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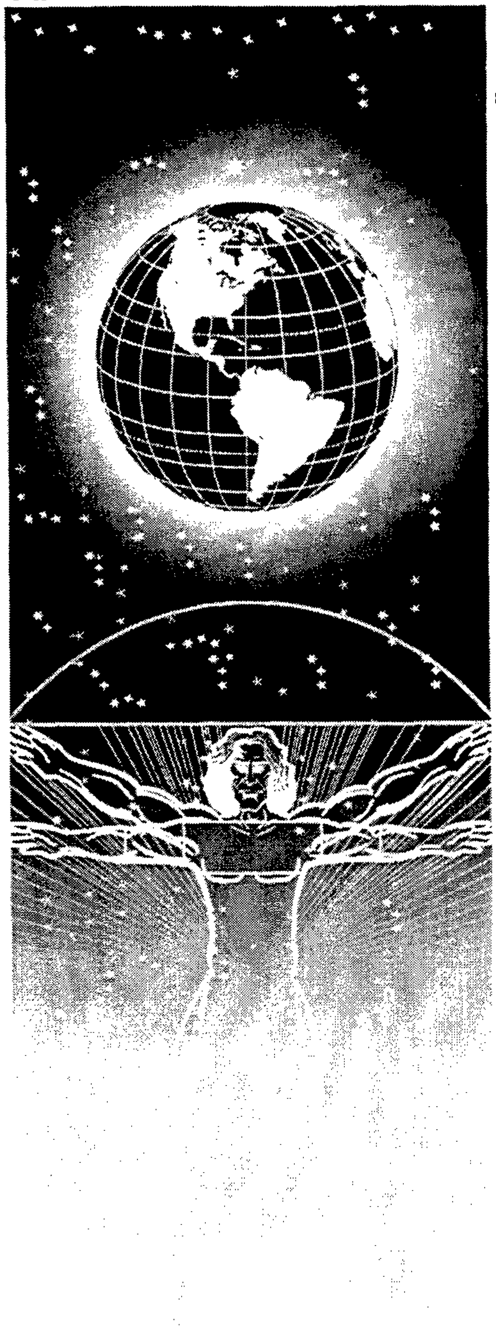

UNITED STATES AIR FORCE
RESEARCH LABORATORY

DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR THE ANESTHETICS HALOTHANE, ISOFLURANE, AND DESFLURANE IN THE PIG (SUS SCROFA)

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August 1999
Interim Report - September 1998 - November 1998

Human Effectiveness Directorate
Deployment and Sustainment Division
Operational Toxicology Branch
2856 G Street
Wright-Patterson AFB OH 45433-7400

NOTICES

DISCLAIMER

TECHNICAL REVIEW AND APPROVAL

AFRL-HE-WP-TR-1999-0236

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.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR

STEPHEN R. CHANNEL, Lt Col, USAF, BSC
Branch Chief, Operational Toxicology Branch
Air Force Research Laboratory

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13. ABSTRACT *(Maximum 200 words)*
The pig has been commonly used in biomedical research studies because of similarities between humans and pigs in various aspects of structure and function. Under consideration is its use for studying the effects of long-term low-level exposure to organophosphates. In spite of the wide use of the pig as an experimental subject there has been no prior attempt to develop a physiologically based pharmacokinetic (PBPK) model to allow linking of external exposure to internal concentrations at sites of effects resulting from xenobiotic exposures. A model was developed with the potential of tracking chemical concentrations in brain, kidney, liver, fat, arterial and venous blood, muscle/skin, and other generally well perfused body organs. As an initial attempt at validating the model, the literature was explored for studies that contained data that were in a form suitable for modeling. Such a study was one in which pigs had been exposed to the anesthetics halothane, isoflurane and desflurane and exhaled concentrations of these chemicals were monitored. These data were used in the initial model validation. The model did an adequate job of simulating the data. Further development and reining of the model will depend on planning actual studies with defined endpoints of interest.

14. SUBJECT TERMS

Pig	Physiologically based pharmacokinetic	PBPK model
Halothane	Isoflurane	Desflurane

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PREFACE

This is one of a series of technical reports describing results of the experimental laboratory programs conducted at the Toxicology Division under the ManTech Geo-Centers Joint Venture contract. This document serves as an interim report on the description of an initial physiologically based pharmacokinetic of the pig. Funding for the work was provided in part by Dr. Harry Salem, SBCCOM/ECBC, Aberdeen Proving Grounds, Maryland. The research described in this report began in September 1998 and was completed in November 1998 under Department of the Air Force Contract No. F41624-96-C-9010. Maj Steve Channel served as the Contracting Officer's Representative for the U.S. Air Force, Air Force Research Laboratory. Darol E. Dodd, Ph.D., served as Program Manager for ManTech Geo-Centers Joint Venture.

