Appendix (Supplementary Materials).

Section A: Supplementary data and Model parameters

Table S1. Parameters used in the PBPK human model.

Parameters	Symbols	Parameters values
Body weight (kg)	Bw	Calculated
Cardiac output (mL/hr/kg)	Qccar	15.36
Tissue volume (fraction of BW unitless)		
Liver	Vli	Calculated
Fat	Vf	Calculated
Rest of the body	Vre	Calculated
Tissue blood volume (fraction tissue volume unitless)		
Liver	VliB0	0.266
Fat	VfB0	0.05
Rest of the body	VreB0	0.03
Tissue blood flow Qt (fraction Qc unitless)		
Liver	Qli0	0.26
Fat	Qf0	0.05
Rest of the body	Qre0	Calculated
Tissue permeability (fraction of Qt unitless)		
Liver	PAliF	0.35
Fat	PAfF	0.12
Rest of the body	PArefF	0.03
Apparent partition coefficient (unitless)		
Liver	Pli	6.0
Fat	Pf	100.0
Rest of the body	Pre	1.5
Metabolism constants		
Urinary clearance elimination (mL/hour)	CLURI	4.17×10^{-8}
Liver (biliary elimination and metabolism; ($hour^{-1}$)	KBILE_LI	Inducible
Interspecies constant ($hour^{-1}$)	Kelv	0.0011
Ah receptor		
Affinity constant in liver (nmol/mL)	KDLI	0.1
Binding capacity in liver (nmol/mL)	LIBMAX	0.35
CYP1A2 induction parameters		
Dissociation constant CYP1A2 (nmol/mL)	KDLI2	40.0
Degradation process CYP1A2 (nmol/mL)	CYP1A2_1OUTZ	1,600.0
Dissociation constant during induction (nmol/mL)	CYP1A2_1EC50	130.0
Basal concentration of CYP1A2 (nmol/mL)	CYP1A2_1A2	1,600.0
First-order rate of degradation ($hour^{-1}$)	CYP1A2_1KOUT	0.1
Time delay before induction process (hour)	CYP1A2_1TAU	0.25
Maximal induction of CYP1A2 (unitless)	CYP1A2_1EMAX	9,300.0
Other constants		
Oral absorption constant ($hour^{-1}$)	KABS	0.06
Gastric non-absorption constant ($hour^{-1}$)	KST	0.01

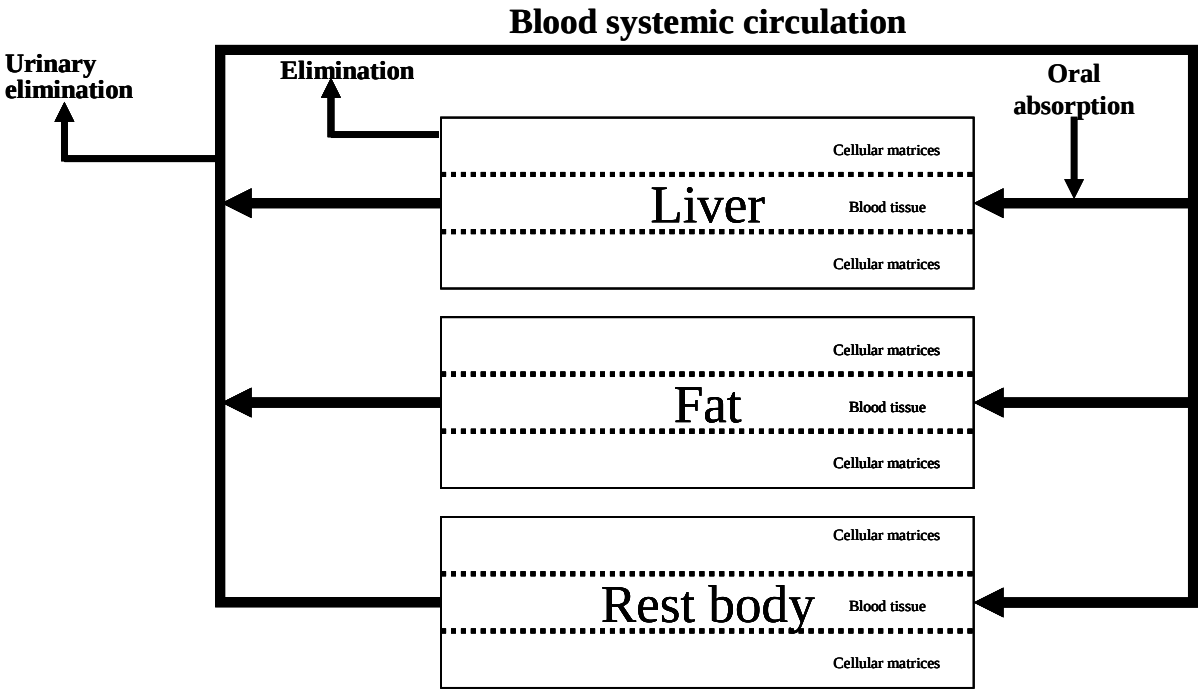


Figure S1. A conceptual representation of the TCDD PBPK model for humans, developed by Emond et al. (2005).

