

## ADME NTP Study S0527 Bromodichloromethane

The contract laboratory used the abbreviation of BDCM for the test article.

Sex/Species: adult male F344 rats.

Vehicles: oral, corn oil.

CASRN 75-27-4

Radiolabeled with carbon-14; Bromodichloro[<sup>14</sup>C]methane

### Studies Performed:

Single 1, 10, 32, or 100 mg/kg oral gavage dose in rats with sacrifice 24 hours (h) postdose.

10-day repeated 10 mg/kg/day or 100 mg/kg/day oral gavage dose in rats with excreta collected 24 hours following doses on days 1, 3, and 10 and sacrifice at 24 hours after final dose.

Kidneys of single 32 mg/kg oral dose and 10-day 100 mg/kg/day repeat dose animals were further dissected to separate cortex from medulla prior to determination of <sup>14</sup>C content. The ratio (mean ± standard deviation) of the radiochemical concentrations of residues of cortex:medulla was 7.9 ± 2.3 to 1 for the single 32 mg/kg dose and 6.1 ± 1.1 to 1 for the 10-day 100 mg/kg/day repeat dosed animals.

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Table 1

Cumulative Excretion of Radioactivity for 24 h after Oral Administration of  $^{14}\text{C}$ -BDCM to Male F-344 Rats (N=4)

1 mg/kg						
End of Interval (h)	Volatiles	CO <sub>2</sub>	% of Dose <sup>a</sup>			Total Excreta
			CO	Urine	Feces	
1	2.1 ± 1.5	9.5 ± 1.1				11.6 ± 1.3
4	2.7 ± 1.8	37.0 ± 3.2	1.5 ± 0.7			41.1 ± 2.8
8		62.9 ± 2.2	2.7 ± 1.1			68.3 ± 1.7
16		76.4 ± 3.2				81.8 ± 2.9
24	3.0 ± 1.6	77.5 ± 3.3	3.3 ± 1.5	4.1 ± 0.2	2.7 ± 1.5	90.7 ± 1.8
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10 mg/kg						
End of Interval (h)	Volatiles	CO <sub>2</sub>	% of Dose <sup>a</sup>			Total Excreta
			CO	Urine	Feces	
1	2.1 ± 1.5	9.5 ± 1.1				11.6 ± 1.3
1	2.0 ± 0.8	8.0 ± 2.0				10.0 ± 1.5
4	2.7 ± 1.1	39.9 ± 3.2	1.9 ± 0.4			44.5 ± 3.0
8		66.0 ± 4.0	3.4 ± 0.9			72.1 ± 3.9
16		81.3 ± 1.7				87.4 ± 1.5
24	2.8 ± 1.1	82.1 ± 1.8	4.3 ± 1.0	4.3 ± 0.2	0.7 ± 0.2	94.2 ± 1.6
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32 mg/kg						
End of Interval (h)	Volatiles	CO <sub>2</sub>	% of Dose <sup>a</sup>			Total Excreta
			CO	Urine	Feces	
1	2.42 ± 1.01	13.4 ± 4.4				15.9 ± 4.4
4	3.19 ± 1.42	40.0 ± 6.0	2.92 ± 0.53			46.1 ± 7.2
8		57.4 ± 6.1	4.32 ± 0.50			64.9 ± 6.1
16		72.3 ± 4.3				79.4 ± 4.2
24	3.36 ± 1.49	76.6 ± 2.8	5.22 ± 0.66	4.89 ± 0.59	1.02 ± 0.14	91.1 ± 1.2
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100 mg/kg						
End of Interval (h)	Volatiles	CO <sub>2</sub>	% of Dose <sup>a</sup>			Total Excreta
			CO	Urine	Feces	
0.5	1.5 ± 1.2	0.4 ± 0.2	ND			1.8 ± 1.2
1	2.6 ± 1.7	1.9 ± 0.9	0.1 ± 0			4.6 ± 1.8
1.5	3.6 ± 1.8	3.8 ± 0.9	0.2 ± 0.1			7.6 ± 2.0
2	4.2 ± 1.9	5.5 ± 1.8	0.3 ± 0.1			10.0 ± 2.9
6				0.6 ± 0.4		10.6 ± 3.0
8	5.7 ± 2.1	33.4 ± 7.4	2.3 ± 0.7			42.0 ± 8.3
24	6.3 ± 2.1	71.0 ± 1.7	5.2 ± 0.3	4.1 ± 0.2	0.7 ± 0.3	87.3 ± 1.6

<sup>a</sup> Values are means ± standard deviations.

