Experiment Number: K08624 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Dermal, IV | **Compound:** Bis 2-Chloroethoxy Methane/ **Analyte:** Bis 2-Chloroethoxy Methane | **Request Time:** 10:03:16

Species/Strain: Rats/F344 | **CAS Number:** 111-91-1 | **Lab:** Battelle Columbus

Male

	Treatment Group (mg/kg)			
	20 IV Plasma[a]	**100 Dermal Plasma[b]**	**200 Dermal Plasma[b]**	**400 Dermal Plasma[b]**
Cmax_pred (ug/mL)	12.4 ± 2.2	5.26 ± 0.68	7.92 ± 0.87	12.2 ± 1.7
Tmax_pred (minute)		14.1 ± 3.8	15.0 ± 3.2	31.7 ± 6.9
Cmax_obs (ug/mL)		4.95 ± 1.81	9.33 ± 3.23	16.5 ± 1.2
Tmax_obs (minute)		5	15	30
Alpha ($minute^{-1}$)		0.0278 ± 0.0062	0.0265 ± 0.0027	0.0111 ± 0.0012
Alpha Half-life (minute)	17.0 ± 2.3	24.9 ± 5.6	26.1 ± 2.7	62.2 ± 6.8
Beta ($minute^{-1}$)		0.00513 ± 0.00152	0.000925 ± 0.000430	0.000712 ± 0.000367
Beta Half-life (minute)	83.4 ± 10.3	135 ± 40	749 ± 348	973 ± 501
k01 ($minute^{-1}$)		0.148 ± 0.075	0.136 ± 0.050	0.0686 ± 0.0260
k01 Half-life (minute)		4.67 ± 2.37	5.10 ± 1.89	10.1 ± 3.8
k10 ($minute^{-1}$)	0.0346 ± 0.0041	0.0240 ± 0.0047	0.0237 ± 0.0026	0.0104 ± 0.0012
k10 Half-life (minute)	20.0 ± 2.4	28.9 ± 5.6	29.2 ± 3.2	66.8 ± 7.7
k12 ($minute^{-1}$)	0.00460 ± 0.00137	0.00303 ± 0.00149	0.00270 ± 0.00073	0.000722 ± 0.000161
k21 ($minute^{-1}$)	0.00976 ± 0.00149	0.00595 ± 0.00203	0.00104 ± 0.00046	0.000776 ± 0.000391
Cl (mL/min/kg)	55.9 ± 5.1			
Cl2 (mL/min/kg)	7.44 ± 1.93			
Cl1_F (mL/min/kg)		312 ± 34	403 ± 42	239 ± 33
Cl2_F (mL/min/kg)		39.5 ± 15.9	45.9 ± 14.8	16.6 ± 5.5
V1 (mL/kg)	1620 ± 290			
V2 (mL/kg)	762 ± 143			
V1_F (mL/kg)		13000 ± 3100	17000 ± 2900	23100 ± 5000
V2_F (mL/kg)		6630 ± 1930	44300 ± 30100	21700 ± 14900
MRT (minute)	42.5 ± 3.3			
AUCinf_pred ($ug*mL^{-1}*min$)	357 ± 32	320 ± 35	496 ± 52	1670 ± 230

Experiment Number: K08624 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Dermal, IV | **Compound:** Bis 2-Chloroethoxy Methane/ **Analyte:** Bis 2-Chloroethoxy Methane | **Request Time:** 10:03:16

