Summary of Inhalation Carcinogenicity Study of 1-Bromo-3-Chloropropane in BDF1 Mice

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Japan Bioassay Research Center

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PREFACE

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on March 25 2005.

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Purpose, materials and methods

1-Bromo-3-chloropropane (BCP, CAS No. 109-70-6) is a colorless liquid with a boiling point of 143.3°C and a melting point of −58.9°C. It is poorly soluble in water and soluble in methanol and diethyl ether.

The carcinogenicity and chronic toxicity of BCP were examined by inhalation exposure of groups of 50 Crj:BDF1 mice of both sexes to BCP vapor at a target concentration of 0 (clean air), 25, 100 or 400 ppm (v/v) for 6 hours/day, 5 days/week for 2 years (104 weeks). The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in the previous 13-week toxicity study. BCP was analyzed for purity and stability by both infrared spectrometry and gas chromatography before and after its use. Stainless-steel inhalation exposure chambers (volume: 3700 L) were used throughout the 2-year exposure period. BCP vapor-air mixture was generated by bubbling clean air through the BCP liquid, and supplied to the inhalation exposure chambers. Air concentrations of BCP vapor in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year exposure period underwent complete necropsy. Urinalysis was performed near the end of the 2-year exposure period. For hematology and blood biochemistry, the surviving animals were bled under ether anesthesia, after they were fasted overnight, at the terminal necropsy. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were fixed and embedded in paraffin. Tissue sections of 5 μm thick were prepared and stained with hematoxylin and eosin and examined for histopathology. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. A positive trend of the dose-response relation for the neoplastic incidence was analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present study was conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

As neoplastic lesions, the incidences of bronchiolar-alveolar carcinomas and adenomas, adenosquamous carcinoma, squamous carcinoma of lung, squamous cell papillomas of the forestomach and Harderian gland adenomas were increased in the BCP-exposed males. The incidences of bronchiolar-alveolar carcinomas and adenomas of lung, squamous cell papillomas and carcinomas of the forestomach, and Harderian gland adenomas were increased in the BCP-exposed females. As pre-neoplastic lesions, the incidences of bronchiolar-alveolar cell hyperplasia and squamous cell hyperplasia of the forestomach in both BCP-exposed males and females and hyperplasia of the Harderian gland in the BCP-exposed males were increased.

As non-neoplastic lesions in the nasal cavity, the incidences of respiratory metaplasia, atrophy, eosinophilic change and appearance of exudates in the olfactory epithelium, respiratory metaplasia in the nasal gland, and eosinophilic change and appearance of exudates in the nasopharynx were increased in the BCP-exposed groups of both sexes. BCP influenced the hematological data.

Conclusions

In mice, there was clear evidence of carcinogenic activity of BCP in males and females, based on the increased incidences of bronchiolar-alveolar adenomas and carcinomas. The increased incidences of squamous cell papillomas of the forestomach and Harderian gland adenomas, and adenosquamous carcinoma and squamous carcinoma of lung in the BCP-exposed males, and the increased incidences of squamous cell papillomas and carcinomas of the forestomach, and Harderian gland adenomas in the BCP-exposed females were noted.

TABLES

TABLES (CONTINUED)

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Weeks on Study	Control Av.Wt.	Control No.of Surviv. <50>	25 ppm Av.Wt.	25 ppm % of cont.	25 ppm No.of Surviv. <50>	100 ppm Av.Wt.	100 ppm % of cont.	100 ppm No.of Surviv. <50>	400 ppm Av.Wt.	400 ppm % of cont.	400 ppm No.of Surviv. <50>
0	23.0 (50)	50/50	23.0 (50)	100	50/50	23.0 (50)	100	50/50	23.0 (50)	100	50/50
1	24.0 (50)	50/50	24.2 (50)	101	50/50	23.8 (50)	99	50/50	23.0 (50)	96	50/50
2	24.9 (50)	50/50	25.0 (50)	100	50/50	24.7 (50)	99	50/50	23.6 (50)	95	50/50
3	25.6 (50)	50/50	25.5 (50)	100	50/50	24.9 (50)	97	50/50	24.1 (50)	94	50/50
4	26.2 (50)	50/50	25.8 (50)	98	50/50	26.9 (50)	103	50/50	25.3 (50)	97	50/50
5	26.7 (50)	50/50	26.3 (50)	99	50/50	26.5 (50)	99	50/50	24.9 (50)	93	50/50
6	27.3 (50)	50/50	27.1 (50)	99	50/50	26.8 (50)	98	50/50	25.6 (50)	94	50/50
7	27.9 (50)	50/50	27.5 (50)	99	50/50	27.1 (50)	97	50/50	26.0 (50)	93	50/50
8	28.3 (50)	50/50	28.1 (50)	99	50/50	27.6 (50)	98	50/50	26.6 (50)	94	50/50
9	29.0 (50)	50/50	28.5 (50)	98	50/50	28.0 (50)	97	50/50	27.1 (50)	93	50/50
10	29.5 (50)	50/50	29.1 (50)	99	50/50	28.4 (50)	96	50/50	27.5 (50)	93	50/50
11	30.0 (50)	50/50	29.7 (50)	99	50/50	29.0 (50)	97	50/50	27.9 (50)	93	50/50
12	30.6 (50)	50/50	30.3 (50)	99	50/50	29.6 (50)	97	50/50	28.1 (50)	92	50/50
13	31.1 (50)	50/50	30.7 (50)	99	50/50	30.1 (50)	97	50/50	28.6 (50)	92	50/50
14	31.7 (50)	50/50	31.4 (50)	99	50/50	30.6 (50)	97	50/50	29.4 (50)	93	50/50
18	33.8 (50)	50/50	33.7 (50)	100	50/50	32.9 (50)	97	50/50	31.4 (50)	93	50/50
22	36.1 (50)	50/50	35.9 (50)	99	50/50	35.1 (50)	97	50/50	33.0 (50)	91	50/50
26	38.0 (50)	50/50	37.9 (50)	100	50/50	36.4 (50)	96	50/50	34.5 (50)	91	50/50
30	39.4 (50)	50/50	39.1 (50)	99	50/50	37.7 (50)	96	50/50	35.5 (50)	90	50/50
34	41.0 (50)	50/50	40.7 (50)	99	50/50	39.2 (49)	96	49/50	36.4 (50)	89	50/50
38	42.2 (50)	50/50	42.0 (50)	100	50/50	40.0 (49)	95	49/50	37.9 (50)	90	50/50
42	43.0 (50)	50/50	42.8 (50)	100	50/50	40.7 (49)	95	49/50	37.3 (50)	87	50/50
46	43.3 (50)	50/50	43.5 (50)	100	50/50	40.9 (49)	94	49/50	38.0 (50)	88	50/50
50	44.0 (49)	49/50	44.8 (50)	102	50/50	41.7 (49)	95	49/50	39.2 (50)	89	50/50
54	45.4 (48)	48/50	45.4 (50)	100	50/50	42.0 (48)	93	48/50	39.8 (50)	88	50/50
58	45.7 (48)	48/50	46.2 (50)	101	50/50	42.2 (48)	92	48/50	40.1 (49)	88	49/50
62	45.9 (46)	46/50	47.1 (49)	103	49/50	43.2 (48)	94	48/50	40.6 (48)	88	48/50
66	47.2 (45)	45/50	47.9 (49)	101	49/50	44.3 (48)	94	48/50	41.3 (48)	88	48/50
70	47.1 (45)	45/50	48.3 (47)	103	47/50	44.6 (48)	95	48/50	41.4 (48)	88	48/50
74	47.5 (45)	45/50	48.4 (47)	102	47/50	45.1 (47)	95	47/50	41.3 (48)	87	48/50
78	47.7 (44)	44/50	48.6 (47)	102	47/50	44.8 (45)	94	45/50	41.6 (48)	87	48/50
82	48.1 (43)	43/50	49.0 (45)	102	45/50	45.3 (44)	94	44/50	42.1 (48)	88	48/50
86	49.2 (42)	42/50	50.0 (44)	102	44/50	46.3 (42)	94	42/50	43.1 (47)	88	47/50
90	48.8 (40)	40/50	49.6 (44)	102	44/50	46.3 (42)	95	42/50	43.5 (45)	89	45/50
94	48.5 (40)	40/50	49.1 (41)	101	41/50	45.6 (41)	94	41/50	42.8 (42)	88	42/50
98	48.3 (40)	40/50	48.3 (40)	100	40/50	45.4 (39)	94	39/50	43.2 (39)	89	39/50
102	47.0 (38)	38/50	45.9 (36)	98	36/50	42.9 (37)	91	37/50	40.8 (38)	87	38/50
104	46.8 (38)	38/50	45.5 (33)	97	33/50	42.2 (37)	90	37/50	40.0 (36)	85	36/50

