Summary of Drinking Water Carcinogenicity Study of Urotropin 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 Labour of Japan on June 27 1997.

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

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Purpose, materials and methods

Urotropin (1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane ; Hexamethylenetetramine : CAS No. 100-97-0) is a white crystalline powder with a sublimation point of 263°C and is soluble in water.

The carcinogenicity and chronic toxicity of urotropin were examined by administering groups of F344/DuCrj (Fischer) rats urotropin in their drinking water for 2 years (104 weeks). Each group of test animals consisted of either 50 male or 50 female rats. The drinking water concentration of urotropin was 0, 7500, 15000 or 30000 ppm (w/w). Both sexes were exposed to each concentration of urotropin. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the urotropin used in these experiments was confirmed by both infrared spectrometry and mass spectrometry, and it was analyzed by gas chromatography before and after its use to affirm its stability. To ensure that the concentration of urotropin in the drinking water remained constant, the concentration of urotropin in the drinking water was determined by gas chromatography at the time of preparation and on the 11th day after preparation; water-urotropin mixtures were 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 body weights and water consumption were measured every 2 weeks thereafter and food consumption was measured every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the administration period. For hematology and blood biochemistry at the terminal necropsy, surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of urotropin induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were

analyzed by the 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 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

Survival rates of both males and females administered 30000 ppm urotropin and females administered 15000 ppm urotropin were decreased compared with their respective controls. No significant increase in the incidence of neoplastic lesions was found in any urotropin-administered group of either sex compared with their respective controls. There was, however, mineralization in the brains and kidneys of dead and moribund rats, and this mineralization may have been the cause of death.

Conclusions

There was no evidence of carcinogenic activity of urotropin in male or female rats.

SELECTED TABLES

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN MALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	7500 ppm Av.Wt.	7500 ppm % of cont. <50>	7500 ppm No.of Surviv.	15000 ppm Av.Wt.	15000 ppm % of cont. <50>	15000 ppm No.of Surviv.	30000 ppm Av.Wt.	30000 ppm % of cont. <50>	30000 ppm No.of Surviv.
0	128 (50)	50/50	128 (50)	100	50/50	128 (50)	100	50/50	128 (50)	100	50/50
1	167 (50)	50/50	166 (50)	99	50/50	162 (50)	97	50/50	159 (50)	95	50/50
2	196 (50)	50/50	193 (50)	98	50/50	190 (50)	97	50/50	185 (50)	94	50/50
3	215 (50)	50/50	212 (50)	99	50/50	208 (50)	97	50/50	202 (50)	94	50/50
4	231 (50)	50/50	227 (50)	98	50/50	225 (50)	97	50/50	216 (50)	94	50/50
5	245 (50)	50/50	240 (50)	98	50/50	239 (50)	98	50/50	227 (50)	93	50/50
6	259 (50)	50/50	253 (50)	98	50/50	251 (50)	97	50/50	240 (50)	93	50/50
7	273 (50)	50/50	268 (50)	98	50/50	267 (50)	98	50/50	254 (50)	93	50/50
8	285 (50)	50/50	281 (50)	99	50/50	279 (50)	98	50/50	267 (50)	94	50/50
9	297 (50)	50/50	294 (50)	99	50/50	291 (50)	98	50/50	277 (50)	93	50/50
10	306 (50)	50/50	304 (50)	99	50/50	302 (50)	99	50/50	286 (50)	93	50/50
11	317 (50)	50/50	315 (50)	99	50/50	313 (50)	99	50/50	296 (50)	93	50/50
12	325 (50)	50/50	323 (50)	99	50/50	322 (50)	99	50/50	305 (50)	94	50/50
13	333 (50)	50/50	333 (50)	100	50/50	330 (50)	99	50/50	314 (50)	94	50/50
14	342 (50)	50/50	341 (50)	100	50/50	337 (50)	99	50/50	322 (50)	94	50/50
16	355 (50)	50/50	356 (50)	100	50/50	351 (50)	99	50/50	335 (50)	94	50/50
18	361 (50)	50/50	362 (50)	100	50/50	356 (50)	99	50/50	344 (50)	95	50/50
20	365 (50)	50/50	366 (50)	100	50/50	363 (50)	99	50/50	350 (50)	96	50/50
22	374 (50)	50/50	375 (50)	100	50/50	368 (50)	98	50/50	357 (50)	95	50/50
24	379 (50)	50/50	381 (50)	101	50/50	375 (50)	99	50/50	365 (50)	96	50/50
26	388 (50)	50/50	389 (50)	100	50/50	384 (50)	99	50/50	375 (50)	97	50/50
28	394 (50)	50/50	396 (50)	101	50/50	391 (50)	99	50/50	382 (50)	97	50/50
30	403 (50)	50/50	406 (50)	101	50/50	399 (50)	99	50/50	391 (50)	97	50/50
32	410 (50)	50/50	413 (50)	101	50/50	406 (50)	99	50/50	397 (50)	97	50/50
34	416 (50)	50/50	420 (50)	101	50/50	412 (50)	99	50/50	403 (50)	97	50/50
36	423 (50)	50/50	427 (50)	101	50/50	419 (50)	99	50/50	410 (50)	97	50/50
38	428 (50)	50/50	433 (50)	101	50/50	424 (50)	99	50/50	415 (50)	97	50/50
40	432 (50)	50/50	438 (50)	101	50/50	431 (50)	100	50/50	421 (50)	97	50/50
42	438 (50)	50/50	443 (50)	101	50/50	435 (50)	99	50/50	425 (50)	97	50/50
44	443 (50)	50/50	448 (50)	101	50/50	439 (50)	99	50/50	429 (50)	97	50/50
46	447 (50)	50/50	453 (50)	101	50/50	443 (50)	99	50/50	432 (50)	97	50/50
48	451 (50)	50/50	457 (50)	101	50/50	447 (50)	99	50/50	436 (50)	97	50/50
50	455 (50)	50/50	460 (50)	101	50/50	451 (50)	99	50/50	438 (50)	96	50/50
52	459 (50)	50/50	465 (50)	101	50/50	455 (50)	99	50/50	443 (50)	97	50/50
54	462 (50)	50/50	468 (50)	101	50/50	459 (50)	99	50/50	447 (50)	97	50/50
56	467 (50)	50/50	472 (50)	101	50/50	461 (50)	99	49/50	451 (50)	97	50/50
58	469 (50)	50/50	473 (50)	101	50/50	464 (49)	99	49/50	451 (50)	96	50/50
60	474 (50)	50/50	477 (50)	101	50/50	467 (49)	99	49/50	455 (50)	96	50/50
62	478 (50)	50/50	481 (49)	101	49/50	470 (48)	98	48/50	457 (50)	96	50/50
64	481 (50)	50/50	484 (49)	101	49/50	474 (48)	99	48/50	459 (50)	95	50/50
66	482 (50)	50/50	487 (49)	101	49/50	475 (48)	99	47/50	461 (50)	96	50/50
68	484 (49)	49/50	491 (49)	101	49/50	483 (47)	100	47/50	463 (50)	96	50/50
70	487 (48)	48/50	489 (49)	100	49/50	482 (47)	99	47/50	463 (50)	95	50/50
72	484 (48)	48/50	488 (49)	101	49/50	479 (47)	99	47/50	462 (50)	95	50/50
74	485 (48)	48/50	489 (49)	101	49/50	479 (47)	99	47/50	463 (50)	95	50/50
76	487 (48)	48/50	490 (49)	101	49/50	478 (47)	98	47/50	463 (50)	95	50/50
78	489 (48)	48/50	492 (47)	101	47/50	481 (46)	98	46/50	462 (50)	94	50/50
80	490 (48)	48/50	493 (47)	101	47/50	480 (46)	98	46/50	464 (48)	95	48/50
82	491 (48)	48/50	492 (46)	100	46/50	480 (46)	98	46/50	463 (48)	94	48/50
84	484 (48)	48/50	491 (46)	101	46/50	475 (45)	98	45/50	457 (48)	94	48/50
86	489 (46)	46/50	489 (46)	100	46/50	474 (45)	97	45/50	457 (46)	93	46/50
88	488 (46)	46/50	490 (46)	100	46/50	470 (45)	96	45/50	452 (46)	93	46/50
90	484 (45)	45/50	486 (46)	100	46/50	463 (45)	96	45/50	448 (46)	93	46/50
92	477 (45)	45/50	480 (46)	101	46/50	459 (42)	96	42/50	442 (46)	93	46/50
94	472 (44)	44/50	479 (46)	101	46/50	453 (42)	96	42/50	435 (44)	92	43/50
96	466 (43)	42/50	477 (46)	102	45/50	451 (40)	97	40/50	432 (41)	93	41/50
98	470 (41)	41/50	460 (43)	98	42/50	444 (40)	94	40/50	421 (39)	90	37/50
100	463 (39)	39/50	455 (42)	98	42/50	436 (38)	94	37/50	413 (33)	89	33/50
102	455 (39)	39/50	450 (40)	99	40/50	436 (35)	96	35/50	414 (30)	91	30/50
104	451 (38)	38/50	445 (39)	99	39/50	428 (34)	95	34/50	398 (30)	88	30/50

