Experiment Number: S0593
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 2-Hydroxy-4-methoxybenzophenone
Analyte: 2-Hydroxy-4-methoxybenzophenone
CAS Number: 131-57-7

Request Date: 7/12/2023
Request Time: 2:40:16
Lab: RTI

Male

	Treatment Group (mg/kg)				
	50 IV Plasma[a,l]	**50 IV Plasma[b,m]**	**100 Gavage Plasma[a,e]**	**100 Gavage Plasma[b,f]**	**100 Gavage Plasma[c,g]**
Cmax_obs (mg/L)	31.7	4.47	0.0799	0.372	
Tmax_obs (minute)	5	5	15	30	
Alpha (minute^{-1})					0.161 ± 0.018
Beta (minute^{-1})	0.0042		0.0028		0.00874 ± 0.0026
Beta Half-life (minute)	166		248		
k01 (minute^{-1})					0.0809 ± 0.038
k10 (minute^{-1})					0.112 ± 0.013
K12 (minute^{-1})					0.0454 ± 0.0095
K21 (minute^{-1})					0.0126 ± 0.0038
Cl (L/min/kg)	0.0736				
Cl1_F (L/min/kg)			6.13		
V1 (L/kg)	17.6				0.720 ± 0.096
V1_F (L/kg)			2189		
MRT (minute)	38.2		352		
AUC_0-T (mg*min/L)		200		60.8	
AUCinf_pred (mg*min/L)	647		15.3		
F			0.0120		

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	Treatment Group (mg/kg)			
	250 Gavage Plasma[a,h]	**250 Gavage Plasma[b,i]**	**500 Gavage Plasma[a,j]**	**500 Gavage Plasma[b,k]**
Cmax_obs (mg/L)	0.346	1.43	0.614	3.24
Tmax_obs (minute)	15	30	60	30
Beta (minute^{-1})	0.0045		0.0044	
Beta Half-life (minute)	154		158	
Cl1_F (L/min/kg)	8.96		6.72	
V1 (L/kg)				
V1_F (L/kg)	1996		1532	
MRT (minute)	183		182	
AUC_0-T (mg*min/L)		151		349
AUCinf_pred (mg*min/L)	30.1		76.5	
F	0.00822		0.0110	

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Male

Treatment Group (ppm)	
1000 Dosed Feed Plasma[d]	10000 Dosed Feed Plasma[d]

Parameters Not Available

Experiment Number: S0593
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Toxicokinetics Data Summary
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Analyte: 2-Hydroxy-4-methoxybenzophenone
CAS Number: 131-57-7

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Lab: RTI

Female

	Treatment Group (mg/kg)				
	50 IV Plasma[a,u]	**50 IV Plasma[b,v]**	**100 Gavage Plasma[a,n]**	**100 Gavage Plasma[b,o]**	**100 Gavage Plasma[c,p]**
Cmax_obs (mg/L)	19.0	3.07	0.112	0.443	
Tmax_obs (minute)	5	5	15	15	
Alpha (minute^{-1})					0.135 ± 0.016
Beta (minute^{-1})	0.0042		0.0051		0.00740 ± 0.0017
Beta Half-life (minute)	164		137		
k01 (minute^{-1})					0.0315 ± 0.016
k10 (minute^{-1})					0.0756 ± 0.0089
k12 (minute^{-1})					0.0533 ± 0.0093
k21 (minute^{-1})					0.0132 ± 0.0030
Cl (L/min/kg)	0.108				
Cl1_F (L/min/kg)			7.59		
V1 (L/kg)	25.4				1.38 ± 0.17
V1_F (L/kg)			1502		
MRT (minute)	59.8		296		
AUC_0-T (mg*min/L)		84.3		24.1	
AUCinf_pred (mg*min/L)	434		12.4		
F			0.0142		

Experiment Number: S0593
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Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
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Analyte: 2-Hydroxy-4-methoxybenzophenone
CAS Number: 131-57-7

Request Date: 7/12/2023
Request Time: 2:40:16
Lab: RTI

Female

	Treatment Group (mg/kg)			
	250 Gavage Plasma[a,q]	**250 Gavage Plasma[b,r]**	**500 Gavage Plasma[a,s]**	**500 Gavage Plasma[b,t]**
Cmax_obs (mg/L)	0.757	2.04	5.30	3.82
Tmax_obs (minute)	30	10	120	15
Beta (minute^{-1})	0.0088		0.0055	
Beta Half-life (minute)	78.5		126	
Cl (L/min/kg)				
Cl1_F (L/min/kg)	4.97		0.774	
V1 (L/kg)				
V1_F (L/kg)	563		140	
MRT (minute)	123		142	
AUC_0-T (mg*min/L)		91.7		275
AUCinf_pred (mg*min/L)	54.7		650	
F	0.0216		0.139	

