

SUPPLEMENTAL MATERIALS

Article title: Physiologically-Based Pharmacokinetics of Lysosomotropic Chloroquine in Rat and Man

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

Tissue	T_{max} (h)		C_{max} ($\mu\text{g/mL}$)		$T_{1/2}$ (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 ($\mu\text{g/mL}$)										
	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 ($\mu\text{g}/\text{mL}$)			
	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.

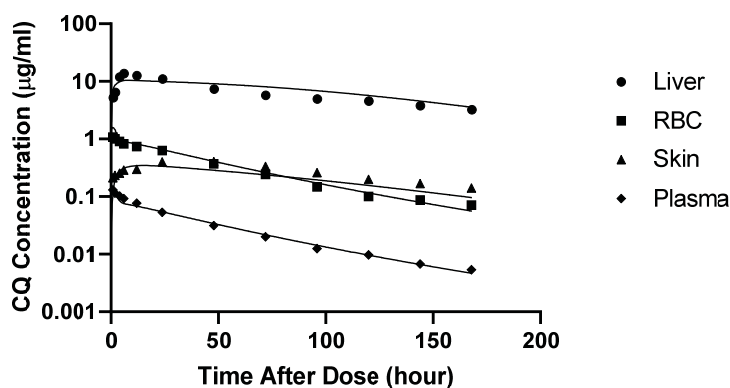


Figure S1. Simulation for rat tissues, RBC and plasma concentrations with PBPK model

Adapt code for rat PBPK model

```
1 c*****
*****
2 C ADAPT *
3 C Version 5 *
4 C*****
5 C *
6 C MODEL *
7 C *
8 C This file contains Fortran subroutines into which the user *
9 C must enter the relevant model equations and constants. *
10 C Consult the User's Guide for details concerning the format for *
11 C entered equations and definition of symbols. *
12 C *
13 C 1. Symbol- Parameter symbols and model constants *
14 C 2. DiffEq- System differential equations *
15 C 3. Output- System output equations *
16 C 4. Varmod- Error variance model equations *
17 C 5. Covmod- Covariate model equations (ITS,MLEM) *
18 C 6. Popinit- Population parameter initial values (ITS,MLEM) *
19 C 7. Prior - Parameter mean and covariance values (ID,NPD,STS) *
20 C 8. Sparam- Secondary parameters *
21 C 9. Amat - System state matrix *
22 C *
23 C*****
24 C#####C
25 Subroutine SYMBOL
26 Implicit None
27 Include 'globals.inc'
28 Include 'model.inc'
29 CC
30 C-----C
31 C Enter as Indicated C
32 C---c-----C
33 NDEqs = 22 ! Enter # of Diff. Eqs.
34 NSParam = 21 ! Enter # of System Parameters.
35 NVparam = 2 ! Enter # of Variance Parameters.
36 NSecPar = 0 ! Enter # of Secondary Parameters.
37 NSecOut = 0 ! Enter # of Secondary Outputs (not used).
38 leqsol = 1 ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
39 Descr = ' simple PBPK of QC '
40 CC
41 C-----C
42 C Enter Symbol for Each System Parameter (eg. Psym(1)='Kel') C
43 C---c-----C
44 Psym(1)='Bmax_liver'
45 Psym(2)='Bmax_kidney'
46 Psym(3)='Bmax_heart'
47 Psym(4)='Bmax_muscle'
48 Psym(5)='Bmax_skin'
49 Psym(6)='Bmax_lung'
50 Psym(7)='Bmax_spleen'
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51 Psym(8)='Bmax_brain'
52 Psym(9)='Bmax_eye'
53 Psym(10)='Bmax_carcass'
54 Psym(11)='KD'
55 Psym(12)='KD2'
56 Psym(13)='kap'
57 Psym(14)='Kal'
58 Psym(15)='CL_u,int'
59 Psym(16)='CL_u,renal'
60 Psym(17)='ft'
61 Psym(18)='PS'
62 Psym(19)='PS2'
63 Psym(20)='PS3'
64 Psym(21)='PS4'
65 CC
66 C-----C
67 C Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'} C
68 C---c-----C
69 PVsym(1)='sigma'
70 PVsym(2)='intercept'
71 CC
72 C-----C
73 C Enter Symbol for Each Secondary Parameter {eg: PSsym(1)='CLt'} C
74 C---c-----C
75 C-----C
76 C-----C
77 C
78 Return
79 End
80 C#####C
81 Subroutine DIFFEQ(T,X,XP)
82 Implicit None
83 Include 'globals.inc'
84 Include 'model.inc'
85 Real*8 T,X(MaxNDE),XP(MaxNDE)
86 Real*8 ka, F, Cl_kidney, Cl_liver, fu
87 Real*8 Bmax_liver, Kp_liver ,Kp_heart,KD3
88 Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Kp_carcass
89 Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD,KD2
90 Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
91 Real*8 Q_slow,Q_rapid, Q_blood,Q_carcass,ft_s,kal
92 Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
93 Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl,ft_m
94 Real*8 Vmaxr,Kmr, Vmaxl,Kml,ft_h,ft_k,ft_l,fi,GFR,ft_c
95 Real*8 Q_lung, Q_spleen, Q_brain, Q_eye, Kp_lung, Kp_spleen
96 Real*8 Kp_brain, Kp_eye, V_lung,V_spleen, V_brain, V_eye
97 Real*8 V_artery, V_vein,Bmax_spleen,ft_b,ft_e,PS,PS2,PS3,PS4
98 Real*8 Bmax_lung,Bmax_eye,Bmax_brain,Bmax_carcass
99 Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
100 real*8 V_spleen2,V_brain2
101 CC
102 C-----C
103 C Enter Differential Equations Below {e.g. XP(1) = -P(1)*X(1) } C

