Model Script Supplemental Data

Content Summary

Murine Intravenous PBPK Model

[INDIVIDUAL]
input = {BW_pop, omega_BW, K2ki_pop, K2li_pop, K2lu_pop, K2ot_pop, K2sp_pop, Kkii2c_pop, Klii2c_pop, Klui2c_pop, Koti2c_pop, Kspi2c_pop, fu_pop, omega_Koti2c, omega_Kspi2c, omega_Klii2c, omega_Klui2c}

DEFINITION:
BW = {distribution=logNormal, typical=BW_pop, sd=omega_BW}
K2ki = {distribution=logNormal, typical=K2ki_pop, no-variability}
K2li = {distribution=logNormal, typical=K2li_pop, no-variability}
K2lu = {distribution=logNormal, typical=K2lu_pop, no-variability}
K2ot = {distribution=logNormal, typical=K2ot_pop, no-variability}
K2sp = {distribution=logNormal, typical=K2sp_pop, no-variability}
Kkii2c = {distribution=logNormal, typical=Kkii2c_pop, no-variability}
Klii2c = {distribution=logNormal, typical=Klii2c_pop, sd=omega_Klii2c}
Klui2c = {distribution=logNormal, typical=Klui2c_pop, sd=omega_Klui2c}
Koti2c = {distribution=logNormal, typical=Koti2c_pop, sd=omega_Koti2c}
Kspi2c = {distribution=logNormal, typical=Kspi2c_pop, sd=omega_Kspi2c}
fu = {distribution=logNormal, typical=fu_pop, no-variability}

[LONGITUDINAL]
input = {b1, b2, b3, b4, b5}
;;;; Included file '1599_IV_Model_Mice.txt'

input={Klui2c, K2lu, Klii2c, K2li, Kkii2c, K2ki, Kspi2c, K2sp, Koti2c, K2ot, BW, fu}

PK:
Vp = 0.00120*(BW/0.028) ;Volume of Venous Blood (L)
depot(adm = 1, target =C_Venous, p = BW/Vp) ;Concentration (mg/L) at mg Dose

