Summary of Drinking Water Carcinogenicity Study of Urotropin in BDF1 Mice

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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 Crj:BDF1 mice urotropin in their drinking water for 2 years (104 weeks). Each group of test animals consisted of either 50 male or 50 female mice. The drinking water concentration of urotropin was 0, 10000, 20000 or 40000 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

There was no significant difference in survival rate between any urotropin-administered group of either sex and their respective controls. In the mammary gland, the combined incidence of adenomas and adenocarcinomas was statistically increased in females. In addition, several age-related non-neoplastic lesions were increased in the nasal cavity: duct ectasia of both males and females; respiratory metaplasia of the nasal gland in both males and females; respiratory metaplasia of the olfactory epithelium of males; and eosinophilic change in the olfactory epithelium of females.

Conclusions

In mice, there was some evidence of carcinogenic activity of urotropin in females based on a marginally increased incidence of adenomas and adenocarcinomas of the mammary gland. There was no evidence of carcinogenic activity of urotropin in males.

SELECTED TABLES

TABLE 15 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN MALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	10000 ppm Av.Wt.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.Wt.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.Wt.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
0	22.5 (50)	50/50	22.5 (50)	100	50/50	22.5 (50)	100	50/50	22.5 (50)	100	50/50
1	24.1 (50)	50/50	23.9 (50)	99	50/50	23.6 (50)	98	50/50	23.4 (50)	97	50/50
2	24.9 (50)	50/50	24.7 (50)	99	50/50	24.7 (50)	99	50/50	24.4 (50)	98	50/50
3	25.9 (50)	50/50	25.9 (50)	100	50/50	25.8 (50)	100	50/50	25.5 (50)	98	50/50
4	27.0 (50)	50/50	26.9 (50)	100	50/50	26.9 (50)	100	50/50	26.4 (50)	98	50/50
5	27.9 (50)	50/50	27.1 (50)	97	50/50	27.3 (50)	98	50/50	26.8 (50)	96	50/50
6	28.6 (50)	50/50	28.3 (50)	99	50/50	28.4 (50)	99	50/50	27.7 (50)	97	50/50
7	29.0 (50)	50/50	28.9 (50)	100	50/50	28.9 (50)	100	50/50	28.2 (50)	97	50/50
8	29.7 (50)	50/50	29.9 (50)	101	50/50	29.7 (50)	100	50/50	29.0 (50)	98	50/50
9	30.4 (50)	50/50	30.8 (50)	101	50/50	30.6 (50)	101	50/50	29.7 (50)	98	50/50
10	31.4 (50)	50/50	31.8 (50)	101	50/50	31.6 (50)	101	50/50	30.7 (50)	98	50/50
11	31.9 (50)	50/50	32.2 (50)	101	50/50	32.1 (50)	101	50/50	31.2 (50)	98	50/50
12	33.1 (50)	50/50	33.3 (50)	101	50/50	33.2 (50)	100	50/50	32.3 (50)	98	50/50
13	33.6 (50)	50/50	33.9 (50)	101	50/50	34.0 (50)	101	50/50	32.9 (50)	98	50/50
14	34.4 (50)	50/50	34.8 (50)	101	50/50	35.1 (50)	102	50/50	33.9 (50)	99	50/50
16	35.7 (50)	50/50	36.0 (50)	101	50/50	36.2 (50)	101	50/50	35.1 (50)	98	50/50
18	37.5 (50)	50/50	38.1 (50)	102	50/50	38.0 (50)	101	50/50	36.6 (50)	98	50/50
20	38.9 (50)	50/50	39.5 (50)	102	50/50	39.5 (50)	102	50/50	38.0 (50)	98	50/50
22	39.4 (50)	50/50	40.3 (50)	102	50/50	40.4 (50)	103	50/50	38.7 (50)	98	50/50
24	40.4 (50)	50/50	40.9 (50)	101	50/50	41.5 (50)	103	50/50	39.5 (50)	98	50/50
26	41.4 (50)	50/50	42.0 (50)	101	50/50	42.6 (50)	103	50/50	40.6 (50)	98	50/50
28	42.3 (50)	50/50	43.0 (50)	102	50/50	43.9 (50)	104	50/50	41.6 (50)	98	50/50
30	43.3 (50)	50/50	44.1 (50)	102	50/50	44.8 (50)	103	50/50	42.6 (50)	98	50/50
32	44.7 (50)	50/50	45.4 (50)	102	50/50	46.4 (50)	104	50/50	43.9 (50)	98	50/50
34	45.2 (50)	50/50	45.8 (50)	101	50/50	46.8 (50)	104	50/50	44.3 (50)	98	50/50
36	45.9 (50)	50/50	46.1 (50)	100	50/50	46.8 (50)	102	50/50	44.4 (50)	97	50/50
38	46.2 (50)	50/50	46.5 (50)	101	50/50	47.1 (50)	102	50/50	44.6 (50)	97	50/50
40	46.6 (50)	50/50	47.0 (50)	101	50/50	47.8 (50)	103	50/50	45.1 (50)	97	50/50
42	47.0 (50)	50/50	47.4 (50)	101	50/50	48.3 (50)	103	50/50	45.2 (50)	96	50/50
44	47.6 (50)	50/50	48.6 (50)	102	50/50	49.1 (50)	103	50/50	46.2 (50)	97	50/50
46	47.8 (50)	50/50	48.3 (50)	101	50/50	49.2 (50)	103	50/50	46.4 (50)	97	50/50
48	48.0 (50)	49/50	48.4 (50)	101	50/50	49.3 (50)	103	50/50	46.7 (50)	97	50/50
50	49.2 (49)	49/50	49.0 (50)	100	50/50	50.0 (50)	102	50/50	47.1 (50)	96	50/50
52	50.2 (49)	49/50	50.0 (50)	100	50/50	50.9 (50)	101	50/50	47.6 (50)	95	50/50
54	49.2 (49)	49/50	49.7 (50)	101	50/50	49.9 (50)	101	50/50	46.8 (49)	95	49/50
56	49.5 (49)	49/50	49.6 (50)	100	50/50	49.8 (50)	101	50/50	46.6 (49)	94	49/50
58	49.2 (49)	49/50	49.4 (50)	100	50/50	50.0 (50)	102	50/50	46.5 (48)	95	48/50
60	50.4 (49)	49/50	50.2 (50)	100	50/50	51.4 (50)	102	50/50	47.9 (48)	95	48/50
62	51.4 (49)	49/50	51.0 (50)	99	50/50	51.9 (50)	101	50/50	49.0 (47)	95	47/50
64	51.5 (49)	49/50	51.5 (50)	100	50/50	52.3 (50)	102	50/50	49.4 (47)	96	47/50
66	51.5 (49)	49/50	51.1 (50)	99	50/50	51.9 (50)	101	50/50	48.9 (46)	95	46/50
68	51.8 (49)	49/50	52.2 (49)	101	49/50	51.9 (50)	100	50/50	48.8 (45)	94	45/50
70	52.2 (48)	48/50	52.1 (49)	100	49/50	52.5 (49)	101	49/50	49.2 (43)	94	43/50
72	52.7 (48)	48/50	52.7 (49)	100	49/50	52.4 (49)	99	49/50	49.5 (43)	94	43/50
74	52.9 (48)	48/50	52.9 (49)	100	49/50	52.6 (48)	99	48/50	49.9 (42)	94	42/50
76	52.9 (47)	47/50	52.7 (49)	100	49/50	53.2 (46)	101	46/50	50.0 (42)	95	42/50
78	53.2 (46)	46/50	53.0 (48)	100	48/50	53.1 (46)	100	46/50	50.0 (42)	94	42/50
80	53.3 (44)	44/50	53.5 (48)	100	48/50	53.3 (46)	100	46/50	51.0 (41)	96	41/50
82	53.7 (44)	44/50	53.1 (48)	99	48/50	52.9 (46)	99	46/50	50.4 (41)	94	41/50
84	53.7 (44)	44/50	53.3 (47)	99	46/50	52.4 (45)	98	45/50	50.9 (40)	95	40/50
86	53.0 (44)	44/50	53.1 (46)	100	46/50	52.9 (43)	100	43/50	50.1 (40)	95	40/50
88	52.4 (44)	44/50	53.6 (45)	102	45/50	52.7 (43)	101	43/50	49.9 (39)	95	39/50
90	51.6 (44)	44/50	53.0 (45)	103	45/50	51.3 (42)	99	42/50	49.3 (38)	96	38/50
92	51.8 (42)	42/50	54.1 (43)	104	43/50	51.9 (41)	100	41/50	50.3 (35)	97	35/50
94	51.5 (42)	42/50	53.4 (43)	104	43/50	50.9 (41)	99	41/50	49.4 (35)	96	34/50
96	51.4 (41)	41/50	53.2 (42)	104	42/50	50.0 (39)	97	39/50	48.1 (33)	94	33/50
98	50.8 (40)	40/50	53.8 (39)	106	39/50	49.3 (37)	97	37/50	47.3 (32)	93	32/50
100	49.9 (39)	39/50	53.1 (38)	106	38/50	49.3 (33)	99	33/50	46.0 (31)	92	31/50
102	49.9 (36)	36/50	52.6 (36)	105	36/50	48.5 (32)	97	32/50	46.4 (29)	93	29/50
104	49.5 (34)	34/50	52.3 (35)	106	35/50	48.0 (30)	97	30/50	46.6 (25)	94	25/50

