Experiment Number: K05097
Route: Gavage, IV
Species/Strain: Rats/Fischer F344

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})	2890 ± 500		
Cmax_obs (ng*mL^{-1})		3004	913.2
Tmax_obs (minute)		2	10
Lambda_z (min^{-1})		0.00622 ± 0.0013	0.00506 ± 0.00153
Half-life (minute)		111 ± 24	137 ± 42
Alpha (min^{-1})	0.0754 ± 0.0120		
Alpha Half-life (min)	9.20 ± 147		
Beta (min^{-1})	0.00624 ± 0.00088		
Beta Half-life (min)	111 ± 16		
k10 (min^{-1})	0.0547 ± 0.0079		
k10 Half-life (min)	12.7 ± 1.8		
k12 (min^{-1})	0.183 ± 0.0049		
K21 (min^{-1})	0.00860 ± 0.00155		
Cl (L*kg^{-1}*min^{-1})	0.19 ± 0.02		
Cl (L*min^{-1}*kg^{-1})		0.168 ± 0.011	0.870 ± 0.058
Vss (L*kg^{-1})	10.8 ± 1.7	10.3 ± 1.2	85.8 ± 11.5
MRT (min)		61.3 ± 6.0	98.6 ± 11.5
AUCinf_pred (ng*min*mL^{-1})	59100 ± 3030	59400 ± 4000	28700 ± 1900

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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})	749.2	2148	1355
Tmax_obs (minute)	7	7	7
Lambda_z (min^{-1})	0.00478 ± 0.0015	0.00498 ± 0.00036	0.00371 ± 0.00081
Half-life (minute)	145 ± 46	139 ± 10	187 ± 41
Cl (L*min^{-1}*kg^{-1})	1.42 ± 0.13	0.501 ± 0.031	0.885 ± 0.072
Vss (L*kg^{-1})	142 ± 26	57.1 ± 5.7	136 ± 20
MRT (min)	99.8 ± 15.9	114 ± 9	154 ± 19
AUCinf_pred (ng*min*mL^{-1})	17600 ± 1600	99700 ± 6200	56500 ± 4600

Experiment Number: K05097
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Toxicokinetics Data Summary
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CAS Number: 75-27-4

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

Male

	Treatment Group (mg/kg)	
	100 Gavage Plasma[b]	**100 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	4370	2611
Tmax_obs (minute)	15	7
Lambda_z (min^{-1})	0.00278 ± 0.00054	0.00256 ± 0.0012
Half-life (minute)	250 ± 49	271 ± 124
Cl (L*kg^{-1}*min^{-1})		
Cl (L*min^{-1}*kg^{-1})	0.281 ± 0.016	0.330 ± 0.038
Vss (L*kg^{-1})	37.6 ± 4.0	53.7 ± 11.4
MRT (min)	134 ± 12	163 ± 29
AUCinf_pred (ng*min*mL^{-1})	356000 ± 20000	303000 ± 35000

Experiment Number: S0553 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Gavage, IV | **Compound:** Bromodichloromethane/ **Analyte:** Bromodichloromethane | **Request Time:** 10:03:16

Species/Strain: Rats/Fischer F344 | **CAS Number:** 75-27-4 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)		
	10 IV Plasma[a]	**10 IV Plasma[b]**	**25 Gavage Plasma[b]**
C_0min (ng*mL^{-1})	3160 ± 1120		
Cmax_obs (ng*mL^{-1})		2186	880.7
Tmax_obs (minute)		2	10
Lambda_z (min^{-1})		0.00835 ± 0.00162	0.00493 ± 0.00361
Half-life (minute)		83.0 ± 16.1	141 ± 100
Alpha (min^{-1})	0.170 ± 0.037		
Alpha Half-life (min)	4.08 ± 0.88		
Beta (min^{-1})	0.00685 ± 0.00139		
Beta Half-life (min)	101 ± 21		
k10 (min^{-1})	0.101 ± 0.026		
k10 Half-life (min)	6.85 ± 1.74		
k12 min^{-1})	0.0640 ± 0.0172		
k21 (min^{-1})	0.0115 ± 0.0032		
Cl (L*kg^{-1}*min^{-1})	0.32 ± 0.05		
Cl (L*min^{-1}*kg^{-1})		0.256 ± 0.022	1.07 ± 0.12
Vss (L*kg^{-1})	20.8 ± 6.1	16.1 ± 2.4	102 ± 40
MRT (min)		62.7 ± 7.6	95.3 ± 35.8
AUCinf_pred (ng*min*mL^{-1})	39000 ± 2700	39000 ± 3400	23400 ± 2500

