Summary of Feed Carcinogenicity Study of Diphenylamine in B6D2F1 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 Health, Labour and Welfare of Japan on August 25, 2011.

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

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Purpose, materials and methods

Diphenylamine (CAS No. 122-39-4) is a colourless solid with a floral odour. and with a melting point of 52.85°C. It is insoluble in water, and soluble alcohol, and ether.

The carcinogenicity and chronic toxicity of diphenylamine were examined in B6D2F1/Crlj mice. Groups of test animals were administered diphenylamine in their food for 2 years (104 weeks). Each group consisted of either 50 male or 50 female mice. The dietary concentration of diphenylamine were 0, 250, 1000 or 4000 ppm (w/w). Both sexes were administered each concentration of diphenylamine. 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 diphenylamine used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by high performance liquid chromatography before and after use to affirm its stability. The concentrations of diphenylamine in the diet were determined by high performance liquid chromatography at the time of preparation and on the 8th day after preparation while stored at room temperature or stored in the refrigerator. 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 4 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year administration period underwent complete necropsy. Urinalysis was performed near the end of the administration period. 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 diphenylamine 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 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

The markedly decreased survival rate of the 4000 ppm-fed male group was attributed to the increased number of deaths due to urinary retention. Survival rates of the females fed 4000 ppm inceased more than the female control at the end of administration period. Brown urine was observed in the 4000 ppm-fed males and females. Body weights were supressed in males fed 4000 ppm diphenylamine throughout the 2-year administration period and in females fed 4000 ppm diphenylamine after 18th week of the administration period. Food consumption in the all administerd group were similar to the respective controls. Due to the markedly decreased survival rate caused by urinary retention and the marked body weights supression, the high dose level of 4000 ppm for males was considered to exceed the MTD.

The incidences of selected neoplastic lesions in male and female mice are presented in the tables below. The combined incidence of hemangioma and/or hemangiosarcoma in spleen was increased in males fed 1000 ppm (Fisher’s exact test). The incidence of hemangioma in all organs including subcutis, bone marrow, spleen, liver and heart was increased in males (Peto test), and the incidence of hemangioma and the combined incidence of hemangioma and/or hemangiosarcoma was increased in males fed 1000 ppm (Fisher’s exact test). The incidence of histiocytic sarcoma in uterus was increased in female mice fed 1000 ppm diphenylamine. But the incidence was within the range of maximum incidence of the JBRC historical control data, so the incidence of histiocytic sarcoma in uterus can not be judged to be attributed to the diphenylamine administration. No significant diphenylamine related increase in incidence of neoplastic lesions was found in females.

In blood and hematopoietic system, methemoglobin concentration was increased in all groups of males and females fed diphenylamine. Anemia caused by the increase of methemoglobin concentration was observed in all groups of males and females fed diphenylamine. Also vearious anemia-related changes in hematology and biochemistry were observed in diphenylamine-fed groups. In the bone marrow, increased hematopoiesis was observed. In the spleen, increased organ weights, increased extramedullary hematopoiesis, deposit of hemosiderin and engorgement of erythrocyte were observed. Deposit of hemosiderin was observed also in liver and kidney. In the liver, hepatocellular hypertrophy were increased in males and females fed 4000 ppm. In the urinary system, urinary retention was observed in males fed 4000 ppm. Plasma urea nitrogen was increaded in females fed 4000 ppm. Kidney weights

were increased in femels fed 1000 ppm above, pyelonephritis was observed in males fed 4000 ppm. In the urinary bladder, dilatation was observed in males fed 4000 ppm and hyaline droplet degeneration was observed in both males and females fed 4000 ppm. The inflammation in urethra was observed in males fed 4000 ppm. In lung, uremic pneumonitis was increased in males fed 4000 ppm and degeneration of blood vessel was observed in both males and females fed 4000 ppm.

In the present two-year feeding study, the effects on blood and hematopoietic system were observed for the lowest dose of 250 ppm in both males and females. The lowest observed-adverse-effect-level (LOAEL) of diphenylamine in the diet was 250 ppm (male : 29 mg/kg body weight per day, female : 36 mg/kg body weight per day).

Conclusions

There was some evidence for carcinogenicity of diphenylamine in male mice based on the increased incidences of vascular tumours in spleen and in all organs included spleen and liver. There was no evidence for carcinogenicity of diphenylamine in female mice.

Incidences of selected neoplastic lesions of male mice in the 2-year feed carcinogenicity study of diphenylamine

Dose (ppm)		0	250	1000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
subcutis	hemangioma	0	0	1	0		
lung	bronchiolar-alveolar adenoma	5	4	7	4		
bone marrow	hemangioma	0	0	0	1		
spleen	hemangioma	1	0	6	2		
liver	hemangioma	2	2	5	3	↑	
	hepatocellular adenoma	9	14	10	2 *		↓↓
Harderian gland	adenoma	4 a)	2	1	1		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	5	6	8	1		
lymph node	malignant lymphoma	6	4	3	2		
spleen	hemangiosarcoma	0	0	3	1		
heart	hemangiosarcoma	0	1	0	0		
liver	histiocytic sarcoma	5	1	1	1		
	hepatocellular carcinoma	7	15 *	5	2		↓↓
	hemangiosarcoma	0	1	2	1		
epididymis	histiocytic sarcoma	1	1	3	1		
spleen	hemangioma+hemangiosarcoma	1	0	9 **	3		
liver	hemangioma+hemangiosarcoma	2	3	7	4	↑	
all organs b)	hemangioma	3	2	10 *	6	↑	
	hemangiosarcoma	0	1	4	1		
	hemangioma＋hemangiosarcoma c)	3	3	14 **	6		

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 animals examined is 49

b: All organs were consisted of spleen, liver, subcutis, bone marrow and heart.

c: Combined analysis of hemangioma+hemangiosarcomain in all organs of Peto test and Cochran-Armitage test was not applied.

Incidences of selected neoplastic lesions of female mice in the 2-year feed carcinogenicity study of diphenylamine

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	1	3	1	2		
liver	hepatocellular adenoma	4	4	3	0		↓
pituitary	adenoma	2	0	5	4		
Harderian gland	adenoma	0	3	1	2		
malignant tumor							
lymph node	malignant lymphoma	18	20	17	15		
spleen	malignant lymphoma	0	3	1	0		
liver	histiocytic sarcoma	4	0	1	1		
	hemangiosarcoma	1	1	2	3		
uterus	histiocytic sarcoma	8	7	17 *	12		

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

SELECTED TABLES (CONTINUED)

TABLE C 1

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN BODY WEIGHTS AND SURVIVAL

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	23.3 (50)	50/50	23.3 (50)	100	50/50	23.3 (50)	100	50/50	23.3 (50)	100	50/50
1	24.2 (50)	50/50	24.1 (50)	100	50/50	24.1 (50)	100	50/50	23.4 (50)	97	50/50
2	24.7 (50)	50/50	24.8 (50)	100	50/50	25.0 (50)	101	50/50	24.1 (50)	98	50/50
3	25.3 (50)	50/50	25.3 (50)	100	50/50	25.5 (50)	101	50/50	24.8 (50)	98	50/50
4	26.4 (49)	49/50	26.1 (50)	99	50/50	26.2 (50)	99	50/50	25.6 (50)	97	50/50
5	27.0 (49)	49/50	27.0 (49)	100	49/50	27.0 (50)	100	50/50	26.2 (50)	97	50/50
6	27.5 (49)	49/50	27.9 (49)	101	49/50	27.6 (50)	100	50/50	26.3 (50)	96	50/50
7	28.2 (49)	49/50	28.8 (49)	102	49/50	28.2 (50)	100	50/50	27.0 (50)	96	50/50
8	28.8 (49)	49/50	29.7 (48)	103	48/50	28.6 (50)	99	50/50	26.9 (50)	93	50/50
9	29.2 (49)	49/50	30.2 (48)	103	48/50	29.0 (50)	99	50/50	27.4 (50)	94	50/50
10	30.2 (49)	49/50	31.2 (48)	103	48/50	30.3 (50)	100	50/50	28.0 (50)	93	50/50
11	30.4 (48)	48/50	31.3 (48)	103	48/50	30.6 (50)	101	50/50	27.8 (50)	91	50/50
12	31.9 (48)	48/50	32.4 (48)	102	48/50	31.7 (50)	99	50/50	28.8 (50)	90	50/50
13	32.5 (48)	48/50	33.1 (48)	102	48/50	32.3 (50)	99	50/50	29.1 (50)	90	50/50
14	32.9 (48)	48/50	33.6 (48)	102	48/50	32.8 (50)	100	50/50	29.4 (50)	89	50/50
18	35.5 (48)	48/50	36.4 (48)	103	48/50	35.0 (50)	99	50/50	30.9 (49)	87	49/50
22	37.7 (48)	48/50	39.1 (48)	104	48/50	37.4 (50)	99	50/50	32.2 (49)	85	49/50
26	39.9 (48)	48/50	41.8 (48)	105	48/50	39.4 (50)	99	50/50	32.9 (49)	82	49/50
30	41.7 (48)	48/50	43.9 (48)	105	48/50	41.2 (50)	99	50/50	34.0 (49)	82	49/50
34	43.2 (48)	48/50	45.6 (48)	106	48/50	43.0 (50)	100	50/50	34.9 (49)	81	49/50
38	45.0 (48)	48/50	47.2 (48)	105	48/50	44.8 (50)	100	50/50	35.9 (48)	80	48/50
42	46.7 (48)	48/50	48.9 (48)	105	48/50	46.6 (50)	100	50/50	36.9 (47)	79	47/50
46	48.2 (48)	48/50	50.4 (48)	105	48/50	47.7 (50)	99	50/50	37.8 (47)	78	47/50
50	48.5 (47)	47/50	50.6 (48)	104	48/50	48.1 (50)	99	50/50	38.7 (45)	80	45/50
54	49.9 (46)	46/50	52.4 (48)	105	48/50	50.5 (48)	101	48/50	40.3 (45)	81	45/50
58	49.9 (45)	45/50	52.3 (48)	105	48/50	50.5 (48)	101	48/50	40.4 (44)	81	44/50
62	50.7 (45)	45/50	52.6 (48)	104	48/50	50.7 (48)	100	48/50	40.6 (44)	80	44/50
66	51.6 (45)	45/50	53.2 (47)	103	47/50	51.4 (48)	100	48/50	41.2 (42)	80	42/50
70	51.9 (45)	45/50	53.3 (47)	103	47/50	52.6 (46)	101	46/50	42.3 (40)	82	40/50
74	52.2 (45)	45/50	52.9 (46)	101	46/50	53.4 (44)	102	44/50	43.4 (37)	83	37/50
78	52.8 (45)	45/50	53.4 (44)	101	44/50	53.5 (44)	101	44/50	44.5 (34)	84	34/50
82	52.2 (44)	44/50	51.3 (42)	98	42/50	54.0 (41)	103	41/50	42.9 (34)	82	34/50
86	52.4 (42)	42/50	54.2 (34)	103	34/50	54.2 (39)	103	39/50	42.8 (28)	82	28/50
90	52.8 (40)	40/50	53.9 (34)	102	34/50	52.8 (39)	100	39/50	43.0 (23)	81	23/50
94	50.7 (39)	39/50	53.2 (32)	105	32/50	51.7 (35)	102	35/50	40.7 (23)	80	23/50
98	51.3 (34)	34/50	53.3 (30)	104	30/50	50.7 (33)	99	33/50	41.7 (19)	81	19/50
102	50.9 (32)	32/50	51.5 (29)	101	29/50	49.0 (32)	96	32/50	41.0 (17)	81	17/50
104	50.6 (31)	31/50	49.7 (29)	98	29/50	48.8 (29)	96	29/50	38.9 (16)	77	16/50

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

TABLE C 2

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

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	19.0 (50)	50/50	19.0 (50)	100	50/50	19.0 (50)	100	50/50	19.0 (50)	100	50/50
1	19.3 (50)	50/50	19.4 (50)	101	50/50	19.5 (50)	101	50/50	19.3 (50)	100	50/50
2	19.8 (50)	50/50	19.8 (50)	100	50/50	19.7 (50)	99	50/50	19.5 (50)	98	50/50
3	20.3 (50)	50/50	20.4 (50)	100	50/50	20.2 (50)	100	50/50	20.1 (50)	99	50/50
4	20.7 (50)	50/50	20.8 (50)	100	50/50	20.9 (50)	101	50/50	20.7 (50)	100	50/50
5	21.2 (50)	50/50	21.3 (50)	100	50/50	21.5 (50)	101	50/50	21.0 (50)	99	50/50
6	21.7 (50)	50/50	21.8 (50)	100	50/50	21.6 (50)	100	50/50	21.5 (50)	99	50/50
7	22.1 (50)	50/50	22.3 (50)	101	50/50	22.1 (50)	100	50/50	21.9 (50)	99	50/50
8	22.7 (50)	50/50	22.6 (50)	100	50/50	22.5 (50)	99	50/50	22.3 (50)	98	50/50
9	22.8 (50)	50/50	22.9 (50)	100	50/50	22.6 (50)	99	50/50	22.4 (50)	98	50/50
10	22.9 (50)	50/50	23.2 (50)	101	50/50	23.1 (50)	101	50/50	22.9 (50)	100	50/50
11	23.5 (50)	50/50	23.2 (50)	99	50/50	23.2 (50)	99	50/50	23.0 (50)	98	50/50
12	23.9 (50)	50/50	23.9 (50)	100	50/50	23.7 (50)	99	50/50	23.2 (50)	97	50/50
13	23.9 (50)	50/50	24.2 (50)	101	50/50	24.0 (50)	100	50/50	23.5 (50)	98	50/50
14	24.3 (50)	50/50	24.2 (50)	100	50/50	24.4 (50)	100	50/50	23.7 (50)	98	50/50
18	25.8 (50)	50/50	26.0 (50)	101	50/50	25.6 (50)	99	50/50	24.6 (50)	95	50/50
22	27.6 (50)	50/50	27.9 (50)	101	50/50	27.0 (50)	98	50/50	25.7 (50)	93	50/50
26	28.7 (50)	50/50	29.4 (50)	102	50/50	28.7 (50)	100	50/50	26.6 (50)	93	50/50
30	30.2 (49)	49/50	30.8 (50)	102	50/50	29.8 (49)	99	49/50	27.1 (50)	90	50/50
34	31.9 (49)	49/50	32.7 (50)	103	50/50	31.4 (49)	98	49/50	27.9 (50)	87	50/50
38	33.1 (49)	49/50	33.8 (50)	102	50/50	32.3 (49)	98	49/50	28.6 (50)	86	50/50
42	33.8 (49)	49/50	34.2 (50)	101	50/50	33.0 (49)	98	49/50	29.0 (50)	86	50/50
46	34.6 (49)	49/50	35.3 (50)	102	50/50	33.9 (49)	98	49/50	29.1 (50)	84	50/50
50	35.3 (49)	49/50	35.6 (49)	101	49/50	33.9 (49)	96	49/50	29.6 (50)	84	50/50
54	36.8 (48)	48/50	36.9 (49)	100	49/50	35.4 (49)	96	49/50	30.4 (50)	83	50/50
58	36.8 (47)	47/50	36.7 (48)	100	48/50	35.5 (49)	96	49/50	30.8 (50)	84	50/50
62	36.8 (47)	47/50	36.9 (48)	100	48/50	35.9 (48)	98	48/50	30.9 (49)	84	49/50
66	37.1 (47)	47/50	37.4 (48)	101	48/50	36.0 (47)	97	47/50	31.2 (49)	84	49/50
70	38.0 (47)	47/50	38.1 (46)	100	46/50	36.6 (47)	96	47/50	31.3 (48)	82	48/50
74	37.9 (47)	47/50	37.4 (43)	99	43/50	36.5 (46)	96	46/50	31.4 (47)	83	47/50
78	38.4 (42)	42/50	37.7 (42)	98	42/50	36.9 (44)	96	44/50	31.4 (46)	82	46/50
82	38.3 (40)	40/50	37.4 (41)	98	41/50	37.2 (44)	97	44/50	31.5 (45)	82	45/50
86	37.8 (37)	37/50	38.1 (40)	101	40/50	37.2 (39)	98	39/50	31.4 (45)	83	45/50
90	38.0 (34)	34/50	37.6 (37)	99	37/50	37.4 (36)	98	36/50	31.6 (42)	83	42/50
94	37.5 (32)	32/50	37.6 (34)	100	34/50	36.4 (30)	97	30/50	31.8 (41)	85	41/50
98	36.2 (30)	30/50	37.4 (30)	103	30/50	36.2 (29)	100	29/50	31.8 (41)	88	41/50
102	35.5 (27)	27/50	35.9 (26)	101	26/50	36.1 (26)	102	26/50	30.7 (35)	86	35/50
104	36.4 (23)	23/50	35.8 (25)	98	25/50	35.7 (25)	98	25/50	31.1 (35)	85	35/50

