PROGRAM: PBPK model for extended release Methylphenidate (MPH) in adult humans.

!! Note parameter values in the csl codes may be replaced by m files

INITIAL

!! MODEL CONSTANTS USED FOR the absorption model

!! EXCHANGE SURFACE AREA, CM^2

CONSTANT ESA_DUO = 19995
CONSTANT ESA_JEJ1 = 77482
CONSTANT ESA_JEJ2 = 69217
CONSTANT ESA_ILL1 = 60952
CONSTANT ESA_ILL2 = 52171
CONSTANT ESA_ILL3 = 43906
CONSTANT ESA_CECUM = 1964
CONSTANT ESA_ASCENDING = 2961

!! INTESTINAL TRANSIT TIMES ARE IN HOUR (Almukainzi 2014)

CONSTANT TSTOMACH = 0.25
CONSTANT TDUO = 0.26
CONSTANT TJEJ1 = 0.95
CONSTANT TJEJ2 = 0.76
CONSTANT TILL1 = 0.59
CONSTANT TILL2 = 0.43
CONSTANT TILL3 = 0.31
CONSTANT Tcecum = 4.5
CONSTANT Tascending = 13.5

!! INTESTINAL PH values (Almukainzi 2014)

CONSTANT PHSTOMACH = 1.3
CONSTANT PHDUO = 6.0
CONSTANT PHJEJ1 = 6.2
CONSTANT PHJEJ2 = 6.4
CONSTANT PHILL1 = 6.6
CONSTANT PHILL2 = 6.9
CONSTANT PHILL3 = 7.4
CONSTANT PHcecum = 6.4
CONSTANT PHascending = 6.8

!! Volume of the lumen (mL) (Almukainzi 2014)

CONSTANT VSTOMACH = 50
CONSTANT VDUO = 48
CONSTANT VJEJ1 = 175
CONSTANT VJEJ2 = 140
CONSTANT VILL1 = 109
CONSTANT VILL2 = 79
CONSTANT VILL3 = 56
CONSTANT Vcecum = 53
CONSTANT Vascending = 57

!! PHYSCHEM PROPERTIES

CONSTANT ION = 1  ! NOTE -1=Acid, 0=Neutral, 1=Base, 2=Zwitterion ! Singh et al. 2005

CONSTANT PKABASE1 = 8.77  ! Singh et al. 2005
CONSTANT PKABASE2 = 8.77
CONSTANT PKAACID1 = 16
CONSTANT PKAACID2 = 16
CONSTANT MW = 233.3062  ! g/mol
CONSTANT MW_WATER = 18.02  ! g/mol

!! SOLUBILITY - Estimated using ADMET Predictor (Simulations Plus, Inc.)

CONSTANT SOL = 9250  ! mg/L
CONSTANT REFPHSOL = 10.58  ! reference pH of the user solubility

!! LOGICAL CONSTANTS
LOGICAL INTESTINAL
CONSTANT INTESTINAL = 0 ! Not intestinal SOL, False

!!CONSTANTS FOR Permeability ESTIMATION (HPEFF AND DIFF)
CONSTANT CACO2PEFF = 24.7! MDCKII 24.7 x 10^-6 cm/s; in the
form of 1 not 1e10^-6 cm/s; (Feng 2008)
CONSTANT CACO2PEFF_cecum = 24.7!
CONSTANT CACO2PEFF_ascending = 24.7!

! For dissolution constant (Kd) calculation (dissolve)
CONSTANT DIFFCOEFF_IR = 1e-4 ! cm^2/min,
default value 10-4 cm2/min
CONSTANT rho = 1 ! particle density in g/mL
CONSTANT rparticle = 5.0 ! radius in um,
default value 5 um; effective drug particle radius !1 um = 0.0001 cm
CONSTANT DLT = 30 ! diffusion layer thickness in um, default 30 um

!!!!!!!!!!!!!!!!!!! Physiological Parameters
!!!!!!!!!!!!!!!!!!!

! Fractional Blood Flows to Tissues (fraction of cardiac output)
CONSTANT QCC = 15.87 ! (L/h/kg^0.75) | Cardiac output
CONSTANT QFatC = 0.053 ! | Fractional blood flow to the fats; female: 0.091
CONSTANT QbrainC = 0.11 ! | Fractional blood flow to the brain;
CONSTANT QgonadC = 0.00054 ! | Fractional blood flow to the gonads; female: 0.00022
CONSTANT QHeartC = 0.038 ! | Fractional blood flow to the heart; female: 0.047
CONSTANT QLiverC = 0.255 ! | Fractional blood flow to the liver; total blood flow, portal plus arterial; 0.27 for female
CONSTANT QDUOC = 0.02375 ! ! Fractioanl blood flow to the duo; 0.025625 for females obtained by QgutC/8
CONSTANT QJEJ1C = 0.02375 !0.025625
CONSTANT QJEJ2C = 0.02375 !0.025625
CONSTANT QILL1C = 0.02375 !0.025625
CONSTANT QILL2C = 0.02375 !0.025625
CONSTANT QILL3C = 0.02375 !0.025625
CONSTANT QCECUMC = 0.02375 !0.025625
CONSTANT QASCENDI NGC = 0.02375 !0.025625

! Fractional Tissue Volumes of BW
CONSTANT BW = 80 !(kg) | Body weight
CONSTANT VplasmaC = 0.0435 !(%BW) | Fractional Volume of the Plasma
CONSTANT VFatC = 0.213 !(%BW) | Fractional Volume of the fat; female: 0.327
CONSTANT VbrainC = 0.02 !(%BW) | Fractional Volume of the brain
CONSTANT VgonadC = 0.0007 !(%BW) | Fractional Volume of the gonads; female: 0.0027
CONSTANT VheartC = 0.0045 !(%BW) | Fractional Volume of the heart; female: 0.0042
CONSTANT VLiverC = 0.026 !(%BW) | Fractional Volume of the liver
CONSTANT VbodyC = 0.6 !(%BW) | Fractional Volume of the body

2002 Table 6.6 and 6.7
CONSTANT VMEMDUOC = 0.000767 ! Female: 0.000877 Valentin
CONSTANT VMEMJEJ1C = 0.00192 ! Female 0.00192
CONSTANT VMEME|E|2C = 0.00192 !Female 0.00192
CONSTANT VMEME|L|L1C = 0.00142 !Female 0.00149
CONSTANT VMEME|L|L2C = 0.00142 !Female 0.00149
CONSTANT VMEME|L|L3C = 0.00142 !Female 0.00149
CONSTANT VMEME|C|O|L|O|M|M|E|M|C = 0.00125 !Female 0.00137 |Fractional

Weight of cecum and ascending colon obtained from ICRP Publication 89, Table 6.9, 6.10

CONSTANT VMEME|C|E|M|C|U|M|M|E|M|C = 0.0004 !!0.0004 !Adjusted based on length
CONSTANT VMEME|A|S|C|E|N|D|I|N|G|M|E|M|C = 0.000848 !!0.00093

!!!!!!!!!!!!!!!!!!!!!!!!!! Chemical Specific Parameters!!!!!!!!!!!!!!!!!!!!!!!!!!

! Partition Coefficients for MPH

CONSTANT PFat = 1.79 !(no units)|Partitioning into the fat (Fat/blood)
CONSTANT Pbrain = 6.07 !(no units)|Partitioning into the brain (Brain/blood)
CONSTANT PRich = 5.66 !(no units)|Partitioning into the richly perfused tissues (Richly perfused/blood)
CONSTANT PSlow = 2.47 !(no units)|Partitioning into the slowly perfused tissues (Slowly perfused/blood)

CONSTANT PGonad = 3.12 !(no units)|Partitioning into the gonads (Gonads/blood)
CONSTANT Pheart = 2.19 !(no units)|Partitioning into the heart (Heart/blood)
CONSTANT PLiver = 5.66 !(no units)|Partitioning into the liver (Liver/blood)
CONSTANT KPGUT = 5.66 !set to the value of liver;
CONSTANT KPliver = 5.66!

! Kinetic Parameters

!! MPH oral uptake and metabolism

CONSTANT Kmliverd = 27600!(ug/L) |Km of d-MPH hydrolysis in the liver
CONSTANT Kmliverl = 10172!(ug/L) |Km of l-MPH hydrolysis in the liver
CONSTANT VmaxliverdC = 25826!(ug/h/kg^0.75)|Vmax of d-MPH hydrolysis in the liver
CONSTANT VmaxliverlC = 52404!(ug/h/kg^0.75)|Vmax of l-MPH hydrolysis in the liver
CONSTANT kmetdC = 0.43 !(L/h/kg^0.75) |Clearance term of d-MPH oxidation in the liver
CONSTANT kmetlC = 0.43 !(L/h/kg^0.75) |Clearance term of l-MPH oxidation in the liver

CONSTANT K5lC = 37 !(1/h/kg^0.75) |Metabolism of d-MPH in the small intestine
CONSTANT K5dC = 37 !(1/h/kg^0.75) |Metabolism of l-MPH in the small intestine

CONSTANT K5lC_cecum = 37 !(1/h/kg^0.75) |Metabolism of d-MPH in the cecum
CONSTANT K5dC_cecum = 37 !(1/h/kg^0.75) |Metabolism of l-MPH in the cecum

CONSTANT K5lC_ascending = 37 !(1/h/kg^0.75) |Metabolism of d-MPH in the ascending colon
CONSTANT K5dC_ascending = 37 !(1/h/kg^0.75) |Metabolism of l-MPH in the ascending colon

CONSTANT Fmetabolized in the gut undergoing hydrolysis = 0.8 !(no units) |Fraction of MPH

!! Urinary excretion of RA
CONSTANT Ku_RAdC = 0.305 !(L/h/kg^0.75) | Urinary excretion of d-RA
CONSTANT Ku_RAlC = 0.168 !(L/h/kg^0.75) | Urinary excretion of l-RA

!!!!!!!!!!!!!!!! Dosing Parameters!!!!!!!!!!!!!!!!!!!!

CONSTANT TSTOP = 24 !(h) | simulation period
CONSTANT tlen = 0.05 !(h) | Length of oral gavage exposure
CONSTANT IVTime = 0.01 !(h) | Length of IV dosing

CONSTANT IVdoseCd = 0.0 !(ug/Kg) | IV dose for d-MPH
CONSTANT IVdoseCl = 0.0 !(ug/Kg) | IV dose for l-MPH

CONSTANT AdosedIR = 0.0 !(ug) | Oral dose of IR-dMPH
CONSTANT AdosedER = 0.0 !(ug) | Oral dose of ER-dMPH

!!MW, MPHHCL = 269.77; MPH: 233.3062; RA: 219.28

END ! INITIAL

DYNAMIC

ALGORITHM IALG = 1!
NSTEMPS NSTP = 1
MAXTERVAL MAXT = 1.0e9
MINTERVAL MINT = 1.0e-9
CINTERVAL CINT = 0.01!

DERIVATIVE

! scaled blood flows
QC = QCC*BW^0.75 !(L/h) | Cardiac Output
QN = QFatC*QC !(L/h) | Blood
QB = QBrainC*QC !(L/h) | Blood
QO = QgonadC*QC !(L/h) | Blood
QL = QLiverC*QC !(L/h) | Blood
QH = QHeartC*QC !(L/h) | Blood
QS = 0.24*QC - QFat - QHeart !(L/h) | Blood
QR = 0.76*QC - QLiver - Qgonad - Qbrain !(L/h) | Blood
QG = QGUTC*QC !(L/h) | Blood
QD = QDUOC*QC !(L/h) | Blood
QD1 = QE1*C*QC !(L/h) | Blood
QD2 = QE2*C*QC !(L/h) | Blood
SBppe PBPK Code.txt

Q1LL1 = Q1LL1C*QC
Q1LL2 = Q1LL2C*QC
Q1LL3 = Q1LL3C*QC
QCECUM = QCECUMC*QC
QASCENDING = QASCENDINGC*QC

!Scaled tissue volumes

VLiver = VLiverC*BW
!(L) Volume of the liver
VFat = VFatC*BW
!(L) Volume of the fat
Vgonad = VgonadC*BW
!(L) Volume of the gonads
VS = 0.60*BW -VFat-Vheart
!(L) Volume of the slowly perfused tissues
VR = 0.33*BW -VLiver-VPlasma
- Vgonad-Vbrain-VMEMDUO-VMEM|E|1-VMEM|E|2-VMEMILL1-VMEMILL2-VMEMILL3
- VMEMCECUM-VMEMASCENDING !(L) Volume of the rapidly perfused tissues
VPlasma = VPlasmaC*BW
!(L) Volume of the plasma
Vbrain = VbrainC*BW
!(L) Volume of the brain
Vheart = VheartC*BW
!(L) Volume of the heart
VMEMDUO = VMEMDUOC*BW
!(L) Volume of the Duodenum
Vbody = VbodyC*BW
!(L) Volume of the body compartment
VMEMASCENDING = BW*VMEMASCENDINGMEMC
VMEMCECUM = BW*VMEMCECUMMEMC
VMEMILL1 = VMEMILL1C*BW
VMEMILL2 = VMEMILL2C*BW
VMEMILL3 = VMEMILL3C*BW

!!!$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$ SET UP GUT PARAMETERS
$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$!!!!! ref: Alex Avdeef 2007 solubility of sparingly-soluble ionizable drugs

!Ionisation terms
IF (ION .EQ. 1 .AND. PKABASE1 .EQ. PKABASE2) THEN ! monoprotic base
HHI NT = 1+(10.0**((PKABASE1 - REFPHSOL))
HHSTOMACH = 1+(10.0**((PKABASE1 - PHSTOMACH))
HHDUO = 1+(10.0**((PKABASE1 - PHDUO))
HH|E|1 = 1+(10.0**((PKABASE1 - PH|E|1))
HH|E|2 = 1+(10.0**((PKABASE1 - PH|E|2))
HHILL1 = 1+(10.0**((PKABASE1 - PHILL1))
HHILL2 = 1+(10.0**((PKABASE1 - PHILL2))
HHILL3 = 1+(10.0**((PKABASE1 - PHILL3))
HHCECUM = 1+(10.0**((PKABASE1 - PHCECUM))
HHASCENDING = 1+(10.0**((PKABASE1 - PHASCENDING))
ELSE IF (ION .EQ. 1) THEN ! diprotic base
HHI NT = 1+(10.0**((max(PKABASE1, PKABASE2) - REFPHSOL)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*REFPHSOL))
HHSTOMACH = 1+(10.0**((max(PKABASE1, PKABASE2) - PHSTOMACH)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHSTOMACH))
HHDUO = 1+(10.0**((max(PKABASE1, PKABASE2) - PHDUO)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHDUO))
HH|E|1 = 1+(10.0**((max(PKABASE1, PKABASE2) - PH|E|1)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PH|E|1))
HH|E|2 = 1+(10.0**((max(PKABASE1, PKABASE2) - PH|E|2)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PH|E|2))
HHILL1 = 1+(10.0**((max(PKABASE1, PKABASE2) - PHILL1)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL1))
HHILL2 = 1+(10.0**((max(PKABASE1, PKABASE2) - PHILL2)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL2))
HHILL3 = 1+(10.0**((max(PKABASE1, PKABASE2) - PHILL3)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL3))
HHCECUM = 1+(10.0**((max(PKABASE1, PKABASE2) - PHCECUM)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHCECUM))
HHASCENDING = 1+(10.0**((max(PKABASE1, PKABASE2) - PHASCENDING)) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHASCENDING))

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Supple PBPK Code.txt

10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL1))
HHILLL2 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHILL2) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL2))
HHILL3 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHILL3) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHILL3))
HHASCENDING = 1+(10.0**(max(PKABASE1, PKABASE2) - PHASCENDING) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHASCENDING))
HHCECUM = 1+(10.0**(PHCECUM - PKABASE2) +
10.0**(PKABASE1, PKABASE2) - PHCECUM) +
10.0**(PKABASE1 + PKABASE2 - 2.0*PHASCENDING))

ELSE IF (ION .EQ. -1 .AND. PKA 1 .EQ. PKA 2) THEN ! monoprotic acid
HHINT = 1+(10.0**(REFPHSOL - PKA 1))
HHSTOMACH = 1+(10.0**(PHSTOMACH - PKA 1))
HDUO = 1+(10.0**(PHDUO - PKA 1))
HHJEJ1 = 1+(10.0**(PHJEJ1 - PKA 1))
HHJEJ2 = 1+(10.0**(PHJEJ2 - PKA 1))
HHILL1 = 1+(10.0**(PHILL1 - PKA 1))
HHILL2 = 1+(10.0**(PHILL2 - PKA 1))
HHILL3 = 1+(10.0**(PHILL3 - PKA 1))
HHASCENDING = 1+(10.0**(PHASCENDING - PKA 1))
HHCECUM = 1+(10.0**(PHCECUM - PKA 1))

