Advancing chemical risk assessment through human physiology-based biochemical process modeling - Supplementary material

Dimosthenis Sarigiannis [1,2,3,*] and Spyros Karakitsios [1,2,3]

[1] HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Balkan Center, Bldg. B, 10th km Thessaloniki-Thermi Road, 57001Thermi, Greece; spyros.karakitsios@gmail.com
[2] Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, University Campus, 54124 Thessaloniki, Greece
[3] Environmental Health Engineering, Department of Science, Technology and Society, University School for Advanced Study (IUSS), Piazza della Vittoria 15, 27100 Pavia, Italy
* Correspondence: denis@eng.auth.gr; Tel.: +30-2310-99-4562

Supplementary material

The following formulas are based on the formulation scheme proposed by Edginton and Ritter 2009):

For non-eliminating organs:

Red blood cells

$$V_{rbc_org}\frac{dC_{rbc_org}}{dt} = Q_{org}\cdot HCT\cdot\left(C_{rbc_art} - C_{rbc_org}\right) + PS_{rbc_org}\cdot f_u\cdot\left(C_{\text{int}_org} - \frac{C_{rbc_org}}{K_{rbc}}\right)$$

Where $V_{rbc_org} = f_{vas_org}\cdot V_{org}\cdot HCT$

Plasma +interstitial

$$V_{\text{int}_org}\frac{dC_{\text{int}_org}}{dt} = Q_{org}\cdot\left(1-HCT\right)\cdot\left(C_{pls_art} - C_{\text{int}_org}\right) - PS_{rbc_org}\cdot f_u\cdot\left(C_{\text{int}_org} - \frac{C_{rbc_org}}{K_{rbc}}\right) - PS_{cell_org}\cdot f_u\cdot\left(C_{\text{int}_org} - \frac{C_{cell_org}}{K_{org}}\right)$$

Where $V_{\text{int}_org} = V_{org}\cdot\left[f_{\text{int}_org} + f_{vas_org}\cdot\left(1-HCT\right)\right]$

Cellular

$$V_{cell_org}\frac{dC_{cell_org}}{dt} = PS_{cell_org}\cdot f_u\cdot\left(C_{\text{int}_org} - \frac{C_{cell_org}}{K_{org}}\right)$$

Where $V_{cell_org} = f_{cell_org}\cdot V_{org}$

Kidney

For kidney in BPA_Glu submodel to incorporate renal plasma clearance (CL_{pls_kid}):

Plasma + Interstitial

$$V_{\text{int}_kid}\frac{dC_{\text{int}_kid}}{dt} = Q_{kid}\cdot\left(1-HCT\right)\cdot\left(C_{pls_art}-C_{\text{int}_kid}\right)$$
$$-PS_{rbc_kid}\cdot f_u\cdot\left(C_{\text{int}_kid}-\frac{C_{rbc_liv}}{K_{rbc}}\right)$$
$$-PS_{cell_kid}\cdot f_u\cdot\left(C_{\text{int}_kid}-\frac{C_{cell_kid}}{K_{kid}}\right)$$
$$-\frac{CL_{pls_kid}\cdot Q_{kid}\cdot\left(1-HCT\right)\cdot C_{\text{int}_kid}}{\left[Q_{kid}\cdot\left(1-HCT\right)-CL_{pls_kid}\right]}$$

Portal vein

Red blood cells

$$HCT\cdot V_{pv}\frac{dC_{rbc_pv}}{dt} = Q_{GI_tract}\cdot HCT\cdot\left(C_{rbc_GI_tract}-C_{rbc_pv}\right)$$
$$+PS_{rbc_pv}\cdot f_u\cdot\left(C_{pls_pv}-\frac{C_{rbc_org}}{K_{rbc}}\right)$$

Plasma + interstitial

$$\left(1-HCT\right)\cdot V_{pv}\cdot\frac{dC_{pls_pv}}{dt} = Q_{GI_tract}\cdot\left(1-HCT\right)\cdot\left(C_{\text{int}_GI_tract}-C_{pv}\right)$$
$$-PS_{rbc_pv}\cdot f_u\cdot\left(C_{pls_pv}-\frac{C_{rbc_pv}}{K_{rbc}}\right)$$

For venous blood

Red blood cells

$$HCT\cdot V_{ven}\cdot\frac{dC_{rbc_ven}}{dt} = \sum_{org}Q_{org}\cdot HCT\cdot C_{rbc_org}$$
$$+PS_{rbc_ven}\cdot f_u\cdot\left(C_{pls_ven}-\frac{C_{rbc_ven}}{K_{rbc}}\right)$$
$$-Q_{lung}\cdot HCT\cdot C_{rbc_ven}$$

