Supplementary materials 2

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;PBK model code human model

;=========================================================================
; physiological parameters
;=========================================================================

    ; Tissue volumes (L or Kg)

     BW = 70                    ; body weight human in kg

    ; All fractions are 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 = 0.037                ; fraction of rapidly perfused tissue
     VSc = 0.58                 ; fraction of blood flow to slowly perfused tissue
                                ; total of fractions = 0.9527

    VL = VLc * BW               ; volume of liver
    VF = VFc * BW               ; volume of fat
    VLu = VLuc * BW             ; volume of lung
    VK = VKc * BW               ; volume of kidney
    VH = VHc * BW               ; volume of heart
    VR = VRc * BW               ; volume of rapidly 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                 ; QC = 15 * BW^0.74 (Brown et al., 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 kidney
      QHc = 0.04                        ; fraction of blood flow to heart
      QSc = 0.291                       ; fraction of blood flow to slowly perfused tissue
      QRc = 0.215                       ; fraction of blood flow to rapidly perfused tissue
                                        ; total of fractions = 1
```

```
    ; all fractions are taken from Brown et al. (1997)
    QL = QLc*QC                 ; blood flow rate to liver in L/h
    QF = QFc*QC                 ; blood flow rate to fat
    QK = QKc * QC               ; blood flow rate to kidney
    QH = QHc*QC                 ; blood flow rate to heart
    QR = QRc*QC                 ; blood flow rate to rapidly perfused tissue
    QS = QSc*QC                 ; blood flow rate to slowly perfused tissue

;====================================================================
; Partition coefficients
;====================================================================
    PFibo = 0.18                ; fat/blood partition coefficient ibogaine
    PSibo = 2.73                ; slowly perfused tissues/blood partition coefficient ibogaine
    PHibo = 0.7                 ; heart/blood partition coefficient ibogaine
    PKibo = 1.02                ; kidney/blood partition coefficient ibogaine
    PLibo = 1.62                ; liver/blood partition coefficient ibogaine
    PRibo = 1.62                ; rapidly perfused tissues/blood partition coefficient ibogaine
    PLuibo = 0.32               ; lung/blood partition coefficient ibogaine

    PFnor = 1.38                ; fat/blood partition coefficient noribogaine
    PSnor= 2.33                 ; slowly perfused tissues/blood partition coefficient noribogaine
    PHnor =7.6                  ; heart/blood partition coefficient noribogaine
    PKnor = 16.9                ; kidney/blood partition coefficient noribogaine
    PLnor = 15.3                ; liver/blood partition coefficient noribogaine
    PRnor = 15.3                ; rapidly perfused tissues/blood partition coefficient
noribogaine
    PLunor = 13.1               ; lung/blood partition coefficient noribogaine

;====================================================================
; Biochemical parameters
;====================================================================
    ; Linear uptake rate (/h)   ; calculated based on Papp values obtained from the current
study using methadone as a reference compound.

