SUPPLEMENTAL MATERIALS

Article title: Physiologically-Based Pharmacokinetics of Lysosomotropic Chloroquine in Rat and Man
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Journal title: Journal of Pharmacology and Experimental Therapeutics
Manuscript number: JPET-AR-2020-000385

Table S1. Comparation of chloroquine pharmacokinetic parameters (Adelusi & Salako, 1982a)

Tissue	T_{max} (h)		C_{max} (μg/mL)		$T_{1/2}$ (h)		β Slope (h^{-1})	
	Original article	PBPK fitting	Original article	PBPK fitting	Original article	PBPK fitting	Original article	PBPK fitting
Liver	7.70	6.00	14.8	10.7	81.7	75.7	0.0085	0.0092
Kidney	10.0	15.5	6.80	5.76	94.1	105	0.0073	0.0066
Lung	22.0	14.3	7.90	8.77	138	97.3	0.0050	0.0071
Spleen	10.0	4.73	9.90	9.12	75.1	80.6	0.0092	0.0086
Heart	16.0	4.73	2.40	2.29	100	79.9	0.0069	0.0087
Muscle	16.0	6.34	0.60	0.424	97.0	71.1	0.0072	0.0098
Skin	24.7	4.06	0.45	0.407	110	67.9	0.0063	0.0102
RBC	1.30	1.69	1.10	1.12	40.0	31.0	0.0170	0.0223
Plasma	1.00	1.69	0.143	0.0969	28.2	31.0	0.0260	0.0223

Table S2. Digitized and recalculated chloroquine plasma and tissue concentration data for rat

Time (h)	Chloroquine Concentration (μg/mL)										
	Liver	Kidney	Lung	Spleen	Heart	Brain	Muscle	Skin	Eye	RBC	Plasma
1	2.992	1.480	1.959	2.322	0.832	0.997	0.223	0.198	0.361	1.012	0.139
2	7.095	3.305	5.496	4.882	1.310	1.202	0.304	0.237	0.650	0.976	0.125
4	13.35	4.478	6.193	7.777	2.694	1.070	0.358	0.284	0.982	0.907	0.107
6	14.64	7.143	8.486	10.58	1.857	0.882	0.449	0.266	1.175	0.615	0.092
12	12.55	7.097	8.646	12.28	1.778	1.253	0.523	0.307	1.137	0.685	0.075
24	10.09	5.857	9.096	8.955	1.718	1.116	0.453	0.381	1.004	0.587	0.051
48	8.459	5.306	8.734	7.665	1.689	1.437	0.393	0.299	1.453	0.375	0.031
72	7.254	4.391	7.962	6.533	1.618	0.864	0.283	0.226	1.076	0.236	0.020
96	5.954	3.648	6.532	5.816	1.530	1.122	0.227	0.194	0.858	0.163	0.013
120	5.012	3.468	5.387	5.145	1.371	0.778	0.185	0.154	0.644	0.127	0.009
144	3.980	2.815	4.765	4.514	1.261	0.540	0.160	0.133	0.636	0.094	0.006
168	2.978	2.028	2.970	3.079	1.209	0.142	0.160	0.098	0.489	0.051	0.005

From: (Adelusi & Salako, 1982a)

Table S3. Digitized plasma chloroquine concentrations in man.

150 mg		300 mg		600 mg	
Time (h)	ng/mL	Time (h)	ng/mL	Time (h)	ng/mL
24	19.74	24	46.51	8	91.32
75	7.177	48	25.69	12	68.83
296	2.031	72	35.24	24	51.89
583	0.948	95	14.77	95	31.30
926	0.778	177	4.720	130	17.02
1342	0.408	308	3.545	144	12.64
1600	0.308	453	2.698	156	9.688
2001	0.205	641	1.315	385	5.132
2345	0.155	815	1.116	581	3.450
3090	0.096	1076	0.913	647	2.258
4050	0.072	1250	0.807	1121	1.164
		1540	0.534	1366	0.866
		2018	0.332	1840	0.487
		2394	0.291	2298	0.347
		3075	0.248	3001	0.310
		4148	0.146	3524	0.292
		5250	0.080	4162	0.210

From (Frisk-Holmberg et al, 1984)

Predictability of the PBPK model for chloroquine in rats for a different data set

A second study of the pharmacokinetics and tissue distribution of chloroquine was carried out by (Adalusi and Salako, 1982b). Groups of Wistar rats were fed with different diets including (commercial rat diet, cassava-based diet [altered carbohydrate source], and kwashiorkorigenic diet [low protein]) to assess effects of malnourishment. The data from the first group were not graphed, so data from the cassava-based diet group were digitized as this group showed similar body weights as the control group. Chloroquine was given intraperitoneally at a dose of 10 mg/kg. Blood and tissues were taken at various times. Graphical data were digitized to yield the numerical values listed in Table S4.

Table S4. Plasma and tissue concentrations of chloroquine

Time (hour)	Chloroquine concentrations (μg/mL)			
	Plasma	RBC	Liver	Skin
1	0.1297	1.076	5.19	0.212
2	0.1148	1.003	6.40	0.233
4	0.1023	0.907	11.88	0.256
6	0.0924	0.821	13.72	0.288
12	0.0768	0.737	12.55	0.298
24	0.0536	0.628	10.94	0.401
48	0.0316	0.369	7.30	0.403
72	0.0201	0.244	5.72	0.332
96	0.0126	0.147	4.94	0.259
120	0.0098	0.100	4.51	0.199
144	0.0068	0.087	3.77	0.169
168	0.0054	0.071	3.20	0.140

The first-stage PBPK model and parameters obtained from the main study were used to simulate the available tissue and plasma profiles from this study. The figure below demonstrates excellent capture of the liver, RBC, skin, and plasma profiles from this study.

