Summary of Inhalation Carcinogenicity Study of Butyl 2,3-Epoxypropyl Ether in BDF1 Mice

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

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 September 28 2005.

This English Summary was translated by JBRC from Japanese complete report.

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Purpose, materials and methods

Butyl 2,3-epoxypropyl ether (BEE, 1-butoxy-2,3-epoxypropane, *n*-butyl glycidyl ether, CAS No. 2426-08-6) is a colorless liquid with a boiling point of 164°C and a vapor pressure of 3.2 mm Hg at 25°C. It is slightly soluble in water (2% at 20°C).

The carcinogenicity and chronic toxicity of BEE were examined by inhalation exposure of groups of 50 Crj:BDF1 mice of both sexes to BEE vapor at a target concentration of 0 (clean air), 5, 15 or 45 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. BEE 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. BEE vapor-air mixture was generated by bubbling clean air through the BEE liquid, and supplied to the inhalation exposure chambers. Air concentrations of BEE 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

Hemangiomas in the nasal cavity occurred in the males exposed to 5 ppm and above, and in the females exposed to 15 and 45 ppm. A statistically significant increase in the incidence of hemangiomas was noted in the males exposed to 15 and 45 ppm and in the 45 ppm-exposed females. Squamous cell carcinomas in the nasal cavity occurred in the males and females, although these tumor incidences were not statistically significant. Nasal lesions in the respiratory epithelium (cuboidal change, nodular hyperplasia of transitional epithelium and eosinophilic change), in the submucosal vessel in the region of respiratory epithelium (angiectasis), and in the olfactory epithelium and the submucosal gland (respiratory metaplasia) were found in the BEE-exposed mice.

Conclusions

In mice, there was some evidence of carcinogenic activity of BEE in males and females, based on the increased incidences of hemangiomas in the nasal cavity.

TABLES

TABLES (CONTINUED)

TABLE 1 CONCENTRATION OF BUTYL 2,3-EPOXYPROPYL ETHER IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
5 ppm	5.0 ± 0.0
15 ppm	15.0 ± 0.1
45 ppm	45.0 ± 0.3

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Week on Study	Control		5 ppm			15 ppm			45 ppm		
	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.
	<50>		<49>			<50>			<49>		
0	23.5 (50)	50 / 50	23.5 (49)	100	49 / 49	23.5 (50)	100	50 / 50	23.5 (49)	100	49 / 49
1	25.0 (50)	50 / 50	24.8 (49)	99	49 / 49	25.0 (50)	100	50 / 50	24.5 (49)	98	49 / 49
2	25.8 (50)	50 / 50	25.6 (49)	99	49 / 49	25.8 (50)	100	50 / 50	24.8 (49)	96	49 / 49
3	26.3 (50)	50 / 50	26.1 (49)	99	49 / 49	26.3 (50)	100	50 / 50	25.2 (49)	96	49 / 49
4	26.9 (50)	50 / 50	26.6 (49)	99	49 / 49	26.8 (50)	100	50 / 50	25.5 (49)	95	49 / 49
5	27.4 (50)	50 / 50	27.1 (49)	99	49 / 49	27.6 (50)	101	50 / 50	25.7 (49)	94	49 / 49
6	28.2 (50)	50 / 50	27.9 (49)	99	49 / 49	28.1 (50)	100	50 / 50	25.9 (49)	92	49 / 49
7	29.1 (50)	50 / 50	28.9 (49)	99	49 / 49	29.0 (50)	100	50 / 50	26.4 (49)	91	49 / 49
8	29.4 (50)	50 / 50	29.2 (49)	99	49 / 49	29.2 (50)	99	50 / 50	26.7 (49)	91	49 / 49
9	30.2 (50)	50 / 50	29.8 (49)	99	49 / 49	30.2 (50)	100	50 / 50	27.1 (49)	90	49 / 49
10	30.7 (50)	50 / 50	30.3 (49)	99	49 / 49	30.9 (50)	101	50 / 50	27.4 (49)	89	49 / 49
11	31.7 (50)	50 / 50	31.6 (49)	100	49 / 49	31.8 (50)	100	50 / 50	27.6 (49)	87	49 / 49
12	32.3 (50)	50 / 50	32.3 (49)	100	49 / 49	32.5 (50)	101	50 / 50	28.0 (49)	87	49 / 49
13	32.7 (50)	50 / 50	33.1 (49)	101	49 / 49	33.1 (50)	101	50 / 50	28.3 (49)	87	49 / 49
14	33.6 (50)	50 / 50	33.8 (49)	101	49 / 49	33.0 (50)	98	50 / 50	28.2 (49)	84	49 / 49
18	36.3 (50)	50 / 50	36.8 (49)	101	49 / 49	36.7 (50)	101	50 / 50	29.5 (49)	81	49 / 49
22	38.5 (50)	50 / 50	39.0 (49)	101	49 / 49	38.7 (50)	101	50 / 50	30.3 (49)	79	49 / 49
26	40.2 (50)	50 / 50	40.8 (49)	101	49 / 49	40.0 (50)	100	50 / 50	31.3 (49)	78	49 / 49
30	41.5 (50)	50 / 50	42.6 (49)	103	49 / 49	41.8 (50)	101	50 / 50	31.9 (49)	77	49 / 49
34	43.1 (49)	49 / 50	44.2 (49)	103	49 / 49	43.6 (50)	101	50 / 50	32.7 (49)	76	49 / 49
38	44.7 (49)	49 / 50	45.7 (48)	102	48 / 49	45.0 (50)	101	50 / 50	33.5 (49)	75	49 / 49
42	45.4 (49)	49 / 50	46.4 (48)	102	48 / 49	45.8 (50)	101	50 / 50	33.7 (49)	74	49 / 49
46	46.5 (49)	49 / 50	47.5 (48)	102	48 / 49	46.7 (50)	100	50 / 50	34.4 (49)	74	49 / 49
50	47.9 (48)	48 / 50	48.5 (48)	101	48 / 49	47.8 (50)	100	50 / 50	35.2 (49)	73	49 / 49
54	48.4 (48)	48 / 50	49.3 (48)	102	48 / 49	48.4 (50)	100	50 / 50	35.7 (49)	74	49 / 49
58	49.1 (48)	48 / 50	49.9 (48)	102	48 / 49	49.3 (48)	100	48 / 50	36.2 (49)	74	49 / 49
62	50.1 (48)	48 / 50	50.7 (48)	101	48 / 49	50.3 (48)	100	48 / 50	37.6 (49)	75	49 / 49
66	50.5 (48)	48 / 50	51.6 (47)	102	47 / 49	51.1 (48)	101	48 / 50	37.5 (49)	74	49 / 49
70	50.8 (48)	48 / 50	51.9 (47)	102	47 / 49	51.0 (48)	100	48 / 50	37.8 (49)	74	49 / 49
74	51.0 (48)	48 / 50	52.4 (47)	103	47 / 49	51.1 (48)	100	48 / 50	38.2 (47)	75	47 / 49
78	51.8 (48)	48 / 50	53.3 (47)	103	47 / 49	51.6 (48)	100	48 / 50	39.0 (46)	75	46 / 49
82	52.2 (47)	47 / 50	53.2 (46)	102	46 / 49	51.3 (48)	98	48 / 50	38.9 (45)	75	45 / 49
86	51.9 (45)	45 / 50	52.8 (46)	102	46 / 49	50.5 (45)	97	45 / 50	38.6 (43)	74	43 / 49
90	51.7 (45)	45 / 50	52.4 (43)	101	43 / 49	48.7 (42)	94	42 / 50	38.2 (42)	74	42 / 49
94	51.8 (42)	42 / 50	52.4 (42)	101	42 / 49	49.1 (40)	95	40 / 50	37.8 (42)	73	42 / 49
98	51.2 (40)	40 / 50	52.0 (39)	102	39 / 49	48.9 (36)	96	36 / 50	38.4 (40)	75	40 / 49
102	51.0 (36)	36 / 50	51.0 (36)	100	36 / 49	46.9 (34)	92	34 / 50	38.1 (37)	75	37 / 49
104	50.1 (35)	35 / 50	50.1 (35)	100	35 / 49	46.5 (32)	93	32 / 50	38.3 (36)	76	36 / 49