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Toxicokinetics Data Summary
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Analyte: 2-Hydroxy-4-methoxybenzophenone
CAS Number: 131-57-7

Request Date: 7/12/2023
Request Time: 2:40:16
Lab: RTI

Female

Treatment Group (ppm)	
1000 Dosed Feed Plasma[d]	**10000 Dosed Feed Plasma[d]**

Parameters Not Available

LEGEND

MODELING SOFTWARE

WINONLIN, Models 200 and 201, Version 1.0

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin (Models 200 and 201), Version 1.0 (Scientific Consulting Inc., 1995), Noncompartmental modeling

[b] WinNonlin Version 1.0 (Scientific Consulting Inc. 1995), Noncompartmental modeling

[c] 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/YHAT weighting where YHAT is the predicted plasma HMBP concentration at a given time.

[d] Winnonlin Version 1.0 (Scientific Consulting Inc., 1995), Feed study plasma concentrations after 7-8 days of dosing were simulated using the simultaneously fitting (2-compartmental model) the iv and low oral data sets parameter. The predicted concentrations were much higher than the observed concentrations although the overall shape of the plasma HMBP concentration versus time curve was similar for observed and simulated data.

EXCEPTIONS

MALE

[e] Actual administered dose is 93.71 mg/kg, Beta range is 60-360, F is absolute bioavailability, V1 is V Beta.

[f] Actual administered dose is 93.71 mg/kg.

[g] Actual administered dose is 47.60 mg/kg iv dose Study AC and 93.71 mg/kg po dose Study AE.

[h] Actual administered dose is 269.61 mg/kg, Beta range is 60-420, F is absolute bioavailability, V1 is V Beta.

[i] Actual administered dose is 269.61 mg/kg.

[j] Actual administered dose is 513.83 mg/kg, Beta range is 600-960, F is absolute bioavailability, V1 is V Beta.

[k] Actual administered dose is 513.83 mg/kg.

EXCEPTIONS (cont'd)

MALE (cont'd)

[l]Actual administered dose is 47.60 mg/kg, Beta range is 90-960, F is absolute bioavailability, V1 is V Beta.

[m]Actual administered dose is 47.60 mg/kg.

FEMALE

[n]Actual administered dose is 94.42 mg/kg, Beta range is 5-360, F is absolute bioavailability, V1 is V Beta.

[o]Actual administered dose is 94.42 mg/kg.

[p]Actual administered dose is 46.64 mg/kg iv dose Study AD and 94.42 mg/kg po dose Study AF.

[q]Actual administered dose is 272.10 mg/kg, Beta range is 120-420, F is absolute bioavailability, V1 is V Beta. Replicate 3 at 2.5 minutes was declared an outlier and excluded from the toxicokinetic analysis.

[r]Actual administered dose is 272.10 mg/kg

[s]Actual administered dose is 503.34 mg/kg, Beta range is 15-960, F is absolute bioavailability, V1 is V Beta.

[t]Actual administered dose is 503.34 mg/kg.

[u]Actual administered dose is 46.64 mg/kg, Beta range is 60-960, F is absolute bioavailability, V1 is V Beta.

[v]Actual administered dose is 46.64 mg/kg.

ANALYTE

2-Hydroxy-4-methoxybenzophenone

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
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 = Half-life of the absorption process to 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_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
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
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

The supernatant of processed plasma was analyzed by High Performance Liquid Chromatography (HPLC) with UV detection (320 nm).

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA

50 mg/kg Male and Female

Animals received a single bolus administration of 2-Hydroxy-4-methoxybenzophenone by intravenous injection or oral gavage. Triplicate blood samples/timepoint for each route/dose level were collected for up to 13 post-dosing timepoints

TK_GAVAGE PLASMA

100 mg/kg,250 mg/kg, 500 mg/kg Male and Female

Animals received a single bolus administration of 2-Hydroxy-4-methoxybenzophenone by intravenous injection or oral gavage. Triplicate blood samples/timepoint for each route/dose level were collected for up to 13 post-dosing timepoints

TK_DOSED FEED PLASMA

ANALYSIS METHOD

The supernatant of processed plasma was analyzed by High Performance Liquid Chromatography (HPLC) with UV detection (320 nm). The two compartmental simultaneously solved for iv and oral data sets model parameters were used to simulate plasma concentrations.

1000 mg/kg, 10000 mg/kg Male and Female

All animals received dosed NTP-2000 powdered feed for 7 days. Dosing was continued ad libitum for 7-8 days. For feed studies, each animal was killed at a specific time of day starting at approximately 10 AM on day 7 of exposure and continuing approximately every 2 hours until about 24 hours had elapsed (11-12 timepoints).