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

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Weeks on Study	Control Av.Wt.	Control No.of Surviv.	25 ppm Av.Wt.	25 ppm % of cont.	25 ppm No.of Surviv.	100 ppm Av.Wt.	100 ppm % of cont.	100 ppm No.of Surviv.	400 ppm Av.Wt.	400 ppm % of cont.	400 ppm No.of Surviv.
	<50>		<49>			<50>			<50>		
0	18.6 (50)	50/50	18.6 (49)	100	49/49	18.6 (50)	100	50/50	18.6 (50)	100	50/50
1	19.1 (50)	50/50	19.3 (49)	101	49/49	19.2 (50)	101	50/50	18.6 (50)	97	50/50
2	20.0 (50)	50/50	20.2 (49)	101	49/49	19.9 (50)	100	50/50	19.1 (50)	96	50/50
3	20.5 (50)	50/50	20.4 (49)	100	49/49	20.3 (50)	99	50/50	19.6 (50)	96	50/50
4	21.0 (50)	50/50	20.9 (49)	100	49/49	21.6 (50)	103	50/50	20.4 (50)	97	50/50
5	21.5 (50)	50/50	21.4 (49)	100	49/49	21.5 (50)	100	50/50	20.6 (50)	96	50/50
6	22.1 (50)	50/50	22.1 (49)	100	49/49	22.1 (50)	100	50/50	21.1 (50)	95	50/50
7	22.4 (50)	50/50	22.3 (49)	100	49/49	22.2 (50)	99	50/50	21.6 (50)	96	50/50
8	22.7 (50)	50/50	22.8 (49)	100	49/49	22.5 (50)	99	50/50	21.9 (50)	96	50/50
9	23.1 (50)	50/50	23.0 (49)	100	49/49	23.2 (50)	100	50/50	21.9 (50)	95	50/50
10	23.2 (50)	50/50	23.2 (49)	100	49/49	23.0 (50)	99	50/50	22.3 (50)	96	50/50
11	23.5 (50)	50/50	23.6 (49)	100	49/49	23.3 (50)	99	50/50	22.7 (50)	97	50/50
12	23.7 (50)	50/50	23.8 (49)	100	49/49	23.8 (50)	100	50/50	23.0 (50)	97	50/50
13	24.0 (50)	50/50	23.7 (49)	99	49/49	23.7 (50)	99	50/50	23.3 (50)	97	50/50
14	24.3 (50)	50/50	24.2 (49)	100	49/49	24.1 (50)	99	50/50	23.5 (50)	97	50/50
18	25.3 (50)	50/50	25.4 (49)	100	49/49	25.1 (50)	99	50/50	24.3 (50)	96	50/50
22	26.2 (50)	50/50	26.2 (49)	100	49/49	25.6 (50)	98	50/50	24.8 (50)	95	50/50
26	26.7 (50)	50/50	27.0 (49)	101	49/49	26.4 (50)	99	50/50	25.4 (50)	95	50/50
30	27.4 (50)	50/50	27.8 (49)	101	49/49	26.8 (50)	98	50/50	25.8 (50)	94	50/50
34	27.9 (50)	50/50	28.5 (49)	102	49/49	27.4 (50)	98	50/50	26.1 (50)	94	50/50
38	28.4 (49)	49/50	28.7 (49)	101	49/49	27.9 (50)	98	50/50	26.6 (50)	94	50/50
42	29.1 (49)	49/51	29.4 (49)	101	49/49	27.9 (50)	96	50/50	26.4 (50)	91	50/50
46	28.8 (49)	49/52	29.4 (49)	102	49/49	27.9 (50)	97	50/50	26.7 (50)	93	50/50
50	29.7 (49)	49/53	29.7 (49)	100	49/49	28.4 (49)	96	49/50	26.9 (50)	91	50/50
54	29.8 (49)	49/54	30.2 (48)	101	48/49	28.6 (49)	96	49/50	27.0 (50)	91	50/50
58	30.0 (49)	49/55	30.7 (48)	102	48/49	28.7 (49)	96	49/50	27.2 (50)	91	50/50
62	30.4 (49)	49/56	31.4 (47)	103	47/49	29.3 (49)	96	49/50	27.0 (49)	89	49/50
66	30.6 (49)	49/57	32.2 (47)	105	47/49	29.6 (49)	97	49/50	27.2 (48)	89	48/50
70	30.7 (49)	49/58	31.5 (46)	103	46/49	29.3 (49)	95	49/50	27.3 (48)	89	48/50
74	31.4 (49)	49/59	32.5 (46)	104	46/49	30.0 (49)	96	49/50	27.2 (47)	87	47/50
78	31.8 (48)	48/50	32.3 (45)	102	45/49	29.7 (46)	93	46/50	27.3 (46)	86	46/50
82	32.0 (45)	45/50	32.2 (41)	101	41/49	29.6 (45)	93	45/50	27.6 (46)	86	46/50
86	31.6 (44)	44/50	33.0 (39)	104	39/49	29.6 (44)	94	44/50	28.3 (44)	90	44/50
90	31.6 (40)	40/50	33.7 (37)	107	37/49	29.4 (44)	93	44/50	28.4 (42)	90	42/50
94	31.5 (38)	38/50	33.2 (32)	105	32/49	30.2 (40)	96	40/50	28.6 (39)	91	39/50
98	32.0 (36)	36/50	33.1 (29)	103	29/49	30.2 (38)	94	38/50	28.8 (36)	90	36/50
102	31.4 (32)	32/50	32.0 (25)	102	25/49	30.5 (33)	97	33/50	28.1 (35)	89	35/50
104	31.6 (30)	30/50	31.9 (24)	101	24/49	30.4 (32)	96	32/50	28.1 (33)	89	33/50

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

TABLE 3 INCIDENCES OF EXTERNAL AND INTERNAL MASSES IN CLINICAL OBSERVATION OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	Control	0/50	0/50	0/50	0/50	0/48	1/45	2/43	2/40	4/50 (1/12)
	25 ppm	0/50	0/50	0/50	0/50	0/50	0/49	1/47	1/43	1/50 (1/17)
	100 ppm	0/50	0/50	0/50	0/49	0/48	0/48	1/45	2/42	3/50 (0/13)
	400 ppm	0/50	0/50	0/50	0/50	0/50	0/48	2/48	5/44	6/50 (1/14)
Internal mass										
	Control	0/50	0/50	0/50	2/50	4/48	2/45	3/43	8/40	12/50 (5/12)
	25 ppm	0/50	0/50	0/50	0/50	0/50	1/49	3/47	8/43	9/50 (6/17)
	100 ppm	0/50	2/50	2/50	3/49	1/48	1/48	3/45	2/42	7/50 (5/13)
	400 ppm	3/50	5/50	5/50	6/50	5/50	3/48	3/48	3/44	7/50 (4/14)

No. of animals with mass / No. of surviving animals at the first week in each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 4 INCIDENCES OF EXTERNAL AND INTERNAL MASSES IN CLINICAL OBSERVATION OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	Control	0/50	0/50	0/50	0/49	0/49	1/49	2/48	5/39	6/50 (3/20)
	25 ppm	0/49	0/49	0/49	0/49	0/49	0/47	0/44	0/35	0/49 (0/26)
	100 ppm	0/50	0/50	0/50	0/50	0/49	1/49	1/46	2/42	3/50 (1/18)
	400 ppm	0/50	0/50	0/50	0/50	0/50	0/48	5/46	5/42	6/50 (1/17)
Internal mass										
	Control	0/50	0/50	2/50	1/49	1/49	2/49	5/48	7/39	11/50 (9/20)
	25 ppm	0/49	0/49	0/49	3/49	5/49	2/47	13/44	14/35	23/49 (17/26)
	100 ppm	0/50	0/50	2/50	2/50	3/49	6/49	6/46	11/42	14/50 (8/18)
	400 ppm	1/50	1/50	1/50	1/50	4/50	3/48	6/46	10/42	16/50 (12/17)