```

104 C---c-----C
105 Bmax_liver=P(1)
106 Bmax_kidney=P(2)
107 Bmax_heart=P(3)
108 Bmax_muscle=P(4)
109 Bmax_skin=P(5)
110 Bmax_lung=P(6)
111 Bmax_spleen=P(7)
112 Bmax_brain=P(8)
113 Bmax_eye=P(9)
114 Bmax_carcass=P(10)
115 KD=P(11)
116 KD2=P(12)
117 ka=P(13)
118 kal=P(14)
119 Cl=P(15)
120 Cl_kidney=P(16)
121 ft_e=1.0
122 ft_k=1.0
123 ft_l=1.0
124 ft_m=P(17)
125 ft_h=1.0
126 ft_b=1.0
127 ft_s=P(17)
128 ft_c=1.0
129 PS=P(18)
130 PS2=P(19)
131 PS3=P(20)
132 PS4=P(21)
133 ! Tissue volume (mL/kg)
134 V_kidney=5.25*0.273
135 V_liver=32.31*0.161
136 V_heart=2.19*0.320
137 V_skin=174.45*0.382
138 V_muscle=422.68*0.118
139 V_lung=2.642*0.336
140 V_spleen=0.973*0.207
141 V_brain=4.643*0.162
142 V_eye=0.74
143 V_artery= 21.1
144 V_vein=42.1
145 V_carcass=290.92
146 V_kidney2=5.25*(1.0-0.273)
147 V_liver2=32.31*(1.0-0.161)
148 V_heart2=2.19*(1.0-0.32)
149 V_skin2=174.45*(1.0-0.382)
150 V_muscle2=422.68*(1.0-0.118)
151 V_lung2=2.642*(1.0-0.336)
152 V_spleen2=0.973*(1.0-0.207)
153 V_brain2=4.643*(1.0-0.162)
154 ! plasma flow was used to describe the flow rate to each tissues (mL/h/kg)
155 Q_kidney=1385
156 Q_liver= 2191

157 Q_heart= 574
158 Q_skin= 758
159 Q_muscle= 3512
160 Q_carcass=1735
161 Q_lung =11181.6
162 Q_spleen=679
163 Q_brain=248
164 Q_eye=99.6
165 GFR=315
166 !Kp
167 fu=0.4
168 Kp_heart=1+Bmax_heart/(KD+X(5))
169 Kp_kidney=1+Bmax_kidney/(KD+X(4))
170 Kp_liver=1+Bmax_liver/(KD+X(3))
171 Kp_muscle=1+Bmax_muscle/(KD2+X(7))
172 Kp_skin=1+Bmax_skin/(KD2+X(6))
173 Kp_lung=1+Bmax_lung/(KD+X(8))
174 Kp_spleen=1+Bmax_spleen/(KD+X(9))
175 Kp_brain=1+Bmax_brain/(KD+X(10))
176 Kp_eye=fu*(1+Bmax_eye/(KD2+fu*X(1)))
177 Kp_carcass=fu*(1+Bmax_carcass/(KD+fu*X(1)))
178 !IP bolus in rat
179 !artery
180 XP(1)=(Q_lung*X(8)/fu+ka*X(2)-fu*GFR*X(1)
181 -(Q_liver+Q_kidney+Q_heart+Q_skin*ft_s+
182 Q_muscle*ft_m+Q_spleen+Q_brain+Q_eye*ft_e+
183 Q_carcass*ft_c)*X(1))/V_artery
184 !vein
185 XP(14)=((Q_liver+Q_spleen)*X(3)/fu+Q_kidney*X(4)/fu+Q_heart*
186 X(5)/fu+Q_skin*ft_s*X(6)/fu+Q_muscle*ft_m*X(7)/fu
187 +Q_brain*ft_b*X(10)/fu+Q_eye*ft_e*X(11)/
188 Kp_eye+
189 Q_carcass*ft_c*X(12)/Kp_carcass-Q_lung*X(14))/V_vein
190 !absorption in plasma
191 XP(2)=-ka*X(2)
192 !absorption in liver
193 XP(13)=-kal*X(13)
194 !liver
195 XP(3)=(Q_liver*(X(1)-X(3)/fu)+Q_spleen*(X(9)/fu-X(3)/fu)
196 +kal*X(13)-PS*(X(3)-
197 X(15)/Kp_liver))/V_liver
198 XP(15)=(PS*(X(3)-X(15)/Kp_liver)-
199 Cl*X(15)/Kp_liver)/V_liver2
200 !kidney
201 XP(4)=(Q_kidney*(X(1)-X(4)/fu)-PS2*(X(4)-
202 X(16)/Kp_kidney))/V_kidney
203 XP(16)=(PS2*(X(4)-X(16)/Kp_kidney)-
204 Cl_kidney*X(16)/Kp_kidney)/V_kidney2
205 !heart
206 XP(5)=(Q_heart*(X(1)-X(5)/fu)-PS3*(X(5)-
207 X(17)/Kp_heart))/V_heart
208 XP(17)=PS3*(X(5)-X(17)/Kp_heart)/V_heart2
209 !skin