EQUATION:

```
odeType=stiff

;Initial conditions
BP = 0.552              ; Blood to plasma ratio
;fu = 0.602             ; Fraction unbound in plasma
fu_ELF = 0.948          ; Fraction unbound in ELF

C_Venous_0 = 0 ; Initial Concentration in Plasma mg/L
C_Arterial_0 = 0
Cb_LU_0 = 0
C_C_Lung_0 = 0
Cb_SP_0 = 0
C_C_Spleen_0 = 0
Cb_LI_0 = 0
C_C_Liver_0 = 0
Cb_KI_0 = 0
C_C_Kidney_0 = 0
Cb_OT_0 = 0
C_C_Other_0 = 0
;C_ELF_0 = 0
;C_IT_0 = 0


; Physiological parameters (reference:PK-Sim)


AF = (BW/0.028)^0.75          #Allometry Scaling Factor

;Blood flow (L/h)
Q_Lung = 0.618*AF ;L/h
Q_Spleen = 0.00695*AF ;L/h
Q_Liver = 0.139*AF ;L/h
Q_Kidney = 0.1*AF ;L/h
Q_Other = 0.371*AF ;L/h
GFR = 0.0168*AF      ; L/h mouse GFR from Davies and Morris


;Organ volume (L) (reference: PK-Sim)

V_Venous = 0.00120*(BW/0.028)     ;L
V_Arterial = 0.000515*(BW/0.028)   ;L

V_Lung = 0.000204*(BW/0.028)
V_Lung_v = V_Lung*0.26  ;L
V_Lung_i = V_Lung*0.19  ;L
V_Lung_c = V_Lung*0.55  ;L
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V_Spleen = 0.000127*(BW/0.028)
V_Spleen_v = V_Spleen*0.22 ;L
V_Spleen_i = V_Spleen*0.2 ;L
V_Spleen_c = V_Spleen*0.58 ;L

V_Liver = 0.00193*(BW/0.028)
V_Liver_v = V_Liver*0.15 ;L
V_Liver_i = V_Liver*0.20 ;L
V_Liver_c = V_Liver*0.64 ;L

V_Kidney = 0.000525*(BW/0.028)
V_Kidney_v = V_Kidney*0.1 ;L
V_Kidney_i = V_Kidney*0.15 ;L
V_Kidney_c = V_Kidney*0.75 ;L

V_Other = 0.023483*(BW/0.028)
V_Other_v = V_Other*0.04 ;L
V_Other_i = V_Other*0.19 ;L
V_Other_c = V_Other*0.77 ;L

V_IT = 0.00005 ;L

Differential Equations

; $$$$$$$$$$$$ disposition of 1599 in Lung $$$$$$$

ddt_C_Venous = (Q_Liver*Cb_LI + Q_Kidney*Cb_KI + Q_Other*Cb_OT - Q_Lung*C_Venous)/V_Venous

C_Plasma = C_Venous/BP

; $$$$$$$$$$$$ disposition of 1599 in Lung $$$$$$$

; Vascular space

ddt_Cb_LU = (Q_Lung*(C_Venous - Cb_LU) - Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU + K2lu*C_C_Lung*V_Lung_c)/(V_Lung_v + (V_Lung_i/BP))

; Cellular Space

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ddt_C_C_Lung  = (Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU -
K2lu*C_C_Lung*V_Lung_c)/V_Lung_c


;ddt_C_ELF =  (-Klui2c*C_ELF*fu_ELF*V_ELF + K2lu*C_C_Lung*V_Lung_c -
Ka*fu_ELF*C_ELF*V_ELF + Ka*fu*Cb_LU*(V_Lung_v + V_Lung_i))/V_ELF


;ddt_C_IT =  -Ka*C_IT


; Lung Tissue

C_Lung = (C_C_Lung*V_Lung_c + Cb_LU*(V_Lung_v + (V_Lung_i/BP)))/V_Lung


;  $$$$$$$$$$$  disposition  of  1599  in  Arterial blood $$$$$$$


ddt_C_Arterial = (Q_Lung*(Cb_LU - C_Arterial))/V_Arterial


;  $$$$$$$$$$$  disposition  of  1599  in  Spleen $$$$$$$

;  Vascular  space

ddt_Cb_SP = (Q_Spleen*(C_Arterial - Cb_SP)  - Kspi2c*(V_Spleen_v +
(V_Spleen_i/BP))*fu*Cb_SP + K2sp*C_C_Spleen*V_Spleen_c)/(V_Spleen_v +
(V_Spleen_i/BP))

;  Cellular  Space

ddt_C_C_Spleen =( Kspi2c*(V_Spleen_v + (V_Spleen_i/BP))*fu*Cb_SP -
K2sp*C_C_Spleen*V_Spleen_c)/V_Spleen_c

; Spleen Tissue

C_Spleen = (C_C_Spleen*V_Spleen_c + Cb_SP*(V_Spleen_v +
(V_Spleen_i/BP)))/V_Spleen

;  $$$$$$$$$$$  disposition  of  1599  in  Liver $$$$$$$

;  Vascular  space
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```
ddt_Cb_LI = ((Q_Liver - Q_Spleen)*C_Arterial + Q_Spleen*Cb_SP  - Q_Liver*Cb_LI -
Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI +
K2li*C_C_Liver*V_Liver_c)/(V_Liver_v + (V_Liver_i/BP))

;  Cellular  Space


ddt_C_C_Liver = (Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI -
K2li*C_C_Liver*V_Liver_c)/V_Liver_c

; Liver Tissue


C_Liver = (C_C_Liver*V_Liver_c + Cb_LI*(V_Liver_v + (V_Liver_i/BP)))/V_Liver


;  $$$$$$$$$$$  disposition  of  1599  in  Kidney $$$$$$$

;  Vascular  space

ddt_Cb_KI = (Q_Kidney*C_Arterial - Q_Kidney*Cb_KI - Kkii2c*(V_Kidney_v +
(V_Kidney_i/BP))*fu*Cb_KI - GFR*fu*(Cb_KI/BP) +
K2ki*C_C_Kidney*V_Kidney_c)/(V_Kidney_v + (V_Kidney_i/BP))


;  Cellular  Space

ddt_C_C_Kidney = (Kkii2c*(V_Kidney_v + (V_Kidney_i/BP))*fu*Cb_KI -
K2ki*C_C_Kidney*V_Kidney_c)/V_Kidney_c


; Kidney Tissue

C_Kidney = (C_C_Kidney*V_Kidney_c + Cb_KI*(V_Kidney_v +
(V_Kidney_i/BP)))/V_Kidney


;  $$$$$$$$$$$  disposition  of  1599  in  Other $$$$$$$

;  Vascular  space

ddt_Cb_OT = (Q_Other*C_Arterial - Q_Other*Cb_OT - Koti2c*(V_Other_v +
(V_Other_i/BP))*fu*Cb_OT + K2ot*C_C_Other*V_Other_c)/(V_Other_v +
(V_Other_i/BP))

;  Cellular  Space
```