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ABBREVIATIONS

ACSL	Advanced Continuous Simulation Language
kg	kilogram
PBPK	physiologically based pharmacokinetic
SD	standard deviation

SECTION I

INTRODUCTION

The pig has been a common animal for use in biomedical research studies (Tumbleson, 1986). Humans and pigs have similarities in structure and function, which include size, digestive physiology, kidney structure and function, lung vascular bed anatomy, coronary artery distribution, respiratory rates and tidal volumes. It has been used to evaluate chronic and acute exposures to various xenobiotics such as alcohol, caffeine and environmental pollutants. In spite of the apparent usefulness of the pig as a human surrogate for various studies there is currently no physiologically based pharmacokinetic (PBPK) model to link xenobiotic exposure with resulting concentrations at target tissue sites of potential effects resulting from the exposures. This report presents an initial PBPK model for the pig and demonstrates the simulation of exposures to several anesthetic agents.

SECTION II

MATERIALS AND METHODS

A PBPK model was developed with the general form of Ramsey and Andersen (1994) but with the addition of brain, kidney, and separate arterial and venous blood compartments. The model was perfusion limited and metabolism was assumed to occur in the liver. Mass balance differential equations were written for each compartment and were solved using ACSL simulation software (Pharsight Corp., Mountain View, CA) operating under WindowsNT (Microsoft Corp., Redmond, WA).

Data on the volumes of physiological compartments and the blood flows to them were taken from several publications (Armstrong et al., 1987; Denac et al., 1977; Doornenbal et al., 1986; Friedman et al., 1994; Lundeen et al., 1983; Mehta et al., 1997; Tranquilli et al., 1982; Tumbleson et al., 1970; Verbrugghe et al., 1982). The major sources for each parameter are indicated in Table 1.

Tissue partition coefficients (Table 2) and pharmacokinetic data used for model development and validation come from Yasuda et al. (1990), where details of collection were described. Briefly, five young healthy female swine (3-4 months old; 20 ± 2 [mean ± SD] kg) were exposed to a mixture of 3.0% desflurane, 0.5% sevoflurane, 0.4% isoflurane, and 0.2% halothane, balance 40% O_2/60% N_2. Exposure occurred for 30 min using a controlled-ventilation nonrebreathing system. End-tidal samples were taken periodically during the 30-min exposure and for up to 3400 min post-exposure. Samples were analyzed for anesthetic concentrations using gas chromatography.

