Experiment Number: S0613
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: Formamide/ **Analyte:** Formamide
CAS Number: 75-12-7

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Midwest Research Institute

Male

	Treatment Group (mg/kg)		
	20 IV Plasma[a]	**60 IV Plasma[b]**	**180 IV Plasma[b]**
Cmax_pred (ug/mL)	49.6	96.6	239
Tmax_pred (hour)			
Alpha ($hour^{-1}$)	0.13		
Alpha Half-life (hour)	5.2		
Beta ($hour^{-1}$)	0.0070		
Beta Half-life (hour)	99		
k01 ($hour^{-1}$)			
k01 Half-life (hour)			
k10 ($hour^{-1}$)	0.065	0.18	0.12
k10 Half-life (hour)	10.7	3.9	5.6
Cl (mL/(hr*kg))	26	110	94
V1 (mL/kg)	403	621	753
Vss (mL/kg)	2390		
V1_F (mL/kg)			
MRT (hour)	93	5.9	6.7
AUCinf_pred (ug*hr/mL)	781	605	1747
F			

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Male

	Treatment Group (mg/kg)		
	120 Gavage Plasma[c,e]	**1000 Gavage Plasma[c,f]**	**2000 Gavage Plasma[c,g]**
Cmax_pred (ug/mL)	152	1436	2443
Tmax_pred (hour)	0.70	0.74	0.60
Alpha ($hour^{-1}$)			
Alpha Half-life (hour)			
Beta ($hour^{-1}$)			
Beta Half-life (hour)			
k01 ($hour^{-1}$)	4.60	5.49	8.6
k01 Half-life (hour)	0.15	0.13	0.081
k10 ($hour^{-1}$)	0.21	0.10	0.053
k10 Half-life (hour)	3.2	6.8	13.0
Cl (mL/(hr*kg))	52	52	50
V1 (mL/kg)			
Vss (mL/kg)			
V1_F (mL/kg)	680	646	793
MRT (hour)	5.5	9.3	19.8
AUCinf_pred (ug*hr/mL)	1170	16593	48536
F	0.51	0.87	1.22

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Female

	Treatment Group (mg/kg)		
	20 IV Plasma[d]	**60 IV Plasma[b]**	**180 IV Plasma[b]**
Cmax_pred (ug/mL)	44.7	85.6	257
Tmax_pred (hour)			
k01 ($hour^{-1}$)			
k01 Half-life (hour)			
k10 ($hour^{-1}$)		0.19	0.19
k10 Half-life (hour)		3.6	3.7
Cl (mL/(hr*kg))		133	131
V1 (mL/kg)		701	701
Vss (mL/kg)	1900		
V1_F (mL/kg)			
MRT (hour)	38	5.3	5.9
AUCinf_pred (ug*hr/mL)	404	644	1962
F			

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Toxicokinetics Data Summary
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Female

	Treatment Group (mg/kg)		
	120 Gavage Plasma[c,h]	**1000 Gavage Plasma[c,i]**	**2000 Gavage Plasma[c,j]**
Cmax_pred (ug/mL)	159	1366	2690
Tmax_pred (hour)	0.81	1.9	1.1
k01 ($hour^{-1}$)	3.70	1.33	3.5
k01 Half-life (hour)	0.19	0.52	0.20
k10 ($hour^{-1}$)	0.22	0.13	0.86
k10 Half-life (hour)	3.2	5.2	8.0
Cl (mL/(hr*kg))	73	71	72
V1 (mL/kg)			
Vss (mL/kg)			
V1_F (mL/kg)	630	567	677
MRT (hour)	5.6	8.0	14.4
AUCinf_pred (ug*hr/mL)	1190	15297	39793
F	0.72	1.08	1.44

LEGEND

MODELING SOFTWARE

WinNonlin, Version 1

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin (Version 1, SCI, Cary, North Carolina) estimated distribution (alpha half-life) and elimination half-lives, volumes of distribution (Vc shown as V1, Vss) and clearance Cl. Model independent methods (CHANKIN) were used to estimate mean residence time (MRTiv) and area under the plasma concentration-time curve (AUCo-inf), two compartment model with first order elimination

