Summary of Inhalation Carcinogenicity Study of Methylamine 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 26, 2012.

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

Summary of Inhalation Carcinogenicity Study of Methylamine in B6D2F1 Mice

Purpose, materials and methods

Methylamine (CAS No. 74-89-5) is a colorless gas with a boiling point of -6.3°C. It is soluble in water, ethanol and acetone.

The carcinogenicity and chronic toxicity of methylamine (greater than 99.97% pure) were examined by inhalation exposure using B6D2F1/Crlj mice. Groups of test animals were exposed to methylamine vapors at target concentrations of 0 (clean air), 5, 15 or 45 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 methylamine 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 methylamine used in these experiments was confirmed by mass spectrometry. It was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 3.7 m^3) were used throughout the 2-year exposure period. Methylamine gas from liquefied methylamine gas cylinder was deluted to each target concentration with filtered freah air and delivered to each inhalation exposure chamber. Air concentrations of the methylamine 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 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. Three 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 methylamine induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for

Testing of Chemicals 451 “Carcinogenicity Studies”.

Results

No significant differences in survival rates and clinical signs were found between any of the groups exposed to methylamine and their respective controls. Body weights of the males exposed to 45 ppm methylamine were slightly suppressed during the first half of the exposure period and the end of the exposure periods. Body weights were suppressed after 26th to 50th week of the exposure period in the females exposed to 15 ppm and above. There was no significant difference in food consumption was found between any methylamine exposed group of males and the control. Food consumption was decreased after 18th to 54th week in all methylamine exposed females.

The incidences of selected neoplastic lesions in male and female mice are presented in the tables below. The incidence of osteosarcoma of bone in females was increased in a concentration-dependent manner, and was above the JBRC histrical control data. However, only three incidences of osteosarcoma of bone were observed in females exposed to 45 ppm, and moreover, one incidence of osteosarcoma of bone was found in female control group. Therefore, the increased incidences of osteosarcoma of bone in females were not attributed to methylamine exposure.The incidences of pituitary adenoma was significantly increased in females exposed to 45 ppm and increased in a concentration-dependent manner, but the incidence of pituitary adenoma in females exposed to 45 ppm was within the JBRC histrical control data. Therefore, the increased incidences of pituitary adenoma in females were not attributed to methylamine exposure.

In the non-neoplastic lesions, the effect of methylamine was observed in the nasal cavity. Inflammation and hyperplasia of the transitinal epithelium in the nasal cavity were increased males exposed 45 ppm and females exposed 15 ppm and above. Squamous metaplasia of the transitinal epithelium and eosinophilic change in the olfactory epithelium were increased females exposed 45 ppm. No effects of methylamine were observed in exposed to 5 ppm

Using nasal lesions as endpoint markers, the no-observed-adverse-effect-level (NOAEL) of methylamine was 5 ppm in both male and female mice when exposed by inhalation.

Conclusions

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

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

Dose (ppm)		0	5	15	45	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	6	4	2	3		
liver	hepatocellular adenoma	9	5	7	7		
Harderian gland	adenoma	1	1	5	0		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	2	5	2	5		
lymph node	malignant lymphoma	11	5	11	8		
spleen	hemangiosarcoma	1	3	2	1		
liver	hepatocellular carcinoma	4	7	3	5		
	hemangiosarcoma	2	6	1	2		
	histiocytic sarcoma	1	3	1	2		

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

Dose (ppm)		0	5	15	45	Peto test	Cochran-Armitage test
Number of examined animals		50 1)	50	50	50 1)		
benign tumor							
lung	bronchiolar-alveolar adenoma	0	2	1	3		
liver	hepatocellular adenoma	4	1	3	3		
pituitary	adenoma	4	9	8	13 *	↑	↑
uterus	endometrial stromal polyp	1	3	0	3		
malignant tumor							
lymph node	malignant lymphoma	16	17	16	20		
liver	histiocytic sarcoma	4	1	2	1		
pituitary	adenocarcinoma	2	2	0	0		
uterus	histiocytic sarcoma	11	13	8	10		
bone	osteosarcoma	1	0	0	3	↑	↑
subcutis	fibrosarcoma	0	3	2	1		

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

1) : Number of animals examined in pituitary is 49.

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)

SELECTED TABLES

TABLE A

CONCENTRATIONS OF METHYLAMINE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

CONCENTRATIONS OF METHYLAMINE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
5 ppm	5.0 ± 0.1
15 ppm	15.0 ± 0.2
45 ppm	45.1 ± 0.5

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0732
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>	5 ppm Av. Wt.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	15 ppm Av. Wt.	15 ppm % of cont. <50>	15 ppm No. of Surviv.	45 ppm Av. Wt.	45 ppm % of cont. <50>	45 ppm No. of Surviv.
0-0	22.9 (50)	50/50	22.9 (50)	100	50/50	22.9 (50)	100	50/50	22.9 (50)	100	50/50
1-7	24.1 (50)	50/50	23.8 (50)	99	50/50	24.1 (50)	100	50/50	23.8 (50)	99	50/50
2-7	24.8 (50)	50/50	24.3 (50)	98	50/50	25.0 (50)	101	50/50	24.7 (50)	100	50/50
3-7	25.5 (50)	50/50	25.3 (50)	99	50/50	25.5 (50)	100	50/50	25.1 (50)	98	50/50
4-7	26.3 (50)	50/50	25.8 (50)	98	50/50	26.1 (50)	99	50/50	25.4 (50)	97	50/50
5-7	26.7 (50)	50/50	26.3 (50)	99	50/50	26.8 (49)	100	49/50	25.9 (50)	97	50/50
6-7	27.3 (50)	50/50	26.5 (50)	97	50/50	27.4 (49)	100	49/50	26.5 (50)	97	50/50
7-7	27.8 (50)	50/50	27.1 (50)	97	50/50	27.9 (49)	100	49/50	27.1 (50)	97	50/50
8-7	28.4 (50)	50/50	27.5 (50)	97	50/50	28.7 (49)	101	49/50	27.6 (50)	97	50/50
9-7	29.0 (50)	50/50	28.1 (50)	97	50/50	29.1 (49)	100	49/50	28.6 (50)	99	50/50
10-7	29.6 (50)	50/50	28.7 (50)	97	50/50	29.7 (49)	100	49/50	28.8 (50)	97	50/50
11-7	30.2 (50)	50/50	29.4 (50)	97	50/50	30.2 (49)	100	49/50	29.4 (50)	97	50/50
12-7	30.9 (50)	50/50	30.1 (50)	97	50/50	31.0 (49)	100	49/50	30.1 (50)	97	50/50
13-7	31.5 (50)	50/50	30.8 (50)	98	50/50	31.6 (49)	100	49/50	30.9 (50)	98	50/50
14-7	31.9 (50)	50/50	31.5 (50)	99	50/50	32.3 (49)	101	49/50	31.3 (50)	98	50/50
18-7	34.1 (50)	50/50	34.1 (50)	100	50/50	34.6 (49)	101	49/50	33.7 (50)	99	50/50
22-7	36.5 (50)	50/50	36.3 (50)	99	50/50	36.9 (49)	101	49/50	35.9 (50)	98	50/50
26-7	38.3 (50)	50/50	38.9 (50)	102	50/50	38.8 (49)	101	49/50	37.7 (50)	98	50/50
30-7	39.8 (50)	50/50	40.4 (50)	102	50/50	40.2 (49)	101	49/50	39.2 (50)	98	50/50
34-7	41.0 (50)	50/50	41.6 (50)	101	50/50	41.5 (48)	101	48/50	40.2 (50)	98	50/50
38-7	41.5 (50)	50/50	42.2 (50)	102	50/50	42.0 (48)	101	48/50	40.6 (50)	98	50/50
42-7	42.3 (50)	50/50	42.9 (50)	101	50/50	42.7 (48)	101	48/50	41.4 (49)	98	49/50
46-7	43.3 (50)	50/50	43.9 (49)	101	49/50	43.4 (48)	100	48/50	41.7 (49)	96	49/50
50-7	44.3 (50)	50/50	44.8 (49)	101	49/50	44.4 (48)	100	48/50	42.3 (49)	95	49/50
54-7	44.7 (50)	50/50	45.6 (49)	102	49/50	45.0 (48)	101	48/50	43.2 (49)	97	49/50
58-7	45.5 (50)	50/50	46.3 (49)	102	49/50	45.6 (48)	100	48/50	43.9 (49)	96	49/50
62-7	46.5 (50)	50/50	47.3 (49)	102	49/50	46.0 (48)	99	48/50	45.0 (48)	97	48/50
66-7	46.9 (50)	50/50	48.0 (49)	102	49/50	46.3 (48)	99	48/50	45.4 (48)	97	48/50
70-7	47.3 (49)	49/50	48.5 (49)	103	49/50	46.8 (48)	99	48/50	45.6 (47)	96	47/50
74-7	47.7 (48)	48/50	48.8 (49)	102	49/50	47.1 (46)	99	46/50	46.0 (47)	96	47/50
78-7	48.2 (48)	48/50	49.0 (48)	102	48/50	47.8 (43)	99	43/50	45.8 (47)	95	47/50
82-7	48.2 (48)	48/50	48.6 (47)	101	47/50	47.9 (42)	99	42/50	45.3 (47)	94	47/50
86-7	48.3 (46)	46/50	48.2 (44)	100	44/50	47.1 (42)	98	42/50	45.0 (45)	93	45/50
90-7	47.5 (45)	45/50	47.8 (39)	101	39/50	46.0 (41)	97	41/50	43.9 (44)	92	44/50
94-7	45.9 (45)	45/50	46.5 (39)	101	39/50	44.4 (40)	97	40/50	42.2 (43)	92	43/50
98-7	45.1 (43)	43/50	46.5 (37)	103	37/50	44.0 (39)	98	39/50	42.3 (40)	94	40/50
102-7	43.9 (42)	42/50	45.9 (35)	105	35/50	42.5 (37)	97	37/50	41.7 (38)	95	38/50
104-7	43.0 (42)	42/50	46.9 (34)	109	34/50	42.4 (36)	99	36/50	41.6 (37)	97	37/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0732
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>	5 ppm Av. Wt.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	15 ppm Av. Wt.	15 ppm % of cont. <50>	15 ppm No. of Surviv.	45 ppm Av. Wt.	45 ppm % of cont. <50>	45 ppm No. of Surviv.
0-0	19.8 (50)	50/50	19.8 (50)	100	50/50	19.8 (50)	100	50/50	19.8 (50)	100	50/50
1-7	20.0 (50)	50/50	19.7 (50)	99	50/50	19.8 (50)	99	50/50	19.6 (50)	98	50/50
2-7	20.5 (50)	50/50	20.1 (50)	98	50/50	20.5 (50)	100	50/50	20.0 (50)	98	50/50
3-7	21.0 (50)	50/50	20.7 (50)	99	50/50	21.3 (50)	101	50/50	20.7 (50)	99	50/50
4-7	21.9 (50)	50/50	21.5 (50)	98	50/50	21.7 (50)	99	50/50	21.4 (50)	98	50/50
5-7	22.1 (50)	50/50	21.9 (50)	99	50/50	22.3 (50)	101	50/50	22.0 (50)	100	50/50
6-7	22.6 (50)	50/50	22.4 (50)	99	50/50	22.9 (50)	101	50/50	22.5 (50)	100	50/50
7-7	23.3 (50)	50/50	23.0 (50)	99	50/50	23.3 (50)	100	50/50	23.2 (50)	100	50/50
8-7	23.8 (50)	50/50	23.4 (50)	98	50/50	23.7 (50)	100	50/50	23.5 (50)	99	50/50
9-7	24.0 (50)	50/50	23.5 (50)	98	50/50	24.2 (50)	101	50/50	23.9 (50)	100	50/50
10-7	24.2 (50)	50/50	23.8 (50)	98	50/50	24.3 (50)	100	50/50	23.9 (50)	99	50/50
11-7	24.4 (50)	50/50	24.1 (50)	99	50/50	24.4 (50)	100	50/50	24.2 (50)	99	50/50
12-7	25.0 (50)	50/50	24.7 (50)	99	50/50	24.7 (50)	99	50/50	24.7 (50)	99	50/50
13-7	25.1 (50)	50/50	24.8 (50)	99	50/50	24.9 (50)	99	50/50	24.8 (50)	99	50/50
14-7	25.1 (50)	50/50	24.9 (50)	99	50/50	25.0 (50)	100	50/50	24.9 (50)	99	50/50
18-7	26.4 (50)	50/50	25.9 (50)	98	50/50	26.1 (50)	99	50/50	26.1 (49)	99	49/50
22-7	27.1 (50)	50/50	26.8 (50)	99	50/50	26.5 (50)	98	50/50	26.3 (49)	97	49/50
26-7	28.3 (50)	50/50	27.2 (50)	96	50/50	27.1 (50)	96	50/50	26.5 (49)	94	49/50
30-7	28.7 (50)	50/50	27.7 (50)	97	50/50	27.5 (50)	96	50/50	27.5 (49)	96	49/50
34-7	29.2 (50)	50/50	28.3 (50)	97	50/50	28.1 (50)	96	50/50	27.6 (49)	95	49/50
38-7	29.3 (50)	50/50	28.6 (50)	98	50/50	28.2 (50)	96	50/50	28.2 (48)	96	48/50
42-7	29.6 (50)	50/50	29.0 (50)	98	50/50	28.8 (50)	97	50/50	28.4 (47)	96	47/50
46-7	30.2 (50)	50/50	29.6 (50)	98	50/50	29.0 (50)	96	50/50	28.5 (47)	94	47/50
50-7	30.4 (50)	50/50	30.1 (50)	99	50/50	29.0 (50)	95	50/50	29.4 (47)	97	47/50
54-7	31.0 (48)	48/50	30.3 (50)	98	50/50	30.0 (50)	97	50/50	29.5 (46)	95	46/50
58-7	31.0 (48)	48/50	30.8 (50)	99	50/50	30.2 (50)	97	50/50	29.9 (46)	96	46/50
62-7	31.5 (48)	48/50	31.0 (50)	98	50/50	30.5 (50)	97	50/50	30.4 (46)	97	46/50
66-7	31.4 (48)	48/50	31.4 (50)	100	50/50	30.9 (50)	98	50/50	30.7 (46)	98	46/50
70-7	31.9 (47)	47/50	31.0 (49)	97	49/50	31.2 (50)	98	50/50	31.1 (46)	97	46/50
74-7	32.1 (46)	46/50	31.8 (48)	99	48/50	31.5 (49)	98	49/50	30.9 (46)	96	46/50
78-7	32.3 (45)	45/50	32.2 (48)	100	48/50	32.7 (47)	101	47/50	32.5 (43)	101	43/50
82-7	32.7 (43)	43/50	32.5 (47)	99	47/50	33.0 (41)	101	41/50	32.4 (42)	99	42/50
86-7	33.1 (41)	41/50	32.8 (47)	99	47/50	32.9 (41)	99	41/50	33.1 (42)	100	42/50
90-7	32.8 (36)	36/50	32.2 (45)	98	45/50	32.6 (40)	99	40/50	32.6 (39)	99	39/50
94-7	32.3 (29)	29/50	33.0 (43)	102	43/50	32.5 (40)	101	40/50	31.7 (35)	98	35/50
98-7	32.6 (26)	26/50	33.0 (41)	101	41/50	32.8 (37)	101	37/50	33.0 (33)	101	33/50
102-7	32.4 (23)	23/50	33.4 (35)	103	35/50	32.9 (33)	102	33/50	32.6 (29)	101	29/50
104-7	32.5 (22)	22/50	34.4 (34)	106	34/50	33.5 (33)	103	33/50	32.6 (29)	100	29/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	22.9± 0.8	24.1± 1.0	24.8± 1.2	25.5± 1.3	26.3± 1.4	26.7± 1.6	27.3± 1.7
5 ppm	22.9± 0.8	23.8± 0.8	24.3± 0.9*	25.3± 1.0	25.8± 1.1	26.3± 1.2	26.5± 1.2*
15 ppm	22.9± 0.8	24.1± 0.9	25.0± 0.9	25.5± 1.2	26.1± 1.3	26.8± 1.4	27.4± 1.6
45 ppm	22.9± 0.8	23.8± 0.8	24.7± 0.8	25.1± 1.0	25.4± 1.0**	25.9± 1.0**	26.5± 1.2*

