Summary of Drinking Water Carcinogenicity Study of *o*-Phenylenediamine Dihydrochloride 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 February 26 2004.

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Purpose, materials and methods

o-Phenylenediamine dihydrochloride (*o*-PD2HCl, 1,2-benzenediamine dihydrochloride, CAS No. 615-28-1) is a light red crystalline powder with a melting point of 258°C and is soluble in water.

The carcinogenicity and chronic toxicity of *o*-PD2HCl were examined in groups of 50 F344/DuCrj (Fischer) rats of both sexes administered *o*-PD2HCl in drinking water for 2 years (104 weeks). The drinking water concentration of *o*-PD2HCl was 0, 500, 1000 or 2000 ppm (w/w) for male rats, and 0, 250, 500 or 1000 ppm for female rats. The highest dose levels were 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. *o*-PD2HCl was analyzed for purity and stability by both infrared spectrometry and high performance liquid chromatography before and after its use. The concentrations of *o*-PD2HCl in drinking water were determined by high performance liquid chromatography at the time of preparation, and on the 8th 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 *o*-PD2HCl-administered group of either sex and the respective control. Body weight and water consumption were significantly decreased in all the *o*-PD2HCl-administered male groups and in the females administered 500 and 1000 ppm. Food consumption was suppressed in the 2000 ppm-administered males and in the 1000 ppm-administered females throughout the 2-year administration period and in both 500 and 1000 ppm-administered males during both the early and late periods of 2-year administration.

The incidence of hepatocellular adenomas was significantly increased in the middle and high-dosed groups of both sexes, while the incidence of hepatocellular carcinomas was significantly increased in the high-dosed groups of both sexes. The incidences of the hepatocellular tumors exceeded the respective maximum incidences of the Japan Bioassay Research Center (JBRC) historical control data. As a pre-neoplastic lesion, the incidence of basophilic cell foci in the liver was significantly increased in the males administered 1000 ppm and above and in all the *o*-PD2HCl-administered female groups. Plasma levels of AST (GOT), ALT (GPT) and γ-GTP were increased in the *o*-PD2HCl-administered males and females. Moreover, the incidences of transitional cell papillomas and carcinomas in the urinary bladder of the 2000 ppm-administered males exceeded the respective maximum incidences of the JBRC historical control data. The combined incidence of transitional cell papillomas and carcinomas was increased in the males administered 2000 ppm, together with the increased incidence of hyperplasia of transitional epithelium. In the kidney, the incidences of papillary necrosis, papillary mineralization and urothelial hyperplasia of the pelvis were increased in the *o*-PD2HCl-administered males and females. In the nasal cavity, eosinophilic change in the olfactory epithelium was observed in the *o*-PD2HCl-administered males and females. Those renal and nasal lesions were thought to be related to the *o*-PD2HCl administration. The incidence of follicular adenomas in the thyroid of the *o*-PD2HCl-administered males was increased, but was not clearly related to the *o*-PD2HCl administration. A no-observed-adverse-effect-level (NOAEL) for *o*-PD2HCl could not determined in the 2-year drinking water study, since the incidences of basophilic cell foci of the liver and urothelial hyperplasia of the pelvis in the *o*-PD2HCl-administered females were increased at the lowest dose level. The lowest-observed-adverse-effect-level (LOAEL) was 250 ppm (0.014 - 0.034 mg/kg/body weight per day for females) for these endpoints. The lower confidence limits of the benchmark dose yielding a response with a 10% extra risk ($BMDL_{10}$) value for the endpoint of urothelial hyperplasia of the pelvis was 148 ppm.

Conclusions

In rats, there was clear evidence of carcinogenic activity of *o*-PD2HCl in males and females,

based on the increased incidences of hepatocellular adenomas and carcinomas in males and females and the increased combined incidences of urinary bladder transitional cell papillomas and carcinomas in males.

TABLES

TABLES (CONTINUED)

TABLES (CONTINUED)

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

Week on Study	Control		500 ppm			1000 ppm			2000 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	118 (50)	50 / 50	118 (50)	100	50 / 50	118 (50)	100	50 / 50	118 (50)	100	50 / 50
1	147 (50)	50 / 50	143 (50)	97	50 / 50	139 (50)	95	50 / 50	129 (50)	88	50 / 50
2	176 (50)	50 / 50	171 (50)	97	50 / 50	166 (50)	94	50 / 50	154 (50)	88	50 / 50
3	202 (50)	50 / 50	194 (50)	96	50 / 50	192 (50)	95	50 / 50	178 (50)	88	50 / 50
4	223 (50)	50 / 50	214 (50)	96	50 / 50	212 (50)	95	50 / 50	196 (50)	88	50 / 50
5	239 (50)	50 / 50	229 (50)	96	50 / 50	228 (50)	95	50 / 50	211 (50)	88	50 / 50
6	251 (50)	50 / 50	239 (50)	95	50 / 50	238 (50)	95	50 / 50	219 (50)	87	50 / 50
7	261 (50)	50 / 50	250 (50)	96	50 / 50	248 (50)	95	50 / 50	227 (50)	87	50 / 50
8	273 (50)	50 / 50	259 (50)	95	50 / 50	257 (50)	94	50 / 50	235 (50)	86	50 / 50
9	282 (50)	50 / 50	268 (50)	95	50 / 50	266 (50)	94	50 / 50	241 (50)	85	50 / 50
10	289 (50)	50 / 50	276 (50)	96	50 / 50	274 (50)	95	50 / 50	247 (50)	85	50 / 50
11	296 (50)	50 / 50	282 (50)	95	50 / 50	281 (50)	95	50 / 50	251 (50)	85	50 / 50
12	303 (50)	50 / 50	288 (50)	95	50 / 50	287 (50)	95	50 / 50	257 (50)	85	50 / 50
13	310 (50)	50 / 50	296 (50)	95	50 / 50	294 (50)	95	50 / 50	263 (50)	85	50 / 50
14	315 (50)	50 / 50	300 (50)	95	50 / 50	297 (50)	94	50 / 50	267 (50)	85	50 / 50
18	330 (50)	50 / 50	319 (50)	97	50 / 50	313 (50)	95	50 / 50	279 (50)	85	50 / 50
22	344 (50)	50 / 50	332 (50)	97	50 / 50	326 (50)	95	50 / 50	289 (50)	84	50 / 50
26	358 (50)	50 / 50	345 (50)	96	50 / 50	338 (50)	94	50 / 50	301 (50)	84	50 / 50
30	368 (50)	50 / 50	354 (50)	96	50 / 50	346 (50)	94	50 / 50	306 (50)	83	50 / 50
34	376 (50)	50 / 50	360 (50)	96	50 / 50	353 (50)	94	50 / 50	313 (50)	83	50 / 50
38	382 (50)	50 / 50	369 (50)	97	50 / 50	361 (50)	95	50 / 50	316 (50)	83	50 / 50
42	388 (50)	50 / 50	375 (50)	97	50 / 50	365 (50)	94	50 / 50	319 (50)	82	50 / 50
46	396 (50)	50 / 50	380 (50)	96	50 / 50	369 (50)	93	50 / 50	322 (50)	81	50 / 50
50	398 (50)	50 / 50	383 (50)	96	50 / 50	373 (50)	94	50 / 50	325 (50)	82	50 / 50
54	404 (50)	50 / 50	387 (50)	96	50 / 50	376 (50)	93	50 / 50	325 (50)	80	50 / 50
58	410 (50)	50 / 50	389 (50)	95	50 / 50	377 (50)	92	50 / 50	327 (49)	80	49 / 50
62	413 (50)	50 / 50	392 (50)	95	50 / 50	379 (50)	92	50 / 50	328 (49)	79	49 / 50
66	420 (50)	50 / 50	394 (50)	94	50 / 50	380 (50)	90	50 / 50	327 (48)	78	48 / 50
70	425 (50)	50 / 50	396 (50)	93	50 / 50	382 (49)	90	49 / 50	330 (48)	78	48 / 50
74	426 (50)	50 / 50	394 (49)	92	49 / 50	384 (49)	90	49 / 50	329 (48)	77	48 / 50
78	426 (50)	50 / 50	400 (47)	94	47 / 50	382 (47)	90	47 / 50	327 (48)	77	48 / 50
82	426 (49)	49 / 50	401 (47)	94	47 / 50	383 (46)	90	46 / 50	327 (48)	77	48 / 50
86	430 (47)	47 / 50	403 (46)	94	46 / 50	381 (46)	89	46 / 50	323 (48)	75	48 / 50
90	430 (46)	46 / 50	399 (46)	93	46 / 50	376 (46)	87	46 / 50	317 (47)	74	47 / 50
94	426 (45)	45 / 50	387 (42)	91	42 / 50	370 (45)	87	45 / 50	309 (46)	73	46 / 50
98	419 (44)	44 / 50	383 (40)	91	40 / 50	362 (43)	86	43 / 50	302 (44)	72	44 / 50
102	413 (42)	42 / 50	377 (39)	91	39 / 50	355 (43)	86	43 / 50	294 (43)	71	43 / 50
104	406 (41)	41 / 50	377 (36)	93	36 / 50	349 (42)	86	42 / 50	287 (42)	71	42 / 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 *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Week on Study	Control		250 ppm			500 ppm			1000 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	110 (50)	100	50 / 50	108 (50)	98	50 / 50	105 (50)	95	50 / 50
2	123 (50)	50 / 50	123 (50)	100	50 / 50	121 (50)	98	50 / 50	118 (50)	96	50 / 50
3	133 (50)	50 / 50	133 (50)	100	50 / 50	130 (50)	98	50 / 50	126 (50)	95	50 / 50
4	141 (50)	50 / 50	140 (50)	99	50 / 50	138 (50)	98	50 / 50	132 (50)	94	50 / 50
5	148 (50)	50 / 50	147 (50)	99	50 / 50	144 (50)	97	50 / 50	137 (50)	93	50 / 50
6	153 (50)	50 / 50	151 (50)	99	50 / 50	149 (50)	97	50 / 50	140 (50)	92	50 / 50
7	157 (50)	50 / 50	156 (50)	99	50 / 50	153 (50)	97	50 / 50	145 (50)	92	50 / 50
8	161 (50)	50 / 50	160 (50)	99	50 / 50	157 (50)	98	50 / 50	149 (50)	93	50 / 50
9	165 (50)	50 / 50	164 (50)	99	50 / 50	160 (50)	97	50 / 50	151 (50)	92	50 / 50
10	167 (50)	50 / 50	166 (50)	99	50 / 50	164 (50)	98	50 / 50	155 (50)	93	50 / 50
11	171 (50)	50 / 50	172 (50)	101	50 / 50	167 (50)	98	50 / 50	158 (50)	92	50 / 50
12	173 (50)	50 / 50	174 (50)	101	50 / 50	170 (50)	98	50 / 50	160 (50)	92	50 / 50
13	175 (50)	50 / 50	176 (50)	101	50 / 50	172 (50)	98	50 / 50	161 (50)	92	50 / 50
14	176 (50)	50 / 50	178 (50)	101	50 / 50	174 (50)	99	50 / 50	163 (50)	93	50 / 50
18	184 (50)	50 / 50	185 (50)	101	50 / 50	181 (50)	98	50 / 50	169 (50)	92	50 / 50
22	189 (50)	50 / 50	188 (50)	99	50 / 50	185 (50)	98	50 / 50	173 (50)	92	50 / 50
26	193 (50)	50 / 50	194 (50)	101	50 / 50	190 (50)	98	50 / 50	178 (50)	92	50 / 50
30	199 (50)	50 / 50	198 (50)	99	50 / 50	196 (50)	98	50 / 50	182 (50)	91	50 / 50
34	204 (50)	50 / 50	204 (50)	100	50 / 50	200 (50)	98	50 / 50	185 (50)	91	50 / 50
38	206 (50)	50 / 50	205 (50)	100	50 / 50	202 (50)	98	50 / 50	187 (50)	91	50 / 50
42	211 (50)	50 / 50	210 (50)	100	50 / 50	205 (50)	97	50 / 50	189 (50)	90	50 / 50
46	215 (50)	50 / 50	213 (50)	99	50 / 50	208 (49)	97	49 / 50	191 (50)	89	50 / 50
50	219 (50)	50 / 50	216 (50)	99	50 / 50	212 (49)	97	49 / 50	196 (50)	89	50 / 50
54	223 (50)	50 / 50	220 (50)	99	50 / 50	216 (49)	97	49 / 50	199 (50)	89	50 / 50
58	227 (50)	50 / 50	223 (50)	98	50 / 50	220 (49)	97	49 / 50	202 (50)	89	50 / 50
62	232 (50)	50 / 50	227 (49)	98	49 / 50	224 (49)	97	49 / 50	204 (50)	88	50 / 50
66	237 (50)	50 / 50	232 (49)	98	49 / 50	228 (49)	96	49 / 50	206 (50)	87	50 / 50
70	243 (49)	49 / 50	236 (49)	97	49 / 50	232 (49)	95	49 / 50	209 (49)	86	49 / 50
74	250 (48)	48 / 50	244 (47)	98	47 / 50	237 (49)	95	49 / 50	214 (49)	86	49 / 50
78	255 (48)	48 / 50	248 (47)	97	47 / 50	240 (49)	94	49 / 50	217 (48)	85	48 / 50
82	263 (47)	47 / 50	252 (46)	96	46 / 50	245 (49)	93	49 / 50	221 (48)	84	48 / 50
86	264 (47)	47 / 50	255 (45)	97	45 / 50	249 (49)	94	49 / 50	219 (48)	83	48 / 50
90	264 (45)	45 / 50	256 (45)	97	45 / 50	251 (49)	95	49 / 50	221 (46)	84	46 / 50
94	265 (45)	45 / 50	253 (45)	95	45 / 50	249 (48)	94	48 / 50	220 (45)	83	45 / 50
98	267 (44)	44 / 50	256 (43)	96	43 / 50	251 (45)	94	45 / 50	219 (44)	82	44 / 50
102	271 (41)	41 / 50	259 (40)	96	40 / 50	250 (44)	92	44 / 50	218 (42)	80	42 / 50
104	269 (41)	41 / 50	253 (38)	94	38 / 50	248 (44)	92	44 / 50	217 (41)	81	41 / 50

