Jepson
ManTech Environmental Technology, Inc.

Dayton, OH 45437-0009 USA

Current standards for egress from potential exposure to halogenated fire suppressants use cardiac sensitization **as** the acute toxic endpoint of concern. Rules are based on the LOAEL (lowest observable adverse effect level) and NOAEL (no observable adverse effect level). The time to egress, based on these endpoints, has been set arbitrarily. Using a physiologically based pharmacokinetic model, it is possible to associate the external exposure concentration, on which the LOAEL and NOAEL are based, with the arterial blood concentration, which is associated with the cardiac sensitization event. The model can then be used to determine whether **a** particular model will allow prediction of the time required to reach this critical blood concentration. Given that individuals vary in physiological characteristics that will affect the pharmacokinetics of **a** chemical in the body, the model must he used in a way that will be protective of a broad part of the population. Consideration of the variability in individuals is taken into account by doing a Monte Carlo simulation. This technique involves performing multiple simulations in which the values of the physiological parameters are sampled randomly from their known distributions. The target blood concentration and time for egress determined with this method will be representative of **a** population rather than just **an** average individual. These determined values can then be used by regulators to set standards for egress in an objective manner.

Two sources relevant to this study are listed below:

Vinegar, A., and G. W. Jepson. "Cardiac sensitization thresholds of halon replacement chemicals predicted in humans by physiologically based pharmacokinetic modeling," ***Risk Analysis,*** 16:571-579, 1996.

Vinegar, **A., G.** W. Jepson, and J. H. Overton. "PBPK modeling of short-term (0 to 5 min) human inhalation exposures to halogenated hydrocarbons," ***Inhalation Toxicology,*** 10411-429, 1998.

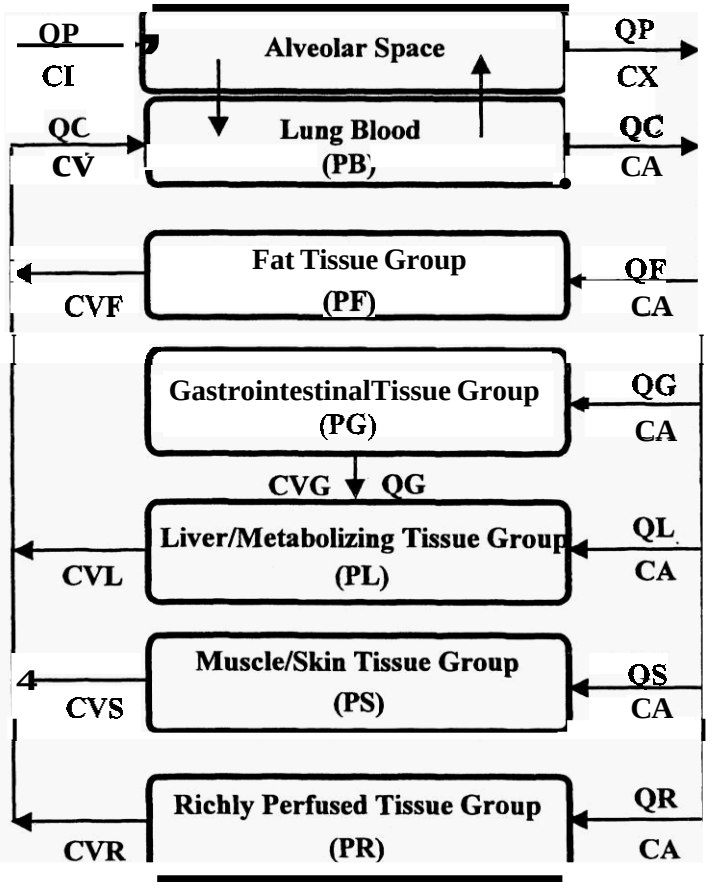
Current Egress Requirements for Total Flooding Agents (OSHA & EPA)

1. Design to NOAEL (cardiac sensitization in dog)
2. Up to LOAEL if Egress in 30 sec to 1 min
3. Above the LOAEL if Egress in Less than 30 sec
4. Egress Times Set Arbitrarily

