Experiment Number: C99037B	**Toxicokinetics Data Summary**	**Date Report Requested:** 12/29/2016
Route: Gavage, IV	**Test Compound:** alpha-Thujone	**Time Report Requested:** 14:32:29
Species/Strain: Rat/Fischer 344	**CAS Number:** 546-80-5	**Lab:** Battelle Columbus

Male

Treatment Groups (mg/kg)

	25 [a]	50 [a]	1.6 IV [a]	25 [b]		
	Brain			**Plasma**		
$C_{0min(pred)}$ (ng/mL)						
$C_{max(pred)}$ (ng/mL)				292	±	39
$T_{max(pred)}$ (minute)				22.4	±	5.0
$C_{max(obs)}$ *	728 ± 38 ng/g	1720 ± 660 ng/g	1590 ± 520 ng/g			
$T_{max(obs)}$ (minute)	15.3	16.7	10.7			
$t_{1/2}$ (minute)	107	86.1	60.0			
$t_{1/2(Alpha)}$ (minute)						
$t_{1/2(Beta)}$ (minute)						
k_{01} (minute^-1)				0.171 ±		0.053
$t_{1/2(k01)}$ (minute)				4.06 ±		1.27
k_{10} (minute^-1)				0.00407 ± 4.4E-4		
$t_{1/2(k10)}$ (minute)				170	±	18
k_{12} (minute^-1)						
k_{21} (minute^-1)						
Cl_1 (mL/min/kg)						
Cl_2 (mL/min/kg)						
$Cl_{1(F)}$ (mL/min/kg)				318	±	33
V_1 (mL/kg)						
V_2 (mL/kg)						
$V_{1(F)}$ (mL/kg)				78100	±	11900
MRT (minute)						
AUC_{0-t} (ng/g*min)	81400	249000	67900	83400		
AUC_{inf} (ng/g*min)	91000	266000	68600	78700	±	8200

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Male

	Treatment Groups (mg/kg)			
	50 [b]		**1.6 IV** [c]	
	Plasma			
$C_{0min(pred)}$ (ng/mL)			684 ± 80	
$C_{max(pred)}$ (ng/mL)	955 ± 215			
$T_{max(pred)}$ (minute)	23.3 ± 8.5			
$C_{max(obs)}$ *				
$T_{max(obs)}$ (minute)				
$t_{1/2}$ (minute)				
$t_{1/2(Alpha)}$ (minute)			8.82 ± 1.07	
$t_{1/2(Beta)}$ (minute)			201 ± 12	
k_{01} (minute^-1)	0.150 ± 0.078			
$t_{1/2(k01)}$ (minute)	4.62 ± 2.40			
k_{10} (minute^-1)	0.00517 ± 7.6E-4		0.0278 ± 0.0029	
$t_{1/2(k10)}$ (minute)	134 ± 20		24.9 ± 2.6	
k_{12} (minute^-1)			0.0445 ± 0.0067	
k_{21} (minute^-1)			0.00973 ± 0.00103	
Cl_{1} (mL/min/kg)			65.1 ± 2.3	
Cl_{2} (mL/min/kg)			104 ± 11	
$Cl_{1(F)}$ (mL/min/kg)	240 ± 45			
V_{1} (mL/kg)			2340 ± 270	
V_{2} (mL/kg)			10700 ± 800	
$V_{1(F)}$ (mL/kg)	46400 ± 12300			
MRT (minute)			200 ± 11	
AUC_{0-t} (ng/g*min)	159000			
AUC_{inf} (ng/g*min)	208000 ± 39000		24600 ± 900	

	Female					
	Treatment Groups (mg/kg)					
	25 [a]	**50** [a]	**1.6 IV** [a]	**25** [b]		
	Brain			**Plasma**		
$C_{0min(pred)}$ (ng/mL)						
$C_{max(pred)}$ (ng/mL)				440	±	110
$T_{max(pred)}$ (minute)				8.31	±	8.37
$C_{max(obs)}$ *	2330 ± 1450 ng/g	5820 ± 1100 ng/g	1810 ± 360 ng/g			
$T_{max(obs)}$ (minute)	14.7	15.7	8.67			
$t_{1/2}$ (minute)	206	149	43.7			
$t_{1/2(Alpha)}$ (minute)						
$t_{1/2(Beta)}$ (minute)						
k_{01} (minute^-1)				0.584	±	0.747
$t_{1/2(k01)}$ (minute)				1.19	±	1.51
k_{10} (minute^-1)				0.00472	±	0.00113
$t_{1/2(k10)}$ (minute)				147	±	35
k_{12} (minute^-1)						
k_{21} (minute^-1)						
Cl_{1} (mL/min/kg)						
Cl_{2} (mL/min/kg)						
$Cl_{1(F)}$ (mL/min/kg)				258	±	56
V_{1} (mL/kg)						
V_{2} (mL/kg)						
$V_{1(F)}$ (mL/kg)				54600	± 14900	
MRT (minute)						
AUC_{0-t} (ng/g*min)	224000	658000	45400	77300		
AUC_{inf} (ng/g*min)	306000	673000	46000	97100	± 21100	