Plasma +interstitial

$$\left(1-HCT\right)\cdot V_{ven}\frac{dC_{pls_ven}}{dt}=\sum_{org}Q_{org}\cdot\left(1-HCT\right)\cdot C_{\text{int}_org}$$
$$-PS_{rbc_ven}\cdot f_u\cdot\left(C_{pls_ven}-\frac{C_{rbc_ven}}{K_{rbc}}\right)$$
$$-Q_{lung}\cdot\left(1-HCT\right)\cdot C_{pls_ven}$$

For arterial blood

Red blood cells

$$HCT\cdot V_{art}\cdot\frac{dC_{rbc_art}}{dt}=-\sum_{org}Q_{org}\cdot HCT\cdot C_{rbc_art}$$
$$+PS_{rbc_art}\cdot f_u\cdot\left(C_{pls_art}-\frac{C_{rbc_art}}{K_{rbc}}\right)$$
$$+Q_{lung}\cdot HCT\cdot C_{rbc_art}$$

Plasma +interstitial

$$\left(1-HCT\right)\cdot V_{art}\frac{dC_{pls_art}}{dt}=-\sum_{org}Q_{org}\cdot\left(1-HCT\right)\cdot C_{\text{int}_art}$$
$$-PS_{rbc_art}\cdot f_u\cdot\left(C_{pls_art}-\frac{C_{rbc_art}}{K_{rbc}}\right)$$
$$+Q_{lung}\cdot\left(1-HCT\right)\cdot C_{pls_art}$$

The rest of the formulas are based on the formulation scheme of Edginton and Ritter with the proper modifications to correspond at the needs of our model.

For liver:

Red blood cells

$$V_{rbc_liv}\frac{dC_{rbc_liv}}{dt}=HCT\cdot\left(Q_{liv}\cdot C_{rbc_art}+Q_{pv}\cdot C_{rbc_pv}\right)$$
$$-\left(Q_{liv}\cdot C_{rbc_art}+Q_{pv}\cdot C_{rbc_pv}\right)$$
$$+PS_{rbc_org}\cdot f_u\cdot\left(C_{\text{int}_org}-\frac{C_{rbc_org}}{K_{rbc}}\right)$$

Plasma + Interstitial

$$V_{\text{int_}liv}\frac{dC_{\text{int_}liv}}{dt}=\left(1-HCT\right)\cdot\left(Q_{liv}\cdot C_{pls_art}+Q_{pv}\cdot C_{pls_pv}\right)$$
$$-\left(Q_{liv}+Q_{pv}\right)\cdot\left(1-HCT\right)\cdot C_{\text{int_}liv}$$
$$-PS_{rbc_liv}\cdot f_u\cdot\left(C_{\text{int_}liv}-\frac{C_{rbc_liv}}{K_{rbc}}\right)$$
$$-PS_{cell_liv}\cdot f_u\cdot\left(C_{\text{int_}liv}-\frac{C_{cell_liv}}{K_{liv}}\right)$$

Cellular

$$V_{cell_liv}\frac{dC_{cell_liv}}{dt}=PS_{cell_liv}\cdot f_u\cdot\left(C_{\text{int_}liv}-\frac{C_{cell_liv}}{K_{li}}\right)$$
$$-\frac{CL_{BPA_liv_gluc}\cdot C_{cell_liv_BPA}\cdot f_{u_BPA}}{K_{liv_BPA}}$$
$$-\frac{CL_{BPA_liv_sulf}\cdot C_{cell_liv_BPA}\cdot f_{u_BPA}}{K_{liv_BPA}}$$

where CL_{BPA_liv} is the intrinsic clearance of BPA and is calculated from the plasma clearance of BPA using the well stirred liver model. This clearance term is positive in the cellular compartment of the BPA-Glu sub-model and represents the only input function to the BPA-Glu sub-model.

For lungs:

$$V_{\text{int_}lung}\cdot\frac{dC_{\text{int_}lung}}{dt}=Q_{lung}\cdot\left(1-HCT\right)\cdot\left(C_{pls_ven}-C_{\text{int_}lung}\right)$$
$$-PS_{rbc_lung}\cdot f_u\cdot\left(C_{\text{int_}lung}-\frac{C_{rbc_lung}}{K_{rbc}}\right)$$
$$-PS_{cell_lung}\cdot f_u\cdot\left(C_{\text{int_}lung}-\frac{C_{cell_lung}}{K_{rbc}}\right)$$
$$+Q_{vent}\cdot C_{amb_air}\cdot P_{air}$$
$$-Q_{vent}\cdot\left(\frac{C_{\text{int_}lung}}{P_{air}}\cdot\left(1-V_{ds}\right)+C_{amb_air}\cdot V_{ds}\right)$$

For uterus:

Plasma +interstitial

$$V_{\text{int}_uterus}\frac{dC_{\text{int}_uterus}}{dt} = Q_{uterus}\cdot(1-HCT)\cdot\left(C_{pls_art}-C_{\text{int}_uterus}\right)$$
$$-K_{d_uterus_pla}\cdot\left(C_{placenta}-C_{uterus_M}\right)$$
$$-PS_{rbc_uterus}\cdot f_u\cdot\left(C_{\text{int}_uterus}-\frac{C_{rbc_uterus}}{K_{rbc}}\right)$$
$$-PS_{cell_uterus}\cdot f_u\cdot\left(C_{\text{int}_uterus}-\frac{C_{cell_uterus}}{K_{rbc}}\right)$$

beside the assumption of equal diffusion flow from uterus to placenta and vice-versa during pregnancy, uterus behaves like other organs.