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

TABLE 16 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN FEMALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	10000 ppm Av.Wt.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.Wt.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.Wt.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
0	18.1 (50)	50/50	18.1 (50)	100	50/50	18.1 (50)	100	50/50	18.1 (50)	100	50/50
1	19.2 (50)	50/50	19.2 (50)	100	50/50	19.0 (50)	99	50/50	19.3 (50)	101	50/50
2	19.8 (50)	50/50	19.9 (50)	101	50/50	19.6 (50)	99	50/50	19.7 (50)	99	50/50
3	20.6 (50)	50/50	20.7 (50)	100	50/50	20.5 (50)	100	50/50	20.7 (50)	100	50/50
4	21.5 (50)	50/50	21.6 (50)	100	50/50	21.3 (50)	99	50/50	21.5 (50)	100	50/50
5	22.0 (50)	50/50	21.7 (50)	99	50/50	21.4 (50)	97	50/50	21.2 (50)	96	50/50
6	22.5 (50)	50/50	22.4 (50)	100	50/50	22.4 (50)	100	50/50	22.2 (50)	99	50/50
7	22.8 (50)	50/50	22.5 (50)	99	50/50	22.6 (50)	99	50/50	22.6 (50)	99	50/50
8	23.2 (50)	50/50	23.1 (50)	100	50/50	23.2 (50)	100	50/50	23.0 (50)	99	50/50
9	23.6 (50)	50/50	23.7 (50)	100	50/50	23.7 (49)	100	49/50	23.5 (50)	100	50/50
10	24.0 (50)	50/50	24.1 (50)	100	50/50	24.0 (49)	100	49/50	24.0 (50)	100	50/50
11	23.9 (50)	50/50	23.9 (50)	100	50/50	23.7 (49)	99	49/50	23.9 (50)	100	50/50
12	24.9 (50)	50/50	24.4 (50)	98	50/50	24.4 (49)	98	49/50	24.3 (50)	98	50/50
13	24.4 (50)	50/50	24.1 (50)	99	50/50	24.1 (49)	99	49/50	24.1 (50)	99	50/50
14	24.7 (50)	50/50	24.7 (50)	100	50/50	24.5 (49)	99	49/50	24.6 (50)	100	50/50
16	25.4 (50)	50/50	25.4 (50)	100	50/50	25.0 (49)	98	49/50	25.0 (50)	98	50/50
18	26.4 (50)	50/50	26.2 (50)	99	50/50	26.1 (49)	99	49/50	25.9 (50)	98	50/50
20	26.8 (50)	50/50	26.8 (50)	100	50/50	26.4 (49)	99	49/50	26.4 (50)	99	50/50
22	27.0 (50)	50/50	27.4 (50)	101	50/50	27.2 (49)	101	49/50	26.9 (50)	100	50/50
24	27.4 (50)	50/50	26.9 (50)	98	50/50	27.5 (49)	100	49/50	27.1 (50)	99	50/50
26	28.1 (50)	50/50	27.9 (50)	99	50/50	27.5 (49)	98	49/50	27.3 (50)	97	50/50
28	29.0 (49)	49/50	28.6 (50)	99	50/50	28.3 (49)	98	49/50	27.4 (50)	94	50/50
30	29.4 (49)	49/50	29.1 (50)	99	50/50	28.4 (49)	97	49/50	28.1 (50)	96	50/50
32	30.4 (49)	49/50	30.4 (50)	100	50/50	30.0 (48)	99	48/50	29.0 (50)	95	50/50
34	30.4 (49)	49/50	30.3 (50)	100	50/50	29.6 (48)	97	48/50	29.6 (50)	97	50/50
36	30.9 (49)	49/50	31.0 (49)	100	49/50	30.5 (48)	99	48/50	29.8 (50)	96	50/50
38	30.6 (49)	49/50	30.8 (49)	101	49/50	30.1 (48)	98	48/50	29.7 (50)	97	50/50
40	31.7 (49)	49/50	31.6 (49)	100	49/50	31.0 (48)	98	48/50	30.3 (50)	96	50/50
42	31.9 (49)	49/50	31.6 (49)	99	49/50	31.3 (48)	98	48/50	29.7 (50)	93	50/50
44	31.9 (49)	49/50	32.0 (49)	100	49/50	31.6 (48)	99	48/50	30.4 (50)	95	50/50
46	31.6 (47)	47/50	31.8 (49)	101	49/50	31.2 (47)	99	47/50	30.4 (50)	96	50/50
48	32.8 (47)	47/50	33.0 (49)	101	49/50	32.1 (47)	98	47/50	30.9 (50)	94	50/50
50	32.6 (47)	47/50	32.8 (49)	101	49/50	32.2 (47)	99	47/50	31.3 (50)	96	50/50
52	33.0 (47)	47/50	32.8 (49)	99	49/50	33.0 (47)	100	47/50	32.0 (50)	97	50/50
54	32.3 (47)	47/50	32.3 (49)	100	49/50	32.4 (46)	100	46/50	31.6 (49)	98	49/50
56	32.8 (46)	46/50	31.6 (49)	96	49/50	31.9 (46)	97	46/50	31.7 (49)	97	49/50
58	33.2 (46)	46/50	32.6 (48)	98	48/50	32.6 (46)	98	46/50	32.4 (49)	98	49/50
60	34.1 (46)	46/50	34.1 (48)	100	48/50	33.9 (46)	99	46/50	33.0 (49)	97	49/50
62	35.3 (45)	45/50	34.8 (48)	99	48/50	34.3 (45)	97	45/50	33.5 (49)	95	49/50
64	35.8 (45)	45/50	35.3 (48)	99	48/50	35.6 (45)	99	45/50	34.6 (49)	97	49/50
66	36.3 (45)	45/50	35.9 (47)	99	47/50	35.2 (44)	97	44/50	34.3 (48)	94	48/50
68	36.5 (45)	45/50	36.2 (47)	99	47/50	35.1 (43)	96	43/50	34.4 (47)	94	47/50
70	36.4 (45)	45/50	36.2 (47)	99	47/50	35.3 (43)	97	43/50	34.4 (47)	95	47/50
72	36.7 (45)	45/50	36.3 (47)	99	47/50	36.3 (43)	99	43/50	34.9 (47)	95	47/50
74	37.4 (43)	43/50	36.7 (46)	98	46/50	36.3 (43)	97	43/50	35.0 (47)	94	47/50
76	37.2 (43)	43/50	37.5 (45)	101	45/50	37.0 (42)	99	42/50	35.9 (46)	97	46/50
78	38.1 (43)	43/50	37.4 (44)	98	44/50	37.1 (42)	97	42/50	36.0 (46)	94	46/50
80	37.8 (42)	42/50	37.8 (42)	100	42/50	37.6 (42)	99	42/50	36.4 (46)	96	46/50
82	38.3 (42)	42/50	38.0 (41)	99	41/50	37.8 (41)	99	41/50	36.2 (45)	95	45/50
84	37.7 (41)	41/50	38.1 (41)	101	41/50	37.6 (39)	100	39/50	36.6 (44)	97	44/50
86	38.0 (40)	40/50	37.1 (41)	98	41/50	37.6 (37)	99	37/50	36.1 (43)	95	43/50
88	37.8 (38)	38/50	36.9 (40)	98	39/50	37.5 (35)	99	35/50	36.3 (43)	96	43/50
90	37.6 (37)	37/50	36.4 (36)	97	36/50	37.1 (32)	99	32/50	35.9 (43)	95	43/50
92	36.8 (37)	37/50	36.7 (35)	100	35/50	36.0 (31)	98	31/50	35.9 (41)	98	41/50
94	37.1 (37)	37/50	36.0 (34)	97	34/50	36.7 (29)	99	29/50	35.9 (39)	97	39/50
96	36.3 (35)	35/50	35.3 (32)	97	32/50	35.9 (27)	99	27/50	35.3 (37)	97	37/50
98	37.6 (33)	33/50	35.3 (31)	94	31/50	35.8 (26)	95	26/50	35.0 (36)	93	36/50
100	36.4 (32)	32/50	36.3 (28)	100	28/50	35.4 (24)	97	24/50	35.4 (35)	97	35/50
102	36.6 (30)	30/50	36.5 (25)	100	25/50	34.7 (23)	95	22/50	34.5 (33)	94	32/50
104	36.2 (29)	29/50	35.4 (25)	98	24/50	36.1 (19)	100	19/50	34.9 (28)	96	28/50

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

TABLE 17 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION IN MALE MOUSE

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	0/49	0/49	1/46	1/44	2/34	4/50(2/16)
10000ppm	0/50	0/50	0/50	0/50	0/50	3/48	2/43	4/35	5/50(2/15)
20000ppm	0/50	0/50	0/50	0/50	0/50	0/46	0/42	1/30	1/50(0/20)
40000ppm	0/50	0/50	0/50	0/50	0/46	0/42	2/36	1/25	3/50(2/25)
Internal mass									
Control	0/50	0/50	0/50	0/49	0/49	2/46	3/44	4/34	6/50(3/16)
10000ppm	0/50	0/50	0/50	0/50	1/50	1/48	2/43	1/35	4/50(4/15)
20000ppm	0/50	0/50	0/49	0/50	1/50	2/46	2/42	3/30	4/50(4/20)
40000ppm	0/50	0/50	0/50	0/50	1/46	0/42	0/36	1/25	2/50(2/25)

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 18 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION IN FEMALE MOUSE

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	0/49	0/47	1/45	1/43	0/37	6/29	7/50(4/21)
10000ppm	0/50	0/50	0/49	0/49	0/48	1/44	3/36	2/24	3/50(3/26)
20000ppm	1/49	0/49	0/48	2/47	0/45	1/42	1/32	1/19	3/50(3/31)
40000ppm	0/50	0/50	0/50	0/50	1/48	3/46	4/43	7/28	7/49(4/22)
Internal mass									
Control	0/50	0/50	0/49	0/47	4/45	4/43	5/37	2/29	12/50(11/21)
10000ppm	0/50	0/50	0/49	0/49	0/48	3/44	5/36	2/24	7/50(7/26)
20000ppm	0/49	0/49	0/48	2/47	1/45	0/42	8/32	5/19	12/50(11/31)
40000ppm	0/50	0/50	0/50	0/50	3/48	4/46	4/43	4/28	9/49(9/22)

