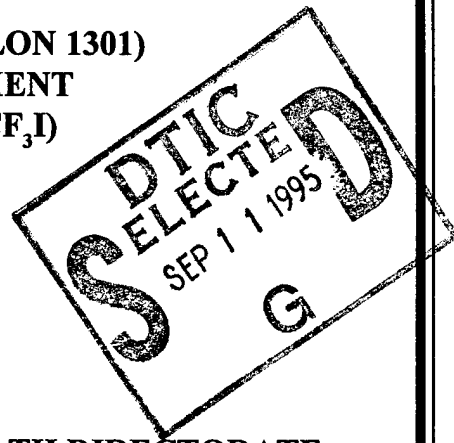


AL/OE-TR-1994-0068



**GAS UPTAKE KINETICS OF  
BROMOTRIFLUOROMETHANE (HALON 1301)  
AND ITS PROPOSED REPLACEMENT  
IODOTRIFLUOROMETHANE (CF<sub>3</sub>I)**

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**January 1994**

**FINAL REPORT FOR THE PERIOD JUNE THROUGH DECEMBER 1993**

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### TECHNICAL REVIEW AND APPROVAL


AL/OE-TR-1994-0068

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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### FOR THE COMMANDER

  
**TERRY A. CHILDRESS**, Lt Col, USAF, BSC  
Director, Toxicology Division  
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**REPORT DOCUMENTATION PAGE**

Form Approved  
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Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

<b>1. AGENCY USE ONLY (Leave Blank)</b>		<b>2. REPORT DATE</b> January 1994	<b>3. REPORT TYPE AND DATES COVERED</b> Final - June-December 1993	
<b>4. TITLE AND SUBTITLE</b> Gas Uptake Kinetics of Bromotrifluoromethane (Halon 1301) and Its Proposed Replacement Iodotrifluoromethane (CF <sub>3</sub> I)			<b>5. FUNDING NUMBERS</b> Contract F33615-90-C-0532 PE 62202F PR 6302 TA 630200 WU 63020002	
<b>6. AUTHOR(S)</b> R.J. Williams, A. Vinegar, J.Z. Byczkowski, J.R. Creech, R.K. Black, S.K. Neurath, and G.W. Jepson				
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> ManTech Environmental Technology, Inc. Toxic Hazards Research Unit P.O. Box 31009 Dayton, OH 45437-0009			<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>  4300-9306	
<b>9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> Armstrong Laboratory, Occupational and Environmental Health Directorate Toxicology Division, Human Systems Center Air Force Materiel Command Wright-Patterson AFB OH 45433-7400			<b>10. SPONSORING; MONITORING AGENCY REPORT NUMBER</b>  AL/OE-TR-1994-0068	
<b>11. SUPPLEMENTARY NOTES</b>				
<b>12a. DISTRIBUTION/AVAILABILITY STATEMENT</b> Approved for public release; distribution is unlimited.			<b>12b. DISTRIBUTION CODE</b>	
<b>13. ABSTRACT (Maximum 200 words)</b>  A physiologically based simulation approach was used to estimate <i>in vivo</i> metabolic constants in male Fischer 344 rats for the two chemicals, bromotrifluoromethane (Halon 1301), and its proposed replacement candidate, iodotrifluoromethane (CF <sub>3</sub> I). A closed recirculating exposure system was used to collect a series of gas uptake curves for both chemicals at equivalent initial exposure concentrations. Additionally, tissue:air partition coefficients were determined experimentally for each chemical and incorporated into a physiologically based pharmacokinetic model, which was then used to simulate the uptake of the chemicals. By iteratively adjusting the constants describing metabolism of the chemical, and optimized fit of the series of uptake curves was obtained for each chemical. This simulation approach adequately described the overall uptake of each chemical from the chamber. Given the relatively low level of partitioning of these chemicals into tissues and their relative inertness, this approach could not be used with certainty to discriminate between metabolism by saturable and/or first-order process and no metabolism at all.				
<b>14. SUBJECT TERMS</b> Gas Uptake Kinetics      CF <sub>3</sub> I Bromotrifluoromethane      Physiologically Based Pharmacokinetic Model Halon 1301      Iodotrifluoromethane			<b>15. NUMBER OF PAGES</b>  36	
			<b>16. PRICE CODE</b>	
<b>17. SECURITY CLASSIFICATION OF REPORT</b> UNCLASSIFIED	<b>18. SECURITY CLASSIFICATION OF THIS PAGE</b> UNCLASSIFIED	<b>19. SECURITY CLASSIFICATION OF ABSTRACT</b> UNCLASSIFIED	<b>20. LIMITATION OF ABSTRACT</b>  UL	

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## PREFACE

The research reported herein was conducted by the Toxic Hazards Research Unit, ManTech Environmental Technology, Inc., and serves as a final report for the determination of the gas uptake kinetics of bromotrifluoromethane (Halon 1301) and its proposed replacement iodotrifluoromethane (CF<sub>3</sub>I). The research described in this report began in June 1993 and was completed in December 1993. It was performed under Department of the Air Force Contract No. F33615-90-C-0532 (Study No. F21). Lt Col James N. McDougal and Lt Col Terry A. Childress served as Contract Technical Monitor, respectively, for the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory, Wright-Patterson Air Force Base, OH.

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## ABBREVIATIONS

°C	Degrees celsius
Halon 1301	Bromotrifluoromethane
F-344	Fischer 344 (rats)
FID	Flame ionization detector
g	Gram
GC	Gas chromatograph(y)
h	Hour
L	Liter
m	Meter
min	Minute
mL	Milliliter
BW	Body weight
GI	Gastrointestinal
mm	Millimeter
PBPK	Physiologically based pharmacokinetic
ppm	Parts per million
CF <sub>3</sub> I	Iodotrifluoromethane

## SECTION 1

### INTRODUCTION

The aim of this study was to measure tissue:air partition coefficients and to describe the kinetics of bromotrifluoromethane (Halon 1301) and its proposed replacement chemical, iodotrifluoromethane (CF<sub>3</sub>I), via recirculating gas uptake exposure methods.

Inhalation pharmacokinetics for both chemicals were determined experimentally in Fischer 344 (F-344) male rats. A physiologically based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of both chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments.

Given the relatively low level of partitioning of these chemicals into tissues and their relative inertness, this approach could not be used with certainty to discriminate between metabolism by saturable and/or a first-order process and no metabolism at all.

## SECTION 2

### MATERIALS AND METHODS

#### TEST CHEMICALS

Bromotrifluoromethane (Halon 1301):

Trade name	FC-13B1
CAS #	75-63-8
Mol. Weight	148.91
Empirical formula	CF <sub>3</sub> Br
Boiling point (°C)	-57.8

Iodotrifluoromethane (CF<sub>3</sub>I):

Trade name	Trifluoromethyl iodide
CAS #	2314-97-8
Mol. Weight	195.9
Empirical formula	CF <sub>3</sub> I
Boiling point (°C)	-22.5

The 1301 and CF<sub>3</sub>I from PCR Inc. (Gainesville, FL) were used in this study.

#### ANIMALS

Male F-344 (200 to 350 g) rats (*Rattus norvegicus*) were obtained from Charles River Breeding Laboratories (Kingston, NY). Animals received Purina Formulab #5008 and softened water *ad libitum*. They were housed in plastic cages (2 to 3/cage) with hardwood chip bedding prior to exposure and were maintained on a 12-h light/12-h dark light cycle at constant temperature (22 ± 1 °C) and humidity (40 to 60%). Cages were changed twice per week. Animals were marked for identification with a tail tattoo.

