

Model S5: Male child model for AOH

METHOD RK4

STARTTIME = 0

STOPTIME = 10

DT = 0.00002

{Type Equations Here.}

{Top model}

{Reservoirs}

$d/dt (ASTAOH) = - \text{transSTtoSI} + \text{oraldose}$

INIT ASTAOH = 0

LIMIT ASTAOH ≥ 0

$d/dt (ASIAOH) = -\text{transSItoSIG} - \text{transSItoLI} + \text{transSTtoSI}$

INIT ASIAOH = 0

LIMIT ASIAOH ≥ 0

$d/dt (ALIAOH) = + \text{transSItoLI} - \text{fecalex} - \text{transLItoL}$

INIT ALIAOH = 0

LIMIT ALIAOH ≥ 0

$d/dt (AGSIAOH) = + \text{transSItoSIG} - \text{venGS}$

INIT AGSIAOH = 0

LIMIT AGSIAOH ≥ 0

$d/dt (FECAOH) = + \text{fecalex}$

INIT FECAOH = 0

LIMIT FECAOH ≥ 0

$d/dt (ALAOH) = - \text{venL} + \text{artL} + \text{venP} + \text{venGS} + \text{transLItoL} - \text{Phase1metab} - \text{AOHglucur}$

INIT ALAOH = 0

LIMIT ALAOH ≥ 0

$d/dt (ABAOH) = + \text{venL} + \text{venS} + \text{venR} + \text{venF} + \text{venK} + \text{venM} - \text{artL} - \text{artP} - \text{artS} - \text{artR} - \text{artF} - \text{artK} - \text{artM}$

INIT ABAOH = 0

LIMIT ABAOH ≥ 0

$d/dt (APAOH) = + \text{artP} - \text{venP}$

INIT APAOH = 0

LIMIT APAOH ≥ 0

$d/dt (ASAOH) = + \text{artS} - \text{venS}$

INIT ASAOH = 0

LIMIT ASAOH ≥ 0

$d/dt (ARAOH) = + \text{artR} - \text{venR}$

INIT ARAOH = 0

LIMIT ARAOH ≥ 0

$d/dt (AFAOH) = + \text{artF} - \text{venF}$

INIT AFAOH = 0

LIMIT AFAOH ≥ 0

$d/dt (AKAOH) = + \text{artK} - \text{venK} - \text{urineAOH}$

INIT AKAOH = 0

LIMIT AKAOH ≥ 0

$d/dt (AUCAOHUr) = + \text{urineAOH}$

INIT AUCAOHUr = 0

$d/dt (AMAOH) = + \text{artM} - \text{venM}$

INIT AMAOH = 0

LIMIT AMAOH ≥ 0

$d/dt (\text{Start}) = - \text{oraldose}$

INIT Start = AODOSEAOH

LIMIT Start ≥ 0

$d/dt (\text{exAOHmetab}) = + \text{Phase1metab}$

INIT exAOHmetab = 0

LIMIT exAOHmetab ≥ 0

$d/dt (\text{exAOHglucur}) = + \text{AOHglucur}$

INIT exAOHglucur = 0

LIMIT exAOHglucur ≥ 0

{Flows}

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

venL = QL*CVLAOH
artL = (QL-QP)*CBAOH
venP = QP*CPAOH
artP = QP*CBAOH
venS = QS*CVSAOH
artS = QS*CBAOH
venR = QR*CVRAOH
artR = QR*CBAOH
venF = QF*CVFAOH
artF = QF*CBAOH
venM = QM*CVMAOH
artM = QM*CBAOH
venK = QK*CVKAOH
artK = QK*CBAOH
venGS = QSI*CVGSIAOH
artGS = QSI*CBAOH

; excretion :

urineAOH = GFR*CVKAOH*60/1000 ; (L/h)
fecalex = Kli*ALIAOH

; gastrointestinal tract :

transSTtoSI = kelST * ASTAOH ; from stomach lumen to small intestine lumen
transSItoSIG = KaAOH*CSIAOH ; from small intestine lumen to gut small intestine tissue
transSItoLI = ASIAOH*Ksi ; from small intestine lumen to large intestine lumen
transLItoL = KbAOH*CLIAOH ; from large intestine lumen to liver tissue

oraldose = PULSE(AODOSEAOH, 0, 24)

