Summary of Feed Carcinogenicity Study

of 2,4-Dichloro-1-Nitrobenzene

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 March 25 2005.

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

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Purpose, materials and methods

2,4-Dichloro-1-nitrobenzene (2,4DCNB, CAS No. 611-06-3) is a light yellow crystal with a melting point of 33°C and a boiling point of 258.5°C, and it is insoluble in water.

The carcinogenicity and chronic toxicity of 2,4DCNB were examined by feeding groups of 50 F344/DuCrj (Fischer) rats of both sexes 2,4DCNB-containing diets for 2 years (104 weeks). The dietary concentration of 2,4DCNB was 0, 750, 1500 or 3000 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. 2,4DCNB was analyzed for purity and stability by both infrared spectrometry and gas chromatography before and after its use. The 2,4DCNB concentrations in the diet were determined by gas chromatography at the time of preparation, and on the 9th day after preparation, while stored at room temperature. 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 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 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

There was no difference in survival rate between any 2,4DCNB-fed group of either sex and the respective control. Terminal body weights of the 3000 ppm-fed males and females were decreased by 14% and 15%, respectively, compared with respective controls. Slightly decreased food consumption was observed sporadically in all the 2,4DCNB-fed groups of both sexes during the early period of 2-year administration. Yellow urine, which was colored by a metabolite of 2,4DCNB, was observed in all the 2,4DCNB-fed groups of both sexes throughout the 2-year administration period.

The incidences of renal tumors (renal cell adenomas and carcinomas) in males and females and preputial gland tumors (adenomas) in males were increased in a dose-related manner. The significantly increased incidence of renal tumors was observed in the males and females fed 1500 ppm and above, while the significantly increased incidence of preputial gland tumor was observed in the males fed 3000 ppm. As a pre-neoplastic lesion in the kidney, the incidence of atypical tubule hyperplasia in the proximal tubules was increased in all the 2,4DCNB-fed groups of both sexes. As non-neoplastic lesions in the kidney, chronic progressive nephropathy (chronic nephropathy, CPN) and eosinophilic droplet in the proximal tubules were observed in all the 2,4DCNB-fed groups of both sexes, and papillary mineralization and urothelial hyperplasia of pelvis were observed in all the 2,4DCNB-fed male groups. These renal lesions occurred in the males and females fed the lowest dose level of 750 ppm.

Conclusions

In rats, there was clear evidence of carcinogenic activity of 2,4DCNB in males and females, based on the increased incidences of renal cell adenomas and carcinomas, and the increased incidences of preputial gland adenomas.

TABLES

TABLES (CONTINUED)