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 19 WATER CONSUMPTION IN MALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.WC.	Control No.of Surviv. <50>	10000 ppm Av.WC.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.WC.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.WC.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
1	4.9 (50)	50/50	5.3 (50)	108	50/50	5.2 (50)	106	50/50	5.6 (49)	114	50/50
2	5.0 (49)	50/50	5.1 (50)	102	50/50	5.2 (50)	104	50/50	5.6 (49)	112	50/50
3	4.7 (49)	50/50	5.0 (50)	106	50/50	5.2 (49)	111	50/50	5.7 (47)	121	50/50
4	6.1 (50)	50/50	5.5 (50)	90	50/50	5.9 (50)	97	50/50	7.0 (50)	115	50/50
5	6.9 (50)	50/50	5.2 (50)	75	50/50	5.6 (50)	81	50/50	7.2 (50)	104	50/50
6	6.6 (50)	50/50	6.3 (50)	95	50/50	6.7 (50)	102	50/50	7.2 (50)	109	50/50
7	9.7 (50)	50/50	6.4 (50)	66	50/50	6.9 (50)	71	50/50	7.8 (50)	80	50/50
8	7.2 (50)	50/50	6.4 (50)	89	50/50	6.9 (50)	96	50/50	7.6 (50)	106	50/50
9	6.3 (50)	50/50	6.2 (50)	98	50/50	6.7 (50)	106	50/50	7.0 (50)	111	50/50
10	5.9 (49)	50/50	5.7 (50)	97	50/50	6.0 (50)	102	50/50	6.4 (50)	108	50/50
11	6.4 (50)	50/50	5.4 (50)	84	50/50	6.5 (50)	102	50/50	6.6 (50)	103	50/50
12	6.4 (49)	50/50	5.8 (50)	91	50/50	5.9 (49)	92	50/50	6.4 (50)	100	50/50
13	6.9 (50)	50/50	5.5 (50)	80	50/50	5.6 (50)	81	50/50	6.0 (50)	87	50/50
14	6.4 (48)	50/50	5.4 (50)	84	50/50	6.1 (50)	95	50/50	6.2 (50)	97	50/50
16	7.2 (49)	50/50	5.6 (50)	78	50/50	5.5 (50)	76	50/50	5.9 (50)	82	50/50
18	6.8 (50)	50/50	4.9 (50)	72	50/50	5.3 (50)	78	50/50	5.7 (50)	84	50/50
20	5.3 (50)	50/50	4.6 (50)	87	50/50	4.9 (50)	92	50/50	5.3 (50)	100	50/50
22	5.2 (50)	50/50	4.7 (50)	90	50/50	5.0 (50)	96	50/50	5.6 (50)	108	50/50
24	5.2 (50)	50/50	4.7 (50)	90	50/50	4.4 (50)	85	50/50	5.2 (50)	100	50/50
26	4.9 (50)	50/50	4.7 (50)	96	50/50	4.5 (50)	92	50/50	4.8 (50)	98	50/50
28	5.2 (50)	50/50	4.4 (50)	85	50/50	4.8 (50)	92	50/50	4.9 (50)	94	50/50
30	5.2 (50)	50/50	4.4 (50)	85	50/50	4.6 (49)	88	50/50	4.7 (50)	90	50/50
32	5.5 (50)	50/50	4.3 (50)	78	50/50	4.6 (50)	84	50/50	5.1 (49)	93	50/50
34	5.0 (50)	50/50	4.4 (50)	88	50/50	4.8 (50)	96	50/50	4.9 (50)	98	50/50
36	4.9 (50)	50/50	4.6 (50)	94	50/50	4.5 (50)	92	50/50	4.8 (50)	98	50/50
38	4.4 (50)	50/50	4.2 (50)	95	50/50	4.6 (50)	105	50/50	4.6 (50)	105	50/50
40	4.9 (50)	50/50	4.4 (50)	90	50/50	4.9 (50)	100	50/50	5.0 (50)	102	50/50
42	4.9 (50)	50/50	4.6 (50)	94	50/50	4.9 (50)	100	50/50	4.8 (50)	98	50/50
44	5.3 (50)	50/50	4.6 (50)	87	50/50	4.9 (50)	92	50/50	5.2 (48)	98	50/50
46	5.6 (50)	50/50	4.4 (50)	79	50/50	4.7 (50)	84	50/50	5.0 (50)	89	50/50
48	6.2 (50)	49/50	4.7 (50)	76	50/50	4.9 (50)	79	50/50	5.4 (50)	87	50/50
50	5.1 (49)	49/50	4.6 (50)	90	50/50	4.7 (50)	92	50/50	5.0 (50)	98	50/50
52	4.5 (49)	49/50	4.3 (50)	96	50/50	4.5 (50)	100	50/50	4.8 (50)	107	50/50
54	5.4 (49)	49/50	4.6 (50)	85	50/50	4.8 (50)	89	50/50	5.2 (49)	96	49/50
56	5.1 (49)	49/50	4.7 (50)	92	50/50	5.0 (50)	98	50/50	5.5 (49)	108	49/50
58	5.2 (49)	49/50	4.5 (50)	87	50/50	5.0 (50)	96	50/50	5.3 (46)	102	48/50
60	5.3 (49)	49/50	4.6 (50)	87	50/50	5.0 (50)	94	50/50	5.2 (47)	98	48/50
62	4.9 (49)	49/50	4.5 (50)	92	50/50	4.5 (50)	92	50/50	4.8 (47)	98	47/50
64	5.3 (49)	49/50	5.5 (50)	104	50/50	4.8 (50)	91	50/50	5.2 (47)	98	47/50
66	5.0 (49)	49/50	5.0 (50)	100	50/50	4.9 (50)	98	50/50	5.2 (46)	104	46/50
68	5.2 (49)	49/50	4.6 (49)	88	49/50	4.9 (50)	94	50/50	5.3 (45)	102	45/50
70	4.7 (48)	48/50	4.4 (48)	94	49/50	4.6 (49)	98	49/50	5.1 (42)	109	43/50
72	5.1 (48)	48/50	4.4 (49)	86	49/50	4.8 (49)	94	49/50	5.5 (43)	108	43/50
74	4.8 (48)	48/50	4.6 (49)	96	49/50	4.8 (48)	100	48/50	5.8 (42)	121	42/50
76	5.6 (47)	47/50	4.5 (49)	80	49/50	5.1 (46)	91	46/50	5.9 (42)	105	42/50
78	5.0 (46)	46/50	4.5 (48)	90	48/50	4.9 (46)	98	46/50	5.5 (42)	110	42/50
80	5.2 (44)	44/50	4.7 (48)	90	48/50	5.1 (46)	98	46/50	5.5 (41)	106	41/50
82	5.2 (44)	44/50	4.6 (48)	88	48/50	5.0 (46)	96	46/50	5.6 (41)	108	41/50
84	5.1 (44)	44/50	4.7 (47)	92	46/50	5.1 (45)	100	45/50	6.0 (40)	118	40/50
86	5.1 (44)	44/50	5.0 (46)	98	46/50	5.4 (43)	106	43/50	6.3 (40)	124	40/50
88	5.9 (44)	44/50	5.0 (45)	85	45/50	5.9 (43)	100	43/50	6.6 (39)	112	39/50
90	5.9 (44)	44/50	4.9 (45)	83	45/50	6.6 (43)	112	42/50	7.2 (38)	122	38/50
92	5.5 (42)	42/50	5.0 (43)	91	43/50	6.7 (41)	122	41/50	7.1 (35)	129	35/50
94	5.3 (42)	42/50	4.7 (43)	89	43/50	6.8 (41)	128	41/50	7.3 (35)	138	34/50
96	5.6 (41)	41/50	5.1 (42)	91	42/50	7.4 (39)	132	39/50	7.3 (33)	130	33/50
98	5.5 (40)	40/50	4.9 (39)	89	39/50	6.9 (37)	125	37/50	8.2 (32)	149	32/50
100	6.2 (39)	39/50	5.0 (38)	81	38/50	6.5 (33)	105	33/50	8.0 (29)	129	31/50
102	6.2 (37)	36/50	5.3 (36)	85	36/50	6.1 (32)	98	32/50	8.0 (30)	129	29/50
104	6.3 (35)	34/50	5.2 (35)	83	35/50	6.5 (30)	103	30/50	8.0 (25)	127	25/50

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

TABLE 20 WATER CONSUMPTION IN FEMALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.WC.	Control No.of Surviv. <50>	10000 ppm Av.WC.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.WC.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.WC.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
1	4.7 (50)	50/50	4.8 (50)	102	50/50	4.9 (50)	104	50/50	5.6 (50)	119	50/50
2	4.6 (48)	50/50	5.0 (50)	109	50/50	5.3 (50)	115	50/50	5.6 (50)	122	50/50
3	4.6 (50)	50/50	4.9 (49)	107	50/50	5.4 (50)	117	50/50	5.7 (50)	124	50/50
4	5.8 (50)	50/50	5.5 (50)	95	50/50	7.2 (50)	124	50/50	7.8 (50)	134	50/50
5	6.0 (49)	50/50	6.3 (50)	105	50/50	7.5 (50)	125	50/50	6.8 (50)	113	50/50
6	6.1 (50)	50/50	7.4 (45)	121	50/50	8.1 (50)	133	50/50	7.7 (49)	126	50/50
7	7.8 (49)	50/50	8.3 (50)	106	50/50	7.4 (50)	95	50/50	8.0 (50)	103	50/50
8	6.3 (50)	50/50	8.9 (50)	141	50/50	7.6 (50)	121	50/50	8.1 (50)	129	50/50
9	7.5 (50)	50/50	8.1 (50)	108	50/50	7.4 (49)	99	49/50	7.5 (50)	100	50/50
10	7.0 (50)	50/50	7.5 (50)	107	50/50	7.6 (49)	109	49/50	6.8 (50)	97	50/50
11	8.0 (50)	50/50	8.1 (50)	101	50/50	8.7 (49)	109	49/50	7.1 (50)	89	50/50
12	7.7 (50)	50/50	8.1 (50)	105	50/50	7.8 (47)	101	49/50	7.3 (50)	95	50/50
13	8.5 (50)	50/50	7.8 (50)	92	50/50	9.4 (49)	111	49/50	8.0 (50)	94	50/50
14	10.0 (49)	50/50	9.4 (50)	94	50/50	9.3 (48)	93	49/50	8.3 (49)	83	50/50
16	8.3 (49)	50/50	7.9 (50)	95	50/50	7.2 (48)	87	49/50	7.0 (50)	84	50/50
18	8.0 (49)	50/50	7.5 (49)	94	50/50	7.7 (49)	96	49/50	7.3 (50)	91	50/50
20	8.4 (49)	50/50	6.7 (50)	80	50/50	6.1 (48)	73	49/50	6.8 (50)	81	50/50
22	7.0 (50)	50/50	6.9 (50)	99	50/50	6.3 (48)	90	49/50	6.1 (50)	87	50/50
24	7.7 (49)	50/50	6.4 (49)	83	50/50	6.2 (49)	81	49/50	7.1 (50)	92	50/50
26	6.7 (48)	50/50	6.1 (50)	91	50/50	6.5 (48)	97	49/50	6.1 (50)	91	50/50
28	7.9 (49)	49/50	6.2 (50)	78	50/50	6.2 (48)	78	49/50	6.4 (50)	81	50/50
30	7.2 (48)	49/50	6.9 (49)	96	50/50	5.9 (47)	82	49/50	6.1 (50)	85	50/50
32	7.3 (48)	49/50	5.8 (50)	79	50/50	6.0 (47)	82	48/50	6.8 (50)	93	50/50
34	6.6 (49)	49/50	5.6 (50)	85	50/50	6.5 (48)	98	48/50	6.1 (50)	92	50/50
36	6.6 (49)	49/50	6.2 (49)	94	49/50	6.4 (48)	97	48/50	6.0 (50)	91	50/50
38	5.9 (49)	49/50	5.8 (49)	98	49/50	6.0 (47)	102	48/50	5.4 (49)	92	50/50
40	6.0 (49)	49/50	6.0 (49)	100	49/50	6.6 (48)	110	48/50	5.8 (50)	97	50/50
42	6.1 (49)	49/50	6.8 (49)	111	49/50	6.6 (48)	108	48/50	5.4 (50)	89	50/50
44	6.1 (49)	49/50	6.6 (49)	108	49/50	7.0 (48)	115	48/50	5.6 (49)	92	50/50
46	5.4 (48)	47/50	6.2 (49)	115	49/50	6.2 (46)	115	47/50	5.6 (50)	104	50/50
48	5.6 (47)	47/50	6.5 (49)	116	49/50	5.9 (47)	105	47/50	5.8 (50)	104	50/50
50	6.3 (47)	47/50	6.5 (48)	103	49/50	6.6 (47)	105	47/50	6.0 (50)	95	50/50
52	5.2 (47)	47/50	5.5 (49)	106	49/50	5.7 (46)	110	47/50	5.3 (50)	102	50/50
54	6.3 (47)	47/50	7.2 (49)	114	49/50	6.1 (46)	97	46/50	5.5 (49)	87	49/50
56	6.5 (47)	46/50	6.2 (49)	95	49/50	5.9 (46)	91	46/50	5.6 (49)	86	49/50
58	5.5 (46)	46/50	5.5 (48)	100	48/50	5.6 (46)	102	46/50	5.1 (49)	93	49/50
60	5.3 (46)	46/50	5.9 (48)	111	48/50	5.9 (46)	111	46/50	5.6 (46)	106	49/50
62	5.1 (45)	45/50	5.1 (48)	100	48/50	5.0 (46)	98	45/50	4.7 (49)	92	49/50
64	4.9 (45)	45/50	5.4 (47)	110	48/50	5.8 (45)	118	45/50	5.3 (49)	108	49/50
66	5.6 (45)	45/50	5.2 (46)	93	47/50	6.0 (44)	107	44/50	4.9 (48)	88	48/50
68	5.0 (45)	45/50	5.1 (47)	102	47/50	5.7 (42)	114	43/50	4.9 (47)	98	47/50
70	4.7 (45)	45/50	4.7 (47)	100	47/50	5.0 (43)	106	43/50	4.9 (46)	104	47/50
72	4.8 (45)	45/50	4.8 (47)	100	47/50	5.5 (43)	115	43/50	5.0 (47)	104	47/50
74	5.1 (43)	43/50	5.1 (46)	100	46/50	5.2 (43)	102	43/50	5.1 (47)	100	47/50
76	4.7 (43)	43/50	5.0 (44)	106	45/50	5.2 (42)	111	42/50	5.0 (46)	106	46/50
78	4.7 (43)	43/50	4.2 (45)	89	44/50	4.9 (42)	104	42/50	4.8 (46)	102	46/50
80	4.8 (43)	42/50	4.8 (42)	100	42/50	5.5 (42)	115	42/50	5.4 (46)	113	46/50
82	4.5 (42)	42/50	4.6 (41)	102	41/50	5.0 (41)	111	41/50	5.1 (45)	113	45/50
84	4.4 (41)	41/50	4.7 (41)	107	41/50	5.0 (40)	114	39/50	5.4 (45)	123	44/50
86	4.4 (40)	40/50	4.5 (41)	102	41/50	5.0 (38)	114	37/50	5.0 (43)	114	43/50
88	4.7 (38)	38/50	4.8 (40)	102	39/50	5.3 (35)	113	35/50	5.4 (43)	115	43/50
90	4.6 (37)	37/50	4.5 (35)	98	36/50	5.4 (32)	117	32/50	5.2 (43)	113	43/50
92	4.3 (37)	37/50	4.6 (36)	107	35/50	5.3 (32)	123	31/50	5.6 (41)	130	41/50
94	4.3 (37)	37/50	4.4 (34)	102	34/50	5.2 (29)	121	29/50	5.9 (39)	137	39/50
96	4.8 (36)	35/50	4.6 (32)	96	32/50	5.4 (27)	113	27/50	6.6 (37)	138	37/50
98	4.7 (33)	33/50	4.4 (31)	94	31/50	5.5 (26)	117	26/50	6.1 (35)	130	36/50
100	4.9 (32)	32/50	5.1 (28)	104	28/50	6.3 (24)	129	24/50	5.8 (35)	118	35/50
102	4.7 (31)	30/50	4.8 (25)	102	25/50	6.4 (23)	136	22/50	5.8 (34)	123	32/50
104	4.7 (29)	29/50	4.7 (25)	100	24/50	5.5 (19)	117	19/50	6.3 (29)	134	28/50

