

Summary of Drinking Water Carcinogenicity Study
of 2-Phenoxyethanol
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 June 26, 2007.

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Summary of Drinking Water Carcinogenicity Study of 2-Phenoxyethanol in F344 Rats

Purpose, materials and methods

2-Phenoxyethanol (CAS No. 122-99-6) is a colorless clear liquid with a melting point of 10-12°C and a boiling point of 244.7°C, and is soluble in water (2.7 wt%).

The carcinogenicity and chronic toxicity of 2-phenoxyethanol were examined in groups of 50 F344/DuCrIj rats of both sexes administered 2-phenoxyethanol in drinking water for 2 years (104 weeks). The drinking water concentration of 2-phenoxyethanol was 0, 2500, 5000 or 10000 ppm (w/w). 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. 2-Phenoxyethanol was analyzed for purity and stability by both infrared spectrometry and high performance liquid chromatography before and after its use. The concentrations of 2-phenoxyethanol in drinking water were determined by high performance liquid chromatography at the time of preparation, and on the 5th day after preparation, while stored at room temperature. The animals were observed daily for clinical signs and mortality. Body weight, water consumption 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 administration period underwent complete necropsy. Urinalysis was performed near the end of the administration 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 dose-response relationship 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, water consumption, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were 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

There was no significant difference in survival rate between any 2-phenoxyethanol-administered group of either sex and the respective control. Soiled fur around genitalia was observed in the 10000 ppm-administered males and in all the 2-phenoxyethanol-administered female groups. Growth rates of the 10000 ppm-administered males and all the 2-phenoxyethanol-administered female groups were suppressed, as compared with the respective controls. Terminal body weights of the 2500, 5000 and 10000 ppm-administered groups were 98%, 98% and 94% for males, and 95%, 96% and 89% for females, as compared with the respective controls. Food consumption was decreased in the 10000 ppm-administered males and in all the 2-phenoxyethanol-administered female groups during the 2-year administration period as compared with the respective controls. Water consumption was decreased in the 5000 and 10000 ppm-administered males and in all the 2-phenoxyethanol-administered female groups during the early half of the 2-year administration period as compared with the respective controls.

No significant increase in the incidence of neoplastic lesions was found in any 2-phenoxyethanol-administered group of either sex as compared with the respective control. Slight changes in MCV and MCHC were noted in the 10000 ppm-administered females. Plasma levels of AST and ALT were increased in the 10000 ppm-administered males, but no corresponding histopathological changes in the liver were found. Total protein and creatinine were slightly decreased in the 10000 ppm-administered males. Blood urea nitrogen was slightly increased, and total bilirubin and triglyceride were slightly decreased in the 10000 ppm-administered females. Lowered urinary pH and decreases in urinary protein and the incidence of positive ketone body in urine were noted in the 10000 ppm-administered females. The lowered urinary pH might be caused by phenoxyacetic acid, a urinary metabolite of 2-phenoxyethanol. The increased kidney weight and the increased incidences of urothelial hyperplasia of the pelvis, and papillary mineralization and necrosis were noted in the 10000 ppm-administered males, while the increased kidney weight was observed in the 10000 ppm-administered females.

Conclusions

In rats, there was no evidence of carcinogenic activity of 2-phenoxyethanol in males or females.

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TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. Wt. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.
0	126 (50)	50 / 50	126 (50)	100	50 / 50	126 (50)	100	50 / 50	126 (50)	100	50 / 50
1	157 (50)	50 / 50	156 (50)	99	50 / 50	155 (50)	99	50 / 50	150 (50)	96	50 / 50
2	187 (50)	50 / 50	185 (50)	99	50 / 50	184 (50)	98	50 / 50	176 (50)	94	50 / 50
3	214 (50)	50 / 50	209 (50)	98	50 / 50	209 (50)	98	50 / 50	200 (50)	93	50 / 50
4	235 (50)	50 / 50	228 (50)	97	50 / 50	228 (50)	97	50 / 50	218 (50)	93	50 / 50
5	249 (50)	50 / 50	243 (50)	98	50 / 50	243 (50)	98	50 / 50	233 (50)	94	50 / 50
6	261 (50)	50 / 50	254 (50)	97	50 / 50	256 (50)	98	50 / 50	246 (50)	94	50 / 50
7	274 (50)	50 / 50	267 (50)	97	50 / 50	269 (50)	98	50 / 50	257 (50)	94	50 / 50
8	283 (50)	50 / 50	275 (50)	97	50 / 50	279 (50)	99	50 / 50	265 (50)	94	50 / 50
9	292 (50)	50 / 50	286 (50)	98	50 / 50	289 (50)	99	50 / 50	274 (50)	94	50 / 50
10	299 (50)	50 / 50	293 (50)	98	50 / 50	296 (50)	99	50 / 50	279 (50)	93	50 / 50
11	305 (50)	50 / 50	300 (50)	98	50 / 50	303 (50)	99	50 / 50	288 (50)	94	50 / 50
12	313 (50)	50 / 50	307 (50)	98	50 / 50	309 (50)	99	50 / 50	293 (50)	94	50 / 50
13	319 (50)	50 / 50	313 (50)	98	50 / 50	316 (50)	99	50 / 50	299 (50)	94	50 / 50
17	334 (50)	50 / 50	328 (50)	98	50 / 50	332 (50)	99	50 / 50	314 (50)	94	50 / 50
21	350 (50)	50 / 50	345 (50)	99	50 / 50	349 (50)	100	50 / 50	328 (50)	94	50 / 50
25	357 (50)	50 / 50	354 (50)	99	50 / 50	356 (50)	100	50 / 50	336 (50)	94	50 / 50
29	367 (50)	50 / 50	365 (50)	99	50 / 50	368 (50)	100	50 / 50	348 (50)	95	50 / 50
33	374 (50)	50 / 50	373 (50)	100	50 / 50	376 (50)	101	50 / 50	353 (50)	94	50 / 50
37	381 (50)	50 / 50	379 (50)	99	50 / 50	385 (50)	101	50 / 50	362 (50)	95	50 / 50
41	385 (50)	50 / 50	384 (50)	100	50 / 50	388 (50)	101	50 / 50	366 (50)	95	50 / 50
45	396 (50)	50 / 50	392 (50)	99	50 / 50	396 (50)	100	50 / 50	374 (50)	94	50 / 50
49	398 (50)	50 / 50	396 (50)	99	50 / 50	401 (50)	101	50 / 50	378 (50)	95	50 / 50
53	406 (50)	50 / 50	402 (50)	99	50 / 50	408 (50)	100	50 / 50	384 (50)	95	50 / 50
57	411 (50)	50 / 50	409 (49)	100	49 / 50	413 (50)	100	50 / 50	390 (50)	95	50 / 50
61	416 (50)	50 / 50	417 (48)	100	48 / 50	420 (50)	101	50 / 50	397 (50)	95	50 / 50
65	423 (50)	50 / 50	423 (48)	100	48 / 50	424 (50)	100	50 / 50	403 (50)	95	50 / 50
69	423 (50)	50 / 50	425 (48)	100	48 / 50	424 (50)	100	50 / 50	404 (49)	96	49 / 50
73	426 (49)	49 / 50	427 (47)	100	47 / 50	428 (49)	100	49 / 50	406 (49)	95	49 / 50
77	429 (49)	49 / 50	432 (47)	101	47 / 50	429 (49)	100	49 / 50	410 (49)	96	49 / 50
78	429 (49)	49 / 50	431 (47)	100	47 / 50	429 (49)	100	49 / 50	409 (49)	95	49 / 50
82	429 (47)	47 / 50	431 (47)	100	47 / 50	428 (49)	100	49 / 50	409 (49)	95	49 / 50
86	419 (43)	43 / 50	431 (45)	103	45 / 50	425 (49)	101	49 / 50	411 (48)	98	48 / 50
90	420 (41)	41 / 50	428 (45)	102	45 / 50	426 (48)	101	48 / 50	407 (48)	97	48 / 50
94	422 (40)	40 / 50	424 (44)	100	44 / 50	421 (48)	100	48 / 50	399 (48)	95	48 / 50
98	423 (38)	38 / 50	418 (44)	99	44 / 50	420 (47)	99	47 / 50	398 (44)	94	44 / 50
102	419 (36)	36 / 50	412 (39)	98	39 / 50	411 (45)	98	45 / 50	397 (40)	95	40 / 50
104	415 (36)	36 / 50	408 (37)	98	37 / 50	405 (45)	98	45 / 50	389 (40)	94	40 / 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 DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. Wt. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.
0	99 (50)	50 / 50	99 (50)	100	50 / 50	99 (50)	100	50 / 50	99 (50)	100	50 / 50
1	115 (50)	50 / 50	114 (50)	99	50 / 50	114 (50)	99	50 / 50	111 (50)	97	50 / 50
2	129 (50)	50 / 50	126 (50)	98	50 / 50	124 (50)	96	50 / 50	122 (50)	95	50 / 50
3	137 (50)	50 / 50	133 (50)	97	50 / 50	132 (50)	96	50 / 50	129 (50)	94	50 / 50
4	144 (50)	50 / 50	140 (50)	97	50 / 50	138 (50)	96	50 / 50	135 (50)	94	50 / 50
5	151 (50)	50 / 50	145 (50)	96	50 / 50	143 (50)	95	50 / 50	140 (50)	93	50 / 50
6	155 (50)	50 / 50	149 (50)	96	50 / 50	147 (50)	95	50 / 50	144 (50)	93	50 / 50
7	158 (50)	50 / 50	152 (50)	96	50 / 50	151 (50)	96	50 / 50	147 (50)	93	50 / 50
8	162 (50)	50 / 50	154 (50)	95	50 / 50	154 (50)	95	50 / 50	148 (50)	91	50 / 50
9	166 (50)	50 / 50	159 (50)	96	50 / 50	158 (50)	95	50 / 50	152 (50)	92	50 / 50
10	168 (50)	50 / 50	161 (50)	96	50 / 50	161 (50)	96	50 / 50	154 (50)	92	50 / 50
11	171 (50)	50 / 50	164 (50)	96	50 / 50	164 (50)	96	50 / 50	157 (50)	92	50 / 50
12	174 (50)	50 / 50	168 (50)	97	50 / 50	168 (50)	97	50 / 50	160 (50)	92	50 / 50
13	177 (50)	50 / 50	170 (50)	96	50 / 50	169 (50)	95	50 / 50	162 (50)	92	50 / 50
17	183 (50)	50 / 50	175 (50)	96	50 / 50	174 (50)	95	50 / 50	166 (50)	91	50 / 50
21	188 (50)	50 / 50	180 (50)	96	50 / 50	180 (50)	96	50 / 50	170 (50)	90	50 / 50
25	193 (49)	49 / 50	183 (50)	95	50 / 50	184 (50)	95	50 / 50	174 (50)	90	50 / 50
29	199 (49)	49 / 50	190 (50)	95	50 / 50	190 (50)	95	50 / 50	180 (50)	90	50 / 50
33	203 (49)	49 / 50	194 (50)	96	50 / 50	194 (50)	96	50 / 50	183 (50)	90	50 / 50
37	206 (49)	49 / 50	196 (50)	95	50 / 50	196 (50)	95	50 / 50	185 (50)	90	50 / 50
41	211 (49)	49 / 50	201 (50)	95	50 / 50	200 (50)	95	50 / 50	190 (50)	90	50 / 50
45	216 (49)	49 / 50	205 (50)	95	50 / 50	204 (50)	94	50 / 50	193 (50)	89	50 / 50
49	219 (49)	49 / 50	208 (50)	95	50 / 50	208 (50)	95	50 / 50	196 (50)	89	50 / 50
53	224 (49)	49 / 50	213 (50)	95	50 / 50	213 (50)	95	50 / 50	200 (50)	89	50 / 50
57	229 (49)	49 / 50	217 (50)	95	50 / 50	219 (50)	96	50 / 50	205 (50)	90	50 / 50
61	233 (49)	49 / 50	221 (50)	95	50 / 50	223 (50)	96	50 / 50	209 (50)	90	50 / 50
65	241 (49)	49 / 50	228 (50)	95	50 / 50	230 (50)	95	50 / 50	214 (50)	89	50 / 50
69	244 (48)	48 / 50	231 (50)	95	50 / 50	233 (50)	95	50 / 50	216 (50)	89	50 / 50
73	252 (46)	46 / 50	237 (50)	94	50 / 50	239 (50)	95	50 / 50	220 (50)	87	50 / 50
77	257 (45)	45 / 50	241 (48)	94	48 / 50	244 (49)	95	49 / 50	224 (50)	87	50 / 50
78	258 (45)	45 / 50	243 (48)	94	48 / 50	245 (49)	95	49 / 50	225 (50)	87	50 / 50
82	265 (45)	45 / 50	249 (48)	94	48 / 50	250 (48)	94	48 / 50	231 (49)	87	49 / 50
86	271 (45)	45 / 50	255 (48)	94	48 / 50	256 (47)	94	47 / 50	236 (49)	87	49 / 50
90	270 (44)	44 / 50	257 (48)	95	48 / 50	256 (47)	95	47 / 50	238 (48)	88	48 / 50
94	275 (42)	42 / 50	257 (46)	93	46 / 50	260 (46)	95	46 / 50	241 (48)	88	48 / 50
98	277 (42)	42 / 50	261 (45)	94	45 / 50	262 (44)	95	44 / 50	239 (48)	86	48 / 50
102	276 (40)	40 / 50	260 (42)	94	42 / 50	263 (40)	95	40 / 50	240 (44)	87	44 / 50
104	273 (39)	39 / 50	260 (40)	95	40 / 50	261 (38)	96	38 / 50	243 (41)	89	41 / 50

