

Experiment Number: K10482B
Route: IV, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1/N

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

	20 IV Plasma ^a	20 Gavage Plasma ^b	60 Gavage Plasma ^b
C ₀ min _{pred} (ng/mL)	62500 ± 14600		
C _{max} _obs (ng/mL)	33700	1360	7830
C _{max} _pred (ng/mL)		756 ± 119	5530 ± 1250
T _{max} _obs (hour)		0.0833	0.0833
T _{max} _pred (hour)		0.131 ± 0.030	0.103 ± 0.057
Alpha Half-life (hour)	0.0645 ± 0.0093	0.119 ± 0.118	0.156 ± 0.071
Beta Half-life (hour)	0.435 ± 0.025	0.895 ± 0.247	0.789 ± 0.185
k ₀₁ (hour ⁻¹)		11.0 ± 11.4	19.4 ± 20.6
k ₀₁ Half-life (hour)		0.0631 ± 0.0655	0.0358 ± 0.0381
k ₁₀ (hour ⁻¹)	8.71 ± 1.21	3.46 ± 2.75	3.16 ± 1.05
k ₁₀ Half-life (hour)	0.0796 ± 0.0111	0.201 ± 0.160	0.220 ± 0.073
k ₁₂ (hour ⁻¹)	1.65 ± 0.46	1.82 ± 2.68	0.922 ± 0.814
k ₂₁ (hour ⁻¹)	1.97 ± 0.18	1.30 ± 0.64	1.23 ± 0.49
Cl ₁ (mL/hr/kg)	2790 ± 340		
Cl ₂ (mL/hr/kg)	529 ± 157		
Cl ₁ _F (mL/hr/kg)		46800 ± 4900	22700 ± 2700
Cl ₂ _F (mL/hr/kg)		24700 ± 18400	6620 ± 4250
V ₁ (mL/kg)	320 ± 75		
V ₂ (mL/kg)	269 ± 65		
V ₁ _F (mL/kg)		13600 ± 11100	7180 ± 2670
V ₂ _F (mL/kg)		19000 ± 7400	5360 ± 1900
MRT (hour)	0.211 ± 0.022		
AUC _{0-T} (mL*hr)	6440	426	2400
AUC _{inf} _pred (ng/mL*hr)	7180 ± 880	427 ± 45	2650 ± 310
F (percent)			6

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Treatment Group (mg/kg)

200 Gavage Plasma^b

200 Gavage Plasma^c

C ₀ min _{pred} (ng/mL)		
C _{max} _obs (ng/g)	17800	17800
C _{max} _pred (ng/mL)	15500 ± 2400	15500 ± 2300
T _{max} _obs (hour)	0.167	0.167
T _{max} _pred (hour)	0.136 ± 0.051	0.134 ± 0.050
Alpha Half-life (hour)	0.262 ± 0.055	0.268 ± 0.054
Beta Half-life (hour)	1.97 ± 0.31	2.10 ± 0.50
k ₀₁ (hour ⁻¹)	16.1 ± 10.5	16.6 ± 10.7
k ₀₁ Half-life (hour)	0.0431 ± 0.0281	0.0417 ± 0.0268
k ₁₀ (hour ⁻¹)	2.18 ± 0.40	2.14 ± 0.38
k ₁₀ Half-life (hour)	0.317 ± 0.058	0.323 ± 0.057
k ₁₂ (hour ⁻¹)	0.384 ± 0.161	0.373 ± 0.153
k ₂₁ (hour ⁻¹)	0.426 ± 0.084	0.398 ± 0.110
Cl ₁ (mL/hr/kg)		
Cl ₂ (mL/hr/kg)		
Cl ₁ _F (mL/hr/kg)	19900 ± 1900	19800 ± 1800
Cl ₂ _F (mL/hr/kg)	3500 ± 1170	3450 ± 1130
V ₁ (mL/kg)		
V ₂ (mL/kg)		
V ₁ _F (mL/kg)	9120 ± 2020	9250 ± 1950
V ₂ _F (mL/kg)	8200 ± 1940	8660 ± 2150
MRT (hour)		
AUC _{0-T} (mL*hr)	10500	10500
AUC _{inf} _pred (ng/mL*hr)	10000 ± 900	10100 ± 900
F (percent)	14	14

