Summary of Inhalation Carcinogenicity Study of Acrylic Acid in B6D2F1 Mice

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on March 30, 2011.

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

Summary of Inhalation Carcinogenicity Study of Acrylic Acid in B6D2F1 Mice

Purpose, materials and methods

Acrylic acid (CAS No. 79-10-7) is a colorless liquid with a boiling point of 141°C. It is soluble in alcohol and water.

The carcinogenicity and chronic toxicity of acrylic acid (purity : greater than 99.7%) were examined by inhalation exposure using B6D2F1/Crlj mice. Groups of test animals were exposed to acrylic acid vapors at target concentrations of 0 (clean air), 2, 8 or 32 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 acrylic acid 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 acrylic acid used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by gas chromatography before and after use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 3.7 m^3) were used throughout the 2-year exposure period. Acrylic acid vapor-air mixtures were generated by bubbling clean air through acrylic acid liquid and the mixtures delivered to the inhalation exposure chambers. Air concentrations of the acrylic acid 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. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of acrylic acid induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, 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

Survival rates of the male mice exposed to 32 ppm acrylic acid were increased over the male control. No significant differences in clinical signs were found between any of the groups exposed to acrylic acid and their respective controls. Body weights of the males exposed to 32 ppm acrylic acid were suppressed during the first half of the exposure period; thereafter the body weights became similar to that of concomitant controls. Body weights of all female mice exposed to acrylic acid were similar to that of their concomitant controls throughout the exposure period. The terminal body weights of the 32 ppm-exposed males and females were 102% and 99% of their respective controls. Food consumption exposed to 32 ppm acrylic acid in males was decreased throughout the exposure period, and sporadically decreased in females. Food consumption of males exposed to 8 ppm acrylic acid was decreased after 11th week in males, and till 42nd week in females.

The incidence of adenoma in Harderian gland was increased in male mice exposed to 32 ppm acrylic acid. But the incidence was within the range of maximum incidence of the JBRC historical control data, so the incidence of adenoma in Harderian gland can not be judged to be attributed to the acrylic acid exposure. No acrylic acid related increases in the incidence of neoplastic lesions was found in any of the acrylic acid-exposed groups of either sex compared with their respective controls.

In the non-neoplastic lesions, the effect of acrylic acid was observed in the nasal cavity and in the nasopharynx. In the nasal cavity, respiratory metaplasia in the olfactory epithelium and in the gland, eosinophilic change in the olfactory epithelium and in the respiratory epithelium were increased both in males and females. Additionally, atrophy in the olfactory epithelium in males, and exudate and hyperplasia in the respiratory epithelium were increased in females. In the nasopharynx, the number of animals bearing eosinophilic change was increased in both males and females. In these findings, respiratory metaplasia in the olfactory epithelium and in the gland, eosinophilic change in the olfactory epithelium and in the respiratory epithelium in males, respiratory metaplasia in the olfactory epithelium and in the gland, eosinophilic change in the olfactory epithelium, and eosinophilic change in the nasopharynx in females were observed at the lowest dose 2 ppm acrylic acid exposure group.

Using nasal and nasopharynx lesions as endpoint markers, the lowest-observed-adverse-effect-level (LOAEL) of acrylic acid, was 2 ppm for both male and female mice when exposed by inhalation.

Conclusions

There was no evidence for carcinogenicity of acrylic acid in male or female mice.

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

Dose (ppm)		0	2	8	32	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	4	3	3	4		
liver	hepatocellular adenoma	18	15	14	14		
gall bladder	papillary adenoma	1	0	3	1		
Harderian gland	adenoma	0	2	4	5 *		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	3	5	6	7		
lymph node	malignant lymphoma	6	10	3	9		
liver	hepatocellular carcinoma	17	13	7 *	3 **		↓↓
	hemangiosarcoma	3	0	2	0		
liver	hepatocellular adenoma + hepatocellular carcinoma	29	24	20	16 **		↓
	hemangioma+hemangiosarcoma	5	0 *	3	1		

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

Dose (ppm)		0	2	8	32	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
liver	hepatocellular adenoma	7	2	2	2		
	hemangioma	1	0	3	2		
pituitary	adenoma	10	7	9	11		
ovary	cystadenoma	4	1	2	1		
malignant tumor							
lymph node	malignant lymphoma	19	13	12	18		
liver	hepatocellular carcinoma	2	2	1	2		
	hemangiosarcoma	3	1	0	0		
	histiocytic sarcoma	4	2	1	4		
uterus	histiocytic sarcoma	17	13	12	13		
mammary gland	adenocarcinoma	3	1	1	2		
liver	hepatocellular adenoma + hepatocellular carcinoma	9	4	3	4		
	hemangioma+hemangiosarcoma	4	1	3	2		

Significant difference

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

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TABLE A

CONCENTRATIONS OF ACRYLIC ACID IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

CONCENTRATIONS OF ACRYLIE ACID IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
2 ppm	2.0 ± 0.0
8 ppm	8.0 ± 0.1
32 ppm	32.2 ± 0.2

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0705
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. <50>	2 ppm Av. Wt.	2 ppm % of cont. <50>	2 ppm No. of Surviv.	8 ppm Av. Wt.	8 ppm % of cont. <50>	8 ppm No. of Surviv.	32 ppm Av. Wt.	32 ppm % of cont. <50>	32 ppm No. of Surviv.
1-7	24.9 (50)	50/50	24.7 (50)	99	50/50	24.9 (50)	100	50/50	24.5 (50)	98	50/50
2-7	25.5 (50)	50/50	25.4 (50)	100	50/50	25.9 (50)	102	50/50	25.4 (50)	100	50/50
3-7	26.6 (50)	50/50	25.9 (50)	97	50/50	26.6 (50)	100	50/50	26.1 (50)	98	50/50
4-7	27.5 (50)	50/50	26.8 (50)	97	50/50	27.4 (50)	100	50/50	26.8 (50)	97	50/50
5-7	28.1 (50)	50/50	27.6 (50)	98	50/50	28.2 (50)	100	50/50	27.4 (50)	98	50/50
6-7	28.8 (50)	50/50	28.3 (50)	98	50/50	29.0 (50)	101	50/50	28.1 (50)	98	50/50
7-7	29.6 (50)	50/50	28.9 (50)	98	50/50	29.7 (50)	100	50/50	28.6 (50)	97	50/50
8-7	30.2 (50)	50/50	29.6 (50)	98	50/50	30.4 (50)	101	50/50	29.3 (50)	97	50/50
9-7	30.9 (50)	50/50	30.2 (50)	98	50/50	31.0 (50)	100	50/50	29.9 (50)	97	50/50
10-7	31.6 (50)	50/50	30.9 (50)	98	50/50	31.7 (50)	100	50/50	30.3 (50)	96	50/50
11-7	32.2 (50)	50/50	31.6 (50)	98	50/50	32.4 (50)	101	50/50	30.8 (50)	96	50/50
12-7	32.8 (50)	50/50	32.2 (50)	98	50/50	33.1 (50)	101	50/50	31.5 (50)	96	50/50
13-7	33.8 (50)	50/50	33.1 (50)	98	50/50	33.6 (50)	99	50/50	32.1 (50)	95	50/50
14-7	34.3 (50)	50/50	33.9 (50)	99	50/50	34.3 (50)	100	50/50	32.8 (50)	96	50/50
18-7	37.0 (50)	50/50	36.1 (50)	98	50/50	37.0 (50)	100	50/50	35.2 (50)	95	50/50
22-7	40.0 (50)	50/50	38.9 (50)	97	49/50	39.5 (50)	99	50/50	37.3 (50)	93	50/50
26-7	41.6 (50)	50/50	40.7 (49)	98	49/50	40.9 (50)	98	50/50	38.9 (50)	94	50/50
30-7	43.7 (50)	50/50	42.9 (49)	98	49/50	43.2 (49)	99	49/50	40.7 (50)	93	50/50
34-7	45.2 (50)	50/50	44.4 (49)	98	49/50	44.6 (49)	99	49/50	42.4 (50)	94	50/50
38-7	46.9 (50)	50/50	46.1 (49)	98	49/50	46.0 (49)	98	49/50	43.8 (50)	93	50/50
42-7	48.8 (50)	50/50	47.6 (49)	98	49/50	47.4 (49)	97	49/50	46.0 (50)	94	50/50
46-7	49.7 (49)	49/50	48.2 (49)	97	49/50	48.5 (48)	98	48/50	46.9 (49)	94	49/50
50-7	50.4 (49)	49/50	49.5 (47)	98	47/50	49.3 (48)	98	48/50	47.8 (49)	95	49/50
54-7	50.8 (49)	49/50	49.7 (47)	98	47/50	49.2 (48)	97	48/50	47.8 (49)	94	49/50
58-7	51.3 (49)	49/50	50.5 (47)	98	47/50	50.4 (48)	98	48/50	48.5 (49)	95	49/50
62-7	52.0 (49)	49/50	50.6 (46)	97	46/50	50.5 (48)	97	48/50	49.3 (49)	95	49/50
66-7	53.0 (49)	49/50	51.3 (45)	97	45/50	51.6 (48)	97	48/50	51.0 (48)	96	48/50
70-7	53.1 (49)	49/50	51.9 (45)	98	45/50	52.0 (48)	98	47/50	51.8 (48)	98	48/50
74-7	52.4 (46)	46/50	51.8 (45)	99	45/50	52.4 (47)	100	47/50	52.1 (48)	99	48/50
78-7	52.9 (44)	44/50	51.4 (44)	97	44/50	52.8 (46)	100	46/50	52.4 (48)	99	48/50
82-7	52.9 (43)	43/50	51.5 (42)	97	42/50	53.0 (46)	100	46/50	53.2 (47)	101	47/50
86-7	51.0 (42)	42/50	49.9 (41)	98	40/50	52.5 (46)	103	45/50	53.1 (46)	104	46/50
90-7	51.0 (36)	36/50	49.8 (37)	98	37/50	52.4 (44)	103	44/50	52.5 (46)	103	46/50
94-7	50.1 (33)	33/50	49.0 (34)	98	34/50	50.8 (41)	101	41/50	51.4 (46)	103	46/50
98-7	50.3 (30)	29/50	49.3 (29)	98	29/50	49.7 (39)	99	39/50	50.6 (46)	101	46/50
102-7	48.6 (28)	28/50	46.9 (29)	97	28/50	47.9 (35)	99	35/50	49.3 (45)	101	45/50
104-7	48.6 (27)	26/50	46.0 (28)	95	27/50	47.0 (35)	97	35/50	49.5 (43)	102	43/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0705
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>	2 ppm Av. Wt.	2 ppm % of cont. <50>	2 ppm No. of Surviv.	8 ppm Av. Wt.	8 ppm % of cont. <50>	8 ppm No. of Surviv.	32 ppm Av. Wt.	32 ppm % of cont. <50>	32 ppm No. of Surviv.
1-7	20.4 (50)	50/50	20.3 (50)	100	50/50	20.1 (50)	99	50/50	20.1 (50)	99	50/50
2-7	20.9 (49)	50/50	20.7 (50)	99	50/50	21.1 (50)	101	50/50	20.8 (50)	100	50/50
3-7	21.5 (50)	50/50	21.3 (50)	99	50/50	21.6 (50)	100	50/50	21.4 (50)	100	50/50
4-7	22.2 (50)	50/50	22.0 (50)	99	50/50	22.0 (50)	99	50/50	21.9 (50)	99	50/50
5-7	22.7 (50)	50/50	22.4 (50)	99	50/50	22.5 (50)	99	50/50	22.3 (50)	98	50/50
6-7	23.2 (50)	50/50	22.9 (50)	99	50/50	22.8 (50)	98	50/50	22.8 (50)	98	50/50
7-7	23.6 (50)	50/50	23.3 (50)	99	50/50	23.6 (50)	100	50/50	23.5 (50)	100	50/50
8-7	24.1 (50)	50/50	23.9 (50)	99	50/50	24.0 (50)	100	50/50	23.9 (50)	99	50/50
9-7	24.5 (50)	50/50	24.4 (50)	100	50/50	24.0 (50)	98	50/50	24.4 (50)	100	50/50
10-7	24.6 (50)	50/50	24.4 (50)	99	50/50	24.3 (50)	99	50/50	24.2 (50)	98	50/50
11-7	24.7 (50)	50/50	24.6 (50)	100	50/50	24.4 (50)	99	50/50	24.3 (50)	98	50/50
12-7	25.0 (50)	50/50	24.7 (50)	99	50/50	25.1 (50)	100	50/50	25.1 (50)	100	50/50
13-7	25.5 (50)	50/50	25.2 (50)	99	50/50	25.1 (50)	98	50/50	25.1 (50)	98	50/50
14-7	25.7 (50)	50/50	25.4 (50)	99	50/50	25.2 (50)	98	50/50	25.4 (50)	99	50/50
18-7	27.2 (50)	50/50	26.7 (50)	98	50/50	27.0 (50)	99	50/50	26.6 (50)	98	50/50
22-7	29.2 (50)	50/50	28.7 (50)	98	50/50	27.9 (50)	96	50/50	27.9 (50)	96	50/50
26-7	29.1 (50)	50/50	28.5 (50)	98	50/50	28.3 (50)	97	50/50	28.5 (50)	98	50/50
30-7	30.3 (50)	50/50	29.5 (50)	97	50/50	29.2 (50)	96	50/50	29.2 (50)	96	50/50
34-7	31.6 (50)	50/50	30.6 (50)	97	50/50	30.6 (50)	97	50/50	30.6 (50)	97	50/50
38-7	33.0 (50)	50/50	31.5 (49)	95	49/50	31.3 (50)	95	50/50	31.0 (50)	94	50/50
42-7	34.1 (50)	50/50	32.8 (49)	96	49/50	32.5 (50)	95	50/50	32.3 (50)	95	50/50
46-7	34.7 (50)	50/50	33.4 (49)	96	49/50	33.3 (50)	96	50/50	33.2 (50)	96	50/50
50-7	35.2 (50)	50/50	33.8 (47)	96	47/50	34.2 (50)	97	50/50	33.9 (50)	96	50/50
54-7	34.9 (50)	50/50	33.9 (47)	97	47/50	33.7 (50)	97	50/50	33.6 (50)	96	50/50
58-7	35.3 (50)	50/50	34.5 (47)	98	47/50	35.2 (50)	100	50/50	33.8 (50)	96	50/50
62-7	35.5 (50)	50/50	34.5 (47)	97	47/50	35.0 (49)	99	49/50	34.5 (50)	97	50/50
66-7	37.6 (50)	50/50	36.1 (47)	96	47/50	36.9 (49)	98	49/50	36.2 (49)	96	49/50
70-7	37.3 (48)	48/50	36.5 (46)	98	46/50	37.6 (46)	101	46/50	36.4 (47)	98	47/50
74-7	37.8 (47)	47/50	36.9 (46)	98	46/50	37.4 (46)	99	46/50	36.9 (45)	98	45/50
78-7	37.9 (46)	45/50	37.5 (44)	99	43/50	38.0 (44)	100	44/50	37.4 (44)	99	44/50
82-7	39.0 (41)	41/50	37.4 (42)	96	42/50	38.6 (42)	99	42/50	37.3 (41)	96	41/50
86-7	38.7 (40)	40/50	37.3 (41)	96	41/50	38.1 (37)	98	37/50	35.9 (38)	93	38/50
90-7	39.0 (37)	37/50	37.6 (38)	96	38/50	38.3 (36)	98	36/50	36.2 (38)	93	38/50
94-7	37.0 (34)	34/50	37.5 (36)	101	36/50	38.0 (34)	103	34/50	36.7 (33)	99	33/50
98-7	37.1 (28)	28/50	37.3 (34)	101	34/50	37.6 (31)	101	31/50	36.4 (33)	98	31/50
102-7	37.0 (22)	22/50	37.8 (29)	102	29/50	38.5 (30)	104	30/50	35.8 (30)	97	30/50
104-7	36.4 (20)	19/50	37.6 (28)	103	28/50	37.4 (27)	103	27/50	36.2 (30)	99	30/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0705
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 1-7	2-7	3-7	4-7	5-7	6-7	7-7
Control	24.9± 1.0	25.5± 1.3	26.6± 1.5	27.5± 1.5	28.1± 1.7	28.8± 1.8	29.6± 2.0
2 ppm	24.7± 1.0	25.4± 1.2	25.9± 1.5*	26.8± 1.4*	27.6± 1.4	28.3± 1.6	28.9± 1.7
8 ppm	24.9± 1.0	25.9± 1.5	26.6± 1.7	27.4± 1.9	28.2± 2.1	29.0± 2.3	29.7± 2.5
32 ppm	24.5± 1.0	25.4± 1.2	26.1± 1.2	26.8± 1.3*	27.4± 1.3*	28.1± 1.5	28.6± 1.5*