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	27.8± 1.8	28.4± 2.1	29.0± 2.1	29.6± 2.2	30.2± 2.4	30.9± 2.4	31.5± 2.6
5 ppm	27.1± 1.3*	27.5± 1.4*	28.1± 1.5*	28.7± 1.6	29.4± 1.7	30.1± 1.9	30.8± 2.0
15 ppm	27.9± 1.6	28.7± 1.8	29.1± 1.8	29.7± 2.0	30.2± 2.1	31.0± 2.3	31.6± 2.4
45 ppm	27.1± 1.4*	27.6± 1.5	28.6± 1.5	28.8± 1.8	29.4± 1.9	30.1± 2.1	30.9± 2.2

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	31.9± 2.8	34.1± 3.3	36.5± 3.6	38.3± 4.1	39.8± 4.3	41.0± 4.4	41.5± 4.5
5 ppm	31.5± 2.2	34.1± 2.6	36.3± 3.2	38.9± 3.6	40.4± 3.8	41.6± 3.9	42.2± 4.1
15 ppm	32.3± 2.4	34.6± 2.5	36.9± 2.7	38.8± 3.1	40.2± 3.4	41.5± 3.6	42.0± 3.8
45 ppm	31.3± 2.4	33.7± 2.6	35.9± 2.9	37.7± 3.3	39.2± 3.7	40.2± 3.8	40.6± 4.1

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	42.3± 4.6	43.3± 4.7	44.3± 4.8	44.7± 4.8	45.5± 5.0	46.5± 5.0	46.9± 5.1
5 ppm	42.9± 4.4	43.9± 4.3	44.8± 4.3	45.6± 4.4	46.3± 4.6	47.3± 4.9	48.0± 5.3
15 ppm	42.7± 3.9	43.4± 4.1	44.4± 4.2	45.0± 4.3	45.6± 4.9	46.0± 4.7	46.3± 5.3
45 ppm	41.4± 4.4	41.7± 4.6	42.3± 4.8	43.2± 4.9	43.9± 5.1	45.0± 5.1	45.4± 5.4

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	47.3± 5.3	47.7± 5.2	48.2± 5.6	48.2± 5.8	48.3± 6.1	47.5± 5.9	45.9± 6.2
5 ppm	48.5± 5.4	48.8± 6.2	49.0± 5.8	48.6± 7.0	48.2± 7.5	47.8± 7.2	46.5± 7.8
15 ppm	46.8± 5.4	47.1± 5.3	47.8± 5.5	47.9± 6.1	47.1± 6.8	46.0± 6.3	44.4± 6.5
45 ppm	45.6± 5.3	46.0± 5.5	45.8± 5.5	45.3± 5.6	45.0± 6.2	43.9± 5.8*	42.2± 6.1*

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

(HAN260)

BAIS 4

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	45.1± 6.2	43.9± 6.4	43.0± 6.4
5 ppm	46.5± 7.9	45.9± 7.9	46.9± 8.6*
15 ppm	44.0± 5.7	42.5± 6.1	42.4± 5.9
45 ppm	42.3± 5.6	41.7± 5.0	41.6± 4.9

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

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	19.8± 0.8	20.0± 0.9	20.5± 1.0	21.0± 1.0	21.9± 1.1	22.1± 0.9	22.6± 1.1
5 ppm	19.8± 0.8	19.7± 0.9	20.1± 0.9*	20.7± 1.0	21.5± 0.9	21.9± 1.1	22.4± 1.2
15 ppm	19.8± 0.8	19.8± 0.9	20.5± 0.9	21.3± 1.0	21.7± 1.0	22.3± 0.8	22.9± 1.0
45 ppm	19.8± 0.8	19.6± 0.8	20.0± 0.7*	20.7± 0.8	21.4± 1.0	22.0± 0.8	22.5± 0.8

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	23.3± 1.2	23.8± 1.2	24.0± 1.0	24.2± 1.3	24.4± 1.2	25.0± 1.4	25.1± 1.2
5 ppm	23.0± 1.1	23.4± 1.3	23.5± 1.1	23.8± 1.3	24.1± 1.3	24.7± 1.3	24.8± 1.2
15 ppm	23.3± 1.1	23.7± 1.1	24.2± 1.3	24.3± 1.4	24.4± 1.1	24.7± 1.2	24.9± 1.0
45 ppm	23.2± 1.1	23.5± 1.0	23.9± 1.0	23.9± 0.9	24.2± 1.2	24.7± 1.2	24.8± 1.1

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	25.1± 1.3	26.4± 1.5	27.1± 1.7	28.3± 2.1	28.7± 2.5	29.2± 1.8	29.3± 2.2
5 ppm	24.9± 1.5	25.9± 1.6	26.8± 1.6	27.2± 2.1**	27.7± 2.1	28.3± 2.1*	28.6± 2.2
15 ppm	25.0± 1.1	26.1± 1.2	26.5± 1.3	27.1± 1.6**	27.5± 1.5*	28.1± 1.7*	28.2± 1.7*
45 ppm	24.9± 1.1	26.1± 1.3	26.3± 1.1	26.5± 1.3**	27.5± 1.5	27.6± 1.6**	28.2± 2.4*

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	29.6± 2.4	30.2± 2.4	30.4± 2.7	31.0± 2.8	31.0± 2.7	31.5± 2.5	31.4± 2.9
5 ppm	29.0± 2.3	29.6± 2.4	30.1± 2.5	30.3± 2.6	30.8± 2.8	31.0± 2.5	31.4± 3.0
15 ppm	28.8± 2.0	29.0± 1.7*	29.0± 1.7**	30.0± 2.1	30.2± 2.3	30.5± 2.2	30.9± 2.6
45 ppm	28.4± 1.8	28.5± 1.9**	29.4± 1.5	29.5± 1.7	29.9± 2.0	30.4± 1.9	30.7± 2.1

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	31.9± 3.0	32.1± 3.2	32.3± 3.4	32.7± 4.0	33.1± 3.1	32.8± 3.7	32.3± 3.9
5 ppm	31.0± 2.2	31.8± 2.7	32.2± 2.9	32.5± 3.1	32.8± 3.0	32.2± 3.5	33.0± 3.5
15 ppm	31.2± 2.9	31.5± 3.3	32.7± 3.6	33.0± 3.3	32.9± 3.2	32.6± 2.9	32.5± 2.7
45 ppm	31.1± 2.1	30.9± 2.5	32.5± 3.6	32.4± 3.3	33.1± 3.1	32.6± 3.8	31.7± 3.1

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	32.6± 2.8	32.4± 3.4	32.5± 3.4
5 ppm	33.0± 3.5	33.4± 3.6	34.4± 4.0
15 ppm	32.8± 3.5	32.9± 3.2	33.5± 3.7
45 ppm	33.0± 4.0	32.6± 4.1	32.6± 5.6