ddt_C_C_Other =(Koti2c*(V_Other_v + (V_Other_i/BP))*fu*Cb_OT - K2ot*C_C_Other*V_Other_c)/V_Other_c

; Other Tissue

C_Other = (C_C_Other*V_Other_c + Cb_OT*(V_Other_v + (V_Other_i/BP)))/V_Other

OUTPUT:
output = {C_Plasma, C_Lung, C_Liver, C_Kidney, C_Spleen}
;;;;

DEFINITION:
Plasma = {distribution=normal, prediction=C_Plasma, errorModel=proportional(b1)}
Lung = {distribution=normal, prediction=C_Lung, errorModel=proportional(b2)}
Liver = {distribution=normal, prediction=C_Liver, errorModel=proportional(b3)}
Kidney = {distribution=normal, prediction=C_Kidney, errorModel=proportional(b4)}
Spleen = {distribution=normal, prediction=C_Spleen, errorModel=proportional(b5)}

Murine Subcutaneous PBPK Model

[INDIVIDUAL]
input = {BW_pop, omega_BW, F_pop, K2ki_pop, K2li_pop, K2lu_pop, K2ot_pop, K2sp_pop, Ka_pop, Kkii2c_pop, Klii2c_pop, omega_Klii2c, Klui2c_pop, omega_Klui2c, Koti2c_pop, omega_Koti2c, Kspi2c_pop, omega_Kspi2c, fu_pop}

