

### Model S3: Male 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  $\geq 0$

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

INIT ASIAOH = 0

LIMIT ASIAOH  $\geq 0$

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

INIT ALIAOH = 0

LIMIT ALIAOH  $\geq 0$

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

INIT AGSIAOH = 0

LIMIT AGSIAOH  $\geq 0$

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

INIT FECAOH = 0

LIMIT FECAOH  $\geq 0$

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

INIT ALAOH = 0

LIMIT ALAOH  $\geq 0$

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

INIT ABAOH = 0

LIMIT ABAOH  $\geq 0$

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

INIT APAOH = 0

LIMIT APAOH  $\geq 0$

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

INIT ASAOH = 0

LIMIT ASAOH  $\geq 0$

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

INIT ARAOH = 0

LIMIT ARAOH  $\geq 0$

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

INIT AFAOH = 0

LIMIT AFAOH  $\geq 0$

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

INIT AKAOH = 0

LIMIT AKAOH  $\geq 0$

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

INIT AUCAOHUr = 0

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

INIT AMAOH = 0

LIMIT AMAOH  $\geq 0$

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

INIT Start = AODOSEAOH

LIMIT Start  $\geq 0$

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

INIT exAOHmetab = 0

LIMIT exAOHmetab  $\geq 0$

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

INIT exAOHglucur = 0

LIMIT exAOHglucur  $\geq 0$

{Flows}

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

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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
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; excretion :

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

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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
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oraldose = PULSE(AODOSEAOH, 0, 24)
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;Liver metabolism :

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

; AOH male model

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; Physiological parameters ;=====

;bodyweight

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BW = 73 ;Kg ; avg. BW in validation study (ICRP)
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; relative tissue volumes

; fraction of BW

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VLc = 0.0319 ; fraction of liver tissue (ICRP)
VPc = 0.0063 ; fraction portal vein perfused tissue (stomach, spleen, pancreas) tissue (ICRP)
VRc = 0.0212 ; fraction of rapidly perfused tis. (Q/V >>1, heart + lungs) tissue (ICRP)
VSc = 0.1963 ; fraction of slowly perfused tissue (bone, skin) tissue (ICRP)
VFc = 0.2036 ; fraction of fat tissue (adipose) tissue (ICRP)
VMc = 0.4074 ; fraction of muscle tissue tissue (ICRP)
VKc = 0.0057 ; fraction of kidneys tissue (ICRP)
VSIc = 0.0117 ; fraction of small intestine tissue (ICRP)
VLIc = 0.0067 ; fraction of large intestine tissue (ICRP)
VBc = 0.0726 ; fraction of blood (ICRP)
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; 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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$VF = VFc \cdot BW$  ;L or Kg ; volume of fat tissue (calculated)  
 $VM = VMc \cdot BW$  ;L or Kg ; volume of muscle tissue (calculated)  
 $VK = VKc \cdot BW$  ;L or Kg ; volume of kidney (calculated)  
 $VB = VBc \cdot BW$  ;L or Kg ; volume of blood (Brown et al, calculated)  
 $VSI = VSIc \cdot BW$  ;L or Kg ; volume of small intestine tissue (calculated)  
 $VLI = VLIc \cdot BW$  ;L or Kg ; volume of large intestine tissue (calculated)  
 $VSIL = 4.45$  ;L or Kg ; volume of small intestine lumen (ICRP, calculated)  
 $VLIL = 2.38$  ;L or Kg ; volume of large intestine lumen (ICRP, calculated)

;-----  
 ;surface areas

$areaSI = 2917.5 \text{ ;dm}^2$  ;surface area of SI lumen (Helander et al)  
 $areaLI = 107.8 \text{ ;dm}^2$  ;surface area of LI lumen (Helander et al)

;-----

;Blood flow rates,

$QCc = 6.5$  ; (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)

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

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; 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

$pKaAOH = 8.44$  ; parent compound Chemaxon playground (v1.6.2)

; logP

$\log PAOH = 3.18$  ; parent compound Chemaxon playground (v1.6.2)

; logD (parent compound)

$\log Dapical = 3.17$  ;Chemaxon playground (v1.6.2)

$\log Dbasal = 2.96$  ; Chemaxon playground (v1.6.2)

; partition coefficients ;calculated by qivivertools.wu.nl (Berezhkovskiy algorithm)

; Alternariol in main model

$PLAOH = 3.21$  ; liver/blood partition coefficient

$PRAOH = 0.893$  ; rapidly perfused tissue/blood partition coefficient

$PSAOH = 4.601$  ; 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

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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 = 36 ;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
;=====
; oral dose
ODOSEAOH = 0.0022*BW ;μg ;oral dose alternariol, variable
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 ;μmol
CLAOH = ALAOH/VL ;umol/L

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CVLAOH = CLAOH/PLAOH          ;partition with liver tissue
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; portal vein perfused tissue compartment
; APAOH = amount of AOH in spleen tissue ;μmol
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  ;μmol
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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