Experiment Number: S0546
Route: IV, Dosed Feed, Gavage
Species/Strain: Hamster/Syrian-Golden

Toxicokinetics Data Summary
Compound: 2,4-Dichlorophenoxyacetic acid
Analyte: 2,4-Dichlorophenoxyacetic acid
C**AS Number:** 94-75-7

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

Male

	Treatment Group (mg/kg)		
	8.0 IV Plasma[a,d]	**2.0 Gavage Plasma[a,e]**	**8.0 Gavage Plasma[a,f]**
C_0min_pred (ug/mL)	223		
Cmax_pred (ug/mL)		6.86	18.2
Tmax_obs (minute)		15	5
Beta Half-life (minute)	21.0	36.9	24.6
Cl (mL*min/kg)	5.30		
Cl1_F (mL*min/kg)		7.85	14.8
MRT (minute)	12.8	103	33.0
AUCinf_pred (ug/mL*min)	1510	255	541
F		0.67	0.36

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	Treatment Group (mg/kg)	
	8.0 Gavage Plasma[b,g]	**40 Gavage Plasma[a,h]**
Cmax_pred (ug/mL)		70.1
Tmax_obs (minute)		5
Beta Half-life (minute)		210
k01 (minute^{-1})	0.0467 ± 0.012	
k10 (minute^{-1})	0.116 ± 0.010	
Cl1_F (mL*min/kg)		3.38
V1 (L/kg)	0.0605 ± 0.0055	
MRT (minute)		306
AUCinf_pred (ug/mL*min)		11830
F		1.57

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	Treatment Group (ppm)	
	100 Dosed Feed Plasma[c]	**1000 Dosed Feed Plasma[c]**

Parameters Not Available

LEGEND

MODELING SOFTWARE

PCNONLIN

MODELING METHOD & BEST FIT MODEL

[a] Models 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Noncompartmental model (not best fit)

[b] Analyzed using compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (PCNONLIN software, SCI Software, Lexington, KY). The hamster data were best fit using a 1-compartment model with simultaneous solution of the iv (Study T) and mid oral (Study V) data. The model underpredicted terminal concentrations for both the iv and oral studies.

[c] Analyzed using compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (PCNONLIN software, SCI Software, Lexington, KY). Simulations of plasma concentrations after dietary exposure were made using the method of superposition (Yuan, 1993) using a program written by R. D. Austin of RTI and food consumption data provided by NTP (hamster calculations used rat consumption data). Yuan, J. (1993) Modeling Blood/Plasma Concentrations in Dosed Feed and Dosed Drinking Water Toxicology Studies. Toxicol. Appl. Pharmacol., 119,131-141. Using the 1-compartment equation derived from fitting the iv and mid oral data from the toxicokinetic studies, plasma concentrations attained after 1 week of dosing with 100 or 1,000 ppm 2,4-D in the feed were simulated. Simulated curves not shown.

EXCEPTIONS

[d] Terminal elimination Beta range is 40 to 120 minutes. In the hamster iv dose data set, the single data point at 150 minutes was declared an outlier.

[e] For AUCinf, Cl_F, F, and MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 120 to 150 minutes.

[f] Terminal elimination Beta range is 30 to 150 minutes. In the mid dose oral data set, the single data point at 240 minutes and replicates 1 and 3 at 360 minutes were declared as outliers.

[g] In the hamster iv dose data set, the single data point at 150 minutes was declared an outlier. In the mid dose oral data set, the single data point at 240 minutes and replicates 1 and 3 at 360 minutes were declared as outliers.

[h] For MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 240 to 360 minutes

ANALYTE

2,4-Dichlorophenoxyacetic acid

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)
Cmax_pred = 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 bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Blood was analyzed by high performance liquid chromatography (HPLC) with UV detection at 286 nm using 4-Chlorophenoxyacetic acid as an internal standard.

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA

8.0 mg/kg Male

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. Blood was collected at selected post-dosing intervals by cardiac puncture under terminal anesthesia for mice and hamsters. Rats were sampled twice from alternating orbital plexus.

TK_GAVAGE PLASMA

2.0 mg/kg, 8.0 mg/kg, 8.0 mg/kg, 40 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. Blood was collected at selected post-dosing intervals by cardiac puncture under terminal anesthesia for mice and hamsters. Rats were sampled twice from alternating orbital plexus.

TK_DOSED FEED PLASMA

100 ppm, 1000 ppm

Date given as first exposure is date blood samples were first taken from that group. Mice and Wistar Furth rats were adminstered 2,4-Dichlorophenoxyacetic acid (2,4-D) 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 4 pm (mice) or 2 pm (rats) on the 9th day and ending at 2 pm on the 10th day (mice and rats). Hamsters were adminstered 2,4-D mixed in 2 percent corn oil then mixed in certified NIH-07 feed (meal for dosed feed) for 7 days and into the 8th day for some. On the 7th day blood was taken from one hamster per time point for 10-11 timepoints beginning at 2 pm on day 7 and ending on 10 am (100 ppm hamster) or noon (1000 ppm hamster) on day 8. Animals had access to feed ad libitum. Mean dose received (mg 2,4-D/kg body weight/day) excluding days 1-2 and 9-end (mouse and rat) or 7-end (hamster) were 4.42, 278.13, 4.78, 121.27, 4.19, and 57.45 for mouse 31 ppm, mouse 1875 ppm, rat 83 ppm, rat 2500 ppm, hamster 100 ppm, and hamster 1000 ppm doses, respectively.