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

TABLE 3 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Week on Study	Control		500 ppm			1000 ppm			2000 ppm		
	Av. WC.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>
1	17.1 (50)	50 / 50	15.7 (50)	92	50 / 50	13.7 (50)	80	50 / 50	11.7 (50)	68	50 / 50
2	18.0 (50)	50 / 50	16.0 (49)	89	50 / 50	14.3 (50)	79	50 / 50	12.3 (50)	68	50 / 50
3	19.1 (49)	50 / 50	17.4 (50)	91	50 / 50	15.3 (50)	80	50 / 50	13.4 (50)	70	50 / 50
4	19.5 (50)	50 / 50	17.2 (50)	88	50 / 50	15.8 (50)	81	50 / 50	13.4 (50)	69	50 / 50
5	19.5 (50)	50 / 50	17.4 (50)	89	50 / 50	16.4 (50)	84	50 / 50	13.2 (50)	68	50 / 50
6	19.8 (50)	50 / 50	16.9 (50)	85	50 / 50	16.2 (50)	82	50 / 50	13.3 (50)	67	50 / 50
7	19.1 (50)	50 / 50	16.8 (50)	88	50 / 50	15.5 (50)	81	50 / 50	12.7 (50)	66	50 / 50
8	19.0 (50)	50 / 50	16.9 (50)	89	50 / 50	15.4 (50)	81	50 / 50	12.7 (50)	67	50 / 50
9	18.7 (50)	50 / 50	17.4 (50)	93	50 / 50	15.8 (50)	84	50 / 50	13.1 (50)	70	50 / 50
10	18.6 (50)	50 / 50	17.5 (50)	94	50 / 50	16.2 (50)	87	50 / 50	13.2 (50)	71	50 / 50
11	18.0 (50)	50 / 50	16.4 (50)	91	50 / 50	15.2 (50)	84	50 / 50	12.9 (50)	72	50 / 50
12	18.1 (49)	50 / 50	16.2 (50)	90	50 / 50	14.9 (50)	82	50 / 50	12.4 (50)	69	50 / 50
13	18.0 (50)	50 / 50	16.1 (50)	89	50 / 50	15.0 (50)	83	50 / 50	12.3 (50)	68	50 / 50
14	18.1 (50)	50 / 50	16.1 (50)	89	50 / 50	14.4 (50)	80	50 / 50	12.4 (50)	69	50 / 50
18	18.0 (50)	50 / 50	16.6 (50)	92	50 / 50	15.2 (50)	84	50 / 50	12.7 (50)	71	50 / 50
22	17.3 (50)	50 / 50	15.5 (50)	90	50 / 50	14.8 (50)	86	50 / 50	12.4 (50)	72	50 / 50
26	17.2 (50)	50 / 50	15.7 (50)	91	50 / 50	14.3 (50)	83	50 / 50	12.2 (50)	71	50 / 50
30	16.1 (50)	50 / 50	14.8 (50)	92	50 / 50	13.7 (50)	85	50 / 50	11.6 (50)	72	50 / 50
34	16.5 (50)	50 / 50	15.1 (50)	92	50 / 50	14.3 (50)	87	50 / 50	12.1 (50)	73	50 / 50
38	16.7 (50)	50 / 50	15.2 (49)	91	50 / 50	14.6 (50)	87	50 / 50	12.5 (50)	75	50 / 50
42	16.5 (50)	50 / 50	15.4 (50)	93	50 / 50	14.4 (50)	87	50 / 50	12.8 (49)	78	50 / 50
46	16.9 (50)	50 / 50	15.3 (50)	91	50 / 50	14.3 (50)	85	50 / 50	12.6 (50)	75	50 / 50
50	16.9 (50)	50 / 50	15.6 (50)	92	50 / 50	14.8 (50)	88	50 / 50	13.4 (50)	79	50 / 50
54	17.0 (50)	50 / 50	15.7 (50)	92	50 / 50	14.8 (50)	87	50 / 50	13.6 (50)	80	50 / 50
58	17.2 (50)	50 / 50	15.1 (50)	88	50 / 50	14.4 (50)	84	50 / 50	13.0 (49)	76	49 / 50
62	17.1 (50)	50 / 50	15.6 (50)	91	50 / 50	14.8 (50)	87	50 / 50	13.5 (49)	79	49 / 50
66	16.6 (50)	50 / 50	14.8 (50)	89	50 / 50	14.2 (50)	86	50 / 50	13.3 (48)	80	48 / 50
70	17.9 (50)	50 / 50	15.5 (50)	87	50 / 50	14.6 (49)	82	49 / 50	13.8 (48)	77	48 / 50
74	17.6 (50)	50 / 50	15.9 (49)	90	49 / 50	14.5 (49)	82	49 / 50	13.0 (48)	74	48 / 50
78	17.7 (50)	50 / 50	16.4 (47)	93	47 / 50	14.8 (47)	84	47 / 50	13.7 (48)	77	48 / 50
82	17.6 (49)	49 / 50	16.3 (47)	93	47 / 50	14.4 (46)	82	46 / 50	13.8 (48)	78	48 / 50
86	18.6 (47)	47 / 50	15.5 (46)	83	46 / 50	14.6 (46)	78	46 / 50	13.9 (48)	75	48 / 50
90	18.6 (46)	46 / 50	15.7 (46)	84	46 / 50	14.5 (46)	78	46 / 50	14.2 (47)	76	47 / 50
94	19.5 (44)	45 / 50	16.7 (42)	86	42 / 50	14.7 (45)	75	45 / 50	14.2 (46)	73	46 / 50
98	20.7 (44)	44 / 50	17.3 (40)	84	40 / 50	15.6 (43)	75	43 / 50	15.1 (44)	73	44 / 50
102	19.5 (42)	42 / 50	17.4 (39)	89	39 / 50	15.3 (42)	78	43 / 50	15.5 (43)	79	43 / 50
104	20.0 (41)	41 / 50	18.2 (36)	91	36 / 50	15.2 (42)	76	42 / 50	15.3 (42)	77	42 / 50