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

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0732
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>	5 ppm Av. FC.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	15 ppm Av. FC.	15 ppm % of cont. <50>	15 ppm No. of Surviv.	45 ppm Av. FC.	45 ppm % of cont. <50>	45 ppm No. of Surviv.
1-7	3.9 (50)	50/50	3.8 (50)	97	50/50	3.8 (50)	97	50/50	3.7 (50)	95	50/50
2-7	3.8 (50)	50/50	3.8 (50)	100	50/50	4.0 (50)	105	50/50	4.1 (50)	108	50/50
3-7	4.0 (50)	50/50	4.1 (50)	103	50/50	4.2 (50)	105	50/50	4.0 (50)	100	50/50
4-7	4.1 (50)	50/50	4.1 (50)	100	50/50	4.2 (49)	102	50/50	4.2 (50)	102	50/50
5-7	4.2 (50)	50/50	4.2 (50)	100	50/50	4.2 (49)	100	49/50	4.2 (50)	100	50/50
6-7	4.2 (50)	50/50	4.3 (50)	102	50/50	4.3 (49)	102	49/50	4.3 (47)	102	50/50
7-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.4 (49)	102	49/50	4.4 (50)	102	50/50
8-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.4 (49)	102	49/50	4.4 (50)	102	50/50
9-7	4.3 (50)	50/50	4.4 (50)	102	50/50	4.4 (49)	102	49/50	4.5 (50)	105	50/50
10-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.5 (49)	102	49/50	4.4 (50)	100	50/50
11-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.4 (49)	100	49/50	4.5 (50)	102	50/50
12-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.5 (49)	102	49/50	4.5 (50)	102	50/50
13-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.5 (49)	100	49/50	4.6 (50)	102	50/50
14-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.5 (49)	102	49/50	4.5 (50)	102	50/50
18-7	4.6 (50)	50/50	4.6 (50)	100	50/50	4.7 (49)	102	49/50	4.7 (50)	102	50/50
22-7	4.8 (50)	50/50	4.8 (50)	100	50/50	4.9 (49)	102	49/50	4.9 (50)	102	50/50
26-7	4.9 (50)	50/50	4.9 (50)	100	50/50	5.0 (49)	102	49/50	4.9 (50)	100	50/50
30-7	4.7 (50)	50/50	4.7 (50)	100	50/50	4.8 (49)	102	49/50	4.6 (50)	98	50/50
34-7	4.7 (50)	50/50	4.8 (50)	102	50/50	4.8 (48)	102	48/50	4.7 (50)	100	50/50
38-7	4.7 (50)	50/50	4.8 (50)	102	50/50	4.7 (48)	100	48/50	4.7 (50)	100	50/50
42-7	4.7 (50)	50/50	4.7 (50)	100	50/50	4.8 (48)	102	48/50	4.7 (49)	100	49/50
46-7	4.8 (50)	50/50	4.8 (49)	100	49/50	4.8 (48)	100	48/50	4.8 (49)	100	49/50
50-7	5.0 (50)	50/50	5.0 (49)	100	49/50	4.9 (48)	98	48/50	4.7 (49)	94	49/50
54-7	4.9 (50)	50/50	5.0 (49)	102	49/50	4.9 (48)	100	48/50	4.7 (49)	96	49/50
58-7	5.0 (50)	50/50	5.0 (49)	100	49/50	4.9 (48)	98	48/50	4.8 (49)	96	49/50
62-7	5.0 (50)	50/50	5.1 (49)	102	49/50	5.0 (48)	100	48/50	5.0 (48)	100	48/50
66-7	4.9 (50)	50/50	5.0 (49)	102	49/50	4.9 (48)	100	48/50	4.9 (48)	100	48/50
70-7	5.0 (49)	49/50	5.0 (49)	100	49/50	5.0 (48)	100	48/50	4.9 (47)	98	47/50
74-7	5.2 (48)	48/50	5.2 (49)	100	49/50	5.1 (46)	98	46/50	5.1 (47)	98	47/50
78-7	5.2 (48)	48/50	5.1 (48)	98	48/50	5.1 (43)	98	43/50	5.1 (47)	98	47/50
82-7	5.3 (47)	48/50	5.0 (47)	94	47/50	5.1 (42)	96	42/50	5.2 (47)	98	47/50
86-7	5.1 (46)	46/50	4.9 (44)	96	44/50	5.0 (40)	98	42/50	5.0 (45)	98	45/50
90-7	4.9 (45)	45/50	4.9 (39)	100	39/50	4.6 (41)	94	41/50	4.8 (44)	98	44/50
94-7	4.8 (45)	45/50	4.8 (39)	100	39/50	4.5 (40)	94	40/50	4.6 (43)	96	43/50
98-7	4.8 (43)	43/50	4.9 (37)	102	37/50	4.7 (39)	98	39/50	4.9 (40)	102	40/50
102-7	5.0 (42)	42/50	4.8 (35)	96	35/50	4.6 (37)	92	37/50	4.9 (38)	98	38/50
104-7	5.0 (42)	42/50	5.0 (34)	100	34/50	4.8 (36)	96	36/50	4.8 (37)	96	37/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0732
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>	5 ppm Av. FC.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	15 ppm Av. FC.	15 ppm % of cont. <50>	15 ppm No. of Surviv.	45 ppm Av. FC.	45 ppm % of cont. <50>	45 ppm No. of Surviv.
1-7	3.3 (50)	50/50	3.2 (50)	97	50/50	3.2 (50)	97	50/50	3.1 (50)	94	50/50
2-7	3.4 (50)	50/50	3.3 (50)	97	50/50	3.6 (50)	106	50/50	3.6 (50)	106	50/50
3-7	3.7 (50)	50/50	3.7 (50)	100	50/50	3.8 (50)	103	50/50	3.8 (50)	103	50/50
4-7	4.0 (50)	50/50	4.0 (50)	100	50/50	4.0 (50)	100	50/50	4.0 (50)	100	50/50
5-7	4.1 (50)	50/50	4.1 (50)	100	50/50	4.1 (50)	100	50/50	4.1 (50)	100	50/50
6-7	4.3 (50)	50/50	4.2 (50)	98	50/50	4.3 (50)	100	50/50	4.3 (50)	100	50/50
7-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.4 (50)	100	50/50	4.5 (50)	102	50/50
8-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.4 (50)	98	50/50	4.4 (50)	98	50/50
9-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.5 (50)	100	50/50	4.5 (50)	100	50/50
10-7	4.5 (50)	50/50	4.4 (50)	98	50/50	4.4 (50)	98	50/50	4.4 (50)	98	50/50
11-7	4.4 (50)	50/50	4.4 (50)	100	50/50	4.3 (50)	98	50/50	4.4 (50)	100	50/50
12-7	4.4 (50)	50/50	4.3 (50)	98	50/50	4.3 (50)	98	50/50	4.4 (50)	100	50/50
13-7	4.4 (50)	50/50	4.3 (50)	98	50/50	4.3 (50)	98	50/50	4.4 (50)	100	50/50
14-7	4.3 (50)	50/50	4.3 (50)	100	50/50	4.3 (50)	100	50/50	4.3 (50)	100	50/50
18-7	4.6 (50)	50/50	4.4 (50)	96	50/50	4.4 (50)	96	50/50	4.5 (49)	98	49/50
22-7	4.8 (50)	50/50	4.7 (50)	98	50/50	4.6 (50)	96	50/50	4.6 (49)	96	49/50
26-7	4.9 (50)	50/50	4.6 (50)	94	50/50	4.6 (50)	94	50/50	4.6 (49)	94	49/50
30-7	4.8 (50)	50/50	4.5 (50)	94	50/50	4.4 (50)	92	50/50	4.5 (49)	94	49/50
34-7	4.6 (50)	50/50	4.3 (50)	93	50/50	4.3 (50)	93	50/50	4.3 (49)	93	49/50
38-7	4.5 (50)	50/50	4.3 (50)	96	50/50	4.3 (50)	96	50/50	4.3 (48)	96	48/50
42-7	4.4 (50)	50/50	4.3 (50)	98	50/50	4.2 (50)	95	50/50	4.3 (47)	98	47/50
46-7	4.5 (50)	50/50	4.3 (50)	96	50/50	4.3 (50)	96	50/50	4.3 (47)	96	47/50
50-7	4.6 (50)	50/50	4.5 (50)	98	50/50	4.3 (50)	93	50/50	4.5 (47)	98	47/50
54-7	4.6 (48)	48/50	4.4 (50)	96	50/50	4.5 (50)	98	50/50	4.4 (46)	96	46/50
58-7	4.6 (48)	48/50	4.5 (50)	98	50/50	4.4 (50)	96	50/50	4.5 (46)	98	46/50
62-7	4.6 (48)	48/50	4.4 (50)	96	50/50	4.4 (50)	96	50/50	4.5 (46)	98	46/50
66-7	4.4 (48)	48/50	4.4 (50)	100	50/50	4.4 (50)	100	50/50	4.6 (46)	105	46/50
70-7	4.5 (47)	47/50	4.4 (49)	98	49/50	4.3 (50)	96	50/50	4.5 (46)	100	46/50
74-7	4.7 (46)	46/50	4.6 (48)	98	48/50	4.7 (49)	100	49/50	4.6 (46)	98	46/50
78-7	4.7 (45)	45/50	4.6 (48)	98	48/50	4.7 (47)	100	47/50	4.9 (43)	104	43/50
82-7	4.9 (43)	43/50	4.7 (47)	96	47/50	4.9 (41)	100	41/50	4.9 (42)	100	42/50
86-7	4.7 (41)	41/50	4.5 (47)	96	47/50	4.7 (41)	100	41/50	4.8 (42)	102	42/50
90-7	4.4 (36)	36/50	4.4 (45)	100	45/50	4.4 (40)	100	40/50	4.5 (39)	102	39/50
94-7	4.5 (29)	29/50	4.5 (43)	100	43/50	4.3 (40)	96	40/50	4.3 (35)	96	35/50
98-7	4.5 (26)	26/50	4.5 (41)	100	41/50	4.5 (37)	100	37/50	4.8 (33)	107	33/50
102-7	4.7 (23)	23/50	4.7 (35)	100	35/50	4.7 (33)	100	33/50	4.9 (29)	104	29/50
104-7	4.7 (22)	22/50	4.7 (34)	100	34/50	4.7 (33)	100	33/50	4.7 (29)	100	29/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 1-7 (7)	2-7 (7)	3-7 (7)	4-7 (7)	5-7 (7)	6-7 (7)	7-7 (7)
Control	3.9± 0.3	3.8± 0.3	4.0± 0.2	4.1± 0.3	4.2± 0.3	4.2± 0.3	4.3± 0.3
5 ppm	3.8± 0.3	3.8± 0.2	4.1± 0.2*	4.1± 0.3	4.2± 0.2	4.3± 0.3	4.3± 0.2
15 ppm	3.8± 0.3	4.0± 0.3**	4.2± 0.5**	4.2± 0.3	4.2± 0.3	4.3± 0.3	4.4± 0.3
45 ppm	3.7± 0.3	4.1± 0.2**	4.0± 0.3	4.2± 0.2	4.2± 0.3	4.3± 0.3	4.4± 0.3

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

(HAN260)

BAIS 4

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 8-7 (7)	9-7 (7)	10-7 (7)	11-7 (7)	12-7 (7)	13-7 (7)	14-7 (7)
Control	4.3± 0.3	4.3± 0.3	4.4± 0.2	4.4± 0.3	4.4± 0.3	4.5± 0.3	4.4± 0.3
5 ppm	4.3± 0.2	4.4± 0.2	4.4± 0.3	4.4± 0.3	4.4± 0.2	4.4± 0.3	4.4± 0.3
15 ppm	4.4± 0.3	4.4± 0.3	4.5± 0.3	4.4± 0.3	4.5± 0.3	4.5± 0.3	4.5± 0.3
45 ppm	4.4± 0.3	4.5± 0.3**	4.4± 0.3	4.5± 0.3	4.5± 0.3*	4.6± 0.3	4.5± 0.3

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

STUDY NO. : 0732
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	4.8± 0.3	4.9± 0.3	4.7± 0.3	4.7± 0.3	4.7± 0.3	4.7± 0.3
5 ppm	4.6± 0.3	4.8± 0.3	4.9± 0.3	4.7± 0.3	4.8± 0.2	4.8± 0.3	4.7± 0.3
15 ppm	4.7± 0.3	4.9± 0.3	5.0± 0.4	4.8± 0.3	4.8± 0.2	4.7± 0.3	4.8± 0.3
45 ppm	4.7± 0.3*	4.9± 0.3	4.9± 0.3	4.6± 0.3	4.7± 0.3	4.7± 0.3	4.7± 0.3

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 46-7 (7)	50-7 (7)	54-7 (7)	58-7 (7)	62-7 (7)	66-7 (7)	70-7 (7)
Control	4.8± 0.3	5.0± 0.3	4.9± 0.3	5.0± 0.4	5.0± 0.3	4.9± 0.4	5.0± 0.4
5 ppm	4.8± 0.3	5.0± 0.3	5.0± 0.3	5.0± 0.3	5.1± 0.4	5.0± 0.3	5.0± 0.3
15 ppm	4.8± 0.3	4.9± 0.3*	4.9± 0.4	4.9± 0.3	5.0± 0.3	4.9± 0.4	5.0± 0.4
45 ppm	4.8± 0.3	4.7± 0.3**	4.7± 0.3	4.8± 0.4**	5.0± 0.3	4.9± 0.3	4.9± 0.3

