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Supplemental Material

Physiologically Based Pharmacokinetic (PBPK) Modeling of the Bisphenols BPA, BPS, BPF, and BPAF with New Experimental Metabolic Parameters: Comparing the Pharmacokinetic Behavior of BPA with Its Substitutes

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Figure S2. Eadie Hofstee plots of enzyme kinetics of BPS, BPF, and BPAF with human liver and intestinal microsomes. Shown are averages (black circles) and ranges from minimal to maximal reaction velocities (whiskers). Abbreviations: BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; $c_{substrate}$, substrate concentration; v, reaction velocity.

Figure S3. Measured and modeled serum concentration–time profiles of BPS and BPS-g after peroral dosing with 8.75 µg BPS/kg bw. Individual measurements (black circles) represent observed serum concentrations (average ± standard deviation) of 7 adults (Oh et al. 2018). Concentration profiles for the respective volunteers (grey solid lines) were modeled using (A) the adjusted PBPK model for BPA further adjusted with BPS-specific metabolism parameters (Table 7) and (B and C) the BPS-specific model calibrated to assume a higher peroral uptake and increased clearance rates of BPS and BPS-g assuming either (B) no EHR or (C) a BPS EHR rate of 67% (see Table 5 for uptake parameters). Abbreviations: BPA, bisphenol A; BPS, bisphenol S; bw, bodyweight; EHR, enterohepatic recirculation; g, glucuronide.

Figure S4. Modeled concentration profiles of unconjugated BPS obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPS, bisphenol S; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

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Figure S6. Modeled concentration profiles of unconjugated BPF obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPF, bisphenol F; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

Figure S7. Modeled concentration profiles of unconjugated BPAF obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPAF, bisphenol AF; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

Figure S8. Measurements of Hormann et al. (2014) (symbols) against modeled individual serum profiles (solid lines) of unconjugated BPA, BPA-g, and BPA-s in three volunteers. They handled receipt paper for 4 min with both hands which were wetted with skin sanitizer and ate 10 French fries with a contaminated hand afterwards during 4 min. One hand was then cleaned and the other hand stayed contaminated until the end of blood collection (90 min in total, see Table S9 for study-specific parameters). Abbreviations: BPA, bisphenol A; g, glucuronide; s, sulfate.

Input tables

Table C1. Input table “Probanden” used in the basic PBPK model code for BPA.

Table C2. Input table “physAge” used in the basic PBPK model code for BPA.

Table C3. Input table “VarInputFem” used in the PBPK model code for the 2D Monte Carlo Analysis of BPA in women (18-45 years).

Table C4. Input table “ChemData” used in the PBPK model code for the 2D Monte Carlo Analysis of BPA in women (18-45 years).

Model code

References

Table S1. Age-group specific physiological model parameters used as input for the basic PBPK models.

Parameters	Newborn	1 year	5 years	15 years	Adult (30 years)
Cardiac output (L/min)[a]	0.600	1.20	3.40	6.10	5.90/6.50[b]
	Blood flows through organs (% of cardiac output)[a]				
Fat	4.27	0.749	4.44	7.55/4.45[b]	7.45/4.43[b]
Liver	21.8	19.1	22.5	24.4/22.6[b]	24.0/22.6[b]
Brain	25.6	43.7	23.4	11.1/11.4[b]	10.5/10.6[b]
Skin	4.27	3.74	4.41	4.45[b]	4.38/4.43[b]
Gonads	0.0427	0.0374	0.0182/ 0.0441[b]	0.0172/ 0.0452[b]	0.0178/ 0.0449[b]
Slow[c]	8.68	6.36	9.92	14.5/17.8[b]	14.2/19.5[b]
Rich[d]	35.3	26.3	35.3	38.0/39.3[b]	39.4/38.4[b]
	Tissue volumes (% of bodyweight)[e]				
Plasma	4.64	2.97	4.42	3.90/4.63[b]	4.00/4.11[b]
Fat	25.4	36.0	26.3	30.2/17.0[b]	31.7/19.9[b]
Liver	3.71	3.30	3.00	2.45/2.32[b]	2.33/2.47[b]
Brain	10.9	9.50	6.55	2.45/2.54[b]	2.17/1.99[b]
Skin	5.00	3.50	3.00	3.21/3.57[b]	3.83/4.52[b]
Gonads	0.00857/ 0.0243[b]	0.00800/ 0.0150[b]	0.0105/ 0.00895[b]	0.0113/ 0.0286[b]	0.0183/ 0.0479[b]
Slow[c]	33.6	30.8	42.3	46.1/57.1[b]	43.0/54.2[b]
Rich[d]	9.60	7.49	6.59	5.65/5.49[b]	5.94/5.43[b]

Body weight, age, height, and sex were scenario-specific and therefore not reported here.
[a]Edginton et al. (2006).
[b]Indicates values for female/male.
[c]Perfusion lower than 0.1 mL/min/g tissue: muscle and skeleton (Edginton et al. 2006; ICRP 2002).
[d]Perfusion higher than 0.1 mL/min/g tissue: heart, kidneys, small and large intestine, pancreas, spleen, and stomach (Edginton et al. 2006; ICRP 2002).
[e]ICRP (2002).
Abbreviations: PBPK, physiologically based pharmacokinetic; rich, richly perfused tissue; slow, slowly perfused tissue.

Table S2. Published measurements of metabolism parameters for bisphenol A.

Reference	K_m, nM±SD	v_{max}[a], nmol/h/mg microsomal protein±SD
Hepatic glucuronidation		
Kurebayashi et al. (2010)[b]	5,300	39.8
Coughlin et al. (2012)	45,800 ± 8,900	283 ± 18
Trdan Lušin et al. (2012)	8,900 ± 800	510 ± 18
Elsby et al. (2001)[c]	71,900 ± 7,900	333 ± 21
Kuester and Sipes (2007)[c]	8,500 ± 2,500	85.2 ± 31.4
Mazur et al. (2010)[c]	4,250 ± 1,350	190 ± 16.9
Street et al. (2017)	23,000 ± 8,000	270 ± 60
Intestinal glucuronidation		
Trdan Lušin et al. (2012)	58,400 ± 7,800	84.0 ± 6.0
Mazur et al. (2010)	80,100 ± 35,900	29.2 ± 7.2
Microsomal protein content in the small intestine (total mass in mg)		
Zhang et al. (1999)	322	
Paine et al. (1997)	2,977	

[a]The following scaling factors were applied: 32 mg microsomal protein/g liver and 99 x 106 cells/ g liver (Barter et al. 2007).
[b]The K_m was derived from an n=1; therefore, no SD was calculated.
[c]The arithmetic mean of female and male kinetics was used in the comparison.
Abbreviations: K_m, Michaelis-Menten constant; SD, standard deviation; v_{max}, maximum enzyme velocity.

Table S3. Comparison between BPA tissue/serum partition coefficients determined experimentally (Doerge et al. (2011), highlighted in grey) and with different QSARs for QSAR selection.

Tissue	Doerge et al. (2011)	DeJongh et al. (1997)	Schmitt (2008)	Zhang and Zhang (2006) (1)	Zhang and Zhang (2006) (2)
Liver	0.73	7.17	11.5	1.61	1.66
Slow[a]	2.7	4.49	13.1	1.52	1.56
Brain	2.8	5.13	16.0	1.36	1.38
Rich[b]	2.8	5.13	16.0	1.36	1.38
Fat	5	109	103	2.25	2.28
Skin	-	5.53[d]	7.84	2.06	2.15
Gonads	2.6[c]	2.55[d]	5.26[e]	1.37	1.41

[a]Value for muscle used.
[b]Value for brain used.
[c]Value for ovaries used.
[d]QSAR did not explicitly parametrize this kind of tissue and we used additional assumptions to calculate this value (skin: water volume=0.95, lipid volume=0.05, parameter A=0.8, parameter B=-0.22; gonads: water volume=0.977, lipid volume=0.023, parameter A=0.8, parameter B=-0.22).
[e]Value for testes used.

Zhang and Zhang (2006) (1) and (2) refer to their equations 5 and 6, two slightly different QSARs.

The following parameters were used: pKa 10.4 (Bautista-Toledo et al. 2005), $\log P_{ow}$ 3.36 (mean of Bayer 1996; Korenman 1973), fu 0.06 (Csanády et al. 2002). For the QSARs by Zhang and Zhang (2006), we used HyperChem Professional 8.0 and Gaussian 03W to calculate parameters necessary.

Abbreviations: BPA, bisphenol A; fu, unbound fraction; QSAR, Quantitative structure-activity relationship; rich, richly perfused tissue; slow, slowly perfused tissue.

Table S4. Observed changes of RSS and C_{max} of the concentration-time curve of unconjugated bisphenol A after decreasing and increasing the values of the individual tissue/serum partition coefficients by 10% and 50%.

	RSS (nM^2)				C_{max} (nM)			
Tissue	**+ 50 %**	**+ 10 %**	**- 10 %**	**- 50 %**	**+ 50 %**	**+ 10 %**	**- 10 %**	**- 50 %**
Liver	$2 \cdot 10^{-6}$	$7 \cdot 10^{-8}$	$7 \cdot 10^{-8}$	$2 \cdot 10^{-6}$	$9 \cdot 10^{-13}$	$2 \cdot 10^{-11}$	$1 \cdot 10^{-14}$	$1 \cdot 10^{-12}$
Slow[a]	$4 \cdot 10^{-1}$	$2 \cdot 10^{-2}$	$3 \cdot 10^{-2}$	$9 \cdot 10^{-1}$	$2 \cdot 10^{-3}$	$2 \cdot 10^{-4}$	$2 \cdot 10^{-4}$	$9 \cdot 10^{-3}$
Rich[b]	$8 \cdot 10^{-1}$	$4 \cdot 10^{-2}$	$4 \cdot 10^{-2}$	$1 \cdot 10^{0}$	$1 \cdot 10^{-2}$	$5 \cdot 10^{-4}$	$5 \cdot 10^{-4}$	$1 \cdot 10^{-2}$
Brain	$6 \cdot 10^{-3}$	$2 \cdot 10^{-4}$	$2 \cdot 10^{-4}$	$6 \cdot 10^{-3}$	$4 \cdot 10^{-5}$	$1 \cdot 10^{-6}$	$1 \cdot 10^{-6}$	$3 \cdot 10^{-5}$
Skin	$5 \cdot 10^{-2}$	$2 \cdot 10^{-3}$	$2 \cdot 10^{-3}$	$6 \cdot 10^{-2}$	$5 \cdot 10^{-4}$	$3 \cdot 10^{-5}$	$3 \cdot 10^{-5}$	$9 \cdot 10^{-4}$
Gonads	$4 \cdot 10^{-6}$	$2 \cdot 10^{-7}$	$2 \cdot 10^{-7}$	$5 \cdot 10^{-6}$	$4 \cdot 10^{-8}$	$2 \cdot 10^{-9}$	$2 \cdot 10^{-9}$	$7 \cdot 10^{-8}$
Fat	$1 \cdot 10^{-1}$	$8 \cdot 10^{-3}$	$1 \cdot 10^{-2}$	$4 \cdot 10^{-1}$	$1 \cdot 10^{-4}$	$9 \cdot 10^{-6}$	$1 \cdot 10^{-5}$	$8 \cdot 10^{-4}$

[a]Perfusion lower than 0.1 mL/min/g tissue: muscle and skeleton (Edginton et al. 2006; ICRP 2002).
[b]Perfusion higher than 0.1 mL/min/g tissue: heart, kidneys, small and large intestine, pancreas, spleen, and stomach (Edginton et al. 2006; ICRP 2002).
Abbreviations: C_{max}, maximal concentration; rich, richly perfused tissue; RSS, residual sum of squares; slow, slowly perfused tissue.

Table S5. Qualitative evaluation and ordinal scaling of uncertainty in the PBPK model. Model parameters were classified into five different categories: Low uncertainty (L), low to medium uncertainty (LM), medium uncertainty (M), medium to high uncertainty (MH), and high uncertainty (H) (EFSA Scientific Committee 2016).

Parameter	Evaluation	Cat.
Age	The age range was defined within the assessments to cover females of the ages 18-45 years. However, the real life age distribution was not considered.	LM
Height, BMI, body weight, cardiac output, blood flow through organs, tissue volumes, gastric emptying time	Physiological model parameters have been evaluated in several studies with human volunteers/patients, so that the central tendencies are well-known. Therefore, the uncertainty around their parameter values is rather small in comparison to the inter-individual variability in physiology. Among these parameters, the uncertainty varies depending on whether invasive measurement techniques are needed. For example, the uncertainty is lower for the height than for the tissue volumes, as height can be measured externally so that more measurement values exist.	LM
Tissue-to-serum partition coefficients (P_{TS})	For BPA, partitioning was investigated in an animal experiment (Doerge et al. 2011). For the other analogues, QSARs needed to be used to derive P_{TS}. Depending on the QSAR applied, different results can be obtained. It is uncertain which QSAR reflects the situation best.	H
Glucuronidation kinetics in liver and gut, sulfation kinetics in the liver	The experiments investigating metabolism kinetics were conducted *in vitro*. The experimental conditions may not have covered all processes that are relevant *in vivo*. In addition, we observed a large variation of reported parameter values for the hepatic and gut glucuronidation of BPA, but cannot depict the study that represents real circumstances best. Therefore, there is a high uncertainty concerning glucuronidation kinetics of BPA, which can be quantified. For metabolism parameters for which only one study exists, the uncertainty is not necessarily smaller. Differences between BPS kinetic parametrizations before and after calibration can be used to estimate the magnitude of uncertainty for the analogues for which we could not calibrate the models.	H
Enzyme concentrations in liver and gut	Several studies investigated the microsomal protein content in the liver and the small intestine. The range of observations is rather narrow for the liver, meaning that the concentration is easy to analyze and/or that it doesn't vary substantially. The range is much larger for the small intestine. This means that the concentration is difficult to determine and/or that there is a large inter-individual variability. Uncertainty should therefore be evaluated for the	MH-H

	enzyme concentration in the small intestine. For consistency reasons, we also investigated the uncertainty of the hepatic enzyme concentration.	
EHR	The pathway of EHR has been observed for molecules with molecular weights (MW) higher than 500 g/mol (Roberts et al. 2002). The MW of bisphenol glucuronides ranges from 376 (BPF-g) to 512 (BPAF-g) g/mol. This means that the probability of EHR taking place could depend on the respective analogue. A comparison of possible PBPK model outputs for BPA (MW of BPA-g: 404 g/mol) with the biomonitoring data by Thayer et al. (2015) showed that BPA equally could or could not undergo EHR. The results of the biomonitoring study by Oh et al. (2018) suggest that EHR plays an important role for BPS.	H
Dermal absorption (fraction)	Several studies investigated the dermal absorption of BPA, but different study designs and solvents were used. In total, reported dermal absorption ranged from 9.3% to 60%. However, the range diminishes if different solvents and study designs are differentiated.	MH
Half-life of dermal penetration	The half-life of dermal penetration varies substantially depending on the solvent used in the experiment. As only few studies investigated this parameter, there is significant uncertainty. Again, the range of half-lives reported diminishes if different solvents are regarded separately.	MH
Peroral absorption (fraction)	The peroral absorption fraction has been derived from recoveries of biomonitoring studies. The two studies available (Thayer et al. 2015; Völkel et al. 2002) report recoveries of 84-109% and 118 ± 21% respectively, indicating complete or nearly complete peroral absorption.	LM
Uptake of BPs and metabolites from gut to liver	The small intestinal transit time has been characterized in humans. For the metabolites, only the direct transition from enterocytes to the liver needs to be regarded. This has been done with optimizations within the models. The parameter is more uncertain for BPF and BPAF, for which we could not calibrate the models.	M-MH
Urinary excretion of BPs and metabolites	The clearance rates have been characterized in biomonitoring studies of BPA and it has been found that the clearance rate of BPA resembles the creatinine clearance of a healthy adult. The individual excretion terms have been further adjusted within the model for BPA and BPS. For BPF and BPAF, we could not calibrate the excretion terms and therefore their parametrization is more uncertain.	M-MH

Abbreviations: BMI, body mass index; BPA, bisphenol A; BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; Cat., category; EHR, enterohepatic recirculation; g, glucuronide; H, high uncertainty; L, low uncertainty; LM, low to medium uncertainty; M, medium uncertainty; MH, medium to high uncertainty; PBPK, physiologically based pharmacokinetic; QSAR, quantitative structure-activity relationship.

Table S6. Trapezoidal distributions used to describe uncertainty in the outer loop of the 2D-MC analysis. A description of how parameters were obtained and respective references can be found in the text.

Parameter	Minimum	Mode 1	Mode 2	Maximum
Microsomal protein content liver (mg protein/g liver)	28.2	32.0	38.0	42.5
Microsomal protein content gut (mg/kg bw)	1.72	4.29	39.7	70.8
Extent of dermal absorption from thermal paper (%)	2.88	9.30	20.0	32.2
Extent of dermal absorption from PCPs (%)	2.88	9.30	60.0	96.5
Half-life of dermal absorption from thermal paper (h)	2.47	6.00	8.50	13.5
Half-life of dermal absorption from PCPs (h)	0.0687	0.167	8.50	13.5
Fraction not subject to EHR				
BPA	0.33	0.8	1	1
BPS	0.095	0.23	0.43	0.683
BPF	0.33	0.8	1	1
BPAF	0.02	0.05	0.43	0.683
EHR unconjugated (1/h/kg $bw^{-0.25}$), BPF andBPAF	0.0824	0.2	0.35	0.556
EHR as glucuronide (1/h/kg $bw^{-0.25}$), BPF and BPAF	0.0824	0.2	2.0	3.18
Correction factor for hepatic sulfation				
BPS	0.0365	0.0886	11.3	17.9
BPF	0.0787	0.191	5.23	8.31
BPAF	0.0614	0.149	6.73	10.7
K_m hepatic glucuronidation (nM)				
BPF	7,730	17,900	28,100	44,000
BPAF	1,820	4,210	6,600	10,360
v_{max} hepatic glucuronidation (nmol/h/mg microsomal protein)				
BPF	9.74	33.1	112.4	192
BPAF	15.3	52.1	176.9	302
K_m intestinal glucuronidation (nM), BPF	24,600	57,000	89,400	140,200
Uptake from the small intestine to the liver (1/h/kg $bw^{-0.25}$), BPF and BPAF	0.495	2.1	5.0	8.82
Urinary excretion unconjugated (1/h/kg $bw^{0.75}$), BPF and BPAF	0.0247	0.06	0.3	0.476
Urinary excretion as glucuronide (1/h/kg $bw^{0.75}$), BPF and BPAF	0.144	0.35	1.2	1.91

If not further specified, the distribution is used for all analogues in the same way.

Abbreviations: BPA, bisphenol A; BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; bw, body weight; EHR, enterohepatic recirculation; Km, Michaelis-Menten constant; 2D-MC, 2-dimensional Monte Carlo; v_{max}, maximum reaction velocity.

Table S7. Parametrizations for truncated normal distributions used to describe variability in the 2D-MC analysis of BPA (around central values from the basic model for females of childbearing age). A description of how parameters were obtained and respective references can be found in the text.

