

Experiment Number: C99028
Route: Dermal, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Test Compound: Bis 2-Chloroethoxy Methane
CAS Number: 111-91-1

Date Report Requested: 02/07/2017
Time Report Requested: 14:05:28
Lab: Battelle Columbus

Male

Treatment Groups (mg/kg)

	300 a, #	300 a, *	600 a, #	600 a, *	50 IV b, #
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Heart

$C_{\max(\text{obs})}$	2.51 ug/g	0.731 ug/g	9.95 ug/g	3.12 ug/g	39.3 ug/g
$T_{\max(\text{obs})}$ (minute)	18.0	180	14.0	240	3.90
$t_{1/2}$ (minute)	23.5	448	25.5	169	8.88

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Treatment Groups (mg/kg)

	300 a, #	300 a, *	600 a, #	600 a, *	50 IV b, #
	Liver				
$C_{\max(\text{obs})}$	3.15 ug/g	48.2 ug/g	13.2 ug/g	88.2 ug/g	1.65 ug/g
$T_{\max(\text{obs})}$ (minute)	17.6	90	32.3	120	6.96
$t_{1/2}$ (minute)	26.4	140	44.3	145	7.66

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	300 a, *	300 c, #	450 a, *	450 c, #	600 a, *
Plasma					
C _{max(pred)} (ug/mL)		2.42 ± 0.50		4.11 ± 0.50	
T _{max(pred)} (minute)		11.9 ± 3.7		13.7 ± 2.3	
C _{max(obs)}	2.32 ug/mL		5.82 ug/mL		7.78 ug/mL
T _{max(obs)} (minute)	240		90		240
t _{1/2} (minute)	188		195		205
Alpha (minute ⁻¹)		0.0607 ± 0.0373		0.0526 ± 0.0157	
t _{1/2(Alpha)} (minute)		11.4 ± 7.0		13.2 ± 3.9	
Beta (minute ⁻¹)		0.00309 ± 0.00889		0.00244 ± 0.00867	
t _{1/2(Beta)} (minute)		224 ± 645		284 ± 1010	
k ₀₁ (minute ⁻¹)		0.114 ± 0.114		0.0991 ± 0.0505	
t _{1/2(k01)} (minute)		6.07 ± 6.05		7.00 ± 3.56	
k ₁₀ (minute ⁻¹)		0.0507 ± 0.0398		0.0484 ± 0.0204	
t _{1/2(k10)} (minute)		13.7 ± 10.7		14.3 ± 6.0	
k ₁₂ (minute ⁻¹)		0.00941 ± 0.01064		0.00399 ± 0.00679	
k ₂₁ (minute ⁻¹)		0.00370 ± 0.00978		0.00265 ± 0.00903	

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Treatment Groups (mg/kg)

300 a, *

300 c, #

450 a, *

450 c, #

600 a, *

Plasma

Cl _{1(F)} (mL/min/kg)	3080 ± 970	2590 ± 480
Cl _{2(F)} (mL/min/kg)	571 ± 791	214 ± 408
V _{1(F)} (mL/kg)	60700 ± 40400	53500 ± 18300
V _{2(F)} (mL/kg)	154000 ± 612000	80600 ± 427000
AUC _{int} (ug/mL*min)	97.5 ± 30.6	174 ± 32

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	Male									
	Treatment Groups (mg/kg)									
	600 c, #		50 IV d, #		100 IV d, #		300 a, *		300 a, #	
	Plasma					Thymus				
C _{max(pred)} (ug/mL)	12.3	± 2.1	38.2	± 4.7	63.1	± 10.5				
T _{max(pred)} (minute)	14.6	± 3.1								
C _{max(obs)}							2.35 ug/g		3.00 ug/g	
T _{max(obs)} (minute)							180		13.2	
t _{1/2} (minute)							746		14.7	
Alpha (minute ⁻¹)	0.0498	± 0.0152								
t _{1/2(Alpha)} (minute)	13.9	± 4.2	4.94	± 0.34	6.85	± 0.58				
Beta (minute ⁻¹)	0.00350	± 0.01301								
t _{1/2(Beta)} (minute)	198	± 734	17.8	± 5.0	28.0	± 13.2				
k ₀₁ (minute ⁻¹)	0.0918	± 0.0555								
t _{1/2(k01)} (minute)	7.55	± 4.56								
k ₁₀ (minute ⁻¹)	0.0488	± 0.0157	0.136	± 0.008	0.0989	± 0.0074				
t _{1/2(k10)} (minute)	14.2	± 4.6	5.11	± 0.30	7.01	± 0.52				
k ₁₂ (minute ⁻¹)	0.000979	± 0.001271	0.00327	± 0.00130	0.00174	± 0.00102				
k ₂₁ (minute ⁻¹)	0.00358	± 0.01320	0.0402	± 0.0118	0.0253	± 0.0123				
Cl (mL/min/kg)			178	± 14	157	± 18				
Cl ₂ (mL/min/kg)			4.28	± 1.55	2.76	± 1.50				

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Male

Treatment Groups (mg/kg)

600 c, # **50 IV d, #** **100 IV d, #**

Plasma

Cl _{1(F)} (mL/min/kg)	1150 ± 180		
Cl _{2(F)} (mL/min/kg)	23.2 ± 34.7		
V ₁ (mL/kg)		1310 ± 160	1590 ± 260
V ₂ (mL/kg)		106 ± 23	109 ± 28
V _{1(F)} (mL/kg)	23700 ± 9400		
V _{2(F)} (mL/kg)	6470 ± 33200		
MRT (minute)		7.97 ± 0.41	10.8 ± 0.7
AUC _{inf} (ug/mL*min)	520 ± 80	282 ± 23	638 ± 72

