Summary of Inhalation Carcinogenicity Study of Butyl 2,3-Epoxypropyl Ether in F344 Rats

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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.

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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 F344/DuCrj (Fischer) rats of both sexes to BEE vapor at a target concentration of 0 (clean air), 10, 30 or 90 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: 7600 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

As the neoplastic lesions, nasal cavity tumors were increased in males and females. The incidence of squamous cell carcinomas in the nasal cavity was significantly increased in the 90 ppm-exposed males and females. Squamous cell papillomas and esthesioneuroepitheliomas in the nasal cavity occurred in the 90 ppm-exposed males, while adenosquamous carcinomas, esthesioneuroepitheliomas and sarcomas in the nasal cavity occurred in the 90 ppm-exposed females. The increased incidence of adenomas in the nasal cavity was noted in the 30-ppm exposed males and females.

Nasal lesions in the respiratory epithelium (squamous cell metaplasia, squamous cell hyperplasia with atypia, inflammation and hyperplasia of the transitional epithelium), in the olfactory epithelium (atrophy, respiratory metaplasia and squamous cell metaplasia) and in the submucosal gland (hyperplasia) and eyes lesions (keratitis) were found in the BEE-exposed rats.

Conclusions

In rats, there was clear evidence of carcinogenic activity of BEE in males and females, based on the increased incidences of squamous cell carcinomas 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
10 ppm	10.1 ± 0.1
30 ppm	30.1 ± 0.2
90 ppm	90.1 ± 0.6

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

Week on Study	Control		10 ppm			30 ppm			90 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	127 (50)	50 / 50	127 (50)	100	50 / 50	127 (50)	100	50 / 50	127 (50)	100	50 / 50
1	159 (50)	50 / 50	156 (50)	98	50 / 50	155 (50)	97	50 / 50	145 (50)	91	50 / 50
2	189 (50)	50 / 50	187 (50)	99	50 / 50	183 (50)	97	50 / 50	168 (50)	89	50 / 50
3	215 (50)	50 / 50	211 (50)	98	50 / 50	208 (50)	97	50 / 50	191 (49)	89	49 / 50
4	235 (50)	50 / 50	231 (50)	98	50 / 50	227 (50)	97	50 / 50	207 (49)	88	49 / 50
5	251 (50)	50 / 50	248 (50)	99	50 / 50	243 (50)	97	50 / 50	220 (49)	88	49 / 50
6	266 (50)	50 / 50	262 (50)	98	50 / 50	258 (50)	97	50 / 50	230 (49)	86	49 / 50
7	280 (50)	50 / 50	275 (50)	98	50 / 50	270 (50)	96	50 / 50	240 (49)	86	49 / 50
8	293 (50)	50 / 50	288 (50)	98	50 / 50	282 (50)	96	50 / 50	247 (49)	84	49 / 50
9	304 (50)	50 / 50	297 (50)	98	50 / 50	292 (50)	96	50 / 50	254 (49)	84	49 / 50
10	313 (50)	50 / 50	305 (50)	97	50 / 50	300 (50)	96	50 / 50	259 (49)	83	49 / 50
11	321 (50)	50 / 50	314 (50)	98	50 / 50	308 (50)	96	50 / 50	266 (49)	83	49 / 50
12	328 (50)	50 / 50	319 (50)	97	50 / 50	317 (50)	97	50 / 50	283 (49)	86	49 / 50
13	334 (50)	50 / 50	327 (50)	98	50 / 50	323 (50)	97	50 / 50	280 (49)	84	49 / 50
14	339 (50)	50 / 50	332 (50)	98	50 / 50	330 (50)	97	50 / 50	280 (49)	83	49 / 50
18	357 (50)	50 / 50	351 (50)	98	50 / 50	348 (50)	97	50 / 50	294 (49)	82	49 / 50
22	372 (50)	50 / 50	367 (50)	99	50 / 50	363 (50)	98	50 / 50	304 (49)	82	49 / 50
26	384 (50)	50 / 50	379 (50)	99	50 / 50	375 (50)	98	50 / 50	314 (49)	82	49 / 50
30	393 (50)	50 / 50	388 (50)	99	50 / 50	385 (50)	98	50 / 50	320 (49)	81	49 / 50
34	404 (50)	50 / 50	399 (50)	99	50 / 50	394 (50)	98	50 / 50	326 (49)	81	49 / 50
38	412 (50)	50 / 50	408 (50)	99	50 / 50	402 (50)	98	50 / 50	332 (49)	81	49 / 50
42	422 (50)	50 / 50	418 (50)	99	50 / 50	413 (50)	98	50 / 50	343 (49)	81	49 / 50
46	429 (50)	50 / 50	424 (50)	99	50 / 50	419 (50)	98	50 / 50	342 (49)	80	49 / 50
50	435 (50)	50 / 50	431 (50)	99	50 / 50	424 (50)	97	50 / 50	348 (49)	80	49 / 50
54	439 (50)	50 / 50	433 (50)	99	50 / 50	424 (49)	97	49 / 50	351 (49)	80	49 / 50
58	442 (50)	50 / 50	436 (49)	99	49 / 50	431 (49)	98	49 / 50	349 (49)	79	49 / 50
62	444 (50)	50 / 50	437 (49)	98	49 / 50	429 (49)	97	49 / 50	348 (48)	78	48 / 50
66	448 (50)	50 / 50	440 (49)	98	49 / 50	434 (48)	97	48 / 50	354 (47)	79	47 / 50
70	451 (50)	50 / 50	443 (49)	98	49 / 50	436 (47)	97	47 / 50	352 (47)	78	47 / 50
74	454 (50)	50 / 50	447 (48)	98	48 / 50	437 (47)	96	47 / 50	347 (46)	76	46 / 50
78	454 (50)	50 / 50	449 (48)	99	48 / 50	438 (46)	96	46 / 50	338 (43)	74	43 / 50
82	452 (50)	50 / 50	451 (47)	100	47 / 50	439 (45)	97	45 / 50	337 (36)	75	36 / 50
86	447 (49)	49 / 50	449 (47)	100	47 / 50	435 (45)	97	45 / 50	322 (32)	72	32 / 50
90	441 (49)	49 / 50	447 (47)	101	47 / 50	436 (42)	99	42 / 50	334 (24)	76	24 / 50
94	434 (43)	43 / 50	440 (47)	101	47 / 50	431 (42)	99	42 / 50	311 (23)	72	23 / 50
98	432 (40)	40 / 50	434 (42)	100	42 / 50	423 (40)	98	40 / 50	319 (15)	74	15 / 50
102	431 (39)	39 / 50	428 (39)	99	39 / 50	421 (38)	98	38 / 50	310 (12)	72	12 / 50
104	422 (38)	38 / 50	423 (38)	100	38 / 50	418 (38)	99	38 / 50	294 (11)	70	11 / 50