Parameter	Mean	SD	Lower bound	Upper bound
Height (cm)	165	6.80	151	178
BMI (lognormal)	25.9	5.11	15.9	35.9
Cardiac output (L/h)	354	81.4	194	514
Blood flows through organs (% of cardiac output)				
Fat	7.45	2.01	3.51	11.4
Liver	24.0	6.49	11.3	36.8
Brain	10.5	2.84	4.95	16.1
Skin	4.38	1.18	2.06	6.69
Gonads	0.0178	0.00481	0.00838	0.0272
Slow[a]	14.2	3.85	6.71	21.8
Rich[b]	39.4	10.6	18.5	60.2
Tissue volumes (% of body weight)				
Plasma	4.00	1.00	2.04	5.96
Fat	31.7	7.92	16.2	47.2
Liver	2.33	0.583	1.19	3.48
Brain	2.17	0.542	1.11	3.23
Skin	3.83	0.958	1.96	5.71
Gonads	0.0183	0.00458	0.00935	0.0273
Slow[a]	43.0	10.8	21.9	64.1
Rich[b]	5.94	1.49	3.03	8.86
Partitioning coefficients for BPA				
Fat	5.00	0.320	1.86	8.14
Liver	0.730	0.234	0.272	1.19
Brain	2.80	0.896	1.04	4.56
Skin	2.15	0.688	0.802	3.50
Gonads	2.60	0.832	0.969	4.23
Slow[a]	2.70	0.864	1.01	4.39
Rich[b]	2.80	0.896	1.04	4.56
Uptake and excretion of BPA				
Dermal absorption from thermal paper (%)	20.0	6.20	7.85	32.2
Dermal absorption from PCPs (%)	60.0	18.6	23.5	96.5
Dermal absorption half-life thermal paper (h)	6.00	1.80	2.47	9.53
Dermal absorption half-life PCPs (h)	0.167	0.0501	0.0688	0.265
Gastric emptying (1/h/kg bw$^{-0.25}$)	3.50	0.945	1.65	5.35
Volume of distribution in small	122	30.6	62.4	182

intestine (ml)				
Peroral uptake from small intestine into liver (1/h/kg $bw^{-0.25}$)	2.10	0.819	0.495	3.71
Urinary excretion (1/h/kg $bw^{-0.25}$)	0.0600	0.0180	0.0247	0.0953
EHR rates of BPA and BPA-g (1/h/kg $bw^{-0.25}$)	0.200	0.0600	0.0824	0.318
Hepatic glucuronidation of BPA				
K_m (nM)	45,800	13,300	19,800	71,800
v_{max} (nmol/h/g liver)	9,040	3,260	2,660	15,400
Microsomal protein content (mg protein/ g liver)	32.0	1.92	28.2	35.8
Glucuronidation of BPA in enterocytes				
K_m (nM)	58,400	16,900	25,200	91,600
v_{max} (nmol/h/kg bw)	361	130	106	616
Microsomal protein content (mg protein/ kg bw)	4.30	1.72	0.929	7.67
Hepatic sulfation of BPA				
K_m (nM)	10,100	2,930	4,360	15,800
v_{max} (nmol/h/g liver)	149	53.7	43.9	254
Glucuronides and sulfates				
Uptake from enterocytes into liver (1/h/kg $bw^{-0.25}$)	50.0	15.0	20.6	79.4
Urinary excretion glucuronide (1/h/kg $bw^{-0.25}$)	0.350	0.105	0.144	0.556
Urinary excretion sulfate (1/h/kg $bw^{-0.25}$)	0.0300	0.00900	0.0124	0.0477

For the age a uniform distribution was used spanning from 18-45 years, the bodyweight was calculated as ($height^2$) * BMI. The volume of distribution was set equal to the plasma volume.

[a]Perfusion lower than 0.1 mL/min/g tissue: muscle and skeleton (Edginton et al. 2006; ICRP 2002).
[b]Perfusion higher than 0.1 mL/min/g tissue: heart, kidneys, small and large intestine, pancreas, spleen, and stomach (Edginton et al. 2006; ICRP 2002).

Abbreviations: BMI, body mass index; BPA, bisphenol A; bw, body weight; K_m, Michaelis-Menten constant; PCPs, personal care products; rich, richly perfused tissue; slow, slowly perfused tissue; 2D-MC, 2-dimensional Monte Carlo; v_{max}, maximum reaction velocity.

Table S8. Tissue/serum partition coefficients for BPS, BPF, and BPAF calculated with the quantitative structure-activity relationships by DeJongh et al. (1997) and Schmitt (2008), partially used as boundaries in the uncertainty distributions.

	DeJongh et al. (1997)			Schmitt (2008)		
Tissue	**BPS**	**BPF**	**BPAF**	**BPS**	**BPF**	**BPAF**
Fat	44.3	99.7	112	3.85	27.3	276
Liver	2.23	5.73	8.05	8.51	9.16	16.8
Brain	1.74	3.64	7.04	10.2	11.6	26.2
Skin	1.91	4.45	6.21	1.74	3.28	18.6
Gonads	1.20	2.15	2.80	5.26	5.26	5.26
Slow[a]	1.70	3.67	4.99	7.30	8.91	23.4
Rich[b]	1.36	2.61	4.63	4.95	5.26	8.84

[a]Perfusion lower than 0.1 mL/min/g tissue: muscle and skeleton (Edginton et al. 2006; ICRP 2002).
[b]Perfusion higher than 0.1 mL/min/g tissue: heart, kidneys, small and large intestine, pancreas, spleen, and stomach (Edginton et al. 2006; ICRP 2002).

Abbreviations: BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; rich, richly perfused tissue; slow, slowly perfused tissue.

Table S9. Scenario specific exposure parameters for the comparison with Hormann et al. (2014).

Exposure	Start time (min)	End time (min)	Dose (µg)	Extent of absorption	Absorption half-life (min)
Dermal exposure 1	0.00	8.00	1,160	0.682/0.755[a]	3.03/2.87[a]
Dermal exposure 2	8.00	90.0	127	0.682/0.755[a]	3.03/2.87[a]
Peroral exposure	4.00	8.00	58.0/15.0[a]	1.00	0.00

Hormann et al. (2014) provided age, gender and weight of the volunteers and we set these parameters accordingly. We used the following exposure scenario: Use hand sanitizer – hold a thermal receipt paper containing bisphenol A – eat 10 French Fries with the contaminated hand.

[a]Indicates values for female/male.

Table S10. PBPK model parameters for bisphenol S before and after the calibration.

Parameter	Uncalibrated	Calibrated model
Peroral uptake from small intestine to liver (1/h/kg $bw^{-0.25}$)	2.1	5.0
Glucuronidation in enterocytes		
K_m (nM)	354,000	555,000[a]
Hepatic glucuronidation		
K_m (nM)	285,000	446,000[a]
v_{max} (nmol/h/g liver)	26,500	7,810[b]
Fraction of glucuronide in the liver taken up directly into serum	0.9	0.33
EHR as BPS-g (1/h/kg $bw^{-0.25}$)	0.2	2.0
EHR as BPS (1/h/kg $bw^{-0.25}$)	0.2	0.35
Urinary excretion BPS (1/h/kg $bw^{0.75}$)	0.06	0.3
Urinary excretion BPS-g (1/h/kg $bw^{0.75}$)	0.35	1.2

[a]Upper bound of truncated normal distribution.
[b]Lower bound of truncated normal distribution.
Abbreviations: EHR, enterohepatic recirculation; g, glucuronide; Km, Michaelis-Menten constant; PBPK, physiologically based pharmacokinetic; v_{max}, maximum reaction velocity.

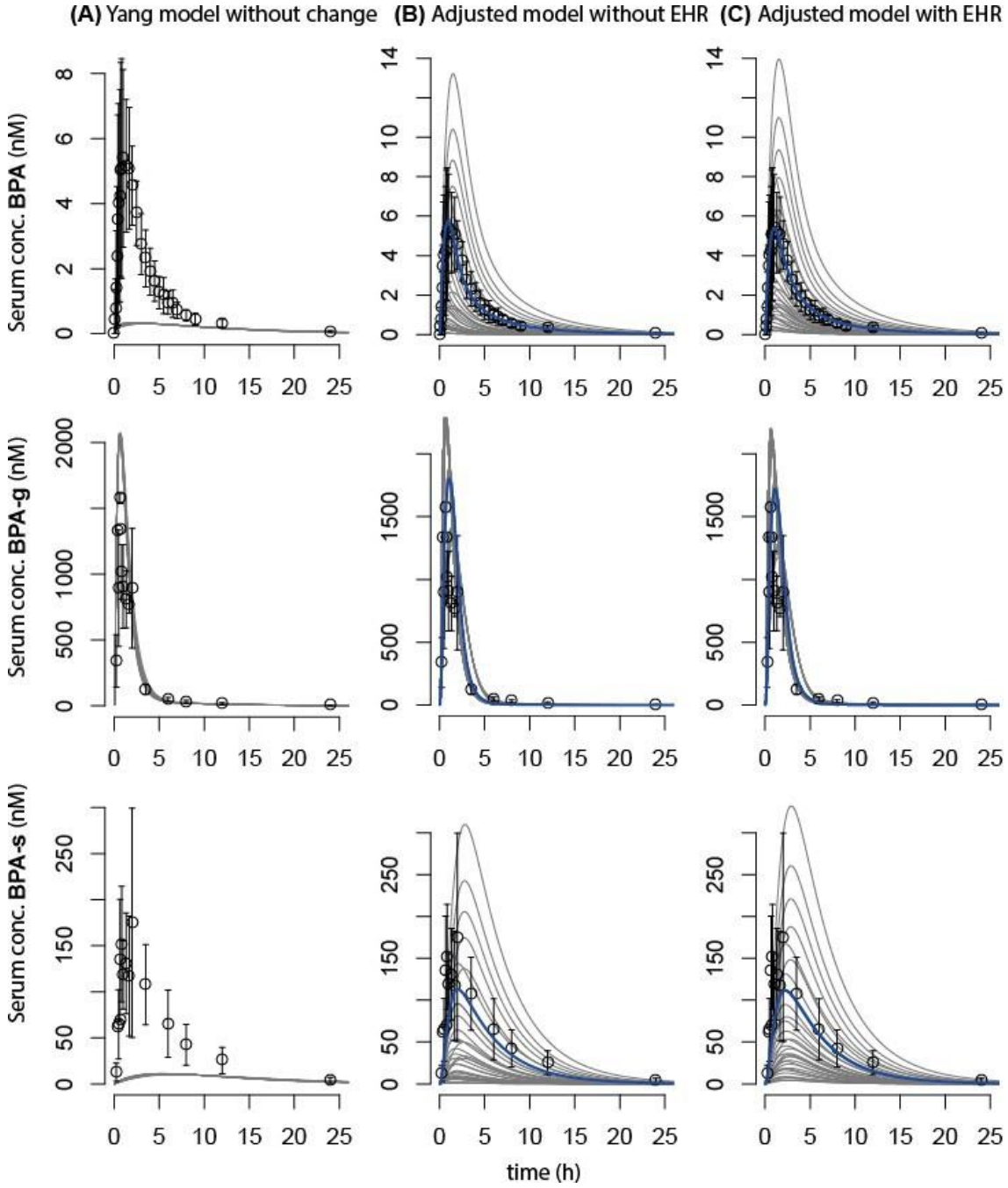

Figure S1. Measured and modeled serum concentration–time profiles of BPA, BPA-g, and BPA-s after peroral dosing with 100 µg BPA/kg bw. Individual measurements (open circles) represent observed serum concentrations (average ± standard deviation) of 14 adults (Thayer et al. 2015). Concentration profiles for the respective volunteers (grey solid lines) were modeled using (A) the published model by Yang et al. (2015) and (B and C) adjusted models with partly different parametrizations (see Tables 7 and 8) assuming either (B) no EHR or (C) a BPA EHR rate of 10% (see Table 5 for uptake parameters). Grey solid lines in the latter two columns depict the model results with varying parameter sets, for the individual with the median BPA concentration-time profile for better clarity (for evaluating the effects of different parameter sets all individuals were considered). The sets describing the biomonitoring data best are highlighted in blue. Abbreviations: BPA, bisphenol A; bw, bodyweight; conc., concentration; EHR, enterohepatic recirculation; g, glucuronide; s, sulfate.

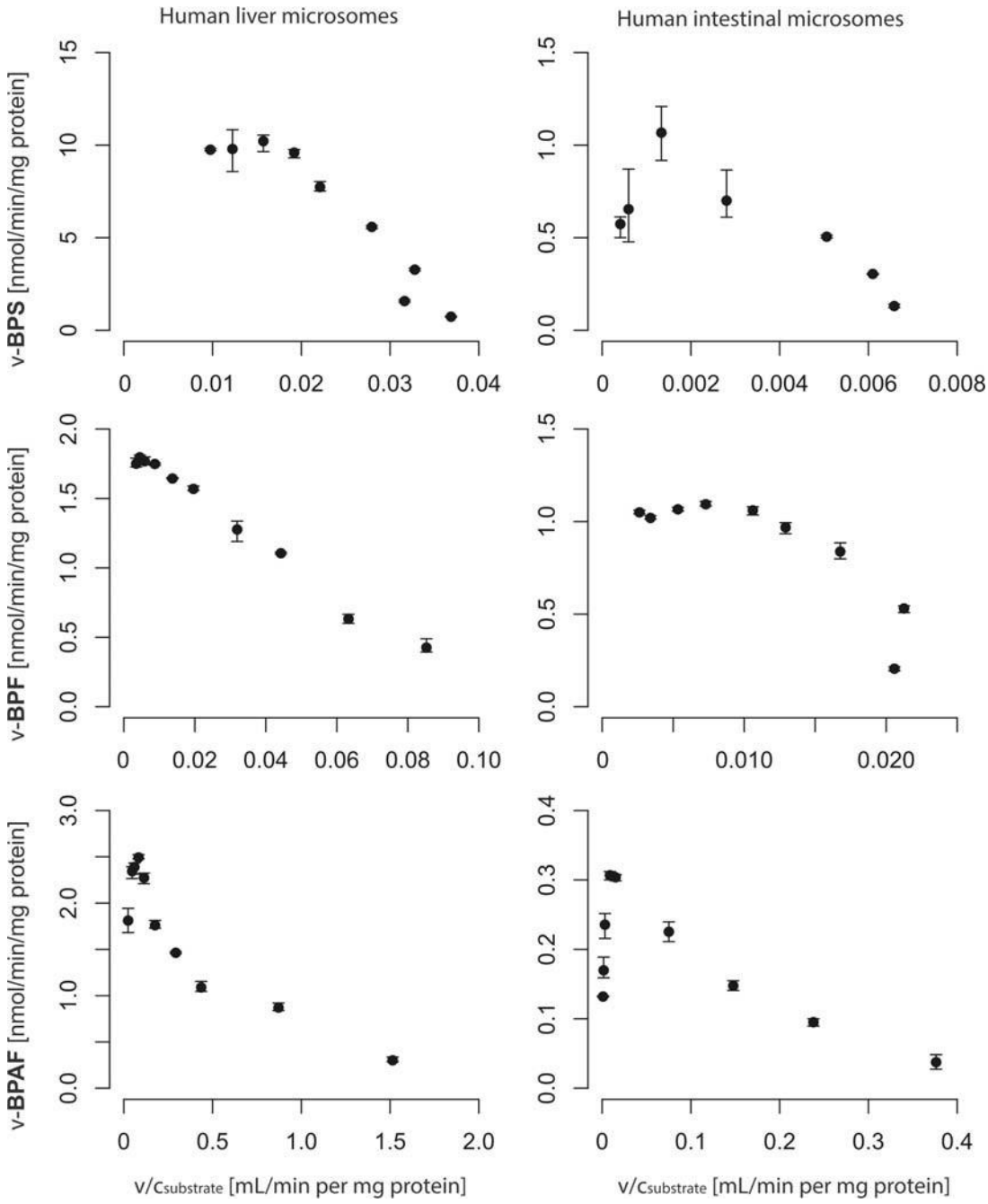

Figure S2. Eadie Hofstee plots of enzyme kinetics of BPS, BPF, and BPAF with human liver and intestinal microsomes. Shown are averages (black circles) and ranges from minimal to maximal reaction velocities (whiskers). Abbreviations: BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; $c_{substrate}$, substrate concentration; v, reaction velocity.

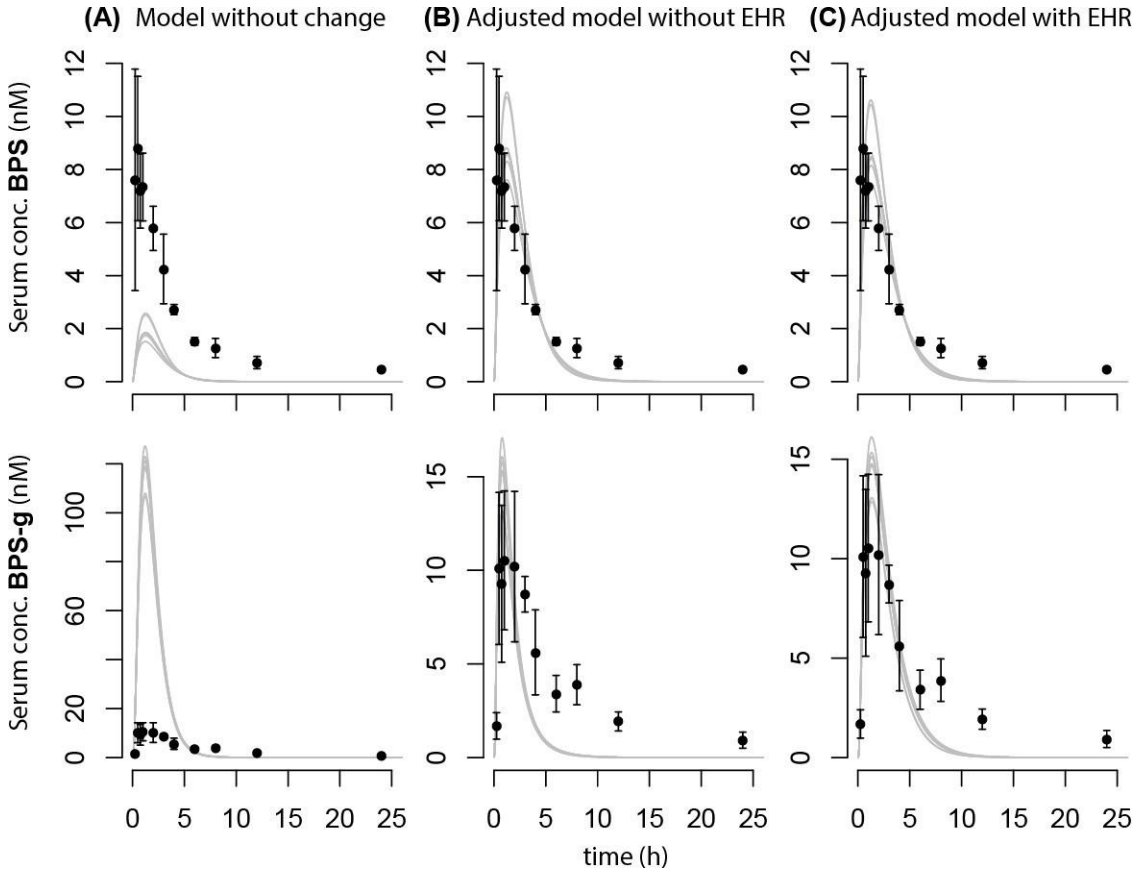

Figure S3. Measured and modeled serum concentration–time profiles of BPS and BPS-g after peroral dosing with 8.75 µg BPS/kg bw. Individual measurements (black circles) represent observed serum concentrations (average ± standard deviation) of 7 adults (Oh et al. 2018). Concentration profiles for the respective volunteers (grey solid lines) were modeled using (A) the adjusted PBPK model for BPA further adjusted with BPS-specific metabolism parameters (Table 7) and (B and C) the BPS-specific model calibrated to assume a higher peroral uptake and increased clearance rates of BPS and BPS-g assuming either (B) no EHR or (C) a BPS EHR rate of 67% (see Table 5 for uptake parameters). Abbreviations: BPA, bisphenol A; BPS, bisphenol S; bw, bodyweight; EHR, enterohepatic recirculation; g, glucuronide.