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Treatment Groups (mg/kg)

600^{a,*}

600^{a,#}

50 IV^{b,#}

Thymus

$C_{\max(\text{obs})}$	10.0 ug/g	14.0 ug/g	32.8 ug/g
$T_{\max(\text{obs})}$ (minute)	480	13.9	3.90
$t_{1/2}$ (minute)	542	14.5	7.91

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Female

Treatment Groups (mg/kg)

	300 a, #	300 a, *	600 a, #	600 a, *	50 IV b, #
	Heart				
$C_{max(obs)}$	6.63 ug/g	0.833 ug/g	17.5 ug/g	2.64 ug/g	34.6 ug/g
$T_{max(obs)}$ (minute)	14.5	240	33.0	240	4.19
$t_{1/2}$ (minute)	10.8	340	61.9	218	6.98

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Female					
Treatment Groups (mg/kg)					
	300 a, *	300 a, #	600 a, #	600 a, *	50 IV b, #
	Liver				
C_{max}(obs)	56.9 ug/g	3.49 ug/g	15.6 ug/g	93.4 ug/g	0.164 ug/g
T_{max}(obs) (minute)	90	14.1	32.3	120	3.52
t_{1/2} (minute)	133	24.0	30.7	140	15.2

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Female										
Treatment Groups (mg/kg)										
	300 a, *		300 c, #		600 a, *		600 c, #		50 IV d, #	
Plasma										
C _{max(pred)} (ug/mL)		5.58	±	0.92		15.5	±	1.8	30.4	± 5.8
T _{max(pred)} (minute)		9.36	±	2.01		14.1	±	1.8		
C _{max(obs)}	1.95 ug/mL				4.33 ug/mL					
T _{max(obs)} (minute)	90				90					
t _{1/2} (minute)	185				214					
Alpha (minute ⁻¹)		0.0824	±	0.0312		0.0547	±	0.0106		
t _{1/2(Alpha)} (minute)		8.41	±	3.18		12.7	±	2.4	4.63	± 0.72
Beta (minute ⁻¹)		0.00841	±	0.00406		0.00453	±	0.00235		
t _{1/2(Beta)} (minute)		82.4	±	39.7		153	±	79	23.7	± 47.7
k ₀₁ (minute ⁻¹)		0.137	±	0.094		0.0900	±	0.0342		
t _{1/2(k01)} (minute)		5.06	±	3.46		7.71	±	2.93		
k ₁₀ (minute ⁻¹)		0.0782	±	0.0291		0.0536	±	0.0103	0.142	± 0.018
t _{1/2(k10)} (minute)		8.87	±	3.30		12.9	±	2.5	4.86	± 0.62
k ₁₂ (minute ⁻¹)		0.00377	±	0.00213		0.000965	±	0.000264	0.00561	± 0.00248
k ₂₁ (minute ⁻¹)		0.00886	±	0.00435		0.00462	±	0.00240	0.0307	± 0.0628
Cl (mL/min/kg)									234	± 25
Cl ₂ (mL/min/kg)									9.21	± 3.54

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Female					
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	300 a, *	300 c, #	600 a, *	600 c, #	50 IV d, #
Plasma					
Cl _{1(F)} (mL/min/kg)		1960 ± 260		959 ± 98	
Cl _{2(F)} (mL/min/kg)		94.2 ± 33.3		17.2 ± 4.2	
V ₁ (mL/kg)					1640 ± 320
V ₂ (mL/kg)					300 ± 585
V _{1(F)} (mL/kg)		25000 ± 10800		17900 ± 4600	
V _{2(F)} (mL/kg)		10600 ± 5100		3730 ± 2210	
MRT (minute)					8.30 ± 3.21
AUC _{inf} (ug/mL*min)		153 ± 20		626 ± 64	214 ± 23

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Treatment Groups (mg/kg)					
	300 a, *	300 a, #	600 a, *	600 a, #	50 IV b, #
Thymus					
$C_{max(obs)}$	2.94 ug/g	5.88 ug/g	6.76 ug/g	13.7 ug/g	30.3 ug/g
$T_{max(obs)}$ (minute)	240	14.4	480	18.6	4.19
$t_{1/2}$ (minute)	447	14.3	300	16.7	5.74

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LEGEND

Data are displayed as mean \pm SEM

MODELING METHOD & BEST FIT MODEL

^a WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Non-compartment model with first order input, first order output, and uniform weighting.

^b WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Non-compartment model with bolus input, first order output, and uniform weighting.

^c WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Two-compartment model with first order input, first order output, and 1/Yhat2 weighting.

^d WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Two-compartment model with bolus input, first order output, and 1/Yhat2 weighting.

ANALYTE

Bis 2-Chloroethoxy Methane

* Thiodiglycolic Acid

TK PARAMETERS

$C_{\max(\text{pred})}$ = Observed or Predicted Maximum plasma (or tissue) concentration

$T_{\max(\text{pred})}$ = Time at which C_{\max} predicted or observed occurs

$C_{\max(\text{obs})}$ = Observed or Predicted Maximum plasma (or tissue) concentration

$T_{\max(\text{obs})}$ = Time at which C_{\max} predicted or observed occurs

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

Alpha = Hybrid rate constant of the alpha phase

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

Beta = Hybrid rate constant of the beta phase

$t_{1/2(\text{beta})}$ = 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 = Clearance, includes total clearance

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

$Cl_{2(F)}$ = Apparent clearance of the secondary compartment

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

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TK PARAMETERS

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

$V_{2(F)}$ = Apparent volume of distribution for the peripheral compartment

MRT = Mean residence time

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

**** END OF REPORT ****