< > : 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 RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Week on Study	Control		10 ppm			30 ppm			90 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	95 (50)	50 / 50	95 (50)	100	50 / 50	95 (50)	100	50 / 50	95 (50)	100	50 / 50
1	110 (50)	50 / 50	108 (50)	98	50 / 50	108 (50)	98	50 / 50	102 (50)	93	50 / 50
2	123 (50)	50 / 50	121 (50)	98	50 / 50	119 (50)	97	50 / 50	113 (50)	92	50 / 50
3	133 (50)	50 / 50	131 (50)	98	50 / 50	130 (50)	98	50 / 50	124 (50)	93	50 / 50
4	141 (50)	50 / 50	139 (50)	99	50 / 50	136 (50)	96	50 / 50	131 (50)	93	50 / 50
5	149 (50)	50 / 50	147 (50)	99	50 / 50	145 (50)	97	50 / 50	140 (50)	94	50 / 50
6	154 (50)	50 / 50	152 (50)	99	50 / 50	149 (50)	97	50 / 50	143 (50)	93	50 / 50
7	159 (50)	50 / 50	158 (50)	99	50 / 50	153 (50)	96	50 / 50	148 (50)	93	50 / 50
8	162 (50)	50 / 50	160 (50)	99	50 / 50	156 (50)	96	50 / 50	151 (50)	93	50 / 50
9	168 (50)	50 / 50	165 (50)	98	50 / 50	161 (50)	96	50 / 50	155 (50)	92	50 / 50
10	171 (50)	50 / 50	168 (50)	98	50 / 50	165 (50)	96	50 / 50	157 (50)	92	50 / 50
11	176 (50)	50 / 50	172 (50)	98	50 / 50	169 (50)	96	50 / 50	162 (50)	92	50 / 50
12	178 (50)	50 / 50	176 (50)	99	50 / 50	173 (50)	97	50 / 50	168 (50)	94	50 / 50
13	180 (50)	50 / 50	178 (50)	99	50 / 50	174 (50)	97	50 / 50	166 (50)	92	50 / 50
14	181 (50)	50 / 50	180 (50)	99	50 / 50	175 (50)	97	50 / 50	165 (50)	91	50 / 50
18	188 (50)	50 / 50	187 (50)	99	50 / 50	183 (50)	97	50 / 50	170 (50)	90	50 / 50
22	195 (50)	50 / 50	194 (50)	99	50 / 50	189 (50)	97	50 / 50	175 (50)	90	50 / 50
26	199 (50)	50 / 50	197 (50)	99	50 / 50	194 (50)	97	50 / 50	179 (50)	90	50 / 50
30	203 (50)	50 / 50	202 (50)	100	50 / 50	200 (50)	99	50 / 50	182 (50)	90	50 / 50
34	207 (50)	50 / 50	207 (50)	100	50 / 50	205 (50)	99	50 / 50	185 (50)	89	50 / 50
38	210 (50)	50 / 50	210 (50)	100	50 / 50	209 (50)	100	50 / 50	188 (50)	90	50 / 50
42	217 (50)	50 / 50	216 (50)	100	50 / 50	216 (50)	100	50 / 50	195 (50)	90	50 / 50
46	222 (50)	50 / 50	220 (50)	99	50 / 50	218 (50)	98	50 / 50	195 (50)	88	50 / 50
50	226 (50)	50 / 50	228 (50)	101	50 / 50	227 (50)	100	50 / 50	201 (50)	89	50 / 50
54	229 (50)	50 / 50	229 (50)	100	50 / 50	229 (50)	100	50 / 50	201 (50)	88	50 / 50
58	233 (50)	50 / 50	232 (50)	100	50 / 50	233 (50)	100	50 / 50	201 (50)	86	50 / 50
62	234 (50)	50 / 50	236 (50)	101	50 / 50	235 (50)	100	50 / 50	203 (50)	87	50 / 50
66	239 (50)	50 / 50	242 (50)	101	50 / 50	241 (50)	101	50 / 50	210 (49)	88	49 / 50
70	242 (49)	49 / 50	248 (50)	102	50 / 50	245 (49)	101	49 / 50	212 (48)	88	48 / 50
74	249 (49)	49 / 50	255 (50)	102	50 / 50	251 (49)	101	49 / 50	212 (48)	85	48 / 50
78	255 (47)	47 / 50	260 (50)	102	50 / 50	256 (47)	100	47 / 50	211 (45)	83	45 / 50
82	258 (47)	47 / 50	262 (50)	102	50 / 50	260 (46)	101	46 / 50	213 (42)	83	42 / 50
86	261 (47)	47 / 50	267 (49)	102	49 / 50	263 (45)	101	45 / 50	214 (37)	82	37 / 50
90	267 (44)	44 / 50	271 (48)	101	48 / 50	266 (44)	100	44 / 50	210 (36)	79	36 / 50
94	269 (44)	44 / 50	272 (48)	101	48 / 50	271 (43)	101	43 / 50	211 (30)	78	30 / 50
98	271 (42)	42 / 50	274 (48)	101	48 / 50	274 (42)	101	42 / 50	206 (25)	76	25 / 50
102	271 (40)	40 / 50	274 (46)	101	46 / 50	274 (42)	101	42 / 50	207 (18)	76	18 / 50
104	269 (40)	40 / 50	272 (45)	101	45 / 50	270 (41)	100	41 / 50	206 (15)	77	15 / 50

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

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

Week on Study	Control		10 ppm			30 ppm			90 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	15.6 (50)	50 / 50	15.4 (50)	99	50 / 50	14.9 (50)	96	50 / 50	12.3 (50)	79	50 / 50
2	16.4 (50)	50 / 50	16.1 (50)	98	50 / 50	15.7 (50)	96	50 / 50	13.7 (50)	84	50 / 50
3	17.4 (50)	50 / 50	16.8 (50)	97	50 / 50	16.5 (50)	95	50 / 50	14.6 (49)	84	49 / 50
4	17.4 (50)	50 / 50	17.2 (50)	99	50 / 50	16.6 (50)	95	50 / 50	14.9 (49)	86	49 / 50
5	17.3 (50)	50 / 50	16.6 (50)	96	50 / 50	16.4 (50)	95	50 / 50	14.7 (49)	85	49 / 50
6	17.1 (50)	50 / 50	16.6 (50)	97	50 / 50	16.4 (50)	96	50 / 50	14.6 (49)	85	49 / 50
7	17.0 (50)	50 / 50	16.6 (50)	98	50 / 50	16.4 (50)	96	50 / 50	14.9 (49)	88	49 / 50
8	16.9 (50)	50 / 50	16.4 (50)	97	50 / 50	16.0 (50)	95	50 / 50	14.0 (49)	83	49 / 50
9	17.1 (50)	50 / 50	16.4 (50)	96	50 / 50	16.3 (50)	95	50 / 50	14.0 (49)	82	49 / 50
10	16.7 (50)	50 / 50	16.4 (50)	98	50 / 50	16.1 (50)	96	50 / 50	14.1 (49)	84	49 / 50
11	16.2 (50)	50 / 50	15.8 (50)	98	50 / 50	16.0 (50)	99	50 / 50	14.5 (49)	90	49 / 50
12	16.7 (50)	50 / 50	16.2 (50)	97	50 / 50	16.5 (50)	99	50 / 50	16.1 (49)	96	49 / 50
13	16.3 (50)	50 / 50	15.6 (50)	96	50 / 50	16.0 (50)	98	50 / 50	14.3 (49)	88	49 / 50
14	16.5 (50)	50 / 50	16.0 (50)	97	50 / 50	15.8 (50)	96	50 / 50	13.7 (49)	83	49 / 50
18	16.4 (50)	50 / 50	16.1 (50)	98	50 / 50	15.9 (50)	97	50 / 50	14.5 (49)	88	49 / 50
22	16.6 (50)	50 / 50	16.2 (50)	98	50 / 50	16.1 (50)	97	50 / 50	14.4 (49)	87	49 / 50
26	16.8 (50)	50 / 50	16.3 (50)	97	50 / 50	15.9 (50)	95	50 / 50	14.7 (49)	88	49 / 50
30	16.5 (50)	50 / 50	16.5 (50)	100	50 / 50	16.2 (50)	98	50 / 50	15.3 (49)	93	49 / 50
34	16.9 (50)	50 / 50	16.7 (50)	99	50 / 50	16.5 (50)	98	50 / 50	15.2 (49)	90	49 / 50
38	17.0 (50)	50 / 50	16.9 (50)	99	50 / 50	16.6 (50)	98	50 / 50	15.5 (49)	91	49 / 50
42	17.2 (50)	50 / 50	17.0 (50)	99	50 / 50	16.8 (50)	98	50 / 50	15.9 (49)	92	49 / 50
46	16.9 (50)	50 / 50	16.8 (50)	99	50 / 50	16.6 (50)	98	50 / 50	15.3 (49)	91	49 / 50
50	17.0 (50)	50 / 50	16.9 (50)	99	50 / 50	16.7 (50)	98	50 / 50	15.9 (49)	94	49 / 50
54	16.7 (50)	50 / 50	16.7 (50)	100	50 / 50	16.4 (49)	98	49 / 50	15.4 (49)	92	49 / 50
58	16.9 (50)	50 / 50	16.9 (49)	100	49 / 50	16.7 (49)	99	49 / 50	15.5 (49)	92	49 / 50
62	17.0 (50)	50 / 50	16.9 (49)	99	49 / 50	16.5 (49)	97	49 / 50	15.4 (48)	91	48 / 50
66	17.2 (50)	50 / 50	17.3 (49)	101	49 / 50	16.8 (48)	98	48 / 50	15.4 (47)	90	47 / 50
70	17.5 (50)	50 / 50	17.5 (49)	100	49 / 50	17.2 (47)	98	47 / 50	16.0 (47)	91	47 / 50
74	17.2 (50)	50 / 50	17.4 (48)	101	48 / 50	16.6 (46)	97	47 / 50	14.8 (46)	86	46 / 50
78	16.8 (50)	50 / 50	17.6 (48)	105	48 / 50	16.7 (46)	99	46 / 50	14.7 (43)	88	43 / 50
82	17.0 (50)	50 / 50	17.6 (47)	104	47 / 50	16.9 (45)	99	45 / 50	14.8 (36)	87	36 / 50
86	16.6 (49)	49 / 50	16.9 (47)	102	47 / 50	15.9 (45)	96	45 / 50	13.9 (32)	84	32 / 50
90	16.0 (49)	49 / 50	16.6 (47)	104	47 / 50	16.6 (42)	104	42 / 50	14.9 (24)	93	24 / 50
94	15.6 (43)	43 / 50	16.7 (47)	107	47 / 50	16.4 (42)	105	42 / 50	13.9 (23)	89	23 / 50
98	16.6 (39)	40 / 50	16.5 (42)	99	42 / 50	16.4 (40)	99	40 / 50	15.0 (15)	90	15 / 50
102	17.1 (39)	39 / 50	16.8 (39)	98	39 / 50	16.6 (38)	97	38 / 50	15.0 (12)	88	12 / 50
104	16.3 (38)	38 / 50	16.6 (38)	102	38 / 50	16.7 (38)	102	38 / 50	13.6 (11)	83	11 / 50