;Liver metabolism :

PhaseImetab = VmaxLAOH * CVLAOH/(KmLAOH + CVLAOH) ; MichaelisMenten
AOHglucur = VmaxLAOHgluc * CVLAOH/(KmLAOHgluc + CVLAOH) ; MichaelisMenten

{Globals}

; AOH male child model

;

; Physiological parameters ;=====

;bodyweight

BW = 19 ;Kg ; avg. BW in validation study (ICRP)

;

; relative tissue volumes

; fraction of BW

VLc = 0.0374 ; fraction of liver tissue (ICRP)
VPc = 0.0068 ; fraction portal vein perfused tissue (stomach, spleen, pancreas) tissue (ICRP)
VRc = 0.0210 ; fraction of rapidly perfused tis. (Q/V >>1, heart + lungs) tissue (ICRP)
VSc = 0.1653 ; fraction of slowly perfused tissue (bone, skin) tissue (ICRP)
VFc = 0.1932 ; fraction of fat tissue (adipose) tissue (ICRP)
VMc = 0.3051 ; fraction of muscle tissue tissue (ICRP)
VKc = 0.0073 ; fraction of kidneys tissue (ICRP)
VSIc = 0.0144 ; fraction of small intestine tissue (ICRP)
VLIc = 0.0079 ; fraction of large intestine tissue (ICRP)
VBc = 0.0737 ; fraction of blood (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)

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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)
VSIL = 0.48      ;L or Kg      ; volume of small intestine lumen (ICPR, calculated)
VLIL = 1.19      ;L or Kg      ; volume of large intestine lumen (ICRP, calculated)
;-----
;surface areas

areaSI = 1771.312;dm2      ;surface area of SI lumen (Helander et al)
areaLI = 73.51;dm2        ;surface area of LI lumen (Helander et al)
;-----
;Blood flow rates,
QCc = 3.4           ; (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 = 1.04          ; 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 = 0.05          ; fraction of blood flow to fat (ICRP)
QMc = 0.17          ; fraction of blood flow to muscle (ICRP)
QKc = 0.19          ; fraction of blood flow to kidneys (ICRP)
QSIc = 0.1          ; fraction of blood flow to small intestine (ICRP)
QLIc = 0.04         ; fraction of blood flow to large intestine (ICRP)

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)
;-----
; glomerular filtration rate
GFR = 125           ;mL/min      ; GFR scaled to body weight (Levey et al.)
;=====
; Physicochemical parameters
;=====
; molecular weights (g/mol)
MWAOH = 258.23 ; parent compound
; pKa1
pKa1AOH = 7.63 ; parent compound Chemaxon playground (v1.6.2)
; pKa2
pKa2AOH = 8.44 ; parent compound Chemaxon playground (v1.6.2)
; logP
logPAOH = 3.18 ; parent compound Chemaxon playground (v1.6.2)
; logD (parent compound)
logDapical = 3.17 ;Chemaxon playground (v1.6.2)
logDbasal = 2.96 ; Chemaxon playground (v1.6.2)

; partition coefficients      ;calculated by qivivetools.wu.nl (Berezhkovskiy algorithm)
; Alternariol in main model
PLAOH = 3.21      ; liver/blood partition coefficient
PRAOH = 0.898     ; rapidly perfused tissue/blood partition coefficient
PSAOH = 4.733     ; slowly perfused tissue/blood partition coefficient
PFAOH = 7.3       ; fat/blood partition coefficient
PMAOH = 2.09      ; muscle/blood partition coefficient
PKAOH = 2.07      ; kidney/blood partition coefficient
FUAOH = 0.06      ; faction unbound plasma according to Lobell&Sivarajah
PSIAOH = 3.97     ; gut/blood partition coefficient
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; absorption/transfer rates
logPappAOH = -5.09 ;log(cm/s) ;log permeability calculated from Caco2 data (Burkhardt et al)
PeffAOH = (3600/10)*(10^(0.6836*LogPappAOH- 0.5579)) ;dm/h ;scaled according toSun et al.

