Experiment Number: K94150C | **Toxicokinetics Data Summary** | **Request Date:** 6/9/2020

Route: Dosed Feed | **Compound/Analyte:** Bisphenol S/Free (unconjugated) Bisphenol S | **Request Time:** 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley | **CAS Number:** 80-09-1 | **Lab:** RTI

Male

	Treatment Group (ppm)		
	338 Feed[a] Plasma	**1125 Feed[a] Plasma**	**3375 Feed[a] Plasma**
Cmax_obs (ng/mL)	161	1150	3040
Tmax_obs (hour)	2.00	4.00	1.21
Lambda_z (hour^-1)	0.144	0.157	0.122
Half-life (hour)	4.82	4.41	5.69
Cl1_F (ppm/(h*ng/mL)	0.279	0.160	0.121
V1_F (ppm/(ng/mL))	1.94	1.02	0.994
AUC_0-T (h*ng/L)	1180	6900	26300
AUCinf_pred (h*ng/L)	1210	7030	27900

Experiment Number: K94150C | **Toxicokinetics Data Summary** | **Request Date:** 6/9/2020

Route: Dosed Feed | **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 (ppm)		
	338 Feed[a] Plasma	**1125 Feed[a] Plasma**	**3375 Feed[a] Plasma**
Cmax_obs (ng/mL)	5730	11800	24700
Tmax_obs (hour)	4.00	1.00	1.21
Lambda_z (hour^-1)	0.0981	0.0872	0.0499
Half-life (hour)	7.07	7.95	13.9
Cl1_F (ppm/(h*ng/mL)	0.00733	0.00876	0.00662
V1_F (ppm/(ng/mL))	0.0789	0.100	0.133
AUC_0-T (h*ng/L)	41100	115000	357000
AUCinf_pred (h*ng/L)	43700	128000	510000

LEGEND

MODELING METHOD & BEST FIT MODEL

[a] Phoenix WinNonlin (Version 6.4, Certara, Princeton, NJ) noncompartmental model (Model 200 for extravascular administration with uniform weighting) Mean concentration values for each time point and time range of 0-24 hours were used. T for AUCo-T was 24 hours. AUCINF was observed not predicted.

ANALYTE

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

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Lambda_z = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim
Half-life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUCinf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

PLASMA

TK Parameters_1

Feed 338 ppm male, Feed 1125 ppm male, Feed 3375 ppm male

Bisphenol S (BPS) was provided via dosed feed to 9 to 11-week old male rats and mice for 7 days beginning on Day 0. Dosed feed was removed (replaced with undosed feed) and blood samples were collected beginning at the time the lights came on in the room on Day 7 through 24 hours later. Concentrations of free (unconjugated) and total (conjugated + unconjugated) BPS in plasma up to 24 hours post dosing were determined. Concentrations were calculated as 23.0 ± 0.84, 76.8 ± 3.94, and 209 ± 17.3 mg/kg/day for free and total BPS for rats exposed to 338, 1125, and 3375 ppm BPS, respectively. Feed vehicle was 5K96 feed meal for rats and along with reverse osmosis water was given ad libitum. Two blood samples were obtained from each rat, with the interim sampling by tail venipuncture (ca. 250 µL). Terminal rat and (all) mouse sampling were by cardiac puncture following CO2 euthanasia. Plasma sample collection time points were 0, 1, 2, 4, 6, 9, 12, 16, 20, and 24 hours for all treatment groups (n=3 and some n=4 per time point/group). For the determination of free and total BPS in plasma, the lower limit of quantitation (LLOQ) was 5.0 ng/mL, and the limit of detection (LOD) was 1.15 ng/mL for free BPS and 0.862 ng/mL for total BPS for both rat and mouse. Food consumption data show that the rats in the 3375 ppm group consumed less of the dosed feed per kg body weight than those in the other dose groups. Mice in all exposure groups were observed removing feed from the food jars and leaving it uneaten in the cage so food jar weights cannot be correlated to actual dose received. Therefore, the exposure level was selected as the dose measure for toxicokinetic analyses. Mouse body weight gain was unaffected by exposure level. Animals were weighed daily from Day -2 to Day 6 and food consumption was measured each day. To mitigate risk of increased variability introduced by this lower consumption (group 3), blood samples were obtained from one of the extra rats at each sampling time point designated for 3-M-06, 3-M-08, and 3-M-11. Therefore, there were 4 plasma samples collected at each of 1, 2, 4, 12, 16, and 20 h for Group 3. Similarly, due to variability in food consumption and spillage noted for all mouse exposure groups, blood samples were obtained from extra mice at 16 hours (1125 and 3375 ppm groups only), 20 and 24 hours (all dose groups), resulting in 4 plasma samples for each of these time points. Noncompartmental analysis of the concentration versus time data to estimate toxicokinetic parameters was conducted using Phoenix WinNonlin (Version 6.4, Certara, Princeton, NJ) using mean values.