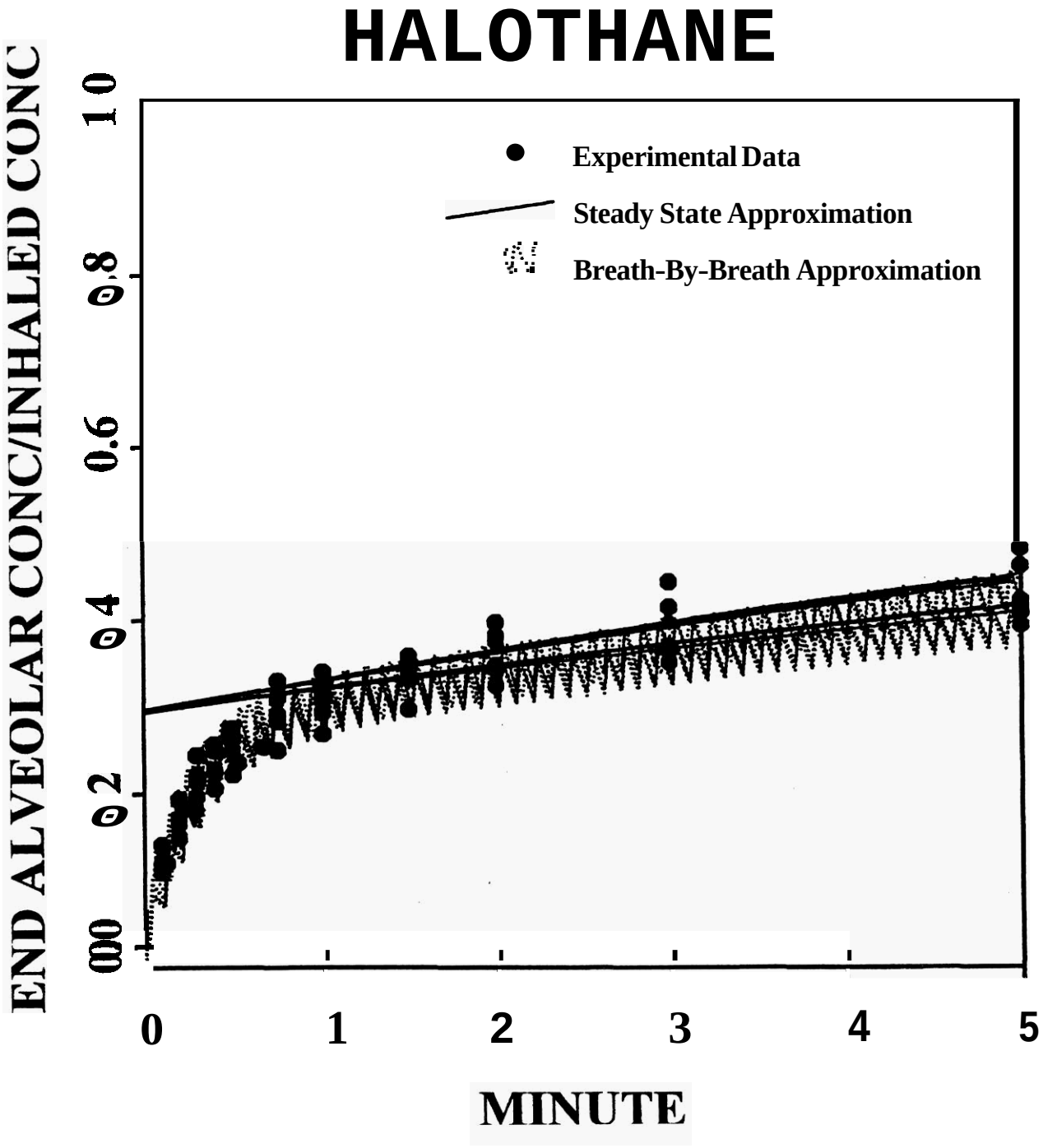
Scientific Approach to Determining Egress Times

