A Permeability- and Perfusion-based PBPK model for Improved Prediction of Concentration-time Profiles

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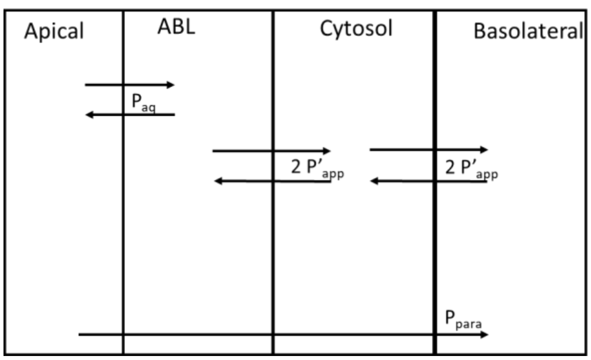
Supplementary Material

1. Derivation of Equations:

Derivation of Eq. 1

$$\boldsymbol{P_{app,cor}} = \frac{\boldsymbol{P_{aq}P_{app} - P_{aq}P_{para}}}{\boldsymbol{P_{aq} + P_{para} - P_{app}}} \qquad \text{Eq. 1}$$

Eq. 1 is derived with the use of net clearance concepts in the accompanying tutorial. Briefly, the derivation is as follows.



Consider the Figure above, where P_{aq} is aqueous boundry layer (ABL) permeability and P_{para} is paracellular permeability. Using net clearances, we know that the permeability across the apical and the basolateral membranes is 2 P'_{app} (Nagar and Korzekwa, DMD 2012; 40: 1649). Thus, the permeability from ABL to basolateral will be the true or 'corrected' permeability or $P_{app,cor}$. A net permeability through a species is the permeability moving forward across the species times the fraction that moves forward. Thus,

$$\boldsymbol{P_{app,corr}} = \frac{\boldsymbol{2\,P'_{app}2\,P'_{app}}}{\boldsymbol{2\,P'_{app} + 2\,P'_{app}}} = \boldsymbol{P'_{app}} \qquad \text{Eq. S1}$$

The permeability from apical to basolateral compartment P_{app} can now we written as the sum of the net permeability from apical to basolateral and the paracellular permeability from apical to basolateral:

$$\boldsymbol{P_{app}} = \frac{\boldsymbol{P_{aq}P_{app,cor}}}{\boldsymbol{P_{aq} + P_{app,cor}}} + \boldsymbol{P_{para}} \qquad \text{Eq. S2}$$

Algebraic rearrangement to solve for $P_{app,cor}$ gives eq. 1.

Derivation of Eq. 3-5

$$\boldsymbol{BP_{corr} = BP - \frac{P_{app,lp}}{P_{app,lp}+P_{app}} f_{up}Hct} \qquad \text{Eq. 3}$$

$$\boldsymbol{BP_{C0} = BP - f_{up}Hct} \qquad \text{Eq. 4}$$

$$\boldsymbol{K_{ery,C0} = \frac{BP_{C0}-(1-Hct)}{f_{up}Hct}} \qquad \text{Eq. 5}$$

For the general concept of blood-to-plasma ratio and erythrocyte partition coefficient, it is useful to start with the mass balance and subsequent steps as detailed in Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications, Appendix D Plasma-to-blood concentration ratio.

The only difference in the present work is the consideration of RBC partitioning of drugs as two components: partitioning into the RBC cytosol, and partitioning into the external RBC membrane (hypothesized partitioning into endothelial glycocalyx).

Thus,

Amount in blood = Amount in plasma + Amount in RBC

Therefore, for either a low-permeability drug or for considering the 'shallow' compartment C0, assuming a fast equilibrium between the drug and the external RBC,

Amount in blood = Amount in plasma + (Total amount in RBC – amount in RBC cytosol)

$C_BV_B = C_pV_p + (C_{RBC}V_{RBC} - C_uV_{RBC})$ Eq. S3

Substituting in hematocrit (Hct) for V_{RBC}/V_B, and $(1\text{-Hct})V_B$ for V_p,

$C_BV_B = C_p(1\text{-Hct})V_B + (C_{RBC}HctV_B - C_u\ HctV_B)$ Eq. S4

Dividing throughout by C_pV_B gives the blood-to-plasma (BP') ratio, C_B/C_p:

$C_B/C_p = 1\text{-Hct} + Hct\ (C_{RBC}/C_p) - f_{up}\ Hct$ Eq. S5

Where $f_{up}=C_u/C_p$. Defining the RBC partition ratio as $K_{pBC} = C_{RBC}/C_u$,

$C_B/C_p = 1+Hct[f_{up}\ K_{pBC} - f_{up} - 1]$ Eq. S6

Comparing eq. S5 for BP' with the equation for BP [Appendix B, Rowland and Tozer text], one can easily see that

$BP' = BP - f_{up}\ Hct$ Eq. S7

A special case of eq. S7 can be derived for low-permeability drugs, where a fast equilibrium between the drug and the external RBC may be missed in an experimental BP; thus, where P_{app} (the MDCK or Caco-2 permeability (10^{-6} cm/sec)), and $P_{app,lp}$ (a low permeability constant set to $2\text{x}10^{-6}$ cm/sec) are used to provide a correction to the experimental BP:

$$\boldsymbol{BP_{corr} = BP - \frac{P_{app,lp}}{P_{app,lp}+P_{app}} f_{up}Hct} \qquad \text{Eq. 3}$$

Thus, for a low permeability drug, the term $P_{app} << P_{app,lp}$ and 'f_{up} Hct' will be subtracted from BP. Eq. S7 can be written for the special case of a shallow compartment C0 as:

$$\boldsymbol{BP_{C0} = BP - f_{up}Hct} \qquad \text{Eq. 4}$$

Finally, analogous to K_{pBC}, we define the partition coefficient for external association with erythrocytes ($K_{ery,C0}$) as $K_{ery,C0} = (C_{RBC}\text{-}C_u)/C_u$. Thus, $K_{ery,C0} = K_{pBC} - 1$, or from eq. S5,

$BP_{C0} = 1\text{-Hct} + f_{up}\ Hct\ [(C_{RBC}\text{-}C_u)/C_u)]$ Eq. S8

Substituting in and solving for $K_{ery,C0} = (C_{RBC}\text{-}C_u)/C_u$ gives:

$$\boldsymbol{K_{ery,C0} = \frac{BP_{C0}-(1-Hct)}{f_{up}Hct}} \qquad \text{Eq. 5}$$

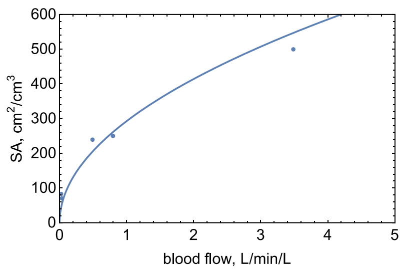
2. Model for capillary SA prediction from blood flow

Tissue	SA	flow
	cm2/cm3	L/min/L
adipose	83	0.0227929
brain	240	0.487857
kidney	500	3.4871
liver	250	0.797253
muscle	70	0.0345357

Data from Crone (26) and Belcik (27). Kidney SA was divided by 0.7 since the reported value was for the cortex only. SA was assumed to be proportiolnal to flow^{½} by dimensional analysis:

$SA = a \text{ flow}^{0.5}$
Weighting 1/Y
$R^2 = 0.97$

Param	Estimate	Std Error	t-Statistic	P-Value
a	292.778	24.7439	11.8323	0.000292



3. References for Table 2

References for training set experimental data in Table 2 are provided below.

f_{up} [1-22]

f_{um} [3, 7, 15, 17, 21, 23-33]

BP [5, 7, 17, 34-40]

P_{app} [2, 41-57]

References for test set experimental data in Table 2 are provided below.

Aprepitant [58-61]

Bumetanide [62-65]

Buprenorphine [66, 67]

Ciprofloxacin [58, 68-72]

Zidovudine [17, 71-74]

Clinical Data References: Cefazolin [75], Diclofenac [76], Furosemide [77], Glyburide [78], Ketoprofen [79], Nafcillin [80], Warfarin [81], Caffeine [82], Diazepam [83], Fluconazole [84], Midazolam [85], Phenytoin [86], Atenolol [87], Betaxolol [88], Carvedilol [89], Diltiazem [90], Diphenhydramine [91], Imipramine [92], Metoprolol [93], Mibefradil [94], Quinidine [95], Ranitidine [96], Terbutaline [97], Verapamil [98], Aprepitant [99], Bumetanide [100], Buprenorphine [101], Ciprofloxacin [102], Zidovudine [103]

References for fe: [104]

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4. Mathematica code for Rodgers and Rowland, memPBPK, and PermQ

Models for Rodgers and Rowland, memPBPK, and PermQ

Drug specific parameters

```
In[]:= ClearAll["Global`*"];

In[]:= SetDirectory["/Users/swatinagar/Dropbox/PermQ"];

In[]:= drugfile = "DatainputPQ11.xlsx";

In[]:= speciesfile = "species.10.xlsx";

In[]:= sheet = 6;

In[]:= {name, class, logp, fup, fum, pkaa, pkab, bp, logdvo, anflag, bflag, pappsec, mw} =
         {"Midazolam", "neutral", 3.15, 0.0345, 0.68,
          14., 6.01, 0.71, 2.16225, 0., 1., 0.0000424, 325.8};

In[]:= name
Out[]= Midazolam

In[]:= dose = 10.;

In[]:= ntp = 15;

In[]:= ivduration = 1.;

In[]:= fe = 0.;

In[]:= avgwt = 70.;

In[]:= kinf = dose / ivduration
Out[]= 10.

In[]:= tt = {5., 10., 15., 30., 45., 60., 90., 120., 180., 240., 300., 360., 480., 600., 720.};

In[]:= ct = {0.321548, 0.264365, 0.244248, 0.204901, 0.164813, 0.140331, 0.105878, 0.0827978,
          0.0489842, 0.0363431, 0.0254625, 0.0196616, 0.00918061, 0.00810542, 0.00713468};

In[]:= ctt = {{5., 0.321548}, {10., 0.264365}, {15., 0.244248}, {30., 0.204901},
         {45., 0.164813}, {60., 0.140331}, {90., 0.105878}, {120., 0.0827978},
         {180., 0.0489842}, {240., 0.0363431}, {300., 0.0254625}, {360., 0.0196616},
         {480., 0.00918061}, {600., 0.00810542}, {720., 0.00713468}}
Out[]= {{5., 0.321548}, {10., 0.264365}, {15., 0.244248}, {30., 0.204901},
        {45., 0.164813}, {60., 0.140331}, {90., 0.105878}, {120., 0.0827978},
        {180., 0.0489842}, {240., 0.0363431}, {300., 0.0254625}, {360., 0.0196616},
        {480., 0.00918061}, {600., 0.00810542}, {720., 0.00713468}}
```