DEFINITION:
BW = {distribution=logNormal, typical=BW_pop, sd=omega_BW}
F = {distribution=logNormal, typical=F_pop, no-variability}
K2ki = {distribution=logNormal, typical=K2ki_pop, no-variability}
K2li = {distribution=logNormal, typical=K2li_pop, no-variability}
K2lu = {distribution=logNormal, typical=K2lu_pop, no-variability}
K2ot = {distribution=logNormal, typical=K2ot_pop, no-variability}
K2sp = {distribution=logNormal, typical=K2sp_pop, no-variability}
Ka = {distribution=logNormal, typical=Ka_pop, no-variability
Kkii2c = {distribution=logNormal, typical=Kkii2c_pop, no-variability}
Klii2c = {distribution=logNormal, typical=Klii2c_pop, sd=omega_Klii2c}
Klui2c = {distribution=logNormal, typical=Klui2c_pop, sd=omega_Klui2c}
Koti2c = {distribution=logNormal, typical=Koti2c_pop, sd=omega_Koti2c}
Kspi2c = {distribution=logNormal, typical=Kspi2c_pop, sd=omega_Kspi2c}

```
fu = {distribution=logNormal, typical=fu_pop, no-variability}

[LONGITUDINAL]
input = {b1, b2, b3, b4, b5}
;;;; Included file '1599_SC_Model_Mice_Final.txt'

input={Klui2c, K2lu, Klii2c, K2li, Kkii2c, K2ki, Kspi2c, K2sp, Koti2c, K2ot, BW, fu,
Ka, F}


PK:
Vp = 0.00005                                    ;SC Injection Volume (L)
depot(adm = 1, target =C_SC, p = F*BW/Vp)       ;Concentration (mg/L) at mg Dose



EQUATION:
odeType=stiff

;Initial conditions
BP = 0.552          ; Blood to plasma ratio
;fu = 0.602         ; Fraction unbound in plasma
fu_ELF = 0.948      ; Fraction unbound in ELF

C_Venous_0 = 0 ; Initial Concentration in Plasma Âµg/mL
C_Arterial_0 = 0
Cb_LU_0 = 0
C_C_Lung_0 = 0
Cb_SP_0 = 0
C_C_Spleen_0 = 0
Cb_LI_0 = 0
C_C_Liver_0 = 0
Cb_KI_0 = 0
C_C_Kidney_0 = 0
Cb_OT_0 = 0
C_C_Other_0 = 0
C_ELF_0 = 0
;C_IT_0 = 0
C_SC_0 = 0


; Physiological parameters (reference:PK-Sim)


AF = (BW/0.028)^0.75        #Allometry Scaling Factor
```

```
;Blood flow (L/h)
Q_Lung = 0.618*AF ;L/h
Q_Spleen = 0.00695*AF ;L/h
Q_Liver = 0.139*AF ;L/h
Q_Kidney = 0.1*AF ;L/h
Q_Other = 0.371*AF ;L/h
GFR = 0.0168*AF      ; L/h mouse GFR from Davies and Morris


;Organ volume (L) (reference: PK-Sim)

V_Venous = 0.00120*(BW/0.028)     ;L
V_Arterial = 0.000515*(BW/0.028)   ;L

V_Lung = 0.000194*(BW/0.028)
V_Lung_v = V_Lung*0.26  ;L
V_Lung_i = V_Lung*0.19  ;L
V_Lung_c = V_Lung*0.55  ;L

V_Spleen = 0.000127*(BW/0.028)
V_Spleen_v = V_Spleen*0.22 ;L
V_Spleen_i = V_Spleen*0.2 ;L
V_Spleen_c = V_Spleen*0.58 ;L

V_Liver = 0.00193*(BW/0.028)
V_Liver_v = V_Liver*0.15 ;L
V_Liver_i = V_Liver*0.20 ;L
V_Liver_c = V_Liver*0.64 ;L

V_Kidney = 0.000525*(BW/0.028)
V_Kidney_v = V_Kidney*0.1 ;L
V_Kidney_i = V_Kidney*0.15 ;L
V_Kidney_c = V_Kidney*0.75 ;L

V_Other = 0.023483*(BW/0.028)
V_Other_v = V_Other*0.04 ;L
V_Other_i = V_Other*0.19 ;L
V_Other_c = V_Other*0.77 ;L

V_ELF = 0.00001*(BW/0.028)
V_IT = 0.00005 ;L
V_SC = 0.00005 ;L

KaIT = 4.67              ;hr-1
```

Differential Equations

;SC Dosing

ddt_C_SC = -Ka*C_SC

; disposition of 1599 in Plasma

ddt_C_Venous = (Ka*C_SC*V_SC + Q_Liver*Cb_LI + Q_Kidney*Cb_KI + Q_Other*Cb_OT - Q_Lung*C_Venous)/V_Venous

C_Plasma = C_Venous/BP

; $$$$$$$$$$$$ disposition of 1599 in Lung $$$$$$$

; Vascular space

ddt_Cb_LU = (Q_Lung*(C_Venous - Cb_LU) - Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU + K2lu*C_C_Lung*V_Lung_c + KaIT*fu_ELF*C_ELF*V_ELF - KaIT*fu*Cb_LU*(V_Lung_v + (V_Lung_i/BP)))/(V_Lung_v + (V_Lung_i/BP))