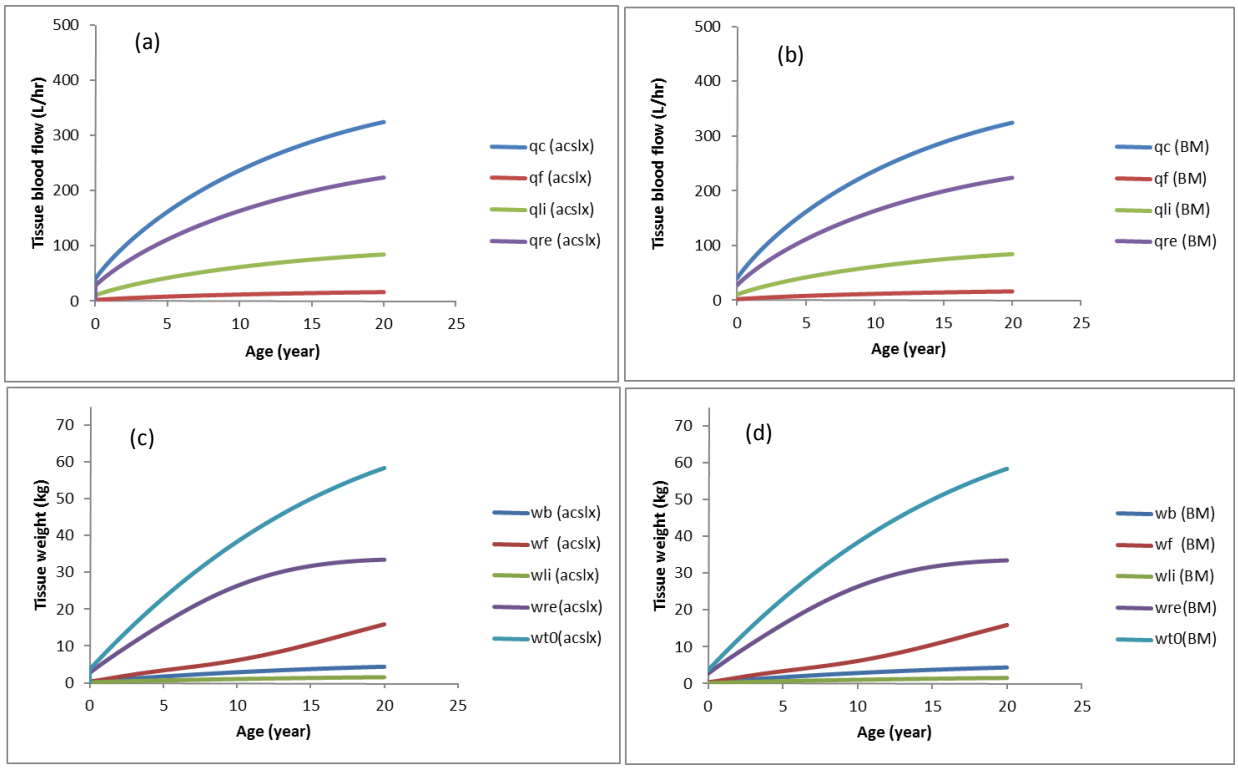
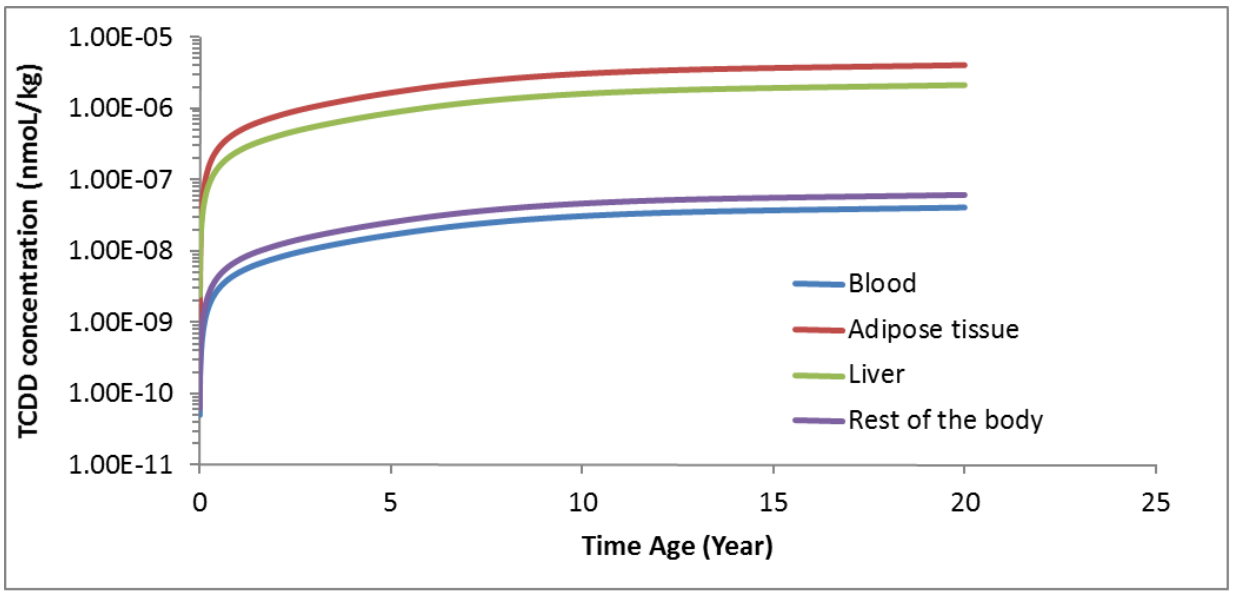
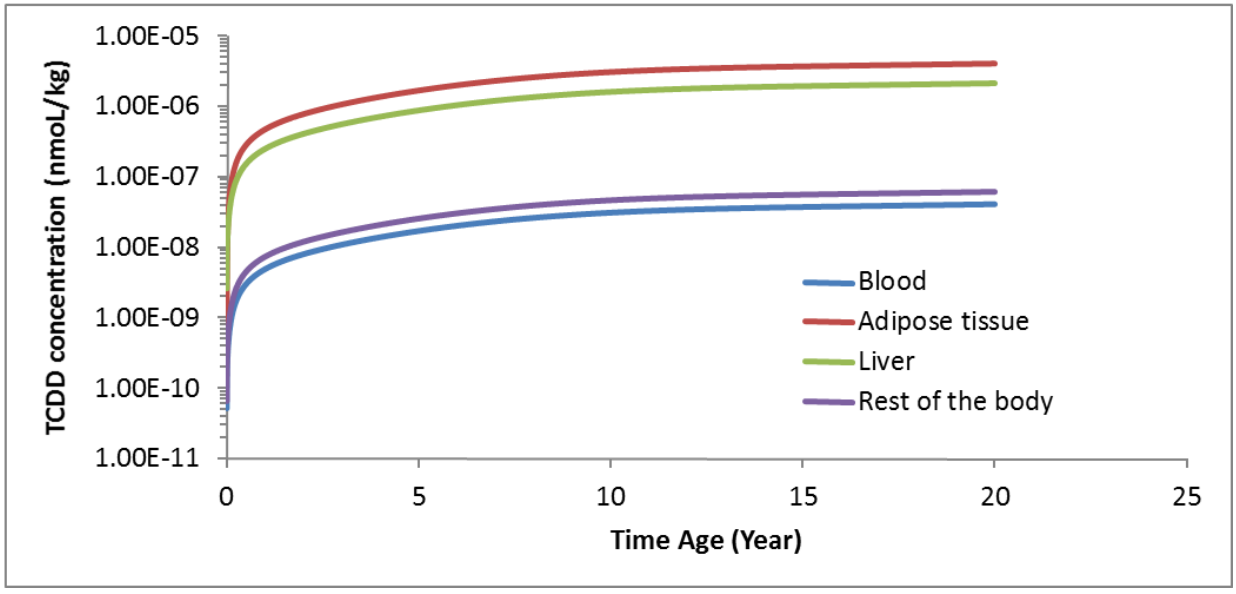


