

Experiment Number: S0571

Route: Intravenous

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Naphthalene/ Analyte: Naphthalene

CAS Number: 91-20-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Male

Treatment Group (mg/kg)

1 IV Whole Blood^a

1 IV Whole Blood^{b,P}

1 IV Whole Blood^{b,Q}

1 IV Whole Blood^{b,i}

Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0337 ± 0.02	0.0736	0.0249	0.0025
Beta Half-life (minute)	106 ± 88	9.42	27.9	282
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	56.1 ± 11	43.5	77.9	46.9
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	3.24 ± 2.4	0.266	1.37	8.07
MRT (minute)	65.2 ± 53	6.12	17.5	172
AUCinf_pred (ug*min/mL)	20.8 ± 3.4	25.3	14.1	23.0

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1 IV Whole Blood^{d,t} 1 IV Whole Blood^d 1 IV Whole Blood^d 1 IV Whole Blood^d

Alpha (minute ⁻¹)	0.367 ± 0.16	0.695 ± 0.21	0.209 ± 0.044	0.197 ± 0.020
Beta (minute ⁻¹)	0.0279 ± 0.016	0.0596 ± 0.025	0.0186 ± 0.023	0.00550 ± 0.0017
Beta Half-life (minute)	58.3 ± 35	11.6 ± 4.9	37.2 ± 46	126 ± 39
k10 (minute ⁻¹)	0.240 ± 0.13	0.490 ± 0.14	0.138 ± 0.037	0.0932 ± 0.013
k12 (minute ⁻¹)	0.113 ± 0.035	0.180 ± 0.077	0.0616 ± 0.025	0.0977 ± 0.017
k21 (minute ⁻¹)	0.0415 ± 0.022	0.0846 ± 0.037	0.0282 ± 0.033	0.0116 ± 0.0031
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	59.6 ± 11	45.6 ± 7.0	81.5 ± 17	51.6 ± 6.2
V1 (L/kg)	0.413 ± 0.16	0.0930 ± 0.038	0.591 ± 0.079	0.554 ± 0.047
Vss (L/kg)	2.46 ± 1.4	0.291 ± 0.12	1.88 ± 1.8	5.21 ± 1.4
MRT (minute)	43.5 ± 29	6.39 ± 2.5	23.1 ± 27	101 ± 36
AUCinf_pred (ug*min/mL)	19.5 ± 3.1	24.1 ± 3.7	13.5 ± 2.8	20.9 ± 2.5

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Treatment Group (mg/kg)

3 IV Whole Blood^{a,r}

3 IV Whole Blood^{b,l}

3 IV Whole Blood^f

3 IV Whole Blood^{b,k}

	3 IV Whole Blood ^{a,r}	3 IV Whole Blood ^{b,l}	3 IV Whole Blood ^f	3 IV Whole Blood ^{b,k}
Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0082	0.0060		0.0104
Beta Half-life (minute)	90.9	115		66.8
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	40.3	47.4		33.1
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	5.08	9.26		0.901
MRT (minute)	111	195		27.3
AUCinf_pred (ug*min/mL)	78.0	63.3		92.6

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Male

Treatment Group (mg/kg)

3 IV Whole Blood^{d,s}

3 IV Whole Blood^d

3 IV Whole Blood^f

3 IV Whole Blood^d

Alpha (minute ⁻¹)	0.616	1.09 ± 12		0.141 ± 0.0060
Beta (minute ⁻¹)	0.00815	0.00309 ± 0.00094		0.0132 ± 0.0025
Beta Half-life (minute)	138	224 ± 68		52.6 ± 10
k10 (minute ⁻¹)	0.0569	0.00886 ± 0.14		0.105 ± 0.0042
k12 (minute ⁻¹)	0.367	0.703 ± 14		0.0316 ± 0.0038
k21 (minute ⁻¹)	0.198	0.379 ± 1.8		0.0177 ± 0.0033
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	39.2	43.2 ± 11		35.1 ± 1.1
V1 (L/kg)	2.61	4.88 ± 79		0.334 ± 0.0098
Vss (L/kg)	7.42	13.9 ± 3.4		0.931 ± 0.13
MRT (minute)	174	322 ± 107		26.5 ± 4.4
AUCinf_pred (ug*min/mL)	78.3	69.4 ± 17		87.1 ± 2.7

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10 IV Whole Blood^a

10 IV Whole Blood^{b,q}

10 IV Whole Blood^{b,p}

10 IV Whole Blood^{b,q}

Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0032 ± 0.00012	0.0030	0.0034	0.0032
Beta Half-life (minute)	219 ± 7.9	234	207	216
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	38.4 ± 2.6	33.2	40.0	41.9
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	2.99 ± 0.13	2.75	3.02	3.20
MRT (minute)	78.4 ± 2.3	82.9	75.7	76.5
AUCinf_pred (ug*min/mL)	249 ± 19	285	237	224