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

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

Week on Study	Control			10 ppm			30 ppm			90 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>			<50>			<50>			<50>		
1	10.9 (50)		50 / 50	10.8 (50)	99	50 / 50	10.7 (50)	98	50 / 50	9.2 (50)	84	50 / 50
2	11.0 (50)		50 / 50	10.9 (50)	99	50 / 50	10.5 (50)	95	50 / 50	9.9 (50)	90	50 / 50
3	11.2 (50)		50 / 50	11.3 (50)	101	50 / 50	10.8 (50)	96	50 / 50	10.6 (50)	95	50 / 50
4	11.1 (50)		50 / 50	11.2 (50)	101	50 / 50	10.8 (50)	97	50 / 50	10.4 (50)	94	50 / 50
5	11.6 (50)		50 / 50	11.6 (50)	100	50 / 50	11.2 (50)	97	50 / 50	11.0 (50)	95	50 / 50
6	10.9 (49)		50 / 50	10.9 (50)	100	50 / 50	10.5 (50)	96	50 / 50	10.4 (50)	95	50 / 50
7	11.0 (50)		50 / 50	11.1 (50)	101	50 / 50	10.7 (50)	97	50 / 50	10.9 (50)	99	50 / 50
8	10.2 (50)		50 / 50	10.2 (50)	100	50 / 50	10.0 (50)	98	50 / 50	9.6 (50)	94	50 / 50
9	10.9 (50)		50 / 50	10.4 (50)	95	50 / 50	10.6 (50)	97	50 / 50	10.0 (50)	92	50 / 50
10	10.1 (50)		50 / 50	10.1 (50)	100	50 / 50	10.1 (50)	100	50 / 50	9.8 (50)	97	50 / 50
11	10.7 (50)		50 / 50	10.4 (50)	97	50 / 50	10.7 (50)	100	50 / 50	10.7 (50)	100	50 / 50
12	10.4 (50)		50 / 50	10.2 (50)	98	50 / 50	10.4 (50)	100	50 / 50	10.6 (50)	102	50 / 50
13	10.5 (50)		50 / 50	10.4 (50)	99	50 / 50	10.2 (50)	97	50 / 50	10.0 (50)	95	50 / 50
14	10.2 (50)		50 / 50	10.1 (50)	99	50 / 50	10.1 (50)	99	50 / 50	9.3 (50)	91	50 / 50
18	9.9 (50)		50 / 50	10.0 (50)	101	50 / 50	10.0 (50)	101	50 / 50	9.9 (50)	100	50 / 50
22	10.2 (50)		50 / 50	10.3 (50)	101	50 / 50	10.1 (50)	99	50 / 50	10.0 (50)	98	50 / 50
26	10.2 (50)		50 / 50	10.1 (50)	99	50 / 50	10.1 (50)	99	50 / 50	10.2 (50)	100	50 / 50
30	10.4 (50)		50 / 50	10.3 (50)	99	50 / 50	10.6 (50)	102	50 / 50	10.4 (50)	100	50 / 50
34	10.2 (50)		50 / 50	10.5 (50)	103	50 / 50	10.6 (50)	104	50 / 50	10.5 (50)	103	50 / 50
38	10.4 (50)		50 / 50	10.5 (50)	101	50 / 50	10.7 (50)	103	50 / 50	10.5 (50)	101	50 / 50
42	10.8 (50)		50 / 50	10.7 (50)	99	50 / 50	10.8 (50)	100	50 / 50	11.0 (50)	102	50 / 50
46	10.7 (50)		50 / 50	10.6 (50)	99	50 / 50	10.4 (50)	97	50 / 50	10.5 (50)	98	50 / 50
50	10.9 (50)		50 / 50	11.1 (50)	102	50 / 50	11.3 (50)	104	50 / 50	11.3 (50)	104	50 / 50
54	10.7 (50)		50 / 50	11.0 (50)	103	50 / 50	10.9 (50)	102	50 / 50	10.2 (50)	95	50 / 50
58	10.8 (50)		50 / 50	10.9 (50)	101	50 / 50	10.8 (50)	100	50 / 50	10.4 (50)	96	50 / 50
62	10.7 (50)		50 / 50	11.1 (50)	104	50 / 50	10.9 (50)	102	50 / 50	10.7 (50)	100	50 / 50
66	11.5 (50)		50 / 50	12.0 (50)	104	50 / 50	11.6 (50)	101	50 / 50	11.1 (49)	97	49 / 50
70	11.3 (49)		49 / 50	12.0 (50)	106	50 / 50	11.8 (49)	104	49 / 50	11.7 (48)	104	48 / 50
74	11.5 (49)		49 / 50	12.2 (50)	106	50 / 50	11.8 (49)	103	49 / 50	10.7 (48)	93	48 / 50
78	11.5 (47)		47 / 50	12.1 (50)	105	50 / 50	11.8 (47)	103	47 / 50	10.5 (45)	91	45 / 50
82	11.6 (47)		47 / 50	11.8 (50)	102	50 / 50	11.9 (46)	103	46 / 50	10.8 (42)	93	42 / 50
86	11.5 (47)		47 / 50	12.1 (49)	105	49 / 50	11.5 (45)	100	45 / 50	10.8 (37)	94	37 / 50
90	11.4 (44)		44 / 50	12.1 (48)	106	48 / 50	11.7 (44)	103	44 / 50	10.1 (36)	89	36 / 50
94	12.3 (43)		44 / 50	12.0 (48)	98	48 / 50	12.3 (43)	100	43 / 50	10.7 (30)	87	30 / 50
98	12.2 (42)		42 / 50	12.2 (48)	100	48 / 50	12.2 (42)	100	42 / 50	9.9 (25)	81	25 / 50
102	11.7 (39)		40 / 50	12.3 (46)	105	46 / 50	12.4 (42)	106	42 / 50	10.5 (18)	90	18 / 50
104	11.5 (40)		40 / 50	11.9 (45)	103	45 / 50	11.7 (41)	102	41 / 50	10.3 (15)	90	15 / 50

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

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

Group Name	Control	10 ppm	30 ppm	90 ppm	
No. of examined animals	38	37	38	8	
HEMOGLOBIN (g/dL)	14.5 ± 2.3	14.0 ± 2.7	13.7 ± 2.8	10.6 ± 3.0	**
HEMATOCRIT (%)	41.7 ± 5.6	40.2 ± 6.6	39.8 ± 6.5	33.2 ± 7.0	**
MCH (pg)	17.3 ± 1.5	17.0 ± 1.2	17.1 ± 1.9	15.8 ± 3.2	**
MCHC (g/dL)	34.7 ± 1.8	34.6 ± 2.0	34.1 ± 2.2	31.4 ± 2.7	**
Differential WBC (%)					
N-SEG	48 ± 8	45 ± 11	45 ± 9	37 ± 13	*

Mean ± S.D.

Significant difference: * : $p \leqq 0.05$ ** : $p \leqq 0.01$ Test of Dunnett

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

Group Name	Control	10 ppm	30 ppm	90 ppm
No. of examined animals	38	37	38	8
ALBUMIN (g/dL)	2.9 ± 0.2	2.8 ± 0.2	2.8 ± 0.3	2.5 ± 0.3 **
T-CHOLESTEROL (mg/dL)	190 ± 84	194 ± 76	172 ± 54	94 ± 22 **
TRIGLYCERIDE (mg/dL)	154 ± 173	146 ± 107	112 ± 62	44 ± 41 **
PHOSPHOLIPID (mg/dL)	275 ± 130	280 ± 110	250 ± 63	164 ± 34 **
AST (IU/L)	103 ± 121	91 ± 55	87 ± 67	156 ± 111 **
ALP (IU/L)	205 ± 57	351 ± 849	237 ± 94	370 ± 144 **
CK (IU/L)	119 ± 146	109 ± 48	111 ± 73	169 ± 105 **
POTASSIUM (mEq/L)	3.8 ± 0.3	3.8 ± 0.3	3.9 ± 0.3	4.2 ± 0.4 *
CALCIUM (mg/dL)	10.4 ± 0.4	10.3 ± 0.4	10.2 ± 0.3	10.0 ± 0.2 *
INORGANIC PHOSPHORUS (mg/dL)	4.0 ± 0.8	4.2 ± 0.5	4.2 ± 0.7	4.9 ± 0.5 **

Mean ± S.D.