Table 2

Tissue Distribution of Radioactivity 24 h after Oral  
Administration of  $^{14}\text{C}$ -BDCM to Male F-344 Rats (N=4)<sup>a</sup>

Tissue	ng-eq BDCM per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
<u>1 mg/kg</u>			
Adipose	14 ± 4	0.83 ± 0.35	0.15 ± 0.04
Blood	18 ± 4	Unity	0.12 ± 0.02
Large Intestine	59 ± 16	3.33 ± 1.08	0.02 ± 0.00
Small Intestine	67 ± 12	3.71 ± 0.09	0.09 ± 0.02
Kidney	88 ± 29	4.93 ± 1.84	0.07 ± 0.01
Liver	784 ± 61	44.46 ± 9.80	3.06 ± 0.15
Muscle	9 ± 2	0.52 ± 0.04	0.47 ± 0.07
Plasma	43 ± 4	2.38 ± 0.25	0.14 ± 0.01
Skin	23 ± 5	1.28 ± 0.19	0.35 ± 0.07
Stomach	77 ± 20	4.21 ± 0.48	0.03 ± 0.01
Total			4.36 ± 0.22
<u>10 mg/kg</u>			
Adipose	87 ± 38	0.42 ± 0.18	0.09 ± 0.04
Blood	212 ± 20	Unity	0.13 ± 0.01
Large Intestine	481 ± 52	2.30 ± 0.41	0.02 ± 0.00
Small Intestine	611 ± 5	2.91 ± 0.24	0.07 ± 0.02
Kidney	1260 ± 159	5.98 ± 0.80	0.09 ± 0.01
Liver	4220 ± 286	20.05 ± 1.98	1.61 ± 0.09
Muscle	82 ± 19	0.39 ± 0.10	0.41 ± 0.10
Plasma	420 ± 15	1.99 ± 0.15	0.14 ± 0.01
Skin	196 ± 61	0.94 ± 0.32	0.29 ± 0.09
Stomach	699 ± 73	3.31 ± 0.33	0.02 ± 0.00
Total			2.74 ± 0.14
<u>32 mg/kg</u>			
Adipose	420 ± 69	0.63 ± 0.10	0.13 ± 0.02
Blood	669 ± 12	Unity	0.13 ± 0.00
Large Intestine	1512 ± 212	2.26 ± 0.29	0.02 ± 0.00
Small Intestine	1884 ± 129	2.82 ± 0.19	0.06 ± 0.01
Kidney	6009 ± 1264	8.97 ± 1.81	0.13 ± 0.03
Liver	11580 ± 651	17.33 ± 1.17	1.32 ± 0.12
Muscle	268 ± 24	0.40 ± 0.04	0.42 ± 0.04
Plasma	1253 ± 50	1.87 ± 0.05	0.13 ± 0.01
Skin	581 ± 67	0.87 ± 0.11	0.27 ± 0.03
Stomach	2715 ± 751	4.06 ± 1.13	0.03 ± 0.01
Total			2.52 ± 0.15%
<u>100 mg/kg</u>			
Adipose	1890 ± 608	0.68 ± 0.14	0.19 ± 0.06
Blood	2825 ± 710	Unity	0.17 ± 0.04
Large Intestine	8162 ± 2231	2.89 ± 0.33	0.02 ± 0.01
Small Intestine	6918 ± 1939	2.45 ± 0.22	0.08 ± 0.03
Kidney	22530 ± 2294	8.22 ± 1.31	0.15 ± 0.04
Liver	31470 ± 4190	11.41 ± 1.56	1.20 ± 0.10
Muscle	1134 ± 141	0.42 ± 0.08	0.56 ± 0.07
Plasma	4393 ± 575	1.56 ± 0.21	0.14 ± 0.02
Skin	2515 ± 612	0.90 ± 0.15	0.37 ± 0.09
Stomach	25400 ± 17680	8.33 ± 3.94	0.09 ± 0.05
Total			2.87 ± 0.33

<sup>a</sup> Values are means ± standard deviations.