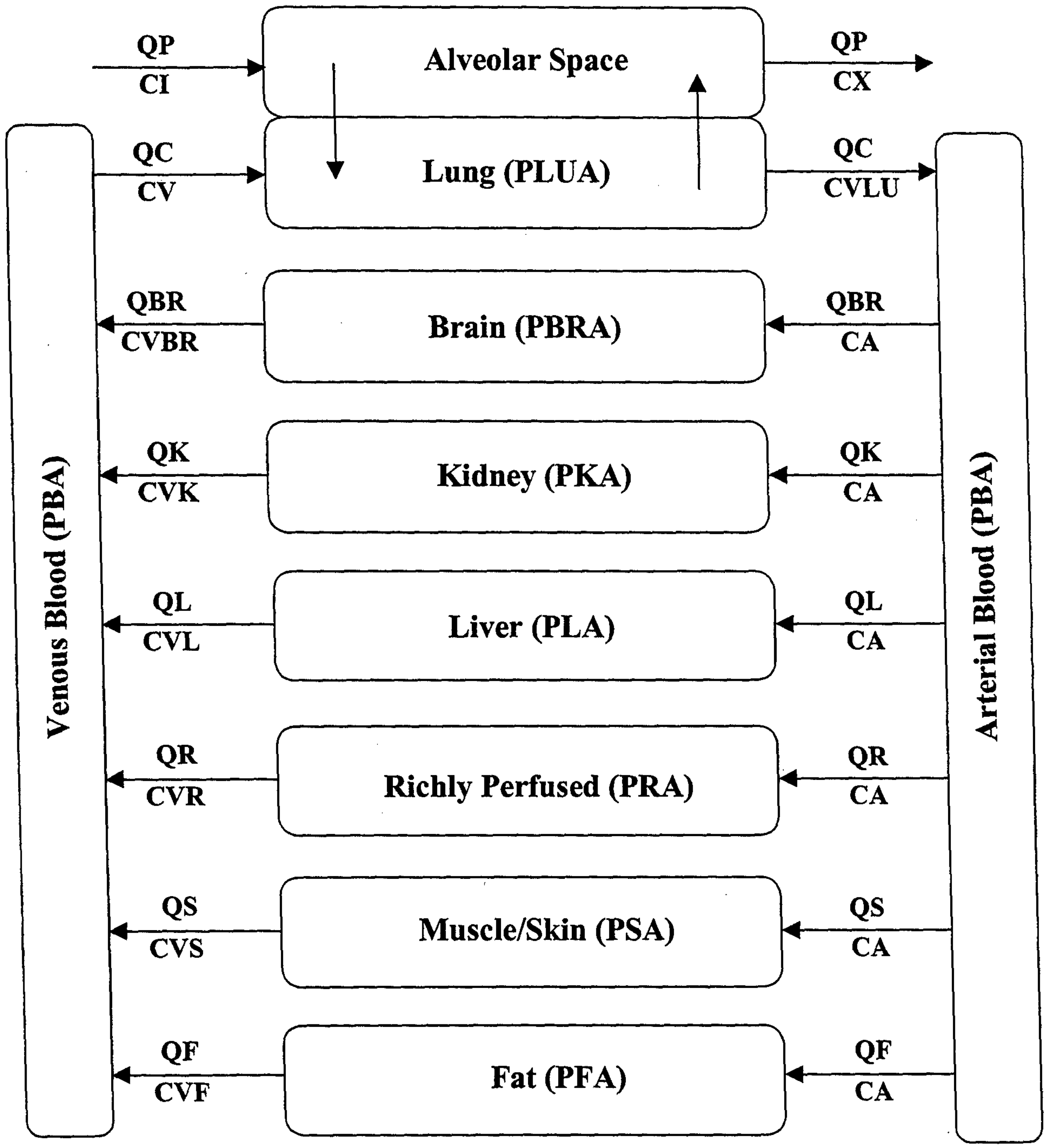

Figure 1 – Physiologicallly Based Pharmacokinetic Model of the Pig (*Sus scrofa*). Abbreviations: CA, arterial concentration; CX, exhaled concentration; CI, inhaled concentration; CV, venous concentration; CVBR, venous brain concentration; CVK, venous kidney concentration; CVL, venous liver concentration; CVR, venous richly perfused concentration; CVS, venous muscle/skin concentration; CVF, venous fat concentration; QP, alveolar ventilation; QC, cardiac output; QBR, brain blood flow; QK, kidney blood flow; QL, liver blood flow; QR, Richly perfused blood flow; QS, Muscle/skin blood flow; QF, fat blood flow; PxA, tissue/air partition coefficient.

TABLE 1. PHYSIOLOGICAL AND ANATOMIC PARAMETERS AND VALUES

Parameter	Value
Body weight (kg)	20.0
Volumes	
Muscle/Skin (% of body weight)	0.48[7]
Fat (% of body weight)	0.23[2]
Richly perfused (% of body weight)	0.084[1]
Liver (% of body weight)	0.025[3,4,7]
Kidney (% of body weight)	0.003[3,4]
Brain (% of body weight)	0.004[7]
Lung (% of body weight)	0.004[7]
Arterial blood (% of body weight)	0.033[1]
Venous blood (% of body weight)	0.066[1]
Flows	
Alveolar ventilation rate (liter/hr/kg)	20.0[5,8]
Cardiac output (liter/hr/kg)	20.0[9]
Muscle/Skin (% of cardiac output)	0.25[1]
Fat (% of cardiac output)	0.05[10]
Richly perfused (% of cardiac output)	0.34[1]
Liver (% of cardiac output)	0.23[4,6]
Kidney (% of cardiac output)	0.12[4,6]
Brain (% of cardiac output)	0.01[4,6]

[1]Armstrong et al. (1987)
[2]Doornebal et al. (1986)
[3]Friedman et al. (1994)
[4]Lundeen et al. (1983)
[5]Mehta et al. (1997)
[6]Tranquilli et al. (1982)
[7]Tumbelson et al. (1970)
[8]Verbrugghe et al. (1982)
[9]Set equal to ventilation
[10]100 – other flows

Table 2. CHEMICAL-SPECIFIC MODEL PARAMETERS AND VALUES[1]

Parameter	Chemical		
	Halothane	Isoflurane	Desflurane
Molecular weight (g/mol)	197.39	184.5	168.0
V_{maxc}, max. metabolic rate (mg/h/kg)	7.4	0 .074	0.0074
Km, affinity constant (mg/L)	0.1	0.1	0.1
Blood:air partition coefficient	2.54	0.94	0.35
Lung:air partition coefficient	4.57	2.26	0.56
Brain:air partition coefficient	4.32	1.88	0.49
Kidney:air partition coefficient	3.30	1.50	0.39
Liver:air partition coefficient	4.57	2.26	0.56
Richly perfused:air partition coefficient	4.57	2.26	0.56
Slowly perfused:air partition coefficient	4.57	2.26	0.42
Fat:air partition coefficient	129.54	53.58	9.8

[1] Metabolic constants are taken from Vinegar and Jepson (1998) and partition coefficients come from Yasuda et al. (1990)

SECTION III

RESULTS

Simulations and data of exhaled breath of pigs exposed to halothane, isoflurane and desflurane are shown in Figure 2. The left-hand column depicts the half-hour of exposure and the first half-hour post-exposure. Results extending to 50 hours (48 hours post-exposure are shown in the right-hand column. Exhaled breath is expressed as an inhalation ratio which during exposure is the ratio of exhaled alveolar concentration to inhaled concentration, post exposure data are expressed as the ratio of exhaled alveolar concentration to the alveolar concentration immediately prior to reverting to air only breathing. At the half-hour point the exhalation ratio becomes one as represented by the blip seen in the simulation at that time.