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Week on Study	Control		750 ppm			1500 ppm			3000 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	161 (50)	50 / 50	160 (50)	99	50 / 50	158 (50)	98	50 / 50	150 (50)	93	50 / 50
2	193 (50)	50 / 50	188 (50)	97	50 / 50	186 (50)	96	50 / 50	174 (50)	90	50 / 50
3	217 (50)	50 / 50	212 (50)	98	50 / 50	208 (50)	96	50 / 50	194 (50)	89	50 / 50
4	237 (50)	50 / 50	229 (50)	97	50 / 50	224 (50)	95	50 / 50	210 (50)	89	50 / 50
5	254 (50)	50 / 50	244 (50)	96	50 / 50	238 (50)	94	50 / 50	225 (50)	89	50 / 50
6	267 (50)	50 / 50	256 (50)	96	50 / 50	252 (50)	94	50 / 50	238 (50)	89	50 / 50
7	279 (50)	50 / 50	269 (50)	96	50 / 50	265 (50)	95	50 / 50	249 (50)	89	50 / 50
8	291 (50)	50 / 50	279 (50)	96	50 / 50	276 (50)	95	50 / 50	259 (50)	89	50 / 50
9	301 (50)	50 / 50	289 (50)	96	50 / 50	285 (50)	95	50 / 50	266 (50)	88	50 / 50
10	309 (50)	50 / 50	297 (50)	96	50 / 50	293 (50)	95	50 / 50	275 (50)	89	50 / 50
11	316 (50)	50 / 50	305 (50)	97	50 / 50	301 (50)	95	50 / 50	282 (50)	89	50 / 50
12	321 (50)	50 / 50	309 (50)	96	50 / 50	306 (50)	95	50 / 50	289 (50)	90	50 / 50
13	326 (50)	50 / 50	316 (50)	97	50 / 50	311 (50)	95	50 / 50	294 (50)	90	50 / 50
14	332 (50)	50 / 50	321 (50)	97	50 / 50	317 (50)	95	50 / 50	301 (50)	91	50 / 50
18	349 (50)	50 / 50	339 (50)	97	50 / 50	336 (50)	96	50 / 50	321 (50)	92	50 / 50
22	362 (50)	50 / 50	354 (50)	98	50 / 50	352 (50)	97	50 / 50	336 (50)	93	50 / 50
26	375 (50)	50 / 50	369 (50)	98	50 / 50	367 (50)	98	50 / 50	351 (50)	94	50 / 50
30	385 (50)	50 / 50	379 (50)	98	50 / 50	376 (50)	98	50 / 50	361 (50)	94	50 / 50
34	395 (50)	50 / 50	391 (50)	99	50 / 50	387 (50)	98	50 / 50	373 (50)	94	50 / 50
38	403 (50)	50 / 50	398 (50)	99	50 / 50	394 (50)	98	50 / 50	378 (50)	94	50 / 50
42	404 (50)	50 / 50	402 (50)	100	50 / 50	397 (50)	98	50 / 50	379 (50)	94	50 / 50
46	410 (50)	50 / 50	408 (50)	100	50 / 50	404 (50)	99	50 / 50	387 (50)	94	50 / 50
50	413 (50)	50 / 50	410 (49)	99	49 / 50	406 (50)	98	50 / 50	389 (50)	94	50 / 50
54	415 (50)	50 / 50	413 (49)	100	49 / 50	408 (50)	98	50 / 50	391 (50)	94	50 / 50
58	417 (50)	50 / 50	414 (49)	99	49 / 50	409 (50)	98	50 / 50	391 (50)	94	50 / 50
62	420 (50)	50 / 50	415 (49)	99	49 / 50	410 (50)	98	50 / 50	391 (50)	93	50 / 50
66	423 (50)	50 / 50	416 (49)	98	49 / 50	409 (50)	97	50 / 50	390 (49)	92	49 / 50
70	424 (50)	50 / 50	415 (49)	98	49 / 50	407 (50)	96	50 / 50	386 (47)	91	47 / 50
74	425 (50)	50 / 50	412 (49)	97	49 / 50	403 (50)	95	50 / 50	381 (47)	90	47 / 50
78	424 (50)	50 / 50	405 (49)	96	49 / 50	398 (50)	94	50 / 50	379 (46)	89	46 / 50
82	422 (50)	50 / 50	402 (47)	95	47 / 50	392 (49)	93	49 / 50	374 (45)	89	45 / 50
86	420 (48)	48 / 50	401 (45)	95	45 / 50	388 (49)	92	49 / 50	369 (45)	88	45 / 50
90	412 (47)	47 / 50	391 (45)	95	45 / 50	379 (48)	92	48 / 50	360 (45)	87	45 / 50
94	406 (47)	47 / 50	380 (45)	94	45 / 50	367 (47)	90	47 / 50	356 (44)	88	44 / 50
98	400 (42)	42 / 50	375 (44)	94	44 / 50	358 (44)	90	44 / 50	342 (43)	86	43 / 50
102	395 (42)	42 / 50	367 (43)	93	43 / 50	353 (40)	89	40 / 50	339 (41)	86	41 / 50
104	388 (39)	39 / 50	360 (42)	93	42 / 50	347 (40)	89	40 / 50	329 (40)	85	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 FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Week on Study	Control		750 ppm			1500 ppm			3000 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	100 (50)	50 / 50	100 (50)	100	50 / 50	100 (50)	100	50 / 50	100 (50)	100	50 / 50
1	114 (50)	50 / 50	114 (50)	100	50 / 50	112 (50)	98	50 / 50	109 (50)	96	50 / 50
2	126 (50)	50 / 50	125 (50)	99	50 / 50	124 (50)	98	50 / 50	120 (50)	95	50 / 50
3	136 (50)	50 / 50	134 (50)	99	50 / 50	131 (50)	96	50 / 50	127 (50)	93	50 / 50
4	143 (50)	50 / 50	141 (50)	99	50 / 50	138 (50)	97	50 / 50	133 (50)	93	50 / 50
5	150 (50)	50 / 50	148 (50)	99	50 / 50	143 (50)	95	50 / 50	139 (50)	93	50 / 50
6	155 (50)	50 / 50	153 (50)	99	50 / 50	149 (50)	96	50 / 50	145 (50)	94	50 / 50
7	159 (50)	50 / 50	157 (50)	99	50 / 50	153 (50)	96	50 / 50	148 (50)	93	50 / 50
8	164 (50)	50 / 50	160 (50)	98	50 / 50	157 (50)	96	50 / 50	151 (50)	92	50 / 50
9	167 (50)	50 / 50	164 (50)	98	50 / 50	160 (50)	96	50 / 50	153 (50)	92	50 / 50
10	172 (50)	50 / 50	167 (50)	97	50 / 50	163 (50)	95	50 / 50	156 (50)	91	50 / 50
11	175 (50)	50 / 50	170 (50)	97	50 / 50	166 (50)	95	50 / 50	159 (50)	91	50 / 50
12	175 (50)	50 / 50	171 (50)	98	50 / 50	167 (50)	95	50 / 50	160 (50)	91	50 / 50
13	178 (50)	50 / 50	173 (50)	97	50 / 50	169 (50)	95	50 / 50	162 (50)	91	50 / 50
14	179 (50)	50 / 50	174 (50)	97	50 / 50	170 (50)	95	50 / 50	163 (50)	91	50 / 50
18	185 (50)	50 / 50	180 (50)	97	50 / 50	174 (50)	94	50 / 50	166 (50)	90	50 / 50
22	190 (50)	50 / 50	185 (50)	97	50 / 50	178 (50)	94	50 / 50	170 (50)	89	50 / 50
26	196 (50)	50 / 50	190 (50)	97	50 / 50	183 (50)	93	50 / 50	176 (50)	90	50 / 50
30	200 (50)	50 / 50	195 (50)	98	50 / 50	185 (50)	93	50 / 50	178 (50)	89	50 / 50
34	204 (50)	50 / 50	200 (50)	98	50 / 50	190 (50)	93	50 / 50	183 (50)	90	50 / 50
38	209 (50)	50 / 50	203 (50)	97	50 / 50	194 (50)	93	50 / 50	187 (50)	89	50 / 50
42	210 (50)	50 / 50	205 (50)	98	50 / 50	195 (49)	93	49 / 50	187 (50)	89	50 / 50
46	215 (50)	50 / 50	209 (50)	97	50 / 50	199 (49)	93	49 / 50	191 (50)	89	50 / 50
50	220 (50)	50 / 50	213 (50)	97	50 / 50	203 (49)	92	49 / 50	195 (50)	89	50 / 50
54	222 (50)	50 / 50	216 (50)	97	50 / 50	206 (49)	93	49 / 50	197 (50)	89	50 / 50
58	227 (50)	50 / 50	220 (50)	97	50 / 50	210 (49)	93	49 / 50	201 (50)	89	50 / 50
62	231 (50)	50 / 50	224 (50)	97	50 / 50	214 (48)	93	48 / 50	204 (50)	88	50 / 50
66	238 (49)	49 / 50	230 (50)	97	50 / 50	220 (47)	92	47 / 50	208 (50)	87	50 / 50
70	246 (49)	49 / 50	237 (50)	96	50 / 50	227 (46)	92	46 / 50	214 (50)	87	50 / 50
74	249 (49)	49 / 50	242 (50)	97	50 / 50	231 (45)	93	45 / 50	218 (50)	88	50 / 50
78	255 (48)	48 / 50	247 (49)	97	49 / 50	236 (45)	93	45 / 50	223 (49)	87	49 / 50
82	258 (46)	46 / 50	252 (48)	98	48 / 50	240 (44)	93	44 / 50	224 (48)	87	48 / 50
86	262 (45)	45 / 50	255 (48)	97	48 / 50	244 (42)	93	42 / 50	227 (48)	87	48 / 50
90	260 (44)	44 / 50	254 (47)	98	47 / 50	245 (42)	94	42 / 50	226 (47)	87	47 / 50
94	264 (41)	41 / 50	257 (46)	97	46 / 50	246 (42)	93	42 / 50	227 (46)	86	46 / 50
98	261 (39)	39 / 50	257 (46)	98	46 / 50	244 (40)	93	40 / 50	225 (45)	86	45 / 50
102	264 (36)	36 / 50	257 (45)	97	45 / 50	242 (39)	92	39 / 50	225 (44)	85	44 / 50
104	263 (35)	35 / 50	257 (44)	98	44 / 50	243 (38)	92	38 / 50	225 (43)	86	43 / 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 FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Week on Study	Control		750 ppm			1500 ppm			3000 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	13.7 (50)	50 / 50	13.3 (50)	97	50 / 50	13.3 (50)	97	50 / 50	12.6 (50)	92	50 / 50
2	14.5 (50)	50 / 50	14.5 (50)	100	50 / 50	14.5 (50)	100	50 / 50	14.5 (50)	100	50 / 50
3	15.0 (50)	50 / 50	14.9 (50)	99	50 / 50	14.7 (50)	98	50 / 50	14.7 (50)	98	50 / 50
4	15.3 (50)	50 / 50	14.7 (50)	96	50 / 50	14.6 (50)	95	50 / 50	14.3 (50)	93	50 / 50
5	15.7 (50)	50 / 50	15.0 (50)	96	50 / 50	15.0 (50)	96	50 / 50	14.8 (50)	94	50 / 50
6	15.5 (50)	50 / 50	15.0 (50)	97	50 / 50	15.3 (50)	99	50 / 50	14.9 (50)	96	50 / 50
7	15.9 (50)	50 / 50	15.4 (50)	97	50 / 50	15.7 (50)	99	50 / 50	15.1 (50)	95	50 / 50
8	15.8 (50)	50 / 50	15.3 (50)	97	50 / 50	15.6 (50)	99	50 / 50	15.2 (50)	96	50 / 50
9	16.0 (50)	50 / 50	15.6 (50)	98	50 / 50	15.8 (50)	99	50 / 50	15.2 (49)	95	50 / 50
10	16.2 (50)	50 / 50	15.0 (50)	93	50 / 50	15.4 (50)	95	50 / 50	15.2 (50)	94	50 / 50
11	15.8 (50)	50 / 50	15.0 (50)	95	50 / 50	15.5 (50)	98	50 / 50	14.9 (50)	94	50 / 50
12	15.4 (50)	50 / 50	14.8 (50)	96	50 / 50	15.4 (50)	100	50 / 50	15.1 (50)	98	50 / 50
13	15.2 (50)	50 / 50	14.5 (50)	95	50 / 50	14.8 (50)	97	50 / 50	14.8 (50)	97	50 / 50
14	15.2 (50)	50 / 50	14.4 (50)	95	50 / 50	15.0 (50)	99	50 / 50	14.8 (49)	97	50 / 50
18	15.6 (50)	50 / 50	15.1 (50)	97	50 / 50	15.6 (50)	100	50 / 50	15.4 (49)	99	50 / 50
22	15.4 (50)	50 / 50	15.1 (50)	98	50 / 50	15.8 (50)	103	50 / 50	15.6 (49)	101	50 / 50
26	16.0 (50)	50 / 50	15.7 (50)	98	50 / 50	16.2 (50)	101	50 / 50	16.0 (49)	100	50 / 50
30	16.3 (49)	50 / 50	16.2 (49)	99	50 / 50	16.6 (49)	102	50 / 50	16.2 (47)	99	50 / 50
34	16.4 (49)	50 / 50	16.2 (49)	99	50 / 50	16.7 (49)	102	50 / 50	16.4 (47)	100	50 / 50
38	16.3 (50)	50 / 50	16.2 (50)	99	50 / 50	16.6 (49)	102	50 / 50	16.2 (47)	99	50 / 50
42	16.1 (50)	50 / 50	16.2 (49)	101	50 / 50	16.6 (48)	103	50 / 50	16.1 (48)	100	50 / 50
46	16.5 (50)	50 / 50	16.8 (49)	102	50 / 50	17.2 (49)	104	50 / 50	16.5 (49)	100	50 / 50
50	16.3 (50)	50 / 50	16.6 (49)	102	49 / 50	16.6 (49)	102	50 / 50	16.0 (48)	98	50 / 50
54	16.3 (49)	50 / 50	16.8 (49)	103	49 / 50	16.9 (50)	104	50 / 50	16.4 (49)	101	50 / 50
58	16.2 (48)	50 / 50	16.4 (47)	101	49 / 50	16.5 (44)	102	50 / 50	15.9 (46)	98	50 / 50
62	16.4 (49)	50 / 50	16.5 (49)	101	49 / 50	16.7 (48)	102	50 / 50	16.2 (48)	99	50 / 50
66	16.5 (48)	50 / 50	16.5 (49)	100	49 / 50	16.6 (49)	101	50 / 50	16.0 (47)	97	49 / 50
70	16.5 (49)	50 / 50	16.5 (48)	100	49 / 50	16.8 (49)	102	50 / 50	16.4 (45)	99	47 / 50
74	16.1 (49)	50 / 50	16.4 (48)	102	49 / 50	16.4 (48)	102	50 / 50	16.0 (44)	99	47 / 50
78	15.9 (48)	50 / 50	16.2 (47)	102	49 / 50	16.7 (48)	105	50 / 50	16.5 (44)	104	46 / 50
82	16.6 (50)	50 / 50	16.5 (44)	99	47 / 50	16.7 (44)	101	49 / 50	16.5 (42)	99	45 / 50
86	15.9 (47)	48 / 50	16.4 (45)	103	45 / 50	16.5 (47)	104	49 / 50	16.1 (43)	101	45 / 50
90	15.9 (47)	47 / 50	16.3 (42)	103	45 / 50	16.7 (43)	105	48 / 50	16.2 (42)	102	45 / 50
94	15.3 (42)	47 / 50	16.0 (41)	105	45 / 50	16.8 (41)	110	47 / 50	16.4 (38)	107	44 / 50
98	16.2 (38)	42 / 50	16.6 (40)	102	44 / 50	17.1 (33)	106	44 / 50	15.6 (34)	96	43 / 50
102	15.6 (38)	42 / 50	16.2 (39)	104	43 / 50	17.0 (31)	109	40 / 50	16.2 (35)	104	41 / 50
104	16.3 (37)	39 / 50	16.2 (38)	99	42 / 50	16.9 (30)	104	40 / 50	16.2 (35)	99	40 / 50

