Summary of Inhalation Carcinogenicity Study of 2,4-Pentanedione 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, 2010.

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

Summary of Inhalation Carcinogenicity Study of 2,4-Pentanedione in B6D2F1 Mice

Purpose, materials and methods

2,4-Pentanedione (CAS No. 123-54-6) is a colorless liquid with a boiling point of 139°C (746 mmHg). It is soluble in ethanol, acetone, and water.

The carcinogenicity and chronic toxicity of 2,4-pentanedione (greater than 99.9% pure) were examined by inhalation exposure using B6D2F1/Crlj mice. Groups of test animals were exposed to 2,4-pentanedione vapors at target concentrations of 0 (clean air), 100, 200 or 400 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 rats. Both sexes were exposed to each concentration of 2,4-pentanedione 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 2,4-pentanedione used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. It was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 3.7m^3) were used throughout the 2-year exposure period. 2,4-Pentanedione vapor-air mixtures were generated by bubbling clean air through 2,4-pentanedione liquid and the mixtures delivered to the inhalation exposure chambers. Air concentrations of the 2,4-pentanedione in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the exposure period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of 2,4-pentanedione 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 2,4-pentanedione and their respective controls. The body weights of the males exposed to 400 ppm 2,4-pentanedione were suppressed during the first half of the exposure period; thereafter the body weights became similar to the controls: the terminal body weights of the 400 ppm-exposed males was 97% of the controls. The body weights of all other 2,4-pentanedione exposed groups, both male and female, were similar to their respective controls throughout the exposure period. Food consumption by the males exposed to 400 ppm 2,4-pentanedione decreased after 30 weeks. Food consumptions of all other 2,4-pentanedione exposed groups, both male and female, were similar to their respective controls throughout the exposure period. There were no 2,4-pentanedione related changes in the hematology parameters or organ weights. Plasma albumin globulin ratios (A/G ratio) and plasma levels of glucose were increased in males exposed to 200 and 400 ppm 2,4-pentanedione and aspartate aminotransferase, alanine aminotransferase, creatine kinase, urea nitrogen and inorganic phosphorus were significantly decreased in males exposed to 400 ppm 2,4-pentanedione. Urinalysis showed an increase in protein and ketone bodies in females exposed to 400 ppm 2,4-pentanedione. Pituitary nodules and enlargement were noted in females exposed to 200 and 400 ppm 2,4-pentanedione.

No significant increases in the incidence of neoplastic lesions was found in any of the 2,4-pentanedione-exposed group of either sex compared with their respective controls. Non-neoplastic lesions in the nasal cavity were noted in both sexes**:** squamous metaplasia (males and females), eosinophilic change (males), ulcer (males and females), necrosis (females) and transitional cell hyperplasia (males) in the respiratory epithelium and atrophy (males and females), respiratory metaplasia (males and females), eosinophilic change (females), necrosis (females) in the olfactory epithelium were observed. Respiratory metaplasia in the submucosal gland was observed in both sexes. The exudate and atrophy in the olfactory epithelium occurred in both males and females exposed to 100 ppm 2,4-pentanedione (the lowest dose tested) and above. Using nasal lesions as endpoint markers, the lowest-observed-adverse-effect-level (LOAEL) of 2,4-pentanedione, exposure by inhalation, was 100 ppm for both male and female mice.

Conclusions

There was no evidence for carcinogenicity of 2,4-pentanedione in male or female mice.

Incidences of selected neoplastic lesions of male mice in the 2-year inhalation carcinogenicity study of 2,4-pentanedione

Dose (ppm)		0	100	200	400	Peto test	Cochran-Armitage test
Number of examined animals		50	50	49	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	4	4	3	5		
liver	hepatocellular adenoma	6	8	18 *	10		
Harderian gland	adenoma	2	4	4	4		
malignant tumor							
lung	bronchiolar-alveolar carcinoma	2	3	2	3		
lymph node	malignant lymphoma	9	6	6	13		
liver	hepatocellular carcinoma	5	8	4	2		
	hemangiosarcoma	6	3	3	3		
all organs	histiocytic sarcoma	3	2	2	4	↑ ↑ [a)]	

Incidences of selected neoplastic lesions of female mice in the 2-year inhalation carcinogenicity study of 2,4-pentanedione

Dose (ppm)		0	100	200	400	Peto test	Cochran-Armitage test
Number of examined animals		50	49	50	50		
benign tumor							
liver	hepatocellular adenoma	1	5	3	3		
pituitary	adenoma	10	11 [b)]	13	12		
ovary	adenoma	1	0	0	3		
Harderian gland	adenoma	1	0	3	2		
malignant tumor							
lymph node	malignant lymphoma	15	14	15	13		
uterus	histiocytic sarcoma	9	7	14	8		

[a)] : Significant in plevalence method only.

[b)] : Numer of examined animal of pituitary is 48.

Significant difference

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

SELECTED TABLES

TABLE A

CONCENTRATIONS OF 2,4-PENTANEDIONE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

CONCENTRATIONS OF 2,4-PENTANEDIONE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
100 ppm	100.9 ± 0.9
200 ppm	200.9 ± 1.4
400 ppm	401.0 ± 1.8

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN BODY WEIGHTS AND SURVIVAL

Week on Study	Control Av. Wt.	Control No. of Surviv. <50>	100 ppm Av. Wt.	100 ppm % of cont. <50>	100 ppm No. of Surviv.	200 ppm Av. Wt.	200 ppm % of cont. <49>	200 ppm No. of Surviv.	400 ppm Av. Wt.	400 ppm % of cont. <50>	400 ppm No. of Surviv.
0	23.5 (50)	50/50	23.5 (50)	100	50/50	23.5 (49)	100	49/49	23.5 (50)	100	50/50
1	24.6 (50)	50/50	24.4 (50)	99	50/50	24.9 (49)	101	49/49	24.3 (50)	99	50/50
2	25.7 (50)	50/50	25.1 (50)	98	50/50	25.6 (49)	100	49/49	24.9 (50)	97	50/50
3	26.3 (50)	50/50	25.3 (50)	96	50/50	26.1 (49)	99	49/49	25.6 (50)	97	50/50
4	26.8 (50)	50/50	25.5 (50)	95	50/50	26.7 (49)	100	49/49	26.1 (50)	97	50/50
5	27.5 (50)	50/50	26.3 (49)	96	49/50	27.5 (49)	100	49/49	26.5 (49)	96	49/50
6	28.1 (50)	50/50	26.9 (49)	96	49/50	27.9 (49)	99	49/49	27.0 (49)	96	49/50
7	28.9 (50)	50/50	27.6 (49)	96	49/50	28.5 (49)	99	49/49	27.5 (49)	95	49/50
8	29.7 (50)	50/50	28.7 (48)	97	48/50	29.3 (49)	99	49/49	28.0 (49)	94	49/50
9	30.3 (50)	50/50	29.2 (48)	96	48/50	29.7 (49)	98	49/49	28.5 (49)	94	49/50
10	30.9 (50)	50/50	29.5 (48)	95	48/50	30.4 (49)	98	49/49	29.1 (49)	94	49/50
11	31.5 (50)	50/50	30.1 (48)	96	48/50	31.2 (49)	99	49/49	29.9 (49)	95	49/50
12	32.5 (50)	50/50	31.2 (48)	96	48/50	31.9 (49)	98	49/49	30.6 (49)	94	49/50
13	33.0 (50)	50/50	31.8 (48)	96	48/50	32.5 (49)	98	49/49	31.1 (49)	94	49/50
14	33.3 (50)	50/50	31.9 (48)	96	48/50	33.0 (49)	99	49/49	31.5 (49)	95	49/50
18	36.1 (50)	50/50	35.0 (48)	97	48/50	35.8 (49)	99	49/49	34.3 (49)	95	49/50
22	38.4 (50)	50/50	38.0 (48)	99	48/50	38.1 (49)	99	49/49	36.6 (49)	95	49/50
26	39.8 (50)	50/50	39.3 (48)	99	48/50	39.8 (49)	100	49/49	38.3 (49)	96	49/50
30	41.6 (50)	50/50	41.5 (48)	100	48/50	41.8 (49)	100	49/49	40.2 (49)	97	49/50
34	43.7 (50)	50/50	43.6 (48)	100	48/50	43.9 (49)	100	49/49	42.5 (49)	97	49/50
38	44.8 (50)	50/50	45.1 (48)	101	48/50	45.1 (49)	101	49/49	43.4 (49)	97	49/50
42	45.7 (50)	50/50	46.0 (48)	101	48/50	45.8 (49)	100	49/49	44.2 (49)	97	49/50
46	46.3 (50)	50/50	46.6 (48)	101	48/50	46.8 (49)	101	49/49	44.6 (49)	96	49/50
50	47.3 (50)	50/50	47.3 (48)	100	48/50	47.6 (48)	101	48/49	45.1 (49)	95	49/50
54	48.2 (50)	50/50	48.3 (46)	100	46/50	47.8 (48)	99	48/49	46.0 (48)	95	48/50
58	48.9 (50)	50/50	48.7 (45)	100	45/50	48.8 (48)	100	48/49	46.6 (48)	95	48/50
62	49.5 (50)	50/50	49.1 (44)	99	44/50	49.0 (48)	99	48/49	47.2 (48)	95	48/50
66	50.2 (50)	50/50	49.5 (44)	99	44/50	49.3 (47)	98	47/49	47.9 (48)	95	48/50
70	51.0 (50)	50/50	50.1 (44)	98	44/50	50.1 (47)	98	47/49	48.6 (48)	95	48/50
74	52.0 (49)	49/50	50.9 (44)	98	44/50	50.4 (47)	97	47/49	49.0 (47)	94	47/50
78	51.7 (49)	49/50	50.6 (42)	98	42/50	50.9 (47)	98	47/49	49.7 (47)	96	47/50
82	51.7 (47)	47/50	51.9 (40)	100	40/50	51.2 (47)	99	47/49	49.9 (46)	97	46/50
86	50.9 (45)	45/50	51.0 (40)	100	40/50	50.8 (43)	100	43/49	49.8 (45)	98	45/50
90	51.5 (40)	40/50	51.2 (37)	99	37/50	50.4 (41)	98	41/49	49.6 (44)	96	44/50
94	51.2 (38)	38/50	50.7 (35)	99	35/50	50.6 (38)	99	38/49	49.3 (44)	96	44/50
98	50.1 (37)	37/50	49.7 (33)	99	33/50	50.5 (37)	101	37/49	49.0 (41)	98	41/50
102	49.1 (36)	36/50	49.6 (31)	101	31/50	49.9 (36)	102	36/49	47.8 (40)	97	40/50
104	49.8 (30)	30/50	48.6 (31)	98	31/50	50.4 (34)	101	34/49	48.3 (39)	97	39/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