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

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Week on Study	Control		5 ppm			15 ppm			45 ppm		
	Av. Wt.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>
0	19.1 (50)	50 / 50	19.1 (50)	100	50 / 50	19.1 (50)	100	50 / 50	19.1 (50)	100	50 / 50
1	19.9 (50)	50 / 50	19.8 (50)	99	50 / 50	19.7 (50)	99	50 / 50	19.6 (50)	98	50 / 50
2	20.7 (50)	50 / 50	20.7 (50)	100	50 / 50	20.6 (50)	100	50 / 50	20.1 (50)	97	50 / 50
3	21.1 (50)	50 / 50	21.2 (50)	100	50 / 50	21.0 (50)	100	50 / 50	20.6 (50)	98	50 / 50
4	21.6 (50)	50 / 50	21.6 (50)	100	50 / 50	21.4 (50)	99	50 / 50	20.7 (50)	96	50 / 50
5	21.7 (50)	50 / 50	22.0 (50)	101	50 / 50	21.6 (50)	100	50 / 50	21.0 (50)	97	50 / 50
6	22.5 (50)	50 / 50	22.7 (50)	101	50 / 50	22.0 (50)	98	50 / 50	21.4 (50)	95	50 / 50
7	23.1 (50)	50 / 50	23.3 (50)	101	50 / 50	23.0 (50)	100	50 / 50	22.0 (50)	95	50 / 50
8	23.1 (50)	50 / 50	23.3 (50)	101	50 / 50	22.9 (50)	99	50 / 50	22.0 (50)	95	50 / 50
9	23.7 (50)	50 / 50	23.7 (50)	100	50 / 50	23.7 (50)	100	50 / 50	22.8 (50)	96	50 / 50
10	23.8 (50)	50 / 50	23.9 (50)	100	50 / 50	23.6 (50)	99	50 / 50	22.7 (50)	95	50 / 50
11	24.3 (50)	50 / 50	24.5 (50)	101	50 / 50	23.9 (50)	98	50 / 50	23.2 (50)	95	50 / 50
12	24.3 (50)	50 / 50	24.4 (50)	100	50 / 50	24.2 (50)	100	50 / 50	23.2 (50)	95	50 / 50
13	24.7 (50)	50 / 50	24.7 (50)	100	50 / 50	24.4 (50)	99	50 / 50	23.4 (50)	95	50 / 50
14	24.9 (50)	50 / 50	25.5 (50)	102	50 / 50	24.4 (50)	98	50 / 50	23.2 (50)	93	50 / 50
18	26.4 (50)	50 / 50	26.7 (50)	101	50 / 50	25.7 (50)	97	50 / 50	24.0 (50)	91	50 / 50
22	27.3 (50)	50 / 50	27.5 (50)	101	50 / 50	26.4 (50)	97	50 / 50	24.4 (50)	89	50 / 50
26	28.0 (50)	50 / 50	28.2 (50)	101	50 / 50	27.3 (50)	98	50 / 50	25.1 (49)	90	49 / 50
30	29.0 (50)	50 / 50	28.9 (50)	100	50 / 50	27.9 (50)	96	50 / 50	25.5 (49)	88	49 / 50
34	29.3 (50)	50 / 50	29.6 (50)	101	50 / 50	28.7 (50)	98	50 / 50	25.7 (48)	88	48 / 50
38	30.0 (50)	50 / 50	30.6 (50)	102	50 / 50	29.0 (50)	97	50 / 50	25.7 (48)	86	48 / 50
42	30.4 (50)	50 / 50	30.7 (50)	101	50 / 50	29.2 (50)	96	50 / 50	25.7 (48)	85	48 / 50
46	31.2 (49)	49 / 50	31.2 (50)	100	50 / 50	30.5 (50)	98	50 / 50	26.1 (48)	84	48 / 50
50	31.3 (48)	48 / 50	31.5 (50)	101	50 / 50	30.3 (49)	97	49 / 50	26.4 (48)	84	48 / 50
54	32.3 (48)	48 / 50	32.6 (50)	101	50 / 50	31.2 (49)	97	49 / 50	26.7 (48)	83	48 / 50
58	32.8 (48)	48 / 50	33.2 (50)	101	50 / 50	32.1 (49)	98	49 / 50	26.9 (45)	82	45 / 50
62	33.3 (47)	47 / 50	33.6 (50)	101	50 / 50	33.2 (48)	100	48 / 50	27.8 (44)	83	44 / 50
66	33.7 (46)	46 / 50	34.2 (50)	101	50 / 50	33.8 (47)	100	47 / 50	27.9 (43)	83	43 / 50
70	33.9 (46)	46 / 50	34.5 (50)	102	50 / 50	34.1 (46)	101	46 / 50	27.7 (41)	82	41 / 50
74	34.6 (46)	46 / 50	34.3 (50)	99	50 / 50	34.9 (44)	101	44 / 50	28.2 (40)	82	40 / 50
78	34.7 (44)	44 / 50	34.9 (50)	101	50 / 50	34.8 (40)	100	40 / 50	28.5 (40)	82	40 / 50
82	34.8 (43)	43 / 50	35.2 (48)	101	48 / 50	35.0 (39)	101	39 / 50	28.5 (37)	82	37 / 50
86	34.4 (43)	43 / 50	35.3 (45)	103	45 / 50	34.8 (36)	101	36 / 50	28.4 (35)	83	35 / 50
90	34.1 (42)	42 / 50	35.6 (43)	104	43 / 50	34.7 (34)	102	34 / 50	28.6 (33)	84	33 / 50
94	34.2 (39)	39 / 50	35.5 (42)	104	42 / 50	34.8 (33)	102	33 / 50	29.4 (31)	86	31 / 50
98	34.0 (38)	38 / 50	36.0 (38)	106	38 / 50	35.2 (31)	104	31 / 50	28.9 (26)	85	26 / 50
102	33.9 (35)	35 / 50	35.6 (34)	105	34 / 50	35.2 (29)	104	29 / 50	29.6 (23)	87	23 / 50
104	33.4 (33)	33 / 50	36.0 (31)	108	31 / 50	35.8 (27)	107	27 / 50	29.6 (22)	89	22 / 50