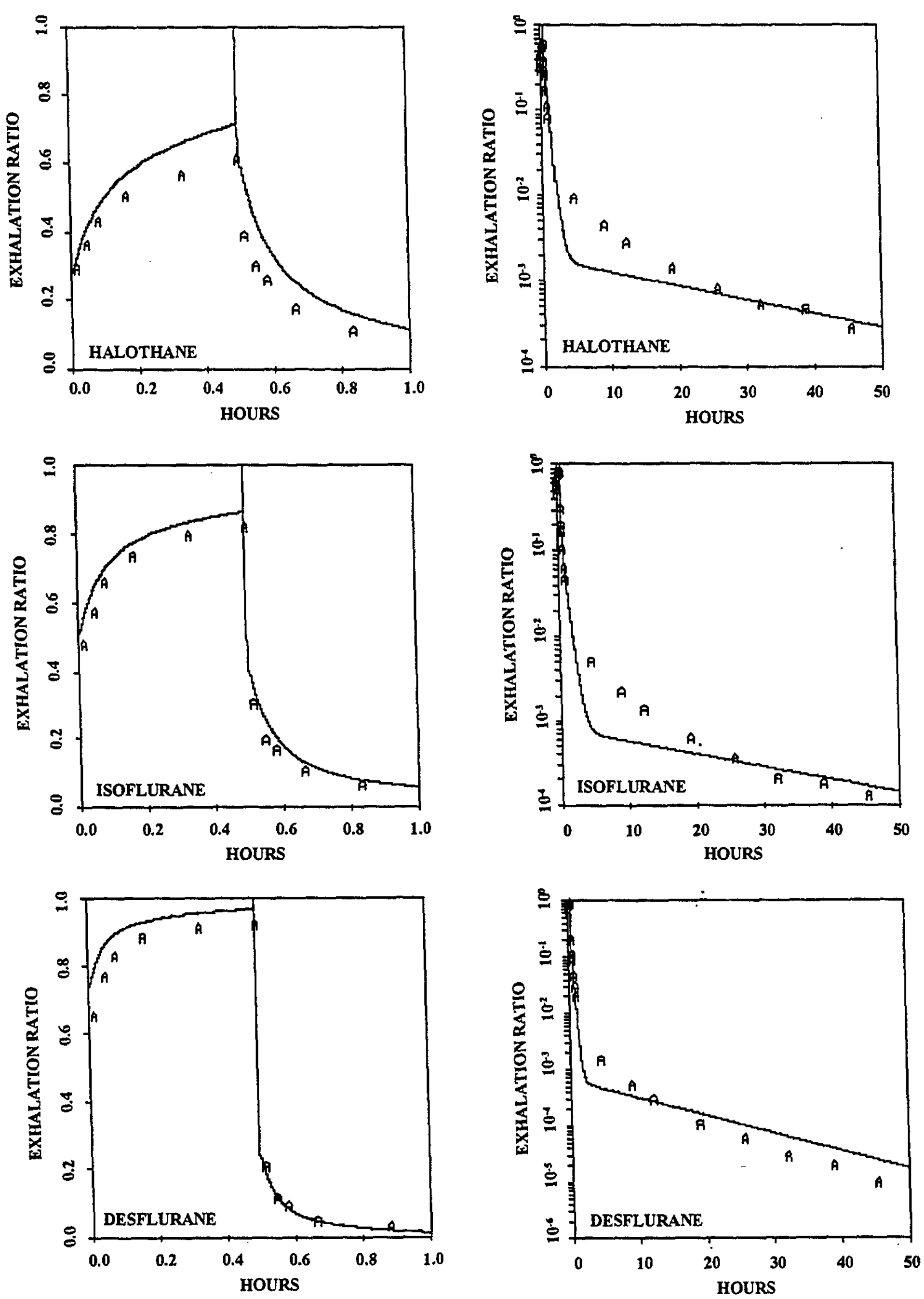

Figure 2 – Exhaled Breath Data From Pigs Exposed To Halothane, Isoflurane, And Desflurane. Continuous lines represent simulations while individual points represent actual data.