    kaibo = 0.79
    kanor = 1.23

    ; Fraction absorbed
    Faibo = 1
    Fanor = 1
```

; Biliary excretion

kbibo=0.575 ; the kb of noribogaine was assumed to be same for ibogaine

kbnor=0.575 ; biliary excretion rate constant (/h) of noribogaine was obtained by fitting CVBnor to reported in vivo data (Glue et al., 2016; Glue et al., 2015a; Glue et al., 2015b).

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; Metabolism of ibogaine in the liver

; Scaling factors;

MPL=32 ; liver microsomal protein yield (mg/gram liver) (Barter et al., 2007)

L=VLc*1000 ; liver =25.7 (gram/kg BW)

; Metabolites of ibogaine, unscaled maximum rate of metabolism (nmol/mg protein/min)

Vmaxc1 = 0.17 ; obtained from in vitro microsomal incubation in the current study.

; Metabolites of ibogaine, scaled maximum rate of metabolism (µmol/h)

Vmax1 = Vmaxc1 / 1000 * 60 * MPL * L * BW

; Metabolites of ibogaine, affinity constants (µmol/L)

Km1 = 0.63 ; obtained from in vitro microsomal incubation in the current study.

; metabolism of noribogaine in the liver

; Metabolites of noribogaine, unscaled maximum rate of metabolism (nmol/mg protein/min)

Vmaxc2 = 0.036 ; obtained from in vitro microsomal incubation in the current study.

; Metabolites of noribogaine, scaled maximum rate of metabolism (µmol/h)

Vmax2 = Vmaxc2 / 1000 * 60 * MPL * L * BW

; Metabolites of noribogaine, affinity constants (µmol/L)

Km2 = 305 ; obtained from in vitro microsomal incubation in the current study.

;==========

; Run settings

;==========

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    ; Molecular weight (g/mol)
        MWibo= 310.4                    ; molecular weight of ibogaine
        MWnor = 296.4                   ; molecular weight of noribogaine

    ; Given dose (mg/kg bw) and oral dose in µmol/kg bw for ibogaine

        TDOSEibo = 0.0000001                        ; whole body total dose (mg)
        GDOSEibo = TDOSEibo / BW                    ; given dose (mg/kg bw)
        ODOSEibo = GDOSEibo * 1e-3 / MWibo*1e6      ; determine odose (µmol/kg bw)
        DOSEibo = ODOSEibo * BW                     ; determine dose (µmol)

        TDOSEnor = 30                               ; whole body total dose (mg)
        GDOSEnor = TDOSEnor  / BW                   ; given dose (mg/kg bw)
        ODOSEnor  = GDOSEnor  * 1e-3 / MWnor *1e6   ; determine odose (µmol/kg bw)
        DOSEnor  = ODOSEnor  * BW                   ; determine dose (µmol)

        doseibo_int = 2400                          ; dosing interval in hours
        dosenor_int = 2400

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

;=============================================================================
; Knetics ibogaine
;=============================================================================
    ; Slowly perfused tissue compartment

    ; ASibo = Amount ibogaine in slowly perfused tissue (µmol)

    ASibo' = QS * (CAibo - CVSibo)
                Init ASibo = 0
                CSibo = ASibo / VS
                CVSibo = CSibo / PSibo

    ;-------------------------------------------------------------------------------------------------------------------
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; Rapidly perfused tissue compartment

;ARibo = Amount ibogaine in rapidly perfused tissue (µmol)

ARibo' = QR * (CAibo - CVRibo)
                Init ARibo = 0
                CRibo = ARibo / VR
                CVRibo = CRibo / PRibo

;-------------------------------------------------------------------------------------------------------------------------------
; Fat compartment

;AFibo = Amount ibogaine in fat tissue (µmol)

AFibo' = QF * (CAibo - CVFibo)
                Init AFibo = 0
                CFibo = AFibo / VF
                CVFibo = CFibo/ PFibo
;-------------------------------------------------------------------------------------------------------------------------------
; Uptake ibogaine from GI tract

;AGIibo= Amount ibogaine remaining in GI tract (µmol)

Init AGIibo = 0
AGIibo' = pulse (DOSEibo* Faibo, 0, doseibo_int) -kaibo * AGIibo

;-------------------------------------------------------------------------------------------------------------------------------
; Liver compartment
;ALibo = Amount ibogaine in liver tissue (µmol)

ALibo' = QL * (CAibo - CVLibo )+ (AGIibo * kaibo) - AMLibo' -ABibo'
                Init ALibo= 0
      CLibo = ALibo/ VL
                CVLibo= CLibo / PLibo

;AMLibo=Amount ibogaine metabolized in liver to noribogaine

                AMLibo' = (Vmax1*CVLibo) / (Km1 + CVLibo)
                init AMLibo = 0
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; ABibo= amount of biliary excretion of ibogaine

                ABibo'=kbibo*ALibo
                init ABibo = 0


;-------------------------------------------------------------------------------------------------------------------------
; Kidney compartment

;AKibo = Amount ibogaine in kidney tissue (µmol)

AKibo' = QK * (CAibo - CVKibo)
                Init AKibo = 0
                CKibo = AKibo / VK
                CVKibo= CKibo/ PKibo
;-------------------------------------------------------------------------------------------------------------------------
;Heart compartment

;AHibo = Amount ibogaine in heart tissue (µmol)

                AHibo' = QH * (CAibo - CVHibo)
                Init AHibo = 0
                CHibo = AHibo / VH
                CVHibo= CHibo / PHibo

;-------------------------------------------------------------------------------------------------------------------------
;Lung compartment

;ALuibo = Amount ibogaine in lung tissue (µmol)

ALuibo' = QC * (CVibo - CALuibo)
Init ALuibo = 0
CLuibo= ALuibo / VLu
CALuibo = CLuibo / PLuibo

;-------------------------------------------------------------------------------------------------------------------------
; Arterial blood compartment

;CAibo = Concentration arterial blood ibogaine
```