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

(HAN260)

BAIS 4

STUDY NO. : 0705
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 8-7	9-7	10-7	11-7	12-7	13-7	14-7
Control	30.2± 2.2	30.9± 2.3	31.6± 2.5	32.2± 2.7	32.8± 2.7	33.8± 2.7	34.3± 3.0
2 ppm	29.6± 1.9	30.2± 1.9	30.9± 2.0	31.6± 2.1	32.2± 2.2	33.1± 2.3	33.9± 2.4
8 ppm	30.4± 2.5	31.0± 2.8	31.7± 2.9	32.4± 2.8	33.1± 2.9	33.6± 3.0	34.3± 3.2
32 ppm	29.3± 1.6	29.9± 1.7*	30.3± 1.7*	30.8± 1.8*	31.5± 1.8*	32.1± 1.9**	32.8± 2.0*

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

(HAN260)

BAIS 4

STUDY NO. : 0705
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 18-7	22-7	26-7	30-7	34-7	38-7	42-7
Control	37.0± 3.5	40.0± 4.1	41.6± 4.5	43.7± 4.7	45.2± 4.7	46.9± 4.7	48.8± 4.7
2 ppm	36.1± 2.9	38.9± 3.3	40.7± 3.7	42.9± 4.1	44.4± 4.1	46.1± 4.1	47.6± 4.7
8 ppm	37.0± 3.8	39.5± 4.0	40.9± 4.4	43.2± 4.3	44.6± 4.3	46.0± 4.2	47.4± 4.3
32 ppm	35.2± 2.2*	37.3± 2.4**	38.9± 2.9**	40.7± 3.5**	42.4± 3.7**	43.8± 3.7**	46.0± 3.7**

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

(HAN260)

BAIS 4

STUDY NO. : 0705
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 46-7	50-7	54-7	58-7	62-7	66-7	70-7
Control	49.7± 4.1	50.4± 4.1	50.8± 4.0	51.3± 4.4	52.0± 4.3	53.0± 4.4	53.1± 5.4
2 ppm	48.2± 5.5	49.5± 4.1	49.7± 4.1	50.5± 4.2	50.6± 4.7	51.3± 5.4	51.9± 5.5
8 ppm	48.5± 4.0	49.3± 3.7	49.2± 3.7	50.4± 3.7	50.5± 3.7	51.6± 3.7	52.0± 4.7
32 ppm	46.9± 3.6**	47.8± 3.6**	47.8± 3.5**	48.5± 3.7**	49.3± 3.7**	51.0± 3.4	51.8± 3.5

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

STUDY NO. : 0705
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 74-7	78-7	82-7	86-7	90-7	94-7	98-7
Control	52.4± 6.6	52.9± 6.8	52.9± 7.6	51.0± 8.9	51.0± 8.7	50.1± 8.9	50.3± 8.1
2 ppm	51.8± 6.0	51.4± 6.3	51.5± 7.0	49.9± 8.2	49.8± 8.4	49.0± 7.8	49.3± 8.1
8 ppm	52.4± 4.1	52.8± 4.6	53.0± 5.9	52.5± 6.7	52.4± 5.2	50.8± 5.6	49.7± 6.1
32 ppm	52.1± 3.6	52.4± 3.6	53.2± 4.0	53.1± 4.3	52.5± 5.0	51.4± 5.5	50.6± 6.0

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

(HAN260)

STUDY NO. : 0705
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 102-7	104-7
Control	48.6± 9.1	48.6± 9.7
2 ppm	46.9± 8.8	46.0± 9.3
8 ppm	47.9± 6.9	47.0± 6.8
32 ppm	49.3± 6.5	49.5± 6.2

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

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0705
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 1-7	2-7	3-7	4-7	5-7	6-7	7-7
Control	20.4± 0.9	20.9± 1.0	21.5± 0.9	22.2± 1.1	22.7± 1.1	23.2± 1.1	23.6± 1.1
2 ppm	20.3± 0.8	20.7± 0.9	21.3± 0.9	22.0± 0.9	22.4± 1.2	22.9± 1.2	23.3± 1.2
8 ppm	20.1± 1.0	21.1± 0.9	21.6± 1.0	22.0± 1.0	22.5± 1.0	22.8± 1.1	23.6± 1.0
32 ppm	20.1± 0.9	20.8± 0.9	21.4± 1.0	21.9± 1.0	22.3± 1.0	22.8± 1.2	23.5± 1.2

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

STUDY NO. : 0705
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 8-7	9-7	10-7	11-7	12-7	13-7	14-7
Control	24.1± 1.5	24.5± 1.6	24.6± 1.5	24.7± 1.4	25.0± 1.6	25.5± 1.8	25.7± 1.9
2 ppm	23.9± 1.2	24.4± 1.5	24.4± 1.3	24.6± 1.4	24.7± 1.2	25.2± 1.6	25.4± 1.5
8 ppm	24.0± 1.1	24.0± 1.5	24.3± 1.4	24.4± 1.4	25.1± 1.6	25.1± 1.8	25.2± 1.5
32 ppm	23.9± 1.3	24.4± 1.5	24.2± 1.5	24.3± 1.3	25.1± 1.6	25.1± 1.5	25.4± 1.9

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

STUDY NO. : 0705
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 18-7	22-7	26-7	30-7	34-7	38-7	42-7
Control	27.2± 2.2	29.2± 3.0	29.1± 3.5	30.3± 3.7	31.6± 4.4	33.0± 5.1	34.1± 5.0
2 ppm	26.7± 1.7	28.7± 2.2	28.5± 2.3	29.5± 2.5	30.6± 2.7	31.5± 2.4	32.8± 3.4
8 ppm	27.0± 1.9	27.9± 2.1*	28.3± 2.8	29.2± 2.8	30.6± 2.9	31.3± 3.4	32.5± 4.0
32 ppm	26.6± 1.9	27.9± 2.2	28.5± 2.7	29.2± 2.9	30.6± 3.6	31.0± 3.8*	32.3± 3.9

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

STUDY NO. : 0705
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 46-7	50-7	54-7	58-7	62-7	66-7	70-7
Control	34.7± 5.2	35.2± 5.8	34.9± 5.4	35.3± 5.7	35.5± 6.0	37.6± 5.4	37.3± 6.2
2 ppm	33.4± 3.8	33.8± 3.5	33.9± 4.0	34.5± 3.5	34.5± 3.7	36.1± 4.3	36.5± 4.7
8 ppm	33.3± 4.3	34.2± 4.2	33.7± 4.2	35.2± 4.4	35.0± 4.6	36.9± 5.4	37.6± 4.8
32 ppm	33.2± 4.5	33.9± 4.6	33.6± 4.7	33.8± 4.6	34.5± 4.9	36.2± 5.0	36.4± 5.9

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

(HAN260)

STUDY NO. : 0705
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 74-7	78-7	82-7	86-7	90-7	94-7	98-7
Control	37.8± 6.0	37.9± 5.9	39.0± 5.7	38.7± 5.7	39.0± 6.1	37.0± 5.7	37.1± 6.2
2 ppm	36.9± 4.9	37.5± 6.2	37.4± 4.9	37.3± 4.9	37.6± 5.2	37.5± 5.4	37.3± 5.9
8 ppm	37.4± 5.5	38.0± 5.3	38.6± 4.8	38.1± 5.2	38.3± 5.2	38.0± 5.2	37.6± 4.5
32 ppm	36.9± 5.4	37.4± 5.4	37.3± 5.3	35.9± 4.9	36.2± 4.8	36.7± 4.2	36.4± 4.3

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

STUDY NO. : 0705
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 102-7	104-7
Control	37.0± 8.1	36.4± 7.6
2 ppm	37.8± 5.3	37.6± 4.9
8 ppm	38.5± 5.0	37.4± 4.0
32 ppm	35.8± 3.4	36.2± 3.5

