Experiment Number: S0593
Route: Gavage, IV
Species/Strain: Rats/F344

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)				
	8 IV Plasma[a,l]	**8 IV Plasma[b,m]**	**100 Gavage Plasma[a,e]**	**100 Gavage Plasma[b,f]**	**100 Gavage Plasma[c,g]**
Cmax_obs (mg/L)	8.57	0.0840	0.220	0.149	
Tmax_obs (minute)	5	5	30	60	
Alpha (minute^{-1})					0.166 ± 0.019
Beta (minute^{-1})	0.0022		0.0067		0.0055 ± 0.0017
Beta Half-life (minute)	313		103		
k01 (minute^{-1})					0.0152 ± 0.0048
k10 (minute^{-1})					0.106 ± 0.015
K12 (minute^{-1})					0.0569 ± 0.012
K21 (minute^{-1})					0.008603 ± 0.0025
Cl (L/min/kg)	0.0381				
Cl1_F (L/min/kg)			4.56		
V1 (L/kg)	17.2				0.429 ± 0.062
V1_F (L/kg)			680		
MRT (minute)	77.1		150		
AUC_0-T (mg*min/L)		6.86		29.4	
AUCinf_pred (mg*min/L)	202		23.6		
F			0.00835		

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Male

	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)	0.367	0.454	2.43	1.41
Tmax_obs (minute)	90	30	60	60
Beta (minute^{-1})	0.0034		0.0037	
Beta Half-life (minute)	206		186	
Cl1_F (L/min/kg)	3.63		1.22	
V1 (L/kg)				
V1_F (L/kg)	1077		327	
MRT (minute)	223		303	
AUC_0-T (mg*min/L)		73.9		246
AUCinf_pred (mg*min/L)	60.8		374	
F	0.0105		0.0313	

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Male

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

Parameters Not Available

Experiment Number: S0593
Route: Gavage, IV
Species/Strain: Rats/F344

Toxicokinetics Data Summary
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CAS Number: 131-57-7

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

Female

	Treatment Group (mg/kg)				
	8 IV Plasma[a,u]	**8 IV Plasma[b,v]**	**100 Gavage Plasma[a,n]**	**100 Gavage Plasma[b,o]**	**100 Gavage Plasma[c,p]**
Cmax_obs (mg/L)	3.70	0.121	0.209	0.203	
Tmax_obs (minute)	5	10	60	60	
Alpha (minute^{-1})					0.0887 ± 0.011
Beta (minute^{-1})	0.0038		0.0060		0.00464 ± 0.0015
Beta Half-life (minute)	180		116		
k01 (minute^{-1})					0.0126 ± 0.0035
k10 (minute^{-1})					0.0579 ± 0.0074
k12 (minute^{-1})					0.0283 ± 0.0071
k21 (minute^{-1})					0.00711 ± 0.0023
Cl (L/min/kg)	0.0776				
Cl1_F (L/min/kg)			6.14		
V1 (L/kg)	20.2				1.39 ± 0.15
V1_F (L/kg)	1020				
MRT (minute)	95.6		175		
AUC_0-T (mg*min/L)	12.4			41.8	
AUCinf_pred (mg*min/L)	100		17.4		
F			0.0127		

Experiment Number: S0593
Route: Gavage, IV
Species/Strain: Rats/F344

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)	0.391	0.570	2.69	1.08
Tmax_obs (minute)	90	30	60	60
Beta (minute^{-1})	0.0062		0.0050	
Beta Half-life (minute)	112		139	
Cl1_F (L/min/kg)	4.08		1.58	
V1_F (L/kg)	660		316	
MRT (minute)	159		172	
AUC_0-T (mg*min/L)		105		278
AUCinf_pred (mg*min/L)	53.5		286	
F	0.0190		0.0491	

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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

WinNonlin (Models 200 and 201), Version 1.0
WinNonlin 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 107.88 mg/kg, Beta range is 15-480, F is absolute bioavailability, V1 is V Beta.

[f] Actual administered dose is 107.88 mg/kg.

[g] Actual administered dose is 7.68 mg/kg iv dose Study U and 107.88 mg/kg po dose Study W.

[h] Actual Actual administered dose is 220.82 mg/kg, Beta range is 180-600, F is absolute bioavailability, V1 is V Beta.

[i] Actual administered dose is 220.82 mg/kg.

[j] Actual administered dose is 455.62 mg/kg, Beta range is 60-960, F is absolute bioavailability, V1 is V Beta. Replicate 1 at 10 minutes was declared an outlier and excluded from the toxicokinetic analysis.

[k] Actual administered dose is 455.62 mg/kg

EXCEPTIONS (cont'd)

MALE (cont'd)

[l]Actual administered dose is 7.68 mg/kg, Beta range is 240-960, F is absolute bioavailability, V1 is V Beta.
[m]Actual administered dose is 7.68 mg/kg.

FEMALE

[n]Actual administered dose is 106.79 mg/kg, Beta range is 10-480, F is absolute bioavailability, V1 is V Beta.
[o]Actual administered dose is 106.79 mg/kg.
[p]Actual administered dose is 7.80 mg/kg iv dose Study V and 106.79 mg/kg po dose Study X.
[q]Actual administered dose is 218.46 mg/kg, Beta range is 15-600, F is absolute bioavailability, V1 is V Beta.
[r]Actual administered dose is 218.46 mg/kg.
[s]Actual administered dose is 451.93 mg/kg, Beta range is 60-960, F is absolute bioavailability, V1 is V Beta.
[t]Actual administered dose is 451.93 mg/kg
[u]Actual administered dose is 7.80 mg/kg, Beta range is 60-960, F is absolute bioavailability, V1 is V Beta.
[v]Actual administered dose is 7.80 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

8 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

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).