Figure S2. S2a-d illustrate the results from the original and recoded PBPK dioxins models for the parameters of tissue blood flow (q_{tissue}) (L/h) and tissue weight (W_{tissue}) (Kg) for the liver, adipose tissue and rest of the body compartments as a function of age (scenario spanning ages 0-20 years). Legend: liver (qli or wli), adipose tissue (qf or wf), rest of the body (qre or wre), and body weight (wt0) respectively. Figure S2a shows the tissue blood flow values across compartments generated by the original PBPK model (acslX); Fig S2b shows the same values generated by the recoded PBPK model (BM); Figure S2c shows the tissue weight values generated by the original PBPK model (acslX); Figure S2d shows the same values generated by the recoded PBPK model (BM).



(a)



(b)

Figure S3. Plots of a simulation of the TCDD concentration in blood, adipose tissue, liver, and rest of the body for a scenario involving women ages 0–20 years who were orally exposed to 1×10^{-7} ng of TCDD per kilogram of body weight, once per day for 20 years. No background exposure was assumed. Fig. S3a shows the data obtained with the original TCDD PBPK model. Fig. S3b shows the data obtained with the TCDD PBPK model recoded in BM.

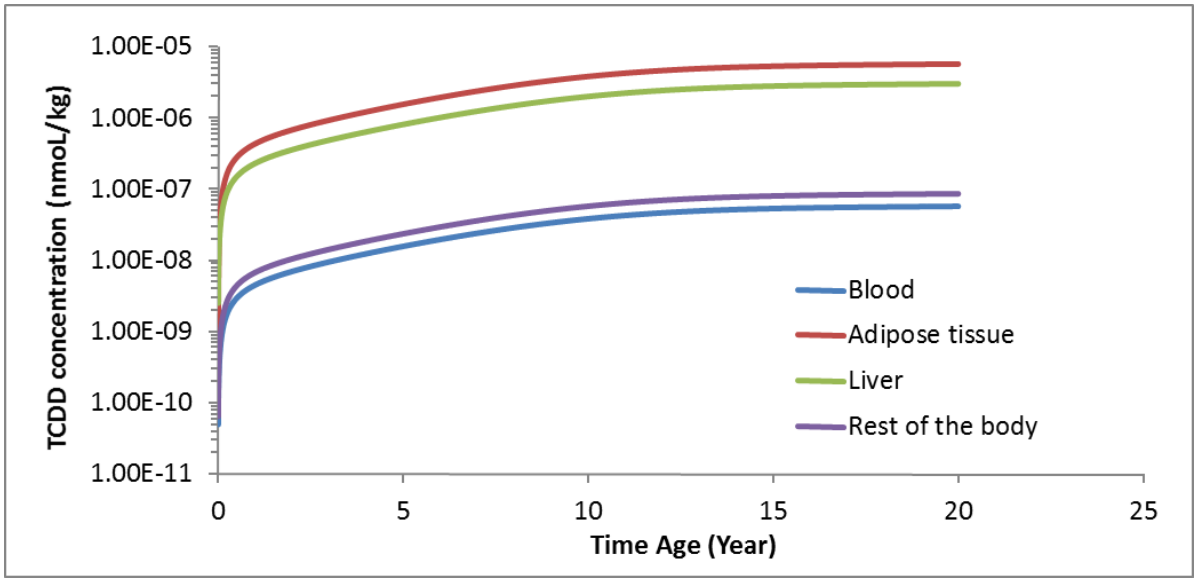
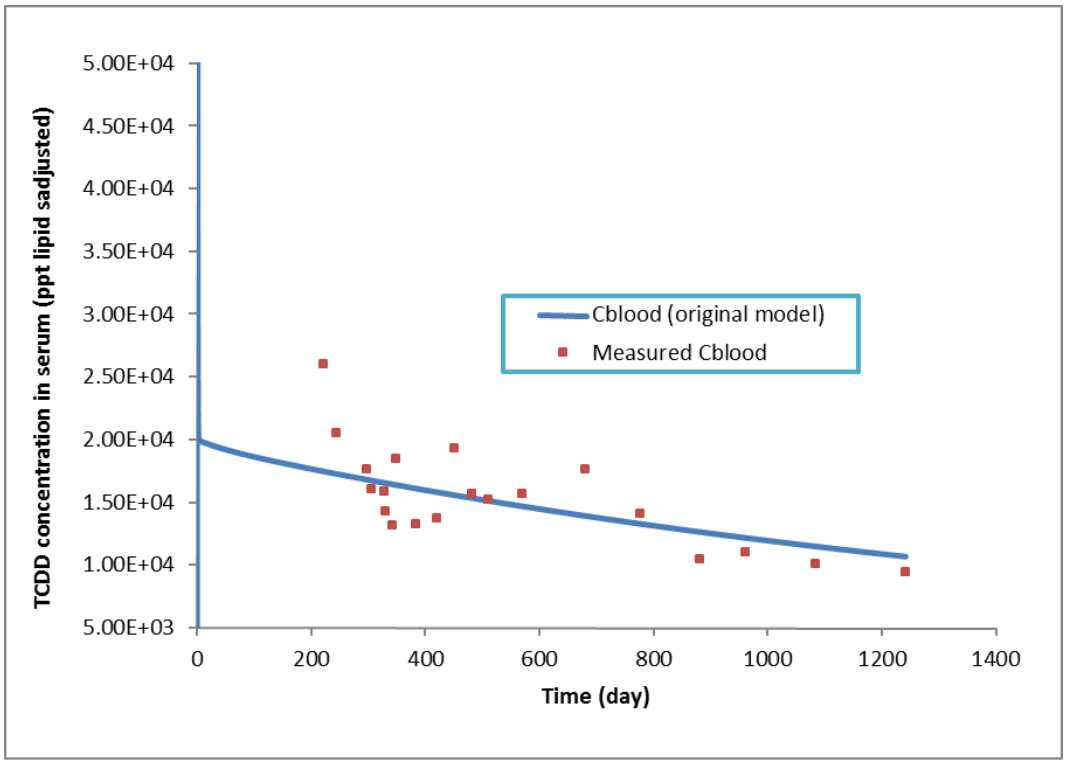
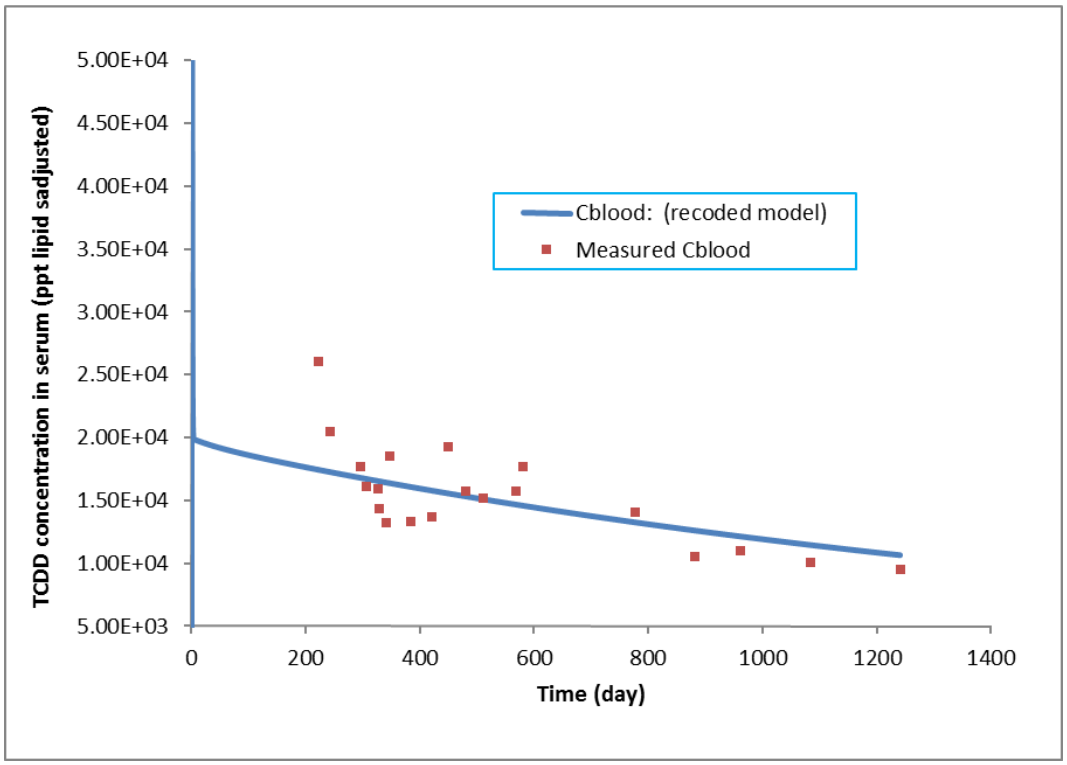


Figure S4. Plots of the data obtained with the model recoded in BM of a simulation in which a man was chronically exposed to TCDD every day from birth to age 20 years. The concentrations in nanomole per kilogram of body weight were reported for blood (cb), adipose tissue (cf), liver (cli), and rest of the body (cre) at different ages.

(a)


5.00E+04
4.50E+04
4.00E+04
3.50E+04
3.00E+04
2.50E+04
2.00E+04
1.50E+04
1.00E+04
5.00E+03
TCDD concentration in serum (ppt lipid sadjusted)
0
200
400
600
800
1000
1200
1400
Time (day)
Cblood (original model)
Measured Cblood

(b)