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

TABLE 3 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. FC. <50>	No. of Surviv.	Av. FC. <50>	% of cont. <50>	No. of Surviv.	Av. FC. <50>	% of cont. <50>	No. of Surviv.	Av. FC. <50>	% of cont. <50>	No. of Surviv.
1	13.8 (50)	50 / 50	13.9 (50)	101	50 / 50	13.6 (50)	99	50 / 50	12.6 (50)	91	50 / 50
2	15.2 (49)	50 / 50	15.3 (50)	101	50 / 50	14.9 (50)	98	50 / 50	13.9 (50)	91	50 / 50
3	- (-)	50 / 50	15.8 (25)	-	50 / 50	15.2 (50)	-	50 / 50	14.6 (50)	-	50 / 50
4	16.2 (50)	50 / 50	15.7 (50)	97	50 / 50	15.6 (50)	96	50 / 50	15.0 (50)	93	50 / 50
5	15.8 (50)	50 / 50	15.6 (50)	99	50 / 50	15.5 (50)	98	50 / 50	14.8 (50)	94	50 / 50
6	15.4 (50)	50 / 50	15.2 (50)	99	50 / 50	15.4 (50)	100	50 / 50	14.6 (50)	95	50 / 50
7	15.4 (50)	50 / 50	15.1 (50)	98	50 / 50	15.4 (50)	100	50 / 50	14.6 (50)	95	50 / 50
8	15.4 (46)	50 / 50	15.1 (41)	98	50 / 50	15.3 (47)	99	50 / 50	14.5 (48)	94	50 / 50
9	15.4 (50)	50 / 50	15.4 (50)	100	50 / 50	15.4 (50)	100	50 / 50	14.3 (50)	93	50 / 50
10	15.1 (50)	50 / 50	14.9 (50)	99	50 / 50	15.1 (50)	100	50 / 50	14.3 (50)	95	50 / 50
11	14.9 (50)	50 / 50	15.0 (50)	101	50 / 50	15.2 (50)	102	50 / 50	14.5 (50)	97	50 / 50
12	14.8 (50)	50 / 50	14.8 (50)	100	50 / 50	14.8 (50)	100	50 / 50	14.3 (50)	97	50 / 50
13	14.7 (50)	50 / 50	14.7 (50)	100	50 / 50	14.8 (50)	101	50 / 50	14.3 (50)	97	50 / 50
17	14.6 (50)	50 / 50	14.6 (50)	100	50 / 50	14.7 (50)	101	50 / 50	14.0 (50)	96	50 / 50
21	15.1 (50)	50 / 50	14.9 (50)	99	50 / 50	15.1 (50)	100	50 / 50	14.4 (50)	95	50 / 50
25	15.9 (50)	50 / 50	15.7 (50)	99	50 / 50	15.9 (50)	100	50 / 50	15.3 (50)	96	50 / 50
29	15.2 (50)	50 / 50	15.3 (50)	101	50 / 50	15.5 (50)	102	50 / 50	14.8 (50)	97	50 / 50
33	15.4 (50)	50 / 50	15.4 (50)	100	50 / 50	15.6 (50)	101	50 / 50	14.7 (50)	95	50 / 50
37	14.9 (50)	50 / 50	15.0 (50)	101	50 / 50	15.3 (50)	103	50 / 50	14.5 (50)	97	50 / 50
41	14.8 (50)	50 / 50	14.9 (50)	101	50 / 50	15.1 (50)	102	50 / 50	14.4 (50)	97	50 / 50
45	15.3 (50)	50 / 50	15.2 (50)	99	50 / 50	15.2 (50)	99	50 / 50	14.8 (50)	97	50 / 50
49	15.5 (50)	50 / 50	15.6 (49)	101	50 / 50	15.9 (50)	103	50 / 50	15.4 (50)	99	50 / 50
53	15.7 (50)	50 / 50	15.7 (50)	100	50 / 50	15.9 (49)	101	50 / 50	15.4 (50)	98	50 / 50
57	16.1 (50)	50 / 50	16.3 (49)	101	49 / 50	16.4 (50)	102	50 / 50	16.1 (50)	100	50 / 50
61	15.9 (50)	50 / 50	16.3 (48)	103	48 / 50	16.1 (50)	101	50 / 50	15.9 (50)	100	50 / 50
65	16.1 (50)	50 / 50	16.4 (48)	102	48 / 50	16.2 (50)	101	50 / 50	16.1 (50)	100	50 / 50
69	15.9 (50)	50 / 50	16.5 (48)	104	48 / 50	16.3 (50)	103	50 / 50	16.0 (49)	101	49 / 50
73	15.9 (49)	49 / 50	16.2 (47)	102	47 / 50	16.1 (49)	101	49 / 50	15.8 (49)	99	49 / 50
77	16.1 (49)	49 / 50	16.6 (47)	103	47 / 50	16.2 (49)	101	49 / 50	16.0 (49)	99	49 / 50
78	16.1 (49)	49 / 50	16.4 (47)	102	47 / 50	16.1 (49)	100	49 / 50	15.7 (49)	98	49 / 50
82	15.4 (46)	47 / 50	15.8 (47)	103	47 / 50	16.0 (49)	104	49 / 50	15.2 (49)	99	49 / 50
86	15.5 (43)	43 / 50	16.4 (45)	106	45 / 50	16.2 (49)	105	49 / 50	16.0 (48)	103	48 / 50
90	15.8 (41)	41 / 50	16.3 (45)	103	45 / 50	16.1 (48)	102	48 / 50	15.4 (48)	97	48 / 50
94	16.1 (40)	40 / 50	16.3 (44)	101	44 / 50	16.0 (48)	99	48 / 50	15.4 (48)	96	48 / 50
98	16.1 (38)	38 / 50	16.1 (44)	100	44 / 50	16.0 (47)	99	47 / 50	15.2 (44)	94	44 / 50
102	16.2 (36)	36 / 50	16.2 (39)	100	39 / 50	15.7 (45)	97	45 / 50	15.4 (40)	95	40 / 50
104	16.2 (36)	36 / 50	16.2 (37)	100	37 / 50	15.7 (45)	97	45 / 50	15.3 (40)	94	40 / 50

