

1 - ブロモブタンのマウスを用いた
吸入による2週間毒性試験報告書

試験番号 : 0481

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2-WEEK INHALATION STUDY OF 1-BROMOBUTANE
(SACRIFICED ANIMALS)

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Week-Day on Study	Control		500ppm			1000ppm			2000ppm			4000ppm			8000ppm		
	Av.Wt.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.
	< 5>		< 5>			< 5>			< 5>			< 5>			< 5>		
0-0	23.1 (5)	5/5	23.1 (5)	100	5/5	23.1 (5)	100	5/5	23.1 (5)	100	5/5	23.1 (5)	100	5/5	23.1 (5)	100	5/5
1-2	23.5 (5)	5/5	22.6 (5)	96	5/5	19.7 (1)	84	1/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
1-4	23.8 (5)	5/5	23.2 (5)	97	5/5	17.2 (1)	72	1/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
1-7	24.4 (5)	5/5	23.5 (5)	96	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
2-3	24.8 (5)	5/5	25.0 (5)	101	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
2-7	25.3 (5)	5/5	24.8 (5)	98	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5

< > : No.of effective animals, () : No.of measured animals Av.Wt. : Average body weight (Unit : g).

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Week-Day on Study	Control		500ppm			1000ppm			2000ppm			4000ppm			8000ppm		
	Av.Wt.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.	Av.Wt.	% of cont.	No.of Surviv.
	< 5>		< 5>			< 5>			< 5>			< 5>			< 5>		
0-0	19.2 (5)	5/5	19.1 (5)	99	5/5	19.1 (5)	99	5/5	19.2 (5)	100	5/5	19.2 (5)	100	5/5	19.2 (5)	100	5/5
1-2	19.2 (5)	5/5	18.5 (5)	96	5/5	18.2 (5)	95	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
1-4	19.4 (5)	5/5	19.3 (5)	99	5/5	19.0 (5)	98	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
1-7	19.6 (5)	5/5	19.3 (5)	98	5/5	19.1 (5)	97	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
2-3	20.7 (5)	5/5	20.4 (5)	99	5/5	18.6 (5)	90	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5
2-7	20.8 (5)	5/5	19.6 (5)	94	5/5	17.5 (5)	84	5/5	- (-)	-	0/5	- (-)	-	0/5	- (-)	-	0/5

< > : No.of effective animals, () : No.of measured animals Av.Wt. : Average body weight (Unit : g).

TABLE 3 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Week-Day on Study	Control		500ppm			1000ppm			2000ppm			4000ppm			8000ppm		
	Av.Fc.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.
	< 5>		< 5>			< 5>			< 5>			< 5>			< 5>		
1-7	4.4 (5)	5/ 5	4.1 (5)	93	5/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5
2-7	4.2 (5)	5/ 5	4.5 (5)	107	5/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5

< > : No.of effective animals, () : No.of measured animals Av.Fc. : Average food consumption (Unit : g).

TABLE 4 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Week-Day on Study	Control		500ppm			1000ppm			2000ppm			4000ppm			8000ppm		
	Av.Fc.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.	Av.Fc.	% of cont.	No.of Surviv.
	< 5>		< 5>			< 5>			< 5>			< 5>			< 5>		
1-7	3.5 (5)	5/ 5	3.7 (5)	106	5/ 5	3.7 (5)	106	5/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5
2-7	3.7 (5)	5/ 5	3.9 (5)	105	5/ 5	3.3 (5)	89	5/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5	- (-)	-	0/ 5

< > : No.of effective animals, () : No.of measured animals Av.Fc. : Average food consumption (Unit : g).

