Physiologically based pharmacokinetic model

ODE system : Algebraic relationships between parameters

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$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
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Physiologically based pharmacokinetic model

ODE system : Time varying state

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// Concentrations in the tissues and in the capillary blood of the tissues
double CA_free = APlas_free/VPlas;        // mg/L, Free PFOSC concentration in the plasma
double CA = CA_free/Free;                 // mg/L, Concentration of total PFOS in plasma

double CL = AL/VL;                        // mg/L, Concentration of parent drug in the tissue of liver
double CVL = CL/PL;                       // mg/L, Concentration of parent drug in the capillary blood of liver

double CKb = AKb/VKb;                     // mg/L, Concentration of PFOS in Kidney blood
double CVK = CKb/PK;
double CK = CVK*PK;                       // mg/L, Concentration of PFOS in Kidney compartment

double CRest = ARest/VRest;               // mg/L, Crest drug concentration in the rest of the body (mg/L)
double CVRest = CRest/PRest;              // mg/L, Concentration of parent drug in the capillary blood of the rest of body

// Kidney compartment plus 2 subcompartment (Proximal Tubule cells: PTC, Filtrate: Fil)
// Concentration in kidney, PTC and fil

double CPTC = APTC/VPTC;                  // mg/L, Concentration of PFOS in PTC blood
double Cfil = AFil/Vfil;                  // mg/L, Concentration of PFOS in FIL blood

// Virtual compartment:
// Basolateral transport : (baso)
// Diffusion             : (dif)
// Apical transport      : (apical)
// efflux clearance      : (efflux)
// Clearance via glormerular filtration (CL)

double RA_baso = (Vmax_baso*CKb)/(Km_baso+CKb);            // mg/h, Rate of basolateral transporters
dxdt_A_baso = RA_baso;                                     // mg, Amount of basolateral transporters
double RA_apical = (Vmax_apical*Cfil)/(Km_apical + Cfil);  // mg/h, Rate of apical transporter
dxdt_A_apical = RA_apical;                                 // mg, Amount of apical transporter
double Rdif = Kdif*(CKb - CPTC);                           // mg/h, Rate of diffusion from into the PTC
dxdt_Adif = Rdif;                                          // mg, Amount moved via glomarular filtration
double RAefflux = Kefflux*APTC;                            // mg/h, Rate of efflux clearance rate from PTC to blood
dxdt_Aefflux = RAefflux;                                   // mg, Amount of efflux clearance rate from PTC to blood
double RCI = CA*GFR*Free;                          // mg/h, Rate of clearance (CL) to via glormerular filtration (GFR)
dxdt_ACI = RCI;                                            // mg, Amount of clearance via GFR
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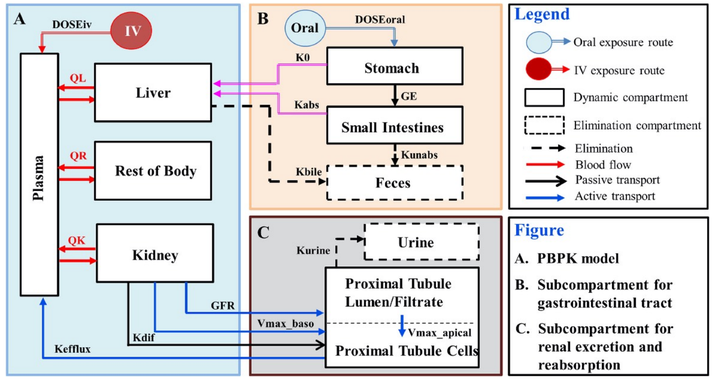


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// PFOS in plasma
double RPlas_free = (QRest*CVRest*Free)+(QK*CVK*Free)+(QL*CVL*Free)-(QC*CA*Free)+RAefflux; // mg/h, Rate of change in the plasma
double RPlas = (QRest*CVRest)+(QK*CVK)+(QL*CVL)-(QC*CA);
dxdt_APlas_free = RPlas_free;                          // mg, Amount in the plasma
dxdt_APlas = RPlas;                                    // mg, Amount in the plasma
dxdt_AUCCA_free = CA_free;                             // mg*h/L, Area under curve of PFOS in liver compartment

// Proximal Tubule Cells (PTC)
double RPTC = Rdif + RA_apical + RA_baso - RAefflux; // mg/h, Rate of change in PTC
dxdt_APTC = RPTC;                                      // mg, Amount moved in PTC
dxdt_AUCCPTC = CPTC;                                   // mg*h/L, Area under curve of PFOS in the compartment of PTC

// Proximal Tubule Lumen/ Filtrate (Fil)
double Rfil = CA*GFR*Free - RA_apical - AFil*Kurine; // mg/h, Rate of change in Fil
dxdt_AFil = Rfil;                                      // mg, Amount moved in Fil
dxdt_AUCfil = Cfil;                                    // mg*h/L, Area under curve of PFOS in the compartment of Fil

// Urine elimination
double Rurine = Kurine*AFil;                           // mg/h, Rate of change in urine
dxdt_Aurine = Rurine;                                  // mg, Amount in urine
double Curine = Rurine/Kvoid; //

// Kidney compartment
double RKb = QK*(CA-CVK)*Free - CA*GFR*Free - Rdif - RA_baso; // mg/h, Rate of change in Kidney compartment
dxdt_AKb = RKb;                                                // mg, Amount in kidney compartment
dxdt_AUCKb = CK;                                               // mg*h/L, Area under curve of PFOS in the Kidney compartment

// PFOS in the compartment of rest of body, flow-limited model
double RRest = QRest*(CA-CVRest)*Free;                 // mg/h, Rate of change in rest of body
dxdt_ARest = RRest;                                    // mg, Amount in rest of body
dxdt_AUCCRest = CRest;                                 // mg*h/L, Area under curve of PFOS in the compartment of rest of body

// Gastrointestinal (GI) tract
// Stomach compartment
double RST = - K0*AST - GE*AST;                        // mg/h, Rate of chagne in Stomach compartment
dxdt_AST = RST;                                        // mg, Amount in Stomach
double RabsST = K0*AST;                                //  mg/h, Rate of absorption in the stomach
dxdt_AabsST = RabsST;                                  // mg, Amount absorbed in the stomach

// Small intestine compartment
double RSI = GE*AST - Kabs*ASI - Kunabs*ASI;           // mg/h, Rate of chagne in Small intestine compartment
dxdt_ASI = RSI;                                        // mg, Amount in Small intestine
double RabsSI = Kabs*ASI;                              // mg/h, Rate of absorption in the Small intestine
dxdt_AabsSI = RabsSI;                                  // mg, Amount absorbed in the Small intestine
double Total_oral_uptake = AabsSI + AabsST;            // mg, Total oral uptake in the GI

// Biliary excretion
double Abile = Kbile*AL;                               // mg, Amount of PFOS in bile excretion
double amount_per_gram_liver = (AL/ML)*1000;           // ug/g, Amount of PFOS in liver per gram liver

// Feces compartment
double Rfeces = Kbile*AL+ Kunabs*ASI;                  // mg/h, Rate of change in feces compartment
dxdt_Afeces = Rfeces;                                  // mg, Amount of the feces compartment

// PFOS in liver compartment, flow-limited model
double RL = QL*(CA-CVL)*Free - Kbile*AL + Kabs*ASI + K0*AST; // mg/h, Rate of chagne in liver compartment
dxdt_AL = RL;                                                // mg, Amount in liver compartment
dxdt_AUCCL = CL;                                             // mg*h/L, Area under curve of PFOS in liver compartment
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