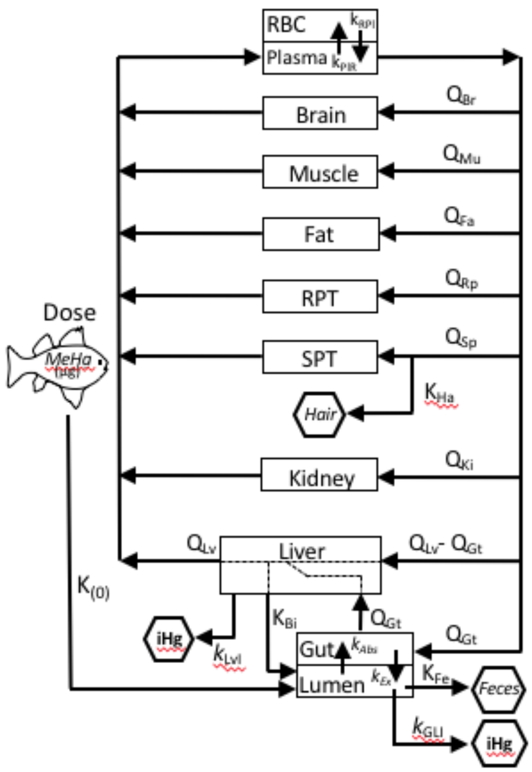
In[∘]:=
```
ClearAll[Evaluate[Context[] <> "*"]]
```