5.00E+04
4.50E+04
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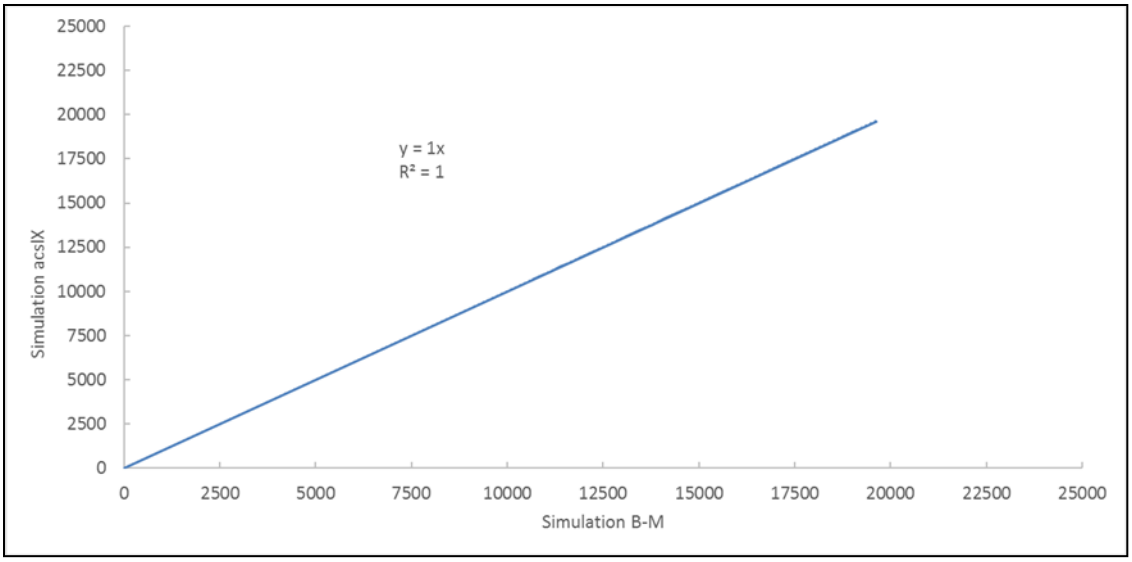
3.50E+04
3.00E+04
2.50E+04
2.00E+04
1.50E+04
1.00E+04
5.00E+03
TCDD concentration in serum (ppt lipid sadjusted)
0
200
400
600
800
1000
1200
1400
Time (day)
Cblood: (recoded model)
Measured Cblood

(c)



(d)

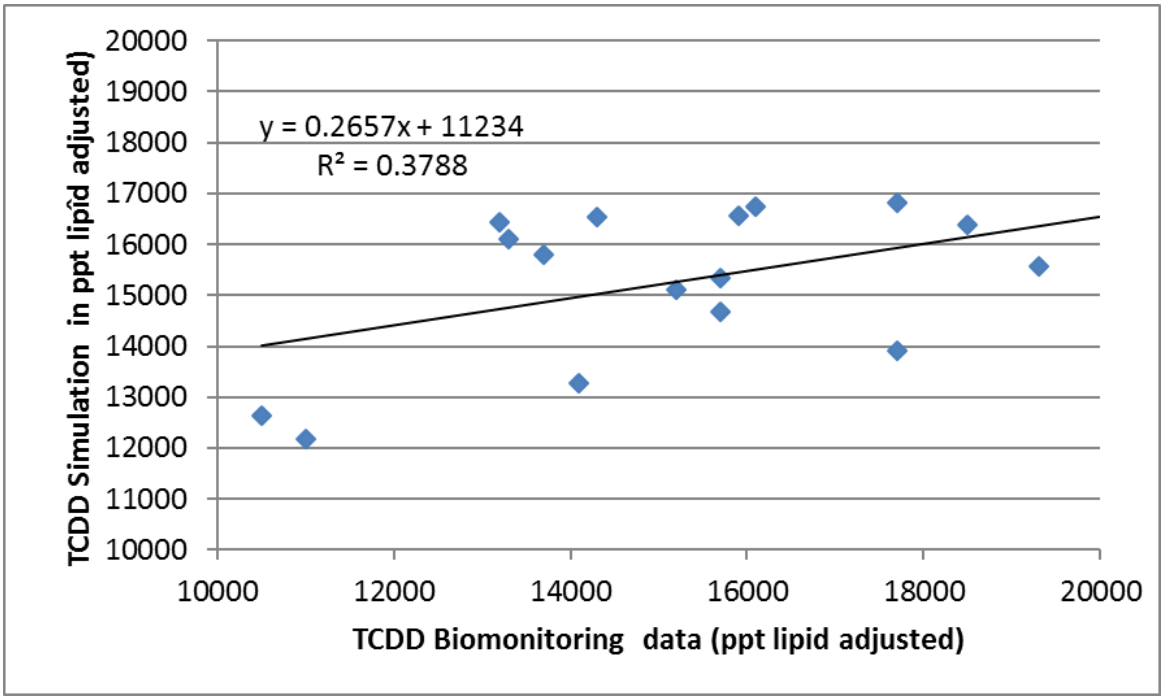


Figure S5. TCDD blood concentrations (ppt lipid adjusted) over time for highly exposed women. The square symbols represent measured concentrations, and the lines represent the model's output. The simulation was performed using (a) the acslX code file, (b) the BM code file software, (c) the determination coefficient (R^2=1) between the prediction of the original model and the recode PBPK model, and (d) is the association between the recoded model and the biomonitoring data of the Vienna woman exposed to TCDD.

Table S2. Measures of predictive performance for TCDD recoded model simulation including

Chemical	R^2	MPE%	MAPE%	RMSPE%
TCDD	0.3788	-3.8816	16.2463	16.2563

the statistic of association between biomonitoring data and the predictive model.