Species/Strain: Rats/F344 | **CAS Number:** 111-91-1 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)		
	20 IV Plasma[a]	**40 IV Plasma[a]**	**100 Dermal Plasma[b]**
Cmax_pred (ug/mL)	13.2 ± 2.3	24.1 ± 2.8	9.41 ± 1.48
Tmax_pred (minute)			15.2 ± 3.4
Cmax_obs (ug/mL)			9.89 ± 3.65
Tmax_obs (minute)			15
Alpha ($minute^{-1}$)			0.0513 ± 0.0410
Alpha Half-life (minute)	13.7 ± 1.7	22.6 ± 2.0	13.5 ± 10.8
Beta ($minute^{-1}$)			0.00916 ± 0.00355
Beta Half-life (minute)	68.5 ± 6.9	86.7 ± 7.9	75.7 ± 29.3
k01 ($minute^{-1}$)			0.0860 ± 0.0852
k01 Half-life (minute)			8.06 ± 7.98
k10 ($minute^{-1}$)	0.0424 ± 0.0046	0.0273 ± 0.0020	0.0445 ± 0.0323
k10 Half-life (minute)	16.3 ± 1.8	25.4 ± 1.9	15.6 ± 11.3
k12 ($minute^{-1}$)	0.00611 ± 0.00156	0.00238 ± 0.00063	0.00544 ± 0.00789
k21 ($minute^{-1}$)	0.0120 ± 0.0015	0.00898 ± 0.00102	0.0106 ± 0.0051
Cl (mL/min/kg)	64.1 ± 5.5	45.4 ± 3.0	
Cl2 (mL/min/kg)	9.22 ± 2.09	3.95 ± 0.93	
Cl1_F (mL/min/kg)			223 ± 31
Cl2_F (mL/min/kg)			27.3 ± 22.6
V1 (mL/kg)	1510 ± 260	1660 ± 190	
V2 (mL/kg)	767 ± 126	440 ± 71	
V1_F (mL/kg)			5020 ± 3900
V2_F (mL/kg)			2590 ± 1170
MRT (minute)	35.5 ± 2.6	46.4 ± 2.3	
AUCinf_pred ($ug*mL^{-1}*min$)	312 ± 27	882 ± 58	448 ± 63

Experiment Number: K08624 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Dermal, IV | **Compound:** Bis 2-Chloroethoxy Methane/ **Analyte:** Bis 2-Chloroethoxy Methane | **Request Time:** 10:03:16

Species/Strain: Rats/F344 | **CAS Number:** 111-91-1 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)	
	200 Dermal Plasma[b]	**400 Dermal Plasma[b]**
Cmax_pred (ug/mL)	9.97 ± 1.24	15.0 ± 2.2
Tmax_pred (minute)	20.9 ± 3.4	27.2 ± 6.9
Cmax_obs (ug/mL)	9.89 ± 1.62	16.8 ± 2.6
Tmax_obs (minute)	15	30
Alpha ($minute^{-1}$)	0.0395 ± 0.0293	0.00985 ± 0.00119
Alpha Half-life (minute)	17.6 ± 13.0	70.4 ± 8.5
Beta ($minute^{-1}$)	0.00608 ± 0.00215	0.00122 ± 0.00044
Beta Half-life (minute)	114 ± 40	570 ± 205
k01 ($minute^{-1}$)	0.0586 ± 0.0496	0.0924 ± 0.0380
k01 Half-life (minute)	11.8 ± 10.0	7.50 ± 3.08
k10 ($minute^{-1}$)	0.0358 ± 0.0250	0.00914 ± 0.00106
k10 Half-life (minute)	19.4 ± 13.5	75.8 ± 8.8
k12 ($minute^{-1}$)	0.00304 ± 0.00401	0.000608 ± 0.000179
k21 ($minute^{-1}$)	0.00670 ± 0.00272	0.00131 ± 0.00049
Cl1_F (mL/min/kg)	321 ± 27.2	188 ± 25
Cl2_F (mL/min/kg)	27.2 ± 20.2	12.5 ± 4.2
V1_F (mL/kg)	8950 ± 6460	20500 ± 4300
V2_F (mL/kg)	4070 ± 1840	9520 ± 3710
AUCinf_pred ($ug*mL^{-1}*min$)	624 ± 84	2130 ± 280

Experiment Number: K08624
Route: Dermal, IV
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: Bis 2-Chloroethoxy Methane/ **Analyte:** Bis 2-Chloroethoxy Methane
CAS Number: 111-91-1

