Summary of Inhalation Carcinogenicity Study of 1-Bromo-3-Chloropropane in F344 Rats

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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 F344/DuCrj (Fischer) rats 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: 7600 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 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 hepatocellular adenomas and carcinomas, and hemangiosarcomas in the liver, bronchiolar-alveolar adenomas in the lung, trichoepitheliomas in the skin/appendage were increased in the BCP-exposed groups of both sexes. In the large intestine, both adenomas and adenocarcinoma in the BCP-exposed males and adenomas in the BCP-exposed females were increased. As pre-neoplastic lesions in the liver, the incidences of clear cell foci and acidophilic cell foci in both BCP-exposed males and females, and basophilic cell foci in the BCP-exposed males were significantly increased.

As non-neoplastic lesions the incidences in the nasal cavity (inflammation and squamous cell metaplasia in the respiratory epithelium, respiratory metaplasia in the nasal gland, and atrophy, necrosis and respiratory metaplasia in the olfactory epithelium) and the incidence in the kidney (chronic progressive nephropathy (chronic nephropathy)) were increased.

Conclusions

In rats, there was clear evidence of carcinogenic activity of BCP in males, based on the increased incidences of hepatocellular carcinomas and adenomas. The increased incidences of bronchiolar-alveolar adenomas in the lung, adenomas and adenocarcinoma in the large intestine, and trichoepitheliomas in the skin/appendage and hemangiosarcomas in the liver were noted. There was clear evidence of carcinogenic activity of BCP in females, based on the increased incidences of hepatocellular carcinomas and adenomas, and hemangiosarcomas in the liver. The incidences of bronchiolar-alveolar adenomas in the lung, adenomas in the large intestine, and trichoepitheliomas in the skin/appendage were increased.

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TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS 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	112 (50)	50/50	112 (50)	100	50/50	112 (50)	100	50/50	112 (50)	100	50/50
1	142 (50)	50/50	141 (50)	99	50/50	140 (50)	99	50/50	131 (50)	92	50/50
2	176 (50)	50/50	176 (50)	100	50/50	175 (50)	99	50/50	158 (50)	90	50/50
3	202 (50)	50/50	204 (50)	101	50/50	203 (50)	100	50/50	179 (50)	89	50/50
4	227 (50)	50/50	228 (50)	100	50/50	227 (50)	100	50/50	195 (50)	86	50/50
5	245 (50)	50/50	246 (50)	100	50/50	246 (50)	100	50/50	209 (50)	85	50/50
6	260 (50)	50/50	262 (50)	101	50/50	262 (50)	101	50/50	221 (50)	85	50/50
7	273 (50)	50/50	275 (50)	101	50/50	276 (50)	101	50/50	230 (50)	84	50/50
8	284 (50)	50/50	286 (50)	101	50/50	288 (50)	101	50/50	239 (50)	84	50/50
9	294 (50)	50/50	296 (50)	101	50/50	299 (50)	102	50/50	251 (50)	85	50/50
10	301 (50)	50/50	306 (50)	102	50/50	307 (50)	102	50/50	257 (50)	85	50/50
11	309 (50)	50/50	312 (50)	101	50/50	314 (50)	102	50/50	260 (50)	84	50/50
12	315 (50)	50/50	318 (50)	101	50/50	322 (50)	102	50/50	266 (50)	84	50/50
13	322 (50)	50/50	325 (50)	101	50/50	328 (50)	102	50/50	272 (50)	84	50/50
14	327 (50)	50/50	331 (50)	101	50/50	335 (50)	102	50/50	277 (50)	85	50/50
18	344 (50)	50/50	348 (50)	101	50/50	352 (50)	102	50/50	292 (50)	85	50/50
22	359 (50)	50/50	365 (50)	102	50/50	369 (50)	103	50/50	305 (50)	85	50/50
26	372 (50)	50/50	376 (50)	101	50/50	381 (50)	102	50/50	320 (50)	86	50/50
30	377 (50)	50/50	382 (49)	101	49/50	390 (49)	103	49/50	327 (50)	87	50/50
34	389 (50)	50/50	395 (49)	102	49/50	401 (49)	103	49/50	342 (49)	88	49/50
38	397 (50)	50/50	401 (49)	101	49/50	407 (49)	103	49/50	351 (49)	88	49/50
42	403 (50)	50/50	407 (49)	101	49/50	415 (48)	103	48/50	349 (49)	87	49/50
46	412 (50)	50/50	418 (49)	101	49/50	422 (48)	102	48/50	339 (48)	82	48/50
50	415 (50)	50/50	421 (49)	101	49/50	425 (48)	102	48/50	345 (48)	83	48/50
54	414 (50)	50/50	423 (49)	102	49/50	425 (48)	103	48/50	347 (48)	84	48/50
58	421 (48)	48/50	427 (49)	101	49/50	431 (48)	102	48/50	351 (48)	83	48/50
62	425 (48)	48/50	429 (49)	101	49/50	433 (48)	102	48/50	355 (48)	84	48/50
66	426 (47)	47/50	432 (48)	101	48/50	435 (48)	102	48/50	351 (47)	82	47/50
70	428 (47)	47/50	434 (48)	101	48/50	439 (48)	103	48/50	352 (47)	82	47/50
74	424 (46)	46/50	432 (47)	102	47/50	436 (48)	103	48/50	349 (46)	82	46/50
78	427 (46)	46/50	435 (45)	102	45/50	436 (48)	102	48/50	347 (45)	81	45/50
82	424 (45)	45/50	436 (45)	103	45/50	434 (48)	102	48/50	339 (45)	80	45/50
86	427 (43)	43/50	428 (44)	100	44/50	435 (46)	102	46/50	338 (43)	79	43/50
90	429 (43)	43/50	430 (40)	100	40/50	435 (46)	101	46/50	334 (42)	78	42/50
94	425 (43)	43/50	424 (40)	100	40/50	431 (46)	101	46/50	329 (41)	77	41/50
98	420 (42)	42/50	416 (39)	99	39/50	414 (44)	99	44/50	324 (38)	77	38/50
102	414 (40)	40/50	412 (35)	100	35/50	420 (39)	101	39/50	313 (35)	76	35/50
104	408 (40)	40/50	405 (35)	99	35/50	412 (38)	101	38/50	305 (30)	75	30/50

< > : 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 RATS 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	91 (50)	50/50	91 (50)	100	50/50	91 (50)	100	50/50	91 (50)	100	50/50
1	106 (50)	50/50	107 (50)	101	50/50	107 (50)	101	50/50	103 (50)	97	50/50
2	121 (50)	50/50	121 (50)	100	50/50	123 (50)	102	50/50	115 (50)	95	50/50
3	133 (50)	50/50	132 (50)	99	50/50	133 (50)	100	50/50	124 (50)	93	50/50
4	142 (50)	50/50	143 (50)	101	50/50	145 (50)	102	50/50	133 (50)	94	50/50
5	148 (50)	50/50	150 (50)	101	50/50	153 (50)	103	50/50	140 (50)	95	50/50
6	155 (50)	50/50	157 (50)	101	50/50	159 (50)	103	50/50	146 (50)	94	50/50
7	160 (50)	50/50	162 (50)	101	50/50	165 (50)	103	50/50	151 (50)	94	50/50
8	164 (50)	50/50	166 (50)	101	50/50	169 (50)	103	50/50	155 (50)	95	50/50
9	169 (50)	50/50	170 (50)	101	50/50	173 (50)	102	50/50	158 (50)	93	50/50
10	173 (50)	50/50	175 (50)	101	50/50	177 (50)	102	50/50	163 (50)	94	50/50
11	176 (50)	50/50	179 (50)	102	50/50	182 (50)	103	50/50	166 (50)	94	50/50
12	178 (50)	50/50	180 (50)	101	50/50	185 (50)	104	50/50	168 (50)	94	50/50
13	181 (50)	50/50	183 (50)	101	50/50	187 (50)	103	50/50	171 (50)	94	50/50
14	183 (50)	50/50	185 (50)	101	50/50	190 (50)	104	50/50	173 (50)	95	50/50
18	189 (50)	50/50	191 (50)	101	50/50	196 (50)	104	50/50	180 (50)	95	50/50
22	197 (50)	50/50	199 (50)	101	50/50	204 (50)	104	50/50	187 (50)	95	50/50
26	203 (50)	50/50	205 (50)	101	50/50	208 (50)	102	50/50	194 (50)	96	50/50
30	206 (50)	50/50	209 (50)	101	50/50	214 (49)	104	49/50	199 (50)	97	50/50
34	212 (50)	50/50	215 (50)	101	50/50	221 (49)	104	49/50	206 (50)	97	50/50
38	217 (50)	50/50	218 (50)	100	50/50	225 (49)	104	49/50	213 (50)	98	50/50
42	220 (50)	50/50	222 (50)	101	50/50	231 (49)	105	49/50	213 (50)	97	50/50
46	227 (50)	50/50	228 (50)	100	50/50	238 (49)	105	49/50	209 (50)	92	50/50
50	227 (50)	50/50	231 (50)	102	50/50	239 (49)	105	49/50	210 (50)	93	50/50
54	230 (50)	50/50	236 (50)	103	50/50	245 (49)	107	49/50	215 (50)	93	50/50
58	234 (50)	50/50	243 (49)	104	49/50	251 (49)	107	49/50	220 (49)	94	49/50
62	236 (50)	50/50	244 (49)	103	49/50	253 (48)	107	48/50	220 (49)	93	49/50
66	242 (50)	50/50	250 (49)	103	49/50	261 (48)	108	48/50	225 (49)	93	49/50
70	247 (48)	48/50	256 (49)	104	49/50	265 (48)	107	48/50	227 (49)	92	49/50
74	252 (47)	47/50	259 (49)	103	49/50	270 (48)	107	48/50	229 (48)	91	48/50
78	255 (47)	47/50	266 (49)	104	49/50	275 (48)	108	48/50	230 (47)	90	47/50
82	259 (44)	44/50	268 (49)	103	49/50	279 (48)	108	48/50	229 (45)	88	45/50
86	259 (43)	43/50	270 (48)	104	48/50	281 (47)	108	47/50	229 (43)	88	43/50
90	269 (42)	42/50	278 (47)	103	47/50	290 (46)	108	46/50	230 (42)	86	42/50
94	269 (42)	42/50	283 (45)	105	45/50	295 (45)	110	45/50	231 (38)	86	38/50
98	273 (40)	40/50	284 (45)	104	45/50	293 (45)	107	45/50	228 (33)	84	33/50
102	274 (38)	38/50	282 (45)	103	45/50	289 (43)	105	43/50	218 (28)	80	28/50
104	272 (38)	38/50	280 (45)	103	45/50	295 (39)	108	39/50	218 (26)	80	26/50