Section A : codes for the model Berkeley Madonna Code

```
{PROGRAM: MODEL PBPK FOR TCDD IN HUMAN NON GESTATION 3 COMPARTMENT
 August 05 EHPTCDD_3CHumPap3MARCH17 (name CHANGE JUNE 9 2009
 Transfert from ACSL11.8 to ACSLX June 9 2009
 NEW NAME:  RAT_3COMP_TCDD_2012 OCTOBER 2009
 HUM_NON_GEST_ICF_F083109.csl SEPTEMBER 2009 UNIFORMIZED
 Transferred from ACSLX to Berkeley Madonna Oct 2011
 Hum_non_gest_icf_f083109.csl September 1 uniformed
 This model was recoding by BioSimulation Consulting, DE, USA
 Final version April 2016
 HNG_3COMP_TCDD_ATSDR2016.mmd}

{Algorithm}

method euler   ;stiff                ; rosenbrock stiff solver (note to self: change to gear)
starttime              = 0           ; delay before begin exposure (hour)
stoptime               =  10000      ; time exposure stop (hour)
dtmin                  = 1e-10       ; minimum (and initial) step size
dtmax                  =10           ; maximum step size
tolerance              =0.01         ; error tolerance for stiff solver
dtout                  = 1            ; communication interval (optional)


{initialization of parameters}

; Simulation parameters
       exptimeon             =      0.0     ; delay before begin exposure (hour)
       exptimeoff     =      180     ;time exposure stop (hour),
       freqexp        =       20     ;time between two exposure cycle (hr)

; time control orale exposure control
        bcktimeon     =      0.0    ;hour delay before background exp. (hour)
       bcktimeoff     =       500    ;hour time when background exp stop. (hour)
       freqexpbg      =         1    ;hour time between two exp. cycle (hr) background source

; time control orale exposure background control
       mstotbckgr     =      0.0     ;oral background exposure dose (ng/kg)
       mstot          =      0.0     ;oral exposure dose (ng/kg)
       doseiv         =      0.0     ;injected dose(ng/kg)
       mw             =      322.0   ;molecular weight g/mole

;oral absorption
       mstotnm                =      mstot/mw       ;amount in nmol/kg
       mstotnmbckgr           =      mstotbckgr/mw  ;amount in [nmol/kg]
;absorption intraveineous
       doseivnm               =      doseiv/mw      ;amount in nmol/kg
;initial guess of the free conc in the ligand in compartment
       cflli0                 =      0.0            ;liver   (nmol/l)
;binding capacity (ahr) for non linear binding (nmol/ml)
       libmax                 =      0.35           ;liver  (nmole/l)
;affinity constant proteins (1a2 or ahr) in compartment (nmol/ml)
       kdli                   =      0.1            ;liver (AhR) (nmol/l) wang et al (1997)
       kdli2                  =     40.0            ;liver (1A2) (nmol/l)emond et al.(2004)
;excretion and absorption constant emond et al (2005)
       kst                    =      0.01           ;gastric empty constant (hr-1)
       kabs                   =      0.06           ;intestinal absorption constant (hr-1)
;elimination constant in different compartment emond et al (2005)
       cluri                  =      4.17e-8  ;     ;urinary clearance in reducing model (l/hr)
;test elimination variable emond et al (2005)
       kelv                   =      0.0011         ;(1/hour)
;operate to divide one input to two outputs wang et al. (1997)
       a                      =             0.7     ;lymphatic fraction
;partition coefficients wang et al. (1997)
       pf                     =       100           ;adipose tissue/blood
       pre                    =       1.5           ;rest of the body/blood
       pli                    =      6.0            ;liver/blood
;parameter for induction of cyp1a2
       pasinduc               =      1.0            ;controle de l'induction
```

```
       cyp1a21outz           =      1600          ;concen in degradation proc (nmol/l),
       cyp1a21a1             =      1600          ;basal conc of 1a1 in t (nmol/l)
       cyp1a21ec50           =       130          ;dis.const in induction proc for 1a2(nmol/l)
       cyp1a21a2             =       1600         ;basal concentration of 1a2 (nmol/l)
       cyp1a21kout           =       0.1          ;first order rate of degradation.(hour-1)
       cyp1a21tau            =       0.25          ;holding time (hour)
       cyp1a21emax           =       9300         ;max induction over basal effect (unitless)
       hill                  =       0.6
;diffusional permeability fraction organ flow
       paff                  =      0.12          ;adipose          (unitless)
       paref                 =      0.03          ;rest of the body (unitless)
       palif                 =      0.35          ;liver            (unitless)
;tissue blood flow fraction of cardiac output (unitless)
       qff                   =             0.05          ;adipose tissue[ref 733]
       qlif                  =             0.26          ;liver [ref 733]
;compartment tissue blood volume fraction
       wfb0                  =             0.050         ;adipose tissue    [same as rat]
       wreb0                 =             0.030         ;rest of the body  [same as rat]
       wlib0                 =             0.266         ;liver            [same as rat]
;cardiac output constant (qc) equation
       qcc                   =      15.36         ;[l/kg.h]  ref emond et al 2004
;fraction of total lipid compartment (unitless), data from emond's thesis 2001
       ftotlip               =      0.8000        ;adipose tissue
       btotlip               =      0.0057        ;blood
       retotlip              =      0.0190        ;rest of the body
       litotlip              =      0.0670               ; liver
       meanlipid             =      974.0
       male                  =      0.0                  ;(1) if male and (0) if female
       female                =      1.0                  ;(0) if male and (1) if female
{end of the initial section}



{dynamic}
;timelimit  = 0.0     ;simulation limit time (hour)
       y0                    =       21            ;age (years) at beginning of simul.
       growon                =       1.0           ;gives body weight/height growth
       day                   =      time/24        ;time in hour
       week                  =      time/168       ;time in term of week
       month                 =      time/730       ;time in term of month
       yearage               =      y0+time/8760   ;time in term of year including age
            timeyear         =       time/8760     ;time in term of year