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210 XP(6)=(Q_skin*ft_s*(X(1)-X(6)/fu)-PS4*(X(6)-
211 X(18)/Kp_skin))/V_skin
212 XP(18)=PS4*(X(6)-X(18)/Kp_skin)/V_skin2
213 !muscle
214 XP(7)=(Q_muscle*ft_m*(X(1)-X(7)/fu)-PS4*(X(7)-
215 X(19)/Kp_muscle))/V_muscle
216 XP(19)=PS4*(X(7)-X(19)/Kp_muscle)/V_muscle2
217 !lung
218 XP(8)=(Q_lung*(X(14)-X(8)/fu)-PS2*(X(8)-
219 X(20)/Kp_lung))/V_lung
220 XP(20)=PS2*(X(8)-X(20)/Kp_lung)/V_lung2
221 !spleen
222 XP(9)=(Q_spleen*(X(1)-X(9)/fu)-PS2*(X(9)-
223 X(21)/Kp_spleen))/V_spleen
224 XP(21)=PS2*(X(9)-X(21)/Kp_spleen)/V_spleen2
225 !brain
226 XP(10)=(Q_brain*(X(1)-X(10)/fu)-PS3*(X(10)-
227 X(22)/Kp_brain))/V_brain
228 XP(22)=PS3*(X(10)-X(22)/Kp_brain)/V_brain2
229 !eye
230 XP(11)=Q_eye*ft_e*(X(1)-X(11)/Kp_eye)/V_eye
231 !carcass
232 XP(12)=Q_carcass*ft_c*(X(1)-X(12)/Kp_carcass)/V_carcass
233 C-----C
234 C-----C
235 C
236 Return
237 End
238 C#####C
239 Subroutine OUTPUT(Y,T,X)
240 Implicit None
241 Include 'globals.inc'
242 Include 'model.inc'
243 Real*8 Y(MaxNOE),T,X(MaxNDE)
244 Real*8 Bmax_liver, Kp_liver ,Kp_heart
245 Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Bmax_blood,fu
246 Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD
247 Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
248 Real*8 Q_eye,Q_slow,Q_rapid, Q_blood,Q_carcass,Kp_blood
249 Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
250 Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Ci
251 Real*8 Vmaxr,Kmr, Vmaxl,Kml
252 Real*8 Vl_liver,Vl_kidney,Vl_heart,Vl_skin,Vl_muscle,Vl_carcass
253 Real*8 At_liver,At_kidney,At_heart,At_skin,At_muscle,At_carcass
254 Real*8 fnc,fnl,N1,N2,EN1,EN2,Pn,PD1,PD2,D1o,D1i,D2o,D2i
255 Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
256 real*8 V_spleen2,V_brain2
257 Real*8 V_lung
258 real*8 V_spleen,V_brain
259 CC
260 C-----C
261 C Enter Output Equations Below {e.g. Y(1) = X(1)/P(2) } C
262 C---c-----C

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263 Kp_blood=11.6
264 ! Tissue volume (mL/kg)
265 V_kidney=5.25*0.273
266 V_liver=32.31*0.161
267 V_heart=2.19*0.320
268 V_skin=174.45*0.382
269 V_muscle=422.68*0.118
270 V_lung=2.642*0.336
271 V_spleen=0.973*0.207
272 V_brain=4.643*0.162
273 V_kidney2=5.25*(1.0-0.273)
274 V_liver2=32.31*(1.0-0.161)
275 V_heart2=2.19*(1.0-0.32)
276 V_skin2=174.45*(1.0-0.382)
277 V_muscle2=422.68*(1.0-0.118)
278 V_lung2=2.642*(1.0-0.336)
279 V_spleen2=0.973*(1.0-0.207)
280 V_brain2=4.643*(1.0-0.162)
281 Y(1)=(X(3)*V_liver+X(15)*V_liver2)/(V_liver+V_liver2)
282 Y(2)=(X(4)*V_kidney+X(16)*V_kidney2)/(V_kidney+V_kidney2)
283 Y(3)=(X(5)*V_heart+X(17)*V_heart2)/(V_heart+V_heart2)
284 Y(4)=X(1)*Kp_blood
285 Y(5)=(X(7)*V_muscle+X(19)*V_muscle2)/(V_muscle+V_muscle2)
286 Y(6)=(X(6)*V_skin+X(18)*V_skin2)/(V_skin+V_skin2)
287 Y(7)=X(1)
288 Y(8)=(X(8)*V_lung+X(20)*V_lung2)/(V_lung+V_lung2)
289 Y(9)=(X(9)*V_spleen+X(21)*V_spleen2)/(V_spleen+V_spleen2)
290 Y(10)=(X(10)*V_brain+X(22)*V_brain2)/(V_brain+V_brain2)
291 Y(11)=X(11)
292 C-----C
293 C-----C
294 C
295 Return
296 End
297 C#####C
298 Subroutine VARMOD(V,T,X,Y)
299 Implicit None
300 Include 'globals.inc'
301 Include 'model.inc'
302 Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
303 CC
304 C-----C
305 C Enter Variance Model Equations Below C
306 C {e.g. V(1) = (PV(1) + PV(2)*Y(1))**2 } C
307 C---c-----C
308 V(1) = (PV(2) + PV(1)*Y(1))**2
309 V(2) = (PV(2) + PV(1)*Y(2))**2
310 V(3) = (PV(2) + PV(1)*Y(3))**2
311 V(4) = (PV(2) + PV(1)*Y(4))**2
312 V(5) = (PV(2) + PV(1)*Y(5))**2
313 V(6) = (PV(2) + PV(1)*Y(6))**2
314 V(7) = (PV(2) + PV(1)*Y(7))**2
315 V(8) = (PV(2) + PV(1)*Y(8))**2

