

Experiment Number: K94150B

Route: Gavage, IV

Species/Strain: Rat/Harlan Sprague-Dawley

Toxicokinetics Data Summary

Compound/Analyte: Bisphenol S/Free (unconjugated) Bisphenol S

CAS Number: 80-09-1

Request Date: 6/4/2020

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)	313 ± 52.4	1140 ± 145	3240 ± 215	73000 ± 27700
Tmax_pred (hour)	0.350 ± 1.02	1.17 ± 0.544	1.97 ± 0.311	
Alpha (hour ⁻¹)				2.69 ± 0.51
Alpha_Half-life (hour)				0.258 ± 0.0488
Beta (hour ⁻¹)				0.149 ± 0.0136
Beta_Half-life (hour)				4.67 ± 0.426
k01 (hour ⁻¹)	13.6 ± 49.8	3.16 ± 2.03	1.80 ± 0.408	
k01_Half-life (hour)	0.0509 ± 0.186	0.219 ± 0.141	0.385 ± 0.0871	
k10 (hour ⁻¹)	0.120 ± 0.0292	0.086 ± 0.0185	0.0582 ± 0.00663	2.45 ± 0.49
k10_Half-life (hour)	5.77 ± 1.40	8.06 ± 1.73	11.9 ± 1.35	0.283 ± 0.564
k12 (hour ⁻¹)				0.225 ± 0.0643
k21 (hour ⁻¹)				0.163 ± 0.0171
Cl1 (mL/h/kg)				1140 ± 261
Cl2 (mL/h/kg)				105 ± 51.6
Cl1_F (mL/h/kg)	12500 ± 2390	7480 ± 1260	5450 ± 474	
V1 (mL/kg)				466 ± 177
V2 (mL/kg)				643 ± 295
Vss (mL/kg)				1110 ± 455
V1_F (mL/kg)	104000 ± 15200	87000 ± 13600	93600 ± 7720	
AUCinf_pred (h*kg/L)	2710 ± 517	14700 ± 2480	62400 ± 5420	29800 ± 6790
F(percent)	9.1	15.2	20.9	

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Female

Treatment Group (mg/kg)

110 Gav^a Plasma

34 IV^b Plasma

Cmax_pred (ng/mL)	804 ± 159	94900 ± 26000
Tmax_pred (hour)	5.88 ± 1.71	
Alpha (hour ⁻¹)		3.77 ± 0.489
Alpha_Half-life (hour)		0.184 ± 0.0238
Beta (hour ⁻¹)		0.929 ± 0.0137
Beta_Half-life (hour)		7.46 ± 1.10
k01 (hour ⁻¹)	0.171 ± 6.58	
k01_Half-life (hour)	4.04 ± 155	
k10 (hour ⁻¹)	0.169 ± 6.43	3.49 ± 0.458
k10_Half-life (hour)	4.11 ± 157	0.198 ± 0.026
k12 (hour ⁻¹)		0.273 ± 0.0753
k21 (hour ⁻¹)		0.100 ± 0.0156
Cl1 (mL/h/kg)		1250 ± 240
Cl2 (mL/h/kg)		97.9 ± 41.4
Cl1_F (mL/h/kg)	8550 ± 2030	
V1 (mL/kg)		358 ± 98.3
V2 (mL/kg)		976 ± 398
Vss (mL/kg)		1330 ± 482
V1_F (mL/kg)	50800 ± 1940000	
AUCinf_pred (h*kg/L)	12900 ± 3050	27200 ± 5200
F(percent)	14.7	

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Toxicokinetics Data Summary

Request Date: 6/4/2020

Route: Gavage, IV

Compound/Analyte: Bisphenol/Total (conjugated + unconjugated) Bisphenol S

Request Time: 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley

CAS Number: 80-09-1

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)	6420 ± 432	18500 ± 1550	32800 ± 1840	114000 ± 23200
Tmax_pred (hour)	0.991 ± 0.224	1.75 ± 0.365	2.77 ± 0.339	
Alpha (hour ⁻¹)				2.02 ± 0.353
Alpha_Half-life (hour)				0.344 ± 0.0601
Beta (hour ⁻¹)				0.109 ± 0.00784
Beta_Half-life (hour)				6.38 ± 0.46
k01 (hour ⁻¹)	4.02 ± 1.24	2.06 ± 0.613	1.29 ± 0.228	
k01_Half-life (hour)	0.172 ± 0.0531	0.336 ± 0.0996	0.537 ± 0.0947	
k10 (hour ⁻¹)	0.0812 ± 0.00941	0.0619 ± 0.00908	0.0403 ± 0.00425	0.884 ± 0.148
k10_Half-life (hour)	8.54 ± 0.989	11.2 ± 1.64	17.2 ± 1.81	0.784 ± 0.131
k12 (hour ⁻¹)				0.995 ± 0.23
k21 (hour ⁻¹)				0.248 ± 0.0379
Cl1 (mL/h/kg)				263 ± 19.1
Cl2 (mL/h/kg)				296 ± 63.1
Cl1_F (mL/h/kg)	397 ± 35.5	331 ± 36.8	373 ± 29.5	
V1 (mL/kg)				298 ± 60.4
V2 (mL/kg)				1190 ± 154
Vss (mL/kg)				1490 ± 189
V1_F (mL/kg)	4890 ± 394	5350 ± 555	9260 ± 642	
AUCinf_pred (h*kg/L)	85700 ± 7670	333000 ± 37000	911000 ± 71900	129000 ± 9360
F(percent)	66.5	79.9	70.7	