In[147]:=
```
(*Part 1 - constant definitions *)

(*System schema:*)
```




```
;

child = 1;
adultMale = 2;
adultFemale = 3;

currentTarget = adultFemale;
(*Edit this to change the target demographic of the model*)

OrganScaleFactor[bodyMass_] :=
  OrganScaleFactor[bodyMass] = bodyMass^1 / weightArray[[currentTarget]]^1;
FlowScaleFactor[bodyMass_] := FlowScaleFactor[bodyMass] =
   bodyMass^0.75 / weightArray[[currentTarget]]^0.75;
RateScaleFactor[bodyMass_] := RateScaleFactor[bodyMass] =
   bodyMass^-0.25 / weightArray[[currentTarget]]^-0.25;

targetWeight = 60; (*kg,
the weight of the person to whom we are applying the model*)
```

```
weightArray = {19.0, 73.0, 60.0}; (*"Average" weight for child, man, woman*)

(* Organ Volumes (L)*)
totalRichlyPerfusedVolArray = {1.00, 3.72, 2.87} OrganScaleFactor[targetWeight];
totalSlowlyPerfusedVolArray = {0.7, 4.0, 4.0} OrganScaleFactor[targetWeight];
brainVolArray = {1.39, 1.34, 1.20} OrganScaleFactor[targetWeight];
kidneyVolArray = {0.09, 0.32, 0.26} OrganScaleFactor[targetWeight];
fatVolArray = {3.60, 14.60, 18.00} OrganScaleFactor[targetWeight];
liverVolArray = {0.50, 1.57, 1.35} OrganScaleFactor[targetWeight];
gutVolArray = {0.28, 1.23, 1.17} OrganScaleFactor[targetWeight];
lumenVolArray = {0.30, 0.9, 0.83} OrganScaleFactor[targetWeight];
(*from ICRP 89 pg. 132 *)
plasmaVolArray = {0.97, 3.46, 2.68} OrganScaleFactor[targetWeight]
bloodcellVolArray = {0.49, 2.36, 1.46} OrganScaleFactor[targetWeight]
skeletalMuscleVolArray = {4.9, 32, 21} OrganScaleFactor[targetWeight];


(* Plasma Flow values for various organs (L/hr) * *Note,
(VPl/(VPl+VRbc)) is the plasma volume fraction. The '60' is for
 a conversion from minutes to hours, (from Price et al. 2003)*)
totalRichlyPerfusedFlowArray =
  (VPl / (VPl + VRbc)) 60 {0.77, 2.60, 2.21} FlowScaleFactor[targetWeight];
totalSlowlyPerfusedFlowArray = (VPl / (VPl + VRbc)) 60
   {0.02, 0.12, 0.12} FlowScaleFactor[targetWeight];
brainFlowArray = (VPl / (VPl + VRbc)) 60 {0.72, 0.68, 0.63}
   FlowScaleFactor[targetWeight];
kidneyFlowArray = (VPl / (VPl + VRbc)) 60 {0.33, 01.17, 0.85}
   FlowScaleFactor[targetWeight];
liverFlowArray = (VPl / (VPl + VRbc)) 60 {0.46, 1.32, 1.35}
   FlowScaleFactor[targetWeight];
gutFlowArray = (VPl / (VPl + VRbc)) 60 {0.22, 0.93, 0.91}
   FlowScaleFactor[targetWeight];
skeletalMuscleFlowArray = (VPl / (VPl + VRbc)) 60
   {0.15, 0.95, 0.63} FlowScaleFactor[targetWeight];
fatFlowArray = (VPl / (VPl + VRbc)) 60 {0.11, 0.29, 0.54} FlowScaleFactor[targetWeight];
(*Total Fat values from Price et al. 2003*)

(*Partition Coefficients for MeHg (unit-less),
X 10 to convert blood value to plasma value*)
PBr = 10 × 3;
PMu = 10 × 2; (*Not given explicitly by Clewell;
using the value for slowly perfused tissue.*)
PRp = 10 × 1;
```

```
PSp = 10 × 2;
PLv = 10 × 5;
PGt = 10 × 1;
PKi = 10 × 4;
PFa = 10 × 0.15; (*Clewell,personal comm.*)
PHa = 10 × 300; (*MR calculation 8/1/20*)

(*Kinetic Parameters (K = L/hr, k = /hr; inferred from model fitting*)
KFeArray = {0.00208, 0.00625, 0.005 } FlowScaleFactor[targetWeight];
(* From ICRP Pub 89,p.130 *)

KHaArray = {0.0000228, 0.0000399, 0.0000336} FlowScaleFactor[targetWeight];
(* From MR calculation 8/1/30; units are L/hr*)

"KBi : "
KBi = 0.00035 ( liverVolArray [[currentTarget]]) 1000
(*this is for flow of MeHg from liver to intestinal lumen. effectively
 a "clearance" value. Male:0.55 L/hr for liver of size 1.57L (1570gm);
0.00035L/hr/gm liver. A multiplier of 1000 is
 needed to convert liver volumes from L to g*)

"kGLI : "
kGLI = 0.08 RateScaleFactor[targetWeight]

"KFe : "
KFe = KFeArray[[currentTarget]]

"KHa : "
KHa = KHaArray[[currentTarget]]
(*flow of hair out of system, MR calulation 8/10/20*)

"kLvI : "
kLvI = 0.001 RateScaleFactor[targetWeight]

kAbs = 0.3 RateScaleFactor[targetWeight];

kEx = 0.10 RateScaleFactor[targetWeight];

(*Oral absobtion half-life,
going from consumption to entry into the intestine (units=hr):*)
AbsorptionHalfLife = 1/10;

Time = 50 * 24; (* x 24 hours = days*)
```

```
Ymax = 10;

n = 1; (*number of doses*)

doseDelay = 7 * 24; (*defines one dose every 7 days*)

NmanipSlowDoses[t_, n_, doseDelay_, Dose_, AbsorptionHalfLife_] :=
```