[b]WinNonlin (Version 1, SCI, Cary, North Carolina) estimated distribution (alpha half-life) and elimination half-lives, volumes of distribution (Vshown as V1) and clearance Cl. Model independent methods (CHANKIN) were used to estimate mean residence time (MRTiv) and area under the plasma concentration-time curve (AUCo-inf), one compartment model with first order elimination

[c]WinNonlin (Version 1, SCI, Cary, North Carolina) estimated Cmax, Tmax, and elimination and absorption half-lives. Model independent methods (CHANKIN) were used to estimate mean residence time (MRToral) and area under the plasma concentration-time curve (AUCo-inf), one-compartment model with first-order absorption and elimination

[d]WinNonlin (Version 1, SCI, Cary, North Carolina) unable to estimate distribution (alpha half-life) and elimination half-lives, volumes of distribution (Vc, Vss) and clearance Cl. Model independent methods (CHANKIN) were used to estimate mean residence time (MRTiv) and area under the plasma concentration-time curve (AUCo-inf). Data from female mice could not be modeled due to the erratic nature of the plasma concentration-time profile.

EXCEPTIONS

[e]Unable to calculate MAT due to rapid absorption.

[f]Extravascular mean absorption time (MAT) is 3.0 hours.

[g]Extravascular mean absorption time (MAT) is 13.5 hours.

[h]Extravascular mean absorption time (MAT) is 0.03 hours.

[i]Extravascular mean absorption time (MAT) is 2.4 hours.

[j]Extravascular mean absorption time (MAT) is 8.4 hours.

ANALYTE

Formamide

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax predicted or observed occurs
Alpha = Hybrid rate constant of the alpha phase
Alpha Half-life = Half-life for the alpha phase
Beta = Hybrid rate constant of the beta 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
Cl = Clearance, includes total clearance
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
Vss = Volume of distribution at steady state
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
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

Only data that were above the limit of detection were used in calculations. WinNonlin software was used for modeling. Also, model independent methods (Statistical Moment, CHANKIN software, Chan, K.K.J., Wnuck, K., Bell, C.L ., Comp. Prog. Biomed., 1986 .) were used to estimate mean residence time (MRT) and area under the plasma concentration-time curve (AUCo-inf), where area under the plasma concentration-time curve (extrapolated to infinity) is equal to the sum of AUCo-t, calculated using the trapezoidal rule, and AUCt-inf, (where AUC t-inf = C(t)/ke, and ke, is the first-order elimination rate constant).

TK_INTRAVENOUS PLASMA

20 mg/kg, 60 mg/kg, 180 mg/kg Male and Female

Animals were administered a single dose by intravenous injection or oral gavage. Three rats or mice/route/dose/sex were sampled at each of 14 or for intravenously administered rats, 16 time points. Final time point ranged from 48-96 hours post-dosing. Plasma samples were analyzed by gas chromatography with thermionic specific detector (TSD) using 12 pentachloropyridine as internal standard. The limit of detection (LOD) of formamide is 0.1 ug/mL and the experimental limit of quantitation (ELOQ) is 1.1 ug/mL.

ANALYSIS METHOD

Only data that were above the limit of detection were used in calculations. WinNonlin software used for modeling. Also, model independent methods (Statistical Moment, CHANKIN software, Chan, K.K.J., Wnuck, K., Bell, C.L ., Comp. Prog. Biomed., 1986 .) were used to estimate mean residence time (MRT) and area under the plasma concentration-time curve (AUCo-inf), where area under the plasma concentration-time curve (extrapolated to infinity) is equal to the sum of AUCo-t, calculated using the trapezoidal rule, and AUCt-inf, (where AUC t-inf = C(t)/ke, and ke, is the first-order elimination rate constant). Bioavailability (F) is equal to (Dose normalized AUC0-inf oral) / (Mean dose normalized AUCo-inf i.v.).

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

120 mg/kg, 1000 mg/kg, 2000 mg/kg Male and Female

Animals were administered a single dose by intravenous injection or oral gavage. Three rats or mice/route/dose/sex were sampled at each of 14 or for intravenously administered rats, 16 time points. Final time point ranged from 48-96 hours post-dosing. Plasma samples were analyzed by gas chromatography with thermionic specific detector (TSD) using 12 pentachloropyridine as internal standard. The limit of detection (LOD) of formamide is 0.1 ug/mL and the experimental limit of quantitation (ELOQ) is 1.1 ug/mL.