PROGRAM

! Initiated by Lingli Huang on 08/18/2014;
! Checked by Zhoumeng Lin on 10/21/2014;

INITIAL

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

!! Physiological parameters

! Blood flow rates

CONSTANT QCC = 5.0 ! Cardiac output (L/h/kg) (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT QLC = 0.27 ! Fraction of blood flow to the liver (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT QKC = 0.12 ! Fraction of blood flow to the kidneys (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT QFC = 0.13 ! Fraction of blood flow to the fat (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT QMC = 0.25 ! Fraction of blood flow to the muscle (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT QGC = 0.18 ! Fraction of blood flow to the GI tract (Tranquillity et al, 1982)

! Tissue volumes

CONSTANT BW = 50 ! Body weight (kg) (Li et al., 2013)

CONSTANT VLC = 0.025 ! Fractional liver tissue (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT VKC = 0.004 ! Fractional kidney tissue (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT VFC = 0.32 ! Fractional fat tissue (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT VMC = 0.40 ! Fractional muscle tissue (Average of Buur et al., 2005 and Upton, 2008)

CONSTANT VGC = 0.05 ! Fractional GI tract (Upton, 2008)
CONSTANT VbloodC = 0.06 ! Blood volume, fraction of BW (Average of Buur et al., 2005 and Upton, 2008)

! Mass Transfer Parameters (Chemical-specific parameters)
CONSTANT MW = 271 ! (g/mol, Molecular weight)

! Partition coefficients for CYA (PC, tissue:plasma)
CONSTANT PLcya = 1.0 ! Liver:plasma PC (Estimated based on Li et al, 2013)
CONSTANT PKcya = 1.28 ! Kidney:plasma PC (Estimated based on Li et al, 2013)
CONSTANT PMcya = 4.55 ! Muscle:plasma PC (Estimated based on Li et al, 2013)
CONSTANT PFcya = 1.98 ! Fat:plasma PC (Estimated based on Li et al, 2013)
CONSTANT POTcya = 1.0 ! GI:plasma PC (Assumed as the same with liver)

! Partition coefficients for BDCYA (PC, tissue:plasma)
CONSTANT PLbdcya = 0.91 ! Liver:plasma PC (Measured from the experiment)
CONSTANT PKbdcya = 2.87 ! Kidney:plasma PC (Measured from the experiment)
CONSTANT PMbdcya = 0.32 ! Muscle:plasma PC (Measured from the experiment)
CONSTANT PFbdcya = 0.30 ! Fat:plasma PC (Measured from the experiment)
CONSTANT POTbdcya = 0.91 ! GI:plasma PC (Assumed as the same with liver)

! Kinetic constants
! Oral absorption rate constants
CONSTANT Ka = 0.0015 ! /h, intestinal absorption rate constant for CYA
CONSTANT Ka1 = 0.0008 ! /h, intestinal absorption rate constant for BDCYA
CONSTANT Kst= 0.2 ! /h, gastric emptying rate constant
CONSTANT Kef = 0.4 ! /h, intestinal transit rate constant for CYA
CONSTANT $K_{ef1} = 0.2 \, /h$, intestinal transit rate constant for BDCYA

CONSTANT Bioavail$ = 0.44 \, /\%$, Bioavailability of CYA in pigs. (Measured by Xu et al, 2012)

CONSTANT PB$ = 0.153 \, /$, plasma protein combination ratio of CYA. (Measured by experiment)

CONSTANT PB1$ = 0.722 \, /$, plasma protein combination ratio of BDCYA. (Measured by experiment)

! Metabolic constants for CYA_BDCYA

CONSTANT $K_{m1C} = 0.01 \, (Liver \, metabolism \, rate \, constant \, of \, CYA)$

CONSTANT $F_L = 0.17 \, (Fraction \, of \, CYA \, to \, be \, metabolized \, into \, BDCYA \, in \, liver)$

CONSTANT $K_{m2C} = 0.04 \, (Intestinal \, metabolism \, rate \, constant \, of \, CYA)$

