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Supplemental Material

Oral Systemic Bioavailability of Bisphenol A and Bisphenol S in Pigs

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Figure S6. Visual Predictive Check (VPC) of plasma BPA and BPAG concentrations obtained with 200 replicates of each animal. A and B: Plasma BPA concentrations (μM) after respective BPA IV (A) and oral administrations. C and D: Plasma BPAG concentrations (μM) after respective BPA IV (C) and oral administrations (D) Red lines: observed quantiles (20, 50 and 80%); Black lines: predicted quantiles by Monte Carlo Simulation (20, 50 and 80%); Black symbols: observed data. When the model ideally predicts the data, the observed and predicted quantiles are expected to be superimposed.

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Figure S8. Visual Predictive Check (VPC) of plasma BPS and BPSG concentrations obtained with 1000 replicates of each animal. A and B: Plasma BPS concentrations (μM) after respective BPS IV (A) and oral administrations. C and D: Plasma BPSG concentrations (μM) after respective IV BPSG (C) and BPS administrations (D). Red lines: observed quantiles (20, 50 and 80%); Black lines: predicted quantiles by Monte Carlo Simulation (20, 50 and 80%); Black symbols: observed data. When the model ideally predicts the data, the observed and predicted quantiles are expected to be superimposed.

Figure S9. Visual Predictive Check (VPC) of the amounts of BPS and BPSG excreted in urine obtained with 1000 replicates of each animal. A and B: Amounts of BPS excreted in urine (μM) after respective BPS IV (A) and oral (B) administrations; C and D: Amounts of BPSG excreted in urine (μM) after respective BPS IV (C) and oral (D) administrations. E: Amounts of BPSG excreted in urine (μM) after BPSG IV administration. Red lines: observed quantiles (20, 50 and 80%); Black lines: predicted quantiles by Monte Carlo Simulation (20, 50 and 80%); Black symbols: observed data. When the model ideally predicts the data, the observed and predicted quantiles are expected to be superimposed.

Table S1: Concentrations of BPA, BPS and BPSG in the dosing solutions.

Experiment	Exp1		Exp2	Exp3		Exp4		Exp5			
Molecule	BPA		BPA	BPS	BPSG	BPS		BPA		BPS	
Route	IV	Oral	IV	IV	IV	IV	Oral	IV	Oral	IV	Oral
Nominal concentration (mg/ml)	50	100	50	25	10	25		23	25	50	25
Measured concentration (mg/ml)*	59.1, 63.4	68.4, 93.8	49.3	26.8	9.8	21.3	NM	18.2, 18.9	18.7, 24.0	39.3, 42.9	17;1; 18.1

*Separate dosing solutions have been prepared for each of the periods of the experiments 1 and 5

BPA: Bisphenol A; BPS: Bisphenol S; BPSG: Bisphenol S glucuronide, Exp: Experiment, IV: Intravenous, NM: Not measured.

Table S2: Limits of quantification (LOQ) of BPA, BPAG, BPS and BPSG (µM).

	Exp1		Exp2		Exp3		Exp4		Exp5	
	Plasma	**Urine**	**Plasma**	**Urine**	**Plasma**	**Urine**	**Plasma**	**Urine**	**Plasma**	**Urine**
BPA	0.0044		0.0044	0.044					0.013	0.11
BPAG	0.049		0.012	2.47					0.074	2.47
BPS					0.012	0.40	0.012	0.40	0.012	0.40
BPSG					0.023	0.23	0.023	0.23	0.023	0.23

The LOQ values were determined for plasma and urine with a precision lower than 20 % and within an accuracy range of 80-120 %

BPA: Bisphenol A; BPAG: Bisphenol A glucuronide; BPS: Bisphenol S; BPSG: Bisphenol S glucuronide, Exp: Experiment.

Table S3: Typical values for the population primary parameters of BPA and BPAG in pigs as obtained with a 9-compartments model.

Parameters (units)	Mean	Median	SE	CV%
tvVBPA (L/kg)	1.03	1.00	0.471	47.30
tvK34 (1/h)	5.90	4.14	5.207	126
tvK43 (1/h)	3.89	3.68	1.347	36.61
tvK30 (1/h)	0.0026	0.002	0.001	57.70
tvVBPAG (L/kg)	0.107	0.112	0.026	23.17
tvK56 (1/h)	1.45	1.45	0.186	12.86
tvK65 (1/h)	0.015	0.015	0.002	10.99
tvK32 (1/h)	3.72	3.31	1.467	44.36
tvK23 (1/h)	1.53	1.32	1.346	102
tvK25 (1/h)	137.08	91.87	117.08	127
tvK12 (1/h)	0.365	0.371	0.062	16.67
tvK10 (1/h)	0.223	0.219	0.077	35.36
tvK110 (1/h)	0.349	0.318	0.150	47.23
tvK105 (1/h)	0.207	0.217	0.030	13.99
tvK50 (1/h)	2.750	2.547	0.743	29.16
tvCMultStdevBPA Plasma	0.410	0.407	0.058	14.28
tvCMultStdevBPAG Plasma	0.459	0.461	0.015	3.35
tvCMultStdevBPA URINE	0.484	0.485	0.052	10.72
tvCMultStdevBPAG URINE	0.295	0.308	0.078	25.23
stdev0 (BPA plasma) µmol/L	0.0093	0.008	0.004	47.49
stdev1 (BPAG plasma) µmol/L	0.0002	0.000	0.000	1195
stdev2 (urine BPA) µmol/kg	0.00005	0.000	0.000	212
stdev3 (urine BPAG) µmol/kg	0.9679	0.026	2.215	8539

BPA: Bisphenol A

BPAG: Bisphenol A glucuronide

The bootstrap procedure was used to estimate the mean, median, standard error (SE) and coefficient of variation (CV%) of the parameter estimates.

VBPA: volume of the BPA central compartment

VBPAG: volume of the BPAG central compartment

K10: rate constant corresponding to the unabsorbed BPA from the gastrointestinal tract

K12: rate constant of BPA absorbed by the enterocytes passing directly into the portal blood

K23, K32, K34, K43: Distribution rate constants between the plasma and the peripheral compartments for BPA.

K25, K56 and K65: Distribution rate constants between the plasma and the peripheral compartments for BPAG.