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

TABLE 21 FOOD COSUMPTION IN MALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Surviv. <50>	10000 ppm Av.FC.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.FC.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.FC.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
1	3.7 (50)	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50	3.6 (50)	97	50/50
2	3.7 (50)	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50	3.6 (50)	97	50/50
3	3.8 (50)	50/50	3.7 (50)	97	50/50	3.7 (50)	97	50/50	3.7 (50)	97	50/50
4	3.7 (50)	50/50	3.6 (50)	97	50/50	3.6 (50)	97	50/50	3.7 (50)	100	50/50
5	3.8 (50)	50/50	3.7 (50)	97	50/50	3.7 (50)	97	50/50	3.6 (50)	95	50/50
6	4.1 (50)	50/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50	3.9 (50)	95	50/50
7	3.7 (50)	50/50	3.7 (50)	100	50/50	3.3 (50)	89	50/50	3.3 (50)	89	50/50
8	3.9 (50)	50/50	3.8 (50)	97	50/50	3.8 (50)	97	50/50	3.7 (50)	95	50/50
9	3.8 (49)	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50
10	4.0 (50)	50/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50	3.8 (50)	95	50/50
11	3.9 (50)	50/50	3.8 (50)	97	50/50	3.8 (50)	97	50/50	3.8 (50)	97	50/50
12	4.0 (50)	50/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50	3.8 (50)	95	50/50
13	3.9 (50)	50/50	3.8 (50)	97	50/50	3.9 (50)	100	50/50	3.8 (50)	97	50/50
14	3.8 (50)	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50	3.7 (50)	97	50/50
18	4.1 (50)	50/50	4.1 (50)	100	50/50	4.1 (50)	100	50/50	3.9 (50)	95	50/50
22	4.2 (50)	50/50	4.1 (50)	98	50/50	4.2 (50)	100	50/50	4.1 (50)	98	50/50
26	4.1 (50)	50/50	4.1 (50)	100	50/50	4.1 (50)	100	50/50	4.0 (50)	98	50/50
30	4.4 (50)	50/50	4.4 (50)	100	50/50	4.4 (50)	100	50/50	4.3 (50)	98	50/50
34	4.4 (50)	50/50	4.4 (50)	100	50/50	4.4 (50)	100	50/50	4.3 (50)	98	50/50
38	4.6 (50)	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50	4.4 (50)	96	50/50
42	4.6 (50)	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50	4.3 (50)	93	50/50
46	4.6 (50)	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50
50	4.7 (49)	49/50	4.7 (50)	100	50/50	4.7 (50)	100	50/50	4.6 (50)	98	50/50
54	4.5 (49)	49/50	4.5 (50)	100	50/50	4.5 (50)	100	50/50	4.3 (49)	96	49/50
58	4.5 (49)	49/50	4.5 (50)	100	50/50	4.5 (50)	100	50/50	4.3 (48)	96	48/50
62	4.7 (49)	49/50	4.4 (50)	94	50/50	4.5 (50)	96	50/50	4.4 (47)	94	47/50
66	4.7 (49)	49/50	4.5 (50)	96	50/50	4.6 (50)	98	50/50	4.5 (46)	96	46/50
70	4.8 (48)	48/50	4.6 (49)	96	49/50	4.6 (49)	96	49/50	4.6 (43)	96	43/50
74	4.8 (48)	48/50	4.7 (49)	98	49/50	4.7 (48)	98	48/50	4.7 (42)	98	42/50
78	4.8 (46)	46/50	4.7 (48)	98	48/50	4.8 (46)	100	46/50	4.8 (42)	100	42/50
82	5.1 (44)	44/50	4.8 (48)	94	48/50	4.9 (46)	96	46/50	4.8 (41)	94	41/50
86	4.9 (44)	44/50	4.9 (46)	100	46/50	4.8 (43)	98	43/50	4.7 (40)	96	40/50
90	4.9 (44)	44/50	4.9 (45)	100	45/50	4.7 (43)	96	42/50	4.8 (38)	98	38/50
94	4.7 (42)	42/50	4.7 (43)	100	43/50	4.8 (41)	102	41/50	4.6 (35)	98	34/50
98	4.6 (40)	40/50	4.8 (39)	104	39/50	4.7 (37)	102	37/50	4.7 (32)	102	32/50
102	4.6 (37)	36/50	4.7 (36)	102	36/50	4.5 (32)	98	32/50	4.4 (30)	96	29/50
104	4.6 (35)	34/50	4.5 (35)	98	35/50	4.4 (30)	96	30/50	4.5 (25)	98	25/50