ELSE IF (ION .EQ. -1) THEN ! diprotic acid
HHINT = 1+(10.0**(REFPHSOL - min(PKA 1, PKA 2)) +
10.0**(2*REFPHSOL - PKA 1 - PKA 2))
HHSTOMACH = 1+(10.0**(PHSTOMACH - min(PKA 1, PKA 2)) +
10.0**(2*PHSTOMACH - PKA 1 - PKA 2))
HDUO = 1+(10.0**(PHDUO - min(PKA 1, PKA 2)) +
10.0**(2*PHDUO - PKA 1 - PKA 2))
HHJEJ1 = 1+(10.0**(PHJEJ1 - min(PKA 1, PKA 2)) +
10.0**(2*PHJEJ1 - PKA 1 - PKA 2))
HHJEJ2 = 1+(10.0**(PHJEJ2 - min(PKA 1, PKA 2)) +
10.0**(2*PHJEJ2 - PKA 1 - PKA 2))
HHILL1 = 1+(10.0**(PHILL1 - min(PKA 1, PKA 2)) +
10.0**(2*PHILL1 - PKA 1 - PKA 2))
HHILL2 = 1+(10.0**(PHILL2 - min(PKA 1, PKA 2)) +
10.0**(2*PHILL2 - PKA 1 - PKA 2))
HHILL3 = 1+(10.0**(PHILL3 - min(PKA 1, PKA 2)) +
10.0**(2*PHILL3 - PKA 1 - PKA 2))
HHCECUM = 1+(10.0**(PHCECUM - min(PKA 1, PKA 2)) +
10.0**(2*PHCECUM - PKA 1 - PKA 2))
HHASCENDING = 1+(10.0**(PHASCENDING - min(PKA 1, PKA 2)) +
10.0**(2*PHASCENDING - PKA 1 - PKA 2))

ELSE IF (ION .EQ. 2) THEN ! zwitterion
HHINT = 1+(10.0**(max(PKABASE1, PKABASE2) - REFPHSOL) +
10.0**(REFPHSOL - min(PKA 1, PKA 2)) +
10.0**(2*PHSTOMACH - PKA 1 - PKA 2))
HHSTOMACH = 1+(10.0**(max(PKABASE1, PKABASE2) - PHSTOMACH) +
10.0**(2*PHSTOMACH - PKA 1 - PKA 2))
HDUO = 1+(10.0**(max(PKABASE1, PKABASE2) - PHDUO) +
10.0**(2*PHDUO - PKA 1 - PKA 2))
HHJEJ1 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHJEJ1) +
10.0**(2*PHJEJ1 - PKA 1 - PKA 2))
HHJEJ2 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHJEJ2) +
10.0**(2*PHJEJ2 - PKA 1 - PKA 2))
HHILL1 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHILL1) +
10.0**(2*PHILL1 - PKA 1 - PKA 2))
HHILL2 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHILL2) +
10.0**(2*PHILL2 - PKA 1 - PKA 2))
HHILL3 = 1+(10.0**(max(PKABASE1, PKABASE2) - PHILL3) +
10.0**(2*PHILL3 - PKA 1 - PKA 2))
HHCECUM = 1+(10.0**(max(PKABASE1, PKABASE2) - PHCECUM) +
10.0**(2*PHCECUM - PKA 1 - PKA 2))
HHASCENDING = 1+(10.0**(max(PKABASE1, PKABASE2) - PHASCENDING) +
10.0**(2*PHASCENDING - PKA 1 - PKA 2))

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ELSE
! Neutrals
HHINT = 1.0
HHSTOMACH = 1.0
HHDUO = 1.0
HHJEJ1 = 1.0
HHJEJ2 = 1.0
HHILL1 = 1.0
HHILL2 = 1.0
HHILL3 = 1.0
HHCECUM = 1.0
HHASCENDING = 1.0
ENDIF

! Correct solubility for reference PH
! Solubility intrinsic, int., in mg/L ug/mL
! SOL is the input solubility in water, fessif or fassif at the reference PH
! in mg/L
SOLINT = SOL / HHINT

! SOLWATER corrected for each compartment in mg/l to account for effect of PH (ionization)
SOLWATER_STOMACH = SOLINT * HHSTOMACH
SOLWATER_DUO = SOLINT * HHDUO
SOLWATER_JEJ1 = SOLINT * HHJEJ1
SOLWATER_JEJ2 = SOLINT * HHJEJ2
SOLWATER_ILL1 = SOLINT * HHILL1
SOLWATER_ILL2 = SOLINT * HHILL2
SOLWATER_ILL3 = SOLINT * HHILL3
SOLWATER_CECUM = SOLINT * HHCECUM
SOLWATER_ASCENDING = SOLINT * HHASCENDING

! Correct solubility for bile effect
! Mithani 1996 Estimation of the increase in solubility of drugs as a function of bile salt concentration
CONSTANT LOGP = 0.2
IF (INTESTINAL) THEN
LOGSR = 0.606 * LOGP + 2.234 ! bile salt solubilization ratio (SR)
SOLBILE_STOMACH = (exp(LOGSR)) * SOLWATER_STOMACH * (MW_WATER / MW) * 1e-6
! Solubility in Bile (SOLBILE) = SR * SCaq; ! SCaq (aqueous solubilization capacity) = (SOL * MW_WATER / MW) = convert sol (mg/L) to moles drug / mol water, unitless, aqueous solubilization capacity
SOLBILE_DUO = (exp(LOGSR)) * SOLWATER_DUO * (MW_WATER / MW) * 1e-6
SOLBILE_JEJ1 = (exp(LOGSR)) * SOLWATER_JEJ1 * (MW_WATER / MW) * 1e-6
SOLBILE_JEJ2 = (exp(LOGSR)) * SOLWATER_JEJ2 * (MW_WATER / MW) * 1e-6
SOLBILE_ILL1 = (exp(LOGSR)) * SOLWATER_ILL1 * (MW_WATER / MW) * 1e-6
SOLBILE_ILL2 = (exp(LOGSR)) * SOLWATER_ILL2 * (MW_WATER / MW) * 1e-6
SOLBILE_ILL3 = (exp(LOGSR)) * SOLWATER_ILL3 * (MW_WATER / MW) * 1e-6
SOLBILE_CECUM = (exp(LOGSR)) * SOLWATER_CECUM * (MW_WATER / MW) * 1e-6
SOLBILE_ASCENDING = (exp(LOGSR)) * SOLWATER_ASCENDING * (MW_WATER / MW) * 1e-6
ENDIF

! Intestinal fluid solubility (SOLIF) in each compartment Bile Con in mM FROM GASTROPLUS, WHICH IS FROM porter 2007
CONSTANT BILE_STOMACH = 0
CONSTANT BILE_DUO = 2.8
CONSTANT BILE_JEJ1 = 2.33
CONSTANT BILE_JEJ2 = 2.03
CONSTANT BILE_ILL1 = 1.41
CONSTANT BILE_ILL2 = 1.16
CONSTANT BILE_ILL3 = 0.14
CONSTANT BILE_CECUM = 0
CONSTANT BILE_ASCENDING = 0
!! estimation of the increase in solubility of drugs as a function of bile salt concentrations.

\[
\text{SOLIF\_STOMACH} = (\text{SOLWATER\_STOMACH} + \text{SOLBILE\_STOMACH} \times \text{MW}\_\text{BILE}\_\text{STOMACH}) \times 0.5
\]

\[
\text{SOLIF\_DUO} = (\text{SOLWATER\_DUO} + \text{SOLBILE\_DUO} \times \text{MW}\_\text{BILE}\_\text{DUO}) \times 0.5
\]

\[
\text{SOLIF\_JEJ1} = (\text{SOLWATER\_JEJ1} + \text{SOLBILE\_JEJ1} \times \text{MW}\_\text{BILE}\_\text{JEJ1}) \times 0.5
\]

\[
\text{SOLIF\_JEJ2} = (\text{SOLWATER\_JEJ2} + \text{SOLBILE\_JEJ2} \times \text{MW}\_\text{BILE}\_\text{JEJ2}) \times 0.5
\]

\[
\text{SOLIF\_ILL1} = (\text{SOLWATER\_ILL1} + \text{SOLBILE\_ILL1} \times \text{MW}\_\text{BILE}\_\text{ILL1}) \times 0.5
\]

\[
\text{SOLIF\_ILL2} = (\text{SOLWATER\_ILL2} + \text{SOLBILE\_ILL2} \times \text{MW}\_\text{BILE}\_\text{ILL2}) \times 0.5
\]

\[
\text{SOLIF\_ILL3} = (\text{SOLWATER\_ILL3} + \text{SOLBILE\_ILL3} \times \text{MW}\_\text{BILE}\_\text{ILL3}) \times 0.5
\]

\[
\text{SOLIF\_CECUM} = (\text{SOLWATER\_CECUM} + \text{SOLBILE\_CECUM} \times \text{MW}\_\text{BILE}\_\text{CECUM}) \times 0.5
\]

\[
\text{SOLIF\_ASCENDING} = (\text{SOLWATER\_ASCENDING} + \text{SOLBILE\_ASCENDING} \times \text{MW}\_\text{BILE}\_\text{ASCENDING}) \times 0.5
\]

! Permeability estimation (used the last one for PAMPA in this model)

! Roche eqn.; \( \text{HPeff\_est} = (10^\left(0.892 \times \text{log(Caco2/1000000)} + 0.626\right)) \)

! GastroPlus eqn.; \( \text{HPeff\_est} = (10^\left(0.5326 \times \text{log(Caco2/100)} + 0.9028\right)) \times 10^{-4} \)

! Yu \text{et al. (2000)} eqn.; \( \text{HPeff\_est} = (10^\left(0.6532 \times \text{log(Caco2)} - 0.3036\right)) \times 10^{-4} \)

! Di 2013 for MDCK cells

! \text{HPeff} in 10^{-4} \text{ cm/s}

! \text{HPeff} experimentally determined or provided by the user in the form of 1

\[
\text{CONSTANT HPeff\_exp = 1.0}
\]

\[
\text{CONSTANT HPeff\_exp\_cecum = 1.0}
\]

\[
\text{CONSTANT HPeff\_exp\_ascending = 1.0}
\]

! Scaling values for calibrating Caco2 Peff

! Reference compound

! None = 0,

! Atenolol = 1

! Metoprolol = 2

! Propranolol = 3

! Cimetidine = 4

! Midazolam = 5

! Verapamil = 6

\[
\text{integer CACO2PEFF\_REFERENCE\_COMPOND}
\]

\[
\text{constant CACO2PEFF\_REFERENCE\_COMPOND} = 0
\]

\[
\text{constant CACO2PEFF\_ATENOLOL\_PUBLISHED} = 3.06
\]

\[
\text{constant CACO2PEFF\_METOPROLOL\_PUBLISHED} = 0.19
\]

\[
\text{constant CACO2PEFF\_PROPRANOLOL\_PUBLISHED} = 21.15
\]

\[
\text{constant CACO2PEFF\_CIMETIDINE\_PUBLISHED} = 20.06
\]

\[
\text{constant CACO2PEFF\_MI_DAZOLAM\_PUBLISHED} = 75.3
\]

\[
\text{constant CACO2PEFF\_VERAPAMI\_L\_PUBLISHED} = 18.8
\]

\[
\text{constant CACO2PEFF\_ATENOLOL\_MEASURED} = 3.06
\]

\[
\text{constant CACO2PEFF\_METOPROLOL\_MEASURED} = 0.19
\]

\[
\text{constant CACO2PEFF\_PROPRANOLOL\_MEASURED} = 21.15
\]

\[
\text{constant CACO2PEFF\_CIMETIDINE\_MEASURED} = 20.06
\]

\[
\text{constant CACO2PEFF\_MI_DAZOLAM\_MEASURED} = 75.3
\]

\[
\text{constant CACO2PEFF\_VERAPAMI\_L\_MEASURED} = 18.8
\]

if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_1} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_ATENOLOL\_PUBLISHED}}{\text{CACO2PEFF\_ATENOLOL\_MEASURED}}
\]

else if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_2} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_METOPROLOL\_PUBLISHED}}{\text{CACO2PEFF\_METOPROLOL\_MEASURED}}
\]

else if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_3} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_PROPRANOLOL\_PUBLISHED}}{\text{CACO2PEFF\_PROPRANOLOL\_MEASURED}}
\]

else if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_4} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_CIMETIDINE\_PUBLISHED}}{\text{CACO2PEFF\_CIMETIDINE\_MEASURED}}
\]

else if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_5} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_MI_DAZOLAM\_PUBLISHED}}{\text{CACO2PEFF\_MI_DAZOLAM\_MEASURED}}
\]

else if (CACO2PEFF\_REFERENCE\_COMPOND \( \text{\_EQ.\_6} \) \text{ then}

\[
\text{SCALAR\_PEFF} = \frac{\text{CACO2PEFF\_VERAPAMI\_L\_PUBLISHED}}{\text{CACO2PEFF\_VERAPAMI\_L\_MEASURED}}
\]
Supplement PBPK Code.txt

SCALAR_PEFF = 1.0
endif

CACO2PEFF_CALIBRATED = CACO2PEFF*SCALAR_PEFF
CACO2PEFF_CALIBRATED_cecum = CACO2PEFF_cecum*SCALAR_PEFF
CACO2PEFF_CALIBRATEDAscending = CACO2PEFFAscending*SCALAR_PEFF

! Hpeff estimated from Caco2 permeability data using three equations
! Caco2Peff in 10^-6 cm/s, which corresponds to Caco2 in the user interface
! Input Caco2pEff is in the form of 1 not 1e-6 cm/s
integer HPEFF_METHOD
constant HPEFF_METHOD = 4 ! 1 = Roche, 2 = Gastro-Plus, 3 = Yu, et al, 4
= equation for MDCK, 5 = experimental
if (HPEFF_METHOD .eq. 1) then
  HPeff_est = 10**(0.892 * log10(CACO2PEFF_CALIBRATED/1e6) + 0.626) ! unit cm/s
  HPeff_est_cecum = 10**(0.892 * log10(CACO2PEFF_CALIBRATED_cecum/1e6) + 0.626)
else if (HPEFF_METHOD .eq. 2) then
  HPeff_est = 10**(0.5326 * log10(CACO2PEFF_CALIBRATED/100) + 0.9028)*1e-4
  HPeff_est_cecum = 10**(0.5326 * log10(CACO2PEFF_CALIBRATED_cecum/100) + 0.9028)*1e-4
else if (HPEFF_METHOD .eq. 3) then
  HPeff_est = 10**(0.6532 * log10(CACO2PEFF_CALIBRATED) - 0.3036)*1e-4
  HPeff_est_cecum = 10**(0.6532 * log10(CACO2PEFF_CALIBRATED_cecum) - 0.3036)*1e-4
else if (HPEFF_METHOD .eq. 4) then
  HPeff_est = 10**(0.92 * log10(CACO2PEFF_CALIBRATED/1e6) + 0.86)
  HPeff_est_cecum = 10**(0.92 * log10(CACO2PEFF_CALIBRATED_cecum/1e6) + 0.86)
endif

! Estimation of diffusion coefficient
! Drug diffusion velocity through the gut membrane, DIFF, in cm^3/h; ml/h
! Exchange surface area in cm^2
! Hpeff is in cm/s
! Rate in ml/h, apical to basolateral, apparent diffusion velocity (Diff)
DIFF_duo                = 60*60 * HPeff_est*ESA_duo
DIFF_JEJ1               = 60*60*HPeff_est*ESA_JEJ1
DIFF_JEJ2               = 60*60*HPeff_est*ESA_JEJ2
DIFF_ILL1               = 60*60*HPeff_est*ESA_ILL1
DIFF_ILL2               = 60*60*HPeff_est*ESA_ILL2
DIFF_ILL3               = 60*60*HPeff_est*ESA_ILL3
DIFF_cecum              = 60*60*HPeff_est_cecum*ESA_cecum
DIFF_ascending          = 60*60*HPeff_est_ascending*ESA_ascending

! UNIONIZED FRACTION (NI) in each gut compartment
NI_duo                  = 1/HHDUO
NI_JEJ1                 = 1/HHJEJ1
NI_JEJ2                 = 1/HHJEJ2

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Supplement PBPK Code.txt

NI_ILL1 = 1/HHILL1
NI_ILL2 = 1/HHILL2
NI_ILL3 = 1/HHILL3
NI_CECUM = 1/HHCECUM
NI_ASCENDING = 1/HHASCENDING

!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! ACAT MODEL!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

! Scaled dosing parameters for iv dosing (Not used)

IVdosed = IVdoseCd*BW !(ug) | intravenous dose of d-MPH
IVdosel = IVdoseCl*BW !(ug) | intravenous dose of l-MPH
rate of d-MPH = (IVdosed)/IVtime !(ug/h) | intravenous dosing rate of d-MPH
rate of l-MPH = (IVdosel)/IVtime !(ug/h) | intravenous dosing point switch
intravenous dosing of d-MPH = IVd*IVZONE !(ug/h) | Scheduled
intravenous dosing of l-MPH = IVl*IVZONE !(ug/h) | Scheduled

AIVd = integ(IVrd,0.0) !(ug) | Amount of d-MPH received by i.v.
AIVl = integ(IVrl,0.0) !(ug) | Amount of l-MPH received by i.v.

