Experiment Number: K94150B
Route: Gavage , IV
Species/Strain: Mice/B6C3F1/N

Toxicokinetics Data Summary
Compound/Analyte: Bisphenol S/Free (unconjugated) Bisphenol S
CAS Number: 80-09-1

Request Date: 6/5/2020
Request Time: 2:30:16
Lab: RTI

Male

	Treatment Group (mg/kg)			
	34 Gav[a] Plasma	**110 Gav[a] Plasma**	**340 Gav[a] Plasma**	**34 IV[b] Plasma**
Cmax_pred (ng/mL)	7540 ± 2770	19400 ± 3590	39200 ± 22700	55900 ± 14300
Tmax_pred (hour)			3.08 ± 3.13	
Alpha (hour^-1)	4.59 ± 1.26	5.21 ± 0.619	2.85 ± 1.76	4.21 ± 0.456
Alpha_Half-life (hour)	0.151 ± 0.0415	0.133 ± 0.0158	0.244 ± 0.151	0.165 ± 0.0178
Beta (hour^-1)	0.242 ± 0.12	0.184 ± 0.0871	0.165 ± 0.124	0.231 ± 0.0358
Beta_Half-life (hour)	2.86 ± 1.41	3.77 ± 1.78	4.21 ± 3.17	3.00 ± 0.464
k10 (hour^-1)	2.95 ± 0.853	3.83 ± 0.566	1.50 ± 0.803	4.04 ± 0.451
k10_Half-life (hour)	0.235 ± 0.0677	0.181 ± 0.0266	0.461 ± 0.246	0.172 ± 0.0192
k12 (hour^-1)	1.50 ± 0.587	1.31 ± 0.274	1.20 ± 1.19	0.161 ± 0.0354
k21 (hour^-1)	0.377 ± 0.185	0.25 ± 0.11	0.312 ± 0.283	0.241 ± 0.0385
Cl1 (mL/h/kg)	13300 ± 2100	21700 ± 1950	13000 ± 4670	2450 ± 424
Cl2 (mL/h/kg)	6760 ± 2140	7420 ± 1740	10400 ± 7600	98.2 ± 36.9
V1 (mL/kg)	4510 ± 1660	5660 ± 1050	8670 ± 5030	608 ± 155
V2 (mL/kg)	18000 ± 10300	29700 ± 17400	33200 ± 26400	407 ± 147
Vss (mL/kg)	22500 ± 11100	35400 ± 17900	41900 ± 27900	1020 ± 292
AUCinf_pred (h*kg/L)	2550 ± 402	5070 ± 455	26100 ± 9350	13900 ± 2390
F(percent)	18.3	11.2	18.7	

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Female

	Treatment Group (mg/kg)	
	110 Gav[a] Plasma	**34 IV[b] Plasma**
Cmax_pred (ng/mL)	21300 ± 13500	59600 ± 19700
Alpha (hour^-1)	5.18 ± 2.14	5.51 ± 0.831
Alpha_Half-life (hour)	0.134 ± 0.552	0.126 ± 0.0189
Beta (hour^-1)	0.211 ± 0.306	0.358 ± 0.0486
Beta_Half-life (hour)	3.29 ± 4.78	1.93 ± 0.262
k10 (hour^-1)	4.00 ± 1.85	5.28 ± 0.814
k10_Half-life (hour)	0.173 ± 0.0804	0.131 ± 0.0202
k12 (hour^-1)	1.12 ± 0.869	0.213 ± 0.0607
k21 (hour^-1)	0.273 ± 0.379	0.374 ± 0.0531
Cl1 (mL/h/kg)	20600 ± 6130	3010 ± 649
Cl2 (mL/h/kg)	5780 ± 4600	121 ± 55.8
V1 (mL/kg)	5150 ± 3270	570 ± 189
V2 (mL/kg)	21200 ± 38400	325 ± 141
Vss (mL/kg)	26300 ± 39900	895 ± 318
AUCinf_pred (h*kg/L)	5340 ± 1590	11300 ± 2430
F(percent)	14.6	

Experiment Number: K94150B | **Toxicokinetics Data Summary** | **Request Date:** 6/5/2020

Route: Gavage ,IV | **Compound/Analyte:** Bisphenol/Total (conjugated + unconjugated) Bisphenol S | **Request Time:** 2:30:16