K30: BPA elimination rate constant from plasma to urine

K50: BPAG elimination rate constant from plasma to urine

K110: rate constant of BPA absorbed by the enterocytes locally subjected to glucuronidation

K105: rate constant of BPAG formed by the enterocytes absorbed into the systemic circulation

MultStdevBPA Plasma: standard deviation of the multiplicative error term ε_1 for BPA plasma concentrations (expressed as a coefficient of variation)

MultStdevBPAG Plasma: standard deviation of the multiplicative error term ε_1 for BPAG plasma concentrations (expressed as a coefficient of variation)

MultStdevBPA URINE: standard deviation of the multiplicative error term ε_1 for BPA urine amount (expressed as a coefficient of variation)

MultStdevBPAG URINE: standard deviation of the multiplicative error term ε_1 for BPAG urine amount (expressed as a coefficient of variation)

Stdev0: standard deviation of the additive error term ε_2 for BPA plasma concentrations

Stdev1: standard deviation of the additive error term ε_2 for BPAG plasma concentrations

Stdev2: standard deviation of the additive error term ε2 for BPA urinary amount

Stdev3: standard deviation of the additive error term ε2 for BPAG urinary amount

Table S4: Typical values for the population primary parameters of BPS and BPSG in pigs as obtained with a 9-compartments model.

Parameters (units)	Mean	Median	SE	CV%
tvVBPS (L/kg)	0.301	0.302	0.053	17.59
tvK34 (1/h)	0.270	0.267	0.040	14.87
tvK43 (1/h)	0.519	0.512	0.071	13.67
tvK30 (1/h)	0.001	0.001	0.0004	30.62
tvVBPSG (L/kg)	0.135	0.137	0.019	14.08
tvK56 (1/h)	0.730	0.655	0.232	31.73
tvK65 (1/h)	0.006	0.006	0.0019	33.29
tvK32 (1/h)	7.119	7.091	2.193	30.81
tvK23 (1/h)	84.0	83.489	13.1	15.58
tvK25 (1/h)	66.6	62.147	21.6	32.38
tvK12 (1/h)	2.042	1.425	1.944	95.20
tvK10 (1/h)	0.018	0.018	0.0032	17.50
tvK110 (1/h)	0.000	0.000	0.0000	11.60
tvK105 (1/h)	0.534	0.523	0.064	11.97
tvK50 (1/h)	1.818	1.832	0.180	9.90
tvCMultStdevBPS	0.460	0.465	0.031	6.76
tvCMultStdevBPSG	0.386	0.373	0.064	16.45
tvCMultStdevBPSURINE	0.738	0.742	0.102	13.80
tvCMultStdevBPSGURINE	0.399	0.393	0.043	10.78
stdev0 (BPS plasma) µmol/L	0.035	0.039	0.016	44.64
stdev1 (BPSG plasma) µmol/L	0.223	0.246	0.120	53.84
stdev2 (urine BPS) µmol/kg	0.0000	0.0000	0.0000	0.0000
stdev3 (urine BPSG) µmol/kg	0.0062	0.0062	0.0000	0.0057

BPS: Bisphenol S

BPSG: Bisphenol S glucuronide

The bootstrap procedure was used to estimate the mean, median, standard error (SE) and coefficient of variation (CV%).

VBPS: volume of the BPS central compartment

VBPSG: volume of the BPSG central compartment

K10: rate constant corresponding to the unabsorbed BPS from the gastrointestinal tract

K12: rate constant of BPS absorbed by the enterocytes passing directly into the portal blood

K23, K32, K34, K43: Distribution rate constants between the plasma and the peripheral compartments for BPS.

K25, K56 and K65: Distribution rate constants between the plasma and the peripheral compartments for BPSG.

K30: BPS elimination rate constant from plasma to urine

K50: BPSG elimination rate constant from plasma to urine

K110: rate constant of BPS absorbed by the enterocytes locally subjected to glucuronidation

K105: rate constant of BPSG formed by the enterocytes absorbed into the systemic circulation

MultStdevBPS: standard deviation of the multiplicative error term ε_1 for BPS plasma concentrations (expressed as a coefficient of variation)

MultStdevBPSG: standard deviation of the multiplicative error term ε_1 for BPSG plasma concentrations (expressed as a coefficient of variation)

MultStdevBPSURINE: standard deviation of the multiplicative error term ε_1 for BPS urine amount (expressed as a coefficient of variation)

MultStdevBPSGURINE: standard deviation of the multiplicative error term ε_1 for BPSG urine amount (expressed as a coefficient of variation)

Stdev0: standard deviation of the additive error term ε_2 for BPS plasma concentrations

Stdev1: standard deviation of the additive error term ε_2 for BPSG plasma concentrations

Stdev2: standard deviation of the additive error term ε_2 for BPSA urinary amount

Stdev3: standard deviation of the additive error term ε2 for BPSG urinary amount

Table S5: Bootstrap estimates of the random variance parameters (diagonal variance-covariance matrix) and BSV for the structural parameters of the BPA toxicokinetic model for which the shrinkage of random effects was lower than 30%.

Label	nK12	nK30	nK25	nK23	nVBPA	nVBPAG	nK50
Omega							
nK12	0.325						
nK30		1.42					
nK25			1.14				
nK23				0.034			
nVBPA					0.117		
nVBPAG						0.883	
nK50							1.67
BSV (CV%)	62	177	146	19	35	119	207

BSV: Between Subject Variability
BPA: Bisphenol A
BPAG: Bisphenol A glucuronide
CV: coefficient of variation
nVBPA: volume of the BPA central compartment
nVBPAG: volume of the BPAG central compartment
nK12: rate constant of BPA absorbed by the enterocytes passing directly into the portal blood
nK23: distribution rate constant between the liver and the plasma for BPA.
nK25: distribution rate constant between the liver and the plasma for BPAG.
nK30: BPA elimination rate constant from plasma to urine
nK50: BPAG elimination rate constant from plasma to urine

Table S6: Bootstrap estimates of the random variance parameters (diagonal variance-covariance matrix) and BSV for the structural parameters of the BPS toxicokinetic model for which the shrinkage of random effects was lower than 30%.