KaAOH = PeffAOH*areaSI ;L/h ;transfer rate of AOH from SI lumen to gut
KbAOH = PeffAOH*areaLI ;L/h ;transfer rate of AOH from LI lumen to gut

; gastric emptying (kelst)
GEstc = 11.8 ; (min) half time of meal in 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 = 34 ;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
KmLAOH = 131 ;μmol/L ;Michaelis constant of hepatic phase I metabolism (Borsos et al)
VmaxLAOHc = 0.00337 ;μmol/mg/min microsomal protein (Borsos et al)
VmaxLAOH = VmaxLAOHc*VLMP*VL*60*10^3 ;μmol/h

;Phase 2 glucuronidation
KmLAOHgluc = 2.7 ;μmol/L ;Michaelis constant of hepatic glucuronidation (in vitro)
VmaxLAOHglucc =0.0069 ;μmol/(mg*min) (in vitro)
VmaxLAOHgluc = VmaxLAOHglucc*VLS9*VL*60*10^3 ;μmol/h
=====
; Run settings
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; oral dose
ODOSEAOH = 0.0031*BW ;μg ;oral dose alternariol, variable
AODOSEAOH = ODOSEAOH/MWAOH ;umol ;oral dose AOH in umol
=====
; Main model calculations/dynamics:
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;ASIAOH: amount of AOH in small intestinal lumen compartment ;μmol
CSIAOH=ASIAOH/VSIL ;umol/L
=====
;large intestine compartment
;ALIAOH: amount of AOH in large intestine lumen ;μmol
CLIAOH = ALIAOH/VLIL ;umol/L
=====
;-----;gut small intestine tissue
compartment

;AGSIAOH: amount of AOH in small intestine tissue ;μmol
CGSIAOH = AGSIAOH/PSIAOH ;μmol/L
CVGSIAOH = CGSIAOH/PSIAOH
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; liver compartment
; ALAOH: amount of AOH in liver ;μmol

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CLAOH = ALAOH/VL          ;umol/L
CVLAOH = CLAOH/PLAOH      ;partition with liver tissue
;-----
; portal vein perfused tissue compartment
; APAOH = amount of AOH in spleen tissue ;umol
CPAOH = APAOH/VP          ;umol/L
;-----
; fat (adipose tissue) compartment
CFAOH = AFAOH/VF          ;umol/L
CVFAOH = CFAOH/PFAOH      ;partition with adipose tissue
;-----
; muscle compartment
; AMAOH = amount of AOH in muscle tissue ;umol
CMAOH = AMAOH/VM          ;umol/L
CVMAOH = CMAOH/PMAOH      ;partition with muscle tissue
;-----
; rapidly perfused tissue
CRAOH = ARAOH/VR          ;umol/L
CVRAOH = CRAOH/PRAOH      ;partition with muscle tissue
;-----
; slowly perfused tissue
CSAOH = ASAOH/VS          ;umol/L
CVSAOH = CSAOH/PSAOH      ;partition with slowly perfused tissue
;-----
; kidney
CKAOH = AKAOH/VK          ;umol/L
CVKAOH = CKAOH/PKAOH      ;partition with kidney tissue
;-----
; blood compartment
CBAOH=ABAOH/VB            ;umol/L
CVBAOH = CBAOH*FUAOH      ;free concentration in plasma
CBAOHug = CBAOH*MWAOH     ;μg/L = ng/mL      ;concentration in blood in ng/ml
;-----
;=====
; Main model: mass balance calculation
;=====
Total = AODOSEAOH
Calculated = ASTAOH + ASIAOH + ALIAOH + AGSIAOH + ALAOH + ABAOH + AKAOH + ARAOH + ASAOH +
AFAOH + APAOH + AMAOH + AUCAOHUr + FECAOH +exAOHmetab +exAOHglucur

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

{End Globals}

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