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

TABLE 4 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Week on Study	Control		250 ppm			500 ppm			1000 ppm		
	Av. WC.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>
1	15.0 (50)	50 / 50	15.2 (50)	101	50 / 50	13.9 (50)	93	50 / 50	11.6 (49)	77	50 / 50
2	17.2 (49)	50 / 50	16.0 (48)	93	50 / 50	15.4 (49)	90	50 / 50	11.8 (50)	69	50 / 50
3	17.4 (49)	50 / 50	16.5 (49)	95	50 / 50	14.3 (50)	82	50 / 50	11.8 (48)	68	50 / 50
4	17.8 (50)	50 / 50	17.1 (49)	96	50 / 50	14.5 (50)	81	50 / 50	11.5 (50)	65	50 / 50
5	17.7 (47)	50 / 50	17.2 (46)	97	50 / 50	15.3 (49)	86	50 / 50	11.4 (50)	64	50 / 50
6	17.1 (46)	50 / 50	19.1 (47)	112	50 / 50	15.9 (50)	93	50 / 50	11.4 (48)	67	50 / 50
7	16.3 (49)	50 / 50	15.3 (48)	94	50 / 50	13.0 (50)	80	50 / 50	10.4 (50)	64	50 / 50
8	18.0 (48)	50 / 50	17.3 (48)	96	50 / 50	13.7 (49)	76	50 / 50	11.2 (50)	62	50 / 50
9	18.2 (49)	50 / 50	18.5 (49)	102	50 / 50	15.5 (50)	85	50 / 50	11.6 (50)	64	50 / 50
10	18.0 (48)	50 / 50	17.7 (48)	98	50 / 50	15.2 (48)	84	50 / 50	11.3 (50)	63	50 / 50
11	17.0 (50)	50 / 50	17.0 (50)	100	50 / 50	14.5 (50)	85	50 / 50	11.0 (50)	65	50 / 50
12	16.7 (49)	50 / 50	16.9 (49)	101	50 / 50	14.5 (50)	87	50 / 50	10.9 (50)	65	50 / 50
13	18.1 (47)	50 / 50	18.0 (46)	99	50 / 50	14.4 (49)	80	50 / 50	10.8 (50)	60	50 / 50
14	20.4 (50)	50 / 50	19.6 (50)	96	50 / 50	14.6 (49)	72	50 / 50	10.9 (50)	53	50 / 50
18	19.2 (47)	50 / 50	17.3 (47)	90	50 / 50	15.4 (49)	80	50 / 50	11.7 (50)	61	50 / 50
22	16.6 (48)	50 / 50	16.5 (50)	99	50 / 50	14.8 (50)	89	50 / 50	11.0 (50)	66	50 / 50
26	16.5 (49)	50 / 50	17.1 (50)	104	50 / 50	14.7 (50)	89	50 / 50	10.8 (50)	65	50 / 50
30	17.8 (50)	50 / 50	15.7 (50)	88	50 / 50	14.0 (50)	79	50 / 50	10.7 (50)	60	50 / 50
34	15.8 (50)	50 / 50	15.4 (50)	97	50 / 50	13.3 (50)	84	50 / 50	10.4 (49)	66	50 / 50
38	15.7 (50)	50 / 50	14.4 (49)	92	50 / 50	13.0 (50)	83	50 / 50	10.6 (48)	68	50 / 50
42	15.4 (50)	50 / 50	14.5 (49)	94	50 / 50	13.6 (50)	88	50 / 50	10.8 (49)	70	50 / 50
46	14.9 (50)	50 / 50	14.3 (49)	96	50 / 50	13.3 (49)	89	49 / 50	10.8 (50)	72	50 / 50
50	14.6 (50)	50 / 50	13.9 (50)	95	50 / 50	12.7 (49)	87	49 / 50	11.1 (50)	76	50 / 50
54	15.2 (50)	50 / 50	14.4 (50)	95	50 / 50	13.5 (49)	89	49 / 50	11.4 (50)	75	50 / 50
58	14.7 (50)	50 / 50	14.1 (50)	96	50 / 50	12.9 (49)	88	49 / 50	11.1 (50)	76	50 / 50
62	14.9 (50)	50 / 50	14.4 (49)	97	49 / 50	12.9 (49)	87	49 / 50	11.3 (50)	76	50 / 50
66	14.6 (50)	50 / 50	13.8 (49)	95	49 / 50	12.9 (49)	88	49 / 50	12.0 (50)	82	50 / 50
70	15.1 (49)	49 / 50	14.0 (49)	93	49 / 50	12.8 (49)	85	49 / 50	11.6 (48)	77	49 / 50
74	14.3 (48)	48 / 50	13.9 (47)	97	47 / 50	12.4 (49)	87	49 / 50	11.3 (49)	79	49 / 50
78	15.8 (48)	48 / 50	14.2 (47)	90	47 / 50	13.1 (49)	83	49 / 50	11.3 (48)	72	48 / 50
82	16.0 (47)	47 / 50	13.9 (46)	87	46 / 50	12.9 (49)	81	49 / 50	11.5 (48)	72	48 / 50
86	15.3 (47)	47 / 50	14.4 (45)	94	45 / 50	13.2 (49)	86	49 / 50	11.2 (47)	73	48 / 50
90	15.6 (45)	45 / 50	14.0 (45)	90	45 / 50	13.2 (49)	85	49 / 50	11.8 (46)	76	46 / 50
94	16.3 (44)	45 / 50	15.1 (45)	93	45 / 50	13.7 (48)	84	48 / 50	12.3 (45)	75	45 / 50
98	16.9 (44)	44 / 50	16.2 (43)	96	43 / 50	13.8 (44)	82	45 / 50	12.3 (42)	73	44 / 50
102	17.7 (40)	41 / 50	15.7 (40)	89	40 / 50	13.7 (44)	77	44 / 50	12.6 (42)	71	42 / 50
104	18.1 (40)	41 / 50	15.8 (38)	87	38 / 50	14.4 (44)	80	44 / 50	12.6 (41)	70	41 / 50

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

TABLE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Week on Study	Control		500 ppm			1000 ppm			2000 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	13.3 (50)	50 / 50	12.7 (50)	95	50 / 50	12.0 (50)	90	50 / 50	10.3 (50)	77	50 / 50
2	14.4 (50)	50 / 50	13.9 (50)	97	50 / 50	13.5 (50)	94	50 / 50	12.2 (50)	85	50 / 50
3	15.7 (50)	50 / 50	14.7 (50)	94	50 / 50	14.6 (50)	93	50 / 50	13.4 (50)	85	50 / 50
4	16.1 (50)	50 / 50	15.4 (50)	96	50 / 50	15.3 (50)	95	50 / 50	14.1 (50)	88	50 / 50
5	15.8 (50)	50 / 50	15.3 (50)	97	50 / 50	15.2 (50)	96	50 / 50	14.2 (50)	90	50 / 50
6	15.9 (50)	50 / 50	15.1 (50)	95	50 / 50	15.1 (50)	95	50 / 50	13.9 (50)	87	50 / 50
7	15.5 (50)	50 / 50	14.8 (50)	95	50 / 50	14.8 (49)	95	50 / 50	13.5 (50)	87	50 / 50
8	15.6 (50)	50 / 50	14.7 (49)	94	50 / 50	14.9 (50)	96	50 / 50	13.6 (50)	87	50 / 50
9	15.5 (50)	50 / 50	14.9 (50)	96	50 / 50	14.8 (50)	95	50 / 50	13.6 (50)	88	50 / 50
10	15.5 (50)	50 / 50	15.1 (50)	97	50 / 50	15.4 (49)	99	50 / 50	13.8 (50)	89	50 / 50
11	15.6 (50)	50 / 50	15.0 (50)	96	50 / 50	15.4 (50)	99	50 / 50	14.0 (50)	90	50 / 50
12	15.6 (50)	50 / 50	15.0 (50)	96	50 / 50	15.6 (50)	100	50 / 50	14.3 (50)	92	50 / 50
13	15.3 (50)	50 / 50	14.8 (50)	97	50 / 50	15.1 (50)	99	50 / 50	13.9 (50)	91	50 / 50
14	15.2 (50)	50 / 50	14.6 (50)	96	50 / 50	14.8 (50)	97	50 / 50	13.7 (50)	90	50 / 50
18	15.0 (50)	50 / 50	14.9 (50)	99	50 / 50	14.6 (50)	97	50 / 50	13.7 (50)	91	50 / 50
22	15.3 (50)	50 / 50	14.9 (50)	97	50 / 50	15.4 (50)	101	50 / 50	14.3 (50)	93	50 / 50
26	15.5 (50)	50 / 50	15.3 (50)	99	50 / 50	15.2 (50)	98	50 / 50	14.4 (50)	93	50 / 50
30	15.1 (50)	50 / 50	14.9 (50)	99	50 / 50	14.9 (50)	99	50 / 50	14.0 (50)	93	50 / 50
34	15.2 (50)	50 / 50	15.3 (50)	101	50 / 50	15.3 (50)	101	50 / 50	14.7 (50)	97	50 / 50
38	15.5 (50)	50 / 50	15.5 (50)	100	50 / 50	15.6 (50)	101	50 / 50	14.6 (50)	94	50 / 50
42	15.5 (50)	50 / 50	15.8 (50)	102	50 / 50	15.7 (50)	101	50 / 50	15.0 (50)	97	50 / 50
46	15.7 (50)	50 / 50	15.7 (50)	100	50 / 50	15.8 (50)	101	50 / 50	14.9 (50)	95	50 / 50
50	15.8 (50)	50 / 50	15.7 (50)	99	50 / 50	15.9 (50)	101	50 / 50	15.0 (50)	95	50 / 50
54	16.2 (50)	50 / 50	16.1 (50)	99	50 / 50	16.2 (50)	100	50 / 50	15.3 (50)	94	50 / 50
58	16.1 (50)	50 / 50	15.8 (50)	98	50 / 50	15.8 (50)	98	50 / 50	15.2 (49)	94	49 / 50
62	15.9 (50)	50 / 50	15.8 (50)	99	50 / 50	15.8 (50)	99	50 / 50	14.7 (49)	92	49 / 50
66	15.9 (50)	50 / 50	15.2 (50)	96	50 / 50	15.1 (50)	95	50 / 50	13.8 (48)	87	48 / 50
70	15.9 (50)	50 / 50	15.3 (50)	96	50 / 50	15.3 (49)	96	49 / 50	14.5 (48)	91	48 / 50
74	16.1 (50)	50 / 50	15.2 (49)	94	49 / 50	15.8 (49)	98	49 / 50	14.5 (48)	90	48 / 50
78	16.1 (50)	50 / 50	16.0 (47)	99	47 / 50	15.8 (47)	98	47 / 50	14.6 (48)	91	48 / 50
82	15.8 (49)	49 / 50	15.7 (47)	99	47 / 50	15.5 (46)	98	46 / 50	14.5 (48)	92	48 / 50
86	15.8 (47)	47 / 50	15.3 (46)	97	46 / 50	15.3 (46)	97	46 / 50	14.0 (48)	89	48 / 50
90	16.3 (46)	46 / 50	15.5 (46)	95	46 / 50	15.3 (46)	94	46 / 50	14.1 (47)	87	47 / 50
94	16.0 (45)	45 / 50	15.3 (42)	96	42 / 50	15.1 (45)	94	45 / 50	13.8 (46)	86	46 / 50
98	15.9 (44)	44 / 50	15.6 (40)	98	40 / 50	15.0 (43)	94	43 / 50	14.0 (44)	88	44 / 50
102	15.7 (42)	42 / 50	15.5 (37)	99	39 / 50	14.9 (43)	95	43 / 50	13.9 (43)	89	43 / 50
104	15.5 (41)	41 / 50	16.2 (36)	105	36 / 50	14.7 (42)	95	42 / 50	13.4 (42)	86	42 / 50

