Experiment Number: K08002D | **Toxicokinetics Data Summary** | **Request Date:** 7/28/2020

Route: Dosed Feed | **Compound/Analyte:** Bisphenol AF/Free Bisphenol AF | **Request Time:** 2:30:16

Species/Strain: Rat/Harlan Sprague Dawley | **CAS Number:** 1478-61-1 | **Lab:** MRI

Male

	Treatment Group (ppm)		
	338 Feed[a] Plasma	**1125 Feed[a] Plasma**	**3750 Feed[a] Plasma**
Cmax_obs (ng/mL)	10.8	41.7	64.3
Tmax_obs (hour)	7.00	0.00	2.00
Lambda_z ($hour^{-1}$)	0.096	0.0660	0.0785
Half-life (hour)	7.10	10.5	8.83
Cl1_F (ppm/(h*ng/mL)	2.86	2.30	5.11
V1_F (ppm/(ng/mL))	29.3	34.8	65.0
AUC_0-T (h*ng/L)	107	355	681
AUCinf_pred (h*ng/L)	118	490	735

Experiment Number: K08002D | **Toxicokinetics Data Summary** | **Request Date:** 7/28/2020

Route: Dosed Feed | **Compound/Analyte:** Bisphenol AF/Total Bisphenol AF | **Request Time:** 2:30:16

Species/Strain: Rat/Harlan Sprague Dawley | **CAS Number:** 1478-61-1 | **Lab:** MRI

Male

	Treatment Group (ppm)		
	338 Feed[a] Plasma	**1125 Feed[a] Plasma**	**3750 Feed[a] Plasma**
Cmax_obs (ng/mL)	1400	5450	8810
Tmax_obs (hour)	4.00	0.00	1.00
Lambda_z ($hour^{-1}$)	0.0932	0.0552	0.0520
Half-life (hour)	7.44	12.6	13.3
Cl1_F (ppm/(h*ng/mL)	0.0225	0.0131	0.0296
V1_F (ppm/(ng/mL))	0.242	0.238	0.569
AUC_0-T (h*ng/L)	13800	58900	87100
AUCinf_pred (h*ng/L)	15000	85700	127000

LEGEND

MODELING METHOD & BEST FIT MODEL

[a] Phoenix WinNonlin (Version 6.4, Certara, Princeton, NJ) noncompartmental methods with uniform weighting (Model 200 for extravascular administration); nominal dose concentrations (ppm) and mean value per timepoint used for modeling. T for AUC0-T is 24 hours (AUCobs 0-24 hours); AUCinf_pred is actually AUCINFobs.

ANALYTE

Free Bisphenol AF
Total Bisphenol AF

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

TK PARAMETERS PROTOCOL

PLASMA

TK Parameters

Feed 338 ppm male, Feed 1125 ppm male, Feed 3750 ppm male

Male 9 week old Harlan Sprague Dawley rats and 8-9 week old B6C3F1/N mice were given bisphenol AF (BPAF) in dosed feed for 7 consecutive days. Bodyweight ranges were 231.3-276.4 g (male rats), 21.0-27.2 g (male mice)). Animals received irradiated and certified Verified 5K96 Casein Diet 10 IF (rats) or NTP-2000 (mice) and tap water ad libitum. Beginning on the morning of Day 8 (when the lights came on in the room), dosed feed was removed and replaced with un-dosed feed and blood was collected at 0, 1, 2, 4, 7, 10, 13, 16, 19, and 24 hours. After blood centrifugation, plasma samples were prepared using protein precipitation with acetonitrile and analyzed for BPAF content with a validated analytical method using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Rat plasma samples were analyzed for both free (unconjugated) and total (conjugated + unconjugated) BPAF concentration. BPAF was deconjugated using a glucuronidase/sulfatase enzyme in the analysis for total BPAF. Approximate LOD and LL0Q = 2.8 ng/mL for rats and mice. Rats were sampled twice; first via retro-orbital sinus and second at termination by exsanguination by cardiac puncture under anesthesia. Mice were sampled once by cardiac puncture. Food consumption and body weight were monitored and recorded daily. In both rats and mice there was evidence of decreasing food consumption at higher doses. Mice spilled more food than consumed, particularly at the high dose, making food consumption data unreliable. The mean daily consumption was calculated as 23.4, 70.5, and 193 mg/kg/day average for 338, 1125, and 3750 ppm respectively, for the rat and calculated as 69.4, 236, and 1590 mg/kg/day for the 338, 1125, and 3750 ppm dose groups, respectively, for the mice. Because of the uncertainty in food consumption, the nominal dose concentration (in ppm) was used as the dose parameter in the toxicokinetic evaluation. The selected time range was 0-24 hours for the fit. Mean concentrations for all time-points was used and when concentrations were not detectable or less than the limit of detection (LOD) those data points were not included in the analysis.