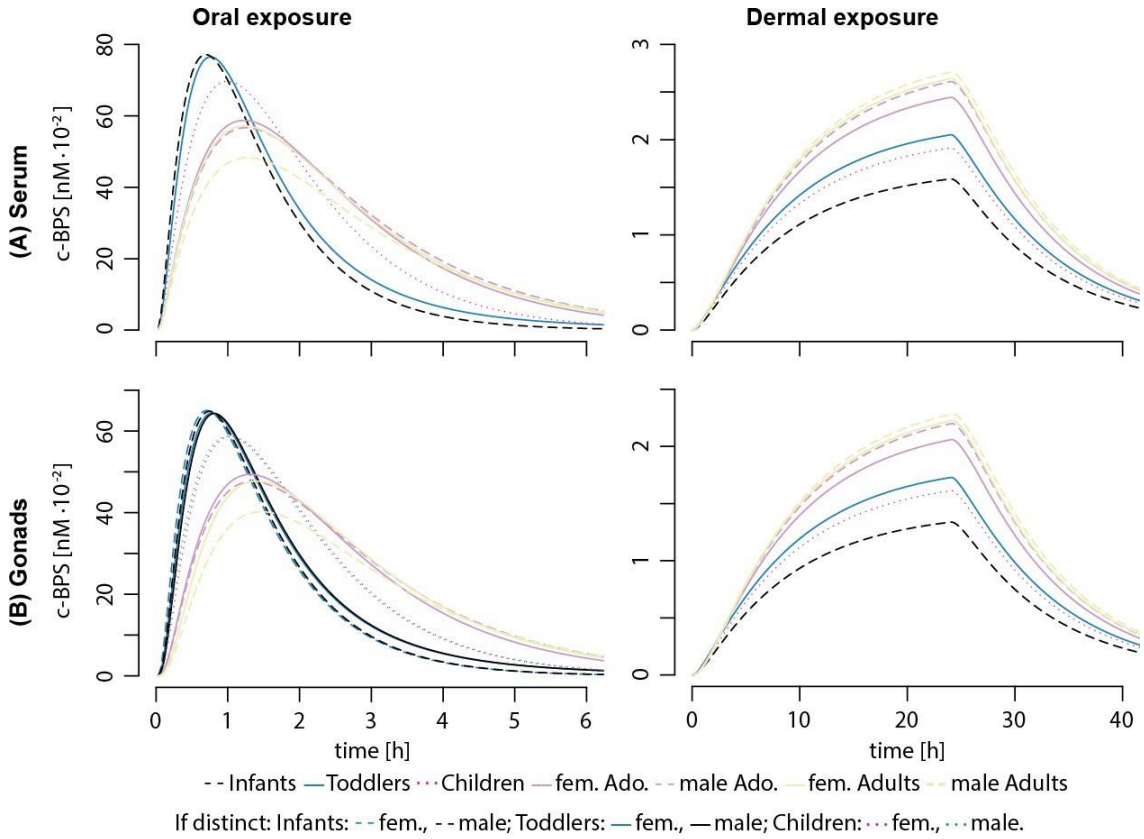

Figure S4. Modeled concentration profiles of unconjugated BPS obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPS, bisphenol S; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

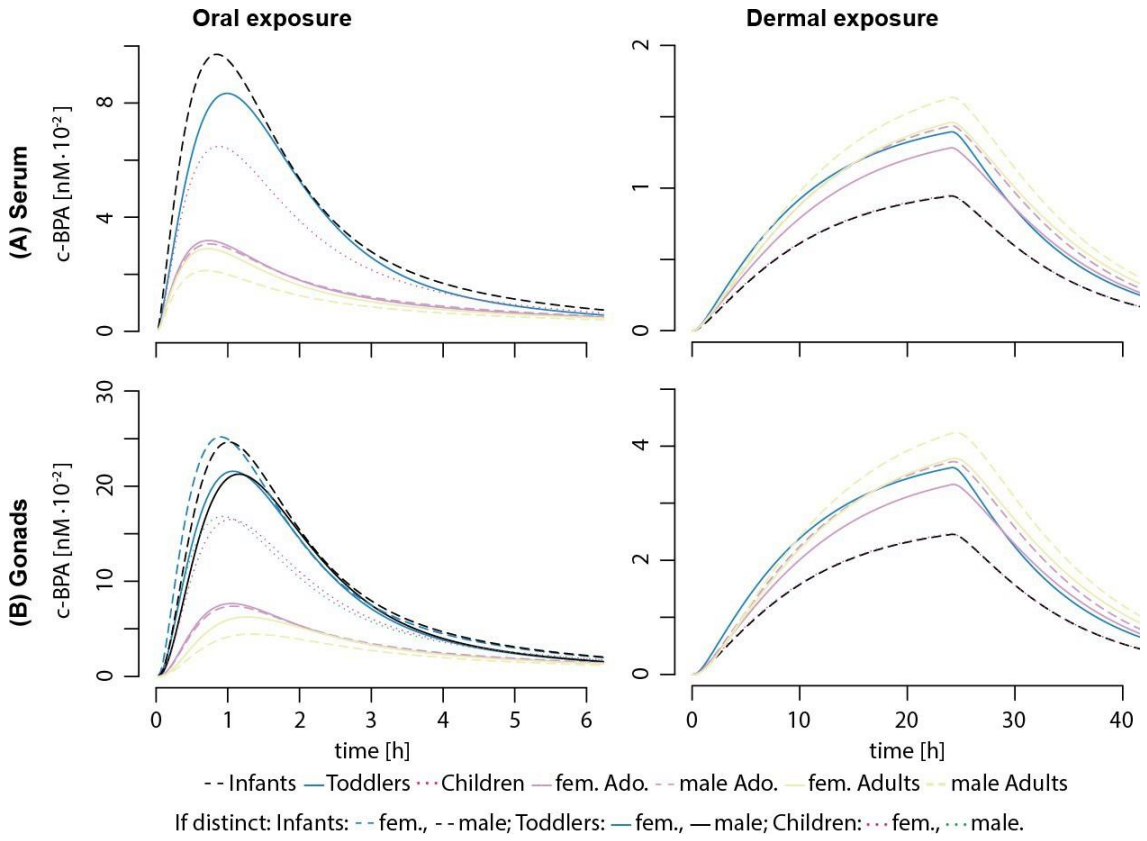

Figure S5. Modeled concentration profiles of unconjugated BPA obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPA, bisphenol A; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

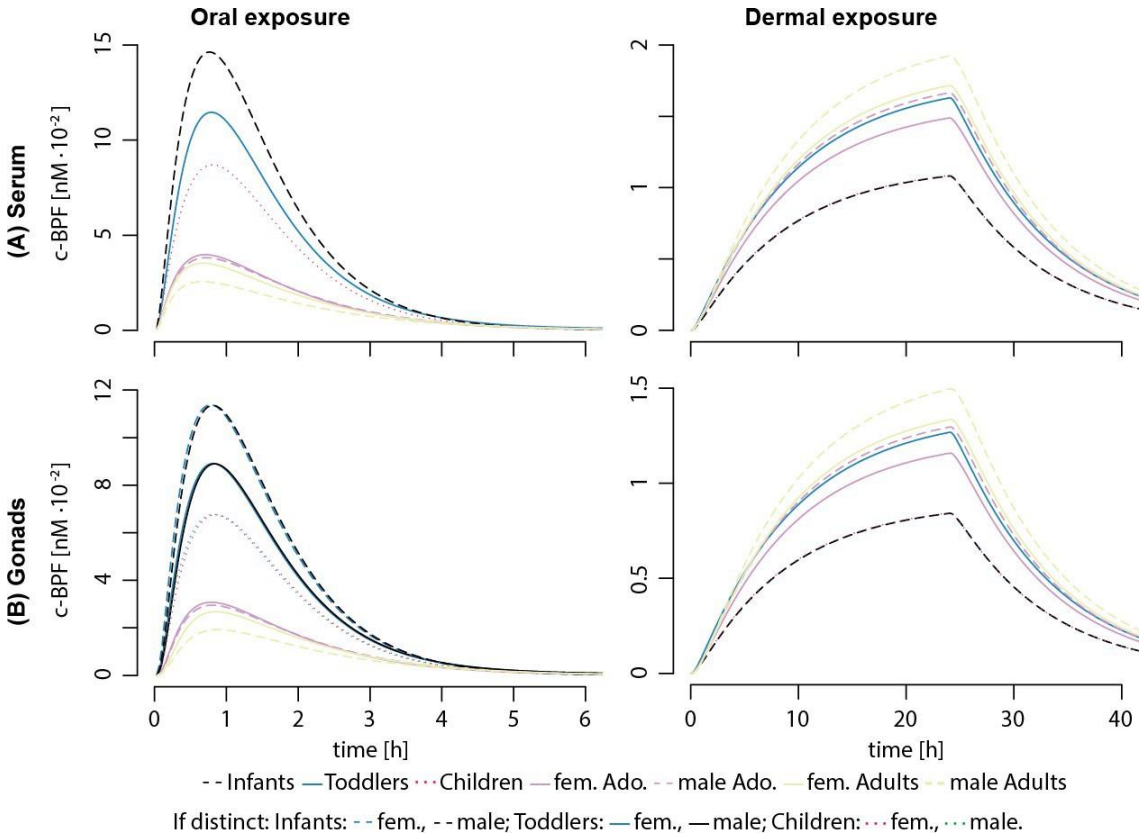

Figure S6. Modeled concentration profiles of unconjugated BPF obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPF, bisphenol F; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

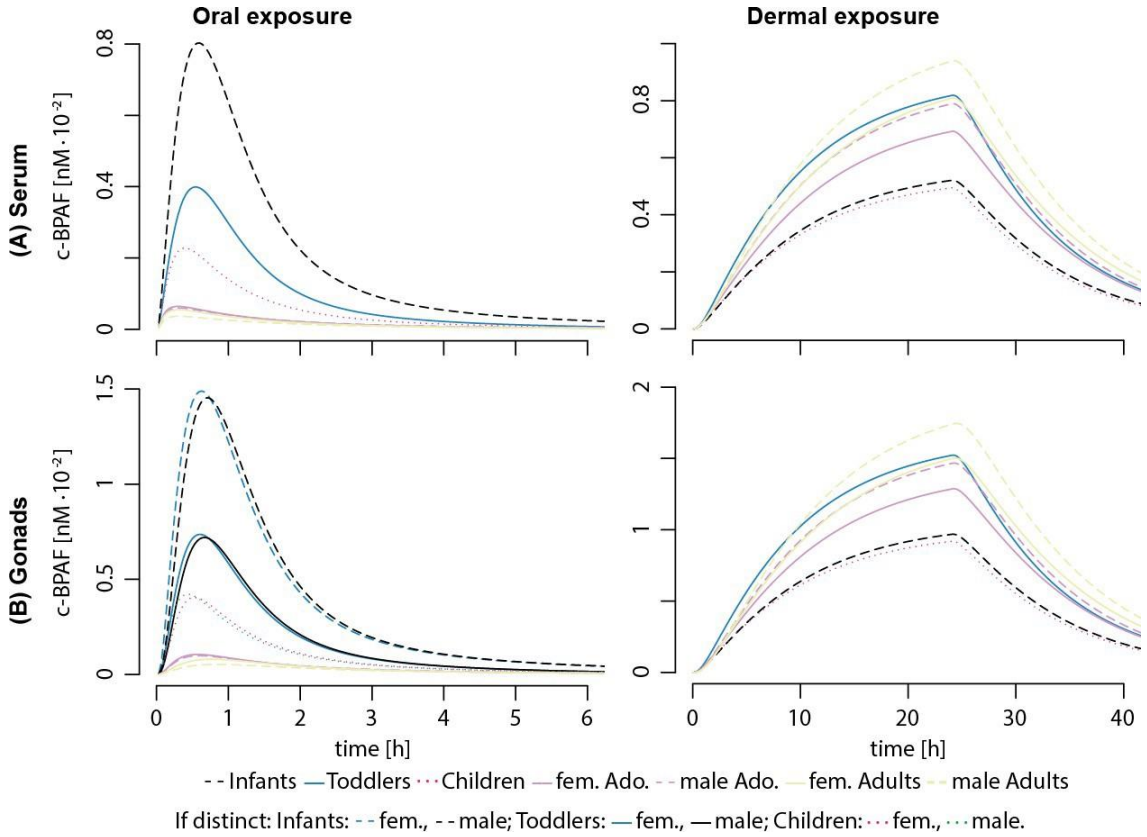

Figure S7. Modeled concentration profiles of unconjugated BPAF obtained with the basic PBPK model in serum (A) and gonads (B) for infants (6 days-3 months), toddlers (1-3 years), children (3-10 years), adolescents (10-18 years), and adults (18-45 years) after 500 ng/kg bw single peroral and dermal exposures (t=0) respectively (rough average of peroral and dermal high BPA exposure estimates for adults by the EFSA CEF Panel (2015)), see Table 5 for uptake parameters. Females are represented by solid lines, males are represented by dotted lines. Abbreviations: BPAF, bisphenol AF; bw, bodyweight; c, concentration; PBPK, physiologically based pharmacokinetic.

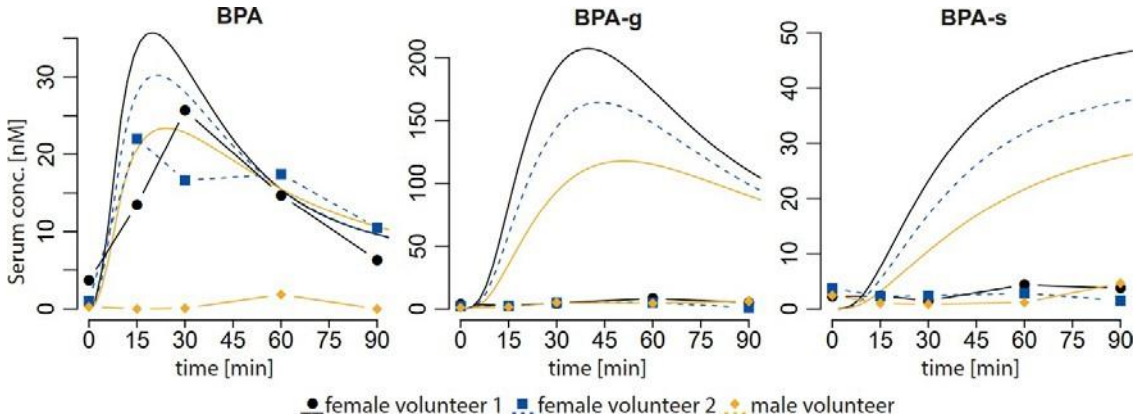

Figure S8. Measurements of Hormann et al. (2014) (symbols) against modeled individual serum profiles (solid lines) of unconjugated BPA, BPA-g, and BPA-s in three volunteers. They handled receipt paper for 4 min with both hands which were wetted with skin sanitizer and ate 10 French fries with a contaminated hand afterwards during 4 min. One hand was then cleaned and the other hand stayed contaminated until the end of blood collection (90 min in total, see Table S9 for study-specific parameters). Abbreviations: BPA, bisphenol A; g, glucuronide; s, sulfate.

Input tables

Table C1. Input table "Probanden" used in the basic PBPK model code for BPA.

ID	bw (kg)	Age (y)	Height (cm)	Sex	Exp. peroral (ng/kg bw/day)	Exp. dermal TP (ng/kg bw/day)	Exp. dermal PCPs (ng/kg bw/day)
1	3.5	0	51	female	615	0	9.4
2	3.5	0	51	male	615	0	9.4
3	10	1	76	female	869	0	5.5
4	10	1	76	male	869	0	5.5
5	19	5	109	female	818	550	4.2
6	19	5	109	male	818	550	4.2
7	53	15	161	female	384	863	4.8
8	56	15	167	male	384	863	4.8
9	60	30	163	female	389	542	4.0
10	73	30	176	male	336	542	4.0

Abbreviations: BPA, bisphenol A; bw, body weight; exp., exposure; ID, person ID; PBPK, physiologically based pharmacokinetic; PCPs, personal care products; TP, thermal paper; y, years.

Table C2. Input table "physAge" used in the basic PBPK model code for BPA.

Par.	Inf.F	Inf.M	Tod.F	Tod.M	Chi.F	Chi.M	Ado.F	Ado.M	Adu.F	Adu.M
Qc	0.60	0.600	0.600	1.20	3.40	3.40	6.10	6.10	5.90	6.50
Qgonad	0.00043	0.00043	0.00037	0.00037	0.00018	0.00044	0.00017	0.00045	0.00018	0.00045
Qliver	0.22	0.22	0.19	0.19	0.23	0.23	0.24	0.23	0.24	0.23
Qfat	0.043	0.043	0.0075	0.0075	0.044	0.044	0.076	0.045	0.074	0.044
Qbrain	0.26	0.26	0.44	0.44	0.23	0.23	0.11	0.11	0.11	0.11
Qskin	0.043	0.043	0.037	0.037	0.044	0.044	0.044	0.045	0.044	0.044
Qslow	0.087	0.087	0.064	0.064	0.099	0.099	0.15	0.18	0.14	0.19
Vplasma	0.046	0.046	0.030	0.030	0.044	0.044	0.039	0.046	0.040	0.041
Vfat	0.25	0.25	0.36	0.36	0.26	0.26	0.30	0.17	0.32	0.20
Vliver	0.037	0.037	0.033	0.033	0.030	0.030	0.025	0.023	0.023	0.025
Vbrain	0.11	0.11	0.095	0.095	0.066	0.066	0.025	0.025	0.022	0.020
Vskin	0.050	0.050	0.035	0.035	0.030	0.030	0.032	0.036	0.038	0.045
Vgonads	0.000086	0.00024	0,000080	0.00015	0.00011	0.000090	0.00011	0.00029	0.00018	0.00048
Vslow	0.34	0.34	0.31	0.31	0.42	0.42	0.46	0.57	0.43	0.54
Vrich	0.096	0.096	0.075	0.075	0.066	0.066	0.056	0.055	0.059	0.054

Abbreviations: Ado, adolescents; Adu, adults; BPA, bisphenol A; Chi, children; F, female; Inf, infants; M, male; Par., parameter; PBPK, physiologically based pharmacokinetic; Q, fractional blood flow (fraction of Qc); Qc, cardiac output (L/min); rich, richly perfused tissue; slow, slowly perfused tissue; Tod, toddlers; V, fractional tissue volume (fraction of body weight).

Table C3. Input table "VarInputFem" used in the PBPK model code for the 2D Monte Carlo Analysis of BPA in women (18-45 years).

parameterVar	meanVar	SDVar	aVar	bVar
BMI	3.25	0.185	15.9	35.9
age	32.0			
height	1.646	0.068	1.51	1.78
QCC	354	81.4	194	514
Qgonad	0.000178	4.81E-05	8.38E-05	0.000272
Qliver	0.240	0.0649	0.113	0.368
Qfat	0.0745	0.0201	0.0350	0.114
Qbrain	0.105	0.0284	0.0495	0.161
Qskin	0.0437	0.0118	0.0206	0.0669
Qslow	0.142	0.0384	0.0670	0.218
Qrich	0.394	0.106	0.185	0.602
Vplasma	0.04	0.01	0.0204	0.0596
Vliver	0.0233	0.00583	0.0119	0.0348
Vgonad	0.000183	4.58E-05	0.0000935	0.000273
Vbrain	0.0217	0.00542	0.0111	0.0323
Vskin	0.0383	0.00958	0.0196	0.0572
Vslow	0.430	0.108	0.219	0.641
Vrich	0.0594	0.0149	0.0303	0.0886
Vsoll	0.93			
Vfat	0.317	0.0792	0.162	0.472

Abbreviations: a, lower boundary; b, upper boundary; BMI, body mass index; BPA, bisphenol A; PBPK, physiologically based pharmacokinetic; Q, fractional blood flow (fraction of QCC); QCC, cardiac output (L/h); rich, richly perfused tissue; SD, standard deviation; slow, slowly perfused tissue; soll, target; V, fractional tissue volume (fraction of body weight);Var, Variability.

Table C4. Input table "ChemData" used in the PBPK model code for the 2D Monte Carlo Analysis of BPA in women (18-45 years).

	MeanVar	SDVar	LowerB	UpperB
MW	228.3			
Fat	5	1.6	1.864	8.136
Liver	0.73	0.234	0.272144	1.188
Brain	2.8	0.896	1.04384	4.556
Skin	2.15	0.688	0.80152	3.498
Gonads	2.6	0.832	0.96928	4.231
Slowly perfused	2.7	0.864	1.00656	4.393
Richly perfused	2.8	0.896	1.04384	4.556
Km HepGl	45,800	13,282	19,767	71,833
Ki HepGl	0	0	0	0
Vmax HepGl	282.6	101.7	83.20	482.0
Km EntGl	58,400	16,936	25,205	91,595
Ki EntGl	0	0	0	0
Vmax EntGl	84	30.24	24.73	143.3

Abbreviations: B, boundary; BPA, bisphenol A; EntGl, glucuronidation in enterocytes; HepGl, hepatic glucuronidation; Ki, Substrate Inhibition constant; Km, Michaelis-Menten constant; MW, molecular weight; PBPK, physiologically based pharmacokinetic; SD, standard deviation; Var, Variability; Vmax, maximum reaction velocity.

