Experiment Number: S0539 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Gavage | **Compound:** 1-Chloro-2-propanol/ **Analyte:** 1-Chloro-2-propanol | **Request Time:** 10:03:16

Species/Strain: Mouse/B6C3F1 | **CAS Number:** 127-00-4 | **Lab:** T.S.I Mason

Male

Treatment Group (mg/kg)

	4.5 Gavage Plasma[a]	22.5 Gavage Plasma[b]	45 Gavage Plasma[c]
No parameters calculated			
C_0min_pred (ug/mL)			19.82
Cmax_obs (ug/mL)		7.64	
Tmax_obs (minute)		5.0	
Lambda_z (minute^{-1})		0.0991	
Half-life (minute)		6.99	
Cl1_F (mL/min/kg)		264.18	
V1 (L/kg)			2.27
AUC_0-T (ug*min/mL)		86.19	449.02
AUCinf_pred (ug*min/mL)		85.17	426.66

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Female

	Treatment Group (mg/kg)		
	4.5 Gavage Plasma[a]	**22.5 Gavage Plasma[b]**	**45.0 Gavage Plasma[c]**
	No parameters calculated		
C_0min_pred (ug/mL)			29.75
Cmax_obs (ug/mL)		9.73	
Tmax_obs (minute)		5.0	
Lambda_z (minute^{-1})		0.0932	
Half-life (minute)		7.43	
Cl1_F (mL/min/kg)		161.35	
V1 (L/kg)			1.51
AUC_0-T (ug*min/mL)		138.61	554.45
AUCinf_pred (ug*min/mL)		139.45	506.70

LEGEND

MODELING METHOD & BEST FIT MODEL

[a] calculations, linear regression - The plasma concentration vs time data for the 4 .5 mg/kg mice could not be determined due to values which were below quantifiable limits.

[b] calculations, linear regression – linear elimination profile

[c] calculations, linear regression - Michaelis-Menten due to saturation of the elimination kinetics (metabolism or excretion) as indicated by the convex profile of the elimination curve. Assuming instantaneous absorption, best fit of the data is a single capacity limited elimination process. Km 26.07, Vm 2.40, intercept Co* 93.12, and C0 is Cmax

ANALYTE

1-Chloro-2-propanol

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)
Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Lambda_z = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim
Half-Life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
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
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

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Plasma was analyzed with a validated method using a gas chromatograph-mass spectrometer (GC/MS) in the selected ion mode to measure levels of 1-chloro-2-propanol. Two standard curve ranges encompassed the range of 0.050 to 8.0 ug/mL and dilutions with control plasma were used to extend the upper limit of quantitation to 80 ug/ml. For the lower standard curve, the limit of detection (LOD) was 0.016 ug/mL and the experimental limit of quantitation (ELOQ) was 0.05 ug/mL For the higher standard curve, LOD was 0.120 ug/mL and ELOQ was 0.6 ug/mL.

TK_GAVAGE PLASMA

4.5 mg/kg, 22.5 mg/kg Male and Female

Mice and F344/N rats were administered a single gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/ timepoint for 8 timepoints in the low and mid dose and 10 timepoints for the higher dose. The average plasma levels of 1-chloro-2-propanol were calculated and the logarithm of these values were plotted as a function of time, The terminal rate constant was determined from the slope of the terminal phase of the log plasma concentration-time profile. The slope was obtained by linear regression of the terminal data points. The half life was calculated as 0.693 divided by lambda. AUC was determined using the trapezoid rule. (last timepoint 120 minutes).

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

45 mg/kg Male and Female

Mice and F344/N rats were administered a single gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/ timepoint for 10 timepoints for the high dose. The average plasma levels of 1-chloro-2-propanol were calculated and the logarithm of these values were plotted as a function of time. For Michaelis-Menten, Co is the plasma concentration extrapolated to zero time and Co* is the intercept from the extrapolated terminal part of the profile. Clearance in a non-linear kinetic disposition (saturable kinetic elimination) is dependent on plasma concentration and consequently on dose. Thus, as the concentration changes so does the clearance, and the half-life also increases with increasing concentrations except at low concentrations. Since the kinetics of disposition of chloropropanol at the high dose (45 mg/kg) in mice was saturable (Michaelis-Menten) the AUCinf values were calculated using AUCinf equals Co divided by Vmax times (Km plus (Co divided by 2)) Where Co is the concentration at time t equals 0, Vmax (the theoretical maximum rate of elimination) and Km are Michaelis-Menten parameters. Cl_tot is equal to Vmax times Vd divided by (Km plus C). (last timepoint 120 minutes).