Experiment Number: S0592
Route: IV, Gavage
Species/Strain: Rats/F344

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)				
	2.5 IV Plasma[a,d]	**2.5 Gavage Plasma[a,e]**	**2.5 Gavage Plasma[b,f]**	**5 Gavage Plasma[a,g]**	**10 Gavage Plasma[a,h]**
Alpha (min^{-1})			0.0675 ± 0.0074		
Beta ($minute^{-1}$)	0.00260	0.00280	0.00258 ± 0.00044	0.00120	0.00140
Beta Half-life (minute)	268	245		594	506
k01 (min^{-1})			0.0171 ± 0.0022		
k10 ($minute^{-1}$)			0.0198 ± 0.0021		
k12 ($minute^{-1}$)			0.0415 ± 0.0056		
k21 ($minute^{-1}$)			0.0881 ± 0.0014		
Cl (mL/min/kg)	47.4				
Cl1_F (mL/min/kg)		57.5		40.2	37.4
V1 (L/kg)	18.3		2.48 ± 0.16		
V1_F (L/kg)		20.3		34.4	27.3
MRT (minute)	264	349		809	737
AUCinf_pred (ug*min/mL)	51.9	32.7		95.6	208
F		0.824		1.18	1.27

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Female

	Treatment Group (mg/kg)				
	2.5 IV Plasma[a,i]	**2.5 Gavage Plasma[a,j]**	**2.5 Gavage Plasma[b,k]**	**5 Gavage Plasma[a,l]**	**10 Gavage Plasma[a,m]**
Alpha (min^{-1})			0.196 ± 0.030		
Beta ($minute^{-1}$)	0.00280	0.00120	0.00350 ± 0.0012	0.00180	0.00140
Beta Half-life (minute)	247	567		395	499
k01 (min^{-1})			0.00385 ± 0.0013		
k10 ($minute^{-1}$)			0.0505 ± 0.010		
k12 ($minute^{-1}$)			0.135 ± 0.026		
k21 ($minute^{-1}$)			0.0136 ± 0.0041		
Cl (mL/min/kg)	48.6				
Cl1_F (mL/min/kg)		34.9		44.0	46.2
V1 (L/kg)	17.3		1.11 ± 0.21		
V1_F (L/kg)		28.5		25.1	33.3
MRT (minute)	254	816		553	662
AUCinf_pred (ug*min/mL)	51.6	53.8		86.8	166
F		1.39		1.10	1.05

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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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CAS Number: 119-61-9

Request Date: 7/11/2023
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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. Although the simulated concentrations were generally higher than the observed BPH concentrations for female rats, the overall shape of the plasma BPH concentration vs . time curve reflected the data.

EXCEPTIONS

[d] 7 minute sample replicate 1 declared outlier and excluded from pharmacokinetic analysis. V1 is Vbeta. Beta is the terminal elimination rate (Beta range is 120-960 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[e] 10 minute sample replicate 3 declared outlier and excluded from pharmacokinetic analysis. V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 60-960 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[f] Simultaneously analyzing iv Study U and low po Study W plasma concentration vs time profiles

[g] V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 180-1440 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT and AUCinf.

[h] V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 60-1440 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT and AUCinf.

EXCEPTIONS (cont'd)

[i] V1 is Vbeta. Beta is the terminal elimination rate (Beta range is 90-960 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 30 - 960 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT and AUCinf.

[k] Simultaneously analyzing iv Study V and low po Study X plasma concentration vs time profiles

[l] V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 60-1440 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT.

[m] V1_F is VbetaF. F is absolute availability. Beta is the terminal elimination rate (Beta range is 360-1440 minutes). (Estimate(0-T) / Estimate(inf) is less than 0.90 for MRT and AUCinf.

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).