Model code

a) PBPK model code as used in the basic model for BPA

```
#########################################################################
### PBPK model for bisphenols (here BPA) as used in the basic model ###
### The model is based on Yang et al. 2015                          ###
#########################################################################

library(deSolve)
library(plyr)

rm(list=ls(all=TRUE))

# data for different age groups, table provided in the SI
Probanden <- read.csv2("DataAgegroups.csv", stringsAsFactors = FALSE)
Probanden[,5] <- as.factor(Probanden[,5])

nPeople <- as.numeric(nrow(Probanden))

# fractional tissue volumes and cardiac output differ among age groups,
table provided in the SI
physAge <- read.csv2("PhysParametersAgegroups.csv")

#empty databases to store results
results <- matrix(0,ncol = nPeople,nrow = 7200)
results <- as.data.frame(results)

gonads <- matrix(0,ncol = nPeople,nrow = 7200)
gonads <- as.data.frame(gonads)

#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#      Physiological Parameters
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

for (i in 1:nPeople) { # run PBPK model for different age groups and gender

# Subject information i
bw           <- as.numeric(Probanden[i,2])     # (kg)            |Body weight
age          <- as.numeric(Probanden[i,3])     # (years)         |Age
height       <- as.numeric(Probanden[i,4]) /100 # (m)             |Height
BMI          <- bw/(height^2)                    #    |Body mass index
gender       <- Probanden[i,5]    #    |1=male, 2=female

# Blood flow rate #
QCC        <- physAge[1,i+1]     # (L/min)           |Cardiac output
# Fractional blood flows
QgonadC    <- physAge[2,i+1]       # (fraction of QC)     |gonads
QliverC    <- physAge[3,i+1]       # (fraction of QC)     |liver
QfatC    <-    physAge[4,i+1]       # (fraction of QC)     |fat
QbrainC   <-   physAge[5,i+1]       # (fraction of QC)     |brain
QskinC   <-   physAge[6,i+1]       # (fraction of QC)     |skin
QmuscleC <- physAge[7,i+1]         # (fraction of QC)     |muscle

# Fractional Tissue Volumes of bw
VplasmaC   <- physAge[8,i+1]       # (fraction of bw)     |plasma
VfatC      <- physAge[9,i+1]       # (fraction of bw)     |fat
VliverC    <- physAge[10,i+1]      # (fraction of bw)     |liver
VbrainC    <- physAge[11,i+1]      # (fraction of bw)     |brain
```

```
VskinC     <- physAge[12,i+1]      # (fraction of bw)     |skin
VgonadC    <- physAge[13,i+1]      # (fraction of bw)     |gonads
VmuscleC   <- physAge[14,i+1]    # (fraction of bw)     |muscle
VrichC     <- physAge[15,i+1]    # (fraction of bw)     |skin
VbodygC    <- VplasmaC           # (fraction of bw)     |Fractional volume
of the distribution for BPAG, set to plasma volume
VbodysC    <- VplasmaC           # (fraction of bw)     |Fractional volume
of the distribution for BPAS, set to plasma volume


#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#      Chemical specific parameters
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

MW          <- 228.28               # (g/mol)        |Molecular weight

# Partition Coefficients  for BPA
pliver      <- 0.73                 #            | (liver/blood)
pfat        <- 5.0                  #            | (fat/blood)
pslow       <- 2.7                  #            | (slowly perfused/blood)
prich       <- 2.8                  #            | (richly perfused/blood)
pgonad      <- 2.6                  #            | (gonads/blood)
pbrain      <- 2.8                  #            | (brain/blood)
pskin       <- 2.15                 #            | (skin/blood)

#BPA peroral uptake and metabolism in the gut
geC         <- 3.5           #  (1/h/bw^-0.25)  |Gastric emptying of BPA
k0C         <- 0             #  (1/h/bw^-0.25)  |Oral uptake of BPA from
the stomach into the liver; set to 0
k1C         <- 2.1           # (1/h/bw^-0.25)   |Oral uptake of BPA from
the small intestine into the liver
k4C         <- 0             # (1/h/bw^-0.25)   |Fecal elimination of BPA
from small intestine after peroral administration; set to 0
kGIingC     <- 50            # (1/h/bw^-0.25)   |Transport of BPAG from
enterocytes into serum
kGIinsC     <- 50            # (1/h/bw^-0.25)   |Transport of BPAS from
enterocytes into serum
kmgutg      <- 58400         # (nM)     |Glucuronidation of BPA in the gut
vmaxgutgC   <- 361           # (nmol/h/kg bw) |Glucuronidation of BPA in
the gut
fgutg       <- 1             #  Correction factor of glucuronidation in the
gut
kmguts      <- 0.001         # (nM)            |Sulfation of BPA in the
gut, not modeled
vmaxgutsC   <- 0.001         # (nmol/h/bw^0.75 |Sulfation of BPA in the gut
fguts       <- 0             # Correction factor of sulfation in the gut -
no sulfation in the gut assumed

#BPA metabolism in the liver
met1g        <- 0.9               #   |Fraction of BPAG in the liver taken
up directly into serum (set to 1 to deactivate EHR)
met1s        <- 1                 #   |Fraction of BPAS in the liver taken
up directly into serum
enterocytes  <- 0.1223                                    # (L)
|Sum of enterocytes weights in duodenum, jujunum and ileum (Gertz 2011)
kmliver      <- 45800         # (nM) |Glucuronidation of BPA in the liver
vmaxliverC   <- 9043.2        # (nmol/h/g liver) |Glucuronidation of BPA in
the liver
fliverg      <- 1
kmlivers     <- 10100         # (nM)             |Sulfation of BPA in the
liver, set to the value for SULT1A1 (Takahito 2002)
vmaxliversC  <- 149    # (nmol/h/g liver) |Sulfation of BPA in the liver
```

```
flivers      <- 1

#EHR and urinary excretion of BPAG
EHRtime           <- 0.00          # (h)        |Time until EHR occurs
EHRrateC          <- 0.2           # (1/h/bw^-0.25)    |EHR of BPAG
k4C_IV            <- 0             # (1/h/bw^-0.25)    |Fecal elimination of
BPAG from the EHR compartment

kurinebpaC        <- 0.06          # (L/h/bw^0.75)     |Clearance of BPA
kurinebpagC       <- 0.35          # (L/h/bw^0.75)     |Clearance of BPAG
kurinebpasC       <- 0.03          # (L/h/bw^0.75)     |Clearance of BPAS
vreabsorptiongC   <- 0             # (nmol/h/bw^0.75) |vmax for renal
reabsorption of BPAG
vreabsorptionsC    <- 0            # (nmol/h/bw^0.75) |vmax for renal
reabsorption of BPAS
kreabsorptiong    <- 9200          # (nmol/L)          |Km for renal
reabsorption of BPAG
kreabsorptions    <- 9200          # (nmol/L)          |Km for renal
reabsorption of  BPAS

kenterobpagC      <- 0.2             # (1/h/bw^-0.25)    |EHR of BPA due to
biliary excretion of BPAG
kenterobpasC      <- 0.0           # (1/h/bw^-0.25)    |EHR of BPA due to
biliary excretion of BPAS


#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#    Dosing Parameters (oral)
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

#Day 1
#Oral Dosing 1
D.o      <- as.numeric(Probanden[i,6])/3                 # (ng/kg bw/d)
|oral   dose is equally distributed among the dosings
dose.O   <- D.o/MW                    # (nmol/kg/d) |oral   dose
EoA.O    <- 1                         #             |extent of peroral   abs.
uptake.O <- bw*dose.O                 # (nmol)      |amount of uptake
period.O <- 3/60                      # (h)         |uptake period
koa      <- uptake.O/period.O         # (nmol/h)    |uptake rate
t0.O     <- 0                         #    time points at which dosing  starts
t1.O     <- t0.O + period.O           #    time at which dosing occurs

#Oral Dosing 2
t0.O2     <- 6                         #   time points at which dosing starts
t1.O2     <- t0.O2 + period.O          #   time at which dosing occurs

#Oral Dosing 3
t0.O3     <- 12                        #   time points at which dosing starts
t1.O3     <- t0.O3 + period.O          #   time at which dosing occurs


#Day 2
#Oral Dosing 1
t0.O4     <- 24                        #   time points at which dosing starts
t1.O4     <- t0.O4 + period.O          #    time at which dosing occurs

#Oral Dosing 2
t0.O5     <- 30                        #   time points at which dosing starts
t1.O5     <- t0.O5 + period.O          #   time at which dosing occurs

#Oral Dosing 3
t0.O6     <- 36                        #   time points at which dosing starts
```

```
t1.O6     <- t0.O6 + period.O        #   time at which dosing occurs

#Day 3
#Oral Dosing 1
t0.O7     <- 48                   #      time points at which dosing starts
t1.O7     <- t0.O7 + period.O     #      time at which dosing occurs

#Oral Dosing 2
t0.O8     <- 54                   #      time points at which dosing starts
t1.O8     <- t0.O8 + period.O     #      time at which dosing occurs

#Oral Dosing 3
t0.O9     <- 60                   #      time points at which dosing starts
t1.O9     <- t0.O9 + period.O     #      time at which dosing occurs

#Day 4
#Oral Dosing 1
t0.O10     <- 72                  #      time points at which dosing starts
t1.O10     <- t0.O10 + period.O   #      time at which dosing occurs

#Oral Dosing 2
t0.O11     <- 78                  #      time points at which dosing starts
t1.O11     <- t0.O11 + period.O   #      time at which dosing occurs

#Oral Dosing 3
t0.O12     <- 84                  #       time points at which dosing starts
t1.O12     <- t0.O12 + period.O   #       time at which dosing occurs

# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#   Dosing Parameters (dermal)
# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

#Day 1
#Dermal uptake from thermal paper 1
D.d      <- as.numeric(Probanden[i,7])/2         # (ng/kg/d)   |dermal dose
(Thermal  paper)
EoA.D    <- 0.2       #             |extent of dermal abs. (Thermal paper)
dose.D   <- D.d/MW                  # (nmol/kg/d) |dermal dose
aHL.D    <- 6               # (h)         |Half-life for dermal penetration
uptake.D <- bw*dose.D               # (nmol)      |amount of uptake
period.D <- 24                      # (h)         |uptake period
kda      <- uptake.D/period.D       # (mg/h)      |uptake rate
t0.D     <- 0                       #    time points at which dosing starts
t1.D     <- t0.D + period.D         #    time at which dosing occurs

# Dermal uptake from thermal paper 2
t0.D3     <- 12                     #    time points at which dosing starts
t1.D3     <- t0.D3 + period.D       #    time at which dosing occurs

#Day 2
#Dermal uptake from thermal paper 1
t0.D5     <- 24                     #    time points at which dosing starts
t1.D5     <- t0.D5 + period.D       #    time at which dosing occurs

# Dermal uptake from thermal paper 2
t0.D7     <- 36                     #    time points at which dosing starts
t1.D7     <- t0.D7 + period.D       #    time at which dosing occurs

#Day 3
#Dermal uptake from thermal paper 1
t0.D9     <- 48                      #   time points at which dosing starts
t1.D9     <- t0.D9 + period.D        #   time at which dosing occurs
```

```
# Dermal uptake from thermal paper 2
t0.D11     <- 60                    #    time points at which dosing starts
t1.D11     <- t0.D11  + period.D    #    time at which dosing  occurs

#Day 4
#Dermal uptake from thermal paper 1
t0.D13     <- 72                    #    time points at which dosing starts
t1.D13     <- t0.D13 + period.D     #    time at which dosing occurs

# Dermal uptake from thermal paper 2
t0.D15     <- 84                    #    time points at which dosing starts
t1.D15     <- t0.D15 + period.D     #    time at which dosing occurs

# Dermal uptake from PCPs
# Day 1
D.d2       <- as.numeric(Probanden[i,8])/2  # (ng/kg/d)  |dermal dose (PCPs)
EoA.D2      <- 0.6    #             |extent of dermal abs. (Thermal paper)
dose.D2    <- D.d2/MW       # (nmol/kg/d) |dermal dose
aHL.D2      <- 0.16         # (h)         |Half-life for dermal penetration
uptake.D2 <- bw*dose.D2    # (nmol)      |amount of uptake
period.D2 <- 24            # (h)         |uptake period
kda2       <- uptake.D2/period.D2      # (mg/h)      |uptake rate
t0.D2      <- 0
t1.D2      <- t0.D2 + period.D2        #         time at which dosing occurs

# Dermal uptake from PCPs 2
t0.D4      <- 12
t1.D4      <- t0.D4 + period.D2        #       time at which dosing occurs

# Day 2
t0.D6      <- 24
t1.D6      <- t0.D6 + period.D2        #       time at which dosing occurs

# Dermal uptake from PCPs 2
t0.D8      <- 36
t1.D8      <- t0.D8 + period.D2        #       time at which dosing occurs

# Day 3
t0.D10     <- 48
t1.D10     <- t0.D10 + period.D2       #       time at which dosing occurs

# Dermal uptake from PCPs 2
t0.D12     <- 60
t1.D12     <- t0.D12 + period.D2       #       time at which dosing occurs

# Day 4
t0.D14     <- 72
t1.D14     <- t0.D14 + period.D2       #       time at which dosing occurs

# Dermal uptake from PCPs 2
t0.D16     <- 84
t1.D16     <- t0.D16 + period.D2       #       time at which dosing occurs

#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#    Derived Parameters
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

#Scaled cardiac output and blood flows
QC          <- QCC*60             # (L/h) |Cardiac output according to ICRP
Qfat        <- QfatC*QC                   # (L/h) |Blood flow to the fat
```

```
Qliver      <- QliverC*QC                 # (L/h) |Blood flow to the liver
Qgonad      <- QgonadC*QC                 # (L/h) |Blood flow to the gonads
Qbrain      <- QbrainC*QC                 # (L/h) |Blood flow to the brain
Qskin       <- QskinC*QC                  # (L/h) |Blood flow to the skin
Qslow       <- QmuscleC*QC #(L/h)|Blood flow to the slowly perfused tissues
Qrich       <- QC-Qliver-Qbrain-Qfat-Qgonad-Qskin-Qslow
# (L/h) |Blood flow to the richly perfused tissues

#Scaled tissue volumes
Vliver      <- VliverC*bw                 # (L)    |Volume of the liver
Vfat        <- VfatC*bw                   # (L)    |Volume of the fat
Vgonad      <- VgonadC*bw                 # (L)    |Volume of the gonads
Vplasma     <- VplasmaC*bw                # (L)    |Volume of the plasma
Vbrain      <- VbrainC*bw                 # (L)    |Volume of the brain
Vskin       <- VskinC*bw                  # (L)    |Volume of the skin
Vslow       <- VmuscleC*bw    # (L)    |Volume of the slowly perfused tissues
Vrich       <- VrichC*bw
Vbodyg      <- VbodygC*bw         # (L) |Volume of the distribution for BPAG
Vbodys      <- VbodysC*bw         # (L) |Volume of the distribution for BPAS

# Scaling of Vmax parameters

vmaxliversCnew <- vmaxliversC*VliverC*1000
vmaxliversCnew <- vmaxliversCnew*bw/(bw^0.75)

vmaxliverCnew <- vmaxliverC*VliverC*1000
vmaxliverCnew <- vmaxliverCnew*bw/(bw^0.75)

vmaxgutgCnew <- vmaxgutgC*bw/(bw^0.75)

#Scaled kinetic parameters
vreabsorptiong    <- vreabsorptiongC*bw^0.75      # (nmol/h)  |vmax of
renal resorption of BPAG
vreabsorptions    <- vreabsorptionsC*bw^0.75      # (nmol/h)  |vmax of
renal resorption of BPAS
EHRrate           <- EHRrateC/(bw^0.25)           # (1/h)     |EHR of BPAG
k0                <- k0C/bw^0.25                  # (1/h)     |Uptake of
BPA from the stomach into the liver
ge                <- geC/bw^0.25    # (1/h)     |Gastric emptying of BPA
k1                <- k1C/bw^0.25                  # (1/h)     |Uptake of
BPA from small intestine into the liver
k4                <- k4C/bw^0.25                  # (1/h)     |Fecal
excretion of BPA after peroral administration from small intestine
k4_IV             <- k4C_IV/bw^0.25               # (1/h)     |Fecal
excretion of BPAG from the EHR compartment
vmaxliver         <- vmaxliverCnew*fliverg*bw^0.75    # (nmol/h)  |vmax of
BPA glucuronidation in the liver
kGIing            <- kGIingC/bw^0.25              # (1/h)     |Uptake of
BPAG from small intestine into serum
met2g             <- 1.0-met1g                    # ()        |Fraction of
BPAG formed subject to EHR
met2s             <- 1.0-met1s                    # ()        |Fraction of
BPAS formed subject to EHR
kurinebpa         <- kurinebpaC*bw^0.75  # (L/h)|Clearance of BPA via urine
kurinebpag        <- kurinebpagC*bw^0.75 #(L/h)|Clearance of BPAG via urine
kurinebpas        <- kurinebpasC*bw^0.75 #(L/h)|Clearance of BPAS via urine
vmaxlivers        <- vmaxliversCnew*flivers*bw^0.75  # (nmol/h)  |vmax of
BPA sulfation in the liver
kGIins            <- kGIinsC/bw^0.25     # (1/h)     |Uptake of BPAS from
small intestine into serum
vmaxgutg          <- vmaxgutgCnew*fgutg*bw^0.75      # (nmol/h)  |vmax of
BPA glucuronidation in the gut
```

```
vmaxguts          <- vmaxgutsC*fguts*bw^0.75      # (nmol/h)  |vmax of BPA
sulfation in the gut
kenterobpag       <- kenterobpagC/bw^0.25         # (1/h)     |EHR of BPA
due to biliary excretion of BPAG
kenterobpas       <- kenterobpasC/bw^0.25         # (1/h)     |EHR of BPA
due to biliary excretion of BPAS


# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
# Compile parameters
# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

para  <- unlist(c(data.frame(
  QC,
  Qfat,
  Qliver,
  Qgonad,
  Qbrain,
  Qskin,
  Qrich,
  Qslow,
  Vliver,
  Vfat,
  Vgonad,
  Vplasma,
  Vbrain,
  Vskin,
  Vslow,
  Vrich,
  Vbodyg,
  Vbodys,
  pliver,
  pfat,
  pslow,
  prich,
  pgonad,
  pbrain,
  pskin,
  kmgutg,
  kmguts,
  met1g,
  met1s,
  enterocytes,
  kmliver,
  kmlivers,
  EHRtime,
  kreabsorptiong,
  kreabsorptions,
  vreabsorptiong,
  vreabsorptions,
  EHRrate,
  k0,
  ge,
  k1,
  k4,
  k4_IV,
  vmaxliver,
  kGIing,
  met2g,
  met2s,
  kurinebpa,
  kurinebpag,
```

```
  kurinebpas,
  vmaxlivers,
  kGIins,
  vmaxgutg,
  vmaxguts,
  kenterobpag,
  kenterobpas,
  koa,
  kda,
  kda2
)))
para


# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
# Initial conditions
# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

yini <- unlist(c(data.frame(
  Input.O        = 0,
  Input.D        = 0,
  Input.D2       = 0,
  AST         = 0,         #   Amount of BPA in stomach
  ASI         = 0,         #   Amount of BPA in small intestine
  Afeces      = 0,         #   Amount of BPA excreted into feces
  AAO      = 0, #   Amount of BPA taken up from small intestine into serum
  AGImet      = 0,         #   Amount of BPAG formed in small intestine
  AGImets     = 0,         #   Amount of BPAS formed in small intestine
  Aoral       = 0,         #   Amount of BPA peroral uptake
  AGIBPAg     = 0,         #   Amount of BPAG in small intestine
  AGIin    = 0, #   Amount of BPAG taken up from small intestine into serum
  AGIBPAs     = 0,         #   Amount of BPAS in small intestine
  AGIins   = 0, #   Amount of BPAS taken up from small intestine into serum
  Aplasma     = 0,         #   Amount of BPA in plasma
  AFat        = 0,         #   Amount of BPA in fat
  Agonad      = 0,         #   Amount of BPA in gonads
  Askin       = 0,         #   Amount of BPA in skin
  ALiver      = 0,         #   Amount of BPA in liver
  Amet_liver  = 0,         #   Amount of BPA glucuronidation in liver
  Amet_livers = 0,         #   Amount of BPA sulfation in liver
  Abrain      = 0,         #   Amount of BPA in brain
  AR          = 0,         #   Amount of BPA in richly perfused tissue
  AS          = 0,         #   Amount of BPA in slowly perfused tissue
  Aurinebpa   = 0,         #   Cummulative amount of BPA excreted into urine
  ABPAg       = 0,         #   Amount of BPAG taken up from the liver into
systemic circulation
  ABPAg_prod_delay = 0,    #   Amount of BPAG excreted from liver into bile
  ABPAg_gut   = 0,         #   Amount of BPAG taken up from the small
intestine into systemic circulation
  ABPAg_prod_delay_gut=0, #   Amount of BPAG excreted from small intestine
into bile
  ABPAs       = 0,         #   Amount of BPAS taken up from the liver into
systemic circulation
  ABPAs_prod_delay = 0,    #   Amount of BPAS excreted from liver into bile
  ABPAs_gut   = 0,         #   Amount of BPAS taken up from the small
intestine into systemic circulation
  ABPAs_prod_delay_gut=0, #   Amount of BPAS excreted from small intestine
into bile
  ABPA_delay  = 0,         #   Amount of BPAG in the gut (EHR compartment)
  ABPA_delayin= 0,         #   Amount of BPAG taken up into the systemic
circulation from the gut (EHR compartment)
```

```
  Afecesiv    = 0,        #   Amount of fecal excretion of BPAG from the
gut(EHR compartment)
  ABPA_delayinbpag = 0,   #   Amount of BPA into the systemic circulation
from the gut (EHR compartment for BPAG)
  Abpac       = 0,        #   Amount of BPAG in the system
  ABPA_delays = 0,        #   Amount of BPAS in the gut (EHR compartment)
  ABPA_delayins = 0,      #   Amount of BPAS taken up into the systemic
circulation from the gut (EHR compartment)
  Afecesivs   = 0,        #   Amount of fecal excretion of BPAS from the
gut(EHR compartment)
  ABPA_delayinbpas = 0,   #   Amount of BPA into the systemic circulation
from the gut (EHR compartment for BPAS)
  Abpasul     = 0,        #   Amount of BPAS in the system
  Aurinebpag  = 0,        #   Amount of BPAG in the bladder
  Areabsorption = 0,      #   Amount of renal reabsorption of BPAG
  Aurineg     = 0,        #   Amount of BPAG excreted
  Aurinebpas  = 0,        #   Amount of BPAS in the bladder
  Areabsorptions = 0,     #   Amount of renal reabsorption of BPAS
  Aurines     = 0,        #   Amount of BPAS excreted
  SSD           = 0,      #   Skin surface depot Thermal paper
  SSD2          = 0,      #   Skin surface depot PCPs
  Cgut          = 0,
  CVLiver       = 0
)))

yini


#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#         Model for BPA
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

PBTKmod <- function(t, y, parms)
{
  with (as.list(c(y, parms)),
        {
          if(t<EHRtime){kentero=0}else{kentero=EHRrate}               #
Time dependent EHR of BPA metabolites

          if(t<=t1.O && t>=t0.O){onoff.O=1} else{onoff.O=0}
          if(t<=t1.O2 && t>=t0.O2){onoff.O2=1} else{onoff.O2=0}
          if(t<=t1.O3 && t>=t0.O3){onoff.O3=1} else{onoff.O3=0}
          if(t<=t1.O4 && t>=t0.O4){onoff.O4=1} else{onoff.O4=0}
          if(t<=t1.O5 && t>=t0.O5){onoff.O5=1} else{onoff.O5=0}
          if(t<=t1.O6 && t>=t0.O6){onoff.O6=1} else{onoff.O6=0}
          if(t<=t1.O7 && t>=t0.O7){onoff.O7=1} else{onoff.O7=0}
          if(t<=t1.O8 && t>=t0.O8){onoff.O8=1} else{onoff.O8=0}
          if(t<=t1.O9 && t>=t0.O9){onoff.O9=1} else{onoff.O9=0}
          if(t<=t1.O10 && t>=t0.O10){onoff.O10=1}else{onoff.O10=0}
          if(t<=t1.O11 && t>=t0.O11){onoff.O11=1}else{onoff.O11=0}
          if(t<=t1.O12 && t>=t0.O12){onoff.O12=1}else{onoff.O12=0}

          if(t<=t1.D && t>=t0.D){onoff.D=1} else{onoff.D=0}
          if(t<=t1.D2 && t>=t0.D2){onoff.D2=1} else{onoff.D2=0}
          if(t<=t1.D3 && t>=t0.D3){onoff.D3=1} else{onoff.D3=0}
          if(t<=t1.D4 && t>=t0.D4){onoff.D4=1} else{onoff.D4=0}
          if(t<=t1.D5 && t>=t0.D5){onoff.D5=1} else{onoff.D5=0}
          if(t<=t1.D6 && t>=t0.D6){onoff.D6=1} else{onoff.D6=0}
          if(t<=t1.D7 && t>=t0.D7){onoff.D7=1} else{onoff.D7=0}
          if(t<=t1.D8 && t>=t0.D8){onoff.D8=1} else{onoff.D8=0}
          if(t<=t1.D9 && t>=t0.D9){onoff.D9=1} else{onoff.D9=0}
          if(t<=t1.D10 && t>=t0.D10){onoff.D10=1}else{onoff.D10=0}
```

```
          if(t<=t1.D11 && t>=t0.D11){onoff.D11=1} else{onoff.D11=0}
          if(t<=t1.D12 && t>=t0.D12){onoff.D12=1} else{onoff.D12=0}
          if(t<=t1.D13 && t>=t0.D13){onoff.D13=1} else{onoff.D13=0}
          if(t<=t1.D14 && t>=t0.D14){onoff.D14=1} else{onoff.D14=0}
          if(t<=t1.D15 && t>=t0.D15){onoff.D15=1} else{onoff.D15=0}
          if(t<=t1.D16 && t>=t0.D16){onoff.D16=1} else{onoff.D16=0}

          #Dermal dosing
          dTPM      <- kda*onoff.D*EoA.D + kda*onoff.D3*EoA.D +
kda*onoff.D5*EoA.D + kda*onoff.D7*EoA.D + kda*onoff.D9*EoA.D +
kda*onoff.D11*EoA.D + kda*onoff.D13*EoA.D+ kda*onoff.D15*EoA.D     # Dermal
dosing Thermal paper
          dPCP      <- kda2*onoff.D2*EoA.D2 + kda2*onoff.D4*EoA.D2+
kda2*onoff.D6*EoA.D2 + kda2*onoff.D8*EoA.D2 + kda2*onoff.D10*EoA.D2 +
kda2*onoff.D12*EoA.D2 + kda2*onoff.D14*EoA.D2 + kda2*onoff.D16*EoA.D2      #
Dermal dosing PCPs

          dInput.D  <- log(2)*(1/aHL.D)*SSD  # input from thermal paper
          dInput.D2  <- log(2)*(1/aHL.D2)*SSD2  # input from PCPs

dSSD      <- -dInput.D + dTPM      # Skin-surface depot from thermal paper
dSSD2      <- -dInput.D2 + dPCP    # Skin-surface depot from thermal paper


          #Oral dosing
          dInput.O  <- koa*onoff.O + koa*onoff.O2 + koa*onoff.O3 +
koa*onoff.O4 + koa*onoff.O5 + koa*onoff.O6 + koa*onoff.O7 + koa*onoff.O8 +
koa*onoff.O9 + koa*onoff.O10 + koa*onoff.O11 + koa*onoff.O12


Cgut      <- ASI/enterocytes   # (nmol/L)  |Concentration of BPA in the
small intestine
RST       <- dInput.O-k0*AST-ge*AST   # (nmol/h)  |Rate of BPA amount
change in the stomach
RGImet    <- vmaxgutg*Cgut/(kmgutg+Cgut)      # (nmol/h)  |Rate of BPA
glucuronidation in the gut
RGImets   <- vmaxguts*Cgut/(kmguts+Cgut)      # (nmol/h)  |Rate of BPA
sulfation in the gut
Rfeces    <- k4*ASI    # (nmol/h)  |Rate of BPA excreted into feces
RAO       <- k1*ASI                           # (nmol/h)  |Uptake rate of
BPA from the small intestine into serum
RSI       <- ge*AST-RGImet-RAO-RGImets        # (nmol/h)  |Rate of BPA
amount change in the small intestine
Roral     <- k0*AST+RAO               # (nmol/h)  |Rate of BPA peroral
uptake

          #Amount of BPAG in GI tract
RGIin     <- kGIing*AGIBPAg                   # (nmol/h)  |Uptake rate of
BPAG from small intestine into serum
RGIBPAg   <- RGImet - RGIin                   # (nmol/h)  |Rate of BPAG
amount change in the small intestine

          #Amount of BPAS in GI tract
RGIins    <- kGIins*AGIBPAs                   # (nmol/h)  |Uptake rate of
BPAS from small intestine into serum
RGIBPAs   <- RGImets - RGIins                 # (nmol/h)  |Rate of BPAS
amount change in the small intestine


          ### C's and CV's ###

CFat       <- AFat/Vfat     # (nmol/L)   |Concentration of BPA in the fat
```

```
CVFat      <- AFat/(Vfat*pfat)    # (nmol/L)   |Venous blood concentration
of BPA leaving the fat
Cgonad     <- Agonad/Vgonad # (nmol/L)  |Concentration of BPA in the gonads
CVgonad    <- Agonad/(Vgonad*pgonad)          # (nmol/L)   |Venous blood
concentration of BPA leaving the gonads
Cskin      <- Askin/Vskin                     # (nmol/L)   |Concentration
of BPA in the skin
CVskin     <- Askin/(Vskin*pskin)             # (nmol/L)   |Venous blood
concentration of BPA leaving the skin
CLiver     <- ALiver/Vliver   # (nmol/L) |Concentration of BPA in the liver
CVLiver    <- ALiver/(Vliver*pliver)          # (nmol/L)   |Venous blood
concentration of BPA leaving the liver
Cbrain     <- Abrain/Vbrain   # (nmol/L) |Concentration of BPA in the brain
CVbrain    <- Abrain/(Vbrain*pbrain)          # (nmol/L)   |Venous blood
concentration of BPA leaving the brain
CR         <- AR/Vrich                             # (nmol/L)
|Concentraitoin of BPA in the rapidly perfused tissues
CVR        <- AR/(Vrich*prich)                # (nmol/L)   |Venous blood
concentration of BPA leaving the rapidly perfused tissues
CVS        <- AS/(Vslow*pslow)                # (nmol/L)   |Venous blood
concentration of BPA leaving the slowly perfused tissues
CS         <- AS/Vslow                        # (nmol/L)   |Concentration
of BPA in the slowly perfused  tissues
CV         <-
(CVLiver*Qliver+CVskin*Qskin+CVFat*Qfat+CVR*Qrich+CVS*Qslow+CVgonad*Qgonad+
CVbrain*Qbrain)/QC   #(nmol/L)         |Concentration of BPA in the venous
plasma.
CA         <- Aplasma/Vplasma
#(nmol/L)         |concentration of BPA in the arterial plasma


          #Excretion of BPA in urine
Rurinebpa   <- kurinebpa*CV   #(nmol/h)|Rate of BPA excreted into the urine

          #Amount of BPA in the plasma
Rplasma     <- QC*(CV-CA)-Rurinebpa     # (nmol/h)   |Rate of BPA amount
change in the plasma.

          #Amount of BPA in the Fat
RAfat <- Qfat*(CA-CVFat) # (nmol/h)   |Rate of BPA amount change in the fat

          #Amount of BPA in the gonads
RAgonad     <- Qgonad*(CA-CVgonad)  # (nmol/h)   |Rate of BPA amount change
in the gonads

          #Amount of BPA in the skin
          RAskin      <- dInput.D+dInput.D2+Qskin*(CA-CVskin)   # (nmol/h)
|Rate of BPA amount change in the skin

          #Amount of BPA in the liver
          RAM         <- vmaxliver*CVLiver/(kmliver+CVLiver)    # (nmol/h)
|Rate of BPA glucuronidation in the liver
          RAMs        <- vmaxlivers*CVLiver/(kmlivers+CVLiver)  # (nmol/h)
|Rate of BPA sulfation in the liver

          #Amount of BPA in the brain
Rbrain      <- Qbrain*(CA-CVbrain) # (nmol/h)   |Rate of BPA amount change
in the brain

          #Amount of BPA in rapidly perfused tissues
RAR         <- Qrich*(CA-CVR)                          # (nmol/h)   |Rate of
BPA amount change in rapidly perfused tissues
```

```
#Amount in slowly perfused tissues
          RAS         <- Qslow*(CA-CVS)                          # (nmol/h)
|Rate of BPA amount change in slowly perfused tissues



#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#         Model for BPAG
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

          #Fate of BPAG formed in the liver
RBPAg_prod   <- met1g*RAM # (nmol/h)    |Taken up into systemic circulation
RBPAg_prod_delay     <- met2g*RAM         # (nmol/h)    |Excreted into bile

          #Fate of BPAG formed in SI
RBPAg_prod_gut<-  met1g*RGIin # (nmol/h)|Taken up into systemic circulation
RBPAg_prod_delay_gut <-  met2g*RGIin   # (nmol/h)    |Excreted into bile

          #Fate of BPAS formed in the liver
RBPAs_prod <-  met1s*RAMs # (nmol/h)    |Taken up into systemic circulation
RBPAs_prod_delay <-  met2s*RAMs   # (nmol/h)    |Excreted into bile

          #Fate of BPAS formed in SI
RBPAs_prod_gut<- met1s*RGIins # (nmol/h)|Taken up into systemic circulation
RBPAs_prod_delay_gut <- met2s*RGIins    # (nmol/h)    |Excreted into bile

          #Amount of BPAG in the gut (EHR compartment)
RBPA_delayin      <- ABPA_delay*kentero       # (nmol/h)|Uptake rate of
BPAG into the systemic circulation from the gut (EHR compartment)
Rfecesiv          <- ABPA_delay*k4_IV         # (nmol/h)|Rate of fecal
excretion of BPAG from the gut (EHR compartment)
RBPA_delayinbpag  <- ABPA_delay*kenterobpag   # (nmol/h)|Uptake rate of BPA
into the systemic circulation from the gut (EHR compartment for BPAG)
Cbpac             <- Abpac/(Vbodyg+1E-34)     # (nmol/L)|Concentration of
BPAG in the system

          #Amount of BPAS in the gut (EHR compartment)
RBPA_delayins     <-  ABPA_delays*kentero     # (nmol/h) |Uptake rate of
BPAS into the systemic circulation from the gut (EHR compartment)
Rfecesivs         <-  ABPA_delays*k4_IV       # (nmol/h) |Rate of fecal
excretion of BPAS from the gut (EHR compartment)
RBPA_delayinbpas  <-  ABPA_delays*kenterobpas # (nmol/h) |Uptake rate of
BPA into the systemic circulation from the gut (EHR compartment for BPAS)
Cbpas             <-  Abpasul/(Vbodys+1E-34)  # (nmol/L) |Concentration of
BPAS in the system

          #Urinary excretion of BPAG
Rreabsorption    <-  vreabsorptiong*Cbpac/(kreabsorptiong+Cbpac)          #
(nmol/h)   |Rate of renal reabsorption of BPAG
Rurinebpag       <-  kurinebpag*Cbpac-Rreabsorption                       #
(nmol/h)   |Rate of BPAG amount change in the bladder
Rurineg          <-  kurinebpag*Cbpac   # (nmo/h)    |Rate of BPAG excreted

          #Urinary excretion of BPAs
Rreabsorptions   <-  vreabsorptions*Cbpas/(kreabsorptions+Cbpas)          #
(nmol/h)|Rate of renal reabsorption of BPAS
Rurinebpas       <-  kurinebpas*Cbpas-Rreabsorptions                      #
(nmol/h)|Rate of BPAS amount change in the bladder
Rurines          <-  kurinebpas*Cbpas    # (nmo/h)|Rate of BPAS excreted
```

```
Rbpas              <- RBPAs_prod+RBPA_delayins+RBPAs_prod_gut-Rurinebpas
# (nmol/h)  |Rate of BPAS amount change in the system
Rbpac              <- RBPAg_prod+RBPAg_prod_gut+RBPA_delayin-Rurinebpag
# (nmol/h)  |Rate of BPAG amount change in the system
RBPA_delay     <-     RBPAg_prod_delay+RBPAg_prod_delay_gut-RBPA_delayin-
Rfecesiv-RBPA_delayinbpag  #  (nmol/h)  |Rate  of  BPAG  amount  change  in
the gut (EHR compartment)
RBPA_delays        <- RBPAs_prod_delay+RBPAs_prod_delay_gut-RBPA_delayins-
Rfecesivs-RBPA_delayinbpas  # (nmol/h)  |Rate of BPAS amount change in the
gut (EHR compartment)
RALiver            <- Qliver*(CA-CVLiver)+Roral-RAM-
RAMs+RBPA_delayinbpag+RBPA_delayinbpas             # (nmol/h)  |Rate of BPA
amount change in the liver

dydt <-
c(dInput.O,dInput.D,dInput.D2,RST,RSI,Rfeces,RAO,RGImet,RGImets,Roral,RGIBP
Ag,RGIin,RGIBPAs,RGIins,Rplasma,RAfat,RAgonad,RAskin,RALiver,RAM,RAMs,Rbrai
n,RAR,RAS,Rurinebpa,

RBPAg_prod,RBPAg_prod_delay,RBPAg_prod_gut,RBPAg_prod_delay_gut,RBPAs_prod,
RBPAs_prod_delay,RBPAs_prod_gut,RBPAs_prod_delay_gut,RBPA_delay,

RBPA_delayin,Rfecesiv,RBPA_delayinbpag,Rbpac,RBPA_delays,RBPA_delayins,Rfec
esivs,RBPA_delayinbpas,Rbpas,Rurinebpag,Rreabsorption,Rurineg,

Rurinebpas,Rreabsorptions,Rurines,dSSD,dSSD2,Cgut,CVLiver)

          conc <- c(CV=CV)
          res  <- list(dydt, conc)
          return(res)
        })}

# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
# Solve the system of differential equations
# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
zeit <- seq(0, 10*24*60, 2)/60   # (h) time
v    <- ode(y=yini, func=PBTKmod, times=zeit, parms=para, method="lsoda")


# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
# Mass Balances
# ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

#Blood balance
Qtotal      <- Qliver + Qfat + Qrich + Qslow + Qgonad + Qbrain + Qskin
Qbal        <- Qtotal - QC

#bw balance
bworgans    <- Vliver + Vrich + Vslow + Vfat + Vgonad + Vbrain + Vskin

#Mass balance (nmoles) for BPA
TMassbpa    <- v[,"Aplasma"] + v[,"ALiver"] + v[,"AFat"] + v[,"AS"] +
v[,"AR"] + v[,"Agonad"] + v[,"Abrain"]   + v[,"Askin"]
Lossbpa     <- v[,"Amet_liver"] + v[,"AGImet"] + v[,"Aurinebpa"] +
v[,"Amet_livers"] + v[,"AGImets"]
BPA         <- v[,"Input.O"] + v[,"Input.D"] - Lossbpa - TMassbpa -
v[,"ASI"] - v[,"AST"]

#Mass balance for BPAG
Massbpagbox <- v[,"ABPAg"] + v[,"ABPAg_gut"] - v[,"Aurinebpag"] -
v[,"Abpac"]
```

```
Massbpasbox <- v[,"ABPAs"] + v[,"ABPAs_gut"] - v[,"Aurinebpas"] -
v[,"Abpasul"]
Massbpagehr <- v[,"ABPAg_prod_delay"] + v[,"ABPAg_prod_delay_gut"] -
v[,"ABPA_delayin"] - v[,"Afecesiv"] - v[,"ABPA_delay"] -
v[,"ABPA_delayinbpag"]
Massbpasehr <- v[,"ABPAs_prod_delay"] + v[,"ABPAs_prod_delay_gut"] -
v[,"ABPA_delayins"] - v[,"Afecesivs"] - v[,"ABPA_delays"] -
v[,"ABPA_delayinbpas"]
perurine    <- (v[,"Aurinebpas"] + v[,"Aurinebpa"] + v[,"Aurinebpag"]) /
(v[,"Input.O"] + v[,"Input.D"])

#Total balance for BPA and BPAG
Mass        <- v[,"Input.O"] + v[,"Input.D"] - TMassbpa - v[,"ASI"] -
v[,"AST"] - v[,"Abpac"] - v[,"Abpasul"] - v[,"Aurinebpa"] -
v[,"Aurinebpag"] - v[,"Aurinebpas"] - v[,"AGIBPAg"] - v[,"AGIBPAs"]

# ++++++++++++++++++++++++++++++++++++++++++++
# From amounts to concentrations
# ++++++++++++++++++++++++++++++++++++++++++++

v[,"Abpac"]  <- v[,"Abpac"]/Vplasma
v[,"Abpasul"]  <- v[,"Abpasul"]/Vplasma
v[,"Aplasma"]  <- v[,"Aplasma"]/Vplasma

v[,"Agonad"] <- v[,"Agonad"]/Vgonad
v[,"ALiver"] <- v[,"ALiver"]/Vliver

#filter out the negative values
v <- v[v[,"Abpac"]>0,]
v <- v[v[,"Abpasul"]>0,]
v <- v[v[,"Aplasma"]>0,]
v <- v[v[,"Aurineg"]>0,]
v <- v[v[,"Aurines"]>0,]
x <- v[v[,"Aurinebpa"]>0,]
v <- v[v[,"Agonad"]>0,]
v <- v[v[,"ALiver"]>0,]


y <- as.data.frame(v)

lengthofy <- as.numeric(nrow(y))
results <- results[1:lengthofy,] # it sometimes messes around with the
number of rows

results[,(i)] <- y$Aplasma
gonads[,(i)] <- y$Agonad

}

results$time <- y$time
gonads$time <- y$time
```