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

TABLE 4 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Week on Study	Control		5 ppm			15 ppm			45 ppm		
	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.
	<50>		<49>			<50>			<49>		
1	4.0 (50)	50 / 50	4.0 (49)	100	49 / 49	3.9 (50)	98	50 / 50	3.8 (49)	95	49 / 49
2	3.9 (50)	50 / 50	3.9 (49)	100	49 / 49	3.9 (50)	100	50 / 50	3.6 (49)	92	49 / 49
3	4.0 (50)	50 / 50	4.0 (49)	100	49 / 49	4.0 (50)	100	50 / 50	3.7 (49)	93	49 / 49
4	4.0 (50)	50 / 50	4.0 (49)	100	49 / 49	3.9 (50)	98	50 / 50	3.7 (49)	93	49 / 49
5	4.0 (50)	50 / 50	4.1 (49)	103	49 / 49	4.0 (50)	100	50 / 50	3.7 (49)	93	49 / 49
6	4.1 (50)	50 / 50	4.1 (49)	100	49 / 49	4.0 (50)	98	50 / 50	3.8 (49)	93	49 / 49
7	4.2 (50)	50 / 50	4.3 (49)	102	49 / 49	4.2 (50)	100	50 / 50	3.8 (49)	90	49 / 49
8	4.3 (50)	50 / 50	4.3 (49)	100	49 / 49	4.2 (50)	98	50 / 50	3.9 (49)	91	49 / 49
9	4.3 (50)	50 / 50	4.3 (49)	100	49 / 49	4.3 (50)	100	50 / 50	4.0 (49)	93	49 / 49
10	4.2 (50)	50 / 50	4.3 (49)	102	49 / 49	4.4 (50)	105	50 / 50	4.0 (49)	95	49 / 49
11	4.4 (50)	50 / 50	4.4 (49)	100	49 / 49	4.4 (50)	100	50 / 50	3.8 (49)	86	49 / 49
12	4.3 (50)	50 / 50	4.3 (49)	100	49 / 49	4.3 (50)	100	50 / 50	3.8 (49)	88	49 / 49
13	4.4 (50)	50 / 50	4.4 (49)	100	49 / 49	4.3 (50)	98	50 / 50	3.8 (49)	86	49 / 49
14	4.3 (50)	50 / 50	4.3 (49)	100	49 / 49	4.3 (50)	100	50 / 50	3.9 (49)	91	49 / 49
18	4.5 (50)	50 / 50	4.5 (49)	100	49 / 49	4.5 (50)	100	50 / 50	3.8 (49)	84	49 / 49
22	4.5 (50)	50 / 50	4.5 (49)	100	49 / 49	4.4 (50)	98	50 / 50	3.7 (49)	82	49 / 49
26	4.6 (50)	50 / 50	4.6 (49)	100	49 / 49	4.5 (50)	98	50 / 50	4.0 (49)	87	49 / 49
30	4.6 (50)	50 / 50	4.6 (49)	100	49 / 49	4.6 (50)	100	50 / 50	3.9 (49)	85	49 / 49
34	4.7 (49)	49 / 50	4.8 (49)	102	49 / 49	4.7 (50)	100	50 / 50	4.0 (49)	85	49 / 49
38	4.7 (49)	49 / 50	4.9 (48)	104	48 / 49	4.7 (50)	100	50 / 50	4.0 (49)	85	49 / 49
42	4.9 (49)	49 / 50	5.0 (48)	102	48 / 49	4.8 (50)	98	50 / 50	3.9 (49)	80	49 / 49
46	4.8 (49)	49 / 50	4.8 (48)	100	48 / 49	4.8 (50)	100	50 / 50	4.1 (49)	85	49 / 49
50	4.7 (48)	48 / 50	4.7 (48)	100	48 / 49	4.7 (50)	100	50 / 50	4.0 (49)	85	49 / 49
54	4.9 (48)	48 / 50	4.9 (48)	100	48 / 49	4.8 (50)	98	50 / 50	4.1 (49)	84	49 / 49
58	4.9 (48)	48 / 50	5.0 (48)	102	48 / 49	4.8 (48)	98	48 / 50	4.0 (49)	82	49 / 49
62	5.1 (48)	48 / 50	5.0 (48)	98	48 / 49	5.0 (48)	98	48 / 50	4.3 (49)	84	49 / 49
66	5.1 (48)	48 / 50	5.1 (47)	100	47 / 49	5.0 (48)	98	48 / 50	4.2 (49)	82	49 / 49
70	4.9 (47)	48 / 50	5.0 (47)	102	47 / 49	4.8 (48)	98	48 / 50	4.1 (49)	84	49 / 49
74	5.0 (48)	48 / 50	5.1 (47)	102	47 / 49	5.0 (48)	100	48 / 50	4.2 (47)	84	47 / 49
78	5.0 (48)	48 / 50	5.1 (47)	102	47 / 49	5.0 (48)	100	48 / 50	4.3 (46)	86	46 / 49
82	5.0 (47)	47 / 50	5.0 (46)	100	46 / 49	5.0 (48)	100	48 / 50	4.2 (45)	84	45 / 49
86	5.0 (45)	45 / 50	5.0 (46)	100	46 / 49	4.9 (45)	98	45 / 50	4.1 (43)	82	43 / 49
90	4.9 (45)	45 / 50	5.0 (43)	102	43 / 49	4.7 (42)	96	42 / 50	4.2 (42)	86	42 / 49
94	4.9 (42)	42 / 50	5.0 (42)	102	42 / 49	5.0 (40)	102	40 / 50	4.1 (42)	84	42 / 49
98	5.1 (40)	40 / 50	5.1 (39)	100	39 / 49	5.0 (36)	98	36 / 50	4.3 (40)	84	40 / 49
102	4.8 (36)	36 / 50	5.0 (36)	104	36 / 49	4.6 (34)	96	34 / 50	4.1 (37)	85	37 / 49
104	4.8 (35)	35 / 50	5.1 (35)	106	35 / 49	4.7 (32)	98	32 / 50	4.4 (36)	92	36 / 49

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

TABLE 5 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Week on Study	Control		5 ppm			15 ppm			45 ppm		
	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>
1	3.3 (50)	50 / 50	3.3 (50)	100	50 / 50	3.3 (50)	100	50 / 50	3.4 (35)	103	50 / 50
2	3.3 (50)	50 / 50	3.5 (50)	106	50 / 50	3.3 (50)	100	50 / 50	3.2 (50)	97	50 / 50
3	3.4 (50)	50 / 50	3.6 (50)	106	50 / 50	3.5 (50)	103	50 / 50	3.4 (50)	100	50 / 50
4	3.5 (50)	50 / 50	3.7 (50)	106	50 / 50	3.5 (50)	100	50 / 50	3.3 (50)	94	50 / 50
5	3.7 (50)	50 / 50	3.8 (50)	103	50 / 50	3.6 (50)	97	50 / 50	3.4 (50)	92	50 / 50
6	3.8 (50)	50 / 50	3.9 (50)	103	50 / 50	3.8 (50)	100	50 / 50	3.6 (50)	95	50 / 50
7	3.9 (50)	50 / 50	4.0 (50)	103	50 / 50	3.9 (50)	100	50 / 50	3.5 (50)	90	50 / 50
8	4.1 (50)	50 / 50	4.2 (50)	102	50 / 50	4.0 (50)	98	50 / 50	3.6 (50)	88	50 / 50
9	4.1 (50)	50 / 50	4.1 (50)	100	50 / 50	4.1 (50)	100	50 / 50	3.8 (50)	93	50 / 50
10	4.0 (50)	50 / 50	4.1 (50)	103	50 / 50	4.1 (50)	103	50 / 50	3.8 (50)	95	50 / 50
11	4.1 (50)	50 / 50	4.2 (50)	102	50 / 50	4.1 (50)	100	50 / 50	3.7 (50)	90	50 / 50
12	4.0 (50)	50 / 50	4.0 (50)	100	50 / 50	4.1 (50)	103	50 / 50	3.6 (50)	90	50 / 50
13	4.0 (50)	50 / 50	4.0 (50)	100	50 / 50	4.1 (50)	103	50 / 50	3.6 (50)	90	50 / 50
14	4.1 (50)	50 / 50	4.2 (50)	102	50 / 50	4.1 (50)	100	50 / 50	3.7 (50)	90	50 / 50
18	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.2 (50)	100	50 / 50	3.7 (50)	88	50 / 50
22	4.3 (50)	50 / 50	4.3 (50)	100	50 / 50	4.2 (50)	98	50 / 50	3.6 (50)	84	50 / 50
26	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.3 (50)	102	50 / 50	3.7 (49)	88	49 / 50
30	4.4 (50)	50 / 50	4.3 (50)	98	50 / 50	4.3 (50)	98	50 / 50	3.8 (49)	86	49 / 50
34	4.4 (50)	50 / 50	4.4 (50)	100	50 / 50	4.4 (50)	100	50 / 50	3.8 (48)	86	48 / 50
38	4.4 (50)	50 / 50	4.5 (50)	102	50 / 50	4.3 (50)	98	50 / 50	3.8 (48)	86	48 / 50
42	4.6 (50)	50 / 50	4.7 (50)	102	50 / 50	4.4 (50)	96	50 / 50	3.8 (48)	83	48 / 50
46	4.5 (49)	49 / 50	4.5 (50)	100	50 / 50	4.5 (50)	100	50 / 50	3.9 (48)	87	48 / 50
50	4.2 (48)	48 / 50	4.2 (50)	100	50 / 50	4.2 (49)	100	49 / 50	3.7 (48)	88	48 / 50
54	4.5 (48)	48 / 50	4.5 (50)	100	50 / 50	4.3 (49)	96	49 / 50	3.7 (48)	82	48 / 50
58	4.5 (48)	48 / 50	4.7 (50)	104	50 / 50	4.5 (49)	100	49 / 50	3.7 (45)	82	45 / 50
62	4.4 (47)	47 / 50	4.5 (50)	102	50 / 50	4.7 (48)	107	48 / 50	4.0 (44)	91	44 / 50
66	4.6 (46)	46 / 50	4.6 (50)	100	50 / 50	4.6 (47)	100	47 / 50	3.9 (43)	85	43 / 50
70	4.4 (46)	46 / 50	4.4 (50)	100	50 / 50	4.4 (46)	100	46 / 50	3.7 (41)	84	41 / 50
74	4.5 (46)	46 / 50	4.5 (50)	100	50 / 50	4.6 (44)	102	44 / 50	3.9 (40)	87	40 / 50
78	4.4 (44)	44 / 50	4.5 (50)	102	50 / 50	4.5 (40)	102	40 / 50	4.0 (40)	91	40 / 50
82	4.5 (43)	43 / 50	4.6 (48)	102	48 / 50	4.3 (39)	96	39 / 50	3.9 (37)	87	37 / 50
86	4.5 (43)	43 / 50	4.6 (45)	102	45 / 50	4.4 (36)	98	36 / 50	3.9 (35)	87	35 / 50
90	4.4 (42)	42 / 50	4.6 (43)	105	43 / 50	4.6 (34)	105	34 / 50	3.8 (26)	86	33 / 50
94	4.4 (39)	39 / 50	4.6 (42)	105	42 / 50	4.6 (33)	105	33 / 50	3.9 (31)	89	31 / 50
98	4.7 (38)	38 / 50	4.7 (38)	100	38 / 50	4.8 (31)	102	31 / 50	4.0 (26)	85	26 / 50
102	4.5 (35)	35 / 50	4.5 (34)	100	34 / 50	4.6 (29)	102	29 / 50	3.9 (23)	87	23 / 50
104	4.6 (33)	33 / 50	4.7 (31)	102	31 / 50	4.9 (27)	107	27 / 50	4.2 (22)	91	22 / 50

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

TABLE 6 HEMATOLOGY OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm
No. of examined animals	34	35	32	35
HEMATOCRIT (%)	43.4 ± 6.8	44.2 ± 4.5	44.4 ± 5.1	46.3 ± 2.5 *
WBC ($10^3/\mu$ L)	4.79 ± 2.67	4.88 ± 3.23	4.70 ± 2.94	2.98 ± 1.28 **

Mean ± S.D.

Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 7 BIOCHEMISTRY OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm	
No. of examined animals	34	35	32	35	
A/G RATIO	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	1.2 ± 0.1	**
T-CHOLESTEROL (mg/dL)	101 ± 19	116 ± 39	109 ± 31	93 ± 49	**
PHOSPHOLIPID (mg/dL)	182 ± 34	203 ± 57	185 ± 50	173 ± 68	**
ALT (IU/L)	104 ± 279	304 ± 1272	65 ± 107	35 ± 65	**
ALP (IU/L)	148 ± 91	178 ± 158	147 ± 129	155 ± 41	*

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

TABLE 8 BIOCHEMISTRY OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm	
No. of examined animals	29	29	26	22	
A/G RATIO	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.5 ± 0.3	**
T-BILIRUBIN (mg/dL)	0.13 ± 0.02	0.13 ± 0.03	0.15 ± 0.05	0.17 ± 0.07	**
ALT (IU/L)	45 ± 18	56 ± 48	49 ± 36	44 ± 52	*
ALP (IU/L)	245 ± 142	208 ± 81	210 ± 88	325 ± 142	*
CK (IU/L)	111 ± 141	92 ± 62	92 ± 65	127 ± 65	*
POTASSIUM (mEq/L)	4.1 ± 0.4	4.0 ± 0.4	4.1 ± 0.5	4.4 ± 0.3	*
CALCIUM (mg/dL)	9.1 ± 0.6	8.8 ± 0.3 *	9.0 ± 0.5	8.7 ± 0.5	*

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

TABLE 9 URINALYSIS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name		Control	5 ppm	15 ppm	45 ppm
No. of examined animals		35	35	33	36
	Grade				
Ketone body	−	17	22	20	2
	±	15	11	10	16
	+	2	2	3	18
	2+	0	0	0	0
	3+	1	0	0	0
	4+	0	0	0	0
	Chi square test				**

Significant difference: * : p≦0.05 ** : p≦0.01

TABLE 10 URINALYSIS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name		Control	5 ppm	15 ppm	45 ppm
No. of examined animals		34	32	29	23
	Grade				
Ketone body	−	11	11	13	2
	±	20	21	15	9
	+	1	0	1	9
	2+	2	0	0	3
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test				**

Significant difference: * : p≦0.05 ** : p≦0.01

TABLE 11 ORGAN WEIGHTS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm	
No. of examined animals	35	35	32	36	
Body weight (g)	46.4 ± 7.8	46.2 ± 6.9	42.7 ± 8.8	35.0 ± 5.0	**
Adrenals (g)	0.009 ± 0.002	0.009 ± 0.002	0.009 ± 0.002	0.009 ± 0.002	
Adrenals (%)	0.021 ± 0.006	0.020 ± 0.005	0.022 ± 0.007	0.026 ± 0.006	**
Testes (g)	0.223 ± 0.033	0.230 ± 0.028	0.218 ± 0.035	0.204 ± 0.032	*
Testes (%)	0.491 ± 0.087	0.506 ± 0.086	0.525 ± 0.105	0.589 ± 0.102	**
Heart (g)	0.226 ± 0.025	0.224 ± 0.021	0.214 ± 0.028	0.185 ± 0.012	**
Heart (%)	0.504 ± 0.132	0.496 ± 0.099	0.520 ± 0.122	0.537 ± 0.061	**
Lungs (g)	0.249 ± 0.167	0.215 ± 0.022	0.236 ± 0.077	0.201 ± 0.025	**
Lungs (%)	0.585 ± 0.581	0.478 ± 0.119	0.581 ± 0.249	0.584 ± 0.094	**
Kidneys (g)	0.730 ± 0.336	0.689 ± 0.211	0.649 ± 0.175	0.573 ± 0.046	**
Kidneys (%)	1.723 ± 1.483	1.542 ± 0.653	1.604 ± 0.682	1.660 ± 0.203	**
Spleen (g)	0.107 ± 0.108	0.125 ± 0.146	0.183 ± 0.295	0.064 ± 0.060	**
Spleen (%)	0.238 ± 0.233	0.289 ± 0.379	0.443 ± 0.639	0.190 ± 0.192	
Liver (g)	1.944 ± 1.181	1.857 ± 0.499	1.698 ± 0.480	1.387 ± 0.523	**
Liver (%)	4.399 ± 3.342	4.119 ± 1.328	4.203 ± 1.908	4.030 ± 1.719	
Brain (g)	0.464 ± 0.018	0.455 ± 0.015	0.457 ± 0.016	0.456 ± 0.021	
Brain (%)	1.035 ± 0.232	1.010 ± 0.182	1.123 ± 0.284	1.329 ± 0.194	**

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

TABLE 12 ORGAN WEIGHTS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm		15 ppm	45 ppm	
No. of examined animals	33	31		27	22	
Body weight (g)	29.4 ± 4.0	32.0 ± 4.8	*	31.7 ± 5.0	26.1 ± 3.2	*
Heart (g)	0.180 ± 0.034	0.185 ± 0.034		0.175 ± 0.029	0.149 ± 0.021	**
Heart (%)	0.618 ± 0.104	0.582 ± 0.091		0.555 ± 0.059	0.578 ± 0.092	
Kidneys (g)	0.503 ± 0.239	0.474 ± 0.092		0.484 ± 0.145	0.422 ± 0.071	*
Kidneys (%)	1.702 ± 0.619	1.489 ± 0.203		1.547 ± 0.502	1.625 ± 0.213	
Liver (g)	1.550 ± 0.424	1.668 ± 0.586		1.612 ± 0.632	1.510 ± 1.075	*
Liver (%)	5.268 ± 1.100	5.171 ± 1.311		5.019 ± 1.243	5.624 ± 3.274	
Brain (g)	0.484 ± 0.017	0.482 ± 0.017		0.480 ± 0.015	0.469 ± 0.013	**
Brain (%)	1.678 ± 0.224	1.540 ± 0.226	*	1.554 ± 0.255	1.820 ± 0.210	

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

TABLE 13 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm	Peto	Cochran-
Number of examined animals	50	49	50	49	test	Armitage test
nasal cavity	<50>	<49>	<50>	<49>		
hemangioma	0 (0 %)	2 (4 %)	14 (28 %) **	8 (16 %) **	↑	↑
schwannoma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
squamous cell carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	2 (4 %)		
histiocytic sarcoma	0 (0 %)	2 (4 %)	0 (0 %)	0 (0 %)		
lung	<50>	<49>	<50>	<49>		
bronchiolar-alveolar adenoma	7 (14 %)	6 (12 %)	3 (6 %)	1 (2 %) *		↓
liver	<50>	<49>	<50>	<49>		
hepatocellular adenoma	11 (22 %)	11 (22 %)	12 (24 %)	1 (2 %) **		↓ ↓

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

TABLE 14 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	5 ppm	15 ppm	45 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
nasal cavity	<50>	<50>	<50>	<50>		
hemangioma	0 (0 %)	0 (0 %)	2 (4 %)	7 (14 %) **	↑ ↑	↑ ↑
squamous cell carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
histiocytic sarcoma	0 (0 %)	0 (0 %)	1 (2 %)	0 (0 %)		
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar adenoma	7 (14 %)	1 (2 %) *	2 (4 %)	1 (2 %) *		
uterus	<50>	<50>	<50>	<50>		
histiocytic sarcoma	6 (12 %)	10 (20 %)	15 (30 %) *	15 (30 %) *	↑ ↑	