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316 V(9) = (PV(2) + PV(1)*Y(9))**2
317 V(10) = (PV(2) + PV(1)*Y(10))**2
318 V(11) = (PV(2) + PV(1)*Y(11))**2
319 C-----C
320 C-----C
321 C
322 Return
323 End
324 C#####C
325 Subroutine COVMOD(Pmean, ICmean, PC)
326 C Defines any covariate model equations (MLEM, ITS)
327 Implicit None
328 Include 'globals.inc'
329 Include 'model.inc'
330 Real*8 PC(MaxNCP)
331 Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
332 CC
333 C-----C
334 C Enter # of Covariate Parameters C
335 C---c-----C
336 NCparam = 0 ! Enter # of Covariate Parameters.
337 CC
338 C-----C
339 C Enter Symbol for Covariate Params {eg: PCSym(1)='CLRenal'} C
340 C---c-----C
341 CC
342 C-----C
343 C For the Model Params. that Depend on Covariates Enter the Equation C
344 C {e.g. Pmean(1) = PC(1)*R(2) } C
345 C---c-----C
346 C-----C
347 C-----C
348 C
349 Return
350 End
351 C#####C
352 Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
353 C Initial parameter values for population program parameters (ITS, MLEM)
354 Implicit None
355 Include 'globals.inc'
356 Include 'model.inc'
357 Integer I,J
358 Real*8 PmeanI(MaxNSP+MaxNDE), ICmeanI(MaxNDE)
359 Real*8 PcovI(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcovI(MaxNDE,MaxNDE)
360 Real*8 PCI(MaxNCP)
361 CC
362 C-----C
363 C Enter Initial Values for Population Means C
364 C { e.g. PmeanI(1) = 10.0 } C
365 C---c-----C
366 CC
367 C-----C
368 C Enter Initial Values for Pop. Covariance Matrix (Lower Triang.) C