Week on Study	Control Av.Wt.	Control No. of Surviv. <50>	100 ppm Av.Wt.	100 ppm % of cont. <49>	100 ppm No. of Surviv.	200 ppm Av.Wt.	200 ppm % of cont. <50>	200 ppm No. of Surviv.	400 ppm Av.Wt.	400 ppm % of cont. <50>	400 ppm No. of Surviv.
0	19.5 (50)	50/50	19.5 (49)	100	49/49	19.5 (50)	100	50/50	19.5 (50)	100	50/50
1	20.0 (50)	50/50	19.7 (49)	99	49/49	19.9 (50)	100	50/50	19.8 (50)	99	50/50
2	20.8 (50)	50/50	20.3 (49)	98	49/49	20.5 (50)	99	50/50	20.3 (50)	98	50/50
3	21.1 (50)	50/50	20.7 (49)	98	49/49	20.9 (50)	99	50/50	20.9 (50)	99	50/50
4	21.6 (50)	50/50	21.3 (49)	99	49/49	21.5 (50)	100	50/50	21.5 (50)	100	50/50
5	22.0 (49)	49/50	21.6 (49)	98	49/49	22.3 (50)	101	50/50	21.9 (50)	100	50/50
6	22.4 (49)	49/50	22.3 (49)	100	49/49	22.7 (50)	101	50/50	22.4 (50)	100	50/50
7	23.0 (49)	49/50	22.8 (49)	99	49/49	22.9 (50)	100	50/50	23.0 (50)	100	50/50
8	23.5 (49)	49/50	23.2 (49)	99	49/49	23.8 (50)	101	50/50	23.3 (50)	99	50/50
9	23.4 (49)	49/50	23.1 (49)	99	49/49	23.9 (50)	102	50/50	23.7 (50)	101	50/50
10	23.7 (49)	49/50	23.5 (49)	99	49/49	24.2 (50)	102	50/50	24.0 (49)	101	49/50
11	24.0 (49)	49/50	23.9 (49)	100	49/49	24.4 (50)	102	50/50	24.4 (49)	102	49/50
12	24.9 (49)	49/50	24.5 (49)	98	49/49	25.0 (50)	100	50/50	24.7 (49)	99	49/50
13	24.7 (49)	49/50	24.5 (49)	99	49/49	25.0 (50)	101	50/50	24.7 (49)	100	49/50
14	24.6 (49)	49/50	24.9 (49)	101	49/49	25.3 (50)	103	50/50	25.1 (49)	102	49/50
18	26.2 (49)	49/50	26.5 (49)	101	49/49	27.0 (50)	103	50/50	26.6 (49)	102	49/50
22	27.1 (49)	49/50	27.4 (49)	101	49/49	27.7 (50)	102	50/50	27.2 (49)	100	49/50
26	27.5 (49)	49/50	28.0 (48)	102	48/49	28.5 (50)	104	50/50	28.0 (49)	102	49/50
30	28.5 (49)	49/50	29.1 (48)	102	48/49	30.0 (50)	105	50/50	29.4 (49)	103	49/50
34	29.9 (49)	49/50	30.5 (48)	102	48/49	31.8 (49)	106	49/50	30.4 (49)	102	49/50
38	30.2 (49)	49/50	30.9 (48)	102	48/49	32.0 (49)	106	49/50	30.5 (49)	101	49/50
42	30.9 (49)	49/50	31.2 (48)	101	48/49	32.6 (49)	106	49/50	31.3 (49)	101	49/50
46	31.1 (49)	49/50	31.9 (48)	103	48/49	33.3 (49)	107	49/50	32.1 (49)	103	49/50
50	31.6 (48)	48/50	32.6 (48)	103	48/49	33.8 (49)	107	49/50	32.1 (48)	102	48/50
54	32.4 (48)	48/50	33.6 (47)	104	47/49	34.5 (49)	106	49/50	31.9 (47)	98	47/50
58	32.5 (47)	47/50	34.1 (47)	105	47/49	34.9 (48)	107	48/50	32.6 (47)	100	47/50
62	32.6 (47)	47/50	33.9 (47)	104	47/49	35.4 (48)	109	48/50	32.7 (47)	100	47/50
66	33.1 (45)	45/50	35.2 (47)	106	47/49	36.0 (47)	109	47/50	33.1 (47)	100	47/50
70	33.8 (45)	45/50	35.6 (46)	105	46/49	36.9 (47)	109	47/50	33.9 (46)	100	46/50
74	34.5 (45)	45/50	36.1 (44)	105	44/49	37.1 (47)	108	47/50	34.3 (46)	99	46/50
78	34.9 (45)	45/50	36.6 (44)	105	44/49	37.0 (46)	106	46/50	34.6 (46)	99	46/50
82	34.9 (44)	44/50	37.0 (43)	106	43/49	37.7 (43)	108	43/50	35.1 (45)	101	45/50
86	34.4 (44)	44/50	36.6 (42)	106	42/49	37.5 (39)	109	39/50	34.6 (43)	101	43/50
90	34.8 (42)	42/50	37.1 (38)	107	38/49	37.6 (38)	108	38/50	35.2 (42)	101	42/50
94	35.0 (41)	41/50	37.3 (36)	107	36/49	37.1 (32)	106	32/50	35.6 (39)	102	39/50
98	33.9 (37)	37/50	37.6 (34)	111	34/49	37.5 (29)	111	29/50	34.3 (37)	101	37/50
102	33.8 (32)	32/50	37.6 (29)	111	29/49	36.7 (26)	109	26/50	34.4 (36)	102	36/50
104	33.7 (31)	31/50	37.3 (27)	111	27/49	37.0 (26)	110	26/50	33.9 (34)	101	34/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	23.5± 0.9	24.6± 1.1	25.7± 1.2	26.3± 1.4	26.8± 1.5	27.5± 1.6	28.1± 1.9
100 ppm	23.5± 0.9	24.4± 1.1	25.1± 1.1*	25.3± 1.4**	25.5± 1.8**	26.3± 1.8**	26.9± 1.9**
200 ppm	23.5± 0.8	24.9± 1.0	25.6± 1.3	26.1± 1.4	26.7± 1.6	27.5± 1.6	27.9± 1.8
400 ppm	23.5± 0.9	24.3± 1.6	24.9± 1.1**	25.6± 1.1*	26.1± 1.3	26.5± 1.4*	27.0± 1.5**

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	28.9± 1.9	29.7± 2.0	30.3± 2.2	30.9± 2.5	31.5± 2.6	32.5± 2.6	33.0± 2.8
100 ppm	27.6± 2.0**	28.7± 1.9*	29.2± 1.9*	29.5± 2.0**	30.1± 2.2**	31.2± 2.2*	31.8± 2.3
200 ppm	28.5± 1.8	29.3± 2.0	29.7± 2.2	30.4± 2.4	31.2± 2.4	31.9± 2.6	32.5± 2.6
400 ppm	27.5± 1.7**	28.0± 1.9**	28.5± 2.0**	29.1± 2.1**	29.9± 2.4**	30.6± 2.4**	31.1± 2.6**

