Experiment Number: S0613

Route: Gavage, IV

Species/Strain: Rats/Fischer 344

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)

	10 IV Plasma[a]	30 IV Plasma[a]	90 IV Plasma[a]
Cmax_pred (ug/mL)	13.3	39.4	139
Tmax_pred (hour)			
k01 (hour^{-1})			
k01 Half-life (hour)			
k10 (hour^{-1})	0.052	0.056	0.049
k10 Half-life (hour)	13.4	12.3	14.2
Cl (mL/(hr*kg))	39	43	32
V1 (mL/kg)	754	761	649
MRT (hour)	19	15	20
AUCinf_pred (ug*hr/mL)	256	655	2847
F			

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Male

Treatment Group (mg/kg)

	36 Gavage Plasma[b,c]	300 Gavage Plasma[b,d]	600 Gavage Plasma[b,e]
Cmax_pred (ug/mL)	49.6	301.3	823.2
Tmax_pred (hour)	1.9	2.4	1.7
k01 (hour^{-1})	1.97	1.7	2.5
k01 Half-life (hour)	0.35	0.42	0.28
k10 (hour^{-1})	0.47	0.037	0.037
k10 Half-life (hour)	14.8	18.8	18.5
Cl (mL/(hr*kg))	39	38	39
V1 (mL/kg)	662	913	684
MRT (hour)	23	25	24
AUCinf_pred (ug*hr/mL)	1201	11099	24717
F	1.3	1.4	1.6

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Female

Treatment Group (mg/kg)

	10 IV Plasma[a]	30 IV Plasma[a]	90 IV Plasma[a]
Cmax_pred (ug/mL)	12.2	41.3	141
Tmax_pred (hour)			
$k01$ (hour^{-1})			
$k01$ Half-life (hour)			
$k10$ (hour^{-1})	0.055	0.070	0.066
$k10$ Half-life (hour)	12.7	10.0	10.4
Cl (mL/(hr*kg))	45	51	43
V1 (mL/kg)	821	727	640
MRT (hour)	19	13	18
AUCinf_pred (ug*hr/mL)	227	573	2284
F			

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Female

Treatment Group (mg/kg)

	36 Gavage Plasma[b,f]	300 Gavage Plasma[b,g]	600 Gavage Plasma[b,h]
Cmax_pred (ug/mL)	50.5	269.4	752.6
Tmax_pred (hour)	1.5	1.5	1.3
$k01$ (hour^{-1})	2.5	2.6	3.6
$k01$ Half-life (hour)	0.28	0.26	0.19
$k10$ (hour^{-1})	0.63	0.055	0.044
$k10$ Half-life (hour)	11.0	12.6	15.8
Cl (mL/(hr*kg))	46	45	44
V1 (mL/kg)	648	1025	755
MRT (hour)	19	17.9	20.4
AUCinf_pred (ug*hr/mL)	934	7961	18977
F	1.2	1.2	1.4

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LEGEND

MODELING SOFTWARE
WinNonlin, Version 1

MODELING METHOD & BEST FIT MODEL
[a]WinNonlin (Version 1, SCI, Cary, North Carolina) estimated elimination half lives (K10_Half-life), volumes of distribution (V shown as V1), and clearance (CI). 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). one compartment model with first order elimination

[b]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), mean absorbance time (MAT) and area under the plasma concentration-time curve (AUCo-inf). one compartment model with first order absorption and elimination

EXCEPTIONS
[c]Extravascular mean absorption time (MAT) is 4.8 hours.
[d]Extravascular mean absorption time (MAT) is 7.1 hours.
[e]Extravascular mean absorption time (MAT) is 5.6 hours.
[f]Extravascular mean absorption time (MAT) is 1.5 hours.
[g]Extravascular mean absorption time (MAT) is 0.9 hours.
[h]Extravascular mean absorption time (MAT) is 3.4 hours.

ANALYTE
Formamide

Experiment Number: S0613   **Toxicokinetics Data Summary**   **Request Date:** 7/11/2023
Route: Gavage, IV   **Compound:** Formamide/ **Analyte:** Formamide   **Request Time:** 10:03:16
Species/Strain: Rats/Fischer 344   **CAS Number:** 75-12-7   **Lab:** Midwest Research Institute

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

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

MRT = Mean residence time

AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

Experiment Number: S0613
Route: Gavage, IV
Species/Strain: Rats/Fischer 344

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

Request Date: 7/11/2023
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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

10 mg/kg, 30 mg/kg, 90 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.).

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TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

<u>36 mg/kg, 300 mg/kg, 600 mg/kg Male and Female</u>

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.