TABLE 5 HEMATOLOGY OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	4	0	0	0	0
RED BLOOD CELL ($10^6/\mu\text{L}$)	11.08 \pm 0.34	10.40 \pm 0.21 **	—	—	—	—
HEMOGLOBIN (g/dL)	16.4 \pm 0.5	15.3 \pm 0.3 **	—	—	—	—
HEMATOCRIT (%)	51.1 \pm 2.0	48.2 \pm 0.8 *	—	—	—	—
Differential WBC(%)						
N-SEG	16 \pm 7	7 \pm 1 *	—	—	—	—
LYMPHO	80 \pm 5	89 \pm 1 *	—	—	—	—

Mean \pm S.D.
^{*)} Significant difference, $p < 0.05$ (Test of t)
^{**)} Significant difference, $p < 0.01$ (Test of t)

TABLE 6 HEMATOLOGY OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	5	5	0	0	0
RED BLOOD CELL ($10^6/\mu\text{L}$)	11.14 \pm 0.19	10.46 \pm 0.23 **	10.49 \pm 0.29 **	—	—	—
HEMOGLOBIN (g/dL)	16.5 \pm 0.2	15.7 \pm 0.4 *	15.5 \pm 0.5 **	—	—	—
HEMATOCRIT (%)	51.0 \pm 0.8	48.4 \pm 0.9 **	47.4 \pm 1.4 **	—	—	—
MCH (pg)	14.8 \pm 0.1	15.0 \pm 0.1 *	14.7 \pm 0.1	—	—	—
WBC ($10^3/\mu\text{L}$)	1.84 \pm 0.79	1.33 \pm 0.23	0.78 \pm 0.45 *	—	—	—

Mean \pm S.D.
^{*)} Significant difference, $p < 0.05$ (Test of Dunnett)
^{**)} Significant difference, $p < 0.01$ (Test of Dunnett)

TABLE 7 BIOCHEMISTRY OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	5	0	0	0	0
TOTAL PROTEIN(g/dL)	5.2 ± 0.3	4.9 ± 0.1 *	—	—	—	—
T-CHOLESTEROL(mg/dL)	75 ± 10	100 ± 15 *	—	—	—	—
ALP(IU/L)	280 ± 16	249 ± 12 **	—	—	—	—
UREA NITROGEN(mg/dL)	28.3 ± 3.8	14.7 ± 1.4 **	—	—	—	—
CHLORIDE (mEq/L)	118 ± 2	121 ± 2 *	—	—	—	—

Mean ± S.D.
^{*)} Significant difference, p<0.05 (Test of t)
^{**)} Significant difference, p<0.01 (Test of t)

TABLE 8 BIOCHEMISTRY OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	5	5	0	0	0
T-CHOLESTEROL(mg/dL)	75 ± 9	92 ± 10	109 ± 23 **	—	—	—
ALP(IU/L)	413 ± 46	328 ± 12 **	340 ± 46 *	—	—	—
UREA NITROGEN(mg/dL)	24.7 ± 2.8	13.4 ± 3.0 **	14.3 ± 7.1 **	—	—	—

Mean ± S.D.
^{*)} Significant difference, p<0.05 (Test of Dunnett)
^{**)} Significant difference, p<0.01 (Test of Dunnett)

TABLE 9 ORGAN WEIGHTS OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	5	0	0	0	0
Body weight (g)	21.4 ± 0.9	21.6 ± 1.0	—	—	—	—
Thymus (g)	0.049 ± 0.006	0.028 ± 0.005 **	—	—	—	—
Thymus (%)	0.227 ± 0.027	0.130 ± 0.023 **	—	—	—	—
Liver (g)	0.962 ± 0.032	1.077 ± 0.084 *	—	—	—	—
Liver (%)	4.490 ± 0.215	4.974 ± 0.224 **	—	—	—	—

Mean ± S.D.
^{*)} Significant difference, p<0.05 (Test of t)
^{**)} Significant difference, p<0.01 (Test of t)

