

Model S8: Female model for AME

METHOD RK4

STARTTIME = 0

STOPTIME = 10

DT = 0.00002

{Type Equations Here.}

{Top model}

{Reservoirs}

d/dt (ASTAME) = - transSTtoSI + oraldose

INIT ASTAME = 0

LIMIT ASTAME >= 0

d/dt (ASIAM) = -transSItoSIG - transSItoLI + transSTtoSI

INIT ASIAM = 0

LIMIT ASIAM >= 0

d/dt (ALIAM) = + transSItoLI - fecalex - transLItoL

INIT ALIAM = 0

LIMIT ALIAM >= 0

d/dt (AGSIAM) = + transSItoSIG - venGS

INIT AGSIAM = 0

LIMIT AGSIAM >= 0

d/dt (FECAME) = + fecalex

INIT FECAME = 0

LIMIT FECAME >= 0

d/dt (ALAME) = - venL + artL + venP + venGS + transLItoL - PhaseI metab - AMEglucur

INIT ALAME = 0

LIMIT ALAME >= 0

d/dt (ABAME) = + venL + venS + venR + venF + venK + venM - artL - artP - artS - artR - artF - artK - artM

INIT ABAME = 0

LIMIT ABAME >= 0

d/dt (APAME) = + artP - venP

INIT APAME = 0

LIMIT APAME >= 0

d/dt (ASAME) = + artS - venS

INIT ASAME = 0

LIMIT ASAME >= 0

d/dt (ARAME) = + artR - venR

INIT ARAME = 0

LIMIT ARAME >= 0

d/dt (AFAME) = + artF - venF

INIT AFAME = 0

LIMIT AFAME >= 0

d/dt (AUAME) = + artU - venU

INIT AUAME = 0

LIMIT AUAME >= 0

d/dt (AKAME) = + artK - venK - urineAME

INIT AKAME = 0

LIMIT AKAME >= 0

d/dt (AUCAMEUr) = + urineAME

INIT AUCAMEUr = 0

d/dt (AMAME) = + artM - venM

INIT AMAME = 0

LIMIT AMAME >= 0

d/dt (Start) = - oraldose

INIT Start = AODOSEAME

LIMIT Start >= 0

d/dt (exAMEmetab) = + PhaseI metab

INIT exAMEmetab = 0

LIMIT exAMEmetab >= 0

d/dt (exAMEglucur) = + AMEglucur

INIT exAMEglucur = 0

LIMIT exAMEglucur >= 0

{Flows}

; arterial (art) and venous (ven) blood flows :

venL = QL*CVLAME

artL = (QL-QP)*CBAME

venP = QP*CPAME

artP = QP*CBAME

venS = QS*CVSAME

artS = QS*CBAME

venR = QR*CVRAME

artR = QR*CBAME

venF = QF*CVFAME

artF = QF*CBAME

venM = QM*CVMAME

artM = QM*CBAME

venK = QK*CVKAME

artK = QK*CBAME

venGS = QSI*CVGSIAME

artGS = QSI*CBAME

venU=QU*CVUAME

artU=QU*CBAME

; excretion :

urineAME = GFR*CVKAME*60/1000 ; (L/h)

fecalex = Kli*ALIAME

; gastrointestinal tract :

transSTtoSI = kelST * ASTAME

; from stomach lumen to small intestine lumen

transSItoSIG = KaAME*CSIAME

; from small intestine lumen to gut small intestine tissue

transSItoLI = ASIAME*Ksi

; from small intestine lumen to large intestine lumen

transLItoL = KbAME*CLIAME

; from large intestine lumen to liver tissue

oraldose = PULSE(AODOSEAME, 0, 24)

;Liver metabolism :

PhaseImetab = VmaxLAME * CVLAME/(KmLAME + CVLAME) ; MichaelisMenten

AMEglucur = VmaxLAMEgluc * CVLAME/(KmLAMEgluc + CVLAME) ; MichaelisMenten

{Globals}

;AME female model

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; Physiological parameters

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;bodyweight

BW = 60 ;Kg ; avg. BW in validation study (ICRP)

; relative tissue volumes

; fraction of BW

VLc = 0.0298

; fraction of liver tissue (ICRP)

VPc = 0.0064

; fraction portal vein perfused tissue (stomach, spleen, pancreas) tissue (ICRP)

VRc = 0.0199

; fraction of rapidly perfused tis. (Q/V >>1, heart + lungs) tissue (ICRP)

VSc = 0.1748

; fraction of slowly perfused tissue (bone, skin) tissue (ICRP)

VFc = 0.3055

; fraction of fat tissue (adipose) tissue (ICRP)

VMc = 0.2985

; fraction of muscle tissue tissue (ICRP)

VKc = 0.0059

; fraction of kidneys tissue (ICRP)

VSIc = 0.0125

; fraction of small intestine tissue (ICRP)