< >:No.of effective animals,( ):No.of measured animals Av.Wt.: g

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN FEMALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	7500 ppm Av.Wt.	7500 ppm % of cont. <50>	7500 ppm No.of Surviv. <50>	15000 ppm Av.Wt.	15000 ppm % of cont. <50>	15000 ppm No.of Surviv. <50>	30000 ppm Av.Wt.	30000 ppm % of cont. <50>	30000 ppm No.of Surviv. <50>
0	100 (50)	50/50	100 (50)	100	50/50	100 (50)	100	50/50	101 (50)	101	50/50
1	120 (50)	50/50	119 (50)	99	50/50	119 (50)	99	50/50	117 (50)	98	50/50
2	131 (50)	50/50	130 (50)	99	50/50	130 (50)	99	50/50	128 (50)	98	50/50
3	140 (50)	50/50	140 (50)	100	50/50	139 (50)	99	50/50	136 (50)	97	50/50
4	148 (50)	50/50	147 (50)	99	50/50	147 (50)	99	50/50	143 (50)	97	50/50
5	155 (50)	50/50	154 (50)	99	50/50	154 (50)	99	50/50	148 (50)	95	50/50
6	159 (50)	50/50	157 (50)	99	50/50	158 (50)	99	50/50	153 (50)	96	50/50
7	165 (50)	50/50	163 (50)	99	50/50	163 (50)	99	50/50	157 (50)	95	50/50
8	167 (50)	50/50	166 (50)	99	50/50	166 (50)	99	50/50	160 (50)	96	50/50
9	173 (50)	50/50	171 (50)	99	50/50	171 (50)	99	50/50	165 (50)	95	50/50
10	176 (50)	50/50	174 (50)	99	50/50	174 (50)	99	50/50	167 (50)	95	50/50
11	181 (50)	50/50	178 (50)	98	50/50	178 (50)	98	50/50	171 (50)	94	50/50
12	183 (50)	50/50	180 (50)	98	50/50	180 (50)	98	50/50	172 (50)	94	50/50
13	186 (50)	50/50	184 (50)	99	50/50	183 (50)	98	50/50	175 (50)	94	50/50
14	190 (50)	50/50	187 (50)	98	50/50	185 (50)	97	50/50	178 (50)	94	50/50
16	195 (50)	50/50	193 (50)	99	50/50	189 (50)	97	50/50	182 (50)	93	50/50
18	199 (50)	50/50	196 (50)	98	50/50	193 (50)	97	50/50	186 (50)	93	50/50
20	202 (50)	50/50	199 (50)	99	50/50	196 (50)	97	50/50	189 (50)	94	50/50
22	205 (50)	50/50	202 (50)	99	50/50	198 (50)	97	50/50	191 (50)	93	50/50
24	209 (50)	50/50	205 (50)	98	50/50	201 (50)	96	50/50	193 (50)	92	50/50
26	212 (50)	50/50	209 (50)	99	50/50	205 (50)	97	50/50	197 (50)	93	50/50
28	214 (50)	50/50	212 (50)	99	50/50	207 (50)	97	50/50	198 (50)	93	50/50
30	217 (50)	50/50	214 (50)	99	50/50	210 (50)	97	50/50	201 (50)	93	50/50
32	220 (50)	50/50	218 (50)	99	50/50	213 (50)	97	50/50	204 (50)	93	50/50
34	221 (50)	50/50	220 (50)	100	50/50	214 (50)	97	50/50	205 (50)	93	50/50
36	224 (50)	50/50	224 (50)	100	50/50	219 (50)	98	50/50	211 (49)	94	49/50
38	228 (50)	50/50	227 (50)	100	50/50	220 (50)	96	50/50	212 (49)	93	49/50
40	231 (50)	50/50	230 (50)	100	50/50	222 (50)	96	50/50	214 (49)	93	49/50
42	234 (50)	50/50	231 (50)	99	50/50	224 (50)	96	50/50	216 (49)	92	49/50
44	236 (50)	50/50	234 (50)	99	50/50	227 (50)	96	50/50	219 (49)	93	49/50
46	238 (50)	50/50	238 (49)	100	49/50	230 (50)	97	50/50	221 (49)	93	49/50
48	241 (50)	50/50	240 (49)	100	49/50	231 (50)	96	50/50	222 (49)	92	49/50
50	245 (50)	50/50	244 (49)	100	49/50	234 (50)	96	50/50	225 (49)	92	49/50
52	250 (50)	50/50	249 (49)	100	49/50	237 (50)	95	50/50	228 (49)	91	49/50
54	252 (50)	50/50	250 (49)	99	49/50	239 (50)	95	50/50	230 (49)	91	49/50
56	255 (50)	50/50	252 (49)	99	49/50	241 (50)	95	50/50	233 (49)	91	49/50
58	259 (50)	50/50	257 (49)	99	49/50	245 (50)	95	50/50	234 (49)	90	49/50
60	262 (50)	50/50	260 (49)	99	49/50	249 (50)	95	50/50	239 (49)	91	49/50
62	267 (50)	50/50	263 (49)	99	49/50	252 (50)	94	50/50	240 (48)	90	48/50
64	271 (50)	50/50	270 (49)	100	49/50	256 (50)	94	50/50	243 (47)	90	47/50
66	274 (50)	50/50	275 (49)	100	49/50	259 (50)	95	50/50	245 (47)	89	47/50
68	277 (50)	50/50	278 (49)	100	49/50	262 (50)	95	50/50	248 (46)	90	46/50
70	280 (50)	50/50	282 (49)	101	49/50	266 (50)	95	50/50	250 (45)	89	44/50
72	283 (50)	50/50	286 (48)	101	48/50	268 (50)	95	50/50	253 (44)	89	44/50
74	287 (50)	50/50	290 (48)	101	48/50	271 (50)	94	50/50	254 (43)	89	43/50
76	292 (50)	50/50	295 (48)	101	48/50	273 (50)	93	50/50	257 (38)	88	38/50
78	295 (50)	50/50	297 (47)	101	47/50	277 (50)	94	50/50	259 (36)	88	36/50
80	298 (50)	50/50	301 (47)	101	47/50	280 (49)	94	49/50	262 (34)	88	32/50
82	302 (50)	50/50	304 (47)	101	47/50	284 (48)	94	48/50	267 (31)	88	31/50
84	304 (50)	50/50	308 (46)	101	46/50	285 (48)	94	48/50	267 (31)	88	31/50
86	307 (50)	50/50	310 (46)	101	46/50	289 (47)	94	47/50	260 (29)	85	28/50
88	309 (50)	50/50	311 (46)	101	46/50	291 (46)	94	46/50	266 (26)	86	26/50
90	308 (50)	50/50	309 (46)	100	46/50	292 (45)	95	45/50	267 (26)	87	26/50
92	306 (50)	49/50	310 (45)	101	45/50	292 (45)	95	43/50	266 (26)	87	26/50
94	309 (49)	49/50	307 (45)	99	44/50	294 (43)	95	43/50	270 (24)	87	24/50
96	316 (48)	48/50	311 (42)	98	41/50	297 (42)	94	41/50	275 (23)	87	23/50
98	317 (47)	47/50	310 (41)	98	41/50	297 (41)	94	41/50	269 (23)	85	23/50
100	316 (47)	47/50	310 (40)	98	40/50	295 (40)	93	40/50	276 (20)	87	20/50
102	314 (47)	47/50	311 (39)	99	39/50	300 (35)	96	35/50	270 (16)	86	16/50
104	313 (47)	47/50	311 (39)	99	39/50	295 (35)	94	35/50	274 (14)	88	14/50

< >:No.of effective animals,( ):No.of measured animals Av.Wt.: g

TABLE 4 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION IN MALE RAT

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	0/50	4/48	8/45	9/38	11/50(3/12)
	7500ppm	0/50	0/50	0/50	2/50	3/49	4/47	7/46	15/39	16/50(4/11)
	15000ppm	0/50	0/50	0/50	0/50	2/48	2/46	2/43	8/34	10/50(3/16)
	30000ppm	0/50	0/50	0/50	0/50	2/50	5/50	6/46	17/30	18/50(8/20)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	1/48	0/45	0/38	1/50(1/12)
	7500ppm	0/50	0/50	0/50	0/50	0/49	0/47	0/46	1/39	1/50(1/11)
	15000ppm	0/50	0/50	0/50	0/50	0/48	1/46	0/43	1/34	2/50(2/16)
	30000ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/46	0/30	0/50(0/20)

No. of animals with mass / No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 5 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION IN FEMALE RAT

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	0/50	4/50	7/47	9/50(2/ 3)
	7500ppm	0/50	0/50	0/50	1/49	1/49	3/47	7/46	8/39	12/50(4/11)
	15000ppm	0/50	0/50	0/50	0/50	0/50	2/50	2/45	8/35	10/50(6/15)
	30000ppm	0/50	0/50	1/49	2/49	2/47	5/36	5/26	7/14	13/50(9/36)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/47	0/50(0/ 3)
	7500ppm	0/50	0/50	0/50	0/49	0/49	0/47	0/46	1/39	1/50(1/11)
	15000ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/45	1/35	1/50(1/15)
	30000ppm	0/50	0/50	0/49	0/49	0/47	0/36	1/26	1/14	2/50(2/36)

No. of animals with mass / No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 6 WATER CONSUMPTION IN MALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.WC.	Control No.of Surviv. <50>	7500 ppm Av.WC.	7500 ppm % of cont.	7500 ppm No.of Surviv. <50>	15000 ppm Av.WC.	15000 ppm % of cont.	15000 ppm No.of Surviv. <50>	30000 ppm Av.WC.	30000 ppm % of cont.	30000 ppm No.of Surviv. <50>
1	19.6 (50)	50/50	20.6 (50)	105	50/50	21.7 (50)	111	50/50	20.4 (50)	104	50/50
2	20.8 (50)	50/50	21.9 (50)	105	50/50	22.8 (50)	110	50/50	20.1 (50)	97	50/50
3	21.8 (50)	50/50	21.6 (50)	99	50/50	22.6 (50)	104	50/50	20.2 (50)	93	50/50
4	22.3 (50)	50/50	22.3 (50)	100	50/50	23.0 (50)	103	50/50	20.8 (50)	93	50/50
5	21.6 (50)	50/50	22.9 (50)	106	50/50	22.9 (50)	106	50/50	20.4 (50)	94	50/50
6	20.8 (50)	50/50	21.9 (50)	105	50/50	22.8 (50)	110	50/50	20.3 (50)	98	50/50
7	20.8 (50)	50/50	21.5 (50)	103	50/50	22.7 (50)	109	50/50	19.9 (50)	96	50/50
8	21.7 (48)	50/50	22.2 (50)	102	50/50	23.0 (50)	106	50/50	20.4 (50)	94	50/50
9	21.9 (50)	50/50	22.4 (50)	102	50/50	23.1 (50)	105	50/50	20.7 (50)	95	50/50
10	21.4 (50)	50/50	21.9 (50)	102	50/50	22.5 (50)	105	50/50	21.0 (50)	98	50/50
11	21.7 (50)	50/50	21.7 (50)	100	50/50	22.1 (50)	102	50/50	21.0 (50)	97	50/50
12	20.7 (50)	50/50	20.9 (50)	101	50/50	21.4 (50)	103	50/50	21.0 (50)	101	50/50
13	21.6 (49)	50/50	21.8 (50)	101	50/50	22.1 (50)	102	50/50	21.4 (50)	99	50/50
14	22.2 (49)	50/50	21.8 (50)	98	50/50	22.8 (50)	103	50/50	21.4 (50)	96	50/50
16	19.7 (50)	50/50	19.6 (50)	99	50/50	20.1 (50)	102	50/50	19.7 (50)	100	50/50
18	19.3 (49)	50/50	19.3 (50)	100	50/50	19.8 (50)	103	50/50	19.8 (50)	103	50/50
20	20.1 (50)	50/50	19.9 (50)	99	50/50	20.7 (50)	103	50/50	19.7 (50)	98	50/50
22	19.1 (50)	50/50	19.4 (50)	102	50/50	19.4 (50)	102	50/50	19.3 (50)	101	50/50
24	18.6 (50)	50/50	19.0 (50)	102	50/50	19.9 (50)	107	50/50	19.7 (50)	106	50/50
26	19.1 (50)	50/50	19.1 (50)	100	50/50	20.3 (49)	106	50/50	20.3 (50)	106	50/50
28	18.6 (50)	50/50	19.5 (50)	105	50/50	19.7 (50)	106	50/50	20.3 (50)	109	50/50
30	18.8 (50)	50/50	19.2 (50)	102	50/50	19.6 (50)	104	50/50	20.0 (50)	106	50/50
32	18.4 (50)	50/50	19.0 (49)	103	50/50	18.9 (50)	103	50/50	19.8 (50)	108	50/50
34	17.5 (50)	50/50	18.0 (50)	103	50/50	18.4 (50)	105	50/50	18.6 (50)	106	50/50
36	18.6 (50)	50/50	18.9 (50)	102	50/50	19.6 (50)	105	50/50	19.9 (50)	107	50/50
38	18.5 (50)	50/50	18.9 (50)	102	50/50	19.2 (50)	104	50/50	19.6 (50)	106	50/50
40	18.8 (50)	50/50	19.2 (50)	102	50/50	19.6 (50)	104	50/50	20.1 (50)	107	50/50
42	18.9 (50)	50/50	19.4 (50)	103	50/50	19.8 (50)	105	50/50	20.3 (50)	107	50/50
44	19.4 (50)	50/50	19.8 (50)	102	50/50	20.7 (50)	107	50/50	21.3 (50)	110	50/50
46	19.5 (50)	50/50	20.0 (50)	103	50/50	20.6 (50)	106	50/50	21.0 (50)	108	50/50
48	20.0 (50)	50/50	20.3 (50)	102	50/50	21.6 (50)	108	50/50	22.0 (50)	110	50/50
50	20.2 (50)	50/50	20.5 (50)	101	50/50	21.1 (50)	104	50/50	21.7 (50)	107	50/50
52	20.0 (50)	50/50	20.5 (50)	103	50/50	20.8 (50)	104	50/50	21.7 (50)	109	50/50
54	20.1 (49)	50/50	20.4 (50)	101	50/50	21.4 (50)	106	50/50	22.6 (50)	112	50/50
56	20.3 (50)	50/50	20.4 (50)	100	50/50	21.1 (49)	104	49/50	22.1 (50)	109	50/50
58	20.5 (50)	50/50	20.5 (50)	100	50/50	21.4 (49)	104	49/50	22.0 (50)	107	50/50
60	20.1 (50)	50/50	20.1 (50)	100	50/50	20.6 (49)	102	49/50	21.7 (50)	108	50/50
62	20.3 (50)	50/50	19.7 (50)	97	49/50	20.9 (48)	103	48/50	22.1 (50)	109	50/50
64	20.0 (50)	50/50	20.3 (49)	102	49/50	21.3 (48)	106	48/50	22.0 (50)	110	50/50
66	20.0 (50)	50/50	20.6 (49)	103	49/50	21.4 (48)	107	47/50	22.0 (50)	110	50/50
68	19.1 (49)	49/50	19.9 (49)	104	49/50	20.5 (47)	107	47/50	21.3 (50)	112	50/50
70	20.6 (48)	48/50	20.4 (49)	99	49/50	21.4 (47)	104	47/50	22.2 (50)	108	50/50
72	19.4 (48)	48/50	19.5 (49)	101	49/50	20.8 (47)	107	47/50	21.6 (50)	111	50/50
74	20.3 (48)	48/50	21.1 (49)	104	49/50	21.9 (47)	108	47/50	22.7 (50)	112	50/50
76	20.8 (48)	48/50	20.9 (49)	100	49/50	22.1 (47)	106	47/50	22.4 (50)	108	50/50
78	22.1 (48)	48/50	22.6 (48)	102	47/50	23.2 (46)	105	46/50	24.4 (50)	110	50/50
80	20.6 (48)	48/50	21.3 (47)	103	47/50	22.0 (46)	107	46/50	23.0 (48)	112	48/50
82	22.1 (48)	48/50	22.3 (46)	101	46/50	23.3 (46)	105	46/50	24.0 (48)	109	48/50
84	21.5 (48)	48/50	22.2 (46)	103	46/50	23.3 (44)	108	45/50	24.3 (48)	113	48/50
86	23.5 (46)	46/50	23.2 (46)	99	46/50	24.3 (45)	103	45/50	24.3 (46)	103	46/50
88	23.5 (43)	46/50	23.8 (45)	101	46/50	23.6 (42)	100	45/50	24.2 (45)	103	46/50
90	23.9 (45)	45/50	23.2 (46)	97	46/50	23.8 (44)	100	45/50	23.9 (46)	100	46/50
92	24.2 (43)	45/50	24.8 (46)	102	46/50	23.9 (40)	99	42/50	25.1 (46)	104	46/50
94	23.8 (43)	44/50	23.4 (43)	98	46/50	24.2 (41)	102	42/50	24.7 (44)	104	43/50
96	23.9 (39)	42/50	24.7 (42)	103	45/50	26.3 (39)	110	40/50	26.5 (41)	111	41/50
98	26.4 (37)	41/50	25.8 (41)	98	42/50	27.6 (40)	105	40/50	25.1 (39)	95	37/50
100	26.1 (33)	39/50	26.2 (37)	100	42/50	26.2 (36)	100	37/50	25.4 (32)	97	33/50
102	29.4 (36)	39/50	26.4 (37)	90	40/50	28.7 (35)	98	35/50	26.7 (29)	91	30/50
104	26.8 (26)	38/50	26.1 (30)	97	39/50	26.2 (27)	98	34/50	26.1 (29)	97	30/50

