Experiment Number: K10075 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: IV, Gavage | **Compound:** Perfluorooctanoic Acid/ **Analyte:** Perfluorooctanoic Acid | **Request Time:** 10:03

Species/Strain: Rats/Harlan Sprague Dawley | **CAS Number:** 335-67-1 | **Lab:** Battelle Columbus

Male

	Treatment Group (mg/kg)			
	6 IV Plasma[c,i]	**6 Gavage Plasma[g,i]**	**12 Gavage Plasma[g,i]**	**48 Gavage Plasma[g,i]**
Cmax_pred (ng/mL)	52400 ± 2500	37200 ± 2800	76400 ± 5400	232000 ± 20000
Tmax_pred (hour)		4.86 ± 0.81	6.37 ± 0.90	8.33 ± 1.28
Cmax_obs (ng/mL)		45800	83200	279000
Tmax_obs (hour)		6.00	12.0	6.00
Alpha Half-life (min)	67.3 ± 33.9			
Beta Half-life (min)	246 ± 28			
k01 ($hour^{-1}$)		1.31 ± 0.26	0.919 ± 0.160	0.639 ± 0.123
k01 Half-life (min)		0.531 ± 0.107	0.754 ± 0.131	1.09 ± 0.21
K10 ($hour^{-1}$)	0.00453 ± 0.00036	0.00231 ± 0.00014	0.00269 ± 0.00013	0.00322 ± 0.00015
k10 Half-life (hour)	153 ± 12	300 ± 17	258 ± 12	215 ± 10
k12 ($hour^{-1}$)	0.00219 ± 0.00179			
k21 ($hour^{-1}$)	0.00639 ± 0.00356			
Cl1(mL/hr/kg)	0.518 ± 0.033			
Cl1_F (mL/hr/kg)		0.369 ± 0.022	0.415 ± 0.023	0.649 ± 0.044
V1 (mL/kg)	114 ± 5			
V2 (mL/kg)	39.2 ± 14.5			
V1_F (mL/kg)		159 ± 12	154 ± 11	202 ± 18
MRT (hour)	296 ± 12			
AUC_0-T (ng/mL*hr)	12400000	13600000	27400000	62000000
AUCinf_pred (ng/mL*hr)	11600000 ± 700000	16300000 ± 1000000	28900000 ± 1600000	73900000 ± 5000000

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Species/Strain: Rats/Harlan Sprague Dawley | **CAS Number:** 335-67-1 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)				
	40 IV Plasma[c,i]	**40 Gavage Plasma[d,i]**	**80 Gavage Plasma[e,j]**	**80 Gavage Plasma[f,k]**	**320 Gavage Plasma[d,i]**
Cmax_pred (ng/mL)	370000 ± 81000	240000 ± 25000	398000 ± 49000	426000 ± 69000	855000 ± 252000
Tmax_pred (hour)		3.22 ± 0.32	2.33 ± 0.38	2.58 ± 0.50	3.01 ± 2.54
Cmax_obs (ng/mL)		123000	244000	244000	469000
Tmax_obs (hour)		3.00	9.00	9.00	1.00
Alpha Half-life (hour)	0.683 ± 0.478	2.73 ± 0.62	3.72 ± 0.41	3.38 ± 0.51	1.35 ± 26.17
Beta Half-life (hour)	5.17 ± 0.32	29.4 ± 9.0	43.7 ± 27.2	1010 ± 5150	17.9 ± 2.7
k01 ($hour^{-1}$)		0.375 ± 0.138	0.826 ± 0.251	0.658 ± 0.258	0.838 ± 6.36
k01 Half-life (min)		1.85 ± 0.68	0.839 ± 0.255	1.05 ± 0.41	0.827 ± 6.272
K10 ($hour^{-1}$)	0.310 ± 0.075	0.252 ± 0.057	0.184 ± 0.020	0.149 ± 0.198	0.0499 ±0.3619
k10 Half-life (hour)	2.23 ± 0.54	2.75 ± 0.62	3.77 ± 0.41	4.65 ± 6.16	13.9 ± 100.9
k12 ($hour^{-1}$)	0.400 ± 0.420	0.00179 ± 0.00067	0.00246 ± 0.00071	0.0556 ± 0.1911	0.103 ± 4.696
k21 ($hour^{-1}$)	0.438 ± 0.255	0.0238 ± 0.0073	0.0161 ± 0.0100	0.000945 ± 0.003619	0.400 ± 4.980
Cl1 (mL/hr/kg)	33.6 ± 3.6				
Cl1_F (mL/hr/kg)		18.5 ± 1.8	24.0 ± 2.6	16.5 ± 21.4	13.6 ± 1.9
V1 (mL/kg)	108 ± 24				
V2 (mL/kg)	98.7 ± 39.8				
V1_F (mL/kg)		73.6 ± 20.6	130 ± 24	111 ± 28	272 ± 1990
V2_F (mL/kg)		5.55 ± 1.62	19.9 ± 12.9	6520 ± 47500	69.9 ± 1849.1
MRT (hour)	6.16 ± 0.51				
AUC_0-T (ng/mL*hr)	1250000	1750000	2740000	2830000	20100000
AUCinf_pred (ng/mL*hr)	1190000 ± 130000	2160000 ± 210000	3340000 ± 360000	4840000 ± 6240000	23600000 ± 3300000

Male

Treatment Group (mg/kg)