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

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0705
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. <50>	2 ppm Av. FC.	2 ppm % of cont. <50>	2 ppm No. of Surviv.	8 ppm Av. FC.	8 ppm % of cont. <50>	8 ppm No. of Surviv.	32 ppm Av. FC.	32 ppm % of cont. <50>	32 ppm No. of Surviv.
1-7	3.8 (50)	50/50	3.7 (50)	97	50/50	3.6 (50)	95	50/50	3.7 (50)	97	50/50
2-7	3.8 (50)	50/50	3.7 (50)	97	50/50	3.8 (50)	100	50/50	3.8 (50)	100	50/50
3-7	4.0 (50)	50/50	3.8 (50)	95	50/50	3.8 (50)	95	50/50	3.8 (50)	95	50/50
4-7	4.1 (50)	50/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50	3.9 (50)	95	50/50
5-7	4.0 (50)	50/50	4.1 (50)	103	50/50	4.0 (50)	100	50/50	3.9 (50)	98	50/50
6-7	4.2 (50)	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
7-7	4.2 (50)	50/50	4.1 (50)	98	50/50	4.0 (50)	95	50/50	4.0 (50)	95	50/50
8-7	4.2 (50)	50/50	4.2 (50)	100	50/50	4.2 (50)	100	50/50	4.1 (50)	98	50/50
9-7	4.2 (50)	50/50	4.3 (50)	102	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
10-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.3 (50)	100	50/50	4.2 (50)	98	50/50
11-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.3 (50)	100	50/50	4.2 (50)	98	50/50
12-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.3 (50)	96	50/50	4.3 (50)	96	50/50
13-7	4.4 (50)	50/50	4.3 (50)	98	50/50	4.3 (50)	98	50/50	4.3 (50)	98	50/50
14-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.3 (50)	96	50/50	4.3 (50)	96	50/50
18-7	4.6 (50)	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50	4.5 (50)	98	50/50
22-7	4.7 (50)	50/50	4.6 (50)	98	49/50	4.5 (50)	96	50/50	4.5 (50)	96	50/50
26-7	4.7 (50)	50/50	4.6 (49)	98	49/50	4.4 (50)	94	50/50	4.4 (50)	94	50/50
30-7	4.8 (50)	50/50	4.7 (49)	98	49/50	4.7 (49)	98	49/50	4.6 (50)	96	50/50
34-7	5.0 (50)	50/50	4.9 (49)	98	49/50	4.9 (49)	98	49/50	4.9 (50)	98	50/50
38-7	5.0 (50)	50/50	4.9 (49)	98	49/50	4.8 (49)	96	49/50	4.8 (50)	96	50/50
42-7	5.0 (50)	50/50	4.8 (49)	96	49/50	4.8 (49)	96	49/50	4.8 (50)	96	50/50
46-7	5.0 (49)	49/50	4.9 (49)	98	49/50	4.9 (48)	98	48/50	4.9 (49)	98	49/50
50-7	5.0 (48)	49/50	4.9 (47)	98	47/50	4.9 (48)	98	48/50	4.9 (49)	98	49/50
54-7	5.0 (49)	49/50	4.9 (47)	98	47/50	4.9 (48)	98	48/50	4.8 (49)	96	49/50
58-7	5.0 (49)	49/50	5.1 (47)	102	47/50	5.0 (48)	100	48/50	4.9 (49)	98	49/50
62-7	5.2 (49)	49/50	5.1 (46)	98	46/50	5.1 (48)	98	48/50	5.2 (49)	100	49/50
66-7	5.2 (49)	49/50	5.2 (45)	100	45/50	5.2 (48)	100	48/50	5.1 (49)	98	48/50
70-7	5.3 (49)	49/50	5.3 (44)	100	45/50	5.2 (48)	98	47/50	5.1 (48)	96	48/50
74-7	5.3 (48)	46/50	5.4 (45)	102	45/50	5.2 (47)	98	47/50	5.2 (48)	98	48/50
78-7	5.5 (45)	44/50	5.3 (44)	96	44/50	5.2 (46)	95	46/50	5.3 (48)	96	48/50
82-7	5.9 (43)	43/50	5.4 (43)	92	42/50	5.3 (46)	90	46/50	5.3 (48)	90	47/50
86-7	5.4 (43)	42/50	5.2 (41)	96	40/50	5.2 (46)	96	45/50	5.2 (46)	96	46/50
90-7	5.3 (37)	36/50	5.0 (38)	94	37/50	4.9 (44)	92	44/50	5.1 (46)	96	46/50
94-7	5.0 (35)	33/50	5.1 (35)	102	34/50	4.7 (44)	94	41/50	5.2 (46)	104	46/50
98-7	5.3 (30)	29/50	5.0 (30)	94	29/50	4.8 (41)	91	39/50	4.9 (46)	92	46/50
102-7	5.4 (29)	28/50	4.9 (29)	91	28/50	4.9 (35)	91	35/50	5.0 (45)	93	45/50
104-7	5.4 (28)	26/50	5.0 (28)	93	27/50	5.0 (35)	93	35/50	5.0 (44)	93	43/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0705
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>	2 ppm Av. FC.	2 ppm % of cont. <50>	2 ppm No. of Surviv.	8 ppm Av. FC.	8 ppm % of cont. <50>	8 ppm No. of Surviv.	32 ppm Av. FC.	32 ppm % of cont. <50>	32 ppm No. of Surviv.
1-7	3.2 (50)	50/50	3.3 (50)	103	50/50	3.1 (50)	97	50/50	3.2 (50)	100	50/50
2-7	3.3 (50)	50/50	3.3 (50)	100	50/50	3.3 (50)	100	50/50	3.4 (50)	103	50/50
3-7	3.6 (50)	50/50	3.5 (50)	97	50/50	3.4 (50)	94	50/50	3.5 (50)	97	50/50
4-7	3.7 (50)	50/50	3.6 (50)	97	50/50	3.5 (50)	95	50/50	3.6 (50)	97	50/50
5-7	3.8 (50)	50/50	3.7 (50)	97	50/50	3.6 (50)	95	50/50	3.7 (50)	97	50/50
6-7	3.9 (50)	50/50	3.9 (50)	100	50/50	3.7 (50)	95	50/50	3.8 (50)	97	50/50
7-7	3.9 (50)	50/50	4.0 (50)	103	50/50	3.8 (50)	97	50/50	3.9 (50)	100	50/50
8-7	4.0 (50)	50/50	4.0 (50)	100	50/50	3.9 (50)	98	50/50	4.0 (50)	100	50/50
9-7	4.1 (50)	50/50	4.2 (50)	102	50/50	3.9 (50)	95	50/50	4.0 (50)	98	50/50
10-7	4.1 (50)	50/50	4.1 (50)	100	50/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50
11-7	4.1 (50)	50/50	4.1 (50)	100	50/50	3.9 (50)	95	50/50	4.0 (50)	98	50/50
12-7	4.2 (50)	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50	4.1 (50)	98	50/50
13-7	4.1 (50)	50/50	4.0 (50)	98	50/50	4.0 (50)	98	50/50	4.1 (50)	100	50/50
14-7	4.2 (50)	50/50	4.1 (50)	98	50/50	3.9 (50)	93	50/50	4.0 (50)	95	50/50
18-7	4.2 (50)	50/50	4.2 (50)	100	50/50	4.2 (50)	100	50/50	4.2 (50)	100	50/50
22-7	4.5 (50)	50/50	4.5 (50)	100	50/50	4.1 (50)	91	50/50	4.2 (50)	93	50/50
26-7	4.3 (50)	50/50	4.1 (50)	95	50/50	4.1 (50)	95	50/50	4.2 (50)	98	50/50
30-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.3 (50)	96	50/50	4.4 (50)	98	50/50
34-7	4.8 (50)	50/50	4.5 (50)	94	50/50	4.6 (50)	96	50/50	4.6 (50)	96	50/50
38-7	5.0 (50)	50/50	4.5 (49)	90	49/50	4.5 (50)	90	50/50	4.6 (50)	92	50/50
42-7	4.8 (50)	50/50	4.5 (49)	94	49/50	4.4 (50)	92	50/50	4.5 (50)	94	50/50
46-7	4.6 (50)	50/50	4.4 (49)	96	49/50	4.5 (50)	98	50/50	4.7 (50)	102	50/50
50-7	4.5 (50)	50/50	4.4 (48)	98	47/50	4.4 (50)	98	50/50	4.6 (50)	102	50/50
54-7	4.5 (50)	50/50	4.4 (47)	98	47/50	4.3 (50)	96	50/50	4.5 (50)	100	50/50
58-7	4.5 (50)	50/50	4.6 (47)	102	47/50	4.6 (50)	102	50/50	4.4 (50)	98	50/50
62-7	4.6 (50)	50/50	4.6 (47)	100	47/50	4.5 (49)	98	49/50	4.5 (50)	98	50/50
66-7	5.0 (50)	50/50	4.8 (47)	96	47/50	4.8 (49)	96	49/50	5.0 (49)	100	49/50
70-7	4.8 (49)	48/50	5.0 (46)	104	46/50	4.7 (47)	98	46/50	4.7 (48)	98	47/50
74-7	4.8 (47)	47/50	4.8 (46)	100	46/50	4.7 (46)	98	46/50	4.8 (46)	100	45/50
78-7	4.9 (45)	45/50	4.9 (44)	100	43/50	4.8 (44)	98	44/50	5.1 (43)	104	44/50
82-7	5.0 (44)	41/50	5.0 (42)	100	42/50	5.0 (43)	100	42/50	5.1 (41)	102	41/50
86-7	4.9 (40)	40/50	4.7 (42)	96	41/50	4.8 (38)	98	37/50	4.4 (39)	90	38/50
90-7	4.7 (38)	37/50	4.6 (38)	98	38/50	4.5 (36)	96	36/50	4.5 (38)	96	38/50
94-7	4.6 (34)	34/50	4.8 (36)	104	36/50	4.5 (35)	98	34/50	4.8 (33)	104	33/50
98-7	4.6 (30)	28/50	4.5 (34)	98	34/50	4.7 (31)	102	31/50	4.5 (33)	98	31/50
102-7	4.9 (22)	22/50	4.7 (29)	96	29/50	4.7 (31)	96	30/50	4.6 (30)	94	30/50
104-7	4.8 (21)	19/50	4.9 (28)	102	28/50	4.4 (28)	92	27/50	4.8 (30)	100	30/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0705
ANIMAL : MOUSE BGD2F1/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	3.8± 0.3	3.8± 0.4	4.0± 0.4	4.1± 0.3	4.0± 0.3	4.2± 0.3	4.2± 0.3
2 ppm	3.7± 0.3	3.7± 0.3	3.8± 0.3	4.0± 0.6	4.1± 0.3	4.1± 0.4	4.1± 0.3
8 ppm	3.6± 0.3	3.8± 0.2	3.8± 0.3	4.0± 0.3	4.0± 0.3	4.1± 0.4	4.0± 0.4
32 ppm	3.7± 0.4	3.8± 0.3	3.8± 0.3*	3.9± 0.3*	3.9± 0.3*	4.1± 0.3	4.0± 0.3

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

STUDY NO. : 0705
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	4.2± 0.4	4.2± 0.3	4.3± 0.3	4.3± 0.3	4.5± 0.3	4.4± 0.3	4.5± 0.3
2 ppm	4.2± 0.3	4.3± 0.4	4.3± 0.4	4.3± 0.3	4.4± 0.4	4.3± 0.3	4.4± 0.4
8 ppm	4.2± 0.3	4.1± 0.4	4.3± 0.4	4.3± 0.3	4.3± 0.3*	4.3± 0.4	4.3± 0.4*
32 ppm	4.1± 0.3	4.1± 0.3*	4.2± 0.3	4.2± 0.3	4.3± 0.3*	4.3± 0.3	4.3± 0.3*

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

STUDY NO. : 0705
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	4.6± 0.3	4.7± 0.4	4.7± 0.3	4.8± 0.4	5.0± 0.3	5.0± 0.4	5.0± 0.5
2 ppm	4.5± 0.3	4.6± 0.3	4.6± 0.3	4.7± 0.3	4.9± 0.4	4.9± 0.3	4.8± 0.7
8 ppm	4.5± 0.3	4.5± 0.3*	4.4± 0.4**	4.7± 0.3	4.9± 0.3*	4.8± 0.3**	4.8± 0.6*
32 ppm	4.5± 0.3	4.5± 0.3*	4.4± 0.3**	4.6± 0.3*	4.9± 0.3*	4.8± 0.3**	4.8± 0.3*

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

STUDY NO. : 0705
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	5.0± 0.3	5.0± 0.3	5.0± 0.3	5.0± 0.3	5.2± 0.3	5.2± 0.4	5.3± 0.4
2 ppm	4.9± 0.5	4.9± 0.3	4.9± 0.3	5.1± 0.4	5.1± 0.3	5.2± 0.4	5.3± 0.4
8 ppm	4.9± 0.4	4.9± 0.3	4.9± 0.3	5.0± 0.4	5.1± 0.3	5.2± 0.5	5.2± 0.6**
32 ppm	4.9± 0.3	4.9± 0.3	4.8± 0.3**	4.9± 0.3	5.2± 0.4	5.1± 0.4	5.1± 0.3**

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

STUDY NO. : 0705
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	5.3± 0.7	5.5± 0.7	5.9± 0.9	5.4± 1.3	5.3± 0.7	5.0± 1.0	5.3± 0.6
2 ppm	5.4± 0.4	5.3± 0.6	5.4± 0.7*	5.2± 0.7	5.0± 0.7*	5.1± 0.6	5.0± 1.1
8 ppm	5.2± 0.4	5.2± 0.4*	5.3± 0.5**	5.2± 0.3	4.9± 0.4**	4.7± 1.2*	4.8± 1.0**
32 ppm	5.2± 0.3	5.3± 0.4*	5.3± 0.8**	5.2± 0.4	5.1± 0.4	5.2± 0.4	4.9± 0.7**

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

STUDY NO. : 0705
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	5.4± 0.6	5.4± 1.0
2 ppm	4.9± 1.1*	5.0± 1.0
8 ppm	4.9± 0.7**	5.0± 0.8
32 ppm	5.0± 0.7*	5.0± 1.0

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

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0705
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	3.2± 0.3	3.3± 0.3	3.6± 0.3	3.7± 0.3	3.8± 0.3	3.9± 0.3	3.9± 0.3
2 ppm	3.3± 0.3	3.3± 0.2	3.5± 0.2	3.6± 0.2	3.7± 0.2	3.9± 0.3	4.0± 0.3
8 ppm	3.1± 0.3	3.3± 0.2	3.4± 0.2**	3.5± 0.3	3.6± 0.3**	3.7± 0.3**	3.8± 0.3
32 ppm	3.2± 0.2	3.4± 0.2	3.5± 0.2*	3.6± 0.2	3.7± 0.2	3.8± 0.2	3.9± 0.3