1. Use physiologically based pharmacokinetic model
2. Develop and validate model in rat
3. Extrapolate model to man and validate with human data (if possible)
4. Use model to predict target blood concentrations associated with cardiac sensitization

Physiologically Based Pharmacokinetic Model



Pulmonary Gas (VGP)
Pulmonary Tissue (VTP)
Pulmonary Capillaries (VCAPP)
Rest of Body
QC
CA
QC
CV
CGDD or CGDP
CGP
Deadspace
Proximal
Distal
CI
CEX
S


HALOTHANE
END ALVEOLAR CONC/INHALED CONC
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
MINUTE
Experimental Data
Steady State Approximation
Breath-By-Breath Approximation

Model for Egress Time

1. Use human physiological parameters
2. Determine partition coefficients and metabolic rates
3. Simulate cardiac sensitizaiton protocol 5-min exposures to estimate blood concentration
4. Use blood concentration as target for further simulations at exposures higher than the LOAEL but with shorter than 5-min duration

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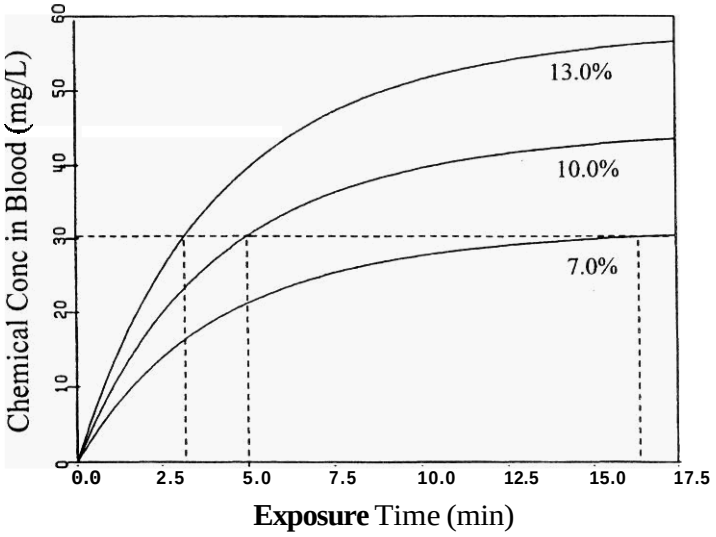
Simulation of Blood Concentrations of Humans During Exposure to HFC-125