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	Treatment Groups (mg/kg)		
	50 [b]	**1.6 IV** [c]	
Plasma			
$C_{0min(pred)}$ (ng/mL)		522 ± 99	
$C_{max(pred)}$ (ng/mL)	2270 ± 450		
$T_{max(pred)}$ (minute)	18.4 ± 7.0		
$C_{max(obs)}$ *	2630 ± 2180 ng/mL		
$T_{max(obs)}$ (minute)	30.0 ± 0.0		
$t_{1/2}$ (minute)			
$t_{1/2(Alpha)}$ (minute)		6.35 ± 0.91	
$t_{1/2(Beta)}$ (minute)		56.7 ± 11.4	
k_{01} (minute^-1)	0.183 ± 0.098		
$t_{1/2(k01)}$ (minute)	3.78 ± 2.02		
k_{10} (minute^-1)	0.00723 ± 6.9E-4	0.0807 ± 0.0109	
$t_{1/2(k10)}$ (minute)	95.9 ± 9.1	8.59 ± 1.15	
k_{12} (minute^-1)		0.0241 ± 0.0051	
k_{21} (minute^-1)		0.0165 ± 0.0036	
Cl_1 (mL/min/kg)		248 ± 20	
Cl_2 (mL/min/kg)		73.8 ± 14.1	
$Cl_{1(F)}$ (mL/min/kg)	140 ± 25		
V_1 (mL/kg)		3070 ± 580	
V_2 (mL/kg)		4470 ± 1060	
$V_{1(F)}$ (mL/kg)	19300 ± 4500		
MRT (minute)		30.4 ± 4.7	
AUC_{0-t} (ng/g*min)	307000		
AUC_{inf} (ng/g*min)	358000 ± 64000	6460 ± 250	

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LEGEND

Data are displayed as mean ± SEM

*Data are displayed as mean ± SD

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Noncompartmental Analysis (NCA).

[b] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; One compartment with first order absorption and elimination with 1/Yhat2 weighting (Model No. 3).

[c] WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Two compartment with bolus input and first order output with 1/Yhat2 weighting (Model No. 8).

ANALYTE

alpha-Thujone

TK PARAMETERS

$C_{0min(pred)}$ = Fitted plasma concentration at time zero (IV only)

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

T_{max} = Time at which C_{max} predicted or observed occurs

$t_{1/2}$ = Lambda$_z$ half-life, $t_{1/2}$, the terminal elimination half-life based on non-compartmental analysis

$t_{1/2(alpha)}$ = Half-life for the alpha phase

$t_{1/2(beta)}$ = Half-life for the beta phase

k_{01} = Absorption rate constant, k_a

$t_{1/2(k01)}$ = Half-life of the absorption process to the central compartment

k_{10} = Elimination rate constant from the central compartment also k_e or k_{elim}

$t_{1/2(k10)}$ = Half-life for the elimination process from the central compartment

k_{12} = Distribution rate constant from first to second compartment etc.

k_{21} = Distribution rate constant from second to first compartment etc.

Cl_1 = Clearance of central compartment, Cl_{app} or apparent clearance for intravenous groups

Cl_2 = Clearance of the secondary compartment

$Cl_{1(F)}$ = Apparent clearance of the central compartment, also $Cl_{(F)}$ for gavage groups in non-compartmental

V_1 = 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

V_2 = Volume of distribution for the peripheral compartment

$V_{1(F)}$ = Apparent volume of distribution for the central compartment includes $V_{d(F)}$, $V_{(F)}$ for oral groups, and $V_{c(F)}$

MRT = Mean residence time

AUC_{0-t} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

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

** END OF REPORT **