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

TABLE C 3

BODY WEIGHT CHANGES: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	23.3± 0.9	24.2± 1.1	24.7± 1.7	25.3± 1.9	26.4± 1.4	27.0± 1.8	27.5± 2.1
250 ppm	23.3± 0.9	24.1± 1.3	24.8± 1.8	25.3± 2.0	26.1± 2.7	27.0± 2.2	27.9± 2.6
1000 ppm	23.3± 0.9	24.1± 1.1	25.0± 0.9	25.5± 1.2	26.2± 1.3	27.0± 1.4	27.6± 1.5
4000 ppm	23.3± 1.0	23.4± 1.2**	24.1± 1.6	24.8± 1.5	25.6± 1.3**	26.2± 1.2**	26.3± 1.2**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HAN260)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	28.2± 2.3	28.8± 2.4	29.2± 3.0	30.2± 2.9	30.4± 2.5	31.9± 2.4	32.5± 2.5
250 ppm	28.8± 2.7	29.7± 2.2	30.2± 2.6	31.2± 2.6	31.3± 2.6	32.4± 2.9	33.1± 2.9
1000 ppm	28.2± 1.7	28.6± 1.9	29.0± 2.9	30.3± 2.1	30.6± 2.2	31.7± 2.3	32.3± 2.5
4000 ppm	27.0± 1.3**	26.9± 1.5**	27.4± 2.2**	28.0± 1.3**	27.8± 1.7**	28.8± 1.8**	29.1± 2.2**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	32.9± 2.4	35.5± 2.8	37.7± 3.5	39.9± 3.9	41.7± 4.3	43.2± 4.5	45.0± 4.7
250 ppm	33.6± 3.0	36.4± 3.4	39.1± 4.1	41.8± 4.6*	43.9± 4.7*	45.6± 4.5*	47.2± 4.2*
1000 ppm	32.8± 2.6	35.0± 3.2	37.4± 3.5	39.4± 4.1	41.2± 4.4	43.0± 4.7	44.8± 4.7
4000 ppm	29.4± 2.0**	30.9± 2.0**	32.2± 2.3**	32.9± 3.0**	34.0± 3.0**	34.9± 3.3**	35.9± 3.5**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	46.7± 4.4	48.2± 4.3	48.5± 4.7	49.9± 4.1	49.9± 3.7	50.7± 4.2	51.6± 4.0
250 ppm	48.9± 4.2*	50.4± 3.9*	50.6± 4.0	52.4± 3.4**	52.3± 3.3**	52.6± 3.9	53.2± 4.4
1000 ppm	46.6± 4.9	47.7± 4.7	48.1± 5.4	50.5± 4.4	50.5± 4.4	50.7± 4.7	51.4± 5.8
4000 ppm	36.9± 4.1**	37.8± 4.9**	38.7± 4.5**	40.3± 5.3**	40.4± 5.6**	40.6± 6.2**	41.2± 6.7**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	51.9± 4.9	52.2± 4.4	52.8± 4.6	52.2± 5.7	52.4± 5.9	52.8± 5.2	50.7± 8.4
250 ppm	53.3± 5.4	52.9± 6.5	53.4± 6.9	51.3± 9.4	54.2± 6.5	53.9± 7.2	53.2± 7.6
1000 ppm	52.6± 6.2	53.4± 5.8	53.5± 6.9	54.0± 6.5	54.2± 6.4	52.8± 7.4	51.7± 8.0
4000 ppm	42.3± 6.8**	43.4± 7.2**	44.5± 7.7**	42.9± 9.2**	42.8± 7.9**	43.0± 7.7**	40.7± 9.0**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98	102	104
Control	51.3± 7.0	50.9± 7.2	50.6± 8.1
250 ppm	53.3± 7.4	51.5± 8.7	49.7± 9.4
1000 ppm	50.7± 8.8	49.0± 9.6	48.8± 9.2
4000 ppm	41.7± 7.7**	41.0± 7.8**	38.9± 8.1**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE C 4

BODY WEIGHT CHANGES: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	19.0± 0.8	19.3± 1.1	19.8± 1.2	20.3± 1.0	20.7± 1.0	21.2± 1.0	21.7± 1.2
250 ppm	19.0± 0.8	19.4± 0.8	19.8± 1.0	20.4± 1.0	20.8± 1.0	21.3± 1.1	21.8± 1.3
1000 ppm	19.0± 0.8	19.5± 1.0	19.7± 1.4	20.2± 1.1	20.9± 1.3	21.5± 1.6	21.6± 1.4
4000 ppm	19.0± 0.8	19.3± 0.9	19.5± 1.0	20.1± 0.9	20.7± 0.9	21.0± 1.1	21.5± 0.9

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	22.1± 1.1	22.7± 1.4	22.8± 1.4	22.9± 1.3	23.5± 1.3	23.9± 1.6	23.9± 1.8
250 ppm	22.3± 1.2	22.6± 1.3	22.9± 1.4	23.2± 1.6	23.2± 1.4	23.9± 1.6	24.2± 1.9
1000 ppm	22.1± 1.3	22.5± 1.5	22.6± 1.8	23.1± 1.7	23.2± 1.6	23.7± 1.6	24.0± 1.8
4000 ppm	21.9± 1.1	22.3± 1.1	22.4± 1.0	22.9± 1.1	23.0± 1.2	23.2± 1.3	23.5± 1.3

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	24.3± 1.8	25.8± 2.2	27.6± 3.2	28.7± 3.3	30.2± 3.4	31.9± 3.8	33.1± 3.8
250 ppm	24.2± 2.0	26.0± 2.3	27.9± 2.8	29.4± 3.0	30.8± 3.4	32.7± 3.6	33.8± 4.3
1000 ppm	24.4± 1.8	25.6± 2.0	27.0± 2.5	28.7± 3.2	29.8± 3.3	31.4± 3.4	32.3± 3.8
4000 ppm	23.7± 1.3	24.6± 1.4**	25.7± 1.6**	26.6± 1.9**	27.1± 2.0**	27.9± 2.0**	28.6± 2.2**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	33.8± 4.1	34.6± 4.5	35.3± 4.4	36.8± 4.5	36.8± 4.5	36.8± 4.5	37.1± 4.4
250 ppm	34.2± 4.0	35.3± 4.2	35.6± 4.5	36.9± 4.9	36.7± 5.0	36.9± 5.2	37.4± 4.9
1000 ppm	33.0± 3.7	33.9± 3.7	33.9± 4.2	35.4± 4.1	35.5± 4.3	35.9± 4.5	36.0± 5.2
4000 ppm	29.0± 2.2**	29.1± 2.5**	29.6± 2.6**	30.4± 2.6**	30.8± 3.4**	30.9± 3.1**	31.2± 3.0**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	38.0± 4.7	37.9± 4.7	38.4± 4.9	38.3± 5.0	37.8± 4.9	38.0± 4.7	37.5± 4.6
250 ppm	38.1± 5.4	37.4± 5.7	37.7± 5.8	37.4± 5.8	38.1± 5.7	37.6± 5.9	37.6± 5.5
1000 ppm	36.6± 5.8	36.5± 5.4	36.9± 5.2	37.2± 5.0	37.2± 5.2	37.4± 5.5	36.4± 5.5
4000 ppm	31.3± 3.1**	31.4± 3.1**	31.4± 3.1**	31.5± 3.3**	31.4± 3.6**	31.6± 3.4**	31.8± 3.3**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98	102	104
Control	36.2± 4.8	35.5± 5.2	36.4± 4.7
250 ppm	37.4± 5.6	35.9± 5.9	35.8± 5.7
1000 ppm	36.2± 5.2	36.1± 5.6	35.7± 5.0
4000 ppm	31.8± 3.9**	30.7± 4.0**	31.1± 4.3**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE D 1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	250 ppm Av. FC.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1	4.1 (50)	50/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50	3.9 (50)	95	50/50
2	3.7 (50)	50/50	3.8 (50)	103	50/50	3.8 (50)	103	50/50	3.9 (50)	105	50/50
3	3.7 (50)	50/50	3.7 (50)	100	50/50	3.8 (50)	103	50/50	3.7 (50)	100	50/50
4	3.9 (49)	49/50	3.9 (49)	100	50/50	3.9 (50)	100	50/50	3.9 (50)	100	50/50
5	4.0 (49)	49/50	3.9 (49)	98	49/50	4.0 (50)	100	50/50	4.0 (50)	100	50/50
6	4.0 (49)	49/50	4.0 (47)	100	49/50	3.9 (50)	98	50/50	3.9 (50)	98	50/50
7	4.0 (49)	49/50	4.0 (49)	100	49/50	3.9 (49)	98	50/50	4.0 (50)	100	50/50
8	4.1 (49)	49/50	4.2 (48)	102	48/50	3.9 (49)	95	50/50	3.9 (50)	95	50/50
9	4.0 (49)	49/50	4.1 (48)	103	48/50	4.0 (50)	100	50/50	4.0 (50)	100	50/50
10	4.2 (49)	49/50	4.3 (48)	102	48/50	4.4 (50)	105	50/50	4.1 (50)	98	50/50
11	4.1 (48)	48/50	4.1 (48)	100	48/50	4.2 (50)	102	50/50	4.0 (50)	98	50/50
12	4.2 (48)	48/50	4.2 (48)	100	48/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
13	4.2 (48)	48/50	4.2 (48)	100	48/50	4.2 (50)	100	50/50	4.0 (50)	95	50/50
14	4.2 (48)	48/50	4.2 (48)	100	48/50	4.2 (49)	100	50/50	4.1 (50)	98	50/50
18	4.4 (48)	48/50	4.4 (48)	100	48/50	4.3 (50)	98	50/50	4.3 (48)	98	49/50
22	4.3 (48)	48/50	4.5 (48)	105	48/50	4.4 (50)	102	50/50	4.3 (49)	100	49/50
26	4.4 (48)	48/50	4.5 (48)	102	48/50	4.4 (50)	100	50/50	4.2 (49)	95	49/50
30	4.5 (48)	48/50	4.5 (48)	100	48/50	4.3 (50)	96	50/50	4.2 (49)	93	49/50
34	4.5 (48)	48/50	4.5 (48)	100	48/50	4.4 (50)	98	50/50	4.3 (49)	96	49/50
38	4.7 (48)	48/50	4.7 (48)	100	48/50	4.6 (50)	98	50/50	4.7 (48)	100	48/50
42	4.7 (48)	48/50	4.8 (48)	102	48/50	4.7 (50)	100	50/50	4.6 (47)	98	47/50
46	4.7 (48)	48/50	4.8 (48)	102	48/50	4.5 (50)	96	50/50	4.6 (43)	98	47/50
50	4.7 (46)	47/50	4.5 (47)	96	48/50	4.5 (50)	96	50/50	4.4 (42)	94	45/50
54	4.6 (46)	46/50	4.7 (48)	102	48/50	4.7 (48)	102	48/50	4.7 (44)	102	45/50
58	4.7 (45)	45/50	4.8 (48)	102	48/50	4.7 (48)	100	48/50	4.7 (44)	100	44/50
62	4.6 (45)	45/50	4.9 (48)	107	48/50	4.6 (48)	100	48/50	4.6 (44)	100	44/50
66	4.8 (45)	45/50	4.9 (47)	102	47/50	4.8 (48)	100	48/50	4.7 (42)	98	42/50
70	4.6 (45)	45/50	4.9 (47)	107	47/50	4.9 (45)	107	46/50	4.8 (40)	104	40/50
74	4.7 (45)	45/50	4.8 (46)	102	46/50	4.8 (43)	102	44/50	5.0 (37)	106	37/50
78	4.8 (45)	45/50	4.8 (44)	100	44/50	4.9 (44)	102	44/50	4.7 (33)	98	34/50
82	4.6 (44)	44/50	4.7 (42)	102	42/50	4.8 (41)	104	41/50	4.9 (34)	107	34/50
86	5.0 (42)	42/50	4.9 (34)	98	34/50	5.0 (39)	100	39/50	5.1 (28)	102	28/50
90	4.8 (40)	40/50	5.0 (34)	104	34/50	4.8 (39)	100	39/50	4.6 (23)	96	23/50
94	4.6 (39)	39/50	4.7 (32)	102	32/50	4.8 (35)	104	35/50	4.4 (23)	96	23/50
98	4.9 (34)	34/50	5.2 (30)	106	30/50	5.0 (33)	102	33/50	5.2 (19)	106	19/50
102	4.9 (32)	32/50	4.9 (28)	100	29/50	4.8 (30)	98	32/50	4.4 (17)	90	17/50
104	4.7 (30)	31/50	4.6 (29)	98	29/50	4.6 (29)	98	29/50	4.7 (15)	100	16/50