Table 3

Distribution of Radioactivity in Excreta Collected for 10 Days after  
Oral Administration of  $^{14}\text{C}$ -BDCM (10 mg/kg/day) to Male F-344 Rats (N=5)

Time at End of Interval (h)	% of Dose Recovered <sup>a</sup>					
	Volatiles	CO <sub>2</sub>	CO	Urine	Feces	Excreta
24	0.16 ± 0.05	8.49 ± 0.14	0.53 ± 0.03	0.46 ± 0.04	0.08 ± 0.03	9.72 ± 0.10
48	0.65 ± 0.71	8.47 ± 0.13	0.51 ± 0.05	0.47 ± 0.12	0.08 ± 0.04	9.65 ± 0.21
72	0.85 ± 0.67	7.42 ± 0.65	0.43 ± 0.02	0.38 ± 0.06	0.15 ± 0.05	9.22 ± 0.33
96	0.08 ± 0.02	7.96 ± 0.43	0.48 ± 0.03	0.41 ± 0.06	0.15 ± 0.04	9.08 ± 0.36
120	0.69 ± 0.68	7.55 ± 0.78	0.38 ± 0.09	0.32 ± 0.10	0.14 ± 0.05	9.09 ± 0.35
144	0.09 ± 0.03	8.21 ± 0.12	0.37 ± 0.11	0.43 ± 0.09	0.19 ± 0.08	9.29 ± 0.22
168	0.13 ± 0.08	8.28 ± 0.12	0.40 ± 0.04	0.36 ± 0.05	0.16 ± 0.03	9.33 ± 0.15
192	0.23 ± 0.17	9.17 ± 0.23	0.45 ± 0.07	0.49 ± 0.07	0.19 ± 0.03	10.53 ± 0.23
216	0.70 ± 0.55	7.80 ± 0.56	0.40 ± 0.08	0.36 ± 0.02	0.18 ± 0.05	9.45 ± 0.13
240	0.25 ± 0.11	8.13 ± 0.21	0.40 ± 0.08	0.48 ± 0.08	0.16 ± 0.06	9.42 ± 0.10
Total	3.31 ± 1.30	81.50 ± 1.48	4.33 ± 0.47	4.16 ± 0.24	1.48 ± 0.17	94.77 ± 0.23

<sup>a</sup> Values are means ± standard deviations.

Table 4

Comparison of Daily Excretion (at days 1, 3 and 10)  
of Radioactivity in Breath Collected  
after Daily Oral Administration  
of  $^{14}\text{C}$ -BDCM (10 mg/kg/day) for 10 Days

Time at End of Interval		% of Dose Recovered as <sup>a</sup>		
		Volatiles	CO <sub>2</sub>	CO
Day 1 (0-24 h)	1	2.0 ± 0.8	8.0 ± 2.0	
	4	0.8 ± 0.3	31.9 ± 2.3	1.9 ± 0.4
	8		26.1 ± 3.4	1.5 ± 0.4
	16		15.2 ± 2.6	
	24	0.1 ± 0.0	0.8 ± 0.1	0.9 ± 0.2
Day 3 (48-72 h)	1	2.8 ± 0.8	4.9 ± 4.0	
	4	5.0 ± 5.0	27.9 ± 12.7	1.4 ± 0.7
	8		31.2 ± 5.7	2.0 ± 0.7
	16		10.7 ± 4.7	
	24	0.8 ± 1.0	1.4 ± 0.7	0.8 ± 0.4
Day 10 (216-240 h)	1	1.2 ± 0.5	8.0 ± 2.4	
	4	1.2 ± 0.6	33.3 ± 1.7	1.8 ± 0.3
	8		30.4 ± 3.5	1.7 ± 0.4
	16		8.4 ± 2.7	
	24	0.1 ± 0.0	1.3 ± 0.1	0.5 ± 0.2

<sup>a</sup> Percent of single day's dose. Values are means ± standard deviations for N=5 rats.