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```

369 C { e.g. Pcovl(2,1) = 0.25 } C
370 C-----C
371 CC
372 C-----C
373 C Enter Values for Covariate Model Parameters C
374 C { e.g. PCI(1) = 2.0 } C
375 C---c-----C
376 C-----C
377 C-----C
378 C
379 Return
380 End
381 C#####C
382 Subroutine PRIOR(Pmean,Pcov,ICmean,ICcov)
383 C Parameter mean and covariance values for MAP estimation (ID,NPD,STS)
384 Implicit None
385 Include 'globals.inc'
386 Include 'model.inc'
387 Integer I,J
388 Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
389 Real*8 Pcov(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcov(MaxNDE,MaxNDE)
390 CC
391 C-----C
392 C Enter Nonzero Elements of Prior Mean Vector C
393 C { e.g. Pmean(1) = 10.0 } C
394 C---c-----C
395 CC
396 C-----C
397 C Enter Nonzero Elements of Covariance Matrix (Lower Triang.) C
398 C { e.g. Pcov(2,1) = 0.25 } C
399 C---c-----C
400 C-----C
401 C-----C
402 C
403 Return
404 End
405 C#####C
406 Subroutine SPARAM(PS,P,IC)
407 Implicit None
408 Include 'globals.inc'
409 Real*8 PS(MaxNSECP), P(MaxNSP+MaxNDE), IC(MaxNDE)
410 CC
411 C-----C
412 C Enter Equations Defining Secondary Paramters C
413 C { e.g. PS(1) = P(1)*P(2) } C
414 C---c-----C
415 C-----C
416 C-----C
417 C
418 Return
419 End
420 C#####C
421 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

```
1 c*****
*****
2 C ADAPT *
3 C Version 5 *
4 C*****
5 C *
6 C MODEL *
7 C *
8 C This file contains Fortran subroutines into which the user *
9 C must enter the relevant model equations and constants. *
10 C Consult the User's Guide for details concerning the format for *
11 C entered equations and definition of symbols. *
12 C *
13 C 1. Symbol- Parameter symbols and model constants *
14 C 2. DiffEq- System differential equations *
15 C 3. Output- System output equations *
16 C 4. Varmod- Error variance model equations *
17 C 5. Covmod- Covariate model equations (ITS,MLEM) *
18 C 6. Popinit- Population parameter initial values (ITS,MLEM) *
19 C 7. Prior - Parameter mean and covariance values (ID,NPD,STS) *
20 C 8. Sparam- Secondary parameters *
21 C 9. Amat - System state matrix *
22 C *
23 C*****
24 C#####C
25 Subroutine SYMBOL
26 Implicit None
27 Include 'globals.inc'
28 Include 'model.inc'
29 CC
30 C-----C
31 C Enter as Indicated C
32 C---c-----C
33 NDEqs = 66 ! Enter # of Diff. Eqs.
34 NSParam = 21 ! Enter # of System Parameters.
35 NVparam = 2 ! Enter # of Variance Parameters.
36 NSecPar = 0 ! Enter # of Secondary Parameters.
37 NSecOut = 0 ! Enter # of Secondary Outputs (not used).
38 leqsol = 1 ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
39 Descr = ' simple PBPK of QC '
40 CC
41 C-----C
42 C Enter Symbol for Each System Parameter (eg. Psym(1)='Kel') C
43 C---c-----C
44 Psym(1)='Bmax_liver'
45 Psym(2)='Bmax_kidney'
46 Psym(3)='Bmax_heart'
47 Psym(4)='Bmax_muscle'
48 Psym(5)='Bmax_skin'
49 Psym(6)='Bmax_lung'
50 Psym(7)='Bmax_spleen'
```

```

51 Psym(8)='Bmax_brain'
52 Psym(9)='Bmax_eye'
53 Psym(10)='Bmax_carcass'
54 Psym(11)='KD'
55 Psym(12)='KD2'
56 Psym(13)='kap'
57 Psym(14)='Kal'
58 Psym(15)='CL_int'
59 Psym(16)='F'
60 Psym(17)='ft'
61 Psym(18)='PS'
62 Psym(19)='PS2'
63 Psym(20)='PS3'
64 Psym(21)='PS4'
65 CC
66 C-----C
67 C Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'} C
68 C---c-----C
69 PVsym(1)='sigma'
70 PVsym(2)='intercept'
71 CC
72 C-----C
73 C Enter Symbol for Each Secondary Parameter {eg: PSsym(1)='CLt'} C
74 C---c-----C
75 C-----C
76 C-----C
77 C
78 Return
79 End
80 C#####C
81 Subroutine DIFFEQ(T,X,XP)
82 Implicit None
83 Include 'globals.inc'
84 Include 'model.inc'
85 Real*8 T,X(MaxNDE),XP(MaxNDE)
86 Real*8 ka, F, Cl_kidney, Cl_liver, fu
87 Real*8 Bmax_liver, Kp_liver ,Kp_heart,KD3
88 Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle,Kp_carcass
89 Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin,KD,KD2
90 Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin,Q_muscle
91 Real*8 Q_slow,Q_rapid, Q_blood,Q_carcass,ft_s,kal
92 Real*8 V_liver,V_kidney, V_muscle,V_blood,V_carcass,V_plasma
93 Real*8 V_heart,V_slow, V_rapid, V_skin, V_gut,Cl,ft_m
94 Real*8 Vmaxr,Kmr, Vmaxl,Kml,ft_h,ft_k,ft_l,fi,GFR,ft_c
95 Real*8 Q_lung, Q_spleen, Q_brain, Q_eye, Kp_lung, Kp_spleen
96 Real*8 Kp_brain, Kp_eye, V_lung,V_spleen, V_brain, V_eye
97 Real*8 V_artery, V_vein,Bmax_spleen,ft_b,ft_e,PS,PS2,PS3,PS4
98 Real*8 Bmax_lung,Bmax_eye,Bmax_brain,Bmax_carcass
99 Real*8 V_liver2,V_kidney2,V_heart2,V_muscle2,V_skin2,V_lung2
100 real*8 V_spleen2,V_brain2,CL_total
101 real*8 Kp_liver2,Kp_heart2,Kp_kidney2,Kp_carcass2,Kp_muscle2
102 real*8 Kp_skin2,Kp_spleen2,Kp_lung2,Kp_brain2, Kp_eye2
103 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)

157 $V_{\text{muscle2}}=400*(1.0-0.118)$