Species/Strain: Mice/B6C3F1/N | **CAS Number:** 80-09-1 | **Lab:** RTI

Male

	Treatment Group (mg/kg)			
	34 Gav[a] Plasma	**110 Gav[a] Plasma**	**340 Gav[c] Plasma**	**34 IV[b], Plasma**
Cmax_pred (ng/mL)	47000 ± 10500	140000 ± 23300	43700 ± 24900	144000 ± 25900
Alpha (hour^-1)	2.69 ± 0.766	3.84 ± 0.561		2.55 ± 0.274
Alpha_Half-life (hour)	0.258 ± 0.0733	0.180 ± 0.0263		0.272 ± 0.0293
Beta (hour^-1)	0.237 ± 0.078	0.228 ± 0.0572		0.235 ± 0.0156
Beta_Half-life (hour)	2.92 ± 0.958	3.04 ± 0.763		2.95 ± 0.196
k01 (hour^-1)			0.477 ± 1.28	
k01_Half-life (hour)			1.55 ± 4.44	
k10 (hour^-1)	1.36 ± 0.283	2.25 ± 0.325	0.227 ± 0.389	2.14 ± 0.233
k10_Half-life (hour)	0.509 ± 0.106	0.309 ± 0.0446	3.05 ± 5.23	0.324 ± 0.0352
k12 (hour^-1)	1.10 ± 0.465	1.44 ± 0.292		0.360 ± 0.0712
k21 (hour^-1)	0.469 ± 0.197	0.39 ± 0.101		0.279 ± 0.0239
Cl (mL/h/kg)			878 ± 619	
Cl1 (mL/h/kg)	986 ± 109	1770 ± 131		506 ± 53.3
Cl2 (mL/h/kg)	794 ± 226	1130 ± 162		85.3 ± 21.5
V1 (mL/kg)	724 ± 162	788 ± 132	3870 ± 7150	237 ± 42.6
V2 (mL/kg)	1690 ± 547	2900 ± 783		305 ± 65.6
Vss (mL/kg)	2420 ± 604	3690 ± 842		542 ± 100
AUCinf_pred (h*kg/L)	34500 ± 3790	62100 ± 4600	387000 ± 273000	67100 ± 7060
F(percent)	51.5	28.7	57.8	

Experiment Number: K94150B | **Toxicokinetics Data Summary** | **Request Date:** 6/5/2020

Route: Gavage ,IV | **Compound/Analyte:** Bisphenol/Total (conjugated + unconjugated) Bisphenol S | **Request Time:** 2:30:16

Species/Strain: Mice/B6C3F1/N | **CAS Number:** 80-09-1 | **Lab:** RTI

Female

	Treatment Group (mg/kg)	
	110 Gav[a] Plasma	**34 IV[b] Plasma**
Cmax_pred (ng/mL)	142000 ± 48000	183000±37500
Alpha (hour^-1)	3.74 ± 1.09	2.67 ± 0.279
Alpha_Half-life (hour)	0.185 ± 0.054	0.260 ± 0.0272
Beta (hour^-1)	0.218 ± 0.136	0.245 ± 0.0215
Beta_Half-life (hour)	3.18 ± 1.99	2.83 ± 0.249
k10 (hour^-1)	2.50 ± 0.704	2.47 ± 0.260
k10_Half-life (hour)	0.277 ± 0.0778	0.280 ± 0.0295
k12 (hour^-1)	1.13 ± 0.569	0.177 ± 0.0430
k21 (hour^-1)	0.325 ± 0.209	0.264 ± 0.0262
Cl1 (mL/h/kg)	1940 ± 325	459 ± 62.5
Cl2 (mL/h/kg)	874 ± 347	32.9 ± 10.6
V1 (mL/kg)	775 ± 262	186 ± 38.1
V2 (mL/kg)	2690 ± 1860	124 ± 35.5
Vss (mL/kg)	3460 ± 1970	310 ± 68.9
AUCinf_pred (h*kg/L)	56700 ± 9500	74100 ± 10100
F(percent)	23.6	

Experiment Number: K94150B | **Toxicokinetics Data Summary** | **Request Date:** 6/5/2020
Route: Gavage, IV | **Compound/Analyte:**Bisphenol S/Free & Total Bisphenol S | **Request Time:** 2:30:16
Species/Strain: Mice/B6C3F1/N | **CAS Number:** 127-07-1 | **Lab:** RTI

LEGEND

MODELING METHOD & BEST FIT MODEL

[a] Phoenix WinNonlin (Version 6.4) two-compartment model (Model 7 with iv-bolus input and first order elimination, weighting 1/y) using individual data

[b]Phoenix WinNonlin (Version 6.4) two-compartment model (Model 7 with iv-bolus input and first order elimination, weighting 1/y^2) using individual data

