Summary of Inhalation Carcinogenicity Study of Isopropyl Acetate in B6D2F1 Mice

March 2009

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 March 31, 2009.

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

Summary of Inhalation Carcinogenicity Study of Isopropyl Acetate in B6D2F1 Mice

Purpose, materials and methods

Isopropyl acetate (CAS No. 108-21-4) is a colorless liquid with a boiling point of 88.6°C. It is soluble in ethanol, acetone and water.

The carcinogenicity and chronic toxicity of isopropyl acetate (greater than 99.9% pure) were examined by inhalation exposure using B6D2F1/Crlj mice. Groups of test animals were exposed to isopropyl acetate vapor at a target concentrations of 0 (clean air), 1000, 2000 or 4000 ppm (v/v) for 6 hours/day, 5 days/week for 2 years (104 weeks). Each group of test animals consisted of either 50 male or 50 female mice. Both sexes were exposed to each concentration of isopropyl acetate vapor. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the isopropyl acetate used in these experiments was confirmed by both infrared spectrometry and mass spectrometry, and it was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 3700 L) were used throughout the 2-year exposure period. Isopropyl Acetate vapor-air mixtures were generated by bubbling clean air through isopropyl acetate liquid and the mixtures supplied to the inhalation exposure chambers. Air concentrations of isopropyl acetate vapor in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the exposure period. For hematology and blood biochemistry at the terminal necropsy, surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of isopropyl acetate induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good

Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 “Carcinogenicity Studies”.

Results

No significant differences in survival rates were found between any of the groups exposed to isopropyl acetate and their respective controls. Growth rates of the males and females exposed to 4000 ppm were suppressed with terminal body weights being 89% of the control for males and 91% of the control for females. Food consumption was decreased throughout the exposure period in both the males and females exposed 4000 ppm, and decreased in the early half of the 2nd year of exposure in both the males and females exposed to 2000 ppm. There were no significant differences in other clinical signs between the groups exposed to isopropyl acetate and their respective controls.

No significant increase in the incidence of neoplastic lesions was found in any of the isopropyl acetate-exposed group of either sex as compared with their respective controls. Increased incidences of atrophy and respiratory metaplasia in the olfactory epithelium and respiratory metaplasia in the submucosal gland were observed in both sexes. Atrophy in the olfactory epithelium occurred in both males and females exposed to 1000 ppm (the lowest dose tested) and higher concentrations of isopropyl acetate.

The lowest-observed-adverse-effect-level (LOAEL) of isopropyl acetate, exposure by inhalation, was 1000 ppm for the endpoint of nasal cavity of both male and female mice.

Conclusions

There was no evidence of carcinogenic activity of isopropyl acetate in male or female mice.

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

Dose (ppm)		0	1000	2000	4000	Peto test	Cochran-Armitage test
	Number of examined animals	49	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	2	3	2	1		
liver	hepatocellular adenoma	15	15	6 *	9		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	5	3	1	1		
lymph node	malignant lymphoma	7	9	4	5		
liver	hepatocellular carcinoma	6	4	3	4		
	histiocytic sarcoma	0	1	3	2		

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

Dose (ppm)		0	1000	2000	4000	Peto test	Cochran-Armitage test
	Number of examined animals	50	50	50	50		
benign tumor							
liver	hepatocellular adenoma	8	4	4	7		
pituitary	adenoma	9	10	6	4		
ovary	hemangioma	3	1	1	1		
uterus	endometrial stromal polyp	1	3	2	1		
Harderian gland	adenoma	4	1	4	1		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	2	3	2	0		
lymph node	malignant lymphoma	16	16	9	9		
liver	hemangiosarcoma	1	5	1	0		
	histiocytic sarcoma	3	2	2	1		
uterus	histiocytic sarcoma	10	9	11	9		
mammary gland	adenocarcinoma	1	0	3	0		

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

TABLE A

CONCENTRATIONS OF ISOPROPYL ACETATE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

CONCENTRATIONS OF ISOPROPYL ACETATE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
1000 ppm	998.7 ± 9.0
2000 ppm	1998.2 ± 15.7
4000 ppm	3998.8 ± 26.2

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN BODY WEIGHTS AND SURVIVAL

Week-Day on Study	Control Av. Wt.	Control No. of Surviv. <49>	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. Wt.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0-0	23.3 (49)	49/49	23.3 (50)	100	50/50	23.3 (50)	100	50/50	23.3 (50)	100	50/50
1-7	24.2 (49)	49/49	24.5 (50)	101	50/50	24.5 (50)	101	50/50	24.1 (50)	100	50/50
2-7	25.1 (49)	49/49	25.1 (50)	100	50/50	25.1 (50)	100	50/50	24.1 (50)	96	50/50
3-7	25.8 (49)	49/49	25.6 (50)	99	50/50	25.8 (50)	100	50/50	24.9 (48)	97	48/50
4-7	26.4 (49)	49/49	26.2 (50)	99	50/50	26.6 (49)	101	49/50	25.7 (48)	97	48/50
5-7	26.9 (49)	49/49	26.4 (50)	98	50/50	26.9 (49)	100	49/50	26.7 (48)	99	48/50
6-7	27.3 (49)	49/49	27.0 (50)	99	50/50	27.4 (49)	100	49/50	27.1 (48)	99	48/50
7-7	27.9 (49)	49/49	27.5 (50)	99	50/50	28.1 (49)	101	49/50	27.8 (48)	100	48/50
8-7	28.5 (49)	49/49	27.9 (50)	98	50/50	28.6 (49)	100	49/50	28.3 (48)	99	48/50
9-7	29.0 (49)	49/49	28.6 (50)	99	50/50	28.9 (49)	100	49/50	28.5 (48)	98	48/50
10-7	29.5 (49)	49/49	29.1 (50)	99	50/50	29.8 (49)	101	49/50	29.2 (48)	99	48/50
11-7	30.1 (49)	49/49	29.5 (50)	98	50/50	30.3 (49)	101	49/50	29.5 (48)	98	48/50
12-7	30.7 (49)	49/49	30.2 (50)	98	50/50	30.9 (48)	101	48/50	29.9 (48)	97	48/50
13-7	31.3 (49)	49/49	31.2 (50)	100	50/50	32.0 (48)	102	48/50	30.9 (48)	99	48/50
14-7	32.1 (49)	49/49	31.8 (50)	99	50/50	32.5 (48)	101	48/50	31.6 (48)	98	48/50
18-7	34.4 (49)	49/49	34.1 (50)	99	50/50	34.8 (48)	101	48/50	33.7 (48)	98	48/50
22-7	36.5 (49)	49/49	36.4 (50)	100	50/50	36.7 (48)	101	48/50	35.5 (48)	97	48/50
26-7	37.9 (49)	49/49	38.0 (50)	100	50/50	38.4 (48)	101	48/50	37.1 (48)	98	48/50
30-7	39.6 (49)	49/49	39.5 (50)	100	50/50	40.4 (48)	102	48/50	38.6 (48)	97	48/50
34-7	41.2 (49)	49/49	41.1 (50)	100	50/50	42.1 (47)	102	47/50	39.7 (48)	96	48/50
38-7	42.6 (49)	49/49	42.2 (50)	99	50/50	43.1 (47)	101	47/50	40.6 (48)	95	48/50
42-7	44.0 (49)	49/49	43.8 (50)	100	50/50	44.5 (46)	101	46/50	42.1 (48)	96	48/50
46-7	44.9 (49)	49/49	44.4 (50)	99	50/50	45.4 (46)	101	46/50	43.0 (47)	96	47/50
50-7	45.9 (49)	49/49	45.3 (50)	99	50/50	45.9 (46)	100	46/50	43.4 (47)	95	47/50
54-7	47.3 (49)	49/49	46.4 (50)	98	50/50	47.2 (46)	100	46/50	45.0 (47)	95	47/50
58-7	48.2 (49)	49/49	47.4 (49)	98	49/50	47.7 (45)	99	45/50	44.5 (46)	92	46/50
62-7	49.1 (49)	49/49	47.8 (49)	97	49/50	48.3 (45)	98	45/50	44.9 (46)	91	46/50
66-7	49.6 (48)	48/49	48.6 (48)	98	48/50	49.0 (45)	99	45/50	45.2 (46)	91	46/50
70-7	49.6 (48)	48/49	48.8 (48)	98	48/50	49.1 (45)	99	45/50	45.2 (46)	91	46/50
74-7	49.1 (47)	47/49	49.8 (48)	101	48/50	50.4 (43)	103	43/50	45.9 (45)	93	45/50
78-7	48.7 (45)	45/49	49.9 (47)	102	47/50	49.9 (43)	102	43/50	45.7 (44)	94	44/50
82-7	48.3 (42)	42/49	50.1 (45)	104	45/50	50.3 (42)	104	42/50	45.2 (44)	94	44/50
86-7	49.2 (41)	41/49	50.6 (45)	103	45/50	51.0 (41)	104	41/50	45.2 (42)	92	42/50
90-7	49.3 (40)	40/49	50.4 (43)	102	43/50	51.3 (41)	104	41/50	45.6 (41)	92	41/50
94-7	48.2 (39)	39/49	50.4 (39)	105	39/50	51.0 (40)	106	40/50	45.2 (41)	94	41/50
98-7	47.8 (37)	37/49	49.3 (39)	103	39/50	49.2 (39)	103	39/50	44.1 (37)	92	37/50
102-7	46.0 (35)	35/49	47.6 (37)	103	37/50	47.9 (38)	104	38/50	42.4 (36)	92	36/50
104-7	47.0 (32)	32/49	47.1 (36)	100	36/50	47.3 (37)	101	37/50	41.6 (35)	89	35/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

Week-Day on Study	Control Av. Wt.	Control No. of Surviv. <50>	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. Wt.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0-0	19.6 (50)	50/50	19.6 (50)	100	50/50	19.6 (50)	100	50/50	19.6 (50)	100	50/50
1-7	20.0 (50)	50/50	19.8 (50)	99	50/50	20.2 (50)	101	50/50	20.5 (50)	103	50/50
2-7	20.7 (50)	50/50	20.5 (50)	99	50/50	20.8 (50)	100	50/50	20.4 (50)	99	50/50
3-7	21.2 (50)	50/50	20.9 (50)	99	50/50	21.1 (50)	100	50/50	20.9 (50)	99	50/50
4-7	21.5 (50)	50/50	21.5 (50)	100	50/50	21.9 (50)	102	50/50	22.0 (50)	102	50/50
5-7	22.3 (50)	50/50	22.1 (50)	99	50/50	22.5 (50)	101	50/50	22.4 (50)	100	50/50
6-7	22.8 (50)	50/50	22.6 (50)	99	50/50	22.8 (50)	100	50/50	23.1 (50)	101	50/50
7-7	23.0 (50)	50/50	23.1 (50)	100	50/50	23.4 (50)	102	50/50	23.4 (50)	102	50/50
8-7	23.6 (50)	50/50	23.5 (50)	100	50/50	23.6 (50)	100	50/50	23.9 (50)	101	50/50
9-7	23.7 (50)	50/50	24.0 (50)	101	50/50	23.6 (50)	100	50/50	24.3 (50)	103	50/50
10-7	24.1 (50)	50/50	24.0 (50)	100	50/50	24.2 (50)	100	50/50	24.5 (50)	102	50/50
11-7	24.5 (50)	50/50	24.4 (50)	100	50/50	24.5 (50)	100	50/50	24.8 (50)	101	50/50
12-7	24.6 (50)	50/50	24.8 (50)	101	50/50	24.7 (50)	100	50/50	25.2 (50)	102	50/50
13-7	24.7 (50)	50/50	25.1 (49)	102	49/50	25.0 (50)	101	50/50	25.3 (50)	102	50/50
14-7	25.1 (50)	50/50	25.1 (49)	100	49/50	25.2 (50)	100	50/50	25.7 (50)	102	50/50
18-7	26.4 (50)	50/50	26.6 (49)	101	49/50	26.5 (50)	100	50/50	26.6 (50)	101	50/50
22-7	27.7 (50)	50/50	28.0 (49)	101	49/50	27.5 (50)	99	50/50	27.8 (50)	100	50/50
26-7	27.6 (50)	50/50	28.9 (49)	105	49/50	28.4 (49)	103	49/50	28.2 (50)	102	50/50
30-7	28.7 (50)	50/50	29.5 (49)	103	49/50	29.1 (49)	101	49/50	28.8 (50)	100	50/50
34-7	29.5 (49)	49/50	30.2 (49)	102	49/50	29.8 (49)	101	49/50	29.5 (50)	100	50/50
38-7	29.9 (49)	49/50	31.1 (49)	104	49/50	30.4 (49)	102	49/50	30.0 (50)	100	50/50
42-7	30.7 (49)	49/50	31.7 (49)	103	49/50	31.2 (49)	102	49/50	30.0 (50)	98	50/50
46-7	31.5 (49)	49/50	32.0 (49)	102	49/50	31.5 (49)	100	49/50	30.5 (50)	97	50/50
50-7	31.7 (49)	49/50	32.5 (49)	103	49/50	31.8 (49)	100	49/50	30.5 (50)	96	50/50
54-7	32.6 (48)	48/50	32.9 (49)	101	49/50	32.7 (48)	100	48/50	31.8 (50)	98	50/50
58-7	32.6 (48)	48/50	33.4 (48)	102	48/50	32.9 (47)	101	47/50	31.1 (50)	95	50/50
62-7	33.4 (48)	48/50	33.8 (47)	101	47/50	33.6 (45)	101	45/50	31.7 (50)	95	50/50
66-7	33.6 (48)	48/50	34.9 (44)	104	44/50	34.0 (45)	101	45/50	31.4 (49)	93	49/50
70-7	33.5 (47)	47/50	34.8 (44)	104	44/50	34.5 (44)	103	44/50	31.7 (48)	95	48/50
74-7	34.4 (46)	46/50	35.3 (43)	103	43/50	34.5 (44)	100	44/50	31.8 (47)	92	47/50
78-7	34.0 (44)	44/50	35.4 (41)	104	41/50	34.9 (43)	103	43/50	31.5 (47)	93	47/50
82-7	34.4 (44)	44/50	35.3 (40)	103	40/50	34.9 (40)	101	40/50	31.9 (47)	93	47/50
86-7	34.6 (43)	43/50	36.1 (40)	104	40/50	35.5 (39)	103	39/50	32.2 (45)	93	45/50
90-7	35.4 (38)	38/50	36.3 (38)	103	38/50	35.9 (38)	101	38/50	32.6 (44)	92	44/50
94-7	35.3 (37)	37/50	36.5 (35)	103	35/50	35.8 (31)	101	31/50	31.9 (42)	90	42/50
98-7	35.1 (30)	30/50	35.7 (31)	102	31/50	35.7 (30)	102	30/50	31.8 (40)	91	40/50
102-7	34.4 (27)	27/50	34.9 (29)	101	29/50	34.9 (28)	101	28/50	32.0 (38)	93	38/50
104-7	35.2 (25)	25/50	34.6 (26)	98	26/50	35.0 (25)	99	25/50	32.0 (37)	91	37/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	23.3± 0.8	24.2± 0.9	25.1± 1.0	25.8± 1.1	26.4± 1.3	26.9± 1.5	27.3± 1.6
1000 ppm	23.3± 0.8	24.5± 0.8	25.1± 1.0	25.6± 1.0	26.2± 1.3	26.4± 1.1	27.0± 1.4
2000 ppm	23.3± 0.8	24.5± 1.0	25.1± 1.3	25.8± 1.4	26.6± 1.4	26.9± 1.9	27.4± 1.8
4000 ppm	23.3± 0.8	24.1± 1.4	24.1± 1.6**	24.9± 1.2**	25.7± 1.1*	26.7± 1.1	27.1± 1.2

