Experiment Number: S0546
Route: IV, Dosed Feed, Gavage
Species/Strain: Mice/B6C3F1

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)		
	1.0 IV Plasma[a,d]	**1.0 Gavage Plasma[a,e]**	**1.0 Gavage Plasma[b,f]**
C_0min_pred (ug/mL)	9.07		
Cmax_pred (ug/mL)		3.49	
Tmax_obs (minute)		5	
Alpha (minute^{-1})			0.0186 ± 0.0053
Beta (minute^{-1})			0.00278 ± 0.0051
Beta Half-life (minute)	90.8	143	
k01 (minute^{-1})			0.129 ± 0.034
k10 (minute^{-1})			0.0149 ± 0.0029
k12 (minute^{-1})			0.00301 ± 0.0027
k21 (minute^{-1})			0.00347 ± 0.0066
Cl (mL*min/kg)	1.36		
Cl1_F (mL*min/kg)		2.71	
V1 (L/kg)			0.124 ± 0.011
MRT (minute)	106	157	
AUCinf_pred (ug/mL*min)	735	369	
F		0.50	

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	Treatment Group (mg/kg)	
	2.0 Gavage Plasma[a,g]	**5.2 Gavage Plasma[a,h]**
Cmax_pred (ug/mL)	6.22	19.2
Tmax_obs (minute)	30	30
Beta Half-life (minute)	63.8	74.8
Cl1_F (mL*min/kg)	2.34	1.15
MRT (minute)	94.4	162
AUCinf_pred (ug/mL*min)	854	4541
F	0.58	1.19

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	Treatment Group (ppm)	
	31 Dosed Feed Plasma[c]	**1875 Dosed Feed Plasma[c]**

Parameters Not Available

LEGEND

MODELING SOFTWARE

Models 200 and 201, PCNONLIN software

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 mouse data were best fit using a 2-compartment model with simultaneous solution of the iv (Study P) and low oral dose (Study Q) data.

[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. Austinof 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 2-compartment equation derived from fitting the iv and low oral data from the toxicokinetic studies, plasma concentrations attained after 9 days of dosing with 31 or 1,875 pprn 2,4-D in the feed were simulated. Simulated curves not shown.

EXCEPTIONS

[d] Terminal elimination Beta range is 180 to 600 minutes.

[e] For MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 120 to 480 minutes. In the mouse low oral data sets, the single data point at 600 minutes was not included in the analyses.

[f] In the mouse low oral data sets, the single data point at 600 minutes was not included in the analyses.

[g] Terminal elimination Beta range is 60 to 360 minutes.

[h] Terminal elimination Beta range is 240 to 600 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
Alpha = Hybrid rate constant of 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
k10 = Elimination rate constant from the central compartment also ke or kelim
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl = Clearance of central compartment, Clapp or apparent clearance for intravenous groups
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

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. 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

1.0 mg/kg, 2.0 mg.kg, 5.2 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

31 ppm, 1875 ppm

Date given as first exposure is date blood samples were first taken from that group. Mice and Wistar Furth rats were administered 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 administered 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.