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

Note: Average food consumption on 3 week could not be calculated, because the remained food has been lost.

TABLE 4 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. FC. <50>	No. of Surviv.	Av. FC.	% of cont. <50>	No. of Surviv.	Av. FC.	% of cont. <50>	No. of Surviv.	Av. FC.	% of cont. <50>	No. of Surviv.
1	10.4 (50)	50 / 50	10.5 (50)	101	50 / 50	10.3 (50)	99	50 / 50	9.6 (50)	92	50 / 50
2	10.9 (50)	50 / 50	10.6 (50)	97	50 / 50	10.2 (50)	94	50 / 50	10.0 (50)	92	50 / 50
3	11.1 (50)	50 / 50	10.5 (50)	95	50 / 50	10.2 (50)	92	50 / 50	9.8 (50)	88	50 / 50
4	10.8 (50)	50 / 50	10.5 (50)	97	50 / 50	10.2 (50)	94	50 / 50	9.8 (50)	91	50 / 50
5	10.7 (50)	50 / 50	10.2 (50)	95	50 / 50	10.2 (50)	95	50 / 50	9.8 (50)	92	50 / 50
6	10.4 (50)	50 / 50	10.0 (50)	96	50 / 50	9.9 (50)	95	50 / 50	9.5 (50)	91	50 / 50
7	10.2 (50)	50 / 50	9.7 (50)	95	50 / 50	9.8 (50)	96	50 / 50	9.4 (50)	92	50 / 50
8	10.1 (50)	50 / 50	9.5 (50)	94	50 / 50	9.5 (50)	94	50 / 50	9.1 (50)	90	50 / 50
9	10.2 (50)	50 / 50	9.7 (50)	95	50 / 50	9.7 (50)	95	50 / 50	9.1 (50)	89	50 / 50
10	9.9 (50)	50 / 50	9.6 (50)	97	50 / 50	9.6 (50)	97	50 / 50	9.0 (50)	91	50 / 50
11	10.1 (50)	50 / 50	9.9 (50)	98	50 / 50	9.9 (50)	98	50 / 50	9.3 (50)	92	50 / 50
12	10.2 (50)	50 / 50	9.7 (50)	95	50 / 50	9.9 (50)	97	50 / 50	9.2 (50)	90	50 / 50
13	10.1 (50)	50 / 50	9.7 (50)	96	50 / 50	9.8 (50)	97	50 / 50	9.4 (50)	93	50 / 50
17	10.4 (50)	50 / 50	10.0 (50)	96	50 / 50	10.0 (50)	96	50 / 50	9.4 (50)	90	50 / 50
21	10.2 (50)	50 / 50	9.9 (50)	97	50 / 50	9.8 (50)	96	50 / 50	9.3 (50)	91	50 / 50
25	10.5 (49)	49 / 50	10.2 (50)	97	50 / 50	10.2 (50)	97	50 / 50	9.6 (50)	91	50 / 50
29	10.7 (49)	49 / 50	10.1 (50)	94	50 / 50	10.1 (50)	94	50 / 50	9.6 (50)	90	50 / 50
33	10.5 (49)	49 / 50	10.4 (50)	99	50 / 50	10.2 (50)	97	50 / 50	9.7 (50)	92	50 / 50
37	10.3 (49)	49 / 50	9.8 (50)	95	50 / 50	9.8 (50)	95	50 / 50	9.3 (50)	90	50 / 50
41	10.6 (49)	49 / 50	10.2 (50)	96	50 / 50	10.3 (50)	97	50 / 50	9.8 (50)	92	50 / 50
45	11.1 (49)	49 / 50	10.8 (50)	97	50 / 50	10.6 (50)	95	50 / 50	10.1 (50)	91	50 / 50
49	10.9 (49)	49 / 50	10.5 (50)	96	50 / 50	10.6 (50)	97	50 / 50	10.1 (50)	93	50 / 50
53	11.1 (49)	49 / 50	11.0 (50)	99	50 / 50	10.8 (50)	97	50 / 50	10.3 (50)	93	50 / 50
57	11.7 (49)	49 / 50	11.0 (50)	94	50 / 50	11.4 (50)	97	50 / 50	10.8 (50)	92	50 / 50
61	11.7 (49)	49 / 50	11.4 (50)	97	50 / 50	11.3 (50)	97	50 / 50	10.9 (50)	93	50 / 50
65	11.7 (49)	49 / 50	11.6 (50)	99	50 / 50	11.4 (50)	97	50 / 50	11.1 (50)	95	50 / 50
69	11.7 (48)	48 / 50	11.2 (50)	96	50 / 50	11.5 (50)	98	50 / 50	10.9 (50)	93	50 / 50
73	12.0 (46)	46 / 50	11.6 (50)	97	50 / 50	11.6 (50)	97	50 / 50	11.2 (50)	93	50 / 50
77	12.2 (45)	45 / 50	11.8 (48)	97	48 / 50	11.8 (49)	97	49 / 50	11.3 (50)	93	50 / 50
78	12.0 (44)	45 / 50	11.7 (46)	98	48 / 50	11.5 (47)	96	49 / 50	11.1 (48)	93	50 / 50
82	12.2 (45)	45 / 50	11.9 (48)	98	48 / 50	11.5 (48)	94	48 / 50	11.3 (49)	93	49 / 50
86	12.7 (45)	45 / 50	12.2 (48)	96	48 / 50	12.2 (47)	96	47 / 50	11.6 (49)	91	49 / 50
90	12.3 (44)	44 / 50	12.0 (48)	98	48 / 50	11.6 (47)	94	47 / 50	11.6 (48)	94	48 / 50
94	12.8 (42)	42 / 50	12.1 (46)	95	46 / 50	12.2 (46)	95	46 / 50	11.8 (48)	92	48 / 50
98	12.7 (42)	42 / 50	12.4 (45)	98	45 / 50	11.7 (44)	92	44 / 50	11.5 (48)	91	48 / 50
102	12.6 (40)	40 / 50	11.9 (42)	94	42 / 50	12.0 (40)	95	40 / 50	11.4 (44)	90	44 / 50
104	12.5 (39)	39 / 50	12.2 (40)	98	40 / 50	12.1 (38)	97	38 / 50	11.7 (41)	94	41 / 50