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

TABLE 4 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Week on Study	Control		750 ppm			1500 ppm			3000 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	10.0 (50)	50 / 50	9.6 (50)	96	50 / 50	9.4 (50)	94	50 / 50	9.1 (50)	91	50 / 50
2	9.9 (50)	50 / 50	9.7 (50)	98	50 / 50	10.0 (50)	101	50 / 50	9.4 (50)	95	50 / 50
3	10.4 (50)	50 / 50	10.4 (50)	100	50 / 50	10.1 (50)	97	50 / 50	9.5 (50)	91	50 / 50
4	10.4 (50)	50 / 50	10.0 (50)	96	50 / 50	10.3 (50)	99	50 / 50	9.5 (50)	91	50 / 50
5	10.7 (50)	50 / 50	9.9 (50)	93	50 / 50	10.3 (50)	96	50 / 50	10.2 (50)	95	50 / 50
6	10.3 (50)	50 / 50	9.8 (50)	95	50 / 50	10.3 (50)	100	50 / 50	10.0 (50)	97	50 / 50
7	10.3 (50)	50 / 50	9.6 (50)	93	50 / 50	10.3 (50)	100	50 / 50	10.0 (50)	97	50 / 50
8	10.2 (50)	50 / 50	9.6 (50)	94	50 / 50	9.9 (50)	97	50 / 50	9.5 (50)	93	50 / 50
9	10.2 (50)	50 / 50	9.6 (50)	94	50 / 50	10.0 (50)	98	50 / 50	9.7 (50)	95	50 / 50
10	10.1 (50)	50 / 50	9.6 (50)	95	50 / 50	9.8 (50)	97	50 / 50	9.5 (50)	94	50 / 50
11	10.2 (50)	50 / 50	9.7 (50)	95	50 / 50	10.2 (50)	100	50 / 50	9.8 (49)	96	50 / 50
12	10.0 (50)	50 / 50	9.5 (50)	95	50 / 50	9.7 (50)	97	50 / 50	9.8 (50)	98	50 / 50
13	9.8 (50)	50 / 50	9.2 (49)	94	50 / 50	9.7 (50)	99	50 / 50	9.6 (50)	98	50 / 50
14	9.7 (50)	50 / 50	9.2 (50)	95	50 / 50	9.4 (50)	97	50 / 50	9.3 (50)	96	50 / 50
18	10.0 (50)	50 / 50	9.7 (50)	97	50 / 50	9.6 (50)	96	50 / 50	10.0 (50)	100	50 / 50
22	9.7 (50)	50 / 50	9.5 (50)	98	50 / 50	9.7 (50)	100	50 / 50	9.7 (50)	100	50 / 50
26	10.3 (50)	50 / 50	10.0 (50)	97	50 / 50	10.2 (50)	99	50 / 50	10.3 (50)	100	50 / 50
30	10.8 (50)	50 / 50	10.7 (50)	99	50 / 50	10.6 (50)	98	50 / 50	11.0 (50)	102	50 / 50
34	11.1 (50)	50 / 50	10.7 (50)	96	50 / 50	10.8 (50)	97	50 / 50	10.7 (50)	96	50 / 50
38	11.1 (50)	50 / 50	10.7 (50)	96	50 / 50	11.0 (50)	99	50 / 50	11.0 (50)	99	50 / 50
42	11.2 (49)	50 / 50	11.3 (50)	101	50 / 50	11.2 (49)	100	49 / 50	11.0 (50)	98	50 / 50
46	11.6 (50)	50 / 50	11.8 (50)	102	50 / 50	11.7 (49)	101	49 / 50	11.3 (50)	97	50 / 50
50	11.6 (50)	50 / 50	11.7 (50)	101	50 / 50	11.7 (49)	101	49 / 50	11.5 (50)	99	50 / 50
54	11.9 (50)	50 / 50	12.1 (50)	102	50 / 50	11.8 (49)	99	49 / 50	11.3 (50)	95	50 / 50
58	12.4 (50)	50 / 50	12.6 (50)	102	50 / 50	12.2 (49)	98	49 / 50	11.9 (50)	96	50 / 50
62	12.1 (50)	50 / 50	12.3 (50)	102	50 / 50	12.5 (48)	103	48 / 50	11.8 (50)	98	50 / 50
66	12.4 (48)	49 / 50	12.4 (50)	100	50 / 50	12.3 (47)	99	47 / 50	11.9 (50)	96	50 / 50
70	12.6 (49)	49 / 50	12.9 (50)	102	50 / 50	12.7 (46)	101	46 / 50	12.4 (50)	98	50 / 50
74	12.6 (49)	49 / 50	12.7 (50)	101	50 / 50	12.5 (45)	99	45 / 50	12.2 (50)	97	50 / 50
78	12.9 (48)	48 / 50	13.3 (49)	103	49 / 50	13.3 (45)	103	45 / 50	12.8 (49)	99	49 / 50
82	13.2 (46)	46 / 50	13.4 (48)	102	48 / 50	13.3 (44)	101	44 / 50	12.6 (48)	95	48 / 50
86	12.7 (44)	45 / 50	12.8 (48)	101	48 / 50	13.0 (42)	102	42 / 50	12.1 (48)	95	48 / 50
90	12.6 (43)	44 / 50	12.4 (47)	98	47 / 50	12.8 (42)	102	42 / 50	11.7 (47)	93	47 / 50
94	12.7 (41)	41 / 50	12.7 (46)	100	46 / 50	13.0 (42)	102	42 / 50	12.5 (46)	98	46 / 50
98	12.7 (39)	39 / 50	13.1 (46)	103	46 / 50	13.0 (40)	102	40 / 50	12.3 (45)	97	45 / 50
102	12.5 (36)	36 / 50	12.8 (45)	102	45 / 50	13.1 (39)	105	39 / 50	12.5 (44)	100	44 / 50
104	13.0 (35)	35 / 50	13.1 (44)	101	44 / 50	13.3 (38)	102	38 / 50	12.4 (43)	95	43 / 50