< > : 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 RATS 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	3/50	3/50	5/47	8/46	11/43	11/50 (0/10)
	25 ppm	0/50	0/50	2/50	4/49	6/49	9/48	8/45	12/40	17/50 (7/15)
	100 ppm	0/50	0/50	0/50	1/48	2/48	6/48	9/48	11/46	12/50 (1/12)
	400 ppm	0/50	0/50	0/50	1/49	2/48	3/47	4/45	7/42	7/50 (3/20)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	0/47	1/46	2/43	3/50 (1/10)
	25 ppm	0/50	0/50	1/50	0/49	0/49	1/48	0/45	0/40	2/50 (2/15)
	100 ppm	0/50	0/50	0/50	0/48	0/48	0/48	0/48	0/46	0/50 (0/12)
	400 ppm	0/50	0/50	0/50	0/49	0/48	0/47	0/45	0/42	0/50 (0/20)

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 RATS 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	0/50	0/50	1/47	10/42	10/50 (1/12)
	25 ppm	0/50	0/50	0/50	0/50	0/50	1/49	3/49	9/46	9/50 (0/5)
	100 ppm	0/50	1/50	0/49	1/49	2/49	2/48	6/48	10/45	12/50 (3/11)
	400 ppm	0/50	0/50	0/50	0/50	2/50	3/49	10/46	11/40	14/50 (7/24)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	1/50	1/47	1/42	2/50 (2/12)
	25 ppm	0/50	0/50	0/50	0/50	0/50	0/49	0/49	0/46	0/50 (0/5)
	100 ppm	0/50	0/50	0/49	0/49	0/49	0/48	1/48	1/45	2/50 (1/11)
	400 ppm	0/50	0/50	0/50	0/50	0/50	0/49	3/46	4/40	5/50 (8/24)

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 RATS 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	14.5 (50)	14.3 (50)	99	14.1 (50)	97	12.6 (50)	87
2	15.9 (50)	16.1 (50)	101	16.2 (50)	102	15.0 (50)	94
3	17.3 (50)	17.5 (50)	101	18.1 (50)	105	16.7 (50)	97
4	17.5 (50)	17.6 (50)	101	18.2 (50)	104	17.2 (50)	98
5	17.5 (50)	17.5 (50)	100	17.9 (50)	102	17.3 (50)	99
6	17.1 (50)	17.4 (50)	102	18.1 (50)	106	17.6 (50)	103
7	17.2 (50)	17.3 (50)	101	17.8 (50)	103	17.4 (50)	101
8	16.6 (50)	16.8 (50)	101	17.5 (50)	105	17.5 (50)	105
9	17.2 (50)	17.4 (50)	101	17.7 (50)	103	17.6 (50)	102
10	16.9 (50)	17.3 (50)	102	17.7 (50)	105	17.4 (50)	103
11	16.8 (50)	17.1 (50)	102	17.4 (50)	104	17.4 (50)	104
12	16.9 (50)	17.0 (50)	101	17.4 (50)	103	17.7 (50)	105
13	16.8 (50)	16.9 (50)	101	17.3 (50)	103	17.8 (50)	106
14	16.8 (50)	16.9 (50)	101	17.4 (50)	104	17.9 (50)	107
18	16.4 (50)	16.6 (50)	101	16.9 (50)	103	17.5 (50)	107
22	17.0 (50)	17.0 (50)	100	17.3 (50)	102	18.0 (50)	106
26	16.8 (50)	16.7 (50)	99	16.8 (50)	100	17.6 (50)	105
30	16.2 (50)	16.2 (49)	100	16.7 (49)	103	17.3 (50)	107
34	17.1 (50)	17.5 (49)	102	17.4 (49)	102	17.9 (49)	105
38	16.6 (50)	16.3 (49)	98	16.7 (49)	101	17.1 (49)	103
42	16.6 (50)	16.6 (49)	100	17.0 (48)	102	16.2 (49)	98
46	17.2 (50)	17.2 (49)	100	17.1 (48)	99	17.8 (48)	103
50	17.1 (50)	17.2 (49)	101	17.2 (48)	101	17.7 (48)	104
54	16.5 (50)	17.0 (49)	103	17.2 (48)	104	17.6 (48)	107
58	17.1 (48)	16.9 (49)	99	17.2 (48)	101	17.4 (48)	102
62	17.5 (48)	17.1 (49)	98	17.2 (48)	98	17.0 (48)	97
66	17.4 (47)	17.4 (48)	100	17.4 (48)	100	16.9 (47)	97
70	17.0 (47)	17.0 (48)	100	17.3 (48)	102	17.2 (47)	101
74	17.2 (46)	17.0 (47)	99	17.2 (48)	100	17.0 (46)	99
78	17.6 (46)	17.4 (45)	99	17.5 (48)	99	17.2 (45)	98
82	16.8 (45)	17.3 (45)	103	17.5 (48)	104	16.9 (44)	101
86	17.2 (43)	16.9 (44)	98	17.1 (46)	99	16.6 (43)	97
90	17.5 (43)	17.1 (40)	98	17.4 (46)	99	16.7 (42)	95
94	16.8 (43)	16.7 (40)	99	17.0 (46)	101	16.5 (41)	98
98	17.2 (42)	16.8 (39)	98	16.1 (44)	94	17.2 (38)	100
102	17.6 (40)	16.8 (35)	95	17.3 (39)	98	16.8 (34)	95
104	17.2 (40)	16.3 (35)	95	17.0 (38)	99	16.7 (30)	97

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

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

TABLE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS 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	10.8 (50)	10.7 (50)	99	10.9 (50)	101	9.8 (50)	91
2	11.0 (50)	11.4 (50)	104	11.9 (50)	108	11.2 (50)	102
3	11.4 (50)	11.6 (50)	102	12.3 (50)	108	11.5 (50)	101
4	11.5 (50)	11.7 (50)	102	12.4 (50)	108	11.9 (49)	103
5	11.3 (50)	11.6 (50)	103	12.7 (50)	112	12.2 (50)	108
6	11.2 (50)	11.5 (50)	103	12.1 (50)	108	12.1 (50)	108
7	11.1 (50)	11.4 (50)	103	11.9 (50)	107	12.2 (50)	110
8	10.8 (50)	10.8 (50)	100	11.4 (50)	106	12.2 (50)	113
9	11.2 (50)	11.2 (50)	100	11.4 (50)	102	12.0 (50)	107
10	11.0 (50)	11.0 (50)	100	11.4 (50)	104	12.0 (50)	109
11	11.0 (50)	11.5 (50)	105	12.0 (50)	109	12.4 (50)	113
12	11.3 (50)	11.3 (50)	100	12.1 (50)	107	12.6 (50)	112
13	11.1 (50)	11.3 (50)	102	11.9 (50)	107	12.7 (50)	114
14	11.3 (50)	11.5 (50)	102	12.2 (50)	108	12.8 (50)	113
18	10.8 (50)	11.2 (50)	104	11.4 (50)	106	12.6 (50)	117
22	11.3 (50)	11.6 (50)	103	11.7 (50)	104	12.6 (50)	112
26	11.0 (50)	11.0 (50)	100	11.1 (50)	101	12.3 (50)	112
30	10.9 (50)	10.9 (50)	100	11.4 (49)	105	12.4 (50)	114
34	10.9 (50)	11.5 (50)	106	12.0 (49)	110	12.6 (50)	116
38	11.3 (50)	11.3 (50)	100	11.8 (49)	104	12.3 (50)	109
42	11.2 (50)	11.2 (50)	100	12.2 (49)	109	11.7 (50)	104
46	11.7 (50)	11.5 (50)	98	12.0 (49)	103	12.4 (50)	106
50	10.9 (50)	11.4 (50)	105	11.7 (49)	107	12.5 (50)	115
54	11.6 (50)	11.9 (50)	103	12.6 (49)	109	13.0 (50)	112
58	11.5 (50)	11.7 (49)	102	12.2 (49)	106	12.7 (49)	110
62	11.6 (50)	11.5 (49)	99	11.9 (48)	103	12.1 (49)	104
66	12.0 (50)	12.0 (49)	100	12.7 (48)	106	12.9 (49)	108
70	12.0 (48)	12.0 (49)	100	12.6 (48)	105	12.6 (49)	105
74	12.1 (47)	12.0 (49)	99	12.5 (48)	103	12.4 (48)	102
78	12.3 (47)	12.6 (49)	102	13.0 (48)	106	12.7 (47)	103
82	12.2 (44)	12.2 (49)	100	12.9 (48)	106	12.8 (45)	105
86	12.0 (43)	12.4 (48)	103	12.8 (47)	107	13.1 (42)	109
90	12.8 (42)	12.5 (47)	98	13.5 (46)	105	13.1 (42)	102
94	12.1 (42)	12.7 (45)	105	13.2 (45)	109	12.8 (38)	106
98	12.6 (40)	13.0 (45)	103	13.2 (45)	105	13.8 (33)	110
102	12.4 (38)	12.6 (45)	102	12.8 (42)	103	13.2 (28)	106
104	12.2 (38)	12.7 (45)	104	12.9 (39)	106	13.3 (26)	109