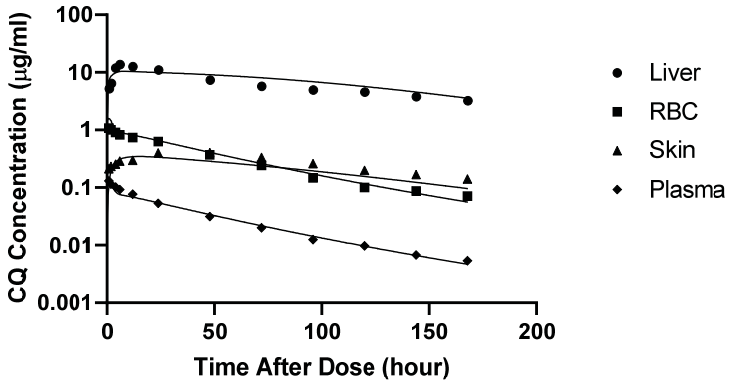

Figure S1. Simulation for rat tissues, RBC and plasma concentrations with PBPK model

Adapt code for rat PBPK model

```
c*****************************************************************************************
**************************************************
C ADAPT *
C Version 5 *
C*********************************************************************
C *
C MODEL *
C *
C This file contains Fortran subroutines into which the user *
C must enter the relevant model equations and constants. *
C Consult the User's Guide for details concerning the format for *
C entered equations and definition of symbols. *
C *
C 1. Symbol- Parameter symbols and model constants *
C 2. DiffEq- System differential equations *
C 3. Output- System output equations *
C 4. Varmod- Error variance model equations *
C 5. Covmod- Covariate model equations (ITS,MLEM) *
C 6. Popinit- Population parameter initial values (ITS,MLEM) *
C 7. Prior - Parameter mean and covariance values (ID,NPD,STS) *
C 8. Sparam- Secondary parameters *
C 9. Amat - System state matrix *
C *
C*********************************************************************
C#####################################################################C
Subroutine SYMBOL
Implicit None
Include 'globals.inc'
Include 'model.inc'
CC
C-------------------------------------------------------------------C
C Enter as Indicated C
C----c--------------------------------------------------------------C
NDEqs = 22 ! Enter # of Diff. Eqs.
NSParam = 21 ! Enter # of System Parameters.
NVparam = 2 ! Enter # of Variance Parameters.
NSecPar = 0 ! Enter # of Secondary Parameters.
NSecOut = 0 ! Enter # of Secondary Outputs (not used).
Ieqsol = 1 ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
Descr = ' simple PBPK of QC '
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each System Parameter (eg. Psym(1)='Kel') C
C----c--------------------------------------------------------------C
Psym(1)='Bmax_liver'
Psym(2)='Bmax_kidney'
Psym(3)='Bmax_heart'
Psym(4)='Bmax_muscle'
Psym(5)='Bmax_skin'
Psym(6)='Bmax_lung'
Psym(7)='Bmax_spleen'
```

```
Psym(8)='Bmax_brain'
Psym(9)='Bmax_eye'
Psym(10)='Bmax_carcass'
Psym(11)='KD'
Psym(12)='KD2'
Psym(13)='kap'
Psym(14)='Kal'
Psym(15)='CL_u,int'
Psym(16)='CL_u,renal'
Psym(17)='ft'
Psym(18)='PS'
Psym(19)='PS2'
Psym(20)='PS3'
Psym(21)='PS4'
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'} C
C----c--------------------------------------------------------------C
PVsym(1)='sigma'
PVsym(2)='intercept'
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each Secondary Parameter {eg: PSsym(1)='CLt'} C
C----c--------------------------------------------------------------C
C-------------------------------------------------------------------C
C-------------------------------------------------------------------C
C
Return
End
C#########################################################################C
Subroutine DIFFEQ(T,X,XP)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 T,X(MaxNDE),XP(MaxNDE)
Real*8 ka, F, Cl_kidney, Cl_liver, fu
Real*8 Bmax_liver, Kp_liver ,Kp_heart,KD3
Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Kp_carcass
Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD,KD2
Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
Real*8 Q_slow,Q_rapid, Q_blood,Q_carcass,ft_s,kal
Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl,ft_m
Real*8 Vmaxr,Kmr, Vmaxl,Kml,ft_h,ft_k,ft_l,fi,GFR,ft_c
Real*8 Q_lung, Q_spleen, Q_brain, Q_eye, Kp_lung, Kp_spleen
Real*8 Kp_brain, Kp_eye, V_lung,V_spleen, V_brain, V_eye
Real*8 V_artery, V_vein,Bmax_spleen,ft_b,ft_e,PS,PS2,PS3,PS4
Real*8 Bmax_lung,Bmax_eye,Bmax_brain,Bmax_carcass
Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
real*8 V_spleen2,V_brain2
CC
C-------------------------------------------------------------------C
C Enter Differential Equations Below {e.g. XP(1) = -P(1)*X(1) } C
```

```
C----c-----------------------------------------------------------------C
Bmax_liver=P(1)
Bmax_kidney=P(2)
Bmax_heart=P(3)
Bmax_muscle=P(4)
Bmax_skin=P(5)
Bmax_lung=P(6)
Bmax_spleen=P(7)
Bmax_brain=P(8)
Bmax_eye=P(9)
Bmax_carcass=P(10)
KD=P(11)
KD2=P(12)
ka=P(13)
kal=P(14)
Cl=P(15)
Cl_kidney=P(16)
ft_e=1.0
ft_k=1.0
ft_l=1.0
ft_m=P(17)
ft_h=1.0
ft_b=1.0
ft_s=P(17)
ft_c=1.0
PS=P(18)
PS2=P(19)
PS3=P(20)
PS4=P(21)
! Tissue volume (mL/kg)
V_kidney=5.25*0.273
V_liver=32.31*0.161
V_heart=2.19*0.320
V_skin=174.45*0.382
V_muscle=422.68*0.118
V_lung=2.642*0.336
V_spleen=0.973*0.207
V_brain=4.643*0.162
V_eye=0.74
V_artery= 21.1
V_vein=42.1
V_carcass=290.92
V_kidney2=5.25*(1.0-0.273)
V_liver2=32.31*(1.0-0.161)