       gyr                   =      y0+growon*(time/8760) ;time in term of year



{derivative, resolution differentials equations}

       b                     =      1.0-a                      ;portal fraction absoption of
dioxin in liver


;parametre corporelle growth up equation, body weight human
;polynomial regression expression write with april 10 2008 optimized with data of pelekis(2001)
;polynomial regression expression write with c huh1 and we bolch1,2 phys. med. biol. 48 (2003)
;reference
;pelekis, m., nicolich, m. j., and gauthier, j. s. (2003). probabilistic framework for the
;estimation of the adult and child toxicokinetic intraspecies uncertainty factors. risk anal
;23(6), 1239-1255

       wt0female      = female* (0.0006*gyr**3 - 0.0912*gyr**2 + 4.3200*gyr + 3.6520)
                        ;equation for female, name changed from "wt0_female"
       wt0male        =  male*(0.00058*gyr**3 - 0.0948*gyr**2 + 4.8434*gyr + 2.2785)
                        ;equation for male, name changed from "wt0_male"
       wt0            = wt0female + wt0male         ;equation changed accordingly
;adipose tissue fraction
       wt0gr          = wt0*1.0e3                   ;body weight in grams

;body mass index calculation
       bh             =  -2e-5*gyr**4+4.2e-3*gyr**3.0-0.315*gyr**2.0+9.7465*gyr+72.098
                                    ;height form 0 to 70 years
```

```
       bhm            = (bh/100.0)          ;human height in meter (bhm)
       hbmi           = wt0/(bhm**2.0)              ;human body mass index (bmi)

;fat fraction was modify to discriminated between male and female
;luecke, r. h., pearce, b. a., wosilait, w. d., slikker, w., and young, j. f. (2007).
;postnatal   growth considerations for pbpk modeling. journal of toxicology
;and environmental health, part a 70(12), 1027-1037.
;and we add the male equation and another to sum both equation depending we consider male or
female.

;equation for female
       wf0female = female*(-6.36e-20*wt0gr**4.0 +1.12e-14*wt0gr**3.0 -5.8e-10*wt0gr**2.0 +1.2e-
5*wt0gr+5.91e-2)
                                                  ;equation for male
       wf0male = male*(-5.26e-20*wt0gr**4.0 +1.09e-14*wt0gr**3.0 -6.99e-10*wt0gr**2.0 +1.59e-
5*wt0gr+3.95e-2)

       wf0            =   wf0female + wf0male  ; fraction of adipose tissue (unitless)

;liver,volume, approach use according to the luecke paper (2007)
       wli0           =  (3.59e-2 -(4.76e-7*wt0gr)+(8.50e-12*wt0gr**2.0)-(5.45e-17*wt0gr**3.0))
       wre0           =       (0.91 -(wlib0*wli0+wfb0*wf0+wli0+wf0))/(1.0+wreb0)
                                                  ;rest of the body fraction; change made per
kk instructions
       qref                   =       1.0-(qff+qlif)       ;rest of the body (unitless)
       qttqf                  =       qff+qref+qlif       ;sum must equal to 1

;compartment volume (l or kg)
       wf                     =       wf0  * wt0                          ;adipose
       wre                    =       wre0 * wt0                          ;rest of the body
       wli                    =       wli0 * wt0                          ;liver
       ;wb                    =       0.075*wt0

;compartment tissue blood (l or kg)
       wfb                    =       wfb0  * wf                          ;adipose
       wreb                   =       wreb0 * wre                         ;rest of the body
       wlib                   =       wlib0 * wli                         ;liver
            wt_blood                          =          wfb+wreb+wlib
            wtot =wf+wre+wli

;cardiac output in relation with (wt0)
       qc                     =       qcc*(wt0**0.75)     ;[l blood/hour]
       qf                     =       qff*qc              ;adipose tissue blood flow rate [l/hr]
       qli                    =       qlif*qc             ;liver tissue blood flow rate [l/hr]
       qre                    =       qref*qc             ;re tissue blood flow rate [l/hr]
       qttq                   =       qf+qre+qli

;permeability organ flow [l/hr]
       paf                    =       paff*qf             ;adipose
       pare                   =       paref*qre           ;rest of the body
       pali                   =       palif*qli           ;liver tissue

;absorption section by intravenous, orale, one dose multidose acute, subchronic and chronic
exposure
       iv                     =       doseivnm * wt0      ;amount in nmol
       msttbckgr              =       mstotnmbckgr *wt0    ;amount in (nmol)
       mstt                   =       mstotnm * wt0        ;amount in (nmol)

;repetitive oral background exposure scenarios
       exposurebg              =      (mod(time,freqexpbg)<dt)
                              ; determine whether exposed or not at the current time
       startexposurebg        =       if  time <= bcktimeon then 0.0 else 1.0
       stopexposurebg         =       if  time <= bcktimeoff then 1.0 else 0.0
       cycleexpbg             =       startexposurebg*stopexposurebg*exposurebg
       msttchbg               =          startexposurebg*stopexposurebg*exposurebg*msttbckgr
;exposed dose
            msttfrbg                  =          msttchbg/dt

;conditional oral exposure
       absmsttbg              =       if msttchbg=msttbckgr then msttfrbg else 0.0
```

```
;repetitive oral main exposure scenario
             exposure         =       if mod(time,freqexp)< dt then 1 else 0.0
                                      ;determine whether exposed or not at the current time
         startexposure        =              if  time <= exptimeon then 0.0 else 1
         stopexposure         =              if  time <= exptimeoff then 1 else 0.0
         cycleexp             =          startexposure *stopexposure*exposure
         msttch               =          startexposure*stopexposure*exposure*mstt
                                                                    ;exposed dose
         msttfr               =          mstt/dt

;conditional oral exposure
        absmstt               =       if msttch=mstt then msttfr else 0.0
;amount change in the lumen
        mst'                  =       -(kst+kabs)*mst+absmstt +absmsttbg
                                      ;rate of change (nmol/h), equation changed accordingly
        init    mst           =       0       ;amount remain in git(nmol)

;absorption in lymph circulation
        lymlum'               =       kabs*mst*a