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

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

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

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	40	35	38	29
MCH (pg)	16.5 ± 1.2	16.3 ± 1.1	16.5 ± 0.9	15.8 ± 0.9 *
PLATELET ($10^3/\mu$ L)	929 ± 241	1004 ± 326	1117 ± 241 **	1045 ± 204

Mean ± S.D.

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

TABLE 8 HEMATOLOGY OF FEMALE RATS 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	45	37	26
MCV (fL)	53.9 ± 3.3	53.1 ± 3.0	54.9 ± 8.7	52.1 ± 4.2 **
MCH (pg)	18.2 ± 0.8	17.8 ± 1.0	18.3 ± 1.9	16.9 ± 1.3 **
MCHC (g/dL)	33.9 ± 1.9	33.5 ± 2.0	33.6 ± 1.7	32.4 ± 1.1 **
PLATELET ($10^3/\mu$ L)	658 ± 92	716 ± 208	721 ± 168	1041 ± 284 **
WBC ($10^3/\mu$ L)	12.46 ± 57.20	2.98 ± 1.48	3.21 ± 3.38	11.62 ± 20.13 **

Mean ± S.D.

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

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

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	40	35	38	29
ALBUMIN (g/dL)	2.9 ± 0.4	2.9 ± 0.2	2.8 ± 0.2	2.7 ± 0.2 **
A/G RATIO	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1 **	0.7 ± 0.1 *
T-CHOLESTEROL (mg/dL)	200 ± 78	189 ± 61	241 ± 65 *	249 ± 56 **
TRIGLYCERIDE (mg/dL)	144 ± 150	108 ± 62	190 ± 132 *	205 ± 130 **
PHOSPHOLIPID (mg/dL)	284 ± 108	271 ± 73	333 ± 81 **	352 ± 66 **
GPT (IU/L)	39 ± 15	35 ± 10	34 ± 20 *	58 ± 54
ALP (IU/L)	214 ± 93	194 ± 43	176 ± 82 **	175 ± 66 **
G-GTP (IU/L)	6 ± 4	5 ± 3	7 ± 4	11 ± 8 *
CPK (IU/L)	109 ± 86	92 ± 11	93 ± 18	99 ± 55 **
UREA NITROGEN (mg/dL)	24.2 ± 12.8	21.0 ± 4.4	26.8 ± 12.2 *	38.8 ± 70.5 **
POTASSIUM (mEq/L)	3.8 ± 0.4	3.5 ± 0.3 *	3.6 ± 0.3	3.8 ± 0.7
CHLORIDE (mEq/L)	106 ± 2	106 ± 1	107 ± 2	111 ± 4 **
CALCIUM (mg/dL)	10.4 ± 0.5	10.4 ± 0.4	10.8 ± 0.7 **	10.7 ± 0.8

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

TABLE 10 BIOCHEMISTRY OF FEMALE RATS 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	45	38	26
ALBUMIN (g/dL)	3.6 ± 0.3	3.6 ± 0.2	3.5 ± 0.3	3.1 ± 0.4 **
A/G RATIO	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1 *	0.9 ± 0.1 **
T-BILIRUBIN (mg/dL)	0.14 ± 0.07	0.14 ± 0.04	0.23 ± 0.60	0.20 ± 0.07 **
GLUCOSE (mg/dL)	155 ± 15	159 ± 18	163 ± 20	136 ± 22 **
T-CHOLESTEROL (mg/dL)	124 ± 25	162 ± 67 **	187 ± 55 **	288 ± 85 **
TRIGLYCERIDE (mg/dL)	53 ± 56	114 ± 146 **	118 ± 104 **	159 ± 107 **
PHOSPHOLIPID (mg/dL)	227 ± 46	287 ± 110 **	321 ± 86 **	437 ± 116 **
GOT (IU/L)	186 ± 194	138 ± 68	143 ± 191	1015 ± 1144 **
GPT (IU/L)	75 ± 38	67 ± 35	63 ± 35	421 ± 622 **
LDH (IU/L)	361 ± 667	243 ± 104	236 ± 110	618 ± 759 **
ALP (IU/L)	144 ± 61	116 ± 53 **	109 ± 64 **	384 ± 284 **
G-GTP (IU/L)	2 ± 1	2 ± 1	2 ± 2	26 ± 27 **
UREA NITROGEN (mg/dL)	20.0 ± 13.7	18.1 ± 2.6	17.7 ± 2.8	22.2 ± 5.2 **
CREATININE (mg/dL)	0.5 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1 **
CHLORIDE (mEq/L)	104 ± 2	104 ± 3	106 ± 2	109 ± 5 **
CALCIUM (mg/dL)	10.3 ± 0.4	10.4 ± 0.3	10.5 ± 0.4	10.6 ± 0.5 **

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

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

Group Name		Control	25 ppm	100 ppm	400 ppm
No. of examined animals		40	35	38	31
	Grade				
pH	5.0	0	0	0	0
	6.0	0	0	0	0
	6.5	4	2	3	8
	7.0	7	3	5	11
	7.5	17	18	16	11
	8.0	12	12	14	1
	8.5	0	0	0	0
	Chi square test				**
Protein	−	0	0	0	0
	±	0	0	0	0
	+	0	0	0	0
	2+	0	1	0	0
	3+	12	15	4	5
	4+	28	19	34	26
	Chi square test			*	

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

TABLE 12 URINALYSIS OF FEMALE RATS 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	45	41	27
	Grade				
pH	5.0	0	0	0	0
	6.0	0	0	2	0
	6.5	2	4	1	6
	7.0	7	7	5	11
	7.5	8	11	10	5
	8.0	17	19	19	4
	8.5	4	4	4	1
	Chi square test				*
Protein	−	1	0	0	0
	±	2	1	0	0
	+	7	13	1	0
	2+	13	10	6	1
	3+	9	10	18	8
	4+	6	11	16	18
	Chi square test			**	**

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

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

Group Name	Control	25 ppm	100 ppm	400 ppm
No. of examined animals	40	35	38	30
Body weight (g)	381 ± 30	378 ± 31	384 ± 45	279 ± 32 **
Adrenals (g)	0.103 ± 0.154	0.106 ± 0.188	0.163 ± 0.528	0.065 ± 0.010 **
Adrenals (%)	0.030 ± 0.056	0.029 ± 0.051	0.041 ± 0.129	0.024 ± 0.006 **
Testes (g)	3.787 ± 1.532	3.685 ± 1.441	3.437 ± 1.460	4.229 ± 1.223
Testes (%)	0.992 ± 0.395	0.979 ± 0.401	0.895 ± 0.367	1.527 ± 0.416 **
Heart (g)	1.251 ± 0.114	1.227 ± 0.099	1.282 ± 0.103	1.148 ± 0.100 **
Heart (%)	0.331 ± 0.040	0.327 ± 0.049	0.337 ± 0.033	0.416 ± 0.050 **
Lungs (g)	1.421 ± 0.102	1.405 ± 0.128	1.462 ± 0.272	1.375 ± 0.146 *
Lungs (%)	0.375 ± 0.037	0.373 ± 0.035	0.387 ± 0.101	0.498 ± 0.069 **
Kidneys (g)	2.772 ± 0.284	2.732 ± 0.235	2.991 ± 0.321 **	2.834 ± 0.261
Kidneys (%)	0.731 ± 0.086	0.729 ± 0.107	0.789 ± 0.130 *	1.023 ± 0.100 **
Spleen (g)	1.271 ± 2.224	0.930 ± 0.230	0.989 ± 0.250	0.968 ± 0.625
Spleen (%)	0.332 ± 0.575	0.247 ± 0.066	0.262 ± 0.083	0.342 ± 0.207 **
Liver (g)	11.401 ± 2.455	11.149 ± 1.059	13.099 ± 1.687 **	13.581 ± 2.917 **
Liver (%)	2.993 ± 0.600	2.965 ± 0.361	3.442 ± 0.509 **	4.877 ± 1.039 **
Brain (g)	2.056 ± 0.058	2.060 ± 0.045	2.050 ± 0.052	1.958 ± 0.054 **
Brain (%)	0.543 ± 0.044	0.549 ± 0.050	0.540 ± 0.051	0.711 ± 0.092 **