< >:No.of effective animals,( ):No.of measured animals Av.WC.: g

TABLE 7 WATER CONSUMPTION IN FEMALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.WC.	Control No.of Surviv. <50>	7500 ppm Av.WC.	7500 ppm % of cont. <50>	7500 ppm No.of Surviv.	15000 ppm Av.WC.	15000 ppm % of cont. <50>	15000 ppm No.of Surviv.	30000 ppm Av.WC.	30000 ppm % of cont. <50>	30000 ppm No.of Surviv.
1	17.3 (50)	50/50	18.8 (50)	109	50/50	17.3 (50)	100	50/50	17.7 (50)	102	50/50
2	18.0 (50)	50/50	20.9 (50)	116	50/50	18.3 (50)	102	50/50	17.1 (50)	95	50/50
3	17.5 (49)	50/50	19.9 (49)	114	50/50	19.0 (50)	109	50/50	16.6 (48)	95	50/50
4	17.7 (50)	50/50	19.1 (46)	108	50/50	18.9 (49)	107	50/50	17.3 (50)	98	50/50
5	17.7 (47)	50/50	18.5 (46)	105	50/50	19.0 (49)	107	50/50	16.2 (48)	92	50/50
6	18.4 (48)	50/50	19.6 (47)	107	50/50	20.3 (49)	110	50/50	17.2 (50)	93	50/50
7	17.6 (47)	50/50	21.1 (48)	120	50/50	18.6 (49)	106	50/50	16.6 (50)	94	50/50
8	18.2 (48)	50/50	20.1 (45)	110	50/50	19.4 (47)	107	50/50	17.5 (48)	96	50/50
9	19.3 (47)	50/50	20.6 (45)	107	50/50	19.5 (47)	101	50/50	16.7 (50)	87	50/50
10	19.3 (48)	50/50	21.2 (44)	110	50/50	18.4 (44)	95	50/50	16.7 (48)	87	50/50
11	19.7 (48)	50/50	20.0 (41)	102	50/50	19.6 (45)	99	50/50	15.7 (46)	80	50/50
12	19.3 (49)	50/50	19.0 (44)	98	50/50	18.6 (47)	96	50/50	17.9 (50)	93	50/50
13	18.7 (44)	50/50	20.2 (46)	108	50/50	17.5 (45)	94	50/50	17.2 (49)	92	50/50
14	20.1 (42)	50/50	20.6 (44)	102	50/50	20.8 (45)	103	50/50	18.0 (49)	90	50/50
16	18.7 (46)	50/50	19.5 (43)	104	50/50	19.5 (49)	104	50/50	15.7 (48)	84	50/50
18	19.5 (44)	50/50	18.8 (41)	96	50/50	19.8 (44)	102	50/50	16.3 (47)	84	50/50
20	19.6 (46)	50/50	18.7 (40)	95	50/50	19.3 (44)	98	50/50	16.8 (47)	86	50/50
22	18.2 (46)	50/50	19.5 (45)	107	50/50	18.2 (45)	100	50/50	16.5 (48)	91	50/50
24	18.5 (45)	50/50	19.0 (41)	103	50/50	19.5 (42)	105	50/50	17.3 (47)	94	50/50
26	18.1 (48)	50/50	20.0 (46)	110	50/50	19.4 (45)	107	50/50	17.8 (48)	98	50/50
28	17.7 (49)	50/50	18.1 (46)	102	50/50	18.1 (45)	102	50/50	16.7 (48)	94	50/50
30	16.5 (46)	50/50	18.7 (43)	113	50/50	17.5 (46)	106	50/50	15.9 (46)	96	50/50
32	15.7 (46)	50/50	17.9 (46)	114	50/50	19.3 (45)	123	50/50	17.7 (49)	113	50/50
34	14.8 (50)	50/50	15.9 (49)	107	50/50	16.0 (49)	108	50/50	14.7 (50)	99	50/50
36	16.7 (49)	50/50	19.9 (48)	119	50/50	18.1 (45)	108	50/50	16.8 (47)	101	49/50
38	15.6 (47)	50/50	17.7 (47)	113	50/50	18.4 (49)	118	50/50	16.4 (47)	105	49/50
40	16.3 (47)	50/50	18.0 (48)	110	50/50	17.6 (46)	108	50/50	16.4 (46)	101	49/50
42	17.3 (50)	50/50	18.9 (50)	109	50/50	17.7 (47)	102	50/50	16.9 (47)	98	49/50
44	16.7 (48)	50/50	17.9 (47)	107	50/50	17.3 (44)	104	50/50	18.3 (49)	110	49/50
46	16.0 (48)	50/50	17.4 (46)	109	49/50	17.8 (47)	111	50/50	18.1 (48)	113	49/50
48	16.7 (48)	50/50	18.0 (46)	108	49/50	18.6 (48)	111	50/50	17.9 (48)	107	49/50
50	17.4 (49)	50/50	19.1 (48)	110	49/50	19.0 (47)	109	50/50	18.4 (48)	106	49/50
52	17.5 (50)	50/50	19.3 (49)	110	49/50	18.3 (50)	105	50/50	19.0 (49)	109	49/50
54	16.2 (49)	50/50	17.9 (48)	110	49/50	16.8 (46)	104	50/50	18.3 (46)	113	49/50
56	15.6 (48)	50/50	17.7 (46)	113	49/50	17.9 (46)	115	50/50	18.9 (48)	121	49/50
58	16.5 (49)	50/50	18.9 (46)	115	49/50	18.7 (50)	113	50/50	18.0 (47)	109	49/50
60	15.7 (48)	50/50	17.6 (47)	112	49/50	18.5 (50)	118	50/50	18.7 (48)	119	49/50
62	16.5 (49)	50/50	18.6 (49)	113	49/50	17.4 (50)	105	50/50	18.0 (47)	109	48/50
64	16.1 (49)	50/50	18.2 (49)	113	49/50	17.2 (50)	107	50/50	17.8 (45)	111	47/50
66	16.0 (49)	50/50	18.3 (49)	114	49/50	16.8 (50)	105	50/50	18.8 (46)	118	47/50
68	14.9 (49)	50/50	16.8 (48)	113	49/50	16.3 (50)	109	50/50	17.5 (43)	117	46/50
70	15.7 (49)	50/50	16.3 (49)	104	49/50	16.4 (50)	104	50/50	17.9 (43)	114	44/50
72	15.3 (48)	50/50	16.9 (47)	110	48/50	17.0 (50)	111	50/50	18.5 (42)	121	44/50
74	15.9 (50)	50/50	17.8 (48)	112	48/50	17.2 (50)	108	50/50	18.2 (43)	114	43/50
76	15.8 (48)	50/50	17.5 (48)	111	48/50	17.7 (50)	112	50/50	17.9 (38)	113	38/50
78	16.9 (49)	50/50	18.0 (47)	107	47/50	18.7 (50)	111	50/50	18.9 (35)	112	36/50
80	15.5 (49)	50/50	17.9 (47)	115	47/50	17.6 (49)	114	49/50	19.0 (33)	123	32/50
82	17.1 (48)	50/50	19.4 (47)	113	47/50	19.2 (48)	112	48/50	19.9 (29)	116	31/50
84	16.5 (48)	50/50	19.1 (46)	116	46/50	17.9 (48)	108	48/50	20.9 (30)	127	31/50
86	17.5 (48)	50/50	19.6 (46)	112	46/50	18.9 (47)	108	47/50	19.8 (27)	113	28/50
88	17.1 (48)	50/50	19.4 (46)	113	46/50	18.8 (46)	110	46/50	19.9 (26)	116	26/50
90	16.9 (49)	50/50	18.6 (46)	110	46/50	18.2 (46)	108	45/50	19.7 (26)	117	26/50
92	17.7 (49)	49/50	19.8 (44)	112	45/50	19.8 (45)	112	43/50	20.9 (25)	118	26/50
94	17.9 (49)	49/50	18.4 (45)	103	44/50	19.0 (43)	106	43/50	20.5 (24)	115	24/50
96	18.9 (47)	48/50	20.8 (42)	110	41/50	20.2 (41)	107	41/50	22.4 (23)	119	23/50
98	19.0 (46)	47/50	20.0 (41)	105	41/50	20.2 (41)	106	41/50	21.7 (23)	114	23/50
100	19.5 (47)	47/50	21.1 (38)	108	40/50	20.9 (40)	107	40/50	21.0 (20)	108	20/50
102	20.5 (45)	47/50	23.0 (38)	112	39/50	22.4 (35)	109	35/50	19.1 (14)	93	16/50
104	20.5 (47)	47/50	22.9 (39)	112	39/50	21.6 (35)	105	35/50	21.6 (14)	105	14/50