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

TABLE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Week on Study	Control		250 ppm			500 ppm			1000 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	10.5 (50)	50 / 50	10.5 (50)	100	50 / 50	10.0 (50)	95	50 / 50	9.3 (50)	89	50 / 50
2	10.7 (50)	50 / 50	10.9 (50)	102	50 / 50	10.6 (50)	99	50 / 50	10.1 (50)	94	50 / 50
3	10.9 (50)	50 / 50	11.0 (50)	101	50 / 50	10.9 (50)	100	50 / 50	10.3 (50)	94	50 / 50
4	11.0 (50)	50 / 50	11.1 (50)	101	50 / 50	10.9 (50)	99	50 / 50	10.1 (50)	92	50 / 50
5	10.9 (50)	50 / 50	10.8 (50)	99	50 / 50	10.6 (50)	97	50 / 50	10.0 (50)	92	50 / 50
6	10.6 (50)	50 / 50	10.6 (50)	100	50 / 50	10.4 (50)	98	50 / 50	9.5 (50)	90	50 / 50
7	10.3 (50)	50 / 50	10.4 (50)	101	50 / 50	10.2 (50)	99	50 / 50	9.5 (50)	92	50 / 50
8	10.5 (50)	50 / 50	10.5 (50)	100	50 / 50	10.3 (50)	98	50 / 50	9.8 (50)	93	50 / 50
9	10.5 (50)	50 / 50	10.7 (50)	102	50 / 50	10.3 (50)	98	50 / 50	9.8 (50)	93	50 / 50
10	10.3 (50)	50 / 50	10.6 (50)	103	50 / 50	10.5 (50)	102	50 / 50	9.8 (50)	95	50 / 50
11	10.5 (50)	50 / 50	10.8 (50)	103	50 / 50	10.5 (50)	100	50 / 50	9.8 (50)	93	50 / 50
12	10.5 (50)	50 / 50	10.8 (50)	103	50 / 50	10.5 (50)	100	50 / 50	9.9 (50)	94	50 / 50
13	10.2 (50)	50 / 50	10.5 (50)	103	50 / 50	10.4 (50)	102	50 / 50	9.7 (50)	95	50 / 50
14	10.1 (50)	50 / 50	10.5 (50)	104	50 / 50	10.2 (50)	101	50 / 50	9.4 (50)	93	50 / 50
18	10.3 (50)	50 / 50	10.5 (50)	102	50 / 50	10.3 (50)	100	50 / 50	9.6 (50)	93	50 / 50
22	10.5 (50)	50 / 50	10.7 (50)	102	50 / 50	10.6 (49)	101	50 / 50	9.9 (50)	94	50 / 50
26	10.5 (50)	50 / 50	10.9 (50)	104	50 / 50	10.8 (50)	103	50 / 50	10.1 (50)	96	50 / 50
30	10.8 (50)	50 / 50	10.9 (50)	101	50 / 50	10.7 (50)	99	50 / 50	10.0 (49)	93	50 / 50
34	10.7 (50)	50 / 50	10.9 (50)	102	50 / 50	10.6 (49)	99	50 / 50	10.0 (50)	93	50 / 50
38	10.7 (50)	50 / 50	10.8 (50)	101	50 / 50	10.5 (49)	98	50 / 50	10.0 (50)	93	50 / 50
42	11.1 (50)	50 / 50	11.2 (50)	101	50 / 50	10.9 (50)	98	50 / 50	10.4 (50)	94	50 / 50
46	11.1 (50)	50 / 50	11.2 (50)	101	50 / 50	10.9 (49)	98	49 / 50	10.4 (50)	94	50 / 50
50	11.2 (50)	50 / 50	11.1 (50)	99	50 / 50	11.0 (49)	98	49 / 50	10.6 (50)	95	50 / 50
54	11.4 (50)	50 / 50	11.3 (50)	99	50 / 50	10.9 (49)	96	49 / 50	10.6 (50)	93	50 / 50
58	11.1 (50)	50 / 50	11.2 (50)	101	50 / 50	11.2 (49)	101	49 / 50	10.6 (50)	95	50 / 50
62	11.2 (50)	50 / 50	11.2 (48)	100	49 / 50	11.0 (49)	98	49 / 50	10.3 (50)	92	50 / 50
66	11.1 (50)	50 / 50	11.0 (49)	99	49 / 50	10.9 (49)	98	49 / 50	10.3 (50)	93	50 / 50
70	11.3 (49)	49 / 50	11.4 (49)	101	49 / 50	11.1 (49)	98	49 / 50	10.4 (49)	92	49 / 50
74	11.3 (48)	48 / 50	11.4 (47)	101	47 / 50	11.1 (49)	98	49 / 50	10.6 (49)	94	49 / 50
78	11.9 (48)	48 / 50	11.7 (46)	98	47 / 50	11.3 (49)	95	49 / 50	10.6 (48)	89	48 / 50
82	12.2 (47)	47 / 50	11.7 (46)	96	46 / 50	11.5 (49)	94	49 / 50	10.9 (48)	89	48 / 50
86	11.7 (47)	47 / 50	11.6 (45)	99	45 / 50	11.3 (49)	97	49 / 50	10.4 (48)	89	48 / 50
90	11.9 (45)	45 / 50	11.9 (45)	100	45 / 50	11.5 (49)	97	49 / 50	10.9 (46)	92	46 / 50
94	11.9 (45)	45 / 50	11.7 (45)	98	45 / 50	11.2 (48)	94	48 / 50	10.7 (45)	90	45 / 50
98	11.9 (44)	44 / 50	12.1 (43)	102	43 / 50	11.4 (45)	96	45 / 50	10.6 (44)	89	44 / 50
102	12.1 (41)	41 / 50	11.8 (40)	98	40 / 50	11.1 (44)	92	44 / 50	10.6 (42)	88	42 / 50
104	11.6 (41)	41 / 50	11.2 (38)	97	38 / 50	11.2 (44)	97	44 / 50	10.5 (40)	91	41 / 50

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

TABLE 7 INCIDENCES OF EXTERNAL AND INTERNAL MASSES IN CLINICAL OBSERVATION OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Time of mass occurrence (week)	0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass									
Control	0/50	0/50	0/50	1/50	2/50	3/50	2/50	7/46	10/50(2/ 9)
500 ppm	1/50	0/50	0/50	2/50	6/50	12/50	15/47	19/45	22/50(7/14)
1000 ppm	0/50	0/50	0/50	0/50	2/50	3/50	7/46	10/46	14/50(2/ 8)
2000 ppm	0/50	0/50	0/50	0/50	5/50	4/48	7/48	8/47	11/50(1/ 8)
Internal mass									
Control	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/46	1/50(1/ 9)
500 ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/47	0/45	0/50(0/14)
1000 ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/46	2/46	2/50(1/ 8)
2000 ppm	0/50	0/50	0/50	0/50	0/50	0/48	0/48	2/47	2/50(0/ 8)

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

TABLE 8 INCIDENCES OF EXTERNAL AND INTERNAL MASSES IN CLINICAL OBSERVATION OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Time of mass occurrence (week)	0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass									
Control	0/50	0/50	0/50	0/50	1/50	2/50	5/48	8/45	9/50(3/ 9)
250 ppm	0/50	0/50	0/50	0/50	1/50	3/49	4/46	6/45	9/50(4/12)
500 ppm	0/50	0/50	0/50	0/50	0/49	1/49	4/49	10/49	11/50(2/ 6)
1000 ppm	0/50	0/50	1/50	1/50	2/50	1/50	3/48	4/46	6/50(4/ 9)
Internal mass									
Control	0/50	0/50	0/50	0/50	0/50	0/50	0/48	0/45	0/50(0/ 9)
250 ppm	0/50	0/50	0/50	0/50	0/50	2/49	0/46	3/45	5/50(2/12)
500 ppm	0/50	0/50	0/50	0/50	0/49	0/49	0/49	0/49	0/50(0/ 6)
1000 ppm	0/50	0/50	0/50	0/50	0/50	0/50	2/48	3/46	4/50(3/ 9)

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

TABLE 9 HEMATOLOGY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	500 ppm	1000 ppm	2000 ppm
No. of examined animals	40	36	42	42
MCV (fL)	50.1 ± 7.7	48.4 ± 2.3	48.8 ± 4.4 *	50.0 ± 3.7
MCH (pg)	16.8 ± 2.0	16.2 ± 1.5 *	16.4 ± 1.3 *	16.8 ± 1.2

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

TABLE 10 HEMATOLOGY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	250 ppm	500 ppm	1000 ppm
No. of examined animals	39	38	43	41
Hemoglobin (g/dL)	14.5 ± 1.8	14.1 ± 3.2	13.9 ± 2.8	14.0 ± 1.8 *
MCV (fL)	53.2 ± 3.4	55.5 ± 14.1	54.4 ± 10.0	52.1 ± 5.8 **
MCH (pg)	18.4 ± 0.8	18.8 ± 2.7	18.5 ± 2.5	17.9 ± 1.9 **
MCHC (g/dL)	34.7 ± 1.0	34.3 ± 2.2	34.2 ± 1.9	34.4 ± 0.8 **
Platelet(10^3/μL)	644 ± 115	578 ± 154	661 ± 156	777 ± 168 **

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

TABLE 11 BIOCHEMISTRY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	500 ppm		1000 ppm		2000 ppm	
No. of examined animals	40	36		42		42	
Total protein(g/dL)	6.8 ± 0.4	6.6 ± 0.4		6.7 ± 0.3		6.5 ± 0.4	**
A/G ratio	1.1 ± 0.1	1.1 ± 0.1		1.1 ± 0.1		1.2 ± 0.1	**
T-cholesterol (mg/dL)	185 ± 72	172 ± 77		155 ± 52		123 ± 39	**
Phospholipid (mg/dL)	272 ± 98	265 ± 103		237 ± 69		201 ± 51	**
GOT (IU/L)	97 ± 49	76 ± 25		167 ± 270		1887 ± 10973	*
GPT (IU/L)	45 ± 23	41 ± 17		90 ± 168		256 ± 1059	*
γ-GTP (IU/L)	12 ± 6	14 ± 6		23 ± 36	*	16 ± 12	
CPK (IU/L)	92 ± 26	82 ± 14		87 ± 31	*	97 ± 88	
Urea nitrogen (mg/L)	19.1 ± 2.0	20.0 ± 2.8		19.6 ± 3.7		26.0 ± 19.2	**
Sodium (mEq/L)	142 ± 2	141 ± 2		141 ± 1	*	141 ± 2	*
Potassium (mEq/L)	3.9 ± 0.3	4.0 ± 0.3		4.1 ± 0.3		4.3 ± 1.0	**
Calcium (mg/dL)	10.3 ± 0.4	10.1 ± 0.3	*	10.2 ± 0.3		10.0 ± 0.4	**

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

TABLE 12 BIOCHEMISTRY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	250 ppm		500 ppm	1000 ppm	
No. of examined animals	39	38		43	41	
Total protein (g/dL)	7.1 ± 0.4	6.8 ± 0.5	**	6.9 ± 0.5	7.0 ± 0.4	
T-cholesterol (mg/dL)	139 ± 36	132 ± 34		139 ± 32	165 ± 36	**
Phospholipid (mg/dL)	257 ± 64	247 ± 64		254 ± 48	290 ± 51	*
GOT (IU/L)	127 ± 82	179 ± 263		179 ± 325	596 ± 928	**
GPT (IU/L)	54 ± 26	62 ± 54		78 ± 218	254 ± 322	**
ALP (IU/L)	139 ± 81	193 ± 313		141 ± 128	206 ± 128	**
γ-GTP (IU/L)	6 ± 5	7 ± 6		9 ± 13	42 ± 56	**
Urea Nitrogen (mg/dL)	17.2 ± 5.3	17.1 ± 2.7		18.8 ± 11.6	18.7 ± 3.2	**
Calcium (mg/dL)	10.3 ± 0.3	10.2 ± 0.3		10.4 ± 0.4	10.5 ± 0.4	*

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

TABLE 13 URINALYSIS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group	Grade	Control	500 ppm	1000 ppm	2000 ppm
Number of examined animals		40	36	42	43
pH	6.0	2	0	2	7
	6.5	4	6	12	12
	7.0	10	11	12	12
	7.5	23	18	12	10
	8.0	1	1	4	2
	8.5	0	0	0	0
	Chi square test				*
Occult blood	−	37	30	33	8
	±	2	2	2	1
	+	1	1	0	1
	2+	0	1	3	4
	3+	0	2	4	29
	Chi square test				**