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

TABLE 5 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. WC. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.
1	18.8 (50)	50 / 50	17.2 (50)	91	50 / 50	16.3 (50)	87	50 / 50	14.7 (50)	78	50 / 50
2	19.3 (50)	50 / 50	18.7 (50)	97	50 / 50	17.1 (50)	89	50 / 50	15.4 (50)	80	50 / 50
3	20.1 (50)	50 / 50	19.6 (50)	98	50 / 50	17.8 (50)	89	50 / 50	17.3 (50)	86	50 / 50
4	20.5 (50)	50 / 50	19.8 (50)	97	50 / 50	18.1 (50)	88	50 / 50	16.5 (50)	80	50 / 50
5	19.7 (50)	50 / 50	19.4 (50)	98	50 / 50	17.6 (50)	89	50 / 50	15.2 (50)	77	50 / 50
6	19.5 (50)	50 / 50	18.8 (50)	96	50 / 50	18.1 (50)	93	50 / 50	15.6 (50)	80	50 / 50
7	19.1 (50)	50 / 50	18.8 (50)	98	50 / 50	17.8 (50)	93	50 / 50	14.9 (49)	78	50 / 50
8	19.0 (50)	50 / 50	19.0 (50)	100	50 / 50	17.7 (50)	93	50 / 50	15.1 (50)	79	50 / 50
9	18.9 (50)	50 / 50	18.3 (50)	97	50 / 50	18.4 (50)	97	50 / 50	15.2 (50)	80	50 / 50
10	18.8 (50)	50 / 50	18.2 (50)	97	50 / 50	17.6 (50)	94	50 / 50	15.7 (50)	84	50 / 50
11	18.4 (50)	50 / 50	17.2 (50)	93	50 / 50	16.9 (49)	92	50 / 50	16.3 (50)	89	50 / 50
12	18.3 (50)	50 / 50	17.3 (50)	95	50 / 50	16.8 (50)	92	50 / 50	16.4 (50)	90	50 / 50
13	18.1 (50)	50 / 50	17.8 (50)	98	50 / 50	16.8 (50)	93	50 / 50	15.1 (50)	83	50 / 50
17	17.2 (50)	50 / 50	16.6 (50)	97	50 / 50	16.4 (50)	95	50 / 50	15.0 (50)	87	50 / 50
21	18.0 (50)	50 / 50	17.1 (50)	95	50 / 50	16.8 (50)	93	50 / 50	15.6 (50)	87	50 / 50
25	17.7 (50)	50 / 50	17.4 (50)	98	50 / 50	18.7 (50)	106	50 / 50	16.8 (50)	95	50 / 50
29	17.7 (50)	50 / 50	17.0 (50)	96	50 / 50	16.9 (50)	95	50 / 50	15.9 (50)	90	50 / 50
33	17.5 (50)	50 / 50	17.2 (48)	98	50 / 50	17.2 (50)	98	50 / 50	16.2 (49)	93	50 / 50
37	17.3 (50)	50 / 50	17.3 (50)	100	50 / 50	17.3 (50)	100	50 / 50	17.7 (50)	102	50 / 50
41	16.0 (50)	50 / 50	16.1 (50)	101	50 / 50	16.8 (50)	105	50 / 50	16.8 (50)	105	50 / 50
45	17.8 (50)	50 / 50	17.5 (50)	98	50 / 50	17.8 (50)	100	50 / 50	17.8 (50)	100	50 / 50
49	17.6 (50)	50 / 50	17.4 (50)	99	50 / 50	18.1 (50)	103	50 / 50	18.3 (50)	104	50 / 50
53	18.2 (50)	50 / 50	17.6 (50)	97	50 / 50	18.7 (50)	103	50 / 50	17.9 (50)	98	50 / 50
57	17.8 (50)	50 / 50	17.7 (49)	99	49 / 50	18.8 (50)	106	50 / 50	18.7 (50)	105	50 / 50
61	17.7 (50)	50 / 50	17.7 (48)	100	48 / 50	19.5 (50)	110	50 / 50	19.2 (50)	108	50 / 50
65	18.1 (50)	50 / 50	18.1 (48)	100	48 / 50	18.8 (50)	104	50 / 50	18.3 (50)	101	50 / 50
69	18.1 (50)	50 / 50	18.2 (48)	101	48 / 50	18.9 (50)	104	50 / 50	19.7 (49)	109	49 / 50
73	18.4 (49)	49 / 50	18.1 (47)	98	47 / 50	19.1 (49)	104	49 / 50	20.2 (49)	110	49 / 50
77	18.3 (49)	49 / 50	18.8 (47)	103	47 / 50	18.9 (49)	103	49 / 50	20.4 (49)	111	49 / 50
78	18.8 (49)	49 / 50	18.8 (47)	100	47 / 50	19.5 (48)	104	49 / 50	20.4 (49)	109	49 / 50
82	18.9 (47)	47 / 50	18.7 (47)	99	47 / 50	20.0 (49)	106	49 / 50	19.5 (49)	103	49 / 50
86	17.8 (43)	43 / 50	19.0 (45)	107	45 / 50	19.4 (48)	109	49 / 50	20.5 (48)	115	48 / 50
90	18.9 (40)	41 / 50	20.0 (45)	106	45 / 50	21.0 (48)	111	48 / 50	21.2 (48)	112	48 / 50
94	19.4 (40)	40 / 50	21.1 (44)	109	44 / 50	20.4 (48)	105	48 / 50	21.0 (47)	108	48 / 50
98	19.5 (38)	38 / 50	20.9 (44)	107	44 / 50	20.1 (47)	103	47 / 50	19.9 (44)	102	44 / 50
102	20.9 (36)	36 / 50	20.7 (36)	99	39 / 50	20.8 (44)	100	45 / 50	20.2 (39)	97	40 / 50
104	21.4 (36)	36 / 50	22.3 (37)	104	37 / 50	22.2 (45)	104	45 / 50	20.1 (39)	94	40 / 50

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

TABLE 6 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm		
	Av. WC. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.	Av. WC.	% of cont. <50>	No. of Surviv.
1	15.0 (49)	50 / 50	14.5 (50)	97	50 / 50	13.5 (50)	90	50 / 50	11.7 (50)	78	50 / 50
2	16.4 (50)	50 / 50	15.4 (50)	94	50 / 50	14.3 (50)	87	50 / 50	12.4 (50)	76	50 / 50
3	16.3 (50)	50 / 50	15.6 (50)	96	50 / 50	14.4 (50)	88	50 / 50	12.3 (50)	75	50 / 50
4	17.4 (50)	50 / 50	15.2 (50)	87	50 / 50	14.5 (50)	83	50 / 50	12.4 (50)	71	50 / 50
5	17.2 (50)	50 / 50	14.3 (50)	83	50 / 50	14.3 (50)	83	50 / 50	12.1 (50)	70	50 / 50
6	18.4 (49)	50 / 50	14.5 (50)	79	50 / 50	13.9 (50)	76	50 / 50	12.0 (50)	65	50 / 50
7	17.1 (47)	50 / 50	13.3 (48)	78	50 / 50	13.9 (50)	81	50 / 50	11.9 (50)	70	50 / 50
8	17.7 (47)	50 / 50	13.7 (48)	77	50 / 50	14.5 (48)	82	50 / 50	11.4 (49)	64	50 / 50
9	17.6 (49)	50 / 50	14.3 (49)	81	50 / 50	14.9 (50)	85	50 / 50	12.1 (50)	69	50 / 50
10	18.4 (48)	50 / 50	14.4 (47)	78	50 / 50	14.2 (48)	77	50 / 50	12.1 (50)	66	50 / 50
11	19.1 (49)	50 / 50	15.0 (49)	79	50 / 50	14.8 (48)	77	50 / 50	12.1 (50)	63	50 / 50
12	18.1 (45)	50 / 50	14.4 (48)	80	50 / 50	15.7 (49)	87	50 / 50	12.7 (50)	70	50 / 50
13	20.4 (49)	50 / 50	15.6 (48)	76	50 / 50	14.7 (48)	72	50 / 50	12.8 (48)	63	50 / 50
17	19.5 (48)	50 / 50	15.7 (48)	81	50 / 50	15.1 (49)	77	50 / 50	12.3 (49)	63	50 / 50
21	20.2 (50)	50 / 50	15.2 (49)	75	50 / 50	17.8 (50)	88	50 / 50	13.6 (49)	67	50 / 50
25	18.7 (48)	49 / 50	14.8 (45)	79	50 / 50	15.9 (49)	85	50 / 50	14.6 (50)	78	50 / 50
29	17.6 (48)	49 / 50	15.9 (50)	90	50 / 50	15.4 (49)	88	50 / 50	14.7 (49)	84	50 / 50
33	18.2 (49)	49 / 50	15.9 (50)	87	50 / 50	15.7 (50)	86	50 / 50	13.8 (49)	76	50 / 50
37	17.2 (49)	49 / 50	15.9 (50)	92	50 / 50	15.6 (49)	91	50 / 50	15.0 (49)	87	50 / 50
41	17.7 (48)	49 / 50	16.8 (50)	95	50 / 50	16.3 (49)	92	50 / 50	16.2 (49)	92	50 / 50
45	16.9 (49)	49 / 50	15.8 (50)	93	50 / 50	16.0 (50)	95	50 / 50	15.3 (50)	91	50 / 50
49	17.3 (49)	49 / 50	15.9 (49)	92	50 / 50	16.8 (50)	97	50 / 50	15.1 (50)	87	50 / 50
53	16.9 (49)	49 / 50	15.7 (50)	93	50 / 50	16.4 (50)	97	50 / 50	15.1 (50)	89	50 / 50
57	15.2 (48)	49 / 50	17.0 (49)	112	50 / 50	15.5 (50)	102	50 / 50	16.3 (49)	107	50 / 50
61	16.4 (49)	49 / 50	16.4 (50)	100	50 / 50	15.4 (50)	94	50 / 50	16.2 (50)	99	50 / 50
65	15.1 (49)	49 / 50	14.8 (50)	98	50 / 50	14.9 (50)	99	50 / 50	16.2 (50)	107	50 / 50
69	15.2 (48)	48 / 50	14.4 (50)	95	50 / 50	15.5 (50)	102	50 / 50	17.6 (50)	116	50 / 50
73	15.5 (46)	46 / 50	15.8 (50)	102	50 / 50	15.6 (50)	101	50 / 50	17.7 (50)	114	50 / 50
77	15.0 (45)	45 / 50	15.7 (48)	105	48 / 50	14.6 (49)	97	49 / 50	17.2 (50)	115	50 / 50
78	15.5 (45)	45 / 50	16.2 (48)	105	48 / 50	15.3 (49)	99	49 / 50	18.0 (50)	116	50 / 50
82	15.5 (45)	45 / 50	15.2 (48)	98	48 / 50	14.5 (48)	94	48 / 50	17.6 (49)	114	49 / 50
86	16.2 (45)	45 / 50	16.0 (48)	99	48 / 50	14.9 (47)	92	47 / 50	17.6 (48)	109	49 / 50
90	17.4 (44)	44 / 50	15.5 (48)	89	48 / 50	15.5 (47)	89	47 / 50	18.5 (48)	106	48 / 50
94	17.1 (42)	42 / 50	16.4 (46)	96	46 / 50	16.4 (46)	96	46 / 50	18.9 (48)	111	48 / 50
98	19.0 (42)	42 / 50	16.8 (45)	88	45 / 50	16.5 (44)	87	44 / 50	18.9 (47)	99	48 / 50
102	18.9 (40)	40 / 50	17.5 (42)	93	42 / 50	17.2 (40)	91	40 / 50	19.1 (44)	101	44 / 50
104	18.8 (39)	39 / 50	18.1 (40)	96	40 / 50	17.3 (38)	92	38 / 50	19.3 (41)	103	41 / 50