TABLE 10 ORGAN WEIGHTS OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE

Group Name	Control	500 ppm	1000 ppm	2000 ppm	4000 ppm	8000 ppm
No. of examined animals	5	5	5	0	0	0
Body weight (g)	17.2 ± 0.8	16.9 ± 1.0	15.3 ± 1.1 *	—	—	—
Thymus (g)	0.061 ± 0.006	0.032 ± 0.002 **	0.022 ± 0.009 **	—	—	—
Thymus (%)	0.356 ± 0.043	0.192 ± 0.018 **	0.141 ± 0.054 **	—	—	—
Adrenals (g)	0.009 ± 0.002	0.010 ± 0.001	0.011 ± 0.002	—	—	—
Adrenals (%)	0.050 ± 0.011	0.057 ± 0.007	0.071 ± 0.011 *	—	—	—
Ovaries (g)	0.022 ± 0.005	0.016 ± 0.004	0.014 ± 0.002 *	—	—	—
Ovaries (%)	0.129 ± 0.027	0.095 ± 0.025	0.092 ± 0.008 *	—	—	—
Lungs (g)	0.124 ± 0.005	0.136 ± 0.012	0.137 ± 0.005 *	—	—	—
Lungs (%)	0.719 ± 0.025	0.802 ± 0.037	0.899 ± 0.085 **	—	—	—
Kidneys (g)	0.231 ± 0.009	0.248 ± 0.016	0.236 ± 0.010	—	—	—
Kidneys (%)	1.346 ± 0.012	1.470 ± 0.096 *	1.546 ± 0.105 **	—	—	—
Spleen (g)	0.036 ± 0.005	0.029 ± 0.002	0.026 ± 0.006 **	—	—	—
Spleen (%)	0.208 ± 0.020	0.172 ± 0.007 *	0.166 ± 0.027 *	—	—	—
Liver (g)	0.753 ± 0.047	0.814 ± 0.045	0.806 ± 0.060	—	—	—
Liver (%)	4.380 ± 0.171	4.825 ± 0.104 *	5.267 ± 0.310 **	—	—	—

Mean ± S.D.
^{*)} Significant difference, p<0.05 (Test of Dunnett)
^{**)} Significant difference, p<0.01 (Test of Dunnett)

TABLE 11 INCIDENCES OF SELECTED LESIONS OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE
(DEAD AND MORIBUND ANIMALS)

Group Name No. of Animals on Study Grade	Control				500ppm				1000ppm				2000ppm				4000ppm				8000ppm			
	0				0				5				5				5				5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
nasal cavity									< 5>				< 5>				< 5>				< 5>			
necrosis:olfactory epithelium	—				—				3	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0
lung									< 5>				< 5>				< 5>				< 5>			
congestion	—				—				1	0	0	0	0	4	1	0	0	0	0	0	0	0	0	0
hemorrhage	—				—				0	0	0	0	0	1	0	0	0	2	0	0	3	0	0	0
edema: alveolus	—				—				0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
edema:perivascular	—				—				3	2	0	0	4	1	0	0	4	0	0	0	0	0	0	0
thymus									< 5>				< 5>				< 5>				< 5>			
atrophy	—				—				0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
spleen									< 5>				< 5>				< 5>				< 5>			
atrophy	—				—				1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
heart									< 5>				< 5>				< 5>				< 5>			
hemorrhage	—				—				0	0	0	0	3	0	0	0	3	2	0	0	0	0	0	0
ground glass appearance	—				—				0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
liver									< 5>				< 5>				< 5>				< 5>			
necrosis:central	—				—				0	0	1	0	5	0	0	0	0	0	0	0	0	0	0	0
vacuolic change	—				—				5	0	0	0	4	1	0	0	5	0	0	0	1	4	0	0
hydropic change	—				—				1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
hemorrhage:central	—				—				0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0
hemorrhage:portal	—				—				0	0	0	0	0	1	0	0	0	2	3	0	0	0	0	0
kidney									< 5>				< 5>				< 5>				< 5>			
tubular necrosis:proximale tubule	—				—				0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 11 INCIDENCES OF SELECTED LESIONS OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE
(DEAD AND MORIBUND ANIMALS) (CONTINUE)

Group Name	Control				500ppm				1000ppm				2000ppm				4000ppm				8000ppm			
No. of Animals on Study	0				0				5				5				5				5			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
testis									< 5>				< 5>				< 5>				< 5>			
germ cell necrosis	—				—				0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0

Grade 1: Slight 2: Moderate 3: Marked 4: Severe
 < > : Number of animals examined at the site
 — : All animals survived at the terminal necropsy

TABLE 12 INCIDENCES OF SELECTED LESIONS OF MALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE (SACRIFICED ANIMALS)