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	33.3± 3.0	36.1± 3.2	38.4± 3.8	39.8± 4.2	41.6± 4.4	43.7± 4.4	44.8± 4.6
100 ppm	31.9± 2.4*	35.0± 2.7	38.0± 3.2	39.3± 3.7	41.5± 3.9	43.6± 4.2	45.1± 4.2
200 ppm	33.0± 2.9	35.8± 3.1	38.1± 3.6	39.8± 4.1	41.8± 4.5	43.9± 4.5	45.1± 4.7
400 ppm	31.5± 2.6**	34.3± 3.1**	36.6± 3.5	38.3± 3.6	40.2± 3.8	42.5± 4.0	43.4± 4.2

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	45.7± 4.6	46.3± 4.5	47.3± 4.8	48.2± 4.6	48.9± 4.7	49.5± 4.4	50.2± 4.5
100 ppm	46.0± 4.3	46.6± 4.2	47.3± 4.5	48.3± 4.1	48.7± 4.2	49.1± 4.0	49.5± 4.0
200 ppm	45.8± 4.7	46.8± 4.8	47.6± 5.0	47.8± 4.9	48.8± 4.9	49.0± 5.1	49.3± 5.4
400 ppm	44.2± 4.1	44.6± 4.1	45.1± 4.1*	46.0± 4.4*	46.6± 4.4*	47.2± 4.4	47.9± 4.3

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	51.0± 4.4	52.0± 4.9	51.7± 6.0	51.7± 6.3	50.9± 6.0	51.5± 6.4	51.2± 6.2
100 ppm	50.1± 4.5	50.9± 4.8	50.6± 5.6	51.9± 5.7	51.0± 6.2	51.2± 6.3	50.7± 6.7
200 ppm	50.1± 5.5	50.4± 6.1	50.9± 6.2	51.2± 6.5	50.8± 6.4	50.4± 7.4	50.6± 6.9
400 ppm	48.6± 4.6	49.0± 4.9	49.7± 5.1	49.9± 6.3	49.8± 5.2	49.6± 5.2	49.3± 5.0

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98	102	104
Control	50.1± 6.9	49.1± 8.1	49.8± 7.7
100 ppm	49.7± 7.8	49.6± 8.2	48.6± 8.7
200 ppm	50.5± 7.0	49.9± 7.4	50.4± 7.0
400 ppm	49.0± 5.3	47.8± 6.5	48.3± 5.5

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

(HAN260)

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	19.5± 0.8	20.0± 0.9	20.8± 1.0	21.1± 1.0	21.6± 0.9	22.0± 1.1	22.4± 1.1
100 ppm	19.5± 0.8	19.7± 0.9	20.3± 1.1	20.7± 0.9	21.3± 1.0	21.6± 1.1	22.3± 0.9
200 ppm	19.5± 0.8	19.9± 0.8	20.5± 1.0	20.9± 0.8	21.5± 1.0	22.3± 1.0	22.7± 1.0
400 ppm	19.5± 0.8	19.8± 0.8	20.3± 0.9	20.9± 0.8	21.5± 0.9	21.9± 1.0	22.4± 1.1

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

(HAN260) BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	23.0± 1.1	23.5± 1.3	23.4± 1.2	23.7± 1.1	24.0± 1.0	24.9± 1.4	24.7± 1.4
100 ppm	22.8± 1.2	23.2± 1.3	23.1± 1.2	23.5± 1.2	23.9± 1.3	24.5± 1.5	24.5± 1.5
200 ppm	22.9± 1.1	23.8± 1.3	23.9± 1.1	24.2± 1.3	24.4± 1.3	25.0± 1.3	25.0± 1.5
400 ppm	23.0± 1.0	23.3± 1.3	23.7± 1.4	24.0± 1.4	24.4± 1.5	24.7± 1.6	24.7± 1.6

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	24.6± 1.4	26.2± 1.6	27.1± 1.7	27.5± 2.1	28.5± 2.4	29.9± 2.8	30.2± 2.6
100 ppm	24.9± 1.5	26.5± 1.6	27.4± 2.3	28.0± 2.4	29.1± 2.5	30.5± 2.8	30.9± 3.1
200 ppm	25.3± 1.6	27.0± 1.8	27.7± 2.0	28.5± 2.5	30.0± 3.5	31.8± 3.4**	32.0± 4.0
400 ppm	25.1± 1.5	26.6± 1.8	27.2± 1.8	28.0± 2.2	29.4± 3.1	30.4± 3.0	30.5± 3.0

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	30.9± 2.9	31.1± 3.2	31.6± 3.3	32.4± 3.3	32.5± 3.6	32.6± 3.9	33.1± 4.2
100 ppm	31.2± 3.1	31.9± 3.3	32.6± 3.7	33.6± 3.6	34.1± 3.9	33.9± 4.0	35.2± 4.2*
200 ppm	32.6± 4.0*	33.3± 4.0**	33.8± 4.2*	34.5± 4.1*	34.9± 4.6**	35.4± 4.8**	36.0± 4.6**
400 ppm	31.3± 3.0	32.1± 3.6	32.1± 3.3	31.9± 3.6	32.6± 3.5	32.7± 3.6	33.1± 3.7

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

(HAN260)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	33.8± 4.4	34.5± 4.5	34.9± 5.3	34.9± 4.2	34.4± 4.1	34.8± 4.6	35.0± 5.0
100 ppm	35.6± 4.9	36.1± 4.9	36.6± 4.8	37.0± 4.5	36.6± 4.6	37.1± 4.9*	37.3± 4.8
200 ppm	36.9± 5.0**	37.1± 5.0*	37.0± 5.4	37.7± 4.5*	37.5± 4.7**	37.6± 6.6*	37.1± 4.9
400 ppm	33.9± 3.8	34.3± 3.8	34.6± 3.8	35.1± 4.0	34.6± 4.0	35.2± 3.9	35.6± 5.3

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98	102	104
Control	33.9± 4.3	33.8± 3.2	33.7± 3.9
100 ppm	37.6± 4.9**	37.6± 4.5**	37.3± 4.1*
200 ppm	37.5± 4.6**	36.7± 4.7*	37.0± 6.3*
400 ppm	34.3± 3.5	34.4± 5.9	33.9± 4.4

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

(HAN260)