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Species/Strain: Rat/Harlan Sprague-Dawley

CAS Number: 80-09-1

Lab: RTI

Female

Treatment Group (mg/kg)

110 Gav^a Plasma

34 IV^b Plasma

Cmax_pred (ng/mL)	13000 ± 1400	155000 ± 41000
Tmax_pred (hour)	0.620 ± 0.494	
Alpha (hour ⁻¹)		2.79 ± 0.675
Alpha_Half-life (hour)		0.248 ± 0.06
Beta (hour ⁻¹)		0.0545 ± 0.0125
Beta_Half-life (hour)		12.7 ± 2.91
k01 (hour ⁻¹)	8.36 ± 8.32	
k01_Half-life (hour)	0.0829 ± 0.0825	
k10 (hour ⁻¹)	0.0485 ± 0.00976	1.34 ± 0.295
k10_Half-life (hour)	14.3 ± 2.88	0.517 ± 0.114
k12 (hour ⁻¹)		1.39 ± 0.453
k21 (hour ⁻¹)		0.114 ± 0.0335
Cl1 (mL/h/kg)		293 ± 33.5
Cl2 (mL/h/kg)		305 ± 99.9
Cl1_F (mL/h/kg)	398 ± 66.1	
V1 (mL/kg)		219 ± 57.9
V2 (mL/kg)		2690 ± 703
Vss (mL/kg)		2910 ± 739
V1_F (mL/kg)	8200 ± 981	
AUCinf_pred (h*kg/L)	277000 ± 459000	116000 ± 13200
F(percent)	73.8	

Experiment Number: K94150B

Route: Gavage, IV

Species/Strain: Rat/Harlan Sprague-Dawley

Toxicokinetics Data Summary

Compound/Analyte: Bisphenol S/Free & Total Bisphenol S

CAS Number: 127-07-1

Request Date: 6/4/2020

Request Time: 2:30:16

Lab: RTI

LEGEND

MODELING METHOD & BEST FIT MODEL

^a Phoenix Winnonlin (Version 6.4) one-compartmental model (Model 3, with first-order input and output; 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/y²) using individual data

ANALYTE

Bisphenol S/Free (unconjugated) Bisphenol S

Total (conjugated + unconjugated) Bisphenol S

TK PARAMETERS

C_{max} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max} = Time at which C_{max} predicted or observed occurs

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

k₀₁ = Absorption rate constant, k_a

k₀₁_Half-life = Half-life of the absorption process to the central compartment

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

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, Cl_{app} or apparent clearance for intravenous groups

Cl₂ = Clearance of the secondary compartment

Cl_{1_F} = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

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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
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
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_1

Gavage 340 mg/kg male

Nine to 10-week old male and female rats 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 72 h post dosing were determined. Blood was collected predose and at 12 time points post-dose (N=3 per time point). Time points were pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 32, 48, and 72 hours post-dose. A maximum of three blood samples were obtained from each rat separated by at least 2 hours for each rat. Terminal rat and 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 $\text{Dose}/V \cdot K_{10}$ and is similar to $\text{AUC}_{0-\infty}$. $F = \frac{\text{"AUCINF_D_obs(oral)"}}{\text{"AUCINF_D_obs(IV)"}} \times 100.63B$

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TK PARAMETERS PROTOCOL (cont'd)

PLASMA

TK Parameters_2

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

Nine to 10-week old male and female rats 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 48 h post dosing were determined. Blood was collected predose and at 11 time points post-dose (N=3 per time point). Time points were pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 32 and 48 hours post-dose. A maximum of three blood samples were obtained from each rat separated by at least 2 h for each rat. Terminal rat and 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 $\text{Dose}/V \cdot K_{10}$ and is similar to $\text{AUC}_{0-\infty}$. $F = \frac{\text{AUCINF_D_obs(oral)}}{\text{AUCINF_D_obs(IV)}} \times 100$.63B

TK Parameters_3

Intravenous 34 mg/kg male, 34 mg/kg female

Nine to 10-week old male and female rats 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, 8, 12, 24, and 32 hours post-dose. A maximum of three blood samples were obtained from each rat separated by at least 2 h for each rat. Terminal rat and 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 $\text{Dose}/V \cdot K_{10}$ and is similar to $\text{AUC}_{0-\infty}$.