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

TABLE 14 ORGAN WEIGHTS OF FEMALE RATS 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	45	39	26
Body weight (g)	253 ± 26	260 ± 29	275 ± 24 **	199 ± 28 **
Adrenals (g)	0.076 ± 0.015	0.076 ± 0.021	0.073 ± 0.008	0.094 ± 0.090
Adrenals (%)	0.030 ± 0.007	0.030 ± 0.014	0.027 ± 0.003	0.047 ± 0.040 **
Ovaries (g)	0.131 ± 0.027	0.199 ± 0.494	0.131 ± 0.026	0.104 ± 0.035 **
Ovaries (%)	0.052 ± 0.011	0.077 ± 0.189	0.048 ± 0.010	0.052 ± 0.016
Heart (g)	0.890 ± 0.084	0.888 ± 0.099	0.936 ± 0.119	0.880 ± 0.081
Heart (%)	0.355 ± 0.052	0.346 ± 0.065	0.342 ± 0.040	0.448 ± 0.060 **
Lungs (g)	1.034 ± 0.205	0.991 ± 0.072	1.059 ± 0.326	1.156 ± 0.387 *
Lungs (%)	0.415 ± 0.111	0.386 ± 0.058	0.390 ± 0.147	0.601 ± 0.281 **
Kidneys (g)	1.738 ± 0.174	1.776 ± 0.229	1.862 ± 0.204 *	2.071 ± 0.167 **
Kidneys (%)	0.694 ± 0.107	0.692 ± 0.149	0.682 ± 0.093	1.055 ± 0.151 **
Spleen (g)	0.798 ± 1.043	0.646 ± 0.608	0.869 ± 1.957	0.943 ± 1.020
Spleen (%)	0.336 ± 0.506	0.263 ± 0.304	0.337 ± 0.839	0.481 ± 0.522 **
Liver (g)	6.543 ± 1.056	7.019 ± 0.902	7.937 ± 1.032 **	15.357 ± 4.930 **
Liver (%)	2.612 ± 0.541	2.714 ± 0.342	2.899 ± 0.378 **	7.969 ± 3.238 **
Brain (g)	1.866 ± 0.053	1.855 ± 0.054	1.848 ± 0.048	1.798 ± 0.049 **
Brain (%)	0.745 ± 0.079	0.722 ± 0.089	0.678 ± 0.064 **	0.918 ± 0.127 **

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

TABLE 15 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE RATS 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
Integumentary system/appandage						
skin/appendage	<50>	<50>	<50>	<50>		
trichoepithelioma	0 (0 %)	1 (2 %)	0 (0 %)	3 (6 %)	↑	↑
Respiratory system						
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar adenoma	2 (4 %)	1 (2 %)	1 (2 %)	7 (14 %)	↑↑	↑↑
bronchiolar-alveolar carcinoma	0 (0 %)	2 (4 %)	0 (0 %)	0 (0 %)		
Digestive system						
large intestine	<50>	<50>	<50>	<50>		
adenoma	0 (0 %)	0 (0 %)	0 (0 %)	3 (6 %)	↑↑	↑↑
adenocarcinoma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
liver	<50>	<50>	<50>	<50>		
hepatocellular adenoma	1 (2 %)	1 (2 %)	2 (4 %)	10 (20 %)**	↑↑	↑↑
hepatocellular carcinoma	0 (0 %)	0 (0 %)	1 (2 %)	6 (12 %)*	↑↑	↑↑
hemangiosarcoma	1 (2 %)	0 (0 %)	0 (0 %)	2 (4 %)		

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 RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

Group Name Number of examined animals	Control 50	25ppm 50	100ppm 50	400ppm 50	Peto test	Cochran-Armitage test
Integumentary system/appandage						
skin/appendage	<50>	<50>	<50>	<50>		
trichoepithelioma	0 (0 %)	0 (0 %)	1 (2 %)	2 (4 %)		
Respiratory system						
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar adenoma	1 (2 %)	0 (0 %)	1 (2 %)	5 (10 %)	↑↑	↑↑
Hematopoietic system						
spleen	<50>	<50>	<50>	<50>		
mononuclear cell leukemia	5 (10 %)	3 (6 %)	5 (10 %)	13 (26 %)*	↑↑	↑↑
Digestive system						
large intestine	<50>	<50>	<50>	<50>		
adenoma	0 (0 %)	0 (0 %)	0 (0 %)	2 (4 %)		
liver	<50>	<50>	<50>	<50>		
hepatocellular adenoma	1 (2 %)	0 (0 %)	2 (4 %)	32 (64 %)**	↑↑	↑↑
hepatocellular carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	38 (76 %)**	↑↑	↑↑
hemangioma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
hemangiosarcoma	0 (0 %)	0 (0 %)	0 (0 %)	6 (12 %)*	↑↑	↑↑

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 RATS 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>			
inflammation:respiratory epithelium	0	0	0	0	6	2	0	0 *	5	2	0	0 *	13	13	0	0 **
squamous cell metaplasia:respiratory epithelium	0	0	0	0	2	0	0	0	1	0	0	0	16	7	0	0 **
hyperplasia with atypia:transitional epithelium	0	0	0	0	0	0	0	0	0	0	0	0	1	3	0	0
respiratory metaplasia:gland	15	15	0	0	14	21	0	0	16	22	0	0	2	37	0	0 **
atrophy:olfactory epithelium	0	0	0	0	0	0	0	0	2	0	0	0	11	18	1	0 **
necrosis:olfactory epithelium	0	0	0	0	0	0	0	0	1	0	0	0	5	3	0	0 *
respiratory metaplasia:olfactory epitheliun	2	2	0	0	4	1	0	0	0	0	0	0	7	9	0	0 *
lung	<50>				<50>				<50>				<50>			
bronchiolar-alveolar cell hyperplasia	0	0	0	0	1	0	0	0	2	0	0	0	3	0	0	0
Hematopoietic system																
spleen	<50>				<50>				<50>				<50>			
deposit of hemosiderin	10	22	0	0	8	25	2	0	5	30	0	0	7	32	3	0 *
Digestive system																
liver	<50>				<50>				<50>				<50>			
clear cell focus	7	9	0	0	9	4	0	0	17	12	0	0 *	0	13	27	0 **
acidophilic cell focus	0	1	0	0	0	0	0	0	2	1	0	0	7	13	0	0 **
basophilic cell focus	2	1	0	0	0	1	0	0	2	5	0	0	1	8	0	0 *
Urinary system																
kidney	<50>				<50>				<50>				<50>			
chronic nephropathy	6	28	6	2	5	35	3	1	1	27	13	5	2	28	14	2

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

TABLE 18 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF FEMALE RATS 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>			
inflammation:respiratory epithelium	0	0	0	0	3	0	0	0	4	0	0	0	12	1	0	0 **
squamous cell metaplasia:respiratory epithelium	0	0	0	0	0	1	0	0	2	0	0	0	16	9	0	0 **
hyperplasia with atypia:transitional epithelium	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0
respiratory metaplasia:gland	17	15	0	0	22	16	0	0	25	18	0	0 *	3	30	0	0 **
atrophy:olfactory epithelium	0	0	0	0	0	0	0	0	0	0	0	0	21	16	2	0 **
necrosis:olfactory epithelium	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0 **
Hematopoietic system																
bone marrow	<50>				<50>				<50>				<50>			
increased hematopoiesis	2	0	0	0	3	0	0	0	2	0	0	0	11	0	0	0 *
spleen	<50>				<50>				<50>				<50>			
deposit of hemosiderin	2	38	4	0	1	43	1	0	1	38	2	0	1	28	0	0 **
Digestive system																
liver	<50>				<50>				<50>				<50>			
clear cell focus	3	1	0	0	0	0	0	0	7	0	0	0	1	12	20	1 **
acidophilic cell focus	0	0	0	0	0	0	0	0	1	0	0	0	4	9	0	0 **
basophilic cell focus	15	8	0	0	9	5	0	0	11	9	0	0	1	5	0	0 **
bile duct hyperplasia	1	3	0	0	4	7	0	0	17	12	0	0 **	13	9	0	0 **
granulation	7	13	1	0	5	5	0	0	0	3	0	0 **	1	2	0	0 **
Urinary system																
kidney	<50>				<50>				<50>				<50>			
chronic nephropathy	20	2	0	0	11	12	1	0 *	19	17	1	1 **	9	31	5	0 **