Label	nK12	nK30	nK25	nK23	nVBPS	nVBPSG	nK50
Omega							
nK12	1.985						
nK30		0.707					
nK25			0.362				
nK23				0.345			
nVBPS					0.202		
nVBPSG						0.214	
nK50							0.212
BSV (CV%)	250.61	101.34	66.04	64.16	47.30	48.91	48.65

BSV: Between Subject Variability
BPS: Bisphenol S
BPSG: Bisphenol S glucuronide
CV: Coefficient of variation
nVBPS: volume of the BPS central compartment
nVBPSG: volume of the BPSG central compartment
nK12: rate constant of BPS absorbed by the enterocytes passing directly into the portal blood
nK23: distribution rate constant between the liver and the plasma for BPS.
nK25: distribution rate constant between the liver and the plasma for BPSG.
nK30: BPS elimination rate constant from plasma to urine
nK50: BPSG elimination rate constant from plasma to urine

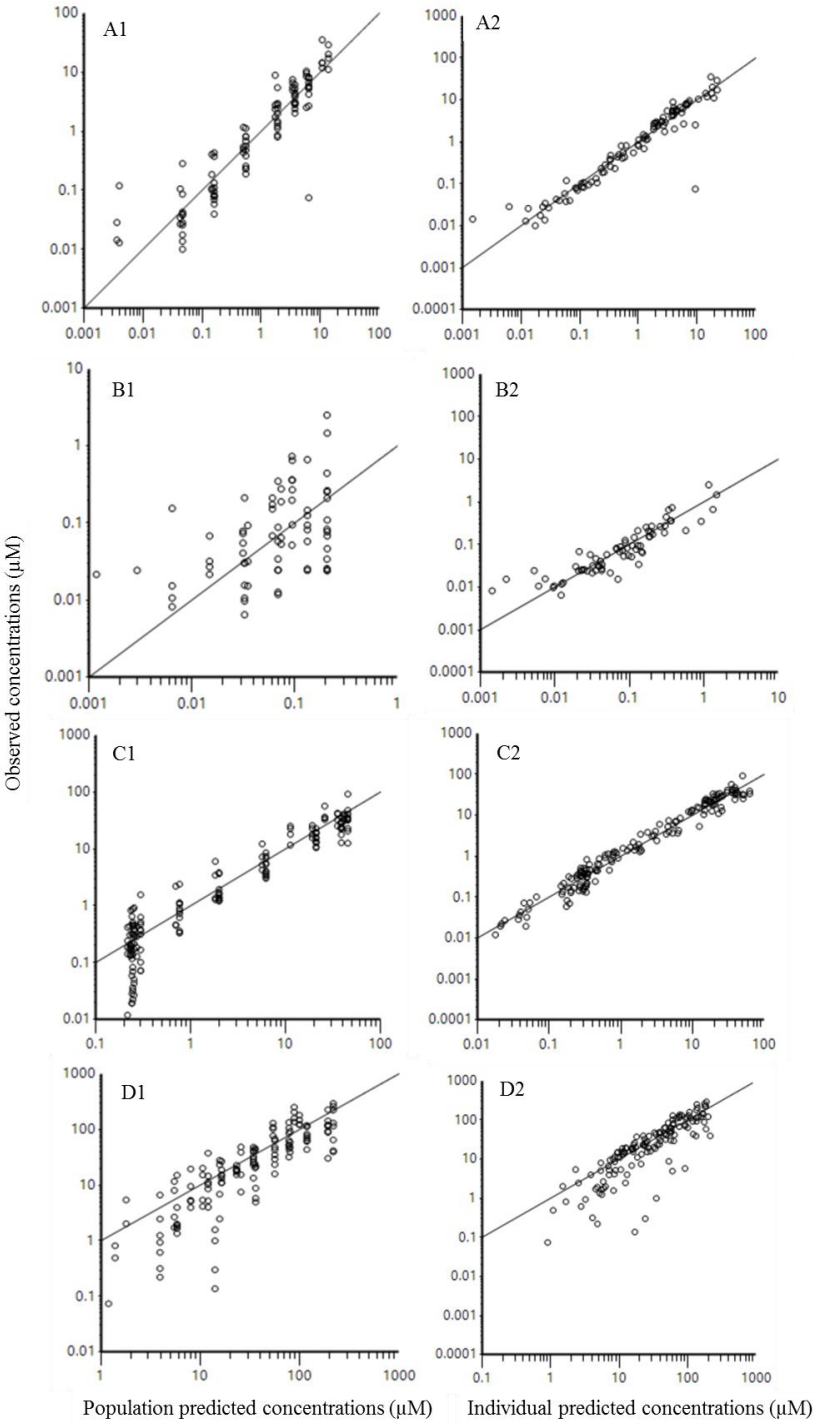


Figure S1: Diagnostic plots of the population and individual model predicted *vs* observed BPA and BPAG plasma concentrations. A1 and B1: Population predicted *vs.* observed BPA plasma concentrations (µM) after respective BPA IV (A1) and oral administrations (B1); C1 and D1: Population predicted *vs.* observed BPAG plasma concentrations (µM) after respective BPA IV (C1) and oral (D1) administrations; A2 and B2: Individual predicted *vs.* observed BPA plasma concentrations (µM) after respective BPA IV (A2) and oral administrations (B2); C2 and D2: Individual predicted *vs.* observed BPAG plasma concentrations (µM) after respective BPA IV (C2) and oral (D2) administrations.
BPA: Bisphenol A; BPAG: Bisphenol A glucuronide; IV: Intravenous