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	27.9± 1.6	28.5± 1.7	29.0± 1.8	29.5± 1.9	30.1± 2.0	30.7± 2.2	31.3± 2.3
1000 ppm	27.5± 1.5	27.9± 1.7	28.6± 1.7	29.1± 1.9	29.5± 1.8	30.2± 2.0	31.2± 2.1
2000 ppm	28.1± 2.1	28.6± 2.1	28.9± 2.5	29.8± 2.6	30.3± 2.6	30.9± 2.6	32.0± 2.6
4000 ppm	27.8± 1.4	28.3± 1.6	28.5± 1.6	29.2± 1.9	29.5± 2.0	29.9± 2.1	30.9± 2.3

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

(HAN260)

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	32.1± 2.6	34.4± 2.8	36.5± 2.9	37.9± 3.5	39.6± 3.8	41.2± 3.9	42.6± 4.5
1000 ppm	31.8± 2.2	34.1± 2.6	36.4± 2.8	38.0± 3.1	39.5± 3.6	41.1± 4.0	42.2± 4.2
2000 ppm	32.5± 2.7	34.8± 3.1	36.7± 3.3	38.4± 3.6	40.4± 4.2	42.1± 4.2	43.1± 4.3
4000 ppm	31.6± 2.5	33.7± 3.1	35.5± 3.5	37.1± 4.0	38.6± 4.4	39.7± 4.8	40.6± 5.3

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	44.0± 5.0	44.9± 5.1	45.9± 5.3	47.3± 5.4	48.2± 5.5	49.1± 5.6	49.6± 5.4
1000 ppm	43.8± 4.6	44.4± 4.7	45.3± 4.7	46.4± 4.7	47.4± 4.7	47.8± 4.8	48.6± 4.5
2000 ppm	44.5± 4.4	45.4± 4.4	45.9± 4.6	47.2± 5.6	47.7± 5.2	48.3± 5.1	49.0± 5.7
4000 ppm	42.1± 5.8	43.0± 5.8	43.4± 6.1	45.0± 6.3	44.5± 5.9**	44.9± 6.2**	45.2± 6.3**

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

(HAN260)

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	49.6± 5.5	49.1± 5.5	48.7± 6.5	48.3± 7.3	49.2± 7.9	49.3± 7.8	48.2± 7.5
1000 ppm	48.8± 4.8	49.8± 4.8	49.9± 5.0	50.1± 5.3	50.6± 5.9	50.4± 6.2	50.4± 5.6
2000 ppm	49.1± 6.3	50.4± 5.7	49.9± 6.4	50.3± 6.0	51.0± 6.2	51.3± 6.4	51.0± 6.1
4000 ppm	45.2± 6.4**	45.9± 6.6*	45.7± 6.7	45.2± 6.8	45.2± 7.3*	45.6± 6.9*	45.2± 7.1

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	47.8± 7.9	46.0± 8.4	47.0± 6.8
1000 ppm	49.3± 5.7	47.6± 5.4	47.1± 5.8
2000 ppm	49.2± 7.4	47.9± 7.4	47.3± 7.8
4000 ppm	44.1± 6.6	42.4± 6.4	41.6± 6.5**

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

(HAN260)

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	19.6± 0.9	20.0± 1.1	20.7± 1.2	21.2± 1.1	21.5± 1.0	22.3± 1.1	22.8± 0.9
1000 ppm	19.6± 0.9	19.8± 1.1	20.5± 1.1	20.9± 1.2	21.5± 1.2	22.1± 1.2	22.6± 1.1
2000 ppm	19.6± 0.9	20.2± 0.9	20.8± 0.9	21.1± 0.9	21.9± 0.9	22.5± 0.9	22.8± 1.0
4000 ppm	19.6± 0.9	20.5± 1.1*	20.4± 0.9	20.9± 0.9	22.0± 0.9	22.4± 1.0	23.1± 1.1

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	23.0± 1.2	23.6± 1.2	23.7± 1.4	24.1± 1.4	24.5± 1.4	24.6± 1.4	24.7± 1.5
1000 ppm	23.1± 1.2	23.5± 1.4	24.0± 1.5	24.0± 1.5	24.4± 1.7	24.8± 1.6	25.1± 1.5
2000 ppm	23.4± 1.2	23.6± 1.0	23.6± 0.9	24.2± 1.1	24.5± 1.2	24.7± 1.1	25.0± 1.3
4000 ppm	23.4± 1.3	23.9± 1.3	24.3± 1.4*	24.5± 1.2	24.8± 1.1	25.2± 1.2*	25.3± 1.4

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

(HAN260)

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	25.1± 1.6	26.4± 1.8	27.7± 2.3	27.6± 2.5	28.7± 2.9	29.5± 3.2	29.9± 3.3
1000 ppm	25.1± 1.3	26.6± 1.7	28.0± 2.2	28.9± 2.5*	29.5± 2.4	30.2± 2.9	31.1± 3.2
2000 ppm	25.2± 1.2	26.5± 1.6	27.5± 1.6	28.4± 1.9	29.1± 2.4	29.8± 2.4	30.4± 2.9
4000 ppm	25.7± 1.5	26.6± 1.6	27.8± 1.9	28.2± 2.0	28.8± 2.6	29.5± 2.8	30.0± 3.0

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	30.7± 3.7	31.5± 3.5	31.7± 3.6	32.6± 3.8	32.6± 4.3	33.4± 4.4	33.6± 4.2
1000 ppm	31.7± 3.3	32.0± 3.5	32.5± 3.7	32.9± 3.7	33.4± 4.3	33.8± 4.7	34.9± 4.2
2000 ppm	31.2± 3.1	31.5± 3.1	31.8± 3.1	32.7± 3.6	32.9± 3.2	33.6± 3.4	34.0± 3.6
4000 ppm	30.0± 3.2	30.5± 3.3	30.5± 2.4	31.8± 3.0	31.1± 2.8	31.7± 3.0	31.4± 3.3*

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	33.5± 3.8	34.4± 4.1	34.0± 4.2	34.4± 4.4	34.6± 4.3	35.4± 5.0	35.3± 4.7
1000 ppm	34.8± 3.8	35.3± 4.0	35.4± 4.3	35.3± 3.9	36.1± 4.7	36.3± 4.7	36.5± 4.6
2000 ppm	34.5± 3.7	34.5± 3.8	34.9± 3.7	34.9± 3.7	35.5± 4.0	35.9± 4.6	35.8± 3.3
4000 ppm	31.7± 3.2	31.8± 3.1**	31.5± 3.0**	31.9± 3.2**	32.2± 3.4*	32.6± 4.4*	31.9± 3.2**

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	35.1± 5.4	34.4± 4.9	35.2± 5.2
1000 ppm	35.7± 4.3	34.9± 4.6	34.6± 4.7
2000 ppm	35.7± 3.2	34.9± 3.8	35.0± 3.4
4000 ppm	31.8± 3.0**	32.0± 3.0*	32.0± 3.5*

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

(HAN260)

