

**Experiment Number:** C99037B  
**Route:** Gavage, IV  
**Species/Strain:** Rat/Fischer 344

**Toxicokinetics Data Summary**  
**Test Compound:** alpha/beta-Thujone mixture  
**CAS Number:** 76231-76-0

**Date Report Requested:** 02/07/2017  
**Time Report Requested:** 10:25:12  
**Lab:** Battelle Columbus

Male					
Treatment Groups (mg/kg)					
	25 <sup>a</sup>	50 <sup>a</sup>	3 IV <sup>a</sup>	25 <sup>b</sup>	
	Brain			Plasma	
C <sub>0min(pred)</sub> (ng/mL)					
C <sub>max(pred)</sub> (ng/mL)				255 ± 29	
T <sub>max(pred)</sub> (minute)				15.1 ± 3.7	
C <sub>max(obs)</sub> (ng/g) *	508 ± 75	1400 ± 210	2560 ± 590		
T <sub>max(obs)</sub> (minute)	42.0	17.0	9.00		
t <sub>1/2</sub> (minute)	80.7	106	54.9		
t <sub>1/2(Alpha)</sub> (minute)					
t <sub>1/2(Beta)</sub> (minute)					
k <sub>01</sub> (minute <sup>-1</sup> )				0.281 ± 0.093	
t <sub>1/2(k01)</sub> (minute)				2.47 ± 0.81	
k <sub>10</sub> (minute <sup>-1</sup> )				0.00435 ± 4.2E-4	
t <sub>1/2(k10)</sub> (minute)				160 ± 16	
k <sub>12</sub> (minute <sup>-1</sup> )					
k <sub>21</sub> (minute <sup>-1</sup> )					
Cl <sub>1</sub> (mL/min/kg)					
Cl <sub>2</sub> (mL/min/kg)					
Cl <sub>1(F)</sub> (mL/min/kg)				400 ± 37	
V <sub>1</sub> (mL/kg)					
V <sub>2</sub> (mL/kg)					
V <sub>1(F)</sub> (mL/kg)				92000 ± 12000	
MRT (minute)					
AUC <sub>0-t</sub>	101000 (ng/g*min)	192000 (ng/g*min)	82700 (ng*min/g)	57500 (ng*min/mL)	
AUC <sub>inf</sub>	107000 (ng/g*min)	218000 (ng/g*min)	83500 (ng*min/g)	62600 ± 5800	

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	Treatment Groups (mg/kg)			
	50 <sup>b</sup>		3 IV <sup>c</sup>	
	Plasma			
C <sub>0min(pred)</sub> (ng/mL)			1110	± 200
C <sub>max(pred)</sub> (ng/mL)	462	± 55		
T <sub>max(pred)</sub> (minute)	12.9	± 3.7		
C <sub>max(obs)</sub> (ng/g) *				
T <sub>max(obs)</sub> (minute)				
t <sub>1/2</sub> (minute)				
t <sub>1/2(Alpha)</sub> (minute)			6.48	± 1.10
t <sub>1/2(Beta)</sub> (minute)			165	± 9
k <sub>01</sub> (minute <sup>-1</sup> )	0.344	± 0.129		
t <sub>1/2(k01)</sub> (minute)	2.01	± 0.75		
k <sub>10</sub> (minute <sup>-1</sup> )	0.00427	± 3.9E-4	0.0349	± 0.0057
t <sub>1/2(k10)</sub> (minute)	162	± 15	19.8	± 3.2
k <sub>12</sub> (minute <sup>-1</sup> )			0.0633	± 0.0127
k <sub>21</sub> (minute <sup>-1</sup> )			0.0129	± 0.0014
Cl <sub>1</sub> (mL/min/kg)			94.2	± 4.2
Cl <sub>2</sub> (mL/min/kg)			171	± 21
Cl <sub>1(F)</sub> (mL/min/kg)	437	± 41		
V <sub>1</sub> (mL/kg)			2700	± 490
V <sub>2</sub> (mL/kg)			13200	± 1000
V <sub>1(F)</sub> (mL/kg)	102000	± 13000		
MRT (minute)			169	± 9
AUC <sub>0-t</sub>	96400	(ng*min/mL)		
AUC <sub>inf</sub>	114000	± 11000 (ng*min/mL)	31800	± 1400 (ng*min/mL)