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

TABLE 14 URINALYSIS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group	Grade	Control	250 ppm	500 ppm	1000 ppm
Number of examined animals		41	39	44	41
pH	6.0	0	3	2	6
	6.5	4	2	13	20
	7.0	10	9	15	11
	7.5	12	10	9	3
	8.0	14	14	5	1
	8.5	1	1	0	0
	Chi square test			*	**
Protein	±	3	1	1	0
	+	12	6	9	4
	2+	13	15	14	15
	3+	6	10	13	17
	4+	7	7	7	5
	Chi square test				*
Ketone body	-	22	11	11	9
	±	18	27	33	32
	+	1	1	0	0
	Chi square test			*	**
Occult blood	−	39	35	39	21
	±	1	0	1	4
	+	0	0	1	0
	2+	0	0	1	3
	3+	1	4	2	13
	Chi square test				**

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

TABLE 15 ORGAN WEIGHTS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	500 ppm	1000 ppm	2000 ppm
No. of examined animals	41	36	42	42
Body weight (g)	382 ± 33	355 ± 47 *	330 ± 22 **	269 ± 29 **
Adrenals (g)	0.082 ± 0.072	0.064 ± 0.009	0.058 ± 0.008 **	0.069 ± 0.108 **
Adrenals (%)	0.022 ± 0.022	0.018 ± 0.003	0.018 ± 0.002	0.026 ± 0.043
Testes (g)	2.751 ± 1.358	3.444 ± 0.946 *	3.796 ± 1.093 **	3.334 ± 1.356
Testes (%)	0.721 ± 0.346	0.983 ± 0.278 **	1.155 ± 0.347 **	1.247 ± 0.483 **
Heart (g)	1.283 ± 0.203	1.195 ± 0.128	1.104 ± 0.084 **	0.975 ± 0.097 **
Heart (%)	0.338 ± 0.065	0.342 ± 0.057	0.336 ± 0.034	0.364 ± 0.027 **
Lungs (g)	1.448 ± 0.319	1.360 ± 0.098	1.383 ± 0.466 **	1.192 ± 0.095 **
Lungs (%)	0.381 ± 0.091	0.388 ± 0.047	0.421 ± 0.157 **	0.447 ± 0.054 **
Kidneys (g)	2.633 ± 0.322	2.564 ± 0.179	2.490 ± 0.171	2.255 ± 0.220 **
Kidneys (%)	0.692 ± 0.093	0.732 ± 0.090 *	0.756 ± 0.049 **	0.845 ± 0.095 **
Spleen (g)	1.290 ± 1.941	0.942 ± 0.396	0.918 ± 0.609	0.589 ± 0.486 **
Spleen (%)	0.342 ± 0.536	0.271 ± 0.128	0.276 ± 0.169	0.223 ± 0.212 **
Liver (g)	11.367 ± 2.693	10.606 ± 1.290	10.651 ± 2.410	9.269 ± 3.410 **
Liver (%)	2.986 ± 0.753	3.009 ± 0.344	3.241 ± 0.818 **	3.461 ± 1.344 **
Brain (g)	2.043 ± 0.060	2.007 ± 0.049 **	1.988 ± 0.046 **	1.929 ± 0.048 **
Brain (%)	0.538 ± 0.045	0.573 ± 0.056 *	0.605 ± 0.043 **	0.726 ± 0.083 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 16 ORGAN WEIGHTS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group name	Control	250 ppm	500 ppm	1000 ppm
No. of examined animals	41	38	44	41
Body weight (g)	253 ± 23	237 ± 30	234 ± 24 **	204 ± 19 **
Adrenals (g)	0.076 ± 0.053	0.070 ± 0.013	0.065 ± 0.012	0.081 ± 0.135 **
Adrenals (%)	0.030 ± 0.020	0.030 ± 0.007	0.028 ± 0.006	0.040 ± 0.069
Ovaries (g)	0.135 ± 0.019	0.125 ± 0.020	0.127 ± 0.024	0.124 ± 0.021
Ovaries (%)	0.053 ± 0.007	0.053 ± 0.008	0.054 ± 0.009	0.061 ± 0.011 **
Heart (g)	0.874 ± 0.063	0.878 ± 0.096	0.870 ± 0.081	0.791 ± 0.079 **
Heart (%)	0.348 ± 0.031	0.377 ± 0.073	0.376 ± 0.054 *	0.389 ± 0.037 **
Lungs (g)	1.015 ± 0.094	1.084 ± 0.303	1.051 ± 0.315	0.957 ± 0.146 **
Lungs (%)	0.404 ± 0.048	0.473 ± 0.190	0.454 ± 0.152	0.474 ± 0.093 **
Kidneys (g)	1.729 ± 0.140	1.715 ± 0.133	1.712 ± 0.126	1.691 ± 0.153
Kidneys (%)	0.688 ± 0.071	0.739 ± 0.139	0.738 ± 0.087 *	0.833 ± 0.085 **
Spleen (g)	0.660 ± 0.566	1.312 ± 2.723	0.697 ± 0.707	0.716 ± 1.332
Spleen (%)	0.264 ± 0.230	0.616 ± 1.402	0.307 ± 0.353	0.363 ± 0.734
Liver (g)	6.694 ± 0.951	6.580 ± 1.098	6.814 ± 1.323	9.406 ± 3.630 **
Liver (%)	2.653 ± 0.338	2.809 ± 0.538	2.934 ± 0.626	4.649 ± 1.846 **
Brain (g)	1.862 ± 0.049	1.854 ± 0.044	1.833 ± 0.043 *	1.826 ± 0.050 **
Brain (%)	0.743 ± 0.071	0.797 ± 0.119	0.792 ± 0.088 *	0.904 ± 0.097 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 17 INCIDENCES OF SELECTED LESIONS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group		Control	500 ppm	1000 ppm	2000 ppm	Peto	Cochran-
Number of examined animals		50	50	50	50	test	Armitage test
Organ / Findings	Grade of nonneoplastic finding						
Nasal cavity							
Mineralization	1+	20	24	22	9		
	Chi square test				*		
Inflammation:foreign body	1+	15	10	10	3		
	2+	1	2	3	2		
	3+	0	1	0	1		
	Chi square test				*		
Eosinophilic change: olfactory epithelium	1+	27	25	21	20		
	2+	4	7	16	22		
	3+	2	1	2	6		
	Chi square test			*	**		
Heart							
Myocardial fibrosis	1+	19	20	16	9		
	Chi square test				*		
Tooth							
Inflammation	1+	11	0	1	8		
	2+	1	0	0	0		
	Chi square test		**	**			
Liver							
Clear cell focus	1+	2	9	8	3		
	2+	0	0	3	0		
	3+	0	0	1	0		
	Chi square test			*			
Basophilic cell focus	1+	18	22	15	25		
	2+	1	9	17	12		
	3+	0	0	4	1		
	4+	0	0	1	0		
	Chi square test		**	**	**		
Hepatocellular adenoma 1)		3	2	12 *	15 **	↑ ↑	↑ ↑
Hepatocellular carcinoma 2)		1	1	6	10 **	↑ ↑	↑ ↑
1)+2)		4	3	16 **	22 **	↑ ↑	↑ ↑
Pancreas							
Islet cell adenoma		7	3	1 *	1 *		↓

Grade 1+: Slight 2+:Moderate 3+:Marked 4+:Severe

Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test for non-neoplastic lesion

Fisher's exact test for neoplastic lesion

↑(↓) : $p<0.05$ ↑ ↑(↓ ↓) : $p<0.01$ Peto or Cochran-Armitage test for neoplastic lesion

The combined incidences indicate the tumor-bearing animals but not the tumors.

TABLE 17 INCIDENCES OF SELECTED LESIONS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE (Continued)

Group		Control	500 ppm	1000 ppm	2000 ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50	test	test
Organ / Findings	Grade of Nonneoplastic finding						
Kidney							
Infract	1+	0	2	2	6		
	2+	0	0	0	1		
	Chi square test				*		
Chronic nephropathy	1+	3	10	8	16		
	2+	25	18	18	19		
	3+	20	13	20	5		
	4+	2	3	0	0		
	Chi square test		*		**		
Papillary necrosis	1+	0	0	0	10		
	2+	0	0	0	5		
	Chi square test				**		
Mineralization:papilla	1+	7	18	16	24		
	2+	0	0	0	2		
	Chi square test		*		**		
Urothelial hyperplasia:pelvis	1+	8	10	17	19		
	2+	0	0	1	3		
	Chi square test				**		
Urinary bladder							
Simple hyperplasia:	1+	1	0	3	6		
transitional epithelium	3+	0	1	0	0		
	Chi square test						
Nodular hyperplasia:	1+	0	1	1	6		
transitional epithelium	Chi square test				*		
Transitional cell papilloma 3)		1	0	0	6	↑↑	↑↑
Transitional cell carcinoma 4)		1	0	0	4	↑	↑
3)+4)		2	0	0	10 *	↑↑	↑↑
Pituitary							
Adenoma		25	20	10 **	13 *		↓↓
Thyroid							
Follicular adenoma 5)		0	1	0	4	↑↑	↑
Follicular adenocarcinoma 6)		1	0	1	1		
5)+6)		1	1	1	5	↑	↑
Testis							
Atrophy	1+	47	46	43	35		
	Chi square test				**		
Intrestitial cell tumor		37	39	45 *	43	↑	

Grade 1+: Slight 2+:Moderate 3+:Marked 4+:Severe

Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test for non-neoplastic lesion

Fisher's exact test for neoplastic lesion

↑(↓) : $p<0.05$ ↑↑(↓↓) : $p<0.01$ Peto or Cochran-Armitage test for neoplastic lesion

The combined incidences indicate the tumor-bearing animals but not the tumors.

TABLE 18 INCIDENCES OF SELECTED LESIONS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

Group		Control	250 ppm	500 ppm	1000 ppm	Peto	Cochran-Armitage
Number of examined animals		50	50	50	50	test	test
Organ / Findings	Grade of nonneoplastic finding						
Nasal cavity							
Mineralization	1+	24	16	16	12		
	Chi square test				*		
Eosinophilic change: olfactory epithelium	1+	20	13	8	6		
	2+	23	17	28	12		
	3+	5	15	11	29		
	4+	0	0	0	1		
	Chi square test		*	*	**		
Lung							
Metastasis :liver tumor		0	0	0	5		
Liver							
Basophilic cell focus	1+	7	15	21	17		
	2+	1	6	13	8		
	3+	0	0	5	8		
	Chi square test		*	**	**		
Bile duct hyperplasia	1+	13	10	10	3		
	Chi square test				*		
Hepatocellular adenoma 1)		1	3	15 **	36 **	↑ ↑	↑ ↑
Hepatocellular carcinoma 2)		0	0	4	18 **	↑ ↑	↑ ↑
1)+2)		1	3	19 **	44 **	↑ ↑	↑ ↑
Pancreas							
Atrophy	1+	0	6	1	4		
	Chi square test		*				
Kidney							
Papillary necrosis	1+	2	1	1	6		
	2+	0	0	0	5		
	Chi square test				*		
Mineralization:papilla	1+	7	8	12	22		
	2+	0	1	0	2		
	Chi square test				**		
Urothelial hyperplasia:pelvis	1+	2	12	10	17		
	Chi square test		**	*	**		
Urinary bladder							
Simple hyperplasia: transitional epithelium	1+	0	1	0	0		
	2+	0	0	0	2		
	Chi square test						
Nodular hyperplasia: transitional epithelium	1+	0	0	0	1		
	Chi square test						
Transitional cell papilloma		1	0	1	1		
Pituitary							
Cyst	1+	12	24	21	15		
	2+	0	2	1	0		
	Chi square test		*				
Adenoma		23	9 **	14 *	11 **		↓

Grade 1+: Slight 2+:Moderate 3+:Marked 4+:Severe

Significant difference * : $p<0.05$ ** : $p<0.01$ Chi square test for non-neoplastic lesion

Fisher's exact test for neoplastic lesion

↑(↓) : $p<0.0$ ↑ ↑(↓ ↓) : $p<0.01$ Peto or Cochran-Armitage test for neoplastic lesion

The combined incidences indicate the tumor-bearing animals but not the tumors.