VLIc = 0.0074

; fraction of large intestine tissue (ICRP)

VBc = 0.065

; fraction of blood (ICRP)

VUc = 0.0016

;fraction of uterus tissue (ICRP)

; calculated tissue volumes

VL = VLc*BW	;L or Kg	; volume of liver tissue (calculated)
VP = VPc*BW	;L or kg	; volume of portal vein perfused tissue
VR = VRc*BW	;L or Kg	; volume of rapidly perfused tissue (calculated)
VS = VSc*BW	;L or Kg	; volume of slowly perfused tissue (calculated)
VF = VFc*BW	;L or Kg	; volume of fat tissue (calculated)
VM = VMc*BW	;L or Kg	; volume of muscle tissue (calculated)
VK = VKc*BW	;L or Kg	; volume of kidney (calculated)
VB = VBc*BW	;L or Kg	; volume of blood (Brown et al, calculated)
VSI = VSIC*BW	;L or Kg	; volume of small intestine tissue (calculated)
VLI = VLIC*BW	;L or Kg	; volume of large intestine tissue (calculated)
VU = VUC*BW	;L or Kg	; volume of uterus tissue (calculated)
VSIL = 4.13	;L or Kg	; volume of small intestine lumen (ICPR, calculated)
VLIL = 2.16	;L or Kg	; volume of large intestine lumen (ICPR, calculated)

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;surface areas
areaSI = 2709.066      ;dm2      ;surface area of SI lumen (Helander et al.)
areaLI = 98.018       ;dm2      ;surface area of LI lumen (Helander et al.)

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;Blood flow rates,
QCc = 5.9              ; (L/min), cardiac output (ICRP)
QPc = 0.05             ; fraction of blood flow to P (spleen, stom., pancreas) (ICRP)
QLc = 0.065           ; fraction of blood flow to liver in total (ICRP)
QRc = 1.05            ; fraction of blood flow to rapidly perfused tissue (heart+lungs) (ICRP)
QSc = 0.1              ; fraction of blood flow to slowly perfused tissue (skin+Bones) (ICRP)
QFc = 0.085           ; fraction of blood flow to fat (ICRP)
QMc = 0.12            ; fraction of blood flow to muscle (ICRP)
QKc = 0.17            ; fraction of blood flow to kidneys (ICRP)
QSIc = 0.11           ; fraction of blood flow to small intestine (ICRP)
QLIc = 0.05           ; fraction of blood flow to large intestine (ICRP)
QUc = 0.004           ; fraction of blood to uterus (ICRP)

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QC = QCc*60	; (L/h)	; cardiac output (calculated)
QP = QPc*QC	;L or Kg	; blood flow to portal vein perfused tissue (calculated)
QL = QLc*QC	;L or Kg	; blood flow to liver total (calculated)
QR = QRc*QC	;L or Kg	; blood flow to rapidly perfused tissue (calculated)
QS = QSc*QC	;L or Kg	; blood flow to slowly perfused tissue (calculated)
QF = QFc*QC	;L or Kg	; blood flow to fat tissue (calculated)
QM = QMc*QC	;L or Kg	; blood flow to muscle tissue (calculated)
QK = QKc*QC	;L or Kg	; blood flow to kidney (calculated)
QSI = QSIc*QC	;L or Kg	; blood flow to small intestine tissue (calculated)
QLI = QLIc*QC	;L or Kg	; blood flow to large intestine tissue (calculated)
QU = QUc*QC	;L or Kg	; blood flow to uterus tissue (calculated)

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; glomerular filtration rate
GFR = 125      ;mL/min      ; GFR scaled to body weight (Levey et al.)

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; Physicochemical parameters

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; molecular weights (g/mol)
MWAME = 272.25      ; parent compound
; pKa1
pKa1AME = 7.71 ; parent compound Chemaxon playground (v1.6.2)
; logP
logPAME = 3.32 ; parent compound Chemaxon playground (v1.6.2)
; logD (parent compound)
logDapical = 3.32 Chemaxon playground (v1.6.2)
logDbasal = 3.1 Chemaxon playground (v1.6.2)

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; partition coefficients      ;calculated by qivivertools.wu.nl (Berezhkovskiy algorithm)
; AME in main model
PLAME = 3.8      ; liver/blood partition coefficient
PRAME = 0.982    ; rapidly perfused tissue/blood partition coefficient
PSAME = 5.551    ; slowly perfused tissue/blood partition coefficient
PFAME = 7.1      ; fat/blood partition coefficient

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PMAME = 2.44          ; muscle/blood partition coefficient
PKAME = 2.41          ; kidney/blood partition coefficient
FUAME = 0.058         ; faction unbound plasma according to Lobell&Sivarajah
PSIAME =4.72          ; gut/blood partition coefficient
;-----
; absorption/transfer rates
logPappAME = -5.11          ;log(cm/s)          ;log permeability estimated
PeffAME = (3600/10)*(10^(0.6836*LogPappAME- 0.5579)) ;dm/h ;scaled according to Sun et al.