158 $V_{\text{lung2}}=7.6*(1.0-0.336)$
159 $V_{\text{spleen2}}=2.6*(1.0-0.207)$
160 $V_{\text{brain2}}=20*(1.0-0.162)$
161 ! plasma flow was used to describe the flow rate to each tissues (mL/h/kg)
162 $Q_{\text{kidney}}=484.6$
163 $Q_{\text{liver}}=628.6$
164 $Q_{\text{heart}}=110.8$
165 $Q_{\text{skin}}=160.6$
166 $Q_{\text{muscle}}=528.9$
167 $Q_{\text{carcass}}=401.5$
168 $Q_{\text{lung}}=2769$
169 $Q_{\text{spleen}}=138.6$
170 $Q_{\text{brain}}=315.7$
171 $Q_{\text{eye}}=0.0738$
172 $GFR=111$
173 !Kp
174 $fu=0.4$
175 !dose 150mg-----
176 $Kp_{\text{heart}}=F*(1+B_{\text{max_heart}}/(KD+X(5)))$
177 $Kp_{\text{kidney}}=F*(1+B_{\text{max_kidney}}/(KD+X(4)))$
178 $Kp_{\text{liver}}=F*(1+B_{\text{max_liver}}/(KD+X(3)))$
179 $Kp_{\text{muscle}}=F*(1+B_{\text{max_muscle}}/(KD2+X(7)))$
180 $Kp_{\text{skin}}=F*(1+B_{\text{max_skin}}/(KD2+X(6)))$
181 $Kp_{\text{lung}}=F*(1+B_{\text{max_lung}}/(KD+X(8)))$
182 $Kp_{\text{spleen}}=F*(1+B_{\text{max_spleen}}/(KD+X(9)))$
183 $Kp_{\text{brain}}=F*(1+B_{\text{max_brain}}/(KD+X(10)))$
184 $Kp_{\text{eye}}=F*(fu*(1+B_{\text{max_eye}}/(KD2+fu*X(1))))$
185 $Kp_{\text{carcass}}=F*(fu*(1+B_{\text{max_carcass}}/(KD+fu*X(1))))$
186 !artery
187 $XP(1)=(Q_{\text{lung}}*X(8)/fu+ka*X(2)-(CL_{\text{kidney}}+GFR)*X(1))*fu$
188 $-(Q_{\text{liver}}+Q_{\text{kidney}}+Q_{\text{heart}}+Q_{\text{skin}}*ft_s+$
189 $Q_{\text{muscle}}*ft_m+Q_{\text{spleen}}+Q_{\text{brain}}+Q_{\text{eye}}*ft_e+$
190 $Q_{\text{carcass}}*ft_c)*X(1))/V_{\text{artery}}$
191 !vein
192 $XP(14)=((Q_{\text{liver}}+Q_{\text{spleen}})*X(3)/fu+Q_{\text{kidney}}*X(4)/fu+Q_{\text{heart}}*$
193 $X(5)/fu+Q_{\text{skin}}*ft_s*X(6)/fu+Q_{\text{muscle}}*ft_m*X(7)/fu$
194 $+Q_{\text{brain}}*ft_b*X(10)/fu$
195 $+Q_{\text{eye}}*ft_e*X(11)/Kp_{\text{eye}}+$
196 $Q_{\text{carcass}}*ft_c*X(12)/Kp_{\text{carcass}}-Q_{\text{lung}}*X(14))/V_{\text{vein}}$
197 !oral plasma
198 $XP(2)=-ka*X(2)$
199 !oral liver
200 $XP(13)=-kal*X(13)$
201 !liver
202 $XP(3)=(Q_{\text{liver}}*(X(1)-X(3)/fu)+Q_{\text{spleen}}*(X(9)/fu-X(3)/fu)$
203 $+kal*X(13)-PS*(X(3)-$
204 $X(15)/Kp_{\text{liver}}))/V_{\text{liver}}$
205 $XP(15)=(PS*(X(3)-X(15)/Kp_{\text{liver}})-$
206 $Cl*X(15)/Kp_{\text{liver}})/V_{\text{liver2}}$
207 !kidney
208 $XP(4)=(Q_{\text{kidney}}*(X(1)-X(4)/fu)-PS2*(X(4)-$
209 $X(16)/Kp_{\text{kidney}}))/V_{\text{kidney}}$

210 $XP(16) = PS2 * (X(4) - X(16)) / Kp_kidney / V_kidney2$
 211 !heart
 212 $XP(5) = (Q_heart * (X(1) - X(5)) / fu) - PS3 * (X(5) -$
 213 $X(17) / Kp_heart) / V_heart$
 214 $XP(17) = PS3 * (X(5) - X(17)) / Kp_heart / V_heart2$
 215 !skin
 216 $XP(6) = (Q_skin * ft_s * (X(1) - X(6)) / fu) - PS4 * (X(6) -$
 217 $X(18) / Kp_skin) / V_skin$
 218 $XP(18) = PS4 * (X(6) - X(18)) / Kp_skin / V_skin2$
 219 !muscle
 220 $XP(7) = (Q_muscle * ft_m * (X(1) - X(7)) / fu) - PS4 * (X(7) -$
 221 $X(19) / Kp_muscle) / V_muscle$
 222 $XP(19) = PS4 * (X(7) - X(19)) / Kp_muscle / V_muscle2$
 223 !lung
 224 $XP(8) = (Q_lung * (X(14) - X(8)) / fu) - PS2 * (X(8) -$
 225 $X(20) / Kp_lung) / V_lung$
 226 $XP(20) = PS2 * (X(8) - X(20)) / Kp_lung / V_lung2$
 227 !spleen
 228 $XP(9) = (Q_spleen * (X(1) - X(9)) / fu) - PS2 * (X(9) -$
 229 $X(21) / Kp_spleen) / V_spleen$
 230 $XP(21) = PS2 * (X(9) - X(21)) / Kp_spleen / V_spleen2$
 231 !brain
 232 $XP(10) = (Q_brain * (X(1) - X(10)) / fu) - PS3 * (X(10) -$
 233 $X(22) / Kp_brain) / V_brain$
 234 $XP(22) = PS3 * (X(10) - X(22)) / Kp_brain / V_brain2$
 235 !eye
 236 $XP(11) = Q_eye * ft_e * (X(1) - X(11)) / Kp_eye / V_eye$
 237 !carcass
 238 $XP(12) = Q_carcass * ft_c * (X(1) - X(12)) / Kp_carcass / V_carcass$
 239 !dose

300mg-----

240 $Kp_heart2 = F * (1 + Bmax_heart / (KD + X(27)))$
 241 $Kp_kidney2 = F * (1 + Bmax_kidney / (KD + X(26)))$
 242 $Kp_liver2 = F * (1 + Bmax_liver / (KD + X(25)))$
 243 $Kp_muscle2 = F * (1 + Bmax_muscle / (KD2 + X(29)))$
 244 $Kp_skin2 = F * (1 + Bmax_skin / (KD2 + X(28)))$
 245 $Kp_lung2 = F * (1 + Bmax_lung / (KD + X(30)))$
 246 $Kp_spleen2 = F * (1 + Bmax_spleen / (KD + X(31)))$
 247 $Kp_brain2 = F * (1 + Bmax_brain / (KD + X(32)))$
 248 $Kp_eye2 = F * (fu * (1 + Bmax_eye / (KD2 + fu * X(23))))$
 249 $Kp_carcass2 = F * (fu * (1 + Bmax_carcass / (KD + fu * X(23))))$
 250 !artery
 251 $XP(23) = (Q_lung * X(30) / fu + ka * X(24) - (GFR + Cl_kidney) * X(23)) * fu$
 252 $- (Q_liver + Q_kidney + Q_heart + Q_skin * ft_s +$
 253 $Q_muscle * ft_m + Q_spleen + Q_brain + Q_eye * ft_e +$
 254 $Q_carcass * ft_c) * X(23) / V_artery$
 255 !vein
 256 $XP(36) = ((Q_liver + Q_spleen) * X(25) / fu + Q_kidney * X(26) / fu + Q_heart *$
 257 $X(27) / fu + Q_skin * ft_s * X(28) / fu + Q_muscle * ft_m * X(29) / fu$
 258 $+ Q_brain * ft_b * X(32) / fu$
 259 $+ Q_eye * ft_e * X(33) / Kp_eye2 +$