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

## DETERMINATION OF PARTITION COEFFICIENTS

Partition coefficients were determined by using a modified version of the vial-equilibration technique described by Gargas et al. (1989). Whole tissue was harvested and minced into a tissue slurry versus prepared as a tissue homogenate in saline. Rats used to determine partition coefficients were euthanatized with CO<sub>2</sub>. Blood was collected from the posterior *vena cava* using a heparinized syringe. Liver (L), muscle (M, quadriceps), fat (F, epididymal and perirenal), and gastrointestinal tract (G, stomach and small intestine) also were removed for analysis. Blood samples (1.0 mL) were placed in 12.4 mL glass vials and incubated/mixed for 3 h at 37 °C with 800 ppm of chemical in the vial headspace. Incubation time was determined by initially exposing samples for 1, 3, 5, or 7 h and observing that no change was seen after 3 h. Chemical concentration was determined by initially using 100, 400, or 800 ppm and observing no difference between 400 and 800 ppm. Whole tissue samples (1.0 g of L and M; 0.50 g of F and G) were minced and incubated/mixed under the same conditions as for blood, except fat was equilibrated for 5 to 8 h.

The chemical concentrations in the headspace were analyzed using a HP19395A headspace sampler (Hewlett-Packard, Avondale, PA) connected to a HP5890 gas chromatograph (GC) (Hewlett-Packard, Palo Alto, CA) equipped with a hydrogen flame ionization detector (FID). Column selection and GC conditions varied for each chemical. For Halon 1301, a 25 m x 0.53 mm Chromopack PoraplotQ (Plot Fused Silica) column was used. Gas chromatography conditions were set with the detector temperature at 250 °C, injection temperature 125 °C, helium carrier gas at 13.0 mL/min column flow plus 13.0 mL/min make-up flow, and oven temperature held constant at 70 °C. For CF<sub>3</sub>I, a 12" x 1/8" stainless steel 10% SE-30, WHP 80/100 Chromosorb column was used. Gas chromatography conditions were set with the detector temperature at 250 °C, injection temperature 125 °C, nitrogen carrier gas flow at 30.0 mL/min, and oven temperature held constant at 60 °C.

## GAS UPTAKE AND METABOLIC CONSTANTS

A closed chamber recirculating gas uptake system with a volume of 8.0 L was used for the estimation of whole animal metabolic constants ( $V_{max}$ ,  $K_m$ , and  $K_i$ ). Three F-344 rats were exposed to each study chemical using a closed recirculating gas uptake system similar to that described by Gargas et al. (1986). Four to five exposure concentrations were performed for 6 h each (Halon 1301 concentrations were 122, 1202, 2993, and 5557 ppm; and CF<sub>3</sub>I concentrations were 112, 648, 1228, 2715, and 5867 ppm). Ascarite (150 g) was used as the CO<sub>2</sub> absorber. Oxygen concentrations were maintained at (21% ± 1) during the exposures. The system flow was maintained at 2.1 L/min with the flow to the sample loop of the GC at 100 mL/min.

The chemical concentrations in the chamber atmosphere were monitored every 5 min for the first 30 min and every 15 min thereafter, using a gas sampling valve connected to a HP5890 GC.

Chromatography was performed on a 25 m x 0.53 mm Chromopack Poraplot Q (Plot Fused Silica) column. The GC was equipped with a hydrogen FID with temperature set at 250 °C, helium carrier flow at 12.1 mL/min with make-up flow of 14.2 mL/min, injection temperature of 125 °C for Halon 1301 and 150 °C for CF<sub>3</sub>I, and oven temperature held constant at 80 °C for 1301 and 125 °C for CF<sub>3</sub>I.

## MODEL DEVELOPMENT

SIMUSOLV (DOW Chemical Co., Midland, MI), a Fortran-based continuous simulation language with optimization capabilities, was used on a VAX/VMS 8530 mainframe computer (Digital Equipment Corp., Maynard, MA). The general form of the PBPK model (Figure 1) followed that of Ramsey and Andersen (1984). The codes that made up the PBPK models are given in the Appendices. Parameters were optimized by SIMUSOLV which is using the log likelihood function as the criterion and either the generalized reduced gradient method for single parameter optimization or the Nelder-Mead search method for multiple parameters optimization to adjust the values.

Physiological constants for calculating volumes of the compartments are shown in Table 1. Tissue volume constants are scaled to the actual body weight (BW) of the rats under study (fat volume was derived from Anderson et al. [1993]); other constants were according to Linstedt (Physiological Parameters Working Group, ILSI Risk Science Institute, unpublished data). Blood flows are expressed as a percentage of cardiac output which was scaled to BW to the exponent 0.75. Alveolar ventilation is also scaled to BW to the exponent 0.75. Cardiac output and alveolar ventilation, based on those described by Gargas et al. (1986) for resting animals, are summarized in Table 1.

Blood:air and tissue:air partition coefficients were obtained as described above. Metabolic constants were determined using the model to obtain a simultaneous fit to the closed chamber gas uptake data. The constants are scaled to BW using the allometric relationship described by Andersen et al. (1987).

**TABLE 1. KINETIC CONSTANTS AND PHYSIOLOGICAL PARAMETERS USED IN PBPK MODELING IN RATS**

<b>Description</b>	<b>[Units] Parameter</b>
Tissue Volumes	[Fraction of Body Weight:BW]
Liver	$V_L C = 0.037$
Fat	$V_F C = 0.01 * (35 * BW + 2.1)$
GI Tract	$V_G C = 0.033$
Slowly Perfused	$V_S C = 0.558$
Rapidly Perfused	$V_R C = 0.031$
Flow Rates	[L/h/kg]
Alveolar Ventilation	$Q_P C = 14.0$
Cardiac Output	$Q_C C = 14.0$
	[Fraction of Cardiac Output]
Liver	$Q_L C = 0.032$
Fat	$Q_F C = 0.058$
GI Tract	$Q_G C = 0.183$
Slowly Perfused	$Q_S C = 0.255$
Rapidly Perfused	$Q_R C = 0.472$

### **PBPK MODEL CONSTRUCTION**

Figure 1 shows the scheme of the PBPK model, essentially as described by Ramsey and Andersen (1984). An additional compartment was added to describe the gastrointestinal (GI) tract.

Mass transfer differential equations describing each compartment of the PBPK model for both chemicals (schematically shown in Figure 1) are presented below.

For simple, well-stirred compartments in which neither metabolism or other losses occurred (rapidly and slowly perfused tissues, fat, and gut), the change in the amount of chemical ( $A_i$ ) over time ( $t$ ) was described as follows:

$$dA_i/dt = Q_i(CA - CV_i)$$

where subscript  $i$  represents "i-th" compartment;  $Q_i$  represents the blood flow through the "i-th" compartment;  $CA$  represents the arterial concentration;  $CV_i$  represents the venous concentration leaving the "i-th" compartment ( $CV_i = C_i/P_i$ ; where  $C_i$  is a concentration in the tissue in "i-th" compartment and  $P_i$  is the tissue/blood partition coefficient for "i-th" compartment.  $C_i = A_i/V_i$ , where  $V_i$  represents the volume of the "i-th" compartment).