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Treatment Group (ppm)

500 Dosed Feed Plasma^d

500 Dosed Feed Plasma^e

1000 Dosed Feed Plasma^d

Cmax_obs (ng/mL)	26.7	26.7	44.6
Tmax_obs (hour)	0	0	0.5
Half-life (hour)	2.36	1.06	4.04
AUC_0-T (ng/mL*hr)	28.6	25.4	70.7
AUCinf_pred (ng/mL*hr)	30.9	25.8	72.2

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Male

Treatment Group (ppm)

1000 Dosed Feed Plasma^f 1000 Dosed Feed Plasma^d 1000 Dosed Feed Plasma^f

Cmax_obs (ng/mL)	44.6	186	186
Tmax_obs (hour)	0.5	0	0
Half-life (hour)	2.09	4.17	2.28
AUC_0-T (ng/mL*hr)	67.4	117	109
AUCinf_pred (ng/mL*hr)	68.1	121	111

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Treatment Group (mg/kg)

20 IV Plasma^g

20 IV Plasma^h

20 Gavage Plasma^b

20 Gavage Plasmaⁱ

C ₀ min _{pred} (ng/mL)	60800 ± 17000	60500 ± 59200		
C _{max} _obs (ng/mL)	10700	29900	779	779
C _{max} _pred (ng/mL)			1040 ± 190	871 ± 175
T _{max} _obs (hour)			0.0333	0.0333
T _{max} _pred (hour)			0.107 ± 0.027	0.0710 ± 0.0232
Alpha Half-life (hour)	0.110 ± 0.018	0.0270 ± 0.0159	0.121 ± 0.045	0.0588 ± 0.0836
Beta Half-life (hour)	0.648 ± 0.189	0.298 ± 0.020	4.13 ± 7.60	0.490 ± 0.116
k ₀₁ (hour ⁻¹)			14.5 ± 9.3	19.0 ± 31.9
k ₀₁ Half-life (hour)			0.0477 ± 0.0303	0.0364 ± 0.0610
k ₁₀ (hour ⁻¹)	5.94 ± 0.88	13.1 ± 9.3	3.48 ± 2.51	6.68 ± 8.60
k ₁₀ Half-life (hour)	0.117 ± 0.017	0.0529 ± 0.0377	0.199 ± 0.144	0.104 ± 0.134
k ₁₂ (hour ⁻¹)	0.306 ± 0.183	10.4 ± 7.0	2.14 ± 1.49	4.02 ± 7.76
k ₂₁ (hour ⁻¹)	1.14 ± 0.36	4.57 ± 1.23	0.276 ± 0.386	2.50 ± 1.01
Cl ₁ (mL/hr/kg)	1960 ± 340	4330 ± 1280		
Cl ₂ (mL/hr/kg)	101 ± 58	3430 ± 2230		
Cl ₁ _F (mL/hr/kg)			36900 ± 18900	74000 ± 8300
Cl ₂ _F (mL/hr/kg)			22800 ± 17700	44600 ± 32000
V ₁ (mL/kg)	329 ± 92	331 ± 323		
V ₂ (mL/kg)	88.5 ± 37.4	750 ± 311		
V ₁ _F (mL/kg)			10600 ± 4100	11100 ± 14500
V ₂ _F (mL/kg)			82400 ± 174000	17900 ± 8100
MRT (hour)	0.214 ± 0.026	0.249 ± 0.067		
AUC _{0-T} (mL*hr)	3320	3320	259	259
AUC _{inf} _pred (ng/mL*hr)	10200 ± 1800	4620 ± 1370	541 ± 277	270 ± 30
F (percent)				

