Supplemental Material

**Berkeley Madonna code**

The code (given below) is based on the works by Diamond, Choudhury, Khoury and others (Choudhury et al 2001; Diamond et al. 2003, Khoury and Diamond 2003), who essentially combined the Kjellström and Nordberg cadmium model (Kjellström and Nordberg 1978; Kjellström and Nordberg 1985) with a model for lead biokinetics (Leggett 1993; Pounds and Leggett, 1998). The eight-compartment model was implemented in the Berkeley Madonna (version 8.3) software.

```
STARTTIME = 0
STOPTIME=365*80
DT = 1
DY = 365
DTOUT = 365/12 ;print result monthly
YEARS = TIME/DY ;conversion from days to years
 ;units are L for volume, kg for weight (i.e. density=1), days for time, µg for cadmium amount, µg/g creatinine for urinary excretion

;------------------------------------------GROWTH------------------------------------------
W = Wb + Wc*YEARS/(H+YEARS) + Wa/(1+K*EXP(-L*Wa*YEARS)) ;growth curve
Wb = 3.5 ;weight at birth
Wc = 22 ;weight of child at max growth rate, 22 kg for females, 23 kg for males
Wa = 3 ;weight at adulthood, 34 kg for females, 50 kg for males
H = 3 ;age when weight is half Wc
K = 600 ;empirically fit logistic constant
L = 0.017 ;idem, 0.017 for females, 0.0095 for males

Wbl = VCbl*W ;blood mass (kg)
Wrbc = VCrbc*Wbl ;red blood cells (kg)
Wki = VCKi*(Wb+Wc)*(W/(Wb+Wc))^(0.85) ;kidney mass (kg)
Wli = VCLI*(Wb+Wc)*(W/(Wb+Wc))^(0.85) ;liver mass (kg)

VCbl = 0.067
VCrbc = 0.42

VCKi = 0.0045
VCLI = 0.025

LBM = W*VCblm ;lean body mass
VCblm = 0.85 ;0.85 for females, 0.88 for males
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\[
CRur = \frac{(LBM/0.0272 - 8.58)}{1000} \quad \text{creatinine excretion (g/day)}
\]

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### ORAL ABSORPTION

- **WKDOSE = 1.5** \(\mu g/\text{kg bw/wk}\)
- **_INGEST = WKDOSE \times 7 \times W** \(\mu g/\text{day}\)
- **AF1 = 0.1** \(\text{fraction available for absorption, e.g. 0.1 for females, 0.05 for males}\)
- **YSTMC' = INGEST - AGSCAL \times RSTMC \times YSTM** \(\mu g/\text{day}\)
- **INIT YSTM = 0** \(\text{initial amount of Cadmium in stomach at birth (µg)}\)
- **RSTMC = 24** \(\text{basal rate of stomach emptying (day-1)}\)
- **AGSCAL = GRAPH (YEARS) (0, 1.66667) (10, 1.66667) (15, 1.33333) (90, 1)**
- **YSIC' = AGSCAL \times RSTMC \times YSTM + H1TOS1 \times RLVR1 + YLVR1 + TOFECE \times CF \times RPLS \times YPLS - AGSCAL \times RISIC \times YSIC** \(\mu g/\text{day}\)
- **INIT YSIC = 0** \(\text{initial amount of Cadmium in small intestine birth (µg)}\)
- **RISIC = 6** \(\text{transfer rate (day-1)}\)
- **YULI' = AGSCAL \times (1 - AF1) \times RULI \times YULI** \(\mu g/\text{day}\)
- **INIT YULI = 0** \(\text{initial amount of Cadmium in upper large intestine birth (µg)}\)
- **RULI = 1.85** \(\text{transfer rate (day-1), taken from AALM}\)
- **YLLI' = AGSCAL \times (1 - AF1) \times RULI \times YULI** \(\mu g/\text{day}\)
- **INIT YLLI = 0** \(\text{initial amount of Cadmium in lower large intestine birth (µg)}\)
- **RLLI = 1** \(\text{transfer rate (day-1)}\)

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### RED BLOOD CELL COMPARTMENT

- **YRBC' = RBCin - ARRBC \times YRBC** \(\mu g/\text{day}\)
- **RBCin = YPLS \times RPLS \times TORBC \times CFRBC** \(\mu g/\text{day}\)
- **RPLS = RPLAS \times TOSUM**
- **RPLAS = 2000** \(\text{default value (day-1)}\)
- **TOSUM = TORBC + TOEVF + TOPROT + TOURIN + TOFECE + TOLVR1 + TOKDN1 + TOKDN2 + TOSOF1**
- **TORBC = 0.05** \(\text{fraction transferred to red blood cells}\)
- **CFRBC = IF RBCONC < RBCNL THEN TORBC ELSE TORBC*(1 - (RBCONC - RBCNL)/(SATRAT - RBCNL))^POWER** \(\mu g/\text{day}\)
- **RBCONC = YRBC/Wrbc** \(\mu g/\text{day}\)
- **RBCNL = 60** \(\mu g/mL\)
- **SATRAT = 350** \(\mu g/mL\)
- **POWER = 1.5** \(\text{unitless}\)
- **INIT YRBC = 0** \(\text{initial amount of Cadmium at birth (µg)}\)

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### EXTRAVASCULAR FLUID COMPARTMENT
EVFin = YPLS*RPLS*TOEVF*CF ; transfer from plasma to extravascular fluid (µg/d)

TOEVF = 0.5 ; fraction transferred to extravascular fluid