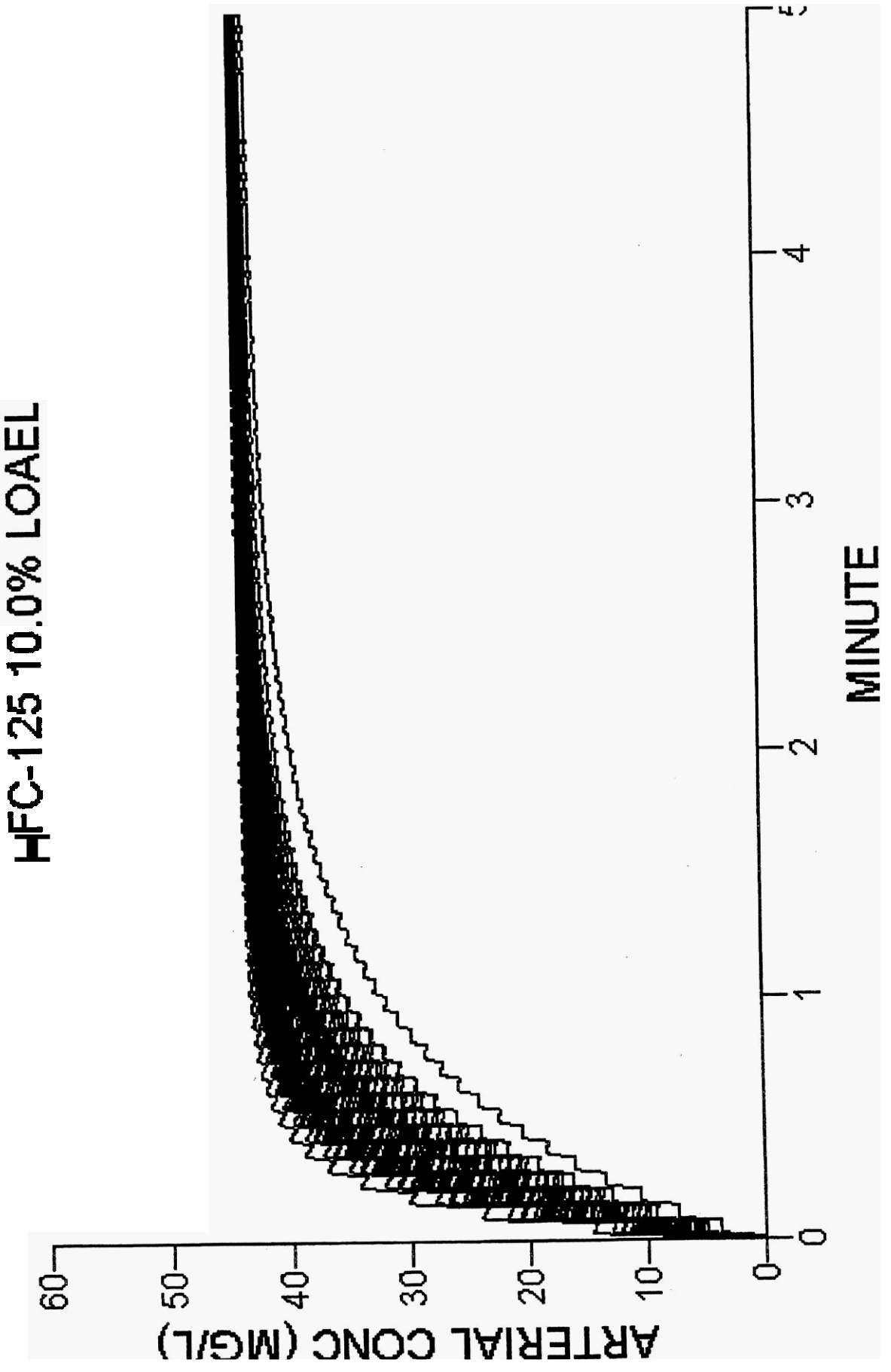


Fluorocarbon 12 – Cardiac Sensitization

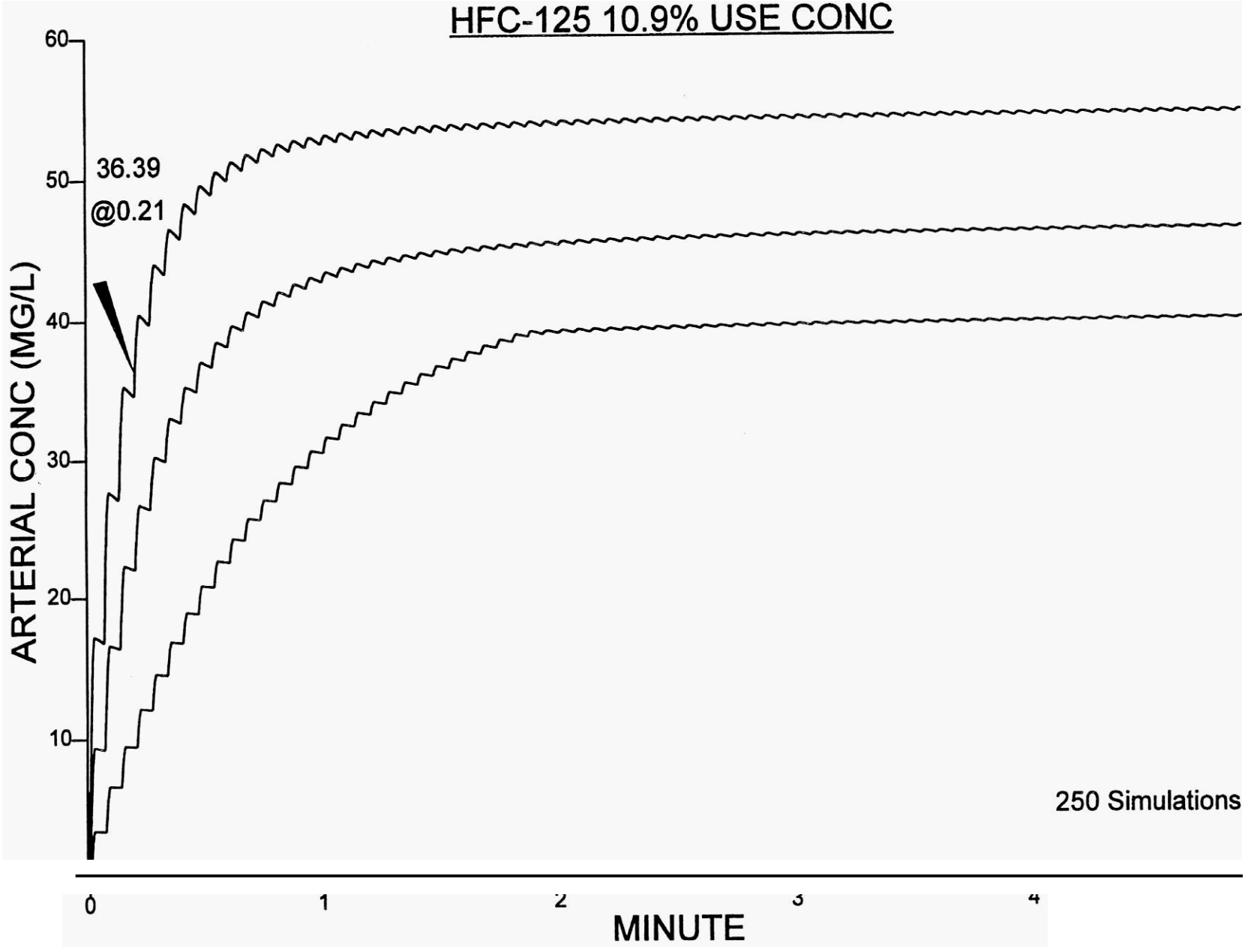
Concentration, % *v/v*	Duration (minutes)	# of Dogs	# of Marked Responses
2.5	5	12	0
2.5	30	6	0
2.5	60	6	0
5	5	12	5
7	0.5	7	0
13.5	0.5	7	**2**

Reinhardt, C.F. A. Azar, M.E. Maxfield, P.E. Smith, Jr., and L.S. Mullin. Arch. Environ. Health, 22:365-279, 1971.

