Supplementary materials 2

Model code for Caucasian population without Monte Carlo simulation. The enantiomeric interaction equations are shown in *italic*.

```
;Model code
;=============================================================================================
; Physiological parameters
;=============================================================================================

;Tissue volumes (L or Kg)

BW = 70                              ; body weight human in kg (Brown et al., 1997)

; all fractions taken from Brown et al. (1997)
 VLc = 0.0257                        ; fraction of liver tissue
 VFc = 0.2142                        ; fraction of fat tissue
 VLuc =   0.0076                     ; fraction of lung tissue
 VAc =  0.0198                       ; fraction of arterial blood: 0.074*1/4
 VVc = 0.0593                        ; fraction of venous blood: 0.074*3/4
 VKc = 0.004                         ; fraction of kidney tissue
 VHc = 0.0047                        ; fraction of heart tissue
 VRc = 0.09-VLc - VLuc - VKc - VHc   ; fraction of richly perfused tissue
 VSc = 0.746-VFc                     ; Fraction of blood flow to slowly perfused tissue
                                     ; total of fractions = 0.9151

VL = VLc * BW                        ; volume of liver
VF = VFc * BW                        ; volume of fat
VLu = VLuc * BW                      ; volume of lungs
VK = VKc * BW                        ; volume of kidneys
VH = VHc * BW                        ; volume of heart
VR = VRc * BW                        ; volume of richly perfused tissue
VS = VSc * BW                        ; volume of slowly perfused tissue
VA = VAc * BW                        ; volume of arterial blood
VV = VVc * BW                        ; volume of venous blood
;-------------------------------------------------------------------------------------------------------------------------------------
----------------------------------
;Blood flow rates (L/h)
  QC = 15 * BW^0.74                  ; Info: QC = 15 * BW^0.74  (Brown, 1997)
  QLc = 0.227                        ; Fraction of blood flow to liver
  QFc = 0.052                        ; Fraction of blood flow to fat
  QKc = 0.175                        ; fraction of blood flow to kidneys
  QHc = 0.04                         ; fraction of blood flow to heart
  QSc = 0.24-QFc                     ; Fraction of blood flow to slowly perfused tissue
  QRc = 0.76-QLc-QKc-QHc             ; fraction of blood flow to rapidly perfused tissue
                                     ; total of fractions = 1

; all fractions taken from Brown 1997
QL = QLc*QC                          ; blood flow rate to liver in L/hr
QF = QFc*QC                          ; blood flow rate to fat
```

```
QK = QKc * QC                    ; blood flow rate to kidneys
QH = QHc*QC                      ; blood flow rate to heart
QR = QRc*QC                      ; blood flow rate to richly perfused tissue
QS = QSc*QC                      ; blood flow rate to slowly perfused tissue

;=================================================================================
; Partition Coefficients
;=================================================================================
; R-Methadone