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

TABLE 15 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control				5 ppm					15 ppm					45 ppm				
Number of examined animals	50				49					50					49				
Grade of non-neoplastic lesion	1	2	3	4	1	2	3	4		1	2	3	4		1	2	3	4	
nasal cavity	<50>				<49>					<50>					<49>				
cuboidal change:respiratory epithelium	0	0	0	0	8	0	0	0	**	27	15	0	0	**	39	7	0	0	**
nodular hyperplasia:transitional epithelium	0	0	0	0	0	0	0	0		4	0	0	0		18	0	0	0	**
angiectasis	0	0	0	0	0	0	0	0		14	0	0	0	**	17	0	0	0	**
eosinophilic change:respiratory epithelium	6	2	0	0	3	1	1	0		9	0	1	0		16	0	0	0	*
respiratory metaplasia:gland	8	2	0	0	8	0	0	0		46	3	0	0	**	4	44	0	0	**
respiratory metaplasia:olfactory epithelium	6	0	0	0	4	0	0	0		38	3	0	0	**	3	44	0	0	**
exudate	1	0	0	0	0	0	0	0		1	0	0	0		20	0	0	0	**
stomach	<50>				<49>					<50>					<49>				
hyperplasia:glandular stomach	25	24	0	0	20	29	0	0		15	32	0	0		28	12	0	0	**
brain	<50>				<49>					<50>					<49>				
mineralization	20	0	0	0	13	0	0	0		16	0	0	0		6	0	0	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 16 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control				5 ppm				15 ppm				45 ppm			
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
nasal cavity	<50>				<50>				<50>				<50>			
cuboidal change:respiratory epithelium	0	0	0	0	4	0	0	0	48	0	0	0 **	50	0	0	0 **
nodular hyperplasia:transitional epithelium	0	0	0	0	0	0	0	0	1	0	0	0	16	0	0	0 **
angiectasis	0	0	0	0	0	0	0	0	4	0	0	0	10	0	0	0 **
squamous cell metaplasia :respiratory epithelium	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
eosinophilic change:respiratory epithelium	39	6	0	0	33	9	0	0	24	0	0	0 **	13	1	0	0 **
respiratory metaplasia:olfactory epithelium	1	0	0	0	12	0	0	0 **	40	1	0	0 **	2	48	0	0 **
respiratory metaplasia:gland	10	0	0	0	12	0	0	0	41	1	0	0 **	2	48	0	0 **
exudate	2	0	0	0	1	0	0	0	1	0	0	0	18	0	0	0 **
nasopharynx	<50>				<50>				<50>				<50>			
eosinophilic change	13	1	0	0	6	2	0	0	3	2	0	0 *	16	3	0	0
spleen	<50>				<50>				<50>				<50>			
extramedullary hematopoiesis	8	3	3	0	3	6	9	0	1	4	16	0 **	9	4	10	0
tooth	<50>				<50>				<50>				<50>			
dysplasia	12	6	0	0	9	5	0	0	1	4	0	0 **	8	6	0	0
stomach	<50>				<50>				<50>				<50>			
hyperplasia:glandular stomach	27	12	0	0	23	16	0	0	23	13	0	0	25	4	0	0 *
adrenal	<50>				<50>				<50>				<50>			
spindle-cell hyperplasia	9	33	8	0	3	44	2	0 *	2	43	5	0 *	8	35	7	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 17 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. (%)
Nasal cavity	1596			
Hemangioma		0	0	0 - 0
Schwannoma		1	0.1	0 - 2
Squamous cell carcinoma		0	0	0 - 0

32 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, 0418, 0422

TABLE 18 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. (%)
Nasal cavity	1596			
Hemangioma		1	0.1	0 - 2
Squamous cell carcinoma		0	0	0 - 0
Uterus	1595			
Histiocytic sarcoma		320	20.1	10 - 32

32 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, 0418, 0422

TABLE 19 CAUSE OF DEATH OF MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

	Male				Female			
Group name	Control	5 ppm	15 ppm	45 ppm	Control	5 ppm	15 ppm	45 ppm
Number of dead or moribund animals	15	14	18	13	17	19	23	28
No microscopical confirmationation	0	1	0	0	0	0	0	2
Cardiovascular lesion	0	0	0	0	0	1	0	0
Hepatic lesion	0	0	1	0	0	0	0	0
Renal lesion	0	0	0	0	0	0	1	1
Reproductive system lesion	0	0	0	0	0	0	1	0
Arteritis	0	1	0	0	0	0	0	0
Hydronephrosis	1	0	0	0	0	0	0	1
Peritonitis	0	0	0	0	0	0	0	2
Tumor death : leukemia	5	5	3	1	8	4	6	7
skin/appendage	0	0	1	1	0	0	0	0
subcutis	1	0	1	1	0	0	1	0
nasal cavity	0	0	0	1	0	0	0	0
lung	0	2	0	0	0	1	1	1
spleen	0	0	0	0	0	2	0	0
bone marrow	0	0	1	1	0	0	0	0
salivary gland	0	1	2	0	0	0	0	0
small intestine	0	2	0	0	0	0	0	0
liver	7	1	8	4	1	4	0	2
pituitary gland	0	0	0	0	1	0	0	1
epididymis	1	0	0	1	—	—	—	—
uterus	—	—	—	—	3	7	13	9
mammary gland	0	0	0	0	1	0	0	1
brain	0	1	0	1	0	0	0	0
peripheral nerves	0	0	0	1	2	0	0	1
muscle	0	0	0	0	1	0	0	0
peritoneum	0	0	0	1	0	0	0	0
retroperitoneum	0	0	1	0	0	0	0	0

FIGURES

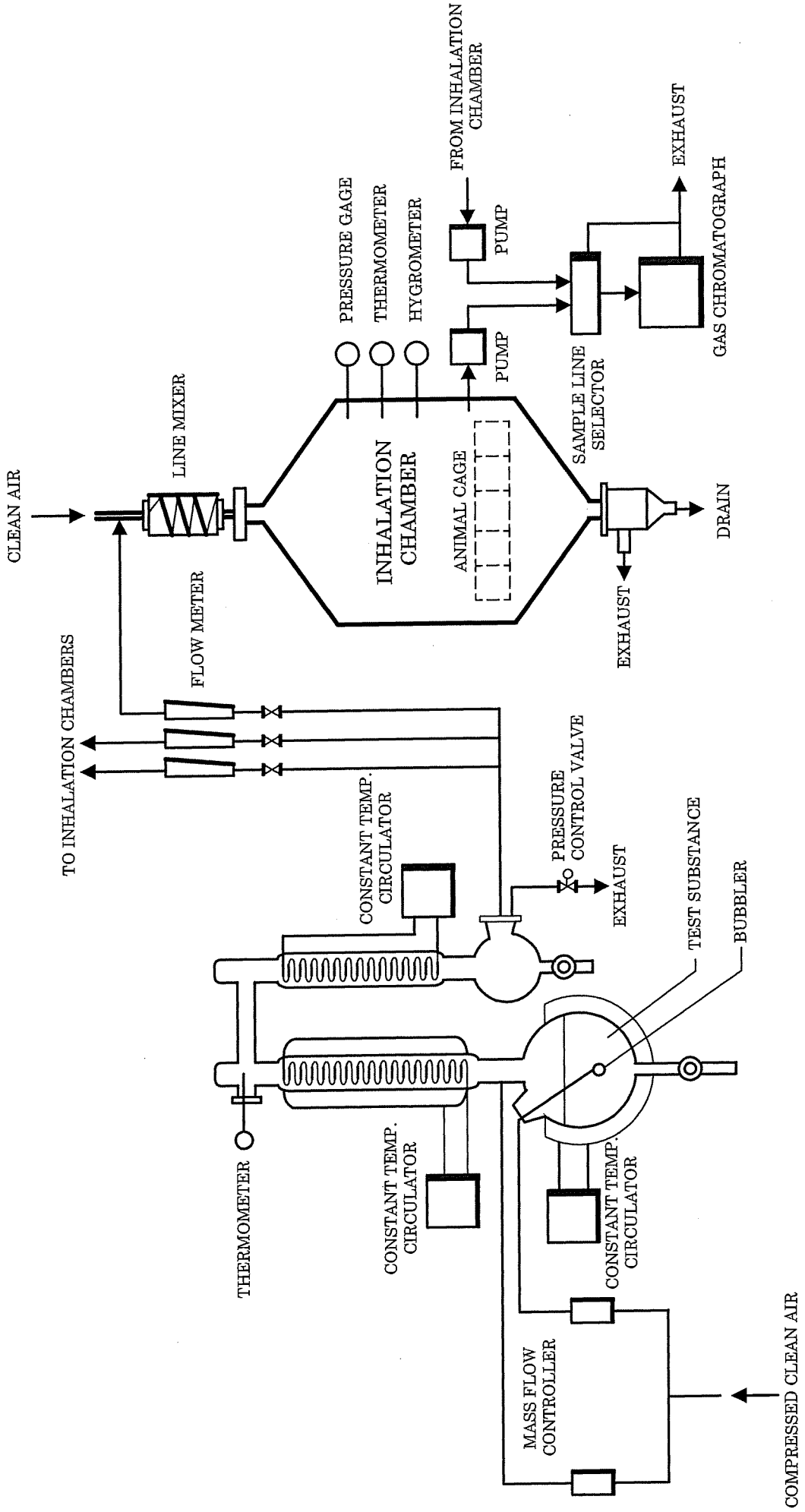


FIGURE 1 BUTYL 2,3-EPOXYPROPYL ETHER VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