No. of animals with mass / No. of surviving animals at the first week in each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 5 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Weeks on Study	Control Av.FC. <50>	25 ppm Av.FC. <50>	25 ppm % of cont.	100 ppm Av.FC. <50>	100 ppm % of cont.	400 ppm Av.FC. <50>	400 ppm % of cont.
1	3.8 (50)	3.8 (50)	100	3.7 (50)	97	3.5 (50)	92
2	3.8 (50)	3.7 (50)	97	3.8 (50)	100	3.5 (50)	92
3	3.7 (50)	3.8 (50)	103	3.7 (50)	100	3.6 (50)	97
4	3.9 (50)	3.9 (50)	100	3.9 (50)	100	3.7 (50)	95
5	4.0 (50)	3.9 (50)	98	4.0 (50)	100	3.8 (50)	95
6	4.1 (50)	4.1 (50)	100	3.8 (50)	93	3.8 (50)	93
7	4.1 (50)	4.0 (50)	98	4.0 (50)	98	3.9 (50)	95
8	4.1 (50)	4.2 (50)	102	4.0 (50)	98	4.0 (50)	98
9	4.1 (50)	4.1 (50)	100	4.0 (50)	98	4.0 (50)	98
10	4.2 (50)	4.2 (50)	100	4.1 (50)	98	4.0 (50)	95
11	4.2 (50)	4.3 (50)	102	4.2 (50)	100	4.1 (50)	98
12	4.3 (50)	4.3 (50)	100	4.3 (50)	100	4.1 (50)	95
13	4.3 (50)	4.3 (50)	100	4.2 (50)	98	4.1 (50)	95
14	4.3 (50)	4.3 (50)	100	4.3 (50)	100	4.2 (50)	98
18	4.4 (50)	4.3 (50)	98	4.3 (50)	98	4.2 (50)	95
22	4.5 (50)	4.5 (50)	100	4.4 (50)	98	4.2 (50)	93
26	4.5 (50)	4.5 (50)	100	4.4 (50)	98	4.4 (50)	98
30	4.6 (50)	4.6 (50)	100	4.5 (50)	98	4.4 (50)	96
34	4.7 (50)	4.7 (50)	100	4.6 (49)	98	4.4 (50)	94
38	4.7 (50)	4.7 (50)	100	4.7 (49)	100	4.5 (50)	96
42	4.7 (50)	4.7 (50)	100	4.6 (49)	98	4.3 (50)	91
46	4.7 (50)	4.7 (50)	100	4.6 (49)	98	4.5 (50)	96
50	4.8 (49)	4.8 (50)	100	4.6 (49)	96	4.6 (50)	96
54	4.8 (48)	4.7 (50)	98	4.7 (48)	98	4.5 (50)	94
58	4.9 (48)	4.9 (50)	100	4.6 (48)	94	4.4 (49)	90
62	4.8 (46)	4.7 (49)	98	4.6 (48)	96	4.5 (48)	94
66	4.9 (45)	4.8 (49)	98	4.7 (48)	96	4.6 (48)	94
70	4.8 (45)	4.8 (47)	100	4.6 (48)	96	4.4 (48)	92
74	4.7 (45)	4.6 (47)	98	4.7 (47)	100	4.4 (48)	94
78	4.9 (44)	4.8 (47)	98	4.7 (45)	96	4.6 (48)	94
82	5.0 (43)	5.0 (45)	100	4.9 (44)	98	4.6 (48)	92
86	5.1 (42)	4.9 (44)	96	4.9 (42)	96	4.7 (47)	92
90	4.9 (40)	4.9 (44)	100	4.8 (42)	98	4.7 (45)	96
94	5.0 (40)	4.9 (41)	98	4.8 (41)	96	4.6 (42)	92
98	4.9 (40)	4.8 (40)	98	4.8 (39)	98	4.6 (39)	94
102	4.8 (38)	4.6 (36)	96	4.6 (37)	96	4.4 (38)	92
104	4.8 (38)	4.7 (33)	98	4.6 (37)	96	4.3 (36)	90

< > : No.of effective animals, ( ) : No.of measured animals

Av.FC. : Averaged food consumption (Unit:g)

TABLE 6 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Weeks on Study	Control Av.FC. <50>	25 ppm Av.FC. <49>	25 ppm % of cont.	100 ppm Av.FC. <50>	100 ppm % of cont.	400 ppm Av.FC. <50>	400 ppm % of cont.
1	3.3 (50)	3.3 (49)	100	3.2 (50)	97	3.1 (50)	94
2	3.2 (50)	3.3 (49)	103	3.3 (50)	103	3.1 (50)	97
3	3.4 (50)	3.4 (49)	100	3.3 (50)	97	3.2 (50)	94
4	3.6 (50)	3.6 (49)	100	3.6 (50)	100	3.4 (50)	94
5	3.7 (50)	3.7 (49)	100	3.7 (50)	100	3.4 (50)	92
6	3.9 (50)	3.8 (49)	97	3.7 (50)	95	3.6 (50)	92
7	3.9 (50)	3.8 (49)	97	3.9 (50)	100	3.7 (50)	95
8	3.9 (50)	3.9 (49)	100	3.9 (50)	100	3.7 (50)	95
9	4.0 (50)	3.9 (49)	98	4.1 (50)	103	3.7 (50)	93
10	4.0 (50)	4.0 (49)	100	4.0 (50)	100	3.7 (50)	93
11	4.0 (50)	4.0 (49)	100	4.2 (50)	105	3.8 (50)	95
12	4.1 (50)	4.0 (49)	98	4.1 (50)	100	3.9 (50)	95
13	4.0 (50)	4.0 (49)	100	4.0 (50)	100	3.9 (50)	98
14	4.1 (50)	4.0 (49)	98	4.1 (50)	100	3.9 (50)	95
18	4.1 (50)	4.0 (49)	98	4.2 (50)	102	3.9 (50)	95
22	4.1 (50)	4.1 (49)	100	4.2 (50)	102	3.9 (50)	95
26	4.2 (50)	4.1 (49)	98	4.3 (50)	102	4.0 (50)	95
30	4.3 (50)	4.3 (49)	100	4.5 (50)	105	4.2 (50)	98
34	4.5 (50)	4.4 (49)	98	4.5 (50)	100	4.3 (50)	96
38	4.3 (49)	4.3 (49)	100	4.5 (50)	105	4.3 (50)	100
42	4.4 (49)	4.2 (49)	95	4.5 (50)	102	4.1 (50)	93
46	4.2 (49)	4.3 (49)	102	4.4 (50)	105	4.1 (50)	98
50	4.4 (49)	4.3 (49)	98	4.4 (49)	100	4.0 (50)	91
54	4.3 (49)	4.2 (48)	98	4.3 (49)	100	4.0 (50)	93
58	4.4 (49)	4.4 (48)	100	4.3 (49)	98	3.9 (50)	89
62	4.4 (49)	4.2 (47)	95	4.3 (49)	98	3.9 (49)	89
66	4.2 (49)	4.4 (47)	105	4.3 (49)	102	3.8 (48)	90
70	4.3 (49)	4.1 (46)	95	4.1 (49)	95	3.8 (48)	88
74	4.1 (49)	4.1 (46)	100	4.3 (49)	105	3.8 (47)	93
78	4.4 (48)	4.3 (45)	98	4.3 (46)	98	3.9 (46)	89
82	4.5 (45)	4.3 (41)	96	4.2 (45)	93	3.9 (46)	87
86	4.4 (44)	4.4 (39)	100	4.2 (44)	95	4.0 (44)	91
90	4.5 (40)	4.3 (37)	96	4.1 (44)	91	4.0 (42)	89
94	4.4 (38)	4.5 (32)	102	4.3 (40)	98	3.9 (39)	89
98	4.5 (36)	4.4 (29)	98	4.2 (38)	93	3.8 (36)	84
102	4.4 (32)	4.3 (25)	98	4.2 (33)	95	3.8 (35)	86
104	4.5 (30)	4.3 (24)	96	4.2 (32)	93	3.8 (33)	84

< > : No.of effective animals, ( ) : No.of measured animals

Av.FC. : Averaged food consumption (Unit:g)

TABLE 7 HEMATOLOGY OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	36	31	34	32
RED BLOOD CELL ($10^6/\mu$ L)	9.66 ± 0.96	10.21 ± 1.25	9.68 ± 0.75	8.55 ± 1.44 **
HEMOGLOBIN (g/dL)	13.6 ± 1.4	13.8 ± 1.7	13.4 ± 1.0	12.3 ± 1.9 **
HEMATOCRIT (%)	44.0 ± 4.4	45.0 ± 6.0	44.0 ± 3.1	40.7 ± 5.6 **
MCV (fL)	45.6 ± 1.5	44.1 ± 2.1 *	45.4 ± 1.3	48.0 ± 3.8 **
MCH (pg)	14.1 ± 0.3	13.5 ± 0.6 **	13.9 ± 0.5	14.5 ± 0.9
MCHC (g/dL)	30.9 ± 0.8	30.6 ± 0.5	30.5 ± 0.6 **	30.2 ± 0.9 **
PLATELET ($10^3/\mu$ L)	1910 ± 287	2034 ± 408	1923 ± 286	1518 ± 539 **
Differential WBC (%)				
EOSINO	2 ± 1	1 ± 1 **	2 ± 2	2 ± 2
OTHER	0 ± 1	0 ± 0	0 ± 1	3 ± 11 **

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 8 HEMATOLOGY OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	30	23	31	31
MCV (fL)	45.0 ± 1.4	45.2 ± 2.3	47.1 ± 5.0 *	47.0 ± 2.1 **
MCHC (g/dL)	31.0 ± 0.8	30.8 ± 1.1	30.7 ± 1.5	30.6 ± 1.1 *
PLATELET ($10^3/\mu$ L)	1296 ± 259	1142 ± 362	1042 ± 384 **	1073 ± 323 *

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 9 BIOCHEMISTRY OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	37	31	34	34
A/G RATIO	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.4 ± 0.2 **
T-CHOLESTEROL (mg/dL)	103 ± 39	118 ± 41	100 ± 34	87 ± 25 *
PHOSPHOLIPID (mg/dL)	194 ± 45	219 ± 61	188 ± 43	163 ± 36 **
GPT (IU/L)	34 ± 59	57 ± 62 *	39 ± 42 *	62 ± 87 **
ALP (IU/L)	141 ± 53	159 ± 120	140 ± 33	187 ± 77 **
G-GTP (IU/L)	1 ± 1	1 ± 1	1 ± 1	2 ± 1 *
UREA NITROGEN (mg/dL)	25.7 ± 9.9	24.1 ± 5.9	21.6 ± 3.2 *	19.1 ± 3.4 **
CHLORIDE (mEq/L)	122 ± 2	122 ± 3	124 ± 3 **	130 ± 4 **

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 10 BIOCHEMISTRY OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	30	23	31	32
TOTAL PROTEIN (g/dL)	5.2 ± 0.6	5.3 ± 0.6	4.8 ± 0.8 **	5.0 ± 0.4
A/G RATIO	1.3 ± 0.2	1.5 ± 0.4	1.6 ± 0.3 **	1.6 ± 0.3 **
CPK (IU/L)	104 ± 62	191 ± 425	136 ± 123	73 ± 44 *
CHLORIDE (mEq/L)	122 ± 3	123 ± 3	124 ± 3	127 ± 4 **

Mean ± S.D.

Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 11 URINALYSIS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name		Control	25 ppm	100 ppm	400 ppm
No. of examined animals		38	34	36	36
	Grade				
pH	5.0	0	0	0	0
	6.0	0	5	5	8
	6.5	4	4	11	22
	7.0	4	5	10	4
	7.5	19	12	5	1
	8.0	7	8	2	0
	8.5	4	0	3	1
	Chi square test			**	**
Protein	−	1	0	0	0
	±	10	8	4	0
	+	25	22	23	17
	2+	2	3	8	17
	3+	0	1	1	2
	4+	0	0	0	0
	Chi square test				**
Ketone body	−	16	22	8	4
	±	20	10	14	9
	+	2	2	12	17
	2+	0	0	2	6
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test			**	**

Significant difference: * : $p<0.05$ ** : $p<0.01$

TABLE 12 URINALYSIS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name		Control	25 ppm	100 ppm	400 ppm
No. of examined animals		30	24	32	33
	Grade				
pH	5.0	0	1	0	0
	6.0	1	1	3	3
	6.5	2	4	3	15
	7.0	2	0	2	3
	7.5	4	3	3	6
	8.0	19	15	18	6
	8.5	2	0	3	0
	Chi square test				**
Protein	−	0	1	0	0
	±	7	4	0	2
	+	13	13	14	12
	2+	7	6	16	16
	3+	3	0	2	3
	4+	0	0	0	0
	Chi square test			*	
Ketone body	−	9	8	0	0
	±	14	13	13	13
	+	6	3	15	9
	2+	1	0	4	11
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test			**	**

Significant difference: * : $p<0.05$ ** : $p<0.01$

TABLE 13 ORGAN WEIGHTS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	38	33	37	36
Body weight (g)	42.5 ± 7.0	41.4 ± 7.7	38.3 ± 7.4 *	36.1 ± 7.3 **
Testes (g)	0.220 ± 0.038	0.213 ± 0.038	0.206 ± 0.031	0.183 ± 0.033 **
Testes (%)	0.525 ± 0.098	0.532 ± 0.123	0.558 ± 0.133	0.522 ± 0.125
Heart (g)	0.218 ± 0.020	0.220 ± 0.020	0.213 ± 0.024	0.203 ± 0.023 *
Heart (%)	0.521 ± 0.068	0.545 ± 0.084	0.576 ± 0.133	0.576 ± 0.082 **
Lungs (g)	0.231 ± 0.171	0.335 ± 0.250	0.309 ± 0.219	0.304 ± 0.169
Lungs (%)	0.604 ± 0.747	0.891 ± 0.876 **	0.879 ± 0.917 **	0.880 ± 0.550 **
Kidneys (g)	0.640 ± 0.186	0.620 ± 0.063	0.624 ± 0.062	1.006 ± 2.200
Kidneys (%)	1.524 ± 0.415	1.529 ± 0.202	1.672 ± 0.258 **	2.598 ± 4.628 **
Spleen (g)	0.144 ± 0.257	0.077 ± 0.032	0.065 ± 0.027	0.102 ± 0.141 *
Spleen (%)	0.354 ± 0.651	0.187 ± 0.072	0.175 ± 0.080	0.312 ± 0.489
Liver (g)	1.543 ± 0.267	1.838 ± 0.737	1.580 ± 0.315	1.729 ± 0.587
Liver (%)	3.679 ± 0.616	4.564 ± 1.937 *	4.246 ± 1.124 **	4.956 ± 2.176 **
Brain (g)	0.455 ± 0.016	0.457 ± 0.018	0.463 ± 0.022	0.442 ± 0.014 **
Brain (%)	1.102 ± 0.198	1.141 ± 0.217	1.268 ± 0.343 *	1.268 ± 0.232 **

Mean ± S.D.
Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 14 ORGAN WEIGHTS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	30	24	32	33
Body weight (g)	27.5 ± 4.5	27.9 ± 4.2	26.3 ± 2.8	25.0 ± 2.4
Heart (g)	0.172 ± 0.022	0.185 ± 0.038	0.171 ± 0.017	0.157 ± 0.015 *
Heart (%)	0.639 ± 0.106	0.668 ± 0.125	0.652 ± 0.071	0.635 ± 0.081
Lungs (g)	0.195 ± 0.023	0.272 ± 0.175 **	0.263 ± 0.191 **	0.266 ± 0.157 **
Lungs (%)	0.721 ± 0.086	1.042 ± 0.940	1.024 ± 0.861 **	1.071 ± 0.626 **
Kidneys (g)	0.576 ± 0.855	0.496 ± 0.309	0.518 ± 0.471	0.441 ± 0.053
Kidneys (%)	2.108 ± 3.014	1.802 ± 1.163	1.926 ± 1.486 *	1.779 ± 0.246 **
Brain (g)	0.494 ± 0.055	0.472 ± 0.023	0.468 ± 0.020 *	0.445 ± 0.016 **
Brain (%)	1.848 ± 0.396	1.727 ± 0.253	1.797 ± 0.188	1.801 ± 0.187

Mean ± S.D.
Significant difference: * : $p<0.05$ ** : $p<0.01$ Test of Dunnett

TABLE 15 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25ppm	100ppm	400ppm	Peto	Cochran-Armitage
Number of examined animals	50	50	50	50	test	test
Respiratory system						
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar adenoma	5 (10 %)	21 (42 %) **	20 (40 %) **	26 (52 %) **	↑↑	↑↑
bronchiolar-alveolar carcinoma	3 (6 %)	29 (58 %) **	26 (52 %) **	26 (52 %) **	↑	↑
adenosquamous carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
squamous cell carcinoma	0 (0 %)	0 (0 %)	1 (2 %)	0 (0 %)		
Digestive system						
stomach	<50>	<50>	<50>	<50>		
squamous cell papilloma	1 (2 %)	1 (2 %)	2 (4 %)	8 (16 %) *	↑↑	↑↑
liver	<50>	<50>	<50>	<50>		
hepatocellular adenoma	4 (8 %)	10 (20 %)	8 (16 %)	14 (28 %) **	↑↑	↑
hepatocellular carcinoma	3 (6 %)	5 (10 %)	3 (6 %)	3 (6 %)		
hepatoblastoma	0 (0 %)	0 (0 %)	1 (2 %)	1 (2 %)		
Special sense organs/appendage						
Harderian gland	<50>	<50>	<50>	<50>		
adenoma	4 (8 %)	4 (8 %)	4 (8 %)	13 (26 %) *	↑↑	↑↑

Significant difference * : $p<0.05$ ** : $p<0.01$ Fisher's exact test for neoplastic lesion
↑(↓) : $p<0.05$ ↑↑(↓↓) : $p<0.01$ Peto or Cochran-Armitage test for neoplastic lesion
< > : Number of animals examined at the site

TABLE 16 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control	25ppm	100ppm	400ppm	Peto	Cochran-
Number of examined animals	50	49	50	50	test	Armitage test
Respiratory system						
lung	<50>	<49>	<50>	<50>		
bronchiolar-alveolar adenoma	2 (4 %)	19 (39 %) **	25 (50 %) **	30 (60 %) **	↑↑	↑↑
bronchiolar-alveolar carcinoma	2 (4 %)	12 (24 %) **	20 (40 %) **	13 (26 %) **		
Digestive system						
stomach	<50>	<49>	<50>	<50>		
squamous cell papilloma	0 (0 %)	0 (0 %)	1 (2 %)	8 (16 %) **	↑↑	↑↑
squamous cell carcinoma	0 (0 %)	1 (2 %)	0 (0 %)	1 (2 %)		
Special sense organs/appendage						
Harderian gland	<50>	<49>	<50>	<50>		
adenoma	3 (6 %)	0 (0 %)	2 (4 %)	14 (28 %) **	↑↑	↑↑

Significant difference * : $p<0.05$ ** : $p<0.01$ Fisher's exact test for neoplastic lesion
↑(↓) : $p<0.05$ ↑↑(↓↓) : $p<0.01$ Peto or Cochran-Armitage test for neoplastic lesion
< > : Number of animals examined at the site