SECTION IV

DISCUSSION

The structure of the model included several compartments that are not normally included in an initial PBPK model: brain, kidney, separate arterial and venous blood compartments. Attempting to find representative values for the volumes of the compartments and blood flows to them presented a challenge because of the diversity of the data available in the literature. No one paper provided all the information. Therefore it was necessary to go to multiple sources and piece together representative values. Multiple factors contributed to apparent inconsistencies between data sets: strain of pig, size, age, anesthetized vs. awake, methodology for determining weights and blood flows. Given that the values assigned to the physiological and anatomic constants represent a first approximation the data are reasonably well represented by the simulations. Clearly, improvements could be made if specific information were available on the actual pigs from which the pharmacokinetic data were collected. As the studies are being designed for which the pigs will ultimately be used it will be useful to determine the appropriate weights and blood flows on those particular animals. This will make the model more useful for conducting meaningful simulations of long term effects.

SECTION V

LITERATURE CITED

Armstrong, R.B., M.D. Delp, E.F. Goljan, and M.H. Laughlin. 1987. Distribution of blood flow in muscles of miniature swine during exercise. J. Appl. Physiol. 62(3):1285-1298.

Denac, M., H. Spörri, and R. Beglinger. 1977. Das Göttlinger Miniaturschwein als Versuchstier 4. Mitteilung: Atmungsparameter. Res. Exp. Med. 170:283-288.

Doornenbal, H., A.K.W. Tong and A.P. Sather. 1986. Relationships among serum characteristics and performance and carcass traits in growing pigs. J. Anim. Sci. 62:1675-1681.

Friedman, L., D.W. Gaines, R.F. Newell, A.O. Sager, R.N. Matthews, and R.C. Braunberg. 1994. Body and organ growth of the developing Hormel-Hanford strain of male miniature swine. Laboratory Animals, 28:376-379.

Lundeen, G., M. Manohar, and C. Parks. 1983. Systemic distribution of blood flow in swine shile awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. Anesth. Analg. 62:499-512.

Mehta, S., S. Magder, and R.D. Levy. 1997. The effects of changes in ventilation and cardiac output on expired nitric oxide. Chest, 111(4):1045-1049.

Ramsey, J.C. and M.E. Andersen. 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73:159-175.

Tranquilli, W.J., C.M. Parks, J.C. Thurmon, G.J. Benson, G.D. Koritz, M. Manohar, and M.C. Theodorakis. 1982. Organ blood flow and distribution of cardiac output in nonanesthetized swine. Am. J. Vet. Res. 43(5):895-897.

Tumbleson, M.E. 1986. Swine in Biomedical Research. Vol. 1-3. Plenum Press, New York and London.

Tumbleson, M.E., O.W. Tinsley, J.B. Mulder, and R.E. Flatt. 1970. Undernutrition in young Sinclair (S-1) miniature swine: body and organ weights. Growth, 34:401-418.

Verbrugghe, C., P. Laurent, and P. Bouverot. 1982. Chemoreflex drive of ventilation in the awake miniature pig. Resp. Physiol. 47:379-391.

Vinegar, A., G.W. Jepson, and J.H. Overton. 1998. PBPK modeling of short-term (0 to 5 min) human inhalation exposures to halogenated hydrocarbons. Inhal. Toxicol. 10:411-429.

Yasuda, N., A.G. Targ, E.I. Eger II, B.H. Johnson, and R.B. Weiskopf. 1990. Pharmacokinetics of desflurane, sevoflurane, isoflurane, and halothane in pigs. Anesth. Analg. 71:340-348.