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Male

Treatment Group (mg/kg)

	10 IV Whole Blood ^{d,v}	10 IV Whole Blood ^d	10 IV Whole Blood ^d	10 IV Whole Blood ^d
Alpha (minute ⁻¹)	0.0911 ± 0.0072	0.100 ± 0.0077	0.0966 ± 0.017	0.0768 ± 0.0061
Beta (minute ⁻¹)	0.00597 ± 0.00019	0.00579 ± 0.0013	0.00636 ± 0.0026	0.00577 ± 0.0016
Beta Half-life (minute)	116 ± 3.7	120 ± 26	109 ± 45	120 ± 34
k10 (minute ⁻¹)	0.0605 ± 0.0036	0.0667 ± 0.0050	0.0606 ± 0.0098	0.0542 ± 0.0039
k12 (minute ⁻¹)	0.0276 ± 0.0037	0.0303 ± 0.0051	0.0322 ± 0.011	0.0202 ± 0.0040
k21 (minute ⁻¹)	0.00898 ± 0.00058	0.00867 ± 0.0019	0.0101 ± 0.0043	0.00818 ± 0.0023
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	42.4 ± 3.2	36.0 ± 1.9	45.4 ± 5.2	45.7 ± 2.5
V1 (L/kg)	0.710 ± 0.090	0.539 ± 0.036	0.750 ± 0.11	0.842 ± 0.049
Vss (L/kg)	2.83 ± 0.21	2.43 ± 0.46	3.13 ± 1.1	2.92 ± 0.66
MRT (minute)	66.8 ± 1.4	67.4 ± 15	68.9 ± 29	64.0 ± 17
AUCinf_pred (ug*min/mL)	225 ± 18	262 ± 14	209 ± 24	205 ± 11

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Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Female

Treatment Group (mg/kg)

1 IV Whole Blood^{a,g}

1 IV Whole Blood^{b,h}

1 IV Whole Blood^g

1 IV Whole Blood^{b,i}

	1 IV Whole Blood ^{a,g}	1 IV Whole Blood ^{b,h}	1 IV Whole Blood ^g	1 IV Whole Blood ^{b,i}
Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0036	0.0016		0.0056
Beta Half-life (minute)	284	444		124
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	56.5	49.0		63.9
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	8.77	13.6		3.93
MRT (minute)	170	278		61.5
AUCinf_pred (ug*min/mL)	20.0	22.5		17.5

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Lab: RTI

Female

Treatment Group (mg/kg)

1 IV Whole Blood^{d,j} 1 IV Whole Blood^d 1 IV Whole Blood^e 1 IV Whole Blood^d

Alpha (minute ⁻¹)	0.239	0.149 ± 0.014		0.328 ± 0.041
Beta (minute ⁻¹)	0.00539	0.00475 ± 0.0032		0.00602 ± 0.0061
Beta Half-life (minute)	131	146 ± 99		115 ± 116
k10 (minute ⁻¹)	0.148	0.0954 ± 0.018		0.201 ± 0.066
k12 (minute ⁻¹)	0.0869	0.0508 ± 0.018		0.123 ± 0.061
k21 (minute ⁻¹)	0.00861	0.00741 ± 0.0041		0.00981 ± 0.0076
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	35.3	61.4 ± 11		70.5 ± 21
V1 (L/kg)	0.497	0.644 ± 0.048		0.350 ± 0.050
Vss (L/kg)	4.90	5.06 ± 3.6		4.73 ± 5.2
MRT (minute)	74.7	82.3 ± 71		67.1 ± 92
AUCinf_pred (ug*min/mL)	16.9	17.9 ± 3.2		15.9 ± 4.8

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Lab: RTI

Female

Treatment Group (mg/kg)

3 IV Whole Blood^a

3 IV Whole Blood^{b,k}

3 IV Whole Blood^{f,l}

3 IV Whole Blood^{b,m}

Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0061 ± 0.0024	0.0111	0.0038	0.0036
Beta Half-life (minute)	146 ± 42	62.4	182	194
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	51.7 ± 11	71.0	52.5	31.5
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	4.10 ± 1.8	2.27	7.66	2.36
MRT (minute)	84.3 ± 33	32.0	146	74.9
AUCinf_pred (ug*min/mL)	67.0 ± 17	43.5	58.3	99.2

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Lab: RTI

Female

Treatment Group (mg/kg)