! Dissolution diffusion layer model Noyes-Whitney equation, ref: Predicting Pharmacokinetics of Drugs Using Physiologically Based Modeling Application to Food Effects Parrott 2009

! Dissolution rate constants: should be in the units of L/(mg*hr)
Kd_IR = 3*(DIFFCOEFF_IR/(rho*rparticle*DLT))*60*100

!! Absorption model
! C in the lumen in ug/ml, C in the enterocytes in ug/L; SOL in mg/l which equals ug/ml, DIFF in ml/h, Qmuc in L/h, V for lumen in ml, V for enterocytes L; T in hr, X in ug
! Amount in stomach in ug

!!! %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% FOR d-MPH
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

! STOMACH

! Lumen solid

X_released_DMPHER_stomach = integ(D_released_DMPHER_stomach, 0.0) ! Amount of ER d-MPH released in the stomach
D_released_DMPHER_stomach = RELEASE_stomach ! Rate of ER d-MPH released in the stomach
D_X_STOMACH_FORM_DT_DMPHER = -D_released_DMPHER_stomach
-X_STOMACH_FORM_DR_DMPHER/Tstomach ! Rate of ER d-MPH (solid) amount change in the stomach
X_STOMACH_FORM_DR_DMPHER = INTEG(D_X_STOMACH_FORM_DT_DMPHER, Adoseder) ! Amount of ER d-MPH (solid) in the stomach
C_STOMACH_FORM_DMPHER = X_STOMACH_FORM_DR_DMPHER/Vstomach ! Concentration of ER d-MPH (solid) in the stomach

D_X_STOMACH_SOLID_DT_DMPHR = -VSTOMACH*Kd_IR*C_STOMACH_SOLID_DMPHR*(SOLIF_STOMACH-C_STOMACH_DISS_DMPH)-X_STOMACH_SOLID_DMPHR/Tstomach ! Rate of IR d-MPH solid amount change in the stomach

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stomach

\[
X_{\text{STOMACH\_SOLID\_DMPHIR}} = \text{BOUND}(0.0, \text{ADOSEDIR}, \text{LIMIT}(D_{X\_\text{STOMACH\_SOLID\_DT\_DMPHIR}}, \text{ADOSEDIR}, 0.0, \text{ADOSEDIR}))
\]

! Amount of IR d-MPH solid in the stomach

\[
C_{\text{STOMACH\_SOLID\_DMPHIR}} = \frac{X_{\text{STOMACH\_SOLID\_DMPHIR}}}{VSTOMACH}
\]

! Concentration of IR d-MPH solid in the stomach

\[
\text{ADOSED} = \text{ADOSEDIR} + \text{ADOSEDER}
\]

! Total dose of d-MPH

\[
D_{\text{dissolve\_solid\_DIR\_STOMACH}} = VSTOMACH \times k_{\text{d\_IR}} \times C_{\text{STOMACH\_SOLID\_DMPHIR}} \times (\text{SOLIF\_STOMACH} - C_{\text{STOMACH\_DISS\_DMPH}})
\]

! Rate of IR d-MPH solid dissolution in the stomach

\[
X_{\text{dissolve\_solid\_DIR\_STOMACH}} = \text{integ}(D_{\text{dissolve\_solid\_DIR\_STOMACH}}, 0.0)
\]

! Amount of IR d-MPH solid dissolved in the stomach

\[
D_{\text{dissolve\_solid\_DISS\_STOMACH}} = D_{\text{released\_DMPHER\_stomach}} + VSTOMACH \times k_{\text{d\_IR}} \times C_{\text{STOMACH\_SOLID\_DMPHIR}} \times (\text{SOLIF\_STOMACH} - C_{\text{STOMACH\_DISS\_DMPH}}) - X_{\text{STOMACH\_DISS\_DMPH}} / T_{\text{stomach}}
\]

! Rate of amount change of dissolved IR and ER d-MPH in the stomach

\[
X_{\text{STOMACH\_DISS\_DMPH}} = \text{integ}(D_{\text{X\_STOMACH\_DISS\_DT\_DMPH}}, 0.0)
\]

! Amount of IR and ER d-MPH dissolved in the stomach

\[
C_{\text{STOMACH\_DISS\_DMPH}} = \frac{X_{\text{STOMACH\_DISS\_DMPH}}}{VSTOMACH}
\]

! Concentration of IR and ER d-MPH dissolved in the stomach

!! DUODENUM

!! Lumen solid

CONSTANT c = 4.0
CONSTANT a = 0.001
CONSTANT b = 10
If (t LE c) Then ! release rate of ER forms
Release_duo = 0.
Release_jej1 = 0.
Release_jej2 = 0.
Release_ill1 = 0.
Release_ill2 = 0.
Release_ill3 = 0.
Release_cecum = 0.
Release_ascending = 0.
RELEASE_stomach = 0.
else
Release_duo = -X_duo\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_jej1 = -X_jej1\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_jej2 = -X_jej2\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_ill1 = -X_ill1\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_ill2 = -X_ill2\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_ill3 = -X_ill3\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_cecum = -X_cecum\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
Release_ascending = -X_ascending\_FORM\_DMPHER*(exp(-(t-c)**(b/a))*(-b/a)*((t-c)**(b-1))
RELEASE_stomach = 0.
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\[
total\ releaserate = \text{Release}_\text{duo} + \text{Release}_\text{jej1} + \text{Release}_\text{jej2} + \text{Release}_\text{ill1} + \text{Release}_\text{ill2} + \text{Release}_\text{ill3} + \text{Release}_\text{cecum} + \text{Release}_\text{ascending}
\]

\[
\text{totalreleaserate} = \frac{(X_{\text{released}_\text{DMPHER}_\text{DUO}} + X_{\text{released}_\text{DMPHER}_\text{jej1}} + X_{\text{released}_\text{DMPHER}_\text{jej2}} + X_{\text{released}_\text{DMPHER}_\text{ill1}} + X_{\text{released}_\text{DMPHER}_\text{ill2}} + X_{\text{released}_\text{DMPHER}_\text{ill3}} + X_{\text{released}_\text{DMPHER}_\text{cecum}} + X_{\text{released}_\text{DMPHER}_\text{ascending}})}{(A_{\text{oseder} + 1e-34})}
\]

\[
X_{\text{released}_\text{DMPHER}_\text{DUO}} = \text{integ}(D_{\text{released}_\text{DMPHER}_\text{DUO}}, 0.0)
\]

\[
D_{\text{released}_\text{DMPHER}_\text{DUO}} = \text{release}_\text{duo}
\]

\[
D_duo\ FORM\ DMPHER^- = -D_{\text{released}_\text{DMPHER}_\text{DUO}} + X_{\text{STOMACH}_\text{FORM}_\text{DR}\text{DMPHER}/T_{\text{stomach}}} -(X_{\text{duo}_\text{FORM}_\text{DMPHER}/T_{\text{DUO}}})
\]

\[
D_{\text{duo}_\text{FORM}_\text{DMPHER}}^- = \text{integ}(D_{\text{duo}_\text{FORM}_\text{DMPHER}}, 0.0)
\]

\[
D_X_{\text{DUO}_\text{SOLID}_\text{DT}\text{DMPHR}}^- = -VDUO*Kd_{IR}*C_{\text{DUO}_\text{SOLID}_\text{DMPHR}}^(-)(\text{SOLIF}_\text{DUO}-C_{\text{DUO}_\text{DISS}_\text{DMPH}})+X_{\text{STOMACH}_\text{SOLID}_\text{DMPHR}/T_{\text{stomach}}} -(X_{\text{DUO}_\text{SOLID}_\text{DMPHR}/T_{\text{DUO}}})
\]

\[
X_{\text{DUO}_\text{SOLID}_\text{DMPHR}}^- = BOUND(0.0, \text{ADOSEDIR}, \text{LIMIT}(D_X_{\text{DUO}_\text{SOLID}_\text{DT}\text{DMPHR}}, 0.0, 0.0, \text{ADOSEDIR}))
\]

\[
C_{\text{DUO}_\text{SOLID}_\text{DMPHR}}^- = X_{\text{DUO}_\text{SOLID}_\text{DMPHR}/T_{\text{DUO}}}
\]

\[
D_{\text{dissolve}\ solid\ dir\ duo}^- = VDUO*Kd_{IR}*C_{\text{DUO}_\text{SOLID}_\text{DMPHR}}^(-)(\text{SOLIF}_\text{DUO}-C_{\text{DUO}_\text{DISS}_\text{DMPH}})
\]

\[
X_{\text{dissolve}\ solid\ dir\ duo}^- = \text{integ}(D_{\text{dissolve}\ solid\ dir\ duo}, 0.0)
\]

\[
D_X_{\text{DUO}_\text{DISS}_\text{DT}\text{DMPH}}^- = VDUO*Kd_{IR}*C_{\text{DUO}_\text{SOLID}_\text{DMPHR}}^(-)(\text{SOLIF}_\text{DUO}-C_{\text{DUO}_\text{DISS}_\text{DMPH}})+X_{\text{STOMACH}_\text{DISS}_\text{DMPHR}/T_{\text{stomach}}} -(X_{\text{DUO}_\text{DISS}_\text{DMPHR}/T_{\text{DUO}}})
\]

\[
X_{\text{DUO}_\text{DISS}_\text{DMPH}}^- = \text{INTEG}(D_X_{\text{DUO}_\text{DISS}_\text{DT}\text{DMPH}}, 0.0)
\]

\[
C_{\text{DUO}_\text{DISS}_\text{DMPH}}^- = X_{\text{DUO}_\text{DISS}_\text{DMPH}/T_{\text{DUO}}}
\]

\[
\text{Enterocytes}
\]

\[
D_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}^- = QDUO*CAD-QDUO*(MEM_{\text{DUO}_\text{DMPH}}/(VMEMDUO*K_{Gut}))*1 - \text{METABOLISM}_\text{DUO}_\text{DMPH} + \text{NI}_\text{DUO}_\text{DIFF}_\text{DUO}^-(-C_{\text{DUO}_\text{MEM}_\text{DMPH}/1000+C_{\text{DUO}_\text{DISS}_\text{DMPH}})+X_{\text{STOMACH}_\text{TS}_{\text{SS}_\text{DMPH}}/T_{\text{DUO}}})
\]

\[
X_{\text{DUO}_\text{MEM}_\text{DMPH}}^- = \text{INTEG}(D_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}, 0.0) \quad \text{ug}
\]

\[
C_{\text{DUO}_\text{MEM}_\text{DMPH}}^- = MEM_{\text{DUO}_\text{DMPH}}/VMEMDUO \quad \text{ug/L}
\]

\[
A_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}^- = \text{integ}(R_{\text{MEM}_\text{DUO}_\text{DMPH}, 0.0}) \quad \text{ug}
\]

\[
R_{\text{MEM}_\text{DUO}_\text{DMPH}}^- = QDUO*(MEM_{\text{DUO}_\text{DMPH}}/(VMEMDUO*K_{Gut}))*1 \quad \text{ug/hr Rate of d-MPH entering portal vein and the liver}
\]

\[
A_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}^- = \text{INTEG}(R_{\text{MEM}_\text{DUO}_\text{DMPH}, 0.0}) \quad \text{ug}
\]

\[
A_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}^- = \text{INTEG}(\text{METABOLISM}_\text{DUO}_\text{DMPH}, 0.0) \quad \text{ug}
\]

\[
A_{\text{MEM}_\text{DUO}_\text{DT}\text{DMPH}}^- = \text{INTEG}(\text{METABOLISM}_\text{DUO}_\text{DMPH}, 0.0) \quad \text{ug}
\]

\[
D_{\text{ABS}_\text{DUO}_\text{DMPH}}^- = NT_{\text{DUO}_\text{DIFF}_\text{DUO}}^-(-C_{\text{DUO}_\text{MEM}_\text{DMPH}/1000+C_{\text{DUO}_\text{DISS}_\text{DMPH}}) \quad \text{ug/hr Rate of d-MPH entering enterocytes from intestinal lumen}
\]

\[
X_{\text{ABS}_\text{DUO}_\text{DMPH}}^- = \text{INTEG}(D_{\text{ABS}_\text{DUO}_\text{DMPH}, 0.0}) \quad \text{ug}
\]

\[
D_{\text{FG}_\text{DUO}_\text{DMPH}}^- = QDUO*CAD+QDUO*(MEM_{\text{DUO}_\text{DMPH}}/(VMEMDUO*K_{Gut}))*1 \quad \text{ug/hr Rate of d-MPH entering blood circulation}
\]

\[
X_{\text{FG}_\text{DUO}_\text{DMPH}}^- = \text{INTEG}(D_{\text{FG}_\text{DUO}_\text{DMPH}, 0.0}) \quad \text{ug}
\]
Supple PBPK Code.txt

\[\text{Da} = \left( \text{X\ ABS\ DUO\ DMPH} + \text{X\ ABS\ jej1\ DMPH} + \text{X\ ABS\ jej2\ DMPH} + \text{X\ ABS\ ill1\ DMPH} + \text{X\ ABS\ ill2\ DMPH} + \text{X\ ABS\ Cecum\ DMPH} + \text{X\ ABS\ ascending\ DMPH} \right) \text{ Total amount of d-MPH entering enterocytes from intestinal lumen} \]

\[\text{La} = \left( \text{X\ ABS\ DUO\ LMPH} + \text{X\ ABS\ jej1\ LMPH} + \text{X\ ABS\ jej2\ LMPH} + \text{X\ ABS\ ill1\ LMPH} + \text{X\ ABS\ ill2\ LMPH} + \text{X\ ABS\ Cecum\ LMPH} + \text{X\ ABS\ ascending\ LMPH} \right) \text{ Total amount of l-MPH entering enterocytes from intestinal lumen} \]

\[\text{Fa} = \frac{(\text{Da} + \text{La})}{(\text{AdosedER} + \text{AdosedIR} + \text{AdoseLER} + \text{AdoseLIR} + 1e^{-34})} \text{ Fraction of total MPH absorbed} \]

\[\text{JEJUNUM1} \]

\[\text{Lumen solid} \]

\[\text{X\ released\ DMPHER\ jej1} = \text{integ}(\text{D\ released\ DMPHER\ jej1}, 0.0) \text{ ug} \]

\[\text{D\ released\ DMPHER\ jej1} = \text{release\ jej1} \]

\[\text{X\ jej1\ FORM\ DMPHER} = \frac{-X\ jej1\ FORM\ DMPHER}{V\ jej1} + X\ DUO\ FORM\ DMPHER / V\ DUO \]

\[\text{C\ jej1\ FORM\ DMPHER} = \frac{X\jej1\ FORM\ DMPHER}{V\jej1} \text{ ug/mL} \]

\[\text{D\ release\ DMPHER\ jej1} = V\jej1\ \text{Kd\ IR}\ \text{C\jej1\ solid\ DMPHER} \left( \text{SOLIF\ jej1} - \text{C\jej1\ Diss\ DMPH} \right) - \frac{X\jej1\ SOLID\ D\MPHIR}{V\jej1} + X\DUO\ SOLID\ D\MPHIR / V\DUO \]