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week-Day on Study	Control Av. FC.	Control No. of Surviv. <49>	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. FC.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1-7	3.9 (49)	49/49	3.9 (50)	100	50/50	3.8 (50)	97	50/50	3.7 (50)	95	50/50
2-7	3.9 (49)	49/49	3.9 (50)	100	50/50	3.8 (50)	97	50/50	3.7 (50)	95	50/50
3-7	4.0 (49)	49/49	3.9 (50)	98	50/50	3.9 (50)	98	50/50	3.8 (48)	95	48/50
4-7	4.0 (49)	49/49	4.1 (50)	103	50/50	4.1 (49)	103	49/50	4.0 (48)	100	48/50
5-7	4.4 (49)	49/49	4.4 (50)	100	50/50	4.3 (49)	98	49/50	4.4 (48)	100	48/50
6-7	4.2 (49)	49/49	4.2 (50)	100	50/50	4.1 (49)	98	49/50	4.1 (48)	98	48/50
7-7	4.2 (49)	49/49	4.3 (50)	102	50/50	4.2 (49)	100	49/50	4.2 (48)	100	48/50
8-7	4.3 (49)	49/49	4.3 (50)	100	50/50	4.1 (49)	95	49/50	4.1 (48)	95	48/50
9-7	4.4 (49)	49/49	4.4 (50)	100	50/50	4.2 (49)	95	49/50	4.2 (48)	95	48/50
10-7	4.4 (49)	49/49	4.5 (50)	102	50/50	4.3 (49)	98	49/50	4.3 (48)	98	48/50
11-7	4.5 (49)	49/49	4.5 (50)	100	50/50	4.3 (49)	96	49/50	4.3 (48)	96	48/50
12-7	4.4 (49)	49/49	4.4 (50)	100	50/50	4.2 (48)	95	48/50	4.2 (48)	95	48/50
13-7	4.5 (49)	49/49	4.7 (50)	104	50/50	4.5 (48)	100	48/50	4.5 (48)	100	48/50
14-7	4.5 (49)	49/49	4.5 (50)	100	50/50	4.3 (48)	96	48/50	4.3 (48)	96	48/50
18-7	4.4 (49)	49/49	4.4 (50)	100	50/50	4.2 (48)	95	48/50	4.2 (48)	95	48/50
22-7	4.6 (49)	49/49	4.6 (50)	100	50/50	4.4 (48)	96	48/50	4.4 (48)	96	48/50
26-7	4.6 (49)	49/49	4.7 (50)	102	50/50	4.5 (48)	98	48/50	4.5 (48)	98	48/50
30-7	4.7 (49)	49/49	4.7 (50)	100	50/50	4.6 (48)	98	48/50	4.7 (48)	100	48/50
34-7	4.9 (49)	49/49	4.8 (50)	98	50/50	4.7 (47)	96	47/50	4.7 (48)	96	48/50
38-7	4.8 (49)	49/49	4.8 (50)	100	50/50	4.6 (47)	96	47/50	4.6 (48)	96	48/50
42-7	4.9 (49)	49/49	4.9 (50)	100	50/50	4.8 (46)	98	46/50	4.8 (48)	98	48/50
46-7	4.9 (49)	49/49	4.9 (50)	100	50/50	4.8 (46)	98	46/50	4.8 (47)	98	47/50
50-7	4.9 (49)	49/49	4.9 (50)	100	50/50	4.7 (46)	96	46/50	4.7 (47)	96	47/50
54-7	5.1 (49)	49/49	5.1 (50)	100	50/50	5.0 (46)	98	46/50	5.3 (47)	104	47/50
58-7	5.0 (49)	49/49	5.0 (49)	100	49/50	4.7 (45)	94	45/50	4.7 (46)	94	46/50
62-7	5.0 (49)	49/49	5.0 (49)	100	49/50	4.9 (45)	98	45/50	4.7 (46)	94	46/50
66-7	5.0 (48)	48/49	5.0 (48)	100	48/50	4.8 (45)	96	45/50	4.6 (46)	92	46/50
70-7	5.1 (48)	48/49	5.1 (48)	100	48/50	4.9 (45)	96	45/50	4.9 (46)	96	46/50
74-7	4.8 (47)	47/49	5.2 (48)	108	48/50	5.0 (43)	104	43/50	4.7 (45)	98	45/50
78-7	5.2 (45)	45/49	5.2 (47)	100	47/50	5.0 (43)	96	43/50	4.8 (44)	92	44/50
82-7	5.1 (42)	42/49	5.2 (45)	102	45/50	5.1 (42)	100	42/50	4.9 (44)	96	44/50
86-7	5.3 (41)	41/49	5.3 (45)	100	45/50	5.2 (41)	98	41/50	4.8 (42)	91	42/50
90-7	5.3 (40)	40/49	5.2 (43)	98	43/50	5.1 (41)	96	41/50	5.0 (41)	94	41/50
94-7	5.0 (39)	39/49	5.3 (39)	106	39/50	5.2 (40)	104	40/50	5.0 (41)	100	41/50
98-7	5.0 (37)	37/49	5.0 (39)	100	39/50	4.9 (39)	98	39/50	4.6 (37)	92	37/50
102-7	5.1 (35)	35/49	4.9 (37)	96	37/50	4.8 (38)	94	38/50	4.5 (36)	88	36/50
104-7	5.1 (32)	32/49	4.9 (36)	96	36/50	4.7 (37)	92	37/50	4.5 (35)	88	35/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week-Day on Study	Control Av. FC.	Control No. of Surviv. <50>	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. FC.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1-7	3.4 (50)	50/50	3.3 (50)	97	50/50	3.4 (50)	100	50/50	3.3 (50)	97	50/50
2-7	3.5 (50)	50/50	3.3 (50)	94	50/50	3.3 (50)	94	50/50	3.3 (50)	94	50/50
3-7	3.7 (50)	50/50	3.5 (50)	95	50/50	3.4 (50)	92	50/50	3.4 (50)	92	50/50
4-7	3.8 (50)	50/50	3.7 (50)	97	50/50	3.7 (50)	97	50/50	3.7 (50)	97	50/50
5-7	4.4 (50)	50/50	4.3 (50)	98	50/50	4.1 (50)	93	50/50	4.1 (50)	93	50/50
6-7	4.1 (50)	50/50	4.0 (50)	98	50/50	3.9 (50)	95	50/50	3.8 (50)	93	50/50
7-7	4.2 (50)	50/50	4.2 (50)	100	50/50	4.0 (50)	95	50/50	3.9 (50)	93	50/50
8-7	4.4 (50)	50/50	4.2 (50)	95	50/50	4.0 (50)	91	50/50	3.9 (50)	89	50/50
9-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.1 (50)	91	50/50	4.2 (50)	93	50/50
10-7	4.5 (50)	50/50	4.3 (50)	96	50/50	4.2 (50)	93	50/50	4.1 (50)	91	50/50
11-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.1 (50)	93	50/50	4.1 (50)	93	50/50
12-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.0 (50)	93	50/50	4.1 (50)	95	50/50
13-7	4.4 (50)	50/50	4.4 (49)	100	49/50	4.2 (50)	95	50/50	4.1 (50)	93	50/50
14-7	4.4 (50)	50/50	4.3 (49)	98	49/50	4.1 (50)	93	50/50	4.1 (50)	93	50/50
18-7	4.3 (50)	50/50	4.2 (49)	98	49/50	4.0 (50)	93	50/50	4.0 (50)	93	50/50
22-7	4.5 (50)	50/50	4.2 (49)	93	49/50	4.1 (50)	91	50/50	4.2 (50)	93	50/50
26-7	4.4 (50)	50/50	4.5 (49)	102	49/50	4.3 (49)	98	49/50	4.2 (50)	95	50/50
30-7	4.7 (50)	50/50	4.6 (49)	98	49/50	4.3 (49)	91	49/50	4.3 (50)	91	50/50
34-7	4.8 (49)	49/50	4.6 (49)	96	49/50	4.4 (49)	92	49/50	4.5 (50)	94	50/50
38-7	4.6 (49)	49/50	4.5 (49)	98	49/50	4.2 (49)	91	49/50	4.3 (50)	93	50/50
42-7	4.7 (49)	49/50	4.6 (49)	98	49/50	4.4 (49)	94	49/50	4.3 (50)	91	50/50
46-7	4.7 (49)	49/50	4.6 (49)	98	49/50	4.3 (49)	91	49/50	4.4 (50)	94	50/50
50-7	4.6 (49)	49/50	4.6 (49)	100	49/50	4.3 (49)	93	49/50	4.3 (50)	93	50/50
54-7	4.7 (48)	48/50	4.5 (49)	96	49/50	4.6 (48)	98	48/50	4.7 (50)	100	50/50
58-7	4.5 (48)	48/50	4.6 (48)	102	48/50	4.2 (47)	93	47/50	4.2 (50)	93	50/50
62-7	4.5 (48)	48/50	4.5 (47)	100	47/50	4.4 (45)	98	45/50	4.3 (50)	96	50/50
66-7	4.5 (48)	48/50	4.5 (44)	100	44/50	4.2 (45)	93	45/50	4.1 (49)	91	49/50
70-7	4.5 (47)	47/50	4.5 (44)	100	44/50	4.4 (44)	98	44/50	4.3 (48)	96	48/50
74-7	4.5 (46)	46/50	4.5 (43)	100	43/50	4.4 (44)	98	44/50	4.2 (47)	93	47/50
78-7	4.7 (44)	44/50	4.7 (41)	100	41/50	4.5 (43)	96	43/50	4.2 (47)	89	47/50
82-7	4.6 (44)	44/50	4.6 (40)	100	40/50	4.4 (40)	96	40/50	4.3 (47)	93	47/50
86-7	4.6 (43)	43/50	4.8 (40)	104	40/50	4.6 (39)	100	39/50	4.4 (45)	96	45/50
90-7	4.8 (38)	38/50	4.8 (38)	100	38/50	4.7 (38)	98	38/50	4.5 (44)	94	44/50
94-7	4.7 (37)	37/50	4.8 (35)	102	35/50	4.7 (31)	100	31/50	4.3 (42)	91	42/50
98-7	4.8 (30)	30/50	4.7 (31)	98	31/50	4.6 (30)	96	30/50	4.2 (40)	88	40/50
102-7	4.7 (27)	27/50	4.5 (29)	96	29/50	4.4 (28)	94	28/50	4.1 (38)	87	38/50
104-7	4.8 (25)	25/50	4.5 (26)	94	26/50	4.5 (25)	94	25/50	4.1 (37)	85	37/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-7(7)	2-7(7)	3-7(7)	4-7(7)	5-7(7)	6-7(7)	7-7(7)
Control	3.9± 0.3	3.9± 0.3	4.0± 0.3	4.0± 0.3	4.4± 0.3	4.2± 0.3	4.2± 0.3
1000 ppm	3.9± 0.2	3.9± 0.3	3.9± 0.3	4.1± 0.3	4.4± 0.3	4.2± 0.3	4.3± 0.3
2000 ppm	3.8± 0.3	3.8± 0.3	3.9± 0.3	4.1± 0.3	4.3± 0.4	4.1± 0.3	4.2± 0.3
4000 ppm	3.7± 0.3*	3.7± 0.4**	3.8± 0.3**	4.0± 0.3	4.4± 0.3	4.1± 0.3	4.2± 0.3

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 8-7(7)	9-7(7)	10-7(7)	11-7(7)	12-7(7)	13-7(7)	14-7(7)
Control	4.3± 0.3	4.4± 0.3	4.4± 0.3	4.5± 0.3	4.4± 0.3	4.5± 0.3	4.5± 0.3
1000 ppm	4.3± 0.3	4.4± 0.3	4.5± 0.3	4.5± 0.3	4.4± 0.3	4.7± 0.3**	4.5± 0.3
2000 ppm	4.1± 0.3*	4.2± 0.4*	4.3± 0.4	4.3± 0.3**	4.2± 0.3**	4.5± 0.3	4.3± 0.2**
4000 ppm	4.1± 0.3**	4.2± 0.3	4.3± 0.3	4.3± 0.3**	4.2± 0.3**	4.5± 0.3	4.3± 0.3**

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 18-7(7)	22-7(7)	26-7(7)	30-7(7)	34-7(7)	38-7(7)	42-7(7)
Control	4.4± 0.3	4.6± 0.3	4.6± 0.3	4.7± 0.3	4.9± 0.3	4.8± 0.3	4.9± 0.3
1000 ppm	4.4± 0.3	4.6± 0.2	4.7± 0.2	4.7± 0.3	4.8± 0.3	4.8± 0.2	4.9± 0.3
2000 ppm	4.2± 0.3**	4.4± 0.3	4.5± 0.2	4.6± 0.3	4.7± 0.3*	4.6± 0.3	4.8± 0.3
4000 ppm	4.2± 0.3**	4.4± 0.3*	4.5± 0.3	4.7± 0.3	4.7± 0.4	4.6± 0.4*	4.8± 0.4

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 46-7(7)	50-7(7)	54-7(7)	58-7(7)	62-7(7)	66-7(7)	70-7(7)
Control	4.9± 0.3	4.9± 0.3	5.1± 0.3	5.0± 0.3	5.0± 0.3	5.0± 0.3	5.1± 0.4
1000 ppm	4.9± 0.3	4.9± 0.3	5.1± 0.3	5.0± 0.3	5.0± 0.4	5.0± 0.3	5.1± 0.4
2000 ppm	4.8± 0.3	4.7± 0.3**	5.0± 0.4	4.7± 0.4**	4.9± 0.4	4.8± 0.4*	4.9± 0.6
4000 ppm	4.8± 0.4	4.7± 0.4**	5.3± 0.4**	4.7± 0.4**	4.7± 0.3**	4.6± 0.4**	4.9± 0.4**

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 74-7(7)	78-7(7)	82-7(7)	86-7(7)	90-7(7)	94-7(7)	98-7(7)
Control	4.8± 0.6	5.2± 0.7	5.1± 0.5	5.3± 0.5	5.3± 0.4	5.0± 0.6	5.0± 0.6
1000 ppm	5.2± 0.6**	5.2± 0.4	5.2± 0.3	5.3± 0.4	5.2± 0.8	5.3± 0.4*	5.0± 0.3
2000 ppm	5.0± 0.3	5.0± 0.5	5.1± 0.3	5.2± 0.4	5.1± 0.4	5.2± 0.4	4.9± 0.5
4000 ppm	4.7± 0.5	4.8± 0.4**	4.9± 0.4*	4.8± 0.4**	5.0± 0.4**	5.0± 0.5	4.6± 0.5**

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 102-7(7)	104-7(7)
Control	5.1± 0.7	5.1± 0.8
1000 ppm	4.9± 0.4	4.9± 0.6
2000 ppm	4.8± 0.5	4.7± 0.7
4000 ppm	4.5± 0.6**	4.5± 0.8**

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

(HAN260)

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-7(7)	2-7(7)	3-7(7)	4-7(7)	5-7(7)	6-7(7)	7-7(7)
Control	3.4± 0.3	3.5± 0.2	3.7± 0.3	3.8± 0.3	4.4± 0.4	4.1± 0.3	4.2± 0.3
1000 ppm	3.3± 0.3	3.3± 0.3*	3.5± 0.2*	3.7± 0.2	4.3± 0.3	4.0± 0.2	4.2± 0.3
2000 ppm	3.4± 0.2	3.3± 0.3**	3.4± 0.2**	3.7± 0.2	4.1± 0.2**	3.9± 0.2**	4.0± 0.3**
4000 ppm	3.3± 0.4	3.3± 0.2**	3.4± 0.3**	3.7± 0.3	4.1± 0.3**	3.8± 0.3**	3.9± 0.3**

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

(HAN260)

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 8-7(7)	9-7(7)	10-7(7)	11-7(7)	12-7(7)	13-7(7)	14-7(7)
Control	4.4± 0.4	4.5± 0.4	4.5± 0.3	4.4± 0.4	4.3± 0.4	4.4± 0.4	4.4± 0.3
1000 ppm	4.2± 0.3	4.4± 0.3	4.3± 0.3	4.4± 0.3	4.3± 0.3	4.4± 0.3	4.3± 0.3*
2000 ppm	4.0± 0.2**	4.1± 0.2**	4.2± 0.3**	4.1± 0.3**	4.0± 0.3**	4.2± 0.3**	4.1± 0.3**
4000 ppm	3.9± 0.3**	4.2± 0.4**	4.1± 0.3**	4.1± 0.3**	4.1± 0.3**	4.1± 0.3**	4.1± 0.3**

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 18-7(7)	22-7(7)	26-7(7)	30-7(7)	34-7(7)	38-7(7)	42-7(7)
Control	4.3± 0.4	4.5± 0.4	4.4± 0.4	4.7± 0.5	4.8± 0.5	4.6± 0.5	4.7± 0.5
1000 ppm	4.2± 0.3	4.2± 0.4**	4.5± 0.4	4.6± 0.4	4.6± 0.5*	4.5± 0.4	4.6± 0.5
2000 ppm	4.0± 0.3**	4.1± 0.3**	4.3± 0.3	4.3± 0.4**	4.4± 0.4**	4.2± 0.3**	4.4± 0.5**
4000 ppm	4.0± 0.3**	4.2± 0.4**	4.2± 0.3**	4.3± 0.4**	4.5± 0.4**	4.3± 0.4**	4.3± 0.5**