PLRmet = 12.53                   ; liver/blood partition coefficient R-Methadone
PFRmet = 3.33                    ; fat/blood partition coefficient R-Methadone
PRRmet = 12.53                   ; richly perfused tissues/blood partition coefficient R-Methadone
PSRmet = 7.71                    ; slowly perfused tissues/blood partition coefficient R-Methadone
PLuRmet = 1.77                   ; lung/blood partition coefficient R-Methadone
PKRmet = 7.6                     ; kidney/blood partition coefficient R-Methadone
PHRmet = 4.93                    ; heart/blood partition coefficient R-Methadone

; S-Methadone
PLSmet = 11.99                    ; liver/blood partition coefficient S-Methadone
PFSmet = 2.54                     ; fat/blood partition coefficient S-Methadone
PRSmet = 11.99                    ; richly perfused tissues/blood partition coefficient S-Methadone
PSSmet = 7.39                     ; slowly perfused tissues/blood partition coefficient S-Methadone
PLuSmet = 1.71                    ; lung/blood partition coefficient S-Methadone
PKSmet = 7.29                     ; kidney/blood partition coefficient S-Methadone
PHSmet = 4.73                     ; heart/blood partition coefficient S-Methadone

;=================================================================================
; Biochemical parameters
;=================================================================================

;Linear uptake rate (/h)
ka = 0.59                        ; obtained from Foster et al. (2000); Wolff et al. (2000)

;Fraction absorbed
Fa = 0.88                        ; obtained from Ke et al. (2013)

;Renal clearance (L/h)
RCLRmet =1.8                     ; average values obtained from Boulton et al. (2001); Kharasch et al. (2009)
Foster et al. (2000)

RCLSmet =1.1                     ; average values obtained from Boulton et al. (2001); Kharasch et al. (2009)
Foster et al. (2000)

;---------------------------------------------------------------------------------------------------------------------------
;Metabolism liver

;Scaling factors
ISEFCYP2B6R=0.13                 ; corrected based on Totah et al. (2007) (2008)
ISEFCYP3A4R=0.04                 ; corrected based on Totah et al. (2007) (2008)
```

```
ISEFCYP2C19R= 0.1                ; corrected based on Totah et al. (2007) (2008)

ISEFCYP2B6S=0.13                 ; corrected based on Totah et al. (2007) (2008)
ISEFCYP3A4S=0.03                 ; corrected based on Totah et al. (2007) (2008)
ISEFCYP2C19S= 0.39               ; corrected based on Totah et al. (2007) (2008)

aCYP2B6 = 17                     ; EM CYP abundance level pmol/mg CYPisoform from Barter et al. (2013)
;aCYP2B6 =6                      ; PM CYP abundance level pmol/mg CYPisoform from Barter et al. (2013)
aCYP3A4 = 93                     ; CYP abundance level pmol/mg CYPisoform from Achour et al. (2014)
n=713
aCYP2C19 = 11                    ; CYP abundance level pmol/mg CYPisoform from Achour et al. (2014),
n=76;

MPL=32                           ; liver microsomal protein yield (mg/gram liver) (Barter et al., 2007)
L=VLc*1000                       ; liver = 25.7 (gram/kg BW)

;in vitro recombinant incubation of R-methadone (pmol/min/nmol CYP)
VmaxRmetCYP2B6m = 36             ; Totah et al. (2007)