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

TABLE 22 FOOD COSUMPTION IN FEMALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Surviv. <50>	10000 ppm Av.FC.	10000 ppm % of cont. <50>	10000 ppm No.of Surviv.	20000 ppm Av.FC.	20000 ppm % of cont. <50>	20000 ppm No.of Surviv.	40000 ppm Av.FC.	40000 ppm % of cont. <50>	40000 ppm No.of Surviv.
1	3.2 (50)	50/50	3.2 (50)	100	50/50	3.2 (50)	100	50/50	3.2 (50)	100	50/50
2	3.2 (50)	50/50	3.3 (50)	103	50/50	3.2 (50)	100	50/50	3.2 (50)	100	50/50
3	3.4 (50)	50/50	3.4 (50)	100	50/50	3.5 (50)	103	50/50	3.5 (50)	103	50/50
4	3.4 (50)	50/50	3.3 (50)	97	50/50	3.5 (50)	103	50/50	3.5 (50)	103	50/50
5	3.4 (50)	50/50	3.5 (50)	103	50/50	3.4 (50)	100	50/50	3.4 (50)	100	50/50
6	3.7 (50)	50/50	3.6 (50)	97	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50
7	3.5 (50)	50/50	3.4 (50)	97	50/50	3.5 (50)	100	50/50	3.5 (50)	100	50/50
8	3.6 (50)	50/50	3.6 (50)	100	50/50	3.6 (50)	100	50/50	3.6 (50)	100	50/50
9	3.6 (50)	50/50	3.6 (50)	100	50/50	3.7 (49)	103	49/50	3.7 (50)	103	50/50
10	3.6 (50)	50/50	3.6 (50)	100	50/50	3.6 (49)	100	49/50	3.6 (50)	100	50/50
11	3.6 (50)	50/50	3.6 (50)	100	50/50	3.6 (49)	100	49/50	3.6 (50)	100	50/50
12	3.7 (50)	50/50	3.7 (50)	100	50/50	3.7 (49)	100	49/50	3.6 (50)	97	50/50
13	3.5 (50)	50/50	3.5 (50)	100	50/50	3.6 (49)	103	49/50	3.5 (50)	100	50/50
14	3.3 (50)	50/50	3.4 (50)	103	50/50	3.4 (49)	103	49/50	3.4 (50)	103	50/50
18	3.8 (50)	50/50	3.8 (50)	100	50/50	3.9 (49)	103	49/50	3.8 (50)	100	50/50
22	3.7 (50)	50/50	3.9 (50)	105	50/50	3.9 (49)	105	49/50	3.7 (50)	100	50/50
26	3.8 (50)	50/50	3.9 (50)	103	50/50	3.8 (49)	100	49/50	3.9 (50)	103	50/50
30	4.1 (49)	49/50	4.1 (50)	100	50/50	4.0 (49)	98	49/50	3.9 (50)	95	50/50
34	4.0 (49)	49/50	4.0 (50)	100	50/50	3.9 (48)	98	48/50	4.2 (50)	105	50/50
38	4.0 (49)	49/50	4.2 (49)	105	49/50	4.1 (48)	103	48/50	4.1 (50)	103	50/50
42	4.1 (49)	49/50	4.1 (49)	100	49/50	4.1 (48)	100	48/50	3.9 (50)	95	50/50
46	4.0 (48)	47/50	4.1 (49)	103	49/50	4.2 (47)	105	47/50	4.2 (50)	105	50/50
50	4.2 (47)	47/50	4.3 (49)	102	49/50	4.4 (47)	105	47/50	4.4 (50)	105	50/50
54	3.9 (47)	47/50	4.1 (49)	105	49/50	4.1 (46)	105	46/50	4.1 (49)	105	49/50
58	4.1 (46)	46/50	4.1 (48)	100	48/50	4.2 (46)	102	46/50	4.2 (49)	102	49/50
62	4.4 (45)	45/50	4.3 (48)	98	48/50	4.3 (46)	98	45/50	4.3 (49)	98	49/50
66	4.1 (45)	45/50	4.1 (47)	100	47/50	4.1 (44)	100	44/50	4.1 (48)	100	48/50
70	4.3 (45)	45/50	4.2 (47)	98	47/50	4.3 (43)	100	43/50	4.2 (47)	98	47/50
74	4.5 (43)	43/50	4.3 (46)	96	46/50	4.3 (43)	96	43/50	4.4 (47)	98	47/50
78	4.4 (43)	43/50	4.2 (45)	95	44/50	4.2 (42)	95	42/50	4.4 (46)	100	46/50
82	4.6 (42)	42/50	4.5 (41)	98	41/50	4.7 (41)	102	41/50	4.6 (45)	100	45/50
86	4.4 (40)	40/50	4.5 (41)	102	41/50	4.4 (38)	100	37/50	4.4 (43)	100	43/50
90	4.4 (37)	37/50	4.3 (36)	98	36/50	4.4 (32)	100	32/50	4.4 (43)	100	43/50
94	4.3 (37)	37/50	4.1 (34)	95	34/50	4.4 (29)	102	29/50	4.5 (39)	105	39/50
98	4.4 (33)	33/50	4.2 (31)	95	31/50	4.1 (26)	93	26/50	4.3 (36)	98	36/50
102	4.6 (31)	30/50	4.5 (25)	98	25/50	4.7 (23)	102	22/50	4.3 (34)	93	32/50
104	4.3 (29)	29/50	4.2 (25)	98	24/50	4.5 (19)	105	19/50	4.7 (29)	109	28/50

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

TABLE 23 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN MALE MOUSE

Group Name	Control	10000ppm	20000ppm	40000ppm
SITE : spleen				
TUMOR : malignant lymphoma(f)				
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	2.94	0.0	6.67	0.0
Terminal rates(c)	1/34(2.9)	0/35(0.0)	2/30(6.7)	0/25(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0074**			
Prevalence method(d)	P=0.5831			
Combined analysis (d)	P=0.0462*			
Cochran-Amitage test(e)	P=0.1347			
Fisher Exact test(e)		P=0.4950	P=0.3235	P=0.3235
SITE : all organ				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	8/50(16.0)	3/50(6.0)	9/50(18.0)	9/50(18.0)
Adjusted rates(b)	14.71	5.71	16.67	10.00
Terminal rates(c)	5/34(14.7)	2/35(5.7)	5/30(16.7)	2/25(8.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0350*			
Prevalence method(d)	P=0.4813			
Combined analysis (d)	P=0.0895			
Cochran-Amitage test(e)	P=0.3961			
Fisher Exact test(e)		P=0.1322	P=0.4846	P=0.4846

(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: 35/800(4.4%); range 2% to 10%
?: 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 24 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN FEMALE MOUSE

Group Name	Control	10000ppm	20000ppm	40000ppm
SITE : uterus				
TUMOR : endometrial stromal polyp[f]				
Tumor rate				
Overall rates(a)	5/50(10.0)	2/50(4.0)	0/50(0.0)	2/50(4.0)
Adjusted rates(b)	17.24	8.33	0.0	4.76
Terminal rates(c)	5/29(17.2)	2/24(8.3)	0/19(0.0)	1/28(3.6)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.9062			
Combined analysis (d)	P=------			
Cochran-Amitage test(e)	P=0.1848			
Fisher Exact test(e)		P=0.2425	P=0.0360*	P=0.2425
SITE : mammary gland				
TUMOR : adenoma[g]				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	1/50(2.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	5.26	7.69
Terminal rates(c)	0/29(0.0)	0/24(0.0)	1/19(5.3)	2/28(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0146*			
Combined analysis (d)	P=------			
Cochran-Amitage test(e)	P=0.0168*			
Fisher Exact test(e)		P=0.5000	P=0.4950	P=0.1325
SITE : mammary gland				
TUMOR : adenoma[g], adenocarcinoma[h]				
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	3/50(6.0)	6/50(12.0)
Adjusted rates(b)	2.94	0.0	5.26	13.16
Terminal rates(c)	0/29(0.0)	0/24(0.0)	1/19(5.3)	3/28(10.7)
Statistical analysis				
Peto test				
Standard method(d)	P=0.2823			
Prevalence method(d)	P=0.0098**			
Combined analysis (d)	P=0.0142*			
Cochran-Amitage test(e)	P=0.0137*			
Fisher Exact test(e)		P=0.2475	P=0.3235	P=0.0724

TABLE 24 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS IN FEMALE MOUSE
(Continued)

Group Name	Control	10000ppm	20000ppm	40000ppm
SITE : all organ				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	12/50(24.0)	16/50(32.0)	12/50(24.0)	16/50(32.0)
Adjusted rates(b)	17.24	16.67	15.79	35.71
Terminal rates(c)	5/29(17.2)	4/24(16.7)	3/19(15.8)	10/28(35.7)
Statistical analysis				
Peto test				
Standard method(d)	P=0.7741			
Prevalence method(d)	P=0.0378*			
Combined analysis (d)	P=0.3240			
Cochran-Amitage test(e)	P=0.5229			
Fisher Exact test(e)		P=0.3253	P=0.4103	P=0.3253

(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: 22/799(2.8%); range 0% to 10%
(g):Historical incidence for 2-year studies: 0/799(0%)
(h):Historical incidence for 2-year studies: 11/799(1.4%); range 0% to 4%
?: 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 25 NUMBER OF MICE WITH SELECTED LESIONS OF NASAL CAVITY

Group name		Male				Female			
		Control	10000ppm	20000ppm	40000ppm	Control	10000ppm	20000ppm	40000ppm
Number of examined		50	50	50	50	50	50	50	50
Duct ectasia:									
olfactory gland		0	0	10	39	0	0	5	40
	+	(0)	(0)	(10)	(39)	(0)	(0)	(5)	(40)
	2+	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	3+	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Respiratory metaplasia:									
gland		14	26	21	37	1	6	9	14
	+	(8)	(19)	(17)	(31)	(1)	(6)	(9)	(13)
	2+	(6)	(7)	(4)	(6)	(0)	(0)	(0)	(1)
	3+	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Respiratory metaplasia:									
olfactory epithelium		13	11	25	32	3	2	10	8
	+	(13)	(11)	(25)	(30)	(2)	(2)	(10)	(8)
	2+	(0)	(0)	(0)	(2)	(1)	(0)	(0)	(0)
	3+	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Eosinophilic change:									
olfactory epithelium		15	12	20	10	3	3	3	15
	+	(15)	(12)	(20)	(10)	(1)	(1)	(2)	(14)
	2+	(0)	(0)	(0)	(0)	(0)	(2)	(1)	(1)
	3+	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

Grade +:Slight 2+:Moderate 3+:Marked
a a:Number of animals with lesion
(b) b:Number of animals with lesion in each grade

TABLE 26 CAUSE OF DEATH IN MICE

Group		Male				Female			
		Control	10000ppm	20000ppm	40000ppm	Control	10000ppm	20000ppm	40000ppm
Number of dead or moribund animals		16	15	20	25	21	26	31	22
No microscopical confirmation		2	0	0	2	1	1	2	2
Integmentary system lesion		0	0	0	0	0	1	0	0
Hepatic lesion		0	0	1	3	0	2	0	0
Renal lesion		0	0	0	2	1	0	0	0
Urinary retention		3	4	5	3	0	0	0	0
Reproductive system lesion		0	0	0	0	0	0	1	1
Body cavity lesion		0	0	0	0	1	0	0	0
Arteritis		0	0	0	0	0	0	2	0
Hydronephrosis		0	0	0	1	2	0	1	1
Tumor death :	leukemia	3	1	4	6	7	12	10	6
	subcutis	1	3	0	1	0	1	0	2
	lung	0	0	1	0	1	0	0	0
	spleen	0	0	1	0	0	0	0	0
	liver	4	7	7	6	1	3	2	0
	pituitary	0	0	0	0	1	1	2	1
	adrenal	0	0	0	0	0	0	0	1
	ovary	–	–	–	–	0	1	0	0
	uterus	–	–	–	–	6	2	9	7
	mammary gland	0	0	0	0	0	1	2	1
	brain	0	0	1	0	0	0	0	0
	peripheral nerve	0	0	0	1	0	1	0	0
	Harder gland	1	0	0	0	0	0	0	0