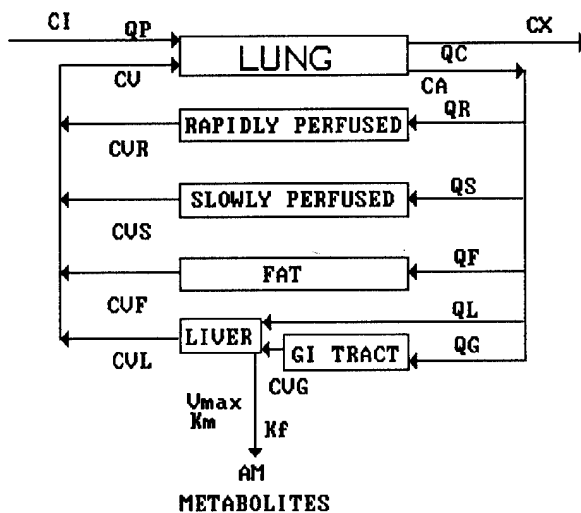


Figure 1. A scheme of PBPK model used for computer simulations of Halon 1301 and CF<sub>3</sub>I disposition and metabolism in rats.

For the liver compartment, a loss term (RAM) was added to the well-stirred compartment description to account for rate of metabolism ( $RAM = V_{max}CV_L/(K_m + CV_L) + K_fCV_LV_L$ ; where  $V_{max}$  is apparent-maximal velocity rate of the metabolism,  $CV_L$  is venous concentration leaving the liver,  $K_m$  is apparent Michaelis-Menten constant,  $K_f$  is the first order rate of metabolism, and  $V_L$  is the volume of liver):

$$dA_L/dt = Q_L(CA - CV_L) + Q_G(CV_G - CV_L) - RAM$$

where  $Q_G$  is the blood flow through the portal circulation (from the GI tract) and  $CV_G$  is a concentration of the chemical that reaches liver via portal circulation (from the GI tract). Units for the above variables are as follows: amounts - mg, concentrations - mg/L, flows - L/h, and rates - mg/h. The actual codes used for computer simulation of Halon 1301 are included in APPENDIX A, and codes used for computer simulation of CF<sub>3</sub>I are included in APPENDIX B.

**SECTION 3**  
**RESULTS**

**PARTITION COEFFICIENTS**

The rat tissue:air partition coefficients determined for Halon 1301 and CF<sub>3</sub>I, which were used in the PBPK model optimization, are shown in Table 2.

**TABLE 2. PARTITION COEFFICIENTS FOR HALON 1301 AND CF<sub>3</sub>I IN RATS**

Partition Coefficients		Ratio ± S.D.	
		Halon 1301 (n=32)	CF3I (n=10)
Blood:air	PB	0.72 ± 0.48	1.75 ± 0.35
Liver:air	PLA	0.85 ± 0.58	1.22 ± 0.22
Fat:air	PFA	3.95 ± 2.91	11.24 ± 1.75
Gut:air	PGA	0.69 ± 0.51	1.57 ± 0.66
Rapidly perfused/air	PRA	0.85 ± 0.58	1.22 ± 0.22
Slowly perfused/air	PSA	0.59 ± 0.40	1.27 ± 0.30

**GAS UPTAKE STUDIES**

The inhalational uptake of both Halon 1301 and CF<sub>3</sub>I by the rat showed two discernable phases: a rapid equilibration phase that lasted up to 60 min followed by a slow linear uptake phase (Figures 2 through 5). Uptake of Halon 1301 (Figure 2) was simulated without the necessity of attributing any metabolic capacity by the rats. Simulation of the uptake of CF<sub>3</sub>I (Figures 3 through 5) required some attribution of metabolic capacity by the rats. Attribution of both saturable ( $V_{maxc}=0.375$ ,  $K_m=0.1$ ) and first order ( $K_{fc}=1.6$ ) metabolism and a chamber loss of 2.7% is shown compared to no metabolism with the same chamber loss rate (Figure 3). The upper curve with each set of data represents the no metabolism condition. Attribution of saturable ( $V_{maxc}=0.375$ ,  $K_m=0.1$ ) metabolism alone and a chamber loss of 4.0% is shown compared to no metabolism with a chamber loss of 2.7% (Figure 4). Again the upper curve with each set of data represents the no metabolism condition. The two sets of simulations with attributed metabolism shown in Figures 3 and 4 are shown compared in Figure 5 indicating virtual overlap, indicating a lack of discrimination between first order metabolism and chamber loss. The constants and rates used for each of the preceding simulations are summarized in Table 3.

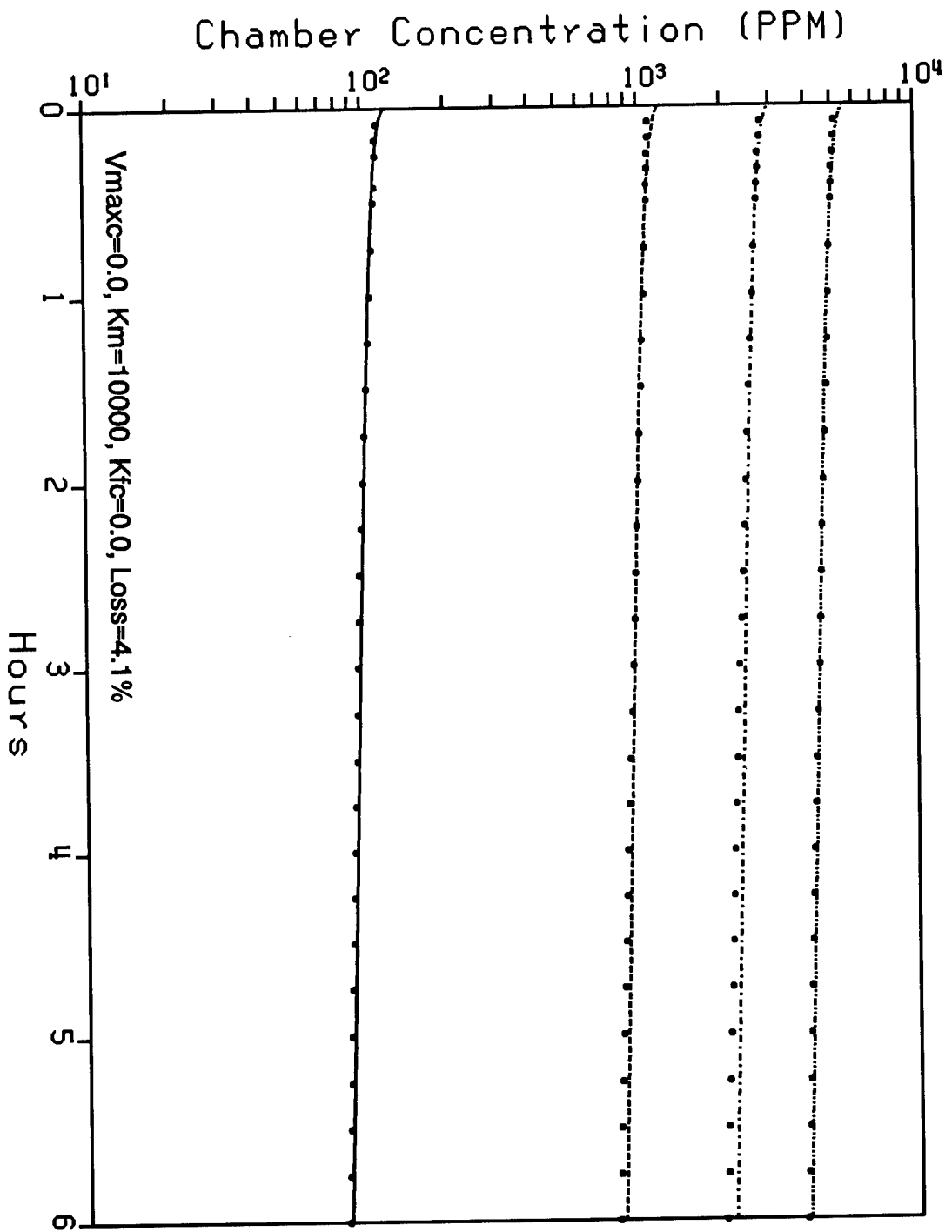


Figure 2. Halon 1301 Gas Uptake.