TABLE 17 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control				25ppm				100ppm				400ppm				
Number of examined animals	50				50				50				50				
Grade of non-neoplastic lesion	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
Respiratory system																	
nasal cavity	<50>				<50>				<50>				<50>				
respiratory metaplasia:olfactory epitheliun	4	1	0	0	3	1	0	0	5	0	0	0	29	19	0	0	**
atrophy:olfactory epithelium	0	1	0	0	0	1	0	0	0	0	0	0	37	0	0	0	**
eosinophilic change:olfactory epithelium	10	1	0	0	14	0	0	0	18	0	0	0	17	5	0	0	*
exudate	0	1	0	0	0	1	0	0	0	1	0	0	3	0	0	0	
respiratory metaplasia:gland	8	0	0	0	9	0	0	0	9	0	0	0	23	23	1	0	**
nasopharynx	<50>				<50>				<50>				<50>				
eosinophilic change	5	0	0	0	3	0	0	0	6	1	0	0	34	3	0	0	**
lung	<50>				<50>				<50>				<50>				
bronchiolar-alveolar cell hyperplasia	3	1	0	0	20	4	0	0	**	23	3	0	0	**	27	6	0	0	**
Digestive system																	
stomach	<50>				<50>				<50>				<50>				
squamous cell hyperplasia:forestomach	2	0	0	0	1	2	0	0	4	0	0	0	17	1	0	0	**
Special sense organs/appendage																	
Harderian gland	<50>				<50>				<50>				<50>				
hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< > : Number of animals examined at the site
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

TABLE 18 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name	Control				25ppm				100ppm				400ppm			
Number of examined animals	50				49				50				50			
Grade of non-neoplastic lesion	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Respiratory system																
nasal cavity	<50>				<49>				<50>				<50>			
respiratory metaplasia:olfactory epithelium	5	0	0	0	6	0	0	0	9	0	0	0	4	42	3	0 **
atrophy:olfactory epithelium	0	0	0	0	0	0	0	0	0	0	0	0	25	0	0	0 **
eosinophilic change:olfactory epithelium	23	3	1	0	16	4	4	0	22	3	0	0	9	32	8	1 **
exudate	0	0	0	0	0	0	0	0	2	0	0	0	20	0	0	0 **
respiratory metaplasia:gland	8	0	0	0	9	0	0	0	11	0	0	0	13	32	1	0 **
nasopharynx	<50>				<49>				<50>				<50>			
eosinophilic change	10	1	0	0	11	3	0	0	22	2	0	0 *	38	5	0	0 **
exudate	0	0	0	0	0	0	0	0	1	0	0	0	17	0	0	0 **
lung	<50>				<49>				<50>				<50>			
bronchiolar-alveolar cell hyperplasia	7	0	0	0	20	1	0	0 **	28	3	0	0 **	20	7	0	0 **
Digestive system																
stomach	<50>				<49>				<50>				<50>			
squamous cell hyperplasia:forestomach	2	2	0	0	2	0	0	0	10	1	0	0 *	18	3	0	0 **
Nervous system																
brain	<50>				<49>				<50>				<50>			
mineralization	21	0	0	0	10	0	0	0 *	16	0	0	0	4	0	0	0 **
Special sense organs/appendage																
Harderian gland	<50>				<49>				<50>				<50>			
hyperplasia	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< > : Number of animals examined at the site
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

TABLE 19 CAUSE OF DEATH OF MALE AND FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

	Male				Female			
Group name	Control	25 ppm	100 ppm	400 ppm	Control	25 ppm	100 ppm	400 ppm
Number of dead or moribund animals	12	17	13	14	20	25	18	17
No microscopical confirmation	0	0	1	0	0	0	1	0
Hydronephrosis	0	0	1	4	1	1	0	0
Urinary retention	3	0	0	0	1	0	0	0
Hemorrhage	1	0	0	0	0	0	0	1
Tumor death : leukemia	4	4	4	4	9	13	5	7
subcutis	0	0	0	0	0	1	0	0
lung	0	6	1	4	1	0	3	0
spleen	0	0	1	0	0	0	0	1
large intestine	0	0	0	0	0	0	1	0
liver	3	7	4	2	1	1	0	0
urinary bladder	1	0	0	0	0	0	0	0
pituitary gland	0	0	0	0	2	3	0	0
adrenal gland	0	0	0	0	0	0	0	1
uterus	—	—	—	—	4	6	7	7
mammary gland	0	0	0	0	1	0	0	0
peripheral nerves	0	0	1	0	0	0	1	0

TABLE 20 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : Crj:BDF$_1$ MALE MICE

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Lung	1495			
Bronchiolar-alveolar adenoma		120	8.0	2 - 18
Bronchiolar-alveolar carcinoma		162	10.8	0 - 24
Adenosquamous carcinoma		0	0.0	0 - 0
Squamous cell carcinoma		0	0.0	0 - 0
Stomach	1495			
Squamous cell papilloma		3	0.2	0 - 2
Liver	1496			
Hepatocellular adenoma		273	18.2	4 - 34
Harderian gland	1495			
Adenoma		69	4.6	0 - 10

30 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0268, 0270, 0279, 0285, 0297, 0319, 0329, 0343, 0348, 0366, 0372, 0402, 0406

TABLE 21 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : Crj:BDF$_1$ FEMALE MICE

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Lung	1498			
Bronchiolar-alveolar adenoma		54	3.6	0 - 10
Bronchiolar-alveolar carcinoma		43	2.9	0 - 8
Stomach	1497			
Squamous cell papilloma		4	0.3	0 - 2
Squamous cell carcinoma		2	0.1	0 - 2
Harderian gland	1498			
Adenoma		47	3.1	0 - 12

30 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0268, 0270, 0279, 0285, 0297, 0319, 0329, 0343, 0348, 0366, 0372, 0402, 0406

FIGURES

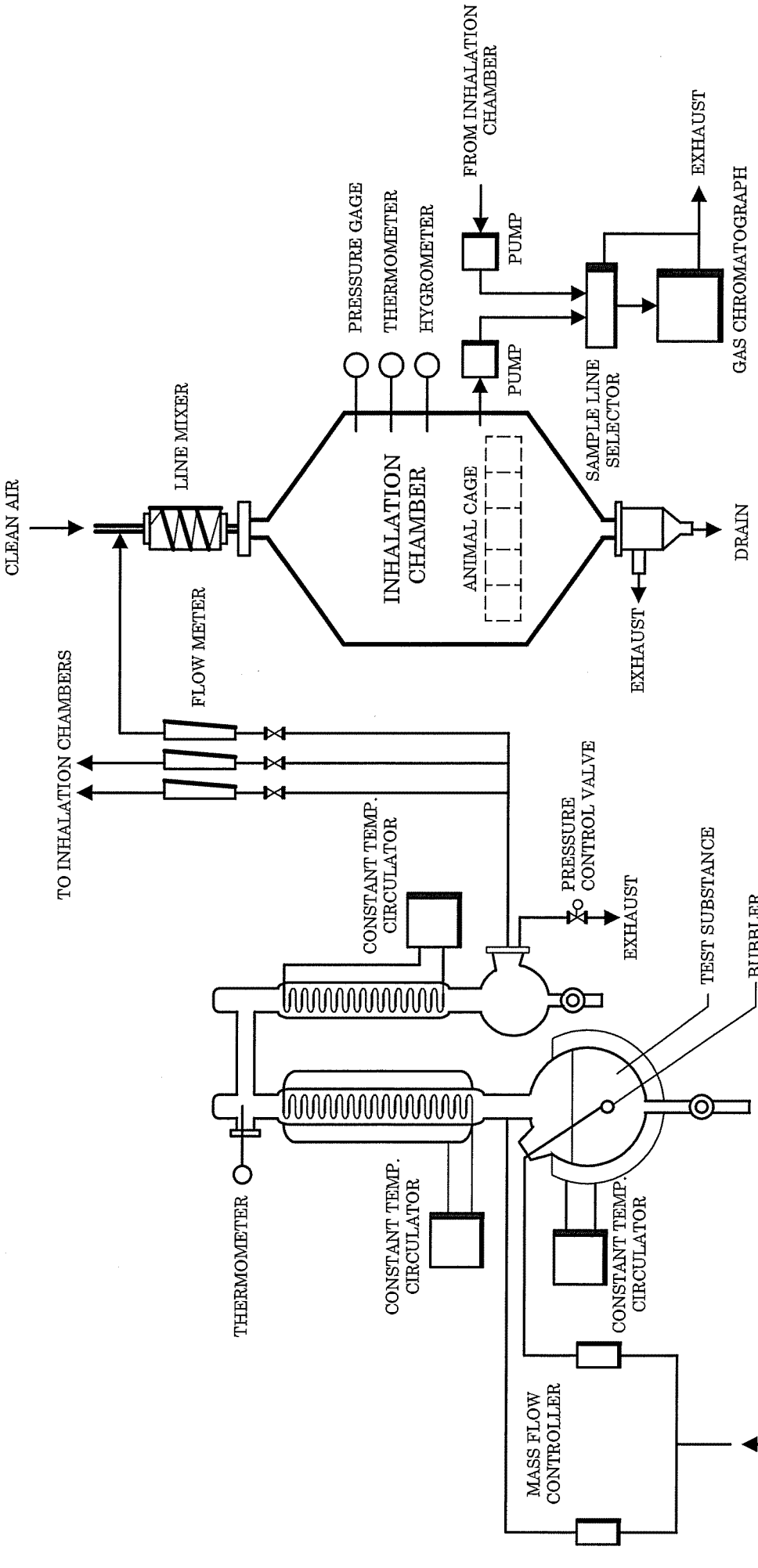


FIGURE 1 1-BROMO-3-CHLOROPROPANE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

