Experiment Number: K08002C
Route: Gavage, Intravenous
Species/Strain: Mice/B6C3F1/N

Toxicokinetics Data Summary
Compound/Analyte: Bisphenol AF/Free Bisphenol AF
CAS Number: 1478-61-1

Request Date: 7/28/2020
Request Time: 2:30:16
Lab: TI

Male

	Treatment Group (mg/kg)	
	34 Gav[a] Plasma	**34 IV[b] Plasma**
Cmax_pred (ng/mL)	64.1 ± 18.9	7490 ± 1750
Tmax_pred (hour)	0.455 ± 0.214	
Alpha (1/hour)	0.414 ± 5.43	1.23 ± 0.262
Alpha_Half-life (hour)	1.67 ± 21.9	0.566 ± 0.121
Beta (1/hour)	0.147 ± 0.18	0.184 ± 0.0155
Beta_Half_life (hour)	4.73 ± 5.8	3.76 ± 0.316
k01 (1/hour)	8.59 ± 7.96	
k01_Half-life (hour)	0.0807 ± 0.0747	
k10 (1/hour)	0.164 ± 0.0912	0.939 ± 0.193
k10_Half-life (hour)	4.22 ± 2.34	0.698 ± 0.135
k12 (1/hour)	0.0271 ± 0.476	0.189 ± 0.0802
k21 (1/hour)	0.369 ± 5.1	0.227 ± 0.0304
Cl1 (L/h/kg)		4.51 ± 0.547
Cl2 (L/h/kg)		0.860 ± 0.324
Cl1_F (L/h/kg)	80 ± 22.5	
Cl2_F (L/h/kg)	13.2 ± 226	
V1 (L/kg)		4.54 ± 1.06
V2 (L/kg)		3.78 ± 1.10
Vss (L/kg)		8.32 ± 1.64
V1_F (L/kg)	487 ±238	
V2_F (L/kg)	35.8 ± 285	
AUCinf_pred (h*ng/mL)	425 ± 119	7540 ± 912
F (percent)	5.64	

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Female

	Treatment Group (mg/kg)	
	34 Gav[a] Plasma	**34 IV[b] Plasma**
Cmax_pred (ng/mL)	105 ± 20.3	92300 ± 32300
Tmax_pred (hour)	0.342 ± 0.0703	
Alpha (1/hour)	3.32 ± 1070	6.56 ± 1.2
Alpha_Half-life (hour)	0.209 ± 67.2	0.106 ± 0.0193
Beta (1/hour)	0.0768 ± 0.0589	0.229 ± 0.0165
Beta_Half_life (hour)	9.02 ± 4.74	3.03 ± 0.218
k01 (1/hour)	3.33 ± 1070	
k01_Half-life (hour)	0.208 ± 66.9	
k10 (1/hour)	0.523 ± 168	5.84 ± 1.11
k10_Half-life (hour)	1.33 ± 426	0.119 ± 0.0225
k12 (1/hour)	2.38 ± 899	0.696 ± 0.19
k21 (1/hour)	0.487 ± 0.497	0.257 ± 0.0225
Cl1 (L/h/kg)		2.15 ± 0.426
Cl2 (L/h/kg)		0.256 ± 0.108
Cl1_F (L/h/kg)	68.7 ± 22.5	
Cl2_F (L/h/kg)	313 ± 17400	
V1 (L/kg)		0.368 ± 0.129
V2 (L/kg)		0.995 ± 0.388
Vss (L/kg)		1.36 ± 0.499
V1_F (L/kg)	131 ± 42200	
V2_F (L/kg)	642 ± 35300	
AUCinf_pred (h*ng/mL)	495 ± 162	15800 ± 3130
F (percent)	3.13	

Experiment Number: K08002C
Route: Gavage, Intravenous
Species/Strain: Mice/B6C3F1/N

Toxicokinetics Data Summary
Compound/Analyte: Bisphenol AF/Total Bisphenol AF
CAS Number: 1478-61-1

Request Date: 7/28/2020
Request Time: 2:30:16
Lab: TI

Male

	Treatment Group (mg/kg)	
	34 Gav[c] Plasma	**34 IV[d] Plasma**
Cmax_pred (ng/mL)	1930 ± 449	11700 ± 2540
Tmax_pred (hour)	0.298 ± 0.071	
Alpha (1/hour)	3.7 ± 845	0.71 ± 0.224
Alpha_Half-life (hour)	0.187 ± 42.7	0.976 ± 0.308
Beta (1/hour)	0.121 ± 0.09	0.159 ± 0.0216
Beta_Half_life (hour)	5.73 ± 3.16	4.37 ± 0.594
k01 (1/hour)	3.72 ± 849	
k01_Half-life (hour)	0.186 ± 42.4	
k10 (1/hour)	0.92 ± 210	0.53 ± 0.109
k10_Half-life (hour)	0.753 ± 171	1.31 ± 0.269
k12 (1/hour)	2.42 ± 635	0.126 ± 0.0997
k21 (1/hour)	0.487 ± 0.542	0.213 ± 0.0622
Cl1 (L/h/kg)		1.54 ± 0. 223
Cl2 (L/h/kg)		0.367 ± 0.267
Cl1_F (L/h/kg)	6.41 ± 1.94	
Cl2_F (L/h/kg)	16.8 ± 586	
V1 (L/kg)		2.91 ± 0.634
V2 (L/kg)		1.73 ± 0.841
Vss (L/kg)		4.64 ± 0.994
V1_F (L/kg)	6.97 ± 1590	
V2_F (L/kg)	34.6 ± 1170	
AUCinf_pred (h*ng/mL)	5300 ± 1600	22100 ± 3190
F (percent)	24.0	

Experiment Number: K08002C | **Toxicokinetics Data Summary** | **Request Date:** 7/28/2020

Route: Gavage, Intravenous | **Compound/Analyte:** Bisphenol AF/Total Bisphenol AF | **Request Time:** 2:30:16

Species/Strain: Mice/B6C3F1/N | **CAS Number:** 1478-61-1 | **Lab:** TI

Female

	Treatment Group (mg/kg)	
	34 Gav[c] Plasma	**34 IV[d] Plasma**
Cmax_pred (ng/mL)	3970 ± 1060	140000 ± 29800
Tmax_pred (hour)	0.275 ± 0.101	
Alpha (1/hour)	4.02 ± 331	2.68 ± 0.38
Alpha_Half-life (hour)	0.172 ± 14.2	0.259 ± 0.0366
Beta (1/hour)	0.115 ± 0.0674	0.201 ± 0.0122
Beta_Half_life (hour)	6.03 ± 3.27	3.45 ± 0.209
k01 (1/hour)	4.09 ± 336	
k01_Half-life (hour)	0.170 ± 13.9	
k10 (1/hour)	0.862 ± 70.6	2.05 ± 0.289
k10_Half-life (hour)	0.804 ± 65.8	0.339 ± 0.0478
k12 (1/hour)	2.74 ± 260	0.572 ± 0.148
k21 (1/hour)	0.536 ± 0.557	0.263 ± 0.0277
Cl1 (L/h/kg)		0.496 ± 0.058
Cl2 (L/h/kg)		0.139 ± 0.0422
Cl1_F (L/h/kg)	2.95 ± 1.08	
Cl2_F (L/h/kg)	9.38 ± 122	
V1 (L/kg)		0.242 ± 0.0157
V2 (L/kg)		0.528 ± 0.125
Vss (L/kg)		0.770 ± 0.163
V1_F (L/kg)	3.43 ± 281	
V2_F (L/kg)	17.5 ± 216	
AUCinf_pred (h*ng/mL)	11500 ± 4210	68500 ± 8000
F (percent)	16.8	

LEGEND

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin Version 6.4 (Certara, Princeton, NJ). Nominal doses (mg/kg) for each group were used. For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUCo to infinity (AUCinf_pred). Free bisphenol AF represents unconjugated bishphenol AF. Two-compartment with first-order input, first-order output, no lag time, micro-constants as primary parameters and 1/y weighting (Model 11)

[b]WinNonlin Version 6.4 (Certara, Princeton, NJ). Nominal doses (mg/kg) for each group were used. For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUCo to infinity (AUCinf_pred). Free bisphenol AF represents unconjugated bishphenol AF. Two-compartment with bolus intravenous dose, first order output and $1/y^2$ weighting (Model 7).

[c]WinNonlin Version 6.4 (Certara, Princeton, NJ). Nominal doses (mg/kg) for each group were used. For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUCo to infinity (AUCinf_pred). Total bisphenol AF represents both conjugated and unconjugated bisphenol AF. Two-compartment with first-order input, first-order output, no lag time, micro-constants as primary parameters and 1/y weighting (Model 11)

[d]WinNonlin Version 6.4 (Certara, Princeton, NJ). Nominal doses (mg/kg) for each group were used. For compartmental models AUC is calculated as Dose/V*K10 and is similar to AUCo to infinity (AUCinf_pred). Total bisphenol AF represents both conjugated and unconjugated bisphenol AF. Two-compartment with bolus intravenous dose, first order output and $1/y^2$ weighting (Model 7).

