

# **Model S6: Male toddler model for AOH**

METHOD RK4

STARTTIME = 0

STOPTIME = 10

DT = 0.00002

{Type Equations Here.}

{Top model}

{Reservoirs}

d/dt (ASTAOH) = - transSTtoSI + oraldose

INIT ASTAOH = 0

LIMIT ASTAOH >= 0

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

INIT ASIAOH = 0

LIMIT ASIAOH >= 0

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

INIT ALIAOH = 0

LIMIT ALIAOH >= 0

d/dt (AGSIAOH) = + transSItoSIG - venGS

INIT AGSIAOH = 0

LIMIT AGSIAOH >= 0

d/dt (FECAOH) = + fecalex

INIT FECAOH = 0

LIMIT FECAOH >= 0

d/dt (ALAOH) = - venL + artL + venP + venGS + transLItoL - Phase1metab - AOHglucur

INIT ALAOH = 0

LIMIT ALAOH >= 0

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

INIT ABAOH = 0

LIMIT ABAOH >= 0

d/dt (APAOH) = + artP - venP

INIT APAOH = 0

LIMIT APAOH >= 0

d/dt (ASAOH) = + artS - venS

INIT ASAOH = 0

LIMIT ASAOH >= 0

d/dt (ARAOH) = + artR - venR

INIT ARAOH = 0

LIMIT ARAOH >= 0

d/dt (AFAOH) = + artF - venF

INIT AFAOH = 0

LIMIT AFAOH >= 0

d/dt (AKAOH) = + artK - venK - urineAOH

INIT AKAOH = 0

LIMIT AKAOH >= 0

d/dt (AUCAOHUr) = + urineAOH

INIT AUCAOHUr = 0

d/dt (AMAOH) = + artM - venM

INIT AMAOH = 0

LIMIT AMAOH >= 0

d/dt (Start) = - oraldose

INIT Start = AODOSEAOH

LIMIT Start >= 0

d/dt (exAOHmetab) = + Phase1metab

INIT exAOHmetab = 0

LIMIT exAOHmetab >= 0

d/dt (exAOHglucur) = + 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 :

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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 :

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

; AOH male toddler model

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; Physiological parameters ;=====

;bodyweight

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BW = 10 ;Kg ; avg. BW in validation study (ICRP)
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; relative tissue volumes

; fraction of BW

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VLc = 0.0380 ; fraction of liver tissue (ICRP)
VPc = 0.0056 ; fraction portal vein perfused tissue (stomach, spleen, pancreas) tissue (ICRP)
VRc = 0.0198 ; fraction of rapidly perfused tis. (Q/V >>1, heart + lungs) tissue (ICRP)
VSc = 0.1570 ; fraction of slowly perfused tissue (bone, skin) tissue (ICRP)
VFc = 0.2343 ; fraction of fat tissue (adipose) tissue (ICRP)
VMc = 0.1953 ; fraction of muscle tissue tissue (ICRP)
VKc = 0.0080 ; fraction of kidneys tissue (ICRP)
VSIc = 0.0104 ; fraction of small intestine tissue (ICRP)
VLIc = 0.0061 ; fraction of large intestine tissue (ICRP)
VBc = 0.05 ; 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)
VF = VFc*BW ;L or Kg ; volume of fat tissue (calculated)
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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 = 0.34 ;L or Kg ; volume of small intestine lumen (ICPR, calculated)  
 VLIL = 0.228 ;L or Kg ; volume of large intestine lumen (ICRP, calculated)

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 ;surface areas

areaSI = 1250.338;dm2 ;surface area of SI lumen (Helander et al)  
 areaLI = 58.81;dm2 ;surface area of LI lumen (Helander et al)

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 ;Blood flow rates,

QCc = 1.2 ; (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)  
 QLILc = 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)

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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)

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

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)

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

; Alternariol in main model

PLAOH = 3.21 ; liver/blood partition coefficient

PRAOH = 0.920 ; rapidly perfused tissue/blood partition coefficient

PSAOH = 4.627 ; 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 = 32 ;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 = 0.0049*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
;-----
; 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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