APPENDIX A – MODEL CODE

```
PROGRAM: PHYSIOLOGICAL PHARMACOKINETIC MODEL -- WITH DATA
'PIG.CSL with separate blood, brain and kidney compartments'
'------------------------------------------------------------'
INITIAL

'**Miscellaneous**'
ALGORITHM IALG=2 $ 'Gear integration algorithm for stiff systems'

'**Timing commands**'

CONSTANT TSTOP=24.  $ 'Length of experiment (hr)'
CONSTANT TCHNG=6.   $ 'Length of inhalation exposure (hr)'
CONSTANT TINF=.01   $ 'Length of IV infusion (hr)'
CONSTANT POINTS=10000. $ 'Number of simulated data points in plot'
CINT=TSTOP/POINTS   $ 'Communication interval (hr)'

'**Physiological Parameters**'

CONSTANT KS=100000. $ 'Suppression rate constant (mg/L)'
CONSTANT BW=20.0    $ 'Body weight (kg) {or L where 1 L/kg}'
CONSTANT QPC=20.    $ 'Alveolar ventilation (L/hr/kg BW)'
CONSTANT QCC=20.    $ 'Cardiac output (L/hr/kg BW)'
CONSTANT QLC=0.23   $ 'Proportion cardiac output to liver'
CONSTANT QFC=0.05   $ 'Proportion cardiac output to fat'
CONSTANT QRC=0.34   $ 'Proportion cardiac output to rapid'
CONSTANT QSC=0.25   $ 'Proportion cardiac output to slow'
CONSTANT QBRC=0.01  $ 'Proportion cardiac output to brain'
CONSTANT QKC=0.12   $ 'Proportion cardiac output to kidney'
CONSTANT VLUC=.004  $ 'Lung volume (L/L BW)'
CONSTANT VLC=0.025  $ 'Liver volume (L/L BW)'
CONSTANT VRC=0.084  $ 'Rapid volume (L/L BW)'
CONSTANT VSC=0.48   $ 'Slow volume (L/L BW)'
CONSTANT VFC=0.23   $ 'Body fat volume (L/L BW)'
CONSTANT VBRC=0.004 $ 'Brain volume (L/L BW)'
CONSTANT VKC=0.003  $ 'Kidney volume (L/L BW)'
CONSTANT VVBC=0.066 $ 'Volume of venous blood (L/L BW)'
CONSTANT VABC=0.033 $ 'Volume of arterial blood (L/L BW)'

'**Toxicant**'

CONSTANT CONC=1000. $ 'Inhaled concentration (ppm)'
CONSTANT MW=152.93  $ 'Molecular weight  (g/mol)'
CONSTANT VMAXC=8.83 $ 'Michaelis-Menten Vmax (mg/hr/kg BW)'
```

```
CONSTANT KM=0.70    $ 'Michaelis-Menten Km (mg/L)'
CONSTANT KFC=0    $ 'First order metabol. rate constant (/hr-1kg)'

CONSTANT PLA=3.29    $ 'Liver/air partition coefficient'
CONSTANT PFA=70.27    $ 'Fat/air partition coefficient'
CONSTANT PSA=2.13    $ 'Slowly perfused tissues/air part. coefficient'
CONSTANT PLUA=2.13    $ 'Lung/air partition coefficient'
CONSTANT PRA=3.29    $ 'Richly perfused tissues/air part. coefficient'
CONSTANT PKA=3.3    $ 'Kidney/air part. coefficient'
CONSTANT PBRA=4.32    $ 'Brain/air partition coefficient'
CONSTANT PB=3.17    $ 'Blood/air partition coefficient'

PL=PLA/PB    $ 'Liver/blood partition coefficient'
PF=PFA/PB  $ 'Fat/blood partition coefficient'
PS=PSA/PB  $ 'Slowly perfused tissues/blood part. coefficient'
PLU=PLUA/PB $ 'Lung/blood partition coefficient'
PR=PRA/PB  $ 'Richly perfused tissues/blood part. coefficient'
PBR=PBRA/PB $ 'Brain/blood partition coefficient'
PK=PKA/PB  $ 'Kidney/blood partition coefficient'

'**Exposure definition**'

CONSTANT PDOSE=0.  $ 'Oral dose (mg/kg)'
CONSTANT KA=5.0    $ 'First-order oral uptake rate (1/hr)'
CONSTANT IVDOSE=0.  $ 'IV dose (mg/kg)'
IF (PDOSE.EQ.0.) KA=0.  $ 'If no oral dose set absorption rate to 0'


'**Scaled and other derived parameters**'

QP=QPC*BW**0.75        $ 'Alveolar ventilation rate (L/hr)'
QC=QCC*BW**0.75        $ 'Cardiac output (L/hr)'
QL=QLC*QC              $ 'Blood flow to liver (L/hr)'
QF=QFC*QC              $ 'Blood flow to fat (L/hr)'
QS=QSC*QC              $ 'Blood flow to slowly perfused tissue (L/hr)'
QR=QRC*QC              $ 'Blood flow to rapidly perfused tissue (L/hr)'
QK=QKC*QC                  $ 'Blood flow to kidney (L/hr)'
QBR=QBRC*QC                $ 'Blood flow to brain (L/hr)'
VL=VLC*BW              $ 'Volume liver (L)'
!VF=(2.59*bw**2+41*bw-248)/1000 $ 'Volume fat (L)'
VF=VFC*BW
VS=VSC*BW              $ 'Volume slowly perfused tissue (L)'
VLU=VLUC*BW                $ 'Volume lung (L)'
VR=VRC*BW              $ 'Volume rapidly perfused tissue (L)'
VK=VKC*BW            $ 'Volume kidney (L)'
VBR=VBRC*BW                $ 'Volume brain (L)'
```

```
VVB=VVBC*BW              $ 'Volume venous blood (L)'
VAB=VABC*BW              $ 'Volume arterial blood (L)'