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 46-7(7)	50-7(7)	54-7(7)	58-7(7)	62-7(7)	66-7(7)	70-7(7)
Control	4.7± 0.5	4.6± 0.5	4.7± 0.5	4.5± 0.5	4.5± 0.5	4.5± 0.5	4.5± 0.5
1000 ppm	4.6± 0.5	4.6± 0.4	4.5± 0.5	4.6± 0.5	4.5± 0.6	4.5± 0.5	4.5± 0.5
2000 ppm	4.3± 0.4**	4.3± 0.4**	4.6± 0.4	4.2± 0.6	4.4± 0.4	4.2± 0.5	4.4± 0.4
4000 ppm	4.4± 0.4**	4.3± 0.3**	4.7± 0.5	4.2± 0.3**	4.3± 0.4	4.1± 0.5**	4.3± 0.5

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

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 74-7(7)	78-7(7)	82-7(7)	86-7(7)	90-7(7)	94-7(7)	98-7(7)
Control	4.5± 0.5	4.7± 0.5	4.6± 0.6	4.6± 0.5	4.8± 0.8	4.7± 0.7	4.8± 0.5
1000 ppm	4.5± 0.6	4.7± 0.6	4.6± 0.6	4.8± 0.7	4.8± 1.0	4.8± 0.7	4.7± 0.6
2000 ppm	4.4± 0.6	4.5± 0.5	4.4± 0.5	4.6± 0.6	4.7± 0.6	4.7± 0.6	4.6± 0.6
4000 ppm	4.2± 0.4**	4.2± 0.5**	4.3± 0.5**	4.4± 0.4*	4.5± 0.5	4.3± 0.6*	4.2± 0.6**

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

(HAN260)

BAIS 4

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 102-7(7)	104-7(7)
Control	4.7± 0.5	4.8± 0.6
1000 ppm	4.5± 0.8	4.5± 0.8
2000 ppm	4.4± 0.7	4.5± 0.6
4000 ppm	4.1± 0.5**	4.1± 0.4**

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

(HAN260)

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[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 fℓ	MCH pg	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	30	9.87± 2.30	14.0± 2.7	45.5± 8.4	46.7± 3.5	14.3± 1.0	30.6± 1.4	1815± 377
1000 ppm	35	10.22± 0.89	14.4± 1.2	46.8± 3.9	45.9± 1.3	14.1± 0.5	30.8± 0.7	1667± 338
2000 ppm	35	10.13± 0.99	14.6± 1.5	47.0± 4.5	46.5± 1.5	14.4± 0.5	31.0± 1.1	1778± 335
4000 ppm	33	10.20± 1.25	15.0± 1.5	48.6± 4.9	47.8± 1.9**	14.8± 0.5**	30.9± 0.6	1789± 342

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

(HCL070)

BAIS 4

STUDY NO. : 0611
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 %
Control	30	2.9± 1.8
1000 ppm	35	2.4± 0.7
2000 ppm	35	2.3± 0.9
4000 ppm	33	2.6± 2.3

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

(HCL070)

BAIS 4

STUDY NO. : 0611
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 (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
Control	30	4.58± 2.17	1± 3	28± 13	2± 1	0± 0	5± 2	63± 17	1± 2
1000 ppm	35	4.32± 1.99	1± 1	30± 13	3± 3	0± 0	5± 2	60± 15	1± 1
2000 ppm	35	4.04± 2.02	1± 1	27± 10	2± 1	0± 0	4± 2	65± 11	0± 1
4000 ppm	33	3.50± 1.83	1± 1	31± 12	2± 1	0± 0	4± 2	61± 11	1± 1

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

(HCL070)

BAIS 4

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0611
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	25	9.96± 1.49	14.1± 1.9	45.5± 5.5	45.9± 2.5	14.2± 0.6	30.9± 0.9	1172± 204
1000 ppm	24	9.64± 2.13	14.0± 3.0	45.5± 8.6	48.4± 6.3	14.6± 0.6*	30.4± 2.4	1097± 278
2000 ppm	24	9.73± 1.31	14.1± 2.1	45.3± 5.9	46.5± 1.4	14.5± 0.5	31.2± 1.0	1245± 330
4000 ppm	36	10.12± 0.95	14.9± 1.3	47.9± 3.5	47.6± 2.8*	14.8± 0.4**	31.2± 1.1	1263± 259

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

(HCL070)

BAIS 4

STUDY NO. : 0611
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 %
Control	25	3.4± 3.5
1000 ppm	24	6.1± 13.9
2000 ppm	24	2.6± 2.0
4000 ppm	36	2.4± 2.7*

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

(HCL070)

BAIS 4

STUDY NO. : 0611
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 (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
Control	25	5.37± 6.89	2± 1	28± 15	2± 2	0± 0	5± 2	60± 15	3± 9
1000 ppm	24	8.48± 13.85	2± 2	28± 14	2± 2	0± 0	4± 2	56± 20	9± 22
2000 ppm	24	3.61± 1.91	1± 1	26± 13	3± 2	0± 0	4± 2	62± 14	3± 12
4000 ppm	36	5.22± 9.41	1± 1	23± 11	2± 1	0± 0	5± 2	64± 16	5± 17

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

(HCL070)

BAIS 4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0611
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	0.9± 0.2	0.14± 0.03	166± 36	121± 51	50± 22
1000 ppm	35	5.4± 0.6	2.5± 0.3	0.9± 0.1	0.14± 0.03	164± 26	120± 78	43± 23
2000 ppm	36	5.1± 0.5	2.5± 0.2	0.9± 0.1	0.15± 0.05	171± 36	106± 22	55± 26
4000 ppm	34	5.2± 0.5	2.5± 0.3	0.9± 0.1	0.15± 0.06	180± 39	119± 34	50± 26

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

(HCL074)

BAIS 4

STUDY NO. : 0611
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	205± 68	111± 112	67± 85	504± 389	151± 88	1± 0	114± 267
1000 ppm	35	194± 83	117± 121	77± 116	473± 397	149± 69	1± 1	62± 30
2000 ppm	36	179± 41	127± 251	51± 94	449± 359	161± 81	1± 1	92± 97
4000 ppm	34	194± 33	187± 518	180± 636	899± 1509	146± 54	1± 1	164± 395

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

(HCL074)

BAIS 4

STUDY NO. : 0611
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	29.8± 36.8	153± 2	4.4± 0.6	121± 3	8.9± 0.6	6.7± 4.4
1000 ppm	35	23.3± 4.6	153± 2	4.3± 0.3	121± 2	8.9± 0.5	6.2± 0.7
2000 ppm	36	25.4± 10.8	153± 2	4.5± 0.4	122± 2	8.7± 0.3	6.6± 1.0**
4000 ppm	34	27.6± 13.1	153± 2	4.3± 0.4	122± 3	8.9± 1.2	6.7± 0.9**

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

(HCL074)

BAIS 4

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0611
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	25	5.3± 0.7	2.6± 0.3	1.0± 0.2	0.14± 0.06	115± 22	102± 73	59± 38
1000 ppm	25	5.1± 0.7	2.4± 0.3	1.0± 0.2	0.17± 0.13	109± 38	81± 27	42± 29
2000 ppm	25	5.5± 1.1	2.7± 0.4	1.0± 0.1	0.14± 0.05	143± 20**	101± 42	41± 17
4000 ppm	35	5.0± 0.4	2.5± 0.2	1.0± 0.1	0.13± 0.04	149± 31**	88± 27	40± 23

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

(HCL074)

BAIS 4

STUDY NO. : 0611
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	25	179± 101	112± 83	49± 37	556± 1129	207± 87	1± 1	88± 49
1000 ppm	25	136± 52	278± 550	122± 256	964± 1502*	204± 91	1± 1	208± 320
2000 ppm	25	176± 68	109± 74	52± 50	426± 188	194± 67	1± 1	98± 65
4000 ppm	35	152± 40	178± 389	84± .199	537± 1007	211± 96	1± 1	125± 249

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

(HCL074)

BAIS4

STUDY NO. : 0611
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	25	17.3±	4.5	151±	2	4.1±	0.4	121±	2	9.1±	0.7	6.1±	0.7
1000 ppm	25	26.8±	25.5	153±	3*	4.3±	0.9	123±	3	9.0±	0.6	6.6±	1.6
2000 ppm	25	17.7±	6.0	152±	2	4.1±	0.4	121±	3	9.3±	1.1	6.1±	0.7
4000 ppm	35	19.2±	13.3	152±	1	4.2±	0.7	122±	6	8.8±	0.4	6.3±	1.6

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

(HCL074)

BAIS4

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0611
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	35	0	5	5	5	9	6	5		0	7	19	7	2	0		35	0	0	0	0	0		25	6	4	0	0	0		32	0	0	1	2	
1000 ppm	37	0	1	6	5	8	10	7		0	8	24	5	0	0		37	0	0	0	0	0		30	3	4	0	0	0		35	0	0	1	1	
2000 ppm	38	0	3	6	4	8	9	8		0	9	24	5	0	0		38	0	0	0	0	0		30	4	3	1	0	0		35	0	0	0	3	
4000 ppm	36	0	3	4	10	8	5	6		0	6	14	14	2	0		36	0	0	0	0	0		15	5	15	1	0	0	*	36	0	0	0	0	

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

(HCL101)

BAIS 4

STUDY NO. : 0611 URINALYSIS
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

Group Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
Control	35	35	0	0	0	0	
1000 ppm	37	37	0	0	0	0	
2000 ppm	38	38	0	0	0	0	
4000 ppm	36	36	0	0	0	0	

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

(HCL101)

BAIS 4

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0611
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	27	0	0	4	1	5	17	0		0	4	12	10	0	1		27	0	0	0	0	0		12	11	1	2	1	0		27	0	0	0	0	
1000 ppm	29	0	0	2	7	9	9	2	*	0	7	15	4	3	0		29	0	0	0	0	0		11	14	1	3	0	0		25	0	1	2	1	
2000 ppm	28	0	0	1	3	5	16	3		0	5	20	1	2	0	*	28	0	0	0	0	0		13	13	2	0	0	0		28	0	0	0	0	
4000 ppm	38	0	3	2	1	9	18	5		0	12	16	9	1	0		38	0	0	0	0	0		14	20	3	1	0	0		37	1	0	0	0	

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

(HCL101)

STUDY NO. : 0611
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	27	27	0	0	0	0	
1000 ppm	29	29	0	0	0	0	
2000 ppm	28	28	0	0	0	0	
4000 ppm	38	38	0	0	0	0	

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

(HCL101)

BAIS 4

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Cr1j[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	42.9± 6.8	0.010± 0.002	0.211± 0.032	0.223± 0.018	0.211± 0.086	0.833± 1.009
1000 ppm	35	43.1± 5.7	0.011± 0.002	0.199± 0.031	0.221± 0.022	0.217± 0.141	1.332± 2.931
2000 ppm	36	43.1± 7.8	0.011± 0.002	0.209± 0.026	0.221± 0.019	0.189± 0.019	0.653± 0.111
4000 ppm	34	38.3± 6.4*	0.011± 0.002	0.212± 0.036	0.207± 0.019**	0.187± 0.016	0.637± 0.065

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

(HCL040)

STUDY NO. : 0611
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	0.129±	0.212	1.756±	0.587	0.463±	0.018
1000 ppm	35	0.173±	0.286	1.699±	0.468	0.462±	0.014
2000 ppm	36	0.092±	0.111	1.570±	0.253	0.451±	0.016**
4000 ppm	34	0.095±	0.069	1.662±	0.523	0.453±	0.013*

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

(HCL040)

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0611
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	25	30.8± 4.9	0.014± 0.002	0.042± 0.023	0.183± 0.024	0.198± 0.027	0.460± 0.060
1000 ppm	26	30.4± 4.8	0.014± 0.002	0.442± 1.410	0.185± 0.027	0.239± 0.141	0.559± 0.483
2000 ppm	25	30.7± 3.6	0.014± 0.002	0.049± 0.041	0.180± 0.026	0.191± 0.018	0.450± 0.060
4000 ppm	36	28.7± 3.4	0.013± 0.002	0.086± 0.164	0.168± 0.017*	0.189± 0.028	0.434± 0.039

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

(HCL040)

STUDY NO. : 0611
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	25	0.241±	0.402	1.737±	0.850	0.489±	0.016
1000 ppm	26	0.218±	0.252	1.662±	1.122	0.490±	0.020
2000 ppm	25	0.351±	0.946	1.547±	0.298	0.482±	0.013
4000 ppm	36	0.151±	0.166	1.430±	0.295	0.466±	0.013**

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

(HCL040)

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0611
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	42.9± 6.8	0.025± 0.006	0.499± 0.085	0.532± 0.096	0.506± 0.219	1.948± 2.190
1000 ppm	35	43.1± 5.7	0.027± 0.006	0.471± 0.106	0.519± 0.073	0.532± 0.459	3.126± 6.511
2000 ppm	36	43.1± 7.8	0.026± 0.007	0.503± 0.120	0.527± 0.093	0.455± 0.097	1.566± 0.398
4000 ppm	34	38.3± 6.4*	0.029± 0.006	0.566± 0.117*	0.552± 0.078	0.502± 0.087	1.696± 0.270

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

(HCL042)

