Physiologically based pharmacokinetic model

ODE system : Coefficients

```
HumanPBK.code <- '
$PARAM @annotated
QCC                 :  12.500   : L/h/kg^0.75, Cardiac output (Brown 1997, Forsyth 1968)
QLC                 :   0.250   : Fraction blood flow to liver (Brown 1997, Fisher 2000)
QKC                 :   0.175   : Fraction blood flow to kidney (Brown 1997, Forsyth 1968)
Htc                 :   0.44    : Hematocrit for human; ICRP Publication 89 (2003)
BW                  :  82.3     : kg, Bodyweight (EPA Factors Handbook, 2011)
VLC                 :   0.026   : Fractional liver tissue (Brown 1997)
VKC                 :   0.004   : Fractional kidney tissue (Brown 1997)
VPlasC              :   0.0428  : L/kg BW, Fractional plasma (Davies 1993)
VfilC               :   4.0e-4  : L/kg BW, Fraction vol. of filtrate
VPTCC               :   1.35e-4 : L/kg kidney, Vol. of proximal tubule cells (60 million PTC cells/gram kidney, 1 PTC = 2250 um3)
FVBK                :   0.160   : Blood volume fraction of kidney (Brown, 1997)
PL                  :   2.67    : Liver/plasma PC; (from human cadaver data, Fabrega, 2014)
PK                  :   1.26    : Kidney/plasma PC; (from human cadaver data, Fabrega, 2014)
PRest               :   0.2     : Restofbody/plasma PC; (from mouse tissue data, Loccisano, 2011)
MW                  : 500.126   : g/mol, PFOS molecular mass
MKC                 :   0.0084  : Fraction mass of kidny (percent of BW); Brown, 1997
Free                :   0.025   : Free fraction of PFOS in plasma (Luccisanno et al., 2011)
Vmax_baso_invitro   : 439.20    : pmol/mg protein/min, Vmax of basolateral transporter; averaged in vitro value of rOAT1 and rOAT3 (Nakagawa, 2007)
Km_baso             : 20100     : ug/L, Km of basolateral transpoter, averaged in vitro value of rOAT1 and rOAT3 (Nakagawa, 2007)
Vmax_apical_invitro : 37400     : pmol/mg protein/min, Vmax of apical transporter; averaged invitro value of Oatp1a1 (Weaver, 2010)
Km_apical           : 77500     : ug/L, Km of apical transpoter, in vitro value for Oatp1a1 (Weaver, 2010)
RAFbaso             :   1       : Relative activity factor, basolateral transpoters (male) (fit to data); 0.01356 (female)
RAFapi              : 0.0007    : Relative acitivty factor, apical transpoters (fit to data); 0.001356 (female)
protein             :  2.0e-6   : mg protein/proximal tubuel cell, Amount of protein in proximal tubule cells
GFRC                :  24.19    : L/hr/kg kiney, Glomerular filtration rate (male); 41.04 (female) (Corley, 2005)
Kdif                :   0.001   : L/h, Diffusion rate from proximal tubule cells
Kabsc               :   2.120   : 1/(h*BW^0.25), Rate of absorption of chemical from small intestine to liver (fit to data)
KunabsC             : 7.06e-5   : 1/(h*BW^0.25), Rate of unabsorbed dose to appear in feces (fit to data)
GEC                 :   3.500   : 1/(h*BW^0.25), Gastric emptying time (Yang, 2013)
K0C                 :   1.000   : 1/(h*BW^0.25),  Rate of uptake from the stomach into the liver (fit to data)
KeffluxC            :   0.100   : 1/(h*BW^0.25), Rate of clearance of PFOS from proximal tubule cells into blood
KbileC              :   0.0001  : 1/(h*BW^0.25), Biliary elimination rate (male); liver to feces storage (fit to data)
KurineC             :   0.063   : 1/(h*BW^0.25), Rate of urine elimination from urine storage (male) (fit to data)
Kvoid               : 0.06974   : (L/hr), Daily urine volume rate (L/hr); Van Haarst, 2004
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Physiologically based pharmacokinetic model

ODE system : Algebraic relationships between parameters

```
$MAIN
double QC = QCC*pow(BW, 0.75)*(1-Htc);          // L/h, Cardiac output (adjusted for plasma)
double QK = QKC*QC;                             // L/h, Plasma flow to kidney
double QL = QLC*QC;                             // L/h, Plasma flow to liver
double QRest = QC-QK-QL;                        // L/h, Plasma flow to the rest of body
double QBal = QC-(QK+QL+QRest);                 // L/h, Balance check of blood flows

double VL = VLC*BW;                             // kg, Liver
double VK = VKC*BW;                             // kg, Kidney
double VPlas = VPlasC*BW;                       // kg, Plasma
double Vfil = VfilC*BW;                         // kg (L), Filtrate compartment
double VPTC = VK*VPTCC*1000;                    // kg (L), proximal tubule cells
double VKb = VK*FVBK;                           // kg, blood in Kidney
double VRest = (0.93*BW)-VL-VK-VPlas-VPTC-Vfil; // Rest of body
double ML = VL*1.05*1000;                       // g, liver weight in gram
double MK = VK*1*1000;                          // g, kidney weight in gram

double PTC = MKC*6e7*1000;                      // cells/kg BW, Number of PTC (cells/kg BW) (based on 60 million PTC/gram kidney,Hsu et al., 2014); Revised original equation (PTC = MKC*6e7) from Worley et al. (2015)
double MPTC = VPTC*1000;                        // g, mass of the proximal tubule cells (assuming density 1 kg/L)
double Vmax_basoC = (Vmax_baso_invitro*RAFbaso*PTC*protein*60*(MW/1e12)*1000000);    // mg/h/kg BW^0.75, Vmax of basolateral transporters (average Oat1 and Oat3)
double Vmax_apicalC = (Vmax_apical_invitro*RAFapi*PTC*protein*60*(MW/1e12)*1000000); // mg/h/kg BW^0.75, Vmax of apical transpoters in in vitro studies (Oatp1a1)
double Vmax_baso = Vmax_basoC*pow(BW,0.75);       // mg/h
double Vmax_apical = Vmax_apicalC*pow(BW,0.75);   // mg/h
double Kbile = KbileC*pow(BW,(-0.25));            // 1/h, Biliary elimination, liver to feces storage
double Kurine = KurineC*pow(BW,(-0.25));          // 1/h, Urinary elimination; from filtrate
double Kefflux = KeffluxC*pow(BW,(-0.25));        // 1/h, Efflux clearance rate from PTC to blood
double GFR = GFRC* VK;                            // L/h, Glomerular filtration rate, scaled to mass of kidney

//GI tract parameters
double Kabs = Kabsc*pow(BW,(-0.25));     // 1/h, rate of absorption of chemical from small intestine to liver
double Kunabs = KunabsC*pow(BW,(-0.25)); // 1/h, rate of unabsorbed dose to appear in feces
double GE = GEC*pow(BW,(-0.25));         // 1/h, Gasric emptying time
double K0 = K0C*pow(BW,(-0.25));         // 1/h, Rate of uptake from the stomach into the liver
```