V_heart2=2.19*(1.0-0.32)
V_skin2=174.45*(1.0-0.382)
V_muscle2=422.68*(1.0-0.118)
V_lung2=2.642*(1.0-0.336)
V_spleen2=0.973*(1.0-0.207)
V_brain2=4.643*(1.0-0.162)
! plasma flow was used to describe the flow rate to each tissues (mL/h/kg)
Q_kidney=1385
Q_liver= 2191
```

```
Q_heart= 574
Q_skin= 758
Q_muscle= 3512
Q_carcass=1735
Q_lung =11181.6
Q_spleen=679
Q_brain=248
Q_eye=99.6
GFR=315
!Kp
fu=0.4
Kp_heart=1+Bmax_heart/(KD+X(5))
Kp_kidney=1+Bmax_kidney/(KD+X(4))
Kp_liver=1+Bmax_liver/(KD+X(3))
Kp_muscle=1+Bmax_muscle/(KD2+X(7))
Kp_skin=1+Bmax_skin/(KD2+X(6))
Kp_lung=1+Bmax_lung/(KD+X(8))
Kp_spleen=1+Bmax_spleen/(KD+X(9))
Kp_brain=1+Bmax_brain/(KD+X(10))
Kp_eye=fu*(1+Bmax_eye/(KD2+fu*X(1)))
Kp_carcass=fu*(1+Bmax_carcass/(KD+fu*X(1)))
!IP bolus in rat
!artery
XP(1)=(Q_lung*X(8)/fu+ka*X(2)-fu*GFR*X(1)
  -(Q_liver+Q_kidney+Q_heart+Q_skin*ft_s+
  Q_muscle*ft_m+Q_spleen+Q_brain+Q_eye*ft_e+
  Q_carcass*ft_c)*X(1))/V_artery
!vein
XP(14)=((Q_liver+Q_spleen)*X(3)/fu+Q_kidney*X(4)/fu+Q_heart*
  X(5)/fu+Q_skin*ft_s*X(6)/fu+Q_muscle*ft_m*X(7)/fu
  +Q_brain*ft_b*X(10)/fu+Q_eye*ft_e*X(11)/
  Kp_eye+
  Q_carcass*ft_c*X(12)/Kp_carcass-Q_lung*X(14))/V_vein
!absorption in plasma
XP(2)=-ka*X(2)
!absorption in liver
XP(13)=-kal*X(13)
!liver
XP(3)=(Q_liver*(X(1)-X(3)/fu)+Q_spleen*(X(9)/fu-X(3)/fu)
  +kal*X(13)-PS*(X(3)-
  X(15)/Kp_liver))/V_liver
XP(15)=(PS*(X(3)-X(15)/Kp_liver)-
  Cl*X(15)/Kp_liver)/V_liver2
!kidney
XP(4)=(Q_kidney*(X(1)-X(4)/fu)-PS2*(X(4)-
  X(16)/Kp_kidney))/V_kidney
XP(16)=(PS2*(X(4)-X(16)/Kp_kidney)-
  Cl_kidney*X(16)/Kp_kidney)/V_kidney2
!heart
XP(5)=(Q_heart*(X(1)-X(5)/fu)-PS3*(X(5)-
  X(17)/Kp_heart))/V_heart
XP(17)=PS3*(X(5)-X(17)/Kp_heart)/V_heart2
!skin
```

```
XP(6)=(Q_skin*ft_s*(X(1)-X(6)/fu)-PS4*(X(6)-
  X(18)/Kp_skin))/V_skin
XP(18)=PS4*(X(6)-X(18)/Kp_skin)/V_skin2
!muscle
XP(7)=(Q_muscle*ft_m*(X(1)-X(7)/fu)-PS4*(X(7)-
  X(19)/Kp_muscle))/V_muscle
XP(19)=PS4*(X(7)-X(19)/Kp_muscle)/V_muscle2
!lung
XP(8)=(Q_lung*(X(14)-X(8)/fu)-PS2*(X(8)-
  X(20)/Kp_lung))/V_lung
XP(20)=PS2*(X(8)-X(20)/Kp_lung)/V_lung2
!spleen
XP(9)=(Q_spleen*(X(1)-X(9)/fu)-PS2*(X(9)-
  X(21)/Kp_spleen))/V_spleen
XP(21)=PS2*(X(9)-X(21)/Kp_spleen)/V_spleen2
!brain
XP(10)=(Q_brain*(X(1)-X(10)/fu)-PS3*(X(10)-
  X(22)/Kp_brain))/V_brain
XP(22)=PS3*(X(10)-X(22)/Kp_brain)/V_brain2
!eye
XP(11)=Q_eye*ft_e*(X(1)-X(11)/Kp_eye)/V_eye
!carcass
XP(12)=Q_carcass*ft_c*(X(1)-X(12)/Kp_carcass)/V_carcass
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine OUTPUT(Y,T,X)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 Y(MaxNOE),T,X(MaxNDE)
Real*8 Bmax_liver, Kp_liver ,Kp_heart
Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Bmax_blood,fu
Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD
Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
Real*8 Q_eye,Q_slow,Q_rapid, Q_blood,Q_carcass,Kp_blood
Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl
Real*8 Vmaxr,Kmr, Vmaxl,Kml
Real*8 Vl_liver,Vl_kidney,Vl_heart,Vl_skin,Vl_muscle,Vl_carcass
Real*8 At_liver,At_kidney,At_heart,At_skin,At_muscle,At_carcass
Real*8 fnc,fnl,N1,N2,EN1,EN2,Pn,PD1,PD2,D1o,D1i,D2o,D2i
Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
real*8 V_spleen2,V_brain2
Real*8 V_lung
real*8 V_spleen,V_brain
CC
C-----------------------------------------------------------------------C
C Enter Output Equations Below {e.g. Y(1) = X(1)/P(2) } C
C----c------------------------------------------------------------------C
```

```
Kp_blood=11.6
! Tissue volume (mL/kg)
V_kidney=5.25*0.273
V_liver=32.31*0.161
V_heart=2.19*0.320
V_skin=174.45*0.382
V_muscle=422.68*0.118
V_lung=2.642*0.336
V_spleen=0.973*0.207
V_brain=4.643*0.162
V_kidney2=5.25*(1.0-0.273)
V_liver2=32.31*(1.0-0.161)
V_heart2=2.19*(1.0-0.32)
V_skin2=174.45*(1.0-0.382)
V_muscle2=422.68*(1.0-0.118)
V_lung2=2.642*(1.0-0.336)
V_spleen2=0.973*(1.0-0.207)
V_brain2=4.643*(1.0-0.162)
Y(1)=(X(3)*V_liver+X(15)*V_liver2)/(V_liver+V_liver2)
Y(2)=(X(4)*V_kidney+X(16)*V_kidney2)/(V_kidney+V_kidney2)
Y(3)=(X(5)*V_heart+X(17)*V_heart2)/(V_heart+V_heart2)
Y(4)=X(1)*Kp_blood
Y(5)=(X(7)*V_muscle+X(19)*V_muscle2)/(V_muscle+V_muscle2)
Y(6)=(X(6)*V_skin+X(18)*V_skin2)/(V_skin+V_skin2)
Y(7)=X(1)
Y(8)=(X(8)*V_lung+X(20)*V_lung2)/(V_lung+V_lung2)
Y(9)=(X(9)*V_spleen+X(21)*V_spleen2)/(V_spleen+V_spleen2)
Y(10)=(X(10)*V_brain+X(22)*V_brain2)/(V_brain+V_brain2)
Y(11)=X(11)
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine VARMOD(V,T,X,Y)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
CC
C-----------------------------------------------------------------------C
C Enter Variance Model Equations Below C
C {e.g. V(1) = (PV(1) + PV(2)*Y(1))**2 } C