BAIS 4

STUDY NO. : 0611
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	0.342± 0.658	4.311± 2.086	1.111± 0.204
1000 ppm	35	0.407± 0.637	4.027± 1.413	1.090± 0.158
2000 ppm	36	0.226± 0.291	3.737± 0.809	1.089± 0.240
4000 ppm	34	0.258± 0.200	4.417± 1.460*	1.220± 0.222

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

(HCL042)

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0611
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	25	30.8± 4.9	0.046± 0.008	0.139± 0.078	0.599± 0.066	0.660± 0.139	1.509± 0.183
1000 ppm	26	30.4± 4.8	0.048± 0.008	1.378± 4.320	0.621± 0.107	0.852± 0.747	1.838± 1.464
2000 ppm	25	30.7± 3.6	0.047± 0.007	0.163± 0.138	0.590± 0.090	0.626± 0.081	1.477± 0.228
4000 ppm	36	28.7± 3.4	0.047± 0.008	0.301± 0.565	0.588± 0.066	0.660± 0.071	1.520± 0.124

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

(HCL042)

BAIS 4

STUDY NO. : 0611
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	25	0.797± 1.325	5.815± 3.316	1.628± 0.253
1000 ppm	26	0.734± 0.868	5.479± 3.729	1.649± 0.238
2000 ppm	25	1.170± 3.220	5.061± 0.980	1.588± 0.185
4000 ppm	36	0.505± 0.474	4.981± 0.758	1.641± 0.175

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

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<49>				<50>				<50>				<50>			
	ulcer		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	erosion		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		3 (6)	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)
{Respiratory system}																		
nasal cavit			<49>				<50>				<50>				<50>			
	exudate		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)
	eosinophilic change:olfactory epithelium		10 (20)	3 (6)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 * (0)	1 (2)	0 (0)	0 (0)	0 ** (0)	2 (4)	0 (0)	0 (0)	0 ** (0)
	eosinophilic change:respiratory epithelium		6 (12)	1 (2)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:olfactory epithelium		10 (20)	0 (0)	0 (0)	0 (0)	17 (34)	0 (0)	0 (0)	0 (0)	25 (50)	1 (2)	0 (0)	0 ** (0)	33 (66)	11 (22)	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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<49>				<50>				<50>				<50>			
	respiratory metaplasia:gland		11 (22)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	16 (32)	3 (6)	0 (0)	0 (0)	20 (40)	11 (22)	0 (0)	0 (0) **
	atrophy:olfactory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0) *	28 (56)	1 (2)	0 (0)	0 (0) **	43 (86)	0 (0)	0 (0)	0 (0) **
	necrosis:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
nasopharynx			<49>				<50>				<50>				<50>			
	eosinophilic change		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
lung			<49>				<50>				<50>				<50>			
	hemorrhage		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)	0 (0)	0 (0)
	edema		2 (4)	0 (0)	2 (4)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
lung			<49>				<50>				<50>				<50>			
	accumulation of foamy cells		3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
{Hematopoietic system}																		
bone marrow			<49>				<50>				<50>				<50>			
	increased hematopoiesis		4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	myelofibrosis		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)
	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)
lymph node			<49>				<50>				<50>				<50>			
	granulation		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 49 1 (%)	Control 49 2 (%)	Control 49 3 (%)	Control 49 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Hematopoietic system}																		
lymph node			<49>				<50>				<50>				<50>			
	proliferation:histiocyte		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)
thymus			<49>				<50>				<50>				<50>			
	atrophy		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)
spleen			<49>				<50>				<50>				<50>			
	extramedullary hematopoiesis		16 (33)	11 (22)	2 (4)	0 (0)	14 (28)	8 (16)	1 (2)	0 (0)	17 (34)	5 (10)	4 (8)	0 (0)	15 (30)	9 (18)	2 (4)	0 (0)
	follicular hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Circulatory system}																		
heart			<49>				<50>				<50>				<50>			
	thrombus		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)	0 (0)	0 (0)
	necrosis:focal		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	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 49 1 (%)	Control 49 2 (%)	Control 49 3 (%)	Control 49 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Circulatory system}																		
heart			<49>				<50>				<50>				<50>			
	mineralization		2 (4)	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)
	arteritis		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)
artery/aort			<49>				<50>				<50>				<50>			
	mineralization		0 (0)	0 (0)	0 (0)	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)
{Digestive system}																		
tongue			<49>				<50>				<50>				<50>			
	arteritis		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)
salivary gl			<49>				<50>				<50>				<50>			
	xanthogranuloma		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
stomach			<49>				<50>				<50>				<50>			
	erosion:forestomach		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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
stomach			<49>				<50>				<50>				<50>			
	ulcer:forestomach		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:forestomach		1 (2)	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)
	erosion:glandular stomach		4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	ulcer:glandular stomach		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)	1 (2)	0 (0)
	hyperplasia:glandular stomach		17 (35)	0 (0)	0 (0)	0 (0)	19 (38)	1 (2)	0 (0)	0 (0)	17 (34)	0 (0)	0 (0)	0 (0)	13 (26)	0 (0)	0 (0)	0 (0)
small intes			<49>				<50>				<50>				<50>			
	diverticula		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)
	inflammation		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)
liver			<49>				<50>				<50>				<50>			
	angiectasis		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)	1 (2)	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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<49>				<50>				<50>				<50>			
	hemorrhage		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)
	necrosis:central		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	necrosis:focal		1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory cell nest		6 (12)	1 (2)	0 (0)	0 (0)	12 (24)	1 (2)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		1 (2)	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)
	clear cell focus		0 (0)	0 (0)	1 (2)	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)
	acidophilic cell focus		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	basophilic cell focus		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)

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				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
liver																		
	biliary cyst		<49>				<50>				<50>				<50>			
			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)
gall bladd																		
	eosinophilic change		<49>				<50>				<50>				<50>			
			1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		3	1	0	0	2	1	0	0	0	0	0	0	1	1	0	0
			(6)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
pancreas																		
	atrophy		<49>				<50>				<50>				<50>			
			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)
	islet cell hyperplasia		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)	(0)
{Urinary system}																		
kidney																		
	hyperplasia:tubular epithelial cell		<49>				<50>				<50>				<50>			
			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				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<49>				<50>				<50>				<50>			
	atrophy		0	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)
	cyst		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyaline droplet		0	1	0	0	3	1	0	0	2	0	0	0	4	1	0	0
			(0)	(2)	(0)	(0)	(6)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(8)	(2)	(0)	(0)
	inflammatory infiltration		0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		3	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(4)	(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	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	inflammatory polyp		1	0	1	0	1	1	1	0	0	0	0	0	0	1	0	0
			(2)	(0)	(2)	(0)	(2)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	hydronephrosis		0	1	5	0	0	2	3	0	0	1	2	0	0	2	3	0
			(0)	(2)	(10)	(0)	(0)	(4)	(6)	(0)	(0)	(2)	(4)	(0)	(0)	(4)	(6)	(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 49 1 (%)	Control 49 2 (%)	Control 49 3 (%)	Control 49 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Urinary system}																		
kidney			<49>				<50>				<50>				<50>			
	mineralization:cortico-medullary junction		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)
	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)
	glomerulosclerosis		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)	0 (0)	0 (0)
	regeneration:proximal tubule		10 (20)	0 (0)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	transitional cell hyperplasia		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)
urin bladd			<49>				<50>				<50>				<50>			
	dilatation		1 (2)	1 (2)	5 (10)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	1 (2)	5 (10)	0 (0)	1 (2)	0 (0)	3 (6)	0 (0)
	inflammation		2 (4)	1 (2)	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)
	xanthogranuloma		0 (0)	2 (4)	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	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Endocrine system}																		
pituitary			<49>				<49>				<50>				<48>			
	thrombus		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)
	cyst		1	0	0	0	1	0	0	0	2	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		3	0	0	0	2	0	0	0	2	0	0	0	3	0	0	0
			(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	Rathke pouch		3	0	0	0	3	0	0	0	2	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
thyroid			<49>				<50>				<50>				<50>			
	cyst		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)
parathyroid			<49>				<50>				<50>				<50>			
	cyst		2	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
adrenal			<49>				<50>				<50>				<50>			
	spindle-cell hyperplasia		5	0	0	0	6	0	0	0	8	0	0	0	4	0	0	0
			(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(8)	(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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Endocrine system}																		
adrenal			<49>				<50>				<50>				<50>			
	hyperplasia:cortical cell		1	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:medulla		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			<49>				<50>				<50>				<50>			
	mineralization		5	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0
			(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
epididymis			<49>				<50>				<50>				<50>			
	lymphocytic infiltration		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)
	granulation		1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	spermatogenic granuloma		7	0	0	0	2	0	0	0	1	1	0	0	1	0	0	0
			(14)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(2)	(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 49 1 (%)	Control 49 2 (%)	Control 49 3 (%)	Control 49 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Reproductive system}																		
semin ves			<49>				<50>				<50>				<50>			
	hemorrhage		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)
	degeneration		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)
prostate			<49>				<50>				<50>				<50>			
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	granulation		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)
prep/cli gl			<49>				<50>				<50>				<50>			
	inflammation		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)
	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)
{Nervous system}																		
brain			<49>				<50>				<50>				<50>			
	mineralization		10 (20)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	6 (12)	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 49				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Nervous system}																		
brain			<49>				<50>				<50>				<50>			
	meningoencephalitis		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)
{Special sense organs/appendage}																		
eye			<49>				<50>				<50>				<50>			
	keratitis		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)
	degeneration:cornea		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)
Harder gl			<49>				<50>				<50>				<50>			
	hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Musculoskeletal system}																		
muscle			<49>				<50>				<50>				<50>			
	mineralization		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	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	49				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Musculoskeletal system}																		
bone			<49>				<50>				<50>				<50>			
	fracture		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)
	osteosclerosis		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)

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 L4

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : FEMALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<50>				<49>				<50>				<50>			
	squamous cell hyperplasia		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)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	exudate		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)
	eosinophilic change:olfactory epithelium		11 (22)	0 (0)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	eosinophilic change:respiratory epithelium		36 (72)	5 (10)	0 (0)	0 (0)	30 (60)	5 (10)	0 (0)	0 (0)	38 (76)	4 (8)	0 (0)	0 (0)	35 (70)	6 (12)	0 (0)	0 (0)
	respiratory metaplasia:olfactory epithelium		4 (8)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)	20 (40)	1 (2)	0 (0)	0 ** (0)	40 (80)	10 (20)	0 (0)	0 ** (0)
	respiratory metaplasia:gland		7 (14)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	18 (36)	1 (2)	0 (0)	0 * (0)	27 (54)	10 (20)	0 (0)	0 ** (0)
	inflammation:transitional epithelium		1 (2)	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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Respiratory system}																		
nasal cavit		<50>																
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	26 (52)	0 (0)	0 (0)	0 ** (0)	40 (80)	2 (4)	0 (0)	0 ** (0)	40 (80)	0 (0)	0 (0)	0 ** (0)
	necrosis:olfactory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
nasopharynx		<50>																
	eosinophilic change		3 (6)	4 (8)	0 (0)	0 (0)	7 (14)	5 (10)	0 (0)	0 (0)	5 (10)	2 (4)	0 (0)	0 (0)	6 (12)	6 (12)	0 (0)	0 (0)
lung		<50>																
	inflammatory infiltration		4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	accumulation of foamy cells		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		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 / No. of Animals on Study / Grade	Control 50				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			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		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
lymph node			<50>				<50>				<50>				<50>			
	follicular hyperplasia		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)
spleen			<50>				<50>				<50>				<50>			
	deposit of hemosiderin		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)
	deposit of melanin		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)
	extramedullary hematopoiesis		12 (24)	5 (10)	2 (4)	0 (0)	13 (26)	9 (18)	3 (6)	0 (0)	9 (18)	8 (16)	6 (12)	0 (0)	11 (22)	4 (8)	1 (2)	0 (0)
	follicular hyperplasia		3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	necrosis:focal		2	2	0	0	2	1	0	0	0	0	0	0	2	0	0	0
			(4)	(4)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	mineralization		1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(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)
artery/aort			<50>				<50>				<50>				<50>			
	arteritis		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)
{Digestive system}																		
tongue			<50>				<50>				<50>				<50>			
	arteritis		1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
salivary gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(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				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			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	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)
stomach			<50>				<50>				<50>				<50>			
	ulcer:forestomach		1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		0	1	0	0	0	1	0	0	1	0	0	0	1	1	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	erosion:glandular stomach		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)	(0)	(4)	(0)	(0)	(0)
	ulcer:glandular stomach		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)	(0)
	hyperplasia:glandular stomach		10	0	0	0	10	0	0	0	11	0	0	0	14	0	0	0
			(20)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(28)	(0)	(0)	(0)
	squamous cell metaplasia: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)
liver			<50>				<50>				<50>				<50>			
	angiectasis		3	0	0	0	0	1	0	0	0	0	0	0	4	2	0	0
			(6)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(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 / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 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>			
	necrosis:central		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	necrosis:focal		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	granulation		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	inflammatory cell nest		18 (36)	0 (0)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	19 (38)	3 (6)	0 (0)	0 (0)	24 (48)	2 (4)	0 (0)	0 (0)
	extramedullary hematopoiesis		4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	clear cell focus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)
	acidophilic cell focus		0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)
	basophilic cell focus		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)	1 (2)	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				1000 ppm				2000 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}																		
liver																		
	biliary cyst		<50>				<50>				<50>				<50>			
			0	0	0	0	1	0	0	0	2	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
gall bladd																		
	inflammation		<50>				<50>				<50>				<50>			
			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)
	hyperplasia		4	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas																		
	inflammatory infiltration		<50>				<50>				<50>				<50>			
			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)
	lymphocytic infiltration		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)
	islet 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)
{Urinary system}																		
kidney																		
	cyst		<50>				<50>				<50>				<50>			
			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)