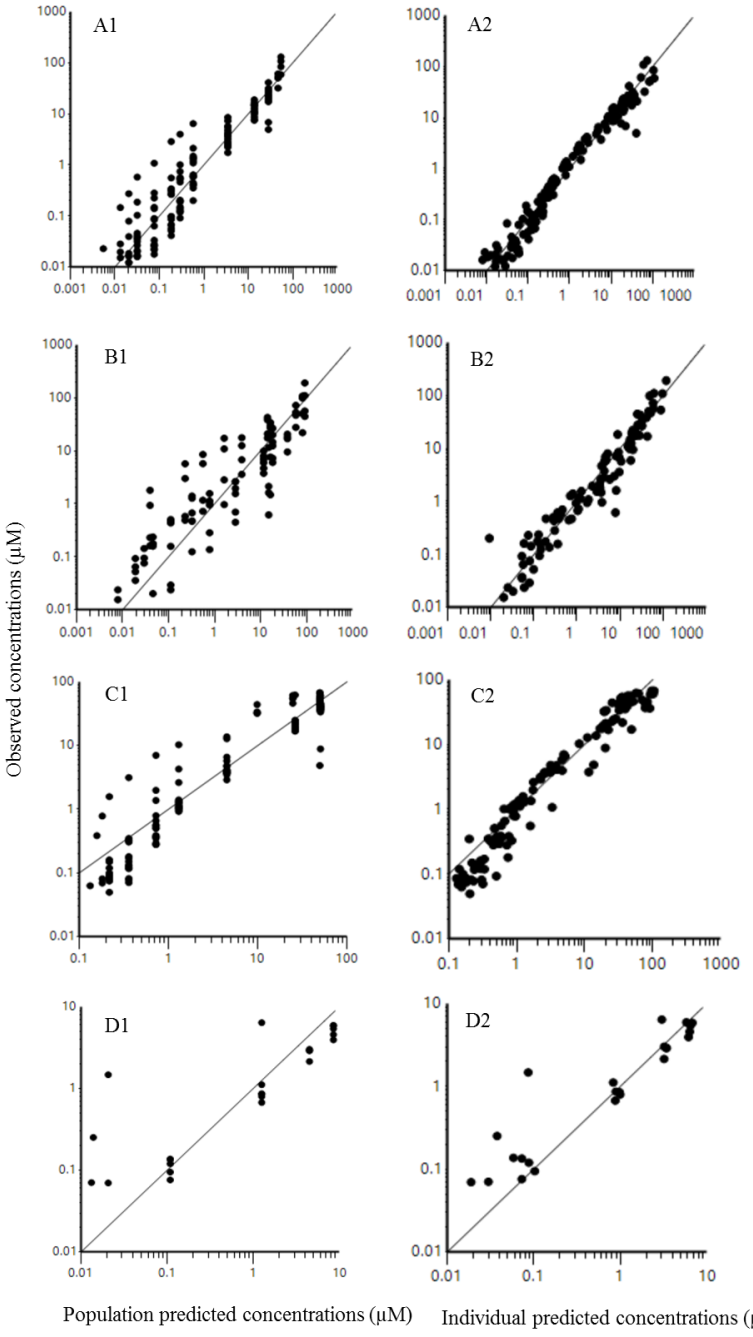


Figure S2: Diagnostic plots of the population and individual model predicted *vs* observed BPS and BPSG plasma concentrations. A1 and B1: Population predicted *vs.* observed BPS plasma concentrations (µM) after respective BPS IV (A1) and oral administrations (B1); C1 and D1: Population predicted *vs.* observed BPSG plasma concentrations (µM) after respective IV administrations of BPS (C1) and BPSG (D1); A2 and B2: Individual predicted *vs.* observed BPS plasma concentrations (µM) after respective BPS IV (A2) and oral administrations (B2); C2 and D2: Individual predicted *vs.* observed BPSG plasma concentrations (µM) after respective IV administrations of BPS (C2) and BPSG (D2).
BPS: Bisphenol S; BPSG: Bisphenol S glucuronide; IV: Intravenous.

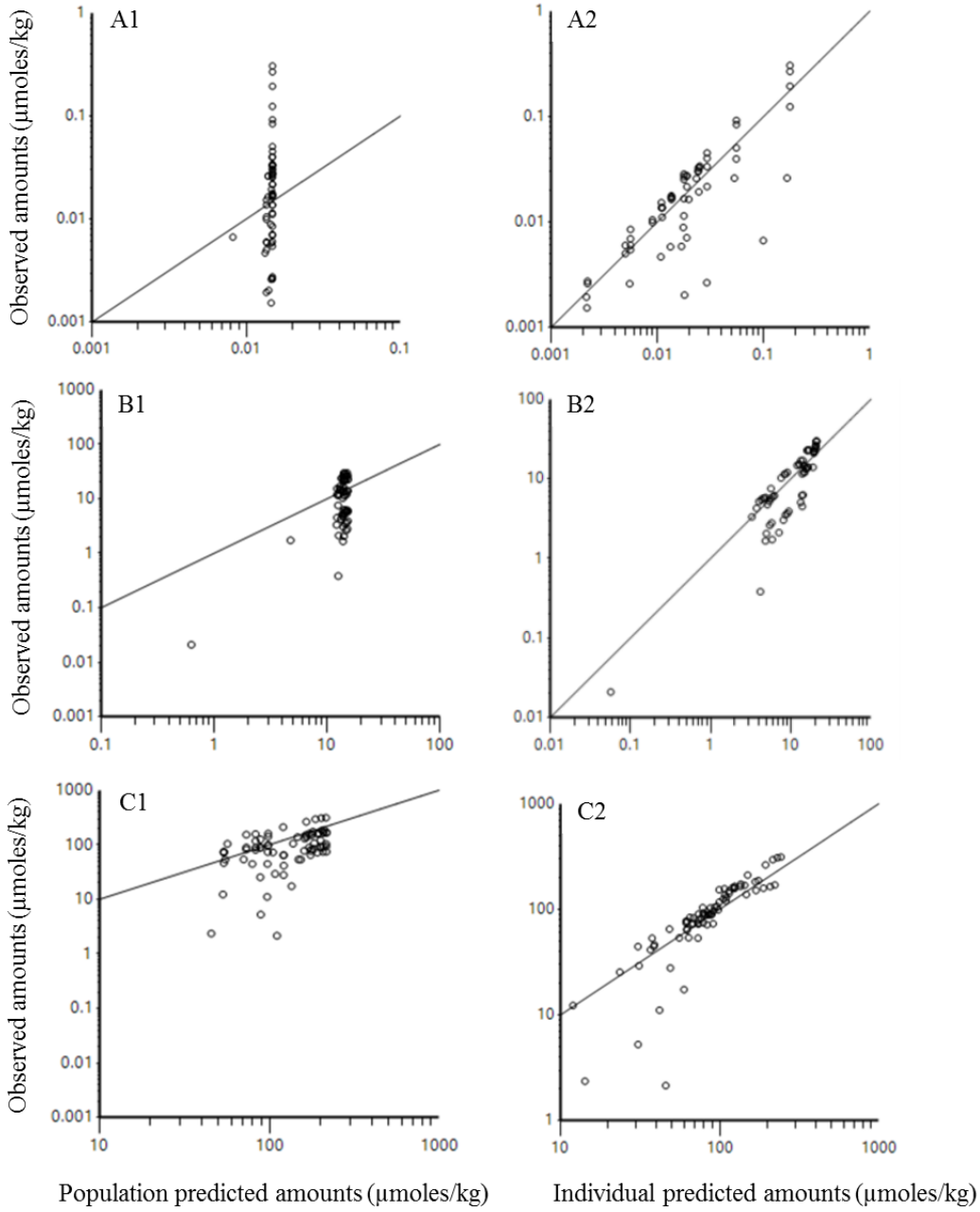


Figure S3: Diagnostic plots of the population and individual model predicted *vs* observed cumulative amounts of BPA and BPAG excreted in urine. A1 and B1: Population predicted *vs.* observed cumulative amounts (µmoles/kg) of BPA (A1) and BPAG (B1) excreted in urine after BPA IV administration; C1: Population predicted *vs.* observed cumulative amounts of BPAG excreted in urine after BPA oral administration; A2 and B2: Individual predicted *vs.* observed cumulative amounts of BPA (A2) and BPAG (B2) excreted in urine after BPA IV administration; C2: Individual predicted *vs.* observed cumulative amounts of BPAG excreted in urine after BPA oral administration.