$$\text{Dose} \sum_{i=0}^{\text{IntegerPart}[n]-1} \partial_t \left(1 - \left(\frac{1}{2}\right)^{\frac{t - i\ \text{doseDelay}}{\text{AbsorptionHalfLife}}}\right) \text{HeavisideTheta}[t - i\ \text{doseDelay}]$$

```
(*The values we define below are what will actually be used in the model. This
 way, they're automatically updated when we change "currentTarget"*)

weight = weightArray[[currentTarget]];
VBr = brainVolArray[[currentTarget]];
VKi = kidneyVolArray[[currentTarget]];
VLv = liverVolArray[[currentTarget]];
VGt = gutVolArray[[currentTarget]];
VGL = lumenVolArray[[currentTarget]];
VPl = plasmaVolArray[[currentTarget]];
VMu = skeletalMuscleVolArray[[currentTarget]];
VFa = fatVolArray[[currentTarget]];
VRbc = bloodcellVolArray[[currentTarget]];
VRp = totalRichlyPerfusedVolArray[[currentTarget]];
VSp = totalSlowlyPerfusedVolArray[[currentTarget]];

QBr = brainFlowArray[[currentTarget]];
QKi = kidneyFlowArray[[currentTarget]];
QFa = fatFlowArray[[currentTarget]];
QLv = liverFlowArray[[currentTarget]];
QGt = gutFlowArray[[currentTarget]];
QMu = skeletalMuscleFlowArray[[currentTarget]];
QRp = totalRichlyPerfusedFlowArray[[currentTarget]];
QSp = totalSlowlyPerfusedFlowArray[[currentTarget]];

"fromRBCToplasma : "
kRPl = 0.3 RateScaleFactor[targetWeight];

"fromplasmaToRBC : "
kPlR = 3 RateScaleFactor[targetWeight];

(*Part 2 - Model definition:  *)
```

```
SystemSolutionAndTime = AbsoluteTiming[NDSolve[{
    (*  16  *)
    ARBC'[t] == -kRPl ARBC[t] + kPlR APl[t],
    ARBC[0] == 0,

    (*  1  *)
    APl'[t] == (QLv ALv[t]/(VLv PLv) - (QLv - QGt) APl[t]/VPl) +
      QBr (ABr[t]/(VBr PBr) - APl[t]/VPl) + QSp (ASp[t]/(VSp PSp) - APl[t]/VPl) + QRp (ARp[t]/(VRp PRp) - APl[t]/VPl) +
      QKi (AKi[t]/(VKi PKi) - APl[t]/VPl) + QMu (AMu[t]/(VMu PMu) - APl[t]/VPl) + QFa (AFa[t]/(VFa PFa) - APl[t]/VPl) -
      QGt APl[t]/VPl + kRPl (ARBC[t]) - kPlR (APl[t]) - KHa (APl[t]/VPl) PHa,
    APl[0] == 0,

    (*  2  *)
    ABr'[t] == - QBr (ABr[t]/(VBr PBr) - APl[t]/VPl),
    ABr[0] == 0,

    (*  3  *)
    AMu'[t] == -QMu (AMu[t]/(VMu PMu) - APl[t]/VPl),
    AMu[0] == 0,

    (*  4  *)
    AFa'[t] == -QFa (AFa[t]/(VFa PFa) - APl[t]/VPl),
    AFa[0]  == 0,

    (*  5  *)
    ARp'[t] == -QRp (ARp[t]/(VRp PRp) - APl[t]/VPl),
    ARp[0] == 0,

    (*  6  *)
    ASp'[t] == -QSp (ASp[t]/(VSp PSp) - APl[t]/VPl),
    ASp[0] == 0,

    (*  7  *)
    ALv'[t] ==
     -(QLv ALv[t]/(VLv PLv) - (QLv - QGt) APl[t]/VPl - QGt AGt[t]/(VGt PGt)) - KBi APl[t]/VPl - kLvI ALv[t],
```

ALv[0] == 0,

(* 8 *)

$$\text{AGt}'[t] == -\text{QGt}\left(\frac{\text{AGt}[t]}{\text{VGt PGt}} - \frac{\text{APl}[t]}{\text{VPl}}\right) + \text{kAbs AGL}[t] - \text{kEx AGt}[t],$$

AGt[0] == 0,

(* 9 **NOTE: THE DOSE AMOUNT IN THIS LINE** *)

$$\text{AGL}'[t] == \text{KBi}\,\frac{\text{APl}[t]}{\text{VPl}} - \text{kAbs AGL}[t] - \text{KFe}\,\frac{\text{AGL}[t]}{\text{VGL}} +$$

NmanipSlowDoses[t, n, doseDelay, 42.0(*dose amount, μg MeHg*) , AbsorptionHalfLife] - kGLI AGL[t] + kEx AGt[t],

AGL[0] == 0,

(* 10 *)

$$\text{AKi}'[t] == -\text{QKi}\left(\frac{\text{AKi}[t]}{\text{VKi PKi}} - \frac{\text{APl}[t]}{\text{VPl}}\right),$$

AKi[0] == 0,

(* 11 *)

AIHGurine'[t] == kLvI ALv[t],

AIHGurine[0] == 0,

(* 12 *)

AIHGfeces'[t] == kGLI AGL[t],

AIHGfeces[0] == 0,

(* 13 *)

$$\text{AMeHgfeces}'[t] == \text{KFe}\,\frac{\text{AGL}[t]}{\text{VGL}},$$

AMeHgfeces[0] == 0,

(* 14 *)

$$\text{ABiTransTot}'[t] == \text{KBi}\,\frac{\text{APl}[t]}{\text{VPl}},$$

ABiTransTot[0] == 0,

(* 15 *)