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

(HAN260)

STUDY NO. : 0705
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	4.0± 0.3	4.1± 0.3	4.1± 0.3	4.1± 0.4	4.2± 0.3	4.1± 0.4	4.2± 0.4
2 ppm	4.0± 0.3	4.2± 0.4	4.1± 0.3	4.1± 0.4	4.1± 0.3	4.0± 0.3	4.1± 0.3
8 ppm	3.9± 0.3	3.9± 0.4**	4.0± 0.3	3.9± 0.3*	4.1± 0.3	4.0± 0.6	3.9± 0.3**
32 ppm	4.0± 0.3	4.0± 0.3	4.0± 0.3	4.0± 0.3	4.1± 0.3	4.1± 0.3	4.0± 0.3**

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

(HAN260)

BAIS 4

STUDY NO. : 0705
ANIMAL : MOUSE BGD2F1/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	4.2± 0.4	4.5± 0.5	4.3± 0.5	4.5± 0.5	4.8± 0.6	5.0± 0.7	4.8± 0.5
2 ppm	4.2± 0.4	4.5± 0.4	4.1± 0.5*	4.4± 0.6	4.5± 0.6	4.5± 0.5**	4.5± 0.5
8 ppm	4.2± 0.4	4.1± 0.4**	4.1± 0.5*	4.3± 0.4	4.6± 0.4	4.5± 0.5**	4.4± 0.5**
32 ppm	4.2± 0.5	4.2± 0.4**	4.2± 0.5	4.4± 0.5	4.6± 0.5	4.6± 0.5	4.5± 0.7*

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

(HAN260)

BAIS 4

STUDY NO. : 0705
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	4.6± 0.5	4.5± 0.6	4.5± 0.5	4.5± 0.6	4.6± 0.6	5.0± 0.6	4.8± 0.9
2 ppm	4.4± 0.6	4.4± 0.7	4.4± 0.6	4.6± 0.4	4.6± 0.5	4.8± 0.7	5.0± 1.1
8 ppm	4.5± 0.6	4.4± 0.6	4.3± 0.5	4.6± 0.6	4.5± 0.7	4.8± 0.9	4.7± 0.8
32 ppm	4.7± 0.5	4.6± 0.6	4.5± 0.5	4.4± 0.5	4.5± 0.6	5.0± 0.6	4.7± 0.6

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

STUDY NO. : 0705
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	4.8± 0.9	4.9± 1.0	5.0± 1.2	4.9± 1.1	4.7± 0.7	4.6± 0.7	4.6± 1.1
2 ppm	4.8± 0.7	4.9± 0.8	5.0± 0.7	4.7± 0.8	4.6± 0.8	4.8± 0.7	4.5± 0.8
8 ppm	4.7± 0.8	4.8± 0.8	5.0± 1.4	4.8± 0.8	4.5± 0.6	4.5± 0.8	4.7± 0.8
32 ppm	4.8± 1.1	5.1± 0.7	5.1± 0.7	4.4± 0.8*	4.5± 1.0	4.8± 0.4	4.5± 0.8

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

(HAN260)

BAIS 4

STUDY NO. : 0705
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	4.9± 0.7	4.8± 1.1
2 ppm	4.7± 0.7	4.9± 1.0
8 ppm	4.7± 1.1	4.4± 0.8
32 ppm	4.6± 0.8	4.8± 0.5

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

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0705
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	25	9.93± 1.84	14.1± 2.3	44.9± 7.0	45.7± 3.8	14.3± 0.7	31.4± 1.4	1686± 424
2 ppm	26	9.95± 1.90	13.7± 2.0	43.9± 5.7	44.6± 3.1	13.9± 0.9	31.3± 1.0	1662± 432
8 ppm	33	9.75± 1.24	13.8± 1.5	43.7± 4.1	45.1± 3.0	14.2± 0.6	31.5± 1.1	1743± 250
32 ppm	43	9.22± 1.68	13.1± 2.3	42.0± 6.4	46.0± 3.2	14.3± 0.5	31.2± 1.5	1660± 348

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

(HCL070)

STUDY NO. : 0705
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	25	3.3±	3.7
2 ppm	26	3.3±	3.2
8 ppm	33	2.4±	0.8
32 ppm	43	3.1±	3.3

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

(HCL070)

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	25	4.92±	2.84	36±	18	58±	19	3±	2	2±	1	0±	0	1±	1
2 ppm	26	7.27±	8.73	36±	17	58±	16	3±	1	2±	2	0±	0	1±	0
8 ppm	33	4.43±	1.66	34±	17	60±	17	3±	2	2±	1	0±	0	1±	1
32 ppm	43	9.92±	38.68	32±	17	61±	18	3±	4	3±	2	0±	1	1±	1

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

(HCL070)

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0705
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	19	8.85± 1.25	13.0± 1.4	41.8± 3.5	47.7± 4.0	14.8± 0.9	31.1± 1.2	897± 389
2 ppm	26	9.18± 1.65	13.3± 2.3	42.0± 6.2	46.2± 2.8	14.5± 0.4	31.4± 1.4	1123± 269
8 ppm	23	9.46± 1.53	13.7± 1.9	43.3± 4.6	46.5± 5.0	14.6± 0.8	31.5± 1.7	1080± 325
32 ppm	30	9.44± 1.10	13.7± 1.6	43.3± 4.4	46.1± 4.5	14.6± 0.9	31.7± 1.4	1051± 370

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

(HCL070)

BAIS 4

STUDY NO. : 0705
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	19	5.3± 4.9
2 ppm	26	4.3± 6.1
8 ppm	23	4.0± 5.1
32 ppm	30	3.8± 5.7

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

(HCL070)

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	19	5.78±	5.74	34±	17	59±	18	3±	1	2±	1	0±	1	2±	1
2 ppm	26	6.10±	8.84	27±	15	65±	17	3±	3	2±	1	0±	0	2±	1
8 ppm	23	14.88±	47.20	23±	12	66±	16	3±	1	3±	2	0±	0	5±	17
32 ppm	30	4.80±	5.55	24±	13	70±	14	3±	2	2±	1	0±	0	2±	1

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

(HCL070)

BAIS 4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0705
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	25	5.4± 0.8	2.6± 0.4	0.9± 0.2	0.13± 0.04	152± 47	139± 79	44± 24
2 ppm	26	5.4± 1.2	2.5± 0.5	0.9± 0.1	0.19± 0.36	155± 46	145± 94	38± 24
8 ppm	33	5.1± 0.7	2.5± 0.4	0.9± 0.1	0.12± 0.02	156± 48	116± 44	36± 23
32 ppm	43	5.1± 0.7	2.4± 0.3	0.9± 0.2	0.11± 0.02	167± 47	104± 31*	38± 16

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

(HCL074)

BAIS 4

STUDY NO. : 0705
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	25	227± 119	164± 248	88± 112	313± 258	264± 146	1± 1	74± 64
2 ppm	26	235± 122	317± 885	200± 479	714± 1737	258± 186	1± 0	73± 61
8 ppm	33	192± 65	142± 230	67± 105	272± 285	219± 137	1± 1	82± 82
32 ppm	43	180± 54	80± 76	32± 33**	293± 439	222± 287	1± 1	73± 66

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

(HCL074)

BAIS 4

STUDY NO. : 0705
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	25	29.8± 26.3	154± 5	4.3± 0.8	122± 6	9.1± 0.6	6.5± 1.2
2 ppm	26	25.8± 8.8	154± 3	4.2± 0.4	122± 3	9.1± 0.8	6.7± 0.8
8 ppm	33	29.9± 17.0	154± 2	4.3± 0.5	123± 3	8.9± 0.5	6.8± 0.8
32 ppm	43	30.5± 23.7	155± 3	4.4± 0.7	123± 3	8.8± 0.3	7.2± 2.7

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

(HCL074)

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0705
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	19	4.9± 0.5	2.5± 0.3	1.0± 0.2	0.14± 0.05	123± 31	76± 40	29± 16
2 ppm	27	5.1± 0.6	2.4± 0.3	1.0± 0.2	0.12± 0.07	120± 30	81± 18	52± 49
8 ppm	24	4.9± 0.4	2.5± 0.2	1.1± 0.2	0.11± 0.03*	126± 20	76± 22	51± 32*
32 ppm	30	5.1± 0.7	2.5± 0.2	1.0± 0.2	0.13± 0.10*	127± 32	88± 82	39± 42

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

(HCL074)

BAIS 4

STUDY NO. : 0705
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	19	142± 66	168± 144	63± 55	573± 1458	247± 117	1± 1	113± 131
2 ppm	27	151± 29	96± 44	42± 33	245± 187	282± 131	2± 7	77± 54
8 ppm	24	146± 38	109± 66	43± 26	253± 405	304± 130	1± 0	63± 30
32 ppm	30	149± 76	133± 121	51± 41	402± 875	287± 102	1± 1	90± 83

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

(HCL074)

BAIS 4

STUDY NO. : 0705
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	19	17.5± 8.4	153± 2	4.0± 0.5	122± 3	9.1± 0.4	6.7± 1.0
2 ppm	27	17.7± 12.1	153± 2	4.0± 0.5	122± 3	9.0± 0.3	6.7± 0.9
8 ppm	24	14.7± 2.9	152± 1	4.0± 0.7	121± 2	9.0± 0.5	7.0± 1.6
32 ppm	30	18.2± 15.7	151± 7	4.0± 0.7	121± 7	9.0± 0.6	7.4± 2.4

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

(HCL074)

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0705
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	28	0	1	5	5	6	10	1		0	3	20	4	1	0		28	0	0	0	0	0		10	16	2	0	0	0		26	0	0	0	2	
2 ppm	28	0	5	6	6	7	4	0		0	2	16	9	1	0		28	0	0	0	0	0		9	18	1	0	0	0		26	1	0	1	0	
8 ppm	35	0	1	9	8	6	8	3		0	1	18	15	1	0		35	0	0	0	0	0		10	24	1	0	0	0		32	1	0	0	2	
32 ppm	44	0	3	8	8	8	16	1		0	1	28	14	1	0		44	0	0	0	0	0		9	32	3	0	0	0		39	3	2	0	0	

Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01

Test of CHI SQUARE

(HCL101)

BAIS 4

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
Control	28	28	0	0	0	0	
2 ppm	28	28	0	0	0	0	
8 ppm	35	35	0	0	0	0	
32 ppm	44	44	0	0	0	0	

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

(HCL101)

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0705
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	21	0	1	1	3	6	7	3		0	12	6	3	0	0		21	0	0	0	0	0		16	2	2	1	0	0		19	0	1	0	1	
2 ppm	29	0	1	3	4	10	7	4		1	11	13	4	0	0		29	0	0	0	0	0		24	3	2	0	0	0		25	1	2	0	1	
8 ppm	29	0	1	3	2	9	11	3		0	16	10	3	0	0		29	0	0	0	0	0		22	3	3	1	0	0		27	0	0	1	1	
32 ppm	30	0	2	3	2	7	10	6		0	17	10	3	0	0		30	0	0	0	0	0		23	2	4	0	1	0		29	0	1	0	0	

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

(HCL101)

BAIS 4

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Urobilinogen ±	1+	2+	3+	4+	CHI
Control	21	21	0	0	0	0	
2 ppm	29	29	0	0	0	0	
8 ppm	29	29	0	0	0	0	
32 ppm	30	30	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. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	Body Weight	ADRENALS	TESTES	HEART	LUNGS	KIDNEYS
Control	25	45.0± 9.4	0.013± 0.002	0.230± 0.050	0.233± 0.024	0.193± 0.016	0.741± 0.161
2 ppm	26	43.3± 8.5	0.013± 0.002	0.220± 0.037	0.226± 0.021	0.214± 0.056	0.683± 0.083
8 ppm	33	42.6± 7.2	0.013± 0.003	0.221± 0.041	0.226± 0.023	0.234± 0.180	0.795± 0.516
32 ppm	43	45.3± 6.9	0.013± 0.003	0.228± 0.032	0.224± 0.022	0.232± 0.122	0.771± 0.228

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

(JICL040)

STUDY NO. : 0705
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	25	0.105± 0.058	2.167± 0.954	0.460± 0.018
2 ppm	26	0.154± 0.153	2.066± 0.793	0.461± 0.012
8 ppm	33	0.085± 0.033	1.692± 0.527**	0.460± 0.012
32 ppm	43	0.120± 0.109	1.712± 0.583*	0.459± 0.017

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

(IICL040)

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0705
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	19	32.6± 6.1	0.017± 0.003	0.175± 0.233	0.186± 0.030	0.195± 0.024	0.483± 0.082
2 ppm	27	33.8± 5.0	0.017± 0.003	0.159± 0.364	0.185± 0.025	0.202± 0.040	0.512± 0.112
8 ppm	25	33.5± 3.9	0.016± 0.002	0.096± 0.136	0.180± 0.023	0.198± 0.041	0.501± 0.131
32 ppm	30	31.9± 3.3	0.017± 0.003	0.129± 0.355	0.179± 0.021	0.202± 0.040	0.567± 0.364