[c]Phoenix WinNonlin (Version 6.4) one-compartmental model (Model 3, with first-order input and output; weighting 1/y) using mean data

ANALYTE

Bisphenol S/Free (unconjugated) Bisphenol S
Total (conjugated + unconjugated) Bisphenol S

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Alpha = Hybrid rate constant of the alpha phase
Alpha Half-life = Half-life for the alpha phase
Beta = Hybrid rate constant of the beta phase
Beta Half-life = Half-life for the beta phase
k10 = Elimination rate constant from the central compartment also ke or kelim
k10_Half-life = Half-life for the elimination process from the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups
Cl2 = Clearance of the secondary compartment

TK Parameters (cont'd)

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies

V2 = Volume of distribution for the peripheral compartment

Vss = Volume of distribution at steady state

AUCinf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

PLASMA

TK Parameters_4

Gavage 34 mg/kg male, Gavage 110 mg/kg male, Gavage 340 mg/kg male, Gavage 110 mg/kg female

Eleven to 12-week old mice were given a single gavage dose of test article bisphenol S (BPS) in 0.5% methylcellulose and allowed food and water ad libitum. BPS was administered at three dose levels (34, 110, or 340 mg/kg) by gavage to male rats and mice, and by gavage at one dose level (110 mg/kg) to female rats and mice. Concentrations of free and total BPS in plasma up to 24 h post dosing were determined. Blood was collected predose and at 9 time points post-dose (N=3 per time point). Time points were pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. All mouse samplings were by cardiac puncture following CO2 euthanasia. The gavage dosing volume was 5 mL/kg body weight for rat and 10 mL/kg body weight for mouse. Limit of detection = 1.15 ng/mL (free), 0.862 ng/mL (total) bisphenol S. Lower limit of quantitation is 5.0 ng/mL. Compartmental analysis (1- and 2-compartment models) of the concentration versus time data to estimate toxicokinetic parameters was conducted using Phoenix WinNonlin (Version 6.4). For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUC0-∞. F = "AUCINF_D_obs(oral)" /"AUCINF_D_obs(IV)" x 100.63B. No absorption phase was observed for any free BPS and most total BPS in gavage data sets, so no Tmax was calculated by WinNonlin (for iv-bolus input models, T=0 is assumed Tmax).

TK PARAMETERS PROTOCOL (cont'd)

PLASMA

TK Parameters_5
Intravenous 34 mg/kg Male

Eleven to 12-week old mice were given a single intravenous dose of test article bisphenol S in 20:10:70 Kolliphor EL: 95% ethanol:deionized water vehicle and allowed food and water ad libitum. Blood was collected predose and at 9 time points post-dose (N=3 per time point). Time points were pre-dose, 0.083, 0.33, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. All mouse samplings were by cardiac puncture following CO2 euthanasia. The intravenous dose volume was 2 mL/kg body weight for rat and 4 mL/kg body weight for mouse. Limit of detection = 1.15 ng/mL (free), 0.862 ng/mL (total) bisphenol S. Lower limit of quantitation is 5.0 ng/mL. Compartmental analysis (1- and 2-compartment models) of the concentration versus time data to estimate toxicokinetic parameters was conducted using Phoenix WinNonlin (Version 6.4). For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUC0-∞.

TK Parameters_6

Intravenous 34 mg/kg female

Eleven to 12-week old mice were given a single intravenous dose of test article bisphenol S in 20:10:70 Kolliphor EL: 95% ethanol:deionized water vehicle and allowed food and water ad libitum. Blood was collected predose and at 9 time points post-dose (N=3 per time point). Time points were pre-dose, 0.083, 0.33, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. All mouse samplings were by cardiac puncture following CO2 euthanasia. The intravenous dose volume was 2 mL/kg body weight for rat and 4 mL/kg body weight for mouse. Due to an inadvertent failure to record the empty syringe weight for 12-F-05 (female mouse intravenously dosed at 5 minutes), a second mouse was dosed (named '12-F-05 redosed' in the record). Blood was collected from both mice and plasma was analyzed; however, since no accurate dose information was available for 12-F-05, plasma concentration data for that animal was excluded from toxicokinetic analysis. Limit of detection = 1.15 ng/mL (free), 0.862 ng/mL (total) bisphenol S. Lower limit of quantitation is 5.0 ng/mL. Compartmental analysis (1- and 2-compartment models) of the concentration versus time data to estimate toxicokinetic parameters was conducted using Phoenix WinNonlin (Version 6.4). For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUC0-∞.