AGtTransTot'[t] == kEx AGt[t],

AGtTransTot[0] == 0,

(* 17 *)

$$\text{AHa}'[t] == \text{KHa}\,\frac{\text{APl}[t]}{\text{VPl}}\,\text{PHa},$$

```
    AHa[0] == 0
   },
   {(*  1  *)APl,
    (*  2  *)ABr,
    (*  3  *)AMu,
    (*  4  *)AFa,
    (*  5  *)ARp,
    (*  6  *)ASp,
    (*  7  *)ALv,
    (*  8  *)AGt,
    (*  9  *)AGL,
    (*  10 *)AKi,
    (*  11 *)AIHGurine,
    (*  12 *)AIHGfeces,
    (*  13 *)AMeHgfeces,
    (*  14 *)ABiTransTot,
    (*  15 *)AGtTransTot,
    (*  16 *)ARBC,
    (*  17 *)AHa

   }, {t, 0, 42 000}, SolveDelayed → True, WorkingPrecision → MachinePrecision]];
Text["Time taken to solve system:"]
SystemSolutionAndTime[[1]]
SystemSolution = SystemSolutionAndTime[[2]];
```

Out[161]= {0.97, 3.46, 2.68}

Out[162]= {0.49, 2.36, 1.46}

Out[177]= KBi :

Out[178]= 0.4725

Out[179]= kGLI :

Out[180]= 0.08

Out[181]= KFe :

Out[182]= 0.005

Out[183]= KHa :

Out[184]= 0.0000336

Out[185]= kLvI :

Out[186]= 0.001

Out[212]= fromRBCToplasma :

Out[214]= fromplasmaToRBC :

Out[217]= Time taken to solve system:

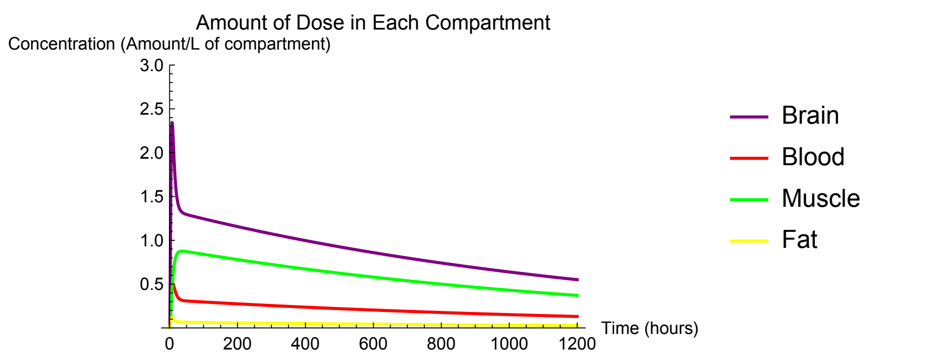
Out[218]= 0.09183

In[236]:=
```
(*Part 3 - Model analysis
  Now that the system takes a few minutes to solve,
it's best if we separate out the analysis from the system solution,
so we don't have to re-solve the system every time*)

Plot[{
  Evaluate[ABr[t ] /. SystemSolution[[1]][[2]]] / VBr,
  (Evaluate[APl[t] /. SystemSolution[[1]][[1]] +
     Evaluate[ARBC[t ] /. SystemSolution[[1]][[16]]]) / (VRbc + VPl),
  Evaluate[AMu[t ] /. SystemSolution[[1]][[3]]] / VMu,
  Evaluate[AFa[t] /. SystemSolution[[1]][[4]]] / VFa
  }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Concentration (Amount/L of compartment)"},
 PlotLegends → {"Brain", "Blood", "Muscle", "Fat"},
 ImageSize → Medium, PlotLabel → "Amount of Dose in Each Compartment",
 PlotStyle → { Purple, Red, Green, Yellow}, PlotRange → {0, 3}, PlotPoints → 200]

Plot[{
  (Evaluate[APl[t] /. SystemSolution[[1]][[1]] +
     Evaluate[ARBC[t ] /. SystemSolution[[1]][[16]]]) / (VRbc + VPl)
 }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Concentration (MeHg (μg/L))"},
 PlotLegends → {"MeHg in Blood"},
 ImageSize → Medium, PlotLabel → "Blood Concentraion of MeHg",
 PlotStyle → {Blue}, PlotRange → {0, 0.6}, PlotPoints → 200]

Plot[{
  Evaluate[APl[t] /. SystemSolution[[1]][[1]]] / VPl,
  Evaluate[ARBC[t ] /. SystemSolution[[1]][[16]]] / VRbc,
  (Evaluate[APl[t] /. SystemSolution[[1]][[1]] +
     Evaluate[ARBC[t ] /. SystemSolution[[1]][[16]]]) / (VRbc + VPl)
  }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Concentration (Amount/L of compartment)"},
 PlotLegends → {"Plasma", "RBC", "Blood",},
 ImageSize → Medium, PlotLabel → "Amount of Dose in Each Compartment",
 PlotStyle → { Orange, Purple, Red}, PlotRange → {0, 2}, PlotPoints → 200]
```

