Experiment Number: K11054C
Route: IV, Gavage
Species/Strain: Rats/Harlan Sprague Dawley

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[a,c]	**10 Gavage Plasma[b]**	**30 Gavage Plasma[b]**	**100 Gavage Plasma[b]**
Cmax_pred (ng/mL)	15700 ± 575	7560 ± 525	30600 ± 1280	98400 ± 7150
Tmax_pred (hour)		0.968 ± 1.115	1.15 ± 0.0863	1.34 ± 0.197
k01 ($hour^{-1}$)		2.49 ± 0.528	2.21 ± 0.284	2.43 ± 0.528
k01 Half-life (hour)		0.278 ± 0.0589	0.314 ± 0.0403	0.285 ± 0.0630
k10 ($hour^{-1}$)	0.384 ± 0.0225	0.298 ± 0.0390	0.226 ± 0.0167	0.110 ± 0.0137
k10 Half-life (hour)	1.81 ± 0.106	2.33 ± 0.304	3.07 ± 0.227	6.33 ± 0.790
Cl (mL/h/kg)	242 ± 11.5			
Cl1_F (mL/h/kg)		296 ± 25.5	171 ± 8.69	96.2 ± 9.22
V1 (mL/kg)	631 ± 23.2			
V1_F (mL/kg)		991 ± 112	757 ± 49.4	878 ± 83.6
AUCinf_pred (h*ng/mL)	40800 ± 1930	33800 ± 2910	176000 ± 8930	1040000 ± 99600
F		82.9	143	255

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Female

	Treatment Group (mg/kg)			
	10 IV Plasma[a,d]	**10 Gavage Plasma[b]**	**30 Gavage Plasma[b]**	**100 Gavage Plasma[b]**
Cmax_pred (ng/mL)	14900 ± 514	8500 ± 529	28700 ± 1600	101000 ± 7000
Tmax_pred (hour)		0.934 ± 0.0954	0.964 ± 0.105	1.47 ± 0.200
k01 ($hour^{-1}$)		2.41 ± 0.465	2.68 ± 0.473	2.13 ± 0.445
k01 Half-life (hour)		0.288 ± 0.0554	0.259 ± 0.0456	0.326 ± 0.0680
k10 ($hour^{-1}$)	0.362 ± 0.0206	0.353 ± 0.0442	0.260 ± 0.0221	0.111 ± 0.0131
k10 Half-life (hour)	1.92 ± 0.109	1.97 ± 0.246	2.67 ± 0.227	6.28 ± 0.743
Cl (mL/h/kg)	240 ± 11.0			
Cl1_F (mL/h/kg)		299 ± 23.1	211 ± 14.5	93.2 ± 8.41
V1 (mL/kg)	664 ± 23.0			
V1_F (mL/kg)		847 ± 92.1	813 ± 66.7	844 ± 78.5
AUCinf_pred (h*ng/mL)	41100 ± 1880	33500 ± 2590	142000 ± 9710	1070000 ± 96800
F		81.4	115	261

LEGEND

MODELING SOFTWARE

Phoenix WinNonlin (Version 6.3)

MODELING METHOD & BEST FIT MODEL

[a] 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.

[b] 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

[c] 7-M-005 (male rat iv, 5 min) was an outlier and not included in the analysis

[d] 8-F-008 (female rat iv, 15 min) was an outlier and not included in the analysis

ANALYTE

Sulfolane

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax predicted or observed occurs
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
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
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

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*K10 and is similar to AUC0-infinity. F = ((AUC/Dose(oral))/(AUC/Dose(iv)))*100.

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA

10 mg/kg Male and Female

Fifteen 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, 15, 30, 60, 120, 240, 480, 720, 1440 minutes (9 post dose time points for gavage) and at Predose, 5, 15, 30, 60, 120, 240, 480, 720 minutes (8 post dose time points for intravenous) . Zero-hour collections were made pre-dose. Each rat was sampled twice. 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

Fifteen 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, 15, 30, 60, 120, 240, 480, 720, 1440 minutes (9 post dose time points for gavage) and at Predose, 5, 15, 30, 60, 120, 240, 480, 720 minutes (8 post dose time points for intravenous) . Zero-hour collections were made pre-dose. Each rat was sampled twice. n=3 per time point. Samples were analyzed by GC/MS using a validated method and sulfolane-d8 as an internal standard.