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 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hyaline droplet		9 (18)	2 (4)	0 (0)	0 (0)	4 (8)	5 (10)	0 (0)	0 (0)	5 (10)	6 (12)	0 (0)	0 (0)	2 (4)	3 (6)	0 (0)	0 (0)
	deposit of amyloid		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)	0 (0)	0 (0)	0 (0)
	deposit of hemosiderin		0 (0)	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)
	hyaline cast		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)
	inflammatory 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)
	lymphocytic infiltration		4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	inflammatory polyp		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	ossification		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	2000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hydronephrosis		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	1 (2)	0 (0)	2 (4)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)
	mineralization:cortex		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)
	glomerulosclerosis		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)
	regeneration:proximal tubule		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	vacuolic change:proximal tubule		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)
urin bladd			<50>				<50>				<50>				<50>			
	inflammation		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)
	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)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		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)

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				1000 ppm				2000 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}																		
pituitary			<50>				<50>				<50>				<50>			
	cyst		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		9	8	3	0	6	2	7	0	7	4	1	0	11	3	1	0
			(18)	(16)	(6)	(0)	(12)	(4)	(14)	(0)	(14)	(8)	(2)	(0)	(22)	(6)	(2)	(0)
thyroid			<50>				<50>				<50>				<50>			
	cyst		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)
	vacuolar change;follicular cell		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)
parathyroid			<50>				<50>				<50>				<50>			
	cyst		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)
adrenal			<50>				<50>				<50>				<50>			
	vacuolic change		0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	extramedullary hematopoiesis		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)

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				1000 ppm				2000 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>			
	spindle-cell hyperplasia		27	0	0	0	14	1	0	0 *	10	0	0	0 **	25	0	0	0
			(54)	(0)	(0)	(0)	(28)	(2)	(0)	(0)	(20)	(0)	(0)	(0)	(50)	(0)	(0)	(0)
	hyperplasia:cortical cell		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)
{Reproductive system}																		
ovary			<50>				<50>				<50>				<50>			
	thrombus		0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	cyst		12	0	0	0	9	0	0	0	17	0	0	0	16	0	0	0
			(24)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(34)	(0)	(0)	(0)	(32)	(0)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	cystic endometrial hyperplasia		30	1	0	0	33	1	0	0	26	1	0	0	28	2	2	0
			(60)	(2)	(0)	(0)	(66)	(2)	(0)	(0)	(52)	(2)	(0)	(0)	(56)	(4)	(4)	(0)
vagina			<50>				<50>				<50>				<50>			
	hyperplasia		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)

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				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	mineralization		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (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 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Harder gl			<50>				<50>				<50>				<50>			
	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)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		0 (0)	0 (0)	0 (0)	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)
	lymphocytic infiltration		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				1000 ppm				2000 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		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

TABLE O1

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : MALE

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	2/49(4.1)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	6.25	8.33	5.41	2.86
Terminal rates(c)	2/32(6.3)	3/36(8.3)	2/37(5.4)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7868			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4533			
Fisher Exact test(e)		P = 0.5097	P = 0.6990	P = 0.4923
	SITE : lung			
	TUMOR : bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	5/49(10.2)	3/50(6.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	12.50	8.33	0.0	0.0
Terminal rates(c)	4/32(12.5)	3/36(8.3)	0/37(0.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3749			
Prevalence method(d)	P = 0.9975			
Combined analysis(d)	P = 0.9775			
Cochran-Armitage test(e)	P = 0.0593			
Fisher Exact test(e)		P = 0.3461	P = 0.0976	P = 0.0976
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	7/49(14.3)	6/50(12.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	18.75	16.67	5.41	2.86
Terminal rates(c)	6/32(18.8)	6/36(16.7)	2/37(5.4)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3749			
Prevalence method(d)	P = 0.9938			
Combined analysis(d)	P = 0.9817			
Cochran-Armitage test(e)	P = 0.0512			
Fisher Exact test(e)		P = 0.4842	P = 0.1507	P = 0.0750

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	7/49(14.3)	9/50(18.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	12.50	25.00	5.41	11.43
Terminal rates(c)	4/32(12.5)	9/36(25.0)	2/37(5.4)	4/35(11.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7476			
Prevalence method(d)	P = 0.7943			
Combined analysis(d)	P = 0.8583			
Cochran-Armitage test(e)	P = 0.3130			
Fisher Exact test(e)		P = 0.4101	P = 0.2505	P = 0.3654
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	15/49(30.6)	15/50(30.0)	6/50(12.0)	9/50(18.0)
Adjusted rates(b)	35.29	27.78	14.63	20.00
Terminal rates(c)	11/32(34.4)	10/36(27.8)	5/37(13.5)	7/35(20.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3322			
Prevalence method(d)	P = 0.9811			
Combined analysis(d)	P = 0.9569			
Cochran-Armitage test(e)	P = 0.0641			
Fisher Exact test(e)		P = 0.6121	P = 0.0210*	P = 0.1093
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	0/49(0.0)	1/50(2.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	0.0	0.0	0.0	0.0
Terminal rates(c)	0/32(0.0)	0/36(0.0)	0/37(0.0)	0/35(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1144			
Prevalence method(d)	P = ------			
Combined analysis(d)	P = 0.1144			
Cochran-Armitage test(e)	P = 0.2121			
Fisher Exact test(e)		P = 0.5051	P = 0.1250	P = 0.2525

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	6/49(12.2)	4/50(8.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	12.50	10.00	8.11	8.57
Terminal rates(c)	4/32(12.5)	3/36(8.3)	3/37(8.1)	3/35(8.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3907			
Prevalence method(d)	P = 0.7792			
Combined analysis(d)	P = 0.7356			
Cochran-Armitage test(e)	P = 0.5033			
Fisher Exact test(e)		P = 0.3574	P = 0.2333	P = 0.3574
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/49(2.0)	2/50(4.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	2.78	2.78	7.32	2.86
Terminal rates(c)	0/32(0.0)	1/36(2.8)	2/37(5.4)	1/35(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5888			
Prevalence method(d)	P = 0.4516			
Combined analysis(d)	P = 0.5297			
Cochran-Armitage test(e)	P = 0.9353			
Fisher Exact test(e)		P = 0.5077	P = 0.3163	P = 0.7576
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	20/49(40.8)	17/50(34.0)	8/50(16.0)	13/50(26.0)
Adjusted rates(b)	44.12	32.50	19.51	28.57
Terminal rates(c)	14/32(43.8)	11/36(30.6)	7/37(18.9)	10/35(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3106			
Prevalence method(d)	P = 0.9781			
Combined analysis(d)	P = 0.9460			
Cochran-Armitage test(e)	P = 0.0725			
Fisher Exact test(e)		P = 0.3111	P = 0.0056**	P = 0.0883

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma			
Tumor rate				
Overall rates(a)	20/49(40.8)	17/50(34.0)	8/50(16.0)	13/50(26.0)
Adjusted rates(b)	44.12	32.50	19.51	28.57
Terminal rates(c)	14/32(43.8)	11/36(30.6)	7/37(18.9)	10/35(28.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3106			
Prevalence method(d)	P = 0.9781			
Combined analysis(d)	P = 0.9460			
Cochran-Armitage test(e)	P = 0.0725			
Fisher Exact test(e)		P = 0.3111	P = 0.0056**	P = 0.0883

(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 ≦ 0.05 ** : P ≦ 0.01
N.C. :Statistical value cannot be calculated and was not significant.

STUDY No. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	6/49(12.2)	3/50(6.0)	6/50(12.0)	5/50(10.0)
Adjusted rates(b)	6.25	0.0	8.11	5.71
Terminal rates(c)	2/32(6.3)	0/36(0.0)	3/37(8.1)	2/35(5.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6172			
Prevalence method(d)	P = 0.3410			
Combined analysis(d)	P = 0.5061			
Cochran-Armitage test(e)	P = 0.9776			
Fisher Exact test(e)		P = 0.2333	P = 0.6346	P = 0.4856

(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 ; * : $P \leqq 0.05$ ** : $P \leqq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

TABLE O2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
SITE : lung				
TUMOR : bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	6.90	11.54	4.44	0.0
Terminal rates(c)	1/25(4.0)	3/26(11.5)	1/25(4.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9350			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1720			
Fisher Exact test(e)		P = 0.5000	P = 0.6913	P = 0.2475
SITE : lung				
TUMOR : bronchiolar-alveolar adenoma,bronchiolar-alveolar carcinoma				
Tumor rate				
Overall rates(a)	4/50(8.0)	4/50(8.0)	4/50(8.0)	2/50(4.0)
Adjusted rates(b)	11.11	15.38	8.89	4.76
Terminal rates(c)	2/25(8.0)	4/26(15.4)	1/25(4.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8054			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3991			
Fisher Exact test(e)		P = 0.6425	P = 0.6425	P = 0.3389
SITE : lymph node				
TUMOR : malignant lymphoma				
Tumor rate				
Overall rates(a)	16/50(32.0)	16/50(32.0)	9/50(18.0)	9/50(18.0)
Adjusted rates(b)	25.93	34.62	16.00	8.11
Terminal rates(c)	6/25(24.0)	9/26(34.6)	4/25(16.0)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8188			
Prevalence method(d)	P = 0.9945			
Combined analysis(d)	P = 0.9910			
Cochran-Armitage test(e)	P = 0.0533			
Fisher Exact test(e)		P = 0.5848	P = 0.0826	P = 0.0826

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	4/50(8.0)	4/50(8.0)	7/50(14.0)
Adjusted rates(b)	32.00	15.38	11.11	17.50
Terminal rates(c)	8/25(32.0)	4/26(15.4)	1/25(4.0)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7033			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9701			
Fisher Exact test(e)		P = 0.1783	P = 0.1783	P = 0.5000
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	0.0	3.85	0.0	2.70
Terminal rates(c)	0/25(0.0)	1/26(3.8)	0/25(0.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9555			
Prevalence method(d)	P = 0.3307			
Combined analysis(d)	P = 0.8822			
Cochran-Armitage test(e)	P = 0.3291			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.3087
	SITE : liver			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	5/50(10.0)	1/50(2.0)	0/50(0.0)
Adjusted rates(b)	2.78	8.33	4.00	0.0
Terminal rates(c)	0/25(0.0)	2/26(7.7)	1/25(4.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7563			
Prevalence method(d)	P = 0.8933			
Combined analysis(d)	P = 0.9335			
Cochran-Armitage test(e)	P = 0.1720			
Fisher Exact test(e)		P = 0.1022	P = 0.7525	P = 0.5000

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	6/50(12.0)	1/50(2.0)	0/50(0.0)
Adjusted rates(b)	2.78	11.54	4.00	0.0
Terminal rates(c)	0/25(0.0)	3/26(11.5)	1/25(4.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7563			
Prevalence method(d)	P = 0.9166			
Combined analysis(d)	P = 0.9472			
Cochran-Armitage test(e)	P = 0.1432			
Fisher Exact test(e)		P = 0.0559	P = 0.7525	P = 0.5000
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	5/50(10.0)	4/50(8.0)	7/50(14.0)
Adjusted rates(b)	36.00	15.38	11.11	17.50
Terminal rates(c)	9/25(36.0)	4/26(15.4)	1/25(4.0)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5967			
Prevalence method(d)	P = 0.7924			
Combined analysis(d)	P = 0.8201			
Cochran-Armitage test(e)	P = 0.6910			
Fisher Exact test(e)		P = 0.1940	P = 0.1168	P = 0.3929
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	10/50(20.0)	6/50(12.0)	4/50(8.0)
Adjusted rates(b)	25.00	30.77	12.00	10.26
Terminal rates(c)	6/25(24.0)	8/26(30.8)	3/25(12.0)	3/37(8.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7700			
Prevalence method(d)	P = 0.9798			
Combined analysis(d)	P = 0.9862			
Cochran-Armitage test(e)	P = 0.0834			
Fisher Exact test(e)		P = 0.5000	P = 0.2883	P = 0.1168

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : ovary			
	TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	7.89	2.56	4.00	2.70
Terminal rates(c)	0/25(0.0)	0/26(0.0)	1/25(4.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.8591			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.3266			
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.3087
	SITE : uterus			
	TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	4.00	11.54	5.26	2.70
Terminal rates(c)	1/25(4.0)	3/26(11.5)	1/25(4.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.7162			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.7450			
Fisher Exact test(e)		P = 0.3087	P = 0.5000	P = 0.7525
	SITE : uterus			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	9/50(18.0)	11/50(22.0)	9/50(18.0)
Adjusted rates(b)	16.00	3.85	8.00	12.82
Terminal rates(c)	4/25(16.0)	1/26(3.8)	2/25(8.0)	4/37(10.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8107			
Prevalence method(d)	P = 0.3632			
Combined analysis(d)	P = 0.7090			
Cochran-Armitage test(e)	P = 0.8801			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.5000

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : mammary gland			
	TUMOR : adenocarcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	0.0	0.0	12.00	0.0
Terminal rates(c)	0/25(0.0)	0/26(0.0)	3/25(12.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9119 ?			
Prevalence method(d)	P = 0.4836			
Combined analysis(d)	P = 0.7040			
Cochran-Armitage test(e)	P = 0.7327			
Fisher Exact test(e)		P = 0.5000	P = 0.3087	P = 0.5000
	SITE : Harderian gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	4/50(8.0)	1/50(2.0)
Adjusted rates(b)	16.00	3.85	11.11	2.27
Terminal rates(c)	4/25(16.0)	1/26(3.8)	2/25(8.0)	0/37(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8872			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3236			
Fisher Exact test(e)		P = 0.1811	P = 0.6425	P = 0.1811

(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 ≦ 0.05 ** : P ≦ 0.01
N.C. :Statistical value cannot be calculated and was not significant.