Group Name No. of Animals on Study Grade	Control				500ppm				1000ppm				2000ppm				4000ppm				8000ppm			
	0				0				0				5				5				5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
nasal cavity	< 5>				< 5>																			
atrophy:olfactory epithelium	0	0	0	0	5	0	0	0	—				—				—				—			
lung	< 5>				< 5>																			
basophilic change:bronchiole	0	0	0	0	5	0	0	0	—				—				—				—			
thymus	< 5>				< 5>																			
atrophy	0	0	0	0	2	0	0	0	—				—				—				—			
stomach	< 5>				< 5>																			
erosion:forestomach	0	0	0	0	1	0	0	0	—				—				—				—			
hyperplasia:forestomach	0	0	0	0	0	2	0	0	—				—				—				—			
liver	< 5>				< 5>																			
necrosis:focal	0	0	0	0	0	1	0	0	—				—				—				—			

Grade 1: Slight 2: Moderate 3: Marked 4: Severe
 < > : Number of animals examined at the site
 — : All animals died before the terminal necropsy

TABLE 13 INCIDENCES OF SELECTED LESIONS OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE
(DEAD AND MORIBUND ANIMALS)

Group Name No. of Animals on Study Grade	Control				500ppm				1000ppm				2000ppm				4000ppm				8000ppm			
	0				0				0				5				5				5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
nasal cavity													< 5>				< 5>				< 5>			
necrosis:olfactory epithelium	—				—				—				4	0	0	0	0	0	0	0	0	0	0	0
lung													< 5>				< 5>				< 5>			
congestion	—				—				—				1	1	0	0	0	0	0	0	0	0	0	0
hemorrhage	—				—				—				0	0	0	0	1	0	0	0	3	0	0	0
edema:perivascular	—				—				—				4	1	0	0	1	0	0	0	0	0	0	0
heart													< 5>				< 5>				< 5>			
hemorrhage	—				—				—				2	0	0	0	1	0	0	0	0	0	0	0
ground glass appearance	—				—				—				0	3	2	0	0	3	1	0	0	0	0	0
liver													< 5>				< 5>				< 5>			
vacuolic change	—				—				—				4	0	0	0	0	5	0	0	0	5	0	0
hemorrhage:central	—				—				—				0	0	5	0	0	0	0	0	0	0	0	0
hemorrhage:portal	—				—				—				0	0	0	0	0	3	1	0	0	0	0	0

Grade 1: Slight 2: Moderate 3: Marked 4: Severe
 < > : Number of animals examined at the site
 — : All animals survived at the terminal necropsy

TABLE 14 INCIDENCES OF SELECTED LESIONS OF FEMALE MICE IN THE 2-WEEK INHALATION STUDY OF 1-BROMOBUTANE (SACRIFICED ANIMALS)

Group Name No. of Animals on Study Grade	Control				500ppm				1000ppm				2000ppm				4000ppm				8000ppm			
	5				5				5				0				0				0			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
nasal cavity	< 5>				< 5>				< 5>															
atrophy:olfactory epithelium	0	0	0	0	5	0	0	0	5	0	0	0	—				—				—			
lung	< 5>				< 5>				< 5>															
basophilic change:bronchiole	0	0	0	0	5	0	0	0	5	0	0	0	—				—				—			
thymus	< 5>				< 5>				< 5>															
atrophy	0	0	0	0	4	0	0	0	5	0	0	0	—				—				—			
stomach	< 5>				< 5>				< 5>															
erosion:forestomach	0	0	0	0	1	0	0	0	0	1	0	0	—				—				—			
ulcer:forestomach	0	0	0	0	1	0	0	0	0	0	0	0	—				—				—			
hyperplasia:forestomach	0	0	0	0	0	3	0	0	1	0	1	0	—				—				—			
adrenal gland	< 5>				< 5>				< 5>															
necrosis:cortex	0	0	0	0	0	0	0	0	0	2	0	0	—				—				—			

Grade 1: Slight 2: Moderate 3: Marked 4: Severe
 < > : Number of animals examined at the site
 — : All animals died before the terminal necropsy