TABLE 19 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 with bearing tumors	Incidence (%)	Min. - Max. (%)
Liver	<1499>			
Hepatocellular adenoma 1)		21	1.4	0 - 6
Hepatocellular carcinoma 2)		4	0.3	0 - 2
1)+2)		25	1.7	0 - 6
Pancreas				
Islet cell adenoma	<1499>	46	2.7	0 - 12
Urinary bladder	<1498>			
Transitional cell papilloma		6	0.4	0 - 2
Pituitary gland	<1494>			
Adenoma		523	35.0	18 - 66
Thyroid	<1493>			
Follicular adenoma 1)		13	0.8	0 - 4
Follicular adenocarcinoma 2)		29	1.9	0 - 8
1)+2)		41	2.7	0 - 8
Peritoneum	<1499>			
Mesothelioma		41	2.7	0 - 8

30 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

TABLE 20 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 with bearing tumors	Incidence (%)	Min. - Max. (%)
Liver	<1447>			
Hepatocellular adenoma 1)		18	1.2	0 - 6
Hepatocellular carcinoma 2)		1	0.1	0 - 2
1)+2)		19	1.3	0 - 8
Urinary bladder	<1445>			
Transtional cell papilloma		8	0.6	0 - 2
Pituitary	<1445>			
Adenoma		570	39.4	16 - 71
Uterus	<1447>			
Endometrial stromal polyp		209	14.4	2 - 28
Mammary gland	<1447>			
Fibroadenoma		162	11.2	0 - 20

29 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

TABLE 21 CAUSE OF DEATH OF RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

		Male				Female			
Group		Control	500 ppm	1000 ppm	2000 ppm	Control	250 ppm	500 ppm	1000 ppm
Number of dead or moribund animals		9	14	8	8	9	12	6	9
No microscopical confirmation		0	1	1	2	0	0	0	0
Digestive system lesion		1	0	0	0	0	0	0	0
Chronic nephropathy		1	0	0	0	0	0	0	0
Urinary retension		0	1	0	0	0	0	0	0
Pneumonia		0	0	0	0	1	0	0	0
Arteritis		0	0	0	0	1	0	0	0
Tumor death	leukemia	1	1	3	0	2	5	2	2
	skin/app	0	1	0	0	0	0	0	1
	subcutis	0	4	1	0	0	0	0	0
	nasopharynx	0	0	0	0	0	0	0	1
	thymus	0	0	0	0	1	0	0	0
	liver	0	0	1	1	0	0	0	3
	kidney	0	0	1	0	0	0	0	0
	urinary bladder	0	0	0	3	0	0	0	0
	pituitary	3	3	0	0	3	3	2	0
	thyroid	1	0	0	1	0	0	0	0
	uterus	—	—	—	—	0	1	1	0
	mammary gland	0	0	0	0	1	0	0	0
	brain	1	1	0	1	0	1	0	0
	spinal cord	1	0	0	0	0	0	0	0
	Zymbal gland	0	0	0	0	0	0	1	1
	bone	0	1	1	0	0	1	0	1
	mediastium	0	1	0	0	0	1	0	0

