Experiment Number: S0629
Route: IV, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: Wyeth-14643/ **Analyte:** Wyeth-14643
CAS Number: 50892-23-4

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: TI

Male

Treatment Group (mg/kg)

2.0 IV Plasma[a,c]

Cmax_pred (ug/mL)	15.7
Beta Half-life (minute)	243
Cl (mL/min/kg)	1.48
MRT (minute)	242
AUCinf_pred (ug/mL*min)	1353

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Male

	Treatment Group (mg/kg)			
	2.0 Gavage Plasma[a,e]	**2.0 Gavage Plasma[b]**	**4.0 Gavage Plasma[a,f]**	**8.0 Gavage Plasma[a,g]**
Cmax_obs (ug/mL)	6.94		14.5	20.5
Tmax_obs (minute)	30		15	15
Beta Half-Life (minute)	64.6		61.6	67.0
k01 (minute^{-1})		0.0374		
k10 (minute^{-1})		0.0230 ± 0.0027		
Cl1_F (mL/min/kg)	1.51		3.30	3.37
V1 (L/kg)		0.1310 ± 0.0132		
MRT (minute)	415		83.9	100
AUCinf_pred (ug/mL*min)	1325		1211	2376
F	0.98		0.45	0.44

Male

	Treatment Group (ppm)	
	50 Dosed Feed Plasma[c,h]	**500 Dosed Feed Plasma[c,h]**
Cmax_obs (ug/mL)	1.26	8.42
Tmax_obs (hour)	1800	0200
AUCinf_pred (ug/mL*min)	777	7060

LEGEND

MODELING SOFTWARE

PCNONLIN software, Version 4.2
Models 200 and 201, PCNONLIN software

MODELINING METHOD AND BEST FIT MODEL

[a]Models 200 and 201, PCNONLIN software, Version 4.2, SCI Software, Lexington, KY, Noncompartmental model
[b]PCNONLIN software, Version 4.2, SCI Software, Lexington, KY, Best fit is one compartmental which simultaneously solves iv and low dose oral data sets. Simultaneous solution of mouse intravenous dose (2.0 mg/kg Study P) and low oral gavage dose (2.0 mg/kg Study Q) fits the data well from time zero to approximately 240 minutes.
[c]PCNONLIN software, Version 4.2, SCI Software, Lexington, KY, Noncompartmental model.

EXCEPTIONS

[d]AUC inf and MRT (Estimate(0-T)/ Estimate(inf) is less than 0.90. Terminal elimination Beta range is 90 to 600 minute.
[e]Terminal elimination Beta range is 60 to 600 minute.
[f]Terminal elimination Beta range is 90 to 480 minute.
[g]Terminal elimination Beta range is 120 to 480 minute.
[h]For feed studies, Tmax is reported as 24-hour clock time

ANALYTE

Wyeth-14643

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Beta Half-Life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k10 = Elimination rate constant from the central compartment also ke or kelim
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
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute availability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Plasma was analyzed for Wyeth 14,643 concentration by high performance liquid chromatography (HPLC) using UV detection at 254 nm and indomethacin as the internal standard.

TK_INTRAVENOUS PLASMA

2.0 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

2.0 mg/kg,4.0 mg/kg,8.0 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints.

ANALYSIS METHOD

Plasma was analyzed for Wyeth 14,643 concentration by high performance liquid chromatography (HPLC) using UV detection at 254 nm and indomethacin as the internal standard. Not shown here are simulations of plasma concentrations after dietary exposure which were made using the method of superposition Yuan,J. 1993. Modeling blood/plasma concentrations in dosed feed and dosed drinking water toxicology studies. Toxicol.Appl.Pharmacol. 119,131-141. A program at RTI was written to perform the computations which used 24-hour feed consumptions data for the rat and mouse provided by NTP. Feed consumption data for the rat were used in hamster simulations. Observed plasma concentrations were greatly over predicted at both dose levels in mice, under predicted by approximately 2-fold (low dose) and 5- fold (high dose) levels for the Sprague-Dawley rat, and although within the range of observed plasma concentrations in the hamster, the shape of the simulated curves were not in good agreement with the hamster data.

TK_DOSED FEED PLASMA

50 ppm, 500 ppm

Date given as first exposure is date blood samples taken. Animals were administered Wyeth 14,643 in certified NIH-07 feed (meal for dosed feed) for 9 days and into the 10th day for some. On the 9th day blood was taken from one animal per time point for 10-11 timepoints. Blood samples were collected beginning at noon on the 9th day and ending at 9 am on the 10th day (mice) or ending on 7 am (Wistar Furth rats) or beginning on 2 pm day 9 and ending on 10 am (100 ppm hamster) or noon (1000 ppm hamster).