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

TABLE 7 HEMATOLOGY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm
No. of examined animals	36	37	44	39
MCH (pg)	17.1 ± 2.5	16.1 ± 1.7 *	16.6 ± 1.8	16.8 ± 1.8

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

TABLE 8 HEMATOLOGY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm
No. of examined animals	38	39	38	41
MCV (fL)	52.5 ± 5.2	54.5 ± 11.5	54.6 ± 9.5	55.0 ± 8.5 **
MCHC (g/dL)	34.3 ± 3.0	34.6 ± 1.6	34.6 ± 1.5	34.3 ± 1.6 **

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

TABLE 9 BIOCHEMISTRY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	
No. of examined animals	36	37	44	39	
TOTAL PROTEIN (g/dL)	6.8 ± 0.4	6.7 ± 0.3	6.7 ± 0.4	6.6 ± 0.3	*
AST (IU/L)	102 ± 85	99 ± 28	117 ± 93	148 ± 175	**
ALT (IU/L)	43 ± 16	47 ± 13	47 ± 22	65 ± 51	**
CREATININE (mg/dL)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	*
Mean ± S.D.					
Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$ Test of Dunnett					

TABLE 10 BIOCHEMISTRY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	
No. of examined animals	39	39	38	41	
T-BILIRUBIN (mg/dL)	0.17 ± 0.15	0.18 ± 0.17	0.39 ± 1.47	0.21 ± 0.48	**
TRIGLYCERIDE (mg/dL)	71 ± 65	57 ± 49	52 ± 38	40 ± 31	**
UREA NITROGEN (mg/dL)	17.4 ± 3.4	17.5 ± 3.5	17.4 ± 2.3	18.8 ± 3.4	*
Mean ± S.D.					
Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$ Test of Dunnett					

TABLE 11 URINALYSIS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name		Control	2500 ppm	5000 ppm	10000 ppm
No. of examined animals		39	41	38	42
pH	Grade				
	5.0	0	0	0	0
	6.0	1	1	0	1
	6.5	3	3	4	12
	7.0	1	5	3	12
	7.5	8	6	10	6
	8.0	23	21	16	10
	8.5	3	5	5	1
	Chi square test				**
Protein	—	0	0	0	0
	±	0	2	2	5
	+	8	5	10	14
	2+	12	14	12	14
	3+	11	16	10	9
	4+	8	4	4	0
		Chi square test			
Ketone body	—	5	10	8	22
	±	34	30	29	20
	+	0	1	1	0
	2+	0	0	0	0
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test				**

Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$

TABLE 12 ORGAN WEIGHTS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	
No. of examined animals	36	37	44	39	
Body weight (g)	390 ± 35	382 ± 28	378 ± 26	366 ± 30	**
Adrenals (g)	0.066 ± 0.009	0.081 ± 0.054 *	0.092 ± 0.116 **	0.088 ± 0.121	
Adrenals (%)	0.017 ± 0.003	0.021 ± 0.013 *	0.024 ± 0.029 **	0.025 ± 0.035 *	
Kidneys (g)	2.767 ± 0.417	2.789 ± 0.334	2.782 ± 0.267	2.849 ± 0.245	
Kidneys (%)	0.714 ± 0.114	0.734 ± 0.105	0.738 ± 0.086	0.783 ± 0.101 *	
Brain (g)	2.062 ± 0.047	2.068 ± 0.048	2.059 ± 0.045	2.063 ± 0.034	
Brain (%)	0.533 ± 0.044	0.544 ± 0.035	0.547 ± 0.036	0.567 ± 0.049 **	
Mean ± S.D.					
Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$ Test of Dunnett					

TABLE 13 ORGAN WEIGHTS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	
No. of examined animals	39	40	38	41	
Body weight (g)	254 ± 39	241 ± 26	242 ± 29	227 ± 21	**
Adrenals (g)	0.075 ± 0.015	0.100 ± 0.176	0.076 ± 0.041	0.067 ± 0.007 *	
Adrenals (%)	0.030 ± 0.009	0.044 ± 0.083	0.032 ± 0.018	0.030 ± 0.003	
Ovaries (g)	0.119 ± 0.025	0.128 ± 0.022	0.151 ± 0.185	0.142 ± 0.097	
Ovaries (%)	0.047 ± 0.008	0.054 ± 0.013 *	0.063 ± 0.080	0.063 ± 0.043 **	
Heart (g)	0.895 ± 0.090	0.893 ± 0.092	0.860 ± 0.085	0.853 ± 0.071	
Heart (%)	0.359 ± 0.053	0.376 ± 0.069	0.358 ± 0.037	0.378 ± 0.034 **	
Kidneys (g)	1.806 ± 0.133	1.787 ± 0.134	1.809 ± 0.148	1.891 ± 0.175 *	
Kidneys (%)	0.726 ± 0.116	0.751 ± 0.121	0.755 ± 0.088	0.839 ± 0.110 **	
Brain (g)	1.892 ± 0.048	1.891 ± 0.043	1.881 ± 0.034	1.864 ± 0.058	
Brain (%)	0.762 ± 0.120	0.793 ± 0.097	0.789 ± 0.111	0.829 ± 0.085 *	
Mean ± S.D.					
Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$ Test of Dunnett					

TABLE 14 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE RATS
IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage
						test
adrenal gland	<50>	<50>	<50>	<50>		
pheochromocytoma ¹⁾	1 (2 %)	4 (8 %)	4 (8 %)	1 (2 %)		
pheochromocytoma: malignant ²⁾	0 (0 %)	2 (4 %)	3 (6 %)	1 (2 %)		
1) + 2)	1 (2 %)	6 (12 %)	7 (14 %)*	2 (4 %)		

Significant difference: * : $p \leq 0.05$ ** : $p \leq 0.01$
 $\uparrow(\downarrow)$: $p \leq 0.05$ $\uparrow\uparrow(\downarrow\downarrow)$: $p \leq 0.01$
 < > : Number of animals examined at the site

Fisher's exact test for neoplastic lesion
 Peto or Cochran-Armitage test for neoplastic lesion

TABLE 15 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF MALE RATS
IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group Name	Control				2500 ppm				5000 ppm				10000 ppm			
Number of examined animals	50				50				50				50			
Grade of non-neoplastic lesion	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
kidney	<50>				<50>				<50>				<50>			
papillary necrosis	0	1	0	0	1	0	0	0	0	0	0	0	3	1	0	0
mineralization: papilla	0	0	0	0	0	0	0	0	1	0	0	0	6	0	0	0 *
urothelial hyperplasia: pelvis	1	0	0	0	1	0	0	0	1	0	0	0	5	3	0	0 *