FIGURES

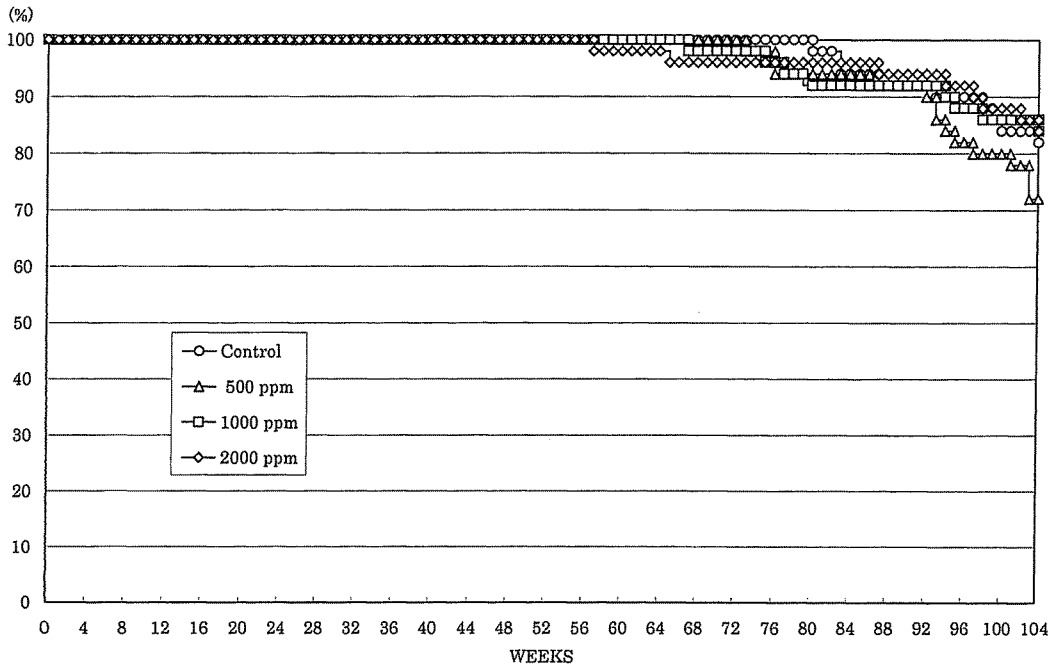


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

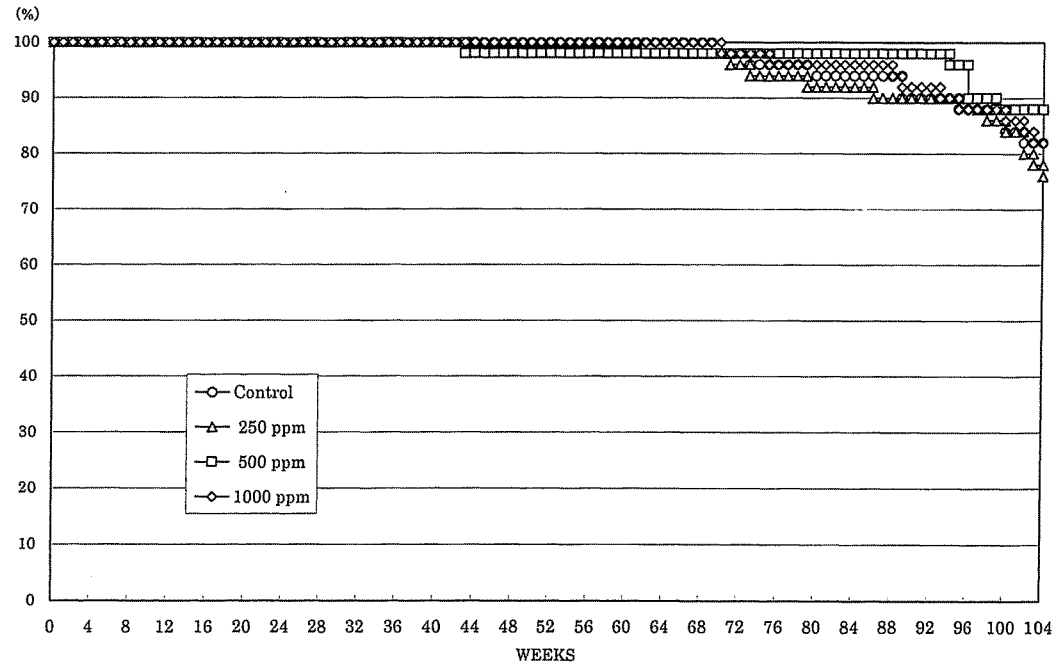


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

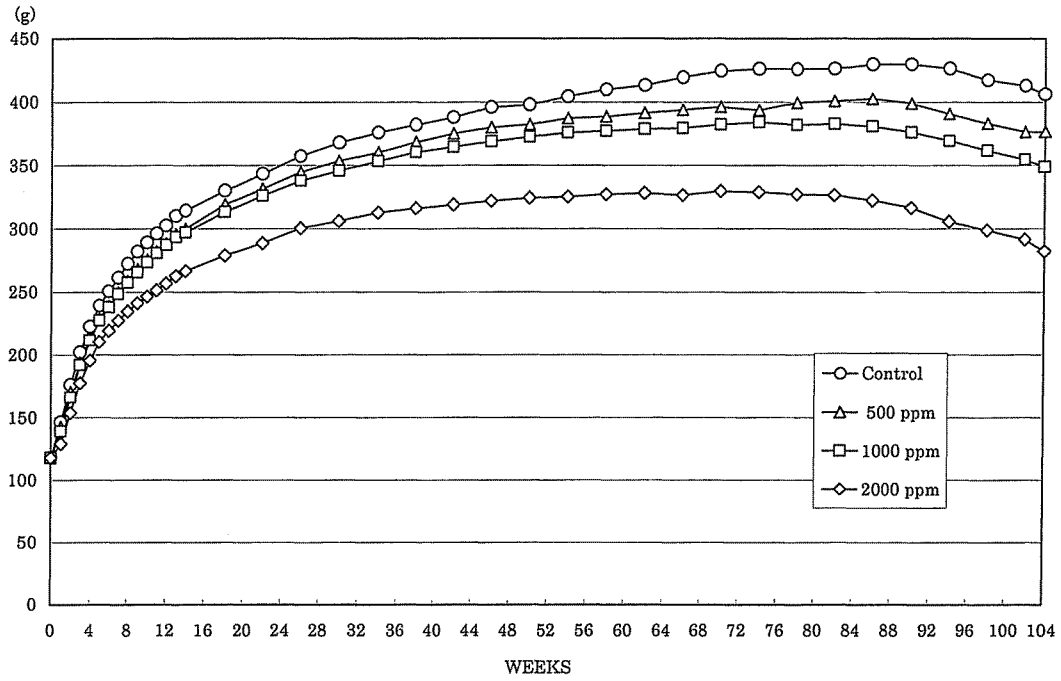


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

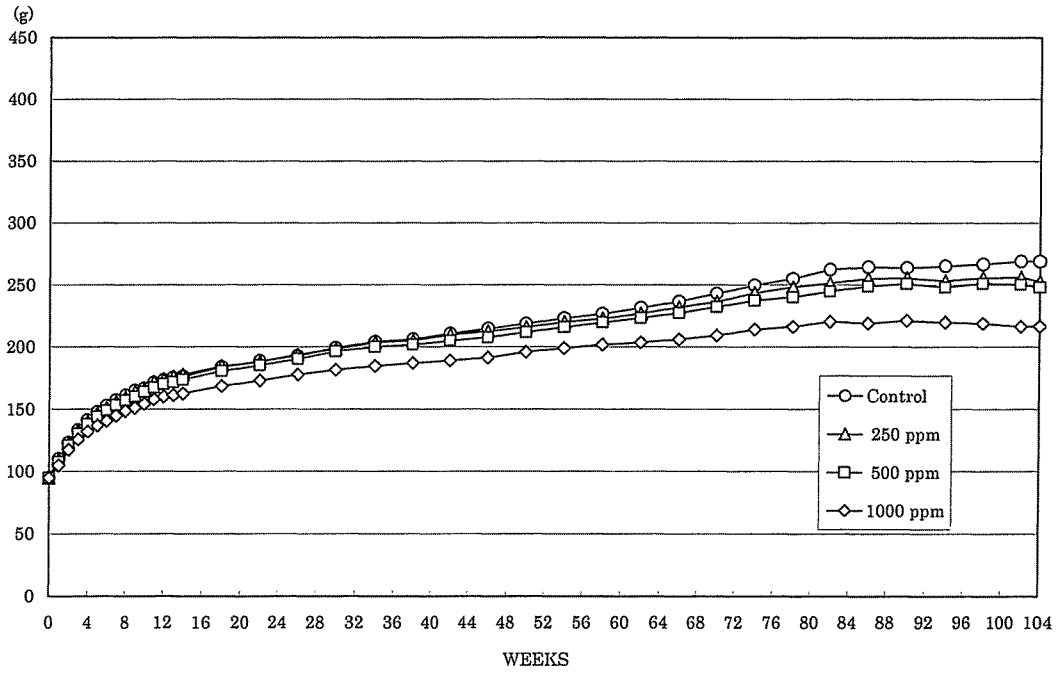


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

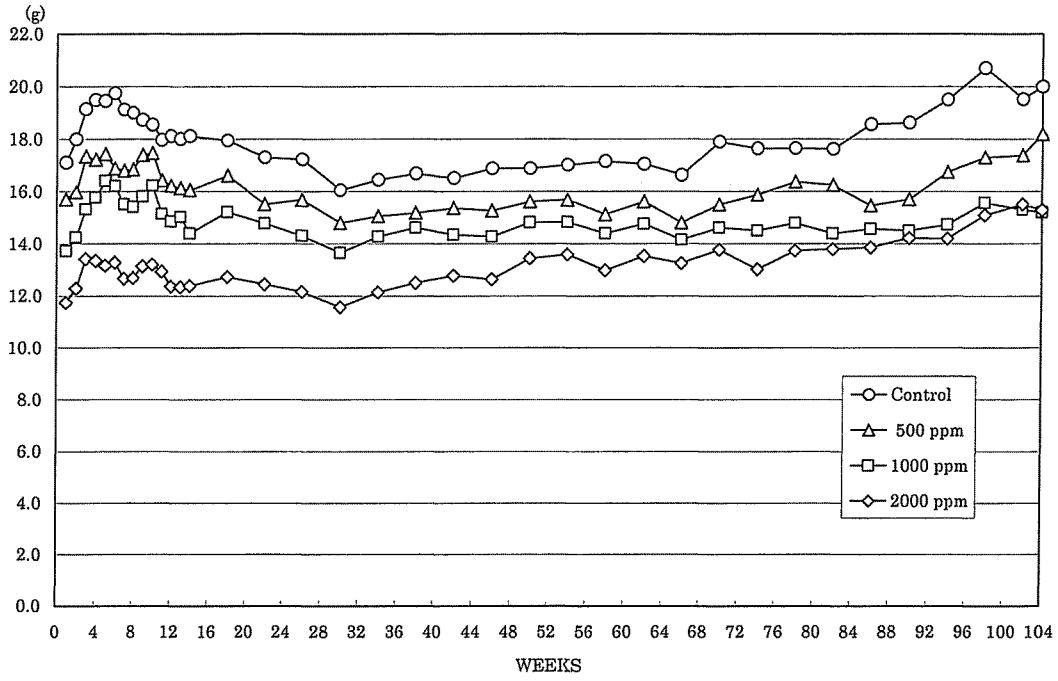


FIGURE 5 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

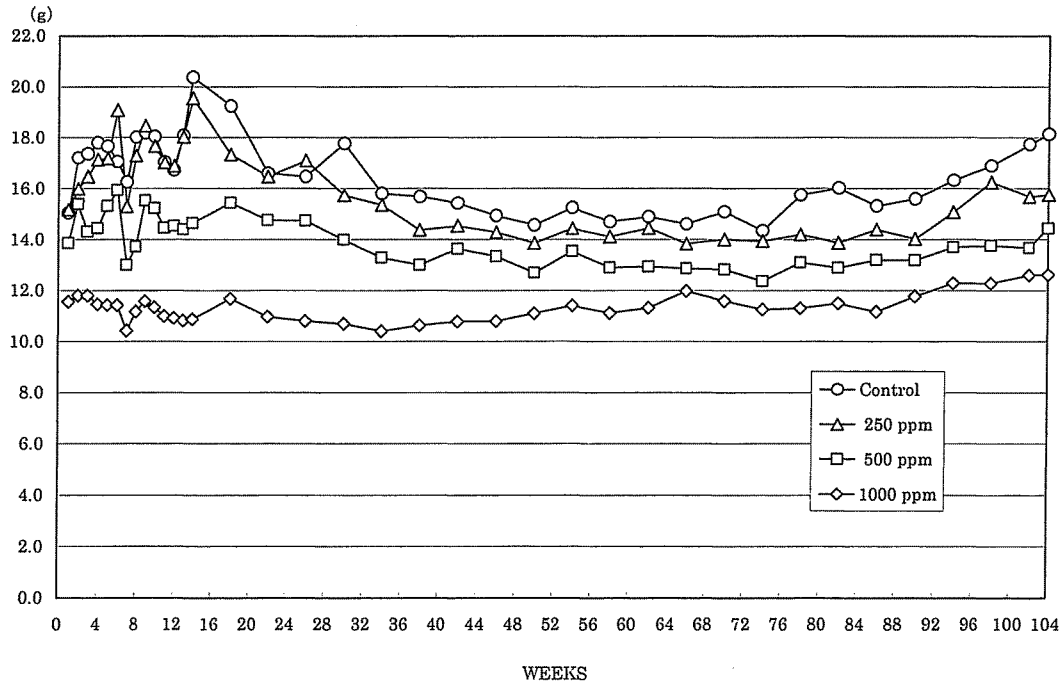


FIGURE 6 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

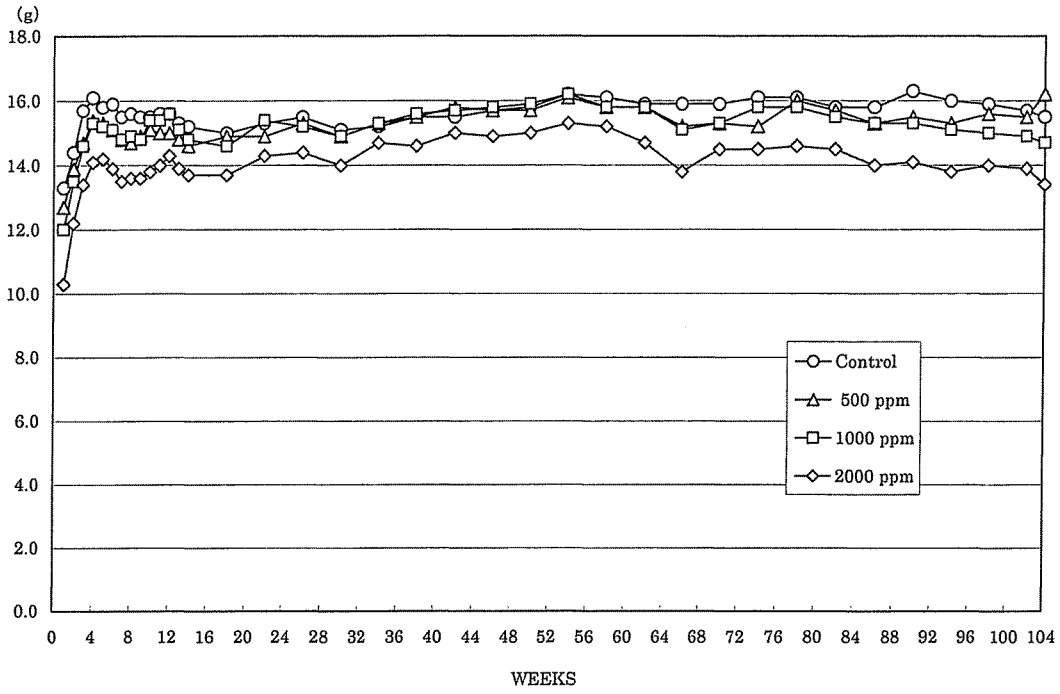


FIGURE 7 FOOD CONSUMPTION CHANGES OF MALE RATS
IN THE 2-YEAR DRINKING WATER STUDY
OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

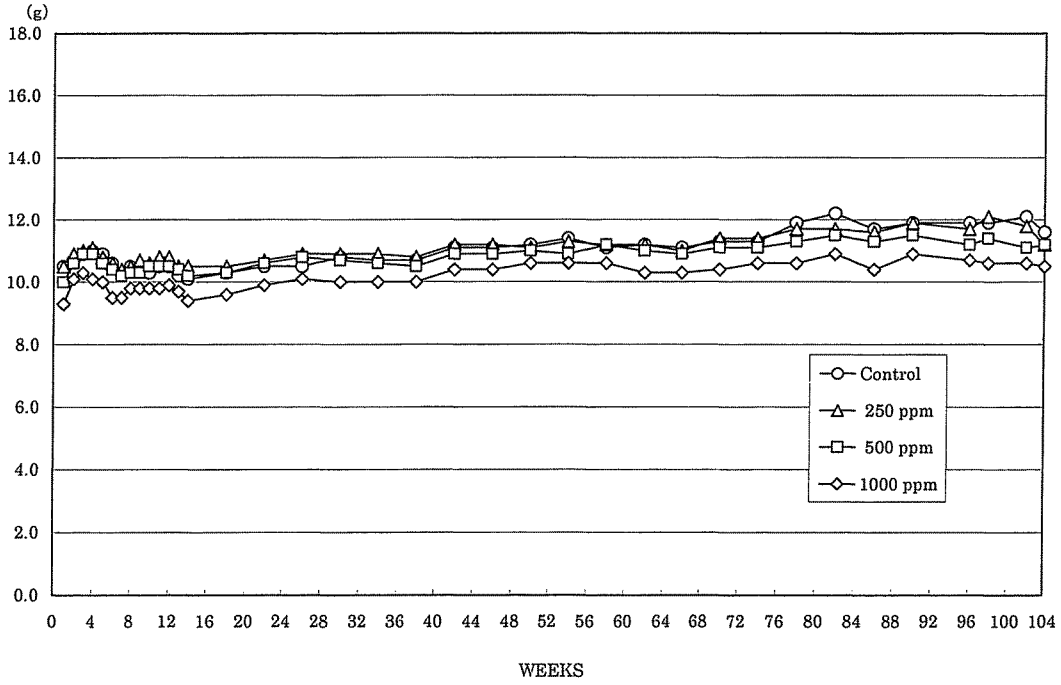


FIGURE 8 FOOD CONSUMPTION CHANGES OF FEMALE RATS
IN THE 2-YEAR DRINKING WATER STUDY
OF *o*-PHENYLENEDIAMINE DIHYDROCHLORIDE