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

STUDY NO. : 0732
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	5.2± 0.4	5.2± 0.4	5.3± 0.8	5.1± 0.4	4.9± 0.4	4.8± 0.4	4.8± 0.5
5 ppm	5.2± 0.5	5.1± 0.6	5.0± 0.6	4.9± 0.8	4.9± 0.5	4.8± 0.5	4.9± 0.5
15 ppm	5.1± 0.4	5.1± 0.4	5.1± 0.4	5.0± 0.4	4.6± 0.4**	4.5± 0.4**	4.7± 0.4
45 ppm	5.1± 0.4	5.1± 0.4	5.2± 0.5	5.0± 0.7	4.8± 0.4	4.6± 0.7	4.9± 0.6

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

STUDY NO. : 0732
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	5.0± 0.5	5.0± 0.8
5 ppm	4.8± 0.8	5.0± 0.6
15 ppm	4.6± 0.5**	4.8± 0.5
45 ppm	4.9± 0.4	4.8± 0.6

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

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0732
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	3.3± 0.2	3.4± 0.3	3.7± 0.3	4.0± 0.3	4.1± 0.3	4.3± 0.3	4.4± 0.3
5 ppm	3.2± 0.3*	3.3± 0.2	3.7± 0.3	4.0± 0.2	4.1± 0.3	4.2± 0.3	4.4± 0.3
15 ppm	3.2± 0.2	3.6± 0.3**	3.8± 0.2**	4.0± 0.3	4.1± 0.3	4.3± 0.3	4.4± 0.3
45 ppm	3.1± 0.2**	3.6± 0.2**	3.8± 0.2**	4.0± 0.2	4.1± 0.3	4.3± 0.3	4.5± 0.3

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

STUDY NO. : 0732
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	4.5± 0.3	4.5± 0.3	4.5± 0.3	4.4± 0.3	4.4± 0.3	4.4± 0.3	4.3± 0.3
5 ppm	4.4± 0.3	4.4± 0.3	4.4± 0.3	4.4± 0.4	4.3± 0.3	4.3± 0.4	4.3± 0.3
15 ppm	4.4± 0.3	4.5± 0.3	4.4± 0.3	4.3± 0.3	4.3± 0.3	4.3± 0.4	4.3± 0.3
45 ppm	4.4± 0.3	4.5± 0.2	4.4± 0.2	4.4± 0.3	4.4± 0.3	4.4± 0.3	4.3± 0.3

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 18-7 (7)	22-7 (7)	26-7 (7)	30-7 (7)	34-7 (7)	38-7 (7)	42-7 (7)
Control	4.6± 0.3	4.8± 0.3	4.9± 0.4	4.8± 0.4	4.6± 0.4	4.5± 0.3	4.4± 0.4
5 ppm	4.4± 0.3*	4.7± 0.3*	4.6± 0.4**	4.5± 0.4**	4.3± 0.3**	4.3± 0.3*	4.3± 0.4
15 ppm	4.4± 0.3*	4.6± 0.3**	4.6± 0.3**	4.4± 0.4**	4.3± 0.3**	4.3± 0.4**	4.2± 0.3*
45 ppm	4.5± 0.3	4.6± 0.3**	4.6± 0.2**	4.5± 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. : 0732
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	4.5± 0.4	4.6± 0.4	4.6± 0.4	4.6± 0.4	4.6± 0.4	4.4± 0.4	4.5± 0.4
5 ppm	4.3± 0.4**	4.5± 0.3	4.4± 0.4**	4.5± 0.4	4.4± 0.4	4.4± 0.4	4.4± 0.4
15 ppm	4.3± 0.3	4.3± 0.3**	4.5± 0.4	4.4± 0.3	4.4± 0.4	4.4± 0.4	4.3± 0.6
45 ppm	4.3± 0.3*	4.5± 0.3	4.4± 0.3**	4.5± 0.3	4.5± 0.4	4.6± 0.4	4.5± 0.4

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

STUDY NO. : 0732
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	4.7± 0.5	4.7± 0.5	4.9± 0.8	4.7± 0.5	4.4± 0.7	4.5± 0.5	4.5± 0.5
5 ppm	4.6± 0.4	4.6± 0.5	4.7± 0.4	4.5± 0.6	4.4± 0.5	4.5± 0.4	4.5± 0.5
15 ppm	4.7± 0.6	4.7± 0.6	4.9± 0.7	4.7± 0.5	4.4± 0.5	4.3± 0.6	4.5± 0.7
45 ppm	4.6± 0.5	4.9± 0.4	4.9± 0.5	4.8± 0.4	4.5± 0.6	4.3± 0.6	4.8± 0.5

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

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 102-7 (7)	104-7 (7)
Control	4.7± 0.5	4.7± 0.5
5 ppm	4.7± 0.5	4.7± 0.6
15 ppm	4.7± 0.6	4.7± 0.7
45 ppm	4.9± 0.8	4.7± 0.8

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

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0732
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	39	9.56± 1.74	13.6± 2.4	43.6± 7.2	45.8± 2.0	14.2± 0.7	31.0± 1.3	1768± 264
5 ppm	32	9.39± 1.52	13.3± 1.8	42.9± 5.4	46.0± 3.0	14.3± 0.7	31.1± 0.8	1694± 367
15 ppm	36	9.30± 1.29	13.2± 1.7	42.5± 4.8	45.9± 2.5	14.2± 0.5	31.0± 1.0	1861± 442
45 ppm	37	9.64± 1.94	13.7± 2.7	43.6± 7.8	46.0± 5.3	14.3± 0.9	31.2± 1.5	1704± 461

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

(HCL070)

BAIS 4

STUDY NO. : 0732
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	39	3.4± 3.9
5 ppm	32	3.3± 2.5
15 ppm	36	3.5± 4.1
45 ppm	37	3.6± 5.2

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

STUDY NO. : 0732
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	39	4.35±	1.90	33±	14	59±	16	4±	5	3±	1	0±	0	1±	1
5 ppm	32	4.73±	2.67	30±	14	64±	14	3±	2	2±	1	0±	0	1±	1
15 ppm	36	3.25±	1.32*	37±	14	57±	15	4±	4	2±	1	0±	0	1±	1
45 ppm	37	3.69±	1.63	34±	12	59±	13	3±	3	2±	1	0±	0	1±	1

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

(HCL070)

BAIS 4

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0732
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	21	10.21± 0.94	14.5± 1.2	46.6± 3.5	45.7± 2.0	14.3± 0.5	31.2± 0.7	1077± 283
5 ppm	32	9.16± 1.93*	13.3± 2.5	42.8± 7.0	47.8± 5.8	14.6± 1.0	30.8± 1.6	1070± 371
15 ppm	33	9.82± 1.14	14.0± 1.7	44.8± 4.6	45.7± 2.3	14.3± 0.8	31.2± 0.9	1127± 255
45 ppm	27	8.78± 2.61	12.9± 3.5	41.9± 9.6	49.5± 7.7**	14.9± 1.4*	30.4± 2.1	924± 395

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

(HCL070)

BAIS4

STUDY NO. : 0732
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	21	2.6± 1.4
5 ppm	32	5.6± 9.9
15 ppm	33	3.1± 2.1
45 ppm	27	7.3± 10.6

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

(HCL070)

STUDY NO. : 0732
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	21	4.75± 6.93	25± 13	68± 14	3± 2	2± 2	0± 0	2± 3
5 ppm	32	3.50± 2.24	30± 14	63± 15	3± 3	2± 1	0± 0	2± 1
15 ppm	33	9.11± 28.31	28± 14	65± 15	3± 2	2± 1	0± 0	1± 1
45 ppm	27	17.88± 68.37	27± 17	64± 22	3± 3	2± 1	0± 0	5± 19

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

(HCL070)

BAIS4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0732
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	39	5.1± 1.1	2.4± 0.4	0.9± 0.2	0.10± 0.07	155± 28	104± 28	41± 46
5 ppm	32	4.9± 0.6	2.3± 0.3	0.9± 0.2	0.10± 0.02	148± 42	114± 30	45± 31
15 ppm	36	5.0± 0.6	2.4± 0.3	0.9± 0.1	0.09± 0.01	145± 32	108± 27	31± 19
45 ppm	37	5.0± 0.5	2.4± 0.3	0.9± 0.2	0.12± 0.10	157± 24	105± 32	40± 38

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

(HCL074)

BAIS 4

STUDY NO. : 0732
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 U/L	ALT U/L	LDH U/L	ALP U/L	G-GTP U/L	CK U/L
Control	39	184± 55	82± 58	47± 51	214± 87	266± 429	0± 1	62± 32
5 ppm	32	193± 53	135± 239	53± 79	223± 136	200± 43	0± 0	75± 97
15 ppm	36	188± 39	85± 74	41± 72	241± 287	197± 69	1± 1	101± 155
45 ppm	37	187± 43	178± 409	82± 177	322± 559	189± 54	1± 1	68± 64

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

STUDY NO. : 0732
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	39	25.6± 9.2	154± 2	4.4± 0.3	123± 2	8.7± 0.4	6.5± 0.8
5 ppm	32	28.6± 20.1	154± 2	4.4± 0.4	123± 3	8.7± 0.4	6.5± 1.0
15 ppm	36	31.8± 18.0	155± 2	4.4± 0.3	124± 2	8.7± 0.4	6.6± 1.0
45 ppm	37	23.3± 6.5	154± 3	4.5± 0.7	124± 3	8.7± 0.4	6.2± 0.6

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

(HCL074)

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0732
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	21	5.1± 0.4	2.5± 0.2	1.0± 0.2	0.10± 0.02	113± 28	82± 23	32± 24
5 ppm	32	5.0± 0.9	2.5± 0.3	1.0± 0.2	0.11± 0.05	110± 32	82± 27	40± 34
15 ppm	33	5.2± 0.7	2.5± 0.3	1.0± 0.2	0.10± 0.02	121± 28	87± 26	46± 51
45 ppm	27	4.8± 0.7	2.4± 0.3	1.1± 0.2	0.15± 0.19	114± 34	75± 20	30± 17

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

STUDY NO. : 0732
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 U/L	ALT U/L	LDH U/L	ALP U/L	G-GTP U/L	CK U/L
Control	21	147± 34	121± 94	37± 24	248± 210	371± 300	1± 1	134± 134
5 ppm	32	149± 47	128± 115	40± 32	635± 1597	324± 158	1± 1	222± 568
15 ppm	33	159± 44	134± 198	44± 57	229± 171	311± 162	1± 1	86± 60
45 ppm	27	132± 36	312± 545	112± 217	622± 1140	393± 345	1± 1	212± 502

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

(HCL074)

STUDY NO. : 0732
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	21	18.8± 7.0	152± 1	4.2± 0.3	122± 3	8.8± 0.3	6.2± 1.0
5 ppm	32	26.6± 22.0	153± 2	4.4± 0.7	123± 3	9.0± 0.6	6.9± 1.8
15 ppm	33	21.0± 16.6	153± 2	4.1± 0.3	123± 3	9.2± 0.8	6.4± 1.2
45 ppm	27	25.6± 19.7	153± 3	4.4± 0.6	124± 4	8.9± 0.5	6.8± 1.7

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

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0732
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	42	0	1	8	10	18	5	0		0	17	18	6	1	0		42	0	0	0	0	0		19	16	6	1	0	0		34	0	0	2	6	
5 ppm	34	0	2	8	8	13	2	1		0	13	16	5	0	0		34	0	0	0	0	0		20	6	7	1	0	0		31	0	0	0	3	
15 ppm	36	0	5	9	6	9	6	1		0	11	18	6	1	0		36	0	0	0	0	0		16	13	7	0	0	0		34	0	0	0	2	
45 ppm	38	0	4	10	12	3	8	1	*	0	13	21	4	0	0		38	0	0	0	0	0		14	15	9	0	0	0		36	0	0	0	2	