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

TABLE 5 HEMATOLOGY OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	39	42		40		38	
MCV (fL)	47.8 ± 2.5	47.0 ± 1.7	*	46.9 ± 1.8	**	47.2 ± 4.0	**
MCH (pg)	16.0 ± 1.5	15.7 ± 0.8	*	15.7 ± 0.5	**	15.5 ± 1.2	**
MCHC (g/dL)	33.4 ± 2.0	33.5 ± 1.1		33.5 ± 0.7	*	32.9 ± 1.6	**

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

TABLE 6 HEMATOLOGY OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	35	44		38		42	
RED BLOOD CELL (10^6/μL)	7.81 ± 1.27	8.26 ± 1.19	**	8.10 ± 0.78		8.29 ± 1.15	**
MCV (fL)	52.1 ± 3.6	52.2 ± 9.6	**	50.2 ± 2.0	**	50.3 ± 3.1	**
MCH (pg)	17.9 ± 1.5	18.1 ± 3.6	**	17.2 ± 0.7	**	17.0 ± 0.7	**
MCHC (g/dL)	34.4 ± 2.4	34.6 ± 1.6		34.3 ± 1.0	**	33.9 ± 1.6	**
PLATELET (10^3/μL)	692 ± 192	706 ± 143		793 ± 142	*	804 ± 135	**
WBC (10^3/μL)	4.65 ± 11.26	12.74 ± 48.58		3.13 ± 1.65		4.07 ± 4.04	*
Differential WBC (%)							
N-BAND	1 ± 2	0 ± 1		0 ± 1		0 ± 1	**

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

TABLE 7 BIOCHEMISTRY OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	39	42		40		38	
TOTAL PROTEIN (g/dL)	6.7 ± 0.5	6.6 ± 0.6		6.6 ± 0.4		6.5 ± 0.3	*
ALBUMIN (g/dL)	3.1 ± 0.3	2.9 ± 0.4	**	2.9 ± 0.2	**	2.8 ± 0.3	**
A/G RATIO	0.9 ± 0.1	0.8 ± 0.1	**	0.8 ± 0.1	**	0.8 ± 0.1	**
T-CHOLESTEROL (mg/dL)	153 ± 50	188 ± 62	*	205 ± 52	**	183 ± 65	
TRIGLYCERIDE (mg/dL)	56 ± 53	80 ± 61		130 ± 89	**	115 ± 95	**
PHOSPHOLIPID (mg/dL)	220 ± 67	265 ± 89	*	294 ± 76	**	274 ± 97	*
GOT (IU/L)	119 ± 193	80 ± 52	*	77 ± 33	*	85 ± 75	*
GPT (IU/L)	44 ± 33	37 ± 27	*	35 ± 16	*	35 ± 21	**
ALP (IU/L)	210 ± 165	235 ± 420		157 ± 59	*	151 ± 63	**
G-GTP (IU/L)	5 ± 2	11 ± 7	**	14 ± 13	**	11 ± 8	**
UREA NITROGEN (mg/dL)	19.5 ± 9.9	25.9 ± 13.2	**	37.7 ± 24.1	**	33.4 ± 16.6	**
CREATININE (mg/dL)	0.6 ± 0.2	0.6 ± 0.1	**	0.9 ± 0.5	**	0.8 ± 0.3	**
POTASSIUM (mEq/L)	3.6 ± 0.3	3.8 ± 0.4	*	3.9 ± 0.3	**	3.9 ± 0.3	*
CHLORIDE (mEq/L)	105 ± 2	104 ± 2		103 ± 3	**	104 ± 2	
CALCIUM (mg/dL)	10.4 ± 0.3	10.5 ± 0.5		10.8 ± 0.7	**	10.6 ± 0.6	
INORGANIC PHOSPHORUS (mg/dL)	4.1 ± 0.8	4.5 ± 0.8		5.3 ± 2.6	**	5.1 ± 2.2	**

Mean ± S.D.

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

TABLE 8 BIOCHEMISTRY OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	35	44		38		42	
TOTAL PROTEIN (g/dL)	6.8 ± 0.5	7.0 ± 0.4		7.1 ± 0.5	**	7.1 ± 0.4	**
A/G RATIO	1.2 ± 0.1	1.2 ± 0.1		1.1 ± 0.1	**	1.1 ± 0.1	**
GLUCOSE (mg/dL)	160 ± 30	163 ± 17		161 ± 19		167 ± 15	**
T-CHOLESTEROL (mg/dL)	129 ± 34	149 ± 21	**	163 ± 39	**	150 ± 36	**
PHOSPHOLIPID (mg/dL)	227 ± 52	256 ± 38	*	272 ± 58	**	250 ± 51	
GOT (IU/L)	136 ± 63	131 ± 207	**	89 ± 33	**	85 ± 32	**
GPT (IU/L)	57 ± 27	50 ± 46		41 ± 14	**	39 ± 15	**
LDH (IU/L)	258 ± 203	205 ± 145	*	175 ± 58	**	168 ± 43	**
ALP (IU/L)	113 ± 36	120 ± 112		106 ± 69	**	98 ± 48	**
G-GTP (IU/L)	2 ± 1	3 ± 2	*	2 ± 1		3 ± 1	**
UREA NITROGEN (mg/dL)	23.8 ± 39.8	17.6 ± 2.6		19.4 ± 5.3	*	20.1 ± 3.4	**
POTASSIUM (mEq/L)	3.7 ± 1.0	3.4 ± 0.4	*	3.3 ± 0.3	*	3.5 ± 0.3	
CHLORIDE (mEq/L)	103 ± 5	102 ± 2	**	103 ± 2		102 ± 2	**

Mean ± S.D.

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

TABLE 9 URINALYSIS OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group name		Control	750 ppm	1500 ppm	3000 ppm
Number of examined animals		42	43	40	41
	Grade				
pH	5.0	0	0	0	0
	6.0	2	0	1	1
	6.5	1	0	3	3
	7.0	1	11	15	13
	7.5	17	15	12	14
	8.0	14	10	6	7
	8.5	7	7	3	3
	Chi square test		*	**	**

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

TABLE 10 URINALYSIS OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group name		Control	750 ppm	1500 ppm	3000 ppm
Number of examined animals		36	45	39	44
	Grade				
Ketone body	−	16	34	34	37
	±	19	11	5	6
	+	1	0	0	1
	2+	0	0	0	0
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test		*	**	**