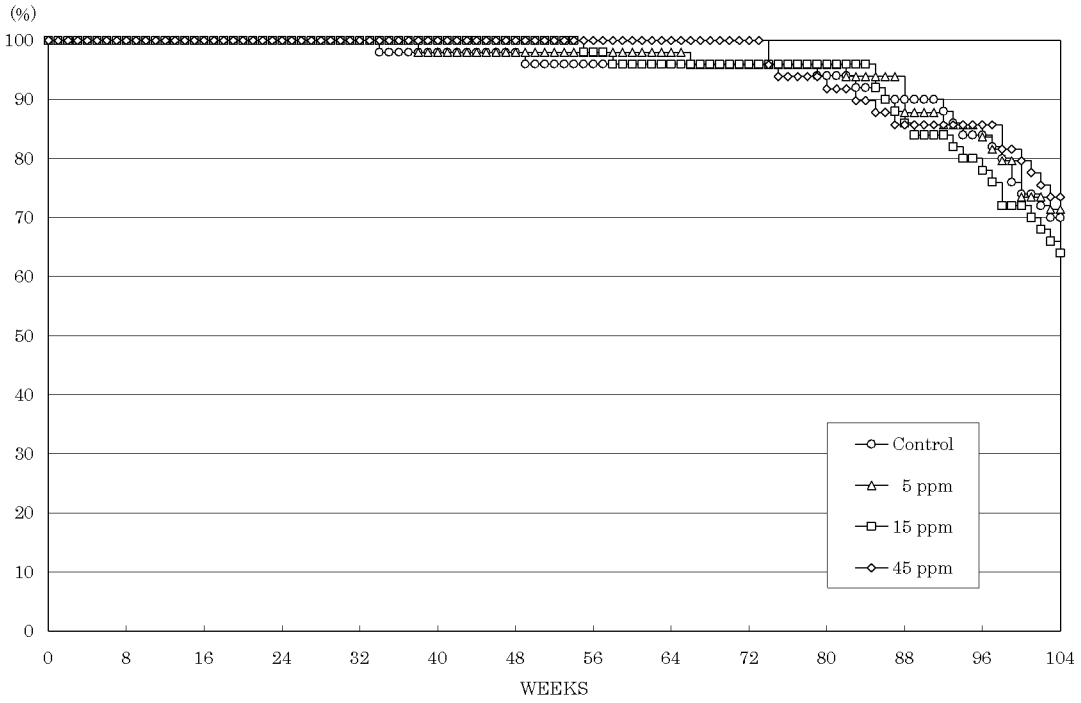


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

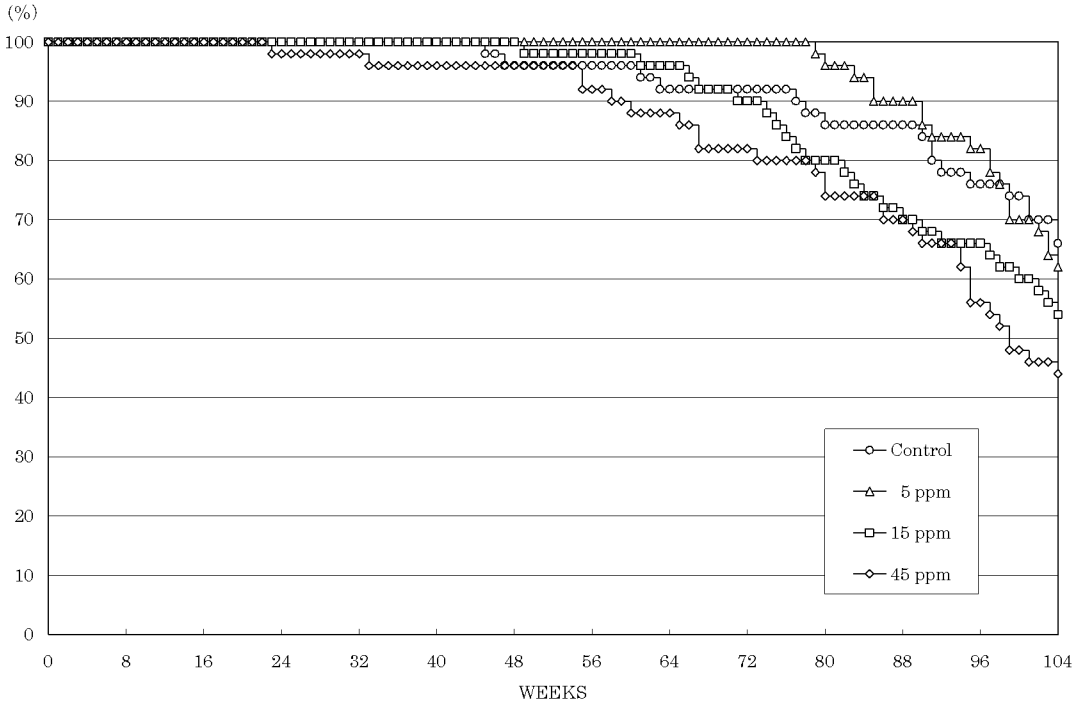


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

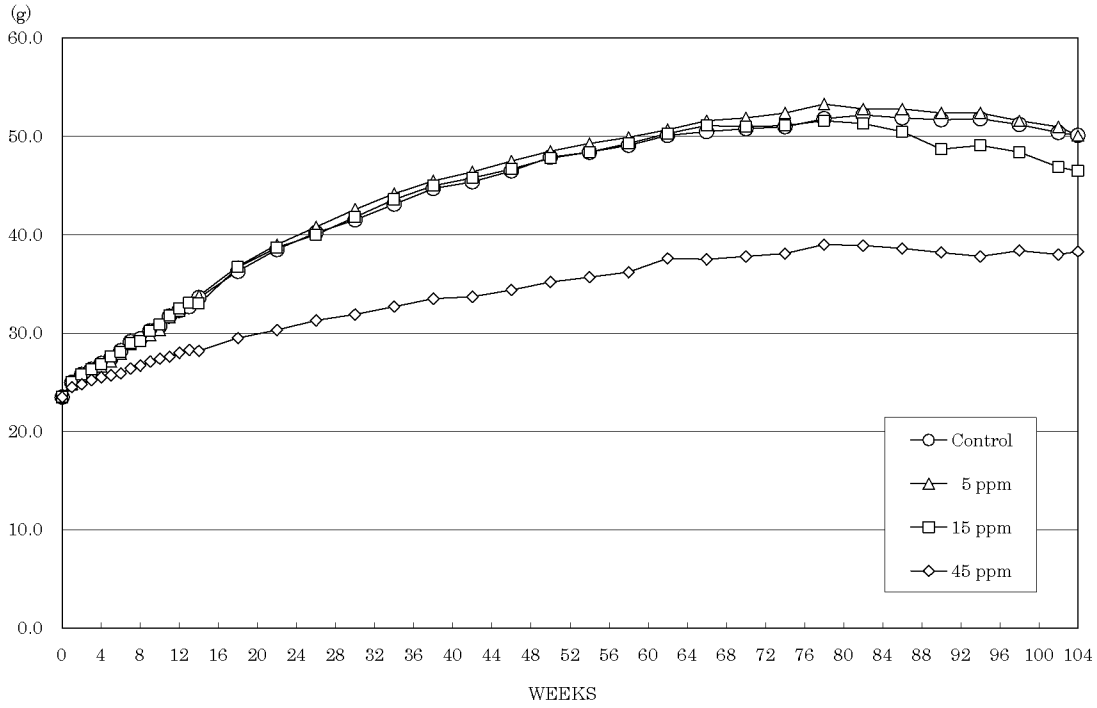


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