Table 5  
 Tissue Distribution of Radioactivity 10 Days  
 after Daily Oral Administration of <sup>14</sup>C-BDCM (10 mg/kg/day)  
 to Male F-344 Rats (N=5)<sup>a</sup>

Tissue	ng-eq BDCM per g Tissue	Tissue-Blood Ratio	% Dose in Total Tissue
Adipose	881 ± 98	1.01 ± 0.13	0.09 ± 0.01
Blood	877 ± 16	Unity	0.06 ± 0.00
Large Intestine	1530 ± 193	1.74 ± 0.20	0.01 ± 0.00
Small Intestine	1680 ± 129	1.91 ± 0.12	0.02 ± 0.00
Kidney	5710 ± 574	6.51 ± 0.63	0.04 ± 0.00
Liver	12500 ± 875	14.30 ± 0.81	0.46 ± 0.01
Muscle	513 ± 39	0.59 ± 0.04	0.26 ± 0.02
Plasma	1160 ± 25	1.32 ± 0.01	0.04 ± 0.00
Skin	1080 ± 123	1.23 ± 0.16	0.16 ± 0.02
Stomach	1760 ± 127	2.01 ± 0.12	0.01 ± 0.00
Total			1.11 ± 0.04%

<sup>a</sup> Values are means ± standard deviations.

Table 6

Distribution of Radioactivity in Excreta Collected for 10 Days after  
Oral Administration of  $^{14}\text{C}$ -BDCM (100 mg/kg/day) to Male F-344 Rats (N=4)

Time at End of Interval (h)	% of Dose Recovered <sup>a</sup>					Total Excreta
	Volatiles	CO <sub>2</sub>	CO	Urine	Feces	
24	0.47 ± 0.17	7.07 ± 0.19	0.49 ± 0.04	0.47 ± 0.06	0.04 ± 0.01	8.55 ± 0.18
48	0.51 ± 0.12	7.71 ± 0.13	0.41 ± 0.17	0.60 ± 0.02	0.17 ± 0.07	9.39 ± 0.25
72	0.76 ± 0.04 <sup>b</sup>	7.01 ± 0.59	0.39 ± 0.03	0.49 ± 0.03	0.13 ± 0.02	9.17 ± 0.24
96	0.68 ± 0.22	7.61 ± 0.33	0.35 ± 0.11	0.54 ± 0.08	0.13 ± 0.01	9.31 ± 0.17
120	0.59 ± 0.13	7.89 ± 0.47	0.40 ± 0.03	0.54 ± 0.02	0.14 ± 0.03	9.56 ± 0.37
144	0.60 ± 0.24	7.72 ± 0.25	0.37 ± 0.07	0.56 ± 0.07	0.17 ± 0.01	9.42 ± 0.20
168	0.65 ± 0.22	7.67 ± 0.27	0.36 ± 0.05	0.50 ± 0.07	0.17 ± 0.04	9.35 ± 0.10
192	0.82 ± 0.40	7.53 ± 0.42	0.35 ± 0.08	0.53 ± 0.07	0.19 ± 0.03	9.41 ± 0.19
216	0.67 ± 0.18	7.94 ± 0.07	0.32 ± 0.07	0.45 ± 0.07	0.17 ± 0.04	9.56 ± 0.20
240	0.61 ± 0.23	8.00 ± 0.24	0.29 ± 0.11	0.57 ± 0.05	0.18 ± 0.02	9.65 ± 0.21
Total	6.74 ± 1.76	76.14 ± 1.83	3.73 ± 0.58	5.24 ± 0.31	1.50 ± 0.09	93.4 ± 0.9

<sup>a</sup> Values are means ± standard deviations.

