

Model S2: Murine 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

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

INIT exAOHgluc = 0

LIMIT exAOHgluc ≥ 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 mouse model

=====

; Physiological parameters

=====

;bodyweight

BW = 0.037 ;Kg ; avg. BW in validation study ;EFSA in vivo study

; relative tissue volumes

; fraction of BW

VLc = 0.0549 ; fraction of liver tissue (Brown et al)
VPc = 0.0155 ; fraction portal vein perfused tissue (stomach, spleen, pancreas) (Brown et al, Crispin et al)
VRc = 0.0123 ; fraction of rapidly perfused tis. (Q/V >>1, heart + lungs) (Brown et al)
VSc = 0.2726 ; fraction of slowly perfused tissue (bone, skin) (Brown et al)
VFc = 0.0048 ; fraction of fat tissue (adipose) (Brown et al)
VMc = 0.3840 ; fraction of muscle tissue (Brown et al)
VKc = 0.0167 ; fraction of kidneys (Brown et al)
VSIc = 0.0253 ;fraction of small intestine tissue (Brown et al)
VLIc = 0.0109 ;fraction of large intestine tissue (Brown et al)

; 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 = 0.08*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 = 0.002851	;L or Kg	; volume of small intestine lumen (Casteleyn et al, calculated)
VLIL = 0.001270	;L or Kg	; volume of large intestine lumen (Casteleyn et al, calculated)

;surface areas

areaSI = 0.3615	;dm2	;surface area of SI lumen	; (Casteleyn et al, calculated)
areaLI = 0.1234	;dm2	;surface area of LI lumen	; (Casteleyn et al, calculated)

;Blood flow rates,

QCc = 0.275*BW^0.75	; (L/min), cardiac output (Brown et al)
QPc = 0.141	; fraction of blood flow to portal vein (Brown et al)
QLc = 0.162	; fraction of blood flow to liver in total (Brown et al)
QRc = 0.071	; fraction of blood flow to rapidly perfused tissue (heart+lungs) (Brown et al)
QSc = 0.18	; fraction of blood flow to slowly perfused tissue (skin+bones) (Brown et al)
QFc = 0.07	; fraction of blood flow to fat (Brown et al)
QMc = 0.159	; fraction of blood flow to muscle (Brown et al)
QKc = 0.091	; fraction of blood flow to kidneys (Brown et al)
QSIc = 0.135	; fraction of blood flow to small intestine (Stott et al)

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 = 0.28	;mL/min	; GFR (Bivona et al)
------------	---------	----------------------

; Physicochemical parameters

; molecular weights (g/mol)

MWAOH = 258.23 ; parent compound

; pKa1

pKa1AOH = 7.63	;Chemaxon playground (v1.6.2)
----------------	-------------------------------

; pKa2

pKaAOH = 8.44	;Chemaxon playground (v1.6.2)
---------------	-------------------------------

; logP

logPAOH = 3.18	;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 = 2.2	; liver/blood partition coefficient
PRAOH = 2.215	; rapidly perfused tissue/blood partition coefficient
PSAOH = 2.621	; slowly perfused tissue/blood partition coefficient
PFAOH = 7.9	; fat/blood partition coefficient
PMAOH = 1.39	; muscle/blood partition coefficient

```

PKAOH = 2.06          ; kidney/blood partition coefficient
FUAOH = 0.06         ; faction unbound plasma according to Lobell&Sivarajah
PSIAOH = 3.07        ; gut/blood partition coefficient
;-----
; absorption/transfer rates
Papp = 5.50E-06
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 to Sun 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 = 74                ; (min) half time of meal in mice stomach (Schwarz et al)

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 = 1.5             ;h          ;passing time through small intestine (Woting et al)
Ksi = 1/tpassSI           ;/h          ;SI to LI transfer constant
tpassLI = 8               ;h          ;passing time through large intestine (Woting et al)
Kli = 1/tpassLI           ;/h          ;LI to excretion transfer constant
;=====
; Kinetic parameters
;=====
;metabolism of rat liver
; scaling factors
VLS9 = 143                ;mg S9 protein/gram liver          ; liver S9 protein yield (Punt et al)
VLMP = 62                 ;mg protein/gram liver          ; liver microsomal protein yield (Smith et al)

;Phase 1 metabolism
KmLAOH = 78.7             ;µmol/L          ;Michaelis constant of hepatic phase I metabolism (Borsos et al)
VmaxLAOHc = 0.00283       ;µmol/mg/min    microsomal protein (Borsos et al)
VmaxLAOH = VmaxLAOHc*VLMP*VL*60*10^3    ;µmol/h

;Phase 2 glucuronidation
KmLAOHgluc = 8.5090       ;µmol/L          ;Michaelis constant of hepatic glucuronidation (in vitro)
VmaxLAOHglucc = 0.021437  ;µmol/(mg*min) (in vitro)
VmaxLAOHgluc = VmaxLAOHglucc*VLS9*VL*60*10^3    ;µmol/h
;=====
; Run settings
;=====
;-----; oral dose
ODOSEAOH = 200000*BW*µg    ;oral dose alternariol, variable (EFSA 2014)
AODOSEAOH = ODOSEAOH/MWAOH    ;umol          ;oral dose AOH in umol
;=====
; Main model calculations/dynamics:
;=====
;-----
;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
;-----
; liver compartment

```

```

; ALAOH: amount of AOH in liver ;umol
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     ;ug/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 + exAOHgluc

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

{End Globals}

```