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	100 ppm Av. FC.	100 ppm % of cont. <50>	100 ppm No. of Surviv.	200 ppm Av. FC.	200 ppm % of cont. <49>	200 ppm No. of Surviv.	400 ppm Av. FC.	400 ppm % of cont. <50>	400 ppm No. of Surviv.
1	3.8 (50)	50/50	3.7 (50)	97	50/50	3.8 (49)	100	49/49	3.7 (50)	97	50/50
2	3.8 (50)	50/50	3.7 (50)	97	50/50	3.8 (49)	100	49/49	3.6 (50)	95	50/50
3	3.8 (50)	50/50	3.7 (50)	97	50/50	3.9 (49)	103	49/49	3.8 (50)	100	50/50
4	3.9 (50)	50/50	3.8 (50)	97	50/50	3.9 (49)	100	49/49	3.8 (50)	97	50/50
5	3.9 (50)	50/50	3.9 (49)	100	49/50	4.0 (49)	103	49/49	3.9 (49)	100	49/50
6	4.0 (50)	50/50	4.0 (49)	100	49/50	4.0 (49)	100	49/49	3.9 (49)	98	49/50
7	4.1 (50)	50/50	4.0 (49)	98	49/50	4.1 (49)	100	49/49	4.0 (49)	98	49/50
8	4.1 (50)	50/50	4.1 (48)	100	48/50	4.1 (49)	100	49/49	4.0 (49)	98	49/50
9	4.2 (50)	50/50	4.2 (48)	100	48/50	4.2 (49)	100	49/49	4.1 (49)	98	49/50
10	4.1 (50)	50/50	4.1 (48)	100	48/50	4.2 (49)	102	49/49	4.1 (49)	100	49/50
11	4.1 (50)	50/50	4.0 (48)	98	48/50	4.1 (49)	100	49/49	4.0 (49)	98	49/50
12	4.4 (50)	50/50	4.4 (48)	100	48/50	4.3 (49)	98	49/49	4.2 (49)	95	49/50
13	4.2 (50)	50/50	4.2 (48)	100	48/50	4.3 (49)	102	49/49	4.3 (49)	102	49/50
14	4.3 (50)	50/50	4.2 (48)	98	48/50	4.3 (49)	100	49/49	4.2 (49)	98	49/50
18	4.5 (50)	50/50	4.5 (48)	100	48/50	4.6 (49)	102	49/49	4.6 (49)	102	49/50
22	4.5 (50)	50/50	4.5 (48)	100	48/50	4.5 (49)	100	49/49	4.4 (49)	98	49/50
26	4.6 (50)	50/50	4.6 (48)	100	48/50	4.7 (49)	102	49/49	4.5 (49)	98	49/50
30	4.8 (50)	50/50	4.8 (48)	100	48/50	4.8 (49)	100	49/49	4.6 (49)	96	49/50
34	4.9 (50)	50/50	4.9 (48)	100	48/50	4.9 (49)	100	49/49	4.7 (49)	96	49/50
38	4.8 (50)	50/50	4.8 (48)	100	48/50	4.9 (49)	102	49/49	4.6 (49)	96	49/50
42	4.8 (50)	50/50	4.7 (48)	98	48/50	4.8 (47)	100	49/49	4.6 (49)	96	49/50
46	4.7 (50)	50/50	4.6 (48)	98	48/50	4.7 (49)	100	49/49	4.5 (49)	96	49/50
50	4.8 (50)	50/50	4.7 (48)	98	48/50	4.7 (48)	98	48/49	4.6 (49)	96	49/50
54	4.8 (50)	50/50	4.8 (46)	100	46/50	4.7 (48)	98	48/49	4.5 (48)	94	48/50
58	4.8 (50)	50/50	4.7 (45)	98	45/50	4.9 (48)	102	48/49	4.5 (48)	94	48/50
62	4.9 (50)	50/50	4.8 (44)	98	44/50	4.7 (48)	96	48/49	4.5 (48)	92	48/50
66	5.0 (50)	50/50	4.9 (44)	98	44/50	4.9 (47)	98	47/49	4.7 (48)	94	48/50
70	5.0 (50)	50/50	4.9 (44)	98	44/50	4.9 (47)	98	47/49	4.7 (48)	94	48/50
74	5.0 (49)	49/50	4.9 (44)	98	44/50	5.1 (46)	102	47/49	4.8 (47)	96	47/50
78	5.2 (49)	49/50	5.0 (42)	96	42/50	5.2 (46)	100	47/49	4.9 (47)	94	47/50
82	5.3 (47)	47/50	5.2 (40)	98	40/50	5.2 (47)	98	47/49	5.0 (46)	94	46/50
86	5.0 (45)	45/50	4.9 (40)	98	40/50	5.1 (43)	102	43/49	4.7 (45)	94	45/50
90	5.3 (40)	40/50	5.1 (37)	96	37/50	5.2 (41)	98	41/49	4.9 (44)	92	44/50
94	5.0 (38)	38/50	4.9 (35)	98	35/50	5.2 (38)	104	38/49	4.8 (44)	96	44/50
98	5.0 (37)	37/50	4.9 (33)	98	33/50	5.3 (37)	106	37/49	4.9 (41)	98	41/50
102	4.9 (36)	36/50	5.0 (31)	102	31/50	5.1 (36)	104	36/49	4.7 (40)	96	40/50
104	5.1 (30)	30/50	5.0 (31)	98	31/50	5.2 (34)	102	34/49	5.1 (39)	100	39/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	100 ppm Av. FC.	100 ppm % of cont. <49>	100 ppm No. of Surviv.	200 ppm Av. FC.	200 ppm % of cont. <50>	200 ppm No. of Surviv.	400 ppm Av. FC.	400 ppm % of cont. <50>	400 ppm No. of Surviv.
1	3.2 (50)	50/50	3.1 (49)	97	49/49	3.1 (50)	97	50/50	3.2 (50)	100	50/50
2	3.2 (50)	50/50	3.2 (49)	100	49/49	3.2 (50)	100	50/50	3.2 (50)	100	50/50
3	3.4 (50)	50/50	3.4 (49)	100	49/49	3.4 (50)	100	50/50	3.4 (50)	100	50/50
4	3.5 (50)	50/50	3.5 (49)	100	49/49	3.6 (50)	103	50/50	3.5 (50)	100	50/50
5	3.6 (49)	49/50	3.6 (49)	100	49/49	3.8 (50)	106	50/50	3.6 (50)	100	50/50
6	3.7 (49)	49/50	3.8 (49)	103	49/49	3.8 (50)	103	50/50	3.7 (50)	100	50/50
7	3.9 (49)	49/50	3.8 (49)	97	49/49	3.9 (50)	100	50/50	3.9 (50)	100	50/50
8	3.9 (49)	49/50	3.8 (49)	97	49/49	3.9 (50)	100	50/50	3.8 (50)	97	50/50
9	3.9 (49)	49/50	3.9 (49)	100	49/49	3.9 (50)	100	50/50	4.0 (50)	103	50/50
10	3.9 (49)	49/50	3.8 (49)	97	49/49	3.9 (50)	100	50/50	4.0 (49)	103	49/50
11	3.8 (49)	49/50	3.7 (49)	97	49/49	3.8 (50)	100	50/50	3.6 (49)	95	49/50
12	4.1 (49)	49/50	4.0 (49)	98	49/49	4.0 (50)	98	50/50	4.0 (49)	98	49/50
13	4.0 (49)	49/50	3.9 (49)	98	49/49	4.0 (50)	100	50/50	4.0 (49)	100	49/50
14	3.9 (49)	49/50	3.9 (49)	100	49/49	4.1 (50)	105	50/50	4.1 (49)	105	49/50
18	4.1 (49)	49/50	4.2 (49)	102	49/49	4.3 (50)	105	50/50	4.3 (49)	105	49/50
22	4.1 (49)	49/50	4.0 (49)	98	49/49	4.2 (50)	102	50/50	4.2 (49)	102	49/50
26	4.3 (49)	49/50	4.2 (48)	98	48/49	4.3 (50)	100	50/50	4.3 (49)	100	49/50
30	4.4 (49)	49/50	4.4 (48)	100	48/49	4.5 (50)	102	50/50	4.4 (49)	100	49/50
34	4.7 (49)	49/50	4.7 (48)	100	48/49	4.7 (49)	100	49/50	4.6 (49)	98	49/50
38	4.5 (49)	49/50	4.4 (48)	98	48/49	4.6 (49)	102	49/50	4.3 (49)	96	49/50
42	4.3 (49)	49/50	4.2 (48)	98	48/49	4.5 (49)	105	49/50	4.2 (49)	98	49/50
46	4.2 (49)	49/50	4.2 (48)	100	48/49	4.3 (49)	102	49/50	4.2 (49)	100	49/50
50	4.4 (48)	48/50	4.2 (48)	95	48/49	4.5 (49)	102	49/50	4.3 (48)	98	48/50
54	4.5 (48)	48/50	4.4 (47)	98	47/49	4.5 (49)	100	49/50	4.1 (47)	91	47/50
58	4.2 (47)	47/50	4.4 (47)	105	47/49	4.5 (48)	107	48/50	4.2 (47)	100	47/50
62	4.1 (47)	47/50	4.0 (47)	98	47/49	4.2 (48)	102	48/50	4.0 (47)	98	47/50
66	4.4 (45)	45/50	4.5 (47)	102	47/49	4.5 (47)	102	47/50	4.2 (47)	95	47/50
70	4.5 (45)	45/50	4.4 (46)	98	46/49	4.6 (47)	102	47/50	4.4 (46)	98	46/50
74	4.5 (45)	45/50	4.5 (44)	100	44/49	4.6 (47)	102	47/50	4.4 (46)	98	46/50
78	4.6 (45)	45/50	4.6 (44)	100	44/49	4.5 (46)	98	46/50	4.5 (46)	98	46/50
82	4.6 (44)	44/50	4.7 (43)	102	43/49	4.6 (43)	100	43/50	4.6 (45)	100	45/50
86	4.4 (44)	44/50	4.5 (42)	102	42/49	4.6 (39)	105	39/50	4.5 (43)	102	43/50
90	4.6 (42)	42/50	4.8 (38)	104	38/49	4.7 (38)	102	38/50	4.7 (42)	102	42/50
94	4.5 (41)	41/50	4.7 (36)	104	36/49	4.6 (32)	102	32/50	4.5 (39)	100	39/50
98	4.5 (37)	37/50	4.8 (34)	107	34/49	5.0 (29)	111	29/50	4.6 (37)	102	37/50
102	4.4 (32)	32/50	4.6 (29)	105	29/49	4.8 (26)	109	26/50	4.4 (36)	100	36/50
104	4.5 (31)	31/50	4.6 (27)	102	27/49	4.8 (26)	107	26/50	4.7 (34)	104	34/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	3.8± 0.2	3.8± 0.2	3.8± 0.3	3.9± 0.3	3.9± 0.3	4.0± 0.2	4.1± 0.3
100 ppm	3.7± 0.3	3.7± 0.3*	3.7± 0.4	3.8± 0.5	3.9± 0.3	4.0± 0.4	4.0± 0.4
200 ppm	3.8± 0.2	3.8± 0.3	3.9± 0.3	3.9± 0.4	4.0± 0.3	4.0± 0.3	4.1± 0.3
400 ppm	3.7± 0.4	3.6± 0.3**	3.8± 0.3	3.8± 0.3**	3.9± 0.3	3.9± 0.3	4.0± 0.3