BPA: Bisphenol A; BPAG: Bisphenol A glucuronide; IV: Intravenous.

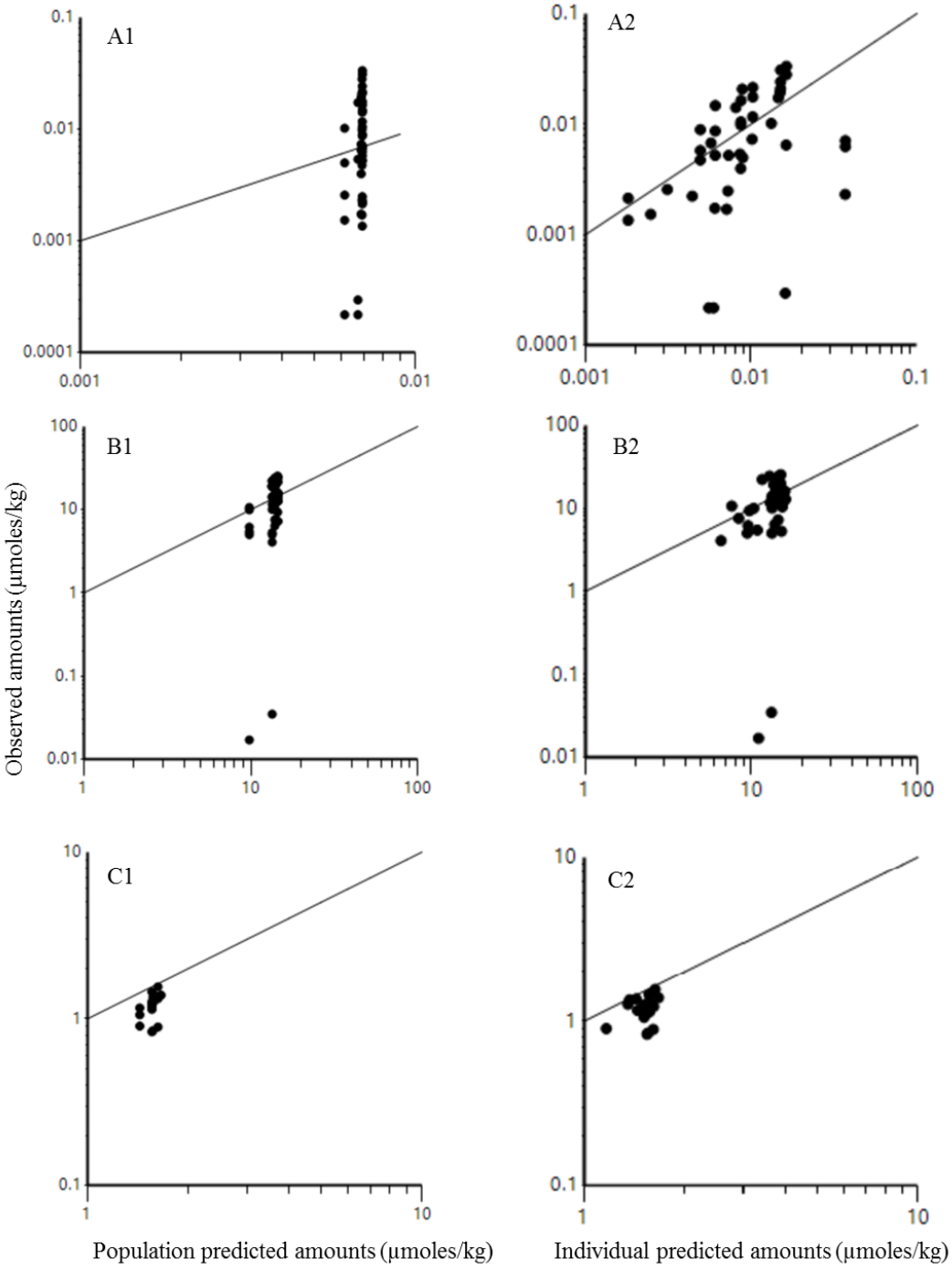


Figure S4: Diagnostic plots of the population and individual model predicted *vs* observed cumulative amounts of BPS and BPSG excreted in urine after IV dosing. A1 and B1: Population predicted *vs.* observed cumulative amounts (µmoles/kg) of BPS (A1) and BPSG (B1) excreted in urine after BPS IV administration; C1: Population predicted *vs.* observed cumulative amounts (µmoles/kg) of BPSG excreted in urine after BPSG IV administration; A2 and B2: Individual predicted *vs.* observed cumulative amounts (µmoles/kg) of BPS (A2) and BPSG (B2) excreted in urine after BPS IV administration; C2: Individual predicted *vs.* observed cumulative amounts (µmoles/kg) of BPSG excreted in urine after IV BPSG administration.
BPS: Bisphenol S; BPSG: Bisphenol S glucuronide; IV: Intravenous.