b) PBPK model code as used in the 2D Monte Carlo analysis for BPA and women of childbearing age

```
#########################################################################
### PBPK model for bisphenols (here BPA) used in the 2D-MC analysis ###
### The model is based on Yang et al. 2015                          ###
#########################################################################

rm(list=ls(all=TRUE))

tOld <- Sys.time() # get start time

library(deSolve)
library(plyr)
library(truncnorm)
library(triangle)
library(EnvStats) # for truncated lognormal distributions
library(trapezoid) # for trapezoidal distributions

nIt <- 1000 # number of variability iterations
nUnc <- 1000 # number of uncertainty iterations

# Input tables

# Tables with Variability distributions for females, provided in the SI
VarInputFem <- read.csv2(InputParVariabilityFem.csv", stringsAsFactors=
FALSE, header = TRUE)

# chemical specific data from variability analysis, provided in the SI
ChemData <- read.csv2(ChemSpecificParBPA.csv",stringsAsFactors =FALSE,
header = TRUE)

# Result outputs
results <- array(0,dim = c(7200,nIt,nUnc)) # 3 dimensional array for data
storage

#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#      Physiological Parameters
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

# Sample from uncertainty distributions before for-loop

pskinUC       <- rtrapezoid(nUnc,min = 0.802,mode1 = 2.15,mode2 = 7.84,max
= 12.76) # Trapezoidal distribution with Zhang and Schmitt LB, UB and mean
values

mcPrCliverUC   <- rtrapezoid(nUnc,min = 28.2,mode1 = 32, mode2 = 38, max=
42.5) # microsomal protein content in liver (mg protein/g liver)
mcPrCgutUC     <- rtrapezoid(nUnc,min = 1.72,mode1 = 4.29, mode2 = 39.7,
max = 70.8) # microsomal protein content in enterocytes (mg protein/kg bw)

EoA.D_UC      <- rtrapezoid(nUnc,min = 0.0288,mode1 = 0.093, mode2 =0.2,
max = 0.322)           # extent of dermal abs. (Thermal paper)
EoA.D2_UC     <- rtrapezoid(nUnc,min = 0.0288,mode1 = 0.093, mode2 =0.6,
max = 0.965)         # extent of dermal abs. (PCPs)

aHL.D_UC     <- rtrapezoid(nUnc,min = 2.47,mode1 = 6, mode2 = 8.5, max =
13.5)        # (h) Minimum is Lower bound of truncated distr. of Demierre,
upper bound is Biedermann estimation
```

```
aHL.D2_UC    <- rtrapezoid(nUnc,min = 0.0687,mode1 = 10/60, mode2 =8.5,
max = 13.5)         # (h)  |Minimum is Lower bound of truncated distr. of
Biedermann ethanol, upper bound is Biedermann tp

kmgutg_UC     <- rtrapezoid(nUnc, min = 25205, mode1 = 58400, mode2 =
80100, max = 125629)
vmaxgutgUS_UC <- rtrapezoid(nUnc, min = 8.6024, mode1 = 29.22, mode2 =
84.00, max = 143.27)

kmliver_UC      <- rtrapezoid(nUnc, min = 2115, mode1 = 4900, mode2 =
66300, max = 103985) # (nm) Glucuronidation of BPA in the liver Mazur -
Elsby for females
vmaxliverUS_UC  <- rtrapezoid(nUnc, min = 9.362, mode1 = 31.8, mode2 =510,
max = 869.9) # (nmol/h/kg protein) | Kurebayashi - Trdan Lusin

met1g_UC      <- rtrapezoid(nUnc,min = 0.33, mode1 = 0.8, mode2 = 1, max =
1) # Fraction not subject to EHR


for (u in 1:nUnc) {

for (i in 1:nIt) {

  gender     <- "female"
  attach(VarInputFem)

  age <- runif(1,min=18, max=45)
  height       <- rtruncnorm(1,a=aVar[3],b=bVar[3],mean =meanVar[3],
sd=SDVar[3])                          # (m)             |Height
  BMI          <- rlnormTrunc(1,meanlog = meanVar[1], sdlog = SDVar[1], min
= aVar[1], max = bVar[1]) # lognormal distribution
  bw           <- (height^2)*BMI                                 # (kg)
|Body weight calculated

  # Blood flow rate [% of cardiac output]
  QCC          <- rtruncnorm(1,a=aVar[4],b=bVar[4],mean =meanVar[4],
sd=SDVar[4])      # (L/min)    |Cardiac output
  QgonadC      <- rtruncnorm(1,a=aVar[5],b=bVar[5],mean = meanVar[5],
sd=SDVar[5])     # (%QC)           |Fractional blood flow to the gonads,
ICRP 89 (alle weiteren Parameter)
  QliverC      <- rtruncnorm(1,a=aVar[6],b=bVar[6],mean = meanVar[6],
sd=SDVar[6])       # (%QC)           |Fractional blood flow to the liver
  QfatC        <- rtruncnorm(1,a=aVar[7],b=bVar[7],mean = meanVar[7],
sd=SDVar[7])       # (%QC)           |Fractional blood flow to the fat
  QbrainC      <- rtruncnorm(1,a=aVar[8],b=bVar[8],mean =meanVar[8],
sd=SDVar[8])                                  # (%QC)
|Fractional blood flow to the brain
  QskinC       <- rtruncnorm(1,a=aVar[9],b=bVar[9],mean =meanVar[9],
sd=SDVar[9])                                   # (%QC)
|Fractional blood flow to the skin
  QmuscleC     <- rtruncnorm(1,a=aVar[10],b=bVar[10],mean = meanVar[10],
sd=SDVar[10])          # (%QC)           |Fractional blood flow to the muscle
= proxy for slowly perfused tissue
  QrichC       <- rtruncnorm(1,a=aVar[11],b=bVar[11],mean =meanVar[11],
sd=SDVar[11])        # Richly perfused tissue

  QtotC <- QgonadC+QliverC+QfatC+QbrainC+QskinC+QmuscleC+QrichC   #
readjustment
  Qdiff <- 1-QtotC

  QgonadC <- (Qdiff*meanVar[5])+QgonadC
  QliverC <- (Qdiff*meanVar[6])+QliverC
```

```
  QfatC <- (Qdiff*meanVar[7])+QfatC
  QbrainC <- (Qdiff*meanVar[8])+QbrainC
  QskinC <- (Qdiff*meanVar[9])+QskinC
  QmuscleC <- (Qdiff*meanVar[10])+QmuscleC
  QrichC <- (Qdiff*meanVar[11])+QrichC


  # Fractional Tissue Volumes of bw
  VplasmaC   <- rtruncnorm(1,a=aVar[12],b=bVar[12],mean =meanVar[12],
sd=SDVar[12])       # (%bw)           |Fractional volume of the plasma
  VliverC    <- rtruncnorm(1,a=aVar[13],b=bVar[13],mean =meanVar[13],
sd=SDVar[13])     # (%bw)           |Fractional volume of the liver
  VgonadC    <- rtruncnorm(1,a=aVar[14],b=bVar[14],mean =meanVar[14],
sd=SDVar[14])     # (%bw)           |Fractional volume of the gonads
  VbrainC    <- rtruncnorm(1,a=aVar[15],b=bVar[15],mean =meanVar[15],
sd=SDVar[15])     # (%bw)           |Fractional volume of the brain
  VskinC     <- rtruncnorm(1,a=aVar[16],b=bVar[16],mean =meanVar[16],
sd=SDVar[16])     # (%bw)           |Fractional volume of the skin
  VbodygC    <- VplasmaC      # (%bw)           |Fractional volume of the
distribution for BPAG, set to plasma volume
  VbodysC    <- VplasmaC      # (%bw)           |Fractional volume of the
distribution for BPAS, set to plasma volume
  VfatC      <- rtruncnorm(1,a=aVar[20],b=bVar[20],mean =meanVar[20],
sd=SDVar[20])     # (%bw)           |Fractional volume of the skin

  VmuscleC   <- rtruncnorm(1,a=aVar[17],b=bVar[17],mean =meanVar[17],
sd=SDVar[17])     # (%bw)           |Fractional volume of the skin
  VrichC     <- rtruncnorm(1,a=aVar[18],b=bVar[18],mean =meanVar[18],
sd=SDVar[18])

  VtotC <- VgonadC+VliverC+VfatC+VbrainC+VskinC+VmuscleC+VrichC

    Vdiff <- meanVar[19]-VtotC # Readjustment

    VplasmaC <- (Vdiff*meanVar[12])+VplasmaC
    VgonadC <- (Vdiff*meanVar[14])+VgonadC
    VliverC <- (Vdiff*meanVar[13])+VliverC
    VfatC <- (Vdiff*meanVar[20])+VfatC
    VbrainC <- (Vdiff*meanVar[15])+VbrainC
    VskinC <- (Vdiff*meanVar[16])+VskinC
    VmuscleC <- (Vdiff*meanVar[17])+VmuscleC
    VrichC <- (Vdiff*meanVar[18])+VrichC

  VtotC <- VgonadC+VliverC+VfatC+VbrainC+VskinC+VmuscleC+VrichC

    Vdiff <- meanVar[19]-VtotC # Readjustment

    VplasmaC <- (Vdiff*meanVar[12])+VplasmaC
    VgonadC <- (Vdiff*meanVar[14])+VgonadC
    VliverC <- (Vdiff*meanVar[13])+VliverC
    VfatC <- (Vdiff*meanVar[20])+VfatC
    VbrainC <- (Vdiff*meanVar[15])+VbrainC
    VskinC <- (Vdiff*meanVar[16])+VskinC
    VmuscleC <- (Vdiff*meanVar[17])+VmuscleC
    VrichC <- (Vdiff*meanVar[18])+VrichC

  detach(VarInputFem)


#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#      Chemical specific parameters
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