12 Gavage Brain[b]

Cmax_obs (ng/g)	1290
Tmax_obs (hour)	12.0
Half-life (hour)	153

Female

Treatment Group (mg/kg)

80 Gavage Brain[a,h]

Cmax_obs (ng/g)	3520
Tmax_obs (hour)	6.00

Male

Treatment Group (mg/kg)

12 Gavage Kidney[b]

Cmax_obs (ng/g)	35400
Tmax_obs (hour)	6.00
Half-life (hour)	224

Female

	Treatment Group (mg/kg)
	80 Gavage Kidney[b]
Cmax_obs (ng/g)	205000
Tmax_obs (hour)	6.00
Half-life (hour)	5.26

Male

Treatment Group (mg/kg)

12 Gavage Liver[b]

Cmax_obs (ng/g)	62700
Tmax_obs (hour)	24.0
Half-life (hour)	313

Female

Treatment Group (mg/kg)

12 Gavage Liver[b]

Cmax_obs (ng/mL)	162000
Tmax_obs (hour)	6.00
Half-life (hour)	5.25

LEGEND

MODELING SOFTWARE

WinNonlin, Version 5.0.1

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartmental model with first order input, first order output, and uniform weighting. Elimination half-life is ND because unable to determine lambda z. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

[b] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartmental model with first order input, first order output, and uniform weighting. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

[c] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two-compartment model with bolus input, first order output and 1/Yhat2 weighting. Yhat2 is a weighting scheme designation for Y predicted. Parameter estimates are reported to three significant figures.

[d] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two-compartment model with first order input, first order output and 1/Yhat2 weighting. Yhat2 is a weighting scheme designation for Y predicted. Parameter estimates are reported to three significant figures.

[e] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two-compartment model with first order input, first order output and 1/Yhat2 weighting. Parameters estimated without 192-hour time point. Yhat2 is a weighting scheme designation for Y predicted. Parameter estimates are reported to three significant figures.

[f] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two-compartment model with first order input, first order output and 1/Yhat2 weighting. Parameters estimated using all time points. Yhat2 is a weighting scheme designation for Y predicted. Parameter estimates are reported to three significant figures.

[g] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, One-compartment model with first order input, first order output and 1/Yhat2 weighting. Yhat2 is a weighting scheme designation for Y predicted. Parameter estimates are reported to three significant figures.

EXCEPTIONS

[h]Not detected, ND. Elimination half-life is ND because unable to determine lambda z.
[i]AUC_0-T observed value
[j]Toxicokinetic parameters estimated without 192 hour time point. AUC_0-T observed value.
[k]Toxicokinetic parameters estimated for all time points. AUC_0-T observed value.

ANALYTE

Perfluorooctanoic Acid

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax predicted or observed occurs
Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Half-life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
Alpha Half-life = Half-life for the alpha phase
Beta Half-life = Half-life for 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 of the absorption process to the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl1 = 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
MRT = Mean residence time
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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

V2 = Volume of distribution for the peripheral compartment

V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F

V2_F = Apparent volume of distribution for the peripheral compartment

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Plasma and tissue PFOA concentrations were measured using liquid chromatography with mass spectroscopy (LC-MS/MS). The target limit of quantitation, LOQ, for plasma from IV and gavage animals was 25 ng/mL.

TK_INTRAVENOUS PLASMA

6 mg/kg Male

The implantation of jugular catheters in the IV rats occurred prior to shipment of the animals. Blood samples were collected at eleven to thirteen time points post-administration using the retro-orbital method. Animals were anesthetized with CO2/O2 prior to bleeding. Three animals/sex were bled at each time point.

40 mg/kg Female

15 animals were received on 1/8/09 and exposed on 1/12/09. Two animals were received on 2/4/09 and exposed on 2/5/09. The implantation of jugular catheters in the IV rats occurred prior to shipment of the animals. Blood samples were collected at eleven to thirteen time points post-administration using the retro-orbital method. Animals were anesthetized with CO2/O2 prior to bleeding. Three animals/sex were bled at each time point.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

6 mg/kg, 12 mg/kg, 48 mg/kg Male, 40 mg/kg, 80 mg/kg, 320 mg/kg Female

Blood samples were collected at eleven to thirteen time points post-administration using the retro-orbital method. Animals were anesthetized with CO2/O2 prior to bleeding. Three animals/sex were bled at each time point.

ANALYSIS METHOD

Plasma and tissue PFOA concentrations were measured using liquid chromatography with mass spectroscopy (LC-MS/MS). Target limit of quantitation for gavage animal tissue samples was 5 ng in tissue.

TK_GAVAGE BRAIN

80 mg/kg Female

Following blood collection at (3, 6, 12 hours and 1, 2, 4, and 8 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.

12 mg/kg Male

Following blood collection (at 3, 6, and 12 hours and 1, 8, 22, and 50 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE KIDNEY

80 mg/kg Female

Following blood collection at (3, 6, 12 hours and 1, 2, 4, and 8 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.

12 mg/kg Male

Following blood collection (at 3, 6, and 12 hours and 1, 8, 22, and 50 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.

TK_GAVAGE LIVER

80 mg/kg Female

Following blood collection at (3, 6, 12 hours and 1, 2, 4, and 8 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.

12 mg/kg Male

Following blood collection (at 3, 6, and 12 hours and 1, 8, 22, and 50 days) each animal was terminated with CO2, and the liver, kidneys, and brain were collected. Samples were digested, extracted, evaporated to dryness and reconstituted in mobile phase.