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

(HCL040)

BAIS 4

STUDY NO. : 0705
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	19	0.243± 0.279	1.717± 0.778	0.489± 0.024
2 ppm	27	0.250± 0.271	1.887± 1.018	0.493± 0.023
8 ppm	25	0.267± 0.404	1.700± 0.501	0.488± 0.015
32 ppm	30	0.248± 0.385	1.672± 0.761	0.487± 0.021

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

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0705
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	25	45.0± 9.4	0.031± 0.009	0.528± 0.136	0.537± 0.108	0.449± 0.113	1.693± 0.382
2 ppm	26	43.3± 8.5	0.030± 0.009	0.519± 0.093	0.541± 0.121	0.515± 0.169	1.623± 0.300
8 ppm	33	42.6± 7.2	0.031± 0.010	0.533± 0.136	0.544± 0.098	0.602± 0.670	1.893± 1.117
32 ppm	43	45.3± 6.9	0.029± 0.009	0.516± 0.107	0.505± 0.084	0.543± 0.363	1.747± 0.598

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

(HCL042)

BAIS 4

STUDY NO. : 0705
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	25	0.250± 0.159	5.231± 3.203	1.069± 0.236
2 ppm	26	0.391± 0.438	5.241± 3.159	1.113± 0.267
8 ppm	33	0.209± 0.101	4.106± 1.761	1.114± 0.212
32 ppm	43	0.284± 0.304	3.871± 1.458	1.041± 0.185

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

(HCL042)

BAIS 4

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0705
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	19	32.6± 6.1	0.053± 0.010	0.554± 0.728	0.585± 0.113	0.615± 0.121	1.500± 0.212
2 ppm	27	33.8± 5.0	0.051± 0.011	0.473± 1.091	0.551± 0.064	0.610± 0.154	1.539± 0.395
8 ppm	25	33.5± 3.9	0.049± 0.009	0.297± 0.456	0.542± 0.082	0.597± 0.118	1.510± 0.431
32 ppm	30	31.9± 3.3	0.053± 0.011	0.396± 1.070	0.564± 0.081	0.637± 0.114	1.786± 1.121

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

(HCL042)

STUDY NO. : 0705
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	19	0.763± 0.929	5.268± 1.939	1.553± 0.301
2 ppm	27	0.723± 0.709	5.562± 2.757	1.494± 0.281
8 ppm	25	0.823± 1.360	5.085± 1.359	1.475± 0.175
32 ppm	30	0.759± 1.068	5.312± 2.664	1.541± 0.187

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

(IICL042)

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				2 ppm 50				8 ppm 50				32 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	ulcer		1	8	0	0	2	4	0	0	1	8	0	0	1	3	0	0
			(2)	(16)	(0)	(0)	(4)	(8)	(0)	(0)	(2)	(16)	(0)	(0)	(2)	(6)	(0)	(0)
	hyperplasia:epidermis		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)
	scab		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)
	epidermal 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)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	exudate		0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	mineralization		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	eosinophilic change:olfactory epithelium		37	1	0	0	37	9	0	0 **	37	10	0	0 **	21	29	0	0 **
			(74)	(2)	(0)	(0)	(74)	(18)	(0)	(0)	(74)	(20)	(0)	(0)	(42)	(58)	(0)	(0)
	eosinophilic change:respiratory epithelium		16	0	0	0	35	2	0	0 **	41	1	0	0 **	42	7	0	0 **
			(32)	(0)	(0)	(0)	(70)	(4)	(0)	(0)	(82)	(2)	(0)	(0)	(84)	(14)	(0)	(0)
	inflammation:foreign body		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)
	respiratory metaplasia:olfactory epithelium		20	1	0	0	22	18	0	0 **	9	33	1	0 **	0	23	27	0 **
			(40)	(2)	(0)	(0)	(44)	(36)	(0)	(0)	(18)	(66)	(2)	(0)	(0)	(46)	(54)	(0)
	respiratory metaplasia:gland		33	5	0	0	30	15	0	0 *	18	24	5	0 **	0	6	44	0 **
			(66)	(10)	(0)	(0)	(60)	(30)	(0)	(0)	(36)	(48)	(10)	(0)	(0)	(12)	(88)	(0)
	squamous cell metaplasia:respiratory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(2)	(0)	(0)
	ulcer:respiratory epithelium		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)	(4)	(0)	(0)	(0)
	atrophy:olfactory epithelium		0	0	0	0	2	0	0	0	8	0	0	0 **	11	1	0	0 **
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(22)	(2)	(0)	(0)

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

Organ	Findings	Group Name	Control				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Respiratory system}																		
nasopharynx			<50>				<50>				<50>				<50>			
	eosinophilic change		1	0	0	0	3	1	0	0	4	0	0	0	37	4	0	0 **
			(2)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(8)	(0)	(0)	(0)	(74)	(8)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	edema		0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		4	1	0	0	5	1	0	0	9	1	0	0	1	0	0	0
			(8)	(2)	(0)	(0)	(10)	(2)	(0)	(0)	(18)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	lymphocytic infiltration		3	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	accumulation of foamy cells		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)
	bronchiolar-alveolar cell hyperplasia		2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	uremic pneumonitis		2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		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)

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 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Hematopoietic system}																		
bone marrow		<50>					<50>				<50>				<50>			
	increased hematopoiesis		4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	myelofibrosis		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)
lymph node		<50>					<50>				<50>				<50>			
	inflammatory infiltration		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)
spleen		<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)
	extramedullary hematopoiesis		16 (32)	15 (30)	0 (0)	0 (0)	15 (30)	10 (20)	2 (4)	0 (0)	12 (24)	10 (20)	0 (0)	0 (0)	19 (38)	2 (4)	3 (6)	0 (0) **
	lymph-follicular hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Circulatory system}																		
heart		<50>					<50>				<50>				<50>			
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	inflammatory infiltration		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)
	myocardial fibrosis		1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
tooth			<50>				<50>				<50>				<50>			
	dysplasia		0	0	0	0	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)
tongue			<50>				<50>				<50>				<50>			
	inflammatory infiltration		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)
stomach			<50>				<50>				<50>				<50>			
	cyst		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)
	ulcer:forestomach		1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(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 / No. of Animals on Study / Grade	Control 50				2 ppm 50				8 ppm 50				32 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	hyperplasia:forestomach		3	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:glandular stomach		5	3	0	0	9	0	0	0	7	1	0	0	8	2	0	0
			(10)	(6)	(0)	(0)	(18)	(0)	(0)	(0)	(14)	(2)	(0)	(0)	(16)	(4)	(0)	(0)
	ulcer:glandular stomach		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:glandular stomach		7	1	0	0	8	0	0	0	3	0	0	0	9	0	0	0
			(14)	(2)	(0)	(0)	(16)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(18)	(0)	(0)	(0)
small intes			<50>				<50>				<50>				<50>			
	inflammation		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)
	invagination		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)
liver			<50>				<50>				<50>				<50>			
	peliosis-like lesion		3	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(6)	(0)	(0)	(0)	(2)	(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 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	necrosis:focal		1 (2)	1 (2)	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)
	degeneration:focal		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)
	inflammatory cell nest		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		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)
	clear cell focus		1 (2)	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)
	acidophilic cell focus		3 (6)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	4 (8)	0 (0)	0 (0)
	basophilic cell focus		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	bile duct 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	Control				2 ppm				8 ppm				32 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			<50>				<50>				<50>				<50>			
	biliary cyst		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)
pancreas			<50>				<50>				<50>				<50>			
	islet cell hyperplasia		2	0	0	0	2	0	0	0	3	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyaline droplet		3	3	0	0	8	0	0	0	3	1	0	0	3	0	0	0
			(6)	(6)	(0)	(0)	(16)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(6)	(0)	(0)	(0)
	hyaline cast		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Urinary system}																		
kidney		<50>					<50>				<50>				<50>			
	lymphocytic infiltration		2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	scar		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	inflammatory polyp		2 (4)	2 (4)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	hydronephrosis		1 (2)	2 (4)	3 (6)	0 (0)	0 (0)	3 (6)	4 (8)	0 (0)	0 (0)	1 (2)	2 (4)	1 (2)	1 (2)	0 (0)	2 (4)	0 (0)
	pyelonephritis		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)	1 (2)	0 (0)	0 (0)
	mineralization:papilla		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:cortex		5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	regeneration:proximal tubule		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	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				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0	1	9	0	0	0	4	0	0	0	7	0	0	0	3	0
			(0)	(2)	(18)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(6)	(0)
	ulcer		0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
	simple hyperplasia:transitional epithelium		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)	(0)
{Endocrine system}																		
pituitary			<49>				<49>				<50>				<50>			
	angiectasis		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)
	cyst		1	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		1	1	0	0	3	0	0	0	1	0	0	0	2	0	0	0
			(2)	(2)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	Rathke pouch		2	0	0	0	3	0	0	0	3	0	0	0	4	0	0	0
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(6)	(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	Control				2 ppm				8 ppm				32 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}																		
thyroid			<50>				<50>				<50>				<50>			
	cyst		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)	(4)	(0)	(0)	(0)
	inflammatory infiltration		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	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)
adrenal			<50>				<50>				<50>				<50>			
	spindle-cell hyperplasia		9	0	0	0	13	0	0	0	9	1	0	0	9	3	0	0
			(18)	(0)	(0)	(0)	(26)	(0)	(0)	(0)	(18)	(2)	(0)	(0)	(18)	(6)	(0)	(0)
	hyperplasia:cortical cell		4	1	0	0	2	0	0	0	3	0	1	0	4	0	1	0
			(8)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(2)	(0)	(8)	(0)	(2)	(0)
{Reproductive system}																		
testis			<50>				<50>				<50>				<50>			
	mineralization		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(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				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
testis			<50>				<50>				<50>				<50>			
	granulation		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)
epididymis			<50>				<50>				<50>				<50>			
	spermatogenic granuloma		2	0	0	0	1	0	0	0	2	0	0	0	5	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	debris of spermatic elements		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)
semin ves			<50>				<50>				<50>				<50>			
	inflammatory infiltration		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)
prostate			<50>				<50>				<50>				<50>			
	inflammatory infiltration		2	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		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)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	cyst		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	Control				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	mineralization		16	0	0	0	22	0	0	0	14	0	0	0	16	0	0	0
			(32)	(0)	(0)	(0)	(44)	(0)	(0)	(0)	(28)	(0)	(0)	(0)	(32)	(0)	(0)	(0)
{Special sense organs/appendage}																		
Harder gl			<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)
{Musculoskeletal system}																		
bone			<50>				<50>				<50>				<50>			
	osteosis		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)
	osteosclerosis		0	0	0	0	1	0	0	0	1	1	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(6)	(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				2 ppm 50				8 ppm 50				32 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	ulcer		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	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)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 * (0)
	hyperplasia:gland		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)
	eosinophilic change:olfactory epithelium		29 (58)	8 (16)	1 (2)	0 (0)	36 (72)	14 (28)	0 (0)	0 ** (0)	27 (54)	21 (42)	0 (0)	0 ** (0)	14 (28)	35 (70)	0 (0)	0 ** (0)
	eosinophilic change:respiratory epithelium		27 (54)	14 (28)	0 (0)	0 (0)	28 (56)	20 (40)	0 (0)	0 (0)	20 (40)	25 (50)	1 (2)	0 (0)	16 (32)	34 (68)	0 (0)	0 ** (0)
	respiratory metaplasia:olfactory epithelium		16 (32)	4 (8)	0 (0)	0 (0)	0 (0)	30 (60)	20 (40)	0 ** (0)	1 (2)	21 (42)	28 (56)	0 ** (0)	1 (2)	6 (12)	43 (86)	0 ** (0)
	respiratory metaplasia:gland		31 (62)	2 (4)	0 (0)	0 (0)	2 (4)	17 (34)	31 (62)	0 ** (0)	0 (0)	16 (32)	34 (68)	0 ** (0)	0 (0)	2 (4)	48 (96)	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 (%)	2 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	8 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	32 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	squamous cell metaplasia:respiratory epithelium		1	0	0	0	2	0	0	0	1	0	0	0	3	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	hyperplasia:transitional epithelium		3	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	atrophy:olfactory epithelium		1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	hyperplasia:respiratory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	7	1	2	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(14)	(2)	(4)	(0)
nasopharynx			<50>				<50>				<50>				<50>			
	eosinophilic change		11	0	0	0	25	0	0	0 **	26	0	0	0 **	41	1	0	0 **
			(22)	(0)	(0)	(0)	(50)	(0)	(0)	(0)	(52)	(0)	(0)	(0)	(82)	(2)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	hemorrhage		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		2	0	0	0	0	0	0	0	3	0	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Respiratory system}																		
lung			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	accumulation of foamy cells		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)
	bronchiolar-alveolar cell hyperplasia		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)	0 (0)	0 (0)	0 (0)
	uremic pneumonitis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	arteritis		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)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		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)
	increased hematopoiesis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	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 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Hematopoietic system}																		
lymph node		<50>																
	inflammatory infiltration		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)
spleen		<50>																
	extramedullary hematopoiesis		7 (14)	10 (20)	4 (8)	0 (0)	5 (10)	4 (8)	4 (8)	0 (0)	7 (14)	8 (16)	3 (6)	0 (0)	13 (26)	5 (10)	1 (2)	0 (0)
	lymph-follicular hyperplasia		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)	1 (2)	0 (0)	0 (0)
{Circulatory system}																		
heart		<50>																
	thrombus		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)	1 (2)	0 (0)	0 (0)
	mineralization		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)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	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	Control				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	myocardial fibrosis		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
salivary gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		0	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
stomach			<50>				<50>				<50>				<50>			
	erosion:forestomach		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)
	hyperplasia:forestomach		0	0	0	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)
	erosion:glandular stomach		7	1	0	0	9	0	0	0	6	0	0	0	4	1	0	0
			(14)	(2)	(0)	(0)	(18)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(8)	(2)	(0)	(0)
	ulcer:glandular stomach		0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(2)	(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				2 ppm				8 ppm				32 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)																		
stomach			<50>				<50>				<50>				<50>			
	hyperplasia:glandular stomach		0	0	0	0	3	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	peliosis-like lesion		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)	(0)
	necrosis:central		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)
	necrosis:focal		1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0
			(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	mineralization		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)
	inflammatory infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	lymphocytic 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)
	inflammatory cell nest		8	0	0	0	10	0	0	0	12	1	0	0	10	0	0	0
			(16)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(24)	(2)	(0)	(0)	(20)	(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				2 ppm				8 ppm				32 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			<50>				<50>				<50>				<50>			
	extramedullary hematopoiesis		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)	0 (0)
	clear cell focus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		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)	1 (2)	0 (0)	0 (0)
	basophilic cell focus		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)	0 (0)	0 (0)	0 (0)
	bile duct hyperplasia		1 (2)	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)
pancreas			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		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)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	2 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	8 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	32 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hyaline droplet		9 (18)	8 (16)	0 (0)	0 (0)	6 (12)	5 (10)	0 (0)	0 (0)	8 (16)	6 (12)	0 (0)	0 (0)	4 (8)	8 (16)	0 (0)	0 (0)
	hyaline cast		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)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	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)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	hydronephrosis		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)
	papillary necrosis		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)
	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)
	urothelial hyperplasia:pelvis		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				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0	0	0	0	0	0	2	0	0	0	1	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
	lymphocytic infiltration		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		2	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	cyst		0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		6	2	1	0	8	2	0	0	9	1	0	0	10	4	1	0
			(12)	(4)	(2)	(0)	(16)	(4)	(0)	(0)	(18)	(2)	(0)	(0)	(20)	(8)	(2)	(0)
	Rathke pouch		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)
adrenal			<50>				<50>				<50>				<50>			
	fatty change		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(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 (%)	2 ppm 50 1 (%)	2 ppm 50 2 (%)	2 ppm 50 3 (%)	2 ppm 50 4 (%)	8 ppm 50 1 (%)	8 ppm 50 2 (%)	8 ppm 50 3 (%)	8 ppm 50 4 (%)	32 ppm 50 1 (%)	32 ppm 50 2 (%)	32 ppm 50 3 (%)	32 ppm 50 4 (%)
{Endocrine system}																		
adrenal		<50>																
	spindle-cell hyperplasia		37	10	0	0	36	5	0	0	38	10	0	0	37	10	1	0
			(74)	(20)	(0)	(0)	(72)	(10)	(0)	(0)	(76)	(20)	(0)	(0)	(74)	(20)	(2)	(0)
{Reproductive system}																		
ovary		<50>																
	cyst		3	0	0	0	4	0	0	0	4	0	0	0	7	0	0	0
			(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	hyperplasia		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)
uterus		<50>																
	cystic endometrial hyperplasia		14	0	0	0	22	0	0	0	23	0	0	0	20	0	0	0
			(28)	(0)	(0)	(0)	(44)	(0)	(0)	(0)	(46)	(0)	(0)	(0)	(40)	(0)	(0)	(0)
prep/cli gl		<50>																
	cyst		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)
{Nervous system}																		
brain		<50>																
	mineralization		12	0	0	0	10	0	0	0	7	0	0	0	9	0	0	0
			(24)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(18)	(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				2 ppm				8 ppm				32 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Special sense organs/appendage}																		
Harder gl			<50>				<50>				<50>				<50>			
	hyperplasia		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)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
bone			<50>				<50>				<50>				<50>			
	osteosclerosis		2	0	0	0	3	0	0	0	2	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(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	2 ppm	8 ppm	32 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	3/50(6.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	13.33	7.50	6.38	9.30
Terminal rates(c)	3/26(11.5)	2/27(7.4)	2/35(5.7)	4/43(9.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5167			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8111			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.6425
	SITE : lung			
	TUMOR : bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	5/50(10.0)	6/50(12.0)	7/50(14.0)
Adjusted rates(b)	5.26	17.24	14.29	15.22
Terminal rates(c)	1/26(3.8)	4/27(14.8)	5/35(14.3)	6/43(14.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7709			
Prevalence method(d)	P = 0.2336			
Combined analysis(d)	P = 0.3423			
Cochran-Armitage test(e)	P = 0.2662			
Fisher Exact test(e)		P = 0.3575	P = 0.2435	P = 0.1589
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma,bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	8/50(16.0)	9/50(18.0)	11/50(22.0)
Adjusted rates(b)	16.67	24.14	20.00	23.91
Terminal rates(c)	4/26(15.4)	6/27(22.2)	7/35(20.0)	10/43(23.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7709			
Prevalence method(d)	P = 0.2915			
Combined analysis(d)	P = 0.3841			
Cochran-Armitage test(e)	P = 0.2902			
Fisher Exact test(e)		P = 0.5000	P = 0.3929	P = 0.2178