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

(HCL101)

STUDY NO. : 0732
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	42	42	0	0	0	0	
5 ppm	34	34	0	0	0	0	
15 ppm	36	36	0	0	0	0	
45 ppm	38	38	0	0	0	0	

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

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0732
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	23	0	0	3	3	6	10	1		0	7	12	3	1	0		23	0	0	0	0	0		9	9	4	1	0	0		22	0	1	0	0	
5 ppm	34	0	4	6	4	3	16	1		0	12	14	5	3	0		34	0	0	0	0	0		10	18	1	5	0	0		32	0	0	0	2	
15 ppm	33	0	5	3	3	6	10	6		1	11	16	5	0	0		33	0	0	0	0	0		14	15	4	0	0	0		32	0	0	0	1	
45 ppm	29	0	4	4	5	3	12	1		0	7	17	4	1	0		29	0	0	0	0	0		11	16	0	2	0	0		27	0	1	1	0	

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

Test of CHI SQUARE

(HCL101)

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Urobilinogen ±	+	2+	3+	4+	CHI
Control	23	23	0	0	0	0	
5 ppm	34	34	0	0	0	0	
15 ppm	33	33	0	0	0	0	
45 ppm	29	29	0	0	0	0	

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

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0732
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	39	39.4± 6.2	0.011± 0.002	0.208± 0.051	0.209± 0.019	0.205± 0.068	0.688± 0.303
5 ppm	33	42.6± 8.9	0.012± 0.002	0.217± 0.034	0.219± 0.022	0.215± 0.123	1.271± 2.727
15 ppm	36	38.0± 6.0	0.012± 0.002	0.220± 0.043	0.211± 0.032	0.204± 0.043	1.305± 2.304
45 ppm	37	37.4± 4.8	0.012± 0.002	0.202± 0.036	0.210± 0.016	0.207± 0.051	0.651± 0.150

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

(HCL040)

STUDY NO. : 0732
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	39	0.156± 0.207	1.599± 0.442	0.452± 0.016
5 ppm	33	0.152± 0.169	1.554± 0.275	0.452± 0.013
15 ppm	36	0.114± 0.070	1.493± 0.284	0.455± 0.016
45 ppm	37	0.144± 0.199	1.537± 0.404	0.457± 0.017

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

(HCL040)

BAIS4

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0732
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	21	28.0± 3.2	0.015± 0.003	0.060± 0.038	0.165± 0.016	0.208± 0.053	0.437± 0.042
5 ppm	32	30.4± 4.2	0.014± 0.002	0.116± 0.238	0.169± 0.024	0.200± 0.024	0.475± 0.118
15 ppm	33	29.0± 3.0	0.014± 0.002	0.073± 0.090	0.168± 0.023	0.198± 0.024	0.481± 0.220
45 ppm	27	29.4± 5.6	0.013± 0.002	0.120± 0.295	0.172± 0.021	0.214± 0.072	0.454± 0.085

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

(HCL040)

BAIS 4

STUDY NO. : 0732
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	21	0.159± 0.118	1.348± 0.183	0.483± 0.019
5 ppm	32	0.218± 0.181	1.669± 0.708	0.478± 0.016
15 ppm	33	0.164± 0.133	1.487± 0.379	0.478± 0.018
45 ppm	27	0.309± 0.465	1.629± 0.714	0.476± 0.016

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

(HCL040)

BAIS4

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0732
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	39	39.4± 6.2	0.029± 0.006	0.538± 0.146	0.538± 0.063	0.541± 0.261	1.795± 0.914
5 ppm	33	42.6± 8.9	0.029± 0.007	0.534± 0.146	0.532± 0.098	0.572± 0.630	2.676± 4.505
15 ppm	36	38.0± 6.0	0.031± 0.007	0.590± 0.148	0.563± 0.098	0.551± 0.139	3.247± 5.158
45 ppm	37	37.4± 4.8	0.031± 0.007	0.544± 0.096	0.569± 0.067	0.565± 0.174	1.751± 0.340

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

(HCL042)

BAIS4

STUDY NO. : 0732
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	39	0.416± 0.565	4.146± 1.302	1.177± 0.194
5 ppm	33	0.365± 0.390	3.741± 0.766	1.111± 0.256
15 ppm	36	0.305± 0.174	3.982± 0.809	1.229± 0.212
45 ppm	37	0.405± 0.625	4.172± 1.283	1.239± 0.151

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

(HCL042)

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0732
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	21	28.0± 3.2	0.053± 0.012	0.215± 0.138	0.594± 0.051	0.750± 0.194	1.566± 0.102
5 ppm	32	30.4± 4.2	0.046± 0.008	0.345± 0.549	0.559± 0.076	0.666± 0.109	1.563± 0.272
15 ppm	33	29.0± 3.0	0.050± 0.006	0.258± 0.331	0.584± 0.084	0.691± 0.099	1.684± 0.897
45 ppm	27	29.4± 5.6	0.047± 0.007	0.414± 0.996	0.598± 0.106	0.756± 0.322	1.570± 0.267

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

(HCL042)

BAIS4

STUDY NO. : 0732
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	21	0.575± 0.423	4.827± 0.497	1.746± 0.195
5 ppm	32	0.723± 0.611	5.449± 1.786	1.599± 0.188
15 ppm	33	0.567± 0.456	5.123± 1.093	1.665± 0.153
45 ppm	27	1.101± 1.715	5.598± 2.193	1.660± 0.235

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

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

Organ	Findings	Group Name	Control				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
[Integumentary system/appandage]																		
skin/app			<50>				<50>				<50>				<50>			
	ulcer		0	6	0	0	0	2	0	0	0	8	0	0	0	3	0	0
			(0)	(12)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(6)	(0)	(0)
	scab		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 system]																		
nasal cavit			<50>				<50>				<50>				<50>			
	exudate		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		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)
	eosinophilic change:olfactory epithelium		19	0	1	0	20	2	0	0	21	0	0	0	24	2	0	0
			(38)	(0)	(2)	(0)	(40)	(4)	(0)	(0)	(42)	(0)	(0)	(0)	(48)	(4)	(0)	(0)
	eosinophilic change:respiratory epithelium		6	2	0	0	4	0	0	0	5	0	0	0	10	1	0	0
			(12)	(4)	(0)	(0)	(8)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(20)	(2)	(0)	(0)
	inflammation:olfactory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
(Respiratory system)																		
nasal cavit			<50>				<50>				<50>				<50>			
	respiratory metaplasia:olfactory epithelium		5 (10)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)
	respiratory metaplasia:gland		27 (54)	0 (0)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	0 * (0)	12 (24)	0 (0)	0 (0)	0 ** (0)	15 (30)	0 (0)	0 (0)	0 * (0)
	inflammation:transitional epithelium		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	22 (44)	0 (0)	0 (0)	0 ** (0)
	hyperplasia:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	19 (38)	0 (0)	0 (0)	0 ** (0)
	squamous cell metaplasia:transitional epithelium		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	erosion:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	ulcer:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Respiratory system}																		
nasopharynx		<50>	1	2	0	0	2	0	0	0	0	0	0	0	0	0	0	0
	eosinophilic change		(2)	(4)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
lung		<50>	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	edema		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	inflammatory infiltration		3	0	0	0	2	0	0	0	5	1	0	0	3	0	0	0
			(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(10)	(2)	(0)	(0)	(6)	(0)	(0)	(0)
	lymphocytic 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)
	accumulation of foamy cells		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)
	bronchiolar-alveolar cell hyperplasia		2	0	0	0	2	0	0	0	1	1	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	uremic pneumonitis		0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow		<50>	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	granulation		(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 1+ (%)	Control 2+ (%)	Control 3+ (%)	Control 4+ (%)	5 ppm 1+ (%)	5 ppm 2+ (%)	5 ppm 3+ (%)	5 ppm 4+ (%)	15 ppm 1+ (%)	15 ppm 2+ (%)	15 ppm 3+ (%)	15 ppm 4+ (%)	45 ppm 1+ (%)	45 ppm 2+ (%)	45 ppm 3+ (%)	45 ppm 4+ (%)
			50				50				50				50			
(Hematopoietic system)																		
bone marrow			<50>				<50>				<50>				<50>			
	increased hematopoiesis		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	granulopoiesis:increased		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
spleen			<50>				<50>				<50>				<50>			
	deposit of melanin		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		15 (30)	3 (6)	0 (0)	0 (0)	9 (18)	10 (20)	0 (0)	0 (0)	12 (24)	5 (10)	0 (0)	0 (0)	18 (36)	4 (8)	0 (0)	0 (0)
	lymph-follicular hyperplasia		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	granulopoiesis:increased		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)
(Circulatory system)																		
heart			<50>				<50>				<50>				<50>			
	mineralization		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Circulatory system}																		
heart		<50>																
	myocardial necrosis		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Digestive system}																		
tongue		<50>																
	fibrosis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
stomach		<50>																
	deposit of amyloid		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)
	ulcer:forestomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:forestomach		1 (2)	1 (2)	2 (4)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	erosion:glandular stomach		16 (32)	0 (0)	0 (0)	0 (0)	14 (28)	2 (4)	0 (0)	0 (0)	13 (26)	1 (2)	0 (0)	0 (0)	15 (30)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Digestive system}																		
stomach		<50>																
	hyperplasia:glandular stomach		5 (10)	0 (0)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	intestinal metaplasia:glandular stomach		3 (6)	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)
	dilated glands		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
small intes		<50>																
	deposit of amyloid		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)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
liver		<50>																
	angiectasis		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)
	hemorrhage		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
(Digestive system)																		
liver		<50>	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	peliosis-like lesion		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:focal		2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	inflammatory cell nest		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	intestinal metaplasia		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		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)
	acidophilic cell focus		2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	basophilic cell focus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	bile duct hyperplasia		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				15 ppm				45 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	1	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
gall bladd			<50>				<50>				<50>				<50>			
	hyperplasia		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)
pancreas			<50>				<50>				<50>				<50>			
	islet cell hyperplasia		0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyaline droplet		1	2	0	0	4	1	0	0	2	1	0	0	2	0	0	0
			(2)	(4)	(0)	(0)	(8)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	inflammatory infiltration		0	1	0	0	1	0	0	0	3	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Urinary system}																		
kidney		<50>	1	0	0	0	1	1	0	0	0	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	lymphocytic infiltration																	
			2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	osseous metaplasia																	
			2	0	0	0	4	1	0	0	4	1	0	0	0	1	0	0
			(4)	(0)	(0)	(0)	(8)	(2)	(0)	(0)	(8)	(2)	(0)	(0)	(0)	(2)	(0)	(0)
	scar																	
			0	3	0	0	1	0	2	0	0	4	2	0	0	1	0	0
			(0)	(6)	(0)	(0)	(2)	(0)	(4)	(0)	(0)	(8)	(4)	(0)	(0)	(2)	(0)	(0)
	inflammatory polyp																	
			0	6	1	0	0	1	2	0	0	3	3	0	0	0	0	1
			(0)	(6)	(2)	(0)	(0)	(2)	(4)	(0)	(0)	(6)	(6)	(0)	(0)	(0)	(0)	(2)
	hydronephrosis																	
			1	0	0	0	0	1	0	0	2	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	pyelonephritis																	
			6	0	0	0	4	0	0	0	3	0	0	0	4	0	0	0
			(12)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	mineralization:cortex																	
			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)
	urothelial hyperplasia:pelvis																	