; Cellular Space

ddt_C_C_Lung = (Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU - K2lu*C_C_Lung*V_Lung_c + Klui2c*fu_ELF*C_ELF*V_ELF)/V_Lung_c

ddt_C_ELF = (-Klui2c*C_ELF*fu_ELF*V_ELF + K2lu*C_C_Lung*V_Lung_c - KaIT*fu_ELF*C_ELF*V_ELF + KaIT*fu*Cb_LU*(V_Lung_v + (V_Lung_i/BP)))/V_ELF

;ddt_C_IT = -Ka*C_IT

; Lung Tissue

C_Lung = (C_C_Lung*V_Lung_c + Cb_LU*(V_Lung_v + (V_Lung_i/BP)) + C_ELF*V_ELF)/(V_Lung + V_ELF)

; $$$$$$$$$$$$ disposition of 1599 in Arterial blood $$$$$$$

ddt_C_Arterial = (Q_Lung*(Cb_LU - C_Arterial))/V_Arterial

; $$$$$$$$$$$ disposition of 1599 in Spleen $$$$$$

; Vascular space

ddt_Cb_SP = (Q_Spleen*(C_Arterial - Cb_SP) - Kspi2c*(V_Spleen_v + (V_Spleen_i/BP))*fu*Cb_SP + K2sp*C_C_Spleen*V_Spleen_c)/(V_Spleen_v + (V_Spleen_i/BP))

; Cellular Space

ddt_C_C_Spleen =(Kspi2c*(V_Spleen_v + (V_Spleen_i/BP))*fu*Cb_SP - K2sp*C_C_Spleen*V_Spleen_c)/V_Spleen_c

; Spleen Tissue

C_Spleen = (C_C_Spleen*V_Spleen_c + Cb_SP*(V_Spleen_v + (V_Spleen_i/BP)))/V_Spleen

; $$$$$$$$$$$ disposition of 1599 in Liver $$$$$$

; Vascular space

ddt_Cb_LI = ((Q_Liver - Q_Spleen)*C_Arterial + Q_Spleen*Cb_SP - Q_Liver*Cb_LI - Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI + K2li*C_C_Liver*V_Liver_c)/(V_Liver_v + (V_Liver_i/BP))

; Cellular Space

ddt_C_C_Liver = (Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI - K2li*C_C_Liver*V_Liver_c)/V_Liver_c

; Liver Tissue

C_Liver = (C_C_Liver*V_Liver_c + Cb_LI*(V_Liver_v + (V_Liver_i/BP)))/V_Liver

; $$$$$$$$$$$ disposition of 1599 in Kidney $$$$$$

; Vascular space

ddt_Cb_KI = (Q_Kidney*C_Arterial - Q_Kidney*Cb_KI - Kkii2c*(V_Kidney_v + (V_Kidney_i/BP))*fu*Cb_KI - GFR*fu*(Cb_KI/BP) + K2ki*C_C_Kidney*V_Kidney_c)/(V_Kidney_v + (V_Kidney_i/BP))

; Cellular Space

ddt_C_C_Kidney = (Kkii2c*(V_Kidney_v + (V_Kidney_i/BP))*fu*Cb_KI - K2ki*C_C_Kidney*V_Kidney_c)/V_Kidney_c

; Kidney Tissue

C_Kidney = (C_C_Kidney*V_Kidney_c + Cb_KI*(V_Kidney_v + (V_Kidney_i/BP)))/V_Kidney

; $$$$$$$$$$$ disposition of 1599 in Other $$$$$$

; Vascular space

ddt_Cb_OT = (Q_Other*C_Arterial - Q_Other*Cb_OT - Koti2c*(V_Other_v + (V_Other_i/BP))*fu*Cb_OT + K2ot*C_C_Other*V_Other_c)/(V_Other_v + (V_Other_i/BP))