< >:No.of effective animals,( ):No.of measured animals Av.WC.: g

TABLE 8 FOOD COSUMPTION IN MALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Suruiv. <50>	7500 ppm Av.FC.	7500 ppm % of cont. <50>	7500 ppm No.of Suruiv.	15000 ppm Av.FC.	15000 ppm % of cont. <50>	15000 ppm No.of Suruiv.	30000 ppm Av.FC.	30000 ppm % of cont. <50>	30000 ppm No.of Suruiv.
1	15.8 (50)	50/50	15.7 (50)	99	50/50	15.4 (50)	97	50/50	14.5 (50)	92	50/50
2	16.3 (50)	50/50	16.2 (50)	99	50/50	16.0 (50)	98	50/50	15.2 (50)	93	50/50
3	16.0 (50)	50/50	15.9 (50)	99	50/50	16.0 (50)	100	50/50	15.1 (50)	94	50/50
4	16.3 (50)	50/50	16.1 (50)	99	50/50	16.3 (50)	100	50/50	15.4 (50)	94	50/50
5	16.4 (50)	50/50	16.0 (50)	98	50/50	16.1 (50)	98	50/50	15.2 (50)	93	50/50
6	15.8 (50)	50/50	15.6 (50)	99	50/50	15.9 (50)	101	50/50	14.4 (50)	91	50/50
7	16.4 (50)	50/50	16.2 (50)	99	50/50	16.5 (50)	101	50/50	14.9 (50)	91	50/50
8	16.4 (50)	50/50	16.3 (50)	99	50/50	16.2 (49)	99	50/50	15.1 (50)	92	50/50
9	16.2 (50)	50/50	16.5 (50)	102	50/50	16.6 (50)	102	50/50	15.2 (50)	94	50/50
10	16.1 (50)	50/50	16.2 (50)	101	50/50	16.5 (50)	102	50/50	15.1 (50)	94	50/50
11	16.5 (50)	50/50	16.7 (50)	101	50/50	16.8 (50)	102	50/50	15.5 (50)	94	50/50
12	16.1 (50)	50/50	16.4 (50)	102	50/50	16.5 (50)	102	50/50	15.3 (50)	95	50/50
13	16.6 (50)	50/50	16.5 (50)	99	50/50	16.7 (50)	101	50/50	15.4 (50)	93	50/50
14	16.5 (50)	50/50	16.3 (50)	99	50/50	16.7 (50)	101	50/50	15.6 (50)	95	50/50
18	15.8 (50)	50/50	16.0 (50)	101	50/50	16.1 (50)	102	50/50	15.4 (50)	97	50/50
22	16.1 (50)	50/50	16.3 (50)	101	50/50	16.0 (49)	99	50/50	15.7 (50)	98	50/50
26	16.2 (50)	50/50	16.5 (50)	102	50/50	16.4 (49)	101	50/50	16.2 (50)	100	50/50
30	16.6 (50)	50/50	17.0 (50)	102	50/50	17.1 (50)	103	50/50	16.3 (50)	98	50/50
34	16.1 (50)	50/50	16.4 (50)	102	50/50	16.7 (50)	104	50/50	15.8 (50)	98	50/50
38	16.1 (50)	50/50	16.5 (50)	102	50/50	16.3 (49)	101	50/50	16.0 (50)	99	50/50
42	16.8 (50)	50/50	17.1 (50)	102	50/50	17.3 (50)	103	50/50	16.4 (50)	98	50/50
46	16.9 (50)	50/50	17.1 (50)	101	50/50	17.1 (50)	101	50/50	16.2 (50)	96	50/50
50	17.0 (50)	50/50	17.1 (50)	101	50/50	17.2 (50)	101	50/50	16.3 (50)	96	50/50
54	17.4 (50)	50/50	17.7 (50)	102	50/50	18.0 (48)	103	50/50	17.1 (50)	98	50/50
58	17.5 (50)	50/50	17.3 (50)	99	50/50	17.4 (49)	99	49/50	17.3 (50)	99	50/50
62	18.0 (50)	50/50	17.7 (50)	98	49/50	18.0 (48)	100	48/50	16.9 (50)	94	50/50
66	17.7 (50)	50/50	18.1 (49)	102	49/50	17.8 (48)	101	47/50	16.7 (50)	94	50/50
70	17.5 (48)	48/50	17.2 (49)	98	49/50	16.7 (47)	95	47/50	16.3 (50)	93	50/50
74	17.6 (48)	48/50	17.5 (49)	99	49/50	17.3 (47)	98	47/50	16.6 (50)	94	50/50
78	17.6 (48)	48/50	17.5 (48)	99	47/50	17.4 (46)	99	46/50	16.4 (50)	93	50/50
82	17.5 (48)	48/50	17.2 (46)	98	46/50	16.7 (46)	95	46/50	16.3 (48)	93	48/50
86	17.3 (46)	46/50	16.9 (46)	98	46/50	16.9 (45)	98	45/50	16.1 (46)	93	46/50
90	17.2 (45)	45/50	17.1 (46)	99	46/50	16.3 (45)	95	45/50	15.9 (46)	92	46/50
94	16.6 (44)	44/50	16.9 (46)	102	46/50	16.1 (42)	97	42/50	15.2 (44)	92	43/50
98	16.9 (41)	41/50	16.4 (43)	97	42/50	16.0 (40)	95	40/50	14.0 (39)	83	37/50
102	16.9 (39)	39/50	16.2 (38)	96	40/50	15.9 (35)	94	35/50	14.6 (30)	86	30/50
104	17.2 (38)	38/50	16.7 (39)	97	39/50	15.7 (35)	91	34/50	13.9 (30)	81	30/50

< >:No.of effective animals,( ):No.of measured animals Av.FC.: g

TABLE 9 FOOD COSUMPTION IN FEMALE RAT (TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Survіv. <50>	7500 ppm Av.FC.	7500 ppm % of cont. <50>	7500 ppm No.of Survіv.	15000 ppm Av.FC.	15000 ppm % of cont. <50>	15000 ppm No.of Survіv.	30000 ppm Av.FC.	30000 ppm % of cont. <50>	30000 ppm No.of Survіv.
1	11.8 (50)	50/50	11.6 (50)	98	50/50	11.9 (50)	101	50/50	11.5 (50)	97	50/50
2	11.2 (50)	50/50	11.2 (50)	100	50/50	11.8 (50)	105	50/50	11.4 (50)	102	50/50
3	11.4 (50)	50/50	11.2 (50)	98	50/50	11.5 (50)	101	50/50	11.2 (50)	98	50/50
4	11.4 (50)	50/50	11.2 (50)	98	50/50	11.8 (50)	104	50/50	11.3 (50)	99	50/50
5	11.4 (50)	50/50	11.2 (50)	98	50/50	11.5 (50)	101	50/50	11.2 (50)	98	50/50
6	10.5 (50)	50/50	10.3 (50)	98	50/50	11.3 (50)	108	50/50	10.5 (50)	100	50/50
7	10.8 (50)	50/50	10.3 (50)	95	50/50	10.9 (50)	101	50/50	10.6 (50)	98	50/50
8	10.4 (50)	50/50	10.1 (50)	97	50/50	10.7 (50)	103	50/50	10.2 (50)	98	50/50
9	10.8 (50)	50/50	10.4 (50)	96	50/50	10.9 (50)	101	50/50	10.6 (50)	98	50/50
10	10.6 (50)	50/50	10.2 (50)	96	50/50	10.6 (50)	100	50/50	10.0 (50)	94	50/50
11	10.7 (50)	50/50	10.1 (50)	94	50/50	10.6 (50)	99	50/50	10.0 (50)	93	50/50
12	10.3 (50)	50/50	10.0 (50)	97	50/50	10.2 (50)	99	50/50	9.7 (50)	94	50/50
13	10.3 (50)	50/50	9.8 (50)	95	50/50	10.0 (50)	97	50/50	9.8 (50)	95	50/50
14	10.7 (50)	50/50	10.4 (50)	97	50/50	10.4 (50)	97	50/50	10.2 (50)	95	50/50
18	11.2 (50)	50/50	10.7 (50)	96	50/50	10.8 (50)	96	50/50	10.3 (50)	92	50/50
22	11.2 (50)	50/50	10.7 (50)	96	50/50	10.9 (50)	97	50/50	10.5 (50)	94	50/50
26	11.3 (50)	50/50	11.1 (50)	98	50/50	11.3 (50)	100	50/50	11.0 (50)	97	50/50
30	11.1 (50)	50/50	10.9 (50)	98	50/50	11.0 (50)	99	50/50	10.7 (50)	96	50/50
34	10.7 (50)	50/50	10.6 (50)	99	50/50	10.8 (50)	101	50/50	10.5 (50)	98	50/50
38	11.2 (50)	50/50	10.7 (50)	96	50/50	10.8 (50)	96	50/50	10.7 (49)	96	49/50
42	11.5 (50)	50/50	10.8 (50)	94	50/50	11.0 (50)	96	50/50	11.1 (49)	97	49/50
46	11.3 (50)	50/50	11.3 (49)	100	49/50	11.3 (50)	100	50/50	11.2 (49)	99	49/50
50	11.8 (50)	50/50	11.7 (49)	99	49/50	11.3 (50)	96	50/50	11.4 (49)	97	49/50
54	12.1 (50)	50/50	11.8 (49)	98	49/50	11.8 (50)	98	50/50	11.9 (49)	98	49/50
58	12.5 (50)	50/50	12.2 (49)	98	49/50	12.1 (50)	97	50/50	11.5 (49)	92	49/50
62	12.7 (50)	50/50	12.3 (49)	97	49/50	12.0 (50)	94	50/50	11.7 (48)	92	48/50
66	12.1 (50)	50/50	12.2 (49)	101	49/50	11.8 (50)	98	50/50	11.6 (47)	96	47/50
70	12.2 (50)	50/50	11.9 (49)	98	49/50	11.9 (50)	98	50/50	11.8 (45)	97	44/50
74	12.6 (50)	50/50	12.6 (48)	100	48/50	12.2 (50)	97	50/50	12.0 (44)	95	43/50
78	12.8 (50)	50/50	12.4 (47)	97	47/50	12.4 (50)	97	50/50	12.0 (36)	94	36/50
82	13.1 (50)	50/50	12.9 (47)	98	47/50	12.6 (48)	96	48/50	12.8 (31)	98	31/50
86	13.0 (50)	50/50	12.6 (46)	97	46/50	12.3 (47)	95	47/50	11.7 (29)	90	28/50
90	12.6 (50)	50/50	12.3 (46)	98	46/50	12.5 (45)	99	45/50	12.2 (26)	97	26/50
94	12.9 (49)	49/50	12.1 (45)	94	44/50	12.6 (43)	98	43/50	12.7 (24)	98	24/50
98	13.0 (47)	47/50	12.3 (41)	95	41/50	12.3 (41)	95	41/50	11.9 (23)	92	23/50
102	13.1 (47)	47/50	12.9 (39)	98	39/50	13.0 (35)	99	35/50	11.2 (16)	85	16/50
104	13.4 (46)	47/50	12.8 (39)	96	39/50	12.3 (35)	92	35/50	11.7 (14)	87	14/50