C----c------------------------------------------------------------------C
V(1) = (PV(2) + PV(1)*Y(1))**2
V(2) = (PV(2) + PV(1)*Y(2))**2
V(3) = (PV(2) + PV(1)*Y(3))**2
V(4) = (PV(2) + PV(1)*Y(4))**2
V(5) = (PV(2) + PV(1)*Y(5))**2
V(6) = (PV(2) + PV(1)*Y(6))**2
V(7) = (PV(2) + PV(1)*Y(7))**2
V(8) = (PV(2) + PV(1)*Y(8))**2
```

```
V(9) = (PV(2) + PV(1)*Y(9))**2
V(10) = (PV(2) + PV(1)*Y(10))**2
V(11) = (PV(2) + PV(1)*Y(11))**2
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine COVMOD(Pmean, ICmean, PC)
C Defines any covariate model equations (MLEM, ITS)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 PC(MaxNCP)
Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
CC
C-----------------------------------------------------------------------C
C Enter # of Covariate Parameters C
C----c------------------------------------------------------------------C
NCparam = 0 ! Enter # of Covariate Parameters.
CC
C-----------------------------------------------------------------------C
C Enter Symbol for Covariate Params {eg: PCsym(1)='CLRenal'} C
C----c------------------------------------------------------------------C
CC
C-----------------------------------------------------------------------C
C For the Model Params. that Depend on Covariates Enter the Equation C
C {e.g. Pmean(1) = PC(1)*R(2) } C
C----c------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C Initial parameter values for population program parameters (ITS, MLEM)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Integer I,J
Real*8 PmeanI(MaxNSP+MaxNDE), ICmeanI(MaxNDE)
Real*8 PcovI(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcovI(MaxNDE,MaxNDE)
Real*8 PCI(MaxNCP)
CC
C-----------------------------------------------------------------------C
C Enter Initial Values for Population Means C
C { e.g. PmeanI(1) = 10.0 } C
C----c------------------------------------------------------------------C
CC
C-----------------------------------------------------------------------C
C Enter Initial Values for Pop. Covariance Matrix (Lower Triang.) C
```

```
C { e.g. PcovI(2,1) = 0.25 } C
C----c----------------------------------------------------------------C
CC
C----------------------------------------------------------------C
C Enter Values for Covariate Model Parameters C
C { e.g. PCI(1) = 2.0 } C
C----c----------------------------------------------------------------C
C----------------------------------------------------------------C
C----------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine PRIOR(Pmean,Pcov,ICmean,ICcov)
C Parameter mean and covariance values for MAP estimation (ID,NPD,STS)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Integer I,J
Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
Real*8 Pcov(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcov(MaxNDE,MaxNDE)
CC
C----------------------------------------------------------------C
C Enter Nonzero Elements of Prior Mean Vector C
C { e.g. Pmean(1) = 10.0 } C
C----c----------------------------------------------------------------C
CC
C----------------------------------------------------------------C
C Enter Nonzero Elements of Covariance Matrix (Lower Triang.) C
C { e.g. Pcov(2,1) = 0.25 } C
C----c----------------------------------------------------------------C
C----------------------------------------------------------------C
C----------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine SPARAM(PS,P,IC)
Implicit None
Include 'globals.inc'
Real*8 PS(MaxNSECP), P(MaxNSP+MaxNDE), IC(MaxNDE)
CC
C----------------------------------------------------------------C
C Enter Equations Defining Secondary Paramters C
C { e.g. PS(1) = P(1)*P(2) } C
C----c----------------------------------------------------------------C
C----------------------------------------------------------------C
C----------------------------------------------------------------C
C
Return
End
C#######################################################################C
Subroutine AMAT(A)
```

```
422 Implicit None
423 Include 'globals.inc'
424 Include 'model.inc'
425 Integer I,J
426 Real*8 A(MaxNDE,MaxNDE)
427 DO I=1,Ndeqs
428 Do J=1,Ndeqs
429 A(I,J)=0.0D0
430 End Do
431 End Do
432 CC
433 C-------------------------------------------------------------------C
434 C Enter non zero elements of state matrix {e.g. A(1,1) = -P(1) } C
435 C----c--------------------------------------------------------------C
436 C-------------------------------------------------------------------C
437 C-------------------------------------------------------------------C
438 C
439 Return
440 End
441 C#####################################################################C
```