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

TABLE D 2

FOOD CONSUMPTION CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE BGD2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	250 ppm Av. FC.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1	3.6 (50)	50/50	3.7 (50)	103	50/50	3.7 (50)	103	50/50	3.6 (50)	100	50/50
2	3.5 (50)	50/50	3.4 (50)	97	50/50	3.3 (50)	94	50/50	3.4 (50)	97	50/50
3	3.3 (50)	50/50	3.5 (50)	106	50/50	3.4 (50)	103	50/50	3.4 (50)	103	50/50
4	3.5 (50)	50/50	3.6 (50)	103	50/50	3.6 (50)	103	50/50	3.5 (50)	100	50/50
5	3.6 (50)	50/50	3.6 (50)	100	50/50	3.6 (50)	100	50/50	3.5 (48)	97	50/50
6	3.6 (50)	50/50	3.6 (50)	100	50/50	3.6 (50)	100	50/50	3.5 (50)	97	50/50
7	3.7 (50)	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50	3.6 (49)	97	50/50
8	3.8 (50)	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50	3.7 (50)	97	50/50
9	3.7 (50)	50/50	3.8 (50)	103	50/50	3.8 (50)	103	50/50	3.6 (50)	97	50/50
10	3.8 (50)	50/50	3.9 (50)	103	50/50	4.0 (50)	105	50/50	3.9 (50)	103	50/50
11	3.9 (50)	50/50	3.9 (50)	100	50/50	3.8 (50)	97	50/50	3.7 (50)	95	50/50
12	3.7 (50)	50/50	3.9 (50)	105	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50
13	3.8 (50)	50/50	3.9 (49)	103	50/50	3.9 (50)	103	50/50	3.8 (50)	100	50/50
14	3.9 (50)	50/50	3.8 (50)	97	50/50	3.9 (50)	100	50/50	3.8 (50)	97	50/50
18	4.0 (50)	50/50	4.0 (50)	100	50/50	3.8 (50)	95	50/50	3.9 (50)	98	50/50
22	4.2 (50)	50/50	4.3 (50)	102	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
26	3.9 (50)	50/50	4.2 (50)	108	50/50	4.2 (50)	108	50/50	4.2 (50)	108	50/50
30	4.1 (49)	49/50	4.2 (50)	102	50/50	4.1 (49)	100	49/50	4.0 (50)	98	50/50
34	4.2 (49)	49/50	4.4 (50)	105	50/50	4.1 (49)	98	49/50	4.1 (50)	98	50/50
38	4.4 (49)	49/50	4.6 (50)	105	50/50	4.4 (49)	100	49/50	4.3 (50)	98	50/50
42	4.5 (49)	49/50	4.6 (50)	102	50/50	4.5 (49)	100	49/50	4.3 (50)	96	50/50
46	4.2 (47)	49/50	4.4 (50)	105	50/50	4.5 (47)	107	49/50	4.3 (49)	102	50/50
50	4.4 (46)	49/50	4.5 (49)	102	49/50	4.6 (48)	105	49/50	4.6 (50)	105	50/50
54	4.3 (48)	48/50	4.3 (49)	100	49/50	4.4 (49)	102	49/50	4.1 (50)	95	50/50
58	4.3 (47)	47/50	4.4 (48)	102	48/50	4.4 (49)	102	49/50	4.3 (50)	100	50/50
62	4.4 (47)	47/50	4.5 (48)	102	48/50	4.6 (48)	105	48/50	4.3 (49)	98	49/50
66	4.3 (47)	47/50	4.4 (48)	102	48/50	4.6 (47)	107	47/50	4.4 (49)	102	49/50
70	4.3 (47)	47/50	4.3 (46)	100	46/50	4.3 (47)	100	47/50	4.2 (48)	98	48/50
74	4.3 (47)	47/50	4.4 (43)	102	43/50	4.4 (46)	102	46/50	4.3 (46)	100	47/50
78	4.5 (41)	42/50	4.4 (42)	98	42/50	4.6 (44)	102	44/50	4.3 (46)	96	46/50
82	4.3 (40)	40/50	4.5 (41)	105	41/50	4.4 (43)	102	44/50	4.3 (45)	100	45/50
86	4.4 (37)	37/50	4.6 (40)	105	40/50	4.6 (39)	105	39/50	4.4 (45)	100	45/50
90	4.2 (34)	34/50	4.5 (37)	107	37/50	4.6 (36)	110	36/50	4.6 (42)	110	42/50
94	4.5 (32)	32/50	4.5 (34)	100	34/50	4.9 (29)	109	30/50	4.7 (41)	104	41/50
98	4.1 (30)	30/50	4.5 (30)	110	30/50	4.6 (29)	112	29/50	4.4 (41)	107	41/50
102	4.4 (27)	27/50	4.5 (25)	102	26/50	4.8 (26)	109	26/50	4.7 (34)	107	35/50
104	4.6 (23)	23/50	4.5 (25)	98	25/50	4.6 (25)	100	25/50	4.4 (35)	96	35/50

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

TABLE D 3

FOOD CONSUMPTION CHANGES: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	4.1± 0.3	3.7± 0.5	3.7± 0.5	3.9± 0.5	4.0± 0.4	4.0± 0.4	4.0± 0.4
250 ppm	4.0± 0.4	3.8± 0.6	3.7± 0.6	3.9± 0.6	3.9± 0.6	4.0± 0.5	4.0± 0.4
1000 ppm	4.0± 0.4	3.8± 0.3	3.8± 0.4	3.9± 0.3	4.0± 0.3	3.9± 0.4	3.9± 0.4
4000 ppm	3.9± 0.5**	3.9± 0.5	3.7± 0.4	3.9± 0.3	4.0± 0.3	3.9± 0.4	4.0± 0.3

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	4.1± 0.5	4.0± 0.6	4.2± 0.6	4.1± 0.4	4.2± 0.4	4.2± 0.3	4.2± 0.4
250 ppm	4.2± 0.4	4.1± 0.5	4.3± 0.5	4.1± 0.4	4.2± 0.5	4.2± 0.4	4.2± 0.5
1000 ppm	3.9± 0.5	4.0± 0.5	4.4± 0.6	4.2± 0.3	4.1± 0.4	4.2± 0.3	4.2± 0.3
4000 ppm	3.9± 0.4	4.0± 0.4	4.1± 0.3*	4.0± 0.4	4.1± 0.5	4.0± 0.5	4.1± 0.4

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	4.4± 0.4	4.3± 0.5	4.4± 0.4	4.5± 0.6	4.5± 0.6	4.7± 0.7	4.7± 0.6
250 ppm	4.4± 0.4	4.5± 0.4	4.5± 0.4	4.5± 0.5	4.5± 0.5	4.7± 0.4	4.8± 0.6
1000 ppm	4.3± 0.4	4.4± 0.4	4.4± 0.5	4.3± 0.5	4.4± 0.5	4.6± 0.4	4.7± 0.4
4000 ppm	4.3± 0.5	4.3± 0.4	4.2± 0.6	4.2± 0.4**	4.3± 0.4*	4.7± 0.6	4.6± 0.5

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	4.7± 0.5	4.7± 0.6	4.6± 0.8	4.7± 0.6	4.6± 0.5	4.8± 0.4	4.6± 0.6
250 ppm	4.8± 0.5	4.5± 0.9	4.7± 0.4	4.8± 0.4	4.9± 0.5*	4.9± 0.6	4.9± 0.4
1000 ppm	4.5± 0.7	4.5± 0.8	4.7± 0.5	4.7± 0.6	4.6± 0.8	4.8± 0.7	4.9± 0.6
4000 ppm	4.6± 0.7	4.4± 0.6	4.7± 0.6	4.7± 0.7	4.6± 0.7	4.7± 0.5	4.8± 0.6

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	4.7± 0.7	4.8± 0.6	4.6± 0.9	5.0± 0.7	4.8± 0.7	4.6± 1.1	4.9± 0.6
250 ppm	4.8± 0.8	4.8± 0.6	4.7± 1.2	4.9± 0.7	5.0± 0.8	4.7± 0.9	5.2± 0.6
1000 ppm	4.8± 0.6	4.9± 0.5	4.8± 0.8	5.0± 0.7	4.8± 0.8	4.8± 0.8	5.0± 0.6
4000 ppm	5.0± 1.0	4.7± 0.9	4.9± 0.8	5.1± 0.9	4.6± 0.8	4.4± 0.9	5.2± 0.7

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HAN260)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	4.9± 0.8	4.7± 0.8
250 ppm	4.9± 1.0	4.6± 0.9
1000 ppm	4.8± 0.6	4.6± 0.8
4000 ppm	4.4± 0.9	4.7± 1.1

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE D 4

FOOD CONSUMPTION CHANGES: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	3.6± 0.3	3.5± 0.4	3.3± 0.3	3.5± 0.2	3.6± 0.3	3.6± 0.3	3.7± 0.3
250 ppm	3.7± 0.2	3.4± 0.3	3.5± 0.3*	3.6± 0.3	3.6± 0.3	3.6± 0.4	3.7± 0.2
1000 ppm	3.7± 0.3	3.3± 0.4	3.4± 0.3	3.6± 0.3	3.6± 0.5	3.6± 0.3	3.7± 0.3
4000 ppm	3.6± 0.4	3.4± 0.4	3.4± 0.3	3.5± 0.3	3.5± 0.4	3.5± 0.3	3.6± 0.3

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	3.8± 0.3	3.7± 0.3	3.8± 0.3	3.9± 0.3	3.7± 0.4	3.8± 0.4	3.9± 0.3
250 ppm	3.8± 0.3	3.8± 0.3	3.9± 0.4	3.9± 0.3	3.9± 0.3	3.9± 0.4	3.8± 0.4
1000 ppm	3.8± 0.4	3.8± 0.5	4.0± 0.4	3.8± 0.3	3.7± 0.3	3.9± 0.4	3.9± 0.4
4000 ppm	3.7± 0.3	3.6± 0.4	3.9± 0.3	3.7± 0.2	3.7± 0.3	3.8± 0.3	3.8± 0.3

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	4.0± 0.4	4.2± 0.6	3.9± 0.6	4.1± 0.5	4.2± 0.6	4.4± 0.6	4.5± 0.6
250 ppm	4.0± 0.5	4.3± 0.6	4.2± 0.7	4.2± 0.7	4.4± 0.5	4.6± 0.8	4.6± 0.7
1000 ppm	3.8± 0.5	4.1± 0.5	4.2± 0.8	4.1± 0.6	4.1± 0.5	4.4± 0.7	4.5± 0.6
4000 ppm	3.9± 0.4	4.1± 0.5	4.2± 0.6	4.0± 0.5	4.1± 0.5	4.3± 0.7	4.3± 0.5

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	4.2± 0.6	4.4± 0.7	4.3± 0.7	4.3± 0.7	4.4± 0.7	4.3± 0.6	4.3± 0.7
250 ppm	4.4± 0.8	4.5± 0.7	4.3± 0.8	4.4± 0.8	4.5± 0.7	4.4± 0.6	4.3± 0.6
1000 ppm	4.5± 0.7	4.6± 0.6	4.4± 0.6	4.4± 0.7	4.6± 0.5	4.6± 0.8	4.3± 0.8
4000 ppm	4.3± 0.5	4.6± 0.8	4.1± 0.6	4.3± 0.6	4.3± 0.6	4.4± 0.5	4.2± 0.5

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	4.3± 0.6	4.5± 0.7	4.3± 0.6	4.4± 0.6	4.2± 0.7	4.5± 0.7	4.1± 0.8
250 ppm	4.4± 0.6	4.4± 0.6	4.5± 0.8	4.6± 0.7	4.5± 0.9	4.5± 0.7	4.5± 0.6
1000 ppm	4.4± 0.8	4.6± 0.8	4.4± 0.8	4.6± 0.5	4.6± 0.8	4.9± 0.5	4.6± 0.8*
4000 ppm	4.3± 0.5	4.3± 0.5	4.3± 0.6	4.4± 0.8	4.6± 0.7	4.7± 0.6	4.4± 0.6

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	4.4± 1.3	4.6± 0.8
250 ppm	4.5± 1.3	4.5± 0.6
1000 ppm	4.8± 0.7	4.6± 0.9
4000 ppm	4.7± 0.9	4.4± 0.7

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE E 1

CHEMICAL INTAKE CHANGES: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1		2		3		4		5		6		7	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	42±	3	38±	4	37±	4	37±	4	36±	4	36±	3	35±	4
1000 ppm	167±	11	153±	10	148±	11	149±	10	148±	10	142±	12	140±	11
4000 ppm	662±	75	655±	73	599±	54	609±	46	614±	39	588±	48	599±	39

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8		9		10		11		12		13		14	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	35±	3	34±	4	34±	4	33±	3	33±	4	32±	3	31±	4
1000 ppm	137±	12	138±	12	145±	20	138±	10	131±	12	131±	11	127±	10
4000 ppm	582±	50	583±	45	586±	45	577±	45	562±	54	556±	47	557±	56

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 18		22		26		30		34		38		42	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	30±	3	29±	3	27±	3	26±	3	25±	3	25±	3	25±	3
1000 ppm	123±	13	117±	10	112±	11	105±	12	104±	10	105±	11	102±	10
4000 ppm	558±	66	537±	52	513±	67	494±	45	488±	42	522±	65	498±	50

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 46		50		54		58		62		66		70	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	24±	2	22±	4	22±	2	23±	2	24±	3	23±	3	23±	3
1000 ppm	95±	15	94±	15	95±	12	94±	12	92±	16	95±	22	95±	20
4000 ppm	500±	108	464±	60	469±	63	470±	66	457±	87	469±	97	461±	92

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 74		78		82		86		90		94		98	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	23±	4	23±	4	23±	6	23±	4	23±	5	22±	5	25±	4
1000 ppm	90±	11	94±	21	88±	13	93±	12	91±	15	94±	15	103±	28
4000 ppm	460±	73	435±	76	472±	114	485±	106	436±	98	453±	134	512±	99

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 102		104	
Control	0±	0	0±	0
250 ppm	23±	5	24±	6
1000 ppm	99±	27	98±	30
4000 ppm	443±	107	489±	153

TABLE E 2

CHEMICAL INTAKE CHANGES: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1		2		3		4		5		6		7	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	48±	3	43±	3	43±	3	43±	3	43±	3	42±	3	42±	2
1000 ppm	190±	13	168±	16	166±	15	170±	12	166±	16	165±	13	167±	11
4000 ppm	753±	78	706±	67	679±	62	680±	44	657±	66	653±	54	654±	48

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8		9		10		11		12		13		14	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	42±	3	41±	3	42±	4	42±	3	41±	2	40±	4	40±	3
1000 ppm	167±	14	166±	18	172±	14	165±	12	158±	13	161±	14	161±	15
4000 ppm	664±	56	651±	69	682±	49	648±	42	637±	51	640±	45	644±	52