VmaxRmetCYP3A4m = 43             ; Totah et al. (2007)
VmaxRmetCYP2C19m = 22            ; Totah et al. (2007)

;metabolites of R-methadone, unscaled maximum rate of metabolism (pmol/mg protein/min)
VmaxRmetCYP2B6c = VmaxRmetCYP2B6m*ISEFCYP2B6R*aCYP2B6
VmaxRmetCYP3A4c = VmaxRmetCYP3A4m*ISEFCYP3A4R*aCYP3A4
VmaxRmetCYP2C19c = VmaxRmetCYP2C19m*ISEFCYP2C19R*aCYP2C19

;metabolites of R-Methadone, scaled maximum rate of metabolism (µmol/h)
VMaxRmetCYP2B6 = VmaxRmetCYP2B6c / 1000000 * 60 * MPL * L * BW
VMaxRmetCYP3A4 = VmaxRmetCYP3A4c / 1000000 * 60 * MPL * L * BW
VMaxRmetCYP2C19= VmaxRmetCYP2C19c / 1000000 * 60 * MPL * L * BW

 ;metabolites of R-methadone, affinity constants (µmol/L)
KmRmetCYP2B6 = 60
KmRmetCYP3A4 = 137
KmRmetCYP2C19 = 97

;in vitro recombinant incubation of S-methadone (pmol/min/nmol CYP)
VmaxSmetCYP2B6m = 15             ; Totah et al. (2007)
VmaxSmetCYP3A4m = 46             ; Totah et al. (2007)
VmaxSmetCYP2C19m = 8             ; Totah et al. (2007)

;metabolites of S-methadone, unscaled maximum rate of metabolism (pmol/mg protein/min)
VmaxSmetCYP2B6c = VmaxSmetCYP2B6m*ISEFCYP2B6S*aCYP2B6
VmaxSmetCYP3A4c =  VmaxSmetCYP3A4m*ISEFCYP3A4S*aCYP3A4
VmaxSmetCYP2C19c = VmaxSmetCYP2C19m*ISEFCYP2C19S*aCYP2C19

; metabolites of S-methadone, scaled maximum rate of metabolism (µmol/h)
VMaxSmetCYP2B6 = VmaxSmetCYP2B6c / 1000000 * 60 * MPL * L * BW
VMaxSmetCYP3A4 = VmaxSmetCYP3A4c / 1000000 * 60 * MPL * L * BW
```

```
VMaxSmetCYP2C19 = VmaxSmetCYP2C19c / 1000000 * 60 * MPL * L * BW

 ;metabolites of S-methadone, affinity constants (umol/L)
KmSmetCYP2B6 = 16
KmSmetCYP3A4 = 149
KmSmetCYP2C19 = 125

;=============================================================================================
;Run settings
;=============================================================================================

;molecular weight (g/mol)
        MWRmet= 309.4                   ; molecular weight
        MWSmet= 309.4                   ; molecular weight

; R-methadone Given dose (mg/kg bw) and oral dose in µmol/kg bw
        TDOSERmet = 30                  ; whole body total dose in mg
        GDOSERmet = TDOSERmet / BW      ; given dose in mg per kg bw
        ODOSERmet = GDOSERmet * 1e-3 / MWRmet *1e6   ; determine odose (µmol/kg bw)
        DOSERmet = ODOSERmet * BW                    ; determine dose in µmol


; S-methadone Given dose (mg/kg bw) and oral dose in µmol/kg bw
        TDOSESmet = 30                  ; whole body total dose in mg
        GDOSESmet = TDOSESmet / BW      ; given dose in mg per kg bw
        ODOSESmet = GDOSESmet * 1e-3 / MWSmet *1e6   ; determine odose (µmol/kg bw)
        DOSESmet = ODOSESmet * BW                    ; determine dose in µmol


        dose_int = 24                                ; dosing interval in hours
;Time
        Starttime = 0                                ; in hrs
        Stoptime = 30*24                             ; in hrs (days * hours in a day)
        DTMIN = 1e-6
        DTMAX = 1
        DTOUT = 0
        TOLERANCE = 0.00001

;=============================================================================================
;Kinetics
;=============================================================================================