Adapt Code for human PBPK model

```
c*****************************************************************************************
**************************************************
C ADAPT *
C Version 5 *
C*********************************************************************
C *
C MODEL *
C *
C This file contains Fortran subroutines into which the user *
C must enter the relevant model equations and constants. *
C Consult the User's Guide for details concerning the format for *
C entered equations and definition of symbols. *
C *
C 1. Symbol- Parameter symbols and model constants *
C 2. DiffEq- System differential equations *
C 3. Output- System output equations *
C 4. Varmod- Error variance model equations *
C 5. Covmod- Covariate model equations (ITS,MLEM) *
C 6. Popinit- Population parameter initial values (ITS,MLEM) *
C 7. Prior - Parameter mean and covariance values (ID,NPD,STS) *
C 8. Sparam- Secondary parameters *
C 9. Amat - System state matrix *
C *
C*********************************************************************
C#####################################################################C
Subroutine SYMBOL
Implicit None
Include 'globals.inc'
Include 'model.inc'
CC
C-------------------------------------------------------------------C
C Enter as Indicated C
C----c--------------------------------------------------------------C
NDEqs = 66 ! Enter # of Diff. Eqs.
NSParam = 21 ! Enter # of System Parameters.
NVparam = 2 ! Enter # of Variance Parameters.
NSecPar = 0 ! Enter # of Secondary Parameters.
NSecOut = 0 ! Enter # of Secondary Outputs (not used).
Ieqsol = 1 ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
Descr = ' simple PBPK of QC '
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each System Parameter (eg. Psym(1)='Kel') C
C----c--------------------------------------------------------------C
Psym(1)='Bmax_liver'
Psym(2)='Bmax_kidney'
Psym(3)='Bmax_heart'
Psym(4)='Bmax_muscle'
Psym(5)='Bmax_skin'
Psym(6)='Bmax_lung'
Psym(7)='Bmax_spleen'
```

```
Psym(8)='Bmax_brain'
Psym(9)='Bmax_eye'
Psym(10)='Bmax_carcass'
Psym(11)='KD'
Psym(12)='KD2'
Psym(13)='kap'
Psym(14)='Kal'
Psym(15)='CL_int'
Psym(16)='F'
Psym(17)='ft'
Psym(18)='PS'
Psym(19)='PS2'
Psym(20)='PS3'
Psym(21)='PS4'
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'} C
C----c--------------------------------------------------------------C
PVsym(1)='sigma'
PVsym(2)='intercept'
CC
C-------------------------------------------------------------------C
C Enter Symbol for Each Secondary Parameter {eg: PSsym(1)='CLt'} C
C----c--------------------------------------------------------------C
C-------------------------------------------------------------------C
C-------------------------------------------------------------------C
C
Return
End
C#########################################################################C
Subroutine DIFFEQ(T,X,XP)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 T,X(MaxNDE),XP(MaxNDE)
Real*8 ka, F, Cl_kidney, Cl_liver, fu
Real*8 Bmax_liver, Kp_liver ,Kp_heart,KD3
Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Kp_carcass
Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD,KD2
Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
Real*8 Q_slow,Q_rapid, Q_blood,Q_carcass,ft_s,kal
Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl,ft_m
Real*8 Vmaxr,Kmr, Vmaxl,Kml,ft_h,ft_k,ft_l,fi,GFR,ft_c
Real*8 Q_lung, Q_spleen, Q_brain, Q_eye, Kp_lung, Kp_spleen
Real*8 Kp_brain, Kp_eye, V_lung,V_spleen, V_brain, V_eye
Real*8 V_artery, V_vein,Bmax_spleen,ft_b,ft_e,PS,PS2,PS3,PS4
Real*8 Bmax_lung,Bmax_eye,Bmax_brain,Bmax_carcass
Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
real*8 V_spleen2,V_brain2,CL_total
real*8 Kp_liver2,Kp_heart2,Kp_kidney2,Kp_carcass2,Kp_muscle2
real*8 Kp_skin2,Kp_spleen2,Kp_lung2,Kp_brain2, Kp_eye2
real*8 Kp_liver3,Kp_heart3,Kp_kidney3,Kp_carcass3,Kp_muscle3
```

```
104 real*8 Kp_skin3,Kp_spleen3,Kp_lung3,Kp_brain3, Kp_eye3
105 CC
106 C-------------------------------------------------------------------------C
107 C Enter Differential Equations Below {e.g. XP(1) = -P(1)*X(1) } C
108 C----c--------------------------------------------------------------------C
109 ! There is no Kp_brain, because it was permeability-limited
110 Bmax_liver=P(1)
111 Bmax_kidney=P(2)
112 Bmax_heart=P(3)
113 Bmax_muscle=P(4)
114 Bmax_skin=P(5)
115 Bmax_lung=P(6)
116 Bmax_spleen=P(7)
117 Bmax_brain=P(8)
118 Bmax_eye=P(9)
119 Bmax_carcass=P(10)
120 KD=P(11)
121 KD2=P(12)
122 ka=P(13)
123 kal=P(14)
124 !CL_total=P(15)
125 Cl=P(15)
126 Cl_kidney=1096
127 F=P(16)
128 ft_e=1.0
129 ft_k=1.0
130 ft_l=1.0
131 ft_m=P(17)
132 ft_h=1.0
133 ft_b=1.0
134 ft_s=P(17)
135 ft_c=1.0