VMAX=VMAXC*BW**0.75    $ 'Vmax for toxicant (mg/hr)'
KF=KFC/BW**0.25        $ 'First-order metabolism of toxicant (1/hr)'
CI=CONC*MW/24450.      $ 'Concentration in inhaled air (mg/L)'
DOSE=PDOSE*BW          $ 'Oral dose (mg)'
IVR=IVDOSE*BW/TINF      $ 'Rate intravenous dosing (mg/hr)'

cxmax=0
END    $ 'End of initial'
'-------------------------------------------------------------'
DYNAMIC
'-------------------------------------------------------------'
DERIVATIVE

'**Condition for termination of run**'
TERMT(T.GE.TSTOP)

Minute=t*60

'**TOXICANT EXPOSURE**'


'**Inhalation exposure**'
CIZONE=RSW((T.LT.TCHNG),1.,0.) $ 'Exposure switch, 0 or 1'
RAI=QP*CI                  $ 'Rate of inhalation (mg/hr)'
AI=INTEG(RAI,0.)           $ 'Amount inhaled (mg)'
CI=RSW((T.LT.TCHNG),CONC*MW/24450.,.0000000000000001)
      'Concentration inhaled (mg/L)'
'CI=CONC*MW/24450.*cizone'   $ 'Concentration of toxicant (mg/L)'
CONSTANT CXEND=5.39105988

if(cx.gt.cxmax) then
cxmax=cx
else
cxmax=cxmax
end if

CXON2=RSW((T.LT.TCHNG),(CX/CI),CX/CXEND)
!CXON2=RSW((T.LT.TCHNG),(CX/CI),CX/CXMAX)


'**Oral dose**'
RMR=-KA*MR         $ 'Rate of change of amount in stomach (mg/hr)'
MR=DOSE*EXP(-KA*T)  $ 'Amount of toxicant in stomach (mg)'
```

```
RAO=KA*MR         $ 'Rate absorption from stomach into blood (mg/hr)'
AO=DOSE-MR         $ 'Amount of dose absorbed (mg)'

'**Intravenous dosing**'
IV=IVR*(1.-STEP(TINF)) $ 'Dose rate (mg/hr)'


'**TOXICANT PHARMACOKINETICS**'

'**Toxicant mass balance**'
TMASS=AAB+AVB+AF+AL+AS+ALU+AR+AK+ABR+AM+AX+MR $ 'Total dose (mg)'
DOSEX=AI+AO+IVR*TINF-AX    $ 'Net amount absorbed (mg)'
Massba=ai-tmass

'**Toxicant exhaled**'
CX=CVLU/PB                    $ 'Exhaled alveolar conc. (mg/L)'
CXPPM=(0.7*CX+0.3*CI)*24450./MW $ 'Exhaled breath conc. (ppm)'
RAX=QP*CX                    $ 'Rate of exhalation (mg/hr)'
AX=INTEG(RAX,0.)              $ 'Amount exhaled (mg)'

'**Toxicant in arterial blood**'
RAAB=QC*(CVLU-CA) $ 'Rate of change (mg/hr)'
AAB=INTEG(RAAB,0.) $ 'Amount (mg)'
CA=AAB/VAB          $ 'Concentration (mg/L)'

'**Toxicant in venous blood**'
RAVB=QF*CVF+QL*CVL+QS*CVS+QR*CVR+QK*CVK+QBR*CVBR-QC*CV+IV
        'Rate of change (mg/hr)'
AVB=INTEG(RAVB,0.)                      $ 'Amount (mg)'
CV=AVB/VVB                              $ 'Concentration (mg/L)'

'**Toxicant in lung**'
RALU=QC*(CV-CVLU)+QP*(CI-CVLU/PB) $ 'Rate of change (mg/hr)'
ALU=INTEG(RALU,0.)               $ 'Amount (mg)'
CVLU=ALU/VLU/PLU                 $ 'Concentration (mg/L)'

'**Toxicant in slowly perfused tissues**'
RAS=QS*(CA-CVS)   $ 'Rate of change (mg/hr)'
AS=INTEG(RAS,0.) $ 'Amount (mg)'
CS=AS/VS        $ 'Concentration (mg/L)'
CVS=CS/PS        $ 'Concentration in venous outflow (mg/L)'

'**Toxicant in fat**'
RAF=QF*(CA-CVF)  $ 'Rate of change (mg/hr)'
AF=INTEG(RAF,0.) $ 'Amount (mg)'
CF=AF/VF        $ 'Concentration (mg/L)'
```

```
CVF=CF/PF        $ 'Concentration in venous outflow (mg/L)'

'**Toxicant in rapidly perfused tissues**'
RAR=QR*(CA-CVR)  $ 'Rate of change (mg/hr)'
AR=INTEG(RAR,0.) $ 'Amount (mg)'
CR=AR/VR         $ 'Concentration (mg/L)'
CVR=CR/PR        $ 'Concentration in venous outflow (mg/L)'

'**Toxicant in kidney**'
RAK=QK*(CA-CVK)  $ 'Rate of change (mg/hr)'
AK=INTEG(RAK,0.) $ 'Amount (mg)'
CK=AK/VK     $ 'Concentation (mg/L)'
CVK=CK/PK    $ 'Concentration in venous outflow (mg/L)'

'**Toxicant in brain**'
RABR=QBR*(CA-CVBR)  $ 'Rate of change (mg/hr)'
ABR=INTEG(RABR,0.) $ 'Amount (mg)'
CBR=ABR/VBR       $ 'Concentration (mg/L)'
CVBR=CBR/PBR      $ 'Concentration in venous outflow (mg/L)'

'**Toxicant in liver**'
RAL=QL*(CA-CVL)-RAM+RAO  $ 'Rate of change (mg/hr)'
AL=INTEG(RAL,0.)        $ 'Amount (mg)'
CL=AL/VL               $ 'Concentration (mg/L)'
CVL=AL/(VL*PL)          $ 'Concentration in venous outflow (mg/L)'
AUCL=INTEG(CL,0.)       $ 'Tissue dose (mg-hr/L)'

'**Toxicant metabolism in liver**'
RAM=(VMAX*CVL)/(KM+CVL*(1+CVL/KS))+KF*CVL*VL  $ 'Rate (mg/hr)'
AM=INTEG(RAM,0.)                $ 'Amount (mg)'


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

APPENDIX B – COMMAND FILE FOR MODEL

