Experiment Number: K05097
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: Bromodichloromethane/ **Analyte:** Bromodichloromethane
CAS Number: 75-27-4

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

Male

	Treatment Group (mg/kg)		
	10 IV Plasma[a]	**10 IV Plasma[b]**	**25 Gavage Plasma[b]**
C_0min_pred (ng*mL^{-1})	4110 ± 3260		
Cmax_obs (ng*mL^{-1})		1570	586.7
Tmax_obs (minute)		2	2
Lambda_z (min^{-1})		0.0700 ± 0.0099	0.00643 ± 0.0032
Half-life (minute)		9.91 ± 1.41	108 ± 54
Alpha (min^{-1})	0.570 ± 0.362		
Alpha Half-life (min)	1.22 ± 0.77		
Beta (min^{-1})	0.0831 ± 0.0072		
Beta Half-life (min)	8.34 ± 0.73		
k10 (min^{-1})	0.326 ± 0.198		
k10 Half-life (min)	2.13 ± 1.29		
k12 (min^{-1})	0.182 ± 0.165		
K21 (min^{-1})	0.146 ± 0.035		
Cl (L*kg^{-1}*min^{-1})	0.79 ± 0.19		
Cl (L*min^{-1}*kg^{-1})		0.794 ± 0.087	3.20 ± 0.51
Vss (L*kg^{-1})	5.47 ± 2.30	7.38 ± 1.49	480 ± 183
MRT (min)		9.30 ± 1.57	150 ± 52
AUCinf_pred (ng*min*mL^{-1})	14700 ± 3400	12600 ± 1400	7820 ± 1240

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Male

	Treatment Group (mg/kg)		
	25 Gavage Plasma[b]	**50 Gavage Plasma[b]**	**50 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	101.4	1813	310.6
Tmax_obs (minute)	5	2	5
Lambda_z (min^{-1})	0.00066 ± 0.0061	0.0714 ± 0.0207	0.00052 ± 0.0030
Half-life (minute)	1050 ± 9770	9.71 ± 2.81	1320 ± 7420
Cl (L*kg^{-1}*min^{-1})			
Cl (L*min^{-1}*kg^{-1})	3.76 ± 29.4	2.35 ± 0.24	2.41 ± 7.63
Vss (L*kg^{-1})	5430 ± 87400	93.8 ± 18.0	2960 ± 24500
MRT (min)	1440 ± 20310	40.0 ± 6.5	1230 ± 9400
AUCinf_pred (ng*min*mL^{-1})	6650 ± 51990	21300 ± 2200	20700 ± 65600

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Male

	Treatment Group (mg/kg)	
	100 Gavage Plasma[b]	**100 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	5162	1965
Tmax_obs (minute)	2	7
Lambda_z (min^{-1})	0.0195 ± 0.0053	0.00452 ± 0.0020
Half-life (minute)	35.5 ± 9.7	153 ± 67
Cl (L*kg^{-1}*min^{-1})		
Cl (L*min^{-1}*kg^{-1})	0.676 ± 0.060	1.56 ± 0.22
Vss (L*kg^{-1})	29.3 ± 5.5	110 ± 27
MRT (min)	43.3 ± 7.2	70.5 ± 14.4
AUCinf_pred (ng*min*mL^{-1})	148000 ± 13000	64200 ± 8900

Female

	Treatment Group (mg/kg)		
	10 IV Plasma[a]	**10 IV Plasma[b]**	**25 Gavage Plasma[b]**
C_0min_pred (ng*mL^{-1})	3040 ± 1490		
Cmax_obs (ng*mL^{-1})		1475	708.3
Tmax_obs (minute)		2	2
Lambda_z (min^{-1})		0.0728 ± 0.018	0.0276 ± 0.0044
Half-life (minute)		9.53 ± 2.40	25.1 ± 4.0
Alpha (min^{-1})	0.360 ± 0.088		
Alpha Half-life (min)	1.93 ± 0.47		
Beta (min^{-1})	0.00576 ± 0.0363		
Beta Half-life (min)	120 ± 756		
k10 (min^{-1})	0.227 ± 0.460		
k10 Half-life (min)	3.05 ± 6.18		
k12 (min^{-1})	0.129 ± 0.419		
k21 (min^{-1})	0.00913 ± 0.0402		
Cl (L*kg^{-1}*min^{-1})	0.75 ± 1.42		
Cl (L*min^{-1}*kg^{-1})		0.896 ± 0.119	4.72 ± 0.62
Vss (L*kg^{-1})	49.8 ± 360.7	7.01 ± 1.56	161 ± 32
MRT (min)		7.82 ± 1.39	34.0 ± 5.0
AUCinf_pred (ng*min*mL^{-1})	16200 ± 29500	11200 ± 1500	5300 ± 700

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Female

	Treatment Group (mg/kg)		
	25 Gavage Plasma[b]	**50 Gavage Plasma[b]**	**50 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	65.58	901.5	435.2
Tmax_obs (minute)	5	2	7
Lambda_z (min^{-1})	0.0330 ± 0.0129	0.0107 ± 0.0039	0.00145 ± 0.00071
Half-life (minute)	21.0 ± 8.2	64.7 ± 23.5	477 ± 230
Cl (L*kg^{-1}*min^{-1})			
Cl (L*min^{-1}*kg^{-1})	27.0 ± 3.4	3.50 ± 0.51	3.72 ± 0.56
Vss (L*kg^{-1})	756 ± 209	279 ± 69	1590 ± 580
MRT (min)	28.0 ± 6.9	79.6 ± 15.9	427 ± 141
AUCinf_pred (ng*min*mL^{-1})	926 ± 120	14300 ± 2100	13400 ± 2000