< >:No.of effective animals,( ):No.of measured animals Av.FC.: g

TABLE 10 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN MALE RAT

Group Name	Control	7500ppm	15000ppm	30000ppm
SITE : skin/appendage				
TUMOR : sebaceous adenoma[f]				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	8.82
Terminal rates(c)	0/38(0.0)	0/39(0.0)	0/34(0.0)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0025**?			
Combined analysis (d)	P=------			
Cochran-Amitage test(e)	P=0.0079**?			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.1325
SITE : thyroid				
TUMOR : C-cell adenoma[g]				
Tumor rate				
Overall rates(a)	12/50(24.0)	5/50(10.0)	5/50(10.0)	4/50(8.0)
Adjusted rates(b)	29.27	12.82	14.71	11.76
Terminal rates(c)	11/38(28.9)	5/39(12.8)	5/34(14.7)	3/30(10.0)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.9671			
Combined analysis (d)	P=------			
Cochran-Amitage test(e)	P=0.0393*			
Fisher Exact test(e)		P=0.0942	P=0.0942	P=0.0539
SITE : mammary gland				
TUMOR : adenoma[h], fibroadenoma[i]				
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	0/50(0.0)	0/50(0.0)
Adjusted rates(b)	7.89	2.44	0.0	0.0
Terminal rates(c)	3/38(7.9)	0/39(0.0)	0/34(0.0)	0/30(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.9858			
Combined analysis (d)	P=------			
Cochran-Amitage test(e)	P=0.0405*			
Fisher Exact test(e)		P=0.3235	P=0.1325	P=0.1325

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimate tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneth the control incidence are the P-values associated with the trend test.
Standard method :Death analysis
Prevalence method :Incidental tumor test
Combined analysis :Death analysis + Incidental tumor test
(e):The Cochran-Amitage and Fisher exact test compare directly the overall incidence rates.
(f):Historical incidence for 2-year studies: 2/850(0.2%); range 0% to 4%
(g):Historical incidence for 2-year studies: 105/850(12.4%); range 4% to 26%
(h):Historical incidence for 2-year studies: 8/850(0.9%); range 0% to 4%
(i):Historical incidence for 2-year studies: 16/850(1.9%); range 0% to 6%
?: The conditional probabilities of the largest and smallest possible out comes can not be estimated or this P-value is beyond the estimated P-value.
------:There is no data which should be statistical analysis.
Significant difference; *:P≦0.05 **:P≦0.01

TABLE 11 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN FEMALE RAT

Group Name	Control	7500ppm	15000ppm	30000ppm
SITE : spleen				
TUMOR : mononuclear cell leukemia[f]				
Tumor rate				
Overall rates(a)	1/50(2.0)	7/50(14.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	2.13	7.69	5.71	7.14
Terminal rates(c)	1/47(2.1)	3/39(7.7)	2/35(5.7)	1/14(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0417*			
Prevalence method(d)	P=0.2161			
Combined analysis (d)	P=0.0349*			
Cochran-Amitage test(e)	P=0.6177			
Fisher Exact test(e)		P=0.0430*	P=0.3235	P=0.1998
SITE : pituitary gland				
TUMOR : adenoma[g]				
Tumor rate				
Overall rates(a)	18/49(36.7)	14/50(28.0)	12/50(24.0)	6/50(12.0)
Adjusted rates(b)	35.42	25.64	25.71	21.43
Terminal rates(c)	16/46(34.8)	10/39(25.6)	9/35(25.7)	3/14(21.4)
Statistical analysis				
Peto test				
Standard method(d)	P=0.4673			
Prevalence method(d)	P=0.9411			
Combined analysis (d)	P=0.9192			
Cochran-Amitage test(e)	P=0.0041**			
Fisher Exact test(e)		P=0.3228	P=0.2121	P=0.0201*
SITE : pituitary gland				
TUMOR : adenoma[g], adenocarcinoma[h]				
Tumor rate				
Overall rates(a)	19/49(38.8)	14/50(28.0)	14/50(28.0)	7/50(14.0)
Adjusted rates(b)	37.50	25.64	28.57	21.43
Terminal rates(c)	17/46(37.0)	10/39(25.6)	10/35(28.6)	3/14(21.4)
Statistical analysis				
Peto test				
Standard method(d)	P=0.1912			
Prevalence method(d)	P=0.9439			
Combined analysis (d)	P=0.8365			
Cochran-Amitage test(e)	P=0.0070**			
Fisher Exact test(e)		P=0.2736	P=0.2736	P=0.0256*
SITE : uterus				
TUMOR : endometrial stromal polyp[i]				
Tumor rate				
Overall rates(a)	14/50(28.0)	5/50(10.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	28.00	12.82	13.04	29.41
Terminal rates(c)	13/47(27.7)	5/39(12.8)	3/35(8.6)	4/14(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0621			
Prevalence method(d)	P=0.6556			
Combined analysis (d)	P=0.4651			
Cochran-Amitage test(e)	P=0.1662			
Fisher Exact test(e)		P=0.0481*	P=0.1246	P=0.1246

TABLE 11 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN FEMALE RAT (Continued)

Group Name	Control	7500ppm	15000ppm	30000ppm
SITE : uterus				
TUMOR : endometrial stromal polyp(i), endometrial stromal sarcoma(j)				
Tumor rate				
Overall rates(a)	14/50(28.0)	5/50(10.0)	9/50(18.0)	8/50(16.0)
Adjusted rates(b)	28.00	12.82	13.33	29.41
Terminal rates(c)	13/47(27.7)	5/39(12.8)	3/35(8.6)	4/14(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0146*			
Prevalence method(d)	P=0.6429			
Combined analysis (d)	P=0.2632			
Cochran-Amitage test(e)	P=0.3195			
Fisher Exact test(e)		P=0.0481*	P=0.2397	P=0.1781

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimate tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneth the control incidence are the P-values associated with the trend test.
Standard method :Death analysis
Prevalence method :Incidental tumor test
Combined analysis :Death analysis + Incidental tumor test
(e):The Cochran-Amitage and Fisher exact test compare directly the overall incidence rates.
(f):Historical incidence for 2-year studies: 125/849(14.7%); range 8% to 26%
(g):Historical incidence for 2-year studies: 360/849(42.4%); range 16% to 70%
(h):Historical incidence for 2-year studies: 19/849(2.2%); range 0% to 14%
(i):Historical incidence for 2-year studies: 127/849(15.0%); range 2% to 28%
(j):Historical incidence for 2-year studies:4/849(0.5%); range 0% to 2%
?: The conditional probabilities of the largest and smallest possible out comes can not be estimated or this P-value is beyond the estimated P-value.
------:There is no data which should be statistical analysis.

TABLE 12 NUMBER OF RATS WITH MINERALIZATION OF HEART

Group name		Control	7500ppm	15000ppm	30000ppm
Male					
Dead and moribund animals		<12>	<11>	<16>	<20>
		2	0	1	11
	+	(1)		(1)	(3)
	2+	(1)			(6)
	3+				(2)
Sacrificed animals		<38>	<39>	<34>	<30>
		0	0	0	2
	+				(2)
	2+				
	3+				
All animals		<50>	<50>	<50>	<50>*
		2	0	1	13
	+	(1)		(1)	(5)
	2+	(1)			(6)
	3+				(2)
Female					
Dead and moribund animals		<3>	<11>	<15>	<36>
		1	0	2	18
	+	(1)			(2)
	2+				(12)
	3+			(2)	(4)
Sacrificed animals		<47>	<39>	<35>	<14>
		0	0	1	0
	+				
	2+				
	3+			(1)	
All animals		<50>	<50>	<50>	<50>**
		1	0	3	18
	+	(1)			(2)
	2+				(12)
	3+			(3)	(4)

Grade +:Slight 2+:Moderate 3+:Marked
<a> a:Number of animals examined at the site
b b:Number of animals with lesion
(c) c:Number of animals with lesion in each grade
Significant difference *:P≦0.05 **:P≦0.01 Test of Chi square

TABLE 13 NUMBER OF RATS WITH MINERALIZATION OF KIDNEY (CORTEX)

Group name		Control	7500ppm	15000ppm	30000ppm
Male					
Dead and moribund animals		<12>	<11>	<16>	<20>
		2	0	2	11
	+	(1)		(2)	(8)
	2+	(1)			(3)
Sacrificed animals		<38>	<39>	<34>	<30>
		0	0	0	2
	+				(2)
	2+				
All animals		<50>	<50>	<50>	<50>**
		2	0	2	13
	+	(1)		(2)	(10)
	2+	(1)			(3)
Female					
Dead and moribund animals		<3>	<11>	<15>	<36>
		1	1	1	26
	+	(1)	(1)		(10)
	2+				(9)
	3+			(1)	(6)
	4+				(1)
Sacrificed animals		<47>	<39>	<35>	<14>
		0	0	1	0
	+				
	2+			(1)	
	3+				
	4+				
All animals		<50>	<50>	<50>	<50>**
		1	1	2	26
	+	(1)	(1)		(10)
	2+			(1)	(9)
	3+			(1)	(6)
	4+				(1)

Grade +:Slight 2+:Moderate 3+:Marked 4+:Severe
<a> a:Number of animals examined at the site
b b:Number of animals with lesion
(c) c:Number of animals with lesion in each grade
Significant difference *:P≦0.05 **:P≦0.01 Test of Chi square

TABLE 14 CAUSE OF DEATH IN RATS

Group	Male				Female			
	Control	7500ppm	15000ppm	30000ppm	Control	7500ppm	15000ppm	30000ppm
Number of dead or moribund animals	12	11	16	20	3	11	15	36
No microscopical confirmation	3	2	1	0	0	0	0	3
Integmentary system lesion	0	0	0	0	0	0	0	1
Cardiovascular lesion	0	0	0	9	0	0	1	14
Renal lesion	0	0	0	0	0	0	0	8
CNS Disorders	0	0	1	0	0	0	0	0
Thrombosis	0	0	1	0	0	0	0	0
Ileus	0	0	0	0	0	0	1	0
Chronic nephropathy	1	0	1	0	1	0	1	1
Tumor death : leukemia	5	0	2	2	0	4	1	3
subcutis	1	3	0	1	0	0	0	1
oral cavity	0	0	0	0	1	0	0	0
tooth	0	0	0	0	0	1	0	0
large intestine	0	0	0	0	0	0	1	0
liver	0	0	1	0	0	0	1	0
pituitary	2	3	3	2	1	3	2	2
adrenal	0	0	1	1	0	0	0	0
uterus	–	–	–	–	0	0	4	2
mammary gland	0	0	0	0	0	1	1	0
preptual/clitoral gland	0	0	1	0	0	1	1	1
brain	0	1	2	1	0	1	0	0
Zymbal gland	0	0	0	1	0	0	1	0
bone	0	0	0	1	0	0	0	0
peritoneum	0	2	2	2	0	0	0	0