KaAME = PeffAME*areaSI      ;L/h ;transfer rate of AME from SI lumen to gut
KbAME = PeffAME*areaLI      ;L/h ;transfer rate of AAME from LI lumen to gut

; gastric emptying (kelst)
GEstc = 11.8              ; (min) half time of meal in mice stomach
GEst = GEstc /60          ; (h)
LNhalf= -0.69314718        ; LN(1/2)
kelST = -LNhalf/ GEst      ; (h-1) constant of gastric excretion          ; from Ct=C0*e^(-kel*t)

tpassSI = 4              ;h          ;passing time through small intestine (ICRP)
Ksi = 1/tpassSI          ;/h          ;SI to LI transfer constant
tpassLI = 48              ;h          ;passing time through large intestine (ICRP)
Kli = 1/tpassLI          ;/h          ;LI to excretion transfer constant
;=====
; Kinetic parameters
;=====
;metabolism of rat liver
; scaling factors
VLS9 = 107.3            ;mg S9 protein/gram liver          ; liver S9 protein yield (Wang et al. 2019)
VLMP = 32                ;mg protein/gram liver          ; liver microsomal protein yield (Barter et al. 2007)

;Phase 1 metabolism
KmLAME = 29.4            ;µmol/L          ;Michaelis constant of hepatic phase I metabolism (Borsos et al)
VmaxLAMEc = 0.000772      ;µmol/mg/min  microsomal protein (Borsos et al)
VmaxLAME = VmaxLAMEc*VLMP*VL*60*10^3      ;µmol/h

;Phase 2 glucuronidation

KmLAMEgluc = 0.97          ;µmol/L          ;Michaelis constant of hepatic glucuronidation (in vitro)
VmaxLAMEglucc =0.0105      ;µmol/(mg*min) (in vitro)
VmaxLAMEgluc = VmaxLAMEglucc*VLS9*VL*60*10^3      ;µmol/h
;=====
; Run settings
;=====
;-----
; oral dose
ODOSEAME = 0.0014*BW ;µg          ;oral dose alternariol, variable
AODOSEAME = ODOSEAME/MWAME      ;umol          ;oral dose AME in umol
;=====
; Main model calculations/dynamics:
;=====
;-----
;ASIAME: amount of AME in small intestinal lumen compartment      ;µmol
CSIAME=ASIAME/VSIL          ;umol/L
;-----
;large intestine compartment
;ALIAME: amount of AME in large intestine lumen          ;µmol
CLIAME = ALIAME/VLIL          ;umol/L
;-----
;gut small intestine tissue compartment
;AGSIAME: amount of AME in small intestine tissue          ;µmol
CGSIAME = AGSIAME/PSIAME      ;umol/L
CVGSIAME = CGSIAME/PSIAME
;-----

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; liver compartment
; ALAME: amount of AME in liver ;μmol
CLAME = ALAME/VL ;umol/L
CVLAME = CLAME/PLAME ;partition with liver tissue
;-----
; portal vein perfused tissue compartment
; APAME = amount of AME in spleen tissue ;μmol
CPAME = APAME/VP ;umol/L
;-----
; fat (adipose tissue) compartment
CFAME = AFAME/VF ;umol/L
CVFAME = CFAME/PFAME ;partition with adipose tissue
;-----
; muscle compartment
; AMAME = amount of AME in muscle tissue ;μmol
CMAME = AMAME/VM ;umol/L
CVMAME = CMAME/PMAME ;partition with muscle tissue
;-----
; rapidly perfused tissue
CRAME = ARAME/VR ;umol/L
CVRAME = CRAME/PRAME ;partition with muscle tissue
;-----
; slowly perfused tissue
CSAME = ASAME/VS ;umol/L
CVSAME = CSAME/PSAME ;partition with slowly perfused tissue
;-----
; kidney
CKAME = AKAME/VK ;umol/L
CVKAME = CKAME/PKAME ;partition with kidney tissue
;-----
; blood compartment
CBAME=ABAME/VB ;umol/LCVBAME = CBAME*FUAME ;free concentration in
plasma
CBAMEug = CBAME*MWAME ;μg/L = ng/mL ;concentration in blood in ng/ml
;-----
; uterus compartment
CUAME=AUAME/VU ;umol/L
CVUAME = CUAME*PMAME ;free concentration in plasma
;-----
;=====
; Main model: mass balance calculation
;=====
Total = AODOSEAME
Calculated = ASTAME + ASIAME + ALIAME + AGSIAME + ALAME+ ABAME+ AKAME + ARAME + ASAME +
AFAME + APAME + AMAME + AUCAMEUr +FECAME+exAMEmetab + exAMEglucur + AUAME

ERROR=((Total-Calculated)/(Total+1E-30))*100
MASSBAL=Total-Calculated + 1

{End Globals}

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