;slowly perfused tissue compartment

;ASRmet = Amount R-methadone in slowly perfused tissue (µmol)
    ASRmet' = QS * (CARmet - CVSRmet)
    Init ASRmet = 0
    CSRmet = ASRmet / VS
    CVSRmet = CSRmet / PSRmet
```

```
;ASSmet = Amount S-methadone in slowly perfused tissue (µmol)
      ASSmet' = QS * (CASmet - CVSSmet)
      Init ASSmet = 0
      CSSmet = ASSmet / VS
      CVSSmet = CSSmet / PSSmet

;-----------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------
; rapid perfused tissue compartment

;ARRmet = Amount R-methadone in richly perfused tissue (µmol)
      ARRmet' = QR * (CARmet - CVRRmet)
      Init ARRmet = 0
      CRRmet = ARRmet / VR
      CVRRmet = CRRmet / PRRmet

;ARSmet = Amount S-methadone in richly perfused tissue (µmol)
      ARSmet' = QR * (CASmet - CVRSmet)
      Init ARSmet = 0
      CRSmet = ARSmet / VR
      CVRSmet = CRSmet / PRSmet
;-----------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------
;fat compartment

;AFRmet = Amount R-methadone in fat tissue (µmol)
      AFRmet' = QF * (CARmet - CVFRmet)
      Init AFRmet = 0
      CFRmet = AFRmet / VF
      CVFRmet = CFRmet / PFRmet

;AFSmet = Amount S-methadone in fat tissue (µmol)
      AFSmet' = QF * (CASmet - CVFSmet)
      Init AFSmet = 0
      CFSmet = AFSmet / VF
      CVFSmet = CFSmet / PFSmet
;-----------------------------------------------------------------------------------------------------------------------------------------------------------
; uptake methadone from GI tract

;AGIRmet = Amount R-methadone remaining in GI tract (µmol)

       Init AGIRmet = 0
       AGIRmet' = pulse(DOSERmet* Fa, 0, dose_int) + AGIRmet * -Ka

;AGISmet = Amount S-methadone remaining in GI tract (µmol)

       Init AGISmet = 0
       AGISmet' = pulse(DOSESmet* Fa, 0, dose_int) + AGISmet * -Ka
```

```
;-------------------------------------------------------------------------------------------------------------------------------------------------------
-----------------------------------
;liver compartment

;ALRmet = Amount R-methadone in liver tissue (µmol)
      ALRmet' =  QL * (CARmet - CVLRmet )+ (AGIRmet * Ka) - AMLRmetCYP2B6' -AMLRmetCYP3A4' -
AMLRmetCYP2C19'
     Init ALRmet = 0
     CLRmet = ALRmet / VL
     CVLRmet = CLRmet / PLRmet

;metabolism described by Michaelis-Menten Kinetics
    ;AMLRmetCYP2B6=Amount R-methadone metabolized in liver to R-EDDP by CYP2B6
    ;AMLRmetCYP2B6' = (VmaxRmetCYP2B6*CVLRmet)  / (KmRmetCYP2B6 + CVLRmet)
    ;init AMLRmetCYP2B6 = 0

    ;AMLRmetCYP3A4=Amount R-methadone metabolized in liver to R-EDDP by CYP3A4
    ;AMLRmetCYP3A4' = (VmaxRmetCYP3A4*CVLRmet)  / (KmRmetCYP3A4 + CVLRmet)
    ;init AMLRMetCYP3A4 = 0

    ;AMLRmetCYP2C19=Amount R-methadone metabolized in liver to R-EDDP by CYP2C19
    ;AMLRmetCYP2C19' = (VmaxRmetCYP2C19*CVLRmet)  / (KmRmetCYP2C19 + CVLRmet)
    ;init AMLRMetCYP2C19 = 0

;metabolism described by enantiomeric interactions equations

        AMLRmetCYP2B6'=VmaxRmetCYP2B6*((CVLRmet*CVLRmet/(ahCYP2B6*KmRmetCYP2B6*KmRmetCY
        P2B6))+(CVLRmet/KmRmetCYP2B6)+(CVLRmet*CVLSmet/(bhCYP2B6*KmRmetCYP2B6*KmSmetCYP2B
        6)))/(1+(CVLRmet*CVLRmet/(ahCYP2B6*KmRmetCYP2B6*KmRmetCYP2B6))+(2*CVLRmet/KmRmetCY
        P2B6)+(CVLSmet*CVLSmet/(ahCYP2B6*KmSmetCYP2B6*KmSmetCYP2B6))+(2*CVLSmet/KmSmetCYP2