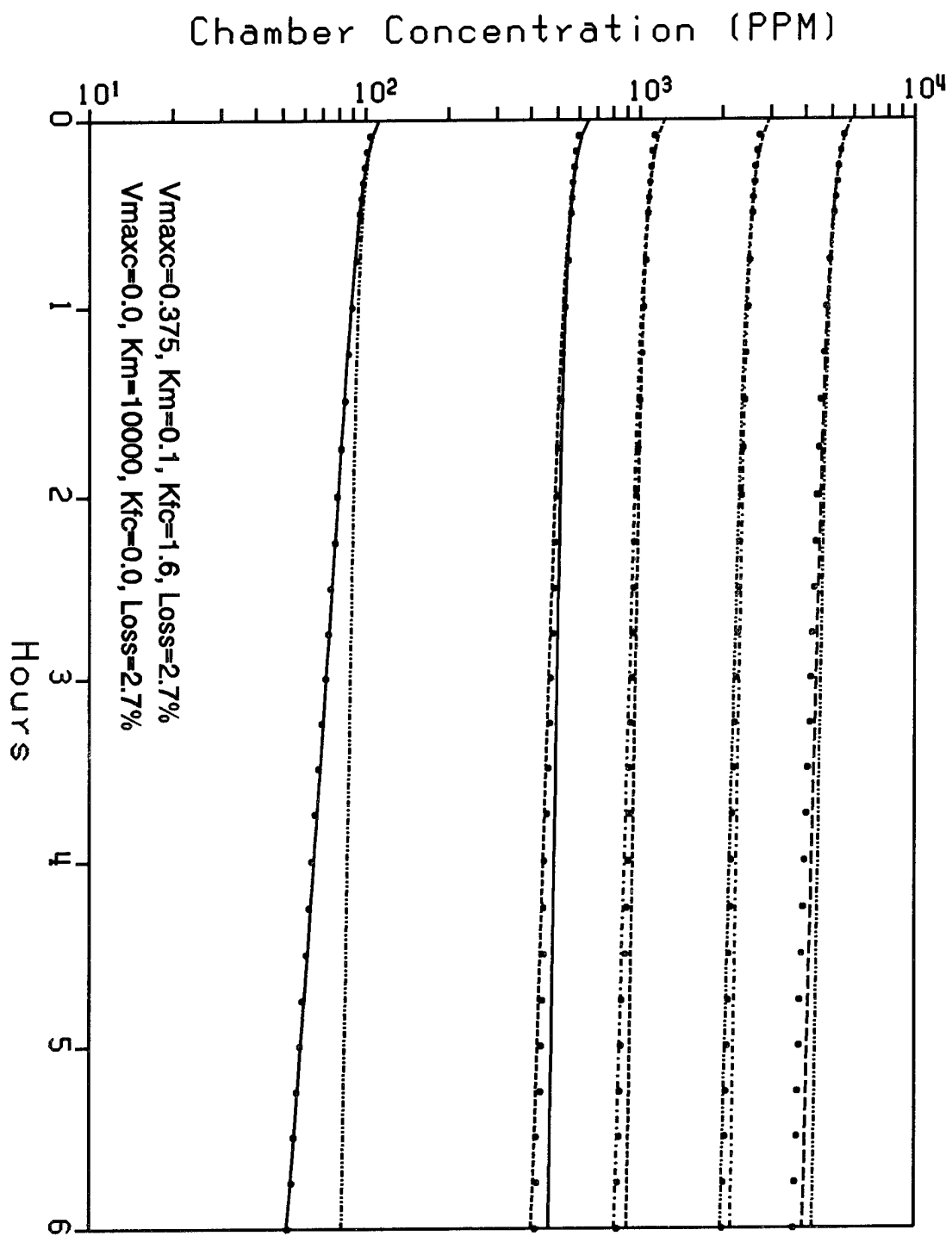


Figure 3. CF<sub>3</sub>I Gas Uptake – Comparison of Metabolism and No Metabolism with Same Loss Rate.

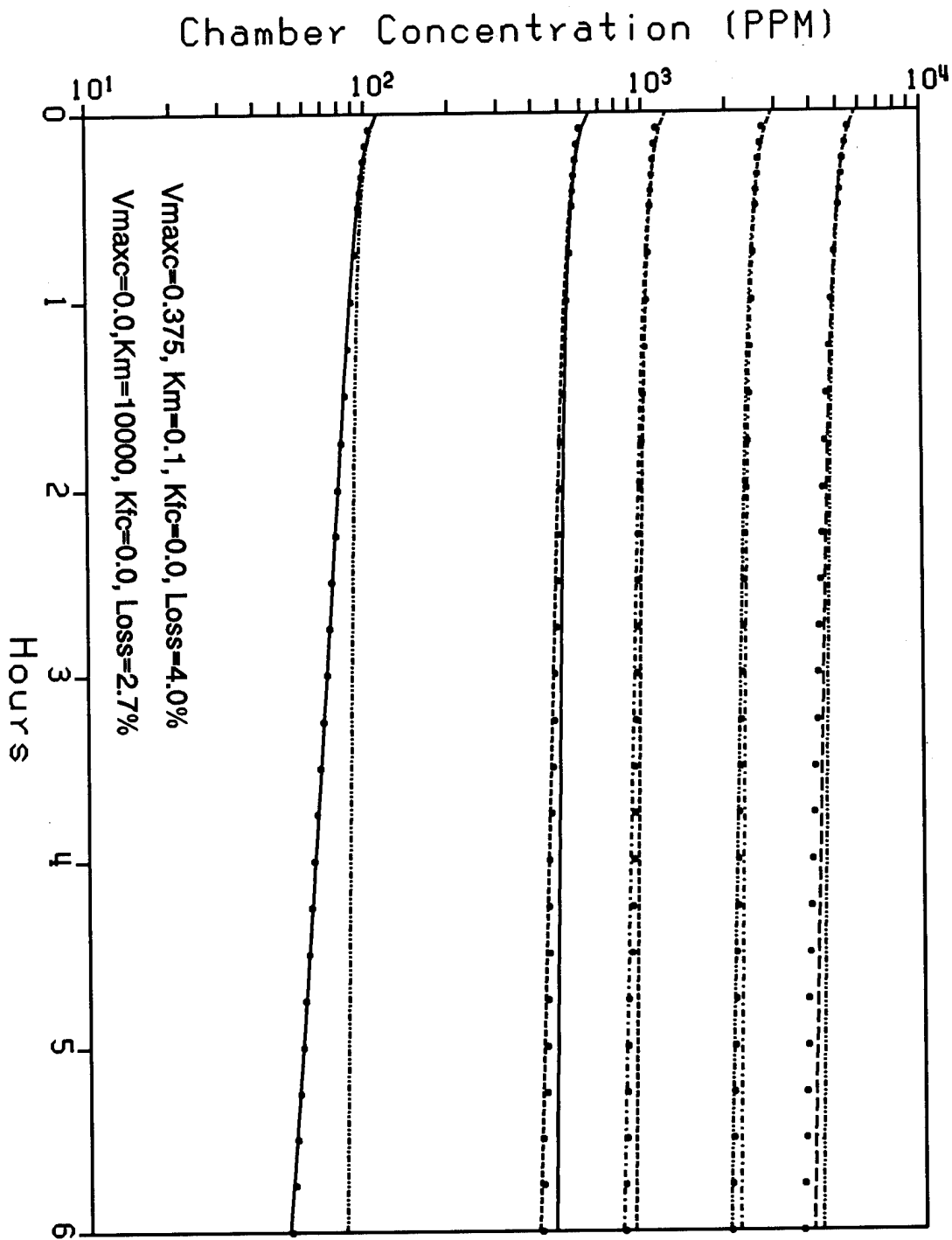


Figure 4.  $CF_3I$  Gas Uptake – Comparison of Metabolism and No Metabolism with Different Loss Rate.

