Experiment Number: K10482B
Route: IV, Gavage, Dosed Feed
Species/Strain: Rats/Harlan Sprague Dawley

Toxicokinetics Data Summary
Compound: N-Butylbenzenesulfonamide
CAS Number: 3622-84-2

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

Male

	Treatment Group (mg/kg)		
	20 IV Plasma[a]	**20 Gavage Plasma[b]**	**60 Gavage Plasma[b]**
C_0min_pred (ng/mL)	10300 ± 1200		
Cmax_obs (ng/g)	14200	613	1810
Cmax_pred (ng/mL)		316 ± 46	1200 ± 290
Tmax_obs (hour)		0.167	0.333
Tmax_pred (hour)		0.355 ± 0.105	0.378 ± 0.266
Alpha Half-life (hour)	0.191 ± 0.021		
Beta Half-life (hour)	0.713 ± 0.109		
k01 ($hour^{-1}$)		8.57 ± 3.74	9.95 ± 9.55
k01 Half-life (hour)		0.0809 ± 0.0353	0.0696 ± 0.0668
k10 ($hour^{-1}$)	3.13 ± 0.26	0.487 ± 0.057	0.254 ± 0.055
k10 Half-life (hour)	0.221 ± 0.018	1.42 ± 0.17	2.72 ± 0.58
k12 ($hour^{-1}$)	0.341 ± 0.125		
k21 ($hour^{-1}$)	1.12 ± 0.22		
Cl1 (mL/hr/kg)	6060 ± 390		
Cl2 (mL/hr/kg)	659 ± 220		
Cl1_F (mL/hr/kg)		26000 ± 3600	11500 ± 2400
V1 (mL/kg)	1940 ± 220		
V2 (mL/kg)	586 ± 112		
V1_F (mL/kg)		53300 ± 9900	45400 ± 12900
MRT (hour)	0.416 ± 0.022		
AUC_0-T (mL*hr)	3610	570	3010
AUCinf_pred (ng/mL*hr)	3300 ± 210	771 ± 107	5190 ± 1100
F (percent)		23	29

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Male

	Treatment Group (mg/kg)	
	60 Gavage Plasma[c]	**200 Gavage Plasma[b]**
C_0min_pred (ng/mL)		
Cmax_obs (ng/g)	1810	4510
Cmax_pred (ng/mL)	1360 ± 170	3440 ± 500
Tmax_obs (hour)	0.333	0.0833
Tmax_pred (hour)	0.189 ± 0.119	0.228 ± 0.183
Alpha Half-life (hour)		
Beta Half-life (hour)		
k01 ($hour^{-1}$)	19.9 ± 16.8	19.2 ± 19.8
k01 Half-life (hour)	0.0349 ± 0.0295	0.0361 ± 0.0373
k10 ($hour^{-1}$)	0.518 ± 0.045	0.257 ± 0.020
k10 Half-life (hour)	1.34 ± 0.12	2.70 ± 0.21
k12 ($hour^{-1}$)		
k21 ($hour^{-1}$)		
Cl1 (mL/hr/kg)		
Cl2 (mL/hr/kg)		
Cl1_F (mL/hr/kg)	20700 ± 2200	14100 ± 1800
V1 (mL/kg)		
V2 (mL/kg)		
V1_F (mL/kg)	40000 ± 5700	54900 ± 8800
MRT (hour)		
AUC_0-T (mL*hr)	2760	12700
AUCinf_pred (ng/mL*hr)	2900 ± 310	14200 ± 1800
F (percent)	29	

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Male

	Treatment Group (ppm)			
	500 Dosed Feed Plasma[d]	**500 Dosed Feed Plasma[e]**	**1000 Dosed Feed Plasma[d]**	**2000 Dosed Feed Plasma[d]**
Cmax_obs (ng/mL)	17.5	17.5	24.3	47.9
Tmax_obs (hour)	0	0	0	0
Half-life (hour)	8.63	1.61	3.48	2.81
AUC_0-T (ng/mL*hr)	46.9	36.2	50.8	86.8
AUCinf_pred (ng/mL*hr)	59.8	38.2	58.6	87.8