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	16/50(32.0)	12/50(24.0)	16/50(32.0)	13/50(26.0)
Adjusted rates(b)	20.00	7.69	12.00	17.95
Terminal rates(c)	5/25(20.0)	2/26(7.7)	3/25(12.0)	6/37(16.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9150			
Prevalence method(d)	P = 0.3214			
Combined analysis(d)	P = 0.8205			
Cochran-Armitage test(e)	P = 0.6912			
Fisher Exact test(e)		P = 0.2522	P = 0.5848	P = 0.3299
	SITE : ALL SITE TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	7/50(14.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	5.56	11.54	4.00	2.70
Terminal rates(c)	1/25(4.0)	3/26(11.5)	1/25(4.0)	1/37(2.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7398			
Prevalence method(d)	P = 0.8694			
Combined analysis(d)	P = 0.9053			
Cochran-Armitage test(e)	P = 0.2648			
Fisher Exact test(e)		P = 0.0798	P = 0.5000	P = 0.5000

(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 ≦ 0.05 ** : P ≦ 0.01
N.C. :Statistical value cannot be calculated and was not significant.

TABLE Q

CAUSE OF DEATH OF MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

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

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
Number of Dead and Moribund Animal	17	14	13	15
no microscop confirm	0	0	2	1
cardiovascular les	2	0	0	0
renal lesion	0	1	0	0
central nervo lesion	1	0	0	0
urinary retention	2	4	2	0
hydronephrosis	2	1	2	5
tumor d:leukemia	3	0	2	1
tumor d:lung	1	0	1	1
tumor d:bone marrow	1	0	0	0
tumor d:spleen	1	0	1	1
tumor d:liver	1	6	3	5
tumor d:kidney	0	0	0	1
tumor d:epididymis	0	1	0	0
tumor d:periph nerv	1	0	0	0
tumor d:peritoneum	2	1	0	0

STUDY NO. : 0611
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : FEMALE

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

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
Number of Dead and Moribund Animal	25	24	25	13
no microscop confirm	0	0	1	0
cardiovascular les	1	0	0	0
hydronephrosis	0	1	1	1
tumor d:leukemia	8	7	5	6
tumor d:subcutis	2	1	0	1
tumor d:spleen	2	0	0	0
tumor d:liver	3	4	2	0
tumor d:pituitary	1	1	2	0
tumor d:uterus	6	8	10	4
tumor d:mammary gl	1	0	0	0
tumor d:muscle	0	1	0	0
tumor d:bone	1	0	0	0
tumor d:peritoneum	0	1	2	1
tumor d:retroperit	0	0	2	0