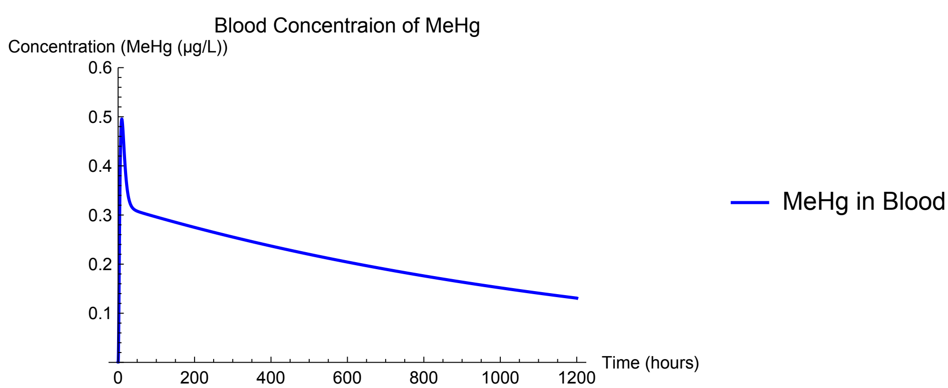
```
Plot[{
   Evaluate[ALv[t ] /. SystemSolution[[1]][[7]]] / VLv,
   Evaluate[AGt[t ] /. SystemSolution[[1]][[8]]] / VGt,
   Evaluate[AKi[t ] /. SystemSolution[[1]][[10]]] / VKi
   }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Concentration (Amount/L of compartment)"},
 PlotLegends → {"Liver", "Gut", "Kidney"},
 ImageSize → Medium, PlotLabel → "Amount of Dose in Each Compartment",
 PlotStyle → {Blue, Brown , Pink}, PlotRange → {0, 10}, MaxRecursion → 7]

Plot[{
   Evaluate[AGL[t ] /. SystemSolution[[1]][[9]]] / VGL
  }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Concentration (Amount/L of compartment)"},
 PlotLegends → {"Gut Lumen"},
 ImageSize → Medium, PlotLabel → "Amount of Dose in Each Compartment",
 PlotStyle → {{DotDashed, Thick, Brown}}, PlotRange → {0, 60}, MaxRecursion → 9]

Plot[{
   Evaluate[AIHGfeces[t ] /. SystemSolution[[1]][[12]]] / 51.1,
   Evaluate[AHa[t ] /. SystemSolution[[1]][[17]]] / 51.1,
   Evaluate[AIHGurine[t ] /. SystemSolution[[1]][[11]]] / 51.1,
   Evaluate[AMeHgfeces[t ] /. SystemSolution[[1]][[13]]] / 51.1
   }, {t, 0, Time},
 AxesLabel → {"Time (hours)", "Amount"},
 PlotLegends → {"iHg feces" , "MeHg hair", "iHg urine", "MeHg feces"},
 ImageSize → Medium,
 PlotLabel → "fraction of dose Eliminated Through Each Outflow",
 PlotStyle → {{Brown}, { Black}, {Dotted, Red}, {Dotted, Brown} },
 PlotRange → {0, 1}]

Plot[Evaluate[AGtTransTot[t] /. SystemSolution[[1]][[15]]] / Evaluate[ABiTransTot[t] /. SystemSolution[[1]][[14]]], {t, 0, Time},
 AxesLabel → {"Time (hours)", "Ratio"}, PlotLegends → { "Gut:Bile"},
 ImageSize → Medium, PlotLabel → "Relative input to gut lumen", PlotRange → {0, 10}]

(* this is used for half-life calculation*)
goodTime = n doseDelay + 2000;
Text["Elimination half-life for the blood compartment in days: "]
(NMinimize[{(Evaluate[APl[t] /. SystemSolution[[1]][[1]]] -
          0.5 Evaluate[ APl[goodTime] /. SystemSolution[[1]][[1]]]) ^2 ,
```

```
        t > goodTime}, t][[2]][[1]][[2]] - goodTime) / 24

LogPlot[Evaluate[APl[t] /. SystemSolution[[1]][[1]]], {t, goodTime, 5 goodTime},
 PlotLabel → "Log Plot of Blood Concentration During Elimination Phase",
 ImageSize → Medium,
 AxesLabel → {"Time (hours)", "Blood Concentration (Amount/L of Compartment)"}]
Text["Half-life of blood concentration as calculated by best fit for log data:"]

modelFit = LinearModelFit[Table[Log[Evaluate[APl[i] /. SystemSolution⟦1⟧⟦1⟧]],
    {i, n doseDelay, n doseDelay + 50}], x, x];
-          Log[2]
  ─────────────────────────
  ∂x Normal[modelFit] 24
Text["R² value for model fit:"]
modelFit["RSquared"]
```

