Summary of Drinking Water Carcinogenicity Study of β-Chloropropionic Acid in BDF_1 Mice

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Japan Bioassay Laboratory

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Labour of Japan. The tests were conducted by Japan Bioassay Laboratory (JBL) and the report was prepared by JBL and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Labour of Japan on December 28, 1994.

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

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Purpose, materials and methods

β-Chloropropionic acid (CAS No. 107-94-8) is a white plates or leaflets with a melting point of 41°C. It is soluble in water, alcohol, and chloroform.

The carcinogenicity and chronic toxicity of β-chloropropionic acid (purity : greater than 99%) were examined in B6D2F1/Crlj mice. Groups of test animals were administered β-chloropropionic acid in their drinking water for 2 years (104 weeks). Each group consisted of either 50 male or 50 female mice. The drinking water concentrations of β-chloropropionic acid were 0, 250, 1000 or 4000 ppm (w/w) for male and 0, 1000, 4000 or 16000 ppm for female. Both sexes were administered each concentration of β-chloropropionic acid. 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 β-chloropropionic acid used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by infrared spectrometry and gas chromatography before and after use to affirm its stability. The concentrations of β-chloropropionic acid in the drinking water were determined by gas chromatography at the time of preparation and on the 4th day after preparation while stored at room temperature. The animals were observed daily for clinical signs and mortality. Body weight, water consumption and food consumption were measured once a week for the first 14 weeks and every 2 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. Hematology and blood biochemistry analysis were performed 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 2-chloropropionic acid 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, water consumption, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present study was conducted with reference to the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

The survival rates of the females administered 16000 ppm β-chloropropionic acid were slightly higher than the controls. Growth rates of the males administered 4000 ppm and females administered 4000 ppm and above were suppressed. Water consumption was decreased in the males and females administered 1000 ppm and above most of the 2-year administration period. Food consumption was decreased in the males administered 4000 ppm in the females administered 16000 ppm most of the 2-year administration period.

The incidences of the malignant lymphoma in lymph node and in all organs were increased in male mice administered 1000 ppm β-chloropropionic acid and the hemangioma in all organs was increased in male mice administered 250 ppm β-chloropropionic acid. But these incidences were not dose related, so the incidence of the malignant lymphoma in lymph node and in all organs and the hemangioma in all organs can not be judged to be attributed to the β-chloropropionic acid administration. The histiocytic sarcoma in all organs in male mice was increased in dose dependently (Peto test). But the incidence was within the range of maximum incidence of the JBRC historical control data, so the incidence of the histiocytic sarcoma in all organs can not be judged to be attributed to the β-chloropropionic acid administration. No β-chloropropionic acid related increase in the incidence of neoplastic lesions was found in any of the β-chloropropionic acid administered groups of either sex compared with their respective controls. The incidences of hepatocellular carcinoma in males were suppressed.

In the non-neoplastic lesions, eosinophilic change in the respiratory epithelium in the nasal cavity in males administered 4000 ppm and in females administered 4000 ppm and above, eosinophilic change in the olfactory epithelium in the nasal cavity in females administered 16000 ppm were increased. Additionally, desquamation in pelvis in the kidney was increased in all female groups administered β-chloropropionic acid. The hyperplasia of glandular stomach was decreased in females administered 4000 ppm and above.

Conclusions

There was no evidence for carcinogenicity of β-chloropropionic acid in male or female mice.

Incidences of selected neoplastic lesions of male mice in the 2-year drinking water carcinogenicity study of β-chloropropionic acid

Dose (ppm)		0	250	1000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	6	11	2	6		
liver	hepatocellular adenoma	7	7	5	3		
all organs	hemangioma	1	7 *	2	2		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	4	5	7	5		
lymph node	malignant lymphoma	1	4	7 *	5		
liver	hepatocellular carcinoma	18	18	8	4 **		↓↓
	hemangiosarcoma	6	7	6	4		
all organs	histiocytic sarcoma	4	3	1	5	↑	
	malignant lymphoma	2	5	9 *	5		

Incidences of selected neoplastic lesions of female mice in the 2-year drinking water carcinogenicity study of β-chloropropionic acid

Dose (ppm)		0	1000	4000	16000	Peto test	Cochran-Armitage test
Number of examined animals		50	49	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	3	4	1	1		
pituitary	adenoma	7	4 [a)]	7	1 [a)]*		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	1	1	3	3		
lymph node	malignant lymphoma	16	13	13	9		
uterus	histiocytic sarcoma	9	2 *	6	7		
all organs	malignant lymphoma	17	16	15	10		

Significant difference

*: p≦0.05		**: p≦0.01		(Fisher test)
↑: p≦0.05	increase	↑↑: p≦0.01	increase	(Peto, Cochran-Armitage test)
↓: p≦0.05	decrease	↓↓: p≦0.01	decrease	(Cochran-Armitage test)

a: Number of examined animal was 48.

SELECTED TABLES

TABLE 14 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN MALE MOUSE (TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	250 ppm Av.Wt.	250 ppm % of cont. <50>	250 ppm No.of Surviv.	1000 ppm Av.Wt.	1000 ppm % of cont. <50>	1000 ppm No.of Surviv.	4000 ppm Av.Wt.	4000 ppm % of cont. <50>	4000 ppm No.of Surviv.
0	23.5 (50)	50/50	23.5 (50)	100	50/50	23.5 (50)	100	50/50	23.5 (50)	100	50/50
1	25.0 (50)	50/50	24.9 (50)	100	50/50	24.8 (50)	99	50/50	23.8 (50)	95	50/50
2	26.0 (50)	50/50	25.6 (50)	98	50/50	25.7 (50)	99	50/50	25.2 (50)	97	50/50
3	26.7 (50)	50/50	26.3 (49)	99	49/50	26.4 (50)	99	50/50	25.7 (50)	96	50/50
4	27.4 (50)	50/50	27.0 (49)	99	49/50	27.1 (50)	99	50/50	26.3 (50)	96	50/50
5	28.3 (50)	50/50	27.9 (49)	99	49/50	28.2 (50)	100	50/50	27.1 (50)	96	50/50
6	29.4 (50)	50/50	28.8 (49)	98	49/50	28.8 (50)	98	50/50	27.7 (50)	94	50/50
7	30.1 (50)	50/50	29.5 (49)	98	49/50	29.7 (50)	99	50/50	28.1 (50)	93	50/50
8	30.5 (50)	50/50	30.1 (49)	99	49/50	30.2 (50)	99	50/50	28.4 (50)	93	50/50
9	31.5 (50)	50/50	31.1 (49)	99	49/50	31.2 (50)	99	50/50	29.2 (50)	93	50/50
10	32.7 (50)	50/50	32.1 (49)	98	49/50	32.2 (50)	98	50/50	30.0 (50)	92	50/50
11	33.6 (50)	50/50	32.9 (49)	98	49/50	32.9 (50)	98	50/50	30.7 (50)	91	50/50
12	34.3 (50)	50/50	33.7 (49)	98	49/50	33.5 (50)	98	50/50	31.2 (50)	91	50/50
13	35.0 (50)	50/50	34.4 (49)	98	49/50	34.3 (50)	98	50/50	29.6 (50)	85	50/50
14	36.0 (50)	50/50	35.1 (49)	98	49/50	34.7 (50)	96	50/50	32.0 (50)	89	50/50
16	37.3 (50)	50/50	36.5 (49)	98	49/50	36.2 (50)	97	50/50	33.2 (50)	89	50/50
18	38.7 (50)	50/50	37.9 (49)	98	49/50	37.2 (50)	96	50/50	34.3 (50)	89	50/50
20	40.1 (50)	50/50	39.1 (49)	98	49/50	38.1 (50)	95	50/50	35.1 (50)	88	50/50
22	40.8 (50)	50/50	39.5 (49)	97	49/50	38.5 (50)	94	50/50	35.7 (50)	88	50/50
24	42.5 (50)	50/50	41.1 (49)	97	49/50	39.8 (50)	94	50/50	36.8 (50)	87	50/50
26	43.7 (50)	50/50	42.3 (49)	97	49/50	40.7 (50)	93	50/50	37.7 (50)	86	50/50
28	44.8 (50)	50/50	43.1 (49)	96	49/50	41.4 (50)	92	50/50	38.3 (50)	85	50/50
30	45.6 (50)	50/50	44.2 (49)	97	49/50	41.8 (50)	92	50/50	38.8 (50)	85	50/50
32	46.7 (50)	50/50	45.3 (49)	97	49/50	42.8 (50)	92	50/50	39.6 (50)	85	50/50
34	47.2 (50)	50/50	45.7 (49)	97	49/50	43.1 (50)	91	50/50	39.9 (50)	85	50/50
36	47.6 (50)	50/50	46.2 (49)	97	49/50	43.6 (50)	92	50/50	40.3 (50)	85	50/50
38	48.5 (50)	50/50	47.1 (49)	97	49/50	44.3 (50)	91	50/50	41.0 (50)	85	50/50
40	48.7 (50)	50/50	47.5 (49)	98	49/50	44.8 (50)	92	50/50	41.0 (49)	84	49/50
42	49.1 (50)	50/50	48.1 (48)	98	48/50	45.5 (50)	93	50/50	41.5 (49)	85	49/50
44	50.1 (50)	50/50	48.9 (48)	98	48/50	46.2 (50)	92	50/50	42.9 (48)	86	48/50
46	50.2 (50)	50/50	49.4 (48)	98	48/50	46.7 (50)	93	50/50	43.2 (48)	86	48/50
48	49.9 (50)	50/50	49.3 (48)	99	48/50	46.5 (50)	93	50/50	43.0 (48)	86	48/50
50	49.9 (50)	50/50	49.1 (48)	98	48/50	46.3 (50)	93	50/50	42.8 (48)	86	48/50
52	50.5 (49)	49/50	49.3 (48)	98	48/50	46.7 (50)	92	50/50	43.0 (48)	85	48/50
54	50.8 (49)	49/50	49.7 (48)	98	48/50	47.2 (50)	93	50/50	43.4 (48)	85	48/50
56	50.9 (49)	49/50	49.6 (48)	97	48/50	47.2 (50)	93	50/50	43.5 (48)	85	48/50
58	51.6 (49)	49/50	51.1 (48)	99	48/50	48.1 (50)	93	50/50	44.5 (48)	86	48/50
60	52.2 (49)	49/50	50.8 (48)	97	48/50	48.1 (50)	92	50/50	44.0 (48)	84	48/50
62	52.3 (49)	49/50	50.9 (48)	97	48/50	48.5 (50)	93	50/50	44.4 (48)	85	48/50
64	52.2 (49)	49/50	50.5 (48)	97	48/50	48.7 (50)	93	50/50	44.5 (48)	85	48/50
66	52.4 (49)	49/50	50.8 (47)	97	47/50	48.6 (50)	93	50/50	44.2 (47)	84	47/50
68	52.7 (49)	49/50	51.2 (47)	97	47/50	49.1 (50)	93	50/50	44.4 (47)	84	47/50
70	52.2 (49)	49/50	50.7 (47)	97	47/50	48.7 (50)	93	50/50	44.1 (47)	84	47/50
72	52.8 (49)	49/50	50.8 (47)	96	47/50	49.1 (50)	93	50/50	44.2 (47)	84	47/50
74	53.5 (49)	49/50	51.4 (46)	96	46/50	49.6 (50)	93	50/50	44.5 (47)	83	47/50
76	53.5 (49)	49/50	51.6 (46)	96	46/50	49.7 (50)	93	49/50	44.6 (47)	83	47/50
78	53.1 (49)	49/50	51.1 (45)	96	45/50	49.2 (49)	93	49/50	44.0 (46)	83	46/50
80	52.6 (49)	49/50	51.2 (44)	97	44/50	49.4 (49)	94	49/50	44.2 (46)	84	46/50
82	53.6 (49)	49/50	51.9 (44)	97	44/50	50.2 (49)	94	49/50	44.5 (46)	83	45/50
84	52.2 (49)	48/50	51.6 (44)	99	44/50	50.0 (48)	96	48/50	44.2 (45)	85	45/50
86	53.4 (47)	47/50	51.3 (43)	96	43/50	49.6 (48)	93	48/50	44.2 (45)	83	45/50
88	53.6 (47)	47/50	51.0 (43)	95	43/50	49.8 (48)	93	48/50	44.6 (45)	83	45/50
90	53.1 (45)	45/50	50.5 (43)	95	43/50	49.1 (48)	92	48/50	44.0 (44)	83	44/50
92	52.9 (45)	45/50	51.1 (40)	97	40/50	48.3 (48)	91	48/50	43.6 (44)	82	44/50
94	52.1 (44)	44/50	50.1 (40)	96	40/50	47.6 (48)	91	48/50	42.8 (44)	82	44/50
96	51.3 (44)	44/50	50.0 (38)	97	38/50	47.1 (46)	92	46/50	42.3 (44)	82	44/50
98	49.9 (42)	41/50	49.0 (36)	98	36/50	46.2 (43)	93	43/50	41.8 (43)	84	43/50
100	50.6 (41)	41/50	49.1 (34)	97	34/50	46.7 (41)	92	40/50	41.4 (42)	82	42/50
102	49.3 (39)	39/50	47.7 (34)	97	34/50	45.9 (39)	93	39/50	40.7 (42)	83	42/50
104	48.5 (38)	38/50	47.3 (33)	98	33/50	45.9 (38)	95	38/50	40.5 (41)	84	40/50