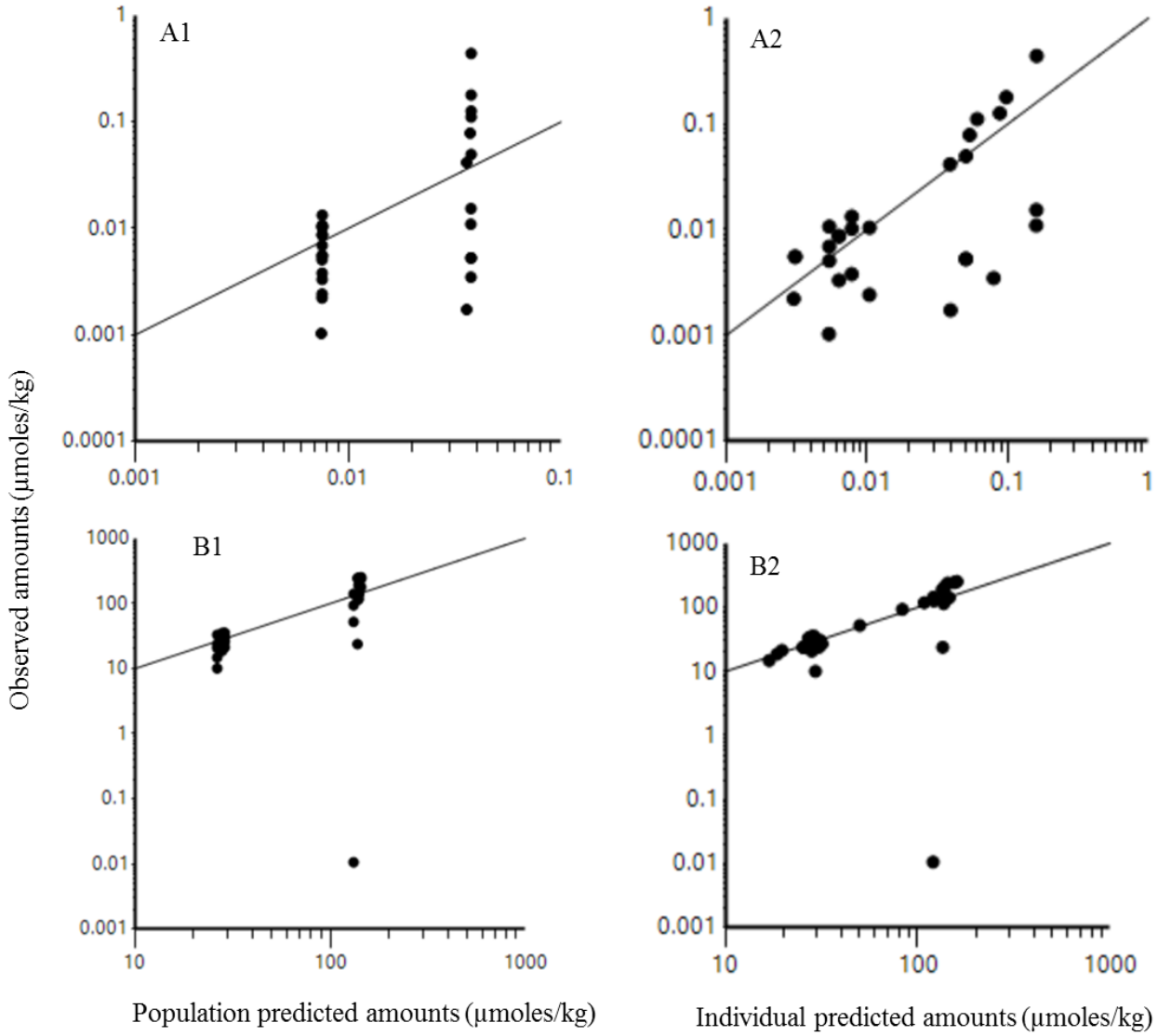
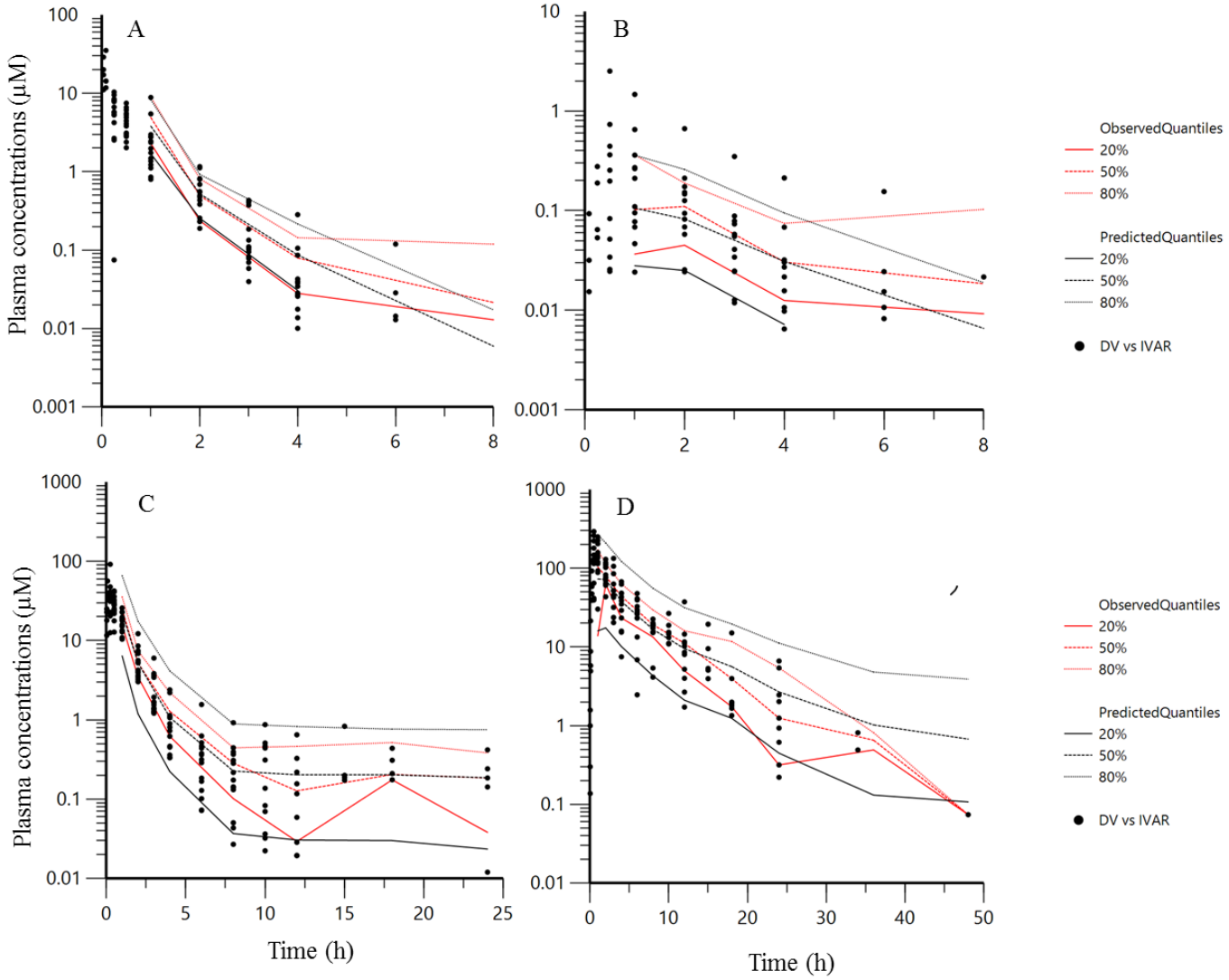


Figure S5: Diagnostic plots of the population and individual model predicted *vs* observed cumulative amounts of BPS and BPSG excreted in urine after oral dosing. A1 and B1: Population predicted *vs.* observed cumulative amounts (µmoles/kg) of BPS (A1) and BPSG (B1) excreted in urine after BPS oral administration; A2 and B2: Individual predicted *vs.* observed cumulative amounts (µmoles/kg) of BPS (A2) and BPSG (B2) excreted in urine after BPS oral administration.
BPS: Bisphenol S; BPSG: Bisphenol S glucuronide.