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

TABLE 19 CAUSE OF DEATH OF MALE AND FEMALE RATS 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	10	15	12	20	12	5	11	24
No microscopical confirmation	1	0	1	3	2	3	1	0
Respiratory system lesion	0	0	0	1	0	0	0	0
Chronic nephropathy	0	0	2	0	0	0	1	0
Renal lesion	0	0	0	0	1	0	0	0
Urinary retention	0	0	0	1	0	0	0	0
Central nervous system lesion	0	0	0	1	0	0	0	0
Hemorrhage	0	0	0	0	1	0	0	0
Tumor death : leukemia	2	2	2	1	3	1	3	8
skin/appendage	0	0	1	1	0	0	0	0
subcutis	0	2	0	0	0	0	1	0
brown fat	0	1	0	0	0	0	0	0
nasal cavity	0	0	0	1	0	0	1	0
spleen	1	1	0	0	0	0	0	0
heart	0	0	0	1	0	0	0	0
oral cavity	0	0	0	2	0	0	0	0
stomach	0	0	0	0	0	0	0	1
small intestine	0	0	1	0	0	0	0	0
large intestine	0	0	0	1	0	0	0	0
liver	0	0	0	3	0	0	0	8
pituitary gland	3	4	2	1	5	0	3	1
thyroid	0	0	0	0	0	0	0	1
adrenal gland	2	1	0	0	0	0	0	0
epididymis	0	0	0	1	0	0	0	0
uterus	—	—	—	—	0	1	0	2
mammary gland	0	1	0	0	0	0	0	0
preputial/clitoral gland	0	0	0	1	0	0	0	1
brain	0	1	1	0	0	0	1	1
Zymbal gland	0	1	0	0	0	0	0	1
bone	1	1	1	0	0	0	0	0
peritoneum	0	0	1	1	0	0	0	0

TABLE 20
HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrj MALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Liver	1749			
Hepatocellular adenoma		30	1.7	0 - 8
Hepatocellular carcinoma		6	0.3	0 - 2
Hemangiosarcoma		0	0.0	0 - 0
Lung	1749			
Bronchiolar-alveolar adenoma		62	3.5	0 - 10
Large intestine	1749			
Adenoma		0	0.0	0 - 0
Adenocarcinoma		0	0.0	0 - 0
Skin/appendage	1747			
Trichoepithelioma		14	0.8	0 - 4

35 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0267, 0269, 0278, 0284, 0288, 0294, 0296, 0318, 0328, 0342, 0347, 0365, 0371, 0396, 0399, 0401, 0407

TABLE 21
HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrj FEMALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Liver	1597			
Hepatocellular adenoma		20	1.3	0 - 6
Hepatocellular carcinoma		2	0.1	0 - 2
Hemangiosarcoma		1	0.1	0 - 2
Lung	1597			
Bronchiolar-alveolar adenoma		30	1.9	0 - 10
Spleen	1597			
Mononuclear cell leukemia		209	13.1	2 - 26
Large intestine	1597			
Adenoma		0	0.0	0 - 0
Skin/appendage	1597			
Trichoepithelioma		3	0.2	0 - 2

32 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0267, 0269, 0278, 0284, 0296, 0303, 0318, 0328, 0342, 0347, 0365, 0371, 0399, 0401

FIGURES

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

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

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

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

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

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

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

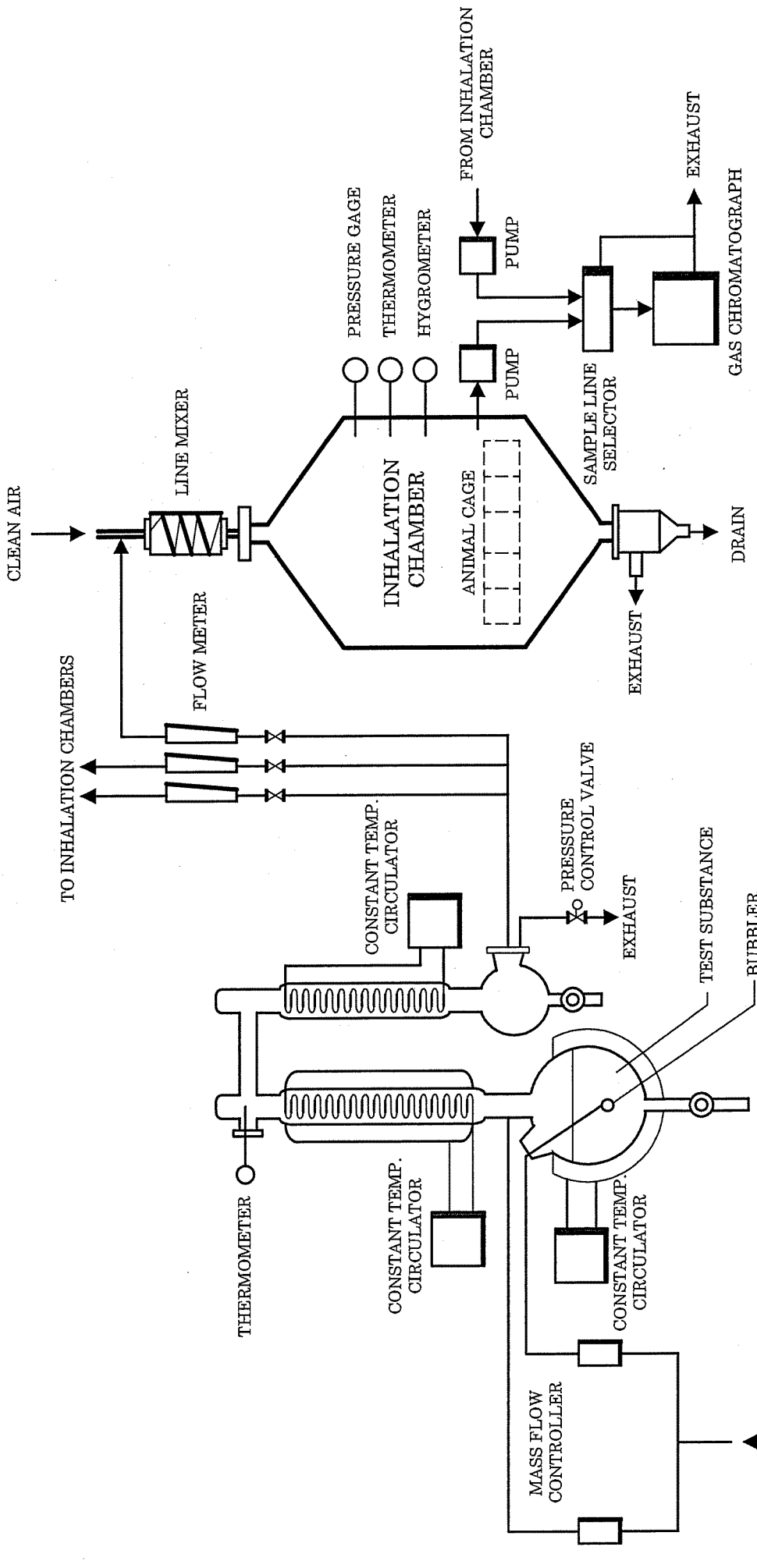


FIGURE 1 1-BROMO-3-CHLOROPROPANE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