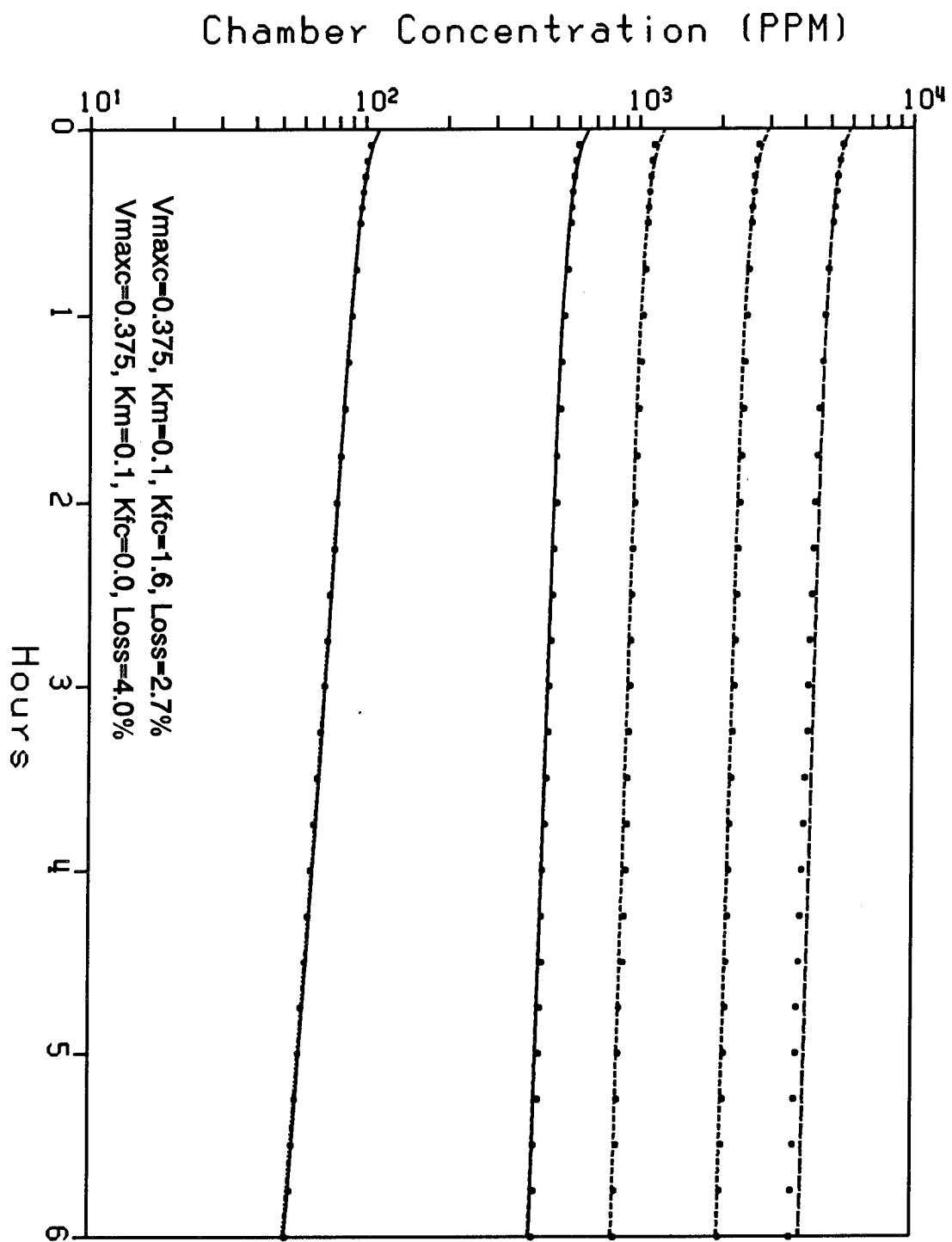


Figure 5.  $CF_3I$  Gas Uptake – Comparison of Saturable and First-Order Metabolism with Saturable Metabolism Alone, Each Having Different Loss Rates

**TABLE 3. SUMMARY OF METABOLIC CONSTANTS AND CHAMBER LOSS RATES USED IN SIMULATING UPTAKE OF HALON 1301 AND CF<sub>3</sub>I BY RATS**

Figure	Chemical	Vmaxc mg/h/kg	Km mg/L	Kfc 1/h/kg	Chamber Loss
2	Halon 1301	0.0	10000	0.0	4.1%
3	CF <sub>3</sub> I	0.375	0.1	1.6	2.7%
	CF <sub>3</sub> I	0.0	10000	0.0	2.7%
4	CF <sub>3</sub> I	0.375	0.1	0.0	4.0%
	CF <sub>3</sub> I	0.0	10000	0.0	2.7%
5	CF <sub>3</sub> I	0.375	0.1	1.6	2.7%
	CF <sub>3</sub> I	0.375	0.1	0.0	4.0%

## SECTION 4

### DISCUSSION

This simulation approach for analysis of gas uptake data has been shown to distinguish between single and multiple metabolic pathways of several previously studied dihalomethanes and numerous other volatile organic compounds. Halon 1301 gas uptake data were simulated successfully by assuming that no metabolism of the chemical was occurring and that after initial uptake by the animal further losses were those occurring in the uptake system itself. Simulation of the  $CF_3I$  required some attribution of metabolism by the rats beyond losses to the system. Another indication that chemical was disappearing beyond that taken up by the chamber is demonstrated by the chromatograms of the chamber air. As gas uptake experiments progressed, a second peak besides that for the parent chemical appeared and increased in size. This could represent a metabolite resulting from the metabolism of the chemical by the rats or could represent a product resulting from spontaneous breakdown of  $CF_3I$  in the chamber. The product appeared only when live rats were in the chamber with the parent chemical. However, further experiments would be necessary to determine the identity and origin of the second chromatographic peak.

**SECTION 5**  
**CONCLUSIONS**

1. The PBPK model adequately describes the disappearance of both chemicals from the chamber atmosphere during gas uptake experiments.
2. Both chemicals had low solubility (partition) in blood and tissues and had minimal, if any, enzymatic metabolism in rats.
3. Further experiments are necessary to determine the identity and origin of the second peak seen during the uptake of  $CF_3I$ .

**SECTION 6**  
**REFERENCES**

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**APPENDIX A**

**CODES AND COMMAND FILE FOR COMPUTER SIMULATION OF HALON 1301 PHARMACOKINETICS**

PROGRAM: CLOSED CHAMBER MODEL 1301 GAS-UPTAKE EXPOSURES

'Based on:'

'Template Model with Code for Gut and Liver - 30 March 1993'

-----  
INTEGER J

ARRAY CONCJ(4), BWJ(4)

CONSTANT CONCJ = 121.5,1201.5,2992.5,5557.