<sup>b</sup> N = 3

Table 7

Percentage<sup>a</sup> of Daily Dose of [<sup>14</sup>C]BDCM (100 mg/kg/day)  
 Appearing as <sup>14</sup>CO<sub>2</sub> During the 8 h Period Post Dosing

Day	
1	29.9 ± 8.5
2	61.2 ± 4.4
3	55.2 ± 5.1
4	56.7 ± 6.1
5	59.3 ± 3.8
6	56.3 ± 5.0
7	58.3 ± 3.0
8	56.4 ± 6.0
9	60.6 ± 6.3
10	61.7 ± 4.2

<sup>a</sup> Values are means ± SD for N = 4 rats, N = 3 for day 1.



Table 8

Comparison of Daily Excretion (at days 1, 3 and 10)  
of Radioactivity in Breath Collected  
after Daily Oral Administration  
of  $^{14}\text{C}$ -BDCM (100 mg/kg/day) for 10 Days

Time at End of Interval		% of Dose Recovered as <sup>a</sup>		
		Volatiles	CO <sub>2</sub>	CO
Day 1 (0-24 h)	1	2.4 ± 0.4	3.1 ± 0.9	
	4	1.0 ± 0.6	13.6 ± 1.8	1.1 ± 0.2
	8		13.8 ± 7.2 <sup>b</sup>	0.9 ± 0.4
	16		32.6 ± 3.9 <sup>b</sup>	
	24	1.4 ± 0.8	7.8 ± 3.3	3.0 ± 0.7
Day 3 (48-72 h)	1	3.9 ± 0.2 <sup>c</sup>	4.5 ± 0.6	
	4	2.6 ± 0.6 <sup>c</sup>	25.1 ± 2.1	1.6 ± 0.2
	8		25.5 ± 4.1	1.5 ± 0.1
	16		13.2 ± 3.4	
	24	1.1 ± 0.3 <sup>c</sup>	1.7 ± 0.9	0.8 ± 0.3
Day 10 (216-240 h)	1	2.6 ± 1.3	4.8 ± 0.6	
	4	2.4 ± 1.0	26.9 ± 1.1	1.2 ± 0.3
	8		30.1 ± 3.2	1.1 ± 0.5
	16		16.6 ± 3.3	
	24	1.0 ± 0.3	1.7 ± 0.3	0.5 ± 0.3

<sup>a</sup> Percent of single day's dose. Values are means ± standard deviations for N = 4 rats, unless otherwise noted.

<sup>b</sup> N = 3 rats (traps for one rat at 8 h not changed).

<sup>c</sup> N = 3 rats (minor dosing problem).

Table 9

Tissue Distribution of Radioactivity 10 Days after Daily Oral Administration of  $^{14}\text{C}$ -BDCM (100 mg/kg/day) to Male F-344 Rats (N=4)<sup>a</sup>

Tissue	$\mu\text{g-eq BDCM}$ per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	9.2 $\pm$ 1.9	1.99 $\pm$ 0.59	0.09 $\pm$ 0.02
Blood	4.7 $\pm$ 0.4	unity	0.03 $\pm$ 0.00
Large Intestine	14.2 $\pm$ 0.8	3.03 $\pm$ 0.45	0.01 $\pm$ 0.00
Small Intestine	14.8 $\pm$ 1.8	3.18 $\pm$ 0.70	0.02 $\pm$ 0.00
Kidney	64.2 $\pm$ 2.4	13.64 $\pm$ 1.55	0.04 $\pm$ 0.00
Liver	69.3 $\pm$ 6.1	14.72 $\pm$ 1.84	0.27 $\pm$ 0.02
Muscle	5.4 $\pm$ 0.2	1.14 $\pm$ 0.12	0.27 $\pm$ 0.01
Plasma	11.7 $\pm$ 0.4	2.49 $\pm$ 0.29	0.04 $\pm$ 0.00
Skin	10.4 $\pm$ 0.8	2.21 $\pm$ 0.31	0.16 $\pm$ 0.01
Stomach	14.0 $\pm$ 2.0	2.99 $\pm$ 0.63	0.01 $\pm$ 0.00
Total			0.90 $\pm$ 0.03

<sup>a</sup> Values are means  $\pm$  standard deviations.