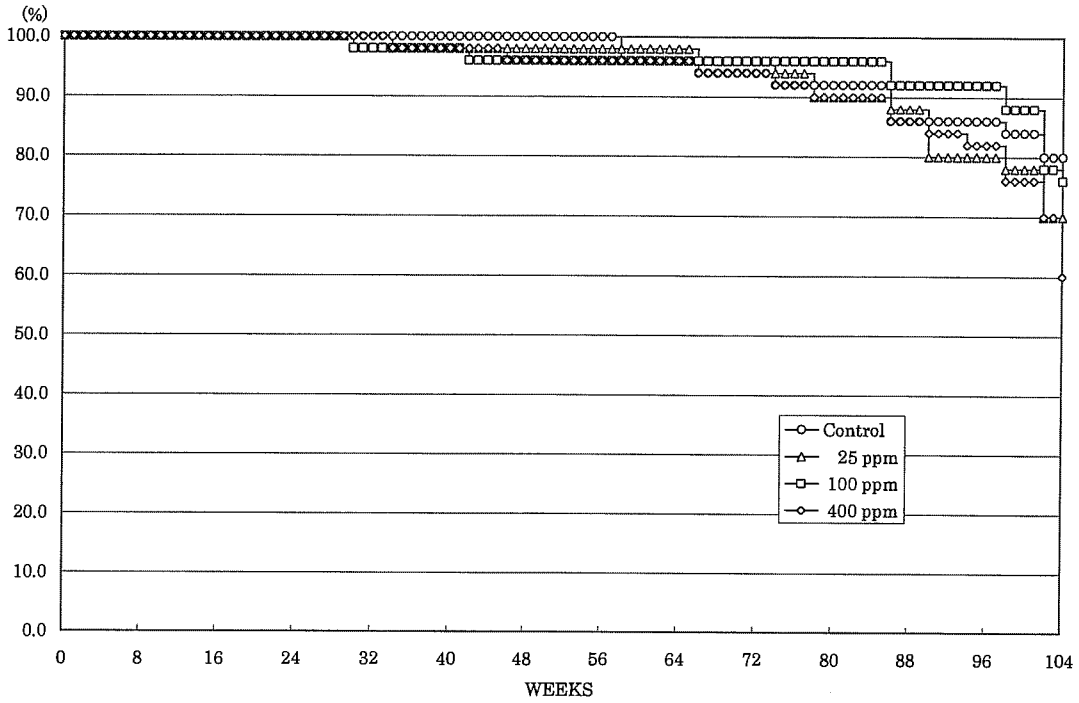


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

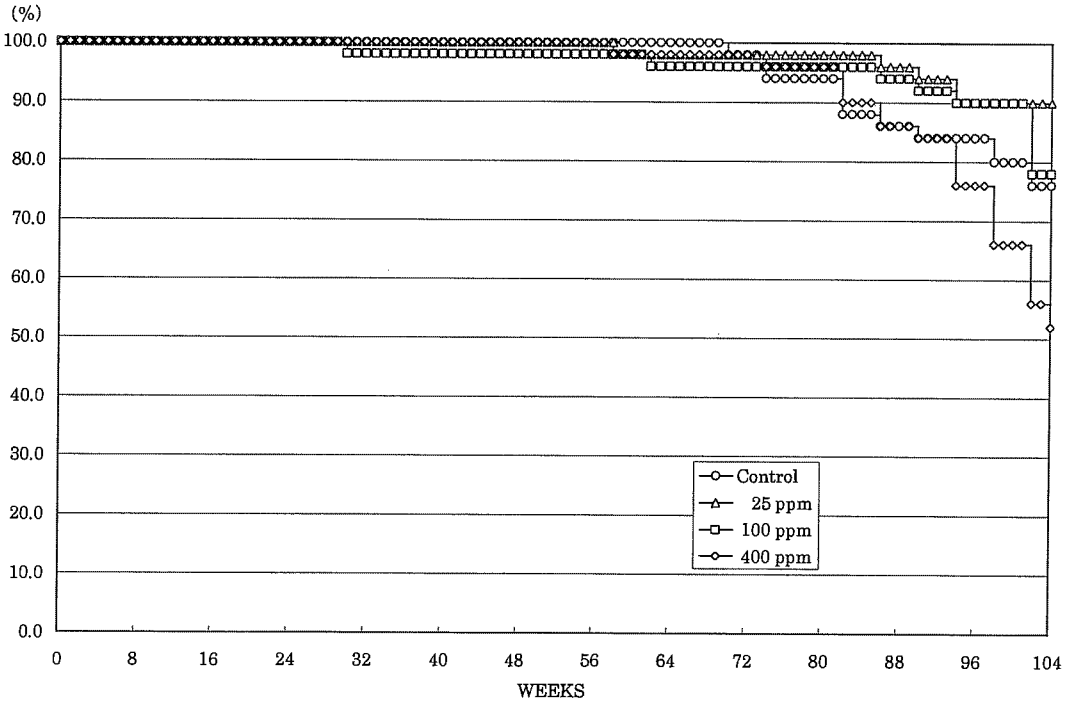


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

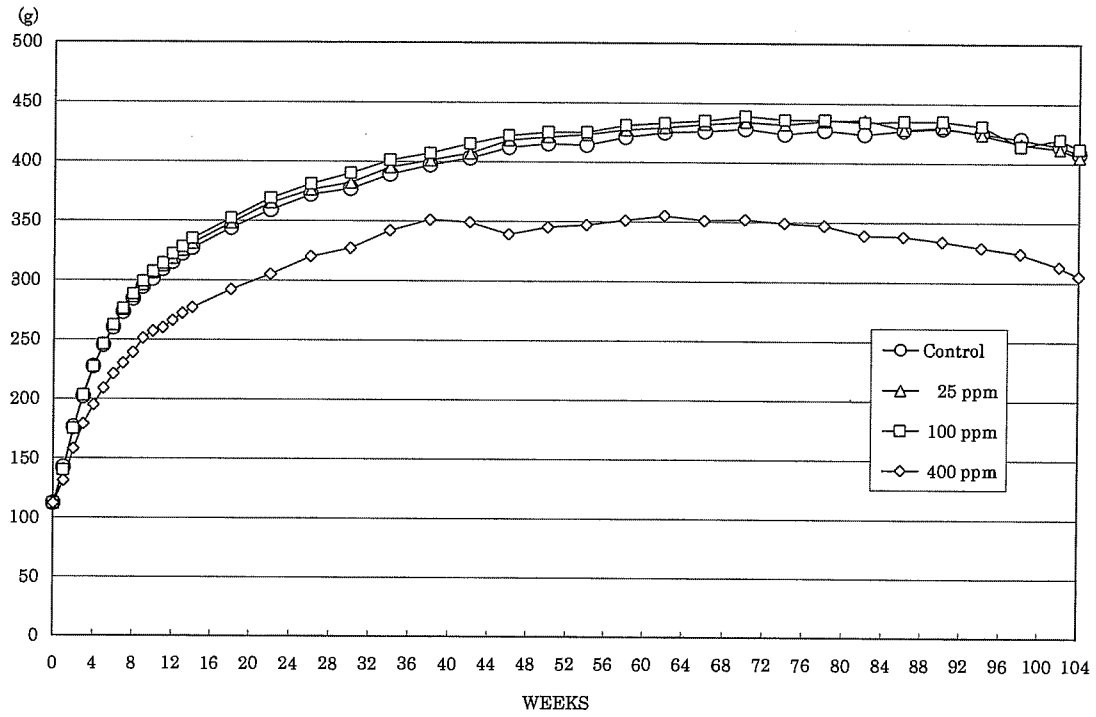


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

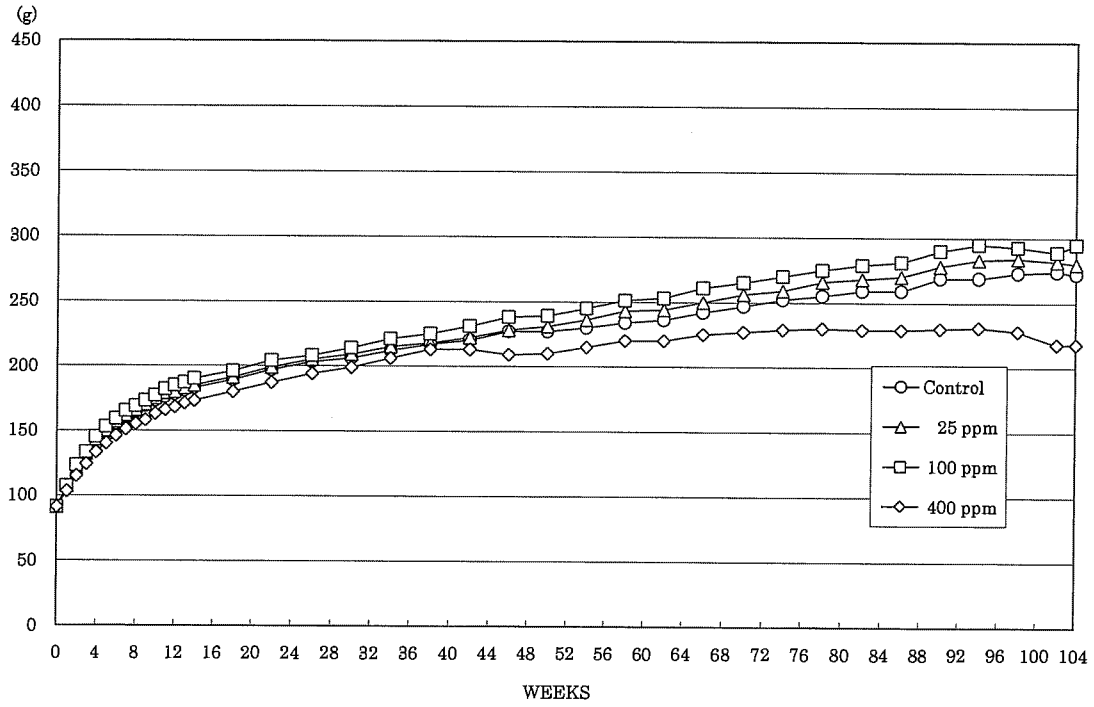


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

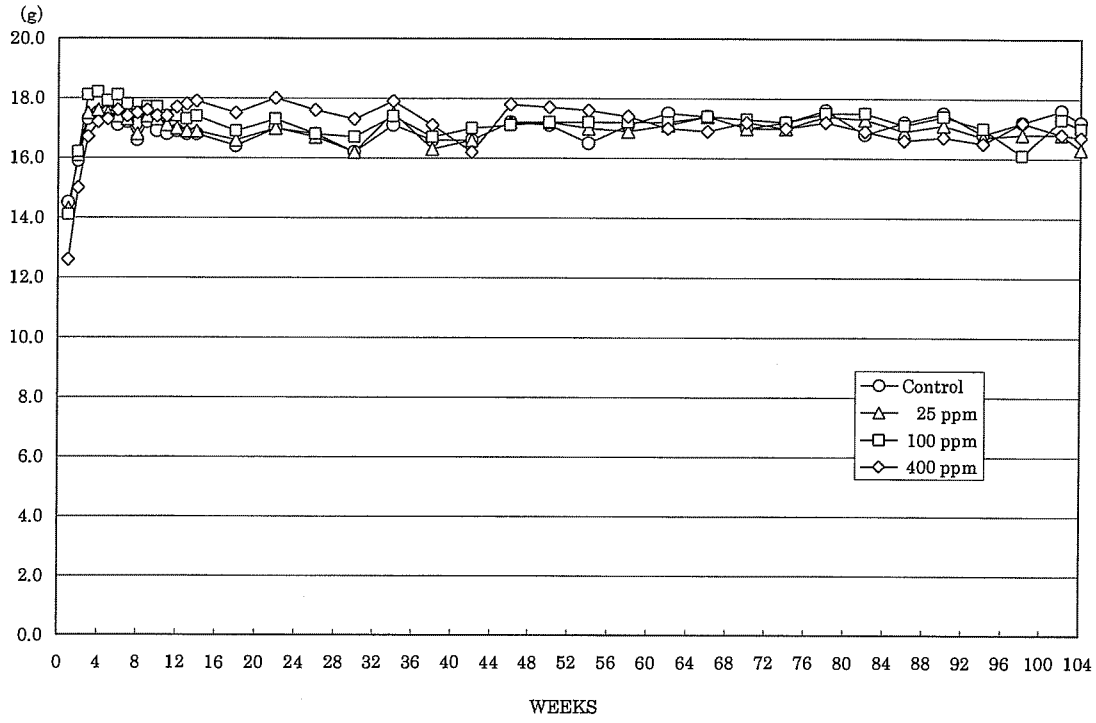