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Female

	Treatment Group (mg/kg)			
	20 IV Plasma[a]	**20 Gavage Plasma[b]**	**60 Gavage Plasma[b]**	**200 Gavage Plasma[b]**
C_0min_pred (ng/mL)	9920 ± 850			
Cmax_obs (ng/g)	10200	2250	4040	9430
Cmax_pred (ng/mL)		1540 ± 250	3890 ± 450	15200 ± 1900
Tmax_obs (hour)		0.167	0.167	0.0833
Tmax_pred (hour)		0.539 ± 0.134	0.392 ± 0.116	0.237 ± 0.175
Alpha Half-life (hour)	0.359 ± 0.057			
Beta Half-life (hour)	1.46 ± 0.85			
k01 ($hour^{-1}$)		4.39 ± 1.81	8.42 ± 3.54	19.7 ± 18.4
k01 Half-life (hour)		0.158 ± 0.065	0.0824 ± 0.0346	0.0353 ± 0.0330
k10 ($hour^{-1}$)	1.61 ± 0.14	0.557 ± 0.071	0.358 ± 0.030	0.195 ± 0.016
k10 Half-life (hour)	0.431 ± 0.038	1.24 ± 0.16	1.93 ± 0.16	3.55 ± 0.28
k12 ($hour^{-1}$)	0.229 ± 0.086			
k21 ($hour^{-1}$)	0.571 ± 0.373			
Cl1 (mL/hr/kg)	3240 ± 170			
Cl2 (mL/hr/kg)	461 ± 151			
Cl1_F (mL/hr/kg)		5370 ± 880	4810 ± 500	2460 ± 270
V1 (mL/kg)	2020 ± 170			
V2 (mL/kg)	808 ± 367			
V1_F (mL/kg)		9640 ± 2250	13400 ± 1900	12600 ± 1800
MRT (hour)	0.871 ± 0.151			
AUC_0-T (mL*hr)	6080	2800	12200	69700
AUCinf_pred (ng/mL*hr)	6170 ± 310	3730 ± 610	12500 ± 1300	81400 ± 9100
F (percent)		60	68	

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Male

	Treatment Group (mg/kg)			
	20 IV Brain[f]	**20 Gavage Brain[g]**	**60 Gavage Brain[g]**	**200 Gavage Brain[g]**
Cmax_obs (ng/g)	61200	1680	4560	13400
Tmax_obs (hour)	0.0679	0.204	0.202	0.116
Half-life (hour)	0.434	0.960	1.42	2.64
AUC_0-T (ng/g*hr)	17400	1300	7080	33600
AUCinf_pred (ng/g*hr)	17500	1370	7220	35100

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Female

	Treatment Group (mg/kg)			
	20 IV Brain[h]	**20 Gavage Brain[g]**	**60 Gavage Brain[g]**	**200 Gavage Brain[g]**
Cmax_obs (ng/g)	42600	4780	11700	25800
Tmax_obs (hour)	0.0674	0.198	0.196	0.113
Half-life (hour)	0.714	1.55	2.47	6.11
AUC_0-T (ng/g*hr)	19000	7410	31000	139000
AUCinf_pred (ng/g*hr)	19200	7580	32000	187000

LEGEND

MODELING SOFTWARE

Phoenix WinNonlin, Version 6.3, 6.4 and 8.0

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA (Parameter estimates are reported to three significant figures. Observed values do not have a reported SEM.), two-compartment with bolus input, first order elimination and 1/Yhat2 weighting (Model #8)

[b]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA (Parameter estimates are reported to three significant figures. Observed values do not have a reported SEM.), one-compartment model with first order input, first order elimination, and 1/Yhat2 weighting (Model #13)

[c]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA (Parameter estimates are reported to three significant figures. Observed values do not have a reported SEM.), one-compartment model with first order input, first order elimination, and 1/Yhat2 weighting (Model #13) with 12 hour data excluded (unexpected increase in plasma concentration at 12 hours).

[d]Phoenix WinNonlin, Version 8.0, Certara L.P., Princeton, NJ library models, non-compartmental analysis, no weighting factor.

[e]Phoenix WinNonlin, Version 8.0, Certara L.P., Princeton, NJ library models, non-compartmental analysis, no weighting factor. Analyzed without 18-hour time point.

[f]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA. (Parameter estimates are reported to three significant figures. NCA does not calculate a standard error.) Noncompartmental analysis (NCA) model with bolus input, first order output and uniform weighting.