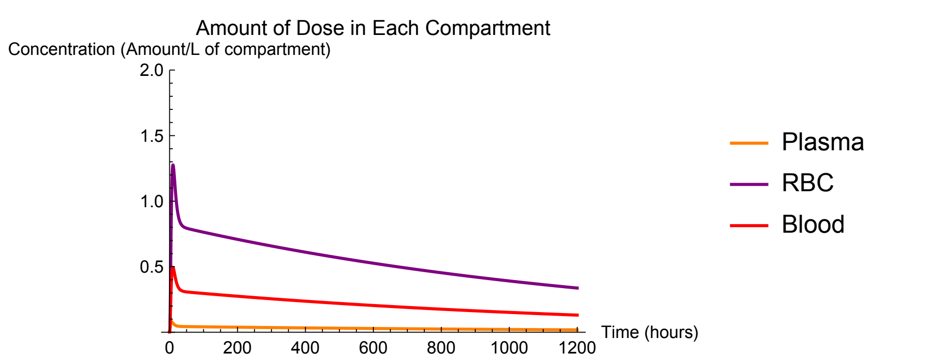
Out[236]=



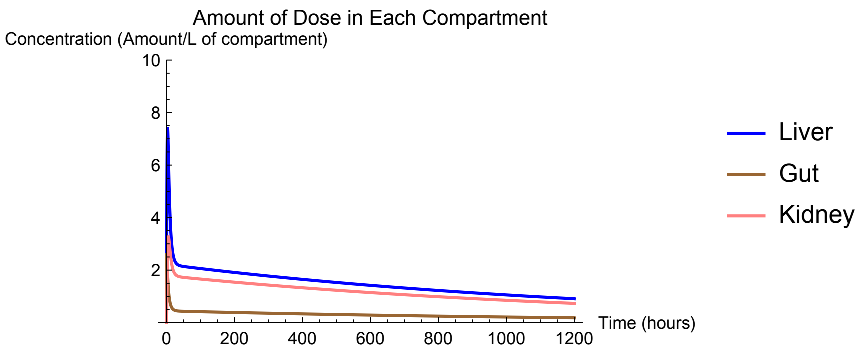
Out[237]=



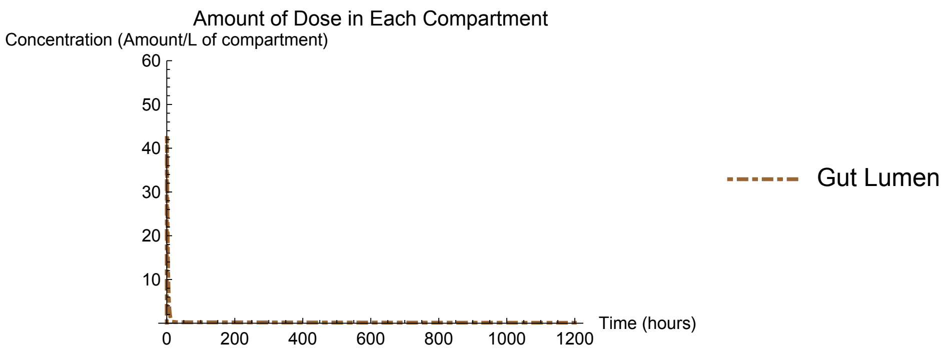
Out[238]=



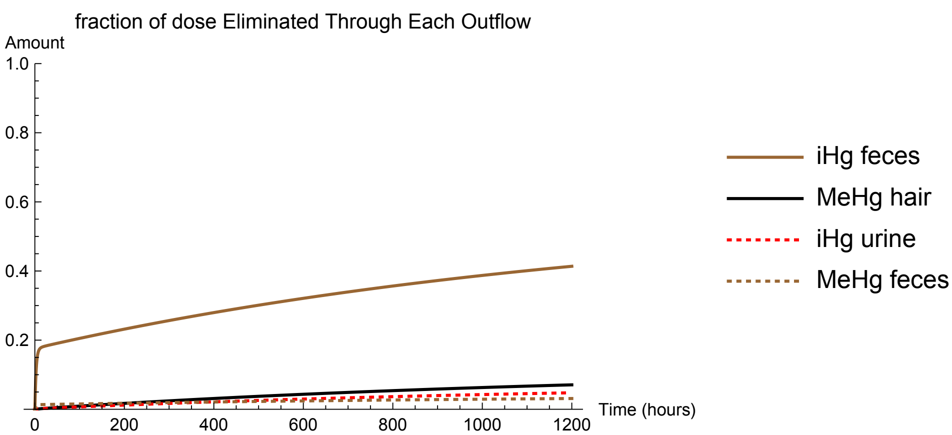
Out[239]=



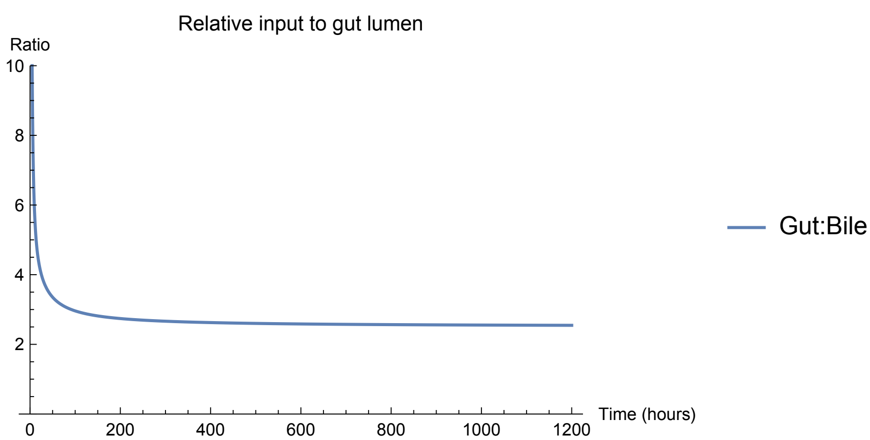
Out[240]=



Out[241]=



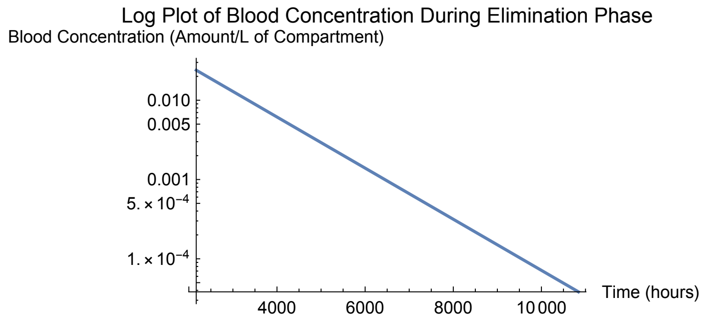
Out[242]=



Out[244]= Elimination half–life for the blood compartment in days:

Out[245]= 38.9031

Out[246]=



Out[247]= Half–life of blood concentration as calculated by best fit for log data:

Out[249]= 38.9031

Out[250]= R^2 value for model fit:

Out[251]= 1.