```
    attach(ChemData)

    MW          <- MeanVar[1]                 # (g/mol)         |Molecular
weight

    # Partition Coefficients for BPA

    pfat        <- rtruncnorm(1,mean =MeanVar[2],sd=SDVar[2],a=LowerB[2],
b=UpperB[2])      #                |Partitioning into the fat (fat/blood)
    pliver      <- rtruncnorm(1,mean =MeanVar[3],sd=SDVar[3],a=LowerB[3],
b=UpperB[3])      #       |Partitioning into the liver (liver/blood)
    pbrain      <- rtruncnorm(1,mean = MeanVar[4],sd=SDVar[4],a=LowerB[4],
b=UpperB[4])     #                |Partitioning into the brain (brain/blood)
    pgonad      <- rtruncnorm(1,mean =MeanVar[6],sd=SDVar[6],a=LowerB[6],
b=UpperB[6])     #          |Partitioning into the gonads (gonads/blood)
    pslow       <- rtruncnorm(1,mean = MeanVar[7],sd=SDVar[7],a=LowerB[7],
b=UpperB[7])     #    |Partitioning into the slowly perfused tissues (slowly
perfused/blood)
    prich       <- rtruncnorm(1,mean =MeanVar[8],sd=SDVar[8],a=LowerB[8],
b=UpperB[8])     #  |Partitioning into the richly perfused tissues (richly
perfused/blood)

    detach(ChemData)

    pskin       <- rtruncnorm(1,mean = pskinUC[u], sd=0.32*pskinUC[u],
a=pskinUC[u]-(1.96*0.32*pskinUC[u]), b=pskinUC[u]+(1.96*0.32*pskinUC[u]))

  #BPA peroral uptake and metabolism in the gut

    geC         <- rtruncnorm(1,mean = 3.5, sd=0.945, a=1.6478,b=5.3522)
# (1/h/bw^-0.25)    |Gastric emptying of BPA
    k0C         <- 0                      # (1/h/bw^-0.25)    |Oral uptake of
BPA from the stomach into the liver; set to 0
    k1C         <- rtruncnorm(1,mean = 2.1, sd=0.819, a=0.4948,b=3.70524)
# (1/h/bw^-0.25)    |Oral uptake of BPA from the small intestine into the
liver
    k4C         <- 0                      # (1/h/bw^-0.25)    |Fecal
elimination of BPA from small intestine after peroral administration; set
to 0
    kGIingC     <- rtruncnorm(1,mean = 50, sd=15, a=20.6,b=79.4)
# (1/h/bw^-0.25)    |Transport of BPAG from enterocytes into serum
    kGIinsC     <- rtruncnorm(1,mean = 50, sd=15, a=20.6,b=79.4)
# (1/h/bw^-0.25)    |Transport of BPAS from enterocytes into serum

  kmliver      <- rtruncnorm(1,mean = kmliver_UC[u], sd=0.29*kmliver_UC[u],
a=kmliver_UC[u]-(1.96*0.29*kmliver_UC[u]), b=
kmliver_UC[u]+(1.96*0.29*kmliver_UC[u]))             # (nm)
|Glucuronidation of BPA in the liver
  mcPrCliver   <- rtruncnorm(1,mean = mcPrCliverUC[u],
sd=0.06*mcPrCliverUC[u], a=mcPrCliverUC[u]-(1.96*0.06*mcPrCliverUC[u]),b=
mcPrCliverUC[u]+(1.96*0.06*mcPrCliverUC[u])) # microsomal protein content
in liver (mg protein/g liver)

  vmaxBorder1      <- (0.0249395*kmliver_UC[u]+0.299274)/mcPrCliver
  # this must be the minimal Vmax, so that rate does to not go below the
rate of Elsby parametrization
  VmaxMinDistr <- vmaxliverUS_UC[u]-(1.96*0.36*vmaxliverUS_UC[u]) #
variable in truncated distribuation

  if(VmaxMinDistr>vmaxBorder1)
    a <- VmaxMinDistr else
```

```
    a <- vmaxBorder1

  vmaxBorder2      <- (9.4279*kmliver_UC[u]+113.1348)/mcPrCliver
  # this must be the minimal Vmax, so that rate does to not go below the
rate of Elsby parametrization
  VmaxMaxDistr <- vmaxliverUS_UC[u]+(1.96*0.36*vmaxliverUS_UC[u]) #
variable in truncated distribuation

  if(VmaxMaxDistr<vmaxBorder2)
    b <- VmaxMaxDistr else
      b <- vmaxBorder2

  vmaxliverUS  <- rtruncnorm(1,mean = vmaxliverUS_UC[u],
sd=0.36*vmaxliverUS_UC[u], a=a, b= b)              # (nmol/h/kg protein)
|Glucuronidation of BPA in the liver


  vmaxliverC   <- mcPrCliver*vmaxliverUS
  fliverg      <- 1

  kmgutg       <- rtruncnorm(1,mean = kmgutg_UC[u], sd=0.29*kmgutg_UC[u],
a=kmgutg_UC[u]-(1.96*0.29*kmgutg_UC[u]), b=
kmgutg_UC[u]+(1.96*0.29*kmgutg_UC[u]))              # (nm)
|Glucuronidation of BPA in the gut
  vmaxgutgUS  <- rtruncnorm(1,mean = vmaxgutgUS_UC[u],
sd=0.36*vmaxgutgUS_UC[u], a=vmaxgutgUS_UC[u]-(1.96*0.36*vmaxgutgUS_UC[u]),
b= vmaxgutgUS_UC[u]+(1.96*0.36*vmaxgutgUS_UC[u]))              #
(nmol/h/bw^0.75) |Glucuronidation of BPA in the gut

  mcPrCgut     <- rtruncnorm(1,mean = mcPrCgutUC[u], sd=0.4*mcPrCgutUC[u],
a=mcPrCgutUC[u]-(1.96*0.4*mcPrCgutUC[u]), b=
mcPrCgutUC[u]+(1.96*0.4*mcPrCgutUC[u])) # microsomal protein content in
enterocytes (mg protein/kg bw)
  vmaxgutgC    <- mcPrCgut*vmaxgutgUS

  fgutg        <- 1               #                   |Correction factor of
glucuronidation in the gut
  kmguts       <- 0.00001               # (nm)             |Sulfation of
BPA in the gut - no sulfation
  vmaxgutsC    <- 0.00001              # (nmol/h/bw^0.75   |Sulfation of BPA
in the gut
  fguts        <- 0.000000             # Correction factor of sulfation in
the gut - no sulfation in the gut assumed

  #BPA metabolism in the liver
  met1g        <- met1g_UC[u]         #                  |Fraction of BPAG
in the liver taken up directly into serum (set to 1 to deactivate EHR)
  met1s        <- 1         #                  |Fraction of BPAS in the
liver taken up directly into serum

  enterocytes  <- rtruncnorm(1,mean = 0.1223,sd=0.030575, a=0.0624,
b=0.182)         # (L)              |Sum of enterocytes weights in
duodenum, jujunum and ileum (Gertz 2011)

  # only for BPA, for the other need to be set 0
  kmlivers     <- rtruncnorm(1,mean = 10100, sd=2929, a=4359, b=15841)
# (nm)             |Sulfation of BPA in the liver, set to the value for
SULT1A1 (Takahito 2002)
  vmaxliversC  <- rtruncnorm(1,mean = 149, sd=53.7, a=43.9, b=254)
# (nmol/h/g liver) |Sulfation of BPA in the liver
  flivers      <- 1
```

```
  #EHR and urinary excretion of BPAG
  EHRtime           <- 0.00          # (h)               |Time until EHR
occurs
  EHRrateC          <- rtruncnorm(1,mean = 0.2, sd=0.06, a=0.0824,
b=0.3176)           # (1/h/bw^-0.25)    |EHR of BPAG set 0 # 1.5?
  k4C_IV            <- 0             # (1/h/bw^-0.25)    |Fecal elimination
of BPAG from the EHR compartment

  kurinebpaC        <- rtruncnorm(1,mean = 0.06 ,sd=0.018, a= 0.0247 , b=
0.0953)          # (L/h/bw^0.75)     |Clearance, urine excretion of BPA
  kurinebpagC       <- rtruncnorm(1,mean = 0.35 ,sd=0.105, a= 0.144,
b=0.556 )          # (L/h/bw^0.75)     |Clearance, urine excretion of BPAG
  kurinebpasC       <- rtruncnorm(1,mean = 0.03 ,sd=0.009, a=0.01236 ,
b=0.04764 )         # (L/h/bw^0.75)     |Clearance, urine excretion of BPAS
  vreabsorptiongC   <- 0             # (nmol/h/bw^0.75) |vmax for renal
reabsorption of BPAG
  vreabsorptionsC   <- 0             # (nmol/h/bw^0.75) |vmax for renal
reabsorption of BPAS
  kreabsorptiong    <- 9200          # (nmol/L)          |Km for renal
reabsorption of BPAG
  kreabsorptions    <- 9200          # (nmol/L)          |Km for renal
reabsorption of BPAS

  kenterobpagC      <- rtruncnorm(1,mean = 0.2, sd=0.06, a=0.0824,
b=0.3176)             # (1/h/bw^-0.25)    |EHR of BPA due to biliary
excretion of BPAG
  kenterobpasC      <- 0.0           # (1/h/bw^-0.25)    |EHR of BPA due to
biliary excretion of BPAS


#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#    Dosing Parameters (oral)
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  #Oral Dosing 1
  D.o      <- 389/3                    # (ng/kg/d)    |oral   dose
  dose.O   <- D.o/MW                  # (nmol/kg/d) |oral   dose
  EoA.O    <- 1                       #               |extent of peroral
abs.
  uptake.O <- bw*dose.O               # (nmol)       |amount of uptake
  period.O <- 3/60                    # (h)          |uptake period
  koa      <- uptake.O/period.O       # (nmol/h)     |uptake rate
  t0.O     <- 0                    #    time points at which dosing starts
  t1.O     <- t0.O + period.O      #         time at which dosing occurs

  #Oral Dosing 2
  t0.O2     <- 6              #        time points at which dosing starts
  t1.O2     <- t0.O2 + period.O         #      time at which dosing occurs

  #Oral Dosing 3
  t0.O3     <- 12                    #   time points at which dosing starts
  t1.O3     <- t0.O3 + period.O        #time at which dosing occurs

  #Day 2
  #Oral Dosing 1
  t0.O4     <- 24               #        time points at which dosing starts
  t1.O4     <- t0.O4 + period.O        #time at which dosing occurs

  #Oral Dosing 2
  t0.O5     <- 30                #       time points at which dosing starts
  t1.O5     <- t0.O5 + period.O        #time at which dosing occurs
```

```
  #Oral Dosing 3
  t0.O6     <- 36                #      time points at which dosing starts
  t1.O6     <- t0.O6 + period.O          #      time at which dosing occurs

  #Day 3
  #Oral Dosing 1
  t0.O7     <- 48                #      time points at which dosing starts
  t1.O7     <- t0.O7 + period.O          #   time at which dosing occurs

  #Oral Dosing 2
  t0.O8     <- 54                  #    time points at which dosing starts
  t1.O8     <- t0.O8 + period.O          #     time at which dosing occurs

  #Oral Dosing 3
  t0.O9     <- 60          #              ime points at which dosing starts
  t1.O9     <- t0.O9 + period.O   #              time at which dosing occurs