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

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

Group Name	Control	10 ppm	30 ppm	90 ppm
No. of examined animals	38	45	41	15
TOTAL PROTEIN (g/dL)	6.7 ± 0.6	7.0 ± 0.4 **	7.0 ± 0.4	6.4 ± 0.7
ALBUMIN (g/dL)	3.4 ± 0.4	3.5 ± 0.3	3.5 ± 0.4	3.1 ± 0.5 *
T-CHOLESTEROL (mg/dL)	126 ± 23	138 ± 28 *	150 ± 53 **	104 ± 38
TRIGLYCERIDE (mg/dL)	62 ± 62	62 ± 30	81 ± 65 *	35 ± 20
PHOSPHOLIPID (mg/dL)	226 ± 38	245 ± 43	267 ± 81 **	192 ± 62
ALP (IU/L)	142 ± 59	140 ± 62	170 ± 150	236 ± 150 **
G-GTP (IU/L)	2 ± 1	3 ± 2	4 ± 4	4 ± 4 *
CK (IU/L)	95 ± 18	108 ± 62	117 ± 82	181 ± 188 **
SODIUM (mEq/L)	141 ± 2	140 ± 2	141 ± 1	140 ± 2 *
CALCIUM (mg/dL)	10.1 ± 0.3	10.3 ± 0.3 **	10.4 ± 0.4 **	10.0 ± 0.3

Mean ± S.D.

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

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

Group Name		Control	10 ppm	30 ppm	90 ppm
No. of examined animals		38	38	38	11
	Grade				
pH	5.0	0	0	0	0
	6.0	0	2	0	0
	6.5	2	4	2	3
	7.0	7	7	1	1
	7.5	15	15	27	5
	8.0	14	10	8	2
	8.5	0	0	0	0
	Chi square test			*	
Ketone body	−	38	38	35	9
	±	0	0	3	2
	+	0	0	0	0
	2+	0	0	0	0
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test				**
Occult blood	−	37	38	38	7
	±	1	0	0	4
	+	0	0	0	0
	2+	0	0	0	0
	3+	0	0	0	0
	Chi square test				**

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

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

Group Name		Control	10 ppm	30 ppm	90 ppm
No. of examined animals		39	46	42	15
	Grade				
Protein	−	1	0	0	1
	±	5	4	4	5
	+	7	8	3	7
	2+	10	13	9	2
	3+	11	14	21	0
	4+	5	7	5	0
	Chi square test				*

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

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

Group Name	Control	10 ppm	30 ppm	90 ppm
No. of examined animals	38	38	38	11
Body weight (g)	396 ± 33	395 ± 27	390 ± 32	275 ± 35 **
Heart (g)	1.176 ± 0.094	1.249 ± 0.116	1.214 ± 0.091	1.204 ± 0.162
Heart (%)	0.298 ± 0.023	0.317 ± 0.038 *	0.312 ± 0.023 *	0.446 ± 0.097 **
Lungs (g)	1.476 ± 0.343	1.620 ± 0.470 *	1.498 ± 0.252	1.810 ± 0.498 **
Lungs (%)	0.376 ± 0.101	0.413 ± 0.134	0.384 ± 0.046	0.682 ± 0.270 **
Kidneys (g)	2.771 ± 0.217	2.819 ± 0.228	2.844 ± 0.278	2.470 ± 0.209 **
Kidneys (%)	0.705 ± 0.072	0.715 ± 0.071	0.732 ± 0.078	0.909 ± 0.129 **
Brain (g)	2.068 ± 0.051	2.083 ± 0.052	2.097 ± 0.063	2.036 ± 0.067
Brain (%)	0.526 ± 0.045	0.529 ± 0.039	0.540 ± 0.042	0.752 ± 0.113 **

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

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

Group Name	Control	10 ppm	30 ppm	90 ppm
No. of examined animals	40	45	41	15
Body weight (g)	251 ± 35	254 ± 24	252 ± 27	195 ± 24 **
Adrenals (g)	0.082 ± 0.097	0.068 ± 0.010	0.065 ± 0.013	0.065 ± 0.009
Adrenals (%)	0.034 ± 0.044	0.027 ± 0.006	0.026 ± 0.005	0.034 ± 0.007 **
Ovaries (g)	0.164 ± 0.332	0.116 ± 0.023	0.192 ± 0.490	0.106 ± 0.015
Ovaries (%)	0.070 ± 0.159	0.046 ± 0.009	0.071 ± 0.159	0.055 ± 0.010 **
Heart (g)	0.858 ± 0.106	0.837 ± 0.052	0.862 ± 0.087	0.796 ± 0.048 *
Heart (%)	0.347 ± 0.056	0.332 ± 0.025	0.345 ± 0.050	0.415 ± 0.055 **
Lungs (g)	1.017 ± 0.123	1.039 ± 0.218	1.050 ± 0.234	1.043 ± 0.179
Lungs (%)	0.413 ± 0.076	0.413 ± 0.096	0.425 ± 0.146	0.544 ± 0.115 **
Kidneys (g)	1.710 ± 0.136	1.754 ± 0.134	1.816 ± 0.309	1.610 ± 0.140
Kidneys (%)	0.691 ± 0.088	0.697 ± 0.085	0.726 ± 0.120	0.836 ± 0.096 **
Brain (g)	1.864 ± 0.046	1.866 ± 0.046	1.872 ± 0.042	1.864 ± 0.033
Brain (%)	0.757 ± 0.107	0.742 ± 0.072	0.751 ± 0.083	0.976 ± 0.163 **

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

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

Group Name	Control	10 ppm	30 ppm	90 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
subcutis	<50>	<50>	<50>	<50>		
fibroma	8 (16 %)	4 (8 %)	6 (12 %)	0 (0 %)**		↓ ↓
nasal cavity	<50>	<50>	<50>	<50>		
squamous cell papilloma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
adenoma	0 (0 %)	0 (0 %)	5 (10 %)*	0 (0 %)		
squamous cell carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	35 (70 %)**	↑ ↑	↑ ↑
ethesioneuroepithelioma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
spleen	<50>	<50>	<50>	<50>		
mononuclear cell leukemia	10 (20 %)	16 (32 %)	19 (38 %)*	7 (14 %)		
pituitary	<50>	<50>	<50>	<50>		
adenoma	8 (16 %)	14 (28 %)	7 (14 %)	2 (4 %)*		↓ ↓
testis	<50>	<50>	<50>	<50>		
interstitial cell tumor	47 (94 %)	38 (76 %)*	40 (80 %)*	24 (48 %)**		↓ ↓

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 RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control	10 ppm	30 ppm	90 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
nasal cavity	<50>	<50>	<50>	<50>		
adenoma	1 (2 %)	1 (2 %)	2 (4 %)	0 (0 %)		
squamous cell carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	28 (56 %) **	↑ ↑	↑ ↑
sarcoma:NOS	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
adenosquamous carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)		
ethesioneuroepithelioma	0 (0 %)	0 (0 %)	0 (0 %)	2 (4 %)		
spleen	<50>	<50>	<49>	<50>		
mononuclear cell leukemia	7 (14 %)	8 (16 %)	5 (10 %)	13 (26 %)	↑ ↑	
pituitary	<50>	<50>	<50>	<50>		
adenoma	15 (30 %)	16 (32 %)	14 (28 %)	5 (10 %) *		↓ ↓

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 RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control				10 ppm				30 ppm				90 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>			
squamous cell metaplasia :respiratory epithelium	0	0	0	0	1	1	0	0	4	6	0	0 **	4	38	0	0 **
squamous cell hyperplasia with atypia	0	0	0	0	0	0	0	0	1	0	0	0	1	30	1	0 **
inflammation:respiratory epithelium	0	0	0	0	1	1	0	0	0	2	0	0	4	17	1	0 **
hyperplasia:transitional epithelium	0	0	0	0	0	0	0	0	5	3	0	0 *	0	0	0	0
hyperplasia with atypia :respiratory epithelium	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
atrophy:olfactory epithelium	0	0	0	0	0	1	0	0	7	2	0	0 **	10	14	0	0 **
respiratory metaplasia:olfactory epithelium	3	0	0	0	0	1	0	0	4	1	0	0	2	6	0	0 *
squamous cell metaplasia :olfactory epithelium	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0
hyperplasia:submucosal gland	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0
eosinophilic change:olfactory epithelium	18	23	1	0	20	20	1	0	11	22	1	0	9	6	0	0 **
inflammation:foreign body	7	17	0	0	8	15	0	0	6	23	0	0	2	7	0	0 **
lung	<50>				<50>				<50>				<50>			
inflammation:foreign body	0	0	0	0	0	0	0	0	0	0	0	0	1	8	0	0 **
metastasis:nasal tumor	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
bone marrow	<50>				<50>				<50>				<50>			
increased hematopoiesis	4	0	0	0	5	0	0	0	5	0	0	0	14	0	0	0 *
lymph node	<50>				<50>				<50>				<50>			
metastasis:nasal tumor	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0
spleen	<50>				<50>				<50>				<50>			
congestion	0	6	0	0	1	3	0	0	1	3	0	0	0	0	0	0 *
heart	<50>				<50>				<50>				<50>			
myocardial fibrosis	14	36	0	0	15	31	0	0	22	27	0	0	24	21	0	0 **
stomach	<50>				<50>				<50>				<50>			
hyperplasia:forestomach	0	4	0	0	2	3	0	0	1	2	0	0	3	0	0	0 *
erosion:glandular stomach	7	1	0	0	1	0	0	0 *	3	0	0	0	8	1	0	0
liver	<50>				<50>				<50>				<50>			
clear cell focus	7	4	0	0	5	8	0	0	3	5	0	0	1	1	0	0 *
kidney	<50>				<50>				<50>				<50>			
chronic nephropathy	16	26	2	0	12	31	2	0	14	25	2	0	18	1	0	0 **