        B6)+(2*CVLRmet*CVLSmet/(bhCYP2B6*KmRmetCYP2B6*KmSmetCYP2B6)))

        ahCYP2B6=5                          ; homotropic interaction factor (Totah et al., 2007)
        bhCYP2B6=7                          ; heterotropic interaction factor (Totah et al., 2007)

        init AMLRmetCYP2B6 = 0

        AMLRmetCYP3A4' =
        (VmaxRmetCYP3A4*((CVLRmet*CVLRmet/(ahCYP3A4*KmRmetCYP3A4*KmRmetCYP3A4))+(CVLRmet/
        KmRmetCYP3A4)))/(1+(CVLRmet*CVLRmet/(ahCYP3A4*KmRmetCYP3A4*KmRmetCYP3A4))+(2*CVLR
        met/KmRmetCYP3A4)+(CVLSmet*CVLSmet/(ahCYP3A4*KmSmetCYP3A4*KmSmetCYP3A4))+(2*CVLSm
        et/KmSmetCYP3A4)+(2*CVLRmet*CVLSmet/(bhCYP3A4*KmRmetCYP3A4*KmSmetCYP3A4)))

        ahCYP3A4=4                          ; homotropic interaction factor (Totah et al., 2007)
        bhCYP3A4=2                          ; heterotropic interaction factor (Totah et al., 2007)

        init AMLRmetCYP3A4 = 0
```

```
        AMLRmetCYP2C19' =
        (VmaxRmetCYP2C19*(CVLRmet/KmRmetCYP2C19))/(1+(CVLRmet*CVLRmet/(ahCYP2C19*KmRmetCYP
        2C19*KmRmetCYP2C19))+(2*CVLRmet/KmRmetCYP2C19)+(CVLSmet*CVLSmet/(ahCYP2C19*KmSmetC
        YP2C19*KmSmetCYP2C19))+(2*CVLSmet/KmSmetCYP2C19)+(2*CVLRmet*CVLSmet/(bhCYP2C19*KmR
        metCYP2C19*KmSmetCYP2C19)))

        ahCYP2C19=42                    ; homotropic interaction factor (Totah et al., 2007)
        bhCYP2C19=3                     ; heterotropic interaction factor (Totah et al., 2007)

        init AMLRmetCYP2C19 = 0

;-------------------------------------------------------------------------------
;S-methadone
;ALSmet = Amount S-methadone in liver tissue (µmol)
     ALSmet' =  QL * (CASmet - CVLSmet )+ (AGISmet * Ka) - AMLSmetCYP2B6' -AMLSmetCYP3A4' -
AMLSmetCYP2C19'
    Init ALSmet = 0
    CLSmet = ALSmet / VL
    CVLSmet = CLSmet / PLSmet

;metabolism described by Michaelis-Menten Kinetics
    ;AMLSmetCYP2B6=Amount Smet metabolized in liver to S-EDDP by CYP2B6
    ;AMLSmetCYP2B6' = (VmaxSmetCYP2B6*CVLSmet)  / (KmSmetCYP2B6 + CVLSmet)
    ;init AMLSmetCYP2B6 = 0

    ;AMLSmetCYP3A4=Amount Smet metabolized in liver to S-EDDP by CYP3A4
    ;AMLSmetCYP3A4' = (VmaxSmetCYP3A4*CVLSmet)  / (KmSmetCYP3A4 + CVLSmet)
    ;init AMLSmetCYP3A4 = 0

    ;AMLSmetCYP2C19=Amount Smet metabolized in liver to S-EDDP by CYP2C19
    ;AMLSmetCYP2C19' = (VmaxSmetCYP2C19*CVLSmet)  / (KmSmetCYP2C19 + CVLSmet)
    ;init AMLSMetCYP2C19 = 0

;metabolism described by enantiomeric interactions equations

        AMLSmetCYP2B6' =
        VmaxSmetCYP2B6*((CVLSmet*CVLSmet/(ahCYP2B6*KmSmetCYP2B6*KmSmetCYP2B6))+(CVLSmet/K
        mSmetCYP2B6)+(CVLRmet*CVLSmet/(bhCYP2B6*KmRmetCYP2B6*KmSmetCYP2B6)))/(1+(CVLRmet*C
        VLRmet/(ahCYP2B6*KmRmetCYP2B6*KmRmetCYP2B6))+(2*CVLRmet/KmRmetCYP2B6)+(CVLSmet*CV
        LSmet/(ahCYP2B6*KmSmetCYP2B6*KmSmetCYP2B6))+(2*CVLSmet/KmSmetCYP2B6)+(2*CVLRmet*CV
        LSmet/(bhCYP2B6*KmRmetCYP2B6*KmSmetCYP2B6)))

        ahCYP2B6=5                      ; homotropic interaction factor (Totah et al., 2007)
        bhCYP2B6=7                      ; heterotropic interaction factor (Totah et al., 2007)

        init AMLSmetCYP2B6 = 0

        AMLSmetCYP3A4' =
        (VmaxSmetCYP3A4*((CVLSmet*CVLSmet/(ahCYP3A4*KmSmetCYP3A4*KmSmetCYP3A4))+(CVLSmet/K
```