CONSTANT $F_I = 0.2 \, (Fraction \, of \, CYA \, to \, be \, metabolized \, into \, BDCYA \, in \, intestine)$

! Elimination rate constant

CONSTANT $Cl_{cya} = 0.035 \, L/h/kg \, (Renal \, clearance \, rate \, of \, CYA, \, Measured \, by \, experiment)$

CONSTANT $Cl_{bdcya} = 0.0044 \, L/h/kg \, (Renal \, clearance \, rate \, of \, BDCYA, \, Measured \, by \, experiment)$

CONSTANT $K_bC = 0.01 \, (bile \, elimination \, rate \, constant \, for \, CYA)$

CONSTANT $K_bC1 = 0.01 \, (bile \, elimination \, rate \, constant \, for \, BDCYA)$

! Parameters for various exposure scenarios

Constant PDOSEoral$ = 20 \, (oral \, dose \, of \, CYA \, in \, pigs(mg/kg \, b.w.)$)

! Determine withdrawal

CONSTANT TL$ = 8000 \, (Tolerance \, of \, BDCYA \, in \, liver)$

CONSTANT TK$ = 3000 \, (Tolerance \, of \, BDCYA \, in \, kidney)$

CONSTANT TM$ = 500 \, (Tolerance \, of \, BDCYA \, in \, muscle)$
CONSTANT TF= 2000 ! (Tolerance of BDCYA in fat)

Twithdrawal=0

END ! INITIAL

DYNAMIC

ALGORITHM IALG = 2
NSTEPS NSTP = 10
MAXTERVAL MAXT = 1.0e9
MINTERVAL MINT = 1.0e-9
CINTERVAL CINT = 0.1

DERIVATIVE
! code for calculating the derivative goes here
! Cardiac output and blood flows to tissues (L/h)
QC = QCC*BW ! Cardiac output
QL = QLC*QC ! Blood flow to the liver
QK = QKC*QC ! Blood flow to the kidney
QF = QFC*QC ! Blood flow to the fat
QM = QMC*QC ! Blood flow to the muscle
QG = QGC*QC ! Blood flow to the GI tract
QOT = QC-QL-QK-QM-QF ! Blood flow to the other tissues
! Tissue volumes (L)

VL = VLC*BW ! Liver

VK = VKC*BW ! Kidney

VF = VFC*BW ! Fat

VM = VMC*BW ! Muscle

VG = VGC*BW ! GI tract

Vblood = VbloodC*BW ! Blood

VOT = BW-VL-VK-VM-VF-Vblood ! Other tissues

! Unit conversion from mg CYA to umol CYA : 1mg = 3.69umol

! 1mg=1000ug

! 1000ug/271g/mol=3.69umol

! 1mg=3.69umol

CONSTANT MWCYA = 3.69 ! Molecular weight of CYA (umol/mg)

! Dosing

DOSEoral = PDOSEoral*BW*MWCYA*Bioavail ! (umol)

!... Dosing, multiple oral gavage

CONSTANT tlen = 0.001 ! Length of oral gavage exposure (h/day)
CONSTANT tinterval = 12 ! Varied dependent on the exposure paradigm(h)

CONSTANT Dstart = 0.0 ! Initiation day of oral gavage (day)

CONSTANT Dstop = 5 ! Termination day of oral gavage (day)

CONSTANT MAXT = 1.0 ! maximum comm. interval

CONSTANT CINTC = 0.1 ! Communication interval

CINT = CINTC ! Communication interval

Tsim = TSTOP ! Tstop in hours

DS = Dstart*24 ! Initiation time point of oral gavage (h)

Doff = (Dstop - Dstart)*24 ! Oral gavage duration (h)

TimeOn = Dstart*24 ! Initiation time point of oral gavage (h)

TimeOff = Dstop*24 + tlen ! Termination time point of oral gavage (h)

Exposure = PULS(0, tinterval, tlen)*PULS(DS, Tsim, Doff)

Rdoseoral = (Doseoral / tlen)*Exposure ! Rate of oral dosage

RAST = Rdoseoral - Kst*AST

AST = INTEG(rast, 0)