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

TABLE 15 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN FEMALE MOUSE

(TWO-YEAR STUDY)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	1000 ppm Av.Wt.	1000 ppm % of cont. <49>	1000 ppm No.of Surviv.	4000 ppm Av.Wt.	4000 ppm % of cont. <50>	4000 ppm No.of Surviv.	16000 ppm Av.Wt.	16000 ppm % of cont. <50>	16000 ppm No.of Surviv.
0	18.3 (50)	50/50	18.3 (49)	100	50/50	18.3 (50)	100	50/50	18.3 (50)	100	50/50
1	19.7 (50)	50/50	19.7 (49)	100	50/50	19.2 (50)	97	50/50	17.7 (50)	90	50/50
2	20.3 (50)	50/50	20.7 (49)	102	50/50	20.3 (50)	100	50/50	18.7 (50)	92	50/50
3	20.6 (50)	50/50	20.9 (49)	101	50/50	20.5 (50)	100	50/50	19.0 (50)	92	50/50
4	21.3 (50)	50/50	21.4 (49)	100	50/50	21.1 (50)	99	50/50	19.4 (50)	91	50/50
5	21.7 (50)	50/50	22.0 (49)	101	50/50	21.5 (50)	99	50/50	19.9 (50)	92	50/50
6	22.5 (50)	50/50	22.7 (49)	101	50/50	22.0 (50)	98	50/50	20.4 (50)	91	50/50
7	23.3 (50)	50/50	23.1 (49)	99	50/50	22.2 (50)	95	50/50	21.0 (50)	90	50/50
8	23.1 (50)	50/50	23.3 (49)	101	50/50	22.5 (50)	97	50/50	21.2 (50)	92	50/50
9	23.5 (50)	50/50	23.8 (49)	101	50/50	23.0 (50)	98	50/50	21.4 (50)	91	50/50
10	24.2 (50)	50/50	24.2 (49)	100	50/50	23.4 (50)	97	50/50	21.9 (50)	90	50/50
11	24.2 (50)	50/50	24.1 (49)	100	50/50	23.3 (50)	96	50/50	22.2 (50)	92	50/50
12	24.9 (50)	50/50	24.5 (49)	98	50/50	23.6 (50)	95	50/50	22.5 (50)	90	50/50
13	24.8 (50)	50/50	24.9 (49)	100	50/50	23.9 (50)	96	50/50	23.3 (50)	94	50/50
14	25.6 (50)	50/50	25.2 (49)	98	50/50	24.1 (50)	94	50/50	23.2 (50)	91	50/50
16	25.8 (50)	50/50	25.6 (49)	99	50/50	24.9 (50)	97	50/50	23.0 (50)	89	50/50
18	26.7 (50)	50/50	26.0 (49)	97	50/50	24.9 (50)	93	50/50	23.0 (50)	86	50/50
20	26.9 (50)	50/50	26.8 (49)	100	50/50	25.6 (50)	95	50/50	23.7 (50)	88	50/50
22	28.4 (50)	50/50	28.0 (49)	99	50/50	26.4 (50)	93	50/50	24.2 (50)	85	50/50
24	28.8 (50)	50/50	28.2 (49)	98	50/50	26.6 (50)	92	50/50	24.5 (50)	85	50/50
26	29.2 (50)	50/50	28.5 (49)	98	49/50	27.0 (50)	92	50/50	24.9 (50)	85	50/50
28	29.7 (50)	50/50	29.1 (48)	98	49/50	27.2 (50)	92	50/50	25.0 (50)	84	50/50
30	30.0 (50)	50/50	29.5 (48)	98	49/50	27.6 (50)	92	50/50	25.0 (50)	83	50/50
32	30.9 (50)	50/50	30.6 (48)	99	49/50	28.1 (50)	91	50/50	25.5 (50)	83	50/50
34	31.8 (50)	50/50	30.5 (48)	96	49/50	28.6 (50)	90	50/50	25.5 (50)	80	50/50
36	32.2 (50)	50/50	30.6 (48)	95	49/50	28.3 (50)	88	50/50	25.7 (50)	80	50/50
38	33.1 (50)	50/50	31.5 (48)	95	49/50	29.6 (49)	89	49/50	26.0 (50)	79	50/50
40	32.8 (50)	50/50	31.5 (48)	96	49/50	29.2 (49)	89	49/50	25.9 (50)	79	50/50
42	33.4 (50)	50/50	31.7 (48)	95	49/50	29.6 (49)	89	49/50	26.5 (50)	79	50/50
44	34.2 (50)	50/50	32.3 (48)	94	49/50	29.7 (49)	87	49/50	26.4 (50)	77	50/50
46	34.0 (50)	50/50	32.4 (48)	95	49/50	30.0 (49)	88	49/50	26.2 (50)	77	50/50
48	33.7 (50)	50/50	32.4 (48)	96	49/50	30.0 (49)	89	49/50	26.3 (50)	78	50/50
50	34.2 (50)	50/50	32.5 (48)	95	49/50	29.8 (49)	87	49/50	26.5 (50)	77	50/50
52	35.0 (50)	50/50	32.6 (48)	93	49/50	30.4 (49)	87	49/50	26.7 (50)	76	50/50
54	35.1 (50)	50/50	33.2 (48)	95	49/50	30.5 (49)	87	49/50	26.7 (50)	76	50/50
56	34.9 (50)	50/50	32.6 (48)	93	49/50	30.3 (49)	87	49/50	26.7 (50)	77	50/50
58	35.5 (50)	50/50	33.4 (48)	94	49/50	30.9 (49)	87	49/50	26.8 (50)	75	50/50
60	35.6 (50)	50/50	32.8 (48)	92	49/50	30.4 (49)	85	49/50	26.9 (50)	76	50/50
62	36.4 (50)	50/50	33.5 (48)	92	49/50	30.7 (49)	84	49/50	26.9 (50)	74	50/50
64	36.9 (50)	50/50	33.1 (48)	90	49/50	31.1 (49)	84	49/50	26.8 (50)	73	50/50
66	37.2 (49)	49/50	33.5 (47)	90	48/50	30.5 (49)	82	49/50	26.8 (50)	72	50/50
68	37.2 (48)	48/50	33.6 (47)	90	48/50	31.4 (49)	84	49/50	27.3 (50)	73	50/50
70	36.2 (47)	47/50	33.0 (47)	91	48/50	30.8 (49)	85	49/50	26.5 (50)	73	50/50
72	36.9 (47)	47/50	33.2 (47)	90	48/50	31.2 (48)	85	48/50	26.7 (50)	72	50/50
74	37.0 (46)	46/50	33.5 (47)	91	48/50	31.1 (48)	84	48/50	26.8 (50)	72	50/50
76	36.9 (46)	46/50	33.0 (47)	89	48/50	31.2 (47)	85	47/50	27.0 (50)	73	50/50
78	36.5 (46)	46/50	33.2 (46)	91	47/50	31.1 (46)	85	46/50	26.3 (48)	72	48/50
80	37.2 (45)	45/50	33.1 (46)	89	46/49	31.2 (46)	84	46/50	26.5 (48)	71	48/50
82	38.3 (45)	45/50	34.5 (45)	90	45/49	32.5 (45)	85	44/50	27.4 (48)	72	48/50
84	38.1 (44)	44/50	33.8 (44)	89	43/49	31.5 (43)	83	43/50	26.8 (46)	70	46/50
86	37.8 (41)	40/50	33.9 (43)	90	43/49	32.0 (42)	85	42/50	26.6 (46)	70	45/50
88	38.1 (39)	39/50	34.4 (41)	90	41/49	32.4 (42)	85	42/50	27.1 (44)	71	44/50
90	37.6 (39)	39/50	34.3 (41)	91	41/49	31.9 (42)	85	42/50	26.8 (44)	71	44/50
92	38.0 (37)	37/50	34.7 (40)	91	40/49	32.4 (38)	85	38/50	27.4 (43)	72	43/50
94	37.3 (36)	36/50	33.5 (40)	90	39/49	31.6 (37)	85	36/50	27.2 (42)	73	42/50
96	37.8 (34)	34/50	33.6 (38)	89	38/49	32.6 (36)	86	36/50	27.0 (41)	71	41/50
98	37.7 (31)	31/50	32.7 (37)	87	37/49	32.1 (35)	85	35/50	27.0 (41)	72	41/50
100	37.5 (31)	30/50	33.3 (36)	89	36/49	31.6 (35)	84	35/50	26.9 (40)	72	40/50
102	36.8 (28)	28/50	32.6 (34)	89	34/49	32.5 (32)	88	32/50	26.4 (39)	72	39/50
104	36.1 (27)	27/50	32.5 (33)	90	33/49	31.6 (30)	88	30/50	26.4 (39)	73	39/50