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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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
[Urinary system]																		
kidney		<50>																
	atypical tubule hyperplasia		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)
	dilated pelvis		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)
	inflammation:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	hyaline cast:urinary tubule		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)
urin bladd		<50>																
	dilatation		0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)
	inflammatory infiltration		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)	1 (2)	0 (0)	0 (0)
	simple hyperplasia:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
urethra		<50>																
	inflammation		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
(Endocrine system)																		
pituitary			<50>				<49>				<50>				<50>			
	angiectasis		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)
	cyst		4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	Rathke pouch		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<50>				<50>				<50>			
	follicular hyperplasia		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)
parathyroid			<50>				<50>				<50>				<50>			
	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)
adrenal			<50>				<50>				<50>				<50>			
	spindle-cell hyperplasia		11 (22)	2 (4)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	15 (30)	1 (2)	0 (0)	0 (0)	8 (16)	2 (4)	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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
(Endocrine system)																		
adrenal		<50>																
	hyperplasia:cortical cell		3 (6)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)
(Reproductive system)																		
testis		<50>																
	mineralization		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)
	interstitial cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
epididymis		<50>																
	atrophy		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)
	inflammatory infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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< a > a : Number of animals examined at the site
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Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Reproductive system}																		
epididymis		<50>																
	spermatogenic granuloma		1	0	0	0	3	1	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
semin ves		<50>																
	inflammatory infiltration		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)	(0)	(0)	(0)	(0)
prostate		<50>																
	inflammatory infiltration		1	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Nervous system}																		
brain		<50>																
	mineralization		19	0	0	0	12	0	0	0	9	0	0	0 *	9	0	0	0 *
			(38)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(18)	(0)	(0)	(0)
{Special sense organs/appendage}																		
eye		<50>																
	cataract		0	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)

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				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	retinal atrophy		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)
	keratitis		0	0	0	0	0	1	0	0	0	1	1	0	1	1	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(2)	(2)	(0)	(0)
Harder gl			<50>				<50>				<50>				<50>			
	hyperplasia		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Musculoskeletal system}																		
bone			<50>				<50>				<50>				<50>			
	osteofibrosis		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

TABLE L4

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : FEMALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Integumentary system/appandage}																		
skin/app		<50>																
	scab		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)
{Respiratory system}																		
nasal cavit		<50>																
	eosinophilic change:olfactory epithelium		27 (54)	1 (2)	0 (0)	0 (0)	30 (60)	0 (0)	0 (0)	0 (0)	27 (54)	1 (2)	0 (0)	0 (0)	39 (78)	4 (8)	0 (0)	0 ** (0)
	eosinophilic change:respiratory epithelium		32 (64)	9 (18)	1 (2)	0 (0)	38 (76)	7 (14)	0 (0)	0 (0)	36 (72)	6 (12)	0 (0)	0 (0)	40 (80)	5 (10)	0 (0)	0 (0)
	inflammation:olfactory epithelium		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)
	respiratory metaplasia:olfactory epithelium		13 (26)	0 (0)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	17 (34)	2 (4)	0 (0)	0 (0)
	respiratory metaplasia:gland		32 (64)	0 (0)	0 (0)	0 (0)	32 (64)	0 (0)	0 (0)	0 (0)	28 (56)	0 (0)	0 (0)	0 (0)	30 (60)	0 (0)	0 (0)	0 (0)
	inflammation:transitional epithelium		8 (16)	0 (0)	0 (0)	0 (0)	13 (26)	0 (0)	0 (0)	0 (0)	30 (60)	0 (0)	0 (0)	0 ** (0)	45 (90)	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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
[Respiratory system]																		
nasal cavit		<50>	<50>				<50>				<50>				<50>			
	hyperplasia:transitional epithelium	4	0	0	0	6	0	0	0	15	0	0	0 *	32	1	0	0 **
		(8)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(64)	(2)	(0)	(0)
	inflammtory infiltration:respiratory epithelium	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)
	squamous cell metaplasia:transitional epithelium	3	0	0	0	2	0	0	0	4	0	0	0	16	1	0	0 **
		(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(32)	(2)	(0)	(0)
	erosion:transitional epithelium	1	0	0	0	2	0	0	0	2	0	0	0	2	0	0	0
		(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	ulcer:transitional epithelium	0	0	0	0	1	0	0	0	2	0	0	0	3	0	0	0
		(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	atrophy:olfactory epithelium	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:respiratory epithelium	0	0	0	0	0	2	0	0	2	0	0	0	0	0	0	0
		(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:olfactory epithelium	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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
(Respiratory system)																		
nasopharynx		<50>																
	eosinophilic change		11 (22)	1 (2)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
lung		<50>																
	hemorrhage		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	edema		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	accumulation of foamy cells		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)
	bronchiolar-alveolar cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	uremic pneumonitis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
(Hematopoietic system)																		
bone marrow			<50>				<50>				<50>				<50>			
	deposit of hemosiderin		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	granulation		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	increased hematopoiesis		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)
	myelofibrosis		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
lymph node			<50>				<50>				<50>				<50>			
	lymphadenitis		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>			
	deposit of melanin		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		8 (16)	10 (20)	4 (8)	0 (0)	11 (22)	7 (14)	1 (2)	0 (0)	7 (14)	4 (8)	1 (2)	0 (0)	13 (26)	5 (10)	3 (6)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}																		
spleen			<50>				<50>				<50>				<50>			
	lymph-follicular hyperplasia		0	0	0	0	1	1	0	0	1	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	myocardial necrosis		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)
	arteritis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
tongue			<50>				<50>				<50>				<50>			
	inflammatory infiltration		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)

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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Digestive system}																		
salivary gl		<50>	1	0	0	0	1	0	0	0	2	0	0	0	1	0	0	0
	lymphocytic infiltration		(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
stomach		<50>	1	1	0	0	0	0	0	0	3	0	0	0	2	1	0	0
	hyperplasia:forestomach		(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(2)	(0)	(0)
	erosion:glandular stomach		7	5	0	0	4	3	1	0	12	1	0	0	10	2	1	0
			(14)	(10)	(0)	(0)	(8)	(6)	(2)	(0)	(24)	(2)	(0)	(0)	(20)	(4)	(2)	(0)
	ulcer:glandular stomach		0	0	0	0	0	0	0	0	2	0	0	0	3	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(2)	(0)	(0)
	hyperplasia:glandular stomach		5	0	0	0	1	0	0	0	4	0	0	0	2	0	0	0
			(10)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	intestinal metaplasia:glandular stomach		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)
	dilated glands		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)
liver		<50>	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
	angiectasis		(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	peliosis-like lesion		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)
	necrosis:focal		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	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)	1 (2)	0 (0)	0 (0)	0 (0)
	inflammatory cell nest		1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	6 (12)	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)	3 (6)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)
	biliary cyst		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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				5 ppm				15 ppm				45 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}																		
gall bladd			<50>				<50>				<50>				<50>			
	malformation		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)
	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)
	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)
	intestinal metaplasia		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	cyst		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)
	hyaline droplet		11	6	0	0	6	6	0	0	9	3	0	0	4	3	0	0
			(22)	(12)	(0)	(0)	(12)	(12)	(0)	(0)	(18)	(6)	(0)	(0)	(8)	(6)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	scar		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	1 (2)	5 (10)	0 (0)	0 (0)
	inflammatory polyp		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hydronephrosis		0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	1 (2)	0 (0)
	mineralization:cortex		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)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				15 ppm				45 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>			
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Endocrine system]																		
pituitary			<49>				<50>				<50>				<49>			
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	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)	2 (4)	0 (0)	0 (0)	0 (0)
	hyperplasia		11 (22)	2 (4)	0 (0)	0 (0)	14 (28)	4 (8)	0 (0)	0 (0)	5 (10)	6 (12)	0 (0)	0 (0)	6 (12)	5 (10)	1 (2)	0 (0)
	Rathke pouch		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<50>				<50>				<50>			
	cyst		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)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Endocrine system}																		
thyroid		<50>					<50>				<50>				<50>			
	ultimobranchial body remanet		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	C-cell hyperplasia		0 (0)	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)
adrenal		<50>					<50>				<50>				<50>			
	spindle-cell hyperplasia		23 (46)	24 (48)	0 (0)	0 (0)	25 (50)	22 (44)	0 (0)	0 (0)	16 (32)	31 (62)	0 (0)	0 (0)	20 (40)	29 (58)	0 (0)	0 (0)
	focal fatty change:cortex		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Reproductive system}																		
ovary		<50>					<50>				<50>				<50>			
	angiectasis		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	thrombus		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				5 ppm				15 ppm				45 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
(Reproductive system)																		
ovary			<50>				<50>				<50>				<50>			
	cyst		8	0	0	0	12	0	0	0	8	0	0	0	12	1	0	0
			(16)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(24)	(2)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	dilatation		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	angiectasis		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)
	cystic endometrial hyperplasia		27	0	0	0	22	1	0	0	33	0	0	0	20	0	1	0
			(54)	(0)	(0)	(0)	(44)	(2)	(0)	(0)	(66)	(0)	(0)	(0)	(40)	(0)	(2)	(0)
(Nervous system)																		
brain			<50>				<50>				<50>				<50>			
	deformity		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)
	vacuolic 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+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	15 ppm 50 1+ (%)	15 ppm 50 2+ (%)	15 ppm 50 3+ (%)	15 ppm 50 4+ (%)	45 ppm 50 1+ (%)	45 ppm 50 2+ (%)	45 ppm 50 3+ (%)	45 ppm 50 4+ (%)
{Nervous system}																		
brain		<50>	3	0	0	0	6	0	0	0	3	0	0	0	1	0	0	0
	mineralization		(6)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Special sense organs/appendage}																		
Harder gl		<50>	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	inflammatory infiltration		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia		1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle		<50>	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	mineralization		(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

TABLE O

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	5 ppm	15 ppm	45 ppm
	SITE : subcutis TUMOR : fibrosarcoma			
Tumor rate				
Overall rates(a)	0/50 (0.0)	3/50 (6.0)	2/50 (4.0)	1/50 (2.0)
Adjusted rates(b)	0.0	4.88	6.06	0.0
Terminal rates(c)	0/22 (0.0)	0/34 (0.0)	2/33 (6.1)	0/29 (0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2387			
Prevalence method(d)	P = 0.7446			
Combined analysis(d)	P = 0.5397			
Cochran-Armitage test(e)	P = 0.8586			
Fisher Exact test(e)		P = 0.1212	P = 0.2475	P = 0.5000
	SITE : lung TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	0/50 (0.0)	2/50 (4.0)	1/50 (2.0)	3/50 (6.0)
Adjusted rates(b)	0.0	4.88	3.03	8.82
Terminal rates(c)	0/22 (0.0)	1/34 (2.9)	1/33 (3.0)	2/29 (6.9)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.0766			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.1378			
Fisher Exact test(e)		P = 0.2475	P = 0.5000	P = 0.1212
	SITE : lung TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	0/50 (0.0)	3/50 (6.0)	1/50 (2.0)	3/50 (6.0)
Adjusted rates(b)	0.0	5.00	3.03	8.82
Terminal rates(c)	0/22 (0.0)	1/34 (2.9)	1/33 (3.0)	2/29 (6.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5534			
Prevalence method(d)	P = 0.0784			
Combined analysis(d)	P = 0.1373			
Cochran-Armitage test(e)	P = 0.2586			
Fisher Exact test(e)		P = 0.1212	P = 0.5000	P = 0.1212

Group Name	Control	5 ppm	15 ppm	45 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	16/50(32.0)	17/50(34.0)	16/50(32.0)	20/50(40.0)
Adjusted rates(b)	27.27	32.35	24.24	36.67
Terminal rates(c)	6/22(27.3)	11/34(32.4)	8/33(24.2)	10/29(34.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5156			
Prevalence method(d)	P = 0.1343			
Combined analysis(d)	P = 0.2398			
Cochran-Armitage test(e)	P = 0.3766			
Fisher Exact test(e)		P = 0.5000	P = 0.5848	P = 0.2661
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	18.18	2.50	9.09	10.34
Terminal rates(c)	4/22(18.2)	0/34(0.0)	3/33(9.1)	3/29(10.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4772			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9116			
Fisher Exact test(e)		P = 0.1811	P = 0.5000	P = 0.5000
	SITE : liver			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	2.86	2.94	4.26	3.45
Terminal rates(c)	0/22(0.0)	1/34(2.9)	0/33(0.0)	1/29(3.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9826			
Prevalence method(d)	P = 0.4599			
Combined analysis(d)	P = 0.8318			
Cochran-Armitage test(e)	P = 0.3013			
Fisher Exact test(e)		P = 0.1811	P = 0.3389	P = 0.1811

