

Experiment Number: K11054C

Route: IV, Gavage

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: Sulfolane/ Analyte: Sulfolane

CAS Number: 126-33-0

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: TI

Male

Treatment Group (mg/kg)

10 IV Plasma<sup>b</sup>

10 Gavage Plasma<sup>a</sup>

30 Gavage Plasma<sup>a</sup>

100 Gavage Plasma<sup>a</sup>

Cmax_pred (ng/mL)	16800 ± 293	5840 ± 212	227000 ± 1090	97300 ± 6000
Tmax_pred (hour)		0.227 ± 0.0160	0.290 ± 0.0276	0.369 ± 0.0553
k01 (hour <sup>-1</sup> )		7.46 ± 1.23	6.68 ± 1.32	7.67 ± 1.76
k01 Half-life (hour)		0.0929 ± 0.0153	0.104 ± 0.0206	0.0903 ± 0.0207
k10 (hour <sup>-1</sup> )	2.33 ± 0.0474	2.32 ± 0.221	1.48 ± 0.177	0.553 ± 0.0546
k10 Half-life (hour)	0.298 ± 0.00605	0.299 ± 0.0284	0.467 ± 0.0557	1.25 ± 0.124
Cl (mL/h/kg)	1400 ± 20.3			
Cl1_F (mL/h/kg)		2350 ± 99.5	1270 ± 80.2	464 ± 38.7
V1 (mL/kg)	602 ± 10.5			
V1_F (mL/kg)		1010 ± 93.8	859 ± 90.0	838 ± 72.8
AUCinf_pred (h*ng/mL)	7200 ± 106	4270 ± 181	23600 ± 1480	216000 ± 18000
F		59.2	109	299

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Female

Treatment Group (mg/kg)

10 IV Plasma<sup>b</sup>

10 Gavage Plasma<sup>a</sup>

30 Gavage Plasma<sup>c</sup>

100 Gavage Plasma<sup>a</sup>

Cmax_pred (ng/mL)	15300 ± 492	6050 ± 173	24300 ± 1840	115000 ± 7300
Tmax_pred (hour)		0.235 ± 0.0140	0.412 ± 0.0536	0.548 ± 0.0691
k01 (hour <sup>-1</sup> )		8.31 ± 0.972	4.00 ± 1.33	4.02 ± 0.878
k01 Half-life (hour)		0.0835 ± 0.00976	0.173 ± 0.0574	0.172 ± 0.0376
k10 (hour <sup>-1</sup> )	1.89 ± 0.0721	1.80 ± 0.105	1.33 ± 0.298	0.626 ± 0.0625
k10 Half-life (hour)	0.367 ± 0.0140	0.385 ± 0.0223	0.521 ± 0.116	1.11 ± 0.111
Cl (mL/h/kg)	1300 ± 37.9			
Cl <sub>1_F</sub> (mL/h/kg)		1950 ± 65.4	950 ± 93.9	387 ± 33.0
V1 (mL/kg)	687 ± 22.1			
V1_F (mL/kg)		1080 ± 61.6	713 ± 155	619 ± 66.1
AUC <sub>inf_pred</sub> (h*ng/mL)	8090 ± 236	5130 ± 172	31600 ± 3120	258000 ± 22000
F		63.4	139	319

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## LEGEND

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### MODELING SOFTWARE

Phoenix WinNonlin (Version 6.3)

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup> Phoenix WinNonlin (Version 6.3), For both rat and mouse, Model 1 (one-compartment with bolus intravenous dose and first order output) was used for intravenous data sets with individual time point data. Model 1 provided a good fit to the data.

<sup>b</sup> Phoenix WinNonlin (Version 6.3), The best fit for both rat and mouse gavage data at all doses was Model 3 (one-compartment with first-order input and output, no lag time) with 1/y weighting. Mean time point data was used for gavage models.

### EXCEPTIONS

<sup>c</sup> 13-F-016 (female mouse, 30 mg/kg gavage group 45 min) was excluded from the analysis because it affected the fitted parameters to the extent it caused poor correlation between observed and predicted data.