 260 $Q_carcass * ft_c * X(34) / Kp_carcass2 - Q_lung * X(36)) / V_vein$

261 loral plasma
 262 $XP(24) = -ka * X(24)$
 263 loral liver
 264 $XP(35) = -kal * X(35)$
 265 lliver
 266 $XP(25) = (Q_liver * (X(23) - X(25) / fu) + Q_spleen * (X(31) / fu - X(25) / fu) + kal * X(35) - PS * (X(25) - X(37) / Kp_liver2)) / V_liver$
 267
 268
 269 $XP(37) = (PS * (X(25) - X(37) / Kp_liver2) - Cl * X(37) / Kp_liver2) / V_liver2$
 270
 271 lkidney
 272 $XP(26) = (Q_kidney * (X(23) - X(26) / fu) - PS2 * (X(26) - X(38) / Kp_kidney2)) / V_kidney$
 273
 274 $XP(38) = PS2 * (X(26) - X(38) / Kp_kidney2) / V_kidney2$
 275 lheart
 276 $XP(27) = (Q_heart * (X(23) - X(27) / fu) - PS3 * (X(27) - X(39) / Kp_heart2)) / V_heart$
 277
 278 $XP(39) = PS3 * (X(27) - X(39) / Kp_heart2) / V_heart2$
 279 lskin
 280 $XP(28) = (Q_skin * ft_s * (X(23) - X(28) / fu) - PS4 * (X(28) - X(40) / Kp_skin2)) / V_skin$
 281
 282 $XP(40) = PS4 * (X(28) - X(40) / Kp_skin2) / V_skin2$
 283 lmuscle
 284 $XP(29) = (Q_muscle * ft_m * (X(23) - X(29) / fu) - PS4 * (X(29) - X(41) / Kp_muscle2)) / V_muscle$
 285
 286 $XP(41) = PS4 * (X(29) - X(41) / Kp_muscle2) / V_muscle2$
 287 llung
 288 $XP(30) = (Q_lung * (X(36) - X(30) / fu) - PS2 * (X(30) - X(42) / Kp_lung2)) / V_lung$
 289
 290 $XP(42) = PS2 * (X(30) - X(42) / Kp_lung2) / V_lung2$
 291 lspleen
 292 $XP(31) = (Q_spleen * (X(23) - X(31) / fu) - PS2 * (X(31) - X(43) / Kp_spleen2)) / V_spleen$
 293
 294 $XP(43) = PS2 * (X(31) - X(43) / Kp_spleen2) / V_spleen2$
 295 lbrain
 296 $XP(32) = (Q_brain * (X(23) - X(32) / fu) - PS3 * (X(32) - X(44) / Kp_brain2)) / V_brain$
 297
 298 $XP(44) = PS3 * (X(32) - X(44) / Kp_brain2) / V_brain2$
 299 leye
 300 $XP(33) = Q_eye * ft_e * (X(23) - X(33) / Kp_eye2) / V_eye$
 301 lcarcass
 302 $XP(34) = Q_carcass * ft_c * (X(23) - X(34) / Kp_carcass2) / V_carcass$
 303 ldose
 600mg-----

 304 $Kp_heart3 = F * (1 + Bmax_heart / (KD + (49)))$
 305 $Kp_kidney3 = F * (1 + Bmax_kidney / (KD + X(48)))$
 306 $Kp_liver3 = F * (1 + Bmax_liver / (KD + X(47)))$
 307 $Kp_muscle3 = F * (1 + Bmax_muscle / (KD2 + X(51)))$
 308 $Kp_skin3 = F * (1 + Bmax_skin / (KD2 + X(50)))$
 309 $Kp_lung3 = F * (1 + Bmax_lung / (KD + X(52)))$
 310 $Kp_spleen3 = F * (1 + Bmax_spleen / (KD + X(53)))$
 311 $Kp_brain3 = F * (1 + Bmax_brain / (KD + X(54)))$

312 $Kp_eye3 = F * (fu * (1 + Bmax_eye / (KD2 + fu * X(45))))$
313 $Kp_carcass3 = F * (fu * (1 + Bmax_carcass / (KD + fu * X(45))))$
314 **!artery**
315 $XP(45) = (Q_lung * X(52) / fu + ka * X(46) - (GFR + CL_kidney) * X(45) * fu$
316 $- (Q_liver + Q_kidney + Q_heart + Q_skin * ft_s +$
317 $Q_muscle * ft_m + Q_spleen + Q_brain + Q_eye * ft_e +$
318 $Q_carcass * ft_c) * X(45) / V_artery$
319 **!vein**
320 $XP(58) = ((Q_liver + Q_spleen) * X(47) / fu + Q_kidney * X(48) / fu + Q_heart *$
321 $X(49) / fu + Q_skin * ft_s * X(50) / fu + Q_muscle * ft_m * X(51) / fu$
322 $+ Q_brain * ft_b * X(54) / fu$
323 $+ Q_eye * ft_e * X(55) / Kp_eye3 +$
324 $Q_carcass * ft_c * X(56) / Kp_carcass3 - Q_lung * X(58) / V_vein$
325 **!oral plasma**
326 $XP(46) = -ka * X(46)$
327 **!oral liver**
328 $XP(57) = -kal * X(57)$
329 **!liver**
330 $XP(47) = (Q_liver * (X(45) - X(47) / fu) + Q_spleen * (X(53) / fu - X(47) / fu)$
331 $+ kal * X(57) - PS * (X(47) -$
332 $X(59) / Kp_liver3) / V_liver$
333 $XP(59) = (PS * (X(47) - X(59) / Kp_liver3) -$
334 $Cl * X(59) / Kp_liver3) / V_liver2$
335 **!kidney**
336 $XP(48) = (Q_kidney * (X(45) - X(48) / fu) - PS2 * (X(48) -$
337 $X(60) / Kp_kidney3) / V_kidney$
338 $XP(60) = PS2 * (X(48) - X(60) / Kp_kidney3) / V_kidney2$
339 **!heart**
340 $XP(49) = (Q_heart * (X(45) - X(49) / fu) - PS3 * (X(49) -$
341 $X(61) / Kp_heart3) / V_heart$
342 $XP(61) = PS3 * (X(49) - X(61) / Kp_heart3) / V_heart2$
343 **!skin**
344 $XP(50) = (Q_skin * ft_s * (X(45) - X(50) / fu) - PS4 * (X(50) -$
345 $X(62) / Kp_skin3) / V_skin$
346 $XP(62) = PS4 * (X(50) - X(62) / Kp_skin3) / V_skin2$
347 **!muscle**
348 $XP(51) = (Q_muscle * ft_m * (X(45) - X(51) / fu) - PS4 * (X(51) -$
349 $X(63) / Kp_muscle3) / V_muscle$
350 $XP(63) = PS4 * (X(51) - X(63) / Kp_muscle3) / V_muscle2$
351 **!lung**
352 $XP(52) = (Q_lung * (X(58) - X(52) / fu) - PS2 * (X(52) -$
353 $X(64) / Kp_lung3) / V_lung$
354 $XP(64) = PS2 * (X(52) - X(64) / Kp_lung3) / V_lung2$
355 **!spleen**
356 $XP(53) = (Q_spleen * (X(45) - X(53) / fu) - PS2 * (X(53) -$
357 $X(65) / Kp_spleen3) / V_spleen$
358 $XP(65) = PS2 * (X(53) - X(65) / Kp_spleen3) / V_spleen2$
359 **!brain**
360 $XP(54) = (Q_brain * (X(45) - X(54) / fu) - PS3 * (X(54) -$
361 $X(66) / Kp_brain3) / V_brain$
362 $XP(66) = PS3 * (X(54) - X(66) / Kp_brain3) / V_brain2$
363 **!eye**
364 $XP(55) = Q_eye * ft_e * (X(45) - X(55) / Kp_eye3) / V_eye$