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 18		22		26		30		34		38		42	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	38±	4	39±	4	36±	7	34±	6	34±	5	34±	5	34±	5
1000 ppm	148±	19	153±	20	148±	27	137±	18	133±	19	136±	20	137±	23
4000 ppm	639±	67	642±	59	634±	90	597±	62	590±	63	608±	91	590±	69

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 46		50		54		58		62		66		70	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	31±	6	32±	7	29±	5	30±	6	31±	5	30±	6	29±	6
1000 ppm	134±	23	138±	23	124±	18	125±	19	131±	18	129±	24	119±	24
4000 ppm	589±	61	618±	100	545±	76	558±	76	563±	66	565±	58	537±	49

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 74		78		82		86		90		94		98	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	30±	6	30±	6	31±	8	31±	8	30±	9	30±	6	30±	6
1000 ppm	120±	20	126±	22	121±	23	124±	17	124±	22	136±	19	127±	21
4000 ppm	545±	56	555±	61	542±	64	563±	103	583±	101	596±	76	554±	80

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 102		104	
Control	0±	0	0±	0
250 ppm	31±	9	32±	6
1000 ppm	134±	14	129±	23
4000 ppm	610±	123	570±	102

TABLE F 1

HEMATOLOGY: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Cr1j[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	30	9.74± 1.07	13.7± 1.1	42.4± 3.1	43.7± 2.1	14.2± 0.8	32.4± 0.7	1674± 465
250 ppm	28	9.15± 1.48	13.2± 1.9	40.8± 5.5**	44.8± 2.0	14.5± 0.7*	32.4± 1.5	1804± 486
1000 ppm	28	7.47± 1.15**	12.6± 1.9**	33.4± 4.5**	45.2± 4.3	17.0± 1.4**	37.6± 2.4**	1758± 319
4000 ppm	15	5.48± 1.42**	10.5± 2.8**	27.7± 4.4**	52.4± 9.3**	19.2± 0.8**	37.7± 6.7**	1957± 675

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Dunnett

(HCL070)

BAIS 4

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %		METHEMOGLOBIN %	
Control	30	2.5±	1.2	0.4±	0.1
250 ppm	28	3.8±	2.9**	1.0±	0.4**
1000 ppm	28	4.8±	5.0**	2.6±	0.7**
4000 ppm	15	1.8±	2.6	5.3±	2.2**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL070)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	30	4.90±	3.03	30±	14	63±	16	4±	2	3±	1	0±	0	1±	1
250 ppm	28	4.77±	2.57	29±	14	64±	14	3±	1	3±	2	0±	0	0±	1
1000 ppm	28	5.76±	2.52	26±	14	67±	16	4±	1	3±	3	0±	0	0±	0
4000 ppm	15	5.42±	2.35	39±	17	55±	17	5±	2	2±	1	0±	0	1±	1

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Dunnett

(HCL070)

BAIS 4

TABLE F 2

HEMATOLOGY: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$		HEMOGLOBIN g/dℓ		HEMATOCRIT %		MCV fℓ		MCH pg		MCHC g/dℓ		PLATELET $10^3/\mu\ell$	
Control	23	10.01±	0.43	14.5±	0.7	44.2±	2.6	44.1±	1.3	14.5±	0.5	32.8±	0.7	1171±	235
250 ppm	25	9.05±	1.15**	13.4±	1.2**	41.1±	3.3**	45.6±	2.0**	14.8±	0.6**	32.5±	0.8	1043±	317
1000 ppm	24	7.46±	1.44**	12.0±	2.2**	34.5±	5.0**	47.1±	5.1**	16.2±	0.8**	34.6±	2.6**	965±	383
4000 ppm	34	5.97±	1.17**	11.2±	2.2**	29.9±	3.9**	51.1±	6.7**	18.8±	1.3**	37.1±	4.1**	1124±	358

Significant difference ; * : $P \leqq 0.05$ ** : $P \leqq 0.01$ Test of Dunnett

(HCL070)

BAIS 4

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %		METHEMOGLOBIN %	
Control	23	2.1±	0.6	0.4±	0.1
250 ppm	25	4.0±	1.9**	0.7±	0.2**
1000 ppm	24	7.0±	5.7**	2.0±	0.6**
4000 ppm	34	3.6±	4.5	4.0±	1.5**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL070)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	23	3.04±	1.23	24±	11	68±	12	3±	2	4±	2	0±	0	1±	1
250 ppm	25	3.91±	3.81	23±	9	70±	10	3±	1	3±	2	0±	0	1±	1
1000 ppm	24	3.40±	1.88	26±	13	65±	16	4±	4	3±	2	0±	0	1±	4
4000 ppm	34	13.05±	42.81	30±	16	61±	17	5±	2**	2±	2*	0±	1	2±	2

Significant difference ; * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of Dunnett

(HCL070)

TABLE G 1

BIOCHEMISTRY: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	TOTAL PROTEIN g／dℓ	ALBUMIN g／dℓ	A/G RATIO	T-BILIRUBIN mg／dℓ	GLUCOSE mg／dℓ	T-CHOLESTEROL mg／dℓ	TRIGLYCERIDE mg／dℓ
Control	30	5.3± 0.7	2.6± 0.4	1.0± 0.2	0.11± 0.02	185± 37	114± 55	52± 25
250 ppm	28	5.6± 0.9	2.8± 0.4	1.1± 0.2	0.12± 0.01*	188± 27	148± 85	70± 44
1000 ppm	27	5.1± 0.7	2.5± 0.4	1.0± 0.2	0.16± 0.07**	182± 44	122± 67	64± 38
4000 ppm	15	5.1± 0.8	2.5± 0.5	1.0± 0.2	0.21± 0.08**	169± 46	117± 43	65± 36

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL074)

BAIS 4

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST IU/ℓ	ALT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	G-GTP IU/ℓ	CK IU/ℓ
Control	30	199± 73	101± 136	57± 78	298± 236	208± 69	1± 1	53± 27
250 ppm	28	245± 103	73± 45	58± 72	250± 145	227± 116	1± 1	42± 11
1000 ppm	27	214± 103	93± 82	52± 53	297± 143	251± 218	1± 1	70± 70
4000 ppm	15	196± 49	147± 138	81± 109	510± 344**	203± 112	1± 1	124± 261

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	UREA NITROGEN mg/dℓ	SODIUM mEq/ℓ	POTASSIUM mEq/ℓ	CHLORIDE mEq/ℓ	CALCIUM mg/dℓ	INORGANIC PHOSPHORUS mg/dℓ
Control	30	22.3± 9.8	153± 2	4.2± 0.3	121± 3	9.0± 0.6	6.3± 0.9
250 ppm	28	21.9± 2.9	152± 1	4.1± 0.3	120± 2	9.2± 0.7	5.9± 0.6
1000 ppm	27	22.3± 8.2	153± 2	4.4± 0.4	121± 3	8.9± 0.6	6.2± 1.1
4000 ppm	15	25.1± 7.3	153± 2	4.4± 0.4	121± 3	8.8± 0.7	6.2± 0.9

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL074)

TABLE G 2

BIOCHEMISTRY: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	TOTAL PROTEIN g/dℓ		ALBUMIN g/dℓ		A/G RATIO		T-BILIRUBIN mg/dℓ		GLUCOSE mg/dℓ		T-CHOLESTEROL mg/dℓ		TRIGLYCERIDE mg/dℓ	
Control	23	4.9±	0.4	2.6±	0.2	1.1±	0.2	0.11±	0.02	154±	30	75±	14	40±	15
250 ppm	25	4.9±	0.6	2.7±	0.3	1.2±	0.2	0.12±	0.04	155±	23	88±	58	51±	27
1000 ppm	24	4.9±	0.8	2.6±	0.4	1.2±	0.3	0.15±	0.05**	155±	23	81±	25	56±	21
4000 ppm	34	5.5±	1.0**	2.9±	0.4**	1.2±	0.3	0.22±	0.09**	144±	38	96±	49	50±	41

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL074)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST IU/ℓ	ALT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	G-GTP IU/ℓ	CK IU/ℓ
Control	23	135± 26	122± 177	54± 71	236± 221	369± 146	0± 1	69± 64
250 ppm	25	160± 103	117± 143	59± 107	223± 144	370± 187	1± 1	54± 30
1000 ppm	24	148± 39	81± 36	31± 16	282± 203	232± 104**	0± 0	68± 56
4000 ppm	34	174± 75**	136± 124	44± 50	542± 622**	295± 113	1± 3	82± 56

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL074)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	UREA NITROGEN mg/dℓ	SODIUM mEq/ℓ	POTASSIUM mEq/ℓ	CHLORIDE mEq/ℓ	CALCIUM mg/dℓ	INORGANIC PHOSPHORUS mg/dℓ
Control	23	16.2± 2.6	151± 2	4.0± 0.3	121± 2	8.7± 0.4	5.4± 0.8
250 ppm	25	17.6± 5.4	152± 2	4.2± 0.4	122± 3	8.9± 0.5	5.9± 1.1
1000 ppm	24	17.7± 4.9	151± 3	4.3± 0.5	121± 3	9.0± 0.7	6.3± 1.0**
4000 ppm	34	23.9± 16.0**	154± 3**	4.4± 0.8	122± 4	9.3± 0.7**	6.5± 1.6**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE H 1

URINALYSIS: MALE

Urinalysis of male mice

In the dosed groups, ketone body could not be measured by urine test paper in some animals, because their urine were colored by metabolite of test substance.

The inspection items and number of animals that could not be measured are shown as followed.

Ketone body: 1000 ppm(2), 4000 ppm(14)

Therefore, ketone body in 4000 ppm dosed group could not be evaluated.

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	±	+	2+	3+	4+	CHI	Occult blood −	±	+	2+	3+	CHI
Control	31	0	2	4	8	8	9	0		0	0	16	13	2	0		31	0	0	0	0	0		4	22	5	0	0	0		28	1	0	1	1	
250 ppm	29	0	3	8	7	7	3	1		0	2	17	9	1	0		29	0	0	0	0	0		4	24	1	0	0	0		29	0	0	0	0	
1000 ppm	28	0	5	5	9	7	2	0		0	3	19	6	0	0		28	0	0	0	0	0		5	17	4	0	0	0		26	0	0	0	2	
4000 ppm	16	0	3	3	2	5	3	0		1	3	7	4	1	0		16	0	0	0	0	0		0	1	1	0	0	0	?	16	0	0	0	0	

Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$ Test of CHI SQUARE

? : Significant test is not applied, because No. of data in this group is less than 3.

(HCL101)

BAIS 4

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
Control	31	31	0	0	0	0	
250 ppm	29	29	0	0	0	0	
1000 ppm	28	28	0	0	0	0	
4000 ppm	16	16	0	0	0	0	

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

TABLE H 2

URINALYSIS: FEMALE

Urinalysis of female mice

In the dosed groups, ketone body could not be measured by urine test paper in some animals, because their urine were colored by metabolite of test substance.

The inspection items and number of animals that could not be measured are shown as followed.

Ketone body: 1000 ppm(2), 4000 ppm(26)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	pH 5.0	6.0	6.5	7.0	7.5	8.0	8.5	CHI	Protein −	±	+	2+	3+	4+	CHI	Glucose −	±	+	2+	3+	4+	CHI	Ketone body −	±	+	2+	3+	4+	CHI	Occult blood −	±	+	2+	3+	CHI
Control	24	0	1	3	3	10	7	0		0	1	17	6	0	0		24	0	0	0	0	0		9	14	1	0	0	0		20	0	0	0	4	
250 ppm	25	0	0	2	4	13	5	1		0	2	15	8	0	0		25	0	0	0	0	0		5	19	1	0	0	0		23	0	0	2	0	*
1000 ppm	26	0	4	2	4	9	7	0		0	4	18	4	0	0		26	0	0	0	0	0		9	15	0	0	0	0		23	0	0	2	1	
4000 ppm	35	0	13	2	4	11	5	0		0	7	26	2	0	0	*	35	0	0	0	0	0		1	8	0	0	0	0		35	0	0	0	0	*

Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
Control	24	24	0	0	0	0	
250 ppm	25	25	0	0	0	0	
1000 ppm	26	26	0	0	0	0	
4000 ppm	35	35	0	0	0	0	

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of CHI SQUARE

TABLE J 1

ORGAN WEIGHT, ABSOLUTE: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	Body Weight	ADRENALS	TESTES	HEART	LUNGS	KIDNEYS
Control	30	47.2± 7.4	0.009± 0.002	0.218± 0.028	0.225± 0.018	0.196± 0.048	0.645± 0.091
250 ppm	28	47.2± 9.1	0.009± 0.002	0.212± 0.032	0.231± 0.022	0.235± 0.186	0.620± 0.078
1000 ppm	28	46.0± 8.2	0.010± 0.002	0.270± 0.212	0.238± 0.025	0.250± 0.191	0.812± 1.020
4000 ppm	15	36.8± 7.5**	0.009± 0.002	0.223± 0.023	0.255± 0.039**	0.250± 0.206	0.624± 0.065

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL040)

BAIS 4

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	SPLEEN		LIVER		BRAIN	
Control	30	0.122±	0.111	1.765±	0.566	0.465±	0.016
250 ppm	28	0.118±	0.048	1.970±	0.777	0.455±	0.014*
1000 ppm	28	0.215±	0.224**	1.821±	0.505	0.462±	0.013
4000 ppm	15	0.353±	0.480**	1.954±	0.476	0.472±	0.012

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE J 2

ORGAN WEIGHT, ABSOLUTE: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	Body Weight	ADRENALS	OVARIES	HEART	LUNGS	KIDNEYS
Control	23	33.8± 4.8	0.013± 0.002	0.044± 0.050	0.164± 0.014	0.171± 0.019	0.408± 0.053
250 ppm	25	33.5± 5.8	0.013± 0.002	0.105± 0.171	0.168± 0.014	0.177± 0.021	0.410± 0.065
1000 ppm	24	33.8± 5.2	0.013± 0.002	0.093± 0.173	0.182± 0.026*	0.182± 0.019*	0.525± 0.284**
4000 ppm	34	28.6± 3.9**	0.012± 0.002	0.045± 0.055	0.183± 0.021**	0.194± 0.051**	0.640± 1.092**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

ORGAN WEIGHT:ABSOLUTE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	SPLEEN		LIVER		BRAIN	
Control	23	0.125±	0.110	1.419±	0.648	0.472±	0.013
250 ppm	25	0.207±	0.160**	1.557±	0.690	0.470±	0.012
1000 ppm	24	0.251±	0.181**	1.827±	1.038**	0.477±	0.014
4000 ppm	34	0.333±	0.453**	1.872±	1.282**	0.474±	0.017

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL040)

