

Experiment Number: S0546

Route: IV, Dosed Feed, Gavage

Species/Strain: Rats/Sprague-Dawley

Toxicokinetics Data Summary

Compound: 2,4-Dichlorophenoxyacetic acid

Analyte: 2,4-Dichlorophenoxyacetic acid

CAS Number: 94-75-7

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Male

Treatment Group (mg/kg)

2.0 IV Plasma^{a,d}

1.5 Gavage Plasma^{a,e}

1.5 Gavage Plasma^{b,f}

| | | | |
|---|------|------|-----------------|
| C _{0min} _pred (ug/mL) | 33.4 | | |
| C _{max} _pred (ug/mL) | | 3.73 | |
| T _{max} _obs (minute) | | 30 | |
| Alpha (minute ⁻¹) | | | 0.223 ± 0.0082 |
| Beta (minute ⁻¹) | | | 0.0200 ± 0.0021 |
| Beta Half-life (minute) | 61.9 | 134 | |
| k ₀₁ (minute ⁻¹) | | | 0.0330 ± 0.0058 |
| k ₁₀ (minute ⁻¹) | | | 0.0461 ± 0.0074 |
| k ₁₂ (minute ⁻¹) | | | 0.0998 ± 0.049 |
| K ₂₁ (minute ⁻¹) | | | 0.0968 ± 0.031 |
| Cl (mL*min/kg) | 2.02 | | |
| Cl _{1_F} (mL*min/kg) | | 2.92 | |
| V ₁ (L/kg) | | | 0.0559 ± 0.0091 |
| MRT (minute) | 61.7 | 180 | |
| AUC _{inf} _pred (ug/mL*min) | 992 | 513 | |
| F | | 0.69 | |

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Treatment Group (mg/kg)

3.56 Gavage Plasma^{a,g} 7.0 Gavage Plasma^{a,h}

| | | |
|-------------------------|------|------|
| Cmax_pred (ug/mL) | 11.0 | 12.0 |
| Tmax_obs (minute) | 30 | 10 |
| Beta Half-life (minute) | 1066 | 176 |
| MRT (minute) | 1417 | 290 |
| AUCinf_pred (ug/mL*min) | 4821 | 2959 |

Experiment Number: S0546

Route: IV, Dosed Feed, Gavage

Species/Strain: Rats/Wistar Furth

Toxicokinetics Data Summary

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Treatment Group (ppm)

83 Dosed Feed Plasma^c

2500 Dosed Feed Plasma^c

Parameters Not Available

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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 rat data were best fit using a 2-compartment model with simultaneous solution of the iv (Study X) and low oral (Study Y) 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, plasma concentrations attained after 9 days of dosing with 83 or 2,500 ppm 2,4-D in the feed were simulated Simulated curves not shown..

EXCEPTIONS

^d For MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 90 to 240 minutes. In the rat iv dose data set, replicate 3 at 210 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 60 to 360 minutes.

^f In the rat iv dose data set, replicate 3 at 210 minutes was declared an outlier.

^g For AUCinf and MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 240 to 480 minutes.

^h For AUCinf and MRT, (Estimate(0-T)/Estimate(inf)) is less than 0.90. Terminal elimination Beta range is 60 to 480 minutes.

ANALYTE

2,4-Dichlorophenoxyacetic acid

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TK PARAMETERS

C_{0min_pred} = Fitted plasma concentration at time zero (IV only)

C_{max_pred} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max_obs} = Time at which C_{max} 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, k_a

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

k₁₂ = Distribution rate constant from first to second compartment

k₂₁ = Distribution rate constant from second to first compartment

Cl = Clearance, includes total clearance

Cl_{1_F} = Apparent clearance of the central compartment, also Cl_{1_F} for gavage groups in non-compartmental model

V₁ = Volume of distribution of the central compartment, includes V_d and V volume of distribution, V_z apparent volume of distribution NCA,
V_{app} apparent volume of distribution for intravenous studies

MRT = Mean residence time

AUC_{inf_pred} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

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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_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

1.5 mg/kg, 3.56 mg/kg, 7.0 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.

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TK PARAMETERS PROTOCOL (cont'd)

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_DOSED FEED PLASMA

83 ppm, 2500 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.