[g]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA. (Parameter estimates are reported to three significant figures. NCA does not calculate a standard error.) NCA model with first order input, first order output, and uniform weighting.

[h]WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA. (Parameter estimates are reported to three significant figures. NCA does not calculate a standard error.) NCA with bolus input, first order output and uniform weighting.

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)
Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax = Time at which Cmax predicted or observed occurs
Half-Life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
Alpha Half-Life = Half-life for the alpha 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 third to central compartment
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
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
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

Blood and brain tissue samples were measured using gas chromatography with mass selective detection (GC/MSD). The target limit of quantitation (LOQ) for N-Butylbenzenesulfonamide (NBBS) (IV and gavage) in plasma was 2.5 ng/mL, for NBBS in brain was 25 ng/g tissue. Samples below the LOQ were designated as below the limit of quantitation (BLOQ).

TK_INTRAVENOUS PLASMA

20 mg/kg Male and Female

Rats were given a single intravenous dose in Cremophor:ethanol:deionized water (1:1:8) vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2-, 5-, 10-, 15-, 20-, 30-, 45-, 60-, 120-, 180-, and 240-min post-dose.

TK_GAVAGE PLASMA

20 mg/kg Male and Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2, 5, 10, 15, 20, 30, 45, 60, 120, 240, and 480 min post-dose.

60 mg/kg, 200 mg/kg Male and Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Pre-dose, 5, 10, 20, 30, 45, 60, 120, 240, 480, 720, and 1440 min post-dose.

TK_PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Whole blood was centrifuged to obtain plasma samples. Plasma samples were processed by liquid-liquid extraction with or without a ten-fold concentration step and analyzed by gas chromatography (GC) with mass selective detection (MSD). The original analytical method had a lower limit of quantitation (LLOQ) of 5 ng/mL with limit of detection (LOD) of 1.57 ng/mL but those samples that were without the ten-fold concentration step and were below the LOD or nondetected were reanalyzed using the ten-fold concentration step and different GC conditions. LLOQ for this second method was 0.5 ng/mL and the LOD was 0.149 ng/mL Samples below the LOD were designated as below the limit of detection (BLOD). For rats, the 500 ppm group had an increase in concentration at the last measurable time point of 18 hour which affected the characterization of the terminal phase. Therefore, the 500 ppm group was also evaluated without the 18 hour time point. Parameter estimates are reported to three significant figures.

TK_DOSED_FEED PLASMA

500 ppm, 1000 ppm, 2000 ppm

Twenty-two Harlan Sprague Dawley rats (10 weeks old and weighing 309 + or - 9 g at randomization) were provided dosed feed for seven consecutive days at concentrations of 500, 1000, or 2000 ppm. Rats were fed irradiated NTP-2000 meal feed ad libitum and tap water was given ad libitum. The average daily food consumption for rats ranged 22.4 to 24.2 g with standard deviations ranging from 2.8 to 10.5. Whole blood samples were collected at 0 (at removal of food), 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours post-dose (last day of dosing, N=3 rats/group/timepoint). The 0-hour sample was scheduled to be collected following dosed feed removal, but prior to offering untreated feed. Rats were typically bled twice with whole blood samples collected under anesthesia, first via the retro-orbital plexus and second via cardiac puncture., N=3 rats/group/timepoint.

ANALYSIS METHOD

Blood and brain tissue samples were measured using gas chromatography with mass selective detection (GC/MSD). The target limit of quantitation (LOQ) for N-Butylbenzenesulfonamide (NBBS) (IV and gavage) in plasma was 2.5 ng/mL, for NBBS in brain was 25 ng/g tissue. Samples below the LOQ were designated as below the limit of quantitation (BLOQ).

TK_PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS BRAIN

20 mg/kg Male and Female

Rats were given a single intravenous dose in Cremophor:ethanol:deionized water (1:1:8) vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2-, 5-, 10-, 15-, 20-, 30-, 45-, 60-, 120-, 180-, and 240-min post-dose.

TK_GAVAGE BRAIN

20 mg/kg Male and Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2-, 5-, 10-, 15-, 20-, 30-, 45-, 60-, 120-, 240-, and 480-min post-dose.

60 mg/kg, 200 mg/kg Male and Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Pre-dose, 5, 10, 20, 30, 45, 60, 120, 240, 480, 720, and 1440 min post-dose.