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    AAibo' = QC * (CALuibo- CAibo);
                    Init AAibo = 0
                    CAibo=  AAibo / VA

    ;-------------------------------------------------------------------------------------------------------------------------
    ; Venous blood compartment

    ;AVibo = amount venous blood ibogaine (µmol)

    AVibo' = (QF * CVFibo + QR * CVRibo + QS * CVSibo + QL * CVLibo + QK * CVKibo + QH *CVHibo-
QC * CVibo)
    Init AVibo = 0
                    CVibo = (AVibo / VV)

;=========================================================================
; Kinetics noribogaine sub-model
;=========================================================================
    ;Slowly perfused tissue compartment

    ; ASnor = Amount noribogaine in slowly perfused tissue (µmol)

    ASnor' = QS * (CAnor- CVSnor)
    Init ASnor = 0
    CSnor = ASnor / VS
    CVSnor = CSnor / PSnor

    ;-------------------------------------------------------------------------------------------------------------------------
    ; Rapidly perfused tissue compartment

    ; ARnor = Amount noribogaine in rapidly perfused tissue (µmol)

    ARnor' = QR * (CAnor - CVRnor)
                    Init ARnor = 0
                    CRnor = ARnor / VR
                    CVRnor= CRnor/ PRnor

    ;-------------------------------------------------------------------------------------------------------------------------
    ; Fat compartment

    ; AFnor= Amount noribogaine in fat tissue (µmol)
```

```
                AFnor' = QF * (CAnor - CVFnor)
                Init AFnor= 0
CFnor= AFnor/ VF
CVFnor = CFnor/ PFnor
;----------------------------------------------------------------------------------------------------------------------------

;----------------------------------------------------------------------------------------------------------------------------
; Uptake noribogaine from GI tract

;AGInor= Amount noribogaine remaining in GI tract (µmol)

Init AGInor = 0
AGInor' = pulse (DOSEnor* Fanor, 0, dosenor_int) + -kanor * AGInor

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

; Liver compartment

; ALnor= Amount noribogaine in liver tissue (µmol)

ALnor' = QL * (CAnor - CVLnor) + (AGInor * kanor) +AMLibo' - ABnor'- AMLnor'
                Init ALnor = 0
                CLnor = ALnor / VL
                CVLnor = CLnor / PLnor

;AMLnor=Amount noribogaine metabolized in liver to noribogaine glucuronide

                AMLnor' = (Vmax2*CVLnor) / (Km2 + CVLnor)
                init AMLnor = 0

; ABnor= amount of biliary excretion of noribogaine

                ABnor'=kbnor*ALnor
                init ABnor = 0
;----------------------------------------------------------------------------------------------------------------------------
; Kidney compartment

; AKnor = Amount noribogaine in kidney tissue (µmol)
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```
AKnor' =QK * (CAnor - CVKnor)
                Init AKnor = 0
                CKnor = AKnor / VK
                CVKnor= CKnor / PKnor
;-------------------------------------------------------------------------------------------------------------------------
; Heart compartment

; AHnor = Amount noribogaine in heart tissue (µmol)

