Experiment Number: S0328
Route: IV, Dosed Feed, Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: Pentachlorophenol, purified/ **Analyte:** Pentachlorophenol, purified
CAS Number: 87-86-5

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: NIEHS_Midwest Research Institute

Male

	Treatment Group (mg/kg)	
	5 IV Plasma[a]	**5 IV Plasma[b]**
Beta ($hour^{-1}$)	0.123 ± 0.008	
k10 Half-life (hour)		2.6
Cl (L/h/kg)	0.016 ± 0.0007	
Cl (mL/h/kg)		11.7
V1 (mL/kg)		46
Vss (L/kg)	0.13 ± 0.006	
Vss (mL/kg)		85
MRT (hour)		7.3
AUCinf_pred (ug*h/mL)	314 ± 14	
AUCinf_pred (ug/mL*h)		428

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Female

	Treatment Group (mg/kg)	
	5 IV Plasma[a]	**5 IV Plasma[b]**
Beta ($hour^{-1}$)	0.073 ± 0.032	
k10 Half-life (hour)		5.8
Cl (L/h/kg)	0.017 ± 0.002	
Cl (mL/h/kg)		13.9
V1 (mL/kg)		125
Vss (L/kg)	0.20 ± 0.04	
Vss (mL/kg)		113
MRT (hour)		8.1
AUCinf_pred (ug*h/mL)	295 ± 34	
AUCinf_pred (ug/mL*h)		359

Male

	Treatment Group (ppm)		
	312 Dosed Feed Plasma[f]	**1250 Dosed Feed Plasma[f]**	**2500 Dosed Feed Plasma[g]**
F (percent)	52	30	

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Male

	Treatment Group (mg/kg)			
	9.5 Gavage Plasma[c]	**18.75 Gavage Plasma[b]**	**75 Gavage Plasma[b]**	**150 Gavage Plasma[d]**
k01 (hour^{-1})	0.87 ± 0.15			
k01 Half-life (hour)		3.6	2.1	
k10 (hour^{-1})	0.081 ± 0.006			
k10 Half-life (hour)		3.8	5.7	
Cl (mL/h/kg)		21.4	22.0	
Cl1 (L/h/kg)	0.015 ± 0.0004			
Vss (L/kg)	0.19 ± 0.014			
Vss (mL/kg)		181	139	
MRT (hour)		15.4	11.9	
AUCinf_pred (ug*h/mL)	613 ± 31			
AUCinf_pred (ug/mL*h)		878	3402	
F (percent)	100 ± 4	0.55	0.53	

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Female

	Treatment Group (mg/kg)			
	38 Gavage Plasma[c]	**18.75 Gavage Plasma[b]**	**75 Gavage Plasma[b]**	**150 Gavage Plasma[d]**
k01 (hour^{-1})	0.49 ± 0.08			
k01 Half-life (hour)		3.8	1.9	
k10 (hour^{-1})	0.110 ± 0.008			
k10 Half-life (hour)		3.1	6.0	
Cl (mL/h/kg)		22.0	28.8	
Cl1 (L/h/kg)	0.016 ± 0.0005			
Vss (L/kg)	0.17 ± 0.014			
Vss (mL/kg)		164	149	
MRT (hour)		11.8	10.8	
AUCinf_pred (ug*h/mL)	2049 ± 94			
AUCinf_pred (ug/mL*h)		852	2613	
F (percent)	86 ± 4	0.63	0.48	

LEGEND

MODELING SOFTWARE

Nonlin84, (Metzler et al.1974)

MODELING METHOD & BEST FIT MODEL

[a] Nonlin84, (Metzler et al. 1974), two-compartment model
[b] No details given, one-compartment open model
[c] Nonlin84, (Metzler et al. 1974), one-compartment model with first-order absorption and elimination kinetics
[d] Not modeled, not modeled, only one 2-hour time point
[e] Nonlin84 (Metzler et al. 1974), two compartment model
[f] Plasma concentrations of PCP in the dosed feed study were analyzed using a computer model based on linear theory. Yuan JH 1993 dosed feed model in Applied Pharmacology
[g] No modeling shown in reports, no modeling shown in reports

ANALYTE

Pentachlorophenol, purified

TK PARAMETERS

Beta = Hybrid rate constant of the beta phase
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
Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups

TK Parameters (cont'd)

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
Vss = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
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

Plasma samples were extracted, derivatized, and then analyzed by gas chromatography with electron capture detection (63Ni pulsed) using 2,4,6-tribromophenol as the internal standard.