FIGURES

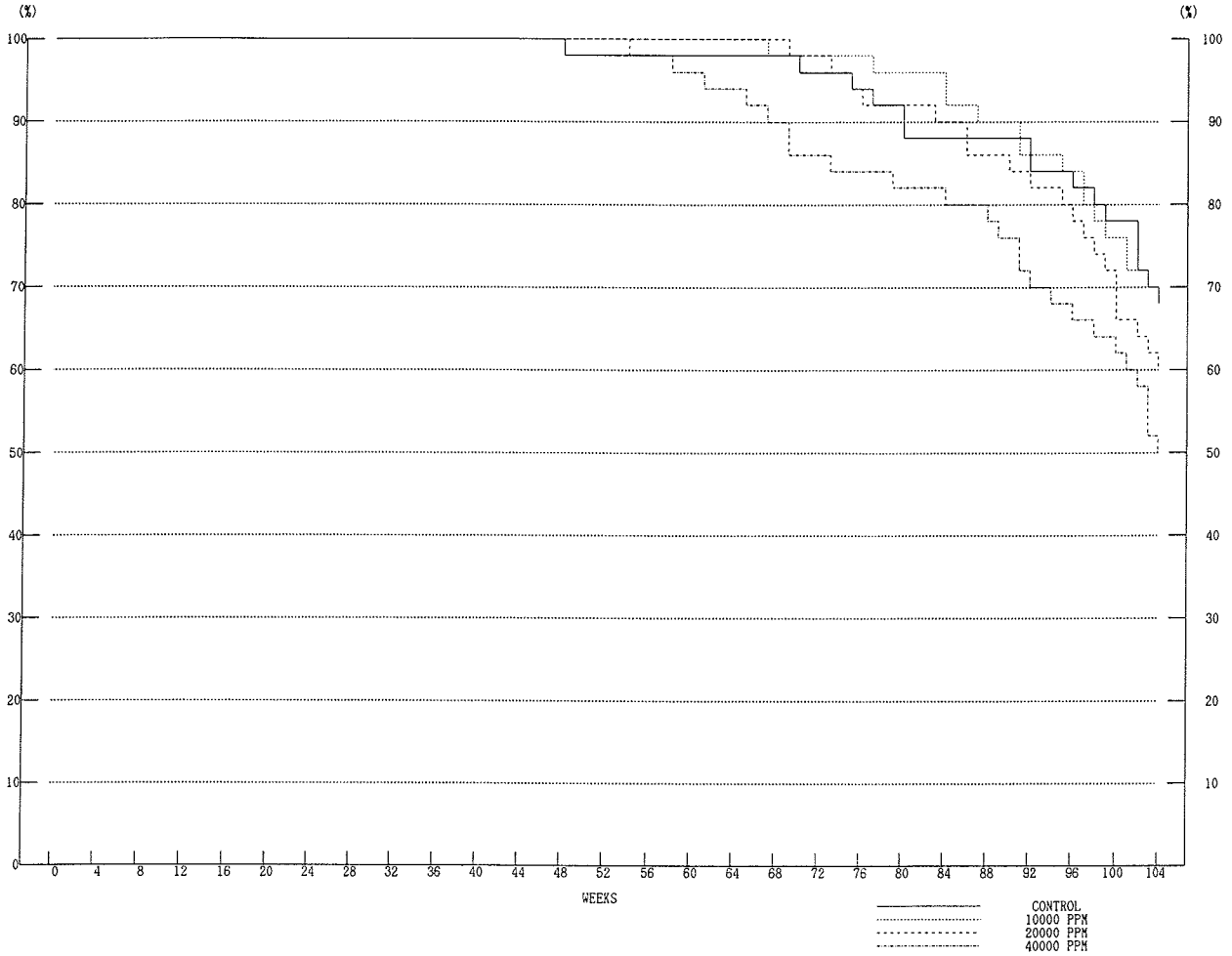

FIGURE 9 SURVIVAL ANIMAL RATE : MOUSE : MALE (TWO-YEAR STUDY)

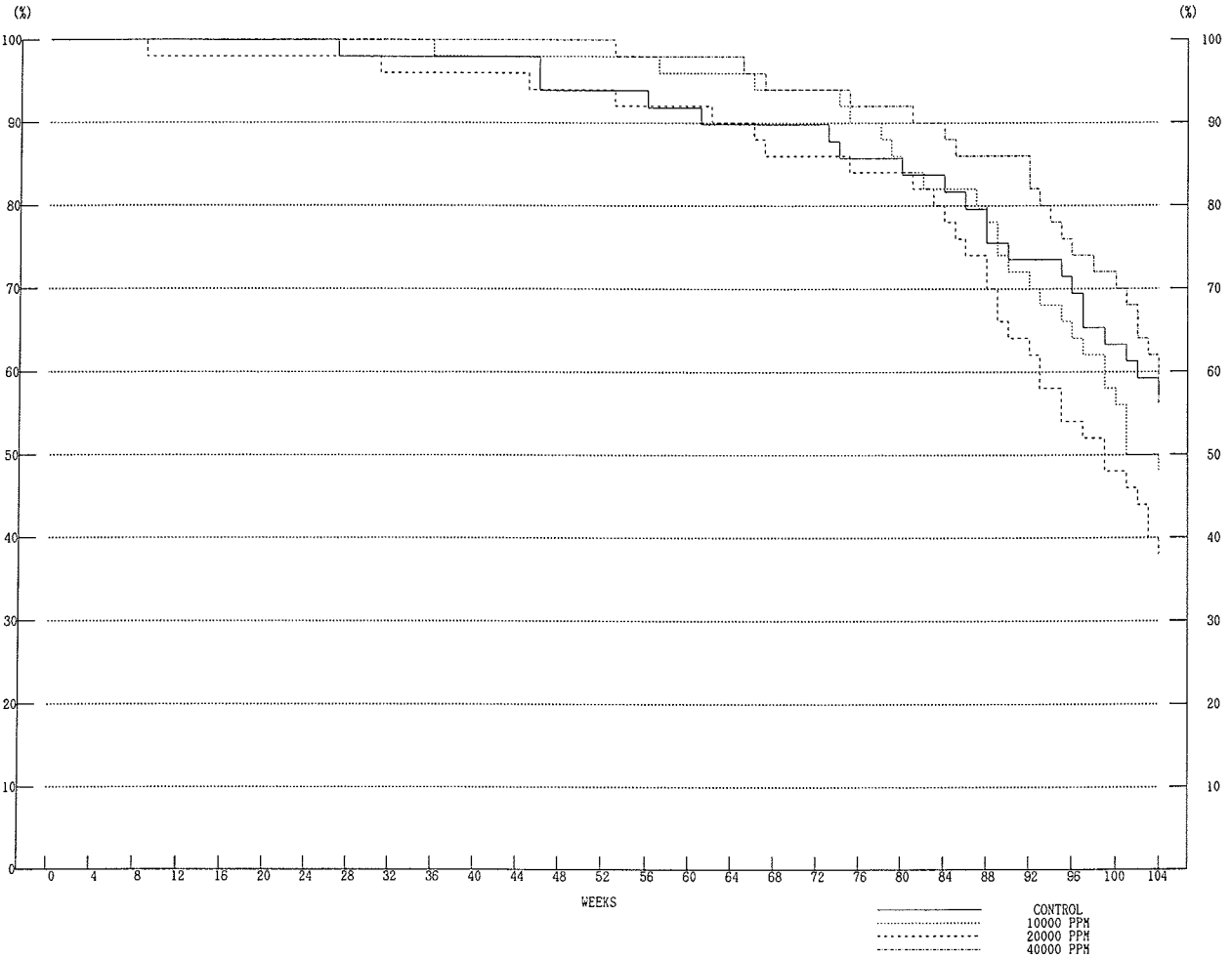

FIGURE 10 SURVIVAL ANIMAL RATE : MOUSE : FEMALE (TWO-YEAR STUDY)

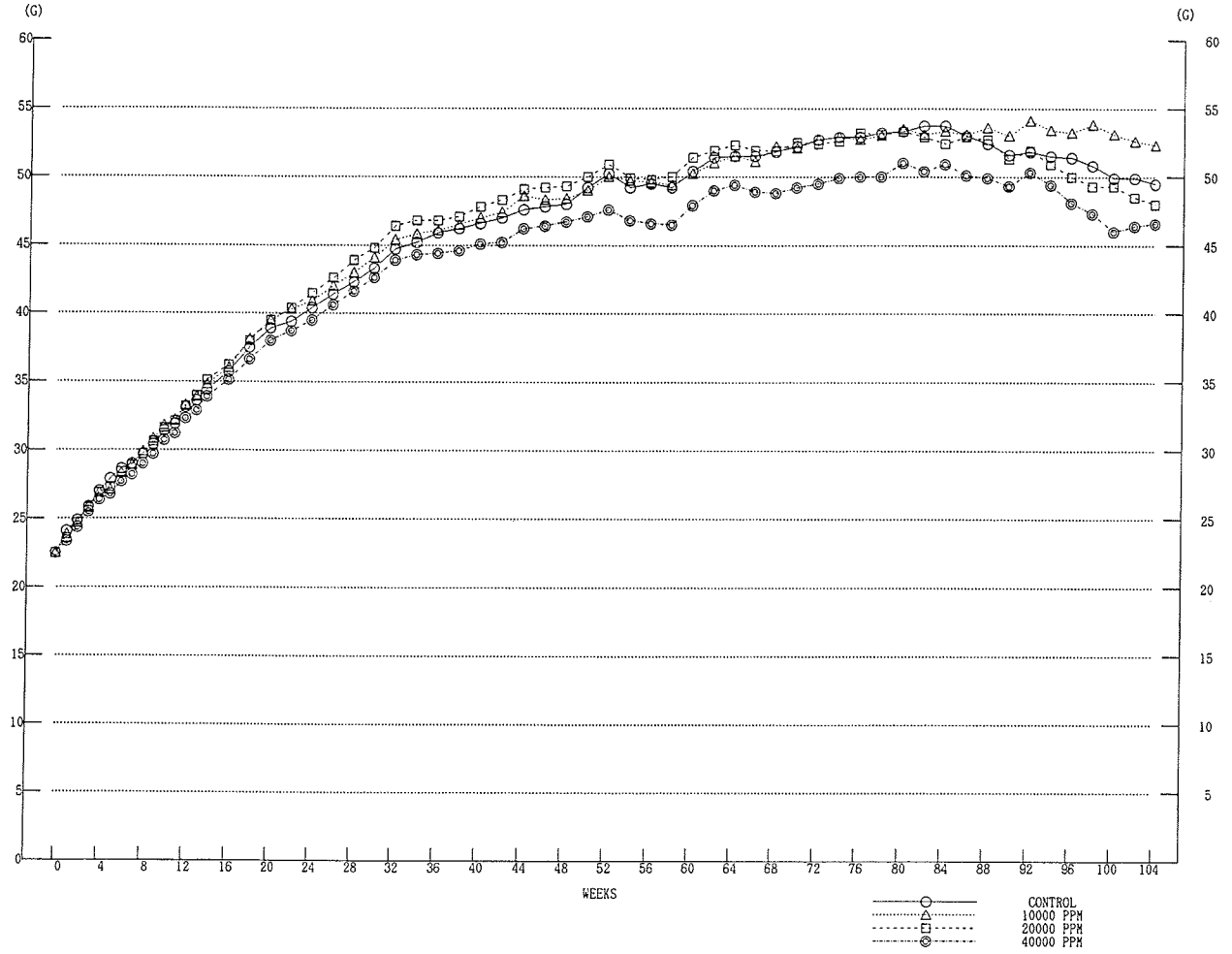

FIGURE 11 BODY WEIGHT CHANGES : MOUSE : MALE (TWO-YEAR STUDY)