136 PS=P(18)
137 PS2=P(19)
138 PS3=P(20)
139 PS4=P(21)
140 ! Tissue volume (mL/kg)
141 V_kidney=4.4*0.273
142 V_liver=25.7*0.161
143 V_heart=4.7*0.320
144 V_skin=37.1*0.382
145 V_muscle=400*0.118
146 V_lung=7.6*0.336
147 V_spleen=2.6*0.207
148 V_brain=20*0.162
149 V_eye=0.214
150 V_artery= 13.7
151 V_vein=32.1
152 V_carcass=452.1
153 V_kidney2=4.4*(1.0-0.273)
154 V_liver2=25.7*(1.0-0.161)
155 V_heart2=4.7*(1.0-0.320)
156 V_skin2=37.1*(1.0-0.382)
```

```
V_muscle2=400*(1.0-0.118)
V_lung2=7.6*(1.0-0.336)
V_spleen2=2.6*(1.0-0.207)
V_brain2=20*(1.0-0.162)
! plasma flow was used to describe the flow rate to each tissues (mL/h/kg)
Q_kidney=484.6
Q_liver= 628.6
Q_heart= 110.8
Q_skin= 160.6
Q_muscle= 528.9
Q_carcass=401.5
Q_lung =2769
Q_spleen=138.6
Q_brain=315.7
Q_eye=0.0738
GFR=111
!Kp
fu=0.4
!dose 150mg----------
Kp_heart=F*(1+Bmax_heart/(KD+X(5)))
Kp_kidney=F*(1+Bmax_kidney/(KD+X(4)))
Kp_liver=F*(1+Bmax_liver/(KD+X(3)))
Kp_muscle=F*(1+Bmax_muscle/(KD2+X(7)))
Kp_skin=F*(1+Bmax_skin/(KD2+X(6)))
Kp_lung=F*(1+Bmax_lung/(KD+X(8)))
Kp_spleen=F*(1+Bmax_spleen/(KD+X(9)))
Kp_brain=F*(1+Bmax_brain/(KD+X(10)))
Kp_eye=F*(fu*(1+Bmax_eye/(KD2+fu*X(1))))
Kp_carcass=F*(fu*(1+Bmax_carcass/(KD+fu*X(1))))
!artery
XP(1)=(Q_lung*X(8)/fu+ka*X(2)-(CL_kidney+GFR)*X(1)*fu
  -(Q_liver+Q_kidney+Q_heart+Q_skin*ft_s+
  Q_muscle*ft_m+Q_spleen+Q_brain+Q_eye*ft_e+
  Q_carcass*ft_c)*X(1))/V_artery
!vein
XP(14)=((Q_liver+Q_spleen)*X(3)/fu+Q_kidney*X(4)/fu+Q_heart*
  X(5)/fu+Q_skin*ft_s*X(6)/fu+Q_muscle*ft_m*X(7)/fu
  +Q_brain*ft_b*X(10)/fu
  +Q_eye*ft_e*X(11)/Kp_eye+
  Q_carcass*ft_c*X(12)/Kp_carcass-Q_lung*X(14))/V_vein
!oral plasma
XP(2)=-ka*X(2)
!oral liver
XP(13)=-kal*X(13)
!liver
XP(3)=(Q_liver*(X(1)-X(3)/fu)+Q_spleen*(X(9)/fu-X(3)/fu)
  +kal*X(13)-PS*(X(3)-
  X(15)/Kp_liver))/V_liver
XP(15)=(PS*(X(3)-X(15)/Kp_liver)-
  Cl*X(15)/Kp_liver)/V_liver2
!kidney
XP(4)=(Q_kidney*(X(1)-X(4)/fu)-PS2*(X(4)-
  X(16)/Kp_kidney))/V_kidney
```

```
XP(16)=PS2*(X(4)-X(16)/Kp_kidney)/V_kidney2
!heart
XP(5)=(Q_heart*(X(1)-X(5)/fu)-PS3*(X(5)-
  X(17)/Kp_heart))/V_heart
XP(17)=PS3*(X(5)-X(17)/Kp_heart)/V_heart2
!skin
XP(6)=(Q_skin*ft_s*(X(1)-X(6)/fu)-PS4*(X(6)-
  X(18)/Kp_skin))/V_skin
XP(18)=PS4*(X(6)-X(18)/Kp_skin)/V_skin2
!muscle
XP(7)=(Q_muscle*ft_m*(X(1)-X(7)/fu)-PS4*(X(7)-
  X(19)/Kp_muscle))/V_muscle
XP(19)=PS4*(X(7)-X(19)/Kp_muscle)/V_muscle2
!lung
XP(8)=(Q_lung*(X(14)-X(8)/fu)-PS2*(X(8)-
  X(20)/Kp_lung))/V_lung
XP(20)=PS2*(X(8)-X(20)/Kp_lung)/V_lung2
!spleen
XP(9)=(Q_spleen*(X(1)-X(9)/fu)-PS2*(X(9)-
  X(21)/Kp_spleen))/V_spleen
XP(21)=PS2*(X(9)-X(21)/Kp_spleen)/V_spleen2
!brain
XP(10)=(Q_brain*(X(1)-X(10)/fu)-PS3*(X(10)-
  X(22)/Kp_brain))/V_brain
XP(22)=PS3*(X(10)-X(22)/Kp_brain)/V_brain2
!eye
XP(11)=Q_eye*ft_e*(X(1)-X(11)/Kp_eye)/V_eye
!carcass
XP(12)=Q_carcass*ft_c*(X(1)-X(12)/Kp_carcass)/V_carcass
!dose
300mg-------------------------------------------------------------------------
-------
Kp_heart2=F*(1+Bmax_heart/(KD+X(27)))
Kp_kidney2=F*(1+Bmax_kidney/(KD+X(26)))
Kp_liver2=F*(1+Bmax_liver/(KD+X(25)))
Kp_muscle2=F*(1+Bmax_muscle/(KD2+X(29)))
Kp_skin2=F*(1+Bmax_skin/(KD2+X(28)))
Kp_lung2=F*(1+Bmax_lung/(KD+X(30)))
Kp_spleen2=F*(1+Bmax_spleen/(KD+X(31)))
Kp_brain2=F*(1+Bmax_brain/(KD+X(32)))
Kp_eye2=F*(fu*(1+Bmax_eye/(KD2+fu*X(23))))
Kp_carcass2=F*(fu*(1+Bmax_carcass/(KD+fu*X(23))))
!artery
XP(23)=(Q_lung*X(30)/fu+ka*X(24)-(GFR+Cl_kidney)*X(23)*fu
  -(Q_liver+Q_kidney+Q_heart+Q_skin*ft_s+
  Q_muscle*ft_m+Q_spleen+Q_brain+Q_eye*ft_e+
  Q_carcass*ft_c)*X(23))/V_artery
!vein
XP(36)=((Q_liver+Q_spleen)*X(25)/fu+Q_kidney*X(26)/fu+Q_heart*
  X(27)/fu+Q_skin*ft_s*X(28)/fu+Q_muscle*ft_m*X(29)/fu
  +Q_brain*ft_b*X(32)/fu
  +Q_eye*ft_e*X(33)/Kp_eye2+
  Q_carcass*ft_c*X(34)/Kp_carcass2-Q_lung*X(36))/V_vein
```

```
!oral plasma
XP(24)=-ka*X(24)
!oral liver
XP(35)=-kal*X(35)
!liver
XP(25)=(Q_liver*(X(23)-X(25)/fu)+Q_spleen*(X(31)/fu-X(25)/fu)
  +kal*X(35)-PS*(X(25)-
  X(37)/Kp_liver2))/V_liver
XP(37)=(PS*(X(25)-X(37)/Kp_liver2)-
  Cl*X(37)/Kp_liver2)/V_liver2
!kidney
XP(26)=(Q_kidney*(X(23)-X(26)/fu)-PS2*(X(26)-
  X(38)/Kp_kidney2))/V_kidney
XP(38)=PS2*(X(26)-X(38)/Kp_kidney2)/V_kidney2
!heart
XP(27)=(Q_heart*(X(23)-X(27)/fu)-PS3*(X(27)-
  X(39)/Kp_heart2))/V_heart
XP(39)=PS3*(X(27)-X(39)/Kp_heart2)/V_heart2
!skin
XP(28)=(Q_skin*ft_s*(X(23)-X(28)/fu)-PS4*(X(28)-
  X(40)/Kp_skin2))/V_skin
XP(40)=PS4*(X(28)-X(40)/Kp_skin2)/V_skin2
!muscle
XP(29)=(Q_muscle*ft_m*(X(23)-X(29)/fu)-PS4*(X(29)-
  X(41)/Kp_muscle2))/V_muscle
XP(41)=PS4*(X(29)-X(41)/Kp_muscle2)/V_muscle2
!lung
XP(30)=(Q_lung*(X(36)-X(30)/fu)-PS2*(X(30)-
  X(42)/Kp_lung2))/V_lung
XP(42)=PS2*(X(30)-X(42)/Kp_lung2)/V_lung2
!spleen