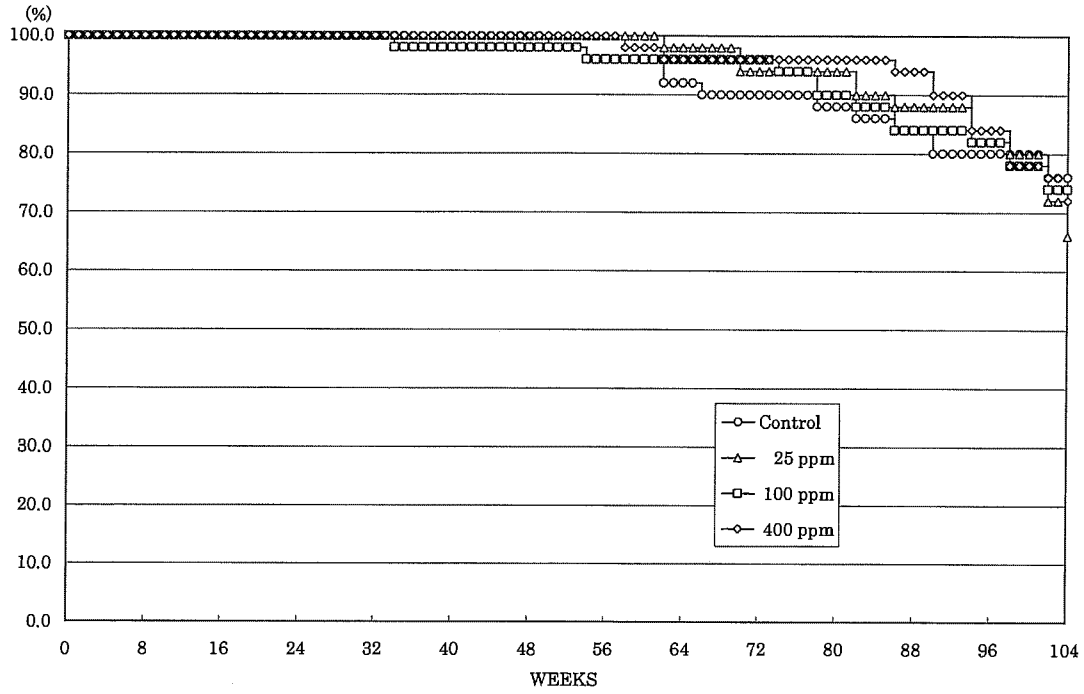


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

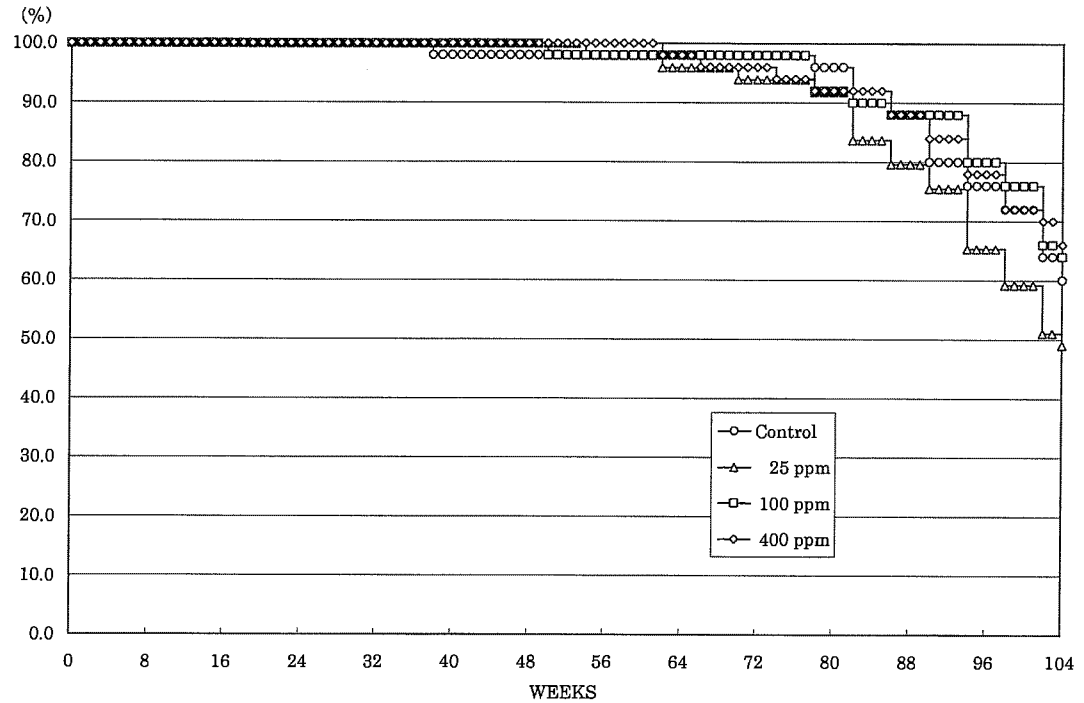


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

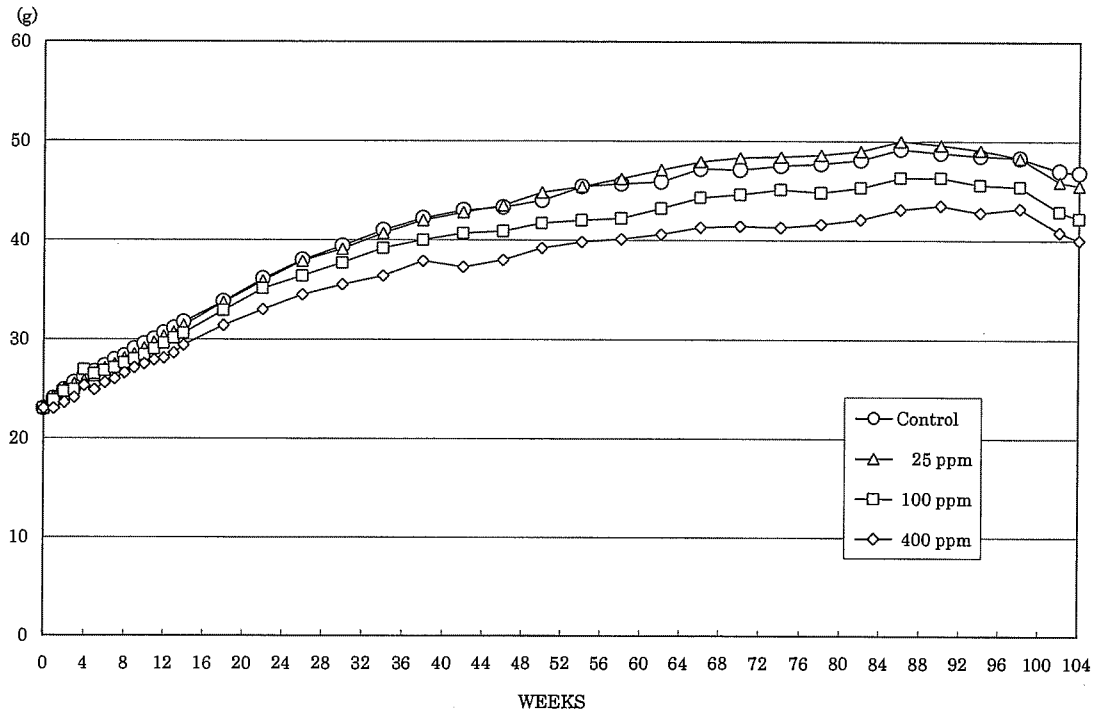


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

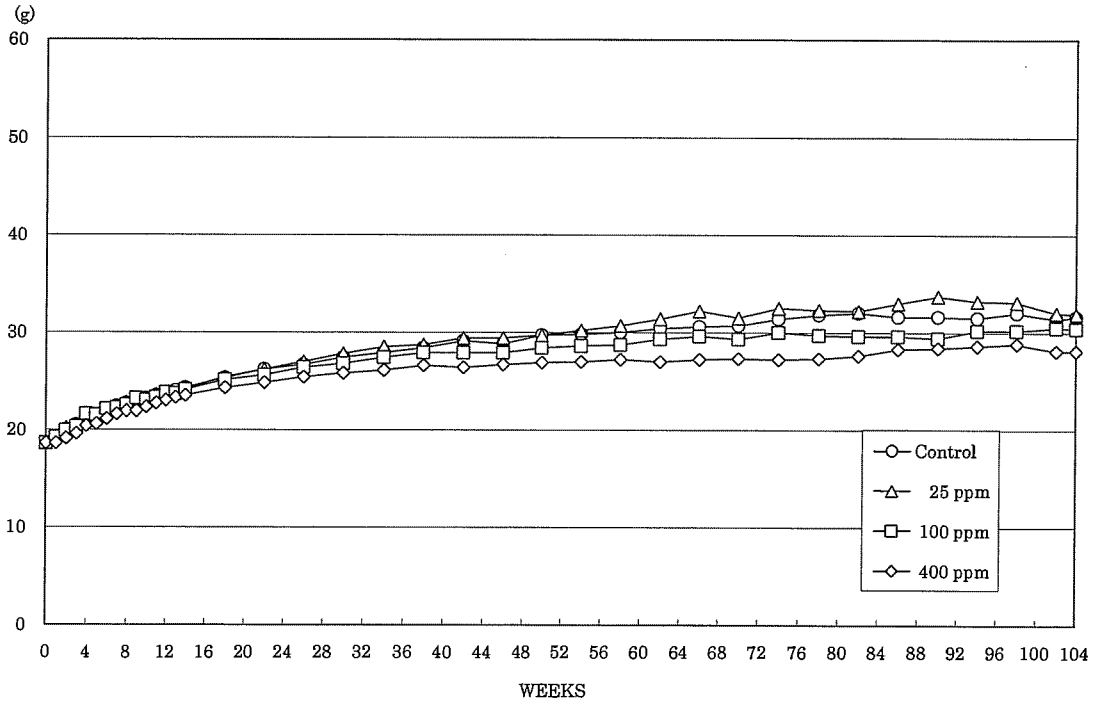