FIGURES

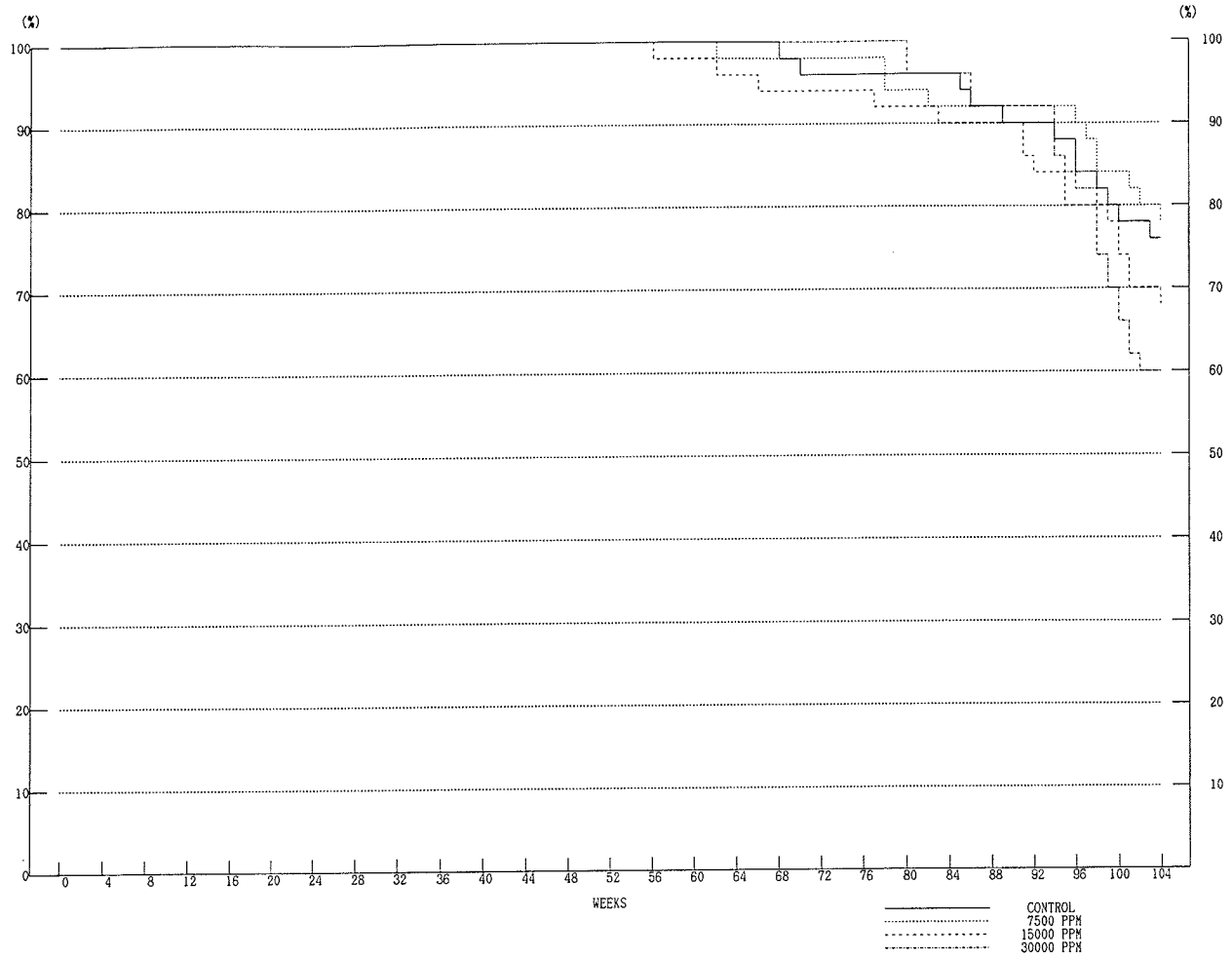

FIGURE 1 SURVIVAL ANIMAL RATE : RAT : MALE (TWO-YEAR STUDY)

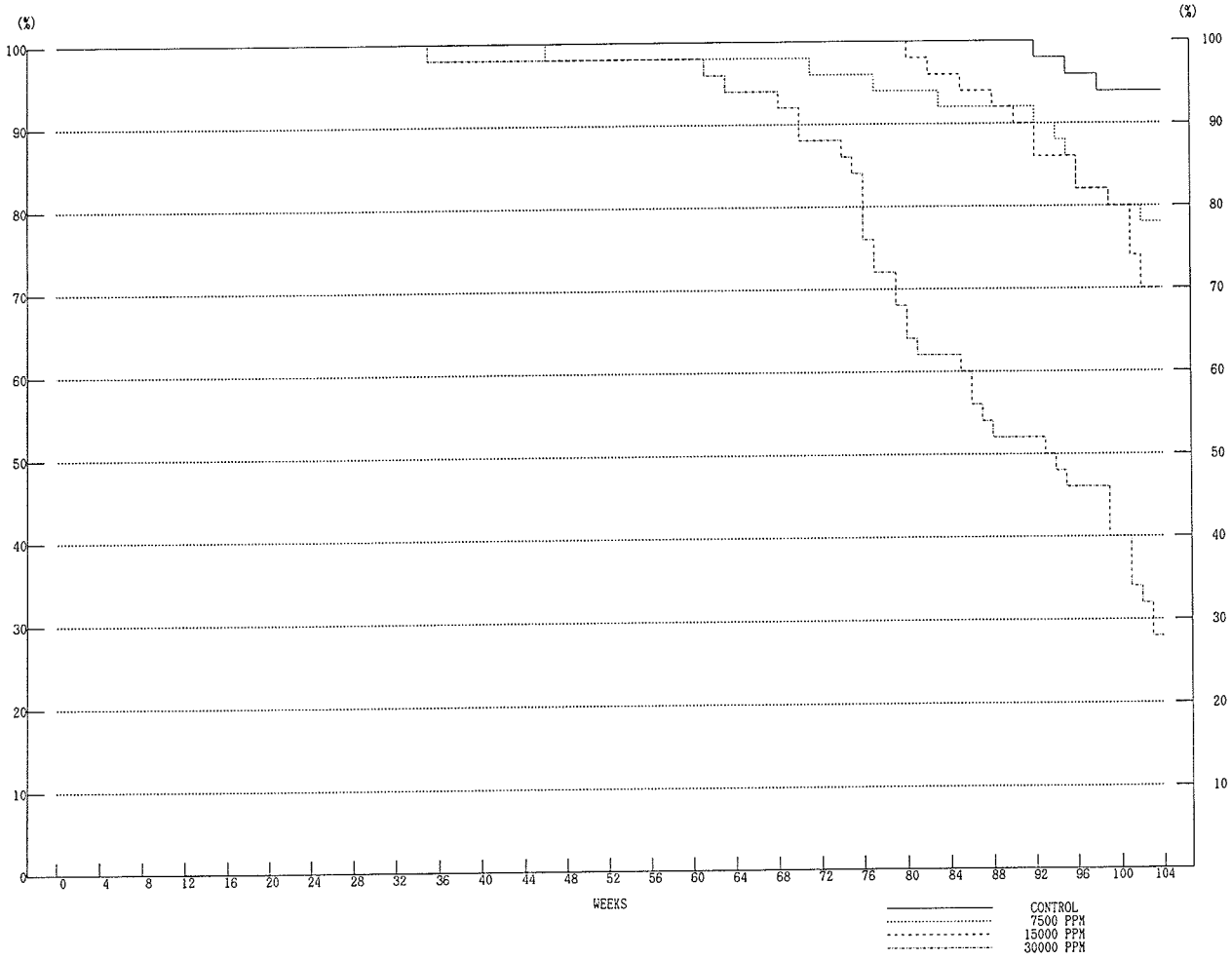

FIGURE 2 SURVIVAL ANIMAL RATE : RAT : FEMALE (TWO-YEAR STUDY)

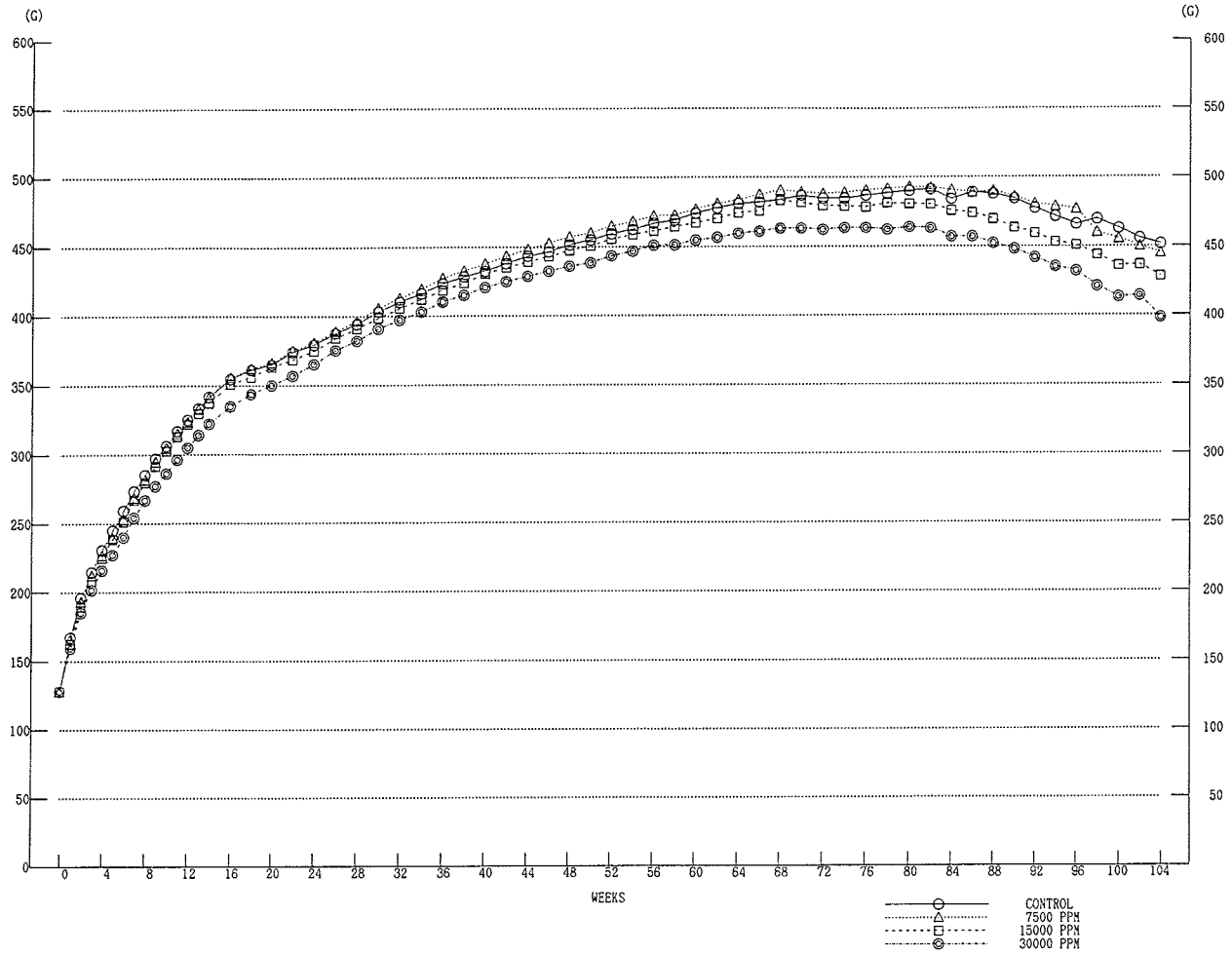

FIGURE 3 BODY WEIGHT CHANGES : RAT : MALE (TWO-YEAR STUDY)

