Experiment Number: S0592
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: Benzophenone/ **Analyte:** Benzophenone
CAS Number: 119-61-9

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: TI

Male

	Treatment Group (mg/kg)				
	15 IV Plasma[a,d]	**15 Gavage Plasma[a,e]**	**15 Gavage Plasma[b,f]**	**30 Gavage Plasma[a,g]**	**60 Gavage Plasma[a,h]**
Alpha (min^{-1})			0.0563 ± 0.0084		
Beta ($minute^{-1}$)	0.0259	0.0159	0.00903 ± 0.0084	0.00610	0.00430
Beta Half-life (minute)	26.7	43.6		113	160
k01 (min^{-1})			0.0980 ± 0.036		
k10 ($minute^{-1}$)			0.0442 ± 0.0052		
k12 ($minute^{-1}$)			0.00961 ± 0.0031		
k21 ($minute^{-1}$)			0.0115 ± 0.011		
Cl (mL/min/kg)	110				
Cl1_F (mL/min/kg)		418		317	231
V1 (L/kg)	4.26		2.65 ± 0.19		
V1_F (L/kg)		26.3		51.8	53.6
MRT (minute)	30.9	99.3		96.1	96.2
AUCinf_pred (ug*min/mL)	140	28.7		74.2	205
F		0.263		0.347	0.475

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Female

	Treatment Group (mg/kg)				
	15 IV Plasma[a,i]	**15 Gavage Plasma[a,j]**	**15 Gavage Plasma[b,k]**	**30 Gavage Plasma[a,l]**	**60 Gavage Plasma[a,m]**
Alpha (min^{-1})			0.0611 ± 0.010		
Beta ($minute^{-1}$)	0.0128	0.00790	0.00821 ± 0.0061	0.00940	0.00640
Beta Half-life (minute)	54.0	87.5		73.9	108
k01 (min^{-1})			0.0747 ± 0.018		
k10 ($minute^{-1}$)			0.0422 ± 0.0062		
k12 ($minute^{-1}$)			0.0153 ± 0.0045		
k21 ($minute^{-1}$)			0.0119 ± 0.0089		
Cl (mL/min/kg)	115				
Cl1_F (mL/min/kg)		246		315	229
V1 (L/kg)	8.96		2.96 ± 0.25		
V1_F (L/kg)		31.0		33.5	35.9
MRT (minute)	42.0	91.4		89.4	112
AUCinf_pred (ug*min/mL)	137	49.2		75.9	211
F		0.468		0.365	0.501

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Male

Treatment Group (ppm)	
312 Dosed Feed Plasma[c]	**1250 Dosed Feed Plasma[c]**

Parameters Not Available

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Lab: TI

Female

Treatment Group (ppm)	
312 Dosed Feed Plasma[c]	**1250 Dosed Feed Plasma[c]**

Parameters Not Available

LEGEND

MODELING SOFTWARE

WinNonlin, Version 1.0

MODELING METHOD & BEST FIT MODEL

[a]Models 200 and 201 of the pharmacokinetic software WinNonlin, Version 1 .0 (Scientific Consulting Inc., 1995), noncompartmental model

[b]Compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (WinNonlin, Version 1 .0, Scientific Consulting Inc., 1995), Best fit is two compartmental which simultaneously solves iv and oral data sets. Analyzed using compartmental modeling techniques with established models or models written to simultaneously solve iv (Study AD) and oral data sets (Study AF) using 1/Y weighting where Y is the observed plasma BPH concentration at a given time.

[c]Compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (WinNonlin, Version 1 .0, Scientific Consulting Inc., 1995). Simulations of plasma BPH concentrations in the multiple exposure dosed feed studies showed that the model did not accurately reflect the observed data. For male and female mice, simulated plasma BPH concentration vs. time profiles were similar in shape to the observed data, yet the model greatly overpredicted peak plasma BPH concentrations for both sexes.

EXCEPTIONS

[d]V1 is Vbeta. Beta is the terminal elimination rate (Beta range is 4 - 180 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[e]V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 45 - 240 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[f]Simultaneously analyzing iv Study AC and low po Study AE plasma concentration vs time profiles

[g]V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 60 - 600 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[h]V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 180-960 minutes)

[i]V1 is Vbeta. Beta is the terminal elimination rate (Beta range is 45 - 180 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[j]V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 45 - 360 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

EXCEPTIONS (cont'd)

[k]Simultaneously analyzing iv Study AD and low po Study AF plasma concentration vs time profiles
[l]V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 30 - 360 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.
[m]15 minute sample replicate 2 declared outlier and excluded from pharmacokinetic analysis. V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 30 - 960 minutes)

ANALYTE

Benzophenone

TK PARAMETERS

Alpha = Hybrid rate constant of 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
k10 = Elimination rate constant from the central compartment also ke or kelim
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl = Clearance, includes total clearance
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
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
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Plasma samples were analyzed by High Performance Liquid Chromatography (HPLC) with UV detection (254 nm) using an internal standard of 0.503 mg of butyrophenone/mL acetonitrile.

TK_INTRAVENOUS PLASMA

15 mg/kg Male and Female

Animals were administered a single dose of benzophenone (BPH) by oral gavage or by iv injection. Blood samples were collected at up to 13 post-dosing timepoints in triplicate for each route/dose level. For multiple dose feed studies, rats and mice received dosed feed ad libitum for 7-8 days. Plasma samples were collected by cardiac puncture at 2 hour intervals for 22 hours from 10 a.m. on day 7 through 8 a.m. on day 8. One animal/species/sex/dose per timepoint (12 timepoints).

TK_GAVAGE PLASMA

15 mg/kg, 30 mg/kg, 60 mg/kg Male and Female

Animals were administered a single dose of benzophenone (BPH) by oral gavage or by iv injection. Blood samples were collected at up to 13 post-dosing timepoints in triplicate for each route/dose level. For multiple dose feed studies, rats and mice received dosed feed ad libitum for 7-8 days. Plasma samples were collected by cardiac puncture at 2 hour intervals for 22 hours from 10 a.m. on day 7 through 8 a.m. on day 8. One animal/species/sex/dose per timepoint (12 timepoints).

TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

312 ppm, 1250 ppm Male and Female

Animals were administered a single dose of benzophenone (BPH) by oral gavage or by iv injection. Blood samples were collected at up to 13 post-dosing timepoints in triplicate for each route/dose level. For multiple dose feed studies, rats and mice received dosed feed ad libitum for 7-8 days. Plasma samples were collected by cardiac puncture at 2-hour intervals for 22 hours from 10 a.m. on day 7 through 8 a.m. on day 8. One animal/species/sex/dose per timepoint (12 timepoints).