CONSTANT BWJ = .307,.326,.310,.311

CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2 '\$Gear method for stiff systems'

'Timing commands'

CONSTANT TSTOP = 6. '\$Length of experiment (hrs)'

CONSTANT CINT = .05 '\$Communication interval'

J = INT(JJ)

CONC = CONCJ(J)

BW = BWJ(J)

CONSTANT KL = .041 '\$FIRST ORDER CHAMBER LOSS (LN AREA CTS/HR)'

CONSTANT BW = 0.31 '\$Body weight (kg)'

CONSTANT QPC = 14.00 '\$Alveolar ventilation rate (l/hr)'

CONSTANT QCC = 14.00 '\$Cardiac output (l/hr)'

CONSTANT QLC = .032 '\$Fractional blood flow to liver'

CONSTANT QGC = .183 '\$Fractional blood flow to gut'

CONSTANT QFC = .058 '\$Fractional blood flow to fat'

CONSTANT QSC = .255 '\$Fractional blood flow to slow'

CONSTANT QRC = .472 '\$Fractional blood flow to rapid'

CONSTANT VLC = .037 '\$Fraction liver tissue'

CONSTANT VGC = .033 '\$Fraction gut tissue'

CONSTANT VSC = .558 '\$Fraction slow tissue'

CONSTANT VRC = .031 '\$Fraction rapid tissue'

VFC = .01\*(35.0\*BW+2.1) '\$Fraction fat tissue'

CONSTANT PLA = 0.85 '\$Liver/air partition coefficient'

CONSTANT PGA = 0.69 '\$Gut/air partition coefficient'

CONSTANT PFA = 3.95 '\$Fat/air partition coefficient'

CONSTANT PSA = 0.59 '\$Slowly perfused tissue/air partition'

CONSTANT PRA = 0.85 '\$Rapidly perfused tissue/air partition'

CONSTANT PB = 0.715 '\$Blood/air partition coefficient'

PL=PLA/PB '\$Liver/blood partition coefficient'

PG=PGA/PB '\$Gut/blood partition coefficient'

PF=PFA/PB '\$Fat/blood partition coefficient'

PS=PSA/PB '\$Slow/blood partition coefficient'

PR=PRA/PB '\$Rapid/blood partition coefficient'

CONSTANT MW = 148.91 '\$Molecular weight (g/mol)'

CONSTANT VMAXC=0.0 '\$Maximum velocity of metabolism (mg/hr-1kg)'

CONSTANT KM =10000 '\$Michaelis-Menten constant (mg/l)'

CONSTANT KFC =0.0 '\$First order metabolism rate constant (/hr-1kg)'

CONSTANT CONC =100. '\$Inhaled concentration (ppm)'

CONSTANT RATS = 3. '\$Number of rats (for closed chamber)'

CONSTANT VCHC = 8. '\$Volume of closed chamber (l)'

CONSTANT SODA = .15 '\$Volume of soda lime (l)'

VCH = VCHC-(RATS\*BW)-SODA \$'Net chamber volume (l)'  
AI0 = CONC\*VCH\*MW/24450. \$'Initial amount in chamber (mg)'

'Scaled parameters'

QC = QCC\*BW\*\*0.75  
QP = QPC\*BW\*\*0.75  
QL = QLC\*QC  
QG = QGC\*QC  
QF = QFC\*QC  
QS = QSC\*QC  
QR = QRC\*QC  
VL = VLC\*BW  
VG = VGC\*BW  
VF = VFC\*BW  
VS = VSC\*BW  
VR = VRC\*BW  
VMAX = VMAXC\*BW\*\*0.75  
KF = KFC/BW\*\*0.25  
VK = VMAXC/KM

END \$'End of initial'

DYNAMIC

DERIVATIVE

'CI = Concentration in inhaled air (mg/l)'  
RAI = RATS\*QP\*(CA/PB-CI)-(KL\*AI)  
AI = INTEG(RAI,AI0) \$ 'CHAMBER'  
CI = AI/VCH \$ 'WITH X RATS'  
CP = CI\*24450./MW

-----  
'CA = Concentration in arterial blood (mg/l)'  
CA = (QC\*CV+QP\*CI)/(QC+(QP/PB))

'AX = Amount exhaled per rat (mg)'  
CX = CA/PB  
CXPPM = (0.7\*CX+0.3\*CI)\*24450./MW  
RAX = QP\*CX  
AX = INTEG(RAX,0.)

'AS = Amount in slowly perfused tissues per rat (mg)'  
RAS = QS\*(CA-CVS)  
AS = INTEG(RAS,0.)  
CVS = AS/(VS\*PS)  
CS = AS/VS

'AR = Amount in rapidly perfused tissues per rat (mg)'  
RAR = QR\*(CA-CVR)  
AR = INTEG(RAR,0.)  
CVR = AR/(VR\*PR)  
CR = AR/VR

'AF = Amount in fat tissue per rat (mg)'  
RAF = QF\*(CA-CVF)  
AF = INTEG(RAF,0.)  
CVF = AF/(VF\*PF)  
CF = AF/VF

'AG = Amount in gut tissue per rat (mg)'  
RAG = QG\*(CA-CVG)  
AG = INTEG(RAG,0.)  
CVG = AG/(VG\*PG)

```
CG = AG/VG

'AL = Amount in liver tissue per rat (mg)'  
RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM  
AL = INTEG(RAL,0.)  
CVL = AL/(VL*PL)  
CL = AL/VL

'AM = Amount metabolized per rat (mg)'  
RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL $(mg/hr)'  
AM = INTEG(RAM,0.) $'Amount (mg)'  
CV = Mixed venous blood concentration per rat (mg/l)'  
CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'  
RINH = QP*CI  
AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'  
TMASS = (AS+AR+AF+AM+AL+AX+AG)  
BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END      $'End of derivative'  
END      $'End of dynamic'  
END      $'End of program'
```

'UPTK1301.CMD'  
'GAS UPTAKE DATA FOR HCFC 1301'

SET TITLE = '1301 Gas Uptake'

PREPAR T, 'ALL'

SET GRDCPL=.F. \$'Turns off grid lines'

PROCED ARRAY1  
SET CONCJ=121.5, 1201.5, 2992.5, 5557.  
SET BWJ=.307,.326,.310,.311  
SET J=1,JJ=1.0  
END

PROCED CONDIT  
SET KL=.041  
SET PLA=.85, PGA=.69, PFA=3.95, PRA=.85  
SET PSA=.59, PB=.715  
SET MW=148.91  
SET RATS=3, VCHC=8., SODA=.15  
SET QPC=14., QCC=14.  
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA  
END

PROCED INHAL

DATA  
T CP JJ INITIAL  
0.0 . 1.0 INITIAL  
0.0833 114.0 .  
0.1670 113.0 .  
0.2500 113.0 .  
0.4170 112.0 .  
0.5000 111.0 .  
0.7500 109.0 .  
1.0000 107.0 .  
1.2500 105.0 .  
1.5000 103.0 .  
1.7500 101.0 .  
2.0000 99.7 .  
2.2500 97.8 .  
2.5000 96.2 .  
2.7500 95.8 .  
3.0000 94.9 .  
3.2500 94.3 .  
3.5000 93.4 .  
3.7500 92.4 .  
4.0000 91.5 .  
4.2500 90.4 .  
4.5000 89.8 .  
4.7500 88.6 .  
5.0000 87.7 .  
5.2500 87.2 .  
5.5000 86.2 .  
5.7500 85.5 .  
6.0000 85.3 .  
0.0 . 2.0 INITIAL  
0.0833 1100.0 .  
0.1670 1100.0 .  
0.2500 1090.0 .  
0.3330 1090.0 .  
0.4170 1080.0 .  
0.5000 1080.0 .