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

TABLE 11 ORGAN WEIGHTS OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	39	42		40		40	
Body weight (g)	370 ± 30	342 ± 31	**	326 ± 29	**	308 ± 33	**
Adrenals (g)	0.067 ± 0.009	0.067 ± 0.014		0.075 ± 0.041		0.067 ± 0.017	
Adrenals (%)	0.018 ± 0.003	0.020 ± 0.005		0.023 ± 0.014	*	0.022 ± 0.007	**
Testes (g)	3.193 ± 1.242	4.361 ± 1.724	**	4.561 ± 1.337	**	5.407 ± 1.288	**
Testes (%)	0.863 ± 0.329	1.266 ± 0.489	**	1.415 ± 0.449	**	1.759 ± 0.403	**
Heart (g)	1.166 ± 0.090	1.111 ± 0.072	*	1.125 ± 0.094		1.123 ± 0.128	*
Heart (%)	0.316 ± 0.026	0.327 ± 0.033		0.346 ± 0.039	**	0.370 ± 0.075	**
Lungs (g)	1.355 ± 0.118	1.446 ± 0.422		1.395 ± 0.092		1.448 ± 0.012	*
Lungs (%)	0.368 ± 0.041	0.427 ± 0.149	**	0.430 ± 0.043	**	0.477 ± 0.112	**
Kidneys (g)	2.634 ± 0.153	2.802 ± 0.261	**	2.900 ± 0.281	**	2.965 ± 0.461	**
Kidneys (%)	0.715 ± 0.055	0.824 ± 0.094	**	0.898 ± 0.139	**	0.970 ± 0.167	**
Spleen (g)	1.071 ± 0.771	0.984 ± 0.250		0.975 ± 0.197		0.950 ± 0.291	
Spleen (%)	0.289 ± 0.204	0.285 ± 0.063	**	0.301 ± 0.063	**	0.305 ± 0.079	**
Liver (g)	10.023 ± 1.185	11.334 ± 1.593	**	12.366 ± 1.547	**	12.052 ± 1.760	**
Liver (%)	2.715 ± 0.297	3.307 ± 0.347	**	3.805 ± 0.469	**	3.945 ± 0.712	**
Brain (g)	2.021 ± 0.057	2.051 ± 0.070		2.045 ± 0.068		2.050 ± 0.081	
Brain (%)	0.549 ± 0.042	0.604 ± 0.068	**	0.631 ± 0.050	**	0.672 ± 0.069	**

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 FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm		1500 ppm		3000 ppm	
No. of examined animals	35	44		38		43	
Body weight (g)	248 ± 36	242 ± 24		228 ± 26	**	210 ± 29	**
Adrenals (g)	0.074 ± 0.022	0.067 ± 0.007		0.066 ± 0.007		0.064 ± 0.009	**
Adrenals (%)	0.031 ± 0.013	0.028 ± 0.004		0.030 ± 0.006		0.031 ± 0.006	
Ovaries (g)	0.154 ± 0.127	0.134 ± 0.028		0.285 ± 0.827		0.125 ± 0.016	
Ovaries (%)	0.061 ± 0.040	0.056 ± 0.012		0.124 ± 0.348		0.060 ± 0.009	*
Heart (g)	0.834 ± 0.091	0.837 ± 0.071		0.832 ± 0.064		0.829 ± 0.103	
Heart (%)	0.344 ± 0.066	0.348 ± 0.037		0.370 ± 0.046	**	0.399 ± 0.057	**
Lungs (g)	0.971 ± 0.068	1.018 ± 0.286		0.973 ± 0.065		1.015 ± 0.189	
Lungs (%)	0.402 ± 0.079	0.428 ± 0.150		0.436 ± 0.092	*	0.492 ± 0.113	**
Kidneys (g)	1.757 ± 0.131	1.876 ± 0.162	**	1.933 ± 0.173	**	1.968 ± 0.253	**
Kidneys (%)	0.723 ± 0.109	0.782 ± 0.102		0.861 ± 0.133	**	0.944 ± 0.110	**
Spleen (g)	0.819 ± 0.786	0.910 ± 1.996		0.557 ± 0.274		0.569 ± 0.260	
Spleen (%)	0.336 ± 0.314	0.410 ± 0.975		0.246 ± 0.119		0.270 ± 0.110	**
Liver (g)	6.462 ± 1.032	7.040 ± 1.161		7.186 ± 0.713	**	7.151 ± 1.371	**
Liver (%)	2.629 ± 0.351	2.940 ± 0.650		3.189 ± 0.425	**	3.400 ± 0.406	**
Brain (g)	1.844 ± 0.070	1.860 ± 0.050		1.853 ± 0.049		1.854 ± 0.073	
Brain (%)	0.766 ± 0.129	0.777 ± 0.087		0.828 ± 0.134	*	0.898 ± 0.130	**

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 FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm	1500 ppm	3000 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
kidney	<50>	<50>	<50>	<50>		
renal cell adenoma	0 (0 %)	0 (0 %)	3 (6 %)	26 (52 %) **	↑ ↑	↑ ↑
renal cell carcinoma	0 (0 %)	0 (0 %)	2 (4 %)	23 (46 %) **	↑ ↑	↑ ↑
preputial gland	<50>	<50>	<50>	<50>		
adenoma	1 (2 %)	4 (8 %)	2 (4 %)	7 (14 %) *	↑	↑
testis	<50>	<50>	<50>	<50>		
interstitial cell tumor	43 (86 %)	48 (96 %)	50 (100 %) **	49 (98 %) *	↑ ↑	↑
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar adenoma	0 (0 %)	1 (2 %)	0 (0 %)	3 (6 %)	↑	↑
pituitary gland	<50>	<50>	<50>	<49>		
adenoma	16 (32 %)	11 (22 %)	6 (12 %) *	5 (10 %) **		↓ ↓
thyroid	<50>	<50>	<50>	<50>		
C-cell adenoma	9 (18 %)	7 (14 %)	4 (8 %)	0 (0 %) **		↓ ↓

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

TABLE 14 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control	750 ppm	1500 ppm	3000 ppm	Peto	Cochran-
Number of examined animals	50	50	50	50	test	Armitage test
kidney	<50>	<50>	<50>	<50>		
renal cell adenoma	0 (0 %)	0 (0 %)	3 (6 %)	26 (52 %) **	↑ ↑	↑ ↑
renal cell carcinoma	0 (0 %)	0 (0 %)	0 (0 %)	12 (24 %) **	↑ ↑	↑ ↑
spleen	<50>	<50>	<50>	<50>		
mononuclear cell leukemia	8 (16 %)	3 (6 %)	3 (6 %)	1 (2 %) *		↓

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

TABLE 15 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control				750 ppm					1500 ppm					3000 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	
kidney	<50>				<50>					<50>					<50>				
atypical tubule hyperplasia	0	0	0	0	36	10	0	0	**	19	27	0	0	**	7	41	0	0	**
chronic nephropathy	30	15	2	1	5	15	27	3	**	1	10	33	6	**	4	19	26	1	**
eosinophilic droplet:proximal tubule	4	0	0	0	44	0	0	0	**	45	1	0	0	**	43	0	0	0	**
mineralization:papilla	0	0	0	0	10	0	0	0	**	32	9	0	0	**	11	32	5	0	**
urothelial hyperplasia:pelvis	0	0	0	0	8	12	3	0	**	3	23	15	0	**	2	27	13	0	**
spleen	<50>				<50>					<50>					<50>				
deposit of hemosiderin	27	0	0	0	39	0	1	0	*	39	2	0	0	**	34	3	0	0	*
liver	<50>				<50>					<50>					<50>				
bile duct hyperplasia	9	41	0	0	24	24	0	0	**	33	17	0	0	**	38	5	0	0	**
nasal cavity	<50>				<50>					<50>					<50>				
eosinophilic change:olfactory epithelium	15	13	5	0	17	10	1	0		7	9	6	0		8	3	0	0	**

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

TABLE 16 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

Group Name	Control				750 ppm					1500 ppm					3000 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	
kidney	<50>				<50>					<50>					<50>				
atypical tubule hyperplasia	0	0	0	0	25	3	0	0	**	31	9	0	0	**	10	40	0	0	**
chronic nephropathy	25	3	1	0	38	4	1	0	*	31	8	4	0	**	27	8	3	0	
eosinophilic droplet:proximal tubule	19	0	0	0	45	0	1	0	**	45	1	0	0	**	46	2	0	0	**
mineralization:papilla	3	0	0	0	2	0	0	0		2	0	0	0		10	0	0	0	
urothelial hyperplasia:pelvis	0	0	0	0	0	0	0	0		1	0	0	0		0	1	0	0	
spleen	<50>				<50>					<50>					<50>				
deposit of hemosiderin	10	23	0	0	8	37	0	0	**	10	30	1	0		8	37	0	0	**
liver	<50>				<50>					<50>					<50>				
basophilic cell focus	19	17	1	0	22	2	0	0	**	12	2	0	0	**	11	1	0	0	**
nasal cavity	<50>				<50>					<50>					<50>				
eosinophilic change:olfactory epithelium	6	8	27	1	12	15	18	2		11	17	15	4	*	16	15	2	1	**