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	4.1± 0.3	4.2± 0.2	4.1± 0.3	4.1± 0.3	4.4± 0.3	4.2± 0.2	4.3± 0.2
100 ppm	4.1± 0.3	4.2± 0.3	4.1± 0.3	4.0± 0.3	4.4± 0.3	4.2± 0.3	4.2± 0.3
200 ppm	4.1± 0.3	4.2± 0.3	4.2± 0.4	4.1± 0.3	4.3± 0.3	4.3± 0.3	4.3± 0.3
400 ppm	4.0± 0.3	4.1± 0.3	4.1± 0.3	4.0± 0.3*	4.2± 0.3	4.3± 0.3	4.2± 0.3

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	4.5± 0.3	4.5± 0.3	4.6± 0.3	4.8± 0.3	4.9± 0.3	4.8± 0.3	4.8± 0.3
100 ppm	4.5± 0.3	4.5± 0.3	4.6± 0.4	4.8± 0.3	4.9± 0.3	4.8± 0.3	4.7± 0.3
200 ppm	4.6± 0.2	4.5± 0.3	4.7± 0.3	4.8± 0.3	4.9± 0.3	4.9± 0.4	4.8± 0.3
400 ppm	4.6± 0.2	4.4± 0.3	4.5± 0.2	4.6± 0.3**	4.7± 0.3	4.6± 0.3**	4.6± 0.3**

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	4.7± 0.3	4.8± 0.3	4.8± 0.3	4.8± 0.3	4.9± 0.2	5.0± 0.3	5.0± 0.3
100 ppm	4.6± 0.3	4.7± 0.3	4.8± 0.3	4.7± 0.3	4.8± 0.3	4.9± 0.3	4.9± 0.3
200 ppm	4.7± 0.3	4.7± 0.3	4.7± 0.7	4.9± 0.3	4.7± 0.5**	4.9± 0.4	4.9± 0.3
400 ppm	4.5± 0.3**	4.6± 0.3**	4.5± 0.3**	4.5± 0.3**	4.5± 0.3**	4.7± 0.3**	4.7± 0.3**

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	5.0± 0.4	5.2± 0.4	5.3± 0.4	5.0± 0.5	5.3± 0.4	5.0± 0.5	5.0± 0.6
100 ppm	4.9± 0.5	5.0± 0.5	5.2± 0.3	4.9± 0.6	5.1± 0.6	4.9± 0.6	4.9± 0.7
200 ppm	5.1± 0.5	5.2± 0.5	5.2± 0.6	5.1± 0.5	5.2± 0.9	5.2± 0.8	5.3± 0.7
400 ppm	4.8± 0.3**	4.9± 0.4**	5.0± 0.6**	4.7± 0.4*	4.9± 0.5**	4.8± 0.4*	4.9± 0.5

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	4.9± 0.9	5.1± 0.8
100 ppm	5.0± 0.6	5.0± 0.6
200 ppm	5.1± 0.7	5.2± 0.6
400 ppm	4.7± 0.6*	5.1± 0.7

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

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	3.2± 0.2	3.2± 0.3	3.4± 0.2	3.5± 0.3	3.6± 0.3	3.7± 0.2	3.9± 0.3
100 ppm	3.1± 0.3	3.2± 0.2	3.4± 0.2	3.5± 0.2	3.6± 0.3	3.8± 0.2	3.8± 0.3
200 ppm	3.1± 0.3	3.2± 0.2	3.4± 0.2	3.6± 0.3	3.8± 0.3*	3.8± 0.3	3.9± 0.3
400 ppm	3.2± 0.2	3.2± 0.2	3.4± 0.2	3.5± 0.2	3.6± 0.2	3.7± 0.3	3.9± 0.3

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	3.9± 0.3	3.9± 0.2	3.9± 0.2	3.8± 0.3	4.1± 0.3	4.0± 0.3	3.9± 0.3
100 ppm	3.8± 0.3	3.9± 0.2	3.8± 0.3	3.7± 0.3	4.0± 0.3	3.9± 0.2	3.9± 0.3
200 ppm	3.9± 0.3	3.9± 0.3	3.9± 0.3	3.8± 0.3	4.0± 0.2	4.0± 0.3	4.1± 0.3*
400 ppm	3.8± 0.3	4.0± 0.2	4.0± 0.3	3.6± 0.3**	4.0± 0.3	4.0± 0.3	4.1± 0.3**

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

(HAN260)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	4.1± 0.3	4.1± 0.3	4.3± 0.4	4.4± 0.4	4.7± 0.4	4.5± 0.4	4.3± 0.4
100 ppm	4.2± 0.3	4.0± 0.5	4.2± 0.3	4.4± 0.4	4.7± 0.4	4.4± 0.3	4.2± 0.5
200 ppm	4.3± 0.3	4.2± 0.4	4.3± 0.4	4.5± 0.4	4.7± 0.4	4.6± 0.4	4.5± 0.4
400 ppm	4.3± 0.4*	4.2± 0.3	4.3± 0.3	4.4± 0.4	4.6± 0.5	4.3± 0.4	4.2± 0.4

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

(HAN260)

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	4.2± 0.5	4.4± 0.4	4.5± 0.4	4.2± 0.4	4.1± 0.5	4.4± 0.4	4.5± 0.4
100 ppm	4.2± 0.3	4.2± 0.4**	4.4± 0.5	4.4± 0.5	4.0± 0.5	4.5± 0.4	4.4± 0.7
200 ppm	4.3± 0.4	4.5± 0.5	4.5± 0.5	4.5± 0.4*	4.2± 0.5	4.5± 0.5	4.6± 0.5
400 ppm	4.2± 0.4	4.3± 0.4	4.1± 0.4**	4.2± 0.3	4.0± 0.4	4.2± 0.5	4.4± 0.4

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

(HAN260)

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	4.5± 0.5	4.6± 0.6	4.6± 0.5	4.4± 0.5	4.6± 0.5	4.5± 0.6	4.5± 0.5
100 ppm	4.5± 0.6	4.6± 0.6	4.7± 0.6	4.5± 0.6	4.8± 0.6	4.7± 0.5	4.8± 0.8*
200 ppm	4.6± 0.6	4.5± 0.6	4.6± 0.5	4.6± 0.5	4.7± 0.7	4.6± 1.0	5.0± 0.8**
400 ppm	4.4± 0.5	4.5± 0.4	4.6± 0.5	4.5± 0.6	4.7± 0.7	4.5± 0.5	4.6± 0.7

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

(HAN260)

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	4.4± 0.6	4.5± 0.6
100 ppm	4.6± 0.6	4.6± 0.5
200 ppm	4.8± 0.6*	4.8± 0.5
400 ppm	4.4± 0.6	4.7± 0.5

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

(HAN260)

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0676
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 f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	30	9.57± 0.79	14.2± 1.4	41.5± 3.6	43.4± 1.3	14.8± 0.6	34.0± 0.8	1648± 384
100 ppm	30	9.35± 1.34	13.7± 1.8	40.5± 4.9	43.5± 2.4	14.7± 0.9	33.8± 0.9	1724± 260
200 ppm	33	9.43± 1.10	14.2± 1.2	41.8± 3.2	44.8± 4.4	15.2± 1.0	33.9± 1.2	1615± 446
400 ppm	39	9.25± 1.29	14.0± 1.9	40.8± 5.2	44.3± 1.8	15.1± 0.5	34.2± 0.9	1595± 344

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

(HCL070)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %	
Control	30	2.1±	0.5
100 ppm	30	2.9±	2.1
200 ppm	33	2.8±	2.9
400 ppm	39	2.7±	2.2

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

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	30	4.65±	4.45	31±	17	62±	17	3±	1	3±	2	0±	0	1±	1
100 ppm	30	3.74±	2.12	31±	13	62±	15	4±	6	2±	1	0±	0	1±	1
200 ppm	33	3.37±	1.67	28±	11	64±	12	4±	3	3±	2	0±	0	1±	1
400 ppm	39	3.22±	1.44	28±	10	64±	11	3±	2	3±	2	0±	0	1±	2

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

(HCL070)

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0676
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	30	9.23± 1.77	14.0± 2.7	40.9± 6.3	44.9± 3.6	15.2± 0.7	33.9± 1.9	1149± 367
100 ppm	27	9.24± 1.73	13.9± 2.6	40.5± 7.1	43.9± 2.1	15.0± 0.7	34.2± 1.1	980± 376
200 ppm	25	9.25± 1.38	14.0± 1.9	40.9± 4.9	44.5± 2.2	15.2± 0.7	34.1± 1.5	989± 364
400 ppm	34	9.31± 1.17	14.1± 1.8	40.8± 4.6	44.0± 2.1	15.1± 0.5	34.4± 1.1	1119± 317

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

(HCL070)

BAIS 4

STUDY NO. : 0676
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	30	4.0±	5.1
100 ppm	27	3.0±	2.4
200 ppm	25	4.1±	4.6
400 ppm	34	3.0±	3.3