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE

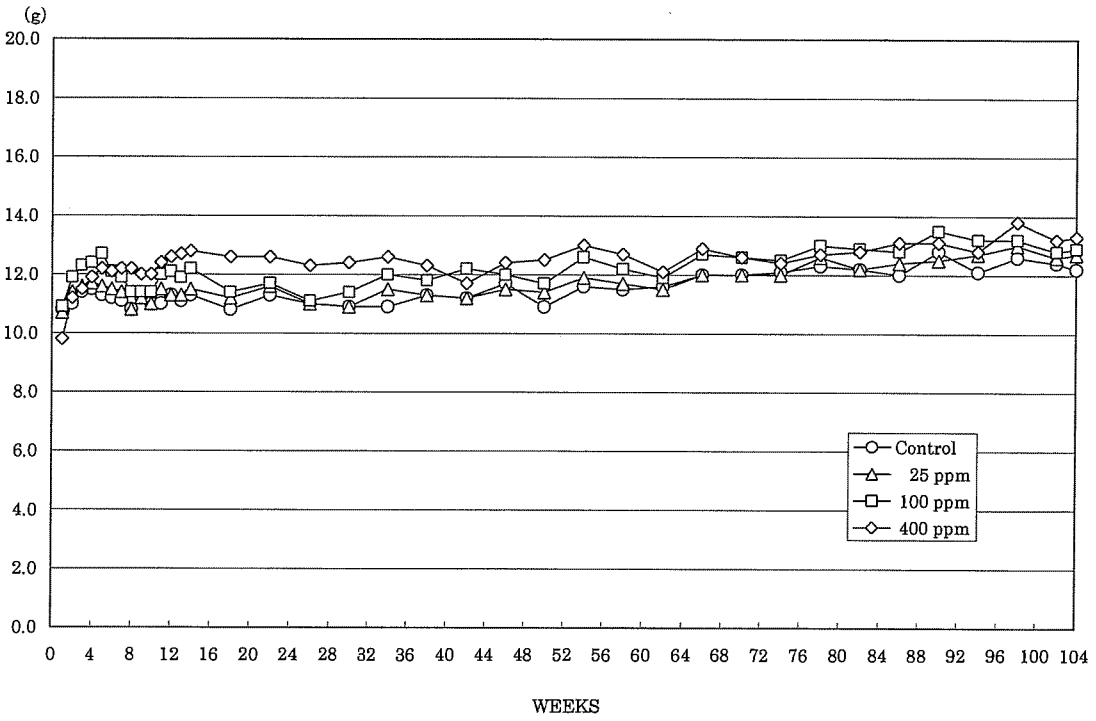
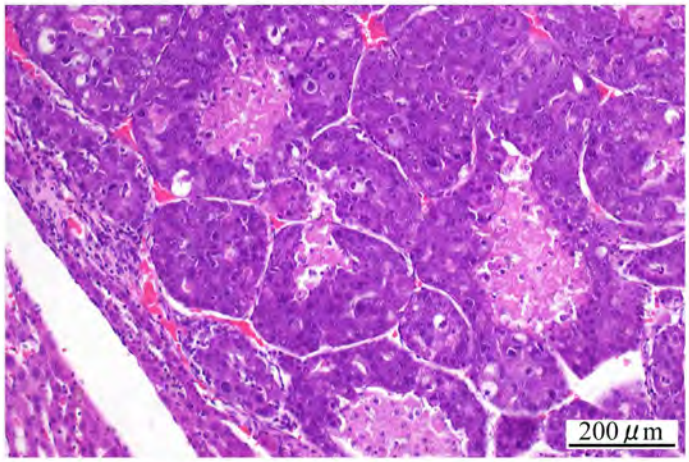
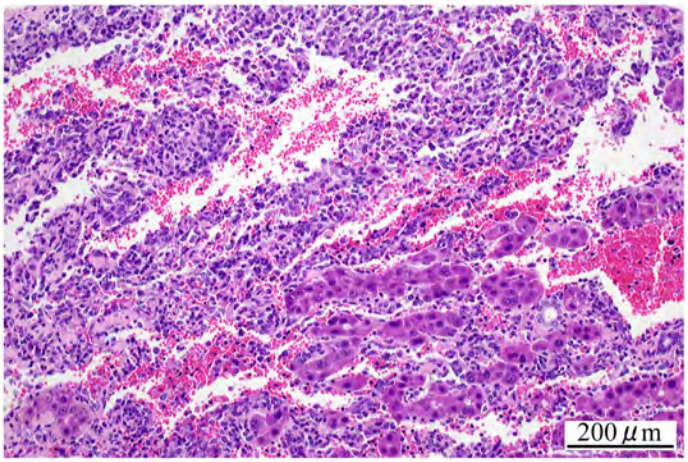


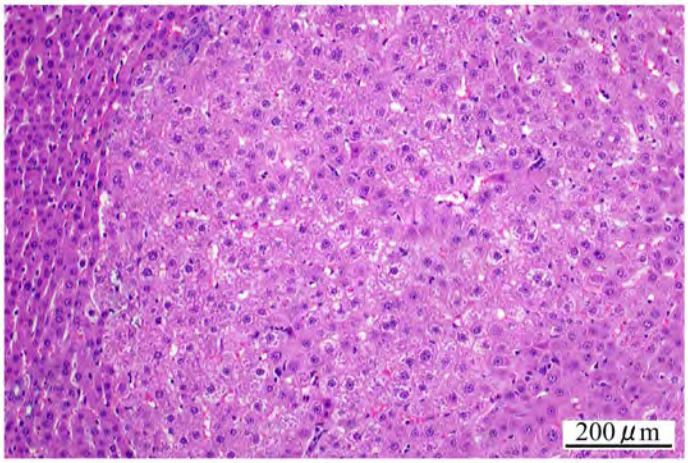
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 1-BROMO-3-CHLOROPROPANE



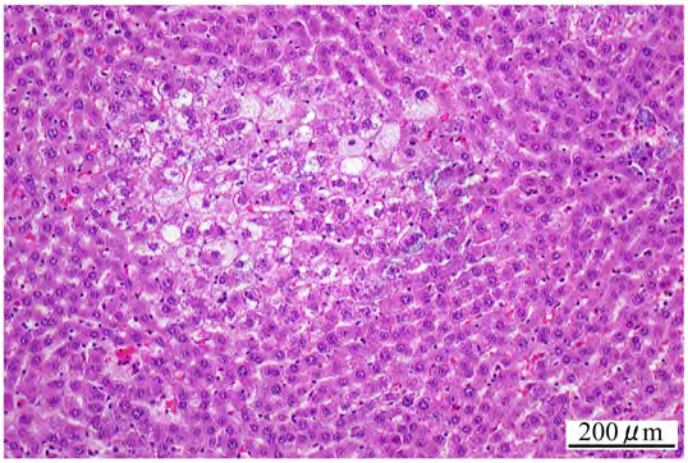
Photograph 1
Liver: Hepatocellular carcinoma
Rat, Female, 400 ppm, Animal No. 0417-2318 (H&E)