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

Group Name	Control				10 ppm				30 ppm				90 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	
testis	<50>				<50>				<50>				<50>				
atrophy	0	3	44	0	0	1	47	0	2	2	43	0	10	6	24	0	**
interstitial cell hyperplasia	0	1	0	0	6	0	0	0	*	4	0	0	0	10	0	0	0	**
prostate	<50>				<50>				<50>				<50>				
hyperplasia	7	1	0	0	9	0	0	0	8	0	0	0	1	0	0	0	*
brain	<50>				<50>				<50>				<50>				
metastasis:nasal tumor	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	
eye	<50>				<50>				<50>				<50>				
retinal atrophy	32	0	8	0	36	0	5	0	40	0	5	0	18	0	2	0	**
keratitis	3	0	0	0	3	0	0	0	0	0	0	0	10	13	3	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 RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

Group Name	Control				10 ppm				30 ppm				90 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>			
squamous cell metaplasia :respiratory epithelium	0	0	0	0	1	0	0	0	6	0	0	0 *	2	41	0	0 **
squamous cell hyperplasia with atypia	0	0	0	0	0	0	0	0	0	0	0	0	9	30	0	0 **
inflammation:respiratory epithelium	0	0	0	0	0	0	0	0	2	0	0	0	8	23	1	0 **
hyperplasia:transitional epithelium	0	0	0	0	0	0	0	0	6	0	0	0 *	0	0	0	0
atrophy:olfactory epithelium	0	0	0	0	0	0	0	0	1	0	0	0	21	8	0	0 **
respiratory metaplasia:olfactory epithelium	0	0	0	0	0	0	0	0	1	0	0	0	5	0	0	0
squamous cell metaplasia :olfactory epithelium	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0 **
eosinophilic change:respiratory epithelium	22	5	0	0	20	6	0	0	11	2	0	0 *	1	0	0	0 **
eosinophilic change:olfactory epithelium	1	35	13	0	2	46	2	0 *	3	46	1	0 **	10	25	0	0 **
lung	<50>				<50>				<50>				<50>			
inflammation:foreign body	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0
liver	<50>				<50>				<50>				<50>			
granulation	12	7	2	0	14	8	6	0	13	8	3	0	4	1	1	0 **
basophilic cell focus	14	8	0	0	7	9	0	0	4	7	0	0 *	3	2	0	0 **
kidney	<50>				<50>				<50>				<50>			
chronic nephropathy	9	4	0	0	18	3	1	0	16	4	2	0	1	0	0	0 **
brain	<50>				<50>				<50>				<50>			
metastasis:nasal tumor	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
eye	<50>				<50>				<50>				<50>			
keratitis	1	1	0	0	0	0	0	0	1	0	0	0	10	12	1	2 **
Harderian gland	<50>				<50>				<50>				<50>			
metastasis:nasal tumor	0	0	0	0	0	0	0	0	0	0	0	0	1	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 17 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. (%)
Nasal cavity	1849			
Squamous cell papilloma		0	0	0 - 0
Adenoma		2	0.1	0 - 2
Squamous cell carcinoma		0	0	0 - 0
Ethesioneuroepithelioma		0	0	0 - 0

37 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, 0417, 0421

TABLE 18 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. (%)
Nasal cavity	1697			
Adenoma		0	0	0 - 0
Squamous cell carcinoma		0	0	0 - 0
Sarcoma NOS		0	0	0 - 0
Adenosquamous carcinoma		0	0	0 - 0
Ethesioneuroepithelioma		0	0	0 - 0
Spleen	1697			
Mononuclear cell leukemia		222	13.1	2 - 26

34 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, 0417, 0421

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

	Male				Female			
Group name	Control	10 ppm	30 ppm	90 ppm	Control	10 ppm	30 ppm	90 ppm
Number of dead or moribund animals	12	12	12	39	10	5	9	35
No microscopical confirmation	3	0	1	1	2	0	0	1
Respiratory system lesion	0	0	0	1	0	0	0	4
Cardiovascular lesion	1	0	0	0	0	0	0	0
Central nervous system lesion	0	0	1	0	0	0	0	0
Urinary retention	0	0	1	0	0	0	0	0
Tumor death : leukemia	3	4	3	4	2	1	1	3
subcutis	2	1	1	0	0	0	0	0
skin/appendage	0	0	0	0	1	0	0	0
nasal cavity	0	0	0	28	0	0	0	24
spleen	0	1	0	0	0	0	0	0
large intestine	0	0	0	0	0	0	1	0
pituitary gland	1	3	1	1	3	2	4	0
thyroid	1	0	0	1	0	0	0	0
adrenal gland	1	1	0	1	0	0	0	0
uterus	—	—	—	—	0	1	2	3
mammary gland	0	0	0	0	0	1	0	0
preputial/clitoral gland	0	0	0	1	0	0	0	0
brain	0	1	1	0	0	0	0	0
spinal cord	0	0	0	0	1	0	0	0
peripheral nerves	0	0	2	0	0	0	0	0
Zymbal gland	0	1	0	0	0	0	1	0
vertebra	0	0	0	0	1	0	0	0
mediastinum	0	0	0	1	0	0	0	0
retroperitoneum	0	0	1	0	0	0	0	0