### ANALYTE

Sulfolane

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#### TK PARAMETERS

C<sub>max\_pred</sub> = Observed or Predicted Maximum plasma (or tissue) concentration

T<sub>max\_pred</sub> = Time at which C<sub>max</sub> predicted or observed occurs

k<sub>01</sub> = Absorption rate constant, k<sub>a</sub>

k<sub>01</sub> Half-life = Half-life of the absorption process to the central compartment

k<sub>10</sub> = Elimination rate constant from the central compartment also k<sub>e</sub> or k<sub>elim</sub>

k<sub>10</sub> Half-life = Half-life for the elimination process from the central compartment

Cl = Clearance, includes total clearance

Cl<sub>1\_F</sub> = Apparent clearance of the central compartment, also Cl<sub>F</sub> for gavage groups in non-compartmental model

V<sub>1</sub> = Volume of distribution of the central compartment, includes V<sub>d</sub> and V volume of distribution, V<sub>z</sub> apparent volume of distribution NCA,  
V<sub>app</sub> apparent volume of distribution for intravenous studies

V<sub>1\_F</sub> = Apparent volume of distribution for the central compartment includes V<sub>d\_F</sub>, V<sub>F</sub> for oral groups, and V<sub>c\_F</sub>

AUC<sub>inf</sub> = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

#### TK PARAMETERS PROTOCOL

##### ANALYSIS METHOD

Samples in which sulfolane was not detectable or where the concentration was less than the limit of detection (LOD) were not included in the analysis. If measured concentrations were between the LOD and the lower limit of quantitation (LLOQ), the value measured was used. For the determination of sulfolane in plasma, the LLOQ was 20.0 ng/mL, and the LOD was 0.516 ng/mL for both rat and mouse. The outliers 7-M-005 (male rat iv, 5 min), 8-F-008 (female rat iv, 15 min), and 13-F-016 (female mouse, 30 mg/kg gavage group 45 min) were excluded. Nominal doses (mg/kg) for each group were used in toxicokinetic modeling. Initial concentration versus time data were modeled using noncompartmental analysis methods using the mean concentration data at each time point but results were not reported. Various compartmental models were tested. One-compartmental models 3 (gavage) and 1 (intravenous) were the best fit. For compartmental models AUC is calculated as Dose/V\*K<sub>10</sub> and is similar to AUC<sub>0-infinity</sub>.  $F = ((AUC/Dose(oral))/(AUC/Dose(iv))) * 100$ .

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#### TK PARAMETERS PROTOCOL

##### TK\_INTRAVENTOUS PLASMA

###### 10 mg/kg Male and Female

Thirty animals per group were given a single oral gavage administration of sulfolane in deionized water or a single intravenous dose in saline. Blood samples were taken at Predose, 5, 10, 15, 30, 45, 90, 180, 360, 540 minutes (9 post dose time points for 30 and 100 gavage dose both sexes), at Predose, 5, 10, 15, 30, 45, 90, 120, 180, 240 minutes (9 post dose time points for 10 mg/kg gavage dose for both sexes) and at Predose, 5, 10, 15, 30, 45, 90, 120, 180, 240 minutes (9 post dose time points for intravenous doses for both sexes). Zero-hour collections were made pre-dose. n=3 per time point. Samples were analyzed by GC/MS using a validated method and sulfolane-d8 as an internal standard.

##### TK\_GAVAGE PLASMA

###### 10 mg/kg, 30 mg/kg, 100 mg/kg Male and Female

Thirty animals per group were given a single oral gavage administration of sulfolane in deionized water or a single intravenous dose in saline. Blood samples were taken at Predose, 5, 10, 15, 30, 45, 90, 180, 360, 540 minutes (9 post dose time points for 30 and 100 gavage dose both sexes), at Predose, 5, 10, 15, 30, 45, 90, 120, 180, 240 minutes (9 post dose time points for 10 mg/kg gavage dose for both sexes) and at Predose, 5, 10, 15, 30, 45, 90, 120, 180, 240 minutes (9 post dose time points for intravenous doses for both sexes). Zero-hour collections were made pre-dose. n=3 per time point. Samples were analyzed by GC/MS using a validated method and sulfolane-d8 as an internal standard.