For placenta:

$$V_{\text{int}_placenta}\frac{dC_{\text{int}_placenta}}{dt} = K_{d_uterus_pla}\cdot\left(C_{\text{int}_placenta}-C_{\text{int}_uterus}\right)$$
$$-K_{d_pla_amniot}\cdot\left(C_{\text{int}_placenta}-C_{amniot}\frac{P_{placenta}}{P_{amniot}}\right)$$
$$+Q_{placenta_fetus}\cdot\left(C_{\text{int}_art_fetus}-\frac{C_{\text{int}_placenta}}{P_{placenta}}\right)$$
$$+K_{glu_deconj}\cdot Q_{placenta_fetus}\cdot C_{\text{int}_placenta_glu}$$
$$-PS_{rbc_placenta}\cdot f_u\cdot\left(C_{\text{int}_placenta}-\frac{C_{rbc_placenta}}{K_{rbc}}\right)$$
$$-PS_{cell_placenta}\cdot f_u\cdot\left(C_{\text{int}_placenta}-\frac{C_{cell_placenta}}{K_{rbc}}\right)$$

For breast:

$$V\frac{dC_{_breast}}{dt} = PS_{_cell_breast}\cdot f_u\cdot\left(C_{_\text{int}_breast}-\frac{C_{_breast}}{K_{_breast}}\right)-L_{excr}$$

and the related excretion via lactation

$$L_{excr} = Q_{_milk}\cdot\frac{C_{_breast}}{K_{_breast}}\cdot P_{_milk/blood}$$

$$P_{_milk/blood} = \frac{K_{ow}\cdot Fl_{_tissue}+Fw_{_tissue}}{K_{ow}\cdot Fl_{_blood}+Fw_{_blood}}$$

Lifetime scaling

The parameters related to organ volumes (***V***) and blood flows (***Q***) were taken from the ICRP (ICPR 2002) report and fitted to time (***t in hours***) in order to derive continuous time depended non lineal polynomial formulas in the form of:

$V = a \cdot t^b + c \cdot t^d + e \cdot t + f$ for organ volumes

$Q = a \cdot t^b + c \cdot t + d$ for organ flows

Table S1. Regression coefficients for lifetime scaling (from conception to adulthood)

	organ volumes (mL)						organ flows (mL/min)			
	a	***b***	***c***	***d***	***e***	***f***	***a***	***b***	***c***	***d***
Portal vein	1.00E-01	1.00E+00	9.80E-02	9.96E-01	0.00E+00	5.70E+01	6.09E-02	-2.61E-02	1.06E+00	1.14E+02
Adipose	2.54E-02	1.00E+00	1.88E+01	5.20E-01	0.00E+00	9.06E+02	1.17E-01	1.00E-01	1.01E+00	3.00E+01
Bones	5.97E-02	1.00E+00	1.26E+00	6.10E-01	0.00E+00	4.52E+02	2.00E-02	1.04E-02	1.05E+00	3.00E+01
Brain	-5.03E-02	1.00E+00	9.07E-01	7.69E-01	0.00E+00	3.95E+02	-3.99E-01	7.10E-01	9.52E-01	1.80E+02
Gonads	8.25E-02	1.00E+00	8.31E-02	9.99E-01	0.00E+00	1.10E+00	3.57E-02	-3.56E-02	1.00E+00	3.00E-01
Heart	4.68E-02	1.00E+00	-3.81E-02	1.01E+00	0.00E+00	2.80E+01	4.08E-03	1.81E-05	1.41E+00	2.40E+01
Kidneys	3.17E-02	1.00E+00	1.44E-02	1.06E+00	0.00E+00	3.80E+01	3.86E-02	-7.90E-03	1.11E+00	1.10E+02
Liver	2.79E-03	1.00E+00	1.10E+00	6.03E-01	0.00E+00	1.60E+02	8.54E-03	-3.51E-04	1.24E+00	3.90E+01
GI tract	8.20E-02	1.00E+00	4.41E-02	1.04E+00	0.00E+00	9.00E+01	6.09E-02	-2.61E-02	1.06E+00	1.14E+02
Muscle	1.26E-01	1.00E+00	7.76E-06	1.76E+00	0.00E+00	9.50E+02	1.00E-01	-1.03E-01	9.92E-01	3.10E+01
Skin	2.88E-01	1.00E+00	2.71E-01	9.98E-01	0.00E+00	2.00E+02	1.06E-02	-2.72E-03	1.10E+00	3.00E+01
Lungs	9.74E-02	1.00E+00	6.33E-02	1.03E+00	0.00E+00	8.40E+01	-4.98E-01	9.94E-01	9.48E-01	5.58E+02
Arterial/venous blood	1.26E-01	1.00E+00	-1.25E-01	9.98E-01	0.00E+00	3.80E+01				
Total blood	1.15E-01	1.00E+00	-1.10E-01	9.92E-01	0.00E+00	1.33E+02				
WEIGHT	3.90E-01	1.00E+00	8.40E+01	3.66E-01	0.00E+00	3.21E+03				
HCT	-1.00E-01	9.66E-12	-1.00E-01	1.55E-06	5.50E-07	5.80E-01				