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. (%)
Kidney	1749			
Renal cell adenoma		2	0.2	0 - 2
Renal cell carcinoma		4	0.2	0 - 4
Prepuputial gland	1749			
Adenoma		47	2.7	0 - 12
Testis	1748			
Interstitial cell tumor		1490	85.2	56 - 98
Lung	1749			
Bronchiolar-alveolar adenoma		62	3.5	0 - 10

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

TABLE 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. (%)
Kidney	1597			
Renal cell adenoma		2	0.1	0 - 2
Renal cell carcinoma		1	0.1	0 - 2
Spleen	1597			
Mononuclear cell leukemia		209	13.1	2 - 26
Mammary gland	1597			
Adenoma		51	3.2	0 - 18

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

TABLE 19 CAUSE OF DEATH OF RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

	Male				Female			
Group name	Control	750 ppm	1500 ppm	3000 ppm	Control	750 ppm	1500 ppm	3000 ppm
Number of dead or moribund animals	11	8	10	10	15	6	12	7
No microscopical confirmation	1	1	0	1	0	1	0	0
Nervous system disorders	0	1	0	0	0	0	0	0
Chronic nephropathy	0	0	2	2	0	0	0	0
Tumor death ：leukemia	2	1	3	0	4	1	2	0
subcutis	2	2	1	2	0	0	0	0
lung	0	0	0	0	1	0	0	0
bone marrow	0	0	0	1	0	0	0	0
spleen	0	1	0	0	0	0	0	0
small intestine	0	0	0	1	0	0	0	0
liver	1	0	0	0	0	0	0	1
kidney	0	0	0	0	0	0	1	0
pituitary gland	3	2	1	0	4	2	2	1
adrenal gland	0	0	0	0	1	0	0	0
ovary	—	—	—	—	1	0	0	0
uterus	—	—	—	—	3	2	4	5
mammary gland	0	0	1	1	0	0	1	0
preputial/clitoral gland	0	0	0	0	0	0	2	0
bone	0	0	0	2	1	0	0	0
peritoneum	1	0	2	0	0	0	0	0
retroperitoneum	1	0	0	0	0	0	0	0