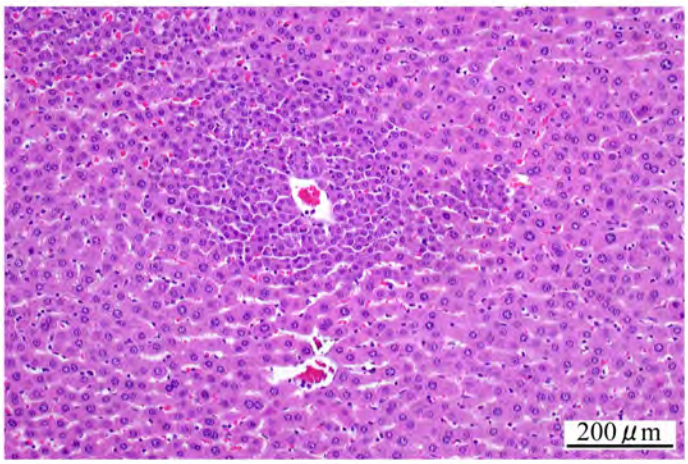
Photograph 2
Liver: Hemangiosarcoma
Rat, Female, 400 ppm, Animal No. 0417-2341 (H&E)



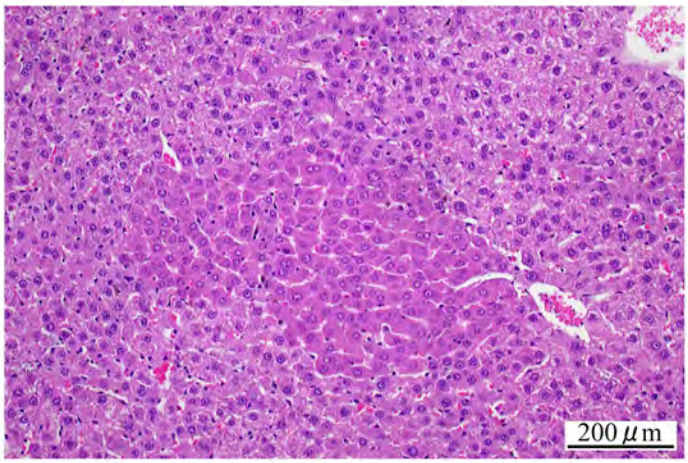
Photograph 3
Liver: Hepatocellular adenoma
Rat, Female, 400 ppm, Animal No. 0417-2316 (H&E)



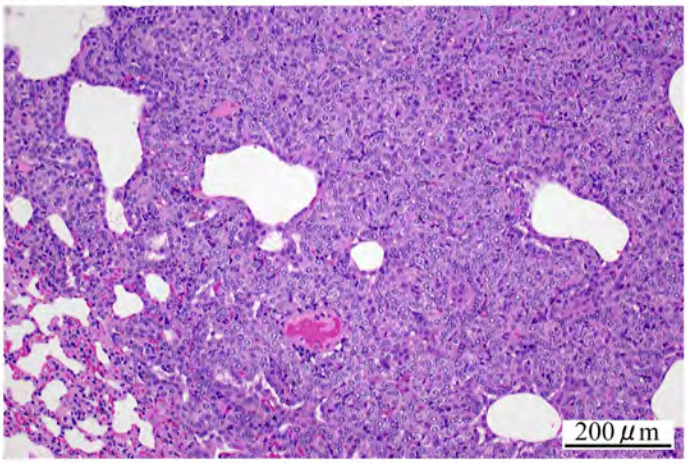
Photograph 4
Liver: Clear cell focus
Rat, Female, 400 ppm, Animal No. 0417-2332 (H&E)



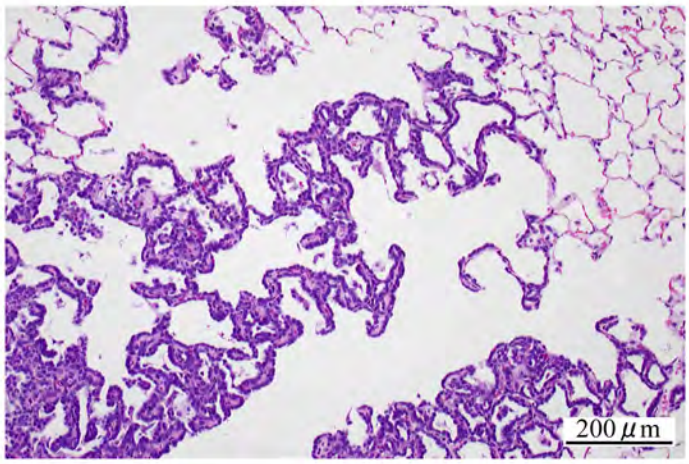
Photograph 5
Liver: Basophilic cell focus
Rat, Male, 400 ppm, Animal No. 0417-1304 (H&E)



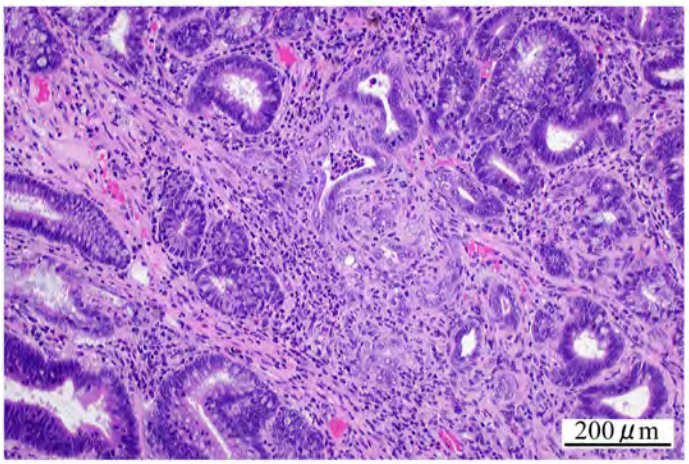
Photograph 6
Liver: Acidophilic cell focus
Rat, Female, 400 ppm, Animal No. 0417-2304 (H&E)



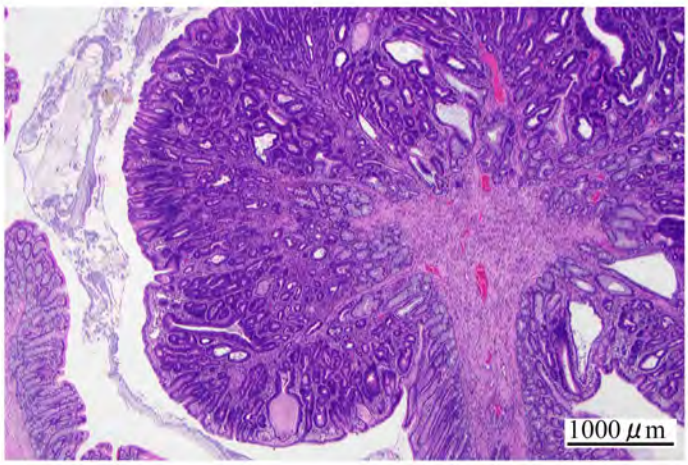
Photograph 7
Lung: Bronchiolar-alveolar adenoma
Rat, Male, 400 ppm, Animal No. 0417-1344 (H&E)



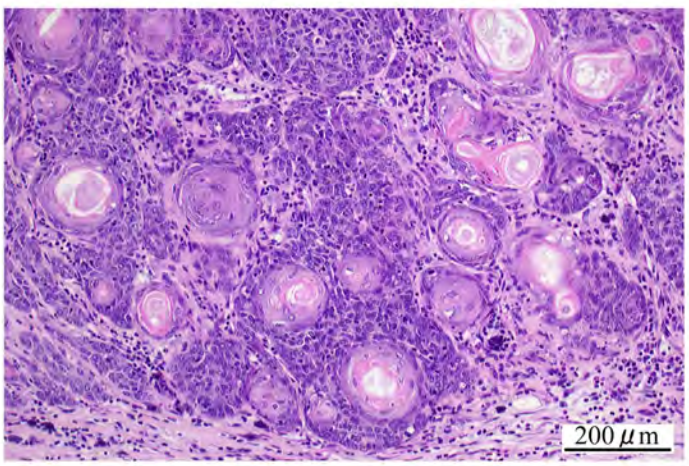
Photograph 8
Lung: Bronchiolar-alveolar cell hyperplasia
Rat, Male, 400 ppm, Animal No. 0417-1346 (H&E)



Photograph 9
Large intestine: Adenocarcinoma
Rat, Male, 400 ppm, Animal No. 0417-1318 (H&E)



Photograph 10
Large intestine: Adenoma
Rat, Male, 400 ppm, Animal No. 0417-1344 (H&E)



Photograph 11
Skin/appendage: Trichoepithelioma
Rat, Male, 400 ppm, Animal No. 0417-1349 (H&E)