  #Day 4
  #Oral Dosing 1
  t0.O10     <- 72           #          time points at which dosing starts
  t1.O10     <- t0.O10 + period.O   #          time at which dosing occurs

  #Oral Dosing 2
  t0.O11     <- 78                #    time points at which dosing starts
  t1.O11     <- t0.O11 + period.O      #       time at which dosing occurs

  #Oral Dosing 3
  t0.O12     <- 84                #       time points at which dosing starts
  t1.O12     <- t0.O12 + period.O      #       time at which dosing occurs

  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  #   Dosing Parameters (dermal)
  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  # Dermal uptake from thermal paper 1
  D.d       <- 542/2       # (ng/kg/d)    |dermal dose (Thermal paper)
  EoA.D     <- rtruncnorm(1,mean = EoA.D_UC[u],sd=0.31*EoA.D_UC[u],
a=EoA.D_UC[u]-(1.96*0.31*EoA.D_UC[u]), b=
EoA.D_UC[u]+(1.96*0.31*EoA.D_UC[u]))          #              |extent of
dermal abs. (Thermal paper)
  dose.D    <- D.d/MW                    # (nmol/kg/d) |dermal dose
  aHL.D     <- rtruncnorm(1,mean = aHL.D_UC[u],sd=0.3*aHL.D_UC[u],
a=aHL.D_UC[u]-(1.96*0.3*aHL.D_UC[u]), b=
aHL.D_UC[u]+(1.96*0.3*aHL.D_UC[u]))         # (h) Minimum is Lower bound of
truncated distr. of Demierre, upper bound is Biedermann estimation
  uptake.D <- bw*dose.D                # (nmol)       |amount of uptake
  period.D <- 24                       # (h)          |uptake period
  kda       <- uptake.D/period.D       # (mg/h)       |uptake rate
  t0.D      <- 0                     #   time points at which dosing starts
  t1.D      <- t0.D + period.D         #       time at which dosing occurs

  # Dermal uptake from thermal paper 2 - extent of dermal abs. and
absorption half-life same as for first handling (Thermal paper)
  t0.D3     <- 12                    #   time points at which dosing starts
  t1.D3     <- t0.D3 + period.D          #       time at which dosing occurs

  #Day 2
  #Dermal uptake from thermal paper 1
  t0.D5     <- 24                #        time points at which dosing starts
  t1.D5     <- t0.D5 + period.D          #       time at which dosing occurs

  # Dermal uptake from thermal paper 2
```

```
  t0.D7     <- 36                    #   time points at which dosing starts
  t1.D7     <- t0.D7 + period.D          #       time at which dosing occurs

  #Day 3
  #Dermal uptake from thermal paper 1
  t0.D9     <- 48                    #    time points at which dosing starts
  t1.D9     <- t0.D9 + period.D          #time at which dosing occurs

  # Dermal uptake from thermal paper 2
  t0.D11     <- 60                   #    time points at which dosing starts
  t1.D11     <- t0.D11 + period.D          #    time at which dosing occurs


#Day 4
  #Dermal uptake from thermal paper 1
  t0.D13     <- 72             #          time points at which dosing starts
  t1.D13     <- t0.D13 + period.D    #          time at which dosing occurs

  # Dermal uptake from thermal paper 2
  t0.D15     <- 84                  #     time points at which dosing starts
  t1.D15     <- t0.D15 + period.D          #    time at which dosing occurs

  # Dermal uptake from PCPs 1
  D.d2       <- 4/2               # (ng/kg/d)    |dermal dose (Thermal paper)
  EoA.D2     <- rtruncnorm(1,mean = EoA.D2_UC[u], sd=0.31*EoA.D2_UC[u],
a=EoA.D2_UC[u]-(1.96*0.31*EoA.D2_UC[u]), b=
EoA.D2_UC[u]+(1.96*0.31*EoA.D2_UC[u]))      #              |extent of dermal
abs. (Thermal paper)
  dose.D2    <- D.d2/MW             # (nmol/kg/d) |dermal dose
  aHL.D2     <- rtruncnorm(1,mean = aHL.D2_UC[u], sd=0.3*aHL.D2_UC[u],
a=aHL.D2_UC[u]-(1.96*0.3*aHL.D2_UC[u]), b=
aHL.D2_UC[u]+(1.96*0.3*aHL.D2_UC[u]))        # (h) |Minimum is Lower bound
of truncated distr. of Biedermann ethanol, upper bound is Biedermann tp
  uptake.D2 <- bw*dose.D2             # (nmol)       |amount of uptake
  period.D2 <- 24                     # (h)          |uptake period
  kda2       <- uptake.D2/period.D2   # (mg/h)       |uptake rate
  t0.D2      <- 0
  t1.D2      <- t0.D2 + period.D2      #       time at which dosing occurs

  # Dermal uptake from PCPs 2
  t0.D4      <- 12
  t1.D4      <- t0.D4 + period.D2      #      time at which dosing occurs

  # Day 2
  t0.D6      <- 24
  t1.D6      <- t0.D6 + period.D2      #       time at which dosing occurs

  # Dermal uptake from PCPs 2
  t0.D8      <- 36
  t1.D8      <- t0.D8 + period.D2      #       time at which dosing occurs

  # Day 3
  t0.D10     <- 48
  t1.D10     <- t0.D10 + period.D2    #       time at which dosing occurs

  # Dermal uptake from PCPs 2
  t0.D12     <- 60
  t1.D12     <- t0.D12 + period.D2    #       time at which dosing occurs

  # Day 4
  t0.D14     <- 72
  t1.D14     <- t0.D14 + period.D2    #       time at which dosing occurs
```

```
  # Dermal uptake from PCPs 2
  t0.D16     <- 84
  t1.D16     <- t0.D16 + period.D2   #       time at which dosing occurs


#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#    Derived Parameters
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  #Scaled cardiac output and blood flows
  QC          <- QCC                          # (L/h) |Cardiac output
  Qfat        <- QfatC*QC                     # (L/h) |Blood flow to the fat
  Qliver      <- QliverC*QC       # (L/h) |Blood flow to the liver
  Qgonad      <- QgonadC*QC       # (L/h) |Blood flow to the gonads
  Qbrain      <- QbrainC*QC       # (L/h) |Blood flow to the brain
  Qskin       <- QskinC*QC                    # (L/h) |Blood flow to the skin
  Qslow <- QmuscleC*QC # (L/h) |Blood flow to the slowly perfused tissues
  Qrich <- QrichC*QC # (L/h) |Blood flow to the richly perfused tissues

  #Scaled tissue volumes
  Vliver      <- VliverC*bw                   # (L)    |Volume of the liver
  Vfat        <- VfatC*bw                     # (L)    |Volume of the fat
  Vgonad      <- VgonadC*bw                   # (L)    |Volume of the gonads
  Vplasma     <- VplasmaC*bw                  # (L)    |Volume of the plasma
  Vbrain      <- VbrainC*bw                   # (L)    |Volume of the brain
  Vskin       <- VskinC*bw                    # (L)    |Volume of the skin
  Vslow       <- VmuscleC*bw # (L) |Volume of the slowly perfused tissues
  Vrich       <- VrichC*bw   # (L) |Volume of the richly perfused tissues

  Vbodyg      <- VbodygC*bw  # (L) |Volume of the distribution for BPAG
  Vbodys      <- VbodysC*bw  # (L) |Volume of the distribution for BPAS

  # Scaling of Vmax parameters

  vmaxliversCnew <- vmaxliversC*VliverC*1000
  vmaxliversCnew <- vmaxliversCnew*bw/(bw^0.75)

  vmaxliverCnew <- vmaxliverC*VliverC*1000
  vmaxliverCnew <- vmaxliverCnew*bw/(bw^0.75)

  vmaxgutgCnew <- vmaxgutgC*bw/(bw^0.75)

  #Scaled kinetic parameters
  vreabsorptiong    <- vreabsorptiongC*bw^0.75      # (nmol/h)  |vmax of
renal resorption of BPAG
  vreabsorptions    <- vreabsorptionsC*bw^0.75      # (nmol/h)  |vmax of
renal resorption of BPAS

  EHRrate           <- EHRrateC/(bw^0.25)     # (1/h)      |EHR of BPAG

  k0                <- k0C/bw^0.25                  # (1/h)     |Uptake of
BPA from the stomach into the liver
  ge                <- geC/bw^0.25                  # (1/h)     |Gastric
emptying of BPA
  k1                <- k1C/bw^0.25                  # (1/h)     |Uptake of
BPA from small intestine into the liver

  k4                <- k4C/bw^0.25                  # (1/h)     |Fecal
excretion of BPA after peroral administration from small intestine
  k4_IV             <- k4C_IV/bw^0.25               # (1/h)     |Fecal
excretion of BPAG from the EHR compartment
```

```
  vmaxliver         <- vmaxliverCnew*fliverg*bw^0.75     # (nmol/h)   |vmax
of BPA glucuronidation in the liver
  kGIing            <- kGIingC/bw^0.25              # (1/h)      |Uptake of
BPAG from small intestine into serum

  met2g         <- 1.0-met1g # () |Fraction of BPAG formed subject to EHR
  met2s         <- 1.0-met1s # () |Fraction of BPAS formed subject to EHR

  kurinebpa     <- kurinebpaC*bw^0.75 # (L/h) |Clearance of BPA via urine
  kurinebpag    <- kurinebpagC*bw^0.75# (L/h) |Clearance of BPAG via urine
  kurinebpas    <- kurinebpasC*bw^0.75 # (L/h)|Clearance of BPAS via urine
  vmaxlivers        <- vmaxliversCnew*flivers*bw^0.75   # (nmol/h)   |vmax of
BPA sulfation in the liver
  kGIins            <- kGIinsC/bw^0.25              # (1/h)      |Uptake of
BPAS from small intestine into serum
  vmaxgutg          <- vmaxgutgCnew*fgutg*bw^0.75       # (nmol/h)   |vmax of
BPA glucuronidation in the gut
  vmaxguts  <- vmaxgutsC*fguts*bw^0.75 # (nmol/h)   |vmax of BPA sulfation
in the gut

  kenterobpag       <- kenterobpagC/bw^0.25          # (1/h)      |EHR of BPA
due to biliary excretion of BPAG
  kenterobpas       <- kenterobpasC/bw^0.25          # (1/h)      |EHR of BPA
due to biliary excretion of BPAS

  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  # Compile parameters
  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  para  <- unlist(c(data.frame(

    QC,
    Qfat,
    Qliver,
    Qgonad,
    Qbrain,
    Qskin,
    Qrich,
    Qslow,
    Vliver,
    Vfat,
    Vgonad,
    Vplasma,
    Vbrain,
    Vskin,
    Vslow,
    Vrich,
    Vbodyg,
    Vbodys,
    pliver,
    pfat,
    pslow,
    prich,
    pgonad,
    pbrain,
    pskin,
    kmgutg,
    kmguts,
    met1g,
    met1s,
    enterocytes,
```

```
    kmliver,
    kmlivers,
    EHRtime,
    kreabsorptiong,
    kreabsorptions,
    vreabsorptiong,
    vreabsorptions,
    EHRrate,
    k0,
    ge,
    k1,
    k4,
    k4_IV,
    vmaxliver,
    kGIing,
    met2g,
    met2s,
    kurinebpa,
    kurinebpag,
    kurinebpas,
    vmaxlivers,
    kGIins,
    vmaxgutg,
    vmaxguts,
    kenterobpag,
    kenterobpas,
    koa,
    kda,
    kda2
  )))
  para


  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  # Initial conditions
  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  yini <- unlist(c(data.frame(
    Input.O        = 0,
    Input.D        = 0,
    Input.D2       = 0,
    AST            = 0,     #   Amount of  BPA in stomach
    ASI            = 0,     #   Amount of  BPA in small intestine

    Afeces         = 0,         #   Amount of BPA excreted into feces

    AAO            = 0,     #    Amount of BPA taken up from small intestine
into serum
    AGImet         = 0,     #    Amount of BPAG formed in small intestine
     AGImets       = 0,     #    Amount of BPAS formed in small intestine
    Aoral          = 0,     #    Amount of BPA peroral uptake
     AGIBPAg       = 0,     #    Amount of BPAG in small intestine
    AGIin          = 0,     #    Amount of BPAG taken up from small intestine
into serum
     AGIBPAs       = 0,     #    Amount of BPAS in small intestine
    AGIins         = 0,     #    Amount of BPAS taken up from small intestine
into serum
     Aplasma       = 0,     #    Amount of BPA in plasma
    AFat           = 0,     #    Amount of BPA in fat
    Agonad         = 0,     #    Amount of BPA in gonads
    Askin          = 0,     #    Amount of BPA in skin
    ALiver         = 0,     #    Amount of BPA in liver
```

```
    Amet_liver     = 0,     #   Amount of BPA glucuronidation in liver
    Amet_livers    = 0,     #   Amount of BPA sulfation in liver
    Abrain         = 0,     #   Amount of BPA in brain
    AR             = 0,     #   Amount of BPA in richly perfused tissue
    AS             = 0,     #   Amount of BPA in slowly perfused tissue
    Aurinebpa      = 0,     #   Cummulative amount of BPA excreted into
urine

    ABPAg       = 0,        #   Amount of BPAG taken up from the liver into
systemic circulation
    ABPAg_prod_delay = 0,   #   Amount of BPAG excreted from liver into
bile
    ABPAg_gut   = 0,        #   Amount of BPAG taken up from the small
intestine into systemic circulation
    ABPAg_prod_delay_gut=0, #   Amount of BPAG excreted from small
intestine into bile
    ABPAs       = 0,        #   Amount of BPAS taken up from the liver into
systemic circulation
    ABPAs_prod_delay = 0,   #   Amount of BPAS excreted from liver into
bile
    ABPAs_gut   = 0,        #   Amount of BPAS taken up from the small
intestine into systemic circulation
    ABPAs_prod_delay_gut=0, #   Amount of BPAS excreted from small
intestine into bile
    ABPA_delay  = 0,        #   Amount of BPAG in the gut (EHR compartment)
    ABPA_delayin= 0,        #   Amount of BPAG taken up into the systemic
circulation from the gut (EHR compartment)
    Afecesiv    = 0,        #   Amount of fecal excretion of BPAG from the
gut(EHR compartment)
    ABPA_delayinbpag = 0,   #   Amount of BPA into the systemic circulation
from the gut (EHR compartment for BPAG)
    Abpac       = 0,        #   Amount of BPAG in the system
    ABPA_delays = 0,        #   Amount of BPAS in the gut (EHR compartment)
    ABPA_delayins = 0,      #   Amount of BPAS taken up into the systemic
circulation from the gut (EHR compartment)
    Afecesivs   = 0,        #   Amount of fecal excretion of BPAS from the
gut(EHR compartment)
    ABPA_delayinbpas = 0,   #   Amount of BPA into the systemic circulation
from the gut (EHR compartment for BPAS)
    Abpasul     = 0,        #   Amount of BPAS in the system
    Aurinebpag  = 0,        #   Amount of BPAG in the bladder
    Areabsorption  = 0,     #   Amount of renal reabsorption of BPAG
    Aurineg     = 0,        #   Amount of BPAG excreted
    Aurinebpas  = 0,        #   Amount of BPAS in the bladder
    Areabsorptions = 0,     #   Amount of renal reabsorption of BPAS
    Aurines     = 0,        #   Amount of BPAS excreted
    SSD            = 0,     #   Skin surface depot Thermal paper
    SSD2           = 0      #   Skin surface depot PCPs
  )))

  yini



#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#         Model for BPA
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  PBTKmod <- function(t, y, parms)
  {
    with (as.list(c(y, parms)),
          {
```

```
            if(t<EHRtime){kentero=0}else{kentero=EHRrate}
# Time dependent EHR of BPA metabolites

            if(t<=t1.O && t>=t0.O){onoff.O=1} else{onoff.O=0}
            if(t<=t1.O2 && t>=t0.O2){onoff.O2=1} else{onoff.O2=0}
            if(t<=t1.O3 && t>=t0.O3){onoff.O3=1} else{onoff.O3=0}
            if(t<=t1.O4 && t>=t0.O4){onoff.O4=1} else{onoff.O4=0}
            if(t<=t1.O5 && t>=t0.O5){onoff.O5=1} else{onoff.O5=0}
            if(t<=t1.O6 && t>=t0.O6){onoff.O6=1} else{onoff.O6=0}
            if(t<=t1.O7 && t>=t0.O7){onoff.O7=1} else{onoff.O7=0}
            if(t<=t1.O8 && t>=t0.O8){onoff.O8=1} else{onoff.O8=0}
            if(t<=t1.O9 && t>=t0.O9){onoff.O9=1} else{onoff.O9=0}
            if(t<=t1.O10 && t>=t0.O10){onoff.O10=1}else{onoff.O10=0}
            if(t<=t1.O11 && t>=t0.O11){onoff.O11=1}else{onoff.O11=0}
            if(t<=t1.O12 && t>=t0.O12){onoff.O12=1}else{onoff.O12=0}

            if(t<=t1.D && t>=t0.D){onoff.D=1} else{onoff.D=0}
            if(t<=t1.D2 && t>=t0.D2){onoff.D2=1} else{onoff.D2=0}
            if(t<=t1.D3 && t>=t0.D3){onoff.D3=1} else{onoff.D3=0}
            if(t<=t1.D4 && t>=t0.D4){onoff.D4=1} else{onoff.D4=0}
            if(t<=t1.D5 && t>=t0.D5){onoff.D5=1} else{onoff.D5=0}
            if(t<=t1.D6 && t>=t0.D6){onoff.D6=1} else{onoff.D6=0}
            if(t<=t1.D7 && t>=t0.D7){onoff.D7=1} else{onoff.D7=0}
            if(t<=t1.D8 && t>=t0.D8){onoff.D8=1} else{onoff.D8=0}
            if(t<=t1.D9 && t>=t0.D9){onoff.D9=1} else{onoff.D9=0}
            if(t<=t1.D10 && t>=t0.D10){onoff.D10=1}else{onoff.D10=0}
            if(t<=t1.D11 && t>=t0.D11){onoff.D11=1}else{onoff.D11=0}
            if(t<=t1.D12 && t>=t0.D12){onoff.D12=1}else{onoff.D12=0}
            if(t<=t1.D13 && t>=t0.D13){onoff.D13=1}else{onoff.D13=0}
            if(t<=t1.D14 && t>=t0.D14){onoff.D14=1}else{onoff.D14=0}
            if(t<=t1.D15 && t>=t0.D15){onoff.D15=1}else{onoff.D15=0}
            if(t<=t1.D16 && t>=t0.D16){onoff.D16=1}else{onoff.D16=0}

            #Dermal dosing
            dTPM      <- kda*onoff.D*EoA.D + kda*onoff.D3*EoA.D +
kda*onoff.D5*EoA.D + kda*onoff.D7*EoA.D + kda*onoff.D9*EoA.D +
kda*onoff.D11*EoA.D + kda*onoff.D13*EoA.D+ kda*onoff.D15*EoA.D     # Dermal
dosing Thermal paper
            dPCP      <- kda2*onoff.D2*EoA.D2 + kda2*onoff.D4*EoA.D2+
kda2*onoff.D6*EoA.D2 + kda2*onoff.D8*EoA.D2 + kda2*onoff.D10*EoA.D2 +
kda2*onoff.D12*EoA.D2 + kda2*onoff.D14*EoA.D2 + kda2*onoff.D16*EoA.D2      #
Dermal dosing PCPs

            dInput.D  <- log(2)*(1/aHL.D)*SSD  # input from thermal paper
            dInput.D2  <- log(2)*(1/aHL.D2)*SSD2  # input from PCPs

            dSSD      <- -dInput.D + dTPM                  # Skin-surface
depot from thermal paper
            dSSD2      <- -dInput.D2 + dPCP                  # Skin-surface
depot from thermal paper


            #Oral dosing
            dInput.O  <- koa*onoff.O + koa*onoff.O2 + koa*onoff.O3 +
koa*onoff.O4 + koa*onoff.O5 + koa*onoff.O6 + koa*onoff.O7 + koa*onoff.O8 +
koa*onoff.O9 + koa*onoff.O10 + koa*onoff.O11 + koa*onoff.O12
# Dosing (oral)
            Cgut      <- ASI/enterocytes                   # (nmol/L)
|Concentration of BPA in the small intestine
            RST       <- dInput.O-k0*AST-ge*AST            # (nmol/h)   |Rate
of BPA amount change in the stomach
```