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

TABLE 16 INCIDENCE AND TIME OF MASS OCCURRENCE IN CLINICAL OBSERVATION :MOUSE :MALE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
The kind of mass										
External mass	Control	0/50	0/50	0/50	2/50	2/49	2/49	2/49	6/45	6/50 (2/12)
	250 ppm	0/50	0/49	0/49	3/49	1/48	1/47	5/44	4/40	9/50 (3/17)
	1000 ppm	0/50	0/50	0/50	0/50	0/50	1/50	2/49	1/48	2/50 (0/12)
	4000 ppm	0/50	0/50	0/50	1/49	1/48	1/47	6/46	6/44	7/50 (1/10)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/49	1/49	2/49	6/45	6/50 (2/12)
	250 ppm	1/50	2/49	2/49	2/49	1/48	1/47	4/44	5/40	8/50 (6/17)
	1000 ppm	0/50	0/50	0/50	1/50	1/50	2/50	3/49	6/48	10/50 (4/12)
	4000 ppm	0/50	1/50	1/50	1/49	1/48	0/47	0/46	4/44	5/50 (1/10)

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 17 INCIDENCE AND TIME OF MASS OCCURRENCE IN CLINICAL OBSERVATION :MOUSE :FEMALE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
The kind of mass										
External mass	Control	0/50	0/50	0/50	3/50	1/50	1/49	2/46	4/37	10/50 (8/23)
	1000 ppm	0/49	0/49	0/49	3/49	1/49	1/47	2/46	4/40	8/49 (2/17)
	4000 ppm	0/50	0/50	0/50	0/49	1/49	1/49	1/46	1/38	3/50 (2/20)
	16000 ppm	0/50	0/50	0/50	0/50	0/50	1/50	1/48	2/43	2/50 (0/11)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	1/49	3/46	5/37	7/50 (5/23)
	1000 ppm	0/49	1/49	0/49	2/49	2/49	2/47	6/46	7/40	13/49 (8/17)
	4000 ppm	0/50	0/50	0/50	0/49	1/49	2/49	9/46	6/38	12/50 (8/20)
	16000 ppm	0/50	0/50	0/50	0/50	2/50	3/50	2/48	4/43	7/50 (4/11)

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 WATER CONSUMPTION IN MALE MOUSE(TWO-YEAR STUDY)

Week-Day on Study	Control Av.WC.	Control No.of Surviv. <50>	250 ppm Av.WC.	250 ppm % of cont. <50>	250 ppm No.of Surviv.	1000 ppm Av.WC.	1000 ppm % of cont. <50>	1000 ppm No.of Surviv.	4000 ppm Av.WC.	4000 ppm % of cont. <50>	4000 ppm No.of Surviv.
1-3	4.0 (50)	50/50	3.8 (50)	95	50/50	3.9 (50)	98	50/50	3.4 (50)	85	50/50
1-7	4.2 (50)	50/50	3.9 (50)	93	50/50	4.0 (50)	95	50/50	2.8 (50)	67	50/50
2-3	4.3 (50)	50/50	4.1 (50)	95	50/50	4.3 (50)	100	50/50	3.2 (50)	74	50/50
2-7	4.2 (50)	50/50	4.0 (50)	95	50/50	4.2 (50)	100	50/50	3.2 (50)	76	50/50
3-3	4.0 (50)	50/50	4.0 (50)	100	49/50	3.9 (50)	98	50/50	3.0 (50)	75	50/50
3-7	4.2 (50)	50/50	4.0 (49)	95	49/50	4.0 (50)	95	50/50	3.1 (50)	74	50/50
4-3	4.2 (50)	50/50	4.2 (49)	100	49/50	4.1 (50)	98	50/50	3.2 (50)	76	50/50
4-7	4.2 (50)	50/50	4.0 (47)	95	49/50	4.0 (50)	95	50/50	3.3 (50)	79	50/50
5-3	4.0 (50)	50/50	4.0 (49)	100	49/50	3.7 (50)	93	50/50	3.4 (50)	85	50/50
5-7	4.1 (50)	50/50	4.3 (49)	105	49/50	4.0 (50)	98	50/50	3.3 (50)	80	50/50
6-3	4.0 (50)	50/50	3.8 (49)	95	49/50	3.5 (50)	88	50/50	3.2 (50)	80	50/50
6-7	4.1 (50)	50/50	4.3 (49)	105	49/50	3.9 (50)	95	50/50	3.5 (50)	85	50/50
7-7	4.1 (50)	50/50	4.1 (48)	100	49/50	3.9 (50)	95	50/50	3.4 (50)	83	50/50
8-3	4.0 (50)	50/50	4.0 (49)	100	49/50	3.7 (50)	93	50/50	3.1 (50)	78	50/50
8-7	4.0 (50)	50/50	4.2 (49)	105	49/50	3.8 (50)	95	50/50	3.3 (50)	83	50/50
9-3	4.1 (50)	50/50	4.1 (49)	100	49/50	3.7 (50)	90	50/50	3.4 (50)	83	50/50
9-7	4.0 (50)	50/50	4.0 (48)	100	49/50	3.7 (50)	93	50/50	3.5 (49)	88	50/50
10-3	4.1 (50)	50/50	4.2 (49)	102	49/50	3.8 (50)	93	50/50	3.6 (50)	88	50/50
10-7	4.0 (50)	50/50	3.9 (49)	98	49/50	3.6 (50)	90	50/50	3.4 (49)	85	50/50
11-3	4.1 (50)	50/50	4.1 (49)	100	49/50	3.7 (50)	90	50/50	3.5 (50)	85	50/50
11-7	3.9 (50)	50/50	3.9 (49)	100	49/50	3.6 (50)	92	50/50	3.4 (50)	87	50/50
12-3	3.9 (50)	50/50	3.9 (49)	100	49/50	3.7 (50)	95	50/50	3.1 (50)	79	50/50
12-7	3.8 (50)	50/50	3.8 (48)	100	49/50	3.6 (50)	95	50/50	3.2 (50)	84	50/50
13-3	3.9 (50)	50/50	4.0 (49)	103	49/50	3.6 (50)	92	50/50	3.4 (50)	87	50/50
13-7	3.6 (50)	50/50	3.5 (48)	97	49/50	3.3 (50)	92	50/50	1.7 (50)	47	50/50
14-3	3.7 (50)	50/50	3.8 (49)	103	49/50	3.4 (50)	92	50/50	3.3 (50)	89	50/50
14-7	3.6 (50)	50/50	3.7 (49)	103	49/50	3.4 (50)	94	50/50	3.0 (50)	83	50/50
16-7	3.6 (50)	50/50	3.6 (49)	100	49/50	3.4 (50)	94	50/50	2.8 (50)	78	50/50
18-7	3.5 (50)	50/50	3.6 (49)	103	49/50	3.3 (50)	94	50/50	2.7 (50)	77	50/50
20-7	3.5 (48)	50/50	3.5 (49)	100	49/50	3.2 (50)	91	50/50	2.7 (50)	77	50/50
22-7	3.4 (50)	50/50	3.5 (49)	103	49/50	3.3 (50)	97	50/50	2.7 (50)	79	50/50
24-7	3.5 (50)	50/50	3.4 (48)	97	49/50	3.2 (50)	91	50/50	2.6 (50)	74	50/50
26-7	3.5 (50)	50/50	3.4 (48)	97	49/50	3.2 (50)	91	50/50	2.7 (50)	77	50/50
28-7	3.7 (50)	50/50	3.8 (49)	103	49/50	3.4 (50)	92	50/50	2.9 (50)	78	50/50
30-7	3.7 (50)	50/50	3.9 (49)	105	49/50	3.4 (50)	92	50/50	2.8 (50)	76	50/50
32-7	3.8 (50)	50/50	3.6 (48)	95	49/50	3.4 (49)	89	50/50	2.8 (50)	74	50/50
34-7	3.7 (50)	50/50	3.6 (49)	97	49/50	3.3 (50)	89	50/50	2.8 (50)	76	50/50
36-7	3.9 (50)	50/50	3.9 (49)	100	49/50	3.6 (50)	92	50/50	3.0 (50)	77	50/50
38-7	3.8 (50)	50/50	3.8 (48)	100	49/50	3.6 (50)	95	50/50	2.9 (50)	76	50/50
40-7	3.9 (50)	50/50	3.9 (48)	100	49/50	3.5 (50)	90	50/50	2.9 (49)	74	49/50
42-7	3.9 (50)	50/50	4.0 (48)	103	48/50	3.5 (50)	90	50/50	3.0 (49)	77	49/50
44-7	4.0 (50)	50/50	3.9 (47)	98	48/50	3.6 (50)	90	50/50	3.0 (48)	75	48/50
46-7	3.9 (50)	50/50	3.9 (47)	100	48/50	3.6 (50)	92	50/50	3.0 (48)	77	48/50
48-7	4.0 (50)	50/50	3.9 (47)	98	48/50	3.5 (50)	88	50/50	2.9 (48)	73	48/50
50-7	4.0 (50)	50/50	4.0 (46)	100	48/50	3.6 (50)	90	50/50	3.1 (48)	78	48/50
52-7	4.0 (49)	49/50	4.1 (47)	103	48/50	3.6 (50)	90	50/50	3.0 (48)	75	48/50
54-7	4.0 (49)	49/50	4.0 (47)	100	48/50	3.6 (50)	90	50/50	3.3 (48)	83	48/50
56-7	4.3 (49)	49/50	4.2 (47)	98	48/50	3.7 (50)	86	50/50	3.2 (48)	74	48/50
58-7	4.3 (49)	49/50	4.3 (48)	100	48/50	3.6 (50)	84	50/50	3.1 (48)	72	48/50
60-7	4.0 (49)	49/50	4.0 (47)	100	48/50	3.6 (50)	90	50/50	3.1 (48)	78	48/50
62-7	3.8 (49)	49/50	4.1 (48)	108	48/50	3.6 (50)	95	50/50	3.2 (48)	84	48/50
64-7	4.6 (49)	49/50	4.7 (47)	102	48/50	4.0 (50)	87	50/50	3.4 (48)	74	48/50
66-7	4.5 (49)	49/50	4.4 (45)	98	47/50	3.9 (50)	87	50/50	3.3 (47)	73	47/50
68-7	4.6 (49)	49/50	4.6 (46)	100	47/50	3.8 (50)	83	50/50	3.4 (47)	74	47/50
70-7	4.6 (49)	49/50	4.6 (47)	100	47/50	3.8 (50)	83	50/50	3.3 (47)	72	47/50
72-7	4.2 (49)	49/50	4.4 (47)	105	47/50	3.7 (50)	88	50/50	3.2 (47)	76	47/50
74-7	4.3 (49)	49/50	4.5 (46)	105	46/50	3.8 (50)	88	50/50	3.2 (47)	74	47/50
76-7	4.4 (49)	49/50	4.5 (45)	102	46/50	3.8 (50)	86	49/50	3.2 (47)	73	47/50
78-7	4.6 (49)	49/50	4.7 (43)	102	45/50	4.0 (49)	87	49/50	3.5 (46)	76	46/50
80-7	4.9 (49)	49/50	4.8 (44)	98	44/50	4.1 (49)	84	49/50	3.5 (46)	71	46/50
82-7	4.9 (49)	49/50	4.9 (44)	100	44/50	4.0 (49)	82	49/50	3.4 (46)	69	45/50
84-7	4.7 (48)	48/50	4.8 (42)	102	44/50	4.2 (48)	89	48/50	3.4 (45)	72	45/50
86-7	4.9 (47)	47/50	4.8 (42)	98	43/50	4.3 (48)	88	48/50	3.5 (45)	71	45/50
88-7	5.0 (46)	47/50	5.0 (41)	100	43/50	4.3 (48)	86	48/50	3.4 (45)	68	45/50
90-7	4.6 (45)	45/50	4.8 (41)	104	43/50	4.0 (48)	87	48/50	3.3 (44)	72	44/50
92-7	4.9 (45)	45/50	4.9 (38)	100	40/50	4.1 (48)	84	48/50	3.4 (44)	69	44/50
94-7	4.9 (44)	44/50	4.7 (37)	96	40/50	3.9 (48)	80	48/50	3.3 (44)	67	44/50
96-7	5.0 (42)	44/50	4.9 (35)	98	38/50	4.1 (46)	82	46/50	3.4 (44)	68	44/50
98-7	4.9 (42)	41/50	5.0 (36)	102	36/50	3.8 (45)	78	43/50	3.4 (44)	69	43/50
100-7	4.8 (39)	41/50	4.8 (35)	100	34/50	4.1 (41)	85	40/50	3.3 (42)	69	42/50
102-7	5.1 (37)	39/50	4.8 (34)	94	34/50	4.1 (39)	80	39/50	3.5 (42)	69	42/50
104-7	5.1 (36)	38/50	5.2 (32)	102	33/50	4.2 (38)	82	38/50	3.6 (41)	71	40/50