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	10/50(20.0)	3/50(6.0)	9/50(18.0)
Adjusted rates(b)	7.69	14.81	0.0	13.95
Terminal rates(c)	2/26(7.7)	4/27(14.8)	0/35(0.0)	6/43(14.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8528			
Prevalence method(d)	P = 0.1698			
Combined analysis(d)	P = 0.5603			
Cochran-Armitage test(e)	P = 0.5438			
Fisher Exact test(e)		P = 0.2070	P = 0.2435	P = 0.2883
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	18/50(36.0)	15/50(30.0)	14/50(28.0)	14/50(28.0)
Adjusted rates(b)	57.69	41.38	28.89	30.23
Terminal rates(c)	15/26(57.7)	11/27(40.7)	9/35(25.7)	13/43(30.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4126			
Prevalence method(d)	P = 0.9155			
Combined analysis(d)	P = 0.9215			
Cochran-Armitage test(e)	P = 0.5432			
Fisher Exact test(e)		P = 0.3355	P = 0.2603	P = 0.2603
	SITE : liver			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	0/50(0.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	3.85	0.0	5.71	0.0
Terminal rates(c)	1/26(3.8)	0/27(0.0)	2/35(5.7)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9283			
Prevalence method(d)	P = 0.8243			
Combined analysis(d)	P = 0.9535			
Cochran-Armitage test(e)	P = 0.1950			
Fisher Exact test(e)		P = 0.1212	P = 0.5000	P = 0.1212

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	17/50(34.0)	13/50(26.0)	7/50(14.0)	3/50(6.0)
Adjusted rates(b)	30.77	32.26	12.82	6.98
Terminal rates(c)	8/26(30.8)	8/27(29.6)	4/35(11.4)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9983			
Prevalence method(d)	P = 0.9990			
Combined analysis(d)	P = 1.0000			
Cochran-Armitage test(e)	P = 0.0008**			
Fisher Exact test(e)		P = 0.2565	P = 0.0169*	P = 0.0004**
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	0/50(0.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	9.38	0.0	8.57	2.33
Terminal rates(c)	2/26(7.7)	0/27(0.0)	3/35(8.6)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9283			
Prevalence method(d)	P = 0.7966			
Combined analysis(d)	P = 0.9182			
Cochran-Armitage test(e)	P = 0.3033			
Fisher Exact test(e)		P = 0.0281*	P = 0.3575	P = 0.1022
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	29/50(58.0)	24/50(48.0)	20/50(40.0)	16/50(32.0)
Adjusted rates(b)	65.38	61.29	39.53	34.88
Terminal rates(c)	17/26(65.4)	16/27(59.3)	13/35(37.1)	15/43(34.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9980			
Prevalence method(d)	P = 0.9911			
Combined analysis(d)	P = 0.9996			
Cochran-Armitage test(e)	P = 0.0167*			
Fisher Exact test(e)		P = 0.2115	P = 0.0545	P = 0.0077**

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : gall bladder TUMOR : papillary adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/48(6.3)	1/50(2.0)
Adjusted rates(b)	3.85	0.0	8.82	2.33
Terminal rates(c)	1/26(3.8)	0/27(0.0)	3/34(8.8)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.6008			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9051			
Fisher Exact test(e)		P = 0.5000	P = 0.2933	P = 0.7525
	SITE : Harderian gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	2/50(4.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	0.0	6.90	10.00	11.63
Terminal rates(c)	0/26(0.0)	1/27(3.7)	3/35(8.6)	5/43(11.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1032			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0503			
Fisher Exact test(e)		P = 0.2475	P = 0.0587	P = 0.0281*

(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	2 ppm	8 ppm	32 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	19/50(38.0)	13/50(26.0)	12/50(24.0)	18/50(36.0)
Adjusted rates(b)	42.11	21.43	33.33	36.67
Terminal rates(c)	8/19(42.1)	6/28(21.4)	9/27(33.3)	11/30(36.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6265			
Prevalence method(d)	P = 0.3119			
Combined analysis(d)	P = 0.4627			
Cochran-Armitage test(e)	P = 0.5733			
Fisher Exact test(e)		P = 0.1419	P = 0.0971	P = 0.5000
	SITE : liver			
	TUMOR : hemangioma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	3.57	0.0	7.41	6.67
Terminal rates(c)	0/19(0.0)	0/28(0.0)	2/27(7.4)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3403			
Prevalence method(d)	P = 0.1638			
Combined analysis(d)	P = 0.2016			
Cochran-Armitage test(e)	P = 0.4166			
Fisher Exact test(e)		P = 0.5000	P = 0.3087	P = 0.5000
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	2/50(4.0)	2/50(4.0)	2/50(4.0)
Adjusted rates(b)	31.58	7.14	7.41	4.55
Terminal rates(c)	6/19(31.6)	2/28(7.1)	2/27(7.4)	1/30(3.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9168			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2378			
Fisher Exact test(e)		P = 0.0798	P = 0.0798	P = 0.0798

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	2/50(4.0)	1/50(2.0)	4/50(8.0)
Adjusted rates(b)	2.86	3.57	0.0	3.33
Terminal rates(c)	0/19(0.0)	1/28(3.6)	0/27(0.0)	1/30(3.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2604			
Prevalence method(d)	P = 0.3985			
Combined analysis(d)	P = 0.2647			
Cochran-Armitage test(e)	P = 0.5514			
Fisher Exact test(e)		P = 0.3389	P = 0.1811	P = 0.6425
	SITE : liver			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	0/50(0.0)	0/50(0.0)
Adjusted rates(b)	10.53	3.57	0.0	0.0
Terminal rates(c)	2/19(10.5)	1/28(3.6)	0/27(0.0)	0/30(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 1.0000 ?			
Prevalence method(d)	P = 0.9572			
Combined analysis(d)	P = 0.9803			
Cochran-Armitage test(e)	P = 0.1133			
Fisher Exact test(e)		P = 0.3087	P = 0.1212	P = 0.1212
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	11.11	3.57	7.41	6.67
Terminal rates(c)	2/19(10.5)	1/28(3.6)	2/27(7.4)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7118			
Prevalence method(d)	P = 0.5185			
Combined analysis(d)	P = 0.6512			
Cochran-Armitage test(e)	P = 0.7028			
Fisher Exact test(e)		P = 0.1811	P = 0.5000	P = 0.3389

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	4/50(8.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	31.58	10.71	11.11	10.00
Terminal rates(c)	6/19(31.6)	3/28(10.7)	3/27(11.1)	3/30(10.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5524			
Prevalence method(d)	P = 0.8179			
Combined analysis(d)	P = 0.8570			
Cochran-Armitage test(e)	P = 0.3556			
Fisher Exact test(e)		P = 0.1168	P = 0.0606	P = 0.1168
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	7/50(14.0)	9/50(18.0)	11/50(22.0)
Adjusted rates(b)	26.32	21.43	24.14	29.03
Terminal rates(c)	5/19(26.3)	6/28(21.4)	6/27(22.2)	8/30(26.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6527			
Prevalence method(d)	P = 0.2051			
Combined analysis(d)	P = 0.2877			
Cochran-Armitage test(e)	P = 0.4798			
Fisher Exact test(e)		P = 0.2977	P = 0.5000	P = 0.5000
	SITE : ovary			
	TUMOR : cystadenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	21.05	3.57	5.13	3.33
Terminal rates(c)	4/19(21.1)	1/28(3.6)	1/27(3.7)	1/30(3.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8715			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3362			
Fisher Exact test(e)		P = 0.1811	P = 0.3389	P = 0.1811