; Cellular Space

ddt_C_C_Other =(Koti2c*(V_Other_v + (V_Other_i/BP))*fu*Cb_OT - K2ot*C_C_Other*V_Other_c)/V_Other_c

; Other Tissue

C_Other = (C_C_Other*V_Other_c + Cb_OT*(V_Other_v + (V_Other_i/BP)))/V_Other

OUTPUT:
output = {C_Plasma, C_Lung, C_Liver, C_Spleen, C_ELF}
;;;;

DEFINITION:
Plasma = {distribution=normal, prediction=C_Plasma, errorModel=proportional(b1)}
Lung = {distribution=normal, prediction=C_Lung, errorModel=proportional(b2)}

Liver = {distribution=normal, prediction=C_Liver, errorModel=proportional(b3)}
Spleen = {distribution=normal, prediction=C_Spleen, errorModel=proportional(b4)}
ELF = {distribution=normal, prediction=C_ELF, errorModel=proportional(b5)}

Murine Intrapulmonary Aerosol PKPB Model

[INDIVIDUAL]
input = {BW_pop, F_pop, K2ki_pop, K2li_pop, K2lu_pop, K2ot_pop, K2sp_pop, Ka_pop, Kkii2c_pop, Klii2c_pop, Klui2c_pop, Koti2c_pop, Kspi2c_pop, fu_pop, omega_Klui2c, omega_Klii2c, omega_Kspi2c, omega_Koti2c, omega_BW}

DEFINITION:
BW = {distribution=logNormal, typical=BW_pop, sd=omega_BW}
F = {distribution=logNormal, typical=F_pop, no-variability}
K2ki = {distribution=logNormal, typical=K2ki_pop, no-variability}
K2li = {distribution=logNormal, typical=K2li_pop, no-variability}
K2lu = {distribution=logNormal, typical=K2lu_pop, no-variability}
K2ot = {distribution=logNormal, typical=K2ot_pop, no-variability}
K2sp = {distribution=logNormal, typical=K2sp_pop, no-variability}
Ka = {distribution=logNormal, typical=Ka_pop, no-variability}
Kkii2c = {distribution=logNormal, typical=Kkii2c_pop, no-variability}
Klii2c = {distribution=logNormal, typical=Klii2c_pop, sd=omega_Klii2c}
Klui2c = {distribution=logNormal, typical=Klui2c_pop, sd=omega_Klui2c}
Koti2c = {distribution=logNormal, typical=Koti2c_pop, sd=omega_Koti2c}
Kspi2c = {distribution=logNormal, typical=Kspi2c_pop, sd=omega_Kspi2c}
fu = {distribution=logNormal, typical=fu_pop, no-variability}

[LONGITUDINAL]
input = {b1, b2, b3, b4, b5}
;;;; Included file '1599_IT_Model_Mice_Final.txt'

input={Klui2c, K2lu, Klii2c, K2li, Kkii2c, K2ki, Kspi2c, K2sp, Koti2c, K2ot, BW, fu, Ka, F}

PK:
Vp = 0.00005 ;SC Injection Volume (L)
depot(adm = 1, target =C_IT, p = F*BW/Vp) ;Concentration (mg/L) at mg Dose