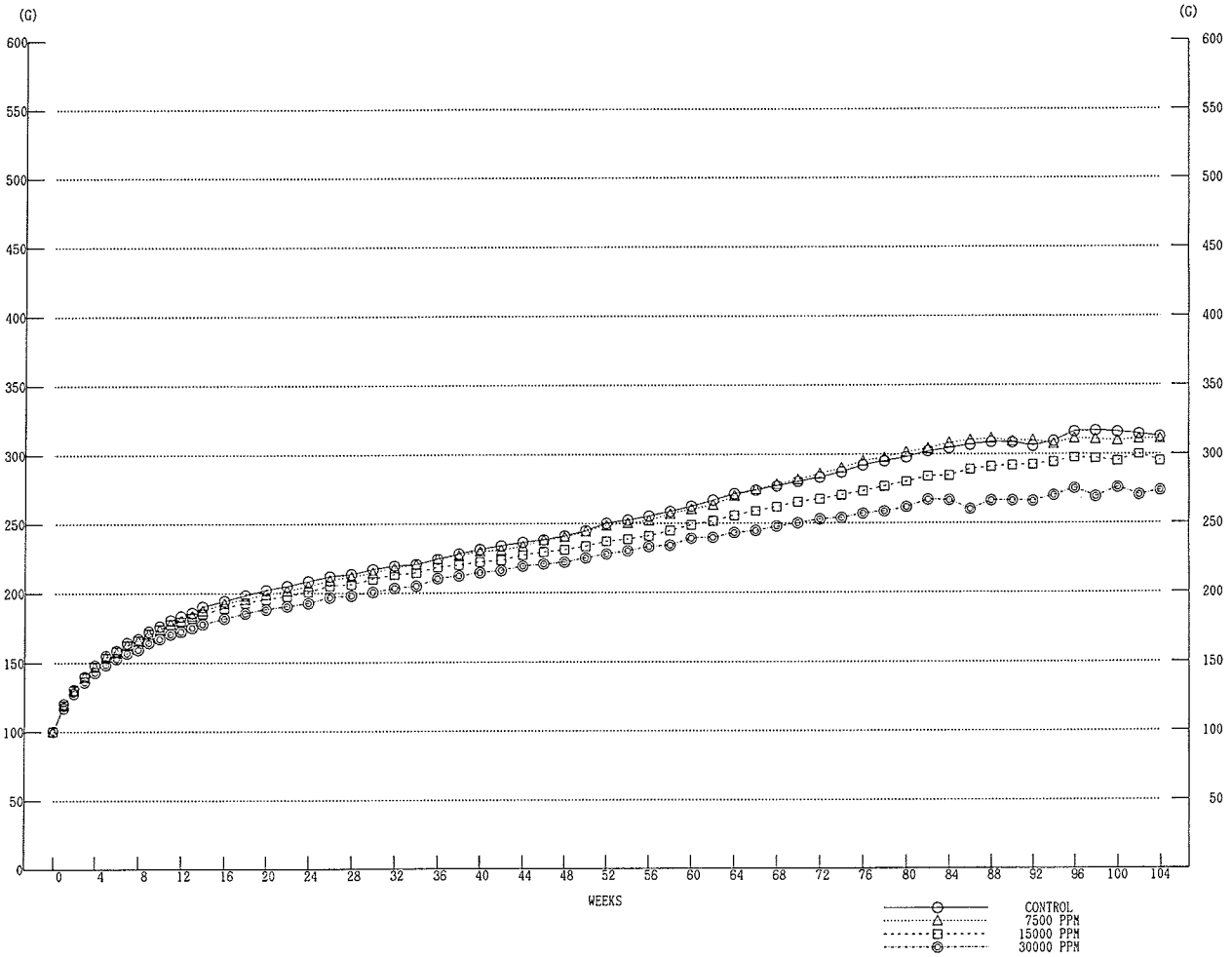

FIGURE 4 BODY WEIGHT CHANGES : RAT : FEMALE (TWO-YEAR STUDY)

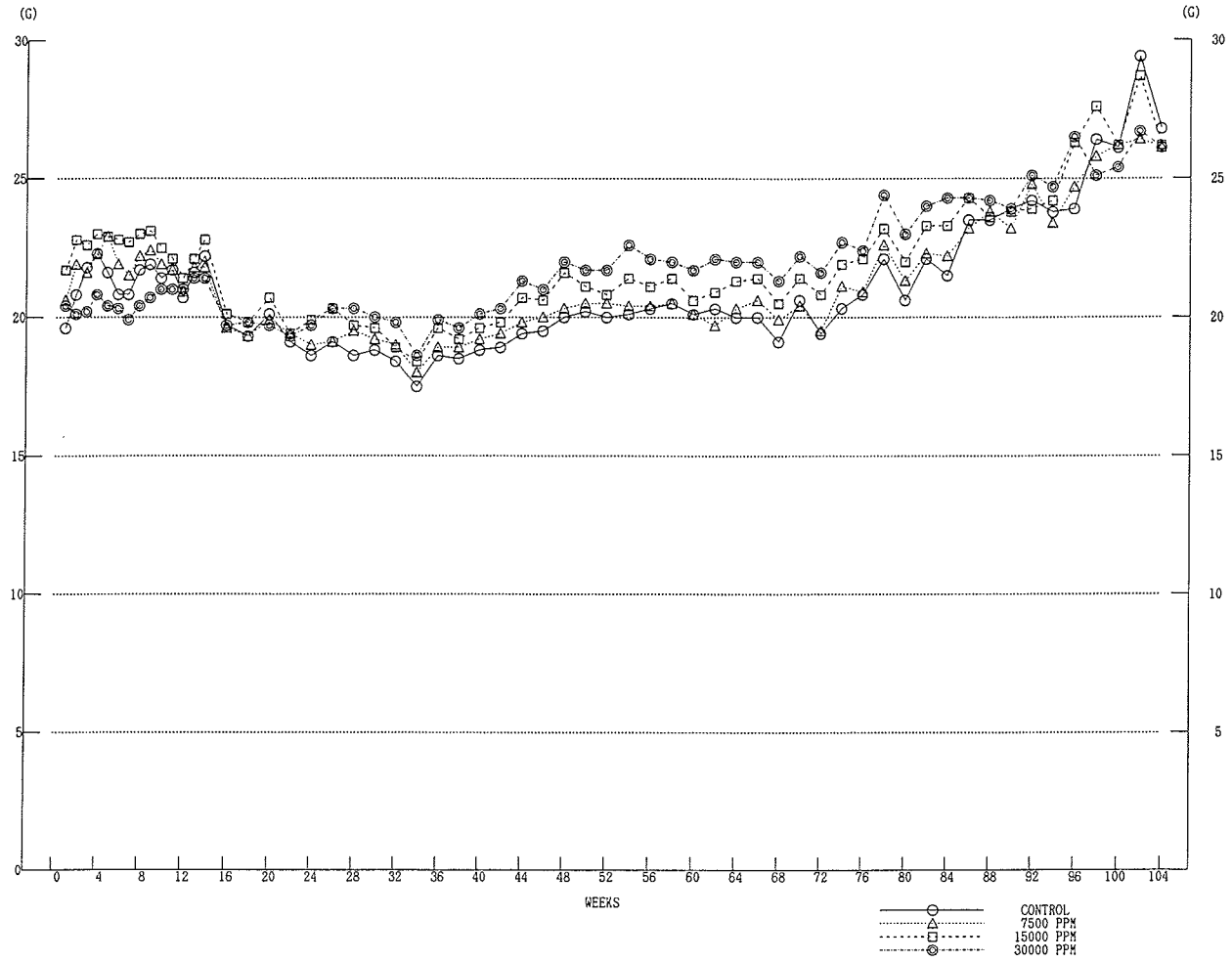

FIGURE 5 WATER CONSUMPTION : RAT : MALE (TWO-YEAR STUDY)

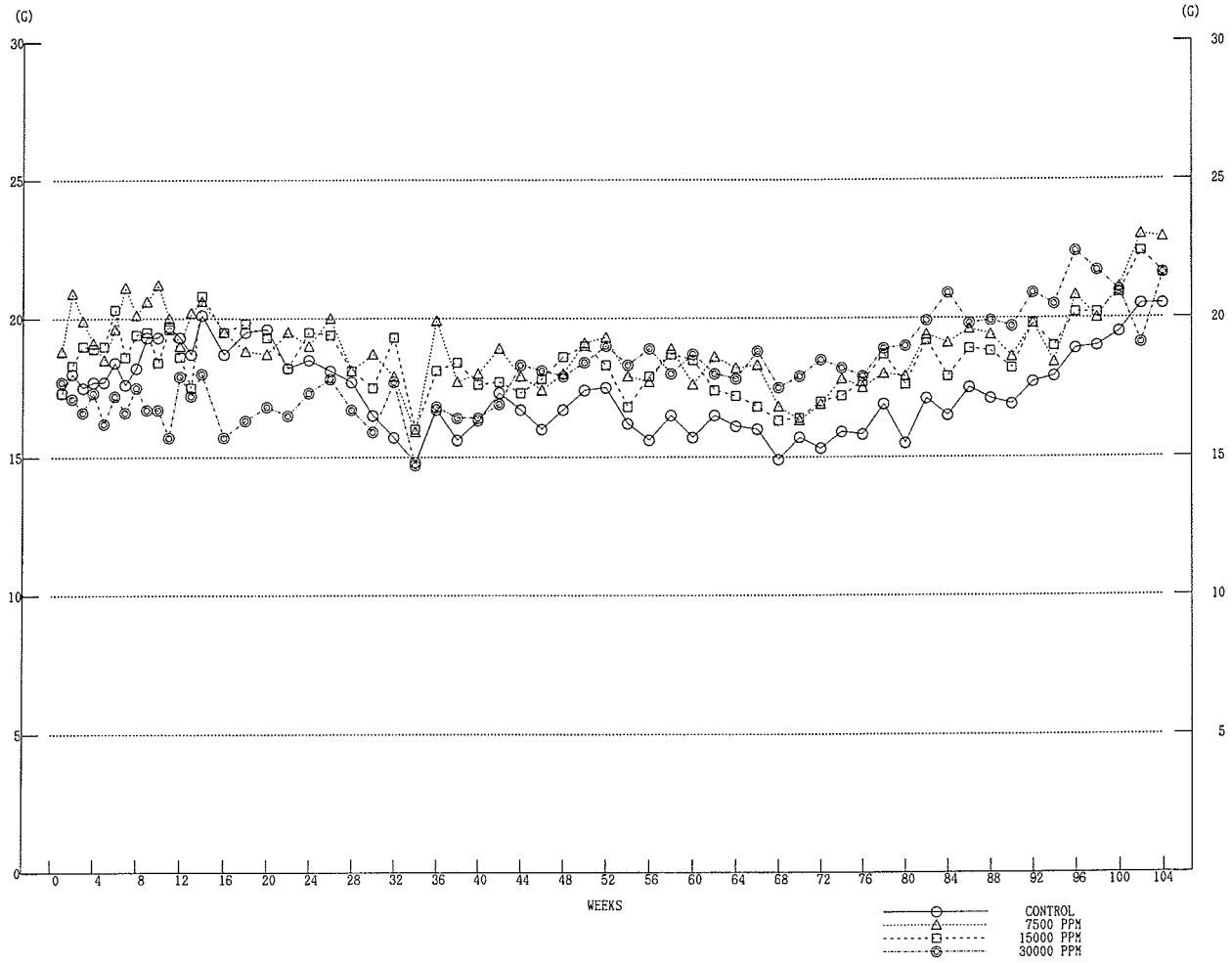

FIGURE 6 WATER CONSUMPTION : RAT FEMALE (TWO-YEAR STUDY)