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

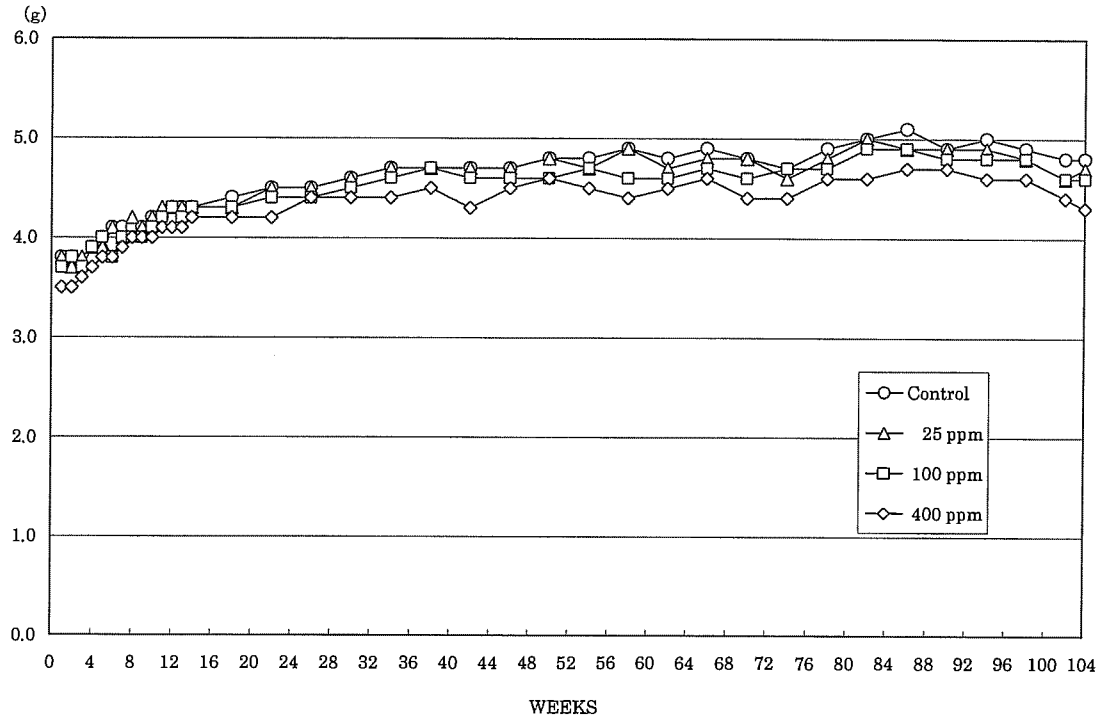


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

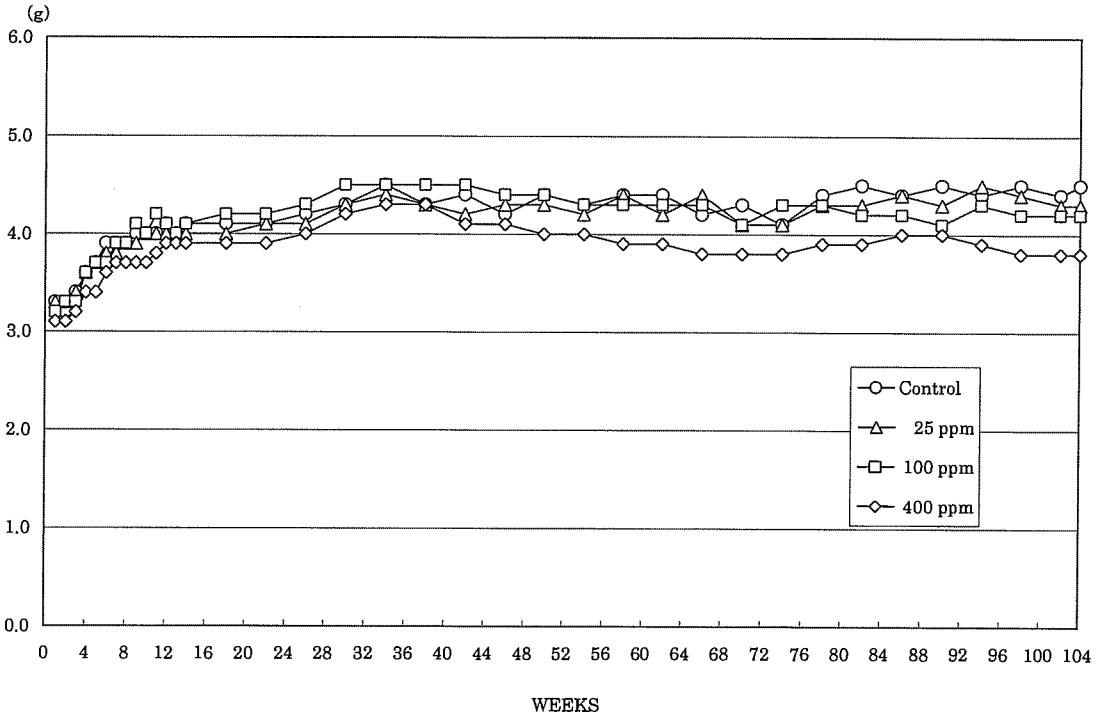
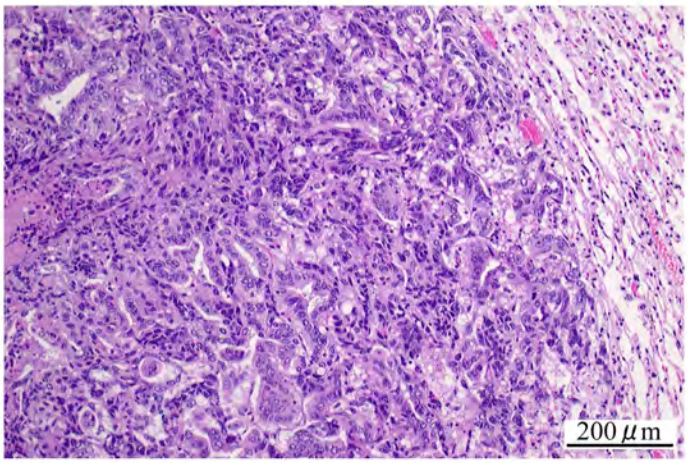
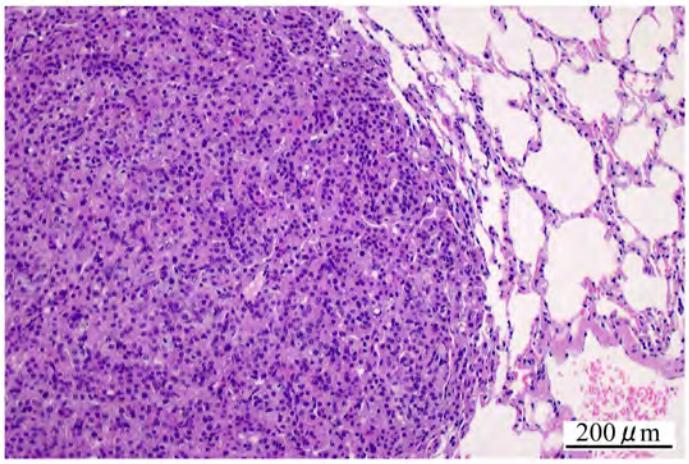


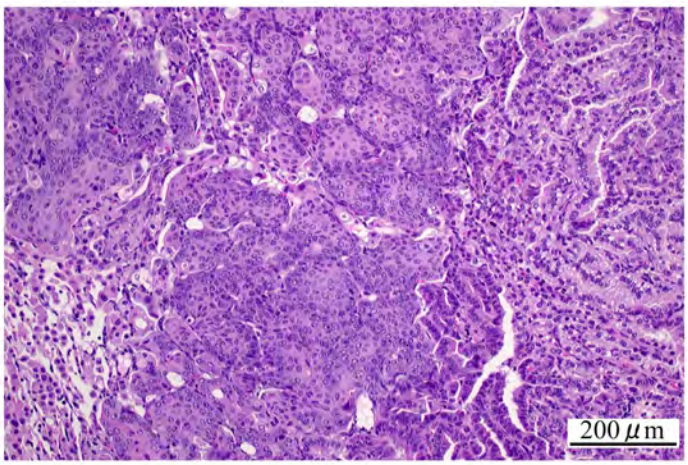
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE



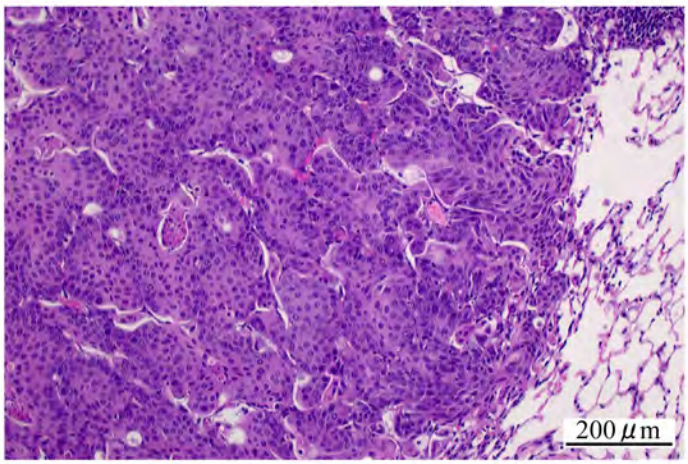
Photograph 1
Lung: Bronchiolar-alveolar carcinoma
Mouse, Male, 400 ppm, Animal No. 0418-1347 (H&E)



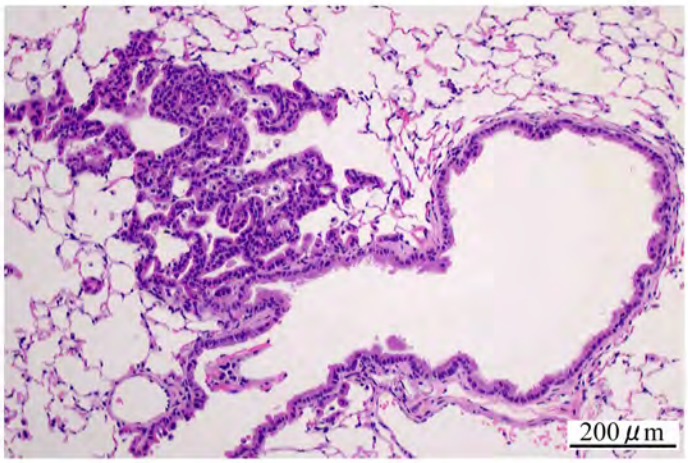
Photograph 2
Lung: Bronchiolar-alveolar adenoma
Mouse, Male, 400 ppm, Animal No. 0418-1326 (H&E)



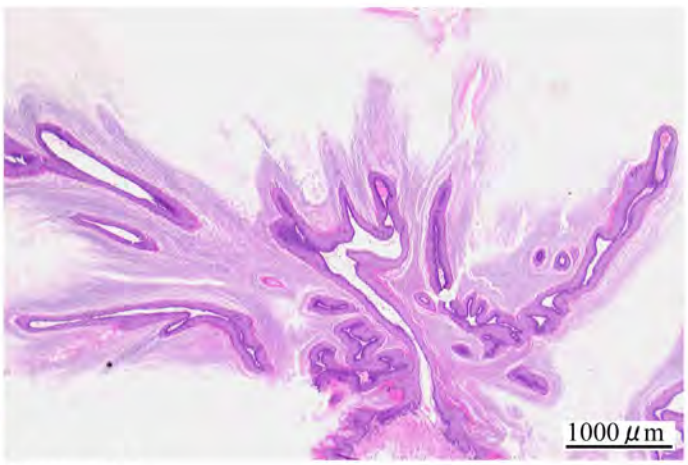
Photograph 3
Lung: Adenosquamous carcinoma
Mouse, Male, 400 ppm, Animal No. 0418-1342 (H&E)



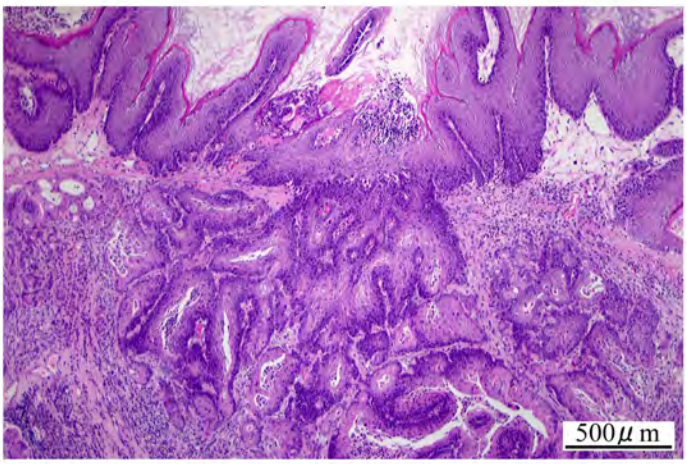
Photograph 4
Lung: Squamous cell carcinoma
Mouse, Male, 100 ppm, Animal No. 0418-1206 (H&E)



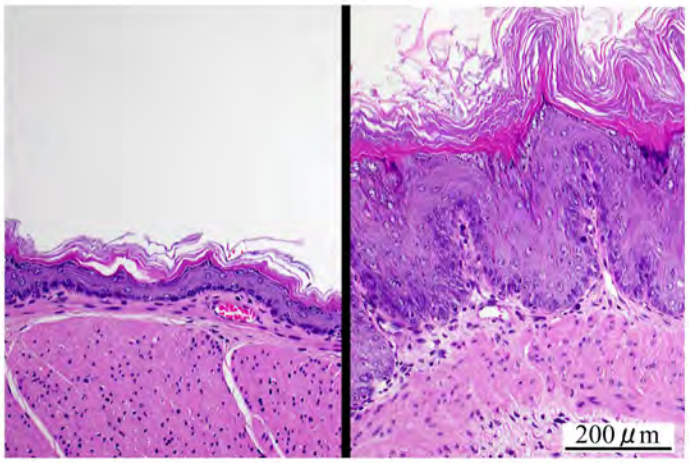
Photograph 5
Lung: Bronchiolar-alveolar cell hyperplasia (Bronchiolar type)
Mouse, Male, 400 ppm, Animal No. 0418-1339 (H&E)



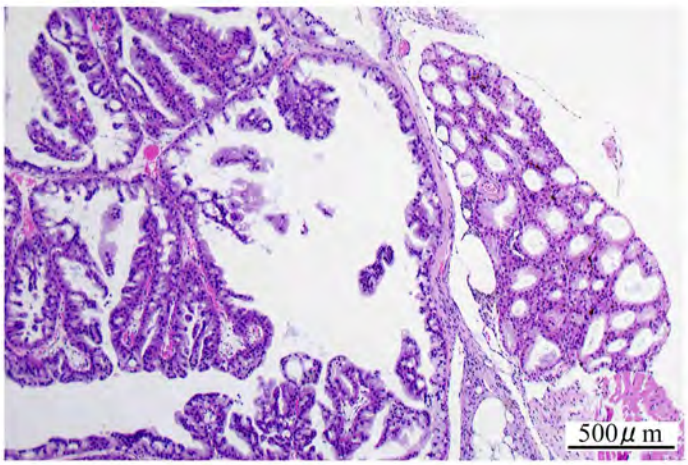
Photograph 6
Forestomach: Squamous cell papilloma
Mouse, Male, 400 ppm, Animal No. 0418-1305 (H&E)



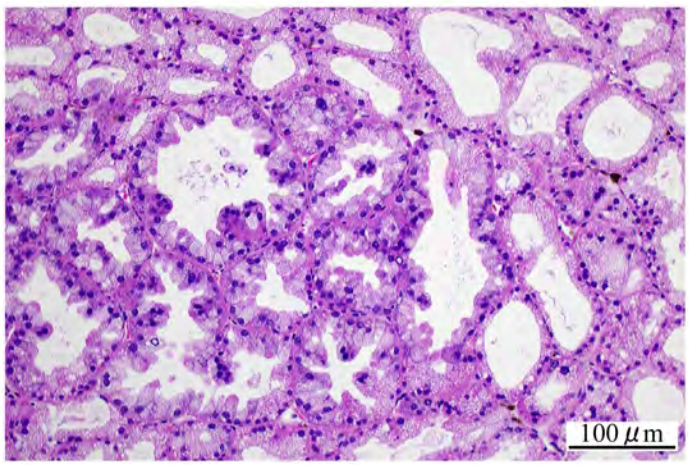
Photograph 7
Forestomach: Squamous cell carcinoma
Mouse, Female, 400 ppm, Animal No. 0418-2318 (H&E)



Photograph 8
Left: Forestomach: Normal
Mouse, Female, Control, Animal No. 0418-2002 (H&E)
Right: Forestomach: Squamous cell hyperplasia
Mouse, Female, 400 ppm, Animal No. 0418-2302 (H&E)



Photograph 9
Harderian gland: Adenoma
Mouse, Male, 400 ppm, Animal No. 0418-1305 (H&E)



Photograph 10
Harderian gland: Hyperplasia
Mouse, Male, 400 ppm, Animal No. 0418-1306 (H&E)