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

STUDY NO. : 0676
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	30	6.99± 13.55	25± 15	67± 16	3± 2	3± 2	0± 0	2± 3
100 ppm	27	2.67± 1.05	27± 11	66± 10	3± 1	3± 2	0± 0	1± 1
200 ppm	25	3.36± 1.55	31± 14	62± 16	3± 1	3± 2	0± 0	1± 1
400 ppm	34	3.32± 2.84	29± 14	64± 15	3± 2	3± 2	0± 0	2± 4

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

(HCL070)

BAIS 4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	TOTAL PROTEIN g／dℓ	ALBUMIN g／dℓ	A/G RATIO	T-BILIRUBIN mg／dℓ	GLUCOSE mg／dℓ	T-CHOLESTEROL mg／dℓ	TRIGLYCERIDE mg／dℓ
Control	30	5.1± 0.5	2.5± 0.3	0.9± 0.1	0.12± 0.02	164± 39	106± 26	47± 24
100 ppm	31	5.4± 0.9	2.6± 0.5	1.0± 0.1	0.13± 0.03	166± 46	132± 107	48± 23
200 ppm	34	5.3± 0.6	2.6± 0.3	1.0± 0.1*	0.13± 0.04	190± 25**	107± 36	45± 22
400 ppm	39	5.1± 0.4	2.6± 0.2	1.1± 0.1**	0.12± 0.03	188± 35**	101± 25	44± 22

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

(HCL074)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST IU/ℓ	ALT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	G-GTP IU/ℓ	CK IU/ℓ
Control	30	189± 42	94± 97	39± 37	294± 335	239± 251	1± 1	81± 103
100 ppm	31	221± 137	148± 239	119± 246	504± 959	316± 341	1± 2	79± 65
200 ppm	34	198± 59	76± 62	47± 53	229± 95	258± 256	1± 1	57± 22
400 ppm	39	182± 37	77± 124*	36± 69*	283± 447	230± 218	1± 1	52± 30*

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

(HCL074)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	UREA NITROGEN mg/dℓ	SODIUM mEq/ℓ	POTASSIUM mEq/ℓ	CHLORIDE mEq/ℓ	CALCIUM mg/dℓ	INORGANIC PHOSPHORUS mg/dℓ
Control	30	25.3± 9.9	153± 4	4.2± 0.3	122± 3	8.8± 0.4	6.8± 0.9
100 ppm	31	25.4± 11.9	154± 2	4.1± 0.5	121± 4	9.0± 0.7	6.7± 1.2
200 ppm	34	22.6± 6.0	153± 3	4.3± 0.4	122± 3	8.8± 0.4	6.7± 0.9
400 ppm	39	24.4± 16.6*	153± 2	4.3± 0.5	122± 2	8.7± 0.3	6.5± 2.3*

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

(HCL074)

BAIS 4

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0676
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	30	5.1± 0.4	2.5± 0.3	1.0± 0.2	0.12± 0.02	121± 27	79± 25	32± 17
100 ppm	27	5.2± 0.5	2.7± 0.3	1.1± 0.2	0.13± 0.07	128± 29	81± 45	27± 19
200 ppm	25	5.6± 1.7	2.5± 0.2	1.0± 0.2	0.15± 0.17	126± 26	78± 34	37± 30
400 ppm	34	5.1± 0.4	2.6± 0.2	1.1± 0.2	0.12± 0.03	134± 32	75± 26	28± 19

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

(HCL074)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST IU/ℓ	ALT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	G-GTP IU/ℓ	CK IU/ℓ
Control	30	135± 33	109± 79	51± 62	220± 181	305± 102	1± 1	117± 155
100 ppm	27	149± 74	108± 91	46± 47	422± 961	328± 130	2± 4	132± 300
200 ppm	25	135± 43	110± 81	58± 83	344± 562	286± 146	1± 1	109± 108
400 ppm	34	135± 45	109± 78	43± 30	329± 491	315± 157	1± 1	127± 291

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

(HCL074)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/CrIj[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	30	25.6± 53.4	152± 3	4.1± 0.9	121± 3	8.9± 0.4	6.4± 3.7
100 ppm	27	16.4± 6.4	152± 2	3.9± 0.5	121± 2	9.0± 0.5	6.4± 1.2
200 ppm	25	20.0± 20.7	152± 2	4.0± 0.4	121± 2	9.0± 0.6	6.6± 2.1
400 ppm	34	17.5± 11.8	151± 2	4.1± 0.4	121± 2	8.7± 0.4	6.2± 1.0

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

(HCL074)

BAIS 4

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0676
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	36	0	2	5	6	11	8	4		0	0	26	7	3	0		36	0	0	0	0	0		4	29	3	0	0	0		32	0	0	0	4	
100 ppm	32	0	1	4	6	5	13	3		0	3	18	10	1	0		32	0	0	0	0	0		9	22	1	0	0	0		29	2	0	1	0	
200 ppm	37	0	2	7	1	7	19	1		0	5	29	3	0	0	*	37	0	0	0	0	0		12	23	2	0	0	0		35	1	0	0	1	
400 ppm	40	0	0	3	3	11	16	7		0	1	26	12	1	0		40	0	0	0	0	0		1	35	4	0	0	0		36	0	1	0	3	

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

(HCL101)

BAIS 4

STUDY NO. : 0676
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	36	36	0	0	0	0	
100 ppm	32	32	0	0	0	0	
200 ppm	37	37	0	0	0	0	
400 ppm	40	40	0	0	0	0	

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

(HCL101)

BAIS 4

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0676
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	34	0	2	3	2	8	12	7		0	25	5	3	1	0		34	0	0	0	0	0		23	3	8	0	0	0		32	0	0	1	1	
100 ppm	30	0	1	1	6	9	6	7		0	20	7	3	0	0		30	0	0	0	0	0		17	7	5	1	0	0		29	0	1	0	0	
200 ppm	26	0	1	3	4	6	8	4		0	14	10	1	1	0		26	0	0	0	0	0		19	3	4	0	0	0		25	0	0	1	0	
400 ppm	36	0	0	3	7	11	11	4		0	11	12	11	2	0	**	36	0	0	0	0	0		11	6	8	9	2	0	**	31	0	0	2	3	

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

Test of CHI SQUARE

(HCL101)

STUDY NO. : 0676
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	34	34	0	0	0	0	
100 ppm	30	30	0	0	0	0	
200 ppm	26	26	0	0	0	0	
400 ppm	36	36	0	0	0	0	

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

(HCL101)

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	Body Weight	ADRENALS	TESTES	HEART	LUNGS	KIDNEYS
Control	30	45.8± 7.6	0.011± 0.002	0.208± 0.038	0.229± 0.022	0.221± 0.112	0.712± 0.262
100 ppm	31	44.9± 8.6	0.011± 0.003	0.210± 0.040	0.225± 0.031	0.217± 0.103	0.685± 0.246
200 ppm	34	46.5± 6.5	0.011± 0.002	0.204± 0.035	0.231± 0.023	0.214± 0.064	0.683± 0.050
400 ppm	39	44.4± 5.5	0.011± 0.002	0.210± 0.045	0.217± 0.026	0.213± 0.071	0.704± 0.332

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

(HCL040)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	SPLEEN		LIVER		BRAIN	
Control	30	0.163±	0.340	1.623±	0.281	0.462±	0.019
100 ppm	31	0.192±	0.449	2.080±	1.054	0.460±	0.016
200 ppm	34	0.102±	0.123	1.791±	0.567	0.458±	0.019
400 ppm	39	0.276±	0.781	1.679±	0.471	0.456±	0.016

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

(HCL040)

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0676
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	30	29.1± 3.4	0.015± 0.003	0.201± 0.557	0.174± 0.026	0.213± 0.098	0.487± 0.219
100 ppm	27	33.2± 3.8**	0.015± 0.004	0.061± 0.043	0.182± 0.034	0.186± 0.015	0.458± 0.071
200 ppm	25	31.9± 4.6*	0.014± 0.002	0.079± 0.067	0.179± 0.023	0.196± 0.027	0.503± 0.241
400 ppm	34	30.1± 4.5	0.013± 0.003	0.063± 0.050	0.175± 0.024	0.194± 0.018	0.459± 0.138

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

STUDY NO. : 0676
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	30	0.246±	0.276	1.438±	0.248	0.483±	0.018
100 ppm	27	0.202±	0.218	1.731±	0.979	0.490±	0.016
200 ppm	25	0.232±	0.244	1.715±	1.070	0.474±	0.016
400 ppm	34	0.173±	0.148	1.417±	0.269	0.483±	0.018

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

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: %

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

Group Name	NO. of Animals	Body Weight (g)	ADRENALS	TESTES	HEART	LUNGS	KIDNEYS
Control	30	45.8± 7.6	0.024± 0.007	0.469± 0.132	0.511± 0.090	0.513± 0.376	1.624± 0.856
100 ppm	31	44.9± 8.6	0.025± 0.010	0.485± 0.136	0.515± 0.112	0.519± 0.344	1.601± 0.814
200 ppm	34	46.5± 6.5	0.023± 0.007	0.448± 0.108	0.501± 0.056	0.476± 0.218	1.498± 0.264
400 ppm	39	44.4± 5.5	0.024± 0.006	0.476± 0.110	0.491± 0.059	0.484± 0.158	1.634± 1.034