EQUATION:
odeType=stiff

;Initial conditions
BP = 0.552 ; Blood to plasma ratio
;fu = 0.602 ; Fraction unbound in plasma
fu_ELF = 0.948 ; Fraction unbound in ELF

```
C_Venous_0 = 0 ; Initial Concentration in Plasma Âµg/mL
C_Arterial_0 = 0
Cb_LU_0 = 0
C_C_Lung_0 = 0
Cb_SP_0 = 0
C_C_Spleen_0 = 0
Cb_LI_0 = 0
C_C_Liver_0 = 0
Cb_KI_0 = 0
C_C_Kidney_0 = 0
Cb_OT_0 = 0
C_C_Other_0 = 0
C_ELF_0 = 0
C_IT_0 = 0
C_SC_0 = 0


; Physiological parameters (reference:PK-Sim)


AF = (BW/0.028)^0.75          #Allometric Scaling Factor

;Blood flow (L/h)
Q_Lung = 0.618*AF ;L/h
Q_Spleen = 0.00695*AF ;L/h
Q_Liver = 0.139*AF ;L/h
Q_Kidney = 0.1*AF ;L/h
Q_Other = 0.371*AF ;L/h
GFR = 0.0168*AF      ; L/h mouse GFR from Davies and Morris


;Organ volume (L) (reference: PK-Sim)

V_Venous = 0.00120*(BW/0.028)     ;L
V_Arterial = 0.000515*(BW/0.028)   ;L

V_Lung = 0.000194*(BW/0.028)
V_Lung_v = V_Lung*0.26  ;L
V_Lung_i = V_Lung*0.19  ;L
V_Lung_c = V_Lung*0.55  ;L

V_Spleen = 0.000127*(BW/0.028)
V_Spleen_v = V_Spleen*0.22 ;L
V_Spleen_i = V_Spleen*0.2 ;L
V_Spleen_c = V_Spleen*0.58 ;L
```

V_Liver = 0.00193*(BW/0.028)
V_Liver_v = V_Liver*0.15 ;L
V_Liver_i = V_Liver*0.20 ;L
V_Liver_c = V_Liver*0.64 ;L

V_Kidney = 0.000525*(BW/0.028)
V_Kidney_v = V_Kidney*0.1 ;L
V_Kidney_i = V_Kidney*0.15 ;L
V_Kidney_c = V_Kidney*0.75 ;L

V_Other = 0.023483*(BW/0.028)
V_Other_v = V_Other*0.04 ;L
V_Other_i = V_Other*0.19 ;L
V_Other_c = V_Other*0.77 ;L

V_ELF = 0.00001*(BW/0.028)
V_IT = 0.00005 ;L
V_SC = 0.00005 ;L

;KaIT = 4.67 ;hr-1

Differential Equations

; disposition of 1599 in Plasma

ddt_C_Venous = (Q_Liver*Cb_LI + Q_Kidney*Cb_KI + Q_Other*Cb_OT - Q_Lung*C_Venous)/V_Venous

C_Plasma = C_Venous/BP

; $$$$$$$$$$$ disposition of 1599 in Lung $$$$$$$

; Vascular space

ddt_Cb_LU = (Q_Lung*(C_Venous - Cb_LU) - Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU + K2lu*C_C_Lung*V_Lung_c + Ka*fu_ELF*C_ELF*V_ELF - Ka*fu*Cb_LU*(V_Lung_v + (V_Lung_i/BP)))/(V_Lung_v + (V_Lung_i/BP))

; Cellular Space

ddt_C_C_Lung = (Klui2c*(V_Lung_v + (V_Lung_i/BP))*fu*Cb_LU - K2lu*C_C_Lung*V_Lung_c + Klui2c*fu_ELF*C_ELF*V_ELF)/V_Lung_c

ddt_C_ELF = (Ka*C_IT*V_IT - Klui2c*C_ELF*fu_ELF*V_ELF + K2lu*C_C_Lung*V_Lung_c - Ka*fu_ELF*C_ELF*V_ELF + Ka*fu*Cb_LU*(V_Lung_v + (V_Lung_i/BP)))/V_ELF

#IPA Dosing

ddt_C_IT = -Ka*C_IT

; Lung Tissue

C_Lung = (C_C_Lung*V_Lung_c + Cb_LU*(V_Lung_v + (V_Lung_i/BP)) + C_ELF*V_ELF)/(V_Lung + V_ELF)