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

TABLE 16 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS
IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCr1Cr1j MALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Adrenal	2098			
Pheochromocytoma 1)		251	12.0	0 - 40
Pheochromocytoma : malignant 2)		37	1.8	0 - 8
1)+2)		283	13.5	2 - 46

42 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, 0246, 0267, 0269, 0278, 0284, 0288, 0294, 0296, 0318, 0328,
0342, 0347, 0365, 0371, 0396, 0399, 0401, 0407, 0417, 0421, 0437, 0448, 0457, 0461

TABLE 17 CAUSE OF DEATH OF RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

Group name	Male				Female			
	Control	2500 ppm	5000 ppm	10000 ppm	Control	2500 ppm	5000 ppm	10000 ppm
Number of dead or moribund animals	14	13	5	10	11	10	12	9
No microscopical confirmation	2	1	0	3	2	0	1	2
cardiovascular lesion	1	0	0	0	0	0	0	1
urinary system lesion	0	0	0	0	0	0	0	1
arteritis	0	1	0	0	0	0	0	0
Tumor death : leukemia	2	3	0	2	2	4	4	1
skin/appendage	0	0	0	1	0	0	0	0
subcutis	2	1	0	0	0	0	0	0
bone marrow	0	0	0	0	1	0	0	0
thymus	1	0	0	0	0	0	0	0
oral cavity	1	0	0	0	0	0	0	0
small intestine	0	1	0	0	0	0	0	0
kidney	0	1	0	0	0	0	0	0
urinary bladder	1	0	0	0	0	0	0	0
pituitary gland	3	3	1	2	0	2	3	1
thyroid	0	1	0	0	0	0	0	0
adrenal gland	0	0	1	0	0	0	0	0
ovary	—	—	—	—	0	0	1	0
uterus	—	—	—	—	3	3	2	3
mammary gland	0	0	0	0	1	0	0	0
preputial gland	0	0	1	0	—	—	—	—
brain	0	0	1	0	2	0	0	0
Zymbal gland	1	0	0	0	0	0	0	0
bone	0	1	0	1	0	1	0	0
peritoneum	0	0	1	1	0	0	1	0

FIGURES

- FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 7 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL
- FIGURE 8 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