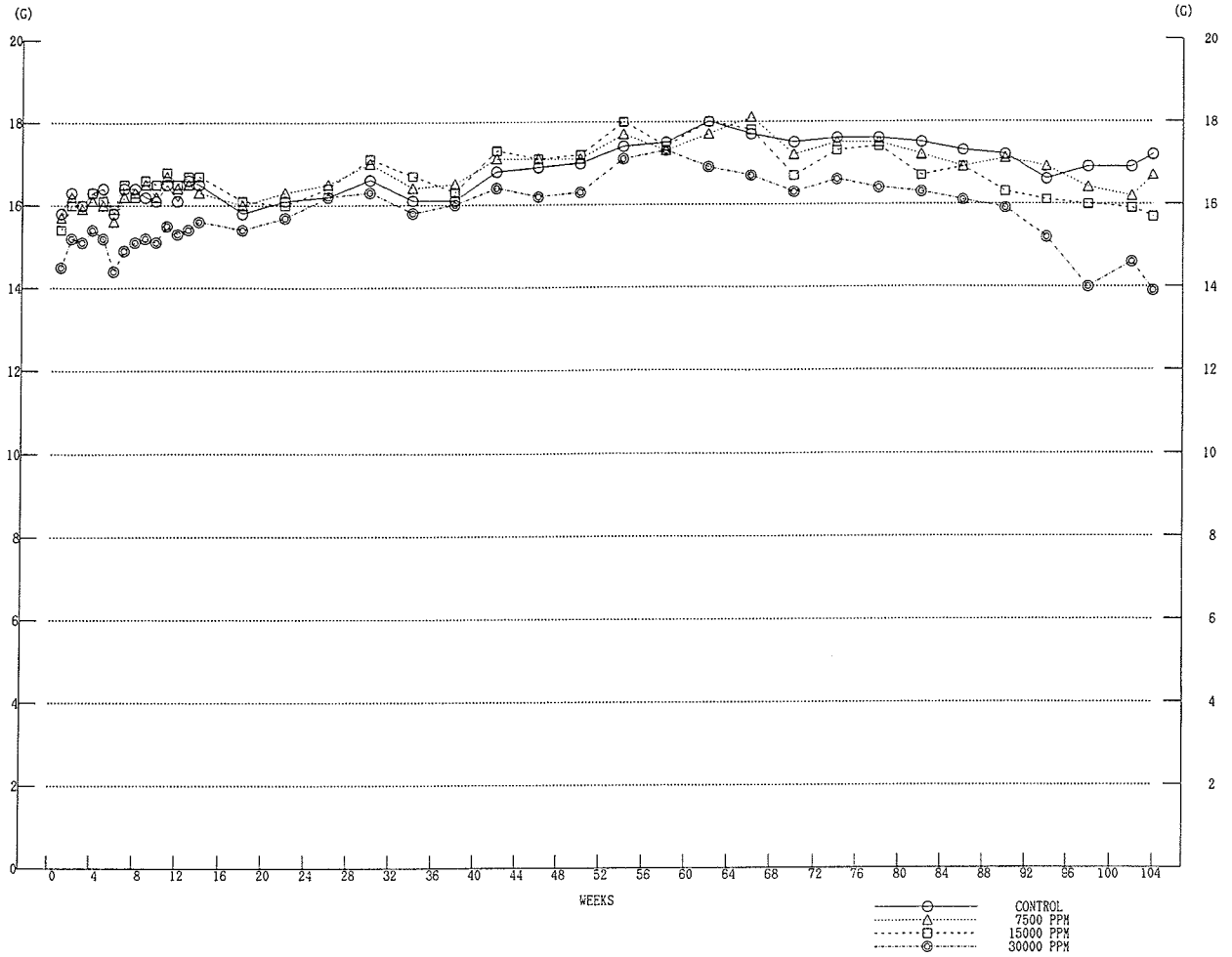

FIGURE 7 FOOD CONSUMPTION : RAT : MALE (TWO-YEAR STUDY)

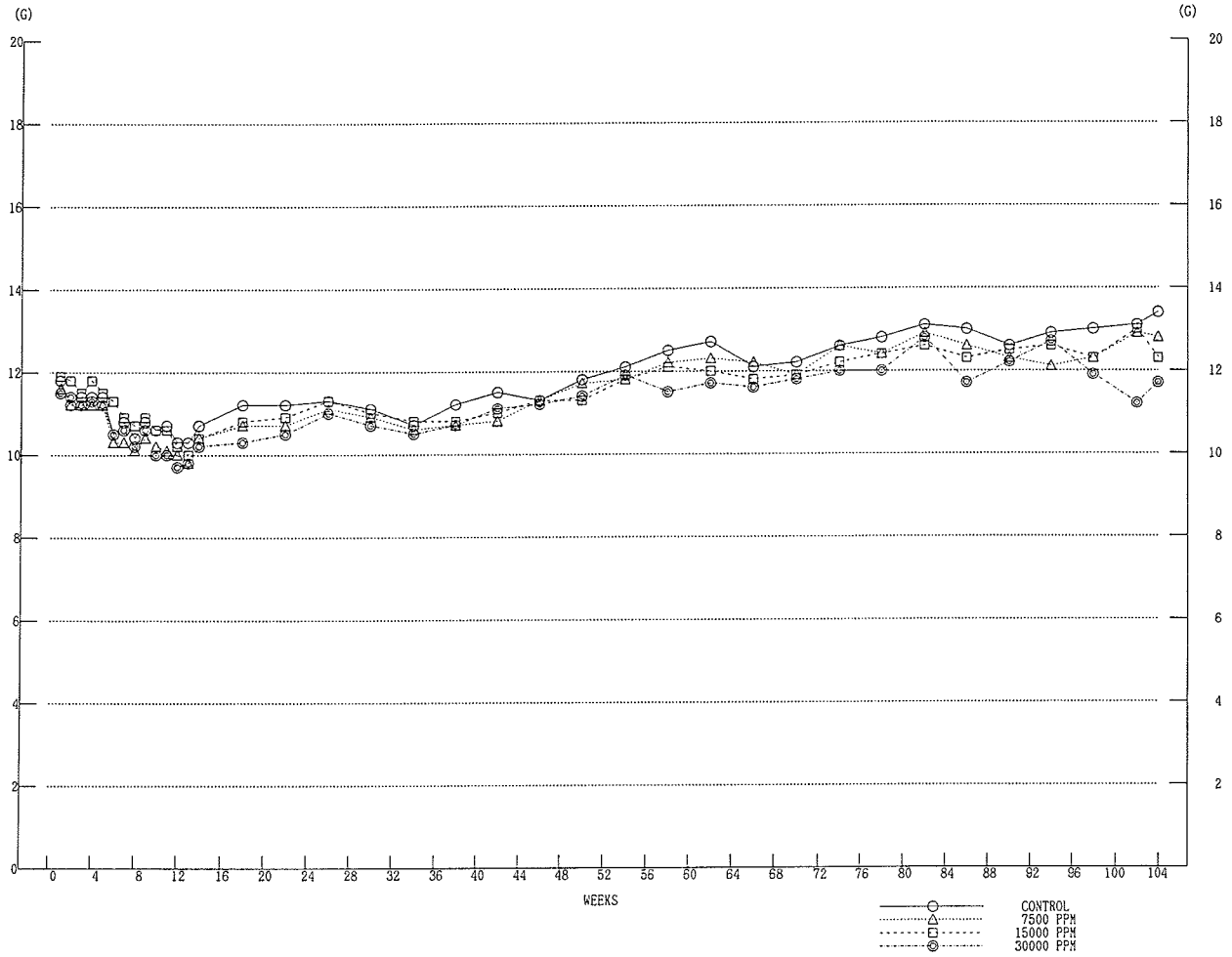

FIGURE 8 FOOD CONSUMPTION : RAT FEMALE (TWO-YEAR STUDY)

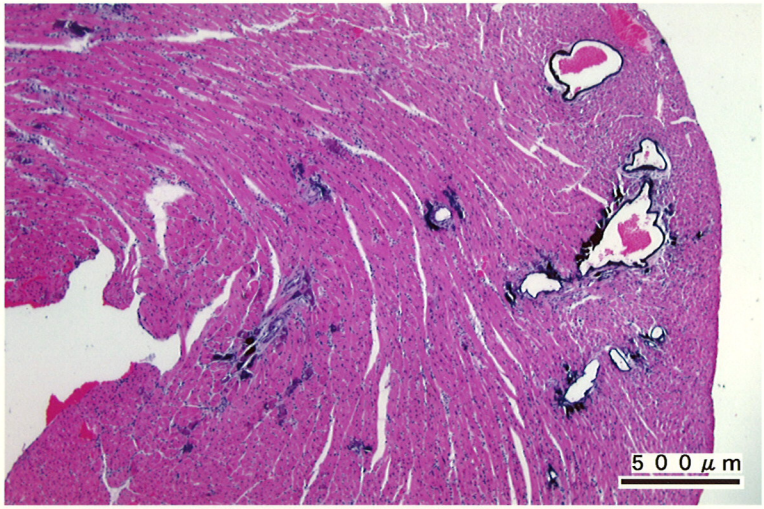

写真１　心臓、鉱質沈着
ラット、雌、30000ppm群、動物No.0224-2341
（H&E染色）

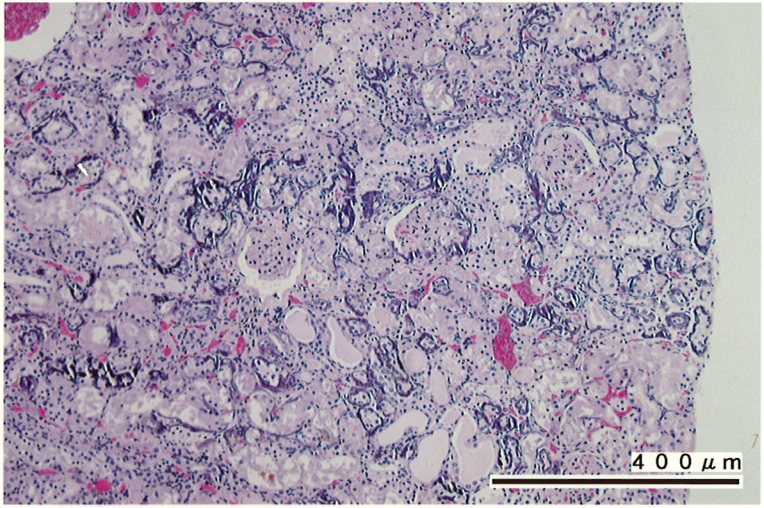

写真２　腎臓、皮質の鉱質沈着
ラット、雌、30000ppm群、動物No.0224-2310
（H&E染色）