3 IV Whole Blood^{d,t}

3 IV Whole Blood^d

3 IV Whole Blood^d

3 IV Whole Blood^d

	3 IV Whole Blood ^{d,t}	3 IV Whole Blood ^d	3 IV Whole Blood ^d	3 IV Whole Blood ^d
Alpha (minute ⁻¹)	0.121 ± 0.0051	0.111 ± 0.025	0.124 ± 0.012	0.128 ± 0.031
Beta (minute ⁻¹)	0.00732 ± 0.0018	0.0106 ± 0.011	0.00458 ± 0.0016	0.00677 ± 0.0078
Beta Half-life (minute)	106 ± 25	65.6 ± 65	151 ± 52	102 ± 118
k10 (minute ⁻¹)	0.0768 ± 0.0068	0.0799 ± 0.017	0.0637 ± 0.0085	0.0868 ± 0.026
k12 (minute ⁻¹)	0.0406 ± 0.0086	0.0271 ± 0.017	0.0564 ± 0.010	0.0382 ± 0.026
k21 (minute ⁻¹)	0.0112 ± 0.0018	0.0147 ± 0.014	0.00895 ± 0.0027	0.0100 ± 0.011
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	55.6 ± 13	77.3 ± 13	55.7 ± 6.5	33.9 ± 8.6
V1 (L/kg)	0.745 ± 0.18	0.968 ± 0.13	0.875 ± 0.061	0.391 ± 0.069
Vss (L/kg)	3.67 ± 1.4	2.76 ± 2.1	6.38 ± 1.9	1.88 ± 2.0
MRT (minute)	68.7 ± 24	35.6 ± 31	115 ± 45	55.5 ± 70
AUCinf_pred (ug*min/mL)	62.3 ± 15	40.0 ± 6.8	54.9 ± 6.4	92.0 ± 23

Experiment Number: S0571

Route: Intravenous

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Naphthalene/ Analyte: Naphthalene

CAS Number: 91-20-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Female

Treatment Group (mg/kg)

10 IV Whole Blood^a

10 IV Whole Blood^{b,n}

10 IV Whole Blood^{b,o}

10 IV Whole Blood^{b,o}

	10 IV Whole Blood ^a	10 IV Whole Blood ^{b,n}	10 IV Whole Blood ^{b,o}	10 IV Whole Blood ^{b,o}
Alpha (minute ⁻¹)				
Beta (minute ⁻¹)	0.0023 ± 0.00019	0.0024	0.0025	0.0019
Beta Half-life (minute)	310 ± 24	294	280	357
k10 (minute ⁻¹)				
k12 (minute ⁻¹)				
k21 (minute ⁻¹)				
Cl (mL/min/kg)	35.0 ± 0.58	35.9	35.1	33.9
Cl1 (mL/min/kg)				
V1 (L/kg)				
Vss (L/kg)	4.09 ± 0.093	3.92	4.12	4.24
MRT (minute)	117 ± 4.6	109	117	125
AUCinf_pred (ug*min/mL)	276 ± 5.2	269	272	286

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CAS Number: 91-20-3

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Request Time: 10:03:16

Lab: RTI

Female

Treatment Group (mg/kg)

10 IV Whole Blood^{d,t} 10 IV Whole Blood^d 10 IV Whole Blood^d 10 IV Whole Blood^d

Alpha (minute ⁻¹)	0.101 ± 0.016	0.0818 ± 0.033	0.0892 ± 0.014	0.132 ± 0.012
Beta (minute ⁻¹)	0.00453 ± 0.00054	0.00510 ± 0.0048	0.00345 ± 0.0027	0.00503 ± 0.0014
Beta Half-life (minute)	158 ± 21	136 ± 127	201 ± 159	138 ± 40
k10 (minute ⁻¹)	0.0667 ± 0.012	0.0482 ± 0.017	0.0630 ± 0.012	0.0889 ± 0.0090
k12 (minute ⁻¹)	0.0320 ± 0.0048	0.0301 ± 0.023	0.0249 ± 0.011	0.0411 ± 0.0079
k21 (minute ⁻¹)	0.00701 ± 0.0011	0.00865 ± 0.0085	0.00489 ± 0.0037	0.00749 ± 0.0020
Cl (mL/min/kg)				
Cl1 (mL/min/kg)	39.5 ± 4.1	47.6 ± 13	35.6 ± 5.5	35.2 ± 2.6
V1 (L/kg)	0.650 ± 0.18	0.989 ± 0.29	0.565 ± 0.081	0.396 ± 0.037
Vss (L/kg)	3.48 ± 0.54	4.43 ± 3.4	3.44 ± 2.6	2.57 ± 0.74
MRT (minute)	87.5 ± 7.3	92.9 ± 86	96.6 ± 85	73.0 ± 24
AUCinf_pred (ug*min/mL)	249 ± 23	203 ± 54	268 ± 41	276 ± 20

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LEGEND

MODELING SOFTWARE

Model 201, WinNonlin, Version 1.0

Model 8, WinNonlin Version 1.0

MODELING METHOD & BEST FIT MODEL

^aData were analyzed using a noncompartmental model for iv dosing (Model 201, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC), Not best fit. Noncompartmental analysis of rats means and standard errors for pharmacokinetic parameters within a dose group.