0.7500	1060.0	.	
1.0000	1050.0	.	
1.2500	1030.0	.	
1.5000	1020.0	.	
1.7500	1000.0	.	
2.0000	988.0	.	
2.2500	974.0	.	
2.5000	962.0	.	
2.7500	953.0	.	
3.0000	938.0	.	
3.2500	926.0	.	
3.5000	910.0	.	
3.7500	899.0	.	
4.0000	886.0	.	
4.2500	878.0	.	
4.5000	868.0	.	
4.7500	858.0	.	
5.0000	845.0	.	
5.2500	835.0	.	
5.5000	824.0	.	
5.7500	818.0	.	
6.0000	811.0	.	
0.0	.	3.0	INITIAL
0.0833	2800.0	.	
0.1670	2780.0	.	
0.2500	2740.0	.	
0.3330	2730.0	.	
0.4170	2710.0	.	
0.5000	2700.0	.	
0.7500	2640.0	.	
1.0000	2600.0	.	
1.2500	2540.0	.	
1.5000	2500.0	.	
1.7500	2460.0	.	
2.0000	2420.0	.	
2.2500	2390.0	.	
2.5000	2360.0	.	
2.7500	2320.0	.	
3.0000	2270.0	.	
3.2500	2240.0	.	
3.5000	2220.0	.	
3.7500	2190.0	.	
4.0000	2160.0	.	
4.2500	2140.0	.	
4.5000	2120.0	.	
4.7500	2100.0	.	
5.0000	2070.0	.	
5.2500	2040.0	.	
5.5000	2010.0	.	
5.7500	2000.0	.	
6.0000	1970.0	.	
0.0	.	4.0	INITIAL
0.0833	5160.0	.	
0.1670	5150.0	.	
0.2500	5100.0	.	
0.3330	5040.0	.	
0.4170	5030.0	.	
0.5000	5000.0	.	
0.7500	4920.0	.	
1.0000	4890.0	.	
1.2500	4840.0	.	
1.5000	4790.0	.	
1.7500	4700.0	.	
2.0000	4610.0	.	

2.2500	4550.0	.
2.5000	4500.0	.
2.7500	4470.0	.
3.0000	4420.0	.
3.2500	4360.0	.
3.5000	4290.0	.
3.7500	4250.0	.
4.0000	4190.0	.
4.2500	4150.0	.
4.5000	4120.0	.
4.7500	4080.0	.
5.0000	4030.0	.
5.2500	4000.0	.
5.5000	3960.0	.
5.7500	3910.0	.
6.0000	3860.0	.

END

START SMOOTH

END

**APPENDIX B**

**CODES AND COMMAND FILE FOR COMPUTER SIMULATION OF CF<sub>3</sub>I PHARMACOKINETICS**

PROGRAM: CLOSED CHAMBER MODEL CF3I GAS-UPTAKE EXPOSURES

'Based on:'

'Template Model with Code for Gut and Liver - 30 March 1993'

-----  
INTEGER J

ARRAY CONCJ(5), BWJ(5)

CONSTANT CONCJ = 111.5,648.4,1228.3,2955.6,5867.

CONSTANT BWJ = .220,.246,.228,.2366,.2385

CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2 \$'Gear method for stiff systems'

'Timing commands'

CONSTANT TSTOP = 6. \$'Length of experiment (hrs)'

CONSTANT CINT = .1 \$'Communication interval'

J = INT(JJ)

CONC = CONCJ(J)

BW = BWJ(J)

CONSTANT KL = .027 \$'FIRST ORDER CHAMBER LOSS (LN AREA CTS/HR)'

CONSTANT BW = 0.23 \$'Body weight (kg)'

CONSTANT QPC = 14.00 \$'Alveolar ventilation rate (l/hr)'

CONSTANT QCC = 14.00 \$'Cardiac output (l/hr)'

CONSTANT QLC = .032 \$'Fractional blood flow to liver'

CONSTANT QGC = .183 \$'Fractional blood flow to gut'

CONSTANT QFC = .058 \$'Fractional blood flow to fat'

CONSTANT QSC = .255 \$'Fractional blood flow to slow'

CONSTANT QRC = .472 \$'Fractional blood flow to rapid'

CONSTANT VLC = .037 \$'Fraction liver tissue'

CONSTANT VGC = .033 \$'Fraction gut tissue'

CONSTANT VSC = .558 \$'Fraction slow tissue'

CONSTANT VRC = .031 \$'Fraction rapid tissue'

VFC = .01\*(35.0\*BW+2.1) \$'Fraction fat tissue'

CONSTANT PLA = 1.223 \$'Liver/air partition coefficient'

CONSTANT PGA = 1.569 \$'Gut/air partition coefficient'

CONSTANT PFA = 11.237 \$'Fat/air partition coefficient'

CONSTANT PSA = 1.269 \$'Slowly perfused tissue/air partition'

CONSTANT PRA = 1.223 \$'Richly perfused tissue/air partition'

CONSTANT PB = 1.746 \$'Blood/air partition coefficient'

PL=PLA/PB \$'Liver/blood partition coefficient'

PG=PGA/PB \$'Gut/blood partition coefficient'

PF=PFA/PB \$'Fat/blood partition coefficient'

PS=PSA/PB \$'Slow/blood partition coefficient'

PR=PRA/PB \$'Rich/blood partition coefficient'

CONSTANT MW = 195.9 \$'Molecular weight (g/mol)'

CONSTANT VMAXC=0.375 \$'Maximum velocity of metabolism (mg/hr-1kg)'

CONSTANT KM = 0.1 \$'Michaelis-Menten constant (mg/l)'

CONSTANT KFC = 1.6 \$'First order metabolism rate constant (/hr-1kg)'

CONSTANT CONC=100. \$'Inhaled concentration (ppm)'

CONSTANT RATS = 3. \$'Number of rats (for closed chamber)'

CONSTANT VCHC = 8.0 \$'Volume of closed chamber (l)'

CONSTANT SODA = .15 \$'Volume of soda lime (l)'

VCH = VCHC-(RATS\*BW)-SODA \$'Net chamber volume (l)'  
AI0 = CONC\*VCH\*MW/24450. \$'Initial amount in chamber (mg)'

'Scaled parameters'

QC = QCC\*BW\*\*0.75  
QP = QPC\*BW\*\*0.75  
QL = QLC\*QC  
QG = QGC\*QC  
QF = QFC\*QC  
QS = QSC\*QC  
QR = QRC\*QC  
VL = VLC\*BW  
VG = VGC\*BW  
VF = VFC\*BW  
VS = VSC\*BW  
VR = VRC\*BW  
VMAX = VMAXC\*BW\*\*0.75  
KF = KFC/BW\*\*0.25  
VK = VMAXC/KM

END \$'End of initial'

DYNAMIC

DERIVATIVE

'CI = Concentration in inhaled air (mg/l)'  
RAI = RATS\*QP\*(CA/PB-CI)-(KL\*AI)  
AI = INTEG(RAI,AI0) \$ 'CHAMBER'  
CI = AI/VCH \$ 'WITH X RATS'  
CP = CI\*24450./MW

'CA = Concentration in arterial blood (mg/l)'  
CA = (QC\*CV+QP\*CI)/(QC+(QP/PB))

'AX = Amount exhaled per rat (mg)'  
CX = CA/PB  
CXPPM = (0.7\*CX+0.3\*CI)\*24450./MW  
RAX = QP\*CX  
AX = INTEG(RAX,0.)