CF = (1-TORBC*CFRBC)/(1-TORBC) ; correction factor

YEVF = YPLS*RPLS*TOEVF*CF - REVF*YEVF ; change in amount of Cadmium in extravascular fluid (µg/d)

INIT YEVF = 0 ; initial amount of Cadmium at birth (µg)

REVF = TOEVF*RPLS/SIZEVF

SIZEVF = 3

;-----------------------------------PLASMA PROTEIN COMPARTMENT-----------------------------------

YPROT' = YPLS*RPLS*TOPROT*CF - RPROT*YPROT ; change in plasma protein bound Cadmium (µg/d)

INIT YPROT = 0 ; initial amount of Cadmium at birth (µg)

TOPROT = 0.0002 ; fraction transferred to bound plasma

RPROT = 0.07 ; rate constant from bound protein

;-----------------------------------BLADDER COMPARTMENT---------------------------------------

URINin = YPLS*RPLS*TOURIN*CF ; transfer from plasma to bladder (µg/d)

TOURIN = 0.000026 ; fraction transferred to bladder

;-------------------------------------FECAL COMPARTMENT------------------------------------------

FECEin = YPLS*RPLS*TOFECE*CF ; transfer from plasma to small intestine (µg/d)

TOFECE = 0.000055 ; fraction transferred to small intestine

;----------------------------------OTHER SOFT TISSUES COMPARTMENT----------------------------------

YSOF1' = YPLS*RPLS*TOSOF1*CF - RSOF1*YSOF1 ; change in amount of Cadmium in extravascular fluid (µg/d)

TOSOF1 = 0.000022 ; fraction transferred to red blood cells

INIT YSOF1 = 0 ; initial amount of Cadmium at birth (µg)

RSOF1 = 0.00014 ; rate constant from other soft tissues

;----------------------------------PLASMA COMPARTMENT------------------------------------------

YPLS' = PLSin - PLSout ; change in Cadmium in plasma (µg/d)

PLSin = RPROT*YPROT + ARRBC*YRBC + REVF*YEVF + RSOF1*YSOF1 +

HITOB1*RLVR1*YLVR1 + ARKDN2*YKDN2 + AF1*AGSCL*RSIC*YSIC

; transfer from all other compartments to plasma (µg/day)

PLSout = YPLS*RPLS*TORBC*CFRBC + YPLS*RPLS*TOEVF*CF +

YPLS*RPLS*TOPROT*CF + URINin + FECEin + YPLS*RPLS*TOFECE*CF +

YPLS*RPLS*TOLVR1*CF + YPLS*RPLS*TOKDN1*CF + YPLS*RPLS*TOKDN2*CF + YPLS*RPLS*TOSOF1*CF

; transfer from plasma to all other compartments

INIT YPLS = 0 ; initial amount of Cadmium in plasma at birth (µg)

ARRBC = GRAPH (YEARS) (0,0.461) (1,0.462) (5,0.277) (10,0.139) (90,0.139)

ARKDN2 = GRAPH (YEARS) (0,0.000006) (25,0.000006) (30, 0.00008) (40,0.00012)

(60,0.00018) (90,0.00018)

; transfer rate constant from "other" kidney tissue to kidney tissue associated with urinary excretion
\[ YLVR1' = YPLS \times RPLS \times TOLVR1 \times CF - YLVR1 \times RLVR1 \times (H1TOBL + H1TOSI) \]

change in Cadmium in liver (µg/d)

\[ TOLVR1 = 0.094 \] ;fraction transferred to liver

\[ INIT YLVR1 = 0 \] ;initial amount of Cadmium in liver at birth (µg)

\[ RLVR1 = 0.00014 \] ;rate constant from liver

\[ H1TOBL = 0.4 \] ;fraction going to plasma

\[ H1TOSI = 0.6 \] ;fraction going to small intestine

\[ YKDN1' = YPLS \times RPLS \times TOKDN1 \times CF - YKDN1 \times RKDN1 \] ;change in Cadmium in kidney (µg/d)

\[ TOKDN1 = 0.000022 \] ;fraction transferred to kidney - urinary pathway

\[ INIT YKDN1 = 0 \] ;initial amount of Cadmium in kidney at birth (µg)

\[ RKDN1 = 1 \] ;default value for all ages

\[ YKDN2' = YPLS \times RPLS \times TOKDN2 \times CF - YKDN2 \times (RKDN2 + ARKDN2) \]

RKDN2 represents the rate coefficient for transfer from the OTHER KIDNEY compartment to PLASMA

\[ TOKDN2 = 0.13 \] ;fraction transferred to other kidney tissues

\[ INIT YKDN2 = 0 \] ;initial amount of Cadmium in kidney at birth (µg)

\[ RKDN2 = 0.00001 \] ;rate constant from other kidney tissue

\[ \text{Ar bladder compartment} \]

\[ YBLAD' = YKDN1 \times RKDN1 + TOURIN \times RPLS \times YPLS \times CF_{BLAD} - YBLAD \times ARBLAD \]

\[ CF_{BLAD} = CF \]

\[ INIT YBLAD = 0 \] ;initial amount of Cadmium in bladder at birth (µg)

\[ ARBLAD = \text{GRAPH} \text{ (YEARS)} (0,12) (0.274,12) (1,15) (5,11) (10,8) (15,7) (90,7) \]

\[ \text{transfer rate constant rate from bladder to urine} \]

\[ UEX = YBLAD \times ARBLAD \] ;excretion in urine (µg/d)

\[ UEXCR = UEX \div CR Ur \] ;excretion in urine (µg/g creatinine)

\[ \text{KIDNEY} = (YKDN1 + YKDN2) \div Wk1 / 1000 \] ;average concentration in kidney (µg/g)

\[ \text{References} \]