RI = Kst*AST - Ka*AI - Kef*AI - Km2*AI ! Rate of CYA in intestine

AI = Integ(RI, 0) ! Amount of dosage in intestine

RAO = Ka*AI ! Rate of absorbed by intestine

AAO = Integ(RAO, 0) ! Amount of absorbed by intestine

AEF = Kef*AI ! Amount of CYA excreted from intestine

AEF1 = Kef1*AI ! Amount of BDCYA excreted from intestine
! Elimination rate constant

$K_{eu} = CL_{cya} \times BW$

$K_{eu1} = CL_{bdcya} \times BW$

$K_{m1} = Km_{1C} \times BW$

$K_{m2} = Km_{2C} \times BW$

$K_{b} = Kb_{C} \times BW$

$K_{b1} = Kb_{C1} \times BW$

! CYA in blood compartment

$CV = \frac{(QL \times CV_{L} + QK \times CV_{K} + QM \times CV_{M} + QF \times CV_{F} + QOT \times CV_{OT})}{QC}$

$RA = QC \times (CV - CA)$

$AA = \text{Integ}(RA, 0)$

$CA = \frac{AA}{V_{\text{blood}} \times (1 - PB)}$

$AUCCV = \text{Integ}(CV, 0.0)$

! CYA in liver compartment

$RL = QL \times (CA - CV_{L}) + RA_{O} - R_{\text{met}} - R_{\text{bile}}$

$AL = \text{Integ}(RL, 0)$

$CL = AL / VL$

$CV_{L} = AL / (VL \times PL_{cya})$

$AUCCL = \text{Integ}(CL, 0.0)$

$CL_{\text{mass}} = CL \times MW$

! Metabolism of CYA in liver
\[ R_{\text{met}} = K_{m1} \cdot C_{VL} \] rate of metabolism of CYA to all metabolites

\[ A_{\text{met}} = \text{integ}(R_{\text{met}}, 0) \]

\[ R_{\text{CYA-BDCYA}} = F_{L} \cdot K_{m1} \cdot C_{VL} \] rate of metabolism of CYA to BDCYA

\[ A_{\text{CYA-BDCYA}} = \text{integ}(R_{\text{CYA-BDCYA}}, 0) \]

! Bile Excretion of CYA

\[ R_{\text{bile}} = K_{b} \cdot C_{VL} \] rate of bile excretion of CYA

\[ A_{\text{bile}} = \text{integ}(R_{\text{bile}}, 0) \]

! CYA in kidney compartment

\[ R_{K} = Q_{K} \cdot (C_{A} - C_{V_{K}}) - R_{\text{urine}} \]

\[ A_{K} = \text{integ}(R_{K}, 0) \]

\[ C_{K} = \frac{A_{K}}{V_{K}} \]

\[ C_{V_{K}} = \frac{A_{K}}{(V_{K} \cdot P_{\text{cya}})} \]

\[ \text{AUC}_{CK} = \text{integ}(C_{K}, 0.0) \]

\[ C_{K_{\text{mass}}} = C_{K} \cdot M_{W} \]

! Urinary excretion of CYA

\[ R_{\text{urine}} = K_{e_{u}} \cdot C_{V_{K}} \]

\[ A_{\text{urine}} = \text{integ}(R_{\text{urine}}, 0) \]

! CYA in muscle compartment

\[ R_{M} = Q_{M} \cdot (C_{A} - C_{V_{M}}) \]

\[ A_{M} = \text{integ}(R_{M}, 0) \]

\[ C_{M} = \frac{A_{M}}{V_{M}} \]
CVM = AM/(VM*PMcya)
AUCCM = Integ(CM,0,0)
CMmass=CM*MW

! CYA in fat compartment
RF = QF*(CA-CVF)
AF = Integ(RF,0)
CF = AF/(VF)
CVF = AF/(VF*PFcya)
AUCCF = Integ(CF,0.0)
CFmass=CF*MW

! CYA in other tissue compartment
ROT = QOT*(CA-CVOT)
AOT = Integ(ROT,0)
COT = AOT/VOT
CVOT = AOT/(VOT*POTcya)
COTmass=COT*MW