FIGURES

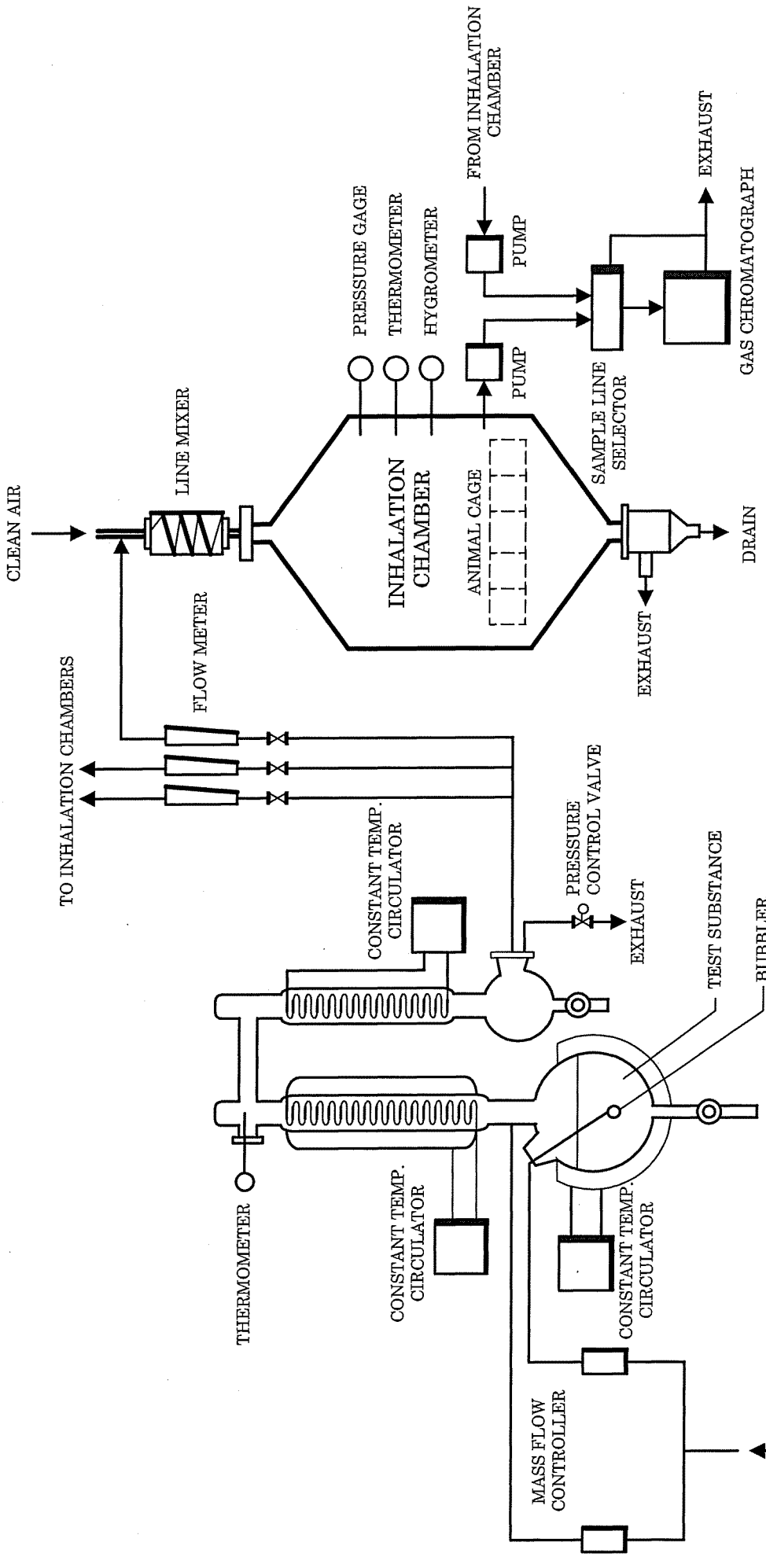


FIGURE 1 BUTYL 2,3-EPOXYPROPYL ETHER VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