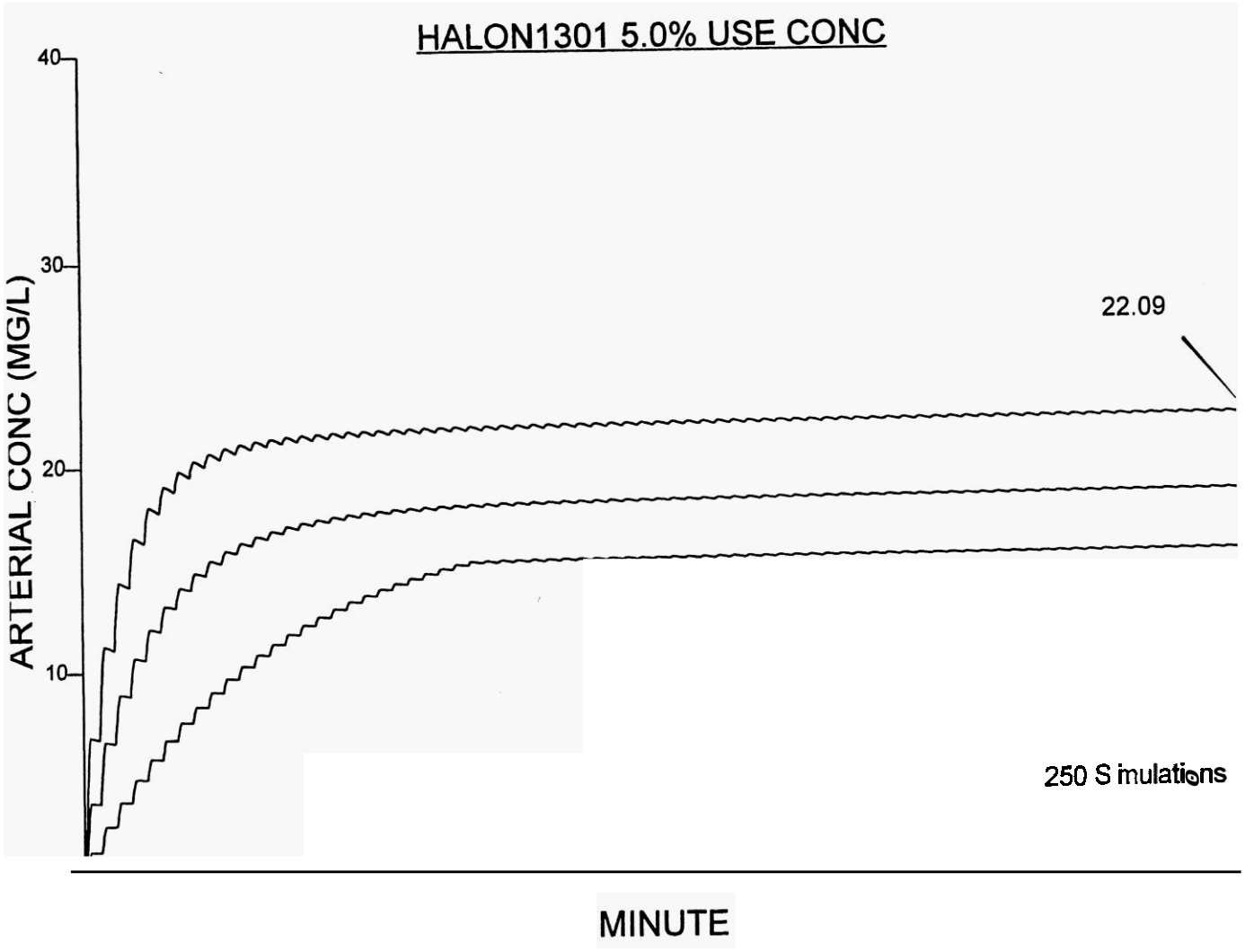
HFC-125 10.0% LOAEL
ARTERIAL CONC (MG/L)
60
50
40
30
20
10
0
0
1
2
3
4
5
MINUTES