Group Name	Control	2 ppm	8 ppm	32 ppm
	SITE : uterus			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	17/50(34.0)	13/50(26.0)	12/50(24.0)	13/50(26.0)
Adjusted rates(b)	26.32	17.86	14.81	12.50
Terminal rates(c)	5/19(26.3)	5/28(17.9)	4/27(14.8)	3/30(10.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7072			
Prevalence method(d)	P = 0.6175			
Combined analysis(d)	P = 0.7385			
Cochran-Armitage test(e)	P = 0.6239			
Fisher Exact test(e)		P = 0.2565	P = 0.1891	P = 0.2565
	SITE : mammary gland			
	TUMOR : adenocarcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	2/50(4.0)
Adjusted rates(b)	10.00	3.57	0.0	6.67
Terminal rates(c)	1/19(5.3)	1/28(3.6)	0/27(0.0)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3442			
Prevalence method(d)	P = 0.4714			
Combined analysis(d)	P = 0.5032			
Cochran-Armitage test(e)	P = 0.9880			
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.5000
	SITE : mammary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	3/50(6.0)
Adjusted rates(b)	10.00	3.57	0.0	8.33
Terminal rates(c)	1/19(5.3)	1/28(3.6)	0/27(0.0)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3442			
Prevalence method(d)	P = 0.2289			
Combined analysis(d)	P = 0.2635			
Cochran-Armitage test(e)	P = 0.5338			
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.6611

Group Name	Control	2 ppm	8 ppm	32 ppm
SITE : mammary gland				
TUMOR : adenoma, adenocarcinoma, adenoacanthoma:malignant				
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	10.00	3.57	0.0	8.33
Terminal rates(c)	1/19(5.3)	1/28(3.6)	0/27(0.0)	2/30(6.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5177			
Prevalence method(d)	P = 0.2289			
Combined analysis(d)	P = 0.2931			
Cochran-Armitage test(e)	P = 0.6021			
Fisher Exact test(e)		P = 0.3087	P = 0.5000	P = 0.6611

(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.

TABLE Q1

CAUSE OF DEATH : MALE

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

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

Group Name	Control	2 ppm	8 ppm	32 ppm
Number of Dead and Moribund Animal	24	23	15	7
integumentary sy les	0	0	0	1
renal lesion	0	1	0	0
ileus	0	1	0	0
urinary retention	6	2	3	0
tooth lesion	0	1	0	0
hydronephrosis	2	3	1	1
tumor d:leukemia	4	6	3	3
tumor d:subcutis	1	0	0	1
tumor d:lung	1	1	1	0
tumor d:spleen	0	1	0	1
tumor d:liver	9	3	5	0
tumor d:kidney	0	0	1	0
tumor d:urin bladd	0	2	0	0
tumor d:pituitary	0	0	1	0
tumor d:epididymis	0	1	0	0
tumor d:periph nerv	1	1	0	0

TABLE Q2

CAUSE OF DEATH : FEMALE

STUDY NO. : 0705
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : FEMALE

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

Group Name	Control	2 ppm	8 ppm	32 ppm
Number of Dead and Moribund Animal	31	22	23	20
digestive sy les	1	0	0	0
renal lesion	0	1	0	0
urinary retention	0	1	1	0
hydronephrosis	0	0	0	1
tumor d:leukemia	10	8	3	7
tumor d:subcutis	0	0	1	0
tumor d:lymph node	0	1	1	0
tumor d:spleen	1	0	0	0
tumor d:liver	4	2	2	3
tumor d:pituitary	2	0	1	1
tumor d:thyroid	0	1	0	0
tumor d:uterus	13	8	8	8
tumor d:vagina	0	0	1	0
tumor d:mammary gl	0	0	2	0
tumor d:muscle	0	0	2	0
tumor d:peritoneum	0	0	1	0