FIGURES

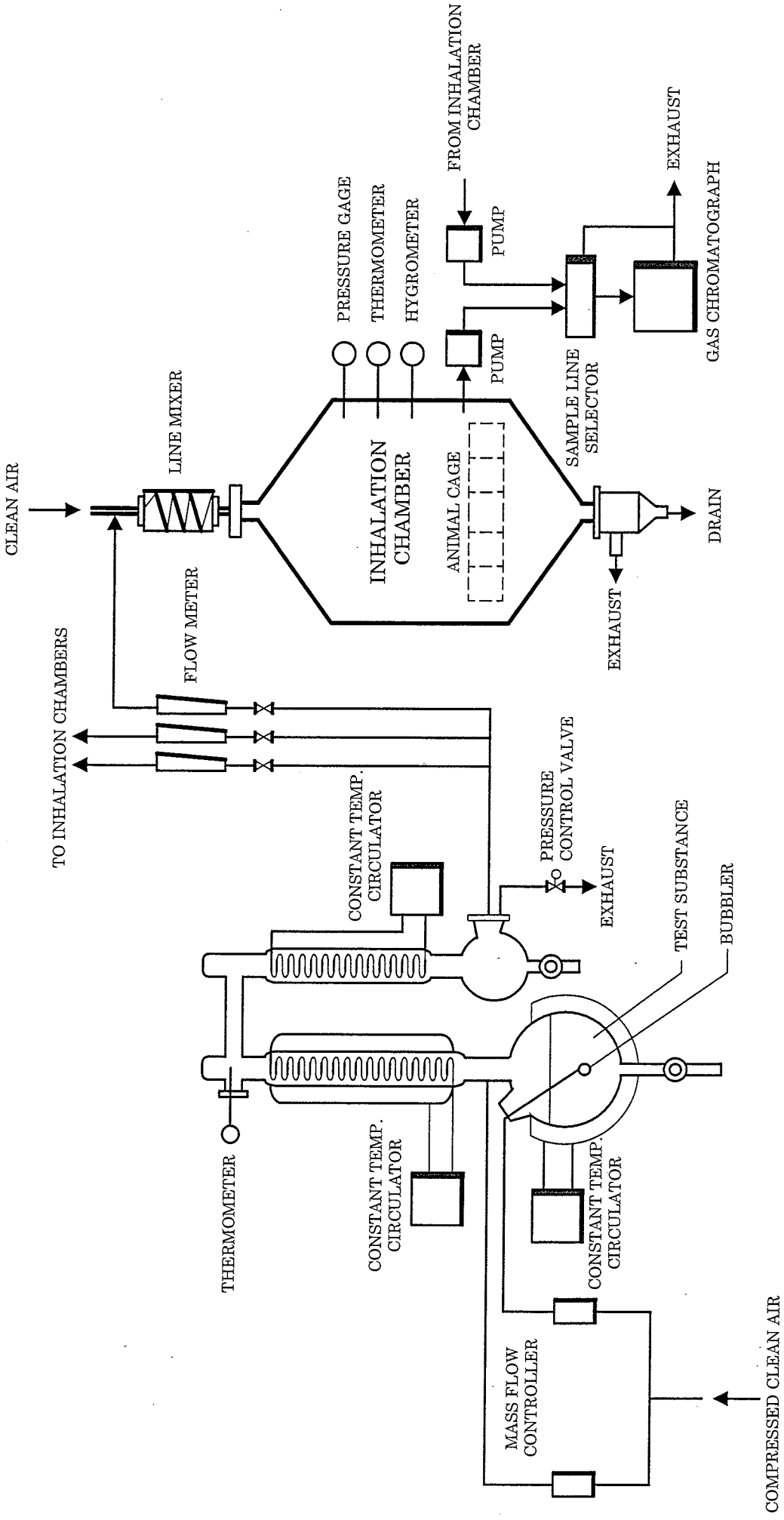


FIGURE 1 ISOPROPYL ACETATE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

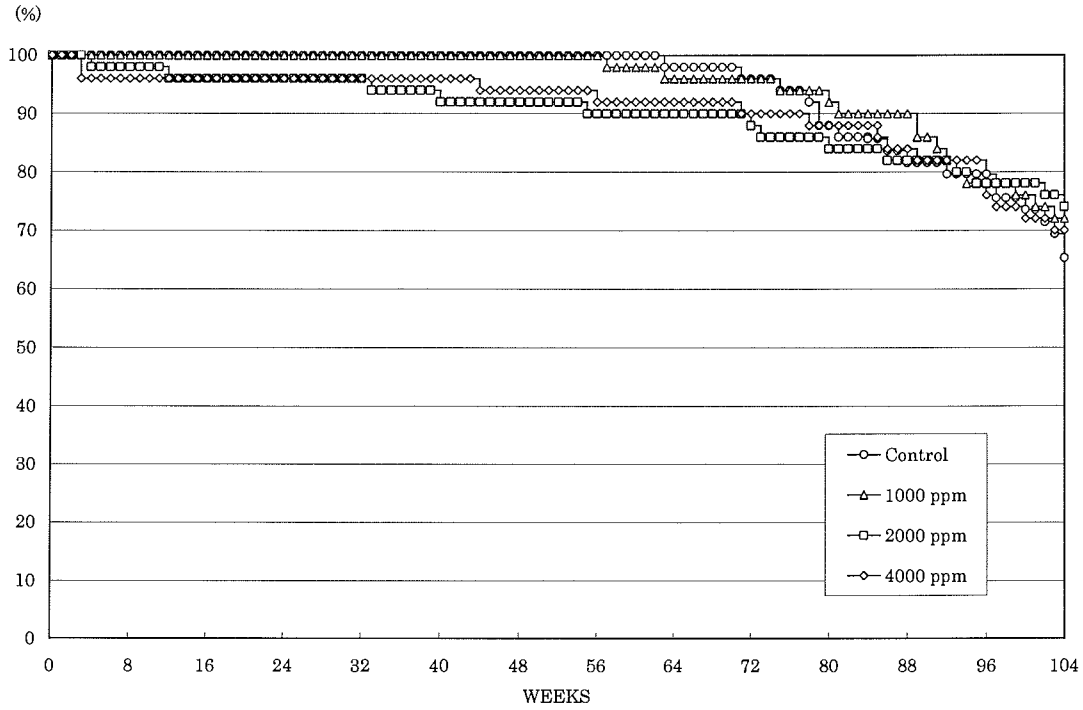


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

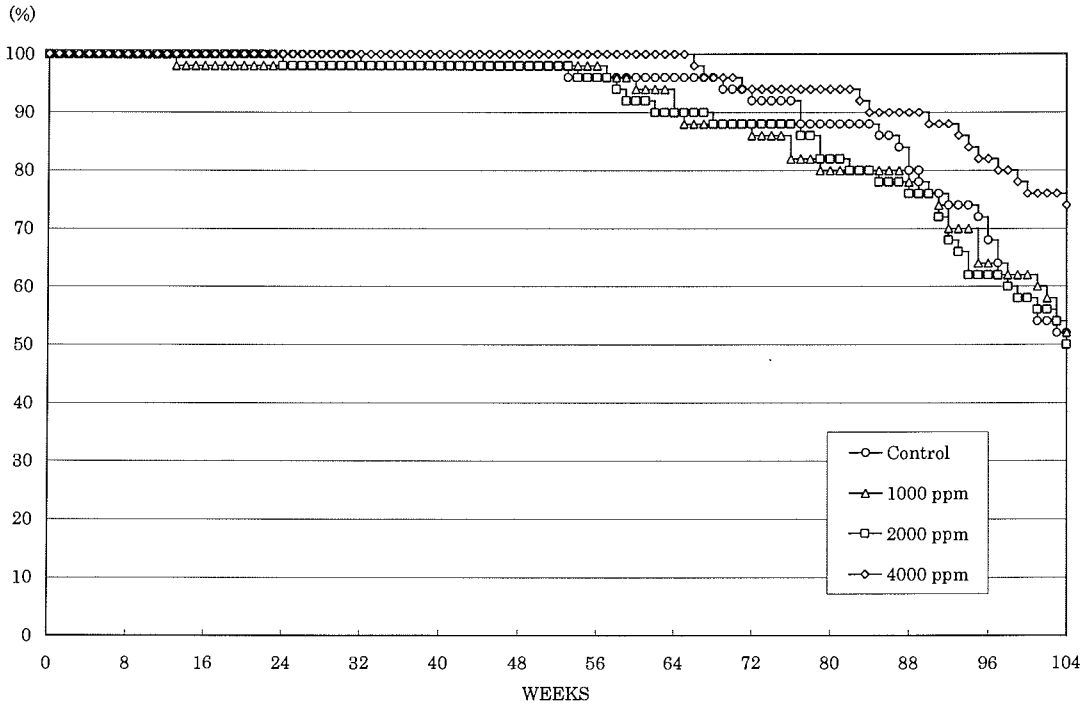


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

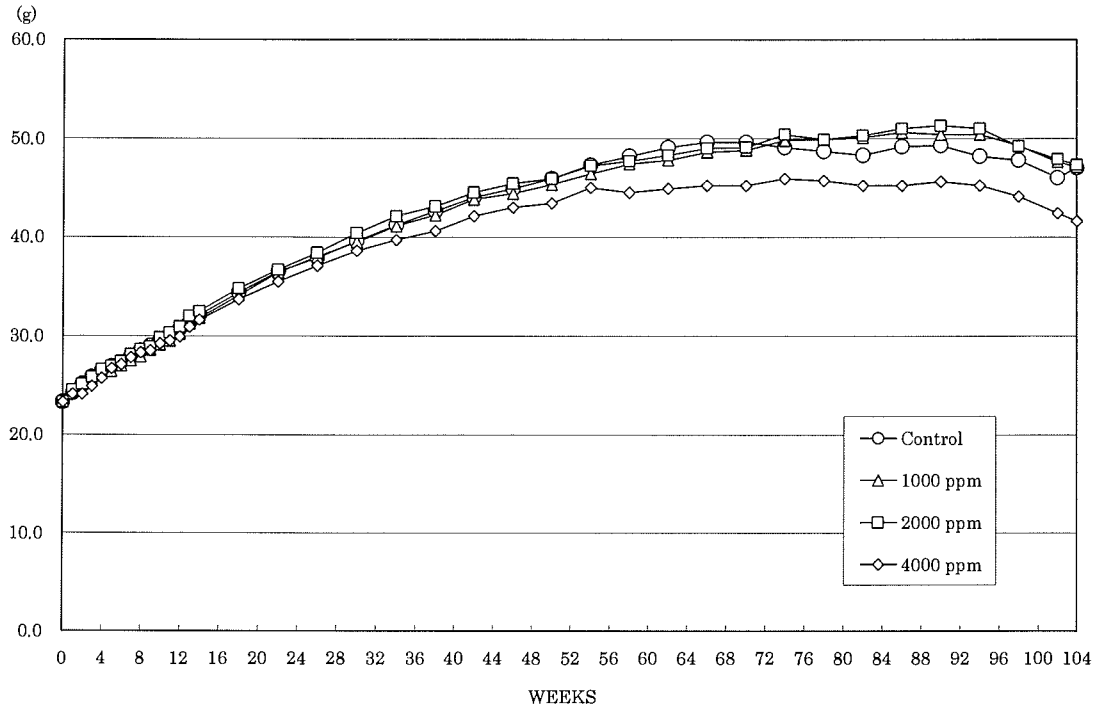


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

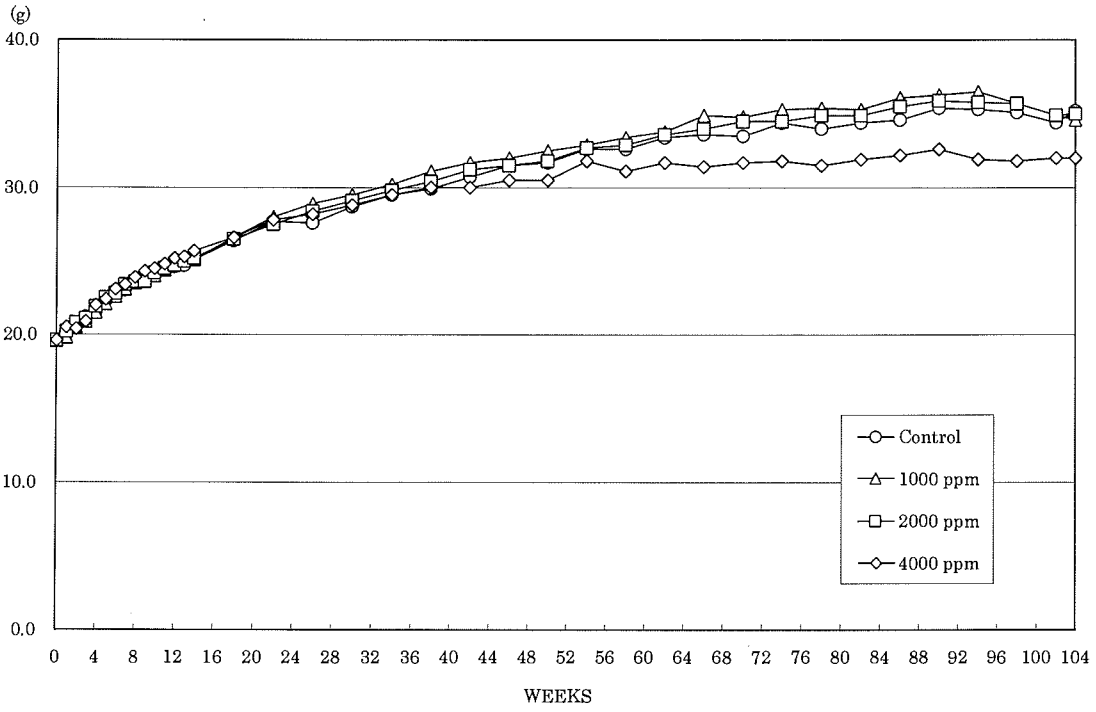


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

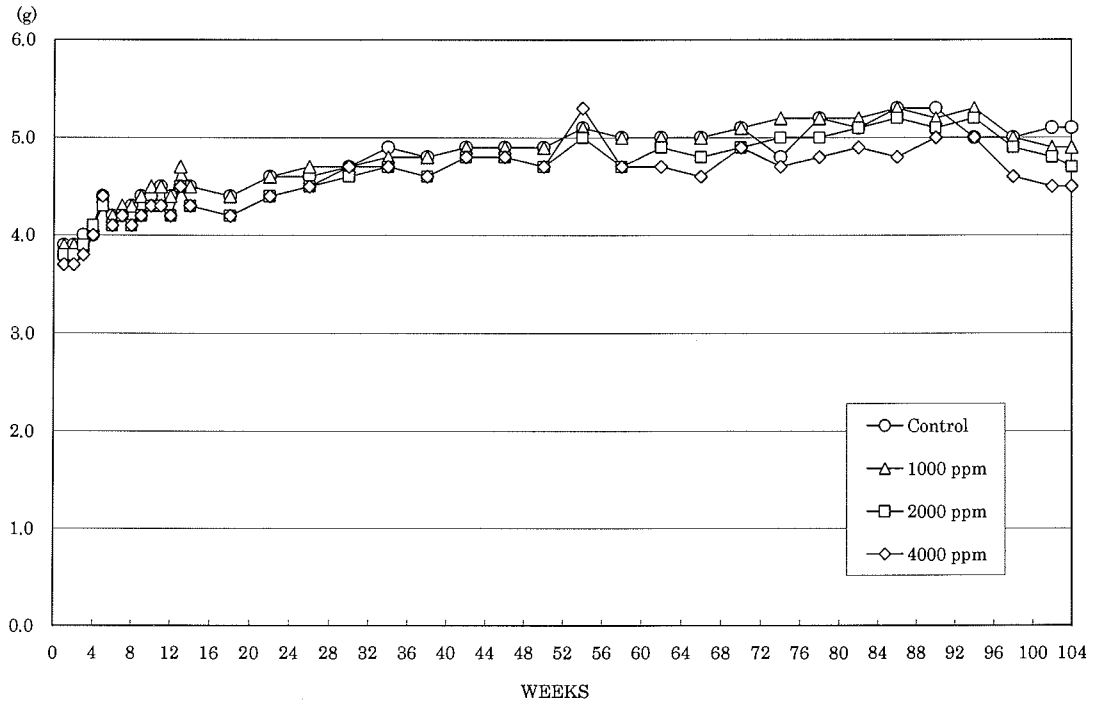


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

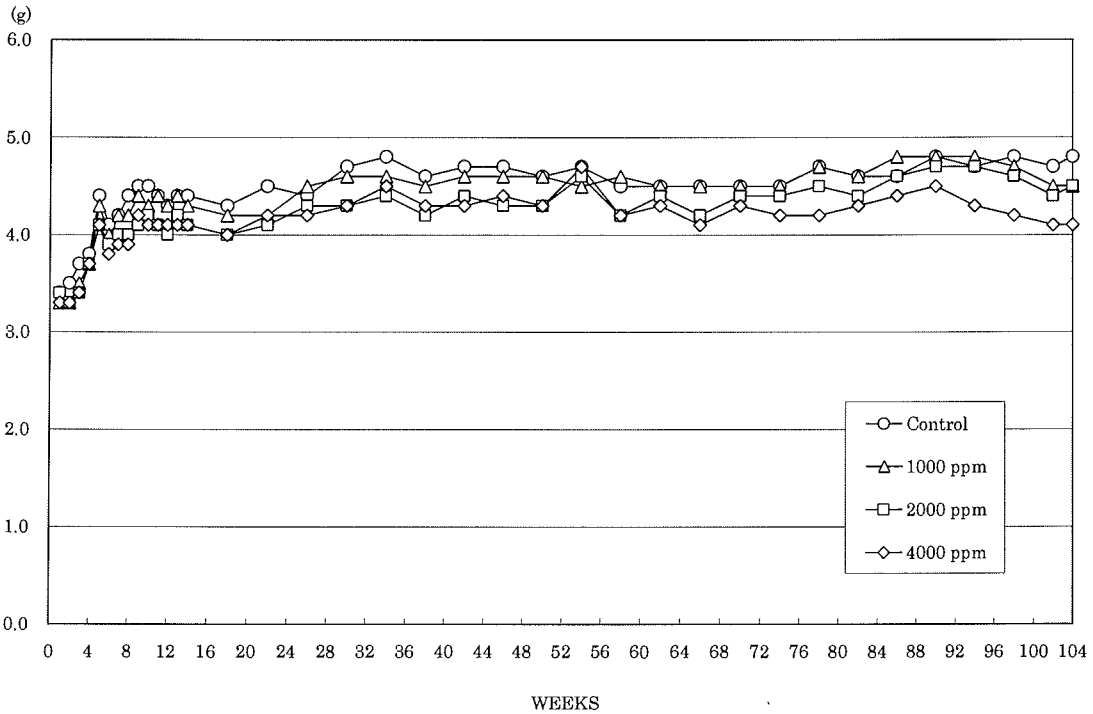
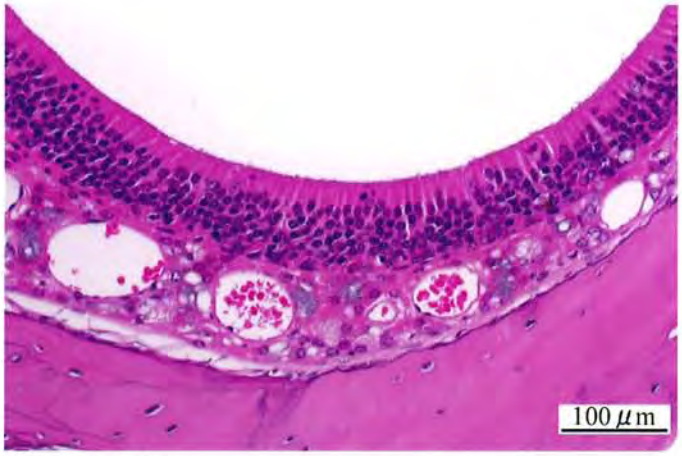
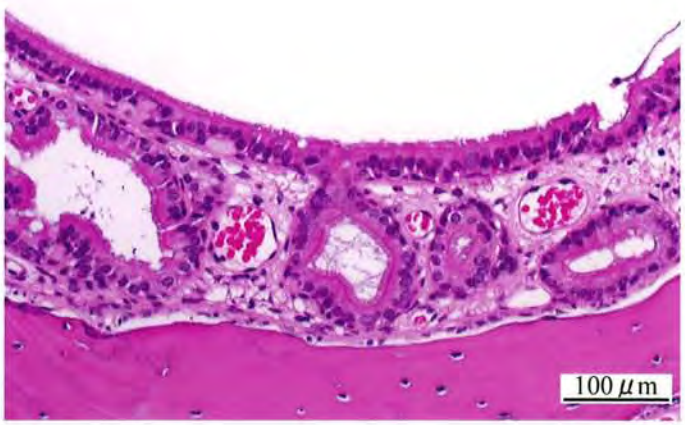


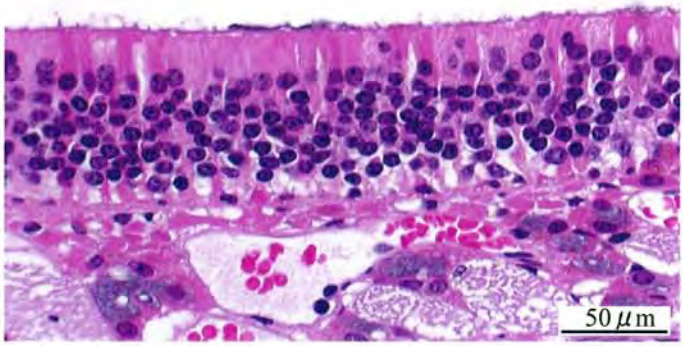
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE



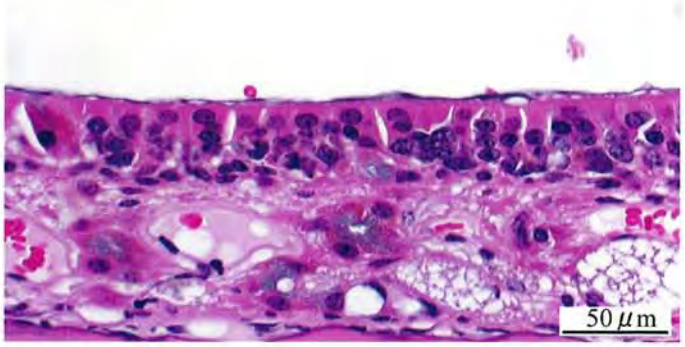
Photograph 1
Nasal cavity: Normal
Mouse, Male, Control, Animal No. 0611-1013 (H&E)



Photograph 2
Nasal cavity: respiratory metaplasia of the olfactory epithelium and submucosal gland
Mouse, Male, 4000 ppm, Animal No. 0611-1327 (H&E)



Photograph 3
Nasal cavity: Normal
Mouse, Male, Control, Animal No. 0611-1002 (H&E)



Photograph 4
Nasal cavity: atrophy of the olfactory epithelium
Mouse, Male, 2000 ppm, Animal No. 0611-1201 (H&E)