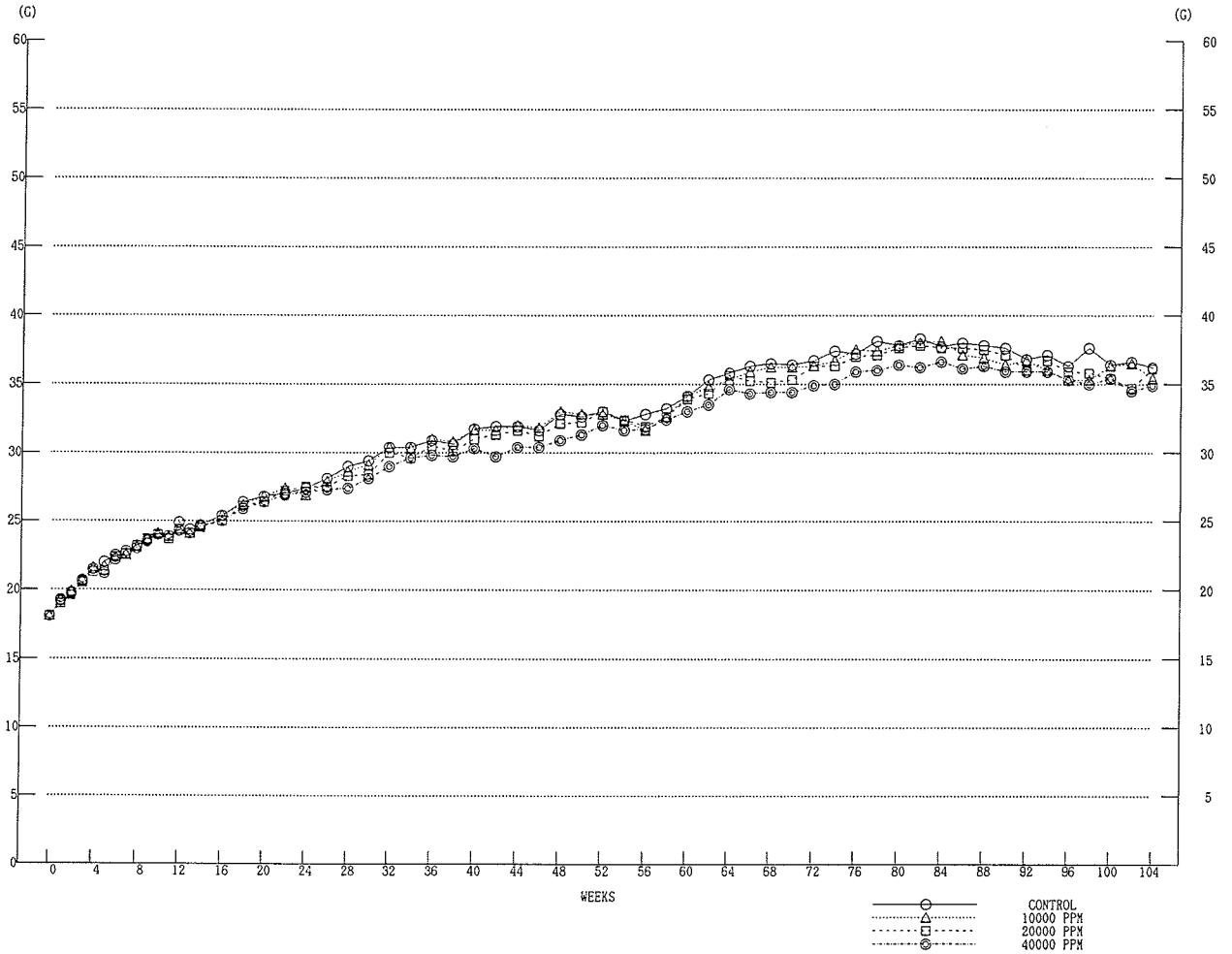

FIGURE 12 BODY WEIGHT CHANGES : MOUSE FEMALE (TWO-YEAR STUDY)

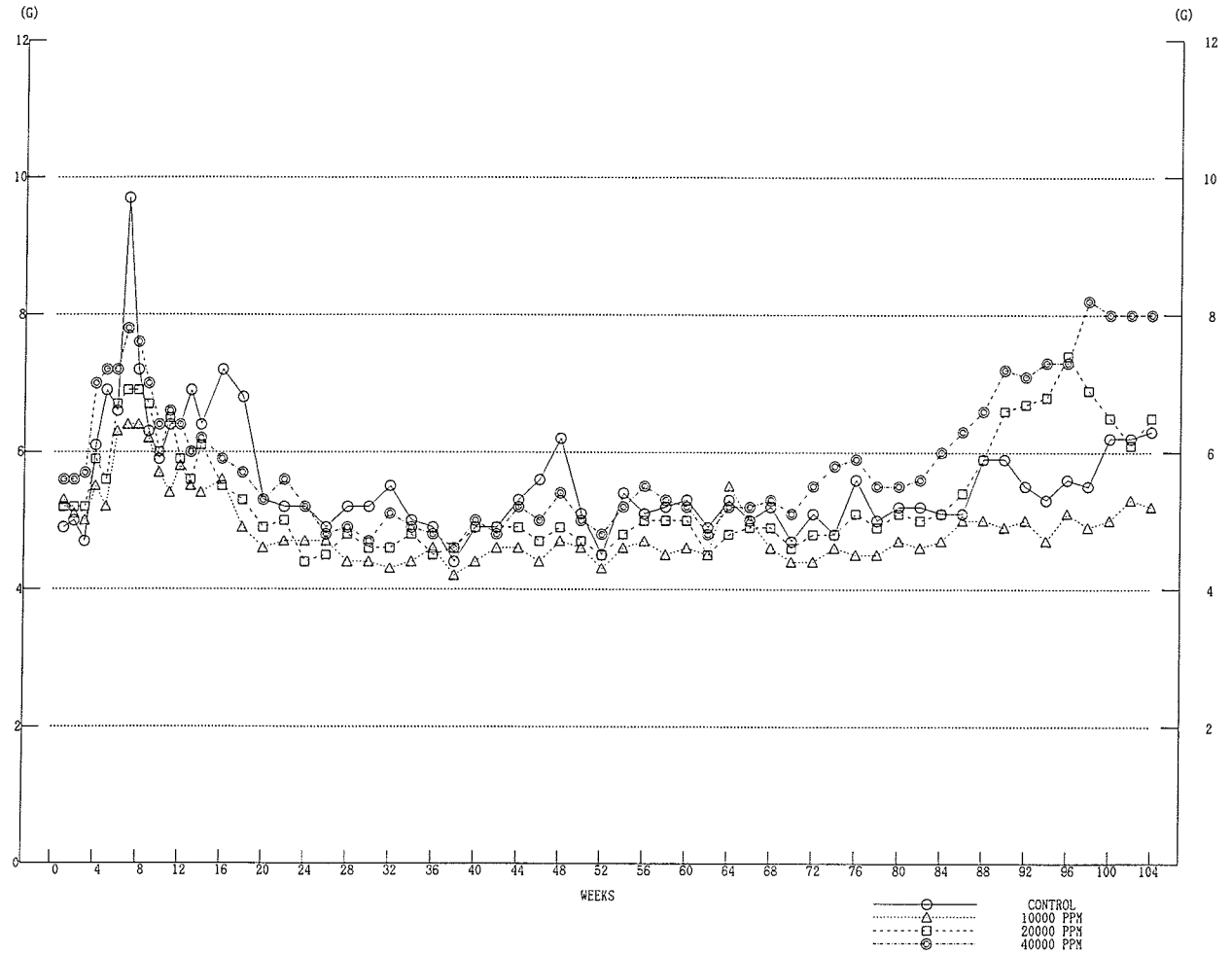

FIGURE 13 WATER CONSUMPTION : MOUSE : MALE (TWO-YEAR STUDY)

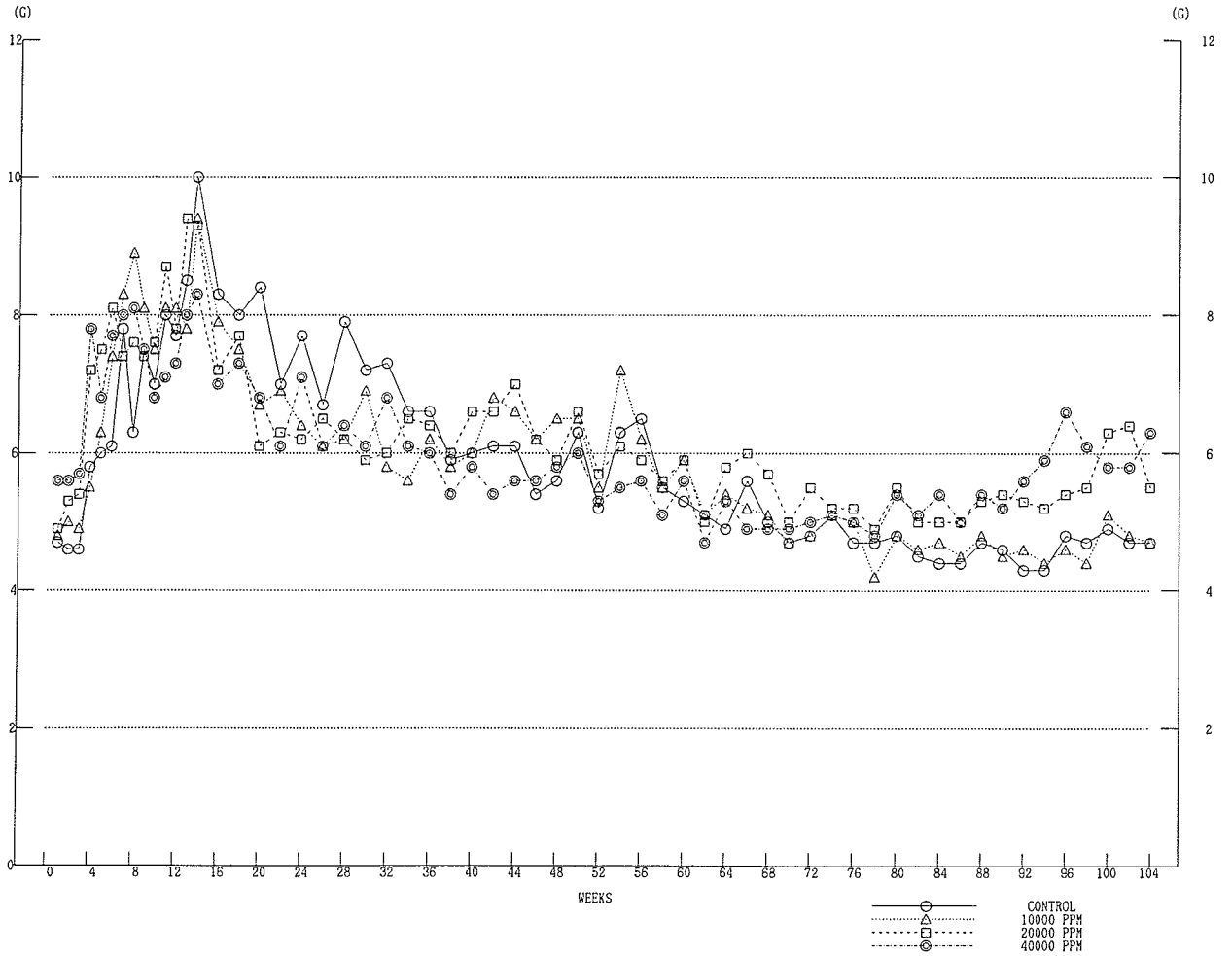

FIGURE 14 WATER CONSUMPTION : MOUSE FEMALE (TWO-YEAR STUDY)