'AS = Amount in slowly perfused tissues per rat (mg)'  
RAS = QS\*(CA-CVS)  
AS = INTEG(RAS,0.)  
CVS = AS/(VS\*PS)  
CS = AS/VS

'AR = Amount in rapidly perfused tissues per rat (mg)'  
RAR = QR\*(CA-CVR)  
AR = INTEG(RAR,0.)  
CVR = AR/(VR\*PR)  
CR = AR/VR

'AF = Amount in fat tissue per rat (mg)'  
RAF = QF\*(CA-CVF)  
AF = INTEG(RAF,0.)  
CVF = AF/(VF\*PF)  
CF = AF/VF

'AG = Amount in gut tissue per rat (mg)'  
RAG = QG\*(CA-CVG)  
AG = INTEG(RAG,0.)  
CVG = AG/(VG\*PG)

```
CG = AG/VG

'AL = Amount in liver tissue per rat (mg)'
RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
AL = INTEG(RAL,0.)
CVL = AL/(VL*PL)
CL = AL/VL

'AM = Amount metabolized per rat (mg)'
RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  '$(mg/hr)''
AM = INTEG(RAM,0.)  '$Amount (mg)''

'CV = Mixed venous blood concentration per rat (mg/l)''
CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
RINH = QP*CI
AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
TMASS = (AS+AR+AF+AM+AL+AX+AG)
BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END  '$End of derivative'
END  '$End of dynamic'
END  '$End of program'
```

'UPTKCF3I.CMD'  
 'GAS UPTAKE DATA FOR HCFC CF3I'

SET TITLE = 'CF3I Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F. \$'Turns off grid lines'

PROCED ARRAY1  
 SET CONCJ=111.5,648.4,1228.,2955.6,5867.  
 SET BWJ=.220,.246,.228,.2366,.2385  
 SET J=1,JJ=1.0  
 END

PROCED CONDIT  
 SET KL=.027  
 SET PLA=1.223, PGA=1.569, PFA=11.237, PRA=1.223  
 SET PSA=1.269, PB=1.746  
 SET MW=195.9,  
 SET RATS=3, VCHC=8., SODA=.15  
 SET QPC=14.0, QCC=14.0  
 DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA  
 END

PROCED INHAL

DATA			
T	CP	JJ	INITIAL
0.0	.	1.0	INITIAL
0.083300	103.618925	.	.
0.167000	100.893179	.	.
0.250000	99.339248	.	.
0.333333	97.735022	.	.
0.417000	96.420210	.	.
0.500000	95.169902	.	.
0.750000	92.512083	.	.
1.000000	89.163992	.	.
1.250000	86.778430	.	.
1.500000	84.245130	.	.
1.750000	81.395859	.	.
2.000000	78.986955	.	.
2.250000	77.540392	.	.
2.500000	74.754263	.	.
2.750000	73.373815	.	.
3.000000	71.748126	.	.
3.250000	69.407132	.	.
3.500000	67.569290	.	.
3.750000	65.621446	.	.
4.000000	63.995923	.	.
4.250000	62.496197	.	.
4.500000	60.925760	.	.
4.750000	59.091267	.	.
5.000000	57.984620	.	.
5.250000	56.400129	.	.
5.500000	54.938278	.	.
5.750000	54.012453	.	.
6.000000	52.333737	.	.
0.0	.	2.0	INITIAL
0.083300	597.686344	.	.
0.167000	583.667563	.	.
0.250000	574.824343	.	.
0.333333	567.096343	.	.
0.417000	564.020850	.	.

0.500000	560.095592	.	
0.750000	546.211894	.	
1.000000	532.538674	.	
1.250000	521.227834	.	
1.500000	514.943337	.	
1.750000	499.971122	.	
2.000000	502.256536	.	
2.250000	490.901717	.	
2.500000	484.813560	.	
2.750000	480.395092	.	
3.000000	473.144594	.	
3.250000	469.871189	.	
3.500000	463.996652	.	
3.750000	458.393852	.	
4.000000	448.158964	.	
4.250000	445.923813	.	
4.500000	447.383023	.	
4.750000	440.391696	.	
5.000000	437.407305	.	
5.250000	434.631822	.	
5.500000	418.682612	.	
5.750000	422.311002	.	
6.000000	415.170456	.	
0.0	.	3.0	INITIAL
0.083300	1128.735825	.	
0.167000	1108.785948	.	
0.250000	1096.012783	.	
0.333333	1086.036758	.	
0.417000	1075.252672	.	
0.500000	1069.827755	.	
0.750000	1050.701084	.	
1.000000	1031.213056	.	
1.250000	1018.777892	.	
1.500000	998.491190	.	
1.750000	983.193834	.	
2.000000	967.493893	.	
2.250000	952.985468	.	
2.500000	946.712079	.	
2.750000	941.000634	.	
3.000000	934.461078	.	
3.250000	925.916938	.	
3.500000	915.480190	.	
3.750000	913.949144	.	
4.000000	906.032083	.	
4.250000	896.361047	.	
4.500000	885.759946	.	
4.750000	859.197012	.	
5.000000	853.643134	.	
5.250000	846.718838	.	
5.500000	842.380954	.	
5.750000	831.830346	.	
6.000000	825.111320	.	
0.0	.	4.0	INITIAL
0.083300	2714.920102	.	
0.167000	2674.022448	.	
0.250000	2626.639409	.	
0.333333	2611.217313	.	
0.417000	2578.882104	.	
0.500000	2562.493075	.	
0.750000	2503.364635	.	
1.000000	2470.860938	.	
1.250000	2430.675022	.	
1.500000	2407.075891	.	
1.750000	2371.307122	.	

2.000000	2337.673807	.
2.250000	2304.666532	.
2.500000	2284.377282	.
2.750000	2266.535068	.
3.000000	2245.370951	.
3.250000	2214.153879	.
3.500000	2195.832079	.
3.750000	2171.075919	.
4.000000	2149.864808	.
4.250000	2134.025118	.
4.500000	2111.121762	.
4.750000	2100.349590	.
5.000000	2074.380379	.
5.250000	2058.847468	.
5.500000	2040.898265	.
5.750000	2015.584043	.
6.000000	1997.317869	.
0.0	.	5.0 INITIAL
0.083300	5508.230988	.
0.167000	5378.203854	.
0.250000	5261.385353	.
0.333333	5215.735645	.
0.417000	5143.595303	.
0.500000	5086.184354	.
0.750000	4891.626035	.
1.000000	4768.083955	.
1.250000	4669.155694	.
1.500000	4552.126697	.
1.750000	4480.472278	.
2.000000	4406.280024	.
2.250000	4352.254110	.
2.500000	4297.984213	.
2.750000	4230.026588	.
3.000000	4183.106058	.
3.250000	4158.387759	.
3.500000	4081.340804	.
3.750000	4032.043993	.
4.000000	3970.043260	.
4.250000	3929.224949	.
4.500000	3885.317569	.
4.750000	3818.980663	.
5.000000	3801.775991	.
5.250000	3750.540150	.
5.500000	3723.417954	.
5.750000	3669.359219	.
6.000000	3635.394650	.

END  
START SMOOTH  
END