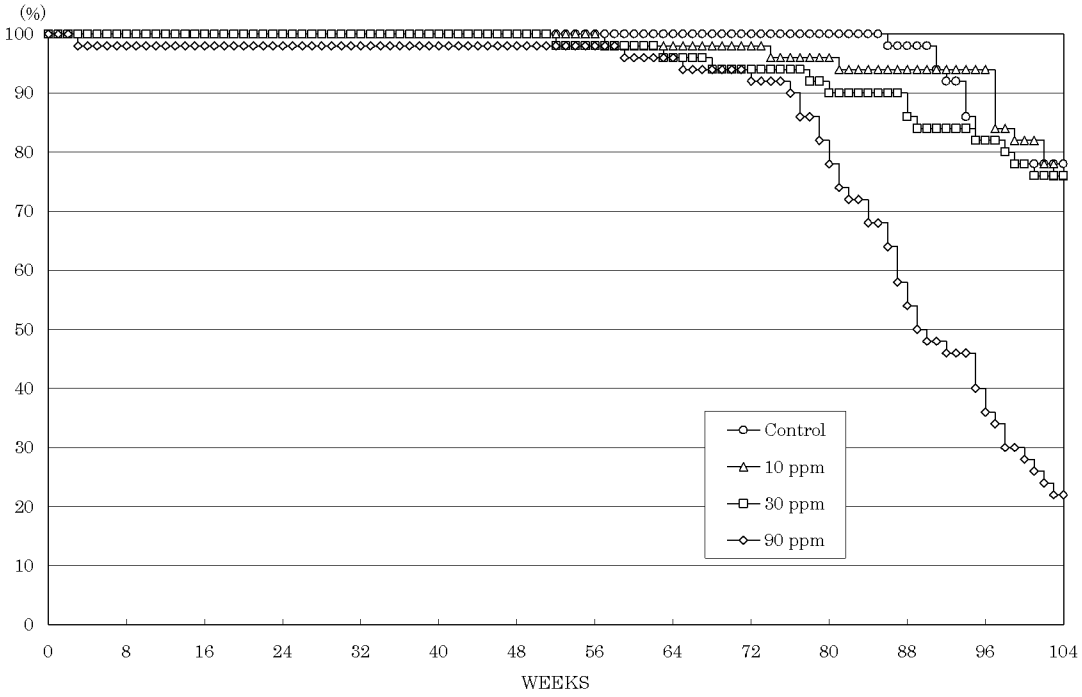


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

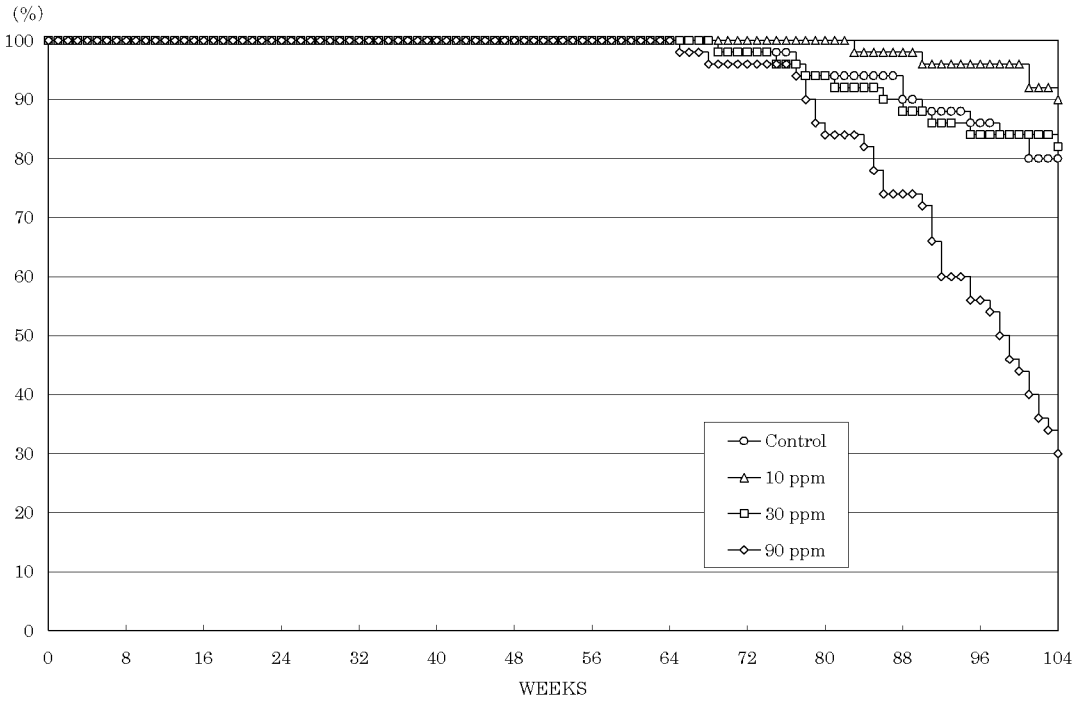


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

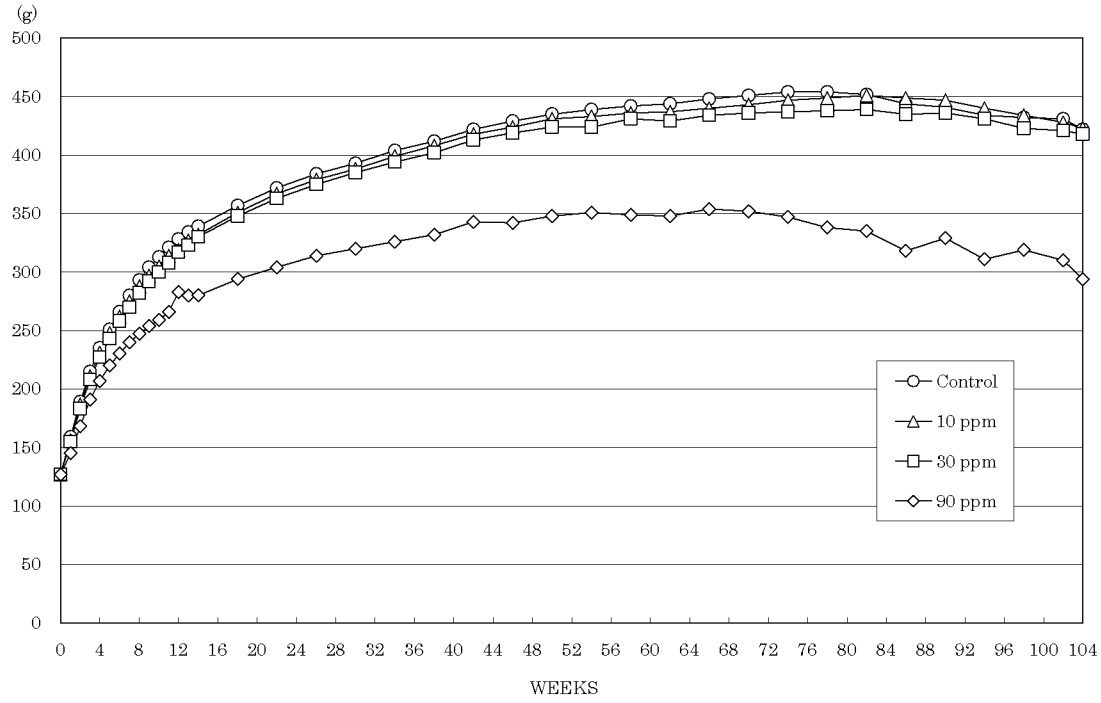


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

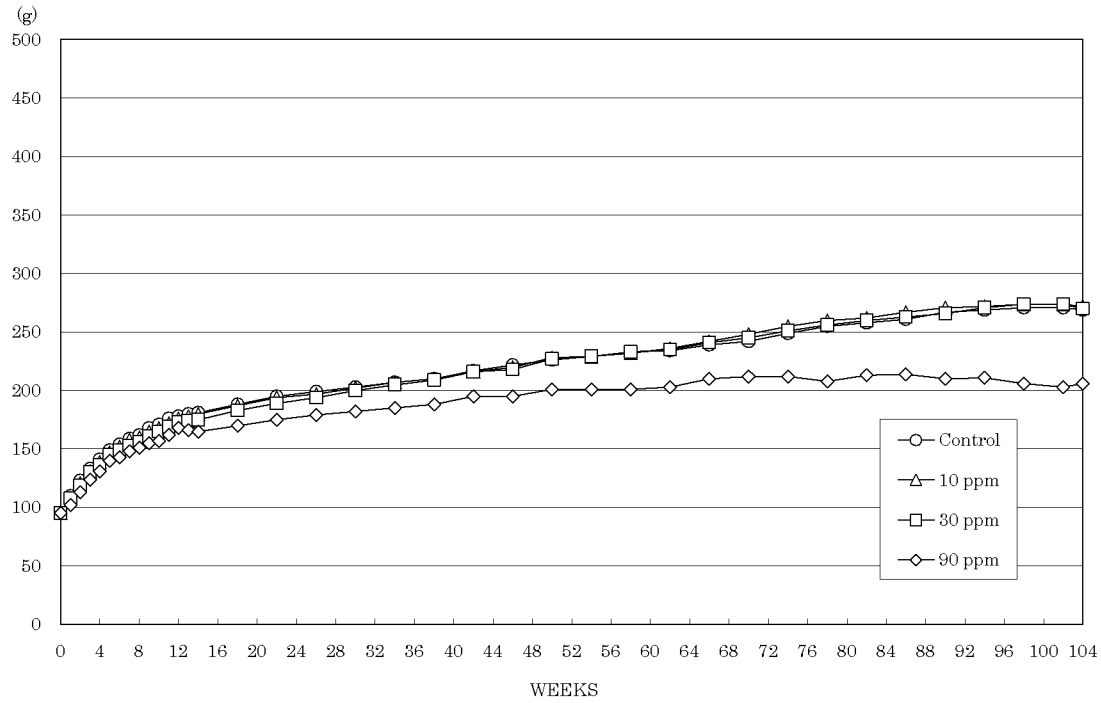


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

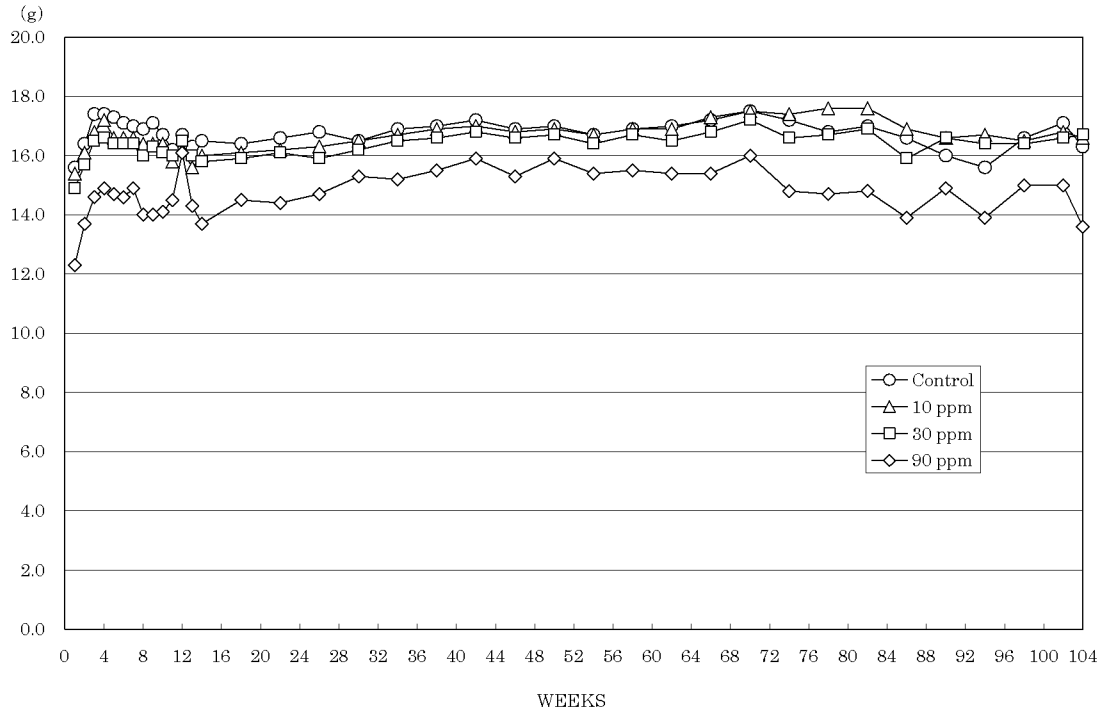


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER

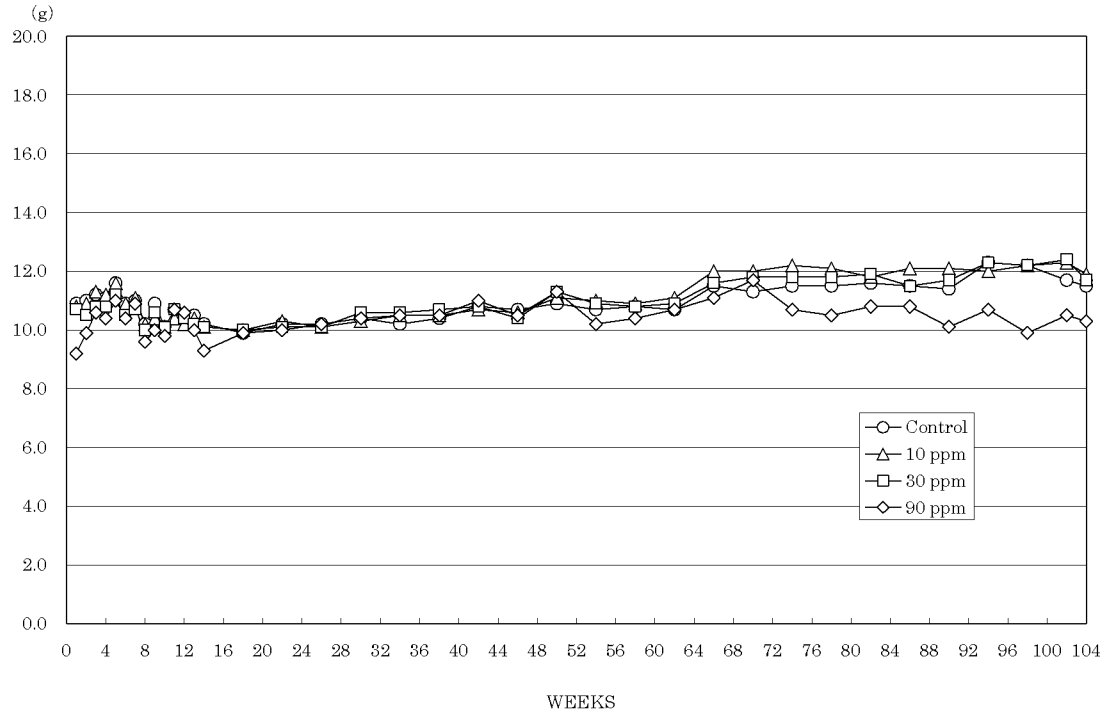
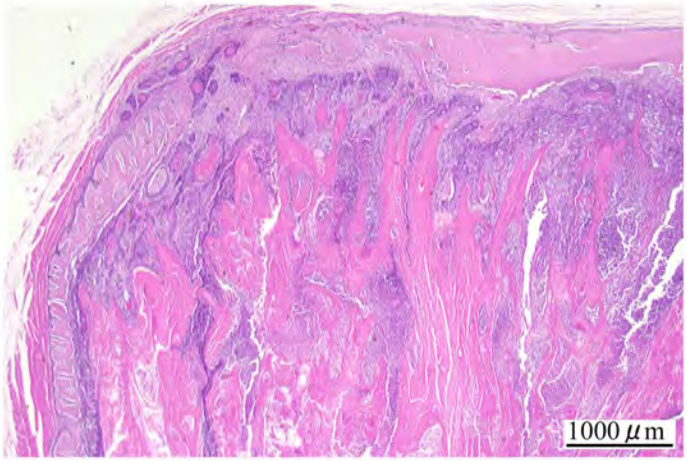
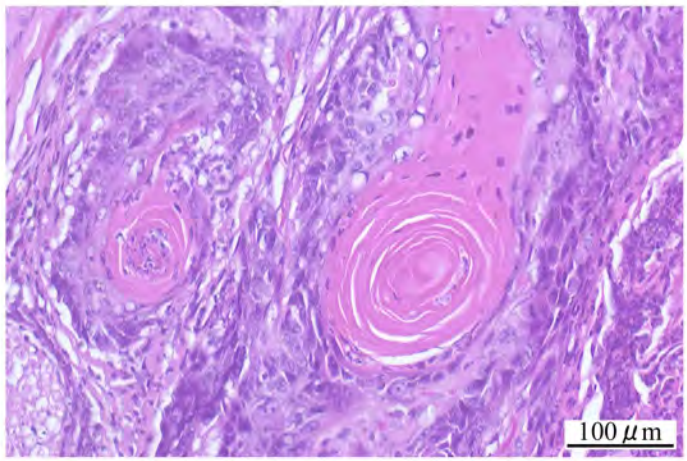