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BPA: Bisphenol A; BPAG: Bisphenol A glucuronide; IV: Intravenous.

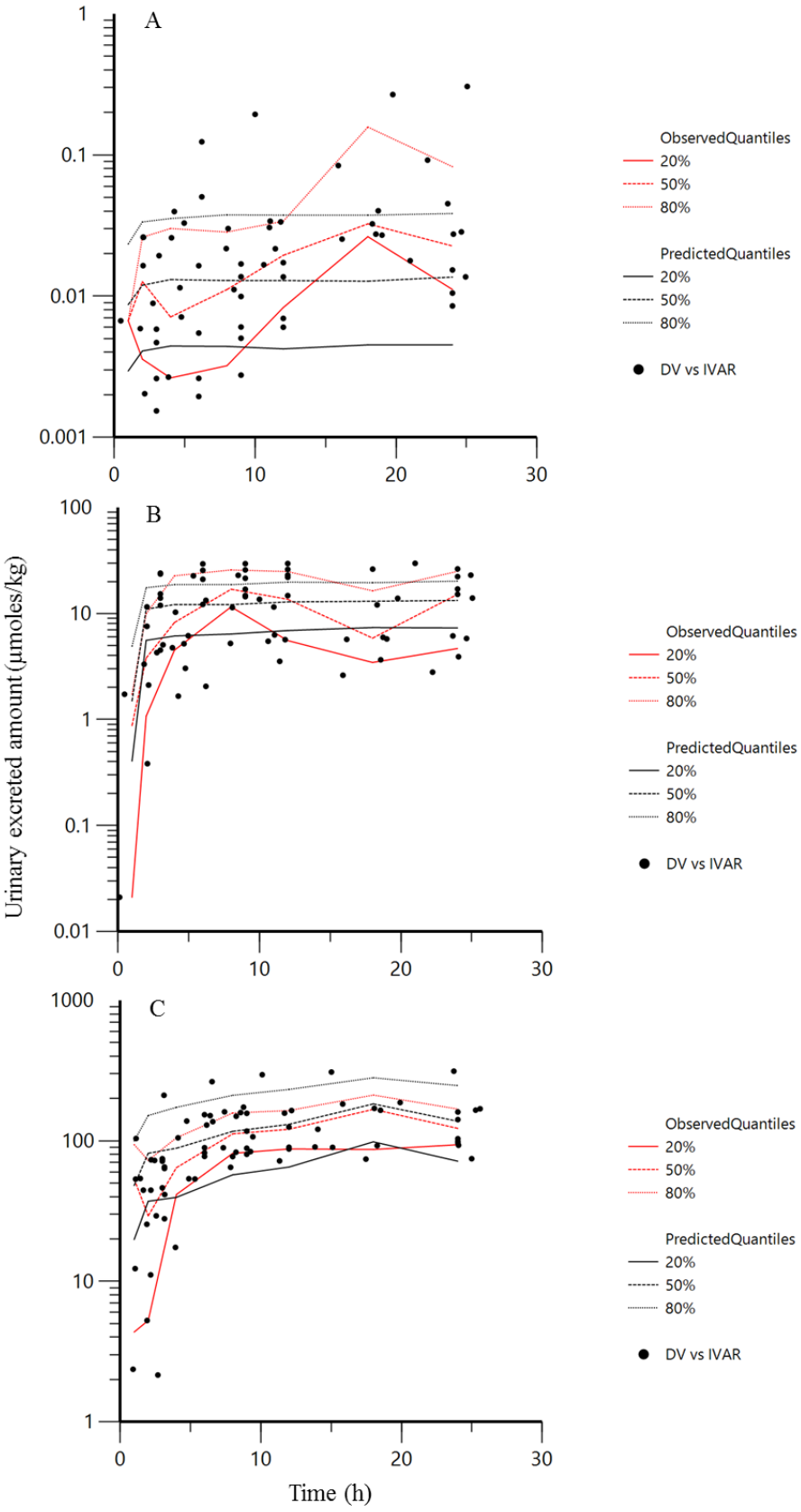


Figure S7: Visual Predictive Check (VPC) of the amounts of BPA and BPAG excreted in urine obtained with 200 replicates of each animal. A: Amounts of BPA excreted in urine (µM) after BPA IV administration; B and C: Amounts of BPAG excreted in urine (µM) after respective BPA IV and oral administrations Red lines: observed quantiles (20, 50 and 80%); Black lines:

predicted quantiles by Monte Carlo Simulation (20, 50 and 80%); Black symbols: observed data. When the model ideally predicts the data, the observed and predicted quantiles are expected to be superimposed.
BPA: Bisphenol A; BPAG: Bisphenol A glucuronide; IV: Intravenous.