Group Name	Control	5 ppm	15 ppm	45 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	4/50 (8.0)	1/50 (2.0)	3/50 (6.0)	4/50 (8.0)
Adjusted rates(b)	18.18	2.50	9.09	10.34
Terminal rates(c)	4/22 (18.2)	0/34 (0.0)	3/33 (9.1)	3/29 (10.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2814			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5505			
Fisher Exact test(e)		P = 0.1811	P = 0.5000	P = 0.6425
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	4/49 (8.2)	9/50 (18.0)	8/50 (16.0)	13/49 (26.5)
Adjusted rates(b)	18.18	19.05	24.24	35.71
Terminal rates(c)	4/22 (18.2)	6/34 (17.6)	8/33 (24.2)	10/28 (35.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2397			
Prevalence method(d)	P = 0.0229*			
Combined analysis(d)	P = 0.0174*			
Cochran-Armitage test(e)	P = 0.0305*			
Fisher Exact test(e)		P = 0.1245	P = 0.1882	P = 0.0153*
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	6/49 (12.2)	11/50 (22.0)	8/50 (16.0)	13/49 (26.5)
Adjusted rates(b)	27.27	21.62	24.24	35.71
Terminal rates(c)	6/22 (27.3)	7/34 (20.6)	8/33 (24.2)	10/28 (35.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3826			
Prevalence method(d)	P = 0.0728			
Combined analysis(d)	P = 0.0741			
Cochran-Armitage test(e)	P = 0.1326			
Fisher Exact test(e)		P = 0.1539	P = 0.4029	P = 0.0619

Group Name	Control	5 ppm	15 ppm	45 ppm
	SITE : uterus TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	4.55	7.32	0.0	7.69
Terminal rates(c)	1/22(4.5)	2/34(5.9)	0/33(0.0)	2/29(6.9)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.2055			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4243			
Fisher Exact test(e)		P = 0.3087	P = 0.5000	P = 0.3087
	SITE : uterus TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	13/50(26.0)	8/50(16.0)	10/50(20.0)
Adjusted rates(b)	4.55	25.00	7.32	17.24
Terminal rates(c)	1/22(4.5)	8/34(23.5)	1/33(3.0)	5/29(17.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7397			
Prevalence method(d)	P = 0.4325			
Combined analysis(d)	P = 0.6533			
Cochran-Armitage test(e)	P = 0.6366			
Fisher Exact test(e)		P = 0.4076	P = 0.3055	P = 0.5000

Group Name	Control	5 ppm	15 ppm	45 ppm
	SITE : bone TUMOR : osteosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	4.55	0.0	0.0	3.03
Terminal rates(c)	1/22(4.5)	0/34(0.0)	0/33(0.0)	0/29(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0156* ?			
Prevalence method(d)	P = 0.3095			
Combined analysis(d)	P = 0.0338*			
Cochran-Armitage test(e)	P = 0.0428*			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.3087

(HPT360A)

BAIS5

(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 Q

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

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

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Pituitary gland	2238			
Adenoma		331	14.8	2 - 34
Bone	2247			
Osteosarcoma		8	0.4	0 - 2

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

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

TABLE R1

CAUSE OF DEATH : MALE

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

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

Group Name	Control	5 ppm	15 ppm	45 ppm
Number of Dead and Moribund Animal	9	16	14	13
urinary retention	2	2	3	6
hydronephrosis	1	1	4	0
tumor d:leukemia	1	2	2	2
tumor d:subcutis	0	0	1	1
tumor d:lung	0	3	0	1
tumor d:lymph node	1	1	0	0
tumor d:spleen	1	0	2	1
tumor d:liver	2	7	1	2
tumor d:kidney	1	0	0	0
tumor d:peritoneum	0	0	1	0

(BIO120)

BAIS5

TABLE R2

CAUSE OF DEATH : FEMALE

STUDY NO. : 0732
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : FEMALE

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

Group Name	Control	5 ppm	15 ppm	45 ppm
Number of Dead and Moribund Animal	28	16	17	21
no microscop confirm	0	0	1	0
hydronephrosis	2	0	0	1
tumor d:leukemia	10	6	8	8
tumor d:subcutis	0	2	2	1
tumor d:lung	0	1	0	0
tumor d:spleen	1	0	1	1
tumor d:liver	3	0	0	1
tumor d:urin bladd	0	1	0	0
tumor d:pituitary	0	2	0	1
tumor d:ovary	1	0	0	0
tumor d:uterus	10	3	5	5
tumor d:periph nerv	1	0	0	0
tumor d:bone	0	0	0	2
tumor d:pleura	0	1	0	1