FIGURES

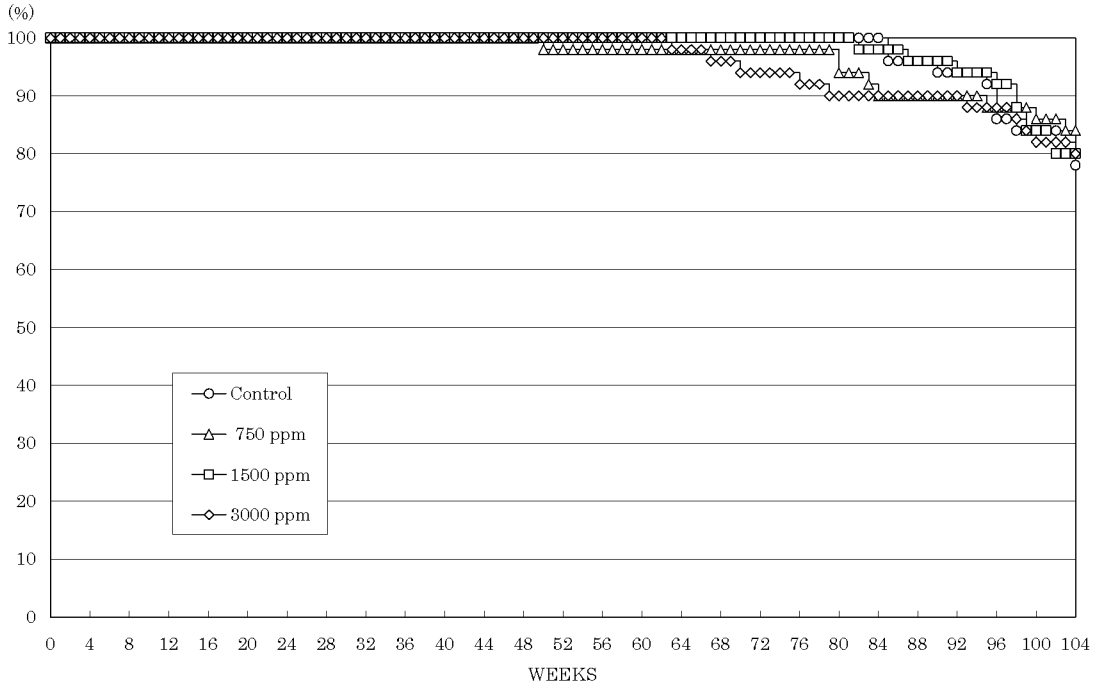


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

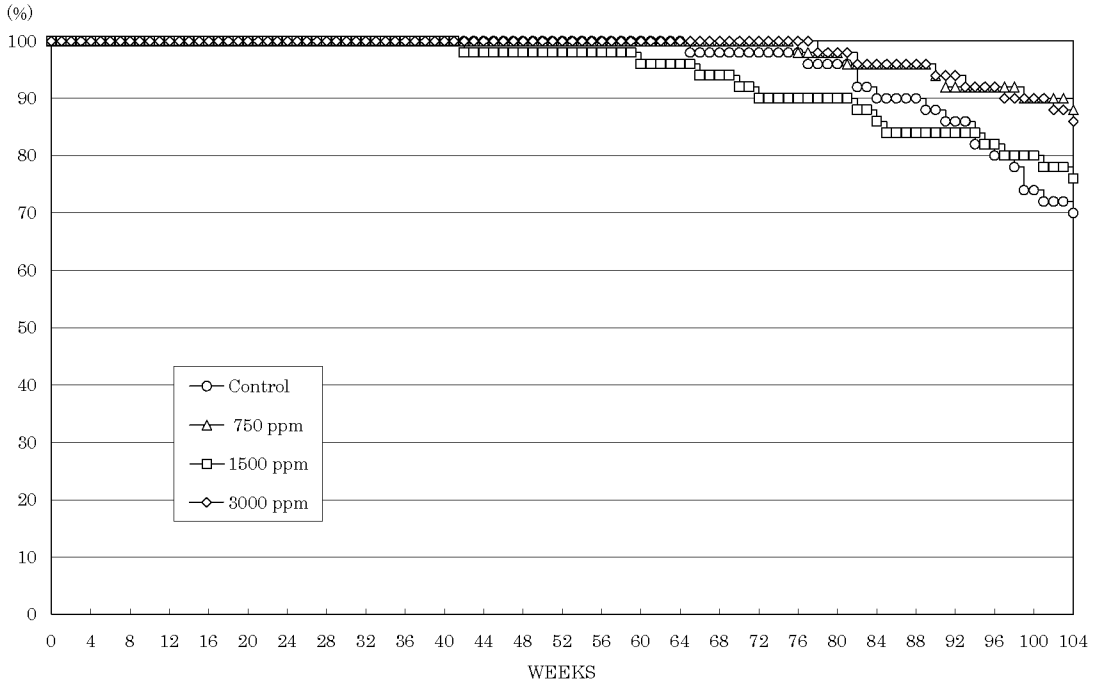


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

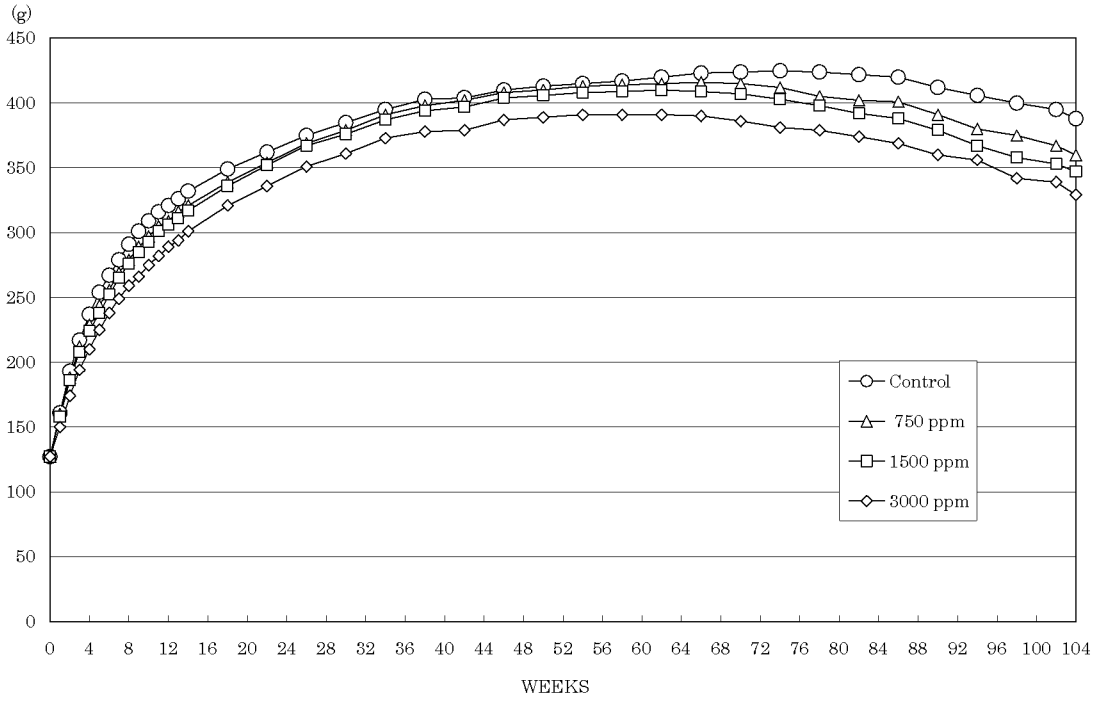


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

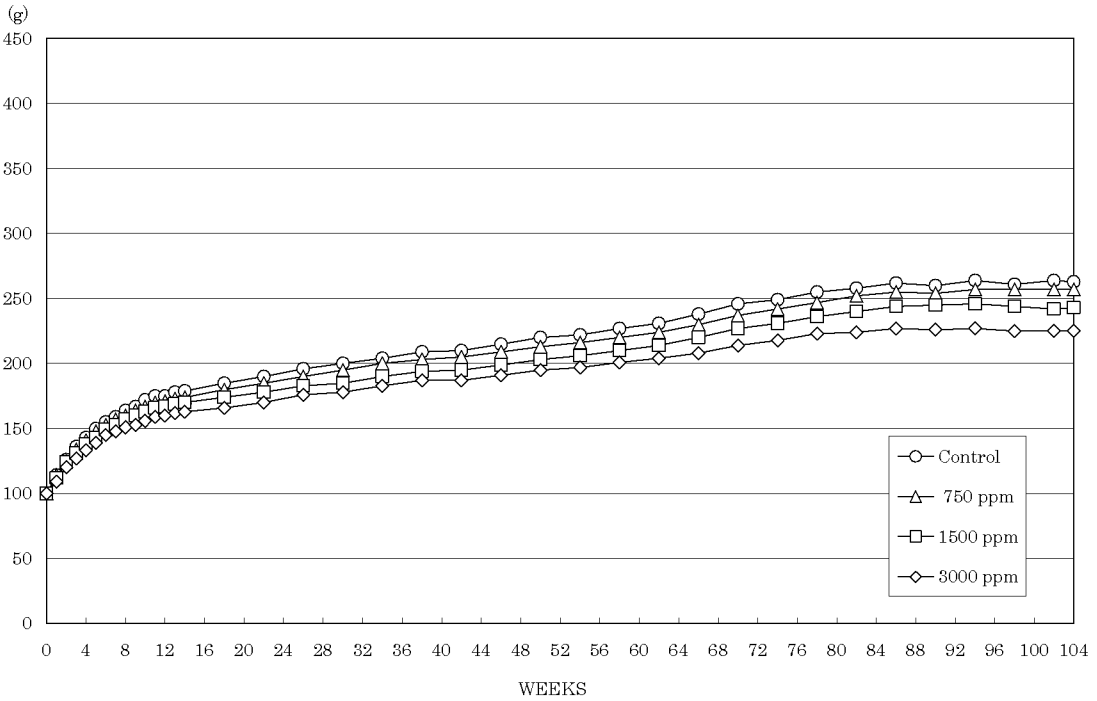


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

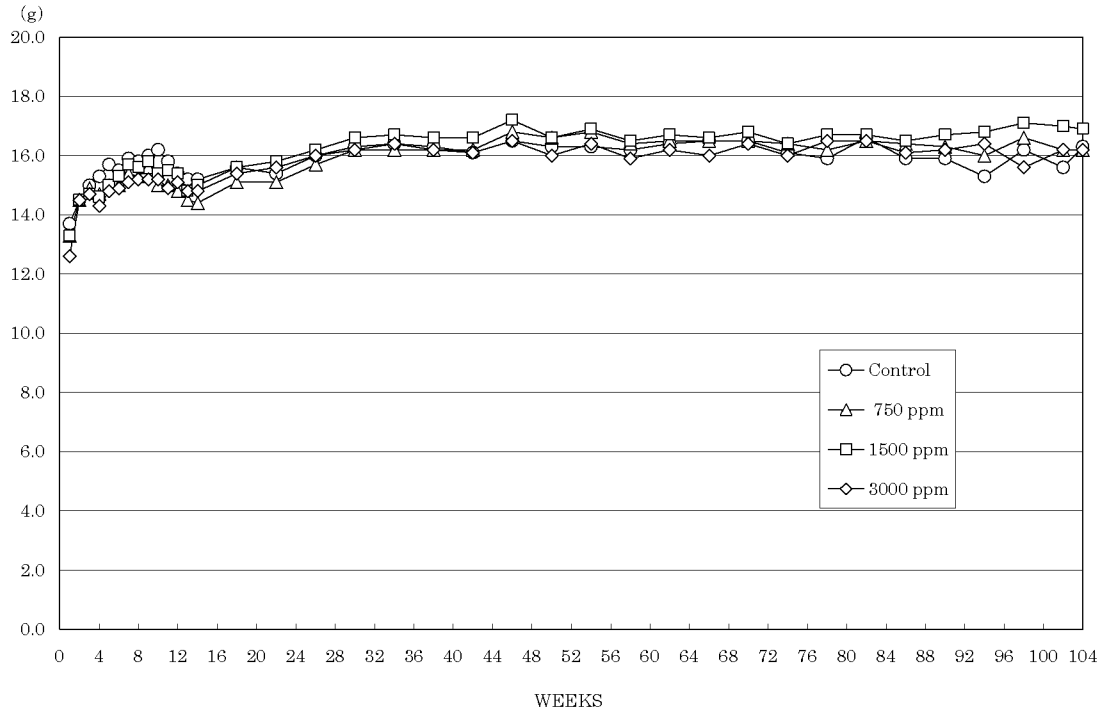


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE

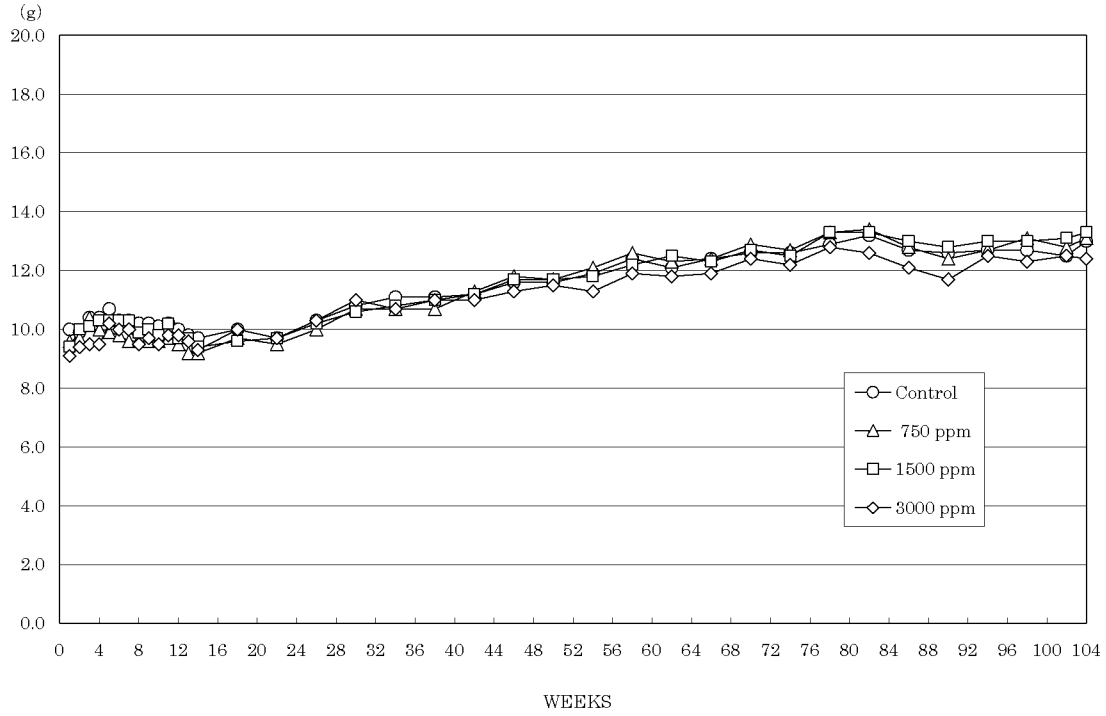
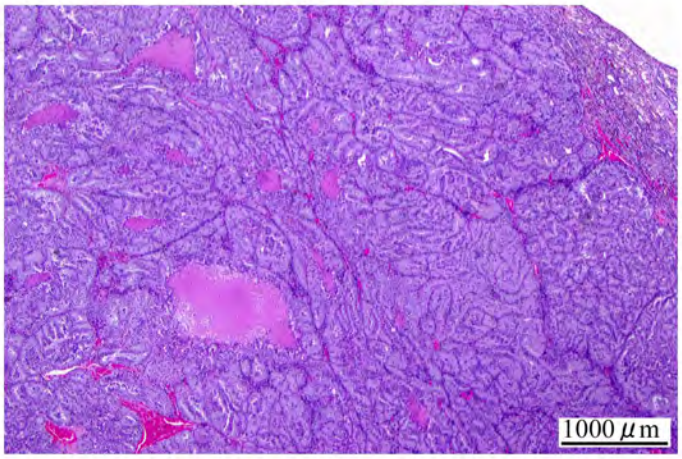
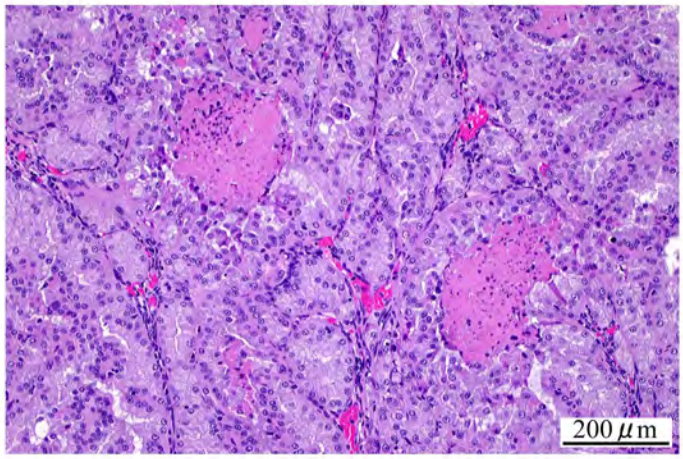