TK_INTRAVENOUS PLASMA

5 mg/kg Male and Female

Rats were given a single administration of pentachlorophenol (PCP) by intravenous injection into the caudal vein. Blood samples were taken from 3 animals/time point at 12 time points (5 minutes to 20 hours) after administration. One laboratory performed the animal study and a second company laboratory analyzed the plasma samples by a validated GC-EC method. Toxicokinetic parameter means plus or minus S.D. were estimated using Nonlin84 program. Toxicokinetic parameters were taken from Yuan JH, Goehl TJ, Murrill E, Moore R, Clark J, Hong HL., and Irwin RD. 1994. Toxicokinetics of pentachlorophenol in F344 rat. Gavage and dosed feed studies. Xenobiotica, 24(6), 553-560.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

18.75 mg/kg, 75 mg/kg,150 mg/kg Male and Female

Rats were given a single administration of 18.75, 75, or 150 mg/kg pentachlorophenol (PCP) by gavage. Blood samples were taken from 3 animals/time point at 12 time points (one time point for 150 mg/kg) after administration. One laboratory performed the animal study and a second company laboratory analyzed the plasma samples by the validated GC-EC method. Toxicokinetic parameters were taken from the analysis report.

ANALYSIS METHOD

Plasma samples were extracted and then analyzed by reverse phase high performance liquid chromatography (HPLC) with UV detection (229 nm) using octanophenone as the internal standard.

TK_GAVAGE PLASMA

9.5 mg/kg, 38 mg/kg Male and Female

Male rats were given a single administration of pentachlorophenol (PCP) of 9.5 and 38 mg/kg by gavage. Blood samples were taken from 3 animals/time point at 12 time points (30 minutes to 40 hours for 9.5 mg/kg and 30 minutes to 60 hours for 38 mg/kg dose) after administration. One laboratory performed the animal study and a second company laboratory analyzed the plasma samples by the validated HPLC method. Toxicokinetic parameter means plus or minus S.D. were estimated using Nonlin84 program. Toxicokinetic parameters were taken from Yuan JH, Goehl TJ, Murrill E, Moore R, Clark J, Hong HL., and Irwin RD. 1994. Toxicokinetics of pentachlorophenol in F344 rat. Gavage and dosed feed studies. Xenobiotica, 24(6), 553-560.

TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

312 ppm, 1250 ppm, 2500 ppm Male

Plasma concentrations of PCP in the dosed feed study were analysed using a computer model based on linear theory (Yuan JH. 1993. Modeling blood/plasma concentrations in dosed feed and dosed drinking water toxicology studies. Toxicology and Applied Pharmacology. 199, 131-141.) The model treats a dosed feed study as a series of consecutive gavage studies with variable doses repeated at a time interval of 0.5 hour. The selection of 0.5 hour as the time interval was based on the absorption rate constant of PCP. The theoretical gavage dose at each time interval was determined from the daily total PCP intake as well as the percentage of the daily feeding activity occurring during each time interval. The feeding activity curve was based on published data (Duffy et al. 1989). Duffy PH., Feuers RJ, Leakey J A, ,Nakamura KD, Turturro A, and Hart RW. 1989. Effect of chronic caloric restriction on physiological variables related to energy metabolism in the male Fischer 344 rat. Mechanisms of Aging and Development, 48, 117-133. Finally, plasma concentrations of PCP were summed from each theoretical small gavage dose at each 0.5-hour time interval as calculated based on the toxicokinetic parameters derived from the previous gavage studies. Assumptions are that the presence of PCP in feed does not alter the feeding pattern of rats and that the toxicokinetics of PCP in rats does not change with time. Groups of male rats were fed dosed feed (NIH-07 diet) for 1 week (ad libitum) after a 1-week acclimatization to undosed powered feed. Blood was collected from each rat once to eliminate the possibility of interrupting the normal feeding pattern. 1-2 rats were sampled at each of 5-8 timepoints/day over 5 days. Actual doses for the feed study were 302 and 1010 ppm for the 312 and 1250 nominal doses, respectively. Food consumption was 16 plus or minus 3 g per rat for the 302 ppm group and 12 plus or minus 3 g per rat for the 1010 ppm group. One laboratory made up the dose formulations and analyzed the plasma samples. A second laboratory performed the study. Toxicokinetic modeling information was taken from Yuan JH, Goehl TJ, Murrill E, Moore R, Clark J, Hong HL, and Irwin RD. 1994. Toxicokinetics of pentachlorophenol in F344 rat. Gavage and dosed feed studies. Xenobiotica, 24(6), 553-560.