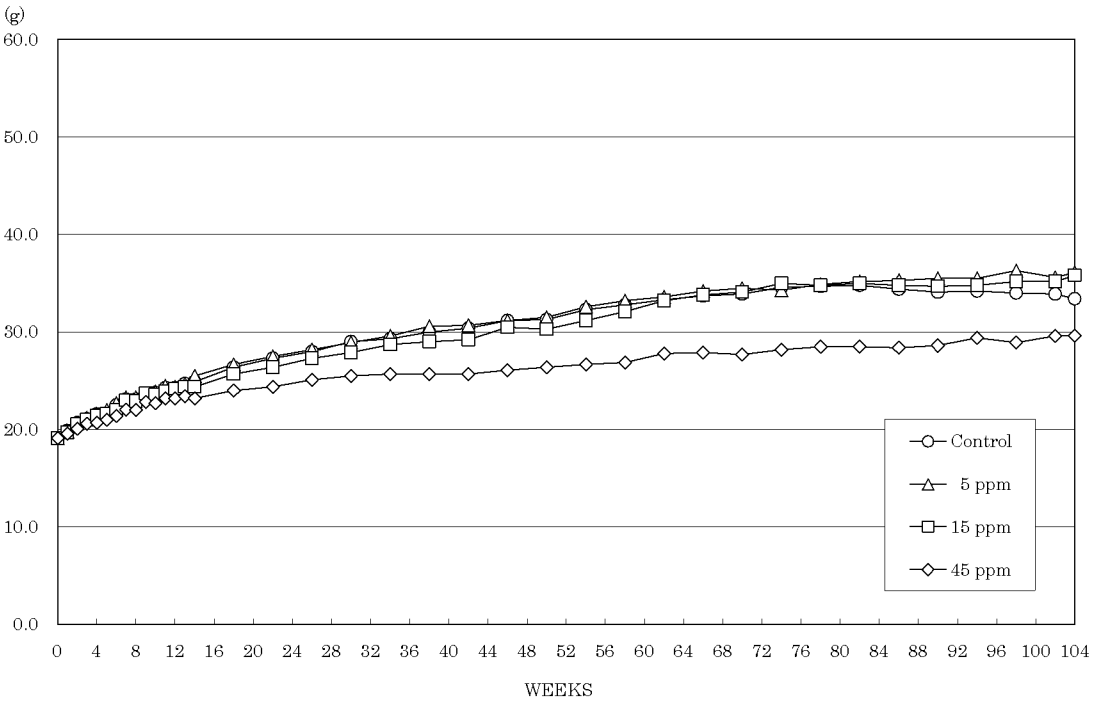


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

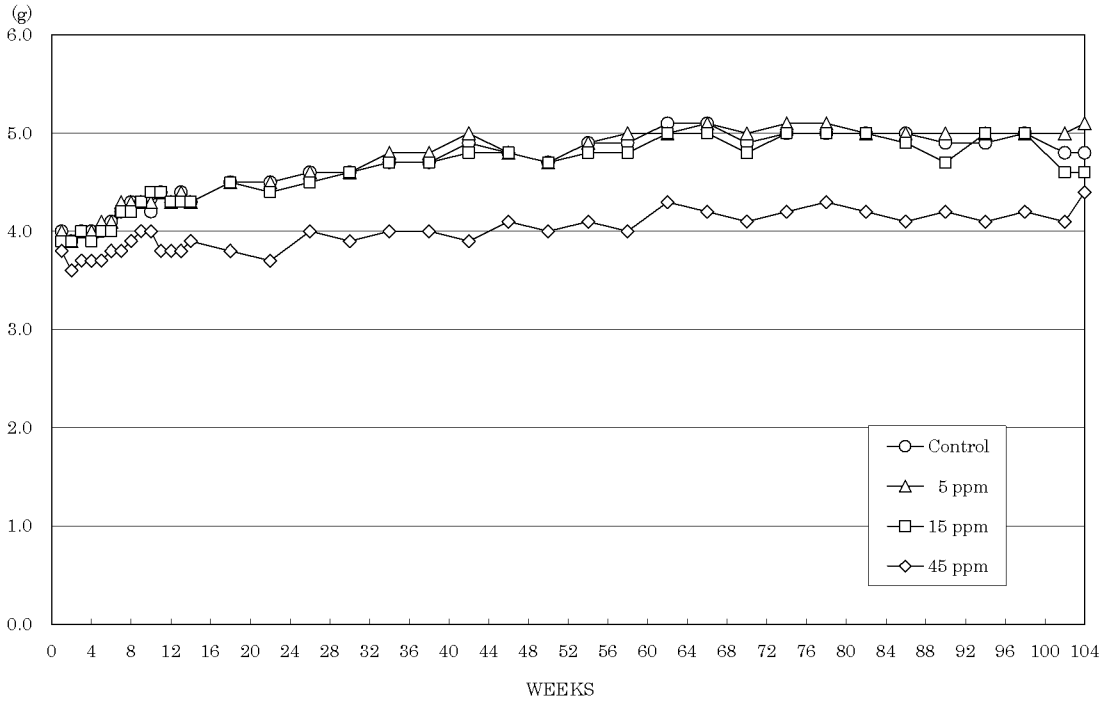


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

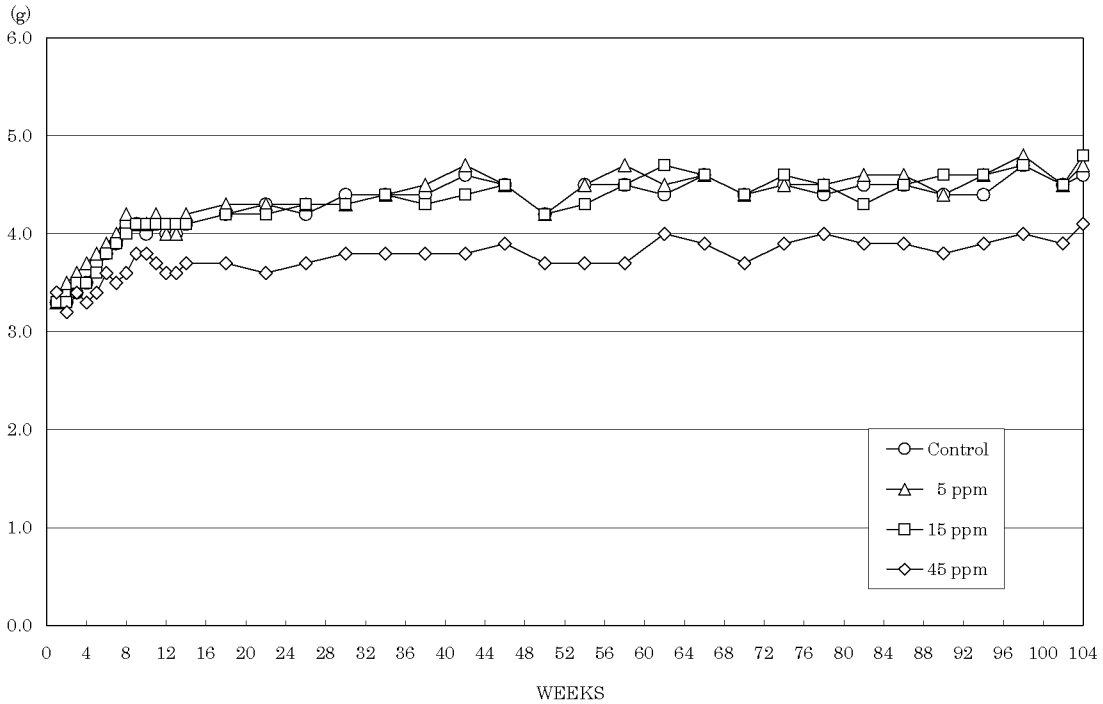
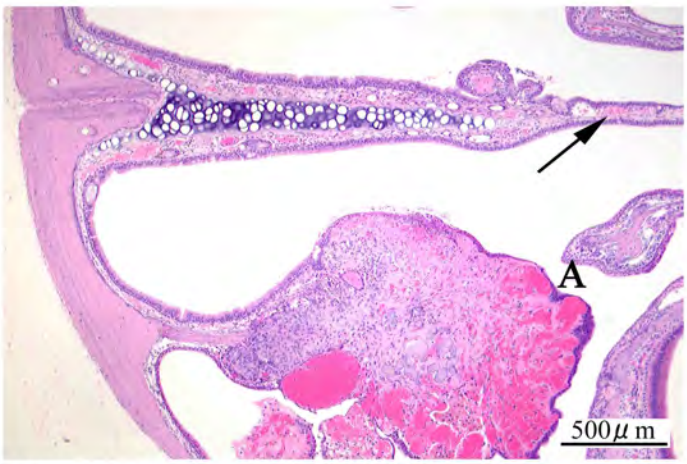
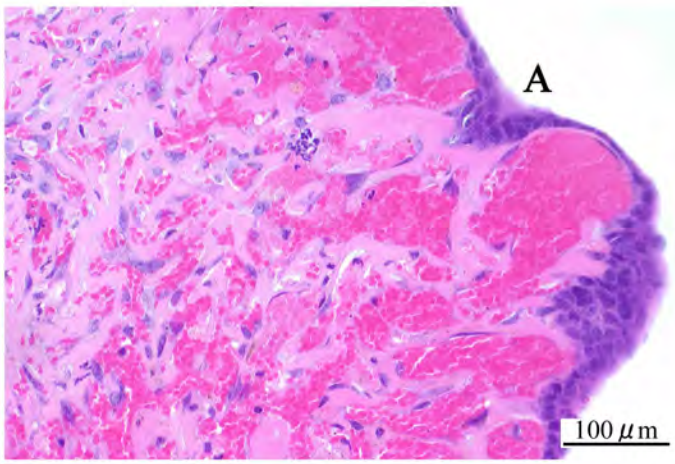