FIGURES

FIGURE 1 ACRYLIC ACID VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

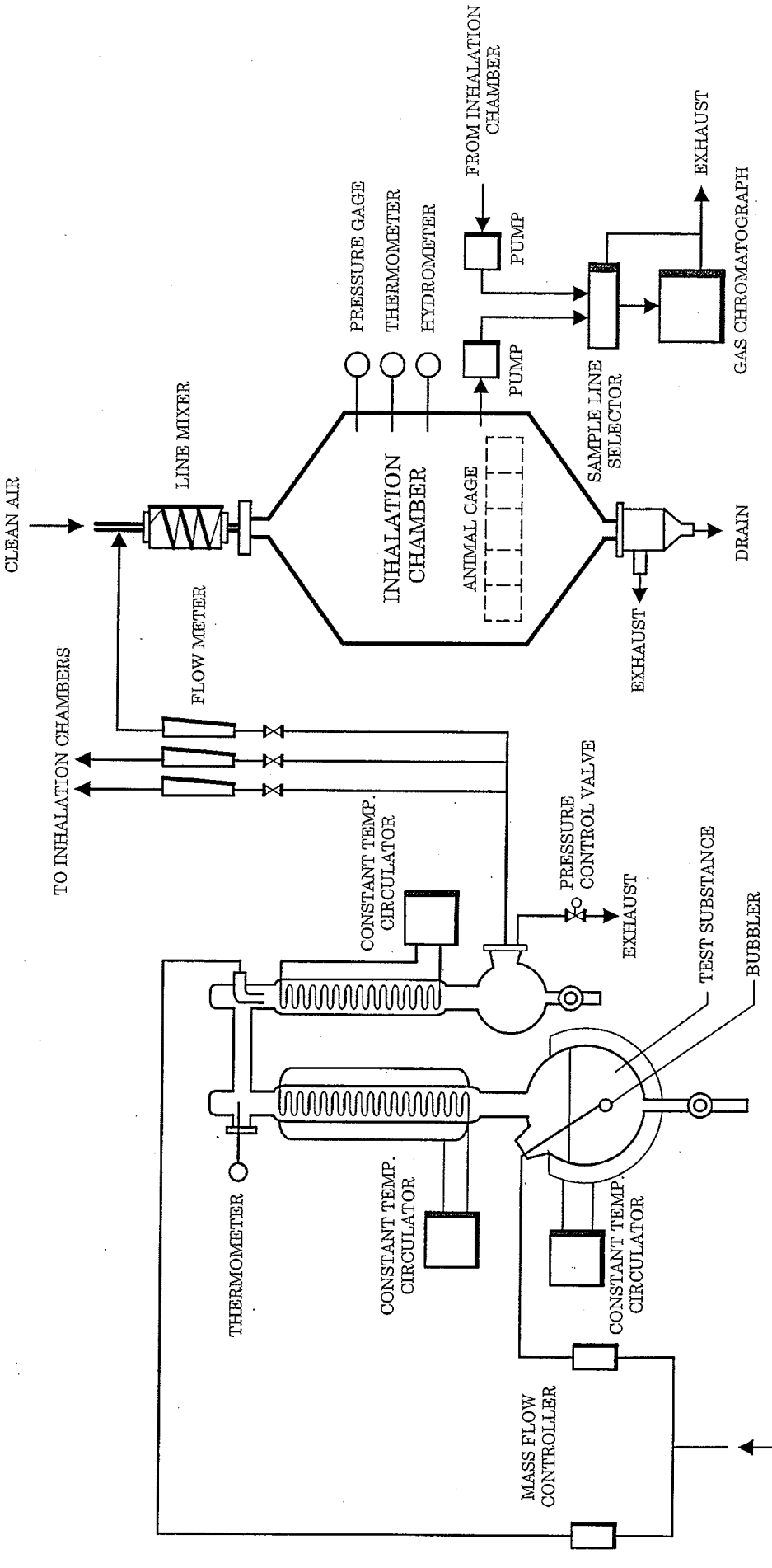


FIGURE 1 ACRYLIC ACID VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

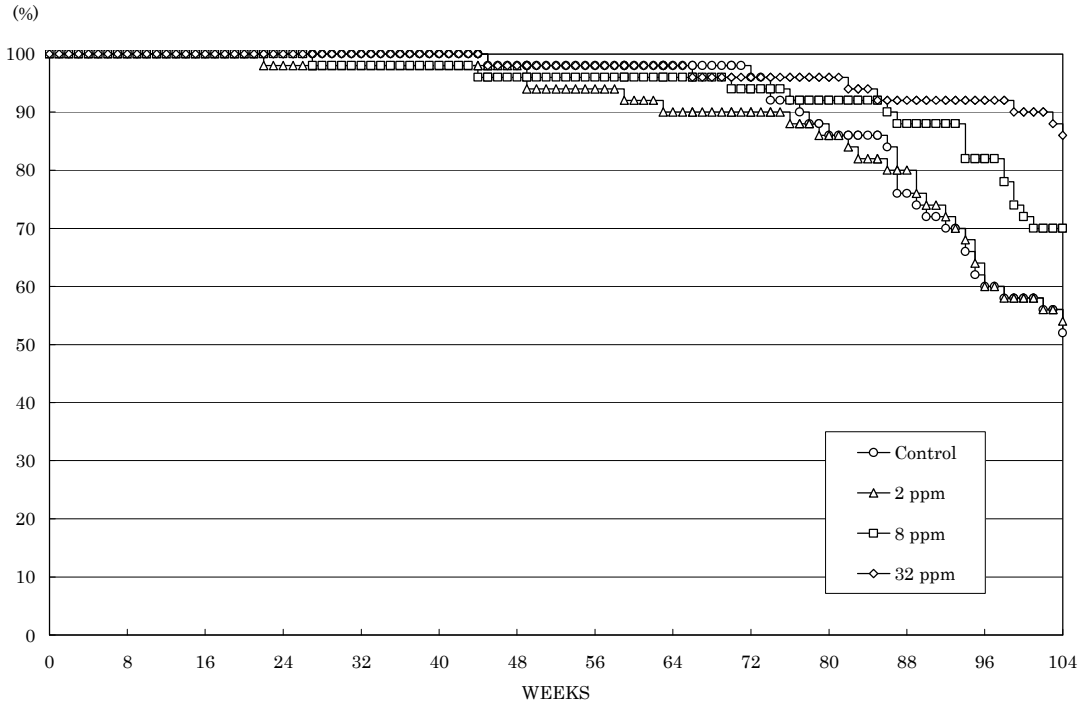


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

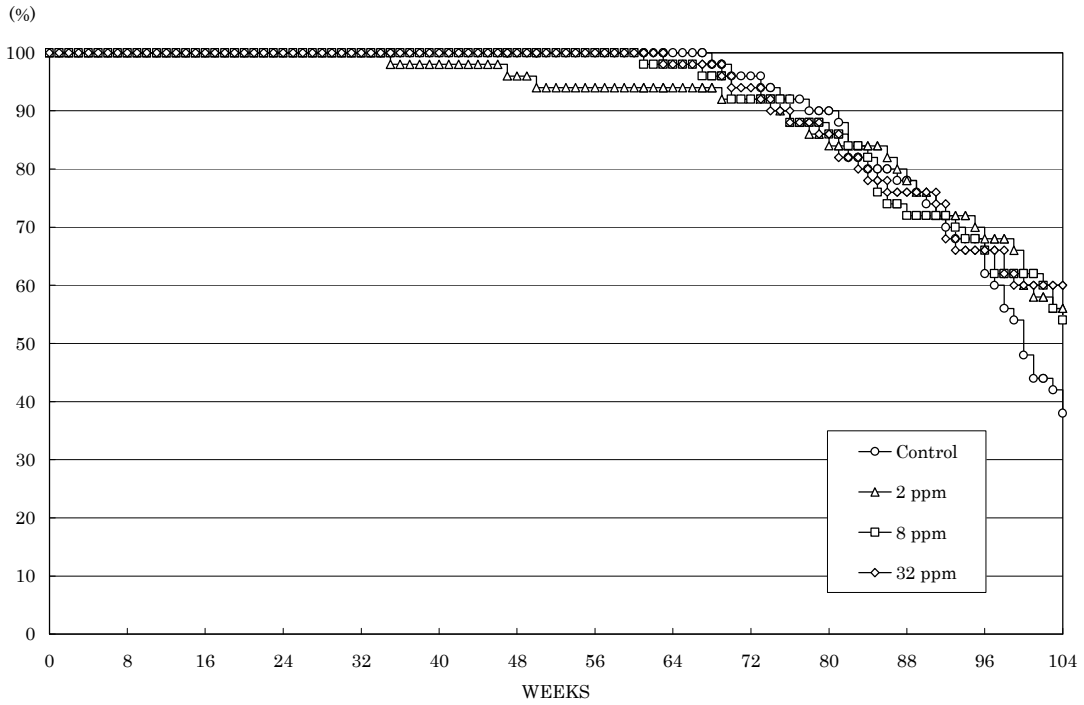


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

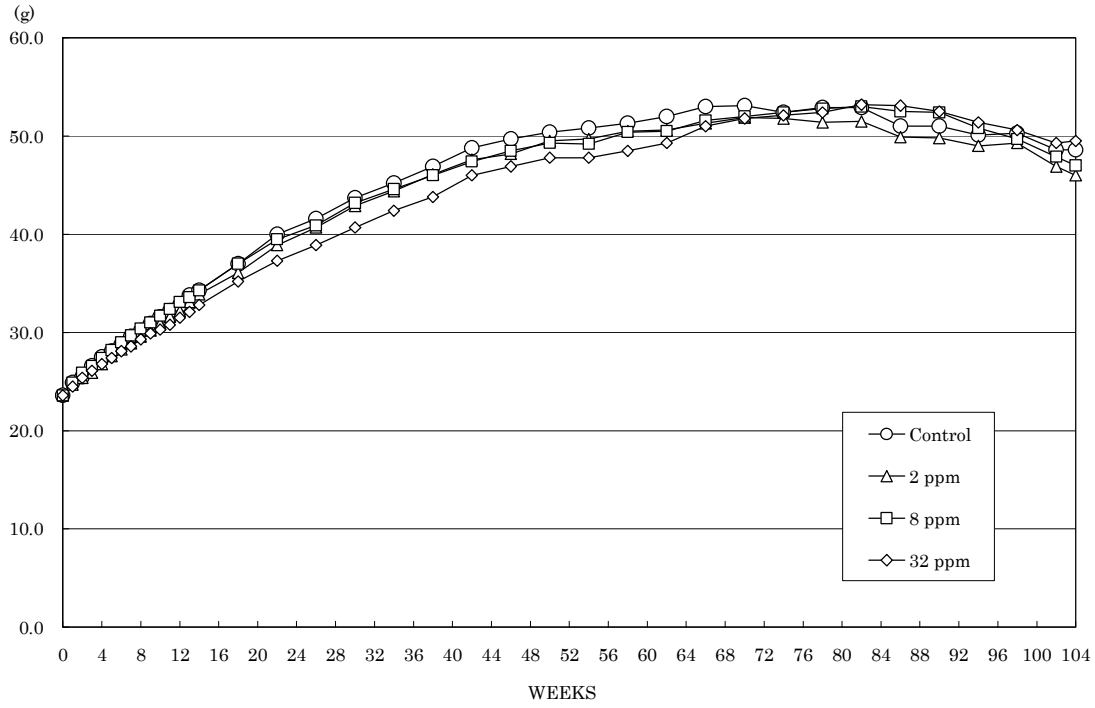


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

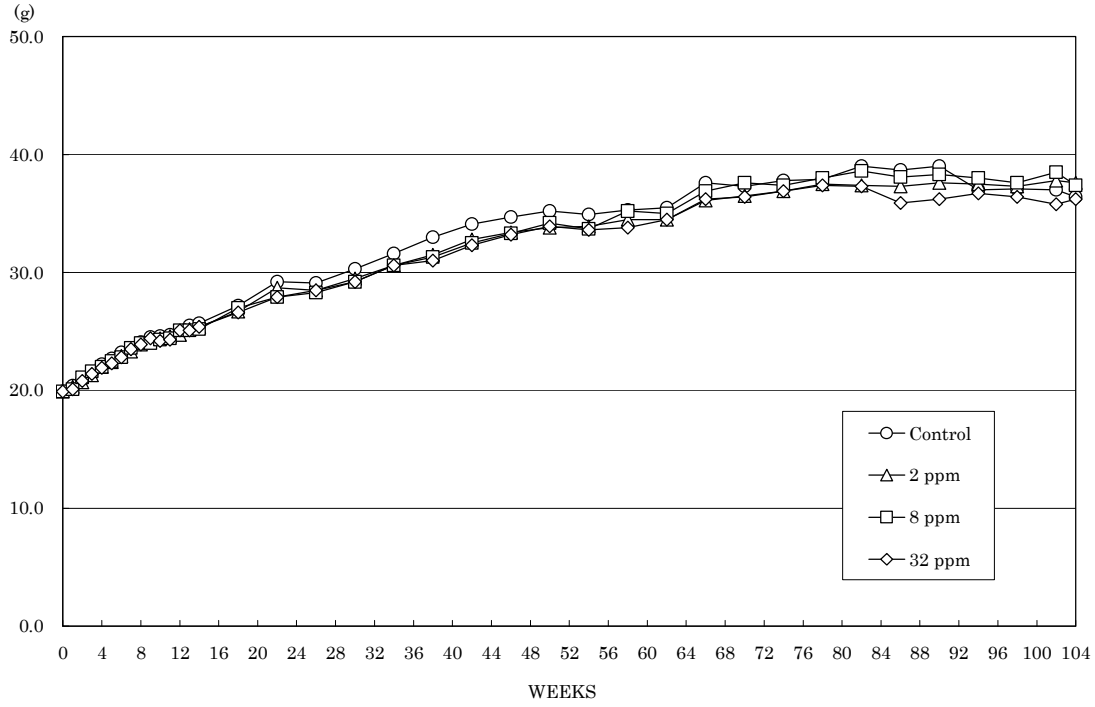


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

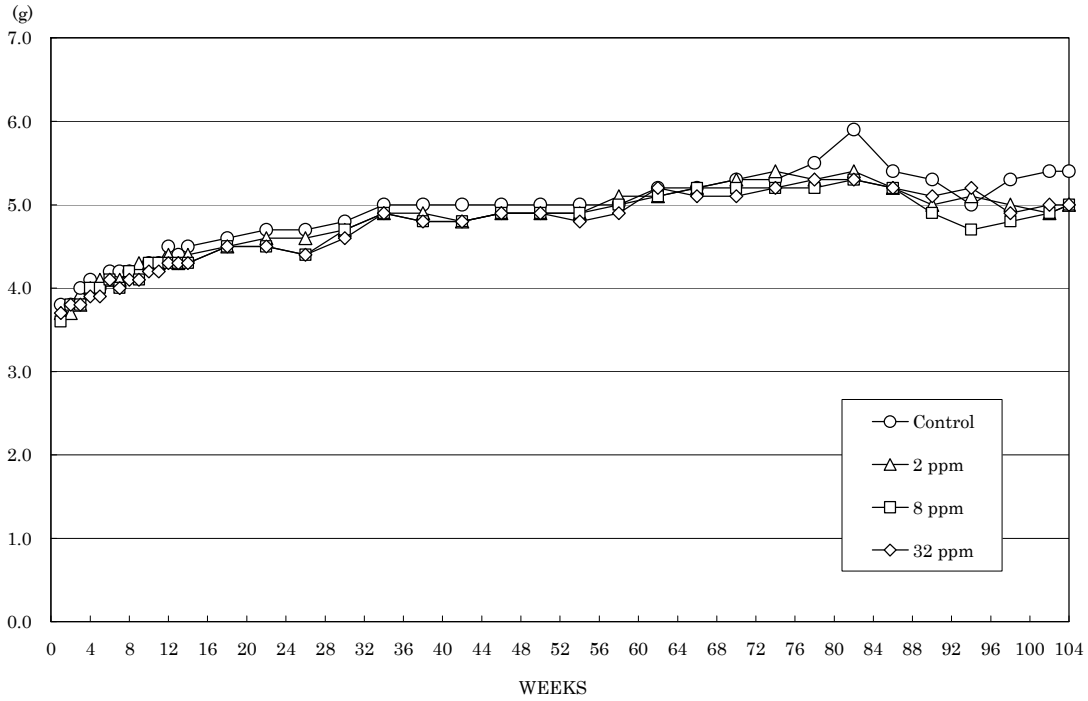


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

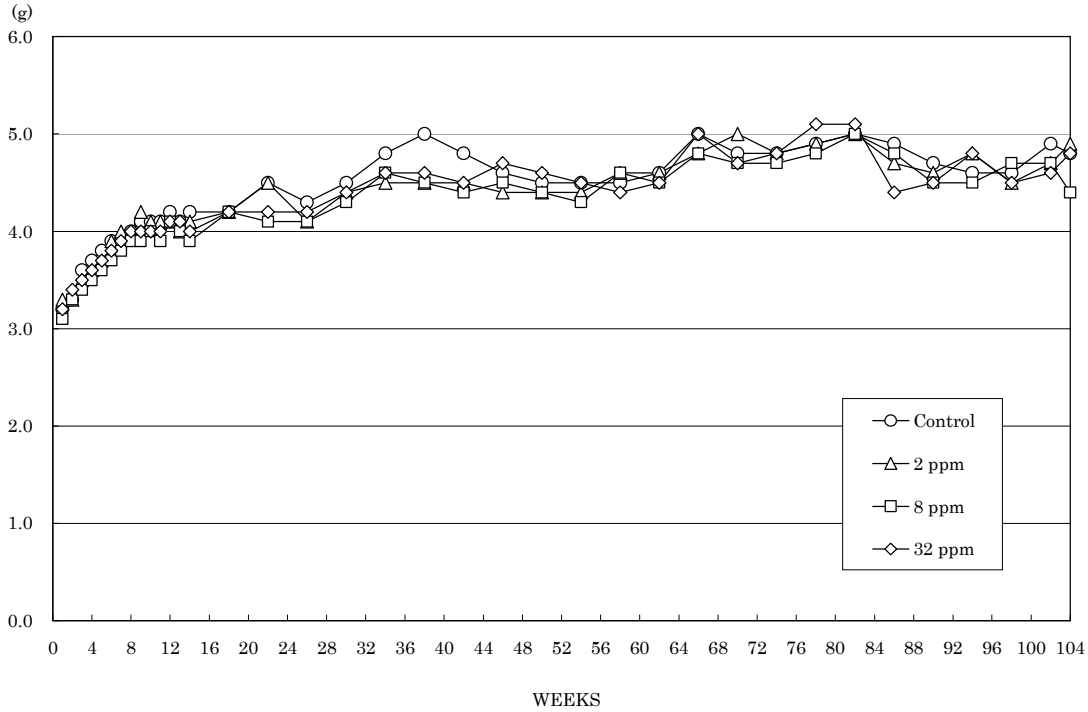
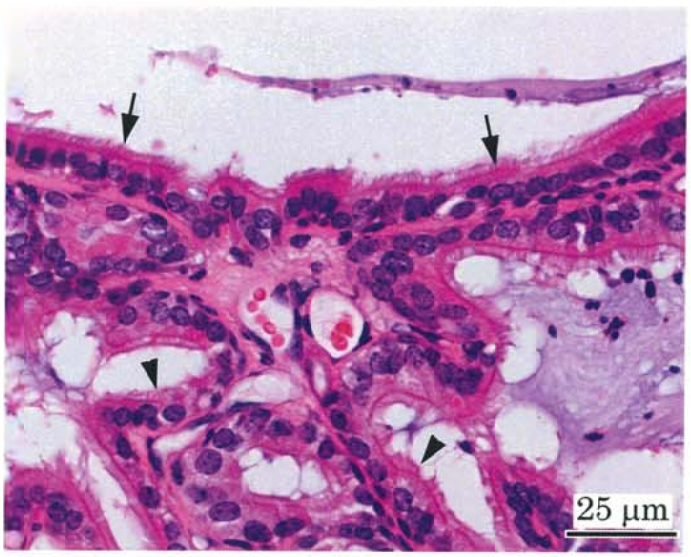


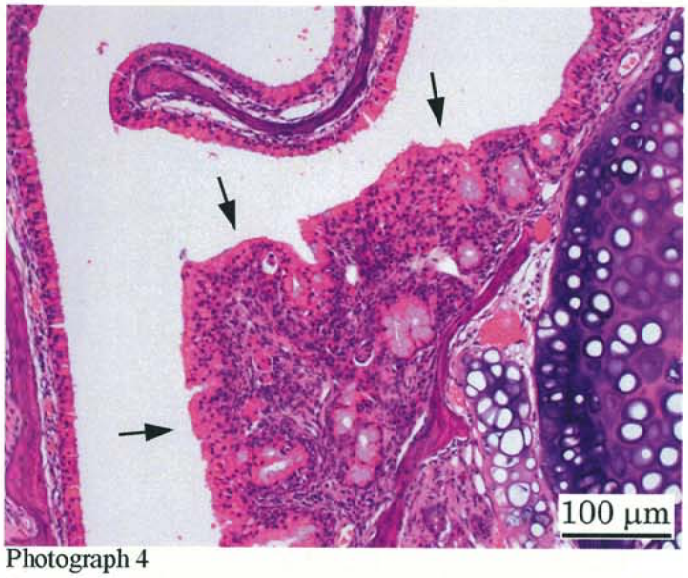
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

Photograph 1
Nasal cavity (Level 3): Atrophy of olfactory epithelium (arrow)
Mouse, Male, 32 ppm, Animal No. 0705-1305 (H&E)



Photograph 2
Nasal cavity (Level 3): Respiratory metaplasia of olfactory epithelium (arrows) and gland (arrow heads)
Mouse, Male, 32 ppm, Animal No. 0705-1342 (H&E)

Photograph 3
Nasal cavity (Level 2): Eosinophylic change of respiratory epithelium (arrows, left side) and normal epithelium (right side)
Mouse, Male, 32 ppm, Animal No. 0705-1350 (H&E)



Photograph 4
Nasal cavity (Level 1): Hyperplasia of respiratory epithelium (arrows)
Mouse, Female, 32 ppm, Animal No. 0705-2306 (H&E)