Table S2. Gestation parameters (from conception to birth)

	organ volumes (mL)						organ flows (mL/min)			
	a	***b***	***c***	***d***	***e***	***f***	***a***	***b***	***c***	***d***
Uterus	3.90E-01	1.00E+00	8.40E+01	3.66E-01	0.00E+00	3.21E+03	3.57E-02	-3.56E-02	1.00E+00	3.00E-01

Placenta	3.90E-01	1.00E+00	8.40E+01	3.66E-01	0.00E+00	3.21E+03	3.57E-02	-3.56E-02	1.00E+00	3.00E-01
Amniotic fluid	3.90E-01	1.00E+00	8.40E+01	3.66E-01	0.00E+00	3.21E+03				
Breast										

Table S3. Partition coefficients (organ/blood)

Organ	Partition coefficient (BPA)	Partition coefficient (BPA-Glu)
Adipose	3.8-8.3	0.18
Bones	1.7	0.42
Brain	3.6	0.75
Gonads	0.79	0.83
Heart	1.6	0.57
Kidneys	1.8	0.68
Liver	1.9	0.65
GI tract	3.8	0.75
Muscle	2.2	0.74
Skin	5.7	0.69
Lungs	2.4	0.58
Uterus	1.35	0.83
Placenta	1.35	0.83
Breast	1.35	0.83

Table S4. Model parameters for MCMC analysis

		Distr.	*Min*	Max	Mean	Std. Dev.
Newborn	**CL_BPA_liver_clearance (mL/h)**	Normal	*39*	117	**78**	14
	CL_BPA_ liver_sulf (mL/h)	Normal	*118*	353	**235**	42
	Dose (µg/kg BW/day)	Normal	*0.1(0.5)*	0.5(8)	0.2(4)	0.05(2)
1 month	**CL_BPA_liver_clearance (mL/h)**	Normal	*90*	269	**179**	33
	CL_BPA_ liver_sulf (mL/h)	Normal	*134*	402	**268**	49
	Dose (µg/kg BW/day)	Normal	*0.1(0.5)*	0.5(8)	0.2(4)	0.05(2)
3 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*338*	1013	**675**	117
	CL_BPA_ liver_sulf (mL/h)	Normal	*169*	506	**337**	59
	Dose (µg/kg BW/day)	Normal	*0.2*	11	5	3
6 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*672*	2016	**1344**	277
	CL_BPA_ liver_sulf (mL/h)	Normal	*202*	605	**403**	69
	Dose (µg/kg BW/day)	Normal	*0.2*	13	8.3	3

9 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*1117*	3351	**2234**	450
	CL_BPA_ liver_sulf (mL/h)	Normal	*224*	671	**447**	75
	Dose (µg/kg BW/day)	Normal	*0.2*	13	6.6	3
12 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*1391*	4173	**2782**	553
	CL_BPA_ liver_sulf (mL/h)	Normal	*246*	737	**491**	83
	Dose (µg/kg BW/day)	Normal	*0.2*	13	5	3
18 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*1864*	5592	**3728**	752
	CL_BPA_ liver_sulf (mL/h)	Normal	*329*	987	**658**	113
	Dose (µg/kg BW/day)	Normal	*0.2*	13	5	3
24 months	**CL_BPA_liver_clearance (mL/h)**	Normal	*2273*	6819	**4546**	929
	CL_BPA_ liver_sulf (mL/h)	Normal	*401*	1203	**802**	139
	Dose (µg/kg BW/day)	Normal	*0.2*	13	5	3
Adult	**CL_BPA_liver_clearance (mL/h)**	Normal	*9260*	27779	**18519**	3000
	CL_BPA_ liver_sulf (mL/h)	Normal	*1634*	4902	**3268**	450
	Dose (µg/kg BW/day)	Normal	*0.2*	5	1.5	0.5