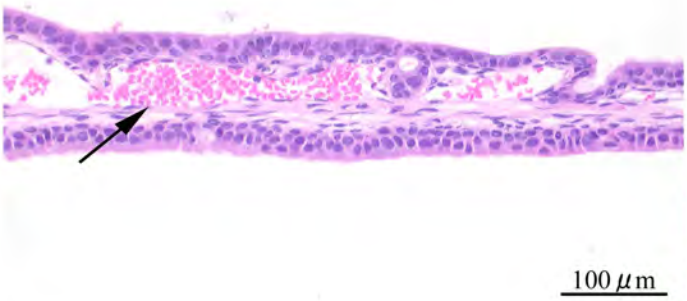
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER



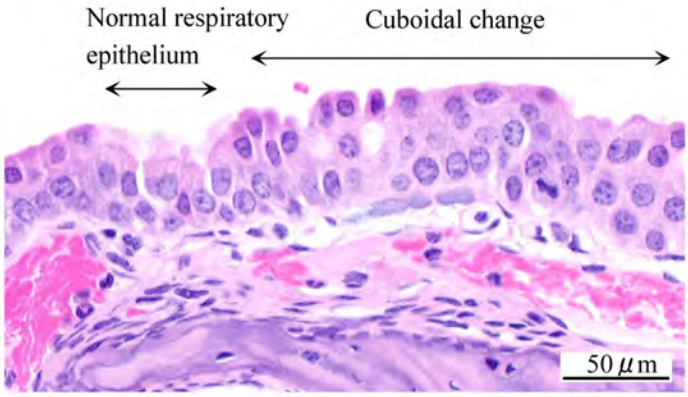
Photograph 1
Nasal cavity: Hemangioma (A) , Angiectasis (Arrow)
Mouse, Female, 45 ppm, Animal No. 0438-2335 (H&E)



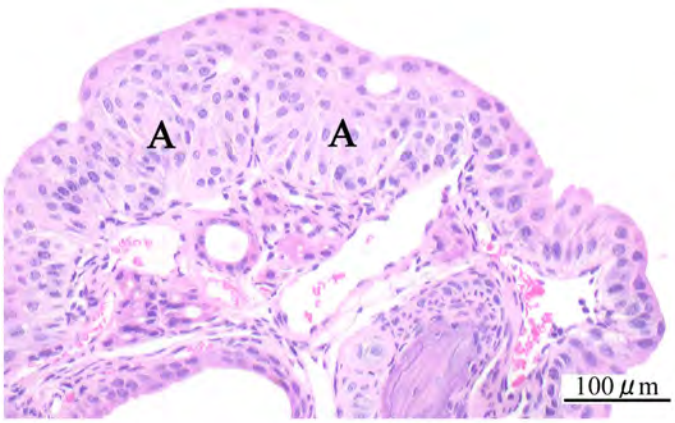
Photograph 2
Nasal cavity: Hemangioma
Higher magnification of photograph 1 (A).
Mouse, Female, 45 ppm, Animal No. 0438-2335 (H&E)



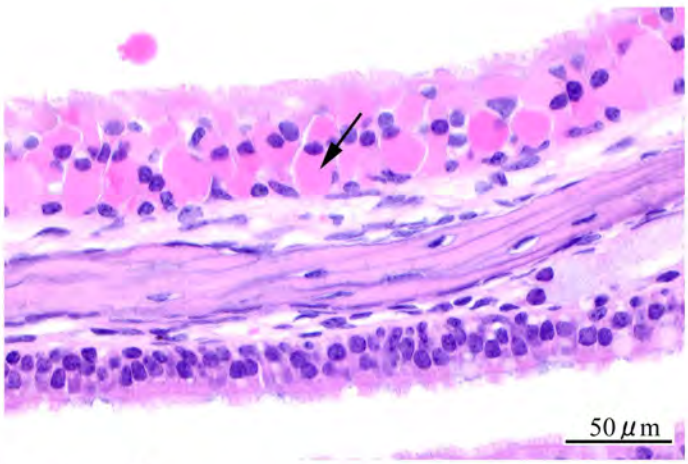
Photograph 3
Nasal cavity: Angiectasis
Higher magnification of photograph 1 (Arrow).
Mouse, Female, 45 ppm, Animal No. 0438-2335 (H&E)



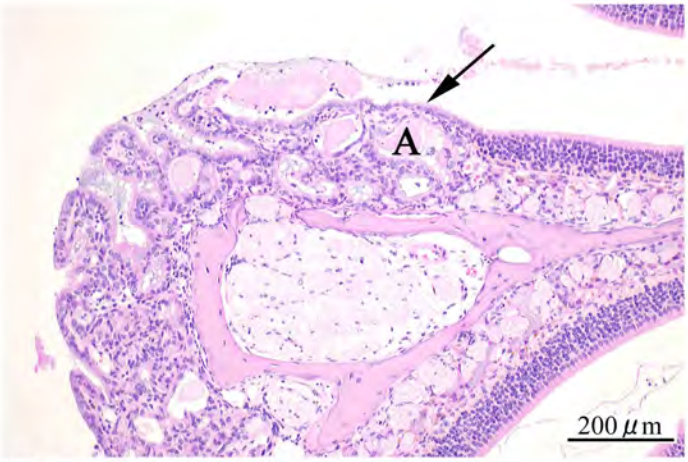
Photograph 4
Nasal cavity (respiratory epithelium): Cuboidal change
Mouse, Male, 15 ppm, Animal No. 0438-1203 (H&E)



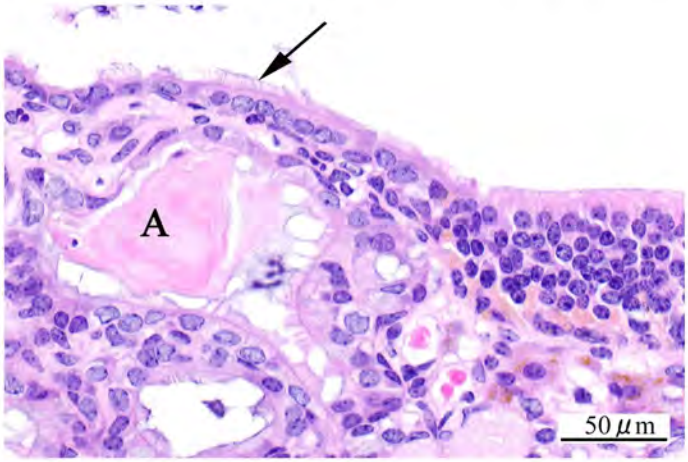
Photograph 5
Nasal cavity (transitional epithelium): Nodular hyperplasia (A)
Mouse, Male, 45 ppm, Animal No. 0438-1303 (H&E)



Photograph 6
Nasal cavity (respiratoly epithelium): Eosinophilic change (Arrow)
Mouse, Male, 45 ppm, Animal No. 0438-1306 (H&E)



Photograph 7
Nasal cavity: Respiratory metaplasia of gland (A) and respiratory metaplasia of olfactory epithelium (Arrow)
Mouse, Male, 45 ppm, Animal No. 0438-1302 (H&E)



Photograph 8
Nasal cavity: Respiratory metaplasia of gland (A) and respiratory metaplasia of olfactory epithelium (Arrow).
Higher magnification of photograph 7.
Mouse, Male, 45 ppm, Animal No. 0438-1302 (H&E)