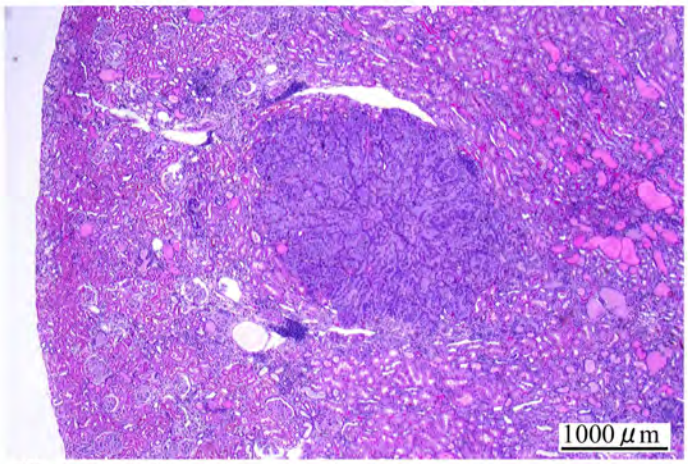
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,4-DICHLORO-1-NITROBENZENE



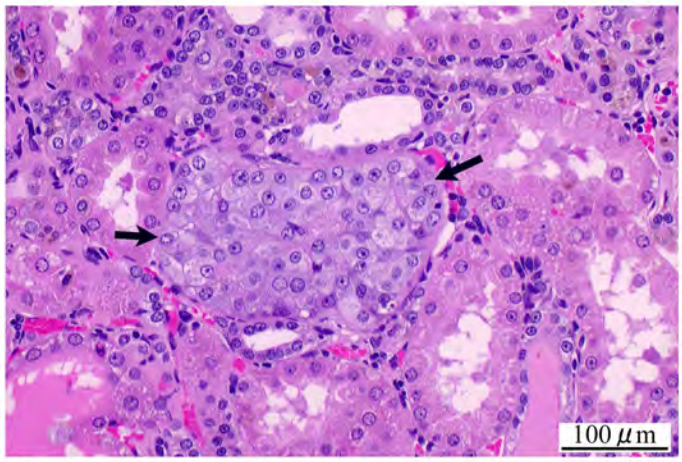
Photograph1
Kidney: Renal cell carcinoma
Rat, Male, 3000 ppm, Animal No. 0421-1309 (H&E)



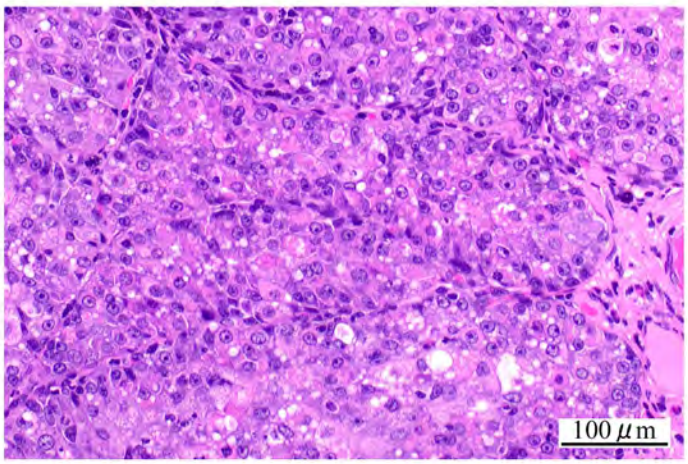
Photograph 2
Kidney: Renal cell carcinoma
Higher magnification of photograph 1



Photograph 3
Kidney: Renal cell adenoma
Rat, Male, 3000 ppm, Animal No. 0421-1330 (H&E)



Photograph 4
Kidney: Atypical tubule hyperplasia (Arrows)
Rat, Male, 1500 ppm, Animal No. 0421-1201 (H&E)



Photograph 5
Preputial gland: Adenoma
Rat, Male, 3000 ppm, Animal No. 0421-1323 (H&E)