XP(31)=(Q_spleen*(X(23)-X(31)/fu)-PS2*(X(31)-
  X(43)/Kp_spleen2))/V_spleen
XP(43)=PS2*(X(31)-X(43)/Kp_spleen2)/V_spleen2
!brain
XP(32)=(Q_brain*(X(23)-X(32)/fu)-PS3*(X(32)-
  X(44)/Kp_brain2))/V_brain
XP(44)=PS3*(X(32)-X(44)/Kp_brain2)/V_brain2
!eye
XP(33)=Q_eye*ft_e*(X(23)-X(33)/Kp_eye2)/V_eye
!carcass
XP(34)=Q_carcass*ft_c*(X(23)-X(34)/Kp_carcass2)/V_carcass
!dose
600mg----------------------------------------------------------------------
-----
Kp_heart3=F*(1+Bmax_heart/(KD+(49)))
Kp_kidney3=F*(1+Bmax_kidney/(KD+X(48)))
Kp_liver3=F*(1+Bmax_liver/(KD+X(47)))
Kp_muscle3=F*(1+Bmax_muscle/(KD2+X(51)))
Kp_skin3=F*(1+Bmax_skin/(KD2+X(50)))
Kp_lung3=F*(1+Bmax_lung/(KD+X(52)))
Kp_spleen3=F*(1+Bmax_spleen/(KD+X(53)))
Kp_brain3=F*(1+Bmax_brain/(KD+X(54)))
```

```
Kp_eye3=F*(fu*(1+Bmax_eye/(KD2+fu*X(45))))
Kp_carcass3=F*(fu*(1+Bmax_carcass/(KD+fu*X(45))))
!artery
XP(45)=(Q_lung*X(52)/fu+ka*X(46)-(GFR+CL_kidney)*X(45)*fu
  -(Q_liver+Q_kidney+Q_heart+Q_skin*ft_s+
  Q_muscle*ft_m+Q_spleen+Q_brain+Q_eye*ft_e+
  Q_carcass*ft_c)*X(45))/V_artery
!vein
XP(58)=((Q_liver+Q_spleen)*X(47)/fu+Q_kidney*X(48)/fu+Q_heart*
  X(49)/fu+Q_skin*ft_s*X(50)/fu+Q_muscle*ft_m*X(51)/fu
  +Q_brain*ft_b*X(54)/fu
  +Q_eye*ft_e*X(55)/Kp_eye3+
  Q_carcass*ft_c*X(56)/Kp_carcass3-Q_lung*X(58))/V_vein
!oral plasma
XP(46)=-ka*X(46)
!oral liver
XP(57)=-kal*X(57)
!liver
XP(47)=(Q_liver*(X(45)-X(47)/fu)+Q_spleen*(X(53)/fu-X(47)/fu)
  +kal*X(57)-PS*(X(47)-
  X(59)/Kp_liver3))/V_liver
XP(59)=(PS*(X(47)-X(59)/Kp_liver3)-
  Cl*X(59)/Kp_liver3)/V_liver2
!kidney
XP(48)=(Q_kidney*(X(45)-X(48)/fu)-PS2*(X(48)-
  X(60)/Kp_kidney3))/V_kidney
XP(60)=PS2*(X(48)-X(60)/Kp_kidney3)/V_kidney2
!heart
XP(49)=(Q_heart*(X(45)-X(49)/fu)-PS3*(X(49)-
  X(61)/Kp_heart3))/V_heart
XP(61)=PS3*(X(49)-X(61)/Kp_heart3)/V_heart2
!skin
XP(50)=(Q_skin*ft_s*(X(45)-X(50)/fu)-PS4*(X(50)-
  X(62)/Kp_skin3))/V_skin
XP(62)=PS4*(X(50)-X(62)/Kp_skin3)/V_skin2
!muscle
XP(51)=(Q_muscle*ft_m*(X(45)-X(51)/fu)-PS4*(X(51)-
  X(63)/Kp_muscle3))/V_muscle
XP(63)=PS4*(X(51)-X(63)/Kp_muscle3)/V_muscle2
!lung
XP(52)=(Q_lung*(X(58)-X(52)/fu)-PS2*(X(52)-
  X(64)/Kp_lung3))/V_lung
XP(64)=PS2*(X(52)-X(64)/Kp_lung3)/V_lung2
!spleen
XP(53)=(Q_spleen*(X(45)-X(53)/fu)-PS2*(X(53)-
  X(65)/Kp_spleen3))/V_spleen
XP(65)=PS2*(X(53)-X(65)/Kp_spleen3)/V_spleen2
!brain
XP(54)=(Q_brain*(X(45)-X(54)/fu)-PS3*(X(54)-
  X(66)/Kp_brain3))/V_brain
XP(66)=PS3*(X(54)-X(66)/Kp_brain3)/V_brain2
!eye
XP(55)=Q_eye*ft_e*(X(45)-X(55)/Kp_eye3)/V_eye
```

```
!carcass
XP(56)=Q_carcass*ft_c*(X(45)-X(56)/Kp_carcass3)/V_carcass
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################################C
Subroutine OUTPUT(Y,T,X)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 Y(MaxNOE),T,X(MaxNDE)
Real*8 Bmax_liver, Kp_liver ,Kp_heart
Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Bmax_blood,fu
Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD
Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
Real*8 Q_eye,Q_slow,Q_rapid, Q_blood,Q_carcass,Kp_blood
Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl
Real*8 Vmaxr,Kmr, Vmaxl,Kml
Real*8 Vl_liver,Vl_kidney,Vl_heart,Vl_skin,Vl_muscle,Vl_carcass
Real*8 At_liver,At_kidney,At_heart,At_skin,At_muscle,At_carcass
Real*8 fnc,fnl,N1,N2,EN1,EN2,Pn,PD1,PD2,D1o,D1i,D2o,D2i
Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
real*8 V_spleen2,V_brain2
Real*8 V_lung
real*8 V_spleen,V_brain
CC
C-----------------------------------------------------------------------C
C Enter Output Equations Below {e.g. Y(1) = X(1)/P(2) } C
C----c------------------------------------------------------------------C
Y(1)=X(1)
Y(2)=X(23)
Y(3)=X(45)
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
Return
End
C#######################################################################################C
Subroutine VARMOD(V,T,X,Y)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
CC
C-----------------------------------------------------------------------C
C Enter Variance Model Equations Below C
C {e.g. V(1) = (PV(1) + PV(2)*Y(1))**2 } C
C----c------------------------------------------------------------------C
V(1) = (PV(2) + PV(1)*Y(1))**2
V(2) = (PV(2) + PV(1)*Y(2))**2
```

```
418 V(3) = (PV(2) + PV(1)*Y(3))**2
419 C-------------------------------------------------------------------C
420 C-------------------------------------------------------------------C
421 C
422 Return
423 End
424 C#####################################################################################C
425 Subroutine COVMOD(Pmean, ICmean, PC)
426 C Defines any covariate model equations (MLEM, ITS)
427 Implicit None
428 Include 'globals.inc'
429 Include 'model.inc'
430 Real*8 PC(MaxNCP)