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Treatment Group (mg/kg)

60 Gavage Plasma^b

200 Gavage Plasma^b

200 Gavage Plasmaⁱ

	60 Gavage Plasma ^b	200 Gavage Plasma ^b	200 Gavage Plasma ⁱ
C _{0min} _pred (ng/mL)			
C _{max} _obs (ng/mL)	2950	16100	16100
C _{max} _pred (ng/mL)	2960 ± 430	13700 ± 2300	14900 ± 2500
T _{max} _obs (hour)	0.0833	0.0833	0.0833
T _{max} _pred (hour)	0.107 ± 0.038	0.133 ± 0.075	0.191 ± 0.065
Alpha Half-life (hour)	0.177 ± 0.042	0.354 ± 0.119	0.310 ± 0.173
Beta Half-life (hour)	0.737 ± 0.135	1.00 ± 0.23	3.12 ± 18.1
k ₀₁ (hour ⁻¹)	19.1 ± 12.5	20.0 ± 18.1	10.3 ± 8.0
k ₀₁ Half-life (hour)	0.0362 ± 0.0236	0.0347 ± 0.0314	0.0674 ± 0.0522
k ₁₀ (hour ⁻¹)	3.14 ± 0.56	1.60 ± 0.35	1.94 ± 1.35
k ₁₀ Half-life (hour)	0.221 ± 0.039	0.432 ± 0.093	0.358 ± 0.249
k ₁₂ (hour ⁻¹)	0.544 ± 0.300	0.200 ± 0.206	0.264 ± 0.313
k ₂₁ (hour ⁻¹)	1.17 ± 0.31	0.844 ± 0.316	0.256 ± 1.44
Cl ₁ (mL/hr/kg)			
Cl ₂ (mL/hr/kg)			
Cl ₁ _F (mL/hr/kg)	43000 ± 3500	18500 ± 1900	17100 ± 6100
Cl ₂ _F (mL/hr/kg)	7460 ± 3250	2310 ± 2030	2340 ± 3480
V ₁ _F (mL/kg)	13700 ± 2900	11500 ± 2700	8860 ± 3570
V ₂ _F (mL/kg)	6360 ± 1650	2730 ± 1610	9130 ± 64500
MRT (hour)			
AUC _{0-T} (mL*hr)	1340	11300	11300
AUC _{inf} _pred (ng/mL*hr)	1390 ± 110	10800 ± 1100	11700 ± 4200
F (percent)	6	25	25

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Male

Treatment Group (mg/kg)

20 IV Brain^k

20 Gavage Brain^l

60 Gavage Brain^l

200 Gavage Brain^l

	20 IV Brain ^k	20 Gavage Brain ^l	60 Gavage Brain ^l	200 Gavage Brain ^l
Cmax_obs (ng/g)	66800	1260	8280	23400
Tmax_obs (hour)	0.0669	0.118	0.120	0.198
Half-life (hour)	0.183	0.315	0.417	0.524
AUC_0-T (ng/g*hr)	20400	258	2390	14100
AUCinf_pred (ng/g*hr)	20500	279	2430	14200

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Female

Treatment Group (mg/kg)

20 IV Brain^k 20 IV Brain^m 20 Gavage Brain^l 60 Gavage Brain^l 200 Gavage Brain^l

	20 IV Brain ^k	20 IV Brain ^m	20 Gavage Brain ^l	60 Gavage Brain ^l	200 Gavage Brain ^l
Cmax_obs (ng/g)	15700	45900	733	2830	18700
Tmax_obs (hour)	0.0738	0.0738	0.199	0.198	0.362
Half-life (hour)	0.352	0.352	0.278	0.329	0.545
AUC_0-T (ng/g*hr)	4110	14600	208	1270	16600
AUCinf_pred (ng/g*hr)	4150	14600	222	1280	16600

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LEGEND

MODELING SOFTWARE

Phoenix WinNonlin, Version 6.3, 6.4 and 8.0

MODELING METHOD & BEST FIT MODEL

^aWinNonlin, 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 $1/Y_{hat}^2$ weighting (Model #8)

^bWinNonlin, 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 model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13)

^cWinNonlin, 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 model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13). Does not include the single concentration at 12 hours.