HFC-125 10.0% LOAEL
ARTERIAL CONC (MG/L)
60
50
40
30
20
10
0
0
1
2
3
4
MINUTE

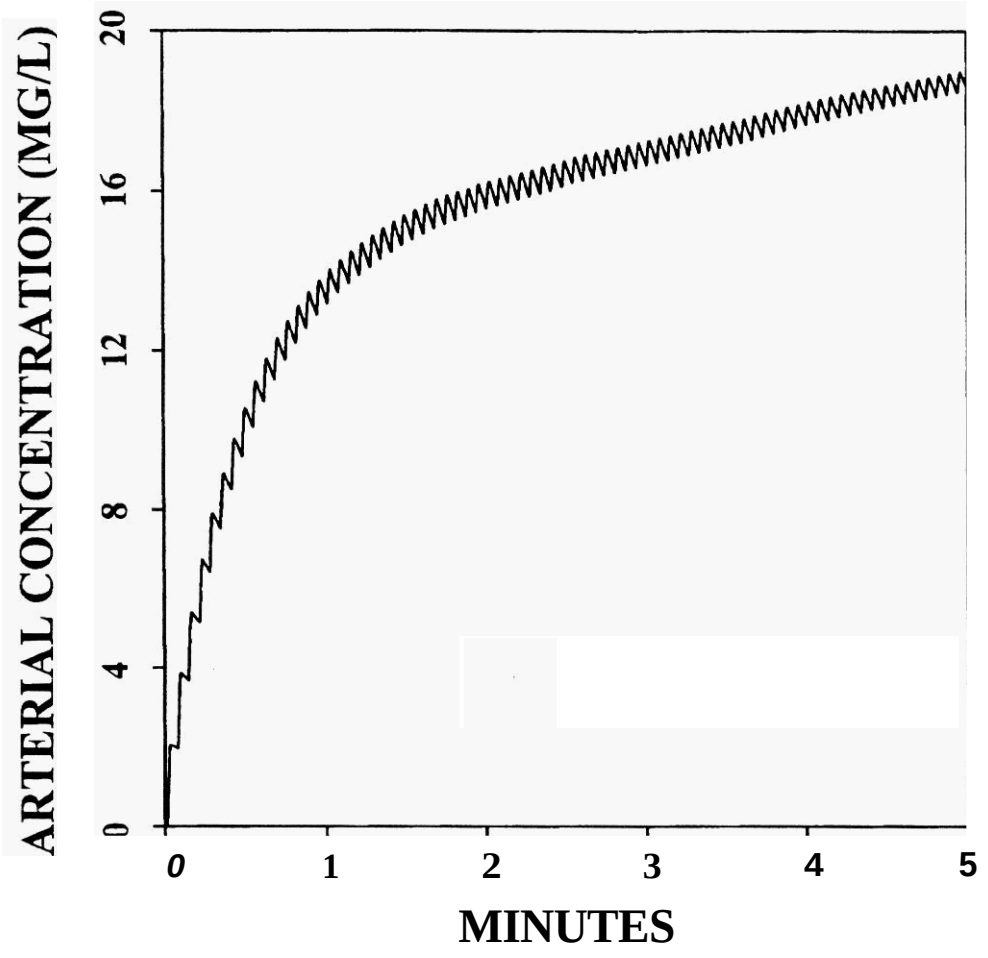
HFC-125 10.0% LOAEL
36.39
250 Simulations
ARTERIAL CONC (MG/L)
MINUTE
0
10
20
30
40
50
60
0
1
2
3
4