TABLE K 1

ORGAN WEIGHT, RELATIVE: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	Body Weight (g)	ADRENALS	TESTES	HEART	LUNGS	KIDNEYS
Control	30	47.2± 7.4	0.020± 0.005	0.471± 0.091	0.490± 0.101	0.428± 0.145	1.402± 0.327
250 ppm	28	47.2± 9.1	0.020± 0.007	0.466± 0.117	0.511± 0.137	0.580± 0.776	1.359± 0.285
1000 ppm	28	46.0± 8.2	0.022± 0.007	0.604± 0.480	0.534± 0.123	0.562± 0.446	1.752± 1.908
4000 ppm	15	36.8± 7.5**	0.026± 0.008*	0.632± 0.157**	0.719± 0.174**	0.724± 0.667**	1.745± 0.304**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN
Control	30	0.275± 0.272	3.848± 1.590	1.011± 0.189
250 ppm	28	0.269± 0.159	4.652± 3.270	1.006± 0.236
1000 ppm	28	0.483± 0.489**	4.088± 1.528	1.040± 0.214
4000 ppm	15	1.061± 1.541**	5.506± 1.795**	1.331± 0.265**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE K 2

ORGAN WEIGHT, RELATIVE: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	Body Weight (g)	ADRENALS	OVARIES	HEART	LUNGS	KIDNEYS
Control	23	33.8± 4.8	0.039± 0.006	0.139± 0.177	0.490± 0.056	0.517± 0.098	1.226± 0.223
250 ppm	25	33.5± 5.8	0.039± 0.005	0.315± 0.496	0.512± 0.071	0.542± 0.111	1.248± 0.228
1000 ppm	24	33.8± 5.2	0.039± 0.007	0.287± 0.543	0.543± 0.068*	0.548± 0.096	1.600± 1.017**
4000 ppm	34	28.6± 3.9**	0.043± 0.008	0.158± 0.197	0.653± 0.108**	0.686± 0.178**	2.179± 3.411**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

(HCL042)

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

ORGAN WEIGHT:RELATIVE (SUMMARY)
SURVIVAL ANIMALS (105W)

Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN
Control	23	0.376± 0.339	4.302± 2.250	1.423± 0.197
250 ppm	25	0.625± 0.475**	4.789± 2.580	1.440± 0.249
1000 ppm	24	0.775± 0.583**	5.435± 2.856	1.440± 0.202
4000 ppm	34	1.117± 1.189**	6.365± 3.181*	1.688± 0.217**

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Dunnett

TABLE L 1

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

MALE: ALL ANIMALS

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE

HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
ALL ANIMALS (0-105W)

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	ulcer		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	erosion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	squamous cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	scab		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)
subcutis			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	exudate		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	eosinophilic change:olfactory epithelium		11	0	0	0	11	0	0	0	8	0	0	0	2	0	0	0 *
			(22)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		15	0	0	0	16	6	1	0 *	13	1	0	0	8	2	0	0
			(30)	(0)	(0)	(0)	(32)	(12)	(2)	(0)	(26)	(2)	(0)	(0)	(16)	(4)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		11	0	0	0	8	1	0	0	4	0	0	0	2	0	0	0 *
			(22)	(0)	(0)	(0)	(16)	(2)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	respiratory metaplasia:gland		8	2	0	0	9	4	0	0	10	2	0	0	4	0	0	0
			(16)	(4)	(0)	(0)	(18)	(8)	(0)	(0)	(20)	(4)	(0)	(0)	(8)	(0)	(0)	(0)
	atrophy:olfactory epithelium		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
nasopharynx			<50>				<50>				<50>				<50>			
	eosinophilic change		1	0	0	0	2	0	1	0	0	1	0	0	3	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(6)	(0)	(0)	(0)
larynx			<50>				<50>				<50>				<50>			
	arthritis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Respiratory system}																		
lung		<50>																
	congestion		0	1	0	0	1	0	0	0	0	0	0	0	0	3	0	0
			(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)
	hemorrhage		0	1	0	0	0	0	0	0	1	2	0	0	0	1	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(0)	(0)	(2)	(0)	(0)
	squamous cell metaplasia		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	accumulation of foamy cells		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	uremic pneumonitis		0	0	0	0	0	1	0	0	0	3	0	0	2	7	0	0 **
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(0)	(0)	(4)	(14)	(0)	(0)
	accumulation:macrophage		0	0	0	0	1	0	0	0	0	1	0	0	1	2	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(4)	(0)	(0)
	degeneration:blood vessel		0	0	0	0	0	1	0	0	0	1	0	0	1	2	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(4)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	increased hematopoiesis		10	0	0	0	12	0	0	0	12	0	0	0	32	0	0	0 **
			(20)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(64)	(0)	(0)	(0)
	granulopoiesis:increased		8	0	0	0	5	0	0	0	9	0	0	0	10	0	0	0
			(16)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
lymph node			<50>				<50>				<50>				<50>			
	lymphadenitis		0	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
thymus			<50>				<50>				<50>				<50>			
	atrophy		0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	atrophy		0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	thrombus		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	deposit of hemosiderin		5	0	0	0	41	1	0	0 **	43	2	0	0 **	36	2	0	0 **
			(10)	(0)	(0)	(0)	(82)	(2)	(0)	(0)	(86)	(4)	(0)	(0)	(72)	(4)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Hematopoietic system}																		
spleen			<50>				<50>				<50>				<50>			
	extramedullary hematopoiesis		16 (32)	4 (8)	0 (0)	0 (0)	21 (42)	5 (10)	0 (0)	0 (0)	16 (32)	17 (34)	1 (2)	0 (0) **	11 (22)	32 (64)	0 (0)	0 (0) **
	engorgement of erythrocyte		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	follicular hyperplasia		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	1 (2)	0 (0)
	mineralization		4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)
	degeneration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	arteritis		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
oral cavity			<50>				<50>				<50>				<50>			
	squamous cell hyperplasia		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
tooth			<50>				<50>				<50>				<50>			
	dysplasia		0	3	1	0	1	1	1	0	0	1	1	0	0	0	0	0
			(0)	(6)	(2)	(0)	(2)	(2)	(2)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)
tongue			<50>				<50>				<50>				<50>			
	arteritis		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
stomach			<50>				<50>				<50>				<50>			
	atrophy:glandular mucosa		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		6	0	0	0	3	0	0	0	1	0	0	0	1	0	0	0
			(12)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				250 ppm 50				1000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	erosion:glandular stomach		1	0	0	0	2	0	0	0	0	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	ulcer:glandular stomach		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:glandular stomach		8	0	0	0	10	0	0	0	8	0	0	0	3	0	0	0
			(16)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
small intes			<50>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	angiectasis		1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:central		0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:focal		2	0	0	0	0	1	2	0	1	2	0	0	4	3	0	0
			(4)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(2)	(4)	(0)	(0)	(8)	(6)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	deposit of hemosiderin		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 ** (0)	40 (80)	0 (0)	0 (0)	0 ** (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	scar		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	clear cell focus		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	basophilic cell focus		2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver																		
	biliary cyst		<50>				<50>				<50>				<50>			
			0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hepatocellular hypertrophy:central		0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
{Urinary system}																		
kidney																		
	cyst		<50>				<50>				<50>				<50>			
			0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyaline droplet		2	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	deposit of hemosiderin		1	0	0	0	0	0	0	0	0	0	0	0	33	0	0	0 **
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(66)	(0)	(0)	(0)
	hyaline cast		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	scar		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)
	inflammatory polyp		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	hydronephrosis		0 (0)	5 (10)	2 (4)	1 (2)	0 (0)	6 (12)	2 (4)	1 (2)	0 (0)	2 (4)	3 (6)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)
	pyelonephritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)
	papillary necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	mineralization:pelvis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:cortex		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	dilatation:tubular lumen		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
	glomerulosclerosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	regeneration:proximal tubule		12 (24)	0 (0)	0 (0)	0 (0)	14 (28)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	10 (20)	2 (4)	0 (0)	0 (0)
ureter			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	2 (4)	25 (50)	0 (0)	0 ** (0)
	simple hyperplasia:transitional epithelium		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	xanthogranuloma		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
urin bladd			<50>				<50>				<50>				<50>			
	hyaline droplet degeneration:superficial cell of transit ional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 ** (0)
urethra			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 * (0)
{Endocrine system}																		
pituitary			<50>				<49>				<49>				<50>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Rathke pouch		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
parathyroid			<50>				<50>				<50>				<50>			
	embryonal rest		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Endocrine system}																		
adrenal			<50>				<50>				<50>				<50>			
	focal fatty change:cortex		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Reproductive system}																		
testis			<50>				<50>				<50>				<50>			
	atrophy		2	0	0	0	2	1	1	0	3	1	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(4)	(2)	(2)	(0)	(6)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
epididymis			<50>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	spermatogenic granuloma		1	0	0	0	2	1	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
prostate			<50>				<50>				<50>				<50>			
	inflammation		0	2	0	0	1	0	0	0	1	0	0	0	1	7	0	0
			(0)	(4)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(14)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
prep/cli gl			<50>				<50>				<50>				<50>			
	duct ectasia		0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	hemorrhage		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		11	0	0	0	12	1	0	0	14	0	0	0	15	0	0	0
			(22)	(0)	(0)	(0)	(24)	(2)	(0)	(0)	(28)	(0)	(0)	(0)	(30)	(0)	(0)	(0)
spinal cord			<50>				<50>				<50>				<50>			
	mineralization		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	keratitis		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	squamous cell metaplasia:cornea		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Harder gl			<49>				<50>				<50>				<50>			
	degeneration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		2	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Body cavities}																		
retroperit			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

TABLE L 4

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

FEMALE: ALL ANIMALS

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	scab		1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	exudate		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		5	0	0	0	3	1	0	0	4	0	0	0	6	0	0	0
			(10)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(8)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		25	5	0	0	30	3	0	0	26	6	0	0	30	6	0	0
			(50)	(10)	(0)	(0)	(60)	(6)	(0)	(0)	(52)	(12)	(0)	(0)	(60)	(12)	(0)	(0)
	inflammation:foreign body		0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		1	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	respiratory metaplasia:gland		5	0	0	0	6	0	0	0	4	0	0	0	2	0	0	0
			(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	squamous cell metaplasia:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	ulcer:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
nasopharynx			<50>				<50>				<50>				<50>			
	eosinophilic change		2 (4)	2 (4)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	3 (6)	0 (0)	0 (0)
lung			<50>				<50>				<50>				<50>			
	congestion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
lung			<50>				<50>				<50>				<50>			
	accumulation of foamy cells		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	accumulation:macrophage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	degeneration:blood vessel		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	4 (8)	0 (0)	0 * (0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	increased hematopoiesis		17 (34)	0 (0)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	18 (36)	0 (0)	0 (0)	0 (0)	36 (72)	0 (0)	0 (0)	0 ** (0)
	granulopoiesis:increased		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}																		
lymph node			<50>				<50>				<50>				<50>			
	lymphadenitis		0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	atrophy		0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	deposit of hemosiderin		19	0	0	0	10	20	0	0 **	9	26	0	0 **	14	29	1	0 **
			(38)	(0)	(0)	(0)	(20)	(40)	(0)	(0)	(18)	(52)	(0)	(0)	(28)	(58)	(2)	(0)
	osseous metaplasia		0	0	0	0	0	0	0	0	0	0	0	0	1	3	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(6)	(0)	(0)
	extramedullary hematopoiesis		11	10	0	0	15	6	1	0	16	16	0	0	28	10	0	0 **
			(22)	(20)	(0)	(0)	(30)	(12)	(2)	(0)	(32)	(32)	(0)	(0)	(56)	(20)	(0)	(0)
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	0	0	0	0	12	1	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(24)	(2)	(0)	(0)
	follicular hyperplasia		0	0	0	0	2	0	1	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Circulatory system}																		
heart		<50>																
	mineralization		3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	degeneration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	arteritis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Digestive system}																		
tooth		<50>																
	dysplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
tongue		<50>																
	arteritis		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
salivary gl			<50>				<50>				<50>				<50>			
	xanthogranuloma		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
stomach			<50>				<50>				<50>				<50>			
	hyperplasia:forestomach		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	erosion:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:glandular stomach		5 (10)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
liver			<50>				<50>				<50>				<50>			
	congestion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	angiectasis		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)
	necrosis:central		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	necrosis:focal		1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	fatty change:central		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	0	0	0	0	2	0	0	0	34	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(68)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	granulation		2	1	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	clear cell focus		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	acidophilic cell focus		1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	hepatocellular hypertrophy:central		0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(14)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
pancreas			<50>				<50>				<50>				<50>			
	atrophy		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hyaline droplet		7	0	0	0	6	0	0	0	10	2	0	0	10	0	0	0
			(14)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(20)	(4)	(0)	(0)	(20)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	1	0	0	0	0	0	0	0	17	0	0	0 **
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(34)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	lymphocytic infiltration		0	0	0	0	3	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	scar		0	1	0	0	0	0	0	0	0	0	0	0	0	6	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(12)	(0)	(0)
	inflammatory polyp		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hydronephrosis		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	papillary necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	mineralization:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	dilatation:tubular lumen		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	regeneration:proximal tubule		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	3 (6)	0 (0)	0 (0)
	desquamation:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyaline droplet degeneration:superficial cell of transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (28)	0 (0)	0 (0)	0 (0) **

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<49>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia		5 (10)	3 (6)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)
	Rathke pouch		3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<50>				<50>				<50>				<50>			
	cyst		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	spindle-cell hyperplasia		12 (24)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
	focal fatty change:cortex		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	fatty change:corticomedullary junction		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Reproductive system}																		
ovary			<50>				<50>				<50>				<50>			
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
ovary			<50>				<50>				<50>				<50>			
	cyst		3	0	0	0	3	0	0	0	7	0	0	0	4	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	dilatation		0	0	0	0	0	1	0	0	0	0	0	0	0	3	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:gland		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	cystic endometrial hyperplasia		10	0	0	0	10	0	0	0	12	0	0	0	7	1	0	0
			(20)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(14)	(2)	(0)	(0)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	hemorrhage		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference : * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	mineralization		10	0	0	0	6	0	0	0	9	0	0	0	14	0	0	0
			(20)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(28)	(0)	(0)	(0)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	keratitis		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)
Harder gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		0	1	0	0	0	1	0	0	2	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
bone			<50>				<50>				<50>				<50>			
	deformity		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				250 ppm				1000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Musculoskeletal system}																		
bone			<50>				<50>				<50>				<50>			
	osteosclerosis		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Body cavities}																		
peritoneum			<50>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
b b : Number of animals with lesion
(c) c : b / a * 100
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