PHOTOGRAPHS

PHOTOGRAPH 1 LIVER: HEPATOCELLULAR CARCINOMA,
RAT, FEMALE, 1000 ppm, ANIMAL NO. 0371-2319 (H&E)

PHOTOGRAPH 2 LIVER: HEPATOCELLULAR ADENOMA, (ARROW)
RAT, FEMALE, 1000 ppm, ANIMAL NO. 0371-2302 (H&E)

PHOTOGRAPH 3 LIVER: BASOPHILIC CELL FOCUS, (ARROW)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1301 (H&E)

PHOTOGRAPH 4 URINARY BLADDER: TRANSITIONAL CELL CARCINOMA
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1319 (H&E)

PHOTOGRAPH 5 URINARY BLADDER: TRANSITIONAL CELL PAPILLOMA, (ARROW)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1328 (H&E)

PHOTOGRAPH 6 URINARY BLADDER: NODULAR HYPERPLASIA OF
TRANSITIONAL EPITHELIUM, (ARROW)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1346 (H&E)

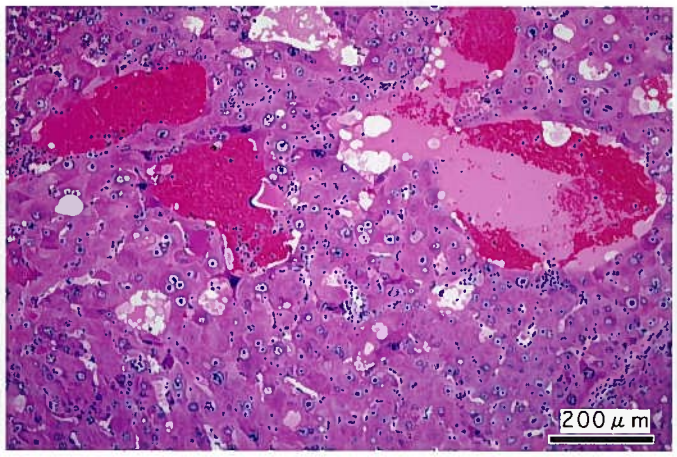
PHOTOGRAPH 7 THYROID: FOLLICLE CELL ADENOMA, (ARROW)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1317 (H&E)

PHOTOGRAPH 8 KIDNEY: PAPILLARY NECROSIS, (ARROW: A)
MINERALIZATION OF PAPILLA, (ARROW: B)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1324 (H&E)

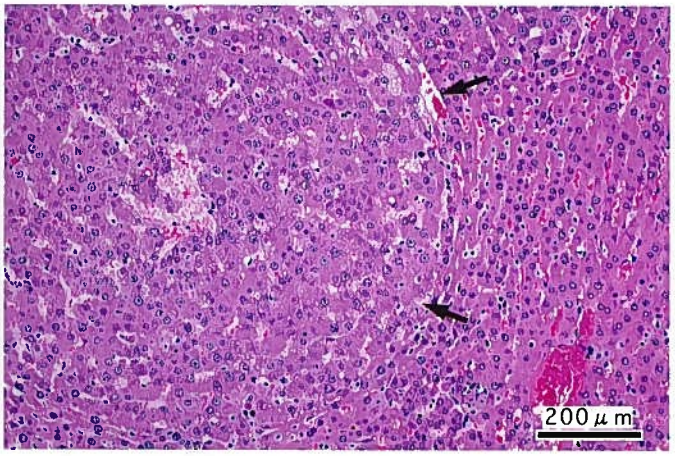
PHOTOGRAPH 9 KIDNEY: UROTHELIAL HYPERPLASIA OF PELVIS, (ARROW)
RAT, MALE,2000 ppm, ANIMAL NO. 0371-1350 (H&E)

PHOTOGRAPH 10 KIDNEY:INFARCT, (ARROW)
RAT, MALE, 2000 ppm, ANIMAL NO. 0371-1329 (H&E)

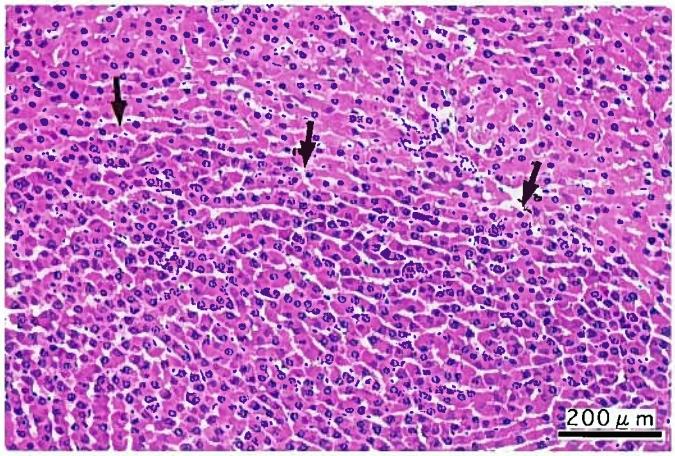
PHOTOGRAPH 11 NASAL CAVITY: NORMAL, (LEFT)
EOSINOPHILIC CHANGE OF OLFACTORY
EPITHERIUM, (RIGHT)
RAT, FEMALE, 1000 ppm, ANIMAL NO. 0371-2317 (H&E)



PHOTOGRAPH 1



PHOTOGRAPH 2



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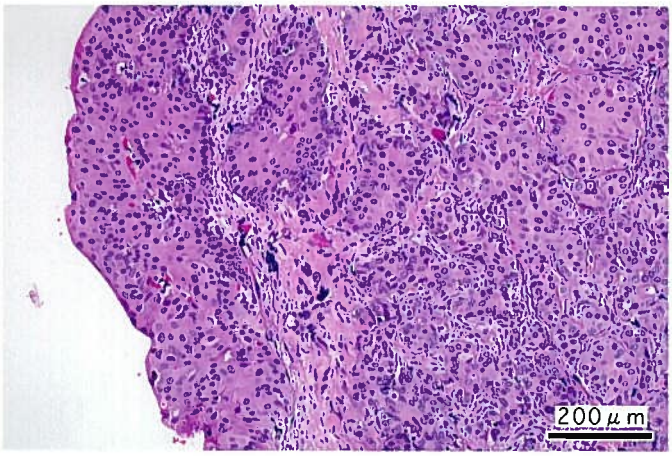
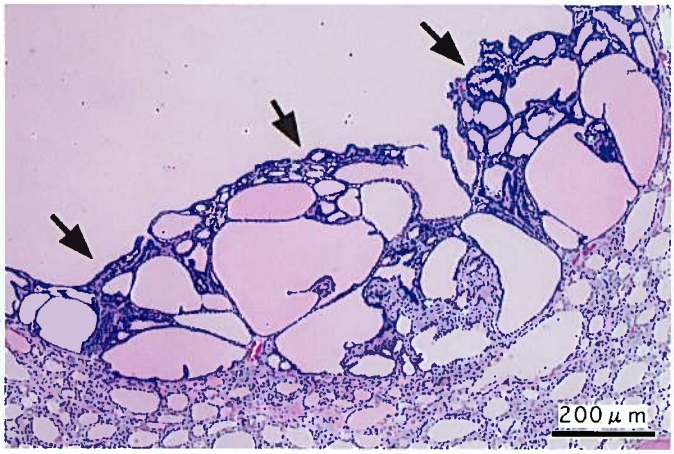


PHOTOGRAPH 4

PHOTOGRAPH 5

PHOTOGRAPH 6



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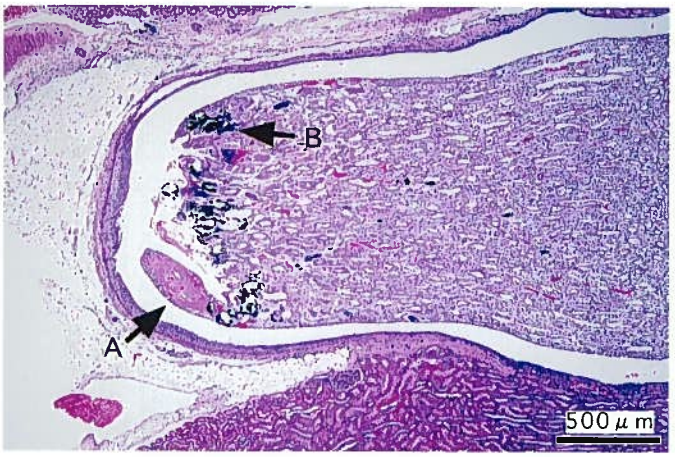
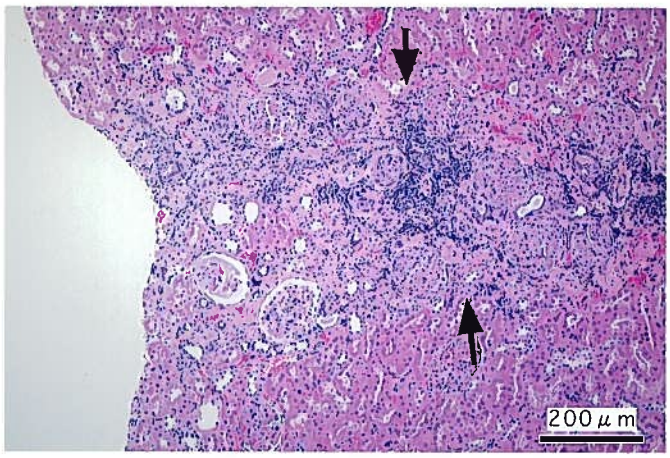
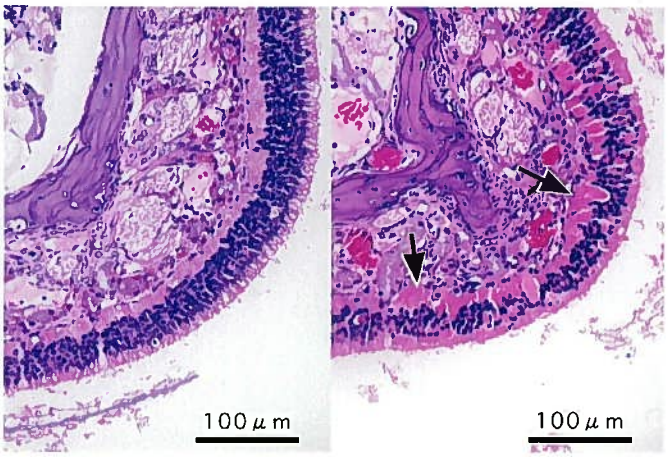


PHOTOGRAPH 8

PHOTOGRAPH 9



PHOTOGRAPH 10



PHOTOGRAPH 11