Preliminary model calibration

- 1st goal : fix non-sensitive parameters
- 2nd goal : estimate prior distribution for the parameters
  - Fit ODE model for sensitive parameters to a “calibration” data sets via optimisation

Table 1
Pharmacokinetic studies in rats, mice, monkeys, and humans used for model development and evaluation.

Reference	Dose regimen	Matrix	Cal	Opt	Eva
Sprague Dawley rat					
3M unpublished data	Single oral dose at 2 mg/kg	Plasma	X		
Chang et al. (2012)	Single oral dose at 4.2 mg/kg	Plasma	X		
Johnson et al. (1979)	Single IV dose at 4.2 mg/kg	Urine	X		
Kim et al. (2016)	Single oral dose at 2 mg/kg	Plasma	X		
Kim et al. (2016)	Single IV dose at 2 mg/kg	Plasma		X	
3M unpublished data	Daily oral dose at 1 mg/kg for 4 weeks	Plasma		X	
3M unpublished data	Single oral dose at 15 mg/kg	Plasma		X	
Chang et al. (2012)	Single oral dose at 15 mg/kg	Urine		X	
Seacat et al. (2003)	Daily oral dose at 0.03, 0.13, 0.34, 1.33 mg/kg for 14 weeks	Plasma; liver			X
CD-1 mouse					
Chang et al. (2012)	Single oral dose at 20 mg/kg	Plasma; liver, kidney, urine	X		
Chang et al. (2012)	Single oral dose at 1 mg/kg	Plasma; liver, kidney, urine		X	
Cynomolgus monkey					
Chang et al. (2012)	Single IV dose at 2 mg/kg	Urine, plasma	X		
Seacat et al. (2002)	Daily oral dose at 0.03, 0.15 and 0.75 mg/kg for 26 weeks	Plasma		X	
Seacat et al. (2002)	Daily oral dose at 0.03, 0.15 and 0.75 mg/kg for 26 weeks	Liver			X
Human: general population					
Haug et al. (2009)	Unknown	Plasma	X	X	
Fabrega et al. (2014)	Unknown	Plasma; liver, kidney			X
Olsen et al. (2003a)	Unknown	Plasma			X
Olsen et al. (2003b)	Unknown	Liver			X
Olsen et al. (2008)	Unknown	Plasma			X

Note: All graphic pharmacokinetic data were extracted from selected studies using WebPlotDigitizer (version 4.10, https://automeris.io/WebPlotDigitizer/; last accessed December 28, 2018.). The 3M unpublished data were extracted from the Loccisano et al. (2012). Cal: Calibration; Opt: Optimized by MCMC algorithm; Eva: Evaluation.

Calibrated (or otherwise fixed) values

Table 2
Values of the species-specific parameters after model calibration for the mouse, rat, monkey and human.

Parameters	Symbol	Mouse	Rat	Monkey	Human
Body weight, (Kg)[a]	BW	0.025	0.3	3.5	82.3
Cardia output, (L/h/kg$^{0.75}$)[b]	QCC	16.5	14	18.96	12.5
Fractional blood flows (% QC)[b]					
Liver	QLC	0.161	0.183	0.194	0.250
Kidney	QKC	0.091	0.141	0.123	0.175
Fractional volumes (% BW)[b]					
Liver	VLC	0.055	0.035	0.026	0.026
Kidney	VKC	0.017	0.0084	0.004	0.004
Plasma	VPlasC	0.049	0.0312	0.0448	0.0428
Filtrate[c]	VfilC	0.0017	0.00084	0.0004	0.0004
Volume of PTCs, (L/g kidney)[c]	VPTCC	1.35e-4	1.35e-4	1.35e-4	1.35e-4
Amount of proteins in PTCs[d] (mg/cell)	Protein	2.0e-6	2.0e-6	2.0e-6	2.0e-6
Hematocrit[e]	Htc	0.48	0.46	0.42	0.44
Partition coefficients[f]					
Liver	PL	7.65*	3.66*	3.72	2.03*
Kidney	PK	0.8	0.8	0.8	1.26
Rest	PRest	0.23*	0.26*	0.15*	0.2
Free fraction of PFOS in plasma[g]	Free	0.02*	0.09	0.016*	0.014*
Glomerular filtration rate constant, (L/h/kg of kidney)[h]	GFRC	59	62.1	21.85	24.19
Gastric emptying rate constant, (/h/kg BW$^{0.25}$)[i]	GEC	0.54	0.54	2.34	3.51
Transporter rates[j]					
Vmax of basolateral (pmol/mg protein/min)	Vmax_baso_invitro	393.45	393.45	439.2	479*
Km of basolateral (mg/L)	Km_baso	27.2	27.2	20.1	20.1
Vmax of apical (pmol/mg protein/min)	Vmax_apical_invitro	4185*	1808*	76972*	51803*
Km of apical transporters (mg/L)	Km_api	52.3	278*	45.2*	64.4*
Relative activity factor[j]					
Apical transporters (unitless)	RAF_api	2.81*	1.90*	0.0014*	0.001*
Basolateral transporters (unitless)	RAF_baso	3.99	4.15*	1	1
Other rate constants (/h/kg BW$^{0.25}$)[j]					
Uptake from stomach to liver,	K0C	1	1	1	1
Absorption from small intestines to liver	KabsC	1.10*	2.12	2.12	2.12
Unabsorbed dose to appear in feces	KunabsC	7.05e-5	7.05e-5	7.05e-5	7.05e-5
Rate of efflux of PFOS from PTCs into blood	KeffluxC	5.60*	2.09*	0.1	0.15*
Diffusion rate from PTCs	Kdif	4.6e-5*	5.1e-4*	0.001	0.001
Biliary elimination rate	KbileC	3.9e-4*	0.0026*	7.8e-4*	1.3e-4*
Urinary elimination rate	KurineC	1.60	1.60	0.092*	0.096*

* Calibrated values were fitted (the initiate values are provided in Table S1) with experiment data using the Levenberg-Marquardt algorithm.
[a] Use measured value if available, or collected from Brown et al. (1997) for rodents and monkeys and from ICRP (2002) for humans.
[b] The baseline value was obtained from Brown et al. (1997).
[c] The baseline value was assumed to be 10% kidney volume based on Worley and Fisher (2015) and Worley et al. (2017b).
[d] The baseline value was obtained from Addis et al. (1936) and Hsu et al. (2014).
[e] The baseline value was obtained from Hejtmancik et al. (2002) (mouse); Davies and Morris (1993) (Rat); Choi et al. (2016) (Monkey); ICRP (2002) (human).
[f] Loccisano et al. (2012) (mouse and rat) and Loccisano et al. (2011) (monkey); Fabrega et al. (2014) (human).
[g] The baseline values were obtained from Loccisano et al. (2012) (mouse and rat) and Loccisano et al. (2011) (monkey and human).
[h] Qi et al. (2004) (mouse), Corley et al. (2005) (rat and human), Iwama et al. (2014) (monkey).
[i] Yang et al. (2015) (mouse, rat and human), Fisher et al. (2011) (monkey).
[j] Initiate values were assumed to be equal to those of PFOA adopted from Worley and Fisher (2015) (rat and mouse) and Worley et al. (2017b) (human and monkey), and then were re-estimated in the present model.