; $$$$$$$$$$$ disposition of 1599 in Arterial blood $$$$$$$

ddt_C_Arterial = (Q_Lung*(Cb_LU - C_Arterial))/V_Arterial

; $$$$$$$$$$$ disposition of 1599 in Spleen $$$$$$$

; Vascular space

ddt_Cb_SP = (Q_Spleen*(C_Arterial - Cb_SP) - Kspi2c*(V_Spleen_v + (V_Spleen_i/BP))*fu*Cb_SP + K2sp*C_C_Spleen*V_Spleen_c)/(V_Spleen_v + (V_Spleen_i/BP))

; Cellular Space

ddt_C_C_Spleen =(Kspi2c*(V_Spleen_v + (V_Spleen_i/BP))*fu*Cb_SP - K2sp*C_C_Spleen*V_Spleen_c)/V_Spleen_c

; Spleen Tissue

C_Spleen = (C_C_Spleen*V_Spleen_c + Cb_SP*(V_Spleen_v + (V_Spleen_i/BP)))/V_Spleen

; $$$$$$$$$$$ disposition of 1599 in Liver $$$$$$$

; Vascular space

```
ddt_Cb_LI = ((Q_Liver - Q_Spleen)*C_Arterial + Q_Spleen*Cb_SP  - Q_Liver*Cb_LI -
Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI +
K2li*C_C_Liver*V_Liver_c)/(V_Liver_v + (V_Liver_i/BP))

;  Cellular  Space


ddt_C_C_Liver = (Klii2c*(V_Liver_v + (V_Liver_i/BP))*fu*Cb_LI -
K2li*C_C_Liver*V_Liver_c)/V_Liver_c

; Liver Tissue


C_Liver = (C_C_Liver*V_Liver_c + Cb_LI*(V_Liver_v + (V_Liver_i/BP)))/V_Liver


;  $$$$$$$$$$$  disposition  of  1599  in  Kidney $$$$$$$

;  Vascular  space

ddt_Cb_KI = (Q_Kidney*C_Arterial - Q_Kidney*Cb_KI - Kkii2c*(V_Kidney_v +
(V_Kidney_i/BP))*fu*Cb_KI - GFR*fu*(Cb_KI/BP) +
K2ki*C_C_Kidney*V_Kidney_c)/(V_Kidney_v + (V_Kidney_i/BP))


;  Cellular  Space

ddt_C_C_Kidney = (Kkii2c*(V_Kidney_v + (V_Kidney_i/BP))*fu*Cb_KI -
K2ki*C_C_Kidney*V_Kidney_c)/V_Kidney_c


; Kidney Tissue

C_Kidney = (C_C_Kidney*V_Kidney_c + Cb_KI*(V_Kidney_v +
(V_Kidney_i/BP)))/V_Kidney


;  $$$$$$$$$$$  disposition  of  1599  in  Other $$$$$$$

;  Vascular  space

ddt_Cb_OT = (Q_Other*C_Arterial - Q_Other*Cb_OT - Koti2c*(V_Other_v +
(V_Other_i/BP))*fu*Cb_OT + K2ot*C_C_Other*V_Other_c)/(V_Other_v +
(V_Other_i/BP))

;  Cellular  Space
```

ddt_C_C_Other =(Koti2c*(V_Other_v + (V_Other_i/BP))*fu*Cb_OT -
K2ot*C_C_Other*V_Other_c)/V_Other_c

; Other Tissue

C_Other = (C_C_Other*V_Other_c + Cb_OT*(V_Other_v + (V_Other_i/BP)))/V_Other

OUTPUT:
output = {C_Plasma, C_Lung, C_Liver, C_Spleen, C_ELF}
;;;;

DEFINITION:
Plasma = {distribution=normal, prediction=C_Plasma, errorModel=proportional(b1)}
Lung = {distribution=normal, prediction=C_Lung, errorModel=proportional(b2)}
Liver = {distribution=normal, prediction=C_Liver, errorModel=proportional(b3)}
Spleen = {distribution=normal, prediction=C_Spleen, errorModel=proportional(b4)}
ELF = {distribution=normal, prediction=C_ELF, errorModel=proportional(b5)}