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

(HCL042)

BAIS 4

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE
UNIT: %

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

Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN
Control	30	0.392± 0.922	3.605± 0.717	1.039± 0.195
100 ppm	31	0.494± 1.241	5.125± 3.803	1.064± 0.231
200 ppm	34	0.234± 0.325	3.923± 1.549	1.004± 0.160
400 ppm	39	0.727± 2.271	3.862± 1.513	1.040± 0.127

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

(HCL042)

BAIS 4

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0676
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	30	29.1± 3.4	0.051± 0.013	0.655± 1.732	0.607± 0.123	0.744± 0.364	1.710± 0.932
100 ppm	27	33.2± 3.8**	0.044± 0.013	0.184± 0.132	0.549± 0.094	0.566± 0.065**	1.382± 0.179*
200 ppm	25	31.9± 4.6*	0.044± 0.008	0.258± 0.246	0.573± 0.108	0.631± 0.144	1.645± 1.052
400 ppm	34	30.1± 4.5	0.045± 0.013	0.208± 0.160	0.594± 0.119	0.658± 0.102	1.549± 0.443

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

(HCL042)

STUDY NO. : 0676
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	30	0.892± 1.154	4.981± 0.945	1.682± 0.194
100 ppm	27	0.599± 0.594	5.181± 2.653	1.494± 0.180**
200 ppm	25	0.777± 0.883	5.499± 3.664	1.516± 0.210*
400 ppm	34	0.572± 0.454	4.760± 0.864	1.642± 0.267

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

(HCL042)

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				100 ppm 50				200 ppm 49				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage)																		
skin/app			<50>				<50>				<49>				<50>			
	ulcer		0	2	0	0	1	1	0	0	2	1	0	0	0	1	0	0
			(0)	(4)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(2)	(0)	(0)
	squamous cell hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
subcutis			<50>				<50>				<49>				<50>			
	inflammation		0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Respiratory system)																		
nasal cavit			<50>				<50>				<49>				<50>			
	exudate		0	0	0	0	4	2	0	0 *	11	35	0	0 **	20	28	1	0 **
			(0)	(0)	(0)	(0)	(8)	(4)	(0)	(0)	(22)	(71)	(0)	(0)	(40)	(56)	(2)	(0)
	mineralization		6	0	0	0	2	0	0	0	3	0	0	0	1	0	0	0
			(12)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	100 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	200 ppm 49 1 (%)	2 (%)	3 (%)	4 (%)	400 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<49>				<50>			
	eosinophilic change:olfactory epithelium		24	2	0	0	27	0	0	0	13	1	0	0	21	0	0	0
			(48)	(4)	(0)	(0)	(54)	(0)	(0)	(0)	(27)	(2)	(0)	(0)	(42)	(0)	(0)	(0)
	eosinophilic change:respiratory epithelium		17	0	0	0	17	0	0	0	40	2	0	0 **	38	1	0	0 **
			(34)	(0)	(0)	(0)	(34)	(0)	(0)	(0)	(82)	(4)	(0)	(0)	(76)	(2)	(0)	(0)
	inflammation:respiratory epithelium		1	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		24	0	0	0	24	0	0	0	38	0	0	0 **	44	0	0	0 **
			(48)	(0)	(0)	(0)	(48)	(0)	(0)	(0)	(78)	(0)	(0)	(0)	(88)	(0)	(0)	(0)
	respiratory metaplasia:gland		36	0	0	0	39	1	0	0	36	3	0	0	39	6	0	0 **
			(72)	(0)	(0)	(0)	(78)	(2)	(0)	(0)	(73)	(6)	(0)	(0)	(78)	(12)	(0)	(0)
	squamous cell metaplasia:respiratory epithelium		1	0	0	0	1	0	0	0	12	0	0	0 **	18	2	0	0 **
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(36)	(4)	(0)	(0)
	ulcer:respiratory epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(2)	(0)
	transitional cell hyperplasia		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 (%)	2 (%)	3 (%)	4 (%)	100 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	200 ppm 49 1 (%)	2 (%)	3 (%)	4 (%)	400 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<49>				<50>			
	xanthogranuloma		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)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	18 (37)	29 (59)	0 (0)	0 ** (0)	23 (46)	26 (52)	0 (0)	0 ** (0)
	necrosis:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
nasopharynx			<50>				<50>				<49>				<50>			
	eosinophilic change		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
lung			<50>				<50>				<49>				<50>			
	congestion		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)
	hemorrhage		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	3 (6)	1 (2)	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 (%)	100 ppm 50 1 (%)	100 ppm 50 2 (%)	100 ppm 50 3 (%)	100 ppm 50 4 (%)	200 ppm 49 1 (%)	200 ppm 49 2 (%)	200 ppm 49 3 (%)	200 ppm 49 4 (%)	400 ppm 50 1 (%)	400 ppm 50 2 (%)	400 ppm 50 3 (%)	400 ppm 50 4 (%)
{Respiratory system}																		
lung			<50>				<50>				<49>				<50>			
	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)
	granulation		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)
	squamous cell metaplasia		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)
	accumulation of foamy cells		1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		0	0	0	0	1	0	0	0	3	1	0	0	1	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(2)	(0)	(0)	(2)	(2)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<49>				<50>			
	angiectasis		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)
	increased hematopoiesis		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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				100 ppm 50				200 ppm 49				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Hematopoietic system}																		
spleen			<50>				<50>				<49>				<50>			
	deposit of melanin		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		6 (12)	2 (4)	2 (4)	0 (0)	12 (24)	8 (16)	0 (0)	0 * (0)	11 (22)	3 (6)	0 (0)	0 (0)	2 (4)	3 (6)	0 (0)	0 (0)
	lymph-follicular hyperplasia		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)	1 (2)	0 (0)	0 (0)
{Circulatory system}																		
heart			<50>				<50>				<49>				<50>			
	mineralization		0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Digestive system}																		
tooth			<50>				<50>				<49>				<50>			
	dysplasia		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				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
{Digestive system}																		
tongue			<50>				<50>				<49>				<50>			
	arteritis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
salivary gl			<50>				<50>				<49>				<50>			
	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)
	xanthogranuloma		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)
stomach			<50>				<50>				<49>				<50>			
	ulcer:forestomach		1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		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)
	erosion:glandular stomach		8	0	0	0	7	1	0	0	5	0	0	0	7	2	0	0
			(16)	(0)	(0)	(0)	(14)	(2)	(0)	(0)	(10)	(0)	(0)	(0)	(14)	(4)	(0)	(0)
	ulcer:glandular stomach		0	0	0	0	1	0	0	0	2	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
stomach			<50>				<50>				<49>				<50>			
	hyperplasia:glandular stomach		4	0	0	0	12	0	0	0	5	1	0	0	8	0	0	0
			(8)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(10)	(2)	(0)	(0)	(16)	(0)	(0)	(0)
liver			<50>				<50>				<49>				<50>			
	angiectasis		0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	necrosis:focal		1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	collapse		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	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)
	granulation		0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	inflammatory cell nest		1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	extramedullary hematopoiesis		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)