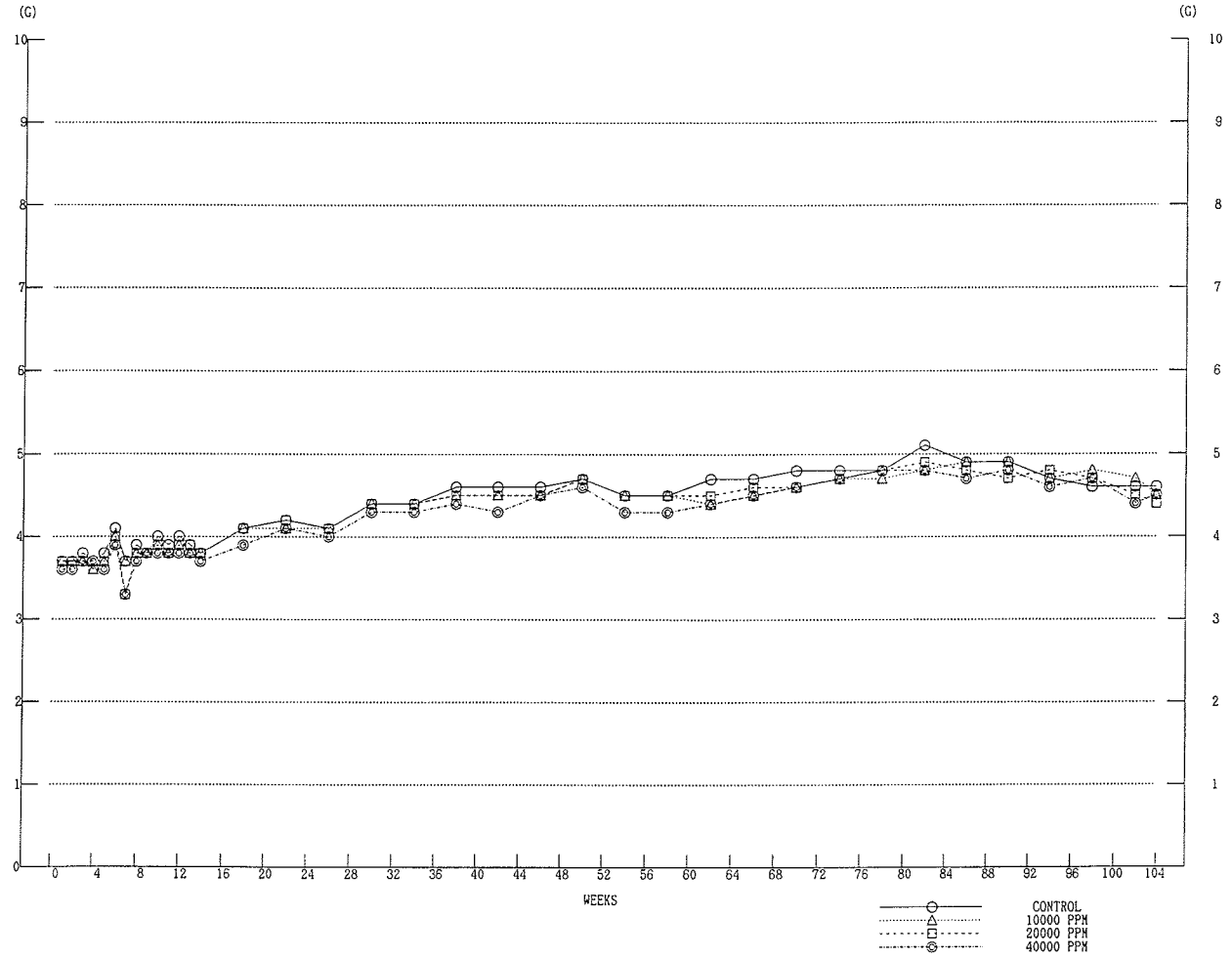

FIGURE 15 FOOD CONSUMPTION : MOUSE : MALE (TWO-YEAR STUDY)

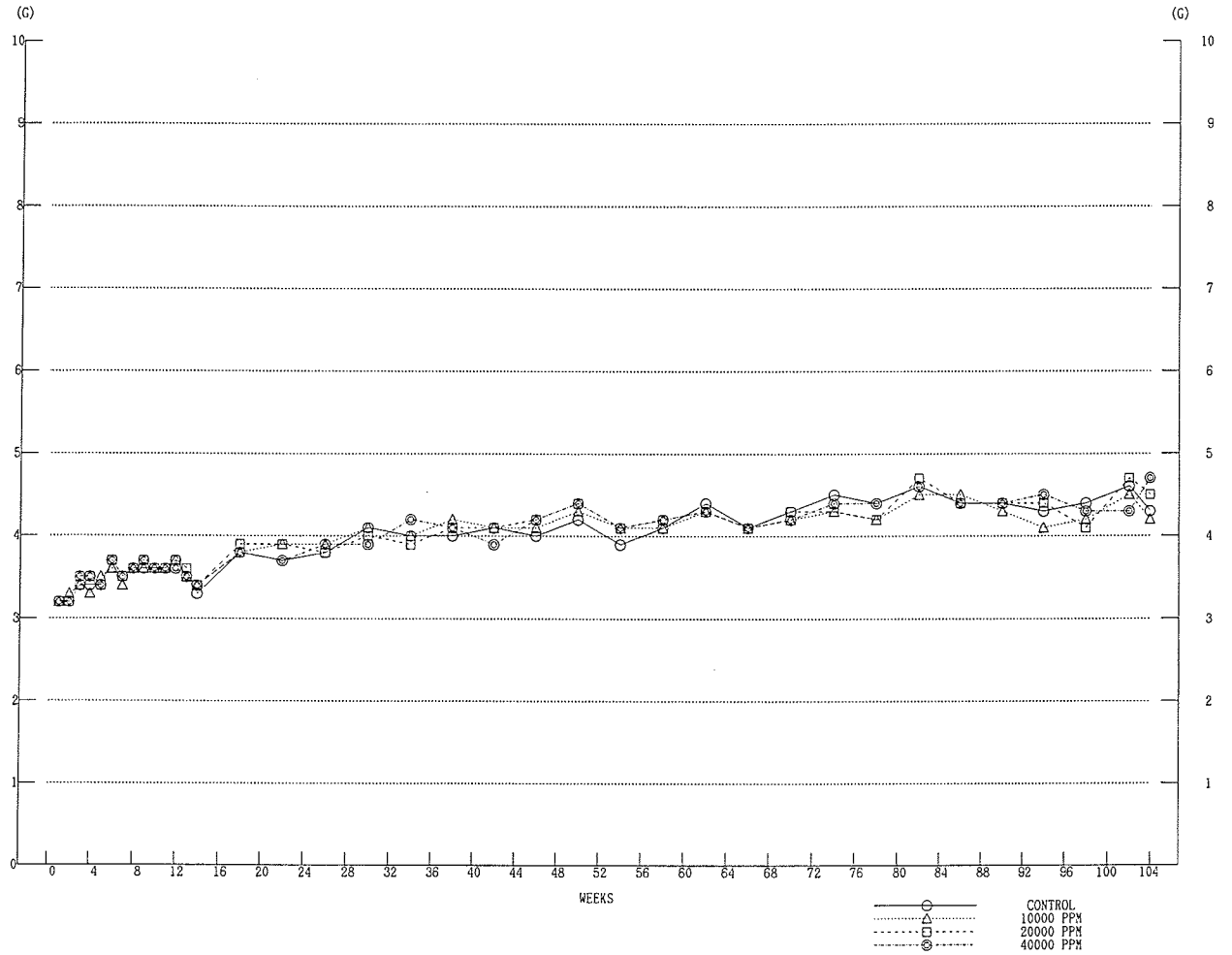

FIGURE 16 FOOD CONSUMPTION : MOUSE : FEMALE (TWO-YEAR STUDY)

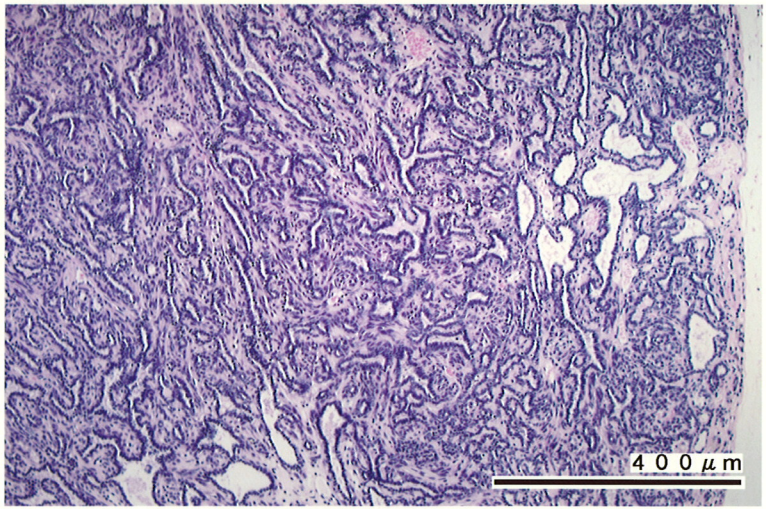

写真３　乳腺、腺癌
マウス、雌、40000ppm群、動物No.0225-2339
（H&E染色）

写真４　鼻腔（レベル３）、嗅腺の導管拡張
マウス、雄、40000ppm群、動物No.0225-1312
（H&E染色）