Experiment Number: S0553 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Gavage, IV | **Compound:** Bromodichloromethane/ **Analyte:** Bromodichloromethane | **Request Time:** 10:03:16

Species/Strain: Rats/Fischer F344 | **CAS Number:** 75-27-4 | **Lab:** Battelle Columbus

Female

	Treatment Group (mg/kg)		
	25 Gavage Plasma[b]	**50 Gavage Plasma[b]**	**50 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	658.0	919.3	1816
Tmax_obs (minute)	7	7	5
Lambda_z (min^{-1})	0.00163 ± 0.00084	0.00509 ± 0.00035	0.00689 ± 0.00151
Half-life (minute)	425 ± 220	136 ± 10	101 ± 22
Cl (L*min^{-1}*kg^{-1})	1.59 ± 0.13	0.807 ± 0.073	0.646 ± 0.079
Vss (L*kg^{-1})	304 ± 109	105 ± 15	51.6 ± 11.1
MRT (min)	192 ± 67	129 ± 14	79.9 ± 14.2
AUCinf_pred (ng*min*mL^{-1})	15800 ± 1300	61900 ± 5600	77400 ± 9500

Experiment Number: S0553
Route: Gavage, IV
Species/Strain: Rats/Fischer F344

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

Female

	Treatment Group (mg/kg)	
	100 Gavage Plasma[b]	**100 Gavage Plasma[b]**
Cmax_obs (ng*mL^{-1})	1783	3791
Tmax_obs (minute)	7	15
Lambda_z (min^{-1})	0.00306 ± 0.00127	0.00203 ± 0.00102
Half-life (minute)	227 ± 94	341 ± 171
Cl (L*min^{-1}*kg^{-1})	0.545 ± 0.058	0.359 ± 0.037
Vss (L*kg^{-1})	79.3 ± 15.0	47.4 ± 9.0
MRT (min)	146 ± 23	132 ± 21
AUCinf_pred (ng*min*mL^{-1})	183000 ± 20000	278000 ± 29000

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 265.7 to 333.7 g. Fischer F344 rats 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 11 time points 2, 5, 10, 15, and 30 minutes and 1, 2, 4, 6, 8, and 12 hours post-administration. Blood was collected from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. 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 182.6 to 324.6 g for first set and 252.1 to 297.5 g for repeat animals. Fischer F344 rats 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 from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. 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 249.4 to 349.1 g. Fischer F344 rats 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 14 time points 2, 5, 7, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-administration. Blood was collected from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. 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 156.4 to 193.8 g. Fischer F344 rats 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 11 time points 2, 5, 10, 15, and 30 minutes and 1, 2, 4, 6, 8, and 12 hours post-administration. Blood was collected from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. 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 135.5 to 190.9 g for first set and 164.2 to 197.7 g for repeat animals. Fischer F344 rats 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 from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. 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 134.2 to 218.1 g. Fischer F344 rats 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 14 time points 2, 5, 7, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-administration. Blood was collected from the retro-orbital sinus from five rats per sex per time point. With the exception of many of the repeat animals, which were bled only once, rats were bled twice. Since BDCM was known to be readily absorbed by plastic, formulations were administered using glass syringes and all-metal needles.