In[∘]:=
```
pow = 10^logp;
```

In[∘]:=
```
dvo = 10^logdvo;
```

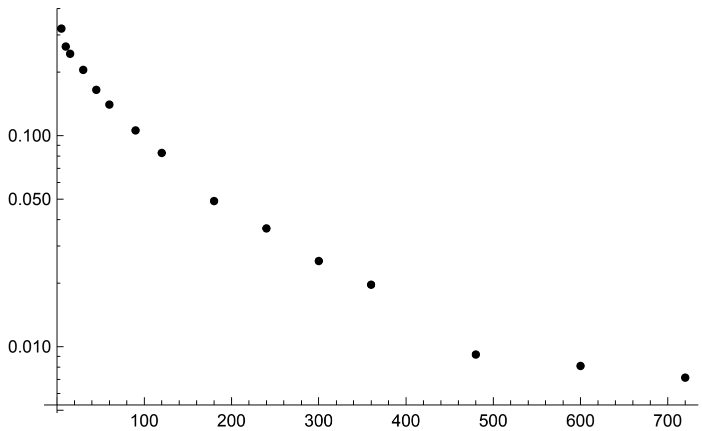
Apply to drug PK model for an IV infusion dose.

In[∘]:=
```
ClearAll[modelpkiv1, modelpkiv2]
```

In[∘]:=
```
colort = {Red, Blue, Orange, Green, Purple, Cyan, Brown};
```

In[∘]:=
```
plotfit1 = ListLogPlot[ctt, PlotStyle → Black]
```

Out[∘]=



In[∘]:=
```
k12init = 0.06;
k21init = 0.09;
k13init = 0.005;
k31init = 0.005;
k10init = 0.01;
V1init = 30;
kinf = dose / ivduration
```

Out[∘]=
```
10.
```

In[∘]:=
```
ClearAll[k12, k21, k13, k31, k10, V1, modelpkiv1, fitiv];
modelpkiv1[k12_?NumericQ, k21_?NumericQ, k13_?NumericQ,
   k31_?NumericQ, k10_?NumericQ, V1_?NumericQ, te_?NumericQ] :=
  (model1[k12, k21, k13, k31, k10, V1][t] = (Xc[te] / V1) /.
     First[NDSolve[{Xc'[t] == k0[t] - (k12 + k13 + k10) Xc[t] + k21 Xp1[t] + k31 Xp2[t],
         Xp1'[t] == k12 Xc[t] - k21 Xp1[t],
         Xp2'[t] == k13 Xc[t] - k31 Xp2[t],
         k0'[t] == 0,
         Xc[0] == 0,
         Xp1[0] == 0,
         Xp2[0] == 0,
         k0[0] == kinf, WhenEvent[t == ivduration, k0[t] → 0.]},
    {Xc, Xp1, Xp2, k0},
       {t, 0, 1.5 ctt[[ntp, 1]]}, MaxSteps → 100 000, PrecisionGoal → ∞]])
```

```
In[ ]:= fitiv = NonlinearModelFit[ctt,
    modelpkiv1[k12, k21, k13, k31, k10, V1, te], {{k12, k12init}, {k21, k21init},
     {k13, k13init}, {k31, k31init}, {k10, k10init}, {V1, V1init}},
    {te}, PrecisionGoal → ∞, MaxIterations → 100 000, Weights → (1 / #2 &)]
```

Out[∘]= FittedModel[modelpkiv1[0.076191, 0.152248, 0.00508624, ≪21≫, ≪21≫, 22.6398, te]]

In[∘]:= fitiv["ParameterTable"]

Out[∘]=

	Estimate	Standard Error	t-Statistic	P-Value
k12	0.076191	0.0623857	1.22129	0.253002
k21	0.152248	0.0574936	2.64809	0.0265592
k13	0.00508624	0.00148771	3.41884	0.00764189
k31	0.00525378	0.00136166	3.85836	0.00385672
k10	0.012971	0.00244904	5.29637	0.000496235
V1	22.6398	4.30817	5.25509	0.000524143

In[∘]:= fitiv["RSquared"]

Out[∘]= 0.998783

In[∘]:= fitiv["AICc"]

Out[∘]= -101.582

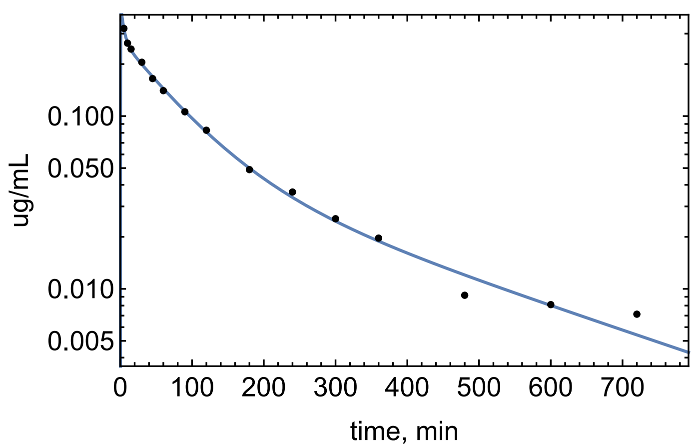
In[∘]:= TableForm[fitiv["CorrelationMatrix"]]

Out[∘]//TableForm=

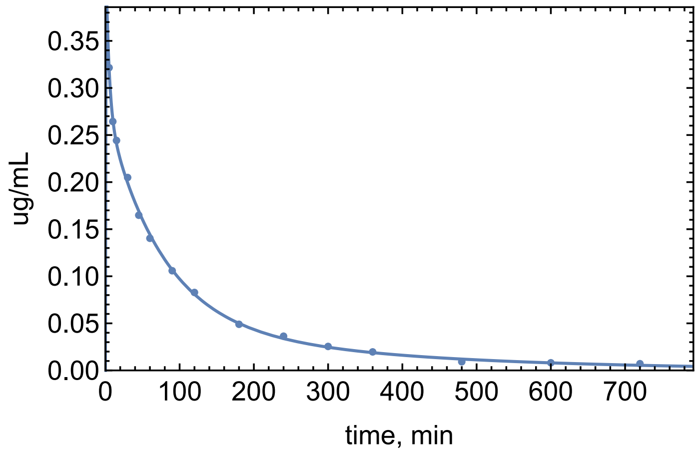
1.	0.914652	0.854205	0.236037	0.9762	-0.981913
0.914652	1.	0.868922	0.393688	0.841364	-0.835222
0.854205	0.868922	1.	0.537698	0.846988	-0.838582
0.236037	0.393688	0.537698	1.	0.27543	-0.201842
0.9762	0.841364	0.846988	0.27543	1.	-0.991668
-0.981913	-0.835222	-0.838582	-0.201842	-0.991668	1.

```
In[∘]:= k12 = fitiv["BestFitParameters"]⟦1, 2⟧;

In[∘]:= k21 = fitiv["BestFitParameters"]⟦2, 2⟧;

In[∘]:= k13 = fitiv["BestFitParameters"]⟦3, 2⟧;

In[∘]:= k31 = fitiv["BestFitParameters"]⟦4, 2⟧;

In[∘]:= k10 = fitiv["BestFitParameters"]⟦5, 2⟧;

In[∘]:= V1 = fitiv["BestFitParameters"]⟦6, 2⟧;

In[∘]:= ClearAll[modelpkiv2];
modelpkiv2 =
  First[NDSolve[{Xc'[t] == k0[t] - (k12 + k13 + k10) Xc[t] + k21 Xp1[t] + k31 Xp2[t],
     Xp1'[t] == k12 Xc[t] - k21 Xp1[t],
     Xp2'[t] == k13 Xc[t] - k31 Xp2[t],
     k0'[t] == 0,
     Xc[0] == 0,
     Xp1[0] == 0,
     Xp2[0] == 0,
     k0[0] == kinf, WhenEvent[t == ivduration, k0[t] → 0.]},
   {Xc, Xp1, Xp2, k0}, {t, 0, 100 000}, MaxSteps → 100 000, PrecisionGoal → ∞]];
```

```
In[]:= auc = NIntegrate[(Xc[t] / V1) /. modelpkiv2, {t, 0, 100 000}]
Out[]= 34.0528

In[]:= aumc = NIntegrate[(t Xc[t] / V1) /. modelpkiv2, {t, 0, 100 000}]
Out[]= 6497.73

In[]:= cl = k10 V1
Out[]= 0.293661

In[]:= vssnc = (aumc / auc - ivduration / 2) cl
Out[]= 55.8876

In[]:= thalfexp =
        0.693 / ((Log[Xc[Max[tt]] / V1] - Log[Xc[1.2 Max[tt]] / V1]) / (1.2 Max[tt] - Max[tt])) /.
         modelpkiv2
Out[]= 214.006

In[]:= plotfit2 = LogPlot[(Xc[t] / V1) /. modelpkiv2, {t, 0, 1.1 Max[tt]},
          PlotRange → {{0, 1.1 Max[tt]}, {0.5 Min[ct], 1.2 Max[ct]}},
          Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
          LabelStyle → (FontFamily → "Arial"), FrameLabel → {"time, min", "ug/mL"}];

In[]:= Show[plotfit2, plotfit1]
Out[]=
```




```
In[]:= plotfit3 = ListPlot[ctt];
       plotfit4 = Plot[(Xc[t] / V1) /. modelpkiv2,
          {t, 0, 1.1 Max[tt]}, PlotRange → {{0, 1.1 Max[tt]}, {0, 1.2 Max[ct]}},
          Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
          LabelStyle → (FontFamily → "Arial"), FrameLabel → {"time, min", "ug/mL"}];

In[]:= Show[plotfit4, plotfit3]
```

Out[∘]=


Physiological Parameters

Plasma and Blood

In[∘]:=
```
{hemat, phiw, php, phbc, fiwbc, taplbc, fnlbc, fnplbc, fnlp, fnplp, qc, vtab, vtvb} =
  {0.45, 7., 7.4, 7.22, 0.603, 0.5, 0.0017, 0.0029, 0.0023, 0.0013, 5.69, 1.89, 3.78};
```

Adipose

In[∘]:=
```
{fiwad, fewad, fnlad, fnplad, r1ad, taplad, qad, vtad, fplad, r2ad} =
  {0.017, 0.135, 0.853, 0.0016, 0.049, 0.4, 0.284, 12.46, 0.002, 0.021952};
```

Bone

In[∘]:=
```
{fiwbone, fewbone, fnlbone, fnplbone, r1bone, taplbone, qbone, vtbone, fplbone,
   r2bone} = {0.364, 0.1, 0.0174, 0.0016, 0.1, 0.67, 0.284, 10.5, 0.002873, 0.0448};
```

Brain

In[∘]:=
```
{fiwbrain, fewbrain, fnlbrain, fnplbrain,
   r1brain, taplbrain, qbrain, vtbrain, fplbrain, r2brain} =
  {0.62, 0.162, 0.0391, 0.0015, 0.048, 0.4, 0.683, 1.4, 0.0019, 0.021504};
```

Gut

In[∘]:=
```
{fiwgut, fewgut, fnlgut, fnplgut, r1gut, taplgut, qgut, vtgut, fplgut, r2gut} =
  {0.475, 0.282, 0.0375, 0.0124, 0.158, 2.41, 1.08, 1.2, 0.01481, 0.070784};
```

Heart

In[∘]:=
```
{fiwheart, fewheart, fnlheart, fnplheart,
   r1heart, taplheart, qheart, vtheart, fplheart, r2heart } =
  {0.456, 0.32, 0.0135, 0.0106, 0.157, 2.25, 0.228, 0.33, 0.01285, 0.070336};
```

Kidney

In[∘]:=
```
{fiwkid, fewkid, fnlkid, fnplkid, r1kid, taplkid, qkid, vtkid, fplkid, r2kid} =
  {0.483, 0.273, 0.0121, 0.024, 0.13, 5.03, 1.081, 0.31, 0.02903, 0.05824};
```

Liver

```
In[•]:= {fiwliver, fewliver, fnlliver, fnplliver,
     r1liver, tapliver, qliver, vtliver, fplliver, r2liver} =
   {0.573, 0.161, 0.0135, 0.0238, 0.086, 4.56, 1.451, 1.82, 0.02836, 0.038528};
```

Lung

```
In[•]:= {fiwlung, fewlung, fnllung, fnpllung,
     r1lung, tapllung, qlung, vtlung, fpllung, r2lung} =
   {0.446, 0.336, 0.0215, 0.0123, 0.212, 3.91, 5.69, 0.53, 0.01621, 0.094976};
```

Muscle

```
In[•]:= {fiwmus, fewmus, fnlmus, fnplmus, r1mus, taplmus, qmus, vtmus, fplmus, r2mus} =
   {0.63, 0.079, 0.022, 0.0078, 0.064, 1.53, 0.967, 28., 0.00933, 0.028672};
```

Rest of Body

```
In[•]:= {fiwrob, fewrob, fnlrob, fnplrob, r1rob, taplrob, qrob, vtrob, fplrob, r2rob} =
   {0.63, 0.079, 0.022, 0.0078, 0.064, 1.53, 0.427, 5., 0.00933, 0.028672};
```

Skin

```
In[•]:= {fiwskin, fewskin, fnlskin, fnplskin,
     r1skin, taplskin, qskin, vtskin, fplskin, r2skin} =
   {0.291, 0.382, 0.0603, 0.0044, 0.277, 1.32, 0.285, 3.15, 0.00572, 0.124096};
```

Spleen

```
In[•]:= {fiwspleen, fewspleen, fnlspleen, fnplspleen,
     r1spleen, taplspleen, qspleen, vtspleen, fplspleen, r2spleen} =
   {0.579, 0.207, 0.0071, 0.0107, 0.097, 3.18, 0.171, 0.17, 0.01388, 0.043456};
```

pH partitioning parameters

```
In[•]:= X = 1 + 10 ^ (pkab - phiw) + 10 ^ (phiw - pkaa);
        Y = 1 + 10 ^ (pkab - php) + 10 ^ (php - pkaa);
```

Clearance is set to the experimental value

```
In[•]:= eh = cl / (qliver bp)
Out[•]= 0.28505

In[•]:= qliver
Out[•]= 1.451
```

Calculate Rodgers Kps for acids and neutrals

In[∘]:=
```
kpad = (X fiwad / Y + fewad + (dvo fnlad + (0.3 dvo + 0.7) fnplad) / Y +
    (1 / fup - 1 - (dvo fnlp + (0.3 dvo + 0.7) fnplp) / Y) r1ad) fup
```
Out[∘]= 4.16274

In[∘]:=
```
kpbone = (X fiwbone / Y + fewbone + (pow fnlbone + (0.3 pow + 0.7) fnplbone) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1bone)) fup
```
Out[∘]= 0.93797

In[∘]:=
```
kpbrain = (X fiwbrain / Y + fewbrain + (pow fnlbrain + (0.3 pow + 0.7) fnplbrain) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1brain)) fup
```
Out[∘]= 1.9205

In[∘]:=
```
kpgut = (X fiwgut / Y + fewgut + (pow fnlgut + (0.3 pow + 0.7) fnplgut) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1gut)) fup
```
Out[∘]= 2.09014

In[∘]:=
```
kpheart = (X fiwheart / Y + fewheart + (pow fnlheart + (0.3 pow + 0.7) fnplheart) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1heart)) fup
```
Out[∘]= 0.940793

In[∘]:=
```
kpkid = (X fiwkid / Y + fewkid + (pow fnlkid + (0.3 pow + 0.7) fnplkid) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1kid)) fup
```
Out[∘]= 1.04048

In[∘]:=
```
kpliver = (X fiwliver / Y + fewliver + (pow fnlliver + (0.3 pow + 0.7) fnplliver) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1liver)) fup
```
Out[∘]= 1.06571

In[∘]:=
```
kplung = (X fiwlung / Y + fewlung + (pow fnllung + (0.3 pow + 0.7) fnpllung) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1lung)) fup
```
Out[∘]= 1.38567

In[∘]:=
```
kpmus = (X fiwmus / Y + fewmus + (pow fnlmus + (0.3 pow + 0.7) fnplmus) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1mus)) fup
```
Out[∘]= 1.21938

In[∘]:=
```
kprob = (X fiwrob / Y + fewrob + (pow fnlrob + (0.3 pow + 0.7) fnplrob) / Y +
    ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1rob)) fup
```
Out[∘]= 1.21938

```
In[ ]:= kpskin = (X fiwskin / Y + fewskin + (pow fnlskin + (0.3 pow + 0.7) fnplskin) / Y +
          ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1skin)) fup
Out[ ]= 3.14181

In[ ]:= kpspleen = (X fiwspleen / Y + fewspleen + (pow fnlspleen + (0.3 pow + 0.7) fnplspleen) / Y +
          ((1 / fup - 1 - (pow fnlp + (0.3 pow + 0.7) fnplp) / Y) r1spleen)) fup
Out[ ]= 0.592745

In[ ]:= vssrod = kpad vtad + kpbone vtbone + kpbrain vtbrain + kpgut vtgut +
          kpheart vtheart + kpkid vtkid + kpliver vtliver + kplung vtlung +
          kpmus vtmus + kprob vtrob + kpskin vtskin + kpspleen vtspleen +
          (1 - hemat) (vtab + vtvb) + hemat (vtab + vtvb) (hemat - 1 + bp) / ( hemat)
Out[ ]= 124.483
```

PBPK model

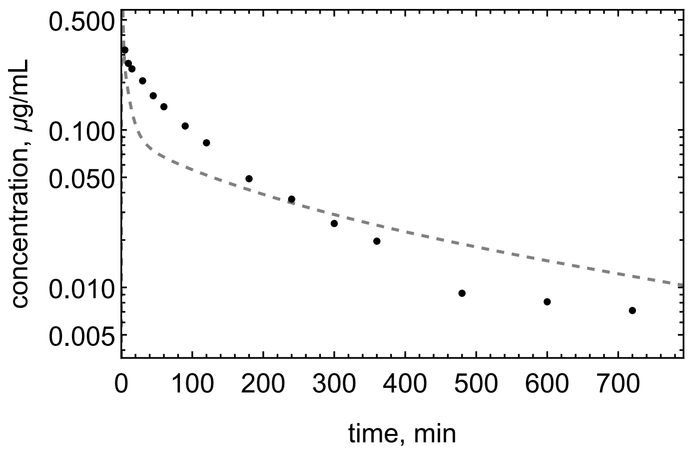
Qc was calculated using the allometric equation: Qc = 0.235 *BW0.75 with a mean BW of 70kg, Unit=L/h
V unit: L (human body weight = 70kg)

In[∘]:=
```
pbpk1 = NDSolve[{
    Clung'[t] == qc (Cvp[t] bp - Clung[t] / (kplung / bp)) / vtlung,
    Cad'[t] == qad (Cab[t] - Cad[t] / (kpad / bp)) / vtad,
     Cbone'[t] == qbone (Cab[t] - Cbone[t] / (kpbone / bp)) / vtbone,
    Cbrain'[t] == qbrain (Cab[t] - Cbrain[t] / (kpbrain / bp)) / vtbrain,
    Cheart'[t] == qheart (Cab[t] - Cheart[t] / (kpheart / bp)) / vtheart,
    Ckid'[t] == qkid (Cab[t] - Ckid[t] / (kpkid / bp)) / vtkid,
    Cmus'[t] == qmus (Cab[t] - Cmus[t] / (kpmus / bp)) / vtmus,
    Cspleen'[t] == qspleen (Cab[t] - Cspleen[t] / (kpspleen / bp)) / vtspleen,
    Cgut'[t] == qgut (Cab[t] - Cgut[t] / (kpgut / bp)) / vtgut,
    Cskin'[t] == qskin (Cab[t] - Cskin[t] / (kpskin / bp)) / vtskin,
    Crob'[t] == qrob (Cab[t] - Crob[t] / (kprob / bp)) / vtrob,
    Cliver'[t] ==
      ((qliver - qgut - qspleen) Cab[t] + qgut Cgut[t] / (kpgut / bp) + qspleen
           Cspleen[t] / (kpspleen / bp) - qliver Cliver[t] / (kpliver / bp)) / vtliver -
       ((qliver - qgut - qspleen) Cab[t] + qgut Cgut[t] / (kpgut / bp) +
          qspleen Cspleen[t] / (kpspleen / bp)) * eh / vtliver,
    Cab'[t] == (qc (Clung[t] / (kplung / bp) - Cab[t])) / vtab,
    Cvp'[t] bp == (qad Cad[t] / (kpad / bp) + qbone Cbone[t] / (kpbone / bp) +
         qbrain Cbrain[t] / (kpbrain / bp) + qheart Cheart[t] / (kpheart / bp) +
         qkid Ckid[t] / (kpkid / bp) + qmus Cmus[t] / (kpmus / bp) +
         qrob Crob[t] / (kprob / bp) + qliver Cliver[t] / (kpliver / bp) +
         qskin Cskin[t] / (kpskin / bp) + k0[t] - qc Cvp[t] bp) / vtvb,
    k0'[t] == 0,
    k0[0] == kinf, WhenEvent[t == ivduration, k0[t] → 0.],
    Cvp[0] bp == 0, Clung[0] == 0, Cad[0] == 0, Cbone[0] == 0, Cbrain[0] == 0,
    Cheart[0] == 0, Ckid[0] == 0, Cmus[0] == 0, Cliver[0] == 0,
    Cspleen[0] == 0, Cgut[0] == 0, Crob[0] == 0, Cskin[0] == 0, Cab[0] == 0},
   {Cvp, Cab, Cad, Clung, Cbone, Cbrain, Cheart, Ckid, Cmus,
    Cliver, Cspleen, Cgut, Cskin}, {t, 0, 20 Max[tt]}];
```

In[∘]:=
```
plot1 = LogPlot[(70. / avgwt Cvp[t]) /. pbpk1, {t, 0, 1.1 Max[tt]}, PlotRange →
    {{0, 1.1 Max[tt]}, {0.5 Min[ct], 1.8 Max[ct]}}, PlotStyle → {Gray, Dashed},
   Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
   LabelStyle → Directive[Plain, FontFamily → "Arial Unicode MS"],
   FrameLabel → {"time, min", "concentration, μg/mL"}, ImageSize → Medium];
```

In[∘]:= `Show[plot1, plotfit1]`

Out[∘]=



In[∘]:= `auc1 = NIntegrate[Cvp[t] /. pbpk1, {t, 0, 20 Max[tt]}][[1]]`

Out[∘]= 34.0529

In[∘]:= `cl1 = dose / auc1`

Out[∘]= 0.293661

In[∘]:= `cl / (cl1)`

Out[∘]= 1.

In[∘]:= `aumc1 = NIntegrate[t Cvp[t] /. pbpk1, {t, 0, 20 Max[tt]}][[1]]`

Out[∘]= 14 284.3

In[∘]:= `mrt1 = aumc1 / auc1`

Out[∘]= 419.474

In[∘]:= `mrt1c = mrt1 - (ivduration / 2)`

Out[∘]= 418.974

In[∘]:= `vss1 = cl1 mrt1`

Out[∘]= 123.183

In[∘]:=
```
thalf1 = 0.693 /
    ((Log[Cvp[Max[tt]]] - Log[Cvp[1.2 Max[tt]]]) / (1.2 Max[tt] - Max[tt])) /. pbpk1[[1]]
```

Out[∘]= 382.76

In[∘]:= `ClearAll["kp*"];`

Calculate memPBPK Kps

In[∘]:= `lkl = (1 - fum) / fum`

Out[∘]= 0.470588

In[∘]:=
```
a = 1383;
b = 0.096;
```

In[∘]:=
$$kpad = r1ad\ (1 - fup) + fiwad\ fup \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) + fewad\ fup + fplad \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) fup\ a\ lkl + fnlad\ fup\ b\ (10 \wedge logp) \left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$$

Out[∘]= 3.72031

In[∘]:=
$$kpbone = r1bone\ (1 - fup) + fiwbone\ fup \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) + fewbone\ fup + fplbone \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) fup\ a\ lkl + fnlbone\ fup\ b\ (10 \wedge logp) \left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$$

Out[∘]= 0.255474

In[∘]:=
$$kpbrain = r1brain\ (1 - fup) + fiwbrain\ fup \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) + fewbrain\ fup + fplbrain \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) fup\ a\ lkl + fnlbrain\ fup\ b\ (10 \wedge logp) \left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$$

Out[∘]= 0.285717

In[∘]:=
$$kpgut = r1gut\ (1 - fup) + fiwgut\ fup \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) + fewgut\ fup + fplgut \left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right) fup\ a\ lkl + fnlgut\ fup\ b\ (10 \wedge logp) \left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$$

Out[∘]= 0.691001

In[ ]:= $$\text{kpheart} = \text{r1heart}\,(1-\text{fup}) + \text{fiwheart}\,\text{fup}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right) + \text{fewheart}\,\text{fup} + \text{fplheart}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right)\text{fup}\;a\;\text{lkl} + \text{fnlheart}\,\text{fup}\;b\;(10\wedge\text{logp})\left(\frac{1}{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}\right)$$

Out[ ]= 0.542182

In[ ]:= $$\text{kpkid} = \text{r1kid}\,(1-\text{fup}) + \text{fiwkid}\,\text{fup}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right) + \text{fewkid}\,\text{fup} + \text{fplkid}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right)\text{fup}\;a\;\text{lkl} + \text{fnlkid}\,\text{fup}\;b\;(10\wedge\text{logp})\left(\frac{1}{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}\right)$$

Out[ ]= 0.894334

In[ ]:= $$\text{kpliver} = \text{r1liver}\,(1-\text{fup}) + \text{fiwliver}\,\text{fup}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right) + \text{fewliver}\,\text{fup} + \text{fplliver}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right)\text{fup}\;a\;\text{lkl} + \text{fnlliver}\,\text{fup}\;b\;(10\wedge\text{logp})\left(\frac{1}{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}\right)$$

Out[ ]= 0.841284

In[ ]:= $$\text{kplung} = \text{r1lung}\,(1-\text{fup}) + \text{fiwlung}\,\text{fup}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right) + \text{fewlung}\,\text{fup} + \text{fpllung}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right)\text{fup}\;a\;\text{lkl} + \text{fnllung}\,\text{fup}\;b\;(10\wedge\text{logp})\left(\frac{1}{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}\right)$$

Out[ ]= 0.709332

In[ ]:= $$\text{kpmus} = \text{r1mus}\,(1-\text{fup}) + \text{fiwmus}\,\text{fup}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right) + \text{fewmus}\,\text{fup} + \text{fplmus}\left(\frac{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}{10^{\text{pkab}-7.4}+10^{7.4-\text{pkaa}}+1}\right)\text{fup}\;a\;\text{lkl} + \text{fnlmus}\,\text{fup}\;b\;(10\wedge\text{logp})\left(\frac{1}{10^{\text{pkab}-7.0}+10^{7.0-\text{pkaa}}+1}\right)$$

Out[ ]= 0.402796

In[∘]:= kprob = r1rob (1 - fup) + fiwrob fup $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ + fewrob fup + fplrob $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ fup a lkl + fnlrob fup b (10 ^ logp) $\left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$

Out[∘]= 0.402796

In[∘]:= kpskin = r1skin (1 - fup) + fiwskin fup $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ + fewskin fup + fplskin $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ fup a lkl + fnlskin fup b (10 ^ logp) $\left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$

Out[∘]= 0.683206

In[∘]:= kpspleen = r1spleen (1 - fup) + fiwspleen fup $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ + fewspleen fup + fplspleen $\left(\frac{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}{10^{pkab-7.4} + 10^{7.4-pkaa} + 1}\right)$ fup a lkl + fnlspleen fup b (10 ^ logp) $\left(\frac{1}{10^{pkab-7.0} + 10^{7.0-pkaa} + 1}\right)$

Out[∘]= 0.482182

```
In[∘]:= vssfum = kpad vtad + kpbone vtbone + kpbrain vtbrain + kpgut vtgut +
    kpheart vtheart + kpkid vtkid + kpliver vtliver + kplung vtlung +
    kpmus vtmus + kprob vtrob + kpskin vtskin + kpspleen vtspleen +
    (1 - hemat) (vtab + vtvb) + hemat (vtab + vtvb) (hemat - 1 + bp) / ( hemat)
```

Out[∘]= 72.1821

PBPK model 2

Qc was calculated using the allometric equation: Qc = 0.235 *BW0.75 with a mean BW of 70kg, Unit=L/h
V unit: L (human body weight = 70kg)

In[ ]:=
```
pbpk2 = NDSolve[{
   Clung'[t] == qc (Cvp[t] bp - Clung[t] / (kplung / bp)) / vtlung,
   Cad'[t] == qad (Cab[t] - Cad[t] / (kpad / bp)) / vtad,
    Cbone'[t] == qbone (Cab[t] - Cbone[t] / (kpbone / bp)) / vtbone,
   Cbrain'[t] == qbrain (Cab[t] - Cbrain[t] / (kpbrain / bp)) / vtbrain,
   Cheart'[t] == qheart (Cab[t] - Cheart[t] / (kpheart / bp)) / vtheart,
   Ckid'[t] == qkid (Cab[t] - Ckid[t] / (kpkid / bp)) / vtkid,
   Cmus'[t] == qmus (Cab[t] - Cmus[t] / (kpmus / bp)) / vtmus,
   Cspleen'[t] == qspleen (Cab[t] - Cspleen[t] / (kpspleen / bp)) / vtspleen,
   Cgut'[t] == qgut (Cab[t] - Cgut[t] / (kpgut / bp)) / vtgut,
   Cskin'[t] == qskin (Cab[t] - Cskin[t] / (kpskin / bp)) / vtskin,
   Crob'[t] == qrob (Cab[t] - Crob[t] / (kprob / bp)) / vtrob,
   Cliver'[t] ==
     ((qliver - qgut - qspleen) Cab[t] + qgut Cgut[t] / (kpgut / bp) + qspleen
         Cspleen[t] / (kpspleen / bp) - qliver Cliver[t] / (kpliver / bp)) / vtliver -
      ((qliver - qgut - qspleen) Cab[t] + qgut Cgut[t] / (kpgut / bp) +
         qspleen Cspleen[t] / (kpspleen / bp)) * eh / vtliver,
   Cab'[t] == (qc (Clung[t] / (kplung / bp) - Cab[t])) / vtab,
   Cvp'[t] bp == (qad Cad[t] / (kpad / bp) + qbone Cbone[t] / (kpbone / bp) +
       qbrain Cbrain[t] / (kpbrain / bp) + qheart Cheart[t] / (kpheart / bp) +
       qkid Ckid[t] / (kpkid / bp) + qmus Cmus[t] / (kpmus / bp) +
       qrob Crob[t] / (kprob / bp) + qliver Cliver[t] / (kpliver / bp) +
       qskin Cskin[t] / (kpskin / bp) + k0[t] - qc Cvp[t] bp) / vtvb,
   k0'[t] == 0,
   k0[0] == kinf, WhenEvent[t == ivduration, k0[t] → 0.],
   Cvp[0] bp == 0, Clung[0] == 0, Cad[0] == 0, Cbone[0] == 0, Cbrain[0] == 0,
   Cheart[0] == 0, Ckid[0] == 0, Cmus[0] == 0, Cliver[0] == 0,
   Cspleen[0] == 0, Cgut[0] == 0, Crob[0] == 0, Cskin[0] == 0, Cab[0] == 0},
  {Cvp, Cab, Cad, Clung, Cbone, Cbrain, Cheart, Ckid, Cmus,
   Cliver, Cspleen, Cgut, Cskin}, {t, 0, 20 Max[tt]}];
```

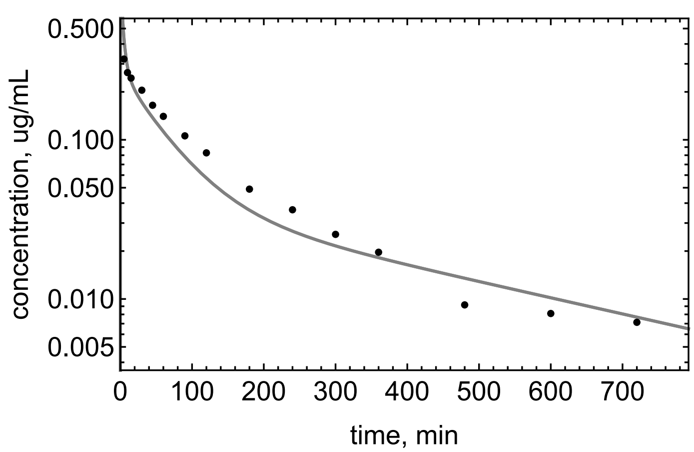
In[ ]:=
```
auc2 = NIntegrate[Cvp[t] /. pbpk2, {t, 0, 20 Max[tt]}][[1]]
```

Out[ ]=
```
34.0529
```

In[ ]:=
```
cl2 = dose / auc2
```

Out[ ]=
```
0.293661
```

In[•]:=
```
cl / (cl2)
```
Out[•]=
```
1.
```
In[•]:=
```
aumc2 = NIntegrate[t Cvp[t] /. pbpk2, {t, 0, 20 Max[tt]}][[1]]
```
Out[•]=
```
8292.1
```
In[•]:=
```
mrt2 = aumc2 / auc2
```
Out[•]=
```
243.507
```
In[•]:=
```
mrt2c = mrt2 - (ivduration / 2)
```
Out[•]=
```
243.007
```
In[•]:=
```
vss2 = cl2 mrt2c
```
Out[•]=
```
71.3616
```
In[•]:=
```
thalf2 = 0.693 /
   ((Log[Cvp[Max[tt]]] - Log[Cvp[1.2 Max[tt]]]) / (1.2 Max[tt] - Max[tt])) /. pbpk2[[1]]
```
Out[•]=
```
296.811
```
In[•]:=
```
plot2 = LogPlot[(70. / avgwt Cvp[t]) /. pbpk2, {t, 0, 1.1 Max[tt]},
   PlotRange → {{0, 1.1 Max[tt]}, {0.5 Min[ct], 1.8 Max[ct]}}, PlotStyle → {Gray},
   Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
   LabelStyle → (FontFamily → "Arial"),
   FrameLabel → {"time, min", "concentration, ug/mL"}];
```
In[•]:=
```
Show[plot2, plot2, plotfit1]
```
Out[•]=



PBPK model 3 - Permeability and perfusion limited

In[•]:=
```
ClearAll[kp, kn, phiw, php, qc]
```

Physiological Parameters

```
In[•]:= {phiw, php, qc, vtab, vtvb, ppcpmw, phcp, phcp2, ecfactor, aconst, bconst, phsl,
            kendoa, kendob, paq, ppara} = {7.1, 7.4, 5.691, 1.527, 3.055, 0.00071934,
            0.000102, 0.00102, 1., 1400., 0.1, 10., 19.0546, 0.694, 0.0001, 2. * 10 ^ -7};

In[•]:= pappsec1 = (paq pappsec - paq ppara) / (paq + ppara - pappsec)

Out[•]= 0.0000730104

In[•]:= bp0 = bp;

In[•]:= pery = 0.000002;

In[•]:= bpc = bp - (pery / (pery + pappsec1) fup 0.45);

In[•]:= If[bpc ≤ 0.55, bp = 0.55001, bp = bpc]

Out[•]= 0.709586

In[•]:= papp = pappsec1 60 / 10

Out[•]= 0.000438062

In[•]:= ppcp = ppcpmw / (mw ^ 0.33)

Out[•]= 0.000106576
```

b=blood
e=extracellular space
c=cytosol
n=neutral lipid
p=phospholipid
am=apical membrane

at 1 mg microsomal protein/mL, kp=(1-fum)/(fum 0.00072) from 1/1390 - Holt et al. 2019

```
In[•]:= kp = aconst (1 - fum) / (fum )

Out[•]= 658.824

In[•]:= kn = bconst pow

Out[•]= 141.254
```

pH partitioning parameters

```
In[•]:= ClearAll[x, y];

In[•]:= x = 1 + phsl ^ (pkab - phiw) + phsl ^ (phiw - pkaa);
        y = 1 + phsl ^ (pkab - php) + phsl ^ (php - pkaa);
```

C1

```
In[•]:= {q1, r1, r2, v1b, v1e, v1c, v1n, v1p, sa1b, sa1e, sa1n, sa1p} =
          {1.359, 0.78018, 0.349521, 0.405, 3.552, 19.301, 0.79,
           0.1933, 21582.9, 323743., 947964., 6.03951 * 10^6};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fue1 = 1 / (1 + re (1 - fup) / fup);
```

adp

```
In[•]:= {qadp, r1, r2, vadpb, vadpe, vadpc, vadpn, vadpp, saadpb, saadpe, saadpn, saadpp} =
          {0.284, 0.362963, 0.162607, 0.18, 1.682, 0.212, 10.624,
           0.0159, 9575.74, 143636., 2.12488 * 10^6, 498400.};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fueadp = 1 / (1 + re (1 - fup) / fup);
```

C2

```
In[•]:= {q2, r1, r2, v2b, v2e, v2c, v2n, v2p, sa2b, sa2e, sa2n, sa2p} = {0.391, 1., 0.448,
           0.104, 1.175, 4.277, 0.201, 0.015, 5534.72, 83020.8, 240828., 470000.};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fue2 = 1 / (1 + re (1 - fup) / fup);
```

C3

```
In[•]:= {q3, r1, r2, v3b, v3e, v3c, v3n, v3p, sa3b, sa3e, sa3n, sa3p} = {0.335, 0.490625,
           0.2198, 0.094, 0.506, 0.72, 0.018, 0.0134, 5000., 75000., 21576.5, 418700.};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fue3 = 1 / (1 + re (1 - fup) / fup);
```

lun

```
In[•]:= {qlun, r1, r2, vlunb, vlune, vlunc, vlunn, vlunp, salunb, salune, salunn, salunp} =
          {5.691, 0.630952, 0.282667, 0.023, 0.178, 0.236,
           0.01, 0.0052, 1226.85, 18402.8, 12109.4, 162975.};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fuelun = 1 / (1 + re (1 - fup) / fup);
```

mes

```
In[•]:= {qmes, r1, r2, vmesb, vmese, vmesc, vmesn, vmesp, samesb, samese, samesn, samesp} =
          {0.972, 0.560284, 0.251007, 0.05, 0.305, 0.513,
           0.038, 0.0107, 2640., 39600., 45385.9, 334800.};

In[•]:= re = r1 anflag + r2 bflag;

In[•]:= fuemes = 1 / (1 + re (1 - fup) / fup);
```

C4

```
In[∘]:= {q4, r1, r2, v4b, v4e, v4c, v4n, v4p, sa4b, sa4e, sa4n, sa4p} = {1.188, 0.47619,
    0.213333, 0.084, 0.426, 0.753, 0.011, 0.03, 4476.85, 67 152.8, 13 665.6, 936 000.};

In[∘]:= re = r1 anflag + r2 bflag;

In[∘]:= fue4 = 1 / (1 + re (1 - fup) / fup);
```

muc

```
In[∘]:= {qmuc, r1, r2, vmucb, vmuce, vmucc, vmucn, vmucp, samucb, samuce, samucn, samucp} =
   {0.108, 0.560284, 0.251007, 0.002, 0.034, 0.057,
    0.004, 0.0012, 97.7778, 1466.67, 5042.88, 37 200.};

In[∘]:= re = r1 anflag + r2 bflag;

In[∘]:= fuemuc = 1 / (1 + re (1 - fup) / fup);
```

spl

```
In[∘]:= {qspl, r1, r2, vsplb, vsple, vsplc, vspln, vsplp, sasplb, sasple, saspln, sasplp} =
   {0.171, 0.468599, 0.209932, 0.009, 0.035, 0.098,
    0.001, 0.0015, 462.778, 6941.67, 1011.84, 45 475.};

In[∘]:= re = r1 anflag + r2 bflag;

In[∘]:= fuespl = 1 / (1 + re (1 - fup) / fup);
```

liv

```
In[∘]:= {qliv, r1, r2, vlivb, vlive, vlivc, vlivn, vlivp, salivb, salive, salivn, salivp} =
   {1.451, 0.534161, 0.239304, 0.079, 0.293, 1.043,
    0.016, 0.0347, 4212.96, 500 000., 19 088.2, 1.0829 * 10 ^ 6};

In[∘]:= re = r1 anflag + r2 bflag;

In[∘]:= fueliv = 1 / (1 + re (1 - fup) / fup);
```

brn

```
In[∘]:= {qbrn, r1, r2, vbrnb, vbrne, vbrnc, vbrnn, vbrnp, sabrnb, sabrne,
    sabrnn, sabrnp, vbrnam} = {0.683, 0.296296, 0.132741, 0.058, 0.227,
    0.868, 0.054, 0.0017, 3111.11, 46 666.7, 65 184., 52 500., 0.0000653333};

In[∘]:= re = r1 anflag + r2 bflag;

In[∘]:= fuebrn = 1 / (1 + re (1 - fup) / fup);
```

Model

rq - net rate blood flow

clbe - net clearance blood to ecf

cleb - net clearance ecf to blood

clec - net clearance ecf to cytosol
clce - net clearance cytosol to ecf
clcn - net clearance cytosol to neutral lipids
clcp - net clearance cytosol to phospholipids
clnc- net clearance neutral lipids to cytosol
clpc- net clearance phospholipids to cytosol
clu1 - hypothetical pinocytosis
clu2 - uptake transporter
clu3 - liver uptake transporter
cle1 - efflux transporter

```
In[]:= (*ClearAll["Global`*"];*)

In[]:= tist = {"1", "adp", "2", "3", "lun", "mes", "4", "muc", "spl", "liv", "brn"};

In[]:= cpt = {ppcp, ppcp, phcp, ppcp, ppcp, ppcp, phcp, phcp, phcp, phcp, phcp2, 0.}

Out[]= {0.000106576, 0.000106576, 0.000102, 0.000106576, 0.000106576,
  0.000106576, 0.000102, 0.000102, 0.000102, 0.000102, 0.00102, 0.}

In[]:= i = 1;
```

In[∘]:=
```
While[i ≤ 11,
  tis = tist[[i]];

  Evaluate[ToExpression["rq" <> tis]] = Evaluate[ToExpression["q" <> tis]] ×
     (Cab[t] - Evaluate[ToExpression["C" <> tis <> "b"]][t]);

  Evaluate[ToExpression["clbe" <> tis]] =
    fup cpt[[i]] × Evaluate[ToExpression["sa" <> tis <> "b"]] / bp +
     fup papp Evaluate[ToExpression["sa" <> tis <> "b"]] / bp;

  Evaluate[ToExpression["cleb" <> tis]] = Evaluate[ToExpression["fue" <> tis]] × cpt[[i]] ×
      Evaluate[ToExpression["sa" <> tis <> "b"]] + Evaluate[ToExpression["fue" <> tis]]
      papp Evaluate[ToExpression["sa" <> tis <> "b"]];

  Evaluate[ToExpression["clec" <> tis]] = Evaluate[ToExpression["fue" <> tis]]
      2 papp Evaluate[ToExpression["sa" <> tis <> "e"]] +
     clu1 + Evaluate[ToExpression["fue" <> tis]] clu2;

  Evaluate[ToExpression["clce" <> tis]] =
    (y / x) 2 papp Evaluate[ToExpression["sa" <> tis <> "e"]];

  Evaluate[ToExpression["clcn" <> tis]] =
    (1 / x) × 4 papp Evaluate[ToExpression["sa" <> tis <> "n"]];

  Evaluate[ToExpression["clcp" <> tis]] =
    4 papp Evaluate[ToExpression["sa" <> tis <> "p"]];

  Evaluate[ToExpression["clnc" <> tis]] =
    4 papp Evaluate[ToExpression["sa" <> tis <> "n"]] / kn;

  Evaluate[ToExpression["clpc" <> tis]] =
    4 papp Evaluate[ToExpression["sa" <> tis <> "p"]] / kp;
  i++];
```

In[∘]:=
```
clu1 = 0.0; clu2 = 0.; clu3 = 0.;
```

Fix the non-normal net clearances

liver discontinuities allow plasma protein diffusion

In[∘]:=
```
clbeliv = phcp2 salivb / bp + fup papp salivb / bp
```

Out[∘]=
```
6.14568
```

```
In[•]:= clebliv = phcp2 salivb + fueliv papp salivb
Out[•]= 4.53699
```

liver to include uptake transport

```
In[•]:= clecliv = fueliv 2 papp salive + clu1 + fueliv clu2 + fueliv clu3;
```

brain apical membrane clearances

```
In[•]:= clbabrn = fup 4 papp sabrnb / bp;
        clabbrn = (4 papp sabrnb) / kp;
        claebrn = (2 papp sabrnb) / (3 kp);
        cleabrn = fuebrn (2 papp sabrnb) / 3;
```

```
In[•]:= ClearAll[clenet, clbnet, clint2, clint]
```

Calculate unbound intrinsic clearance

```
In[•]:= clh = (1 - fe) cl
Out[•]= 0.293661

In[•]:= clenet = clecliv clint2 / (clceliv + clint2)
```

Out[•]= $\frac{56.9131\ \text{clint2}}{421.636 + \text{clint2}}$

```
In[•]:= clbnet = clbeliv clenet / (clebliv + clenet)
```

Out[•]= $\frac{349.77\ \text{clint2}}{(421.636 + \text{clint2}) \times \left(4.53699 + \frac{56.9131\ \text{clint2}}{421.636+\text{clint2}}\right)}$

```
In[•]:= soln = Solve[clh / bp == qliver clbnet / (qliver + clbnet), clint2]〚1〛
Out[•]= {clint2 → 3.52516}

In[•]:= clint = clint2 /. soln
Out[•]= 3.52516
```

```
In[•]:= ClearAll[rqlun, rqliv];

In[•]:= rqlun = qlun (Cvb[t] - Clunb[t]);

In[•]:= rqliv = (qliv - qmes - qmuc - qspl) Cab[t] +
           qmes Cmesb[t] + qmuc Cmucb[t] + qspl Csplb[t] - qliv Clivb[t];
```

Binding to acidic groups on endothelial cells - kd in M

```
In[•]:= kon = 1000.;

In[•]:= bp2 = If[(bp0 - fup 0.45) < 0.55, 0.55001, (bp0 - fup 0.45)]
Out[•]= 0.694475
```

In[]:=
```
kery = (bp2 - 0.55) / (0.45 fup)
```
Out[]=
```
9.30596
```
In[]:=
```
ka = kendoa kery ^ kendob
```
Out[]=
```
89.6025
```
In[]:=
```
koff = kon / ka
```
Out[]=
```
11.1604
```
In[]:=
```
Cneg = 1;
```

In[]:=
```
pbpk3 = NDSolve[{
    C1b'[t] == (rq1 - C1b[t] clbe1 + C1e[t] cleb1) / v1b,
    C1e'[t] == (C1b[t] clbe1 - C1e[t] cleb1 - C1e[t] clec1 + C1c[t] clce1) / v1e,
    C1c'[t] == (C1e[t] clec1 - C1c[t] clce1 -
        C1c[t] clcn1 - C1c[t] clcp1 + C1n[t] clnc1 + C1p[t] clpc1) / v1c,
    C1n'[t] == (C1c[t] clcn1 - C1n[t] clnc1) / v1n,
    C1p'[t] == (C1c[t] clcp1 - C1p[t] clpc1) / v1p,

    Cadpb'[t] == (rqadp - Cadpb[t] clbeadp + Cadpe[t] clebadp) / vadpb,
    Cadpe'[t] == (Cadpb[t] clbeadp -
        Cadpe[t] clebadp - Cadpe[t] clecadp + Cadpc[t] clceadp) / vadpe,
    Cadpc'[t] == (Cadpe[t] clecadp - Cadpc[t] clceadp - Cadpc[t] clcnadp -
        Cadpc[t] clcpadp + Cadpn[t] clncadp + Cadpp[t] clpcadp) / vadpc,
    Cadpn'[t] == (Cadpc[t] clcnadp - Cadpn[t] clncadp) / vadpn,
    Cadpp'[t] == (Cadpc[t] clcpadp - Cadpp[t] clpcadp) / vadpp,

    C2b'[t] == (rq2 - C2b[t] clbe2 + C2e[t] cleb2) / v2b,
    C2e'[t] == (C2b[t] clbe2 - C2e[t] cleb2 - C2e[t] clec2 + C2c[t] clce2) / v2e,
    C2c'[t] == (C2e[t] clec2 - C2c[t] clce2 -
        C2c[t] clcn2 - C2c[t] clcp2 + C2n[t] clnc2 + C2p[t] clpc2) / v2c,
    C2n'[t] == (C2c[t] clcn2 - C2n[t] clnc2) / v2n,
    C2p'[t] == (C2c[t] clcp2 - C2p[t] clpc2) / v2p,

    C3b'[t] == (rq3 - C3b[t] clbe3 + C3e[t] cleb3) / v3b,
    C3e'[t] == (C3b[t] clbe3 - C3e[t] cleb3 - C3e[t] clec3 + C3c[t] clce3) / v3e,
    C3c'[t] == (C3e[t] clec3 - C3c[t] clce3 -
        C3c[t] clcn3 - C3c[t] clcp3 + C3n[t] clnc3 + C3p[t] clpc3) / v3c,
    C3n'[t] == (C3c[t] clcn3 - C3n[t] clnc3) / v3n,
    C3p'[t] == (C3c[t] clcp3 - C3p[t] clpc3) / v3p,

    Clunb'[t] == (rqlun - Clunb[t] clbelun + Clune[t] cleblun) / vlunb,
    Clune'[t] == (Clunb[t] clbelun -
        Clune[t] cleblun - Clune[t] cleclun + Clunc[t] clcelun) / vlune,
```

```
Clunc'[t] == (Clune[t] cleclun - Clunc[t] clcelun - Clunc[t] clcnlun -
     Clunc[t] clcplun + Clunn[t] clnclun + Clunp[t] clpclun) / vlunc,
Clunn'[t] == (Clunc[t] clcnlun - Clunn[t] clnclun) / vlunn,
Clunp'[t] == (Clunc[t] clcplun - Clunp[t] clpclun) / vlunp,

Cmesb'[t] == (rqmes - Cmesb[t] clbemes + Cmese[t] clebmes) / vmesb,
Cmese'[t] == (Cmesb[t] clbemes -
     Cmese[t] clebmes - Cmese[t] clecmes + Cmesc[t] clcemes) / vmese,
Cmesc'[t] == (Cmese[t] clecmes - Cmesc[t] clcemes - Cmesc[t] clcnmes -
     Cmesc[t] clcpmes + Cmesn[t] clncmes + Cmesp[t] clpcmes) / vmesc,
Cmesn'[t] == (Cmesc[t] clcnmes - Cmesn[t] clncmes) / vmesn,
Cmesp'[t] == (Cmesc[t] clcpmes - Cmesp[t] clpcmes) / vmesp,

C4b'[t] == (rq4 - C4b[t] clbe4 + C4e[t] cleb4) / v4b,
C4e'[t] == (C4b[t] clbe4 - C4e[t] cleb4 - C4e[t] clec4 + C4c[t] clce4) / v4e,
C4c'[t] == (C4e[t] clec4 - C4c[t] clce4 -
     C4c[t] clcn4 - C4c[t] clcp4 + C4n[t] clnc4 + C4p[t] clpc4) / v4c,
C4n'[t] == (C4c[t] clcn4 - C4n[t] clnc4) / v4n,
C4p'[t] == (C4c[t] clcp4 - C4p[t] clpc4) / v4p,

Cmucb'[t] == (rqmuc - Cmucb[t] clbemuc + Cmuce[t] clebmuc) / vmucb,
Cmuce'[t] == (Cmucb[t] clbemuc -
     Cmuce[t] clebmuc - Cmuce[t] clecmuc + Cmucc[t] clcemuc) / vmuce,
Cmucc'[t] == (Cmuce[t] clecmuc - Cmucc[t] clcemuc - Cmucc[t] clcnmuc -
     Cmucc[t] clcpmuc + Cmucn[t] clncmuc + Cmucp[t] clpcmuc) / vmucc,
Cmucn'[t] == (Cmucc[t] clcnmuc - Cmucn[t] clncmuc) / vmucn,
Cmucp'[t] == (Cmucc[t] clcpmuc - Cmucp[t] clpcmuc) / vmucp,

Csplb'[t] == (rqspl - Csplb[t] clbespl + Csple[t] clebspl) / vsplb,
Csple'[t] == (Csplb[t] clbespl -
     Csple[t] clebspl - Csple[t] clecspl + Csplc[t] clcespl) / vsple,
Csplc'[t] == (Csple[t] clecspl - Csplc[t] clcespl - Csplc[t] clcnspl -
     Csplc[t] clcpspl + Cspln[t] clncspl + Csplp[t] clpcspl) / vsplc,
Cspln'[t] == (Csplc[t] clcnspl - Cspln[t] clncspl) / vspln,
Csplp'[t] == (Csplc[t] clcpspl - Csplp[t] clpcspl) / vsplp,

Clivb'[t] == (rqliv - Clivb[t] clbeliv + Clive[t] clebliv) / vlivb,
Clive'[t] == (Clivb[t] clbeliv -
     Clive[t] clebliv - Clive[t] clecliv + Clivc[t] clceliv) / vlive,
Clivc'[t] == (Clive[t] clecliv - Clivc[t] clceliv - Clivc[t] clcnliv - Clivc[t]
      clcpliv + Clivn[t] clncliv + Clivp[t] clpcliv - Clivc[t] clint) / vlivc,
Clivn'[t] == (Clivc[t] clcnliv - Clivn[t] clncliv) / vlivn,
Clivp'[t] == (Clivc[t] clcpliv - Clivp[t] clpcliv) / vlivp,
```

```
Cbrnb'[t] == (rqbrn - Cbrnb[t] clbabrn + Cbrnam[t] clabbrn) / vbrnb,
Cbrnam'[t] ==
 (Cbrnb[t] clbabrn - Cbrnam[t] clabbrn - Cbrnam[t] claebrn + Cbrne[t] cleabrn) /
  vbrnam, Cbrne'[t] == (Cbrnam[t] claebrn - Cbrne[t] cleabrn -
    Cbrne[t] clecbrn + Cbrnc[t] clcebrn) / vbrne,
Cbrnc'[t] == (Cbrne[t] clecbrn - Cbrnc[t] clcebrn - Cbrnc[t] clcnbrn -
    Cbrnc[t] clcpbrn + Cbrnn[t] clncbrn + Cbrnp[t] clpcbrn) / vbrnc,
Cbrnn'[t] == (Cbrnc[t] clcnbrn - Cbrnn[t] clncbrn) / vbrnn,
Cbrnp'[t] == (Cbrnc[t] clcpbrn - Cbrnp[t] clpcbrn) / vbrnp,

Cab'[t] == (qc (Clunb[t] - Cab[t])) / vtab,
Cvb'[t] == (q1 C1b[t] + qadp Cadpb[t] + q2 C2b[t] + q3 C3b[t] + q4 C4b[t] +
     qliv Clivb[t] + qbrn Cbrnb[t] - Cvb[t] fe cl / bp + k0[t] - qc Cvb[t]) / vtvb -
  Cneg Cvb[t] (1000. / mw) fup / bp kon + Cnegd[t] koff,

Cnegd'[t] == Cneg Cvb[t] (1000. / mw) fup / bp kon - Cnegd[t] koff,

k0'[t] == 0, k0[0] == kinf, WhenEvent[t == ivduration, k0[t] → 0.],
C1b[0] == 0, C1e[0] == 0, C1c[0] == 0, C1n[0] == 0, C1p[0] == 0, Cadpb[0] == 0,
Cadpe[0] == 0, Cadpc[0] == 0, Cadpn[0] == 0, Cadpp[0] == 0, C2b[0] == 0, C2e[0] == 0,
C2c[0] == 0, C2n[0] == 0, C2p[0] == 0, C3b[0] == 0, C3e[0] == 0, C3c[0] == 0, C3n[0] == 0,
C3p[0] == 0, Clunb[0] == 0, Clune[0] == 0, Clunc[0] == 0, Clunn[0] == 0, Clunp[0] == 0,
Cmesb[0] == 0, Cmese[0] == 0, Cmesc[0] == 0, Cmesn[0] == 0, Cmesp[0] == 0, C4b[0] == 0,
C4e[0] == 0, C4c[0] == 0, C4n[0] == 0, C4p[0] == 0, Cmucb[0] == 0, Cmuce[0] == 0,
Cmucc[0] == 0, Cmucn[0] == 0, Cmucp[0] == 0, Csplb[0] == 0, Csple[0] == 0, Csplc[0] == 0,
Cspln[0] == 0, Csplp[0] == 0, Clivb[0] == 0, Clive[0] == 0, Clivc[0] == 0,
Clivn[0] == 0, Clivp[0] == 0, Cbrnb[0] == 0, Cbrnam[0] == 0, Cbrne[0] == 0,
Cbrnc[0] == 0, Cbrnn[0] == 0, Cbrnp[0] == 0, Cvb[0] == 0, Cab[0] == 0, Cnegd[0] == 0},
{C1b, C1e, C1c, C1n, C1p, Cadpb, Cadpe, Cadpc, Cadpn, Cadpp, C2b, C2e, C2c, C2n,
C2p, C3b, C3e, C3c, C3n, C3p, Clunb, Clune, Clunc, Clunn, Clunp, Cmesb, Cmese,
Cmesc, Cmesn, Cmesp, C4b, C4e, C4c, C4n, C4p, Cmucb, Cmuce, Cmucc, Cmucn, Cmucp,
Csplb, Csple, Csplc, Cspln, Csplp, Clivb, Clive, Clivc, Clivn, Clivp, Cbrnb,
Cbrnam, Cbrne, Cbrnc, Cbrnn, Cbrnp, Cvb, Cab, k0, Cnegd}, {t, 0, 20 Max[tt]}];
```

Calculate Kp,uu liver

```
In[•]:= Clivc[Max[tt]] /. pbpk3
Out[•]= {0.000550734}

In[•]:= fup Cvb[Max[tt]] / bp /. pbpk3
Out[•]= {0.000226382}

In[•]:= kpuuliver = (Clivc[Max[tt]] ) / (fup Cvb[Max[tt]] / bp ) /. pbpk3
Out[•]= {2.43276}
```

In[•]:=
```
auc3 = NIntegrate[(Cvb[t] / bp) /. pbpk3, {t, 0, 20 Max[tt]}][[1]]
```
Out[•]= 34.0529

In[•]:=
```
cl3 = dose / auc3
```
Out[•]= 0.293661

In[•]:=
```
cl / cl3
```
Out[•]= 1.