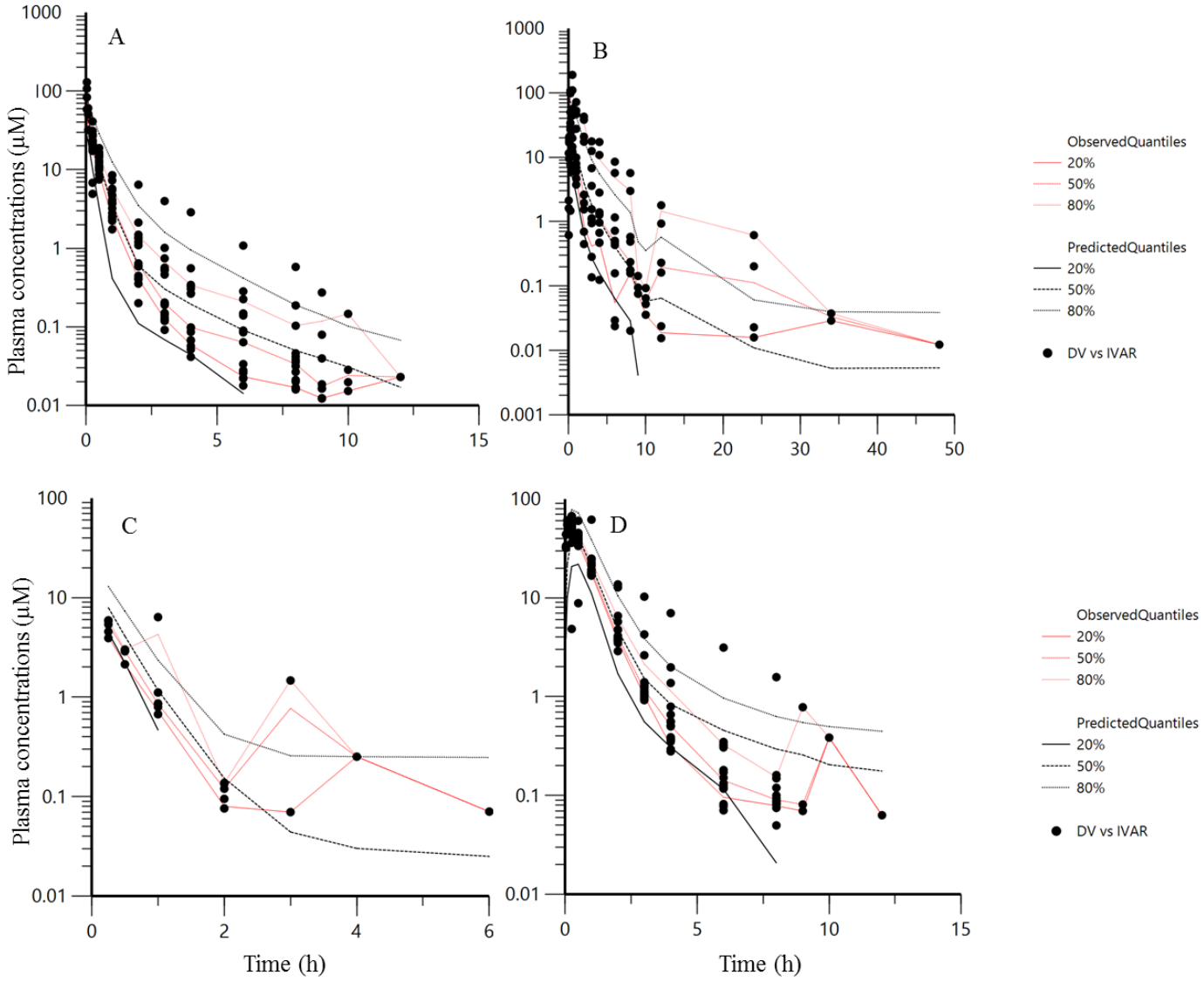
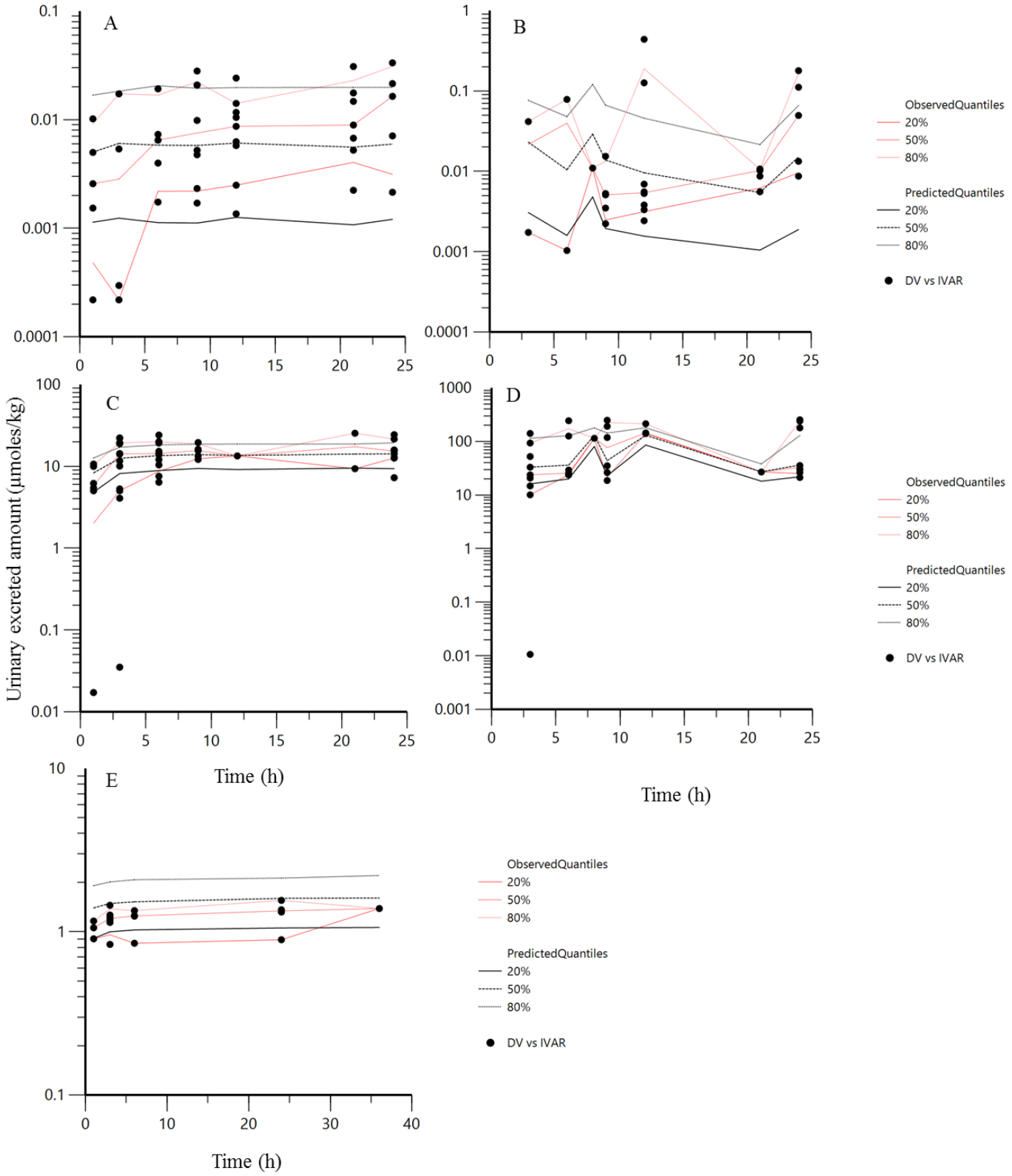


Figure S8: Visual Predictive Check (VPC) of plasma BPS and BPSG concentrations obtained with 1000 replicates of each animal. A and B: Plasma BPS concentrations (µM) after respective BPS IV (A) and oral administrations. C and D: Plasma BPSG concentrations (µM) after respective IV BPSG (C) and BPS administrations (D). Red lines: observed quantiles (20, 50 and 80%); Black lines: predicted quantiles by Monte Carlo Simulation (20, 50 and 80%); Black symbols: observed data. When the model ideally predicts the data, the observed and predicted quantiles are expected to be superimposed.
BPS: Bisphenol S; BPSG: Bisphenol S glucuronide; IV: Intravenous.



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