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Battelle Columbus

Male

	Treatment Group (mg/kg)		
	20 IV Heart[c]	**100 Dermal Heart[e]**	**400 Dermal Heart[e]**
Cmax_obs (ug/mL)	12.6	2.95	18.2
Tmax_obs (minute)	14.9	34.0	34.7
Half-life (minute)	69.9	71.5	91.0

Female

	Treatment Group (mg/kg)		
	20 IV Heart[d]	**100 Dermal Heart[e]**	**400 Dermal Heart[e]**
Cmax_obs (ug/mL)	11.6	8.87	20.4
Tmax_obs (minute)	15.0	15.5	34.7
Half-life (minute)	68.1	63.0	387

Experiment Number: K08624
Route: Dermal, IV
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: Bis 2-Chloroethoxy Methane/ **Analyte:** Bis 2-Chloroethoxy Methane
CAS Number: 111-91-1

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Battelle Columbus

Male

	Treatment Group (mg/kg)		
	20 IV Liver[c]	**100 Dermal Liver[f]**	**400 Dermal Liver[e]**
Cmax_obs (ug/g)	3.89	1.66	11.1
Tmax_obs (minute)	43.7	34.0	64.3
Half-life (minute)	39.1	58.4	86.1

Female

	Treatment Group (mg/kg)		
	20 IV Liver[c]	**100 Dermal Liver[f]**	**400 Dermal Liver[e]**
Cmax_obs (ug/g)	1.70	2.26	14.5
Tmax_obs (minute)	14.8	34.3	64.0
Half-life (minute)	25.7	46.7	199

Male

	Treatment Group (mg/kg)		
	20 IV Thymus[c]	**100 Dermal Thymus[e]**	**400 Dermal Thymus[e]**
Cmax_obs (ug/g)	48.7	6.07	28.7
Tmax_obs (minute)	14.8	34.0	34.7
Half-life (minute)	80.5	65.5	175

Female

	Treatment Group (mg/kg)		
	20 IV Thymus[c]	**100 Dermal Thymus[e]**	**400 Dermal Thymus[e]**
Cmax_obs (ug/g)	42.7	8.37	27.6
Tmax_obs (minute)	14.9	15.6	34.3
Half-life (minute)	164	43.8	187

Experiment Number: K08624 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Dermal | **Compound:** Bis 2-Chloroethoxy Methane/ **Analyte:** Thiodiglycolic Acid | **Request Time:** 10:03:16

Species/Strain: Rats/F344 | **CAS Number:** 111-91-1 | **Lab:** Battelle Columbus

Male

	Treatment Group (mg/kg)			
	400 Dermal Plasma[f]	**400 Dermal Heart[f]**	**400 Dermal Thymus[f]**	**400 Dermal Liver[f]**
Cmax_obs (ug/mL)	5.51	3.35	5.47	84.4
Tmax_obs (min)	180	360	480	360
Half-Life (min)	322	422	853	296

Experiment Number: K08624 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Dermal | **Compound:** Bis 2-Chloroethoxy Methane/ **Analyte:** Thiodiglycolic Acid | **Request Time:** 10:03:16

Species/Strain: Rats/F344 | **CAS Number:** 111-91-1 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)			
	400 Dermal Plasma[f]	**400 Dermal Heart[f]**	**400 Dermal Thymus[f]**	**400 Dermal Liver[f]**
Cmax_obs (ug/mL)	10.8	6.80	11.0	123
Tmax_obs (min)	360	360	480	480
Half-Life (min)	386	548	652	373

LEGEND

MODELING SORFTWARE

WinNonlin Version 5.0.1

MODELING METHOD & BEST FIT MODEL

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

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

[c]WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartment model with bolus input, first order output, and 1/Y2 weighting. Non-compartmental analysis does not calculate a standard error for half-life.

[d]WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartment model with bolus input, first order output, and 1/Y2 weighting. Non-compartmental analysis does not calculate a standard error for half-life. User defined value used for half-life shown here (68.1), NCA gave poor visual fit of terminal phase. NCA half life was 39.1.