In[•]:=
```
aumc3 = NIntegrate[(t Cvb[t] / bp) /. pbpk3, {t, 0, 20 Max[tt]}][[1]]
```
Out[•]= 11 567.2

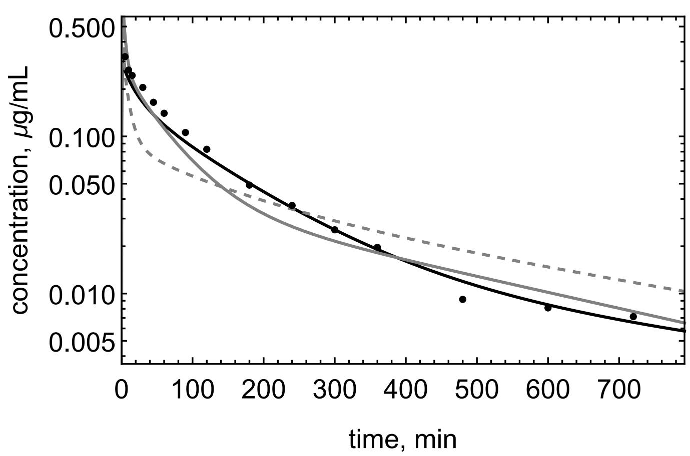
In[•]:=
```
mrt3 = aumc3 / auc3 - (ivduration / 2)
```
Out[•]= 339.183

In[•]:=
```
vss3 = cl3 mrt3
```
Out[•]= 99.6049

In[•]:=
```
thalf3 = 0.693 / ((Log[Cvb[Max[tt]] / bp] - Log[Cvb[1.2 Max[tt]] / bp]) /
      (1.2 Max[tt] - Max[tt])) /. pbpk3[[1]]
```
Out[•]= 407.744

In[•]:=
```
plot3 = LogPlot[(70. / avgwt Cvb[t] / bp) /. pbpk3, {t, 0, 1.1 Max[tt]},
    PlotRange → {{0, 1.1 Max[tt]}, {0.5 Min[ct], 1.8 Max[ct]}}, PlotStyle → {Black},
    Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
    LabelStyle → Directive[Plain, FontFamily → "Arial Unicode MS"],
    FrameLabel → {"time, min", "concentration, μg/mL"}, ImageSize → Medium];
```

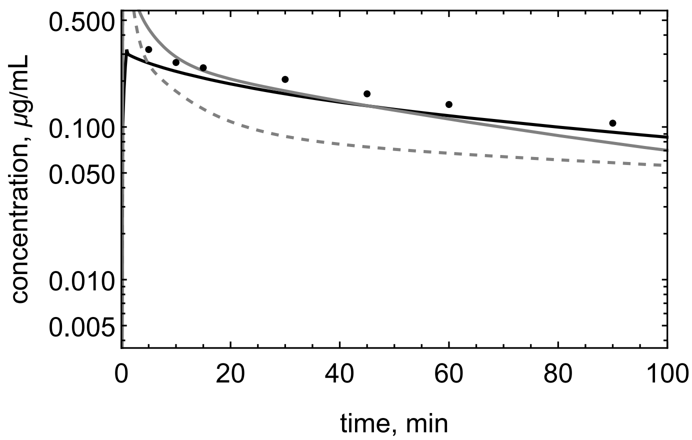
In[•]:=
```
Show[plot3, plot2, plot1, plotfit1]
```
Out[•]=



In[∘]:=
```
plot4 = LogPlot[(70. / avgwt Cvb[t] / bp) /. pbpk3, {t, 0, 1.1 Max[tt]},
    PlotRange → {{0, 100}, {0.5 Min[ct], 1.8 Max[ct]}}, PlotStyle → {Black},
    Frame → True, FrameStyle → Directive[Black, 14, Thickness[0.003]],
    LabelStyle → Directive[Plain, FontFamily → "Arial Unicode MS"],
    FrameLabel → {"time, min", "concentration, μg/mL"}, ImageSize → Medium];
```

In[∘]:=
```
Show[plot4, plot2, plot1, plotfit1]
```

Out[∘]=



Calculate Overlaps

In[∘]:=
```
aucintIV = NIntegrate[(Xc[t] / V1) /. modelpkiv2, {t, 0, 20 Max[tt]}]
```

Out[∘]= 34.0528

In[∘]:=
```
overlap1 = NIntegrate[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvp[t]) /. pbpk1],
   {t, 0, 20 Max[tt]}, PrecisionGoal → 4]
```

Out[∘]= 24.2541

In[∘]:=
```
overlap2 = NIntegrate[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvp[t]) /. pbpk2],
   {t, 0, 20 Max[tt]}, PrecisionGoal → 4]
```

Out[∘]= 29.0016

In[∘]:=
```
overlap3 = NIntegrate[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvb[t] / bp) /. pbpk3],
   {t, 0, 20 Max[tt]}, PrecisionGoal → 4]
```

Out[∘]= 30.8028

In[∘]:=
```
eocrodgers = overlap1 / aucintIV
```

Out[∘]= 0.712247

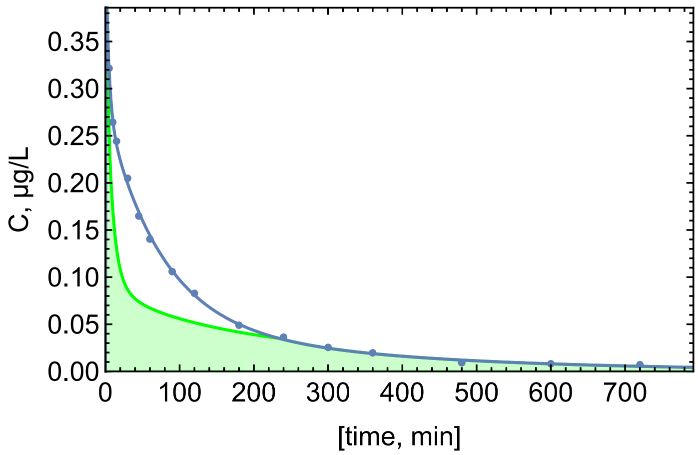
In[∘]:=
```
eocfum = overlap2 / aucintIV
```

Out[∘]= 0.851665

In[]:=
```
eocpqnet = overlap3 / aucintIV
```
Out[]=
```
0.904557
```

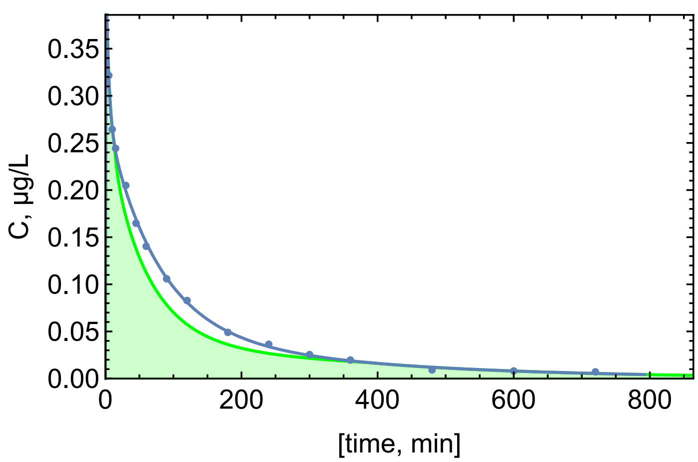
In[]:=
```
plotoverlap1 = Plot[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvp[t]) /. pbpk1],
    {t, 0, Max[tt] 1.2}, PlotRange → {{0, 1.1 Max[tt]}, {0, 1.2 Max[ct]}},
    PlotStyle → Green, Filling → Axis, Frame → True,
    FrameStyle → Directive[Black, 14, Thickness[0.003]],
    LabelStyle → (FontFamily → "Arial"), FrameLabel → {"[time, min]", "C, µg/L"}];
```

In[]:=
```
Show[plotoverlap1, plotfit4, plotfit3]
```
Out[]=



In[]:=
```
plotoverlap2 = Plot[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvp[t]) /. pbpk2],
    {t, 0, Max[tt] 1.2}, PlotRange → {{0, Max[tt] 1.2}, {0, 1.2 Max[ct]}},
    PlotStyle → Green, Filling → Axis, Frame → True,
    FrameStyle → Directive[Black, 14, Thickness[0.003]],
    LabelStyle → (FontFamily → "Arial"), FrameLabel → {"[time, min]", "C, µg/L"}];
```

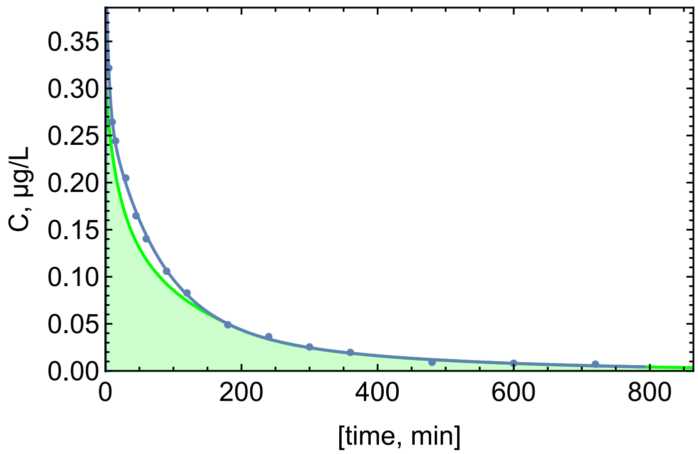
In[]:=
```
Show[plotoverlap2, plotfit4, plotfit3]
```
Out[]=



In[∘]:=
```
plotoverlap3 = Plot[Min[(Xc[t] / V1) /. modelpkiv2, (70. / avgwt Cvb[t] / bp) /. pbpk3],
   {t, 0, Max[tt] 1.2}, PlotRange → {{0, Max[tt] 1.2}, {0, 1.2 Max[ct]}},
   PlotStyle → Green, Filling → Axis, Frame → True,
   FrameStyle → Directive[Black, 14, Thickness[0.003]],
   LabelStyle → (FontFamily → "Arial"), FrameLabel → {"[time, min]", "C, μg/L"}];
```

In[∘]:=
```
Show[plotoverlap3, plotfit4, plotfit3]
```

Out[∘]=



In[∘]:=
```
TableForm[{{"Vss expt", "Vss RR", "Vss fum", "Vss PermQ", "t^1/2 expt", "t^1/2 RR",
   "t^1/2 fum", "t^1/2 PermQ", "EOC RR", "EOC fum", "EOC PermQ"}, {vssnc, vss1,
   vss2, vss3, thalfexp, thalf1, thalf2, thalf3, eocrodgers, eocfum, eocpqnet}}]
```

Out[∘]//TableForm=

Vss expt	Vss RR	Vss fum	Vss PermQ	$t^{1/2}$ expt	$t^{1/2}$ RR	$t^{1/2}$ fum	$t^{1/2}$ P
55.8876	123.183	71.3616	99.6049	214.006	382.76	296.811	407.7