        init    lymlum =      0

;absorption in portal circulation
        limlum'               =       kabs*mst*b
        init    limlum        =       0

;decribed % dose remainning in the gi tract
        prctremaingit         =       100.0*mst/(mstt+1e-30)


;iv absortpion scenario
;turn dose on/off

ivinject                      =       dt             ; time of injection (hour)

turnoffiv = if time < ivinject then 1.0 else 0.0

            vdose             =       iv/ivinject * turnoffiv
             expiv'           =       (step(vdose,time))
         init   expiv         =       0.0



        cb                    =       (qf*cfb+qre*creb+qli*clib+expiv'+lymlum')/(qc+cluri)
                                              ;equation changed accordingly
        ca                    =       cb                          ;concentration (nmol/l)

;urinary excretion
        auri'                 =       cluri *cb
        init auri             =       0.0

;concentration unit
        prctb                 =       100.0*cb/(mstt+1e-30)    ;of dose/kg
             cbsngkgliadj     =       cb*mw/(0.55*btotlip)    ;serum conc in lipid adjust (pg/g)
        auccbsngkgliadj'      =       cb*mw/(0.55*btotlip)     ;serum conc in lipid adjust (pg/g)
        cbppt                 =       cbsngkgliadj             ;equation changed accordingly
        cbngkg                =       cb*mw
        cbpptrh               =       cb*mw*10000/(0.55*meanlipid)
                                      ;serum concentration in lipid adjust (pg/g lipid=ppt)
        init    auccbsngkgliadj       =       0.0

;adipose tissue compartment
        afb'                  =       qf*(ca-cfb)-paf*(cfb-cf/pf)          ;(nmol/hr)
        init    afb           =       0                                    ;(nmole)
                cfb           =       afb/wfb                              ;(nmole/kg)
;tissue subcompartment, modification on nov 5 2009
                af'           =       paf*(cfb-cf/pf)                             ;(nmol/hr)
        init    af            =       0                                    ;(nmole)
                cf            =       af/wf                                       ;(nmol/kg)

;post simulation unit conversion
```

```
               cftotal               =      (af + afb)/(wf + wfb) ;total concentration in
nmol/ml
               prctf          =      100.0*cftotal/(mstt+1e-30)
               cfngkg         =      cftotal*mw

;rest of the body compartment
       areb'                  =      qre*(ca-creb)-pare*(creb-cre/pre)    ;(nmol/hr)
       init    areb           =      0                                    ;(nmole)
               creb           =      areb/wreb                            ;(nmol/kg)

;tissue subcompartment
       are'                   =      pare*(creb-cre/pre)                  ;(nmol/hr)
       init    are            =      0                                  ;(nmole)
               cre            =      are/wre                              ;(nmol/kg)

;post simulation unit conversion
               cretotal       =      (are + areb)/(wre + wreb)   ;total conc. in nmol/ml
               prctre         =      100.0*cretotal/(mstt+1e-30)
crengkg                       =      cretotal*mw


;liver compartment
;tissue blood subcompartment
       alib'                  =      qli*(ca-clib)-pali*(clib-cfllir)+limlum'     ;(nmol/hr)
       init    alib           =      0                                            ;(nmole)
               clib           =      alib/wlib                                    ;(nmoL/kg)
       ali'                   =      pali*(clib-cfllir)-excli'                    ;(nmol/hr)
       init    ali            =      0                                            ;(nmole)
               cli            =      ali/wli                                      ;(nmol/kg)


;free tcdd in liver

       cfllir'                       =      cli-
(cfllir*pli+(libmax*cfllir/(kdli+cfllir))+((cyp1a21o3*cfllir/(kdli2+cfllir)*pasinduc)))-cfllir
               init cfllir    =      cflli0
               cbndli         =      (libmax*cfllir)/(kdli+cfllir)               ;conc bound


;post simulation unit conversion
               clitotal       =      (ali + alib)/(wli + wlib)            ;total conc. in nmol/l
               prctli         =      100.0*clitotal/(mstt+1.0e-30)
       recoccahr      =      100.0*cfllir/(kdli+cfllir+1.0)       ;% of ahr occupancy
       protocc1a2     =      100.0*cfllir/(kdli2+cfllir)          ;% of 1a2 occupancy,
               clingkg        =      clitotal*mw                          ;[ng tcdd/kg]
               cbndlingkg     =      cbndli*mw


;fraction increase of induction of cyp1a2
               foldind        =      cyp1a21out/cyp1a21a2
               variationofac  =      (cyp1a21out-cyp1a21a2)/cyp1a21a2

;variable elimination based on the cyp1a2
               kbilelit       =      kelv*variationofac
               excli'         = kbilelit*cfllir*wli
       init    excli          =      0.0

;chemical in cyp450 (1a2) compartment, parameter for induction of cyp1a2
       cyp1a21kinp            = cyp1a21kout*cyp1a21outz
               cyp1a21out'            = cyp1a21kinp * (1.0 + cyp1a21emax *(cbndli+1.0e-30)**hill
                              /(cyp1a21ec50**hill + (cbndli+1.0e-30)**hill))
                              - cyp1a21kout*cyp1a21out
       init    cyp1a21out     =      cyp1a21outz                                  ;

       cyp1a21o2'             =      (cyp1a21out - cyp1a21o2)/ cyp1a21tau         ;
init   cyp1a21o2              =      cyp1a21a1                                    ;
       cyp1a21o3'             =      (cyp1a21o2 - cyp1a21o3)/ cyp1a21tau          ; changed from
"cyp1a2_1o3'", equation changed accordingly
       init    cyp1a21o3      =      cyp1a21a2                                    ;

;control mass balance
```

```
       bdose                 =       lymlum+limlum+expiv
       bmasse                =       excli+auri+afb+af+areb+are+alib+ali
       bdiff                 =       bdose-bmasse

;body burden in term of (ng/kg)
       aucbbngkg'            =       (afb+af+areb+are+alib+ali)*mw/wt0          ;
       init    aucbbngkg     =       0                                          ;

       bb                    =       (afb+af+areb+are+alib+ali)*mw              ;(amount ng)

{end of the derivative section}
{end of the dynamic section}
{end of program}
```