*mSmetCYP3A4)))/(1+(CVLRmet*CVLRmet/(ahCYP3A4*KmRmetCYP3A4*KmRmetCYP3A4))+(2*CVLRmet/KmRmetCYP3A4)+(CVLSmet*CVLSmet/(ahCYP3A4*KmSmetCYP3A4*KmSmetCYP3A4))+(2*CVLSmet/KmSmetCYP3A4)+(2*CVLRmet*CVLSmet/(bhCYP3A4*KmRmetCYP3A4*KmSmetCYP3A4)))*

ahCYP3A4=4 ; homotropic interaction factor (Totah et al., 2007)
bhCYP3a4=2 ; heterotropic interaction factor (Totah et al., 2007)

init AMLSmetCYP3A4 = 0

AMLSmetCYP2C19' = (VmaxSmetCYP2C19(CVLSmet/KmSmetCYP2C19))/(1+(CVLRmet*CVLRmet/(ahCYP2C19*KmRmetCYP2C19*KmRmetCYP2C19))+(2*CVLRmet/KmRmetCYP2C19)+(CVLSmet*CVLSmet/(ahCYP2C19*KmSmetCYP2C19*KmSmetCYP2C19))+(2*CVLSmet/KmSmetCYP2C19)+(2*CVLRmet*CVLSmet/(bhCYP2C19*KmRmetCYP2C19*KmSmetCYP2C19)))*

ahCYP2C19=42 ; homotropic interaction factor (Totah et al., 2007)
bhCYP2C19=3 ; heterotropic interaction factor (Totah et al., 2007)

init AMLSmetCYP2C19 = 0

;---

;kidney compartment

;AKRmet = Amount R-methadone in kidney tissue (µmol)
AKRmet' = QK * (CARmet - CVKRmet)- ACLRmet'
Init AKRmet = 0
CKRmet = AKRmet / VK
CVKRmet = CKRmet / PKRmet

;ACLRmet=Amount R-methadone cleared renally
ACLRmet'=RCLRmet*CVKRmet
init ACLRmet = 0

;AKSmet = Amount S-methadone in kidney tissue (µmol)
AKSmet' = QK * (CASmet - CVKSmet)- ACLSmet'
Init AKSmet = 0
CKSmet = AKSmet / VK
CVKSmet = CKSmet / PKSmet

;ACLSmet=Amount S-methadone cleared renally
ACLSmet'=RCLSmet*CVKSmet
init ACLSmet = 0