[e]WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartment model with first order input, first order output, and uniform weighting. Non-compartmental analysis does not calculate a standard error.

[f]WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Non-compartment model with first order input, first order output, and uniform weighting.

ANALYTE

Bis 2-Chloroethoxy Methane
Thiodiglycolic Acid

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax= Time at which Cmax predicted or observed occurs
Half-Life = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim
Alpha = Hybrid rate constant of the alpha phase
Alpha Half-life = Half-life for the alpha phase
Beta = Hybrid rate constant of the beta phase
Beta Half-life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k01 Half-life = Half-life of the absorption process to the central compartment
k10 = Elimination rate constant from the central compartment also ke or kelim
k10 Half-life = Half-life for the elimination process from the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl = Clearance, includes total clearance
Cl2 = Clearance of the secondary compartment
Cl1_F= Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
Cl2_F = Apparent clearance of the secondary compartment
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
V2 = Volume of distribution for the peripheral compartment
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
V2_F = Apparent volume of distribution for the peripheral compartment
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

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 2, 5, 10, 15, 20, 30, 40, 50, 60, and 90 minutes. SE is the standard error of the mean. Parameter estimates are reported to three significant figures. Cmax (predicted) based on the model prediction at time 0 minutes.

TK_INTRAVENOUS PLASMA

50 mg/kg Male and Female

Animals were given a single bolus injection of Bis 2-Chloroethoxy Methane (CEM) through a jugular catheter. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 360 minutes. SE is the standard error of the mean. Parameter estimates are reported to three significant figures. Cmax (predicted) based on the model prediction at time 0 minutes.

100 mg/kg Male

Animals were given a single bolus injection of Bis 2-Chloroethoxy Methane (CEM) through a jugular catheter. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. SE is the standard error of the mean. Parameter estimates are reported to three significant figures except for observed Tmax.

300 mg/kg Male and Female, 450 mg/kg Male

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. SE is the standard error of the mean. Parameter estimates are reported to three significant figures except for observed Tmax.

600 mg/kg Male and Female

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

TK_DERMAL HEART

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 2, 5, 10, 15, 20, 30, 40, 50, 60, and 90 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

50 mg/kg Male and Female

Animals were given a single bolus injection of Bis 2-Chloroethoxy Methane (CEM) through a jugular catheter. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models using WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

300 mg Male and Female

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animals was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

600 mg/kg Male and Female

Following blood collection, each animals was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

TK_DERMAL LIVER

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 2, 5, 10, 15, 20, 30, 40, 50, 60, and 90 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

50 mg/kg Male and Female

Animals were given a single bolus injection of Bis 2-Chloroethoxy Methane (CEM) through a jugular catheter. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models using WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

300 mg Male and Female

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood colle ction, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

600 mg/kg Male and Female

Following blood collection, each animals was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

TK_DERMAL THYMUS

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 2, 5, 10, 15, 20, 30, 40, 50, 60, and 90 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

50 mg/kg Male and Female

Animals were given a single bolus injection of Bis 2-Chloroethoxy Methane (CEM) through a jugular catheter. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models using WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

300 mg Male and Female

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

600 mg/kg Male and Female

Following blood collection, each animals was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 90, 120, 180, 240, and 360 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

ANALYSIS METHOD

Following blood collection, each animal was terminated with CO2 and the heart, thymus, and liver were collected. Blood collection time points for this group are 5, 10, 15, 30, 60, 180, 360, 480, 720, 960, 1440, and 1800 minutes. Parameter estimates are reported to three significant figures. Non-compartmental analysis does not calculate a standard error.

TK_DERMAL PLASMA

400 mg/kg Male & Female

Animals were given a single dermal administration of Bis 2-Chloroethoxy Methane (CEM) in 95 percent ethanol. Concentrations time data sets were evaluated using non-compartmental analysis and, when possible, compartmental models. WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA