Summary of Inhalation Carcinogenicity Study of Tetrachloroethylene 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 March 31, 1993.

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

Summary of Inhalation Carcinogenicity Study of Tetrachloroethylene in BDF1 Mice

Purpose, materials and methods

Tetrachloroethylene (CAS No. 127-18-4) is a colorless liquid with a boiling point of 121.2°C. It is insoluble in water and soluble ethanol, ether, chloroform and benzene.

The carcinogenicity and chronic toxicity of tetrachloroethylene (purity : 99.0%) were examined by inhalation exposure using Crj:BDF1 mice. Groups of test animals were exposed to tetrachloroethylene vapors at target concentrations of 0 (clean air), 10, 50 or 250 ppm (v/v) for 6 hours/day, 5 days/week for 2 years (104 weeks). Each group of test animals consisted of either 50 male or 50 female mice. Both sexes were exposed to each concentration of tetrachloroethylene vapor. 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 tetrachloroethylene used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by both infrared spectrometry and gas chromatography before and after use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 3.7 m^3) were used throughout the 2-year exposure period. Tetrachloroethylene vapor-air mixtures were generated by bubbling clean air through tetrachloroethylene liquid and the mixtures delivered to the inhalation exposure chambers. Air concentrations of the tetrachloroethylene in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 2 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 exposure period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under 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 tetrachloroethylene 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 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

Survival rates of the tetrachloroethylen-exposed groups of both sexes tended to be decreased as compared with the respective controls in a dose-related manner. The decreased survival rates in both sexes were causally related to the increased incidences of hepatocellular carcinoma. Body weights was significantly suppressed 6th week and afterward of 250 ppm-exposed males. Body weights was significantly suppressed 80th week and afterward of 250 ppm-exposed females. Food consumption of the 250 ppm-exposed of both sexes tended to be decreased as compared with the respective controls. No overt clinical sign was observed in any tetrachloroethylen-exposed mice of both sexes.

AST and ALT were significantly increased in the 50 and 250 ppm-exposed males and 250 ppm-exposed females. Total bilirubin, LDH and ALP were significantly increased in the 250 ppm-exposed mice of both sexes. Total protein and total cholesterol were significantly increased in the 50 ppm-exposed males. Glucose and triglyceride were significantly decreased in the 50 ppm-exposed males.

The incidences of selected neoplastic lesions in male and female rats are presented in the tables below. The incidences of hepatocellular adenomas and hepatocellular carcinomas were significantly increased in the 250 ppm-exposed mice of both sexes, and were increased dose-dependently as indicated by a significant positive trend by Peto’s test in both sexes. The incidence of hemangioendothelioma in the liver was increased dose-dependently as indicated by a significant positive trend by Peto’s test in males. In the Harderian gland, the incidence of adenoma was increased dose-dependently as indicated by a significant positive trend by Peto’s test in males. In the spleen, the incidences of hemangioendothelioma was increased dose-dependently as indicated by a significant positive trend by Peto’s test in males. The incidence of hemangioendothelioma in all organs including spleen and liver was increased dose-dependently as indicated by a significant positive trend by Peto’s test in males and females.

As non-neoplastic lesions in the liver, the incidence of angiectasis was increased in males exposed to 50 ppm and above and females exposed to 250 ppm. The incidence of centrolobular degeneration were increased in the 250 ppm-exposed males and females. The incidence of focal necrosis were increased in the 250 ppm-exposed males. In the kidney, nuclear enlargement in the proximal tubule was increased in males exposed to 50 ppm and above and females exposed to 250 ppm. Atypical tubular dilation in the proximal tubule was increased in the 250 ppm-exposed females.

Conclusions

In mice, there was clear evidence of carcinogenic activity of tetrachloroethylene in males and females based on the increased incidences of hepatocellular carcinomas, hepatocellular adenomas in males and females and increased incidence of Harderian gland adenomas in males.

Incidences of selected neoplastic lesions of male mice in the 2-year inhalation carcinogenicity study of tetrachloroethylene

Dose (ppm)		0	10	50	250	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	9	7	5	4		
liver	hepatocellular adenoma	7	13	8	26 **	↑↑	↑↑
Harderian gland	adenoma	2	2	2	8	↑↑	↑↑
malignant tumor							
lung	bronchiolar-alveolar carcinoma	2	3	3	0		
lymph node	malignant lymphoma	9	7	7	9		
spleen	hemangioendothelioma	1	1	3	5	↑	↑
liver	hepatocellular carcinoma	7	8	12	25 **	↑↑	↑↑
	hemangioendothelioma	1	1	5	5	↑	
	histiocytic sarcoma	2	0	1	1		
seminal vesicle	histiocytic sarcoma	3	0	0	1		
All Site	hemangioendothelioma	2	1	6	8	↑↑	↑
liver	hepatocellular adenoma＋hepatocellular carcinoma	13	21	19	40 **	↑↑	↑↑

Tumors occurred more than 5% of examined animals at least in one group were presented.

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)

Incidences of selected neoplastic lesions of female mice in the 2-year inhalation carcinogenicity study of tetrachloroethylene

Dose (ppm)		0	10	50	250	Peto test	Cochran-Armitage test
Number of examined animals		50	47	49	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	5	2	0	1		
liver	hepatocellular adenoma	3	3	7	26 ** 1)	↑↑	↑↑
pituitary	adenoma	9	11	4 2)	9	↑	
Harderian gland	adenoma	4	3	3	2		
malignant tumor							
lymph node	malignant lymphoma	14	10	16	10		
spleen	malignant lymphoma	3	1	5 2)	3		
liver	hepatocellular carcinoma	0	0	0	14 **	↑↑	↑↑
uterus	histiocytic sarcoma	11	12	10	11		
All Site	hemangioendothelioma	1	0	2	3	↑↑	
liver	hepatocellular adenoma＋ hepatocellular carcinoma	3	3	7	33 **	↑↑	↑↑

Tumors occurred more than 5% of examined animals at least in one group were presented.

1)：Number of examined animals is 49.

2)：Number of examined animals is 48.

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)

SELECTED TABLES

(Study No. 0104, 0105)

TABLE 29 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN MALE MOUSE

(TWO-YEAR STUDIES)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	10 ppm Av.Wt.	10 ppm % of cont. <50>	10 ppm No.of Surviv.	50 ppm Av.Wt.	50 ppm % of cont. <50>	50 ppm No.of Surviv.	250 ppm Av.Wt.	250 ppm % of cont. <50>	250 ppm No.of Surviv.
0	22.7 (50)	50/50	22.7 (50)	100	50/50	22.7 (50)	100	50/50	22.7 (50)	100	50/50
1	24.6 (50)	50/50	24.4 (50)	99	50/50	24.4 (50)	99	50/50	24.4 (50)	99	50/50
2	25.3 (50)	50/50	24.8 (50)	98	50/50	25.3 (50)	100	50/50	25.3 (50)	100	50/50
3	26.3 (50)	50/50	25.8 (50)	98	50/50	26.0 (50)	99	50/50	25.9 (49)	98	50/50
4	27.0 (50)	50/50	26.4 (50)	98	50/50	26.6 (50)	99	50/50	26.4 (50)	98	50/50
5	27.8 (50)	50/50	27.4 (50)	99	50/50	27.7 (50)	100	50/50	27.2 (50)	98	50/50
6	28.5 (50)	50/50	27.8 (50)	98	50/50	28.3 (50)	99	50/50	27.6 (50)	97	50/50
7	29.0 (50)	50/50	28.0 (50)	97	50/50	28.8 (50)	99	50/50	28.2 (50)	97	50/50
8	29.8 (50)	50/50	28.6 (50)	96	50/50	29.6 (50)	99	50/50	28.5 (50)	96	50/50
9	30.2 (50)	50/50	29.0 (50)	96	50/50	30.2 (50)	100	50/50	29.0 (50)	96	50/50
10	30.7 (50)	50/50	29.6 (50)	96	50/50	30.9 (50)	101	50/50	29.4 (50)	96	50/50
11	31.5 (50)	50/50	30.5 (50)	97	50/50	31.4 (50)	100	50/50	30.0 (50)	95	50/50
12	32.2 (50)	50/50	30.9 (50)	96	50/50	31.8 (50)	99	50/50	30.3 (50)	94	50/50
13	32.9 (50)	50/50	31.8 (50)	97	50/50	32.5 (50)	99	50/50	30.6 (50)	93	50/50
14	33.4 (50)	50/50	32.4 (50)	97	50/50	33.2 (50)	99	50/50	31.2 (50)	93	50/50
16	34.9 (50)	50/50	33.9 (50)	97	50/50	34.5 (50)	99	50/50	32.7 (50)	94	50/50
18	36.3 (50)	50/50	35.5 (50)	98	50/50	36.1 (50)	99	50/50	33.9 (50)	93	50/50
20	37.2 (50)	50/50	36.6 (50)	98	50/50	37.1 (50)	100	50/50	35.5 (50)	95	50/50
22	37.5 (50)	50/50	37.2 (50)	99	50/50	38.0 (50)	101	50/50	35.7 (50)	95	50/50
24	38.2 (50)	50/50	38.2 (50)	100	50/50	38.8 (50)	102	50/50	36.1 (50)	95	50/50
26	39.3 (50)	50/50	39.3 (50)	100	50/50	39.8 (50)	101	50/50	36.7 (50)	93	50/50
28	39.9 (50)	49/50	40.7 (50)	102	50/50	40.9 (50)	103	50/50	38.0 (50)	95	50/50
30	41.5 (49)	49/50	41.1 (50)	99	50/50	41.7 (50)	100	50/50	38.0 (50)	92	50/50
32	41.9 (49)	49/50	42.1 (50)	100	50/50	42.4 (50)	101	50/50	39.0 (49)	93	49/50
34	43.0 (49)	49/50	42.7 (50)	99	50/50	43.3 (50)	101	50/50	39.4 (49)	92	49/50
36	43.3 (49)	49/50	43.2 (50)	100	50/50	43.9 (50)	101	50/50	39.8 (49)	92	49/50
38	44.3 (49)	49/50	44.0 (50)	99	50/50	44.5 (50)	100	50/50	41.5 (49)	94	49/50
40	44.9 (49)	49/50	45.1 (49)	100	49/50	44.9 (50)	100	50/50	41.6 (49)	93	49/50
42	45.9 (48)	48/50	46.0 (49)	100	49/50	46.4 (49)	101	49/50	42.2 (49)	92	49/50
44	46.4 (48)	48/50	46.9 (49)	101	49/50	46.8 (49)	101	49/50	42.9 (49)	92	49/50
46	46.6 (48)	48/50	47.3 (49)	102	49/50	47.2 (49)	101	49/50	43.1 (49)	92	49/50
48	47.6 (47)	47/50	47.9 (49)	101	49/50	47.6 (49)	100	49/50	43.5 (49)	91	49/50
50	48.0 (46)	46/50	48.4 (49)	101	49/50	48.0 (49)	100	49/50	43.6 (49)	91	49/50
52	48.6 (46)	46/50	49.0 (49)	101	49/50	48.4 (48)	100	48/50	44.4 (49)	91	49/50
54	48.4 (46)	46/50	48.9 (49)	101	49/50	48.3 (48)	100	48/50	44.4 (49)	92	49/50
56	48.4 (46)	46/50	49.0 (48)	101	48/50	48.5 (48)	100	48/50	44.5 (49)	92	49/50
58	48.6 (46)	46/50	49.2 (48)	101	48/50	48.7 (48)	100	48/50	44.3 (49)	91	49/50
60	48.6 (46)	46/50	48.6 (48)	100	48/50	48.3 (48)	99	48/50	43.9 (49)	90	49/50
62	48.5 (46)	46/50	48.4 (48)	100	48/50	48.2 (48)	99	48/50	44.0 (49)	91	49/50
64	48.9 (46)	46/50	48.9 (47)	100	47/50	48.6 (47)	99	47/50	44.0 (49)	90	49/50
66	49.1 (46)	46/50	48.9 (47)	100	47/50	48.4 (47)	99	47/50	43.7 (48)	89	48/50
68	49.7 (46)	46/50	49.2 (47)	99	47/50	48.8 (47)	98	46/50	43.5 (48)	88	48/50
70	50.2 (46)	46/50	49.7 (47)	99	47/50	48.7 (46)	97	46/50	43.4 (47)	86	47/50
72	50.3 (46)	46/50	50.7 (47)	101	47/50	48.3 (46)	96	46/50	43.9 (47)	87	47/50
74	49.6 (46)	46/50	50.5 (47)	102	47/50	48.6 (45)	98	44/50	43.3 (47)	87	47/50
76	50.3 (45)	45/50	50.7 (47)	101	47/50	49.2 (43)	98	43/50	43.7 (46)	87	46/50
78	51.1 (44)	44/50	51.5 (47)	101	47/50	49.4 (43)	97	43/50	43.3 (46)	85	46/50
80	51.2 (44)	44/50	51.1 (47)	100	47/50	49.7 (42)	97	42/50	43.3 (45)	85	45/50
82	51.1 (44)	44/50	51.4 (47)	101	47/50	50.3 (41)	98	41/50	42.7 (44)	84	44/50
84	51.9 (42)	42/50	50.6 (47)	97	47/50	50.4 (41)	97	41/50	42.2 (44)	81	44/50
86	51.9 (42)	42/50	50.7 (46)	98	46/50	50.0 (41)	96	41/50	42.6 (40)	82	40/50
88	52.1 (42)	42/50	50.6 (46)	97	46/50	50.1 (39)	96	39/50	41.7 (39)	80	39/50
90	51.8 (42)	42/50	50.7 (46)	98	46/50	49.4 (38)	95	38/50	40.9 (39)	79	39/50
92	51.7 (41)	41/50	50.4 (45)	97	45/50	49.1 (37)	95	36/50	40.1 (37)	78	37/50
94	51.4 (41)	41/50	50.1 (44)	97	44/50	48.5 (35)	94	34/50	39.5 (35)	77	35/50
96	51.4 (38)	38/50	49.4 (44)	96	43/50	47.8 (32)	93	32/50	38.5 (34)	75	34/50
98	51.4 (36)	36/50	49.3 (41)	96	40/50	47.1 (31)	92	31/50	38.3 (31)	75	31/50
100	50.2 (36)	36/50	49.3 (39)	98	38/50	46.5 (30)	93	30/50	37.8 (27)	75	27/50
102	50.0 (35)	34/50	49.3 (37)	99	37/50	45.8 (30)	92	30/50	36.8 (25)	74	25/50
104	50.3 (31)	31/50	49.2 (35)	98	35/50	45.3 (28)	90	28/50	36.4 (23)	72	22/50

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

(Study No. 0104, 0105)

TABLE 30 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES IN FEMALE MOUSE

(TWO-YEAR STUDIES)

Week on Study	Control Av.Wt.	Control No.of Surviv. <50>	10 ppm Av.Wt.	10 ppm % of cont. <47>	10 ppm No.of Surviv.	50 ppm Av.Wt.	50 ppm % of cont. <49>	50 ppm No.of Surviv.	250 ppm Av.Wt.	250 ppm % of cont. <50>	250 ppm No.of Surviv.
0	18.6 (50)	50/50	18.5 (47)	99	50/50	18.5 (49)	99	50/50	18.6 (50)	100	50/50
1	20.0 (50)	50/50	19.9 (47)	100	50/50	19.5 (49)	98	50/50	19.7 (50)	99	50/50
2	20.5 (50)	50/50	20.5 (47)	100	50/50	20.2 (49)	99	50/50	20.4 (50)	100	50/50
3	21.2 (50)	50/50	21.0 (47)	99	50/50	20.9 (49)	99	50/50	21.3 (50)	100	50/50
4	22.0 (50)	50/50	21.7 (47)	99	50/50	21.6 (49)	98	50/50	22.1 (50)	100	50/50
5	22.4 (50)	50/50	22.4 (47)	100	50/50	22.2 (49)	99	50/50	23.1 (50)	103	50/50
6	23.0 (50)	50/50	22.8 (47)	99	50/50	22.8 (49)	99	50/50	23.1 (50)	100	50/50
7	23.4 (50)	50/50	23.1 (47)	99	49/49	23.1 (49)	99	50/50	23.7 (50)	101	50/50
8	24.1 (50)	50/50	23.5 (47)	98	49/49	23.9 (49)	99	50/50	24.1 (50)	100	50/50
9	23.9 (50)	50/50	23.6 (47)	99	49/49	23.9 (49)	100	50/50	24.4 (50)	102	50/50
10	24.4 (50)	50/50	23.8 (47)	98	49/49	24.0 (49)	98	50/50	24.6 (50)	101	50/50
11	24.9 (50)	50/50	24.2 (47)	97	49/49	24.2 (49)	97	50/50	24.6 (50)	99	50/50
12	24.9 (50)	50/50	24.5 (47)	98	49/49	24.6 (49)	99	50/50	24.8 (50)	100	50/50
13	24.9 (50)	50/50	24.9 (47)	100	49/49	24.7 (49)	99	50/50	25.2 (50)	101	50/50
14	25.2 (50)	50/50	25.1 (47)	100	49/49	25.1 (49)	100	50/50	25.1 (50)	100	50/50
16	26.1 (50)	50/50	25.6 (47)	98	49/49	25.6 (49)	98	50/50	26.0 (50)	100	50/50
18	27.0 (50)	50/50	26.6 (47)	99	49/49	26.2 (49)	97	50/50	26.8 (50)	99	50/50
20	27.5 (50)	50/50	27.1 (47)	99	49/49	27.1 (49)	99	50/50	27.3 (50)	99	50/50
22	27.4 (50)	50/50	27.2 (47)	99	49/49	27.1 (49)	99	50/50	27.7 (50)	101	50/50
24	27.2 (50)	50/50	27.5 (47)	101	49/49	27.1 (49)	100	49/49	27.5 (50)	101	50/50
26	28.3 (50)	50/50	27.9 (47)	99	49/49	27.5 (49)	97	49/49	28.8 (50)	102	50/50
28	28.3 (50)	50/50	29.0 (47)	102	49/49	27.9 (49)	99	49/49	28.7 (50)	101	50/50
30	29.7 (50)	50/50	29.2 (47)	98	49/49	28.8 (49)	97	49/49	29.2 (50)	98	50/50
32	29.4 (50)	50/50	29.6 (47)	101	49/49	28.5 (49)	97	49/49	29.0 (50)	99	50/50
34	30.3 (50)	50/50	29.9 (47)	99	49/49	29.1 (49)	96	49/49	29.9 (50)	99	50/50
36	29.7 (50)	50/50	30.3 (47)	102	49/49	29.9 (49)	101	49/49	30.0 (50)	101	50/50
38	30.3 (50)	50/50	31.2 (47)	103	49/49	30.2 (49)	100	49/49	31.1 (50)	103	50/50
40	31.0 (50)	50/50	31.8 (47)	103	49/49	31.1 (48)	100	48/49	31.0 (50)	100	50/50
42	32.4 (50)	50/50	32.3 (47)	100	49/49	32.1 (48)	99	48/49	31.8 (50)	98	50/50
44	32.7 (50)	50/50	33.5 (47)	102	49/49	32.1 (48)	98	48/49	32.7 (50)	100	50/50
46	33.1 (50)	50/50	33.6 (47)	102	49/49	32.3 (48)	98	48/49	32.9 (50)	99	50/50
48	33.9 (50)	50/50	34.1 (47)	101	49/49	33.3 (48)	98	48/49	33.6 (50)	99	50/50
50	33.9 (50)	50/50	34.6 (47)	102	49/49	33.6 (48)	99	48/49	33.5 (50)	99	50/50
52	34.9 (50)	50/50	35.3 (47)	101	49/49	34.6 (48)	99	48/49	34.3 (50)	98	50/50
54	34.6 (50)	50/50	34.8 (47)	101	48/48	34.4 (48)	99	47/49	34.9 (50)	101	50/50
56	35.4 (50)	50/50	35.8 (47)	101	48/48	34.5 (47)	97	47/49	34.2 (50)	97	50/50
58	35.7 (50)	50/50	35.8 (47)	100	48/48	34.7 (47)	97	47/49	34.7 (50)	97	50/50
60	35.0 (50)	50/50	35.5 (47)	101	48/48	34.0 (47)	97	47/49	33.7 (50)	96	50/50
62	35.2 (50)	50/50	35.2 (47)	100	48/48	34.0 (47)	97	47/49	33.9 (50)	96	50/50
64	35.6 (50)	50/50	35.2 (45)	99	46/48	34.7 (47)	97	47/49	34.3 (50)	96	50/50
66	35.6 (50)	50/50	35.2 (45)	99	46/48	34.2 (47)	96	47/49	34.1 (50)	96	50/50
68	36.0 (49)	49/50	35.5 (44)	99	45/48	35.5 (47)	99	47/49	34.6 (50)	96	50/50
70	36.6 (49)	49/50	36.5 (44)	100	45/48	35.5 (47)	97	47/49	34.8 (50)	95	50/50
72	36.9 (48)	48/50	36.4 (44)	99	45/48	35.7 (46)	97	46/49	35.2 (50)	95	50/50
74	37.0 (46)	46/50	36.4 (44)	98	45/48	36.2 (46)	98	46/49	34.7 (50)	94	50/50
76	37.1 (46)	46/50	37.1 (42)	100	43/48	36.0 (45)	97	44/49	35.6 (49)	96	49/50
78	38.3 (46)	46/50	38.0 (42)	99	43/48	37.8 (44)	99	44/49	35.7 (49)	93	49/50
80	39.0 (46)	46/50	37.8 (42)	97	43/48	37.2 (42)	95	42/49	36.1 (49)	93	49/50
82	38.9 (44)	44/50	39.0 (41)	100	42/48	37.6 (41)	97	40/49	35.9 (47)	92	47/50
84	38.9 (43)	43/50	37.8 (41)	97	42/48	37.9 (40)	97	39/49	35.7 (43)	92	43/50
86	39.3 (43)	43/50	38.4 (40)	98	41/48	38.0 (37)	97	37/49	36.4 (41)	93	41/50
88	39.2 (43)	43/50	38.0 (39)	97	41/48	38.0 (37)	97	37/49	35.3 (41)	90	41/50
90	39.6 (43)	43/50	38.5 (39)	97	40/48	38.2 (34)	96	34/49	34.9 (40)	88	40/50
92	39.3 (41)	41/50	37.8 (39)	96	40/48	37.7 (34)	96	34/49	34.9 (35)	89	35/50
94	39.5 (41)	41/50	37.5 (38)	95	38/47	37.5 (33)	95	33/49	34.0 (33)	86	33/50
96	38.8 (41)	41/50	37.2 (35)	96	34/47	37.2 (32)	96	32/49	33.8 (31)	87	31/50
98	38.6 (39)	39/50	37.8 (32)	98	32/47	36.8 (32)	95	32/49	33.7 (29)	87	29/50
100	38.1 (38)	38/50	37.6 (30)	99	30/47	36.5 (27)	96	27/49	31.6 (27)	83	27/50
102	38.5 (37)	37/50	37.9 (29)	98	28/47	35.6 (25)	92	25/49	31.6 (24)	82	24/50
104	37.3 (34)	32/50	37.3 (27)	100	27/47	35.5 (23)	95	22/49	31.1 (17)	83	17/50

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

TABLE 31 INCIDENCE AND TIME OF MASS OCCURRENCE(CLINICAL OBSERVATION) :MOUSE :MALE

Time of mass occurrence		Dosing week 0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
The kind of mass		No. of animals with mass (No. of dead and moribund animals with mass)								
Internal mass										
	Control	0	0	0	1	3	8	10	11	18(12)
	10 ppm	0	0	0	0	3	14	9	16	26(9)
	50 ppm	0	0	0	1	3	17	18	20	31(14)
	250 ppm	0	0	0	1	4	11	12	20	30(18)
External mass	Control	0	0	0	0	0	0	4	3	5(3)
	10 ppm	0	0	0	0	0	2	2	4	5(3)
	50 ppm	0	0	0	0	2	1	5	5	6(3)
	250 ppm	0	0	0	0	1	2	7	10	12(7)

TABLE 32 INCIDENCE AND TIME OF MASS OCCURRENCE(CLINICAL OBSERVATION) :MOUSE :FEMALE

Time of mass occurrence		Dosing week 0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
The kind of mass		No. of animals with mass (No. of dead and moribund animals with mass)								
Internal mass										
	Control	0	0	0	1	3	7	7	8	18(14)
	10 ppm	0	0	0	1	2	7	7	8	16(14)
	50 ppm	0	0	0	2	9	9	8	7	21(13)
	250 ppm	0	0	0	1	1	7	9	13	22(18)
External mass	Control	0	0	0	0	0	2	4	4	8(4)
	10 ppm	0	0	0	0	0	1	1	4	4(2)
	50 ppm	0	0	0	0	2	1	5	6	8(7)
	250 ppm	0	0	0	0	1	2	3	3	5(3)

(Study No. 0104, 0105)

TABLE 33 FOOD CONSUMPTION IN MALE MOUSE (TWO-YEAR STUDIES)

Week on Study	Control Av.FC.	Control No.of Surviv. <50>	10 ppm Av.FC.	10 ppm % of cont. <50>	10 ppm No.of Surviv.	50 ppm Av.FC.	50 ppm % of cont. <50>	50 ppm No.of Surviv.	250 ppm Av.FC.	250 ppm % of cont. <50>	250 ppm No.of Surviv.
1	3.8 (50)	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50
2	3.8 (50)	50/50	3.6 (50)	95	50/50	3.7 (50)	97	50/50	3.8 (50)	100	50/50
3	3.9 (50)	50/50	3.7 (50)	95	50/50	3.7 (50)	95	50/50	3.8 (50)	97	50/50
4	4.0 (50)	50/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50
5	4.0 (50)	50/50	3.9 (50)	98	50/50	4.0 (50)	100	50/50	3.9 (50)	98	50/50
6	4.1 (50)	50/50	3.9 (50)	95	50/50	3.9 (50)	95	50/50	3.9 (50)	95	50/50
7	4.1 (50)	50/50	3.8 (50)	93	50/50	4.0 (50)	98	50/50	3.9 (50)	95	50/50
8	4.1 (50)	50/50	4.0 (50)	98	50/50	4.1 (50)	100	50/50	4.0 (50)	98	50/50
9	4.2 (50)	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
10	4.1 (50)	50/50	4.1 (50)	100	50/50	4.1 (50)	100	50/50	4.0 (50)	98	50/50
11	4.2 (50)	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
12	4.3 (50)	50/50	4.1 (50)	95	50/50	4.2 (50)	98	50/50	4.2 (50)	98	50/50
13	4.2 (50)	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50	4.0 (50)	95	50/50
14	4.2 (50)	50/50	4.2 (50)	100	50/50	4.2 (50)	100	50/50	4.2 (50)	100	50/50
18	4.4 (50)	50/50	4.2 (50)	95	50/50	4.4 (50)	100	50/50	4.3 (50)	98	50/50
22	4.4 (50)	50/50	4.4 (50)	100	50/50	4.4 (50)	100	50/50	4.1 (50)	93	50/50
26	4.6 (50)	50/50	4.5 (50)	98	50/50	4.6 (50)	100	50/50	4.4 (50)	96	50/50
30	4.6 (49)	49/50	4.5 (50)	98	50/50	4.6 (50)	100	50/50	4.4 (50)	96	50/50
34	4.6 (49)	49/50	4.5 (50)	98	50/50	4.6 (50)	100	50/50	4.5 (49)	98	49/50
38	4.8 (49)	49/50	4.6 (50)	96	50/50	4.7 (50)	98	50/50	4.7 (49)	98	49/50
42	4.7 (48)	48/50	4.6 (49)	98	49/50	4.6 (49)	98	49/50	4.5 (49)	96	49/50
46	4.6 (48)	48/50	4.7 (49)	102	49/50	4.6 (49)	100	49/50	4.5 (49)	98	49/50
50	4.7 (46)	46/50	4.6 (49)	98	49/50	4.7 (49)	100	49/50	4.6 (49)	98	49/50
52	4.7 (46)	46/50	4.6 (49)	98	49/50	4.8 (48)	102	48/50	4.5 (49)	96	49/50
54	4.7 (46)	46/50	4.5 (49)	96	49/50	4.8 (48)	102	48/50	4.6 (49)	98	49/50
58	5.0 (46)	46/50	4.8 (48)	96	48/50	5.1 (48)	102	48/50	4.8 (49)	96	49/50
62	4.7 (46)	46/50	4.7 (48)	100	48/50	4.9 (48)	104	48/50	4.6 (49)	98	49/50
66	4.8 (46)	46/50	4.7 (47)	98	47/50	4.9 (47)	102	47/50	4.7 (49)	98	48/50
70	4.8 (46)	46/50	4.7 (47)	98	47/50	4.8 (46)	100	46/50	4.7 (48)	98	47/50
74	4.8 (46)	46/50	4.9 (47)	102	47/50	4.7 (46)	98	44/50	4.4 (47)	92	47/50
78	5.1 (44)	44/50	5.0 (47)	98	47/50	5.1 (43)	100	43/50	5.0 (46)	98	46/50
82	5.2 (44)	44/50	5.0 (47)	96	47/50	5.2 (42)	100	41/50	4.9 (44)	94	44/50
86	5.2 (42)	42/50	5.0 (46)	96	46/50	5.1 (41)	98	41/50	4.6 (41)	88	40/50
90	5.2 (42)	42/50	5.0 (46)	96	46/50	5.1 (39)	98	38/50	4.8 (39)	92	39/50
94	5.0 (41)	41/50	4.9 (44)	98	44/50	4.9 (36)	98	34/50	4.6 (36)	92	35/50
98	5.0 (36)	36/50	5.0 (41)	100	40/50	5.1 (31)	102	31/50	4.6 (33)	92	31/50
102	4.9 (36)	34/50	4.8 (37)	98	37/50	4.9 (30)	100	30/50	4.4 (25)	90	25/50
104	5.1 (32)	31/50	4.8 (35)	94	35/50	4.7 (28)	92	28/50	4.5 (24)	88	22/50

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

TABLE 34 FOOD CONSUMPTION IN FEMALE MOUSE (TWO-YEAR STUDIES)

Week on Study	Control Av.FC.	Control No.of Surviv. <50>	10 ppm Av.FC.	10 ppm % of cont. <47>	10 ppm No.of Surviv.	50 ppm Av.FC.	50 ppm % of cont. <49>	50 ppm No.of Surviv.	250 ppm Av.FC.	250 ppm % of cont. <50>	250 ppm No.of Surviv.
1	3.2 (50)	50/50	3.3 (47)	103	50/50	3.1 (49)	97	50/50	3.2 (50)	100	50/50
2	3.1 (50)	50/50	3.1 (47)	100	50/50	3.2 (49)	103	50/50	3.2 (50)	103	50/50
3	3.4 (50)	50/50	3.2 (47)	94	50/50	3.4 (49)	100	50/50	3.5 (50)	103	50/50
4	3.6 (50)	50/50	3.5 (47)	97	50/50	3.6 (49)	100	50/50	3.7 (50)	103	50/50
5	3.7 (50)	50/50	3.6 (47)	97	50/50	3.7 (49)	100	50/50	3.8 (50)	103	50/50
6	3.9 (50)	50/50	3.7 (47)	95	50/50	3.8 (49)	97	50/50	3.7 (50)	95	50/50
7	3.9 (50)	50/50	3.8 (47)	97	49/49	3.9 (49)	100	50/50	3.8 (50)	97	50/50
8	4.0 (50)	50/50	3.9 (47)	98	49/49	4.0 (49)	100	50/50	3.9 (50)	98	50/50
9	4.0 (50)	50/50	3.9 (47)	98	49/49	3.9 (49)	98	50/50	4.0 (50)	100	50/50
10	4.0 (50)	50/50	3.9 (47)	98	49/49	3.8 (49)	95	50/50	3.9 (50)	98	50/50
11	4.0 (50)	50/50	3.9 (47)	98	49/49	3.9 (49)	98	50/50	3.9 (50)	98	50/50
12	3.9 (50)	50/50	3.9 (47)	100	49/49	4.0 (49)	103	50/50	4.0 (50)	103	50/50
13	3.9 (50)	50/50	3.8 (47)	97	49/49	3.9 (49)	100	50/50	3.9 (50)	100	50/50
14	3.9 (50)	50/50	3.9 (47)	100	49/49	4.0 (49)	103	50/50	4.0 (50)	103	50/50
18	4.2 (50)	50/50	4.1 (47)	98	49/49	4.1 (49)	98	50/50	4.3 (50)	102	50/50
22	4.3 (50)	50/50	4.1 (47)	95	49/49	4.1 (49)	95	50/50	4.1 (50)	95	50/50
26	4.5 (50)	50/50	4.4 (47)	98	49/49	4.4 (49)	98	49/49	4.5 (50)	100	50/50
30	4.5 (50)	50/50	4.4 (47)	98	49/49	4.5 (49)	100	49/49	4.4 (50)	98	50/50
34	4.7 (50)	50/50	4.5 (47)	96	49/49	4.5 (49)	96	49/49	4.5 (50)	96	50/50
38	4.6 (50)	50/50	4.6 (47)	100	49/49	4.6 (49)	100	49/49	4.7 (50)	102	50/50
42	4.6 (50)	50/50	4.4 (47)	96	49/49	4.6 (48)	100	48/49	4.5 (50)	98	50/50
46	4.4 (50)	50/50	4.4 (47)	100	49/49	4.3 (48)	98	48/49	4.5 (50)	102	50/50
50	4.4 (50)	50/50	4.4 (47)	100	49/49	4.4 (48)	100	48/49	4.5 (50)	102	50/50
52	4.7 (50)	50/50	4.5 (47)	96	49/49	4.6 (48)	98	48/49	4.5 (50)	96	50/50
54	4.5 (50)	50/50	4.3 (47)	96	48/48	4.4 (48)	98	47/49	4.7 (50)	104	50/50
58	4.9 (50)	50/50	4.7 (44)	96	48/48	4.7 (47)	96	47/49	4.7 (50)	96	50/50
62	4.5 (50)	50/50	4.4 (47)	98	48/48	4.4 (47)	98	47/49	4.4 (50)	98	50/50
66	4.5 (49)	50/50	4.5 (45)	100	46/48	4.4 (47)	98	47/49	4.4 (50)	98	50/50
70	4.6 (49)	49/50	4.6 (44)	100	45/48	4.4 (47)	96	47/49	4.6 (50)	100	50/50
74	4.4 (48)	46/50	4.7 (44)	107	45/48	4.4 (46)	100	46/49	4.3 (50)	98	50/50
78	4.8 (46)	46/50	4.7 (42)	98	43/48	5.0 (44)	104	44/49	4.9 (49)	102	49/50
82	4.9 (45)	44/50	4.9 (42)	100	42/48	4.9 (41)	100	40/49	4.7 (48)	96	47/50
86	5.0 (43)	43/50	4.9 (40)	98	41/48	4.8 (38)	96	37/49	4.8 (41)	96	41/50
90	4.8 (43)	43/50	5.0 (39)	104	40/48	4.8 (35)	100	34/49	4.7 (41)	98	40/50
94	4.9 (41)	41/50	4.7 (38)	96	38/47	4.6 (34)	94	33/49	4.6 (35)	94	33/50
98	4.8 (40)	39/50	4.5 (34)	94	32/47	4.6 (31)	96	32/49	4.8 (30)	100	29/50
102	4.6 (38)	37/50	4.6 (29)	100	28/47	4.3 (27)	93	25/49	4.3 (24)	93	24/50
104	4.1 (37)	32/50	4.4 (28)	107	27/47	4.7 (24)	115	22/49	4.0 (18)	98	17/50

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

TABLE 35 NEOPLASTIC LESIONS (SPLEEN) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE:MALE

Group Name	Control	10 ppm	50 ppm	250 ppm
SITE : spleen				
TUMOUR : hemangioendothelioma				
Overall Rates(a)	1/50 (2.0)	1/50 (2.0)	3/50 (6.0)	5/50 (10.0)
Adjusted Rates(b)	3.23	0.0	6.38	12.00
Terminal Rates(c)	1/31 (3.2)	0/35 (0.0)	0/28 (0.0)	2/22 (9.1)
Standard Rates(d)	P=0.5167			
Prevalence Rates(d)	P=0.0177*			
Combind analysis(d)	P=0.0340*			
Cochran-Armitage Test(e)	P=0.0420*			
Fisher Exact Test(e)		P=0.2475	P=0.3235	P=0.1210
SITE : spleen				
TUMOUR : hemangioendothelioma:benign,hemangioendothelioma				
Overall Rates(a)	2/50 (4.0)	2/50 (4.0)	3/50 (6.0)	6/50 (12.0)
Adjusted Rates(b)	6.45	2.86	6.38	12.90
Terminal Rates(c)	2/31 (6.5)	1/35 (2.9)	0/28 (0.0)	2/22 (9.1)
Standard Rates(d)	P=0.5167			
Prevalence Rates(d)	P=0.0276*			
Combind analysis(d)	P=0.0458*			
Cochran-Armitage Test(e)	P=0.0608			
Fisher Exact Test(e)		P=0.3088	P=0.4909	P=0.1606

(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
Combind analysis : Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates.
? :The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value beyond the estimated P-value.
-------:There is no data which should be statistic analysis.

TABLE 36 NEOPLASTIC LESIONS (LIVER) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE:MALE

Group Name	Control	10 ppm	50 ppm	250 ppm
SITE : liver TUMOUR : hepatocellular adenoma				
Overall Rates(a)	7/50 (14.0)	13/50 (26.0)	8/50 (16.0)	26/50 (52.0)
Adjusted Rates(b)	15.22	34.29	20.59	77.27
Terminal Rates(c)	4/31 (12.9)	12/35 (34.3)	5/28 (17.9)	17/22 (77.3)
Standard Rates(d)	P=1.0000 ?			
Prevalence Rates(d)	P<0.0001**			
Combind analysis(d)	P<0.0001**			
Cochran-Armitage Test(e)	P<0.0001**			
Fisher Exact Test(e)		P=0.1634	P=0.4854	P=0.0029**
SITE : liver TUMOUR : hemangioendothelioma				
Overall Rates(a)	1/50 (2.0)	1/50 (2.0)	5/50 (10.0)	5/50 (10.0)
Adjusted Rates(b)	0.0	2.17	3.57	13.64
Terminal Rates(c)	0/31 (0.0)	0/35 (0.0)	1/28 (3.6)	3/22 (13.6)
Standard Rates(d)	P=0.2158			
Prevalence Rates(d)	P=0.0270*			
Combind analysis(d)	P=0.0332*			
Cochran-Armitage Test(e)	P=0.0883			
Fisher Exact Test(e)		P=0.2475	P=0.1210	P=0.1210
SITE : liver TUMOUR : hepatocellular carcinoma				
Overall Rates(a)	7/50 (14.0)	8/50 (16.0)	12/50 (24.0)	25/50 (50.0)
Adjusted Rates(b)	16.13	16.67	25.00	45.45
Terminal Rates(c)	5/31 (16.1)	5/35 (14.3)	7/28 (25.0)	10/22 (45.5)
Standard Rates(d)	P=0.0010**			
Prevalence Rates(d)	P=0.0002**			
Combind analysis(d)	P<0.0001**			
Cochran-Armitage Test(e)	P<0.0001**			
Fisher Exact Test(e)		P=0.4854	P=0.2119	P=0.0041**
SITE : liver TUMOUR : hepatocellular adenoma, hepatocellular carcinoma				
Overall Rates(a)	13/50 (26.0)	21/50 (42.0)	19/50 (38.0)	40/50 (80.0)
Adjusted Rates(b)	26.47	50.00	39.39	90.91
Terminal Rates(c)	8/31 (25.8)	17/35 (48.6)	11/28 (39.3)	20/22 (90.9)
Standard Rates(d)	P=0.0020**			
Prevalence Rates(d)	P<0.0001**			
Combind analysis(d)	P<0.0001**			
Cochran-Armitage Test(e)	P<0.0001**			
Fisher Exact Test(e)		P=0.1615	P=0.2359	P=0.0018**

(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
Combind analysis : Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates.
? :The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value beyond the estimated P-value.
-------:There is no data which should be statistic analysis.

TABLE 37 NEOPLASTIC LESIONS (LIVER) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE:FEMALE

Group Name	Control	10 ppm	50 ppm	250 ppm
SITE : liver TUMOUR : hepatocellular adenoma				
Overall Rates(a)	3/50 (6.0)	3/47 (6.4)	7/49 (14.3)	26/49 (53.1)
Adjusted Rates(b)	9.38	11.11	30.43	64.00
Terminal Rates(c)	3/32 (9.4)	3/27 (11.1)	6/22 (27.3)	9/17 (52.9)
Standard Rates(d)	P=------			
Prevalence Rates(d)	P<0.0001**?			
Combind analysis(d)	P=------			
Cochran-Armitage Test(e)	P<0.0001**			
Fisher Exact Test(e)		P=0.3673	P=0.1836	P=0.0001**
SITE : liver TUMOUR : hepatocellular carcinoma				
Overall Rates(a)	0/50 (0.0)	0/47 (0.0)	0/49 (0.0)	14/49 (28.6)
Adjusted Rates(b)	0.0	0.0	0.0	23.33
Terminal Rates(c)	0/32 (0.0)	0/27 (0.0)	0/22 (0.0)	3/17 (17.6)
Standard Rates(d)	P<0.0001**?			
Prevalence Rates(d)	P<0.0001**?			
Combind analysis(d)	P<0.0001**?			
Cochran-Armitage Test(e)	P<0.0001**?			
Fisher Exact Test(e)		P=0.5000	P=0.5000	P=0.0001**
SITE : liver TUMOUR : hepatocellular adenoma, hepatocellular carcinoma				
Overall Rates(a)	3/50 (6.0)	3/47 (6.4)	7/49 (14.3)	33/49 (67.3)
Adjusted Rates(b)	9.38	11.11	30.43	69.70
Terminal Rates(c)	3/32 (9.4)	3/27 (11.1)	6/22 (27.3)	10/17 (58.8)
Standard Rates(d)	P<0.0001**?			
Prevalence Rates(d)	P<0.0001**?			
Combind analysis(d)	P<0.0001**?			
Cochran-Armitage Test(e)	P<0.0001**?			
Fisher Exact Test(e)		P=0.3673	P=0.1836	P<0.0001**

(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
Combind analysis : Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates.
? :The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value beyond the estimated P-value.
------:There is no data which should be statistic analysis.

TABLE 38 NUMBER OF MOUSE WITH SELECTED LIVER LESIONS

	Male				Female			
Group	Control	10ppm	50ppm	250ppm	Control	10ppm	50ppm	250ppm
Number of examined	50	50	50	50	50	47	49	50
Anigectasis	1	3	12	30	6	9	8	26
Degeneration:central	1	1	4	37	0	1	2	30
Necrosis:central	0	0	2	3	1	1	1	0
Necrosis:focal	3	4	8	13	1	1	1	0
Hyperplasia	1	0	3	3	0	1	0	0
Clear cell focus	2	2	3	5	1	1	0	4
Acidophilic cell focus	1	1	0	0	0	0	0	1
Basophilic cell focus	2	3	4	5	0	0	0	1
Vacuolic cell focus	0	0	0	0	1	0	0	1
Mixed cell focus	0	0	0	0	2	1	1	0
Hepatocellular adenoma	7	13	8	26	3	3	7	26
Cholangiocellular adenoma	0	0	0	0	0	1	0	0
Histiocytic sarcoma	2	0	1	1	1	1	1	0
Hemangioendothelioma	1	1	5	5	0	0	0	1
Hepatocellular carcinoma	7	8	12	25	0	0	0	14

TABLE 39 NUMBER OF MOUSE WITH SELECTED KIDNEY LESIONS

	Male				Female			
Group	Control	10ppm	50ppm	250ppm	Control	10ppm	50ppm	250ppm
Number of examined	50	50	50	50	50	47	49	50
Nuclear enlargement: proximal tubule	0	0	6	38	0	0	1	49
Atypical tubular dilation: proximal tubule	0	0	0	1	0	0	0	6
Renal cell adenoma	0	1	0	0	0	0	0	0
Renal cell carcinoma	0	0	1	0	0	0	0	0

TABLE 40 NEOPLASTIC LESIONS (HARDERIAN GLAND) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE:MALE

Group Name	Control	10 ppm	50 ppm	250 ppm
SITE : Harderian gland				
TUMOUR : adenoma				
Overall Rates(a)	2/50 (2.0)	2/50 (4.0)	2/50 (4.0)	8/50 (16.0)
Adjusted Rates(b)	6.45	5.26	6.45	23.08
Terminal Rates(c)	2/31 (6.5)	1/35 (2.9)	0/28 (0.0)	4/22 (18.2)
Standard Rates(d)	P=------			
Prevalence Rates(d)	P=0.0024**			
Combind analysis(d)	P=------			
Cochran-Armitage Test(e)	P=0.0046**			
Fisher Exact Test(e)		P=0.3088	P=0.3088	P=0.0671

TABLE 41 NEOPLASTIC LESIONS (PITUITARY GLAND) INCIDENCE AND STATISTICAL ANALYSIS : MOUSE:FEMALE

Group Name	Control	10 ppm	50 ppm	250 ppm
SITE : pituitary gland				
TUMOUR : adenoma				
Overall Rates(a)	9/49 (18.4)	11/47 (23.4)	4/48 (8.3)	9/50 (18.0)
Adjusted Rates(b)	23.08	31.03	13.64	27.78
Terminal Rates(c)	7/32 (21.9)	8/27 (29.6)	3/22 (13.6)	4/17 (23.5)
Standard Rates(d)	P=0.0154*			
Prevalence Rates(d)	P=0.6810			
Combind analysis(d)	P=0.2327			
Cochran-Armitage Test(e)	P=0.9190			
Fisher Exact Test(e)		P=0.4032	P=0.1655	P=0.3839

(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
Combind analysis : Death analysis + Incidental tumor test
(e):The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates.
? :The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value beyond the estimated P-value.
------:There is no data which should be statistic analysis.

TABLE 42 CAUSE OF DEATH :MOUSE

Group	Male				Female			
	Control	10ppm	50ppm	250ppm	Control	10ppm	50ppm	250ppm
Number of dead/moriboud animal	19	15	22	28	18	20	27	33
No microscopical confirmation	2	2	1	0	0	1	2	0
Cardiovascular lesion	0	0	0	0	0	1	2	0
Respiratory sy. lesion	1	0	0	1	0	0	0	0
Hepatic lesion	0	1	1	4	0	0	0	1
Urinary sy. lesion	0	0	0	1	0	0	0	0
Renal lesion	3	1	4	1	1	2	0	1
Urinary retention	1	3	2	0	0	0	0	0
Amyloidosis	0	1	0	0	0	0	0	0
Arteritis	2	0	1	0	0	0	0	0
Tumor death : leukemia	4	3	3	4	6	4	13	10
: subcutis	0	0	0	1	0	2	0	1
: stomach	0	0	0	0	1	0	0	0
: lung	1	0	1	0	0	0	0	0
: lymph node	0	0	0	1	0	0	0	0
: spleen	0	1	0	0	0	0	0	0
: liver	4	3	8	13	0	1	1	7
: pituitary gland	0	0	0	0	1	2	2	4
: ovary	0	0	0	0	0	0	0	1
: uterus	0	0	0	0	8	8	8	9
: mammary gland	0	0	0	0	0	0	1	0
: epididymis	0	0	0	1	5	2	2	2
: seminal vesicle	1	0	0	1	1	0	0	0
: bone	0	0	1	0	1	2	2	1

(Study No. 0104, 0105)

SELECTED FIGURES

(Study No.0104, 0105)

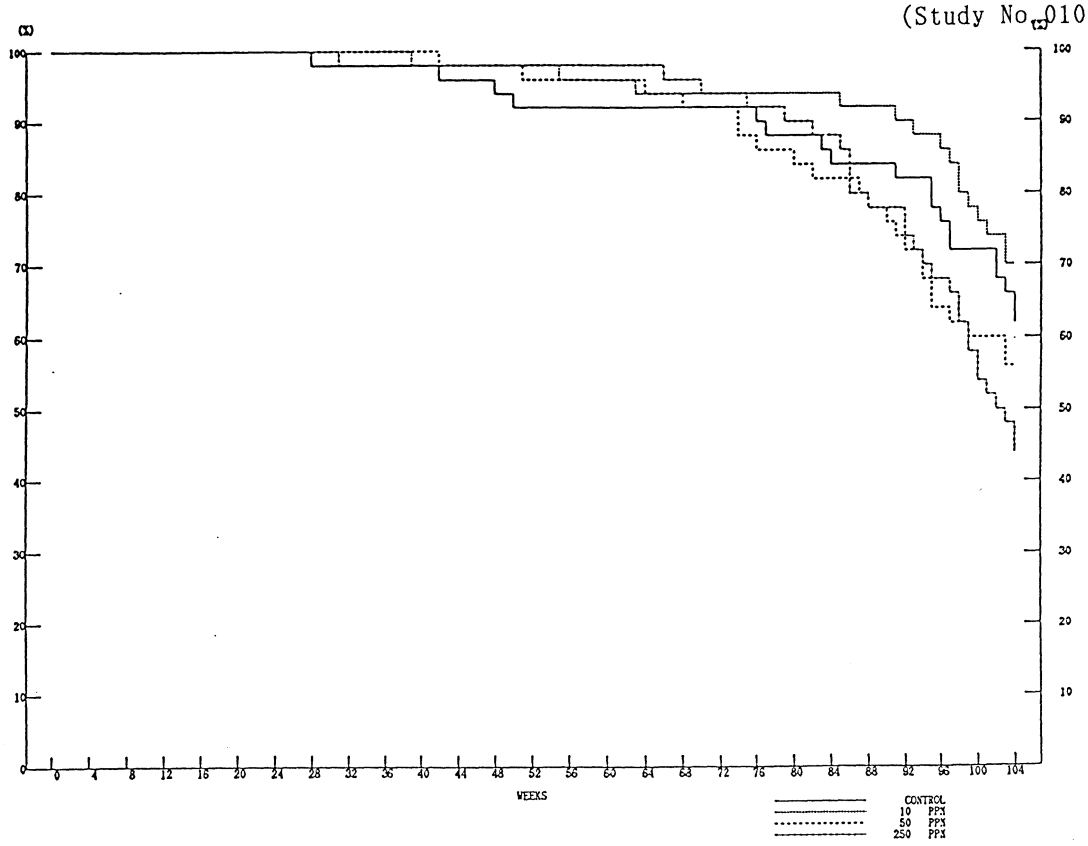


FIGURE 9 SURVIVAL ANIMAL RATE : MOUSE:MALE(TWO-YEAR STUDIES)

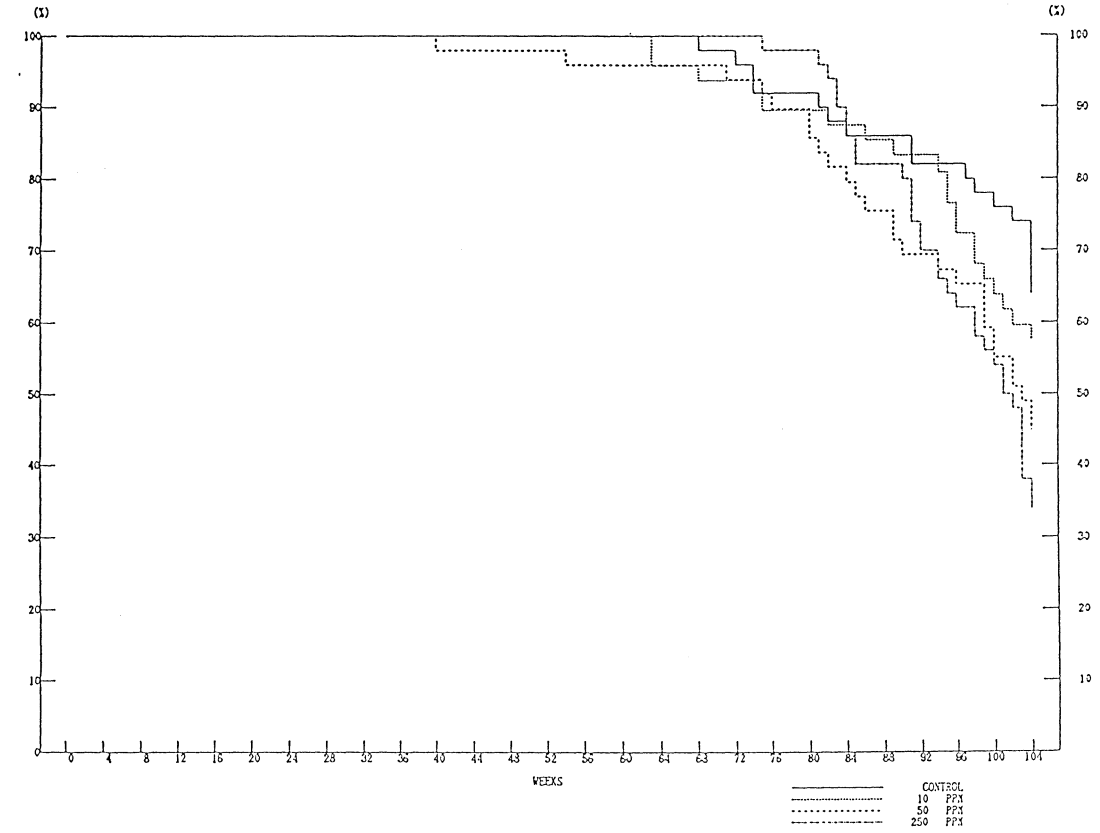


FIGURE 10 SURVIVAL ANIMAL RATE : MOUSE:FEMALE(TWO-YEAR STUDIES)

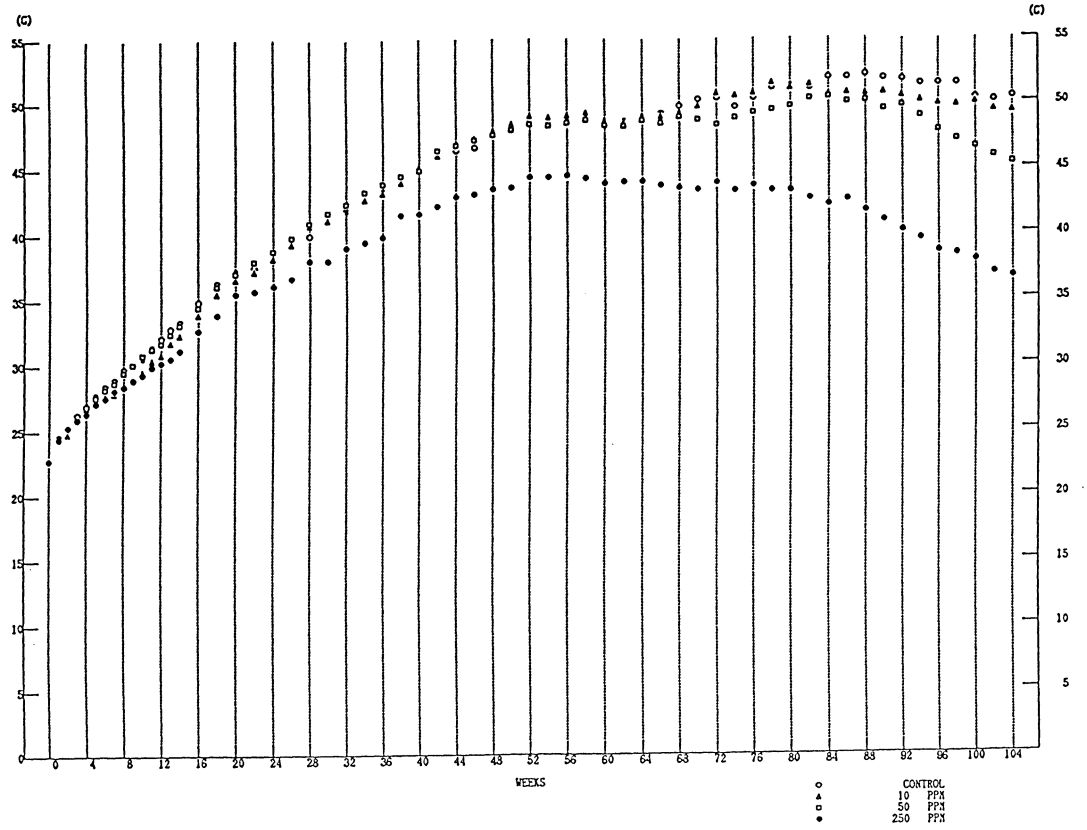


FIGURE 11 BODY WEIGHT CHANGES : MOUSE:MALE(TWO-YEAR STUDIES)

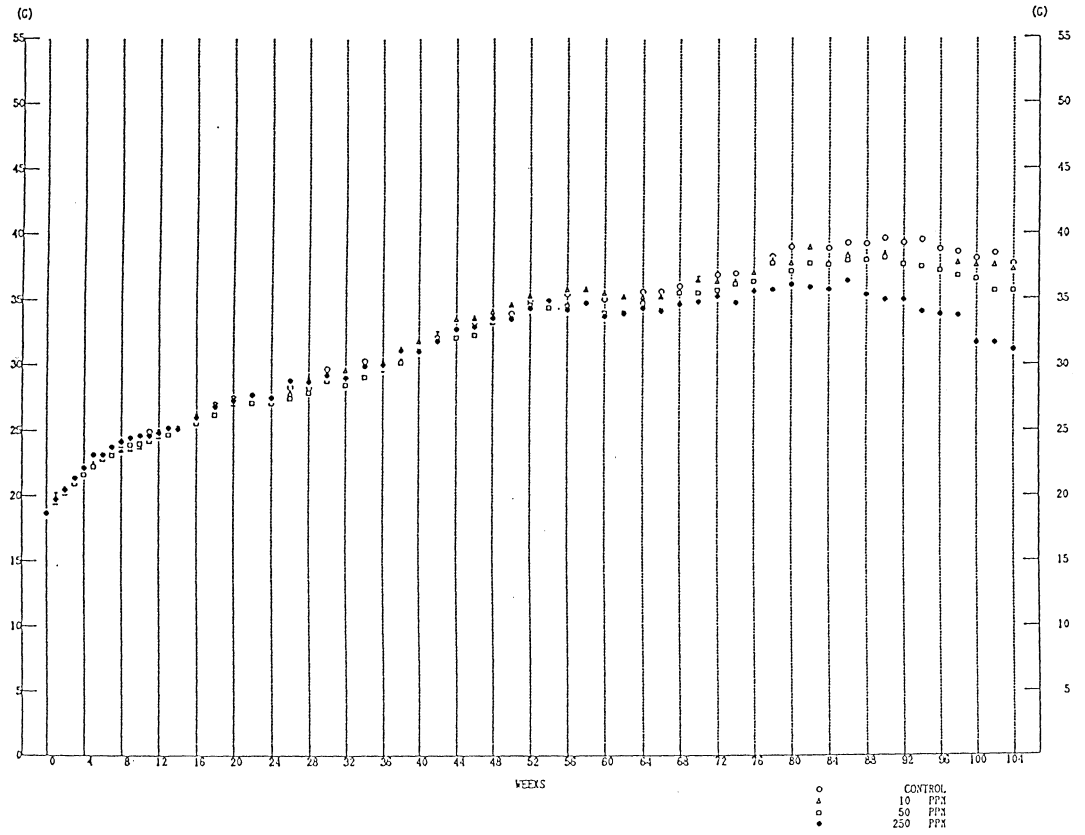


FIGURE 12 BODY WEIGHT CHANGES : MOUSE:FEMALE(TWO-YEAR STUDIES)

(Study No. 0104, 0105)

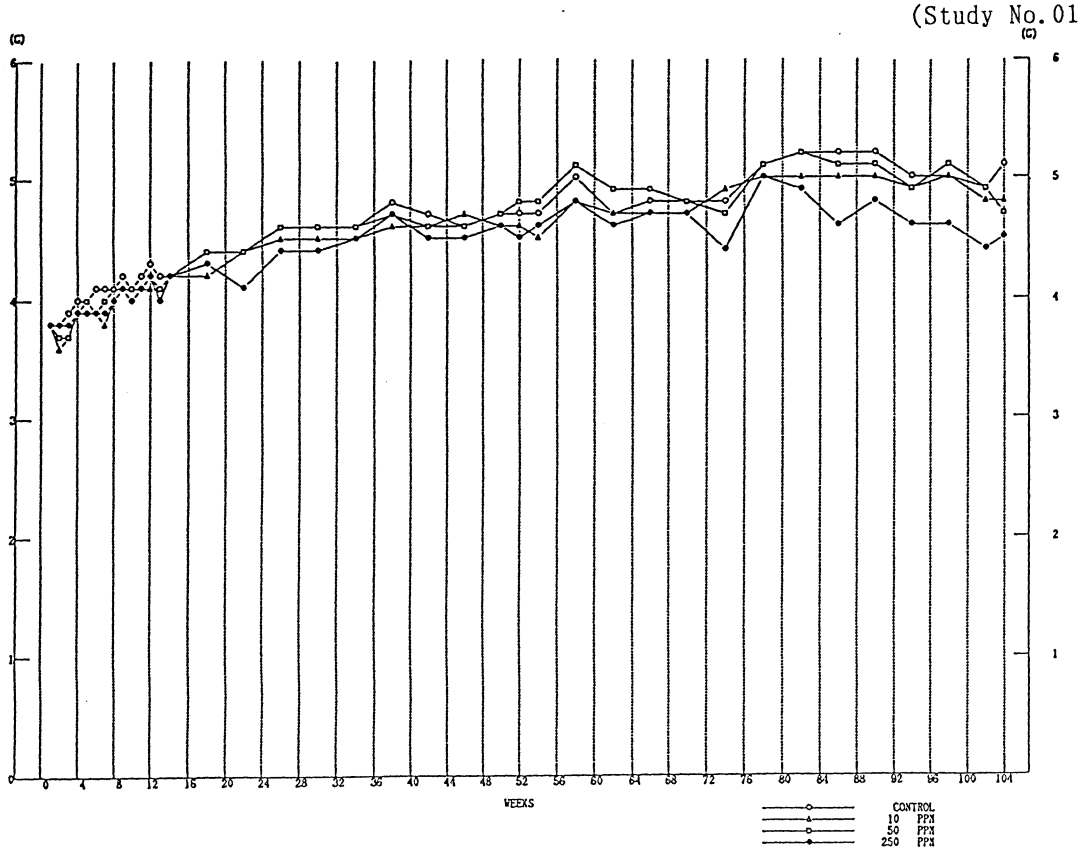


FIGURE 13 FOOD CONSUMPTION : MOUSE:MALE(TWO-YEAR STUDIES)

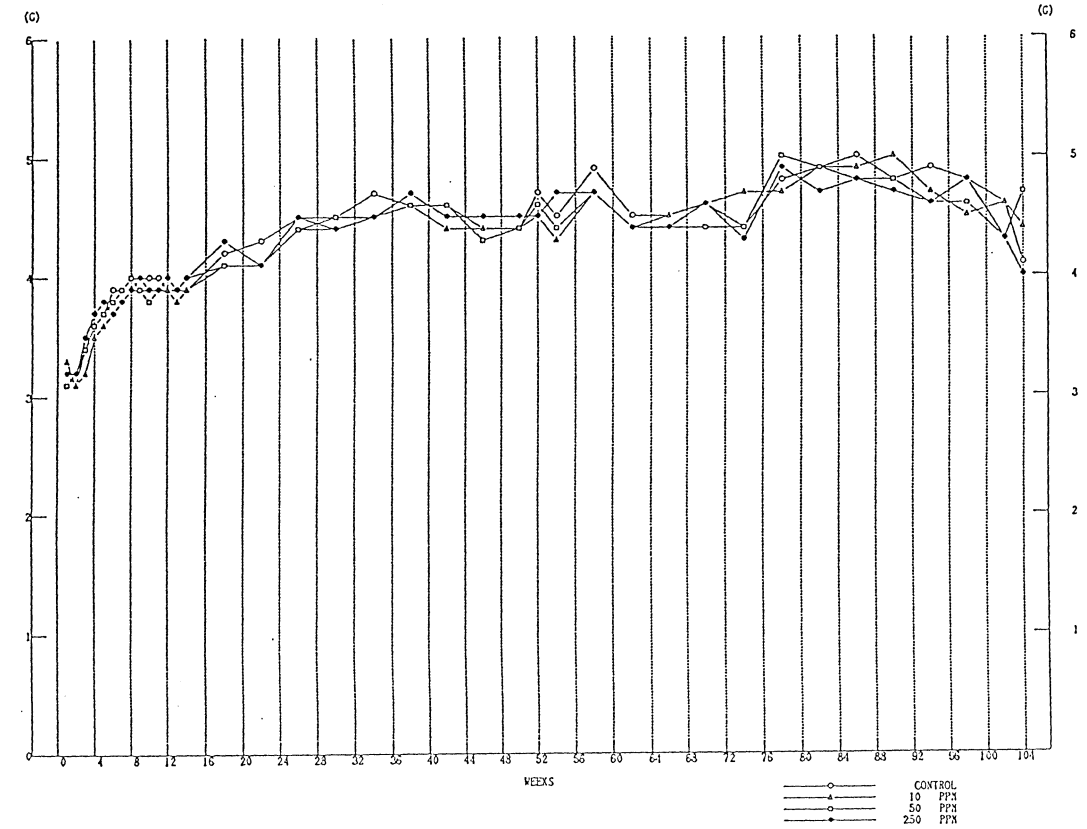


FIGURE 14 FOOD CONSUMPTION : MOUSE:FEMALE(TWO-YEAR STUDIES)

PHOTOGRAPHS

PHOTOGRAPH 7
LIVER, HEPATOCELLULAR ADENOMA :A
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO.0105-1307
(H. E., X152)

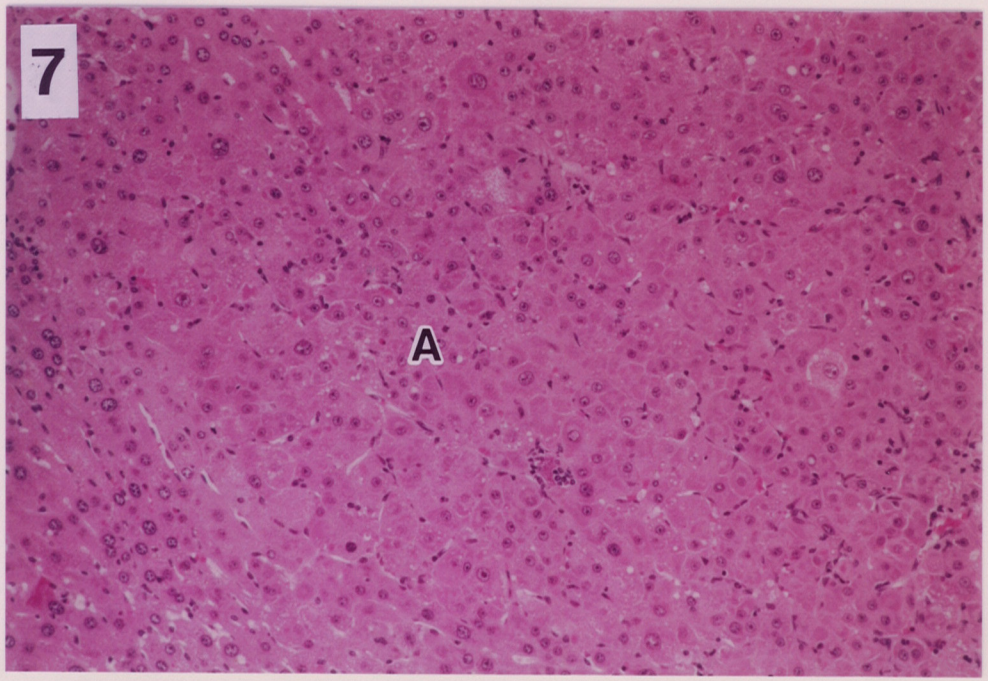
PHOTOGRAPH 8
LIVER, HEPATOCELLULAR CARCINOMA
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO. 0105-1346
(H. E., X152)

PHOTOGRAPH 9
LIVER, HEMANGIOENDOTHELIOMA
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO. 0105-1345
(H. E., X152)

PHOTOGRAPH 10
LIVER, ANGIECTASIS :A
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO.0105-1307
(H. E., X60)

PHOTOGRAPH 11
SPLEEN, HEMANGIOENDOTHERIOMA :A
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO.0105-1347
(H. E., X152)

PHOTOGRAPH 12
KIDNEY, NUCLEAR ENLARGMENT:PROXIMAL TUBULE :A
TWO-YEAR STUDY, MOUSE, MALE, 250 ppm, ANIMAL NO.0105-1306
(H. E., X304)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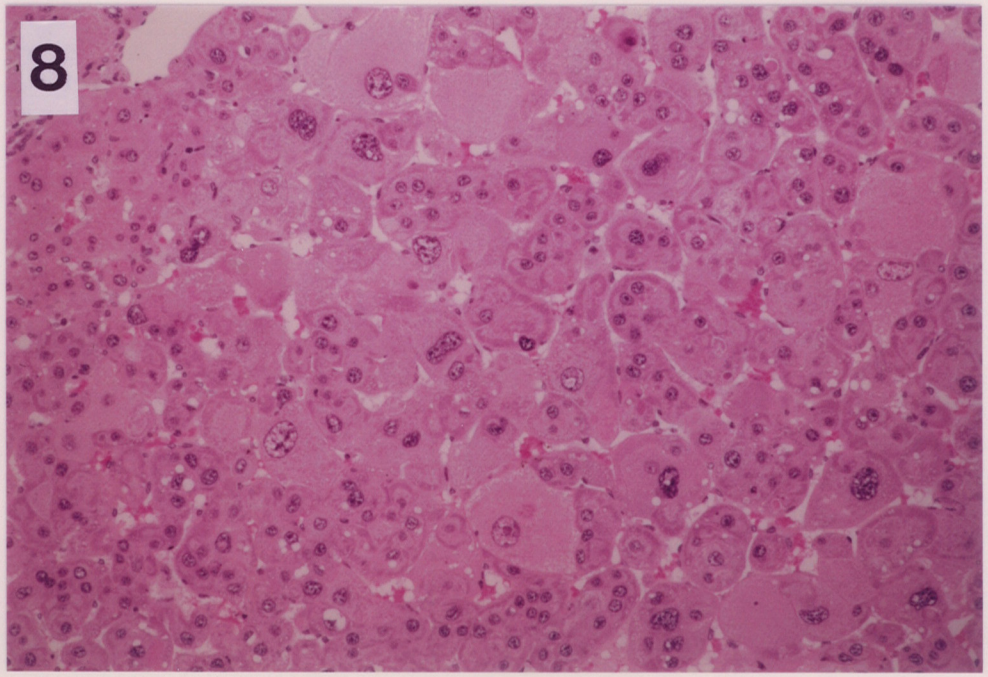
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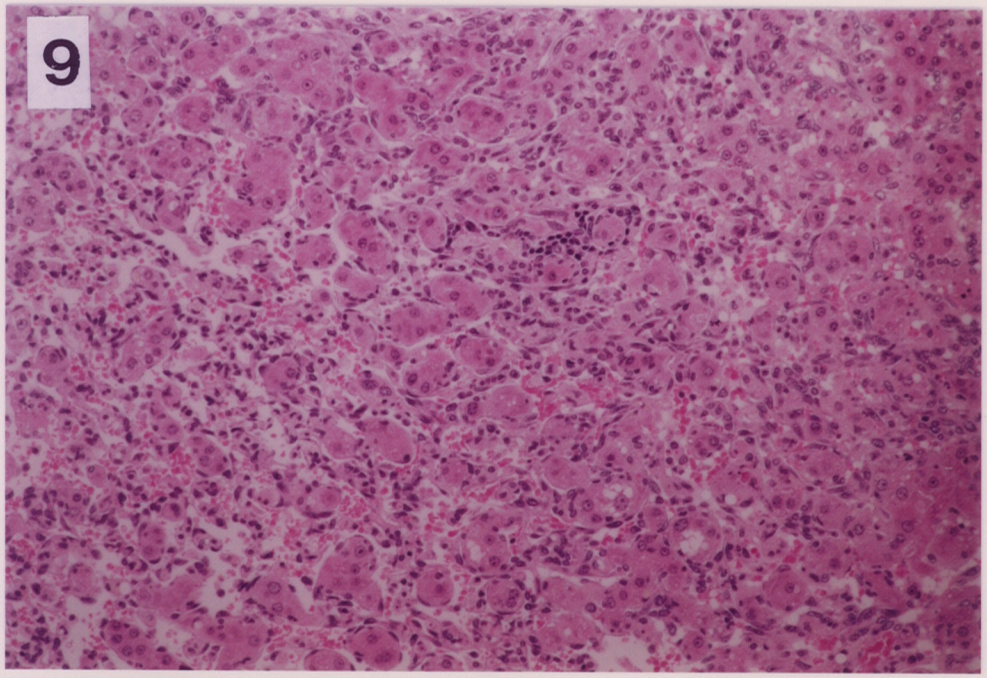
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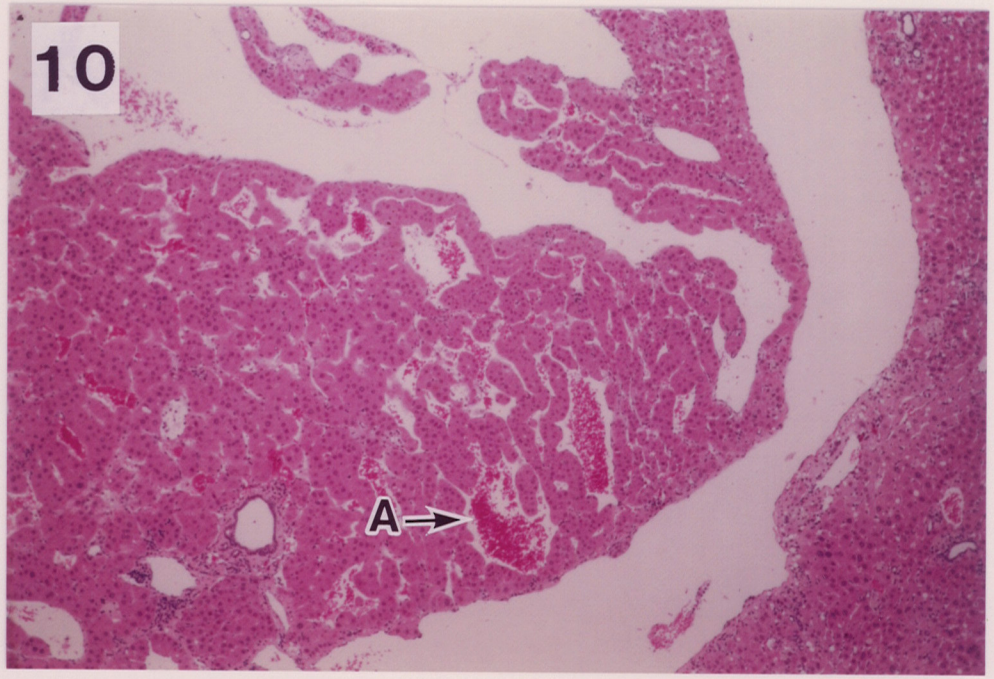
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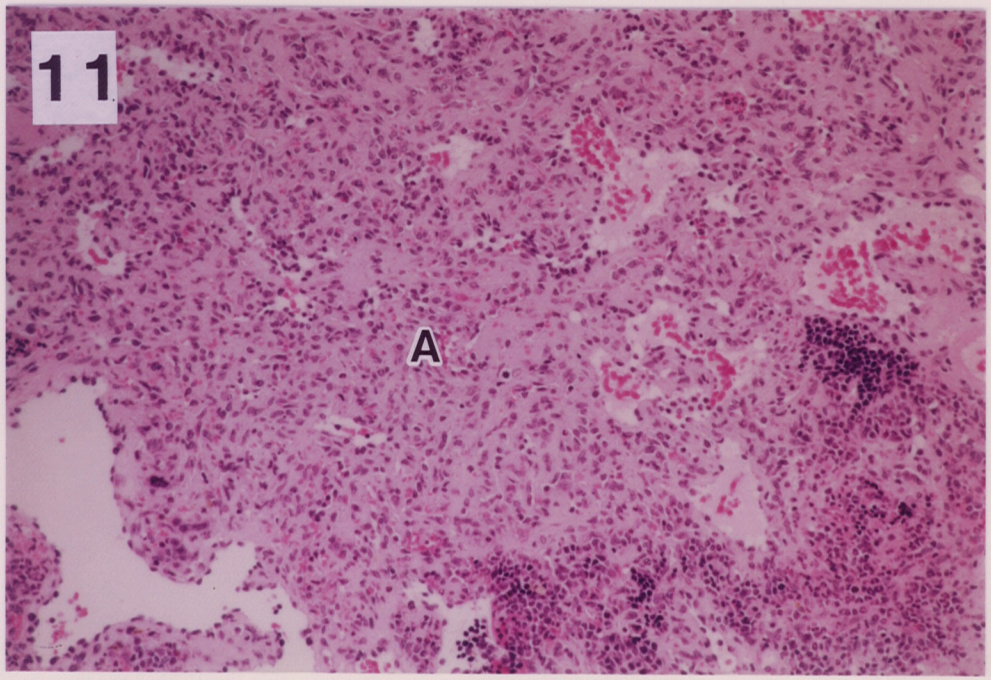
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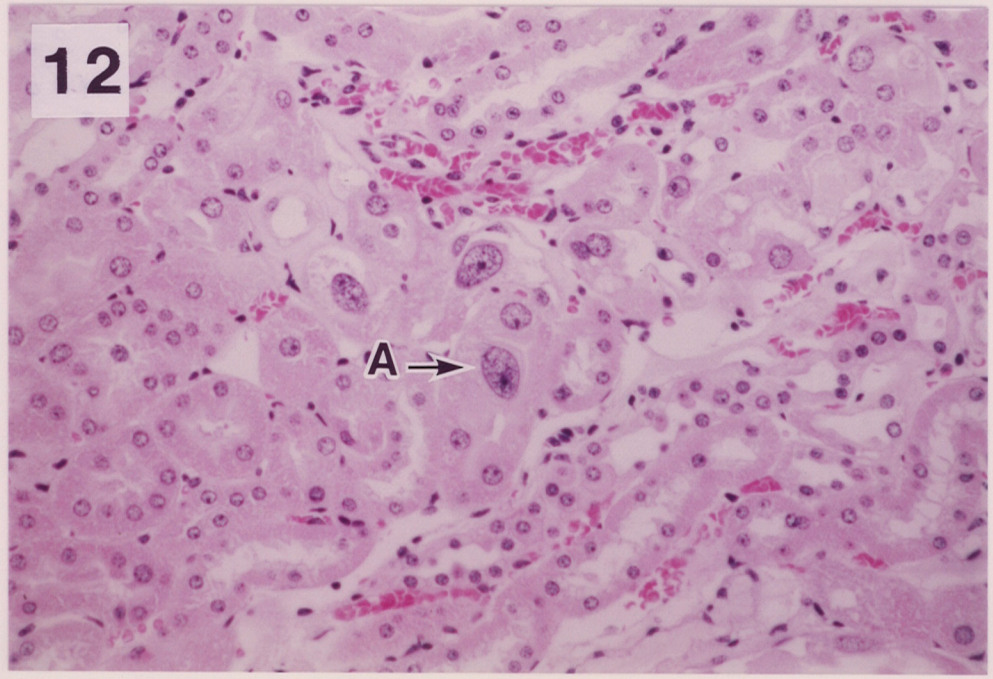
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