

Experiment Number: S0571
Route: Intravenous
Species/Strain: Mouse/B6C3F1

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)

3 IV Whole Blood^{a,f}

3 IV Whole Blood^b

10 IV Whole Blood^{a,g}

Alpha (minute ⁻¹)		0.590 ± 0.14	
Beta (minute ⁻¹)	0.0647	0.104 ± 0.021	0.0590
Beta Half-life (minute)	10.7	6.65 ± 1.3	11.8
k10 (minute ⁻¹)		0.407 ± 0.072	
k12 (minute ⁻¹)		0.136 ± 0.054	
k21 (minute ⁻¹)		0.151 ± 0.040	
Cl (mL/min/kg)	104		98.9
Cl1 (mL/min/kg)		109 ± 8.3	
V1 (L/kg)		0.268 ± 0.063	
Vss (L/kg)	0.481	0.509 ± 0.085	0.591
MRT (minute)	4.63	4.67 ± 0.59	5.98
AUCinf_pred (ug*min/mL)	39.9	38.0 ± 2.9	97.4

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Treatment Group (mg/kg)

10 IV Whole Blood^b

30 IV Whole Blood^{a,h}

30 IV Whole Blood^b

Alpha (minute ⁻¹)	0.360 ± 0.067		0.199 ± 0.019
Beta (minute ⁻¹)	0.0578 ± 0.0089	0.0190	0.0292 ± 0.0086
Beta Half-life (minute)	12.0 ± 1.9	36.5	23.8 ± 7.0
k10 (minute ⁻¹)	0.282 ± 0.050		0.172 ± 0.013
k12 (minute ⁻¹)	0.0617 ± 0.016		0.0226 ± 0.0067
k21 (minute ⁻¹)	0.0737 ± 0.013		0.0338 ± 0.011
Cl (mL/min/kg)		64.0	
Cl1 (mL/min/kg)	100 ± 13		74.8 ± 4.0
V1 (L/kg)	0.354 ± 0.11		0.436 ± 0.050
Vss (L/kg)	0.650 ± 0.162	0.532	0.727 ± 0.11
MRT (minute)	6.50 ± 0.88	8.31	9.72 ± 1.4
AUCinf_pred (ug*min/mL)	96.3 ± 12	435	372 ± 20

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Treatment Group (mg/kg)

3 IV Whole Blood^{a,c}

3 IV Whole Blood^b

10 IV Whole Blood^{a,d}

Alpha (minute ⁻¹)		0.371 ± 0.022	
Beta (minute ⁻¹)	0.082	0.0659 ± 0.014	0.0511
Beta Half-life (minute)	8.46	10.5 ± 2.2	13.6
k10 (minute ⁻¹)		0.324 ± 0.014	
k12 (minute ⁻¹)		0.0377 ± 0.0072	
k21 (minute ⁻¹)		0.0755 ± 0.017	
Cl (mL/min/kg)	129		121
Cl1 (mL/min/kg)		137 ± 3.3	
V1 (L/kg)		0.423 ± 0.023	
Vss (L/kg)	0.531	0.633 ± 0.051	0.808
MRT (minute)	4.13	4.63 ± 0.37	6.68
AUCinf_pred (ug*min/mL)	32.4	30.4 ± 0.73	78.2

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Treatment Group (mg/kg)

10 IV Whole Blood^b

30 IV Whole Blood^{a,e}

30 IV Whole Blood^b

Alpha (minute ⁻¹)	0.367 ± 0.38		0.321 ± 0.058
Beta (minute ⁻¹)	0.0521 ± 0.0046	0.0421	0.0505 ± 0.0086
Beta Half-life (minute)	13.3 ± 1.2	16.4	13.7 ± 2.3
k10 (minute ⁻¹)	0.287 ± 0.030		0.244 ± 0.040
k12 (minute ⁻¹)	0.0656 ± 0.0089		0.0614 ± 0.017
k21 (minute ⁻¹)	0.0666 ± 0.0065		0.0666 ± 0.013
Cl (mL/min/kg)		81.5	
Cl1 (mL/min/kg)	118 ± 9.0		87.8 ± 9.3
V1 (L/kg)	0.413 ± 0.073		0.360 ± 0.095
Vss (L/kg)	0.819 ± 0.12	0.576	0.692 ± 0.15
MRT (minute)	6.92 ± 0.58	7.07	7.88 ± 1.1
AUCinf_pred (ug*min/mL)	79.9 ± 6.1	344	319 ± 34

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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 3 mice/dose/sex over 10 time points.

^bData 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. Mouse parameter estimates had low standard errors, which indicated that these were relatively stable estimates .

EXCEPTIONS

^cTerminal elimination Beta range is 15-50 minutes.

^dTerminal elimination Beta range is 15-90 minutes.

^eTerminal elimination Beta range is 10-150 minutes.

^fTerminal elimination Beta range is 20-60 minutes.

^gTerminal elimination Beta range is 10-90 minutes.

^hTerminal elimination Beta range is 90-150 minutes.

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

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

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TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENTOUS WHOLE BLOOD

3 mg/kg, 10 mg/kg, 30 mg/kg Male and Female

Bodyweight ranges are for all male mice or all female mice in the studies. In the mouse studies, three mice were sacrificed at each timepoint to determine mean blood naphthalene (NAP) concentrations, and composite blood NAP concentration vs . time profiles were generated

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