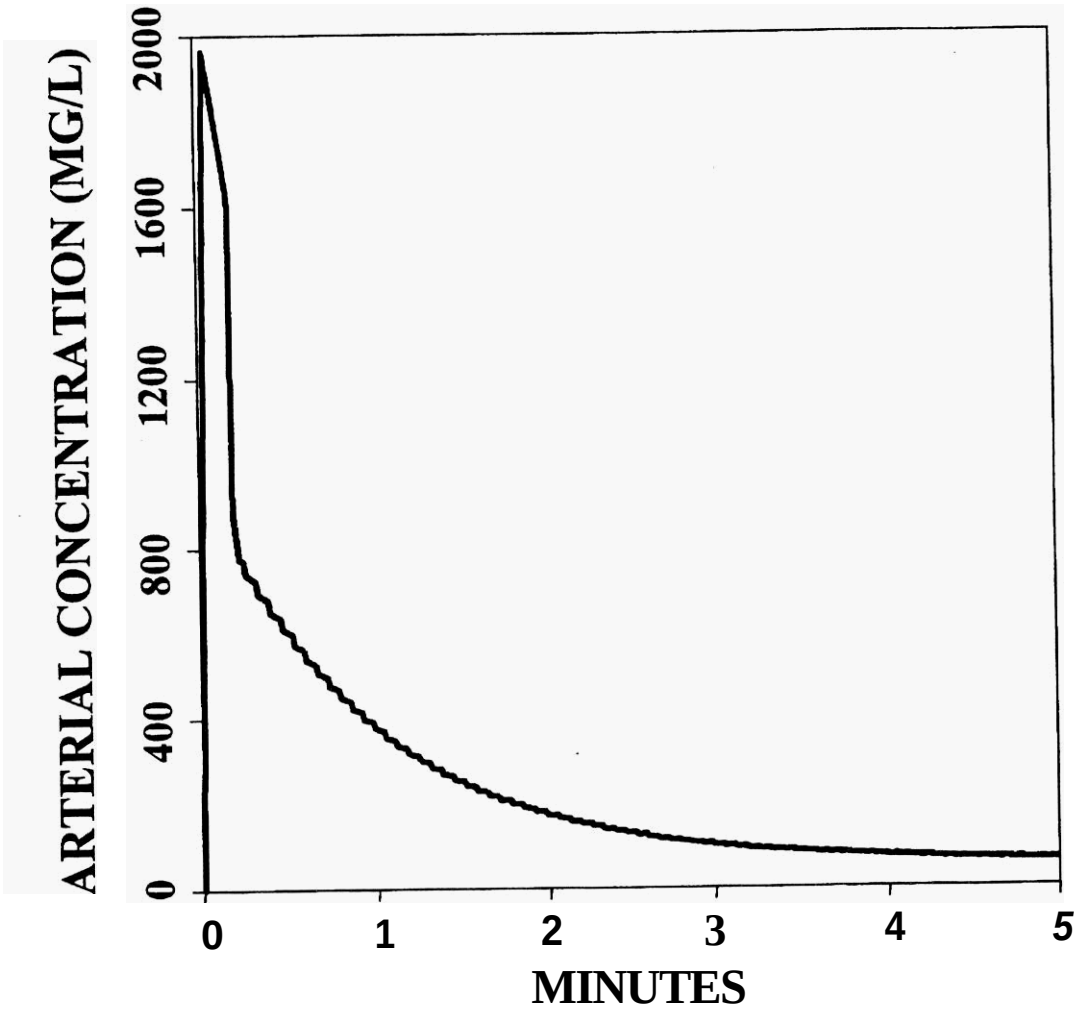

HFC-125 10.9% USE CONC
ARTERIAL CONC (MG/L)
60
50
40
30
20
10
36.39
@0.21
250 Simulations
0
1
2
3
4
MINUTE

HALON1301 7.5% LOAEL
ARTERIAL CONC (MG/L)
40
30
20
10
0
MINUTES
250 Simulations
Z3.20


HALON1301 5.0% USE CONC
ARTERIAL CONC (MG/L)
40
30
20
10
22.09
250 Simulations
MINUTE

CF3I - CONSTANT EXPOSURE (LOAEL)




ARTERIAL CONCENTRATION (MG/L)
0
400
800
1200
1600
2000
0
1
2
3
4
5
MINUTES

CF_3I LOAEL in F344 rat with epinephrine challenge

Male F344 rat (200-35Og) anesthetized with 2% Halothane.

Rat weight (kg)	Epinephrine threshold level (ug/kg)	CF_3I Exposure Concentration (ppm)	+ or – response?
0.298	6.3	4,672 11,862 31,714	- - +
0.340	5.5	5,393 10,836 7,897	- + +

Therefore, at this time the CF_3I LOAEL is between 5393 – 7897 ppm. Present work will determine a more specific LOAEL.

CF_3I **LOAEL** in F344 rat without epinephrine challenge

Male **F344** rat (200-350g) anesthetized with 2% Halothane.
Rat was exposed to **42%** CF_3I, 1% Halothane, 12% O_2, **45%** N_2

Results:

- At T=O min, exposure started
- At T=0.86 min, BP showed considerable drop
- At T=1.5 min, BP less than ½ starting BP
- At T=2.0 min, respiratory depression begins
- At T=3 – 5 min, BP and respiration continue to drop
- At T=5.5 min, BP = 0
- At T=6.6 min, respiration = 0 BPM
- At T=7.5 min, **ECG** shows no response

Summary

1. Egress times for flooding agents currently set arbitrarily
2. Egress times can be set basecl on knowlecige of safe exposure times
3. Safe exposure times can be set basecl on knowlecige of the pharmacokinetics of the agents
4. Physiologically basecl pharmacokinetic mocleling is a tool for helping determine safe exposure times