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Treatment Groups (mg/kg)					
	25 <sup>a</sup>	50 <sup>a</sup>	3 IV <sup>a</sup>	25 <sup>b</sup>	
	Brain			Plasma	
C <sub>0min(pred)</sub> (ng/mL)					
C <sub>max(pred)</sub> (ng/mL)				383	± 88
T <sub>max(pred)</sub> (minute)				16.0	± 7.0
C <sub>max(obs)</sub> (ng/g) *	2180 ± 260	2900 ± 500	3090 ± 200		
T <sub>max(obs)</sub> (minute)	16.3	16.0	10.7		
t <sub>1/2</sub> (minute)	121	141	61.5		
t <sub>1/2(Alpha)</sub> (minute)					
t <sub>1/2(Beta)</sub> (minute)					
k <sub>01</sub> (minute <sup>-1</sup> )				0.213	± 0.135
t <sub>1/2(k01)</sub> (minute)				3.25	± 2.07
k <sub>10</sub> (minute <sup>-1</sup> )				0.00807	± 0.00142
t <sub>1/2(k10)</sub> (minute)				85.9	± 15.1
k <sub>12</sub> (minute <sup>-1</sup> )					
k <sub>21</sub> (minute <sup>-1</sup> )					
Cl <sub>1</sub> (mL/min/kg)					
Cl <sub>2</sub> (mL/min/kg)					
Cl <sub>1(F)</sub> (mL/min/kg)				464	± 85
V <sub>1</sub> (mL/kg)					
V <sub>2</sub> (mL/kg)					
V <sub>1(F)</sub> (mL/kg)				57400	± 16200
MRT (minute)					
AUC <sub>0-t</sub>	188000 (ng/g*min)	396000 (ng/g*min)	95600 (ng*min/g)	44300 (ng*min/mL)	
AUC <sub>inf</sub>	191000 (ng/g*min)	407000 (ng/g*min)	96600 (ng*min/g)	53900	± 9800 (ng*min/mL)

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	Treatment Groups (mg/kg)			
	50 <sup>b</sup>		3 IV <sup>c</sup>	
	Plasma			
C <sub>0min(pred)</sub> (ng/mL)			885	± 185
C <sub>max(pred)</sub> (ng/mL)	483	±	87	
T <sub>max(pred)</sub> (minute)	16.0	±	6.5	
C <sub>max(obs)</sub> (ng/g) *				
T <sub>max(obs)</sub> (minute)				
t <sub>1/2</sub> (minute)				
t <sub>1/2(Alpha)</sub> (minute)			6.79	± 1.17
t <sub>1/2(Beta)</sub> (minute)			53.2	± 10.8
k <sub>01</sub> (minute <sup>-1</sup> )	0.259	±	0.142	
t <sub>1/2(k01)</sub> (minute)	2.68	±	1.46	
k <sub>10</sub> (minute <sup>-1</sup> )	0.00446	±	6.7E-4	0.0746 ± 0.0113
t <sub>1/2(k10)</sub> (minute)	156	±	23	9.29 ± 1.41
k <sub>12</sub> (minute <sup>-1</sup> )				0.0227 ± 0.0061
k <sub>21</sub> (minute <sup>-1</sup> )				0.0178 ± 0.0042
Cl <sub>1</sub> (mL/min/kg)			253	± 22
Cl <sub>2</sub> (mL/min/kg)			76.8	± 17.2
Cl <sub>1(F)</sub> (mL/min/kg)	430	±	63	
V <sub>1</sub> (mL/kg)			3390	± 710
V <sub>2</sub> (mL/kg)			4310	± 970
V <sub>1(F)</sub> (mL/kg)	96400	±	19600	
MRT (minute)			30.5	± 4.2
AUC <sub>0-t</sub>	106000	(ng*min/mL)		
AUC <sub>inf</sub>	116000	±	17000	(ng*min/mL)
			11900	± 1000 (ng*min/mL)

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## LEGEND

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Data are displayed as mean  $\pm$  SEM

\*Data are displayed as mean  $\pm$  SD

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup> WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Noncompartmental Analysis (NCA).

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

<sup>c</sup> WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Two compartment with bolus input and first order elimination 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 model

$V_1$  = 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 \*\***