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

TABLE 19 WATER CONSUMPTION IN FEMALE MOUSE(TWO-YEAR STUDY)

Week-Day on Study	Control Av.WC.	Control No.of Surviv. <50>	1000 ppm Av.WC.	1000 ppm % of cont. <50>	1000 ppm No.of Surviv.	4000 ppm Av.WC.	4000 ppm % of cont. <50>	4000 ppm No.of Surviv.	16000 ppm Av.WC.	16000 ppm % of cont. <50>	16000 ppm No.of Surviv.
1-3	3.7 (50)	50/50	3.7 (50)	100	50/50	3.1 (50)	84	50/50	1.4 (50)	38	50/50
1-7	4.1 (50)	50/50	3.9 (50)	95	50/50	2.8 (50)	68	50/50	1.9 (50)	46	50/50
2-3	3.9 (50)	50/50	3.8 (50)	97	50/50	3.1 (50)	79	50/50	2.1 (50)	54	50/50
2-7	3.9 (50)	50/50	3.7 (50)	95	50/50	2.9 (50)	74	50/50	2.0 (50)	51	50/50
3-3	3.6 (50)	50/50	3.5 (50)	97	50/50	2.9 (50)	81	50/50	1.8 (50)	50	50/50
3-7	3.8 (50)	50/50	3.9 (50)	103	50/50	3.1 (50)	82	50/50	2.0 (50)	53	50/50
4-3	3.9 (50)	50/50	4.1 (50)	105	50/50	3.2 (50)	82	50/50	2.1 (50)	54	50/50
4-7	4.2 (50)	50/50	4.1 (47)	98	50/50	3.3 (50)	79	50/50	2.1 (50)	50	50/50
5-3	4.0 (50)	50/50	4.2 (49)	105	50/50	3.2 (50)	80	50/50	2.3 (50)	58	50/50
5-7	4.2 (50)	50/50	4.2 (48)	100	50/50	3.2 (50)	76	50/50	2.3 (50)	55	50/50
6-3	4.1 (50)	50/50	4.3 (50)	105	50/50	3.3 (50)	80	50/50	2.4 (50)	59	50/50
6-7	4.3 (50)	50/50	4.4 (47)	102	50/50	3.3 (50)	77	50/50	2.5 (50)	58	50/50
7-7	4.4 (50)	50/50	4.4 (47)	100	50/50	3.3 (50)	75	50/50	2.2 (50)	50	50/50
8-3	4.0 (50)	50/50	4.1 (49)	103	50/50	3.4 (50)	85	50/50	2.3 (50)	58	50/50
8-7	4.3 (50)	50/50	4.3 (49)	100	50/50	3.4 (50)	79	50/50	2.3 (50)	53	50/50
9-3	4.1 (50)	50/50	4.3 (50)	105	50/50	3.3 (50)	80	50/50	2.3 (50)	56	50/50
9-7	4.1 (50)	50/50	4.3 (49)	105	50/50	3.6 (49)	88	50/50	2.4 (50)	59	50/50
10-3	4.1 (50)	50/50	4.4 (50)	107	50/50	3.6 (50)	88	50/50	2.4 (50)	59	50/50
10-7	4.0 (50)	50/50	4.3 (49)	108	50/50	3.5 (49)	88	50/50	2.4 (50)	60	50/50
11-3	4.0 (50)	50/50	4.2 (50)	105	50/50	3.4 (50)	85	50/50	2.2 (50)	55	50/50
11-7	4.1 (50)	50/50	4.0 (50)	98	50/50	3.5 (50)	85	50/50	2.4 (50)	59	50/50
12-3	4.0 (50)	50/50	4.1 (50)	103	50/50	3.5 (50)	88	50/50	2.3 (50)	58	50/50
12-7	4.1 (50)	50/50	4.1 (49)	100	50/50	3.5 (49)	85	50/50	2.4 (50)	59	50/50
13-3	4.0 (50)	50/50	4.1 (50)	103	50/50	3.4 (50)	85	50/50	2.4 (50)	60	50/50
13-7	3.9 (50)	50/50	4.1 (50)	105	50/50	3.5 (50)	90	50/50	3.9 (50)	100	50/50
14-3	4.1 (50)	50/50	4.0 (50)	98	50/50	3.5 (50)	85	50/50	2.2 (50)	54	50/50
14-7	4.1 (50)	50/50	4.0 (50)	98	50/50	3.4 (50)	83	50/50	2.6 (50)	63	50/50
16-7	4.1 (50)	50/50	4.0 (49)	98	50/50	3.4 (49)	83	50/50	2.5 (50)	61	50/50
18-7	4.1 (50)	50/50	3.9 (49)	95	50/50	3.2 (50)	78	50/50	2.5 (50)	61	50/50
20-7	4.1 (50)	50/50	3.8 (48)	93	50/50	3.2 (50)	78	50/50	2.5 (50)	61	50/50
22-7	4.1 (50)	50/50	3.7 (49)	90	50/50	3.2 (49)	78	50/50	2.5 (50)	61	50/50
24-7	4.0 (49)	50/50	3.6 (49)	90	50/50	3.0 (50)	75	50/50	2.3 (50)	58	50/50
26-7	3.8 (48)	50/50	3.4 (49)	89	49/50	3.0 (49)	79	50/50	2.3 (50)	61	50/50
28-7	4.1 (50)	50/50	3.7 (47)	90	49/50	3.2 (50)	78	50/50	2.6 (50)	63	50/50
30-7	4.2 (49)	50/50	4.2 (47)	100	49/50	3.8 (49)	90	50/50	3.1 (50)	74	50/50
32-7	3.9 (49)	50/50	3.5 (46)	90	49/50	3.1 (49)	79	50/50	2.4 (50)	62	50/50
34-7	3.8 (48)	50/50	3.6 (48)	95	49/50	3.2 (50)	84	50/50	2.4 (50)	63	50/50
36-7	4.0 (50)	50/50	3.9 (48)	98	49/50	3.2 (49)	80	50/50	2.5 (50)	63	50/50
38-7	3.9 (49)	50/50	3.7 (48)	95	49/50	3.2 (48)	82	49/50	2.5 (50)	64	50/50
40-7	4.0 (50)	50/50	3.7 (47)	93	49/50	3.2 (48)	80	49/50	2.6 (50)	65	50/50
42-7	4.1 (50)	50/50	3.7 (48)	90	49/50	3.3 (49)	80	49/50	2.5 (50)	61	50/50
44-7	4.1 (50)	50/50	3.5 (47)	85	49/50	3.2 (49)	78	49/50	2.5 (50)	61	50/50
46-7	3.9 (49)	50/50	3.6 (48)	92	49/50	3.2 (49)	82	49/50	2.3 (50)	59	50/50
48-7	4.0 (50)	50/50	3.5 (47)	88	49/50	3.1 (49)	78	49/50	2.4 (50)	60	50/50
50-7	4.0 (50)	50/50	3.6 (48)	90	49/50	3.2 (48)	80	49/50	2.6 (50)	65	50/50
52-7	4.1 (50)	50/50	3.5 (47)	85	49/50	3.2 (49)	78	49/50	2.6 (50)	63	50/50
54-7	4.0 (49)	50/50	3.4 (48)	85	49/50	3.1 (49)	78	49/50	2.5 (50)	63	50/50
56-7	4.1 (50)	50/50	3.7 (48)	90	49/50	3.2 (49)	78	49/50	2.5 (50)	61	50/50
58-7	4.2 (50)	50/50	3.7 (48)	88	49/50	3.2 (49)	76	49/50	2.4 (50)	57	50/50
60-7	3.9 (50)	50/50	3.5 (48)	90	49/50	3.0 (49)	77	49/50	2.4 (50)	62	50/50
62-7	4.0 (50)	50/50	3.7 (47)	93	49/50	3.0 (49)	75	49/50	2.5 (50)	63	50/50
64-7	3.9 (50)	50/50	3.4 (48)	87	49/50	3.2 (49)	82	49/50	2.5 (50)	64	50/50
66-7	4.3 (49)	49/50	3.8 (46)	88	48/50	3.1 (49)	72	49/50	2.5 (50)	58	50/50
68-7	4.0 (48)	48/50	3.6 (46)	90	48/50	3.2 (49)	80	49/50	2.5 (50)	63	50/50
70-7	4.1 (48)	47/50	3.8 (46)	93	48/50	3.2 (49)	78	49/50	2.5 (50)	61	50/50
72-7	4.1 (47)	47/50	3.6 (47)	88	48/50	3.1 (48)	76	48/50	2.4 (50)	59	50/50
74-7	4.1 (46)	46/50	3.6 (46)	88	48/50	3.2 (48)	78	48/50	2.4 (50)	59	50/50
76-7	3.9 (46)	46/50	3.6 (47)	92	48/50	3.0 (47)	77	47/50	2.4 (50)	62	50/50
78-7	4.1 (46)	46/50	3.7 (46)	90	47/50	3.3 (46)	80	46/50	2.5 (48)	61	48/50
80-7	4.2 (45)	45/50	3.9 (46)	93	46/49	3.3 (46)	79	46/50	2.5 (48)	60	48/50
82-7	4.2 (45)	45/50	3.8 (45)	90	45/49	3.3 (45)	79	44/50	2.5 (48)	60	48/50
84-7	4.1 (44)	44/50	3.9 (44)	95	43/49	3.3 (43)	80	43/50	2.4 (47)	59	46/50
86-7	4.4 (41)	40/50	3.7 (43)	84	43/49	3.5 (42)	80	42/50	2.5 (46)	57	45/50
88-7	4.3 (39)	39/50	3.8 (41)	88	41/49	3.4 (42)	79	42/50	2.5 (44)	58	44/50
90-7	4.1 (39)	39/50	3.6 (41)	88	41/49	3.3 (42)	80	42/50	2.4 (44)	59	44/50
92-7	4.4 (37)	37/50	3.9 (40)	89	40/49	3.3 (39)	75	38/50	2.5 (42)	57	43/50
94-7	4.1 (36)	36/50	3.6 (40)	88	39/49	3.3 (37)	80	36/50	2.4 (42)	59	42/50
96-7	4.2 (32)	34/50	3.6 (38)	86	38/49	3.2 (36)	76	36/50	2.4 (40)	57	41/50
98-7	4.2 (31)	31/50	3.5 (37)	83	37/49	3.2 (36)	76	35/50	2.4 (41)	57	41/50
100-7	4.2 (31)	30/50	3.7 (36)	88	36/49	3.3 (35)	79	35/50	2.5 (40)	60	40/50
102-7	4.6 (28)	28/50	3.6 (34)	78	34/49	3.5 (32)	76	32/50	2.5 (39)	54	39/50
104-7	4.6 (27)	27/50	3.6 (32)	78	33/49	3.5 (30)	76	30/50	2.4 (39)	52	39/50

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

TABLE 20 FOOD CONSUMPTION IN MALE MOUSE(TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Suruiv. <50>	250 ppm Av.FC.	250 ppm % of cont. <50>	250 ppm No.of Suruiv.	1000 ppm Av.FC.	1000 ppm % of cont. <50>	1000 ppm No.of Suruiv.	4000 ppm Av.FC.	4000 ppm % of cont. <50>	4000 ppm No.of Suruiv.
1	3.9 (50)	50/50	4.0 (50)	103	50/50	4.0 (50)	103	50/50	3.8 (50)	97	50/50
2	3.8 (50)	50/50	3.7 (50)	97	50/50	3.8 (50)	100	50/50	3.9 (50)	103	50/50
3	3.7 (50)	50/50	3.6 (49)	97	49/50	3.6 (50)	97	50/50	3.7 (50)	100	50/50
4	3.7 (50)	50/50	3.7 (49)	100	49/50	3.8 (50)	103	50/50	3.7 (50)	100	50/50
5	3.7 (50)	50/50	3.7 (49)	100	49/50	3.8 (50)	103	50/50	3.8 (50)	103	50/50
6	3.8 (50)	50/50	3.8 (49)	100	49/50	3.8 (50)	100	50/50	3.7 (49)	97	50/50
7	3.9 (50)	50/50	3.8 (49)	97	49/50	3.9 (50)	100	50/50	3.8 (50)	97	50/50
8	3.8 (50)	50/50	3.9 (49)	103	49/50	3.8 (50)	100	50/50	3.7 (50)	97	50/50
9	4.0 (50)	50/50	4.0 (49)	100	49/50	4.0 (50)	100	50/50	4.3 (50)	108	50/50
10	4.1 (50)	50/50	4.1 (49)	100	49/50	4.1 (50)	100	50/50	4.0 (50)	98	50/50
11	4.0 (50)	50/50	4.0 (49)	100	49/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50
12	4.1 (50)	50/50	4.1 (49)	100	49/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50
13	4.0 (50)	50/50	4.0 (49)	100	49/50	4.0 (50)	100	50/50	3.4 (50)	85	50/50
14	4.1 (50)	50/50	4.1 (49)	100	49/50	4.0 (50)	98	50/50	4.2 (50)	102	50/50
18	4.3 (50)	50/50	4.3 (49)	100	49/50	4.1 (50)	95	50/50	4.2 (50)	98	50/50
22	4.5 (50)	50/50	4.5 (49)	100	49/50	4.4 (50)	98	50/50	4.4 (50)	98	50/50
26	4.4 (50)	50/50	4.4 (49)	100	49/50	4.2 (50)	95	50/50	4.1 (50)	93	50/50
30	4.4 (50)	50/50	4.5 (49)	102	49/50	4.3 (50)	98	50/50	4.1 (50)	93	50/50
34	4.5 (50)	50/50	4.0 (49)	89	49/50	4.3 (50)	96	50/50	4.1 (50)	91	50/50
38	4.5 (50)	50/50	4.5 (49)	100	49/50	4.4 (50)	98	50/50	4.3 (50)	96	50/50
42	4.4 (50)	50/50	4.4 (49)	100	48/50	4.3 (50)	98	50/50	4.1 (49)	93	49/50
46	4.4 (50)	50/50	4.6 (48)	105	48/50	4.4 (50)	100	50/50	4.3 (48)	98	48/50
50	4.8 (50)	50/50	4.9 (48)	102	48/50	4.6 (50)	96	50/50	4.5 (48)	94	48/50
54	5.0 (49)	49/50	5.1 (48)	102	48/50	4.9 (50)	98	50/50	4.8 (48)	96	48/50
58	4.9 (49)	49/50	5.0 (48)	102	48/50	4.7 (50)	96	50/50	4.6 (48)	94	48/50
62	5.2 (49)	49/50	5.2 (48)	100	48/50	4.8 (50)	92	50/50	4.6 (48)	88	48/50
66	4.9 (49)	49/50	4.8 (48)	98	47/50	4.7 (50)	96	50/50	4.6 (47)	94	47/50
70	5.0 (49)	49/50	4.9 (47)	98	47/50	4.7 (50)	94	50/50	4.6 (47)	92	47/50
74	5.0 (49)	49/50	5.0 (46)	100	46/50	4.8 (50)	96	50/50	4.5 (47)	90	47/50
78	5.0 (49)	49/50	5.1 (45)	102	45/50	4.9 (49)	98	49/50	4.5 (47)	90	46/50
82	5.0 (49)	49/50	5.0 (44)	100	44/50	4.9 (49)	98	49/50	4.6 (46)	92	45/50
86	5.2 (47)	47/50	5.1 (24)	98	43/50	5.1 (39)	98	48/50	4.6 (45)	88	45/50
88	5.2 (47)	47/50	5.3 (43)	102	43/50	5.1 (48)	98	48/50	4.7 (45)	90	45/50
90	4.7 (47)	45/50	5.0 (43)	106	43/50	4.7 (48)	100	48/50	4.5 (45)	96	44/50
94	5.0 (44)	44/50	5.1 (40)	102	40/50	4.8 (48)	96	48/50	4.5 (44)	90	44/50
98	4.7 (43)	41/50	5.0 (36)	106	36/50	4.6 (45)	98	43/50	4.5 (44)	96	43/50
102	5.0 (39)	39/50	4.9 (34)	98	34/50	4.9 (39)	98	39/50	4.5 (42)	90	42/50
104	4.8 (38)	38/50	5.0 (33)	104	33/50	4.7 (38)	98	38/50	4.4 (41)	92	40/50

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

TABLE 21 FOOD CONSUMPTION IN FEMALE MOUSE(TWO-YEAR STUDY)

Week on Study	Control Av.FC.	Control No.of Surviv. <50>	1000 ppm Av.FC.	1000 ppm % of cont. <49>	1000 ppm No.of Surviv.	4000 ppm Av.FC.	4000 ppm % of cont. <50>	4000 ppm No.of Surviv.	16000 ppm Av.FC.	16000 ppm % of cont. <50>	16000 ppm No.of Surviv.
1	3.3 (50)	50/50	3.5 (49)	106	50/50	3.2 (50)	97	50/50	2.7 (50)	82	50/50
2	3.3 (50)	50/50	3.4 (49)	103	50/50	3.4 (50)	103	50/50	3.0 (49)	91	50/50
3	3.2 (50)	50/50	3.2 (49)	100	50/50	3.1 (50)	97	50/50	2.7 (50)	84	50/50
4	3.3 (50)	50/50	3.3 (49)	100	50/50	3.2 (50)	97	50/50	2.8 (50)	85	50/50
5	3.3 (50)	50/50	3.4 (49)	103	50/50	3.3 (50)	100	50/50	2.8 (50)	85	50/50
6	3.4 (50)	50/50	3.4 (49)	100	50/50	3.4 (50)	100	50/50	3.0 (50)	88	50/50
7	3.5 (50)	50/50	3.4 (49)	97	50/50	3.4 (50)	97	50/50	3.3 (49)	94	50/50
8	3.3 (50)	50/50	3.4 (49)	103	50/50	3.3 (50)	100	50/50	3.1 (50)	94	50/50
9	3.5 (50)	50/50	3.5 (49)	100	50/50	3.5 (50)	100	50/50	3.3 (50)	94	50/50
10	3.7 (50)	50/50	3.7 (49)	100	50/50	3.6 (50)	97	50/50	3.4 (50)	92	50/50
11	3.8 (50)	50/50	3.9 (49)	103	50/50	4.0 (50)	105	50/50	3.7 (50)	97	50/50
12	3.9 (50)	50/50	3.7 (49)	95	50/50	3.7 (50)	95	50/50	3.4 (50)	87	50/50
13	3.6 (50)	50/50	3.7 (49)	103	50/50	3.7 (50)	103	50/50	3.7 (50)	103	50/50
14	3.8 (50)	50/50	3.7 (49)	97	50/50	3.7 (50)	97	50/50	3.3 (50)	87	50/50
18	3.9 (50)	50/50	3.8 (49)	97	50/50	3.7 (50)	95	50/50	3.4 (50)	87	50/50
22	4.3 (50)	50/50	4.3 (49)	100	50/50	4.2 (50)	98	50/50	3.8 (50)	88	50/50
26	4.0 (50)	50/50	3.9 (49)	98	49/50	3.7 (50)	93	50/50	3.6 (50)	90	50/50
30	4.1 (50)	50/50	4.0 (48)	98	49/50	3.9 (50)	95	50/50	3.6 (50)	88	50/50
34	4.2 (50)	50/50	4.1 (48)	98	49/50	4.0 (50)	95	50/50	3.6 (50)	86	50/50
38	4.2 (50)	50/50	4.1 (48)	98	49/50	3.9 (48)	93	49/50	3.5 (50)	83	50/50
42	4.3 (50)	50/50	4.1 (48)	95	49/50	3.9 (49)	91	49/50	3.8 (50)	88	50/50
46	4.3 (50)	50/50	4.2 (48)	98	49/50	4.1 (49)	95	49/50	3.7 (50)	86	50/50
50	4.1 (50)	50/50	4.1 (48)	100	49/50	3.9 (49)	95	49/50	3.8 (50)	93	50/50
54	4.5 (50)	50/50	4.6 (48)	102	49/50	4.3 (49)	96	49/50	4.1 (50)	91	50/50
58	4.3 (50)	50/50	4.4 (48)	102	49/50	4.1 (49)	95	49/50	3.7 (50)	86	50/50
62	4.7 (50)	50/50	4.6 (48)	98	49/50	4.3 (49)	91	49/50	3.9 (50)	83	50/50
66	4.5 (49)	49/50	4.2 (48)	93	48/50	3.8 (49)	84	49/50	3.7 (50)	82	50/50
70	4.5 (48)	47/50	4.3 (47)	96	48/50	4.0 (49)	89	49/50	3.8 (50)	84	50/50
74	4.5 (46)	46/50	4.3 (47)	96	48/50	4.0 (48)	89	48/50	3.8 (50)	84	50/50
78	4.5 (46)	46/50	4.4 (47)	98	47/50	4.3 (46)	96	46/50	3.8 (49)	84	48/50
82	4.6 (45)	45/50	4.5 (45)	98	45/49	4.3 (45)	93	44/50	3.9 (48)	85	48/50
86	4.7 (19)	40/50	4.5 (43)	96	43/49	4.5 (34)	96	42/50	3.9 (46)	83	45/50
88	4.8 (40)	39/50	4.6 (42)	96	41/49	4.5 (42)	94	42/50	4.1 (44)	85	44/50
90	4.4 (39)	39/50	4.2 (41)	95	41/49	4.0 (42)	91	42/50	3.6 (44)	82	44/50
94	4.4 (36)	36/50	4.3 (40)	98	39/49	4.4 (37)	100	36/50	4.0 (42)	91	42/50
98	4.5 (32)	31/50	4.2 (37)	93	37/49	4.3 (36)	96	35/50	3.8 (41)	84	41/50
102	4.6 (28)	28/50	4.3 (34)	93	34/49	4.4 (32)	96	32/50	3.8 (39)	83	39/50
104	4.4 (27)	27/50	4.2 (33)	95	33/49	4.1 (30)	93	30/50	3.7 (39)	84	39/50

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

TABLE 22 NEOPLASTIC LESIONS (LIVER) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE : MALE

Group Name	Control	1000 ppm	4000 ppm	16000 ppm
SITE : liver TUMOUR : hepatocellular carcinoma				
Tumor Rates				
Overall Rates(a)	18/50 (36.0)	18/50 (36.0)	8/50 (16.0)	4/50 (8.0)
Adjusted Rates(b)	31.71	44.44	20.00	10.00
Terminal Rates(c)	12/38 (31.6)	14/33 (42.4)	6/38 (15.8)	4/40 (10.0)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.9952			
Prevalence Method(d)	P=0.9996			
Combined analysis(d)	P=1.0000			
Cochran-Armitage Test(e)	P=0.0003**			
Fisher Exact Test(e)		P=0.4230	P=0.0617	P=0.0053**
SITE : liver TUMOUR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor Rates				
Overall Rates(a)	23/50 (46.0)	24/50 (48.0)	13/50 (26.0)	7/50 (14.0)
Adjusted Rates(b)	44.74	61.11	32.50	15.00
Terminal Rates(c)	17/38 (44.7)	20/33 (60.6)	11/38 (28.9)	6/40 (15.0)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.9293			
Prevalence Method(d)	P=1.0000			
Combined analysis(d)	P=1.0000			
Cochran-Armitage Test(e)	P=0.0001**			
Fisher Exact Test(e)		P=0.4774	P=0.1075	P=0.0078**

TABLE 23 NEOPLASTIC LESIONS (PITUITARY GLAND) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE : FEMALE

Group Name	Control	1000 ppm	4000 ppm	16000 ppm
SITE : pituitary gland TUMOUR : adenoma				
Tumor Rates				
Overall Rates(a)	7/50 (14.0)	4/48 (8.3)	7/50 (14.0)	1/48 (2.1)
Adjusted Rates(b)	22.22	6.06	21.88	2.70
Terminal Rates(c)	6/27 (22.2)	2/33 (6.1)	6/30 (20.0)	1/37 (2.7)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.9243			
Prevalence Method(d)	P=0.9746			
Combined analysis(d)	P=0.9917			
Cochran-Armitage Test(e)	P=0.0544			
Fisher Exact Test(e)		P=0.3191	P=0.3882	P=0.0484*
SITE : pituitary gland TUMOUR : adenoma, adenocarcinoma				
Tumor Rates				
Overall Rates(a)	7/50 (14.0)	5/48 (10.4)	8/50 (16.0)	1/48 (2.1)
Adjusted Rates(b)	22.22	9.09	21.88	2.70
Terminal Rates(c)	6/27 (22.2)	3/33 (9.1)	6/30 (20.0)	1/37 (2.7)
Statistical Analysis				
Peto Test				
Standard Method(d)	P=0.9053			
Prevalence Method(d)	P=0.9826			
Combined analysis(d)	P=0.9943			
Cochran-Armitage Test(e)	P=0.0418*			
Fisher Exact Test(e)		P=0.4331	P=0.4854	P=0.0484*

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimate tumor incidence at the end of 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-Armitage and Fisher exact test compare directly the overall incidence rates.

TABLE 24 NUMBER OF MOUSE WITH SELECTED NASAL CAVITY LESIONS

	Male				Female			
Group	Control	250ppm	1000ppm	4000ppm	Control	1000ppm	4000ppm	16000ppm
Number of examined	50	50	50	50	50	49	50	50
eosinophilic change: olfactory epithelium	24	18	29	13	2	7	6	19
eosinophilic change: respiratory epithelium	29	16	9	42	31	26	48	46
respiratory metaplasia:gland	30	9	8	7	6	11	4	3

TABLE 25 NUMBER OF MOUSE WITH DESQUAMATION OF PELVIS IN KIDNEY

	Male				Female			
Group	Control	250ppm	1000ppm	4000ppm	Control	1000ppm	4000ppm	16000ppm
Number of examined	50	50	50	50	50	49	50	50
desquamation:pelvis	0	0	0	1	1	13	16	19

TABLE 26 CAUSE OF DEATH :MOUSE

Group	Male				Female			
	Control	250ppm	1000ppm	4000ppm	Control	1000ppm	4000ppm	16000ppm
Number of dead/moribund animal	12	17	12	10	23	16	20	11
No microscopical confirmation	1	2	0	1	1	2	3	1
Renal lesion	1	0	0	0	0	0	0	0
Thrombosis	0	0	0	0	1	0	0	0
Hemorrhage	0	1	0	0	0	0	0	0
Urinary retention	1	0	0	0	0	0	0	0
Arteritis	0	1	0	0	0	1	0	0
Hydronephrosis	0	2	1	0	0	1	1	1
Tumor death : leukemia	1	3	5	1	12	5	8	3
: subcutis	0	0	0	1	1	1	0	0
: lung	2	1	3	1	1	0	0	1
: spleen	0	0	0	0	0	1	0	0
: heart	0	1	0	0	0	0	0	0
: small intestine	0	0	0	1	0	0	0	0
: large intestine	1	0	0	0	0	0	1	0
: liver	5	6	2	4	0	0	2	1
: pituitary gland	0	0	0	0	1	2	1	0
: uterus	0	0	0	0	5	2	4	4
: peripheral nerve	0	0	0	1	0	0	0	0
: bone	0	0	0	0	1	0	0	0
: peritoneum	0	0	1	0	0	1	0	0

SELECTED FIGURES

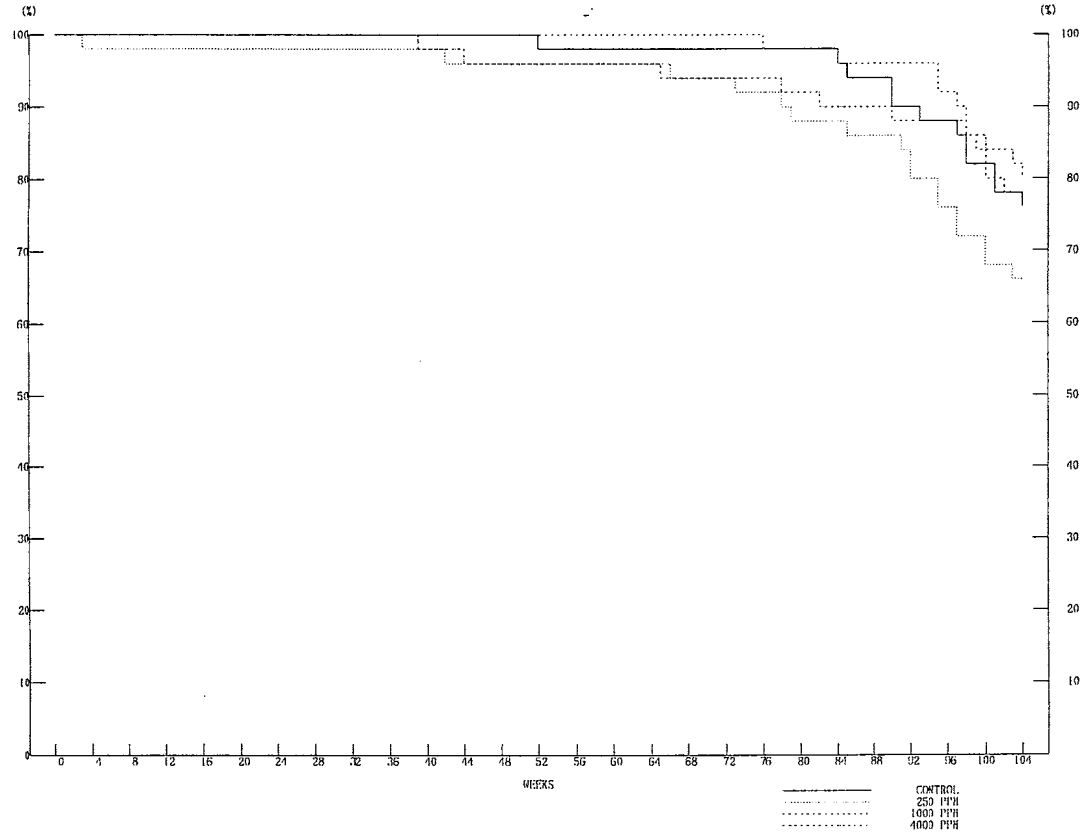


FIGURE 9 SURVIVAL ANIMAL RATE : MOUSE:MALE(TWO-YEAR STUDY)

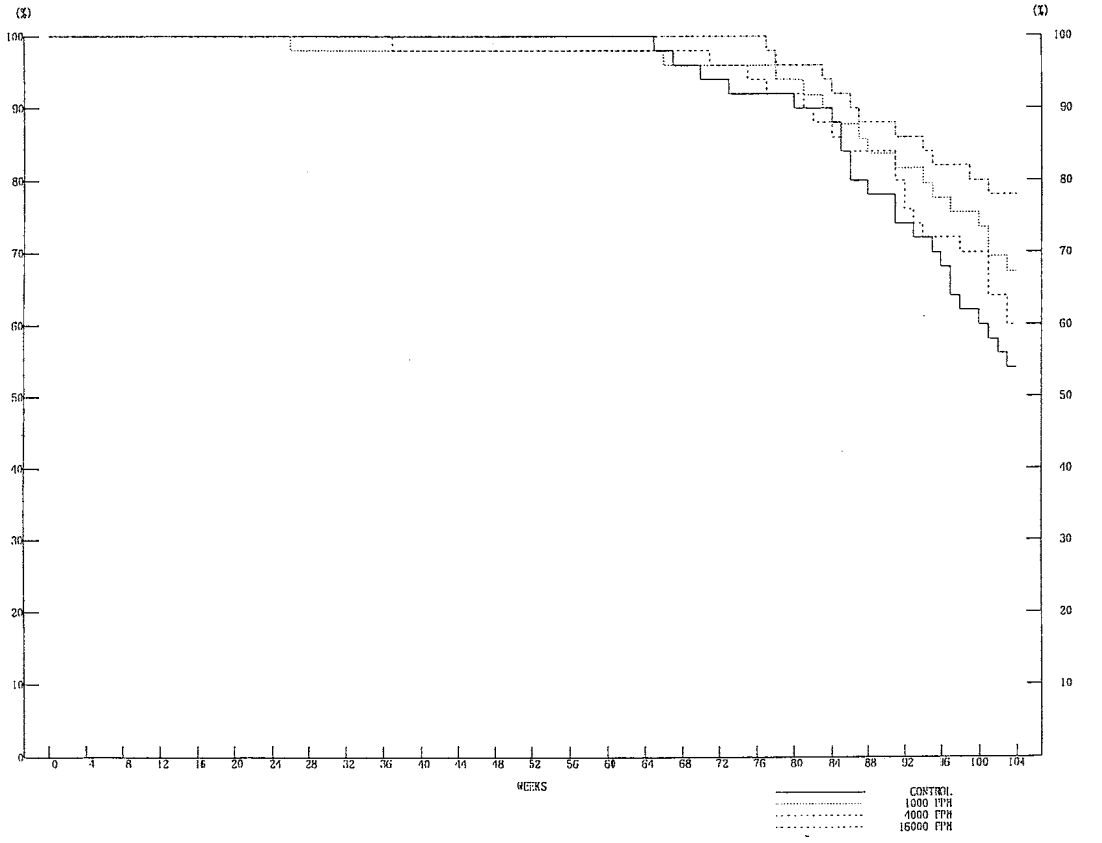


FIGURE 10 SURVIVAL ANIMAL RATE : MOUSE:FEMALE(TWO-YEAR STUDY)

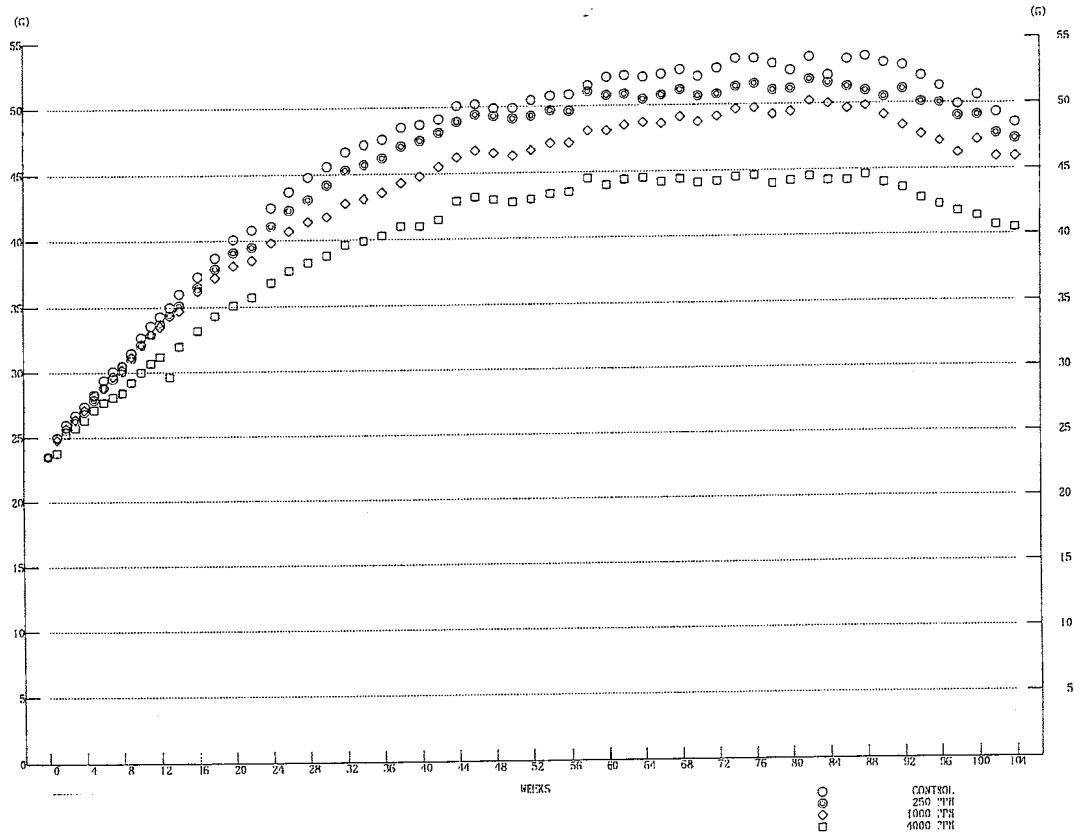


FIGURE 11 BODY WEIGHT CHANGES : MOUSE:MALE(TWO-YEAR STUDY)

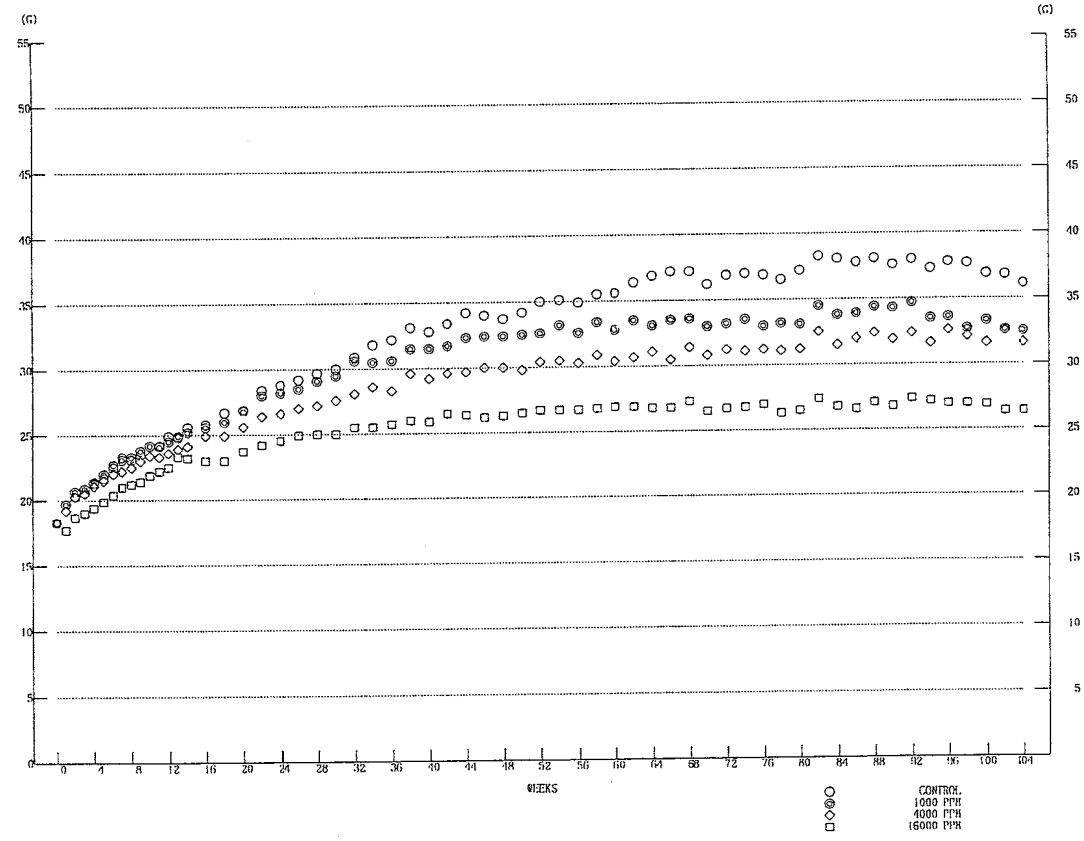


FIGURE 12 BODY WEIGHT CHANGES : MOUSE:FEMALE(TWO-YEAR STUDY)

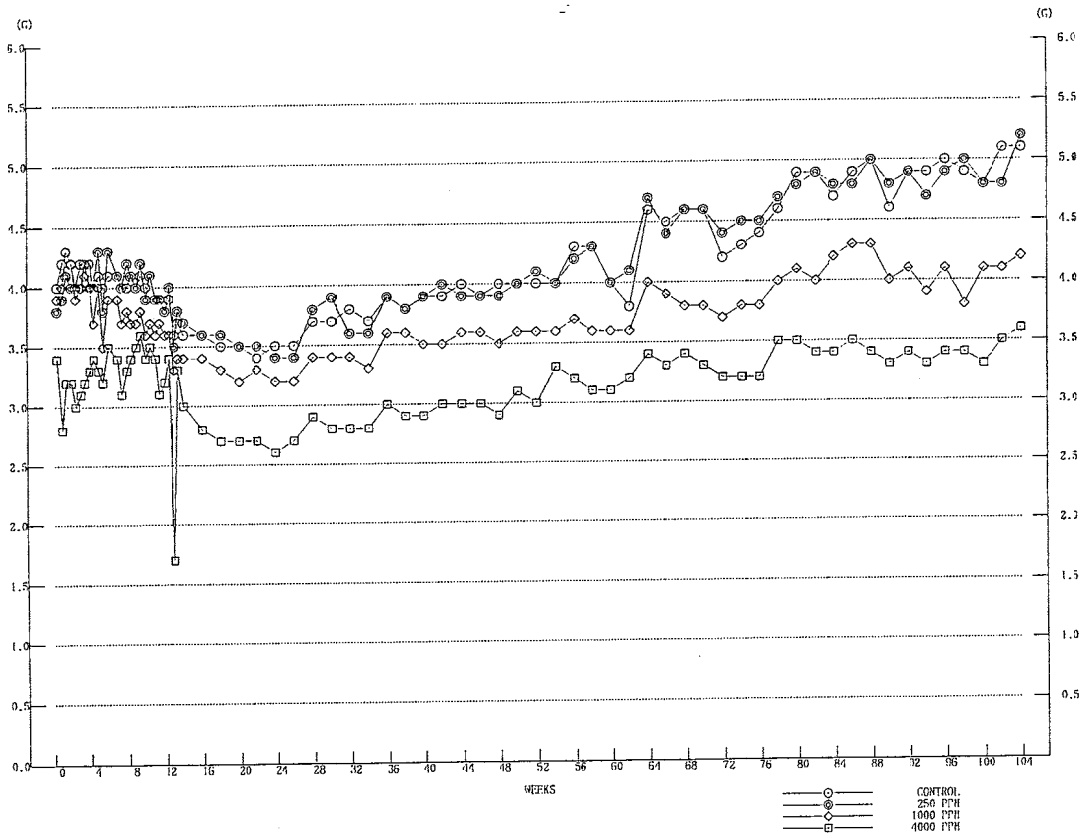


FIGURE 13 WATER CONSUMPTION : MOUSE:MALE(TWO-YEAR STUDY)

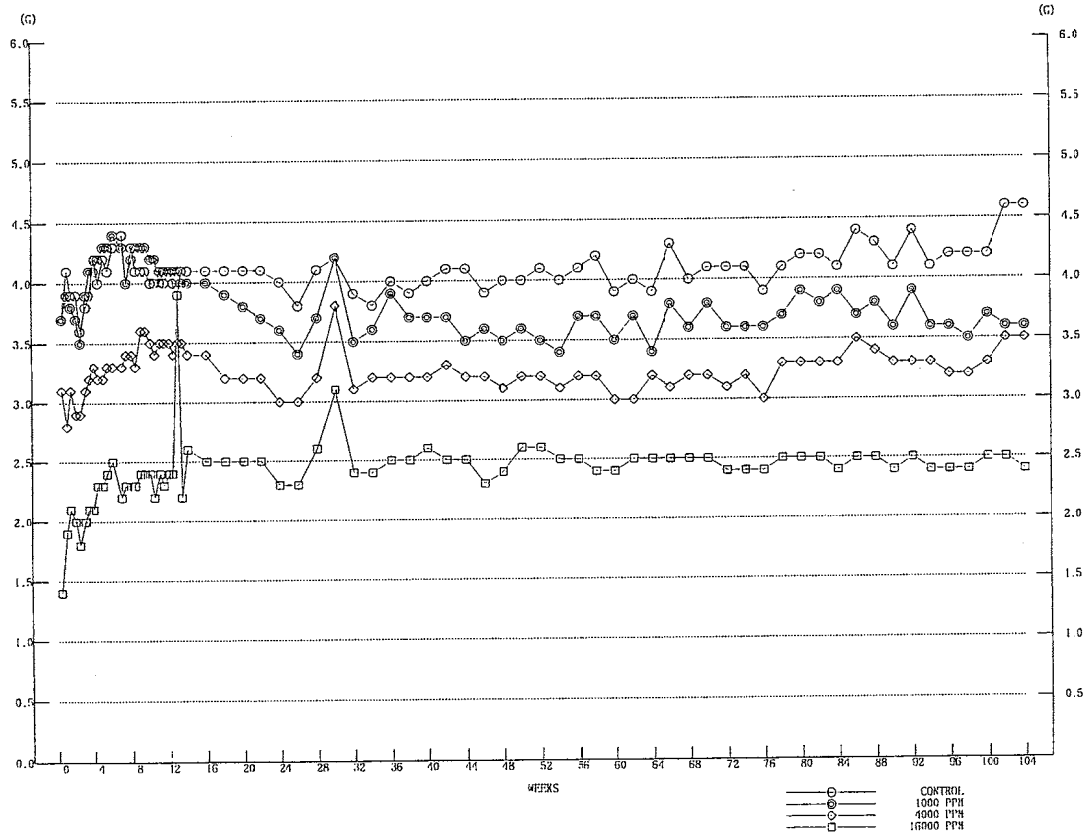


FIGURE 14 WATER CONSUMPTION : MOUSE:FEMALE(TWO-YEAR STUDY)

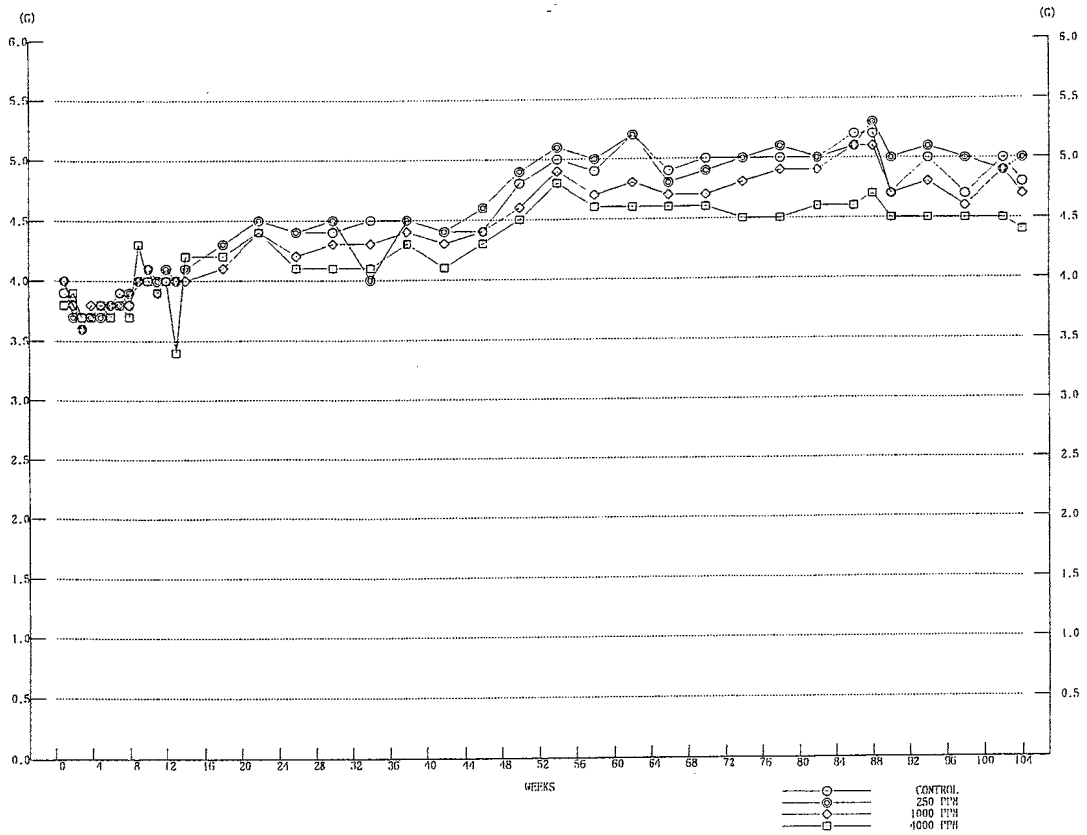


FIGURE 15 FOOD CONSUMPTION : MOUSE:MALE(TWO-YEAR STUDY)

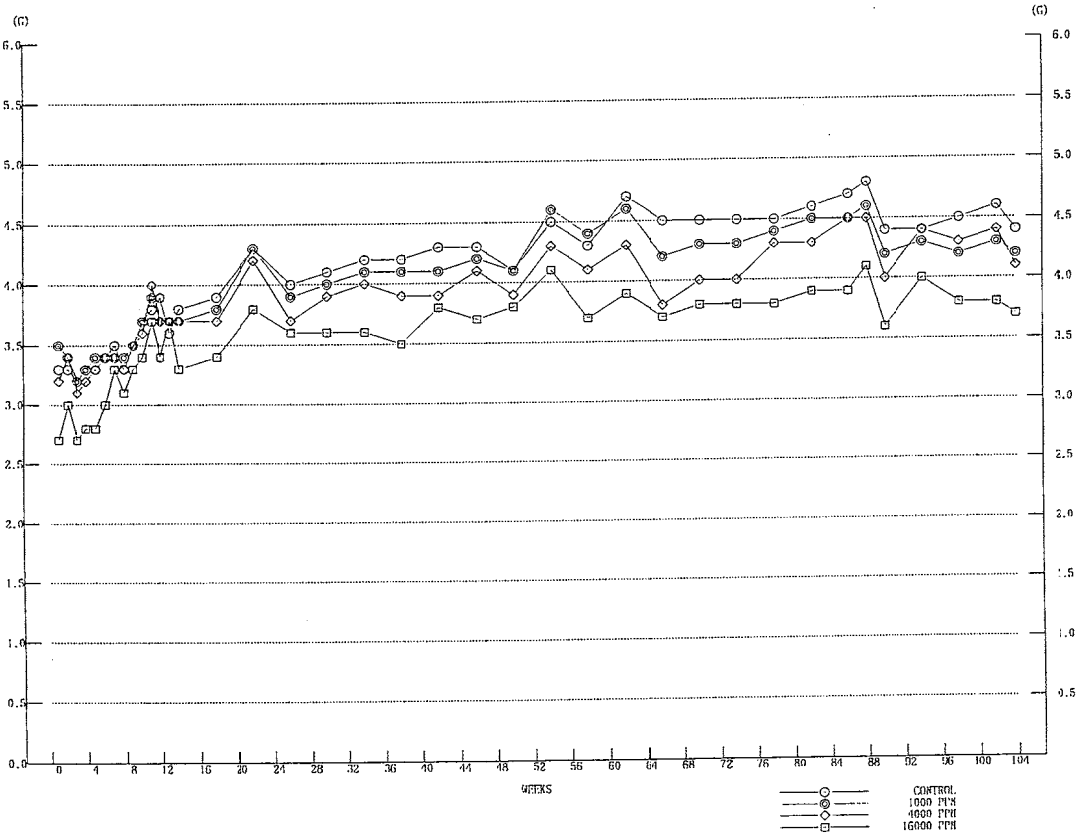
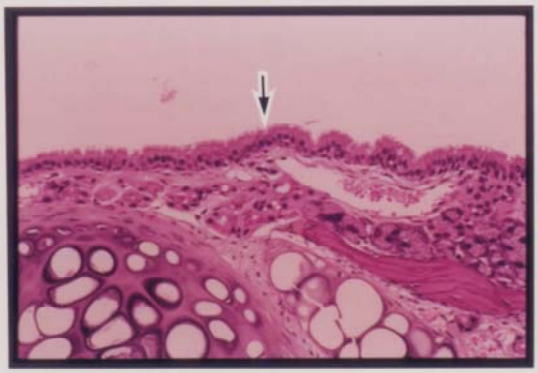


FIGURE 16 FOOD CONSUMPTION : MOUSE:FEMALE(TWO-YEAR STUDY)



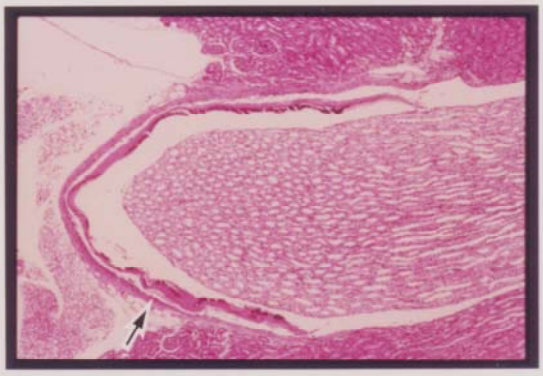
PHOTOGRAPH 7
NASAL CAVITY
(LEVEL 1, NASAL SEPTUM)
NORMAL RESPIRATORY EPITHLIUM
FEMALE, CONTROL,
ANIMAL No. 0140-2016 (H. E., X160)

PHOTOGRAPH 8
NASAL CAVITY
(LEVEL 1, NASAL SEPTUM)
EOSIONOPHILIC CHANGE :
RESPIRATORY EPITHELIUM
FEMALE, 16000ppm,
ANIMAL No. 0140-2303 (H. E., X160)

PHOTOGRAPH 9
NASAL CAVITY
(LEVEL 3, ETHMOTURBINATE)
NORMAL OLFACTORY EPITHELIUM
FEMALE, CONTROL,
ANIMAL No. 0140-2016 (H. E., X160)

PHOTOGRAPH 10
NASAL CAVITY
(LEVEL 3, ETHMOTURBINATE)
EOSIONOPHILIC CHANGE : OLFACTORY
EPITHELIUM
FEMALE, 16000ppm,
ANIMAL No. 0140-2332 (H. E., X160)

PHOTOGRAPH 11
KIDNEY (PELVIS)
NORMAL EPITHELIUM
FEMALE, CONTROL,
ANIMAL No. 0140-2019 (H. E., X32)



PHOTOGRAPH 12
KIDNEY (PELVIS),
DESQUAMATION OF PELVIS
FEMALE, 14000ppm,
ANIMAL No. 0140-2321 (H. E., X32)