

Experiment Number: K94150C
Route: Dosed Feed
Species/Strain: Mice/B6C3F1/N

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

Request Date: 6/9/2020
Request Time: 2:30:16
Lab: RTI

Male

Treatment Group (ppm)

	338 Feed^a Plasma	1125 Feed^a Plasma	3375 Feed^a Plasma
Cmax_obs (ng/mL)	155	496	1270
Tmax_obs (hour)	0.117	0.172	0.222
Lambda_z (hour ⁻¹)	0.113	0.0664	0.102
Half-life (hour)	6.11	10.4	6.82
Cl1_F (ppm/(h*ng/mL))	0.657	0.393	0.607
V1_F (ppm/(ng/mL))	5.80	5.91	5.97
AUC_0-T (h*ng/L)	472	2220	4980
AUCinf_pred (h*ng/L)	514	2860	5560

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

Request Date: 6/9/2020
Request Time: 2:30:16
Lab: RTI

Male

Treatment Group (ppm)

	338 Feed^a Plasma	1125 Feed^a Plasma	3375 Feed^a Plasma
Cmax_obs (ng/mL)	2280	7460	23200
Tmax_obs (hour)	0.117	0.172	0.222
Lambda_z (hour ⁻¹)	0.107	0.0879	0.113
Half-life (hour)	6.51	7.89	6.11
Cl1_F (ppm/(h*ng/mL))	0.0337	0.0232	0.0304
V1_F (ppm/(ng/mL))	0.316	0.264	0.268
AUC_0-T (h*ng/L)	8840	40500	101000
AUCinf_pred (h*ng/L)	10000	48400	111000

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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 AUC_{0-T} was 24 hours. AUC_{INF} was observed not predicted.

ANALYTE

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

TK PARAMETERS

C_{max_obs} = Observed or Predicted Maximum plasma (or tissue) concentration
T_{max_obs} = Time at which C_{max} 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
Cl_{1_F} = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
V_{1_F} = Apparent volume of distribution for the central compartment includes V_{d_F}, V_F for oral groups, and V_{c_F}
AUC_{0-T} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}
AUC_{inf} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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TK PARAMETERS PROTOCOL

PLASMA

TK Parameters_2

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. Dose concentrations were calculated as 131.4 ± 28.6 , 428.2 ± 68.6 , and 1176 ± 444 mg/kg/day for free and total BPS for exposure to 338, 1125, or 3375 ppm, respectively. Feed vehicle was NTP-2000 feed for mice and along with reverse osmosis water was given ad libitum. All mouse sampling was 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.