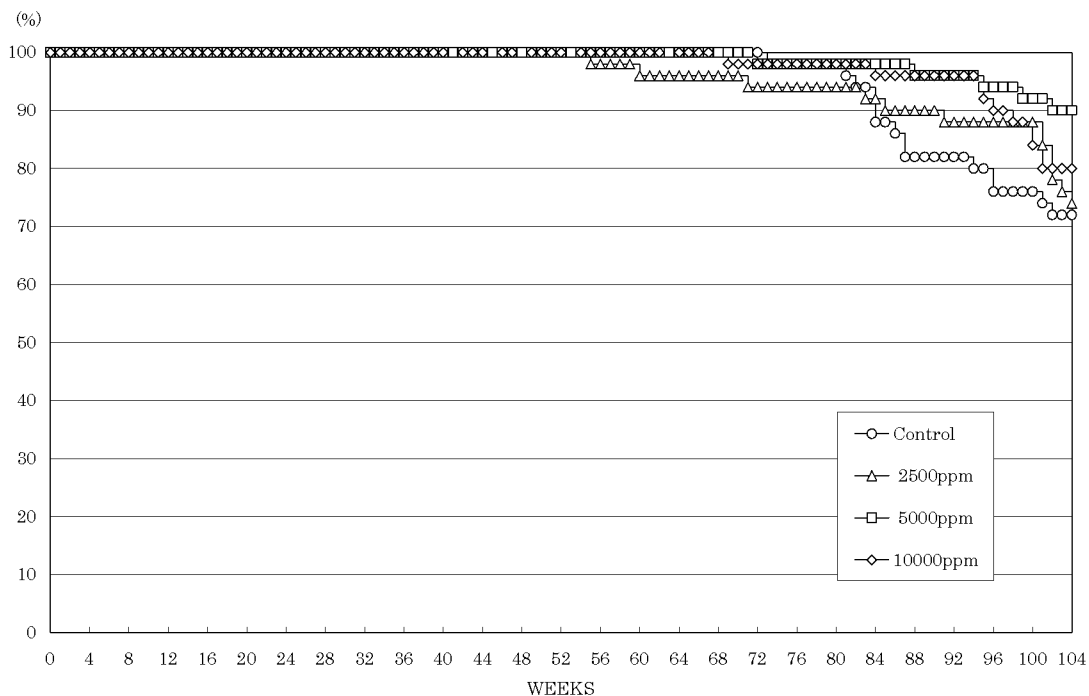


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

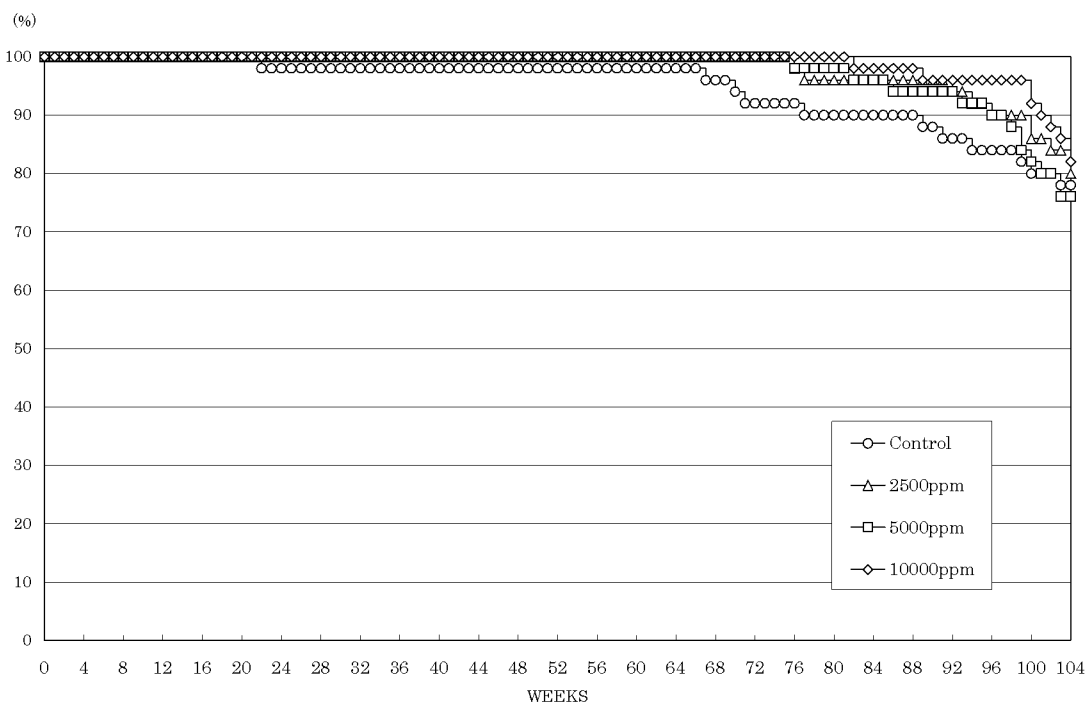


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

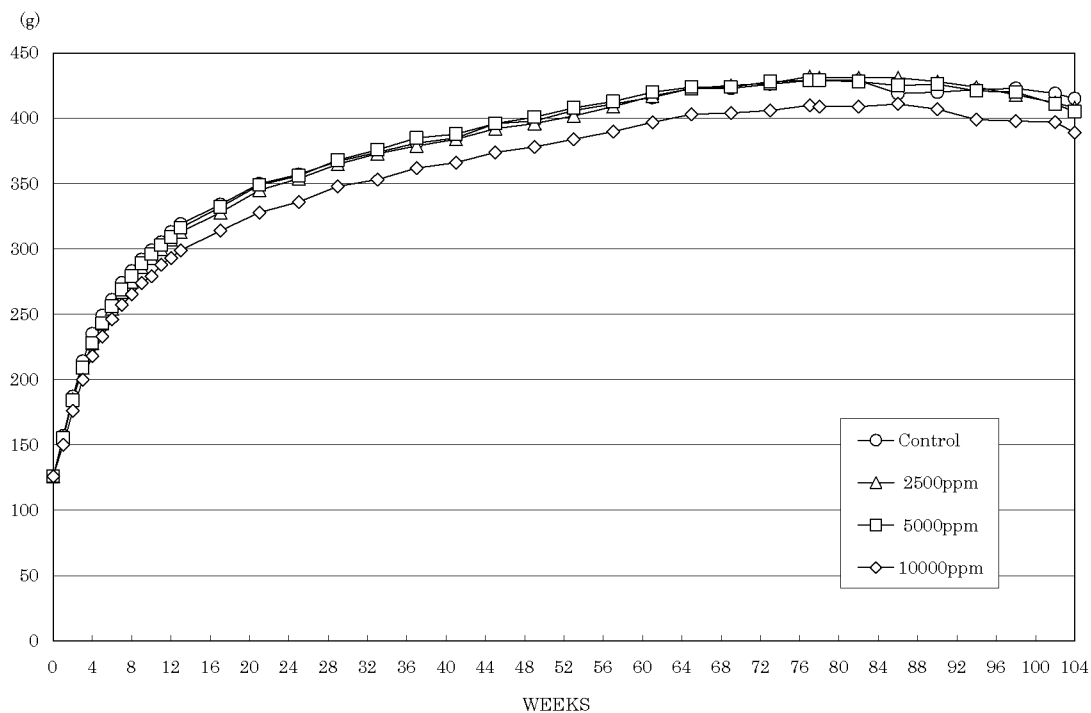


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

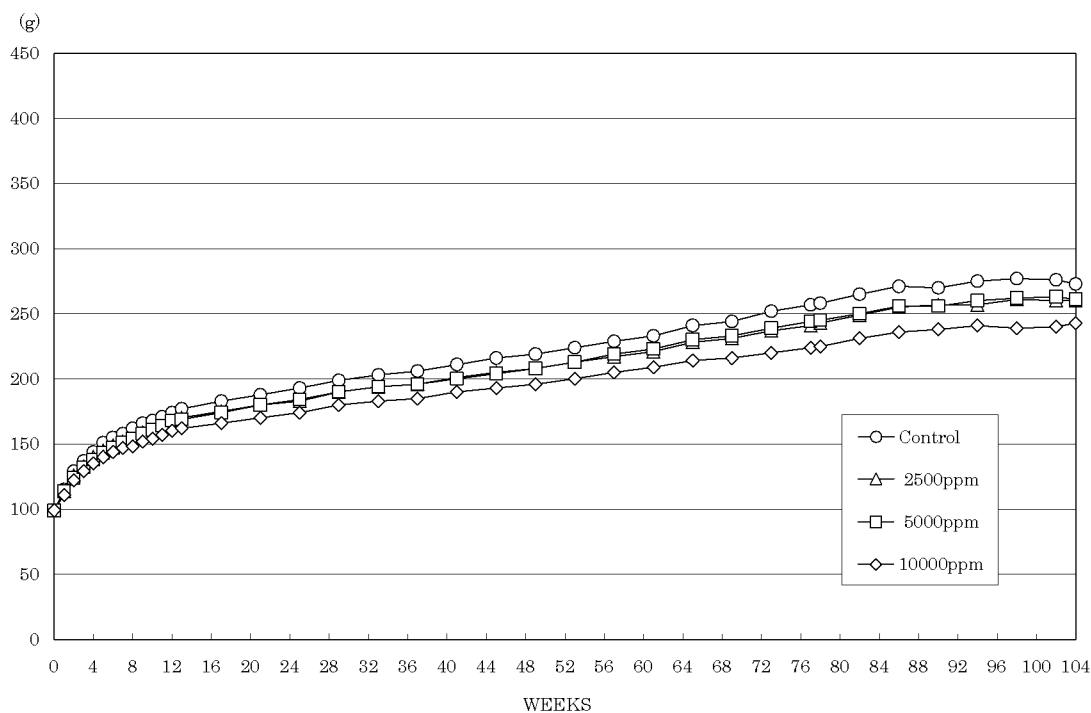


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

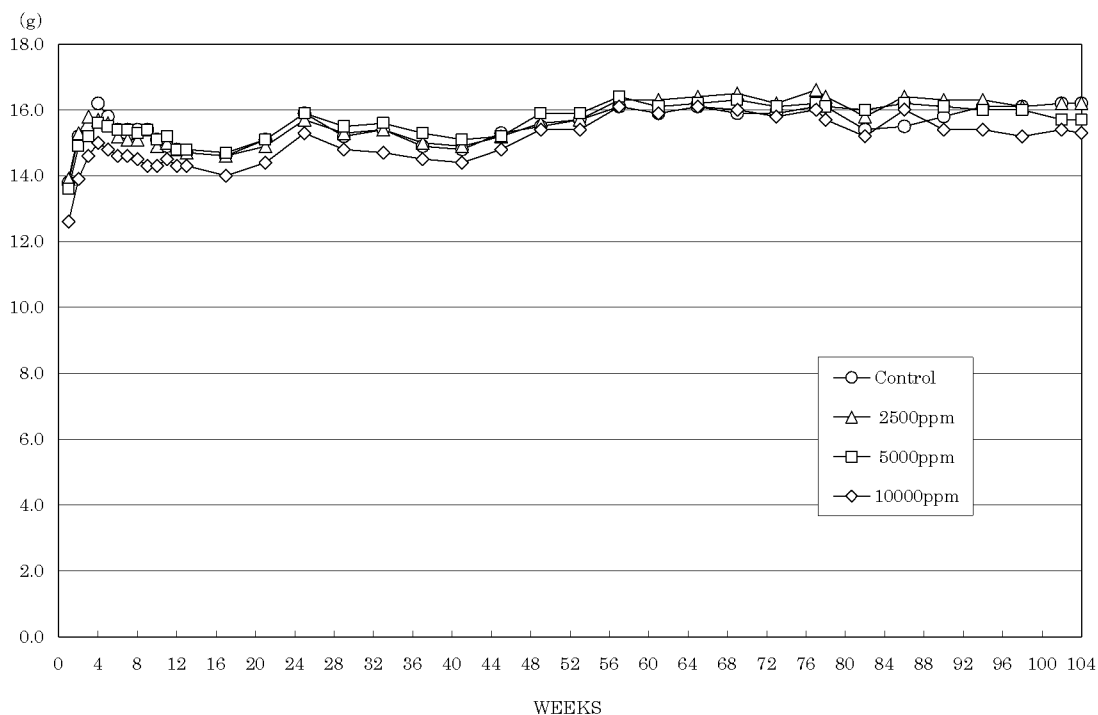


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY 2-PHENOXYETHANOL

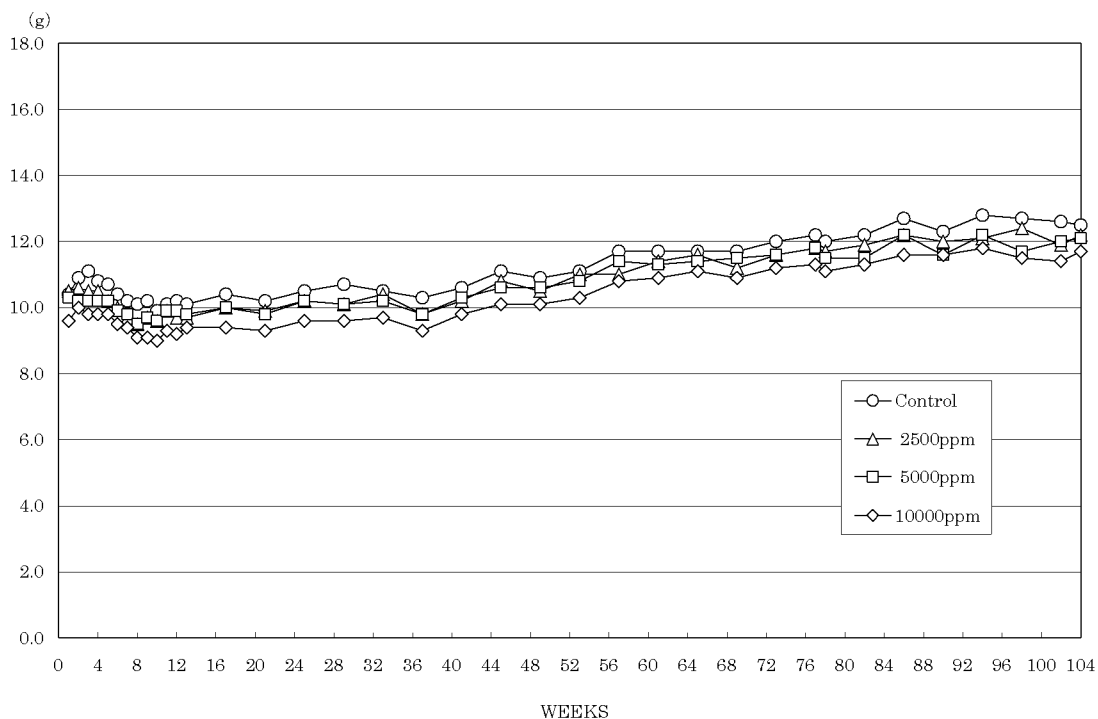


FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

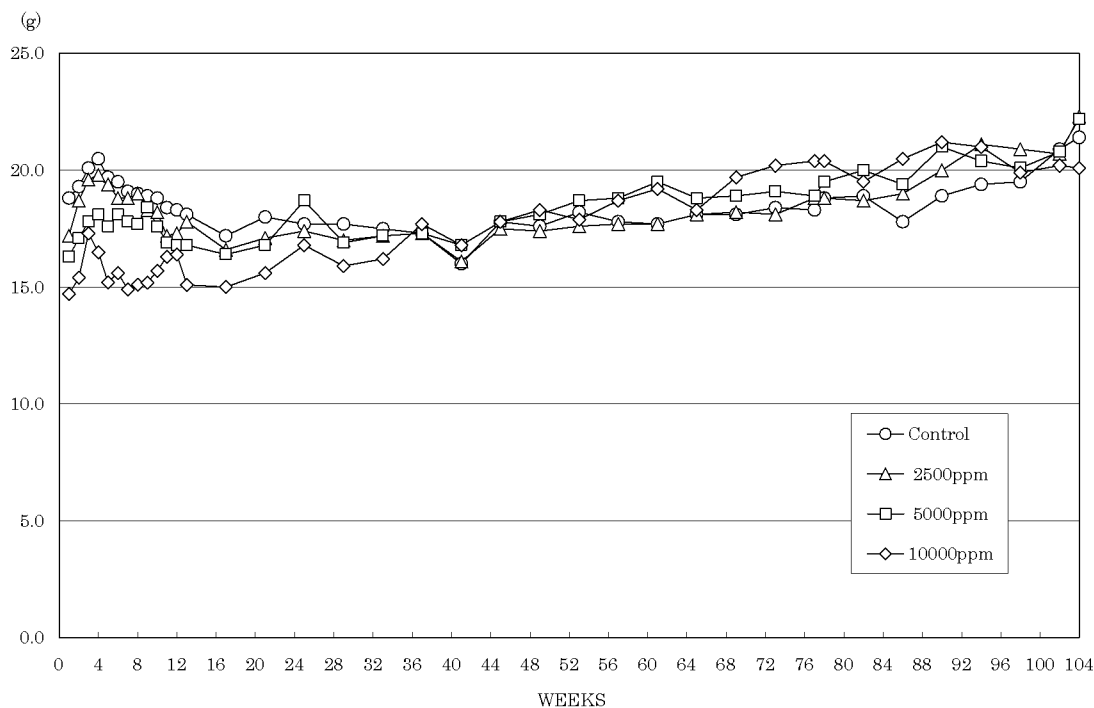


FIGURE 7 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL

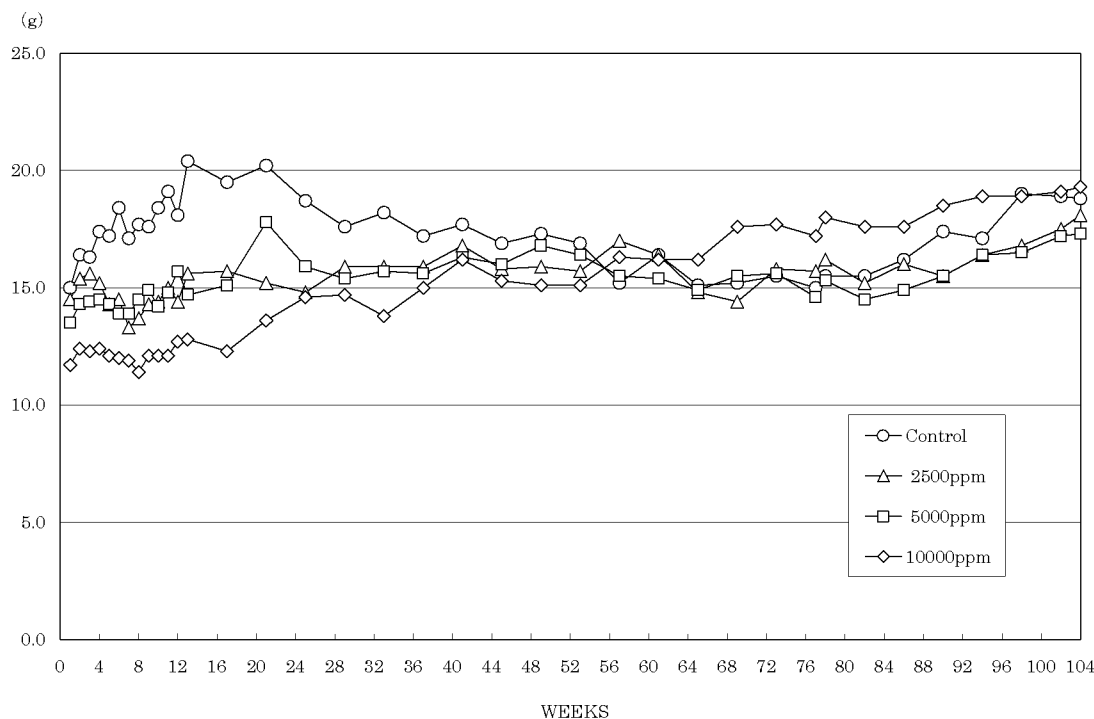
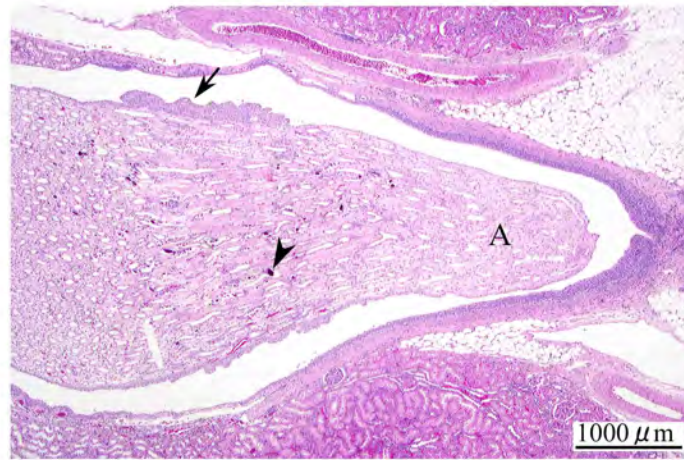
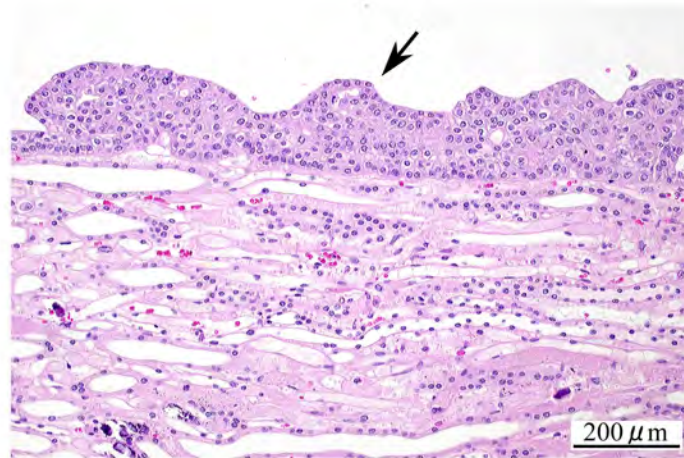


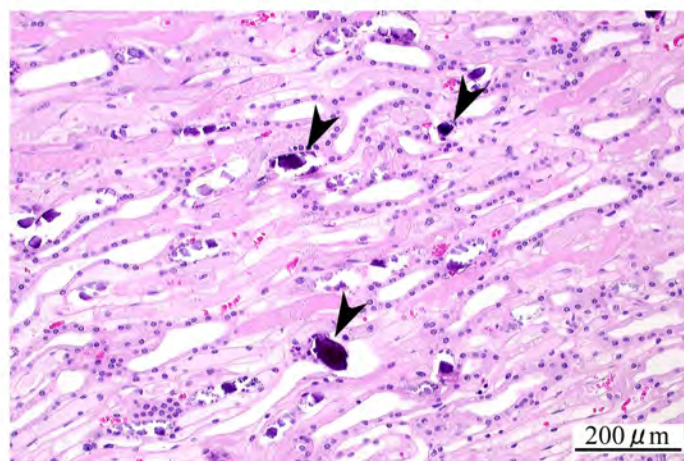
FIGURE 8 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF 2-PHENOXYETHANOL



Photograph 1
Kidney: urothelial hyperplasia (arrow) and mineralization (arrowhead) of pelvis, and papillary necrosis (A)
Rat, Male, 10000 ppm, Animal No. 0497-1304 (H&E)



Photograph 2
Higher magnification of photograph 1
Kidney: urothelial hyperplasia of pelvis (arrow)
Rat, Male, 10000 ppm, Animal No. 0497-1304 (H&E)



Photograph 3
Higher magnification of photograph 1
Kidney: mineralization of pelvis (arrowheads)
Rat, Male, 10000 ppm, Animal No. 0497-1304 (H&E)