^dPhoenix WinNonlin, Version 8.0, Certara L.P., Princeton, NJ library models, non-compartmental analysis, no weighting factor.

^ePhoenix WinNonlin, Version 8.0, Certara L.P., Princeton, NJ library models, non-compartmental analysis, no weighting factor, analyzed without the 8-hour time point.

^fPhoenix WinNonlin, Version 8.0, Certara L.P., Princeton, NJ library models, non-compartmental analysis, no weighting factor, analyzed without the 18-hour time point.

^gWinNonlin, 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 model with bolus input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #8)

^hWinNonlin, 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 model with bolus input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #8). Does not include the single concentration at 4 hours or two concentrations at 0.0333 hours

ⁱWinNonlin, 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 model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13). Does not include the single concentration at 4 hours.

^jWinNonlin, 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 model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13). Does not include the single concentration at 8 hours.

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MODELING METHOD & BEST FIT MODEL (cont'd)

^kWinNonlin, 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 bolus input, first order output, and uniform weighting.

^lWinNonlin, 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.

^mWinNonlin, 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 bolus input, first order output, and uniform weighting. Does not include two concentrations at 0.0333 hours.

TK PARAMETERS

C_{0min_pred} = Fitted plasma concentration at time zero (IV only)

C_{max} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max} = Time at which C_{max} predicted or observed occurs

Half-life = λ_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, k_a

k₀₁ Half-life = Half-life of the absorption process to the central compartment

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

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, Cl_{app} or apparent clearance for intravenous groups

Cl₂ = Clearance of the secondary compartment

Cl_{1_F} = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

Cl_{2_F} = Apparent clearance of the secondary compartment

V₁ = Volume of distribution of the central compartment, includes V_d and V volume of distribution, V_z apparent volume of distribution NCA,

V_{app} apparent volume of distribution for intravenous studies

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TK_PARAMETERS (cont'd)

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

V2_F = Apparent volume of distribution for the peripheral compartment

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_INTRAVENTOUS PLASMA

20 mg/kg Male and Female

Mice were give 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.

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TK_PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

20 mg/kg Male and Female

Mice 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

Mice 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_DOSED_FEED PLASMA

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 mice, the 500 ppm group had an increase in concentration at the last measurable time point of 8 hour and the 1000 and 2000 ppm groups had increases at their last measurable time point of 18 hours. These values affected the characterization of the terminal phases. Therefore, the 500 ppm group was also evaluated without the 8 hour time point, and the 1000 and 2000 ppm groups were also evaluated without the 18 hour time point. Parameter estimates are reported to three significant figures.

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TK_PARAMETERS PROTOCOL (cont'd)

500 ppm, 1000 ppm Male

Forty mice (11 weeks old and weighing 26.2 + or - 1.4 g at randomization) were provided dosed feed for seven consecutive days at concentrations of 500, 1000, or 2000 ppm. Mice were fed irradiated NTP-2000 meal feed ad libitum and tap water was given ad libitum. The average daily food consumption for mice ranged from 4.2 to 4.8 g with standard deviations ranging from 0.8 to 1.4. 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 mice/group/timepoint). The 0-hour sample was scheduled to be collected following dosed feed removal, but prior to offering untreated feed. Whole blood samples were collected via cardiac puncture from anesthetized mice.

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_INTRAVENTOUS BRAIN

20 mg/kg Male and Female

Mice were give 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.

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TK_PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE BRAIN

20 mg/kg Male and Female

Mice 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

Mice 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.