TABLE O 1

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: MALE

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	4/50(8.0)	7/50(14.0)	4/50(8.0)
Adjusted rates(b)	11.43	10.34	19.35	10.00
Terminal rates(c)	3/31(9.7)	3/29(10.3)	5/29(17.2)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.4743			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.7395			
Fisher Exact test(e)		P = 0.5000	P = 0.3798	P = 0.5000
	SITE : lung			
	TUMOR : bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	6/50(12.0)	8/50(16.0)	1/50(2.0)
Adjusted rates(b)	13.89	16.67	19.35	6.25
Terminal rates(c)	4/31(12.9)	4/29(13.8)	5/29(17.2)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5588			
Prevalence method(d)	P = 0.8797			
Combined analysis(d)	P = 0.8969			
Cochran-Armitage test(e)	P = 0.0595			
Fisher Exact test(e)		P = 0.5000	P = 0.2768	P = 0.1022
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	10/50(20.0)	14/50(28.0)	5/50(10.0)
Adjusted rates(b)	25.00	26.67	35.48	12.50
Terminal rates(c)	7/31(22.6)	7/29(24.1)	10/29(34.5)	2/16(12.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5588			
Prevalence method(d)	P = 0.8084			
Combined analysis(d)	P = 0.8305			
Cochran-Armitage test(e)	P = 0.1002			
Fisher Exact test(e)		P = 0.5984	P = 0.2415	P = 0.1312

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	4/50(8.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	9.68	10.34	10.34	6.25
Terminal rates(c)	3/31(9.7)	3/29(10.3)	3/29(10.3)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5931			
Prevalence method(d)	P = 0.6406			
Combined analysis(d)	P = 0.6976			
Cochran-Armitage test(e)	P = 0.1956			
Fisher Exact test(e)		P = 0.3703	P = 0.2435	P = 0.1343
	SITE : spleen			
	TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	6/50(12.0)	2/50(4.0)
Adjusted rates(b)	3.23	0.0	14.63	6.25
Terminal rates(c)	1/31(3.2)	0/29(0.0)	3/29(10.3)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.2366			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.6399			
Fisher Exact test(e)		P = 0.5000	P = 0.0559	P = 0.5000
	SITE : spleen			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	0.0	0.0	8.82	6.25
Terminal rates(c)	0/31(0.0)	0/29(0.0)	2/29(6.9)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.1556			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.5794			
Fisher Exact test(e)		P = N.C.	P = 0.1212	P = 0.5000

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : spleen			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	9/50(18.0)	3/50(6.0)
Adjusted rates(b)	3.23	0.0	21.95	12.50
Terminal rates(c)	1/31(3.2)	0/29(0.0)	5/29(17.2)	2/16(12.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.1265			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.4788			
Fisher Exact test(e)		P = 0.5000	P = 0.0078**	P = 0.3087
	SITE : liver			
	TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	2/50(4.0)	2/50(4.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	3.23	0.0	7.50	13.04
Terminal rates(c)	1/31(3.2)	0/29(0.0)	2/29(6.9)	2/16(12.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8249			
Prevalence method(d)	P = 0.0450*			
Combined analysis(d)	P = 0.2212			
Cochran-Armitage test(e)	P = 0.7439			
Fisher Exact test(e)		P = 0.6913	P = 0.2180	P = 0.5000
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	14/50(28.0)	10/50(20.0)	2/50(4.0)
Adjusted rates(b)	25.81	41.38	30.00	7.69
Terminal rates(c)	8/31(25.8)	12/29(41.4)	8/29(27.6)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.9834			
Combined analysis(d)	P = --------			
Cochran-Armitage test(e)	P = 0.0043**			
Fisher Exact test(e)		P = 0.1710	P = 0.5000	P = 0.0256*

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	1/50(2.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	5.26	0.0	0.0	0.0
Terminal rates(c)	1/31(3.2)	0/29(0.0)	0/29(0.0)	0/16(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5823			
Prevalence method(d)	P = 0.9227			
Combined analysis(d)	P = 0.7689			
Cochran-Armitage test(e)	P = 0.2348			
Fisher Exact test(e)		P = 0.1022	P = 0.1022	P = 0.1022
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	15/50(30.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	15.63	32.35	13.79	12.50
Terminal rates(c)	4/31(12.9)	9/29(31.0)	4/29(13.8)	2/16(12.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8807			
Prevalence method(d)	P = 0.9694			
Combined analysis(d)	P = 0.9877			
Cochran-Armitage test(e)	P = 0.0073**			
Fisher Exact test(e)		P = 0.0448*	P = 0.3798	P = 0.0798
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	7/50(14.0)	4/50(8.0)
Adjusted rates(b)	3.23	3.45	10.34	18.75
Terminal rates(c)	1/31(3.2)	1/29(3.4)	3/29(10.3)	3/16(18.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8021			
Prevalence method(d)	P = 0.0248*			
Combined analysis(d)	P = 0.1437			
Cochran-Armitage test(e)	P = 0.6531			
Fisher Exact test(e)		P = 0.5000	P = 0.0798	P = 0.3389

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	15/50(30.0)	24/50(48.0)	13/50(26.0)	4/50(8.0)
Adjusted rates(b)	37.50	58.62	36.67	18.75
Terminal rates(c)	11/31(35.5)	17/29(58.6)	10/29(34.5)	3/16(18.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8807			
Prevalence method(d)	P = 0.9963			
Combined analysis(d)	P = 0.9984			
Cochran-Armitage test(e)	P = 0.0001**			
Fisher Exact test(e)		P = 0.0502	P = 0.4120	P = 0.0047**
	SITE : epididymis			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	0.0	3.45	6.90	0.0
Terminal rates(c)	0/31(0.0)	1/29(3.4)	2/29(6.9)	0/16(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2543			
Prevalence method(d)	P = 0.5152			
Combined analysis(d)	P = 0.3570			
Cochran-Armitage test(e)	P = 0.8709			
Fisher Exact test(e)		P = 0.7525	P = 0.3087	P = 0.7525

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : Harderian gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	4/49(8.2)	2/50(4.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	12.12	6.90	3.45	2.27
Terminal rates(c)	3/31(9.7)	2/29(6.9)	1/29(3.4)	0/16(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7661			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2532			
Fisher Exact test(e)		P = 0.3292	P = 0.1748	P = 0.1748

(HPT360A)

BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath 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.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	10/50(20.0)	6/50(12.0)
Adjusted rates(b)	6.45	0.0	20.00	25.00
Terminal rates(c)	2/31(6.5)	0/29(0.0)	5/29(17.2)	4/16(25.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8249			
Prevalence method(d)	P = 0.0109*			
Combined analysis(d)	P = 0.0616			
Cochran-Armitage test(e)	P = 0.3156			
Fisher Exact test(e)		P = 0.5000	P = 0.0357*	P = 0.2435
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	3/50(6.0)	7/50(14.0)	3/50(6.0)
Adjusted rates(b)	8.11	6.90	13.79	6.25
Terminal rates(c)	2/31(6.5)	2/29(6.9)	4/29(13.8)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5267			
Prevalence method(d)	P = 0.5907			
Combined analysis(d)	P = 0.6033			
Cochran-Armitage test(e)	P = 0.2585			
Fisher Exact test(e)		P = 0.0999	P = 0.5000	P = 0.0999
	SITE : ALL SITE TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	4/50(8.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	9.68	10.34	13.79	6.25
Terminal rates(c)	3/31(9.7)	3/29(10.3)	4/29(13.8)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6003			
Prevalence method(d)	P = 0.6316			
Combined analysis(d)	P = 0.6915			
Cochran-Armitage test(e)	P = 0.1863			
Fisher Exact test(e)		P = 0.3703	P = 0.5000	P = 0.1343

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	4/50(8.0)	1/50(2.0)
Adjusted rates(b)	0.0	3.45	10.34	6.25
Terminal rates(c)	0/31(0.0)	1/29(3.4)	3/29(10.3)	1/16(6.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2713			
Prevalence method(d)	P = 0.1989			
Combined analysis(d)	P = 0.2187			
Cochran-Armitage test(e)	P = 0.9223			
Fisher Exact test(e)		P = 0.5000	P = 0.0587	P = 0.5000

(HPT360A)

BAIS1

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath 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.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference : * : $P \leqq 0.05$ ** : $P \leqq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

TABLE O 2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: FEMALE

Group Name	Control	250 ppm	1000 ppm	4000 ppm
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	1/50(2.0)	2/50(4.0)
Adjusted rates(b)	2.63	7.50	4.00	5.71
Terminal rates(c)	0/23(0.0)	0/25(0.0)	1/25(4.0)	2/35(5.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.4889			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.8920			
Fisher Exact test(e)		P = 0.3087	P = 0.7525	P = 0.5000
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	4/50(8.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	2.63	7.50	4.00	8.57
Terminal rates(c)	0/23(0.0)	0/25(0.0)	1/25(4.0)	3/35(8.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6699			
Prevalence method(d)	P = 0.2868			
Combined analysis(d)	P = 0.4082			
Cochran-Armitage test(e)	P = 0.7028			
Fisher Exact test(e)		P = 0.1811	P = 0.5000	P = 0.3087
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	18/50(36.0)	20/50(40.0)	17/50(34.0)	15/50(30.0)
Adjusted rates(b)	17.39	28.00	20.00	28.57
Terminal rates(c)	4/23(17.4)	7/25(28.0)	5/25(20.0)	10/35(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9970			
Prevalence method(d)	P = 0.2508			
Combined analysis(d)	P = 0.9576			
Cochran-Armitage test(e)	P = 0.3586			
Fisher Exact test(e)		P = 0.4185	P = 0.5000	P = 0.3355

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : spleen TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	1/50(2.0)	0/50(0.0)
Adjusted rates(b)	0.0	4.00	4.00	0.0
Terminal rates(c)	0/23(0.0)	1/25(4.0)	1/25(4.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8237			
Prevalence method(d)	P = 0.7389			
Combined analysis(d)	P = 0.9038			
Cochran-Armitage test(e)	P = 0.2676			
Fisher Exact test(e)		P = 0.1212	P = 0.5000	P = N.C.
	SITE : spleen TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	2/50(4.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	0.0	7.69	8.00	0.0
Terminal rates(c)	0/23(0.0)	1/25(4.0)	2/25(8.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3471			
Prevalence method(d)	P = 0.8620			
Combined analysis(d)	P = 0.8587			
Cochran-Armitage test(e)	P = 0.3844			
Fisher Exact test(e)		P = 0.2475	P = 0.1212	P = N.C.
	SITE : liver TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	4/50(8.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	13.79	16.00	12.00	0.0
Terminal rates(c)	2/23(8.7)	4/25(16.0)	3/25(12.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9956			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0423*			
Fisher Exact test(e)		P = 0.6425	P = 0.5000	P = 0.0587

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : liver TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	0/50(0.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	2.38	0.0	2.08	2.86
Terminal rates(c)	0/23(0.0)	0/25(0.0)	0/25(0.0)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9607			
Prevalence method(d)	P = 0.3422			
Combined analysis(d)	P = 0.7745			
Cochran-Armitage test(e)	P = 0.4549			
Fisher Exact test(e)		P = 0.0587	P = 0.1811	P = 0.1811
	SITE : liver TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	4.35	4.00	4.00	5.71
Terminal rates(c)	1/23(4.3)	1/25(4.0)	1/25(4.0)	2/35(5.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2237			
Prevalence method(d)	P = 0.3524			
Combined analysis(d)	P = 0.2290			
Cochran-Armitage test(e)	P = 0.2219			
Fisher Exact test(e)		P = 0.7525	P = 0.5000	P = 0.3087
	SITE : liver TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	1/50(2.0)	3/50(6.0)	5/50(10.0)
Adjusted rates(b)	4.35	4.00	8.00	8.57
Terminal rates(c)	1/23(4.3)	1/25(4.0)	2/25(8.0)	3/35(8.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4033			
Prevalence method(d)	P = 0.0979			
Combined analysis(d)	P = 0.1161			
Cochran-Armitage test(e)	P = 0.0865			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.2180

Group Name	Control	250 ppm	1000 ppm	4000 ppm
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	5/50(10.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	13.79	20.00	12.00	2.13
Terminal rates(c)	2/23(8.7)	5/25(20.0)	3/25(12.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ----------			
Prevalence method(d)	P = 0.9787			
Combined analysis(d)	P = ----------			
Cochran-Armitage test(e)	P = 0.1129			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.1811
SITE : pituitary gland				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	0/50(0.0)	5/50(10.0)	4/49(8.2)
Adjusted rates(b)	4.35	0.0	12.00	8.11
Terminal rates(c)	1/23(4.3)	0/25(0.0)	3/25(12.0)	2/35(5.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2792			
Prevalence method(d)	P = 0.1904			
Combined analysis(d)	P = 0.1533			
Cochran-Armitage test(e)	P = 0.1897			
Fisher Exact test(e)		P = 0.2475	P = 0.2180	P = 0.3292
SITE : uterus				
TUMOR : histiocytic sarcoma				
Tumor rate				
Overall rates(a)	8/50(16.0)	7/50(14.0)	17/50(34.0)	12/50(24.0)
Adjusted rates(b)	14.29	4.00	28.00	12.20
Terminal rates(c)	3/23(13.0)	1/25(4.0)	7/25(28.0)	4/35(11.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4025			
Prevalence method(d)	P = 0.3987			
Combined analysis(d)	P = 0.3683			
Cochran-Armitage test(e)	P = 0.3354			
Fisher Exact test(e)		P = 0.5000	P = 0.0317*	P = 0.2270

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : Harderian gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	3/50(6.0)	1/50(2.0)	2/50(4.0)
Adjusted rates(b)	0.0	6.38	4.00	4.65
Terminal rates(c)	0/23(0.0)	0/25(0.0)	1/25(4.0)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3124			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6260			
Fisher Exact test(e)		P = 0.1212	P = 0.5000	P = 0.2475

(HPT360A)

BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath 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.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	2/50(4.0)	4/50(8.0)	4/50(8.0)	2/50(4.0)
Adjusted rates(b)	4.35	15.38	13.33	4.08
Terminal rates(c)	1/23(4.3)	3/25(12.0)	3/25(12.0)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 1.0000 ?			
Prevalence method(d)	P = 0.7200			
Combined analysis(d)	P = 0.7969			
Cochran-Armitage test(e)	P = 0.6076			
Fisher Exact test(e)		P = 0.3389	P = 0.3389	P = 0.6913
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	12/50(24.0)	7/50(14.0)	19/50(38.0)	14/50(28.0)
Adjusted rates(b)	14.29	4.00	28.00	17.14
Terminal rates(c)	3/23(13.0)	1/25(4.0)	7/25(28.0)	6/35(17.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6129			
Prevalence method(d)	P = 0.2035			
Combined analysis(d)	P = 0.3884			
Cochran-Armitage test(e)	P = 0.3902			
Fisher Exact test(e)		P = 0.1540	P = 0.0971	P = 0.4100
	SITE : ALL SITE TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	18/50(36.0)	23/50(46.0)	18/50(36.0)	15/50(30.0)
Adjusted rates(b)	17.39	32.00	24.00	28.57
Terminal rates(c)	4/23(17.4)	8/25(32.0)	6/25(24.0)	10/35(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9983			
Prevalence method(d)	P = 0.3395			
Combined analysis(d)	P = 0.9781			
Cochran-Armitage test(e)	P = 0.2193			
Fisher Exact test(e)		P = 0.2081	P = 0.5824	P = 0.3355

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	4.35	4.00	4.00	5.71
Terminal rates(c)	1/23(4.3)	1/25(4.0)	1/25(4.0)	2/35(5.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2782			
Prevalence method(d)	P = 0.3524			
Combined analysis(d)	P = 0.2616			
Cochran-Armitage test(e)	P = 0.2824			
Fisher Exact test(e)		P = 0.7525	P = 0.3087	P = 0.3087

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath 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.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference : * : $P \leq 0.05$ ** : $P \leq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

TABLE Q 1

HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER: B6D2F1/Crlj MALE MICE

TABLE Q 1 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : B6D2F1/Crlj MALE MICE

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Spleen	2244			
Hemangioma		48	2.1	0 - 10
Hemangiosarcoma		59	2.6	0 - 10
Hemangioma+Hemangiosarcoma		107	4.8	0 - 14
Liver	2245			
Hemangioma		70	3.1	0 - 14
Hemangiosarcoma		96	4.3	0 - 14
Hemangioma+Hemangiosarcoma		166	7.4	0 - 16
All site	2245			
Hemangioma		145	6.5	0 - 18
Hemangiosarcoma		157	7.0	0 - 18
Hemangioma+Hemangiosarcoma		279	12.4	0 - 22

45 carcinogenicity studies examined in Japan Bioassay Research Center were used.