```
            RGImet    <- vmaxgutg*Cgut/(kmgutg+Cgut)       # (nmol/h)  |Rate
of BPA glucuronidation in the gut
            RGImets   <- vmaxguts*Cgut/(kmguts+Cgut)       # (nmol/h)  |Rate
of BPA sulfation in the gut
            Rfeces    <- k4*ASI                                # (nmol/h)
|Rate of BPA excreted into feces
            RAO       <- k1*ASI                            # (nmol/h)
|Uptake rate of BPA from the small intestine into serum
            RSI       <- ge*AST-RGImet-RAO-RGImets         # (nmol/h)  |Rate
of BPA amount change in the small intestine
            Roral     <- k0*AST+RAO                        # (nmol/h)  |Rate
of BPA peroral uptake

            #Amount of BPAG in GI tract
            RGIin     <- kGIing*AGIBPAg                    # (nmol/h)
|Uptake rate of BPAG from small intestine into serum
            RGIBPAg   <- RGImet - RGIin                    # (nmol/h)  |Rate
of BPAG amount change in the small intestine

            #Amount of BPAS in GI tract
            RGIins    <- kGIins*AGIBPAs                    # (nmol/h)
|Uptake rate of BPAS from small intestine into serum
            RGIBPAs   <- RGImets - RGIins                  # (nmol/h)  |Rate
of BPAS amount change in the small intestine


            ### C's and CV's ###

            CFat      <- AFat/Vfat                         # (nmol/L)
|Concentration of BPA in the fat
            CVFat     <- AFat/(Vfat*pfat)                  # (nmol/L)
|Venous blood concentration of BPA leaving the fat
            Cgonad    <- Agonad/Vgonad                     # (nmol/L)
|Concentration of BPA in the gonads
            CVgonad   <- Agonad/(Vgonad*pgonad)            # (nmol/L)
|Venous blood concentration of BPA leaving the gonads
            Cskin     <- Askin/Vskin                       # (nmol/L)
|Concentration of BPA in the skin
            CVskin    <- Askin/(Vskin*pskin)               # (nmol/L)
|Venous blood concentration of BPA leaving the skin
            CLiver    <- ALiver/Vliver                         # (nmol/L)
|Concentration of BPA in the liver
            CVLiver   <- ALiver/(Vliver*pliver)            # (nmol/L)
|Venous blood concentration of BPA leaving the liver
            Cbrain    <- Abrain/Vbrain                     # (nmol/L)
|Concentration of BPA in the brain
            CVbrain   <- Abrain/(Vbrain*pbrain)            # (nmol/L)
|Venous blood concentration of BPA leaving the brain
            CR        <- AR/Vrich                            # (nmol/L)
|Concentraitoin of BPA in the rapidly perfused tissues
            CVR       <- AR/(Vrich*prich)                  # (nmol/L)
|Venous blood concentration of BPA leaving the rapidly perfused tissues
            CVS       <- AS/(Vslow*pslow)                  # (nmol/L)
|Venous blood concentration of BPA leaving the slowly perfused tissues
            CS        <- AS/Vslow                          # (nmol/L)
|Concentration of BPA in the slowly perfused tissues
            CV        <-
(CVLiver*Qliver+CVskin*Qskin+CVFat*Qfat+CVR*Qrich+CVS*Qslow+CVgonad*Qgonad+
CVbrain*Qbrain)/QC    #(nmol/L)          |Concentration of BPA in the venous
plasma.
            CA        <- Aplasma/Vplasma
#(nmol/L)          |concentration of BPA in the arterial plasma
```

```
            #Excretion of BPA in urine
            Rurinebpa   <- kurinebpa*CV                                  #
(nmol/h)    |Rate of BPA excreted into the urine

            #Amount of BPA in the plasma
            Rplasma     <- QC*(CV-CA)-Rurinebpa                         #
(nmol/h)    |Rate of BPA amount change in the plasma.

            #Amount of BPA in the Fat
            RAfat       <- Qfat*(CA-CVFat)                              #
(nmol/h)    |Rate of BPA amount change in the fat

            #Amount of BPA in the gonads
            RAgonad     <- Qgonad*(CA-CVgonad)                          #
(nmol/h)    |Rate of BPA amount change in the gonads

            #Amount of BPA in the skin
            RAskin      <- dInput.D+Qskin*(CA-CVskin)                    #
(nmol/h)    |Rate of BPA amount change in the skin

            #Amount of BPA in the liver
            RAM         <- vmaxliver*CVLiver/(kmliver+CVLiver)          #
(nmol/h)    |Rate of BPA glucuronidation in the liver
            RAMs        <- vmaxlivers*CVLiver/(kmlivers+CVLiver)        #
(nmol/h)    |Rate of BPA sulfation in the liver

            #Amount of BPA in the brain
            Rbrain      <- Qbrain*(CA-CVbrain)                          #
(nmol/h)    |Rate of BPA amount change in the brain

            #Amount  of BPA in rapidly perfused tissues
            RAR         <- Qrich*(CA-CVR)                               #
(nmol/h)    |Rate of BPA amount change in rapidly perfused tissues

            #Amount in slowly perfused tissues
            RAS         <- Qslow*(CA-CVS)                               #
(nmol/h)    |Rate of BPA amount change in slowly perfused tissues



#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
#         Model for BPAG
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

            #Fate of BPAG formed in the liver
            RBPAg_prod          <- met1g*RAM                                #
(nmol/h)    |Taken up into systemic circulation
            RBPAg_prod_delay    <- met2g*RAM                                #
(nmol/h)    |Excreted into bile

            #Fate of BPAG formed in SI
            RBPAg_prod_gut      <-  met1g*RGIin                             #
(nmol/h)    |Taken up into systemic circulation
            RBPAg_prod_delay_gut <-  met2g*RGIin                            #
(nmol/h)    |Excreted into bile

            #Fate of BPAS formed in the liver
            RBPAs_prod          <-  met1s*RAMs                              #
(nmol/h)    |Taken up into systemic circulation
```

```
            RBPAs_prod_delay     <-  met2s*RAMs                                 #
(nmol/h)    |Excreted into bile

            #Fate of BPAS formed in SI
            RBPAs_prod_gut          <- met1s*RGIins                            #
(nmol/h)    |Taken up into systemic circulation
            RBPAs_prod_delay_gut    <- met2s*RGIins                            #
(nmol/h)    |Excreted into bile

            #Amount of BPAG in the gut (EHR compartment)
            RBPA_delayin      <- ABPA_delay*kentero                            #
(nmol/h)|Uptake rate of BPAG into the systemic circulation from the gut
(EHR compartment)
            Rfecesiv          <- ABPA_delay*k4_IV                              #
(nmol/h)|Rate of fecal excretion of BPAG from the gut (EHR compartment)
            RBPA_delayinbpag  <- ABPA_delay*kenterobpag                        #
(nmol/h)|Uptake rate of BPA into the systemic circulation from the gut (EHR
compartment for BPAG)
            Cbpac             <- Abpac/(Vbodyg+1E-34)                          #
(nmol/L)|Concentration of BPAG in the system

            #Amount of BPAS in the gut (EHR compartment)
            RBPA_delayins     <-  ABPA_delays*kentero                          #
(nmol/h) |Uptake rate of BPAS into the systemic circulation from the gut
(EHR compartment)
            Rfecesivs         <-  ABPA_delays*k4_IV                            #
(nmol/h) |Rate of fecal excretion of BPAS from the gut (EHR compartment)
            RBPA_delayinbpas  <-  ABPA_delays*kenterobpas                      #
(nmol/h) |Uptake rate of BPA into the systemic circulation from the gut
(EHR compartment for BPAS)
            Cbpas             <-  Abpasul/(Vbodys+1E-34)                       #
(nmol/L) |Concentration of BPAS in the system


            #Concentration of BPAG
            #Cbpac            <- Abpac/(Vplasma)           # (nmol/L)
|Concentration of BPAG in the system

            #Concentration of BPAS
            #Cbpas            <-  Abpasul/(Vplasma)        # (nmol/L)
|Concentration of BPAS in the system

            #Urinary excretion of BPAG
            Rreabsorption    <-
vreabsorptiong*Cbpac/(kreabsorptiong+Cbpac)    # (nmol/h)    |Rate of renal
reabsorption of BPAG
            Rurinebpag       <-  kurinebpag*Cbpac-Rreabsorption
# (nmol/h)    |Rate of BPAG amount change in the bladder
            Rurineg          <-  kurinebpag*Cbpac
# (nmo/h)     |Rate of BPAG excreted

            #Urinary excretion of BPAs
            Rreabsorptions   <-
vreabsorptions*Cbpas/(kreabsorptions+Cbpas)    # (nmol/h)    |Rate of renal
reabsorption of BPAS
            Rurinebpas       <-  kurinebpas*Cbpas-Rreabsorptions
# (nmol/h)    |Rate of BPAS amount change in the bladder
            Rurines          <-  kurinebpas*Cbpas
# (nmo/h)     |Rate of BPAS excreted
```

```
            Rbpas              <- RBPAs_prod+RBPA_delayins+RBPAs_prod_gut-
Rurinebpas                                  # (nmol/h)  |Rate of BPAS amount
change in the system
            Rbpac              <- RBPAg_prod+RBPAg_prod_gut+RBPA_delayin-
Rurinebpag                                  # (nmol/h)  |Rate of BPAG amount
change in the system
            RBPA_delay         <- RBPAg_prod_delay+RBPAg_prod_delay_gut-
RBPA_delayin-Rfecesiv-RBPA_delayinbpag     # (nmol/h)  |Rate of BPAG amount
change in the gut (EHR compartment)
            RBPA_delays        <- RBPAs_prod_delay+RBPAs_prod_delay_gut-
RBPA_delayins-Rfecesivs-RBPA_delayinbpas  # (nmol/h)  |Rate of BPAS amount
change in the gut (EHR compartment)
            RALiver            <- Qliver*(CA-CVLiver)+Roral-RAM-
RAMs+RBPA_delayinbpag+RBPA_delayinbpas             # (nmol/h)  |Rate of BPA
amount change in the liver

            dydt <-
c(dInput.O,dInput.D,dInput.D2,RST,RSI,Rfeces,RAO,RGImet,RGImets,Roral,RGIBP
Ag,RGIin,RGIBPAs,RGIins,Rplasma,RAfat,RAgonad,RAskin,RALiver,RAM,RAMs,Rbrai
n,RAR,RAS,Rurinebpa,

RBPAg_prod,RBPAg_prod_delay,RBPAg_prod_gut,RBPAg_prod_delay_gut,RBPAs_prod,
RBPAs_prod_delay,RBPAs_prod_gut,RBPAs_prod_delay_gut,RBPA_delay,

RBPA_delayin,Rfecesiv,RBPA_delayinbpag,Rbpac,RBPA_delays,RBPA_delayins,Rfec
esivs,RBPA_delayinbpas,Rbpas,Rurinebpag,Rreabsorption,Rurineg,
                      Rurinebpas,Rreabsorptions,Rurines,dSSD,dSSD2)


            conc <- c(CV=CV)
            res  <- list(dydt, conc)
            return(res)
          })}

  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  # Solve the system of differential equations
  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  zeit <- seq(0, 10*24*60, 2)/60   # (h) time
  v    <- ode(y=yini, func=PBTKmod, times=zeit, parms=para, method="lsoda")


  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  # Mass Balances
  # ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

  #Blood balance
  Qtotal      <- Qliver + Qfat + Qrich + Qslow + Qgonad + Qbrain + Qskin
  Qbal        <- Qtotal - QC

  #bw balance
  bworgans    <- Vliver + Vrich + Vslow + Vfat + Vgonad + Vbrain + Vskin

  #Mass balance (nmoles) for BPA
  TMassbpa    <- v[,"Aplasma"] + v[,"ALiver"] + v[,"AFat"] + v[,"AS"] +
v[,"AR"] + v[,"Agonad"] + v[,"Abrain"]  + v[,"Askin"]
  Lossbpa     <- v[,"Amet_liver"] + v[,"AGImet"] + v[,"Afeces"] +
v[,"Aurinebpa"] + v[,"Amet_livers"] + v[,"AGImets"]
  BPA         <- v[,"Input.O"] + v[,"Input.D"] - Lossbpa - TMassbpa -
v[,"ASI"] - v[,"AST"] + v[,"ABPA_delayinbpas"] + v[,"ABPA_delayinbpag"]

  #Mass balance for BPAG
```

```
  Massbpagbox <- v[,"ABPAg"] + v[,"ABPAg_gut"] + v[,"ABPA_delayin"] -
v[,"Aurinebpag"] - v[,"Abpac"]
  Massbpasbox <- v[,"ABPAs"] + v[,"ABPAs_gut"] + v[,"ABPA_delayins"] -
v[,"Aurinebpas"] - v[,"Abpasul"]
  Massbpagehr <- v[,"ABPAg_prod_delay"] + v[,"ABPAg_prod_delay_gut"] -
v[,"ABPA_delayin"] - v[,"Afecesiv"] - v[,"ABPA_delay"] -
v[,"ABPA_delayinbpag"]
  Massbpasehr <- v[,"ABPAs_prod_delay"] + v[,"ABPAs_prod_delay_gut"] -
v[,"ABPA_delayins"] - v[,"Afecesivs"] - v[,"ABPA_delays"] -
v[,"ABPA_delayinbpas"]
  perurine    <- (v[,"Aurinebpas"] + v[,"Aurinebpa"] + v[,"Aurinebpag"]) /
(v[,"Input.O"] + v[,"Input.D"])

  #Total balance for BPA and BPAG
  Mass        <- v[,"Input.O"] - TMassbpa - v[,"ASI"] - v[,"AST"] -
v[,"ABPA_delay"] - v[,"ABPA_delays"] - v[,"Abpac"] - v[,"Abpasul"] -
v[,"Aurinebpa"] - v[,"Aurinebpag"] - v[,"Aurinebpas"] - v[,"AGIBPAg"] -
v[,"AGIBPAs"] - v[,"Afeces"] - v[,"Afecesiv"] - v[,"Afecesivs"]


  # ++++++++++++++++++++++++++++++++++++++++++++
  # From amounts to concentrations
  # ++++++++++++++++++++++++++++++++++++++++++++

  v[,"Abpac"]  <- v[,"Abpac"]/Vplasma
  v[,"Abpasul"]  <- v[,"Abpasul"]/Vplasma
  v[,"Aplasma"]  <- v[,"Aplasma"]/Vplasma

  #filter out the negative values
  v <- v[v[,"Abpac"]>0,]
  v <- v[v[,"Abpasul"]>0,]
  v <- v[v[,"Aplasma"]>0,]
  v <- v[v[,"Aurineg"]>0,]
  v <- v[v[,"Aurines"]>0,]
  v <- v[v[,"Aurinebpa"]>0,]


  y <- as.data.frame(v)


  results[,(i),(u)] <- y$Aplasma
  }
  }
```

References

Barter ZE, Bayliss MK, Beaune PH, Boobis AR, Carlile DJ, Edwards RJ, et al. 2007. Scaling Factors for the Extrapolation of In Vivo Metabolic Drug Clearance From In Vitro Data: Reaching a Consensus on Values of Human Micro-somal Protein and Hepatocellularity Per Gram of Liver. Curr Drug Metab 8:33–45; doi:10.2174/138920007779315053.

Bautista-Toledo I, Ferro-García MA, Rivera-Utrilla J, Moreno-Castilla C, Vegas Fernández FJ. 2005. Bisphenol A Removal from Water by Activated Carbon. Effects of Carbon Characteristics and Solution Chemistry. Environ Sci Technol 39:6246–6250; doi:10.1021/es0481169.

Bayer AG. 1996. Studies on the EcologicaI Behavior of Bisphenol A.

Coughlin JL, Thomas PE, Buckley B. 2012. Inhibition of Genistein Glucuronidation by Bisphenol A in Human and Rat Liver Microsomes. Drug Metab Dispos 40:481–485; doi:10.1124/dmd.111.042366.

Csanády GA, Oberste-Frielinghaus HR, Semder B, Baur C, Schneider KT, Filser JG. 2002. Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. Arch Toxicol 76:299–305; doi:10.1007/s00204-002-0339-5.

DeJongh J, Verhaar HJM, Hermens JLM. 1997. A quantitative property-property relationship (QPPR) approach to estimate in vitro tissue-blood partition coefficients of organic chemicals in rats and humans. Arch Toxicol 72:17–25; doi:10.1007/s002040050463.

Doerge DR, Twaddle NC, Vanlandingham M, Brown RP, Fisher JW. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats. Toxicol Appl Pharmacol 255:261–270; doi:10.1016/j.taap.2011.07.009.

Edginton AN, Schmitt W, Willmann S. 2006. Development and Evaluation of a Generic Physiologically Based Pharmacokinetic Model for Children. Clin Pharmacokinet 45:1013–1034; doi:10.2165/00003088-200645100-00005.

EFSA CEF Panel. 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA J 20151313978.

EFSA Scientific Committee. 2016. Guidance on Uncertainty in EFSA Scientific Assessment - Revised Draft for Internal Testing.

Elsby R, Maggs JL, Ashby J, Park BK. 2001. Comparison of the Modulatory Effects of Human and Rat Liver Microsomal Metabolism on the Estrogenicity of Bisphenol A: Implications for Extrapolation to Humans. J Pharmacol Exp Ther 297: 103–113.

Hormann AM, vom Saal FS, Nagel SC, Stahlhut RW. 2014. Holding Thermal Receipt Paper and Eating Food after Using Hand Sanitizer Results in High Serum Bioactive and Urine Total Levels of Bisphenol A (BPA). PLoS ONE 9.

ICRP. 2002. Basic anatomical and physiological data for use in radiological protection: reference values: ICRP Publication 89. Ann ICRP 32:1–277; doi:10.1016/S0146-6453(03)00002-2.

Korenman YI. 1973. Solvates of Xylenols in Homologous. Russ J Phys Chem 47: 1045.

Kuester RK, Sipes IG. 2007. Prediction of Metabolic Clearance of Bisphenol A (4,4 ′-Dihydroxy-2,2-diphenylpropane) using Cryopreserved Human Hepatocytes. Drug Metab Dispos 35:1910–1915; doi:10.1124/dmd.107.014787.

Kurebayashi H, Okudaira K, Ohno Y. 2010. Species difference of metabolic clearance of bisphenol A using cryopreserved hepatocytes from rats, monkeys and humans. Toxicol Lett 198:210–215; doi:10.1016/j.toxlet.2010.06.017.

Mazur CS, Kenneke JF, Hess-Wilson JK, Lipscomb JC. 2010. Differences between Human and Rat Intestinal and Hepatic Bisphenol A Glucuronidation and the Influence of Alamethicin on In Vitro Kinetic Measurements. Drug Metab Dispos 38:2232–2238; doi:10.1124/dmd.110.034819.

Oh J, Choi JW, Ahn Y-A, Kim S. 2018. Pharmacokinetics of bisphenol S in humans after single oral administration. Environ Int 112:127–133; doi:10.1016/j.envint.2017.11.020.

Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, et al. 1997. Characterization of Interintestinal and Intraintestinal Variations in Human CYP3A-Dependent Metabolism. J Pharmacol Exp Ther 283: 1552–1562.

Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. 2002. Enterohepatic Circulation. Clin Pharmacokinet 41:751–790; doi:10.2165/00003088-200241100-00005.

Schmitt W. 2008. General approach for the calculation of tissue to plasma partition coefficients. Toxicol In Vitro 22:457–467; doi:10.1016/j.tiv.2007.09.010.

Street CM, Zhu Z, Finel M, Court MH. 2017. Bisphenol-A glucuronidation in human liver and breast: identification of UDP-glucuronosyltransferases (UGTs) and influence of genetic polymorphisms. Xenobiotica 47:1–10; doi:10.3109/00498254.2016.1156784.

Thayer KA, Doerge DR, Hunt D, Schurman SH, Twaddle NC, Churchwell MI, et al. 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environ Int 83:107–115; doi:10.1016/j.envint.2015.06.008.

Trdan Lušin T, Roškar R, Mrhar A. 2012. Evaluation of bisphenol A glucuronidation according to UGT1A1*28 polymorphism by a new LC–MS/MS assay. Toxicology 292:33–41; doi:10.1016/j.tox.2011.11.015.

Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. 2002. Metabolism and Kinetics of Bisphenol A in Humans at Low Doses Following Oral Administration. Chem Res Toxicol 15:1281–1287; doi:10.1021/tx025548t.

Zhang H, Zhang Y. 2006. Convenient Nonlinear Model for Predicting the Tissue/Blood Partition Coefficients of Seven Human Tissues of Neutral, Acidic, and Basic Structurally Diverse Compounds. J Med Chem 49:5815–5829; doi:10.1021/jm051162e.

Zhang Q-Y, Dunbar D, Ostrowska A, Zeisloft S, Yang J, Kaminsky LS. 1999. Characterization of Human Small Intestinal Cytochromes P-450. Drug Metab Dispos 27: 804–809.