^bData were analyzed using a noncompartmental model for iv dosing (Model 201, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC), Not best fit. Noncompartmental analysis of concentration vs time curve of individual rat over 10 time points.

^cData were analyzed using a noncompartmental model for iv dosing (Model 201, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC), Data from rat F2 was not successfully fit using the noncompartmental model.

^dData were analyzed using a 2-compartment model (Model 8, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC). Blood concentration data were weighted as 1/YHAT, where YHAT is the predicted value of blood concentration at a given time, Best fit two compartment model (WinNonlin, Model 8) with 1/YHAT weighting

^eData were analyzed using a 2-compartment model (Model 8, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC). Blood concentration data were weighted as 1/YHAT, where YHAT is the predicted value of blood concentration at a given time, Data from rat F2 was not successfully fit.

^fData were analyzed using a noncompartmental model for iv dosing (Model 201, WinNonlin, Version 1.0 (SCI Software, Morrisville, NC), Data from animal D2 were deemed unreliable and were not considered in pharmacokinetic analyses.

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EXCEPTIONS

^gN is equal to 2. Data from rat F2 was not successfully fit using the noncompartmental model.

^hTerminal elimination Beta range is 60-360 minutes.

ⁱTerminal elimination Beta range is 120-480 minutes.

^jN is equal to 2. Data from rat F2 was not successfully fit using the noncompartmental model. V1 represents V. Vss represents volume of distribution at steady state.

^kTerminal elimination Beta range is 60-240 minutes.

^lTerminal elimination Beta range is 40-480 minutes.

^mTerminal elimination Beta range is 120-360 minutes.

ⁿTerminal elimination Beta range is 360-720 minutes.

^oTerminal elimination Beta range is 240-720 minutes.

^pTerminal elimination Beta range is 2-60 minutes.

^qTerminal elimination Beta range is 20-60 minutes.

^rN is equal to 2. Data from rat D2 were deemed unreliable and were not considered in pharmacokinetic analyses.

^sN is equal to 2. Data from rat D2 were deemed unreliable and were not considered in pharmacokinetic analyses. V1 represents V. Vss represents volume of distribution at steady state.

^tV1 represents V. Vss represents volume of distribution at steady state.

ANALYTE

Naphthalene

Experiment Number: S0571

Route: Intravenous

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Naphthalene/ **Analyte:** Naphthalene

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TK PARAMETERS

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

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, includes total clearance

Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups

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 = Volume of distribution at steady state

MRT = Mean residence time

AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

TK_INTRAVENTOUS WHOLE BLOOD

ANALYSIS METHOD

WinNonlin was also used to calculate the blood concentration of NAP at time zero (Co), by back extrapolation using the first two observed data points, and to determine the upper and lower limits on time to be included in the estimation of Beta. Means plus and minus standard errors (SE) for rats within a dose group were calculated from individual animal parameter estimates, n is equal to 3 unless otherwise noted. Whole blood samples were analyzed using an high performance liquid chromatography (HPLC) system with UV detection at 250 nm. Anthracene was used as the internal standard.

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TK PARAMETERS PROTOCOL (cont'd)

1 mg/kg, 3 mg/kg, 10 mg/kg Male and Female

Bodyweight ranges are for all male rats or all female rats in the studies. In the rat studies, individual animals had surgically implanted jugular cannulae such that multiple blood samples could be taken from a single animal. The time course for each animal was analyzed separately and the means plus and minus standard errors for each group shown were calculated from individual animal parameters.

ANALYSIS METHOD

Means plus and minus standard errors (SE) for rats within a dose group were calculated from individual animal parameter estimates, n is equal to 3 unless otherwise noted. Whole blood samples were analyzed using an high performance liquid chromatography (HPLC) system with UV detection at 250 nm. Anthracene was used as the internal standard.

1 mg/kg, 3 mg/kg, 10 mg/kg Male and Female

Bodyweight ranges are for all male rats or all female rats in the studies. In the rat studies, individual animals had surgically implanted jugular cannulae such that multiple blood samples could be taken from a single animal. The time course for each animal was analyzed separately and the means plus and minus standard errors for each group shown were calculated from individual animal parameters.

ANALYSIS METHOD

Whole blood samples were analyzed using an HPLC system with UV detection at 250 nm. Anthracene was used as the internal standard.

1 mg/kg, 3 mg/kg, 10 mg/kg Male and Female

Bodyweight ranges are for all male rats or all female rats in the studies. In the rat studies, individual animals had surgically implanted jugular cannulae such that multiple blood samples could be taken from a single animal. The time course for each animal was analyzed separately and the means plus and minus standard errors for each group shown were calculated from individual animal parameters.