431 Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
432 CC
433 C-------------------------------------------------------------------C
434 C Enter # of Covariate Parameters C
435 C----c--------------------------------------------------------------C
436 NCparam = 0 ! Enter # of Covariate Parameters.
437 CC
438 C-------------------------------------------------------------------C
439 C Enter Symbol for Covariate Params {eg: PCsym(1)='CLRenal'} C
440 C----c--------------------------------------------------------------C
441 CC
442 C-------------------------------------------------------------------C
443 C For the Model Params. that Depend on Covariates Enter the Equation C
444 C {e.g. Pmean(1) = PC(1)*R(2) } C
445 C----c--------------------------------------------------------------C
446 C-------------------------------------------------------------------C
447 C-------------------------------------------------------------------C
448 C
449 Return
450 End
451 C#####################################################################################C
452 Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
453 C Initial parameter values for population program parameters (ITS, MLEM)
454 Implicit None
455 Include 'globals.inc'
456 Include 'model.inc'
457 Integer I,J
458 Real*8 PmeanI(MaxNSP+MaxNDE), ICmeanI(MaxNDE)
459 Real*8 PcovI(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcovI(MaxNDE,MaxNDE)
460 Real*8 PCI(MaxNCP)
461 CC
462 C-------------------------------------------------------------------C
463 C Enter Initial Values for Population Means C
464 C { e.g. PmeanI(1) = 10.0 } C
465 C----c--------------------------------------------------------------C
466 CC
467 C-------------------------------------------------------------------C
468 C Enter Initial Values for Pop. Covariance Matrix (Lower Triang.) C
469 C { e.g. PcovI(2,1) = 0.25 } C
470 C----c--------------------------------------------------------------C
```

```
CC
C-----------------------------------------------------------------C
C Enter Values for Covariate Model Parameters C
C { e.g. PCl(1) = 2.0 } C
C----c------------------------------------------------------------C
C-----------------------------------------------------------------C
C-----------------------------------------------------------------C
C
Return
End
C#################################################################################C
Subroutine PRIOR(Pmean,Pcov,ICmean,ICcov)
C Parameter mean and covariance values for MAP estimation (ID,NPD,STS)
Implicit None
Include 'globals.inc'
Include 'model.inc'
Integer I,J
Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
Real*8 Pcov(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcov(MaxNDE,MaxNDE)
CC
C-----------------------------------------------------------------C
C Enter Nonzero Elements of Prior Mean Vector C
C { e.g. Pmean(1) = 10.0 } C
C----c------------------------------------------------------------C
CC
C-----------------------------------------------------------------C
C Enter Nonzero Elements of Covariance Matrix (Lower Triang.) C
C { e.g. Pcov(2,1) = 0.25 } C
C----c------------------------------------------------------------C
C-----------------------------------------------------------------C
C-----------------------------------------------------------------C
C
Return
End
C#################################################################################C
Subroutine SPARAM(PS,P,IC)
Implicit None
Include 'globals.inc'
Real*8 PS(MaxNSECP), P(MaxNSP+MaxNDE), IC(MaxNDE)
CC
C-----------------------------------------------------------------C
C Enter Equations Defining Secondary Paramters C
C { e.g. PS(1) = P(1)*P(2) } C
C----c------------------------------------------------------------C
C-----------------------------------------------------------------C
C-----------------------------------------------------------------C
C
Return
End
C#################################################################################C
Subroutine AMAT(A)
Implicit None
Include 'globals.inc'
```

```
524 Include 'model.inc'
525 Integer I,J
526 Real*8 A(MaxNDE,MaxNDE)
527 DO I=1,Ndeqs
528 Do J=1,Ndeqs
529 A(I,J)=0.0D0
530 End Do
531 End Do
532 CC
533 C-------------------------------------------------------------------C
534 C Enter non zero elements of state matrix {e.g. A(1,1) = -P(1) } C
535 C----c--------------------------------------------------------------C
536 C-------------------------------------------------------------------C
537 C-------------------------------------------------------------------C
538 C
539 Return
540 End
541 C#####################################################################C
```