LEGEND (cont'd)

ANALYTE

Free Bisphenol AF
Total Bisphenol AF

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax 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, ka
k01 Half-life = Half-life of the absorption process to the central compartment
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
Cl = Clearance, includes total clearance
Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups
Cl2 = Clearance of the secondary compartment
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
Cl2_F = Apparent clearance of the secondary compartment
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

TK PARAMETERS (cont'd)

V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
V2_F = Apparent volume of distribution for the peripheral compartment
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

PLASMA

TK Parameters (Analyte Free Bisphenol AF)

Gavage 34 mg/kg Male, Gavage 34 mg/kg Female

Thirty-six animals per group were given a single oral gavage administration of bisphenol AF in corn oil. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Blood samples were taken at 0, 5, 15, 30, 60 minutes and 2, 4, 8, 12, 24, 32, and 48 hours for both rat and mouse. Zero-hour collections were made pre-dose. Each mouse was sampled once. n=3 per time point. Free is unconjugated (parent) bisphenol AF. For free and total analysis, plasma samples were prepared using acetonitrile protein precipitation and analyzed using a validated liquid chromatography with mass spectrometric detection (LC/MS/MS) method. A glucuronidase/sulfate enzyme was used to deconjugate BPAF in the analysis for total BPAF. The method was linear over the range of approximately 2.8 to approximately 105 ng/mL in plasma. Limit of detection was 0.82 ng/mL.

34 mg/kg Intravenous Male, Intravenous 34 mg/kg Female

Thirty-six animals per group were given a single intravenous administration of bisphenol AF in deionized water/Cremophor EL/95 percent ethanol (67/23/10) (v/v/v). Doses were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Blood samples were taken at 0, 5, 15, 30, 60 minutes and 2, 4, 8, 12, 24, 32, and 48 hours for both rat and mouse. Zero-hour collections were made pre-dose. Each mouse was sampled once. n=3 per time point. Free is unconjugated (parent) bisphenol AF. For free and total analysis, plasma samples were prepared using acetonitrile protein precipitation and analyzed using a validated liquid chromatography with mass spectrometric detection (LC/MS/MS) method. A glucuronidase/sulfate enzyme was used to deconjugate BPAF in the analysis for total BPAF. The method was linear over the range of approximately 2.8 to approximately 105 ng/mL in plasma. Limit of detection was 0.82 ng/mL.

TK PARAMETERS PROTOCOL

PLASMA

TK Parameters (Analyte Total Bisphenol AF)

Gavage 34 mg/kg Male, Gavage 34 mg/kg Female

Thirty-six animals per group were given a single oral gavage administration of bisphenol AF in corn oil. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Blood samples were taken at 0, 5, 15, 30, 60 minutes and 2, 4, 8, 12, 24, 32, and 48 hours for both rat and mouse. Zero-hour collections were made pre-dose. Each mouse was sampled once. n=3 per time point. Total is conjugated plus unconjugated (free) bisphenol AF. For free and total analysis, plasma samples were prepared using acetonitrile protein precipitation and analyzed using a validated liquid chromatography with mass spectrometric detection (LC/MS/MS) method. A glucuronidase/sulfate enzyme was used to deconjugate BPAF in the analysis for total BPAF. The method was linear over the range of approximately 2.8 to approximately 105 ng/mL in plasma. Limit of detection was 0.82 ng/mL.

34 mg/kg Intravenous Male, Intravenous 34 mg/kg Female

Thirty-six animals per group were given a single intravenous administration of bisphenol AF in deionized water/Cremophor EL/95 percent ethanol (67/23/10) (v/v/v). Doses were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Blood samples were taken at 0, 5, 15, 30, 60 minutes and 2, 4, 8, 12, 24, 32, and 48 hours for both rat and mouse. Zero-hour collections were made pre-dose. Each mouse was sampled once. n=3 per time point. Total is conjugated plus unconjugated (free) bisphenol AF. For free and total analysis, plasma samples were prepared using acetonitrile protein precipitation and analyzed using a validated liquid chromatography with mass spectrometric detection (LC/MS/MS) method. A glucuronidase/sulfate enzyme was used to deconjugate BPAF in the analysis for total BPAF. The method was linear over the range of approximately 2.8 to approximately 105 ng/mL in plasma. Limit of detection was 0.82 ng/mL.