! Mass balance
Qbal = QC-QL-QK-QOT-QM-QF
Tmass = AA+AL+AK+AM+AF+AOT+Aurine+Amet+Abile
BALCYA = AAO-Tmass ! Flow-limited model mass balance
Submodel for BDCYA

BDCYA in blood

BDCYA in blood compartment

\[ CV_1 = \frac{Q_L*CV_L + Q_K*CV_K + Q_M*CV_M + Q_F*CV_F + Q_OT*CV_OT}{QC} \]

\[ RA_1 = QC*(CV_1 - CA_1) \]

\[ AA_1 = \text{Integ}(RA_1, 0) \]

\[ CA_1 = \frac{AA_1}{V_{\text{blood}}}(1 - PB_1) \]

\[ AUCCV_1 = \text{Integ}(CV_1, 0.0) \]

BDCYA in liver compartment

AL_1 = amount of BDCYA in the liver

\[ RL_1 = Q_L*(CA_1 - CV_L) + R_{\text{met}}*FL + RAO_1 - R_{\text{bile}} \]

\[ AL_1 = \text{Integ}(RL_1, 0) \]

\[ CL_1 = \frac{AL_1}{VL} \]

\[ CVL_1 = \frac{AL_1}{VL*P_{\text{bdcya}}} \]

\[ AUCCL_1 = \text{Integ}(CL_1, 0.0) \]

\[ CL_{\text{mass}}_1 = CL_1*MW \]

AAO_1 = Amount of BDCYA absorbed from the intestine

\[ RI_1 = Km_2*FI*AI_1 - Ka_1*AI_1 - kef_1*AI_1 \] Rate of BDCYA in intestine

\[ AI_1 = \text{Integ}(RI_1, 0) \] Amount of BDCYA in intestine

\[ RAO_1 = Ka_1*AI_1 \] Rate of BDCYA absorbed by intestine

\[ AAO_1 = \text{Integ}(RAO_1, 0) \] Amount of BDCYA absorbed by intestine
! Bile Excretion of BDCYA

Rbile1 = Kb1*CVL1 !rate of bile excretion of BDCYA

Able1 = integ(Rbile1,0)

! BDCYA in kidney compartment

RK1 = QK*(CA1-CVK1)-Rurine1

AK1 = Integ(RK1,0)

CK1 = AK1/VK

CVK1 = AK1/(VK*PKbdcya)

AUCCK1 = Integ(CK1,0.0)

CKmass1=CK1*MW

! Urinary excretion of BDCYA

Rurine1 = Keu1*CVK1

Aurine1 = Integ(Rurine1,0)

! CYA in muscle compartment

RM1 = QM*(CA1-CVM1)

AM1 = Integ(RM1,0)

CM1 = AM1/(VM)

CVM1 = AM1/(VM*PMbdcya)

AUCCM1 = Integ(CM1,0.0)

CMmass1=CM1*MW

! CYA in fat compartment
RF1 = QF*(CA1-CVF1)
AF1 = Integ(RF1,0)
CF1 = AF1/(VF)
CVF1 = AF1/(VF*PFbdcya)
AUCCF1 = Integ(CF1,0.0)
CFmass1=CF1*MW

! CYA in other tissue compartment
ROT1 = QOT*(CA1-CVOT1)
AOT1 = Integ(ROT1,0)
COT1 = AOT1/(VOT)
CVOT1 = AOT1/(VOT*POTbdcya)
COTmass1=COT1*MW

! Mass balance of BDCYA
! Tmass1=mass balance of BDCYA

Tmass1 = AA1+AL1+AK1+AM1+AF1+AOT1+Aurine1+Abile1
BALBDCYA = ACYA_BDCYA+AAO1-Tmass1 ! Flow-limited model mass balance

END ! DERIVATIVE

! Add discrete events here as needed
!DISCRETE

!END

! code that is executed once at each communication interval goes here

CONSTANT TSTOP = 300.0
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

END ! PROGRAM