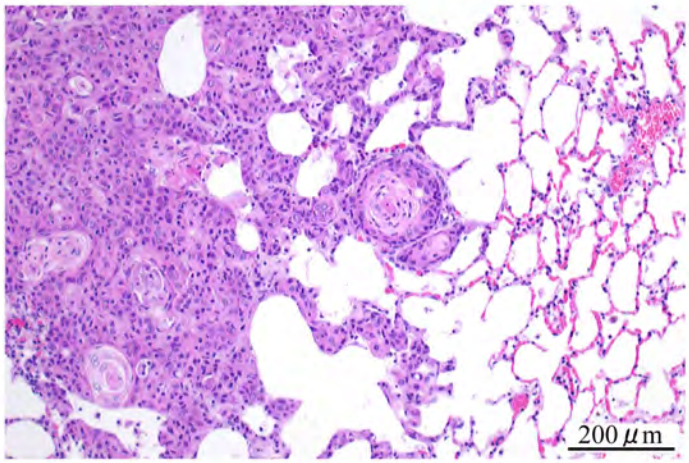
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF BUTYL 2,3-EPOXYPROPYL ETHER



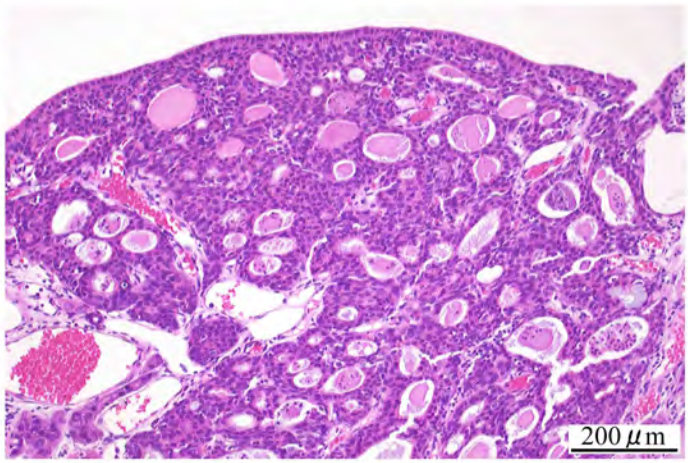
Photograph 1
Nasal cavity: Squamous cell carcinoma
Rat, Male, 90 ppm, Animal No. 0437-1322 (H&E)



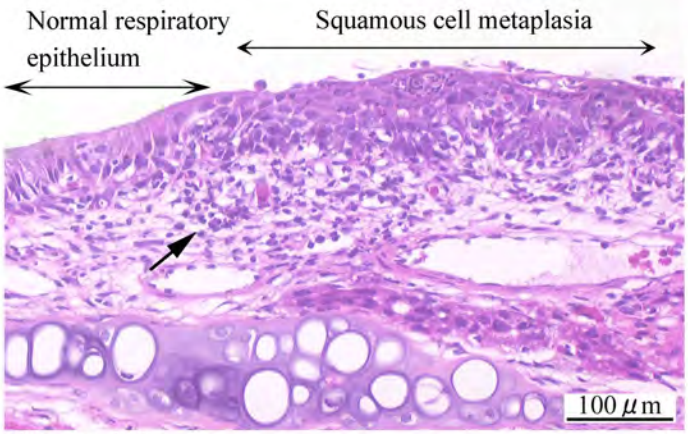
Photograph 2
Nasal cavity: Squamous cell carcinoma
Higher magnification of photograph 1.
Rat, Male, 90 ppm, Animal No. 0437-1322 (H&E)



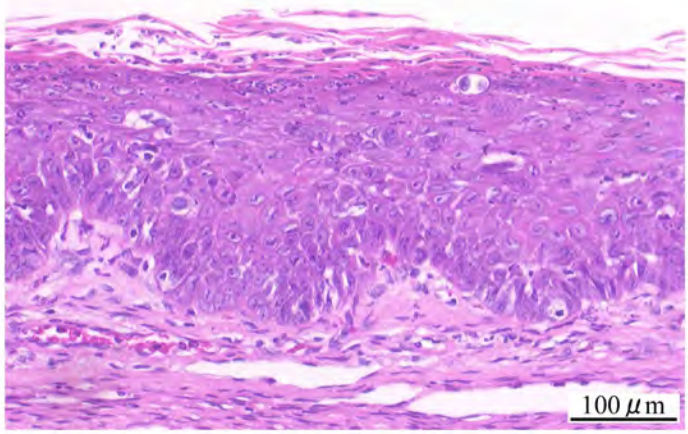
Photograph 3
Lung: Metastasis of nasal cavity tumor
(squamous cell carcinoma)
Rat, Male, 90 ppm, Animal No. 0437-1301 (H&E)



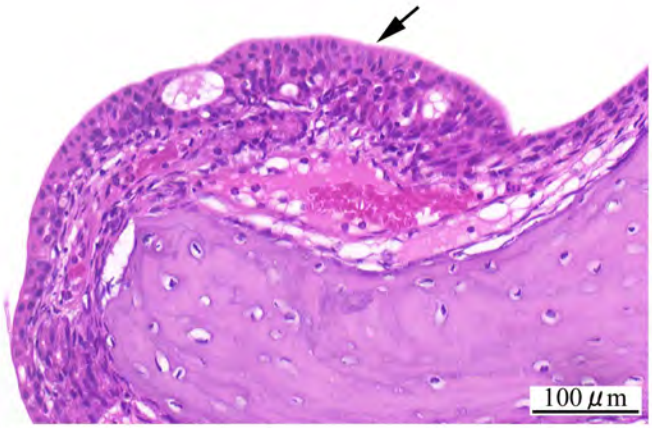
Photograph 4
Nasal cavity: Adenoma
Rat, Male, 30 ppm, Animal No. 0437-1210 (H&E)



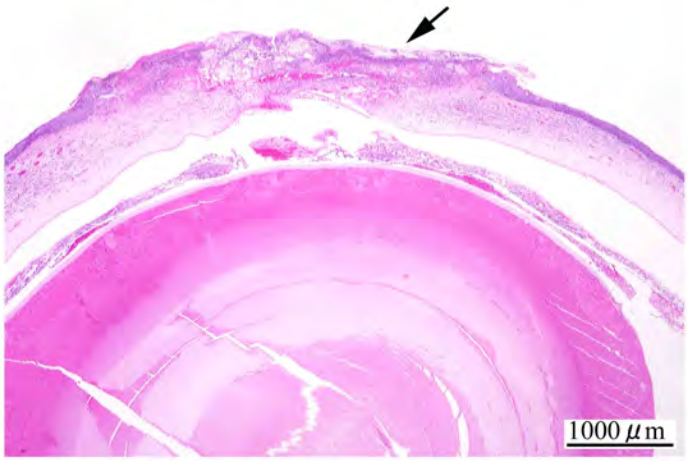
Photograph 5
Nasal cavity (respiratory epithelium): Squamous cell metaplasia and inflammation (Arrow)
Rat, Male, 90 ppm, Animal No. 0437-1336 (H&E)



Photograph 6
Nasal cavity (respiratory epithelium): Squamous cell metaplasia with hyperplasia
Rat, Male, 90 ppm, Animal No. 0437-1307 (H&E)



Photograph 7
Nasal cavity (transitional epithelium): Hyperplasia (Arrow)
Rat, Male, 30 ppm, Animal No. 0437-1246 (H&E)



Photograph 8
Eye: Keratitis (Arrow)
Rat, Male, 90 ppm, Animal No. 0437-1343 (H&E)