;---

;Heart compartment

;AHRmet = Amount R-methadone in heart tissue (µmol)

```
      AHRmet' = QH * (CARmet - CVHRmet)
      Init AHRmet = 0
      CHRmet = AHRmet / VH
      CVHRmet = CHRmet / PHRmet

;AHSmet = Amount S-methadone in heart tissue (µmol)
      AHSmet' = QH * (CASmet - CVHSmet)
      Init AHSmet = 0
      CHSmet = AHSmet / VH
      CVHSmet = CHSmet / PHSmet

;--------------------------------------------------------------------------------------------------------------------------------------------------------
;lung compartment

;ALuRmet = Amount R-methadone in lung tissue (µmol)
      ALuRmet' = QC * (CVRmet - CALuRmet)
      Init ALuRmet = 0
      CLuRmet = ALuRmet / VLu
      CALuRmet = CLuRmet / PLuRmet


;ALuSmet = Amount S-methadone in lung tissue (µmol)
     ALuSmet' = QC * (CVSmet - CALuSmet)
     Init ALuSmet = 0
     CLuSmet = ALuSmet / VLu
     CALuSmet = CLuSmet / PLuSmet

;--------------------------------------------------------------------------------------------------------------------------------------------------------
---------------------------------
; arterial blood compartment

;CARmet = Concentration arterial blood R-methadone
      AARmet' = QC * (CALuRmet- CARmet);
      Init AARmet = 0
      CARmet=  AARmet / VA

;CASmet = Concentration arterial blood S-methadone
      AASmet' = QC * (CALuSmet- CASmet);
      Init AASmet = 0
      CASmet=  AASmet / VA

;--------------------------------------------------------------------------------------------------------------------------------------------------------
---------------------------------
; venous blood compartment

;AVRmet = amount venous blood R-methadone (µmol)
      AVRmet' = (QF * CVFRmet + QR * CVRRmet + QS * CVSRmet + QL * CVLRmet + QK * CVKRmet + QH
*CVHRmet- QC * CVRmet)
      Init AVRmet = 0
```

```
    CVRmet = (AVRmet / VV)


;AVSmet = amount venous blood S-methadone (µmol)
    AVSmet' = (QF * CVFSmet + QR * CVRSmet + QS * CVSSmet + QL * CVLSmet + QK * CVKSmet + QH
*CVHSmet- QC * CVSmet)
    Init AVSmet = 0
    CVSmet = (AVSmet / VV)

;================================================================================
;Mass balance calculations
;================================================================================
{Mass Balance}
TotalRMet' = pulse(DOSERmet *Fa, 0, dose_int)
init TotalRmet = 1E-50

CalculatedRmet = AFRMet + ASRmet+ ARRmet + ALRmet+ AVRmet+ AARmet + AGIRmet + AMLRmetCYP2B6 +
AMLRmetCYP3A4 + AMLRmetCYP2C19+ALuRmet + AKRmet + AHRmet + ACLRmet


ERRORRmet = ((TotalRmet - CalculatedRmet) / (TotalRmet + 1E-30)) * 100
MASSBALRmet = TotalRmet - CalculatedRmet + 1

;--------------------------------------------------------------------------------------------------------------------------------

TotalSMet' = pulse(DOSESmet *Fa, 0, dose_int)
init TotalSmet = 1E-50

CalculatedSmet = AFSMet + ASSmet+ ARSmet + ALSmet+ AVSmet+ AASmet + AGISmet + AMLSmetCYP2B6 +
AMLSmetCYP3A4 + AMLSmetCYP2C19 + ALuSmet + AKSmet + AHSmet + ACLSmet


ERRORSmet = ((TotalSmet - CalculatedSmet) / (TotalSmet + 1E-30)) * 100
MASSBALSmet = TotalSmet - CalculatedSmet + 1

;================================================================================
;Calculation with model
;================================================================================

CVRmetB = CVRmet * MWRmet          ; concentration of R-methadone in venous blood (µg/L)
AUCRmet' = CVRmetB                 ; calculate AUC for R-methadone
init AUCRmet = 0

CVSmetB = CVSmet * MWSmet          ; concentration of S-methadone in venous blood (µg/L)
AUCSmet' = CVSmetB                 ; calculate AUC for S-methadone
init AUCSmet = 0
;-----------------------------------------------------------------------------------------
CVheartRmet= CVHRmet*MWRmet        ; concentration of R-methadone in the heart venuos blood (µg/L)
CVheartSmet= CVHSmet*MWSmet        ; concentration of S-methadone in the heart venuos blood (µg/L)
```

Supplementary materials 3

Model code of Monte Carlo simulation for Caucasian population

```
;CYP2B6 EM
;aCYP2B6c = init(exp(normal(2.38, 0.955)))
;aCYP2B6 = IF aCYP2B6c >0.61 AND aCYP2B6c < 189.01 THEN aCYP2B6c ELSE 100001  ;Values higher or lower than 3 times the SD are removed

;CYP2B6 PM
aCYP2B6c = init(exp(normal(0.99, 1.269)))
aCYP2B6 = IF aCYP2B6c >0.06 AND aCYP2B6c < 120.66 THEN aCYP2B6c ELSE 100001  ;Values higher or lower than 3 times the SD are removed

;CYP3A4 general population n=713
aCYP3A4c = init(exp(normal(4.28, 0.71)))
aCYP3A4 = IF aCYP3A4c >8.58 AND aCYP3A4c < 608.6 THEN aCYP3A4c ELSE 100001  ;Values higher or lower than 3 times the SD are removed

;CYP2C19 general population n=76
aCYP2C19c = init(exp(normal(2.14, 0.717)))
aCYP2C19 = IF aCYP2C19c >0.99 AND aCYP2C19c < 73.12 THEN aCYP2C19c ELSE 100001  ;Values higher or lower than 3 times the SD are removed
```