                AHnor' = QH * (CAnor- CVHnor)
                Init AHnor = 0
                CHnor = AHnor / VH
                CVHnor = CHnor / PHnor

;-------------------------------------------------------------------------------------------------------------------------
;Lung compartment

; ALunor = Amount noribogaine in lung tissue (µmol)

                ALunor' = QC * (CVnor - CALunor)
                Init ALunor = 0
                CLunor = ALunor / VLu
                CALunor = CLunor / PLunor

;-------------------------------------------------------------------------------------------------------------------------
; Arterial blood compartment

; CAnor= Concentration arterial blood noribogaine(µmol)

AAnor' = QC * (CALunor- CAnor)
Init AAnor = 0
CAnor =  AAnor / VA
;-------------------------------------------------------------------------------------------------------------------------
; Venous blood compartment

; AVnor = Amount venous blood noribogaine (µmol)

AVnor' = (QF * CVFnor + QR * CVRnor+ QS * CVSnor+ QL * CVLnor + QK * CVKnor + QH *CVHnor-
QC * CVnor)
                Init AVnor = 0
```

```
CVnor= (AVnor/ VV)

;=========================================================================
    ; Mass balance calculations of ibogaine
;=========================================================================
    Totalibo' = pulse (DOSEibo *Faibo, 0, doseibo_int)
    init Totalibo = 1E-50

    Calculatedibo = AFibo + ASibo+ ARibo + ALibo+ AVibo+ AAibo + AGIibo + AMLibo + ALuibo + AKibo
+ AHibo+ABibo


    ERRORibo = ((Totalibo - Calculatedibo) / (Totalibo + 1E-30)) * 100
    MASSBALibo = Totalibo - Calculatedibo + 1

;=========================================================================
; Mass balance calculations of noribogaine
;=========================================================================
    Totalnor' = AMLibo'+pulse (DOSEnor *Fanor, 0, dosenor_int)
    init Totalnor = 1E-50+AMLibo

    Calculatednor = AFnor + ASnor+ ARnor + ALnor + AVnor+ AAnor+ ALunor + AKnor + AHnor
+ABnor+ AMLnor + AGInor

    ERRORnor= ((Totalnor - Calculatednor) / (Totalnor + 1E-30)) * 100
    MASSBALnor = Totalnor - Calculatednor + 1

;=========================================================================
; Calculation with model
;=========================================================================
    ; Calculations to evaluate the model performance of ibogaine

    CViboB = CVibo* MWibo                    ; Concentration of ibogaine in venous blood (µg/l)

    AUCibo' = CViboB                         ; Calculate AUC for ibogaine
    init AUCibo = 0

    CVheartibo= CVHibo*MWibo                 ; Concentration of ibogaine in heart venous blood (µg/l)
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; Calculations to evaluate the model performance of noribogaine

CVnorB = CVnor * MWnor ; Concentration of noribogaine in venous blood (µg/l)

AUCnor' = CVnorB ; Calculate AUC for noribogaine

init AUCnor = 0

CVheartnor= CVHnor*MWnor ; Concentration of noribogaine in heart venous blood (ug/l)

BPribo=2.5 ;blood to plasma ratio of ibogaine, assumed to be same as noribogaine

BPrnor=2.5 ;blood to plasma ratio of noribogaine (Mash et al. 2016)

fupibo=0.04 ;fraction unbound in plasma of ibogaine obtained from the current study

fupnor=0.26 ;fraction unbound in plasma of ibogaine obtained from the current study

; toxic equivalency factor based on in vitro cardiotoxic potency ($BMCL_{10}$ of ibogaine =0.11 µM $BMCL_{10}$ of noribogaine= 0.15µM) obtained in the hiPSC-CM MEA assay in the current study.

TEFibo=1

TEFnor=0.73

; toxic equivalency concentration upon the oral exposure of ibogaine

fCVheartTEQ=CVheartibo* (fupibo/BPribo) *TEFibo+CVheartnor* (fupnor/BPrnor) *TEFnor