FIGURES

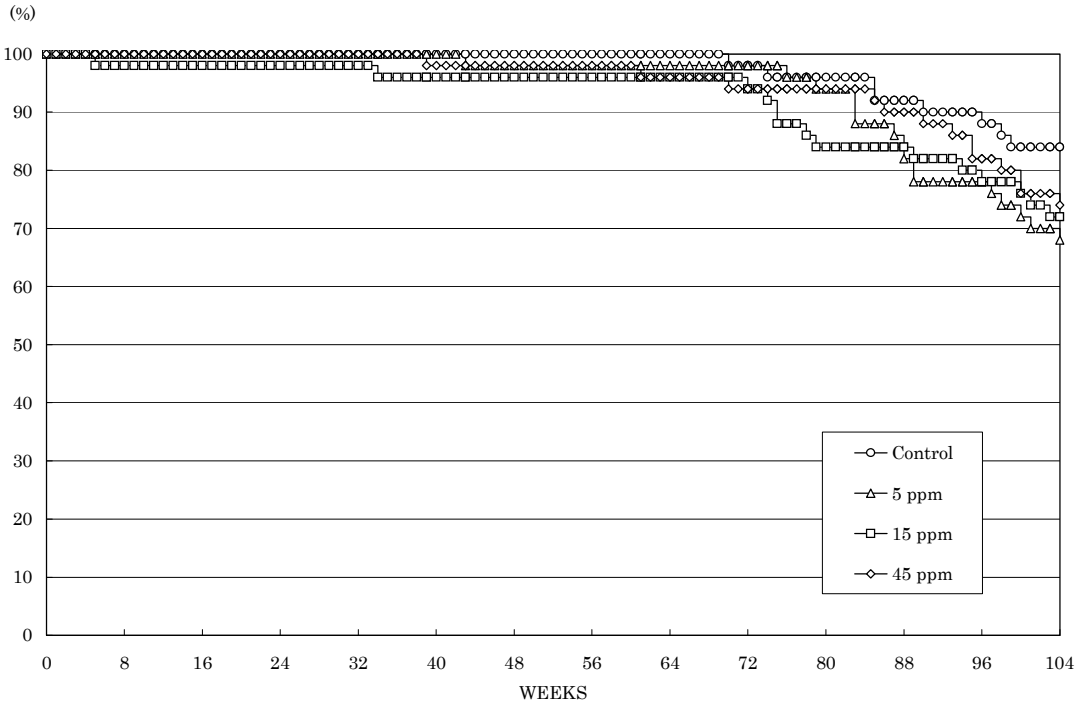


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

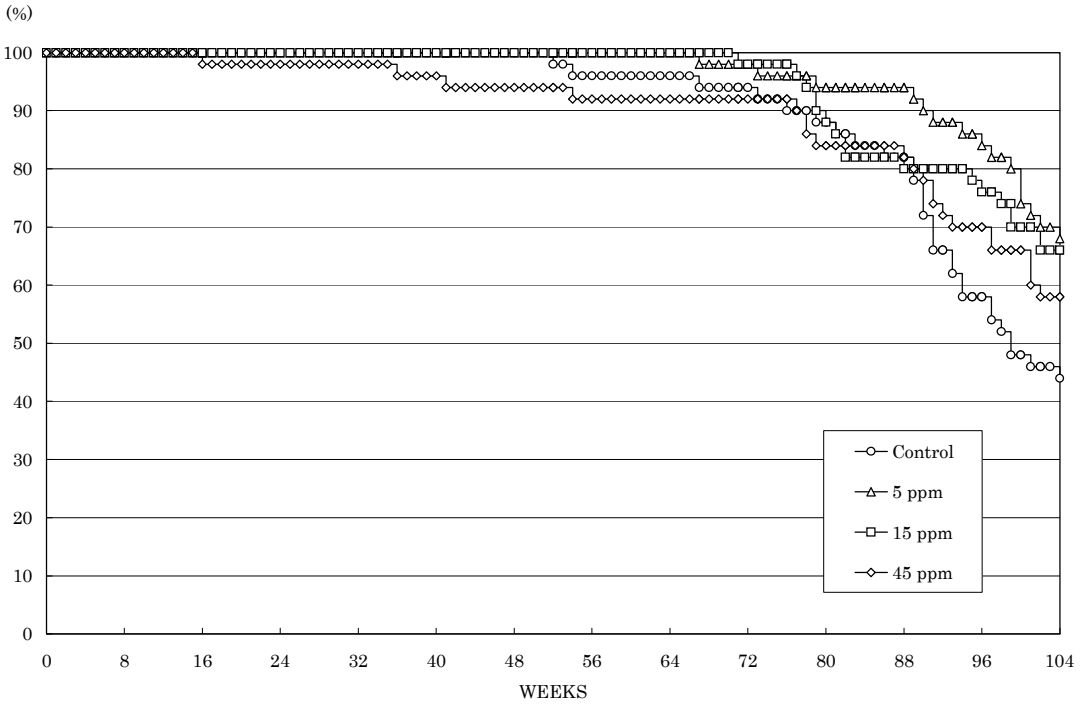


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

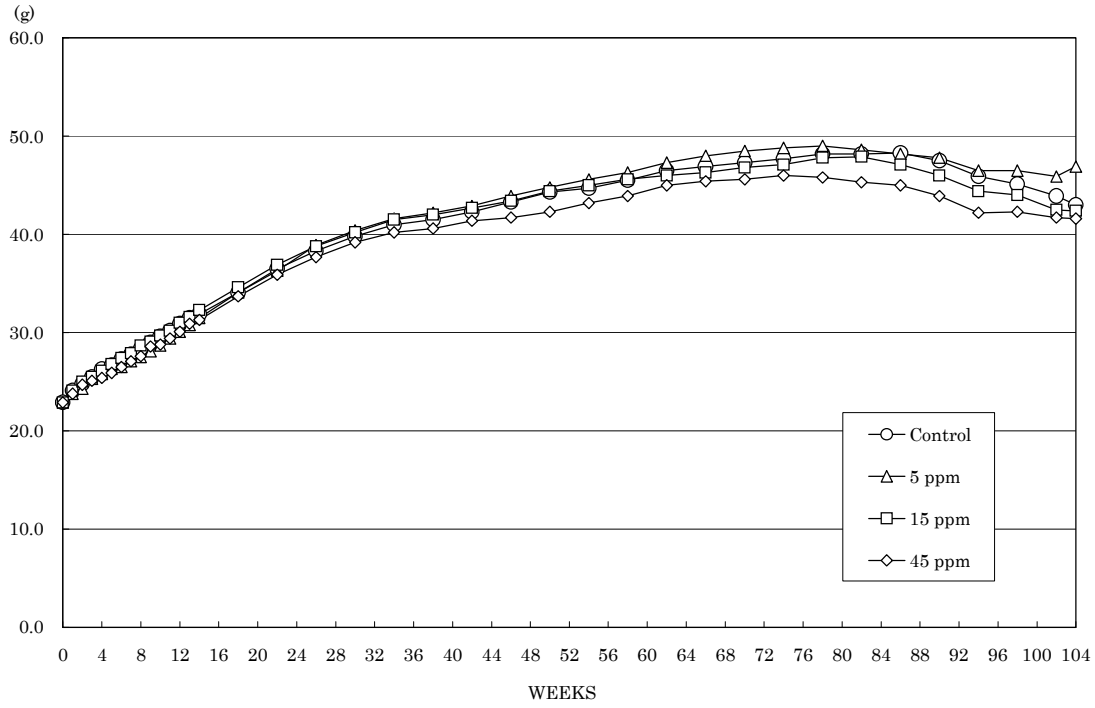


FIGURE 3 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

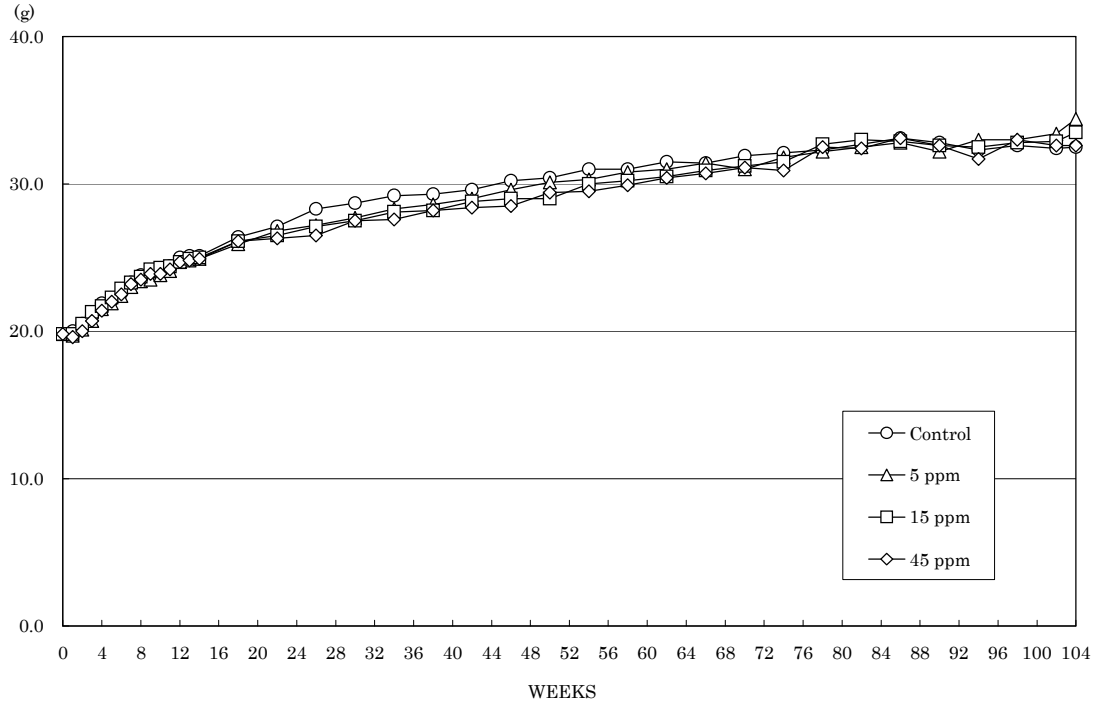


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

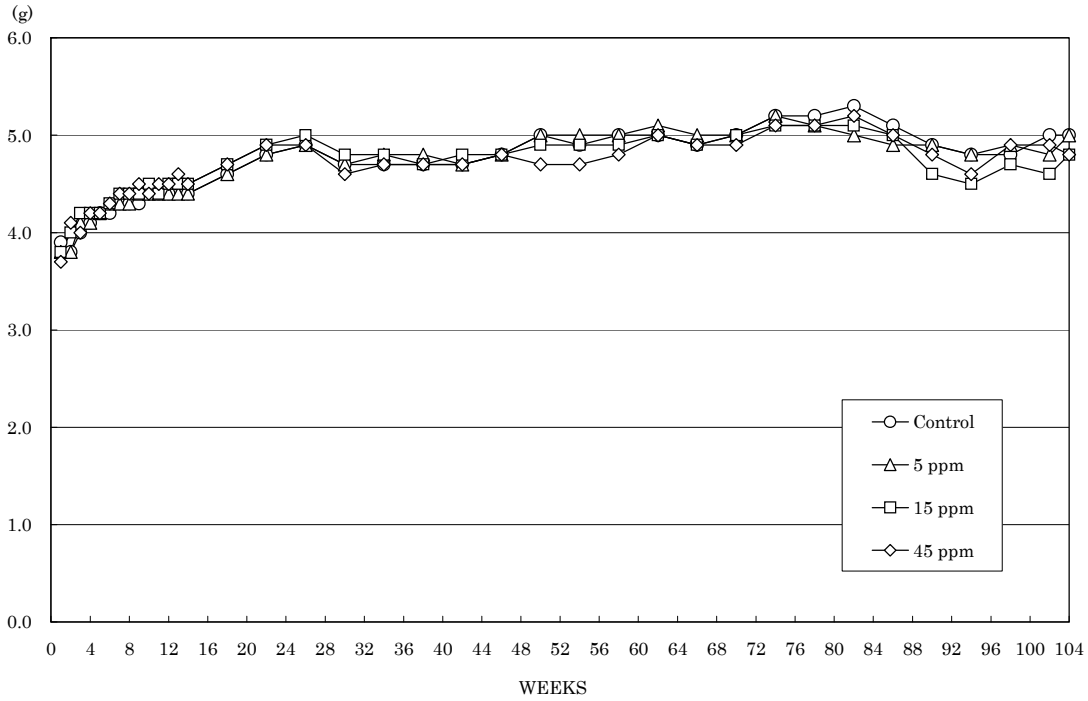


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

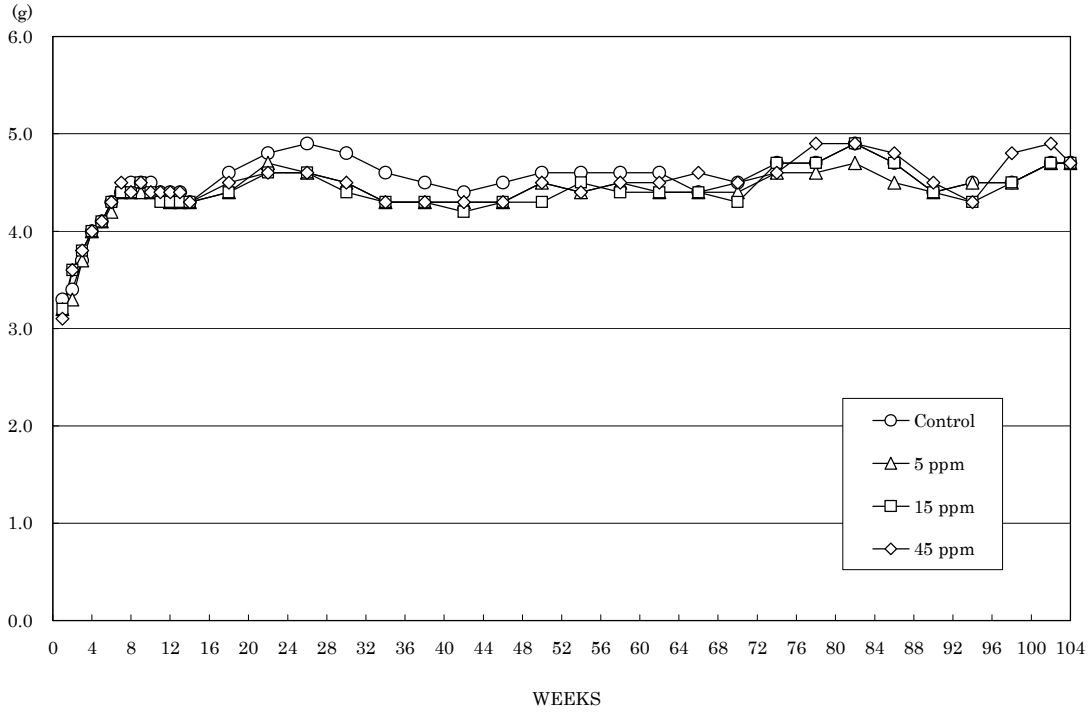
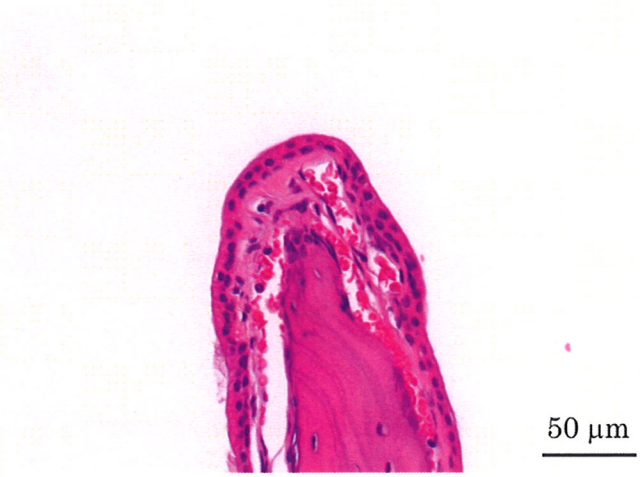
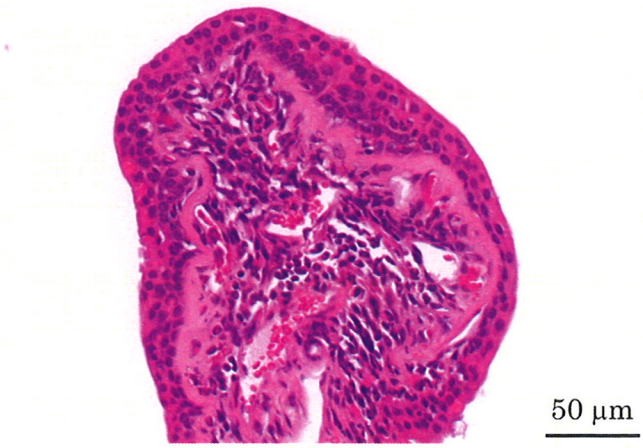


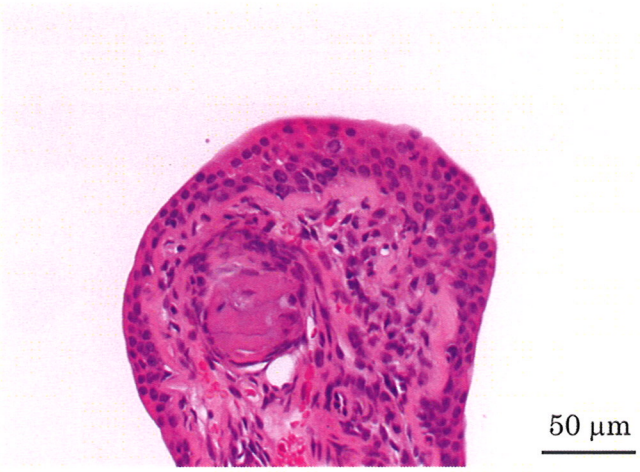
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE



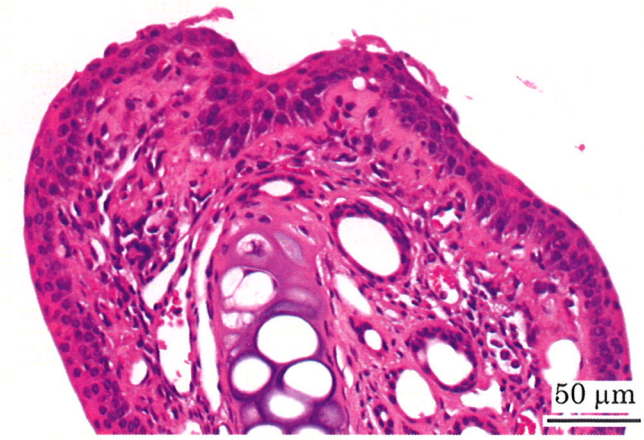
Photograph 1
Nasal cavity (Level 1): Normal, transitional epithelium
Mouse, Male, Control, Animal No. 0732-1006 (H&E)



Photograph 2
Nasal cavity (Level 1): Inflammation of transitional epithelium
Mouse, Male, 45 ppm, Animal No. 0732-1311 (H&E)



Photograph 3
Nasal cavity (Level 1): Hyperplasia of transitional epithelium
Mouse, Male, 45 ppm, Animal No. 0732-1332 (H&E)



Photograph 4
Nasal cavity (Level 1): Squamous metaplasia
of transitional epithelium
Mouse, Female, 45 ppm, Animal No. 0732-2304 (H&E)