```
'The following results are from experiments'
'reported in Yasuda, N., A.G. Targ, E.I. Eger II,'
'B.H. Johnson, and R.B. Weiskopf.'
'Pharmacokinetics of desflurane, sevoflurane, isoflurane, and halothane'
'in humans. Anesth Analg, 71:340-348, 1990.'

PREPAR 'ALL'

SET CINT=.0001,TSTOP=.5,TCHNG=.5


PROCED ISOFLUR
SET PB=0.94,PLA=2.26,PRA=2.26,PSA=2.26,PFA=53.58,PLUA=2.26
SET PKA=1.50,PBRA=1.88
SET MW=184.5
SET VMAXC=.74,KM=.1,KFC=0.0,KS=100000.
END

PROCED HALO
SET PB=2.54,PLA=4.57,PRA=4.57,PSA=4.57,PFA=129.54,PLUA=4.57
SET PKA=3.30,PBRA=4.32
SET MW=197.39
SET VMAXC=7.4,KM=0.1,KFC=0.0,KS=18.1
END

PROCED DES
SET PB=.35,PLA=.56,PRA=.56,PSA=.42,PFA=9.8,PLUA=0.56
SET PKA=0.39,PBRA=0.49
SET MW=168.
SET VMAXC=0.0074,KM=.1,KFC=0.0,KS=100000
END


PROC PIGISO
ISOFLUR
SET TITLE='Pig, ISOFLURANE   '
SET BW=20,CONC=4000.
END

DATA PIGISO &
(T, MINUTE, CXON2)
0.0          0.0   0.0
0.017        1.0   0.482
```

```
0.05          3.0    0.575
0.083         5.0    0.664
0.167         10.0   0.741
0.333         20.0   0.800
0.5           30.0   0.823
0.517         31.0   0.308
0.550         33.0   0.198
0.583         35.0   0.169
0.667         40.0   0.106
0.833         50.0   0.064
1.0           60.0   0.047
4.662         280.0  0.00519
9.092         546    0.00224
12.333        740    0.00138
19.138        1148   0.00062
25.693        1542   0.00036
32.189        1931   0.00021
38.906        2334   0.00018
45.479        2729   0.00013
END

PROC PIGDES
DES
SET TITLE='Pig, DESFLURANE      '
SET BW=20,CONC=30000.
END

DATA PIGDES &
(T, MINUTE, CXON2)
0.0           0.0    0.0
0.017         1.0    0.656
0.05          3.0    0.772
0.083         5.0    0.830
0.167         10.0   0.889
0.333         20.0   0.915
0.5           30.0   0.927
0.517         31.0   0.211
0.550         33.0   0.114
0.583         35.0   0.091
0.667         40.0   0.048
0.883         50.0   0.03
1.0           60.0   0.021
4.644         279    0.00153
9.119         547    0.00054
12.262        736    0.0003
19.075        1145   0.00011
```

```
25.685        1541  0.00006
32.160        1930  0.00003
38.864        2332  0.00002
45.441        2726  0.00001
END

PROC PIGHAL
HALO
SET TITLE='Pig, HALOTHANE     '
SET BW=20,CONC=2000.
END

DATA PIGHAL &
(T, MINUTE, CXON2)
0.0           0.0   0.0
0.017         1.0   0.294
0.05          3.0   0.363
0.083         5.0   0.433
0.167         10.0  0.506
0.333         20.0  0.567
0.5           30.0  0.613
0.517         31.0  0.389
0.550         33.0  0.302
0.583         35.0  0.258
0.667         40.0  0.175
0.833         50.0  0.111
1.0           60.0  0.082
4.744         285   0.00935
9.118         547   0.00441
12.380        743   0.00277
19.055        1143  0.00141
25.719        1543  0.0008
32.205        1932  0.00052
38.892        2333  0.00047
45.562        2734  0.00028
END


SET NPCCPL=100000
SET WESITG=.F.,GRDCPL=.F.
```