Study No. : 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0268, 0270, 0279, 0285, 0297, 0319, 0329, 0343, 0348, 0366, 0372, 0402, 0406, 0418, 0422, 0438, 0449, 0458, 0462, 0498, 0515, 0561, 0580, 0611, 0613, 0642, 0676, 0705

TABLE Q 2

HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER: B6D2F1/CrlCrlj FEMALE MICE

TABLE Q 2 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : B6D2F1/Crlj FEMALE MICE

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Uterus	2245			
Histiocytic sarcoma		464	20.7	10 - 34

45 carcinogenicity studies examined in Japan Bioassay Research Center were used.

Study No. : 0044, 0060, 0062, 0064, 0066, 0068, 0096, 0105, 0116, 0140, 0159, 0163, 0190, 0206, 0211, 0225, 0243, 0268, 0270, 0279, 0285, 0297, 0319, 0329, 0343, 0348, 0366, 0372, 0402, 0406, 0418, 0422, 0438, 0449, 0458, 0462, 0498, 0515, 0561, 0580, 0611, 0613, 0642, 0676, 0705

TABLE R 1

CAUSE OF DEATH: MALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

COUSE OF DEATH (SUMMARY)
(0-105W)

Group Name	Control	250 ppm	1000 ppm	4000 ppm
Number of Dead and Moribund Animal	19	21	21	34
no microscop confirm	0	2	0	3
renal lesion	0	1	1	2
thrombosis	0	0	1	3
urinary retention	2	6	8	21
hydronephrosis	3	3	2	2
tumor d:leukemia	3	1	1	1
tumor d:subcutis	2	0	0	0
tumor d:lung	0	1	1	0
tumor d:salivary gl	0	0	1	0
tumor d:small intes	1	0	0	0
tumor d:liver	6	6	5	1
tumor d:kidney	1	1	0	0
tumor d:epididymis	1	0	1	1

TABLE R 2

CAUSE OF DEATH: FEMALE

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : FEMALE

COUSE OF DEATH (SUMMARY)
(0-105W)

Group Name	Control	250 ppm	1000 ppm	4000 ppm
Number of Dead and Moribund Animal	27	25	25	15
no microscop confirm	0	2	0	0
thrombosis	0	1	0	0
arteritis	1	0	0	0
hydronephrosis	0	0	1	0
tumor d:leukemia	14	15	10	5
tumor d:subcutis	2	0	1	1
tumor d:lung	0	1	1	0
tumor d:spleen	0	0	1	0
tumor d:liver	4	0	2	1
tumor d:pituitary	1	0	0	1
tumor d:uterus	4	6	9	7
tumor d:muscle	1	0	0	0