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Female

	Treatment Group (mg/kg)	
	100 Gavage Plasma[b]	**100 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	4839	1546
Tmax_obs (minute)	2	7
Lambda_z (min^{-1})	0.0472 ± 0.0129	0.00518 ± 0.00163
Half-life (minute)	14.7 ± 4.0	134 ± 42
Cl (L*min^{-1}*kg^{-1})	0.927 ± 0.100	1.55 ± 0.32
Vss (L*kg^{-1})	46.8 ± 8.3	191 ± 65
MRT (min)	50.5 ± 7.1	123 ± 33
AUCinf_pred (ng*min*mL^{-1})	108000 ± 1200	64700 ± 13400

LEGEND

MODELING SOFTWARE

PROC NLIN SAS 8.2

MODELING METHOD & BEST FIT MODEL

[a]PROC NLIN IN SAS 8.2 (SAS Institute Inc., Cary, NC), Two-compartment model with bolus input, first-order elimination. Plasma BDCM concentrations declined in a biexponential fashion with rapid early alpha phase and a terminal beta phase that was approximately 6.9-fold lower.

[b]PROC NLIN IN SAS 8.2 (SAS Institute Inc., Cary, NC) , non-compartmental analysis

ANALYTE

Bromodichloromethane

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)
Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax = Time at which Cmax predicted or observed occurs
Lambda_z = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim
Half-life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
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 alpha phase
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

TK PARAMETERS (cont'd)

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

Plasma bromochloromethane (BDCM) concentrations were measured using validated headspace capillary gas chromatography method with electron data capture. The lower limit of quantitation (LLOQ) was 2.0 ng/mL and the upper limit of quantitation (ULOQ) was 99 ng/mL. Concentration-time data sets were evaluated using non-compartmental analysis (NCA) and, when possible, compartmental models using PROC NLIN.

TK_INTRAVENOUS PLASMA

10 mg/kg Male

Body weight range for animal pool is 22.5 to 36.9 g for first set and 25.9 to 32.1 g for repeat animals. B6C3F1 mice were given a single intravenous (IV) administration of bromodichloromethane (BDCM) in 9 to 1 deionized water-Cremophor at a dosage of 10 mg/kg in the tail vein. Blood samples were collected at 9 time points 2, 5, 10, 15, 20, 30, and 45 minutes and 1 and 1.25 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Plasma bromochloromethane (BDCM) concentrations were measured using validated headspace capillary gas chromatography method with electron data capture. The lower limit of quantitation (LLOQ) was 2.0 ng/mL and the upper limit of quantitation (ULOQ) was 99 ng/mL. Concentration-time data sets were evaluated using non-compartmental analysis (NCA) and, when possible, compartmental models using PROC NLIN.

TK_GAVAGE PLASMA

25 mg/kg, 50 mg/kg, 100 mg/kg Male

Body weight range for animal pool is 19.9 to 36.9 g. B6C3F1 mice were given a single gavage administration of bromodichloromethane (BDCM) in 9 to 1 deionized water-Cremophor at a dosage of 25, 50, or 100 mg/kg. Blood samples were collected at 14 time points 2, 5, 7, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, and 8 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.

25 mg/kg, 50 mg/kg, 100 mg/kg Male

Body weight range for animal pool is 19.7 to 37.2 g. B6C3F1 mice were given a single gavage administration of bromodichloromethane (BDCM) in corn oil at a dosage of 25, 50, or 100 mg/kg. Blood samples were collected at 13 time points 2, 5, 7, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, and 8 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Plasma bromochloromethane (BDCM) concentrations were measured using validated headspace capillary gas chromatography method with electron data capture. The lower limit of quantitation (LLOQ) was 2.0 ng/mL and the upper limit of quantitation (ULOQ) was 99 ng/mL. Concentration-time data sets were evaluated using non-compartmental analysis (NCA) and, when possible, compartmental models using PROC NLIN.

TK_INTRAVENOUS PLASMA

10 mg/kg Female

Body weight range for animal pool is 16.1 to 28.9 g for first set and 21.9 to 26.0 g for repeat animals. B6C3F1 mice were given a single intravenous (IV) administration of bromodichloromethane (BDCM) in 9 to 1 deionized water-Cremophor at a dosage of 10 mg/kg in the tail vein. Blood samples were collected at 9 time points 2, 5, 10, 15, 20, 30, and 45 minutes and 1 and 1.25 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.

TK_GAVAGE PLASMA

25 mg/kg, 50 mg/kg, 100 mg/kg Female

Body weight range for animal pool is 16.5 to 27.1 g. B6C3F1 mice were given a single gavage administration of bromodichloromethane (BDCM) in 9 to 1 deionized water-Cremophor at a dosage of 25, 50, or 100 mg/kg. Blood samples were collected at 14 time points 2, 5, 7, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, and 8 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Plasma bromochloromethane (BDCM) concentrations were measured using validated headspace capillary gas chromatography method with electron data capture. The lower limit of quantitation (LLOQ) was 2.0 ng/mL and the upper limit of quantitation (ULOQ) was 99 ng/mL. Concentration-time data sets were evaluated using non-compartmental analysis (NCA) and, when possible, compartmental models using PROC NLIN.

TK_GAVAGE PLASMA

25mg/kg, 50 mg/kg, 100 mg/kg Female

Body weight range for animal pool is 13.5 to 26.8 g. B6C3F1 mice were given a single gavage administration of bromodichloromethane (BDCM) in corn oil at a dosage of 25, 50, or 100 mg/kg. Blood samples were collected at 13 time points 2, 5, 7, 15, 30, and 45 minutes and 1, 1.25, 1.5, 2, 4, 8, and 12 hours post-administration. Blood was collected by cardiac puncture from six mice per sex per time point. Animals were anesthetized with an approximately 70 percent CO2-30 percent O2 mixture prior to sample collection. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.