\[\text{X\jej1\ SOLID\ D\MPHIR} = \text{BOUND}(0.0, \text{ADOSEDIR}, \text{LIMIT}(\text{D\ release\ DMPHER\ jej1}, 0.0, 0.0, \text{ADOSEDIR})) \text{ ug} \]

\[\text{C\jej1\ SOLID\ D\MPHIR} = \frac{X\jej1\ SOLID\ D\MPHIR}{V\jej1} \]

\[\text{D\ dissolve\ solid\ dir\ jej1} = V\jej1\ Kd\ IR\ \text{C\jej1\ solid\ DMPHER} \left( \text{SOLIF\jej1} - \text{C\jej1\ Diss\ DMPH} \right) \]

\[\text{X\ dissolve\ solid\ dir\ jej1} = \text{integ}(\text{D\ dissolve\ solid\ dir\ jej1}, 0.0) \text{ ug/mL} \]

\[\text{JEJUNUM2} \]

\[\text{Lumen solid} \]

\[\text{X\ released\ DMPHER\ jej2} = \text{integ}(\text{D\ released\ DMPHER\ jej2}, 0.0) \text{ ug} \]

\[\text{D\ released\ DMPHER\ jej2} = \text{release\ jej2} \]

\[\text{X\ jej2\ FORM\ DMPHER} = \frac{-X\jej2\ FORM\ DMPHER}{V\jej2} + X\DUO\ FORM\ DMPHER / V\DUO \]

\[\text{C\jej2\ FORM\ DMPHER} = \frac{X\jej2\ FORM\ DMPHER}{V\jej2} \text{ ug/mL} \]

\[\text{D\ release\ DMPHER\ jej2} = V\jej2\ \text{Kd\ IR}\ \text{C\jej2\ solid\ DMPHER} \left( \text{SOLIF\jej2} - \text{C\jej2\ Diss\ DMPH} \right) \]

\[\text{X\release\ DMPHER\ jej2} = \text{integ}(\text{D\ release\ DMPHER\ jej2}, 0.0) \text{ ug/mL} \]
\[
+X_{\text{JEJ}2}^{\text{FORM DMPHER}} \text{/ TJ} \text{EJ}1 - X_{\text{JEJ}2}^{\text{FORM DMPHER}} \text{/ TJ} \text{EJ}2
\]
\[
X_{\text{JEJ}2}^{\text{FORM DMPHER}} = \text{integ}(D_{\text{JEJ}2}^{\text{FORM DMPHER}}, 0, 0) \text{ !! ug}
\]
\[
C_{\text{JEJ2}}^{\text{FORM DMPHER}} = X_{\text{JEJ2}}^{\text{FORM DMPHER}} / V_{\text{JEJ2}} \text{ !! ug/mL}
\]
\[
D_{X_{\text{JEJ2}}^{\text{SOLID DT DMPHER}}} = -V_{\text{JEJ2}}^{*}K_b^{*}I_r*C_{\text{JEJ2}}^{\text{SOLID DMPHER}}*\left(\text{SOLIF}_{\text{JEJ2}} - C_{\text{JEJ2}}^{\text{DISS DMPHER}}\right) + X_{\text{JEJ1}}^{\text{SOLID DMPHER}} / V_{\text{TJEJ1}} - (X_{\text{JEJ2}}^{\text{SOLID DMPHER}} / V_{\text{TJEJ2}})
\]
\[
X_{\text{JEJ2}}^{\text{SOLID DMPHER}} = \text{BOUND}(0.0, \text{ADOSEDIR}, \text{LTMT}(D_{X_{\text{JEJ2}}^{\text{SOLID DT DMPHER}}} / V_{\text{JEJ2}}, 0.0, 0.0, 0.0, \text{ADOSEDIR})) \text{ !! ug!}
\]
\[
C_{\text{JEJ2}}^{\text{SOLID DMPHER}} = X_{\text{JEJ2}}^{\text{SOLID DMPHER}} / V_{\text{JEJ2}}
\]

\[\text{Lumen dissolved}\]
\[
D_{X_{\text{JEJ2}}^{\text{DISS DT DMPHER}}} = V_{\text{JEJ2}}^{*}K_b^{*}I_r*C_{\text{JEJ2}}^{\text{DISS DMPHER}}*\left(\text{SOLIF}_{\text{JEJ2}} - C_{\text{JEJ2}}^{\text{DISS DMPHER}}\right) + D_{\text{released DMPHER}}_{\text{JEJ2}} - \text{NI}_{\text{JEJ2}}^{*}\text{DIFF}_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / 1000 + C_{\text{JEJ2}}^{\text{DISS DMPHER}}) / V_{\text{JEJ2}} - X_{\text{JEJ1}}^{\text{DISS DMPHER}} / V_{\text{TJEJ1}} - X_{\text{JEJ2}}^{\text{DISS DMPHER}} / V_{\text{TJEJ2}}
\]
\[
X_{\text{JEJ2}}^{\text{DISS DMPHER}} = \text{INTEG}(D_{X_{\text{JEJ2}}^{\text{DISS DT DMPHER}}} / V_{\text{JEJ2}}, 0.0)
\]
\[
C_{\text{JEJ2}}^{\text{DISS DMPHER}} = X_{\text{JEJ2}}^{\text{DISS DMPHER}} / V_{\text{JEJ2}}
\]

\[\text{Enterocytes}\]
\[
D_{\text{MEM}_{\text{JEJ2}}^{\text{DT DMPH}}} = Q_{\text{JEJ2}}^{*}\text{CAD} - Q_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / V_{\text{MEMJEJ2}} * K_p^{\text{Gut}}]*)\text{*}1 - \text{METABOLISM}_{\text{JEJ2}}^{\text{DMPH}} + \text{NI}_{\text{JEJ2}}^{*}\text{DIFF}_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / 1000 + C_{\text{JEJ2}}^{\text{DISS DMPHER}}) / V_{\text{JEJ2}} - \text{NI}_{\text{JEJ2}}^{*}\text{DIFF}_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / 1000 + C_{\text{JEJ2}}^{\text{DISS DMPHER}}) / V_{\text{JEJ2}}
\]
\[
\text{MEM}_{\text{JEJ2}}^{\text{DMPH}} = \text{INTEG}(D_{\text{MEM}_{\text{JEJ2}}^{\text{DT DMPH}}} / V_{\text{JEJ2}}, 0.0) \text{ !! ug/L}
\]
\[
R_{\text{MEM}_{\text{JEJ2}}^{\text{DMPH}}} = Q_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / V_{\text{MEMJEJ2}} * K_p^{\text{Gut}}]*)\text{*}1
\]
\[
A_{\text{MEM}_{\text{JEJ2}}^{\text{DMPH}}} = \text{INTEG}(R_{\text{MEM}_{\text{JEJ2}}^{\text{DMPH}}} / V_{\text{JEJ2}}, 0.0) \text{ !! ug/hr}
\]
\[
\text{METABOLISM}_{\text{JEJ2}}^{\text{DMPH}} = K_{S}\text{D}_{\text{MEM}_{\text{JEJ2}}^{\text{DMPH}}}^{*}K_p^{\text{Gut}}^{*}1
\]
\[
A_{\text{MEM}_{\text{JEJ2}}^{\text{DMPH}}} = \text{INTEG}(\text{METABOLISM}_{\text{JEJ2}}^{\text{DMPH}} / V_{\text{JEJ2}}, 0.0) \text{ !! ug/hr}
\]
\[
D_{\text{ABS}_{\text{JEJ2}}^{\text{DMPH}}} = \text{NI}_{\text{JEJ2}}^{*}\text{DIFF}_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / 1000 + C_{\text{JEJ2}}^{\text{DISS DMPHER}}) / V_{\text{JEJ2}}
\]
\[
X_{\text{ABS}_{\text{JEJ2}}^{\text{DMPH}}} = \text{INTEG}(D_{\text{ABS}_{\text{JEJ2}}^{\text{DMPH}}} / V_{\text{JEJ2}}, 0.0)
\]
\[
D_{\text{FG}_{\text{JEJ2}}^{\text{DMPH}}} = -Q_{\text{JEJ2}}^{*}\text{CAD} + Q_{\text{JEJ2}}^{*}(\text{C}_{\text{JEJ2}}^{\text{MEM DMPH}} / V_{\text{MEMJEJ2}} * K_p^{\text{Gut}}]*)\text{*}1
\]
\[
X_{\text{FG}_{\text{JEJ2}}^{\text{DMPH}}} = \text{INTEG}(D_{\text{FG}_{\text{JEJ2}}^{\text{DMPH}}} / V_{\text{JEJ2}}, 0.0)
\]

\[\text{ILEUM1}\]
\[
X_{\text{released DMPHER}}_{\text{ILL1}} = \text{INTEG}(D_{\text{released DMPHER}}_{\text{ILL1}}, 0.0) \text{ !! ug}
\]
\[
D_{\text{released DMPHER}}_{\text{ILL1}} = \text{release}_{\text{ILL1}}
\]
\[
D_{\text{ILL1 FORM DMPHER}} = -D_{\text{released DMPHER}}_{\text{ILL1}} + X_{\text{JEJ2}}^{\text{SOLID DMPHER}} / V_{\text{TJEJ2}} - X_{\text{JEJ1}}^{\text{SOLID DMPHER}} / V_{\text{TJEJ1}}
\]
\[
X_{\text{ILL1 FORM DMPHER}} = \text{INTEG}(D_{\text{ILL1 FORM DMPHER}}, 0.0) \text{ !! ug/mL}
\]
\[
D_{X_{\text{ILL1 SOLID DT DMPH}} = -V_{\text{ILL1}}^{*}K_b^{*}I_r*C_{\text{ILL1 SOLID DMPHER}}*\left(\text{SOLIF}_{\text{ILL1}} - C_{\text{ILL1 DISS DMPHER}}\right) + X_{\text{JEJ2 SOLID DMPHER}} / V_{\text{TJEJ2}} - (X_{\text{ILL1 SOLID DMPHER}} / V_{\text{TILL1}})
\]
\[
X_{\text{ILL1 SOLID DMPHER}} = \text{BOUND}(0.0, \text{ADOSEDIR}, \text{LTMT}(D_{X_{\text{ILL1 SOLID DT DMPH}}, 0.0, 0.0, 0.0, \text{ADOSEDIR})) \text{ !! ug!}
\]
\[\text{Dissolved}\]
\[
D_{X_{\text{ILL1 DISS DT DMPH}}} = V_{\text{ILL1}}^{*}K_b^{*}I_r*C_{\text{ILL1 DISS DMPHER}}*\left(\text{SOLIF}_{\text{ILL1}} - C_{\text{ILL1 DISS DMPHER}}\right) + D_{\text{released DMPHER}}_{\text{ILL1}} + D_{\text{ILL1 FORM DMPHER}} - D_{\text{released DMPHER}}_{\text{ILL1}} + X_{\text{JEJ2 DISS DMPHER}} / V_{\text{TJEJ2}} - X_{\text{ILL1 DISS DMPHER}} / V_{\text{TILL1}}
\]
\[
X_{\text{ILL1 DISS DMPHER}} = \text{INTEG}(D_{X_{\text{ILL1 DISS DT DMPH}}, 0.0)
\]
\[ C_{\text{ILL1 DISS DMPH}} = X_{\text{ILL1 DISS DMPH}} / V_{\text{ILL1}} \]

\[ D_{\text{dissolve solid dir ILL1}} = V_{\text{ILL1}} K_d I R \cdot C_{\text{ILL1 SOLID DMPH IR}} \cdot (S_{\text{ILL1}} - C_{\text{ILL1 DISS DMPH}}) \]

\[ X_{\text{dissolve solid dir ILL1}} = \text{INTEGRATE}(D_{\text{dissolve solid dir ILL1}}, 0.0) \]

**Enterocytes**

\[ D_{\text{MEM ILL1 DT DMPH}} = Q_I L_{1} * C_A D - Q_I L_{1} * (M_{\text{MEM ILL1 DMPH}} / (V_{\text{MEM ILL1 Kp Gut}})) \cdot 1 - \text{METABOLISM ILL1 DMPH} \]

\[ + N_I \cdot I L_{1} / D I F F \cdot I L_{1} / ((-C_{\text{ILL1 MEM DMPH}} / 1000) + C_{\text{ILL1 DISS DMPH}}) \]

\[ \cdot \text{EFFLUX DUO} + \text{INFLUX DUO} \]

\[ \text{MEM ILL1 DMPH} = \text{INTEGRATE}(\text{D_{MEM ILL1 DT DMPH}}, 0.0) \]

\[ C_{\text{ILL1 MEM DMPH}} = \text{MEM ILL1 DMPH} / V_{\text{MEM ILL1}} \]

\[ R_{\text{MEM ILL1 DMPH}} = Q_I L_{1} * (M_{\text{MEM ILL1 DMPH}} / (V_{\text{MEM ILL1 Kp Gut}})) \cdot 1 \]

\[ \text{A_MEM ILL1 DMPH} = \text{INTEGRATE}(\text{R_{MEM ILL1 DMPH}}, 0.0) \]

\[ \text{METABOLISM ILL1 DMPH} = K_5 D^* \text{MEM ILL1 DMPH} \]

**Ileum2**

**Lumen**

\[ X_{\text{released DMPHER ILL2}} = \text{INTEGRATE}(\text{D_{released DMPHER ILL2}}, 0.0) \]

\[ D_{\text{released DMPHER ILL2}} = \text{release ILL2} \]

\[ D_{\text{ILL2 FORM DMPHER}} = - D_{\text{released DMPHER ILL2}} + X_{\text{ILL2 FORM DMPHER}} / V_{\text{ILL2}} \cdot (X_{\text{ILL2 SOLID DMPHER}} / T_{\text{ILL2}}) - \]

\[ X_{\text{ILL2 FORM DMPHER}} = \text{INTEGRATE}(D_{\text{ILL2 FORM DMPHER}}, 0.0) \]

\[ C_{\text{ILL2 FORM DMPHER}} = X_{\text{ILL2 FORM DMPHER}} / V_{\text{ILL2}} \]

**Lumen dissolved**

\[ D_{\text{X ILL2 DISS DT DMPH IR}} = \]

\[ V_{\text{ILL2 Kd IR}} \cdot C_{\text{ILL2 SOLID DMPH IR}} \cdot (S_{\text{ILL2}} - C_{\text{ILL2 DISS DMPH}}) + X_{\text{ILL2 SOLID DMPHER}} / T_{\text{ILL2}} - \]

\[ X_{\text{ILL2 SOLID DMPHER}} = \text{BOUND}(0.0, \text{ADOSEDIR}, \text{INT}(D_{\text{X ILL2 SOLID DT DMPH IR}}, 0.0, 0.0, \text{ADOSEDIR})) \]

\[ C_{\text{ILL2 SOLID DMPHER}} = X_{\text{ILL2 SOLID DMPHER}} / V_{\text{ILL2}} \]

**Enterocytes**

\[ D_{\text{MEM ILL2 DT DMPH}} = Q_I L_{2} * C_A D - Q_I L_{2} * (M_{\text{MEM ILL2 DMPH}} / (V_{\text{MEM ILL2 Kp Gut}})) \cdot 1 - \text{METABOLISM ILL2 DMPH} \]

\[ + N_I \cdot I L_{2} / D I F F \cdot I L_{2} / ((-C_{\text{ILL2 MEM DMPH}} / 1000) + C_{\text{ILL2 DISS DMPH}}) \]

\[ \cdot \text{EFFLUX DUO} + \text{INFLUX DUO} \]

\[ \text{MEM ILL2 DMPH} = \text{INTEGRATE}(\text{D_{MEM ILL2 DT DMPH}}, 0.0) \]

\[ C_{\text{ILL2 MEM DMPH}} = \text{MEM ILL2 DMPH} / V_{\text{MEM ILL2}} \]

\[ R_{\text{MEM ILL2 DMPH}} = Q_I L_{2} * (M_{\text{MEM ILL2 DMPH}} / (V_{\text{MEM ILL2 Kp Gut}})) \cdot 1 \]

\[ \text{A_MEM ILL2 DMPH} = \text{INTEGRATE}(R_{\text{MEM ILL2 DMPH}}, 0.0) \]

\[ \text{METABOLISM ILL2 DMPH} = K_5 D^* \text{MEM ILL2 DMPH} \]

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AMETABOLISM_ILL2_DMPH = INTEG(METABOLISM_ILL2_DMPH, 0.0) !!ug

D_ABS_ILL2_DMPH = NT_ILL2*DIFF_ILL2*(-C_ILL2_MEM_DMPH/1000+C_ILL2_DISS_DMPH)
X_ABS_ILL2_DMPH = INTEG(D_ABS_ILL2_DMPH, 0.0)

D_FG_ILL2_DMPH = -Q_ILL2*CAD+Q_ILL2*(MEM_ILL2_DMPH/(VMEM_ILL2*KpGut))*1
X_FG_ILL2_DMPH = INTEG(D_FG_ILL2_DMPH, 0.0)

!!ILEUM3
X_released_DMPHER_ILL3 = integ(D_released_DMPHER_ILL3, 0.0) !!ug
D_released_DMPHER_ILL3 = release_ill3
D_ILL3_FORM_DMPHER = -D_released_DMPHER_ILL3 +X_ILL2_FORM_DMPHER/TILL2 -X_ILL3_FORM_DMPHER/TILL3
X_ILL3_FORM_DMPHER = integ(D_ILL3_FORM_DMPHER, 0.0) !!ug
C_ILL3_FORM_DMPHER = X_ILL3_FORM_DMPHER/VILL3 !!ug/mL

D_X_ILL3_SOLID_DT_DMPHR = VILL3*Kd_IR*C_ILL3_SOLID_DMPHR*(SOLIF_ILL3-C_ILL3_DISS_DMPH)+X_ILL2_SOLID_DMPHR/TILL2 -(X_ILL3_SOLID_DMPHR/TILL3)
X_ILL3_SOLID_DMPHR = BOUND(0.0, 0, ADOSEDIR, LIMIT(D_X_ILL3_SOLID_DT_DMPHR, 0.0, 0.0, ADOSEDIR))
C_ILL3_SOLID_DMPHR = X_ILL3_SOLID_DMPHR/VILL3

!!Lumen dissolved
D_X_ILL3_DISS_DT_DMPHR = VILL3*Kd_IR*C_ILL3_SOLID_DMPHR*(SOLIF_ILL3-C_ILL3_DISS_DMPH)+D_released_DMPHER_ILL3
R_ILL3 = NT_ILL3*DIFF_ILL3*(-C_ILL3_MEM_DMPH/1000+C_ILL3_DISS_DMPH)+(X_ILL2_DISS_DMPH/TILL2) -(X_ILL3_DISS_DMPH/TILL3)
X_ILL3_DISS_DMPHR = INTEG(D_X_ILL3_DISS_DT_DMPHR, 0.0)
C_ILL3_DISS_DMPHR = X_ILL3_DISS_DMPHR/VILL3

!!Enterocytes
D_MEM_ILL3_DMPH = Q_ILL3*CAD-Q_ILL3*(MEM_ILL3_DMPH/(VMEM_ILL3*KpGut))*1 - METABOLISM_ILL3_DMPH + NI_ILL3*DIFF_ILL3*(-C_ILL3_MEM_DMPH/1000+C_ILL3_DISS_DMPH) !!ug/hr
MEM_ILL3_DMPH = INTEG(D_MEM_ILL3_DMPH, 0.0) !!ug
C_MEM_ILL3_DMPH = MEM_ILL3_DMPH/VMEM_ILL3 !!ug/L
R_MEM_ILL3_DMPH = Q_ILL3*(MEM_ILL3_DMPH/(VMEM_ILL3*KpGut))*1 !!ug/hr
A_MEM_ILL3_DMPH = integ(R_MEM_ILL3_DMPH, 0.0) !!ug
AMETABOLISM_ILL3_DMPH = K5D*MEM_ILL3_DMPH !!ug/hr

!!Cecum
D_ABS_ILL3_DMPH = NT_ILL3*DIFF_ILL3*(-C_ILL3_MEM_DMPH/1000+C_ILL3_DISS_DMPH)
X_ABS_ILL3_DMPH = INTEG(D_ABS_ILL3_DMPH, 0.0)

D_FG_ILL3_DMPH = -Q_ILL3*CAD+Q_ILL3*(MEM_ILL3_DMPH/(VMEM_ILL3*KpGut))*1
X_FG_ILL3_DMPH = INTEG(D_FG_ILL3_DMPH, 0.0) !!ug/mL

!Lumen SOLID
X_released_DMPHER_CECUM = integ(D_released_DMPHER_CECUM, 0.0) !!ug
D_released_DMPHER_CECUM = release_cecum
D_CECUM_FORM_DMPHER = -D_released_DMPHER_CECUM +X_CECUM_FORM_DMPHER/TCECUM
X_CECUM_FORM_DMPHER = integ(D_CECUM_FORM_DMPHER, 0.0) !!ug
C_CECUM_FORM_DMPHER = X_CECUM_FORM_DMPHER/VCECUM !!ug/mL

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D_X_CECUM_SOLID_DT_DMPH =
-VCECUM*Kd_IR*C_CECUM_SOLID_DMPH*(SOLIF_CECUM-C_CECUM_DISS_DMPH) +
X_ILL3_SOLID_DMPH/TTILL3*(X_CECUM_SOLID_DMPH/TCECUM) !
X_CECUM_SOLID_DMPH = BOUND(0.0, ADosedIR, limit(D_X_CECUM_SOLID_DT_DMPH, 0.0, 0.0, ADosedIR))
C_CECUM_SOLID_DMPH = X_CECUM_SOLID_DMPH/VCECUM

! Lumen dissolved
D_X_CECUM_DISS_DT_DMPH =
VCECUM*Kd_IR*C_CECUM_SOLID_DMPH*(SOLIF_CECUM-C_CECUM_DISS_DMPH)+
D_released_DMPHER_CECUM-NI_CECUM*DIFF_CECUM*(-C_CECUM_MEM_DMPH/1000+C_CECUM_DISS_DMPH) +
(X_ILL3_DISS_DMPH/TTILL3)-(X_CECUM_DISS_DMPH/TCECUM) !
X_CECUM_DISS_DMPH = INTEG(D_X_CECUM_DISS_DT_DMPH, 0.0)
C_CECUM_DISS_DMPH = X_CECUM_DISS_DMPH/VCECUM

D_dissolve_solid_dir_cecum =
VCECUM*Kd_IR*C_CECUM_SOLID_DMPH*(SOLIF_CECUM-C_CECUM_DISS_DMPH)
X_dissolve_solid_dir_cecum = integ(D_dissolve_solid_dir_cecum, 0.0) ! Enterocytes

D_MEM_CECUM_DT_DMPH =
QCECUM*CAD-QCECUM*(MEM_CECUM_DMPH/(VMEMCECUM*Kpcolon))*1 -
METABOLISM_CECUM_DMPH +NI_CECUM*DIFF_CECUM*(-C_CECUM_MEM_DMPH/1000+C_CECUM_DISS_DMPH) ! - EFFLUX_DUO +
+ INFLUX_DUO ! ug/hr
MEM_CECUM_DMPH = INTEG(D_MEM_CECUM_DT_DMPH, 0.0) ! ug
C_CECUM_MEM_DMPH = MEM_CECUM_DMPH/VMEMCECUM ! ug/L
R_MEM_CECUM_DMPH = QCECUM*(MEM_CECUM_DMPH/(VMEMCECUM*Kpcolon))*1 ! ug/hr
AMETABOLISM_CECUM_DMPH = INTEG(METABOLISM_CECUM_DMPH, 0.0) ! ug

D_ABS_CECUM_DMPH =
N_CECUM*DIFF_CECUM*(-C_CECUM_MEM_DMPH/1000+C_CECUM_DISS_DMPH)
X_ABS_CECUM_DMPH = INTEG(D_ABS_CECUM_DMPH, 0.0) ! ug/mL

D_FG_CECUM_DMPH =
-QCECUM*CAD+QCECUM*(MEM_CECUM_DMPH/(VMEMCECUM*Kpcolon))*1
X_FG_CECUM_DMPH = INTEG(D_FG_CECUM_DMPH, 0.0) ! ug/mL

! Ascending Colon

D_X_ASCENDING_SOLID_DT_DMPH =
-VASCENDING*Kd_IR*C_ASCENDING_SOLID_DMPH*(SOLIF_ASCENDING-C_ASCENDING_DISS_DMPH) +
X_ASCENDING_SOLID_DMPH/TCECUM*(X_ASCENDING_SOLID_DMPH/TASCENDING) !
X_ASCENDING_SOLID_DMPH = BOUND(0.0, ADosedIR, limit(D_X_ASCENDING_SOLID_DT_DMPH, 0.0, 0.0, ADosedIR))
C_ASCENDING_SOLID_DMPH = X_ASCENDING_SOLID_DMPH/VASCENDING

! Lumen dissolved
D_X_ASCENDING_DISS_DT_DMPH =
VASCENDING*Kd_IR*C_ASCENDING_SOLID_DMPH*(SOLIF_ASCENDING-C_ASCENDING_DISS_DMPH) +
D_released_DMPHER_ASCENDING+(N_ASCENDING*DIFF_ASCENDING*(-C_ASCENDING_MEM_DMPH/1000+C_ASCENDING_DISS_DMPH)) +X_ASCENDING_DISS_DMPH/TASCENDING!
X_ASCENDING_DISS_DMPH = X_ASCENDING_SOLID_DMPH/VASCENDING

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X_ASCENDING_DISS_DMPH = INTEG(D_ASCENDING_DISS_DT_DMPH, 0.0)
C_ASCENDING_DISS_DMPH = X_ASCENDING_DISS_DMPH / VASCENDING

D_dissolve_solid_dir_ascending = VASCENDING * Kd_IR * C_ASCENDING_SOLID_DMPHIR *(SOLIF_ASCENDING - C_ASCENDING_DISS_DMPH)

x_dissolve_solid_dir_ascending = integ(D_dissolve_solid_dir_ascending, 0.0)

! Enterocytes
D_MEM_ASCENDING_DT_DMPH =
Q_ASCENDING * CAD - Q_ASCENDING * (MEM_ASCENDING_DMPH / (VMEMASCENDING * Kpcolon)) * 1 - METABOLISM_ASCENDING_DMPH
+ NI_ASCENDING * DIFF_ASCENDING * (-C_ASCENDING_MEM_DMPH/1000 + C_ASCENDING_DISS_DMPH)

MEM_ASCENDING_DMPH = INTEG(D_MEM_ASCENDING_DT_DMPH, 0.0)  !!}ug
C_ASCENDING_MEM_DMPH = MEM_ASCENDING_DMPH / VMEMASCENDING

!!ug/L
R_MEM_ASCENDING_DMPH =
Q_ASCENDING * (MEM_ASCENDING_DMPH / (VMEMASCENDING * Kpcolon)) * 1  !!}ug/hr

AMETABOLISM_ASCENDING_DMPH = INTEG(METABOLISM_ASCENDING_DMPH, 0.0)  !!}ug/hr

D_ABS_ASCENDING_DMPH =
- Q_ASCENDING * CAD + Q_ASCENDING * (MEM_ASCENDING_DMPH / (VMEMASCENDING * Kpcolon)) * 1

X_ABS_ASCENDING_DMPH = INTEG(D_ABS_ASCENDING_DMPH, 0.0)

D_FG_ASCENDING_DMPH =
- Q_ASCENDING * CAD + Q_ASCENDING * (MEM_ASCENDING_DMPH / (VMEMASCENDING * Kpcolon)) * 1

X_FG_ASCENDING_DMPH = INTEG(D_FG_ASCENDING_DMPH, 0.0)

D_Terminal_SOLID_DMPH =
X_ASCENDING_SOLID_DMPH / TASCENDING + X_ASCENDING_FORM_DMPHER / TASCENDING

D_Terminal_DISS_DMPH = X_ASCENDING_DISS_DMPH / TASCENDING

! Add the absorption rate constants up

RBS_DMPH =
Q_DUO * (MEM_DUO_DMPH / (VMEMDUO * Kgut)) * 1 + QJE1 * (MEM_JE1_DMPH / (VMEMJE1 * Kgut)) * 1 + QJE2 * (MEM_JE2_DMPH / (VMEMJE2 * Kgut)) * 1 + QILL1 * (MEM_ILL1_DMPH / (VMEMILL1 * Kgut)) * 1 + QILL2 * (MEM_ILL2_DMPH / (VMEMILL2 * Kgut)) * 1 + QILL3 * (MEM_ILL3_DMPH / (VMEMILL3 * Kgut)) * 1

AMETABOLISM_SI_DMPH = AMETABOLISM_DUO_DMPH + AMETABOLISM_JEJ1_DMPH + AMETABOLISM_JEJ2_DMPH + AMETABOLISM_IL1_DMPH + AMETABOLISM_IL2_DMPH + AMETABOLISM_IL3_DMPH + AMETABOLISM_CECUM_DMPH + AMETABOLISM_ASCENDING_DMPH

METABOLISM_SI_DMPH =
AMETABOLISM_SI_DUO_DMPH + AMETABOLISM_SI_JE1_DMPH + AMETABOLISM_SI_JE2_DMPH + AMETABOLISM_SI_ILL1_DMPH + AMETABOLISM_SI_ILL2_DMPH + AMETABOLISM_SI_ILL3_DMPH + AMETABOLISM_SI_CECUM_DMPH + AMETABOLISM_SI_ASCENDING_DMPH

!!%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% FOR
L-MPH%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

X_released_LMPHER_stomach = integ (D_released_LMPHER_stomach, 0.0)
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D_released_LMPHER_stomach = RELEASE_stomach
D_X_STOMACH_FORM_DT_LMPHER = -D_released_LMPHER_stomach
-X_STOMACH_FORM_DR_LMPHER/Tstomach
X_STOMACH_FORM_DR_LMPHER = INTEG(D_X_STOMACH_FORM_DT_LMPHER, AdoselIR)
C_STOMACH_FORM_LMPHER = X_STOMACH_FORM_DR_LMPHER/Vstomach

D_X_STOMACH_SOLID_DT_LMPHER = -VSTOMACH*Kd_IR*C_STOMACH_SOLID_LMPHER*(SOLIF_STOMACH-C_STOMACH_DISS_LMPH)-X_STOMACH_SOLID_LMPHER/Tstomach ! ug/hr (ok)
X_STOMACH_SOLID_LMPHER = BOUND(0.0, AdoselIR, LIMIT(D_X_STOMACH_SOLID_DT_LMPHER,AdoselIR, 0.0, AdoselIR)) ! ug (ok)
C_STOMACH_SOLID_LMPHER = X_STOMACH_SOLID_LMPHER/VSTOMACH ! ug/ml (ok)

Adosel = AdoselIR+AdoselER

!! Lumen dissolved
D_X_STOMACH_DISS_DT_LMPH = VSTOMACH*Kd_IR*C_STOMACH_SOLID_LMPHER*(SOLIF_STOMACH-C_STOMACH_DISS_LMPH)-X_STOMACH_DISS_LMPH/Tstomach+D_released_LMPHER_stomach
X_STOMACH_DISS_LMPH = INTEG(D_X_STOMACH_DISS_DT_LMPH,0.0) ! ug (ok)
C_STOMACH_DISS_LMPH = X_STOMACH_DISS_LMPH/VSTOMACH ! ug/ml (ok)

D_dissolve_solid_LIR_stomach = VSTOMACH*Kd_IR*C_STOMACH_SOLID_LMPHER*(SOLIF_STOMACH-C_STOMACH_DISS_LMPH)
X_dissolve_solid_LIR_stomach = INTEG(D_dissolve_solid_LIR_stomach,0.0) ! ug/ml (ok)

!! DUODENUM
!! Lumen solid
X_released_LMPHER_DUO = INTEG(D_released_LMPHER_DUO,0.0) ! ug
D_released_LMPHER_DUO = release_duo
D_duo_FORM_LMPHER = -D_released_LMPHER_DUO + X_STOMACH_FORM_DR_LMPHER/Tstomach-(X_duo_FORM_LMPHER/VDUO)
X_duo_FORM_LMPHER = INTEG(D_duo_FORM_LMPHER, 0.0) ! ug
C_DUO_FORM_LMPHER = X_duo_FORM_LMPHER/VDUO ! ug/ml

D_X_DUO_SOLID_DT_LMPHIR = -VDUO*Kd_IR*C_DUO_SOLID_LMPHIR*(SOLIF_DUO-C_DUO_DISS_LMPH)+X_STOMACH_SOLID_LMPHIR/Tstomach-(X_DUO_SOLID_LMPHIR/VDUO)
X_DUO_SOLID_LMPHIR = BOUND(0.0, AdoselIR, LIMIT(D_X_DUO_SOLID_DT_LMPHIR,0.0, 0.0, AdoselIR)) ! ug
C_DUO_SOLID_LMPHIR = X_DUO_SOLID_LMPHIR/VDUO ! ug/mL

!! Lumen dissolved
D_X_DUO_DISS_DT_LMPHIR = -VDUO*Kd_IR*C_DUO_SOLID_LMPHIR*(SOLIF_DUO-C_DUO_DISS_LMPH)+D_released_LMPHER_DUO
+NI_DUO*DIFF_DUO*(-C_DUO_MEM_LMPH/1000+C_DUO_DISS_LMPH)
+C_DUO_DISS_LMPHIR = INTEG(D_X_DUO_DISS_DT_LMPHIR,0.0)
X_DUO_DISS_LMPH = INTEG(D_X_DUO_DISS_DT_LMPHIR,0.0)

D_dissolve_solid_LIR_duo = VDUO*Kd_IR*C_DUO_SOLID_LMPHIR*(SOLIF_DUO-C_DUO_DISS_LMPH)
X_dissolve_solid_LIR_duo = INTEG(D_dissolve_solid_LIR_duo, 0.0)

!! Enterocytes
D_MEM_DUO_DT_LMPH = VDUO*CAL-QDUO*(MEM_DUO_LMPH/(VMEMDUO*KpGut)) * 1 - METABOLISM_DUO_LMPH
+NI_DUO*DIFF_DUO*(-C_MEM_DUO_LMPH/1000+C_DUO_DISS_LMPH) ! - EFFLUX_DUO + INFLUX_DUO ! ug/hr
MEM_DUO_MEM_LMPH = INTEG(D_MEM_DUO_DT_LMPH,0.0) ! ug/L
Supple PBPK Code.txt

\[ R_{MEM\_DUO\_LMPH} = \text{QDUO} \ast (**(MEM\_DUO\_LMPH)/(V\_MEMDUO*KpGut)\)) \ast 1 !\text{ug/hr} \]

\[ A_{MEM\_DUO\_LMPH} = \text{integ}(R_{MEM\_DUO\_LMPH}, 0.0) !\text{ug} \]

\[ M\_METABOLISM\_DUO\_LMPH = K5l \ast **(MEM\_DUO\_LMPH) !\text{ug/hr} \]

\[ \text{AMETABOLISM\_DUO\_LMPH} = \text{INTEG}(M\_METABOLISM\_DUO\_LMPH, 0.0) !\text{ug} \]

\[ D\_ABS\_DUO\_LMPH = \text{NT}_{DUO\_DIFF\_DUO} \ast (**(C\_DUO\_MEM\_LMPH/1000+C\_DUO\_DISS\_LMPH)) \]

\[ X\_ABS\_DUO\_LMPH = \text{INTEG}(D\_ABS\_DUO\_LMPH, 0.0) \]

\[ D\_FG\_DUO\_LMPH = \text{QDUO}\ast**CAL+QDUO\ast**(MEM\_DUO\_LMPH/(V\_MEMDUO*KpGut)) \ast 1 \]

\[ X\_FG\_DUO\_LMPH = \text{INTEG}(D\_FG\_DUO\_LMPH, 0.0) \]

\[ R\_JEJUNUM1!\text{Lumen solid} \]

\[ X\_released\_LMPHER\_JEJ1 = \text{integ}(D\_released\_LMPHER\_JEJ1,0.0) !\text{ug} \]

\[ D\_released\_LMPHER\_JEJ1 = \text{release}_{JEJ1} \]

\[ D\_JEJ1\_FORM\_LMPHER = -D\_released\_LMPHER\_JEJ1 \]

\[ -X\_JEJ1\_FORM\_LMPHER/TJEJ1 +X\_DUO\_FORM\_LMPHER/TDUO \]

\[ X\_JEJ1\_FORM\_LMPHER = \text{INTEG}(D\_JEJ1\_FORM\_LMPHER, 0.0) !\text{ug} \]

\[ C\_JEJ1\_FORM\_LMPHER = X\_JEJ1\_FORM\_LMPHER/VJEJ1 !\text{ug/mL} \]

\[ D\_dissolve\_solid\_LIR\_JEJ1 = VJEJ1\ast Kd\_IR\ast C\_JEJ1\_FORM\_LMPHER \ast (**(SOLIF\_JEJ1-C\_JEJ1\_DISS\_LMPH)) \]

\[ \text{Dissolve}_{solid\_LIR\_JEJ1} = \text{INTEG}(D\_dissolve\_solid\_LIR\_JEJ1, 0.0) \]

\[ \text{EFFLUX\_DUO} + \text{INFLUX\_DUO} !\text{ug/hr} \]

\[ \text{MEM}\_JEJ1\_LMPH = \text{INTEG}(D\_MEM\_JEJ1\_DT\_LMPH, 0.0) !\text{ug} \]

\[ C\_JEJ1\_LMPH = \text{MEM}\_JEJ1\_LMPH/VJEJ1 !\text{ug/L} \]

\[ \text{AMETABOLISM\_JEJ1\_LMPH} = K5l \ast **(MEM\_JEJ1\_LMPH) !\text{ug/hr} \]

\[ \text{METABOLISM\_JEJ1\_LMPH} = \text{INTEG}(\text{METABOLISM}\_JEJ1\_LMPH, 0.0) !\text{ug} \]

\[ D\_ABS\_JEJ1\_LMPH = \text{NT}_{JEJ1\_DIFF\_JEJ1} \ast (**(C\_JEJ1\_MEM\_LMPH/1000+C\_JEJ1\_DISS\_LMPH)) \]

\[ X\_ABS\_JEJ1\_LMPH = \text{INTEG}(D\_ABS\_JEJ1\_LMPH, 0.0) \]

\[ D\_FG\_JEJ1\_LMPH = \text{QJEJ1}\ast**CAL+QJEJ1\ast**(MEM\_JEJ1\_LMPH/(V\_MEMJEJ1*KpGut)) \ast 1 \]

\[ X\_FG\_JEJ1\_LMPH = \text{INTEG}(D\_FG\_JEJ1\_LMPH, 0.0) \] Page 20
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D_released_LMPHER_JEJ2 = release_jej2
D_released_LMPHER_JEJ2 = -D_released_LMPHER_JEJ2
+X_EJ1 FORM_LMPHER/TJEJ1 - X_Bound_LMPHER_JEJ2
X_EJ1 FORM_LMPHER = integ(D_EJ1 FORM_LMPHER, 0.0) !! ug/mL
C_EJ1 FORM_LMPHER = X_EJ1 FORM_LMPHER/VJEJ2 !! ug/mL

D_X_EJ2 FORM_LMPHER = -D_released_LMPHER_JEJ2 + X_JEJ1 FORM_LMPHER/TJEJ1 - X_JEJ2 FORM_LMPHER/TJEJ2
X_JEJ2 FORM_LMPHER = integ(D_X_EJ2 FORM_LMPHER, 0.0) !! ug/mL
C_JEJ2 FORM_LMPHER = X_JEJ2 FORM_LMPHER/VJEJ2 !! ug/mL

D_X_JEJ2 SOLID_DT_LMPH = -VJEJ2*Kd_IR*C_JEJ2 SOLID_LMPH*(SOLIF_JEJ2-C_JEJ2 DISS_LMPH) + X_JEJ2 SOLID_LMPH/TJEJ2
X_JEJ2 SOLID_LMPHER = BOUND(0.0, AdoselIR, LIMINT(D_X_JEJ2 SOLID_DT_LMPH, 0.0, 0.0, AdoselIR)) !! ug/mL
C_JEJ2 SOLID_LMPHER = X_JEJ2 SOLID_LMPHER/VJEJ2

D_dissolve_solid_JEJ2 = VJEJ2*Kd_IR*C_JEJ2 SOLID_LMPH*(SOLIF_JEJ2-C_JEJ2 DISS_LMPH)
X_dissolve_solid_JEJ2 = integ(D_dissolve_solid_JEJ2, 0.0) !! ug/mL

D_MEM_JEJ2 DT_LMPH = QJEJ2*CAL-QJEJ2*(MEM_JEJ2 LMPH/(VMEMJEJ2*KpGut))*1 - METABOLISM_JEJ2 LMPH + NI JJEJ2*DIFF_JEJ2*(-C_JEJ2_MEM_LMPH/1000+C_JEJ2 DISS_LMPH)
MEM_JEJ2 LMPH = integ(D_MEM_JEJ2 DT_LMPH, 0.0) !! ug/mL
C_JEJ2 MEM_LMPH = MEM_JEJ2 LMPH/VMEMJEJ2 !! ug/mL
R_MEM_JEJ2 = QJEJ2*(MEM_JEJ2 LMPH/(VMEMJEJ2*KpGut))*1 !! ug/hr
A_MEM_JEJ2_LMPH = integ(R_MEM_JEJ2 LMPH, 0.0) !! ug/hr
AMETABOLISM_JEJ2_LMPH = K5l*MEM_JEJ2 LMPH !! ug/hr
AMETABOLISM_JEJ2_LMPH = integ(METABOLISM_JEJ2 LMPH, 0.0) !! ug/hr

D_FG_JEJ2_LMPH = -QJEJ2*CAL+QJEJ2*(MEM_JEJ2 LMPH/(VMEMJEJ2*KpGut))*1
X_FG_JEJ2_LMPH = integ(D_FG_JEJ2_LMPH, 0.0) !! ug/mL

D_released_LMPHER_ILL1 = release_ill1
D_released_LMPHER_ILL1 = -D_released_LMPHER_ILL1 + X_JEJ2 FORM_LMPHER/TJEJ2
X_JEJ2 FORM_LMPHER = integ(D_JEJ2 FORM_LMPHER, 0.0) !! ug/mL
C_JEJ2 FORM_LMPHER = X_JEJ2 FORM_LMPHER/VJEJ2 !! ug/mL

D_X_ILL1 SOLID_DT_LMPH = -VILL1*Kd_IR*C_ILL1 SOLID_LMPH*(SOLIF_ILL1-C_ILL1 DISS_LMPH) + X_ILL1 SOLID_LMPHER/TILL1
X_ILL1 SOLID_LMPHER = BOUND(0.0, AdoselIR, LIMINT(D_X_ILL1 SOLID_DT_LMPH, 0.0, 0.0, AdoselIR)) !! ug/mL
C_ILL1 SOLID_LMPHER = X_ILL1 SOLID_LMPHER/VILL1

D_X_ILL1 SOLID_DT_LMPH = -VILL1*Kd_IR*C_ILL1 SOLID_LMPH*(SOLIF_ILL1-C_ILL1 DISS_LMPH) + D_released_LMPHER
R_ILL1 NI_ILL1*DIFF_ILL1*(-C_ILL1 MEM_LMPH/1000+C_ILL1 DISS_LMPH)
X_ILL1 FORM_LMPHER = integ(D_ILL1 FORM_LMPHER, 0.0) !! ug/mL
C_ILL1 FORM_LMPHER = X_ILL1 FORM_LMPHER/VILL1 !! ug/mL
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LMPH/TJ/EJ2 - X_ILL1_DISS_LMPH/TILL1
X_ILL1_DISS_LMPH = INTEG(D_X_ILL1_DISS_DT_LMPH, 0.0)
C_ILL1_DISS_LMPH = X_ILL1_DISS_LMPH/VILL1

D_dissolve_solid_LIR_ILL1 =
VILL1*Kd_IR*C_ILL1_SOLID_LMPHIR*(SOLIF_ILL1-C_ILL1_DISS_LMPH)
X_dissolve_solid_LIR_ILL1 = INTEG(D_dissolve_solid_LIR_ILL1, 0.0)

! Enterocytes
D_MEM_ILL1_LMPH = QILL1*CAL-QILL1*(MEM_ILL1_LMPH/(VMEMILL1*KpGut))*1 - METABOLISM_ILL1_LMPH +NI_ILL1*DIFF_ILL1*(-C_ILL1_MEM_LMPH/(VMEMILL1*KpGut))*1 - EFFLUX_DUO + INFLUX_DUO !!ug/hr
MEM_ILL1_LMPH = INTEG(D_MEM_ILL1_LMPH, 0.0) !!ug
C_ILL1_MEM_LMPH = MEM_ILL1_LMPH/VMMEMILL1 !!ug/L
R_MEM_ILL1_LMPH = QILL1*(MEM_ILL1_LMPH/(VMEMILL1*KpGut))*1 !!ug/hr
A_MEM_ILL1_LMPH = INTEG(R_MEM_ILL1_LMPH, 0.0) !!ug
METABOLISM_ILL1_LMPH = K5l*MEM_ILL1_LMPH !!ug/hr
AMETABOLISM_ILL1_LMPH = INTEG(METABOLISM_ILL1_LMPH, 0.0) !!ug

D_ABS_ILL1_LMPH =
M_ILL1*DIFF_ILL1*(-C_ILL1_MEM_LMPH/1000+C_ILL1_DISS_LMPH)
X_ABS_ILL1_LMPH = INTEG(D_ABS_ILL1_LMPH, 0.0)
D_FG_ILL1_LMPH =
-VILL1*Kd_IR*C_ILL1_SOLID_LMPHIR*(SOLIF_ILL1-C_ILL1_DISS_LMPH)+X_ILL1_DISS_LMPH/TILL1-X_ILL2_DISS_LMPH/TILL2
X_FG_ILL1_LMPH = INTEG(D_FG_ILL1_LMPH, 0.0)

! ILEUM2
! Lumen
X_released_LMPHER_ILL2 = INTEG(D_released_LMPHER_ILL2, 0.0) !!ug
D_released_LMPHER_ILL2 = release_ill2
D_ILL2_FORM_LMPHER = -D_released_LMPHER_ILL2 +
X_ILL2_FORM_LMPHER/TILL2-X_ILL1_FORM_LMPHER/TILL1
X_ILL2_FORM_LMPHER = INTEG(D_ILL2_FORM_LMPHER, 0.0) !!ug
C_ILL2_FORM_LMPHER = X_ILL2_FORM_LMPHER/VILL2 !!ug/mL
R_ILL2-NI_ILL2*DIFF_ILL2*(-C_ILL2_MEM_LMPH/1000+C_ILL2_DISS_LMPH)
X_ILL2_DISS_LMPHER = INTEG(D_X_ILL2_DISS_DT_LMPH, 0.0)
C_ILL2_DISS_LMPHER = X_ILL2_DISS_LMPHER/VILL2

! Lumen dissolved
D_X_ILL2_DISS_LMPH =
-VILL2*Kd_IR*C_ILL2_SOLID_LMPHIR*(SOLIF_ILL2-C_ILL2_DISS_LMPH)+D_released_LMPHER
R_X_ILL2_DISS_LMPHER = INTEG(D_X_ILL2_DISS_LMPH, 0.0)
C_ILL2_DISS_LMPHER = X_ILL2_DISS_LMPHER/VILL2

D_dissolve_solid_LIR_ILL2 =
VILL2*Kd_IR*C_ILL2_SOLID_LMPHIR*(SOLIF_ILL2-C_ILL2_DISS_LMPH)
X_dissolve_solid_LIR_ILL2 = INTEG(D_dissolve_solid_LIR_ILL2, 0.0)

! Enterocytes
D_MEM_ILL2_LMPH = QILL2*CAL-QILL2*(MEM_ILL2_LMPH/(VMEMILL2*KpGut))*1 - METABOLISM_ILL2_LMPH +NI_ILL2*DIFF_ILL2*(-C_ILL2_MEM_LMPH/(VMEMILL2*KpGut))*1 - EFFLUX_DUO + INFLUX_DUO !!ug/hr
MEM_ILL2_LMPH = INTEG(D_MEM_ILL2_LMPH, 0.0) !!ug
C_ILL2_MEM_LMPH = MEM_ILL2_LMPH/VMMEMILL2 !!ug/L
R_MEM_ILL2_LMPH = QILL2*(MEM_ILL2_LMPH/(VMEMILL2*KpGut))*1 !!ug/hr

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A_MEM_ILL2_LMPH = integ(R_MEM_ILL2_LMPH, 0.0) !!ug
METABOLISM_ILL2_LMPH = K5L*MEM_ILL2_LMPH !!ug/hr
AMETABOLISM_ILL2_LMPH = integ(METABOLISM_ILL2_LMPH, 0.0) !!ug

D_ABS_ILL2_LMPH =
N1_ILL2*DIFF_ILL2*(-C_ILL2_MEM_LMPH/1000+C_ILL2_DISS_LMPH)
X_ABS_ILL2_LMPH = integ(D_ABS_ILL2_LMPH, 0.0)

D_FG_ILL2_LMPH =
-Q2_ILL2*CAL+Q1_ILL2*(MEM_ILL2_LMPH/(VMEMILL2*KpGut))*1
X_FG_ILL2_LMPH = integ(D_FG_ILL2_LMPH, 0.0)

LILLEUM3
X_released_LMPHER_ILL3 = integ(D_released_LMPHER_ILL3, 0.0) !! ug
D_released_LMPHER_ILL3 = release_ill3
D_ILL3_FORM_LMPHER = -D_released_LMPHER_ILL3+X_ILL2_FORM_LMPHER/TILL2
- X_ILL3_FORM_LMPHER/TILL3
X_ILL3_FORM_LMPHER = integ(D_ILL3_FORM_LMPHER, 0.0) !! ug
C_ILL3_FORM_LMPHER = X_ILL3_FORM_LMPHER/VILL3 !! ug/mL

D_X_ILL3_SOLID_DT_LMPHIR =
-VILL3*Kd_IR*C_ILL3_SOLID_LMPHIR*(SOLIF_ILL3-C_ILL3_DISS_LMPH)+X_ILL2_SOLID_LMPHIR/TILL2
- X_ILL3_SOLID_LMPHIR/TILL3
ABooseI_FIFO_LMTN(D_X_ILL3_SOLID_DT_LMPHIR, 0.0, 0.0, 0.0, AdoseIR)) !!ug
C_ILL3_SOLID_LMPHIR = X_ILL3_SOLID_LMPHIR/VILL3

D_dissolve_solid_LIR_ILL3 =
VILL3*Kd_IR*C_ILL3_SOLID_LMPHIR*(SOLIF_ILL3-C_ILL3_DISS_LMPH)
X_dissolve_solid_LIR_ILL3 = integ(D_dissolve_solid_LIR_ILL3, 0.0)

Enterocytes
D_MEM_ILL3_LMPH = QILL3*CAL-QILL3*(MEM_ILL3_LMPH/(VMEMILL3*KpGut))*1 - METABOLISM_ILL3_LMPH
+NI_ILL3*DIFF_ILL3*(-C_ILL3_MEM_LMPH/1000+C_ILL3_DISS_LMPH) !!EFFLUX_DUO + INFLUX_DUO !!ug/hr
MEM_ILL3_LMPH = integ(D_MEM_ILL3_DT_LMPH, 0.0) !!ug
C_MEM_ILL3_LMPH = MEM_ILL3_LMPH/VMEMILL3 !!ug/L
R_MEM_ILL3_LMPH = QILL3*(MEM_ILL3_LMPH/(VMEMILL3*KpGut))*1
!!ug/hr
A_MEM_ILL3_LMPH = integ(R_MEM_ILL3_LMPH, 0.0) !!ug
METABOLISM_ILL3_LMPH = K5L*MEM_ILL3_LMPH !!ug/hr
AMETABOLISM_ILL3_LMPH = integ(METABOLISM_ILL3_LMPH, 0.0) !!ug

D_ABS_ILL3_LMPH =
N1_ILL3*DIFF_ILL3*(-C_ILL3_MEM_LMPH/1000+C_ILL3_DISS_LMPH)
X_ABS_ILL3_LMPH = integ(D_ABS_ILL3_LMPH, 0.0)

D_FG_ILL3_LMPH =
-Q1_ILL3*CAL+Q1_ILL3*(MEM_ILL3_LMPH/(VMEMILL3*KpGut))*1
X_FG_ILL3_LMPH = integ(D_FG_ILL3_LMPH, 0.0)

Cecum
X_released_LMPHER_CECUM = integ(D_released_LMPHER_CECUM, 0.0) !! ug
D_released_LMPHER_CECUM = release_cecum
D_CECUM_FORM_LMPHER = -D_released_LMPHER_CECUM + X_ILL3_FORM_LMPHER/TILL3
- X_CECUM_FORM_LMPHER/TCECUM
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X_CECUM_FORM_LMPHER = integ(D_CECUM_FORM_LMPHER, 0.0) !! ug
C_CECUM_FORM_LMPHER = X_CECUM_FORM_LMPHER / VCECUM !! ug/mL

D_X_CECUM_SOLID_DT_LMPHER =
- VCECUM * Kd_IR * C_CECUM_SOLI D_LMPHER * (SOLIF_CECUM - C_CECUM_DISS_LMPH) +
X_ILL3_SOLI D_LMPHER / TILL3 - (X_CECUM_SOLID_LMPHER / TCECUM) -
(X_CECUM_SOL I D_LMPHER / TCECUM) +
AdoselIR * LIMIT(D_X_CECUM_SOLID_DT_LMPHER, 0.0, 0.0, AdoselIR)) ! ug
C_CECUM_SOLI D_LMPHER = X_CECUM_SOLI D_LMPHER / VCECUM ! Lumen_dissolved

D_X_CECUM_DISS_DT_LMPHER =
VCECUM * Kd_IR * C_CECUM_SOLI D_LMPHER * (SOLIF_CECUM - C_CECUM_DISS_LMPH) +
D_released_LMPHER_CECUM - NI_CECUM * DIFF_CECUM * (-C_CECUM_MEM_LMPH / 1000 + C_CECUM_DISS_LMPH) +
(X_ILL3_DISS_LMPHER / TILL3) - (X_CECUM_DISS_LMPHER / TCECUM)

D_X_CECUM_DISS_DT_LMPHER =
- VCECUM * Kd_IR * C_CECUM_SOLID_LMPHER * (SOLIF_CECUM - C_CECUM_DISS_LMPH) +
D_released_LMPHER_CECUM - NI_CECUM * DIFF_CECUM * (-C_CECUM_MEM_LMPH / 1000 + C_CECUM_DISS_LMPH) +
(X_ILL3_DISS_LMPHER / TILL3) - (X_CECUM_DISS_LMPHER / TCECUM)

D_dissolve_solid_LIR_CECUM =
VCECUM * Kd_IR * C_CECUM_SOLID_LMPHER * (SOLIF_CECUM - C_CECUM_DISS_LMPH)
X_dissolve_solid_LIR_CECUM = integ(D_dissolve_solid_LIR_CECUM, 0.0)

D_ABS_CECUM_LMPH =
- NI_CECUM * DIFF_CECUM * (-C_CECUM_MEM_LMPH / 1000 + C_CECUM_DISS_LMPH)
X_ABS_CECUM_LMPH = integ(D_ABS_CECUM_LMPH, 0.0)

D_FG_CECUM_LMPH =
- QCECUM * CAL - QCECUM * (MEM_CECUM_LMPH / (VMEMCECUM * Kp colon)) * 1

D_MEM_CECUM_DT_LMPH =
QCECUM * CAL - QCECUM * (MEM_CECUM_LMPH / (VMEMCECUM * Kp colon)) * 1 - METABOLISM_CECUM LMPH

R_MEM_CECUM_LMPH = QCECUM * (MEM_CECUM_LMPH / (VMEMCECUM * Kp colon)) * 1

D_ASCENDING_FORM_LMPHER =
- VASCENDING * Kd_IR * C_ASCENDING_FORM_LMPHER * (SOLIF_ASCENDING - C_ASCENDING_DISS_LMPH) +
X_CASCENDING_FORM_LMPHER / TCECUM -
(X_ASCENDING_FORM_LMPHER / TASCENDING)

C_ASCENDING_FORM_LMPHER = integ(D_ASCENDING_FORM_LMPHER, 0.0) !! ug/mL

D_ASCENDING_SOLID_LMPHER =
- VASCENDING * Kd_IR * C_ASCENDING_SOLID_LMPHER * (SOLIF_ASCENDING - C_ASCENDING_DISS_LMPH) +
X_CASCENDING_SOLID_LMPHER / TCECUM -
(X_ASCENDING_SOLID_LMPHER / TASCENDING)

C_ASCENDING_SOLID_LMPHER = integ(D_ASCENDING_SOLID_LMPHER, 0.0) !! ug/mL
\[
\text{Supple PBPK Code.txt}
\]

\[
\text{VASSENDING*Kd\_IR*C\_ASCENDING\_SOLID\_LMPH*R*(SOLF\_ASCENDING\_C\_ASCENDING\_DISS\_LMPH/1000\_C\_ASCENDING\_DISS\_LMPH/TCECUM)}+\text{X\_CECUM\_DISS\_LMPH/TASCENDING}
\]

\[
X\_ASCENDING\_DISS\_LMPH = \text{integ}(D\_X\_ASCENDING\_DISS\_DT\_LMPH, 0.0)
\]

\[
C\_ASCENDING\_DISS\_LMPH = X\_ASCENDING\_DISS\_LMPH/VASCENDING
\]

\[
D\_dissolve\_solid\_LIR\_ASCENDING = VASCENDING*Kd\_IR*C\_ASCENDING\_SOLID\_LMPH*R*(SOLF\_ASCENDING\_C\_ASCENDING\_DISS\_LMPH/1000\_C\_ASCENDING\_DISS\_LMPH/TASCENDING)
\]

\[
X\_dissolve\_solid\_LIR\_ASCENDING = \text{INTEG}(D\_dissolve\_solid\_LIR\_ASCENDING, 0.0)
\]

\[
\text{Enterocytes}
\]

\[
D\_MEM\_ASCENDING\_DT\_LMPH = QASCENDING*CAL-QASCENDING*(\text{MEM\_ASCENDING\_LMPH}/(\text{VMEMASCENDING\_NG*Kpcolon}))*1 - \text{METABOLISM\_ASCENDING\_LMPH} + NI\_ASCENDING\_DIFF\_ASCENDING\_NG*(-C\_ASCENDING\_MEM\_LMPH/1000+C\_ASCENDING\_DISS\_LMPH) ! - \text{EFFLUX\_DUO} + \text{INFLUX\_DUO} !ug/hr
\]

\[
\text{MEM\_ASCENDING\_LMPH} = \text{INTEG}(D\_MEM\_ASCENDING\_DT\_LMPH, 0.0) !ug
\]

\[
C\_ASCENDING\_MEM\_LMPH = \text{MEM\_ASCENDING\_LMPH}/\text{VMEMASCENDING}
\]

\[
R\_MEM\_ASCENDING\_LMPH = QASCENDING*(\text{MEM\_ASCENDING\_LMPH}/(\text{VMEMASCENDING\_NG*Kpcolon}))*1 !ug/hr
\]

\[
\text{METABOLISM\_ASCENDING\_LMPH} = \text{KSL\_ASCENDING\_NG}\_\text{MEM\_ASCENDING\_LMPH}
\]

\[
A\_MEM\_ASCENDING\_LMPH = \text{INTEG}(R\_MEM\_ASCENDING\_LMPH, 0.0) !ug/hr
\]

\[
\text{AMETABOLISM\_ASCENDING\_LMPH} = \text{INTEG}(\text{METABOLISM\_ASCENDING\_LMPH}, 0.0) !ug/hr
\]

\[
D\_ABS\_ASCENDING\_LMPH = NI\_ASCENDING\_DIFF\_ASCENDING\_NG*(-C\_ASCENDING\_MEM\_LMPH/1000+C\_ASCENDING\_DISS\_LMPH)
\]

\[
X\_ABS\_ASCENDING\_LMPH = \text{INTEG}(D\_ABS\_ASCENDING\_LMPH, 0.0)
\]

\[
D\_FG\_ASCENDING\_LMPH = -QASCENDING*CAL-QASCENDING*(\text{MEM\_ASCENDING\_LMPH}/(\text{VMEMASCENDING\_NG*Kpcolon}))*1
\]

\[
X\_FG\_ASCENDING\_LMPH = \text{INTEG}(D\_FG\_ASCENDING\_LMPH, 0.0)
\]

\[
\text{Terminal\_unabsorbed\_LMPH\_IR}
\]

\[
D\_Terminal\_SOLID\_LMPH = X\_ASCENDING\_SOLID\_LMPH/R\_TASCENDING+X\_ASCENDING\_FORM\_LMPHER/R\_TASCENDING
\]

\[
D\_Terminal\_DISS\_LMPH = X\_ASCENDING\_DISS\_LMPHER/R\_TASCENDING
\]

\[
A\_Terminal\_SOLID\_LMPH = \text{BOUND}(0.0, \text{ADOSEL}, \text{LMTN}(D\_Terminal\_SOLID\_LMPH, 0.0, 0.0, \text{ADOSEL}))
\]

\[
A\_Terminal\_DISS\_LMPH = \text{INTEG}(D\_Terminal\_DISS\_LMPHER, 0.0)
\]

\[
D\_TERMINAL\_IR\_LMPH = X\_ASCENDING\_SOLID\_LMPH/R\_TASCENDING
\]

\[
X\_TERMINAL\_IR\_LMPH = \text{INTEG}(D\_TERMINAL\_IR\_LMPHER, 0.0)
\]

\[
D\_TERMINAL\_ER\_LMPH = X\_ASCENDING\_FORM\_LMPHER/R\_TASCENDING
\]

\[
X\_TERMINAL\_ER\_LMPH = \text{INTEG}(D\_TERMINAL\_ER\_LMPHER, 0.0)
\]

\[
RBS\_LMPH = QDUO*(\text{MEM\_DUO\_LMPH/}(\text{VMEMDUO\_NG*KpGut}))*1+QJE1*(\text{MEM\_JE1\_LMPH/}(\text{VMEMJE1\_NG*1*KpGut}))*1
\]

\[
+QJE2*(\text{MEM\_JE2\_LMPH/}(\text{VMEMJE2\_NG*1*KpGut}))*1+QLLE1*(\text{MEM\_LLE1\_LMPH/}(\text{VMEMLLE1\_NG*KpGut}))*1+QLLE2*(\text{MEM\_LLE2\_LMPH/}(\text{VMEMLLE2\_NG*KpGut}))*1+QLLE3*(\text{MEM\_LLE3\_LMPH/}(\text{VMEMLLE3\_K})}
Supple PBPK Code.txt

pGut())*1+
QCECUM*(MEM_CECUM_LMPH/(VMEMCECUM*Kpcolon))*1+QASCENDING*(MEM_ASCENDING_LMPH/(VMEMASCENDING*Kpcolon))*1

ABS_LMPH = integ(RBS_LMPH, 0.0)

AMETABOLISM_SI_LMPH = AMETABOLISM_DUO_LMPH+AMETABOLISM_JEJ1_LMPH+AMETABOLISM_JEJ2_LMPH+AMETABOLISM_ILL1_LMPH+AMETABOLISM_ILL2_LMPH+AMETABOLISM_ILL3_LMPH+AMETABOLISM_CECUM_LMPH+AMETABOLISM_ASCENDING_LMPH

!Scaled kinetic parameters

K5d = K5dC*BW^0.75 !(1/h)|Enterocyte

K5l = K5lC*BW^0.75 !(1/h)|Enterocyte

K5d_cecum = K5dC_cecum*BW^0.75 !(1/h)|Enterocyte

K5l_cecum = K5lC_cecum*BW^0.75 !(1/h)|Enterocyte

K5d_ascending = K5d_ascending *BW^0.75 !(1/h)|Enterocyte

K5l_ascending = K5l_ascending *BW^0.75 !(1/h)|Enterocyte

Vmaxliver = VmaxliverdC*BW^0.75 !(ug/h)|Vmax of d-MPH hydrolysis in the liver

Vmaxliver = VmaxliverlC*BW^0.75 !(ug/h)|Vmax of l-MPH hydrolysis in the liver

Ku_RA = Ku_RAdC*BW**0.75 !(L/h) |Urinary excretion of d-RA

Ku_RA = Ku_RAldC*BW**0.75 !(L/h) |Urinary excretion of l-RA

Kmet d = Kmet dC*B*BW**0.75 !(L/h) |Clearance of d-MPH in the liver via oxidation

Kmet l = Kmet lC*B*BW**0.75 !(L/h) |Clearance of l-MPH in the liver via oxidation

!-----Amount of d-MPH in the plasma

Rplasmad = QC*(Cv -CAd ) !(ug/h)|Rate of d-MPH amount change in the plasma.

APlasmad = integ(Rplasmad , 0.0) !(ug) |Amount of d-MPH in the plasma.

CAd = Aplasmad /Vplasma !(ug/L)|d-MPH concentration in the artery plasma.

CVD = (CVLiverd*QLiver + CVFatd*QFat + CVRd*QR
+CVSd*QS+ CVgondad*Qgond + CVbraind*Qbrain+CVheArt d*QheArt +IVRd)/QC

!(ug/L)|d-MPH concentration in the venous plasma.

!-----Amount of d-MPH in the fat

RAFatd = QFatd*(CAd -CVfatd ) !(ug/h)|Rate of d-MPH amount change in the fat.

AFatd = integ(RAFatd , 0.0) !(ug) |Amount of d-MPH in the fat.

CVFatd = AFatd /(VFat*PFat) !(ug/L)|venous blood concentration of d-MPH leaving the fat.
Supple PBPK Code.txt

$\text{CFatd} = \frac{\text{AFatd}}{\text{VFat}} \ (\text{ug/L})|\text{d-MPH concentration in the fat.}$

--- Amount of d-MPH in the gonads

$\text{RAgonadd} = \frac{\text{Qgonadd}(\text{Cad} - \text{CVgonadd})}{\text{VFat}} \ (\text{ug/h})|\text{Rate of d-MPH amount change in the gonads.}$

$\text{Agonadd} = \int \text{RAgonadd} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH in the gonads.}$

$\text{CVgonadd} = \frac{\text{Agonadd}}{(\text{Vgonad} \cdot \text{Pgonad})} \ (\text{ug/L})|\text{venous blood concentration of d-MPH leaving the gonads.}$

$\text{Cgonadd} = \frac{\text{Agonadd}}{\text{Vgonad}} \ (\text{ug/L})|\text{d-MPH concentration in the gonads.}$

--- Amount of d-MPH in the liver

$\text{RALIVERD} = \{\text{QLiver} - \text{QDUO} - \text{QIL1} - \text{QIL2} - \text{QI L3} - \text{Qcecum} - \text{Qascending}\} \cdot \text{CAD} - \text{QLIVER} \cdot \text{CVLIVERD} - \text{Rmetd} - \text{Rmet_liverd} + \text{RBS_DMPH}$

$\text{ALiverd} = \int \text{RALIVERD} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH in the liver.}$

$\text{CVLiverd} = \frac{\text{ALiverd}}{(\text{VLiver} \cdot \text{PLiver})} \ (\text{ug/L})|\text{venous blood concentration of d-MPH leaving the liver.}$

$\text{CLiverd} = \frac{\text{ALiverd}}{\text{VLiver}} \ (\text{ug/L})|\text{d-MPH concentration in the liver.}$

$\text{Rmetd} = \frac{\text{Kmetd} \cdot \text{CVliverd}}{\text{Kmliverd}} \ (\text{ug/h})|\text{Rate of d-MPH oxidation in the liver}$

$\text{Ametd} = \int \text{Rmetd} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH oxidation in the liver}$

$\text{Rmet_liverd} = \frac{\text{Vmax_liverd} \cdot \text{CVliverd}}{(\text{Kmliverd} \cdot (1+\text{CVliverd}/\text{Kmliverd}) + \text{CVliverd})} \ (\text{ug/h})|\text{Rate of d-MPH hydrolysis in the liver}$

$\text{Amet_liverd} = \int \text{Rmet_liverd} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH hydrolysis in the liver}$

--- Amount of d-MPH in the brain

$\text{Rbraind} = \frac{\text{Qbrain}(\text{Cad} - \text{CVbraind})}{\text{VFat}} \ (\text{ug/h})|\text{Rate of d-MPH amount change in the brain.}$

$\text{Abra in d} = \int \text{Rbraind} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH in the brain.}$

$\text{CVbraind} = \frac{\text{Abra in d}(\text{Vbrain} \cdot \text{Pbrain})}{\text{VS} \cdot \text{PSlow}} \ (\text{ug/L})|\text{venous blood concentration of d-MPH leaving the brain.}$

$\text{Cbraind} = \frac{\text{Abra in d}}{\text{Vbrain}} \ (\text{ug/L})|\text{d-MPH concentration in the brain.}$

--- Amount of d-MPH in rapidly perfused tissues

$\text{RARd} = \frac{\text{QR}(\text{Cad} - \text{CVrd})}{\text{VFat}} \ (\text{ug/h})|\text{Rate of d-MPH amount change in the rapidly perfused tissues.}$

$\text{ARD} = \int \text{RARd} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH in the rapidly perfused tissues.}$

$\text{CVRD} = \frac{\text{ARD}(\text{VR} \cdot \text{P Rich})}{\text{VR}} \ (\text{ug/L})|\text{venous blood concentration of d-MPH leaving the rapidly perfused tissues.}$

$\text{CRd} = \frac{\text{ARD}}{\text{VR}} \ (\text{ug/L})|\text{d-MPH concentration in the rapidly perfused tissues.}$

--- Amount of d-MPH in slowly perfused tissues

$\text{RASd} = \frac{\text{QS}(\text{Cad} - \text{CVsd})}{\text{VFat}} \ (\text{ug/h})|\text{Rate of d-MPH amount change in the slowly perfused tissues.}$

$\text{ASd} = \int \text{RASd} \, \text{dt}, \ 0.0 \ (\text{ug})|\text{Amount of d-MPH in the slowly perfused tissues.}$

$\text{CVSD} = \frac{\text{ASd}(\text{VS} \cdot \text{PSlow})}{\text{VS}} \ (\text{ug/L})|\text{venous blood concentration of d-MPH leaving the slowly perfused tissues.}$

$\text{CSd} = \frac{\text{ASd}}{\text{VS}} \ (\text{ug/L})|\text{d-MPH concentration in the slowly perfused tissues.}$
Supple PBPK Code.txt

!---- Amount of d-MPH in the heart
Rheartd = QHeart*(CAD - CVheartd) !(ug/h) | Rate of d-MPH

amount change in the heart
Aheardt = INTEG(Rheartd, 0.0) !(ug) | Amount of d-MPH

in the heart
CVheartd = Aheartd/(Vheart*Pheart) !(ug/L) | venous blood

concentration of d-MPH leaving the heart
Cper formed into the system
Aheard = Aheartd/Vheart !(ug/L) | d-MPH

concentration in the heart

!! Model for d-RA
Rmet_RAd = Rmet_liverd*(220/233.3062) !(ug/h) | Formation rate

of d-RA in the liver
Amet_RAd = Integ (Rmet_RAd, 0.0) !(ug) | Amount of d-RA

excretion into the liver
RRAurined = Ku_RAd*CVRAd !(ug/h) | rate of d-RA

excretion into the urine
ARAurined = integ(RRAurined, 0.0) !(ug) | Amount of d-RA

RxRAd = METABOLISM_SI_DMPH*F*(220/233.3062)
!(ug/h) | Formation and uptake rate of d-RA from the gut into the system

AxRAd = Integ (RxRAd, 0.0) !(ug) | Amount of d-RA

formation in the gut and taken up into the system
Rplasmarad = Rmet_RAd - RRAurined + RxRAd !(ug/h) | Rate of

d-RA amount change in the system

APlasmarad = INTEG(Rplasmarad, 0.0) !(ug) | Amount of d-RA

concentration in the system

!!!!!!! %%%%%%%%%%%%%%%%%%%%% PBPK model for LMPH
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

!---- Amount of l-MPH in the plasma
Rplasmal = QC*(CVl - CAl) !(ug/h) | Rate of d-MPH

amount change in the plasma
APlasmal = Integ (Rplasmal, 0.0) !(ug) | Amount of d-MPH

in the plasma
CAl = APlasmal/Vplasma !(ug/L) | d-MPH

concentration in the artery plasma.
CVl = (CVLiverl*QLiver + CVFatl*QFat + CVRl*QR +CVSl*QS+Cvgonadel*Qgonad + CVbrainl*Qbrain+CVheartl*Qheart+IVRI)/QC
!(ug/L) | d-MPH concentration in the venous plasma.

!---- Amount of l-MPH in the fat
Rfatl = QFat*(CAI - CVfatl) !(ug/h) | Rate of d-MPH

amount change in the fat.
AFatl = Integ(Rfatl, 0.0) !(ug) | Amount of d-MPH in the fat.

CFatl = AFatl/(VFat*PFat) !(ug/L) | venous blood

concentration of d-MPH leaving the fat.
Cfatl = AFatl/VFat !(ug/L) | d-MPH

concentration in the fat.

!---- Amount of l-MPH in the gonads
Rgonadl = Qgonad*(CAI - Cvgonadl) !(ug/h) | Rate of d-MPH

amount change in the gonads.
Agonadl = Integ(Rgonadl, 0.0) !(ug) | Amount of d-MPH in the gonads.

Cgonadl = Agonadl/(Vgonad*Pgonad) !(ug/L) | venous blood

concentration of d-MPH leaving the gonads.
Cgonadl = Agonadl/Vgonad !(ug/L) | d-MPH

concentration in the gonads.
!---- Amount of l-MPH in the liver
RALIVER = (QLiver-QDUO-QJEJ1-QJEJ2-QILL1-QILL2-Qcecum-Qascending)*CAL-QLIVER*CVLIVER
ALIVER = INTEGRAL(RALIVER ,0.0) ! (ug) | Amount of d-MPH in the liver.

CVLiver = ALIVER/(VLiver*PLiver) ! (ug/L) | venous blood concentration of d-MPH leaving the liver.
CLiver = ALIVER/VLiver ! (ug/L) | d-MPH concentration in the liver.

Rmet = Kmetl*CVliver ! (ug/h) | Rate of d-MPH oxidation in the liver.

Amet = INTEGRAL(Rmet ,0.0) ! (ug) | Amount of d-MPH oxidation in the liver.

RmetLiver = VmaxLiver*CVliver/(Kmliver*(1+CVLiverD/KMLIVERD)+CVliver) ! (ug/h) | Rate of d-MPH hydrolysis in the liver.

AmetLiver = INTEGRAL(RmetLiver ,0.0) ! (ug) | Amount of d-MPH hydrolysis in the liver.

!---- Amount of l-MPH in the brain
Rbrain = Qbrain*(CAL-CVbrainL) ! (ug/h) | Rate of d-MPH amount change in the brain.

Abrain = INTEGRAL(Rbrain ,0.0) ! (ug) | Amount of d-MPH in the brain.

CVbrain = Abrain/(Vbrain*Pbrain) ! (ug/L) | venous blood concentration of d-MPH leaving the brain.
Cbrain = Abrain/Vbrain ! (ug/L) | d-MPH concentration in the brain.

!---- Amount of l-MPH in rapidly perfused tissues
RARL = QR*(CAL-CVRL) ! (ug/h) | Rate of d-MPH amount change in the rapidly perfused tissues.

ARL = INTEGRAL(RARL ,0.0) ! (ug) | Amount of d-MPH in the rapidly perfused tissues.

CVRL = ARL/(VR*PRich) ! (ug/L) | venous blood concentration of d-MPH leaving the rapidly perfused tissues.
CRL = ARL/VR ! (ug/L) | d-MPH concentration in the rapidly perfused tissues.

!---- Amount of l-MPH in slowly perfused tissues
RASL = QS*(CAL-CVSL) ! (ug/h) | Rate of d-MPH amount change in the slowly perfused tissues.

ASL = INTEGRAL(RASL ,0.0) ! (ug) | Amount of d-MPH in the slowly perfused tissues.

CVSL = ASL/(VS*PSlow) ! (ug/L) | venous blood concentration of d-MPH leaving the slowly perfused tissues.
CSL = ASL/VS ! (ug/L) | d-MPH concentration in the slowly perfused tissues.

!---- Amount of l-MPH in the heart
Rheart = QHeart*(CAL-CVheartL) ! (ug/h) | Rate of d-MPH amount change in the heart.

Aheart = INTEGRAL(Rheart ,0.0) ! (ug) | Amount of d-MPH in the heart.

CVheart = Aheart/(Vheart*PHearth) ! (ug/L) | venous blood concentration of d-MPH leaving the heart.
Cheart = Aheart/Vheart ! (ug/L) | d-MPH concentration in the heart.

!! Model for l-RA
Rmet_RAL = RmetLiver*(220/233.3062) ! (ug/h) | formation rate of d-RA in the liver.

Amet_RAL = INTEGRAL(Rmet_RAL ,0.0) ! (ug) | Amount of d-RA in the liver.
**Supple PBPK Code.txt**

d-RA formed in the liver

\[ RRA_{\text{urineL}} = K_u \cdot RAL \cdot CVRL \] ! (ug/h) | rate of d-RA excretion into the urine

\[ ARA_{\text{urineL}} = \text{integ}(RRA_{\text{urineL}}, 0.0) \] ! (ug) | Amount of d-RA excretion into the urine

\[ RxRAL = METABOLISM_SI_{\text{LMPH}}\cdot F*(220/233.3062) \] ! (ug/h) | Formation and uptake rate of d-RA from the gut into the system

\[ AxRAL = \text{integ}(RxRAL, 0.0) \] ! (ug) | Amount of d-RA formed in the gut and taken up into the system

\[ RplasmaraL = R_{\text{metRAL}} - RRA_{\text{urineL}} + RxRAL \] ! (ug/h) | Rate of d-RA amount change in the system

\[ APlasmaraL = \text{INTEG}(RplasmaraL, 0.0) \] ! (ug) | Amount of d-RA concentration in the system

!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!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!! MPH In THE ENTEROCYTES

CELLDMPH =
MEM_DUO_DMPH+MEM_JEJ1_DMPH+MEM_JEJ2_DMPH+MEM_ILL1_DMPH +MEM_ILL2_DMPH+MEM_ILL3_DMPH+MEM_ASCENDING_DMPH+MEM_CECUM_DMPH

CELLLMPH =
MEM_DUO_LMPH+MEM_JEJ1_LMPH+MEM_JEJ2_LMPH+MEM_ILL1_LMPH +MEM_ILL2_LMPH+MEM_ILL3_LMPH+MEM_ASCENDING_LMPH+MEM_CECUM_LMPH

!! TOTAL MPH IN THE GUT
GUTDMPH = LUMENDMPHform+LUMENDMPHDISS+CELLDMPH
GUTLMPH = LUMENLMPHform+LUMENLMPHDISS+CELLLMPH

!! MASS FOR MPH MODEL
MPHBOX = GUTDMPH + GUTLMPH+ALiverd+ALIVERl+
Aplasma+Aplasma+AFat+d+AFATl+ASd+ASI+ARd+ARI+Agonadd+AGONADI+
Abraind+ABRAINl+Aheartd+AHEARTl
LossMPHLIVER = AmetL +Ametd+Amet_liverd +Amet_liverl
LOSSMPGUT = AMETABOLISM_SI_LMPH+AMETABOLISM_SI_DMPH
BALMPH =
ALv+ALvi+ADOSEDIR+ADOSEDER+ADOSELER-MPHBOX-LOSSMPHLIVER-LOSSMPGUT

!! ra
RABOX = APlasmaD +APlasmaL
RATOMPH = RABOX *(233.3062/220)
balar = Amet_ral +AMET_RAD+ARAL+
ARAD-RABOX-ARAurined-ARAurinel
!(ug)|Mass balance for RA

!! TOTAL BALANCE
BAL = ALv+ALvi+ADOSEDIR+ADOSEDER+ADOSELER-
RATOMPH-MPHBOX-(ARAurined+AR Aurinel)*(233.3062/220)-AmetL-AmetD-AMETABOLISM_SI_DMPH*(1-F)- AMETABOLISM_SI_LMPH*(1-F)
Ratio_liver = (AmetL+Ametd)/(AmetL+Ametd+Amet_liverd +
Amet_liverl+1e-34)
Ratio_total =
(AmetL+Ametd+AMETABOLISM_SI_DMPH*(1-F)+AMETABOLISM_SI_LMPH*(1-F))/(AmetL+Ametd +Amet_liverd +Amet_liverl+1e-34+AMETABOLISM_SI_DMPH+AMETABOLISM_SI_LMPH)
Ratio_gut =
(AMETABOLISM_SI_DMPH*(1-F)+AMETABOLISM_SI_LMPH*(1-F))/(AMETABOLISM_SI_DMPH+AME
TABOLISM_SI_LMPH+1e-34)

auccv = INTEG(CTOTAL, 0)
QSC = QS/QC
QRC = QR/QC
VSC = VS/BW
VRC = VR/BW

END ! DERIVATIVE
! Add discrete events here as needed
! DISCRETE
! END

! code that is executed once at each communication interval goes here
TERMT (T.GE.TSTOP, 'checked on communication interval: REACHED TSTOP')

END ! DYNAMIC

TERMINAL
! code that is executed once at the end of a simulation run goes here

END ! TERMINAL