FIGURES

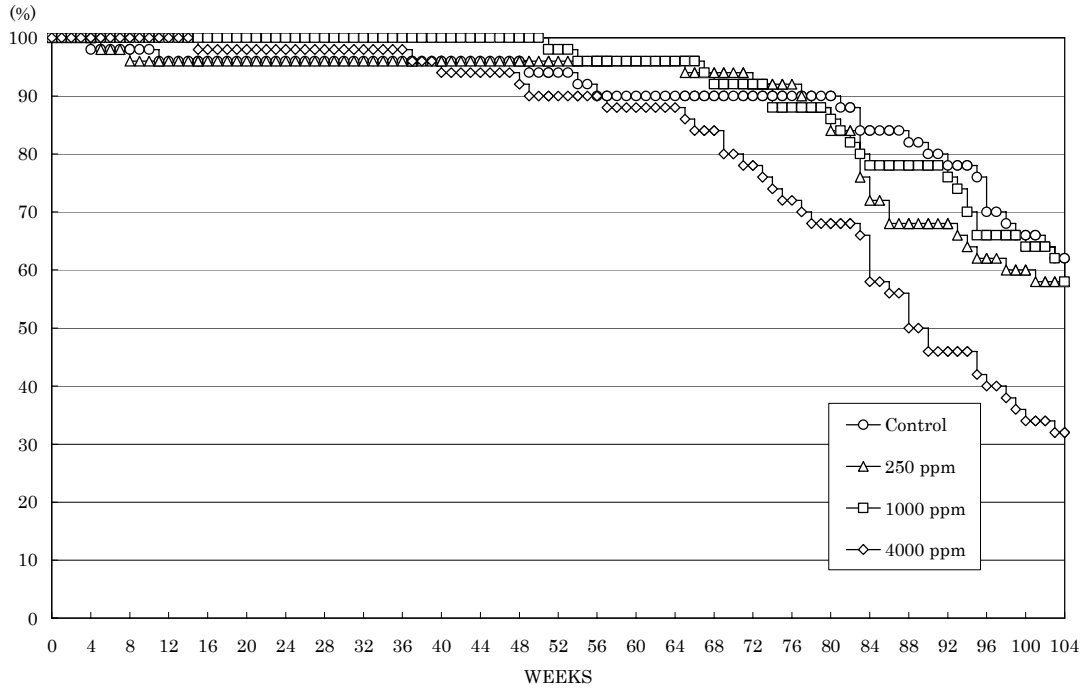


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

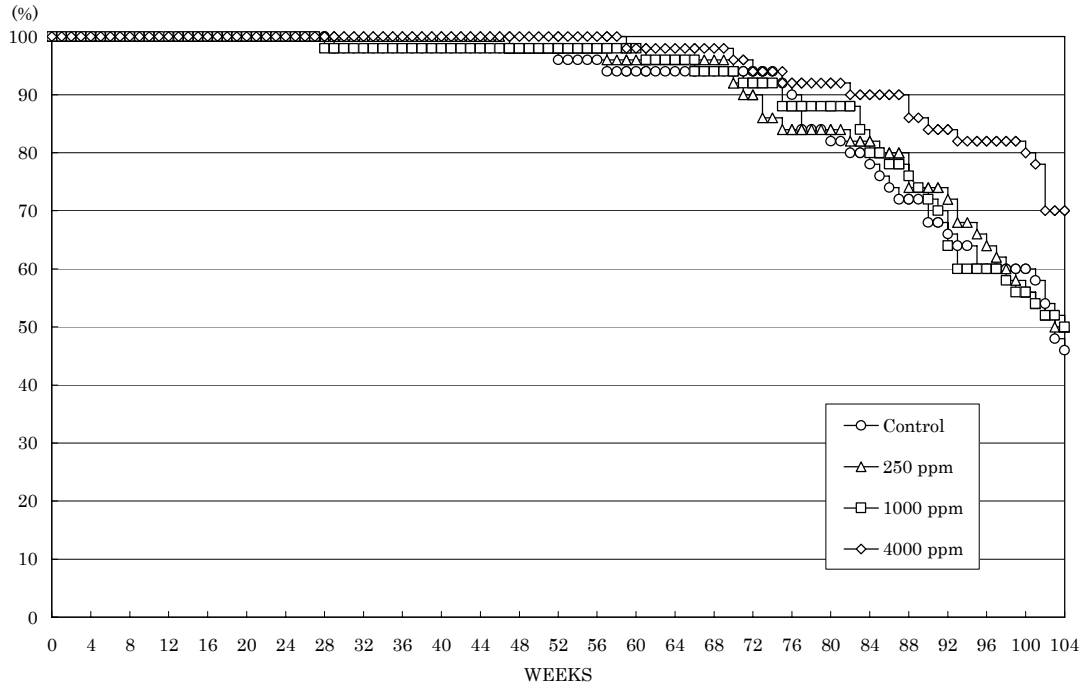


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

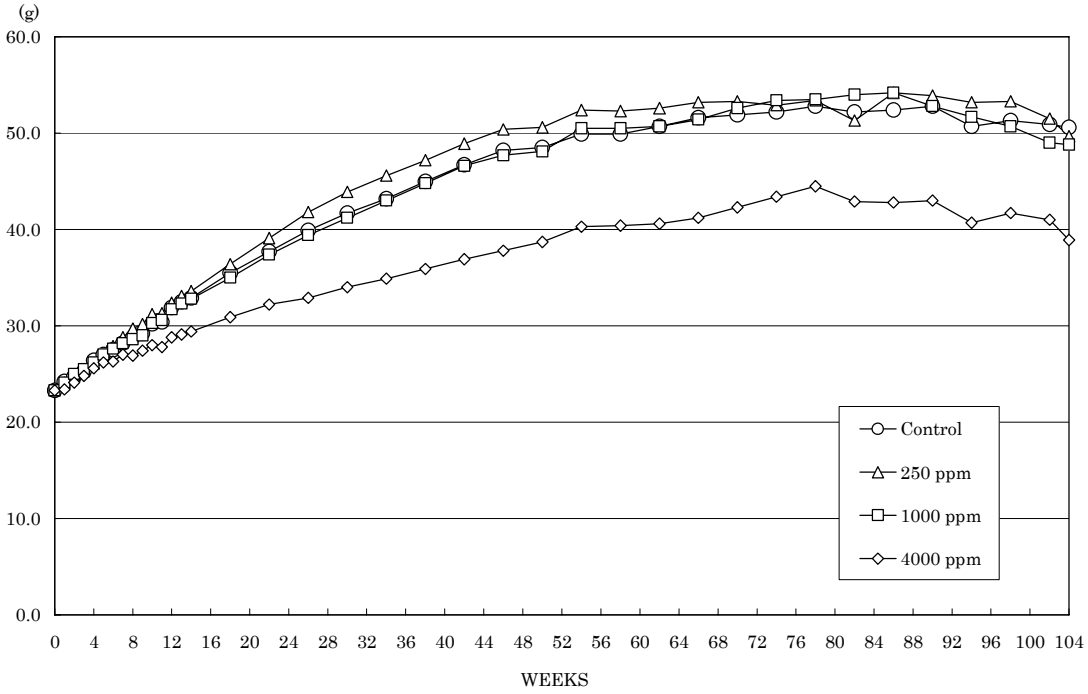


FIGURE 3 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

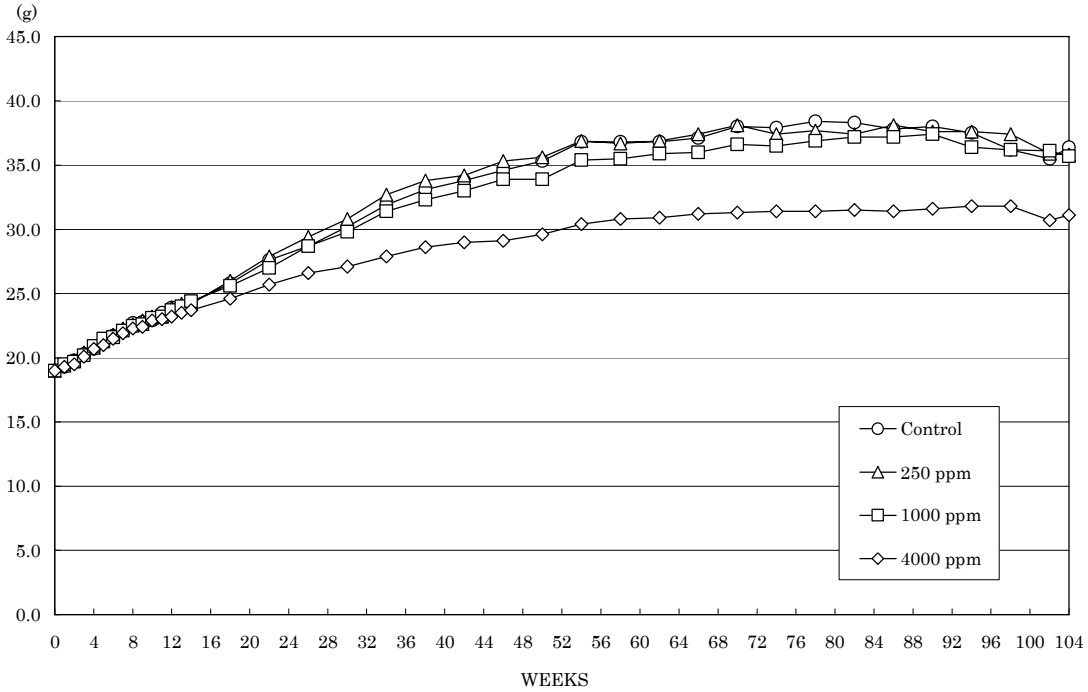


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

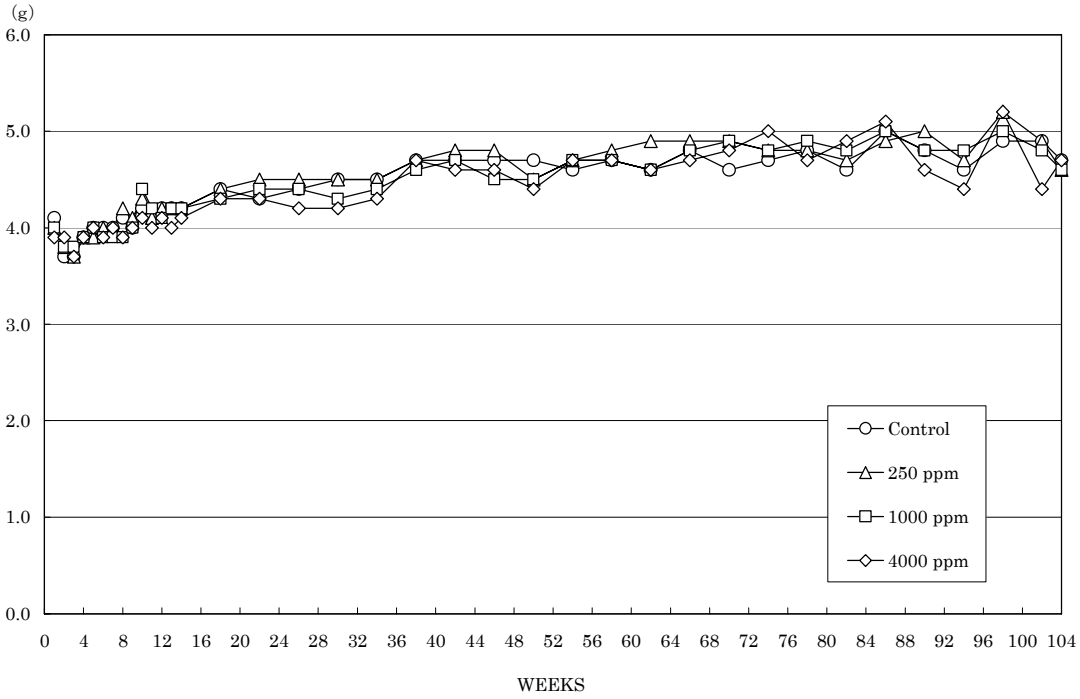


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

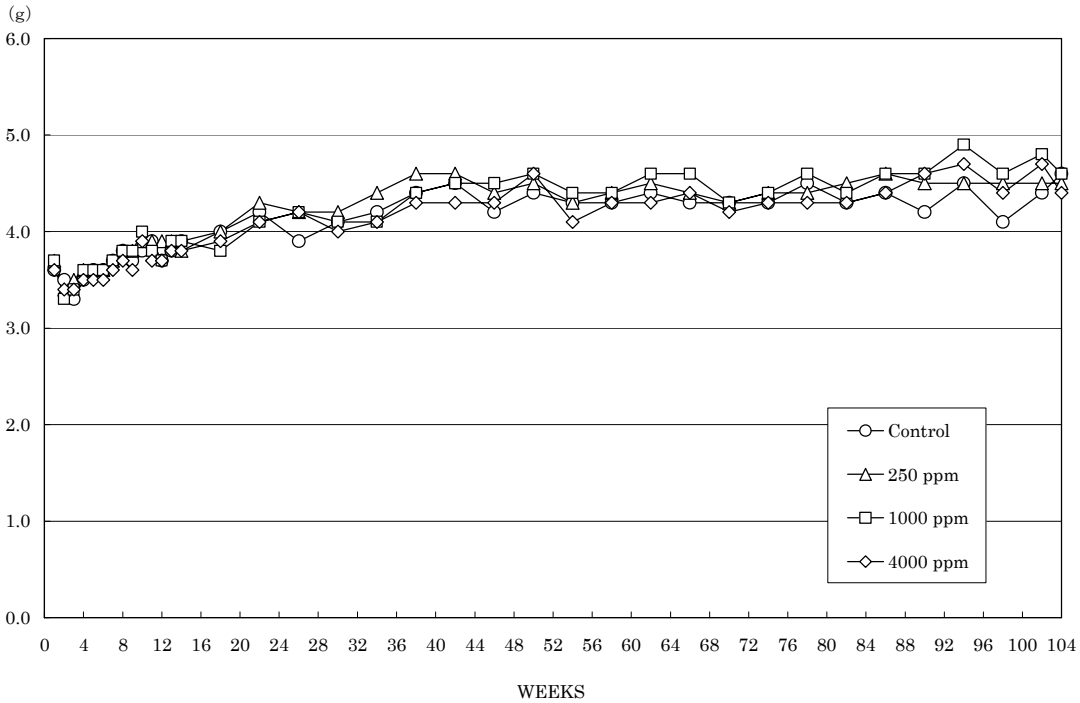
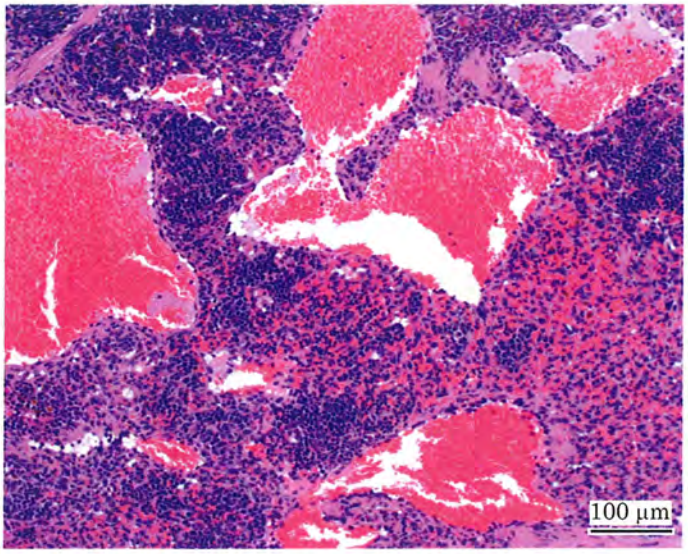
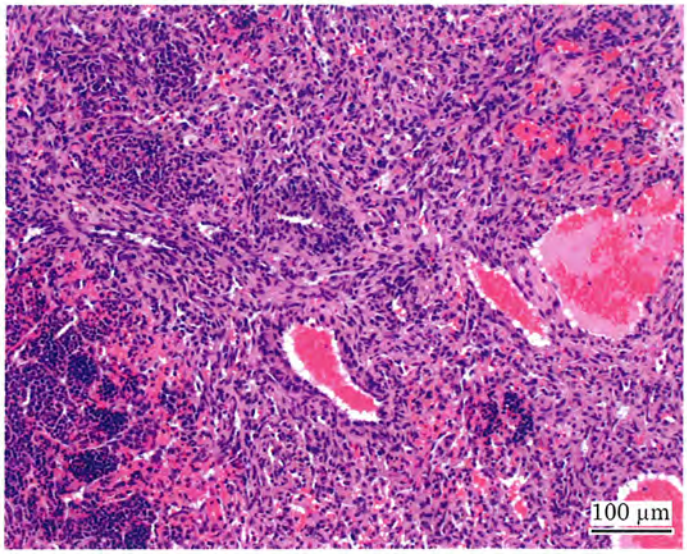


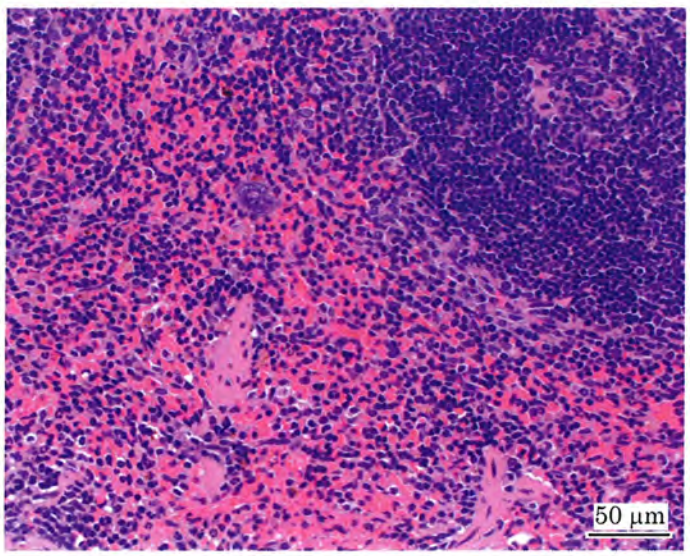
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE



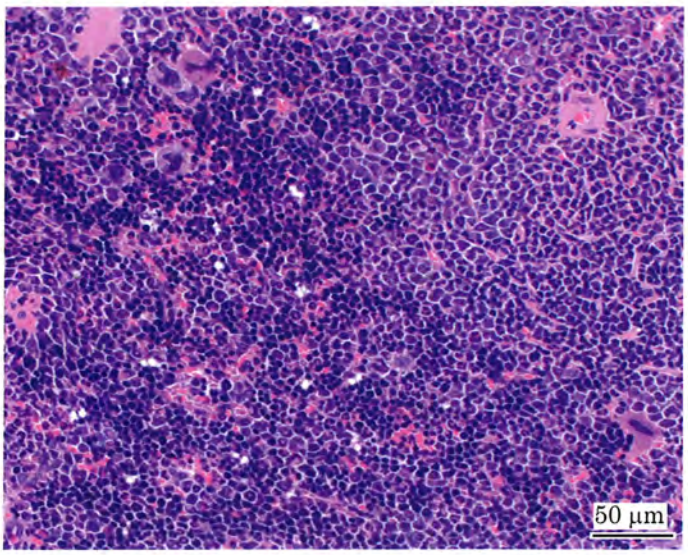
Photograph 1
Spleen: Hemangioma
Rat, Male, 1000 ppm, Animal No. 0685-1208 (H&E)



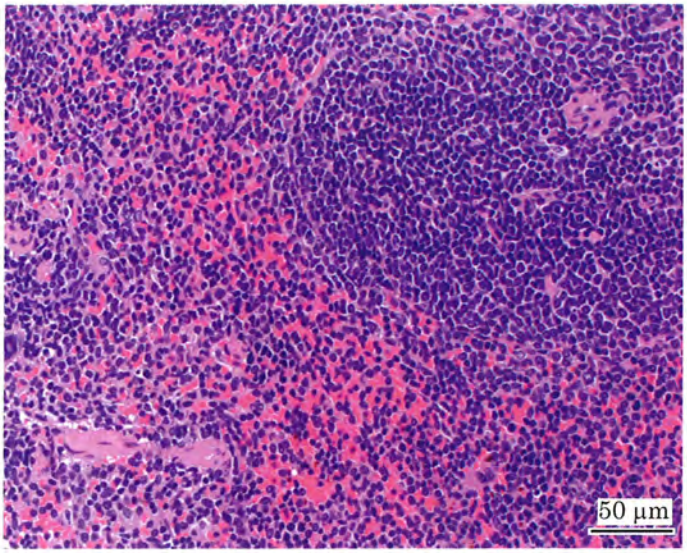
Photograph 2
Spleen: Hemangiosarcoma
Rat, Male, 1000 ppm, Animal No. 0685-1222 (H&E)



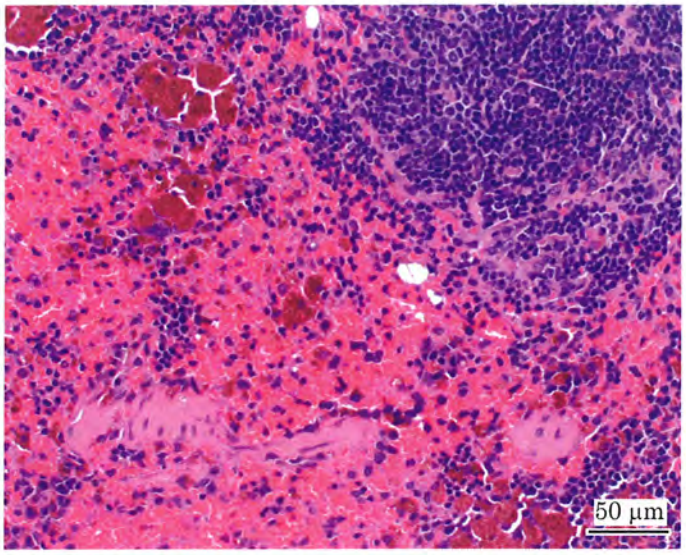
Photograph 3
Spleen: Normal
Rat, Male, Control, Animal No. 0685-1004 (H&E)



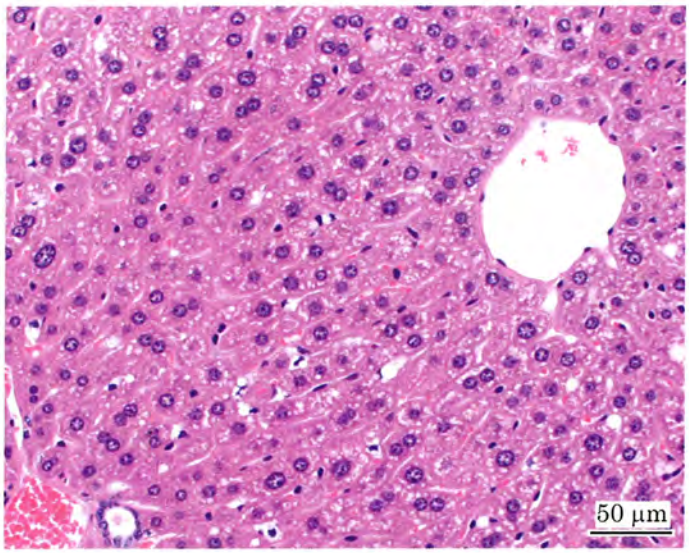
Photograph 4
Spleen: Extramedullary hematopoiesis
Rat, Male, 1000 ppm, Animal No. 0685-1202 (H&E)



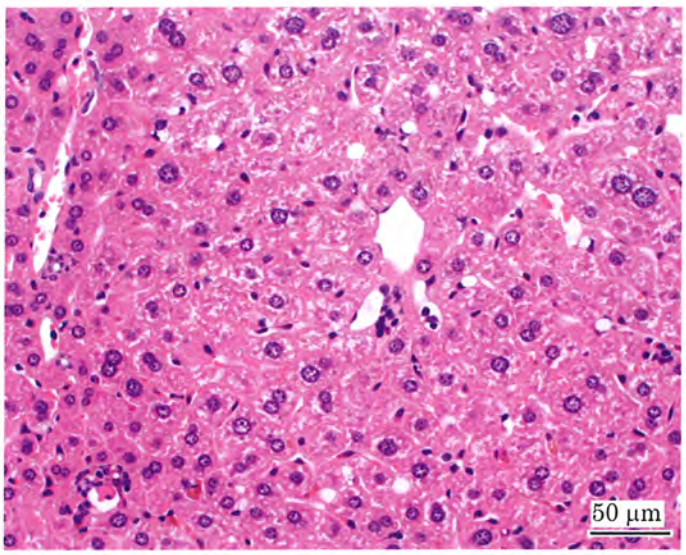
Photograph 5
Spleen: Normal
Rat, Female, Control, Animal No. 0685-2002 (H&E)



Photograph 6
Spleen: Engorgement erythrocyte and deposit of hemosiderin
Rat, Female, 1000 ppm, Animal No. 0685-2333 (H&E)



Photograph 7
Liver: Normal
Rat, Female, Control, Animal No. 0685-2002 (H&E)



Photograph 8
Liver: Hepatocellular hypertrophy
Rat, Female, 4000 ppm, Animal No. 0685-2301 (H&E)