```

365 !carcass
366 XP(56)=Q_carcass*ft_c*(X(45)-X(56)/Kp_carcass3)/V_carcass
367 C-----C
368 C-----C
369 C
370 Return
371 End
372 C#####C
373 Subroutine OUTPUT(Y,T,X)
374 Implicit None
375 Include 'globals.inc'
376 Include 'model.inc'
377 Real*8 Y(MaxNOE),T,X(MaxNDE)
378 Real*8 Bmax_liver, Kp_liver, Kp_heart
379 Real*8 Kp_kidney, Bmax_kidney, Bmax_muscle, Bmax_blood, fu
380 Real*8 Bmax_heart, Kp_muscle, Kp_skin, Bmax_skin, KD
381 Real*8 Q_liver, Q_heart, Q_gut, Q_kidney, Q_skin, Q_muscle
382 Real*8 Q_eye, Q_slow, Q_rapid, Q_blood, Q_carcass, Kp_blood
383 Real*8 V_liver, V_kidney, V_muscle, V_blood, V_carcass, V_plasma
384 Real*8 V_heart, V_slow, V_rapid, V_skin, V_gut, Cl
385 Real*8 Vmaxr, Kmr, Vmaxl, Kml
386 Real*8 Vl_liver, Vl_kidney, Vl_heart, Vl_skin, Vl_muscle, Vl_carcass
387 Real*8 At_liver, At_kidney, At_heart, At_skin, At_muscle, At_carcass
388 Real*8 fnc, fnl, N1, N2, EN1, EN2, Pn, PD1, PD2, D1o, D1i, D2o, D2i
389 Real*8 V_liver2, V_kidney2, V_heart2, V_muscle2, V_skin2, V_lung2
390 real*8 V_spleen2, V_brain2
391 Real*8 V_lung
392 real*8 V_spleen, V_brain
393 CC
394 C-----C
395 C Enter Output Equations Below {e.g. Y(1) = X(1)/P(2) } C
396 C---c-----C
397 Y(1)=X(1)
398 Y(2)=X(23)
399 Y(3)=X(45)
400 C-----C
401 C-----C
402 C
403 Return
404 End
405 C#####C
406 Subroutine VARMOD(V,T,X,Y)
407 Implicit None
408 Include 'globals.inc'
409 Include 'model.inc'
410 Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
411 CC
412 C-----C
413 C Enter Variance Model Equations Below C
414 C {e.g. V(1) = (PV(1) + PV(2)*Y(1))**2 } C
415 C---c-----C
416 V(1) = (PV(2) + PV(1)*Y(1))**2
417 V(2) = (PV(2) + PV(1)*Y(2))**2

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```

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

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471 CC
472 C-----C
473 C Enter Values for Covariate Model Parameters C
474 C { e.g. PCI(1) = 2.0 } C
475 C---c-----C
476 C-----C
477 C-----C
478 C
479 Return
480 End
481 C#####C
482 Subroutine PRIOR(Pmean,Pcov,ICmean,ICcov)
483 C Parameter mean and covariance values for MAP estimation (ID,NPD,STS)
484 Implicit None
485 Include 'globals.inc'
486 Include 'model.inc'
487 Integer I,J
488 Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
489 Real*8 Pcov(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcov(MaxNDE,MaxNDE)
490 CC
491 C-----C
492 C Enter Nonzero Elements of Prior Mean Vector C
493 C { e.g. Pmean(1) = 10.0 } C
494 C---c-----C
495 CC
496 C-----C
497 C Enter Nonzero Elements of Covariance Matrix (Lower Triang.) C
498 C { e.g. Pcov(2,1) = 0.25 } C
499 C---c-----C
500 C-----C
501 C-----C
502 C
503 Return
504 End
505 C#####C
506 Subroutine SPARAM(PS,P,IC)
507 Implicit None
508 Include 'globals.inc'
509 Real*8 PS(MaxNSECP), P(MaxNSP+MaxNDE), IC(MaxNDE)
510 CC
511 C-----C
512 C Enter Equations Defining Secondary Paramters C
513 C { e.g. PS(1) = P(1)*P(2) } C
514 C---c-----C
515 C-----C
516 C-----C
517 C
518 Return
519 End
520 C#####C
521 Subroutine AMAT(A)
522 Implicit None
523 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
```