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				100 ppm 50				200 ppm 49				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<50>				<49>				<50>			
	clear cell focus		1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
	acidophilic cell focus		2	0	0	0	4	1	0	0	4	1	0	0	5	0	0	0
			(4)	(0)	(0)	(0)	(8)	(2)	(0)	(0)	(8)	(2)	(0)	(0)	(10)	(0)	(0)	(0)
	basophilic cell focus		0	0	0	0	2	0	0	0	1	0	0	0	2	0	1	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(2)	(0)
	hyperplasia:Ito-cell		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)
gall bladd			<50>				<50>				<49>				<50>			
	cyst		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas			<50>				<50>				<49>				<50>			
	islet cell hyperplasia		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	xanthogranuloma		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				100 ppm 50				200 ppm 49				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<49>				<50>			
	hemorrhage		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)
	thrombus		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)
	cyst		2 (4)	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)
	hyaline droplet		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	basophilic change		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory polyp		0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hydronephrosis		1 (2)	1 (2)	1 (2)	0 (0)	0 (0)	3 (6)	6 (12)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<50>				<50>				<49>				<50>			
	dilated pelvis		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)
urin bladd			<50>				<50>				<49>				<50>			
	dilatation		0	0	8	0	0	0	5	0	0	0	2	0	0	0	0	0 **
			(0)	(0)	(16)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)
	nodular hyperplasia:transitional 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)
{Endocrine system}																		
pituitary			<50>				<49>				<49>				<50>			
	angiectasis		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		1	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	hyperplasia		0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(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				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Endocrine system}																		
pituitary			<50>				<49>				<49>				<50>			
	Rathke pouch		0	0	0	0	1	1	0	0	0	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
parathyroid			<50>				<50>				<49>				<50>			
	cyst		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
adrenal			<50>				<50>				<49>				<50>			
	spindle-cell hyperplasia		11	0	0	0	8	0	0	0	8	0	0	0	12	0	0	0
			(22)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(24)	(0)	(0)	(0)
	hyperplasia:cortical cell		9	0	0	0	11	1	0	0	8	1	0	0	5	2	0	0
			(18)	(0)	(0)	(0)	(22)	(2)	(0)	(0)	(16)	(2)	(0)	(0)	(10)	(4)	(0)	(0)
{Reproductive system}																		
testis			<50>				<50>				<49>				<50>			
	mineralization		3	0	0	0	2	0	0	0	1	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	interstitial cell hyperplasia		0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0
			(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
testis			<50>				<50>				<49>				<50>			
	spermatogenic granuloma		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)
epididymis			<50>				<50>				<49>				<50>			
	spermatogenic granuloma		0	0	0	0	2	0	0	0	1	0	0	0	1	1	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
semin ves			<50>				<50>				<49>				<50>			
	hemorrhage		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
prostate			<50>				<50>				<49>				<50>			
	inflammatory infiltration		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
prep/cli gl			<50>				<50>				<49>				<50>			
	cyst		1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Nervous system}																		
brain			<50>				<50>				<49>				<50>			
	hemorrhage		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	100 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	200 ppm 49 1 (%)	2 (%)	3 (%)	4 (%)	400 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Nervous system}																		
brain			<50>				<50>				<49>				<50>			
	mineralization		18 (36)	0 (0)	0 (0)	0 (0)	17 (34)	0 (0)	0 (0)	0 (0)	21 (43)	0 (0)	0 (0)	0 (0)	18 (36)	0 (0)	0 (0)	0 (0)
{Special sense organs/appendage}																		
eye			<50>				<50>				<49>				<50>			
	keratitis		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)	0 (0)	0 (0)	0 (0)
	phthisis bulbi		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)	0 (0)
Harder gl			<50>				<50>				<49>				<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)
{Musculoskeletal system}																		
muscle			<50>				<50>				<49>				<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)

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				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				50				49				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Musculoskeletal system}																		
bone			<50>				<50>				<49>				<50>			
	ostitis fibrosa		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)
{Body cavities}																		
peritoneum			<50>				<50>				<49>				<50>			
	cyst		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

TABLE L4

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : FEMALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	100 ppm 49 1 (%)	2 (%)	3 (%)	4 (%)	200 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	400 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<50>				<49>				<50>				<50>			
	exudate		1	0	0	0	6	7	2	0 **	7	15	25	0 **	15	23	10	0 **
			(2)	(0)	(0)	(0)	(12)	(14)	(4)	(0)	(14)	(30)	(50)	(0)	(30)	(46)	(20)	(0)
	mineralization		0	0	0	0	4	0	0	0	2	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		27	0	0	0	20	0	0	0	22	1	0	0	45	1	0	0 **
			(54)	(0)	(0)	(0)	(41)	(0)	(0)	(0)	(44)	(2)	(0)	(0)	(90)	(2)	(0)	(0)
	eosinophilic change:respiratory epithelium		41	4	0	0	19	1	0	0 **	34	1	0	0 *	41	3	1	0
			(82)	(8)	(0)	(0)	(39)	(2)	(0)	(0)	(68)	(2)	(0)	(0)	(82)	(6)	(2)	(0)
	inflammation:respiratory epithelium		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)
	respiratory metaplasia:olfactory epithelium		15	0	0	0	23	0	0	0	27	1	0	0 *	36	10	0	0 **
			(30)	(0)	(0)	(0)	(47)	(0)	(0)	(0)	(54)	(2)	(0)	(0)	(72)	(20)	(0)	(0)
	respiratory metaplasia:gland		34	0	0	0	30	0	0	0	40	0	0	0	47	0	0	0 **
			(68)	(0)	(0)	(0)	(61)	(0)	(0)	(0)	(80)	(0)	(0)	(0)	(94)	(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 (%)	100 ppm 49 1 (%)	100 ppm 49 2 (%)	100 ppm 49 3 (%)	100 ppm 49 4 (%)	200 ppm 50 1 (%)	200 ppm 50 2 (%)	200 ppm 50 3 (%)	200 ppm 50 4 (%)	400 ppm 50 1 (%)	400 ppm 50 2 (%)	400 ppm 50 3 (%)	400 ppm 50 4 (%)
{Respiratory system}																		
nasal cavit			<50>				<49>				<50>				<50>			
	squamous cell metaplasia:respiratory epithelium		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	19 (38)	1 (2)	0 (0)	0 ** (0)	22 (44)	8 (16)	1 (2)	0 ** (0)
	ulcer:respiratory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	3 (6)	0 (0)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	6 (12)	5 (10)	1 (2)	0 ** (0)	10 (20)	16 (32)	22 (44)	0 ** (0)	7 (14)	33 (66)	7 (14)	0 ** (0)
	necrosis:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	necrosis:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (14)	1 (2)	0 (0)	0 * (0)	5 (10)	0 (0)	0 (0)	0 (0)
nasopharynx			<50>				<49>				<50>				<50>			
	eosinophilic change		4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
larynx			<50>				<49>				<50>				<50>			
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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< 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				100 ppm 49				200 ppm 50				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
trachea			<50>				<49>				<50>				<50>			
	eosinophilic change		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)
lung			<50>				<49>				<50>				<50>			
	inflammatory infiltration		2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	accumulation of foamy cells		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
{Hematopoietic system}																		
bone marrow			<50>				<49>				<50>				<50>			
	increased hematopoiesis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Hematopoietic system}																		
bone marrow	granulopoiesis:increased		<50> 1 (2)	0 (0)	0 (0)	0 (0)	<49> 1 (2)	0 (0)	0 (0)	0 (0)	<50> 0 (0)	0 (0)	0 (0)	0 (0)	<50> 0 (0)	0 (0)	0 (0)	0 (0)
spleen	deposit of melanin		<50> 0 (0)	0 (0)	0 (0)	0 (0)	<49> 0 (0)	0 (0)	0 (0)	0 (0)	<49> 0 (0)	0 (0)	0 (0)	0 (0)	<50> 1 (2)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		3 (6)	8 (16)	0 (0)	0 (0)	6 (12)	2 (4)	0 (0)	0 (0)	4 (8)	3 (6)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 * (0)
	lymph-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)	2 (4)	0 (0)	0 (0)	0 (0)
{Circulatory system}																		
heart	mineralization		<50> 0 (0)	0 (0)	0 (0)	0 (0)	<49> 1 (2)	0 (0)	0 (0)	0 (0)	<50> 1 (2)	0 (0)	0 (0)	0 (0)	<50> 0 (0)	0 (0)	0 (0)	0 (0)
	myocardial fibrosis		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

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(c) c : b / a * 100
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Organ	Findings	Group Name	Control				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				49				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Circulatory system}																		
heart			<50>				<49>				<50>				<50>			
	arthritis		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)
{Digestive system}																		
salivary gl			<50>				<49>				<50>				<50>			
	lymphocytic infiltration		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)
stomach			<50>				<49>				<50>				<50>			
	hyperplasia:forestomach		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)
	erosion:glandular stomach		5	1	0	0	6	0	0	0	4	3	0	0	3	1	0	0
			(10)	(2)	(0)	(0)	(12)	(0)	(0)	(0)	(8)	(6)	(0)	(0)	(6)	(2)	(0)	(0)
	ulcer:glandular stomach		0	0	1	0	0	1	0	0	0	0	0	0	0	1	1	0
			(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)
	hyperplasia:glandular stomach		3	0	0	0	2	0	0	0	4	0	0	0	5	0	0	0
			(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(10)	(0)	(0)	(0)

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			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
(Digestive system)																		
liver			<50>				<49>				<50>				<50>			
	angiectasis		1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	necrosis:focal		1 (2)	1 (2)	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)
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	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)	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		4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				100 ppm 49				200 ppm 50				400 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<49>				<50>				<50>			
	clear cell focus		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)	1 (2)	0 (0)	0 (0)
	acidophilic cell focus		1 (2)	0 (0)	1 (2)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	2 (4)	1 (2)	0 (0)
	bile duct hyperplasia		3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Urinary system}																		
kidney			<50>				<49>				<50>				<50>			
	cyst		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)
	hyaline droplet		13 (26)	1 (2)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	inflammatory polyp		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)

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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 (%)	100 ppm 49 1 (%)	100 ppm 49 2 (%)	100 ppm 49 3 (%)	100 ppm 49 4 (%)	200 ppm 50 1 (%)	200 ppm 50 2 (%)	200 ppm 50 3 (%)	200 ppm 50 4 (%)	400 ppm 50 1 (%)	400 ppm 50 2 (%)	400 ppm 50 3 (%)	400 ppm 50 4 (%)
{Urinary system}																		
kidney			<50>				<49>				<50>				<50>			
	hydronephrosis		1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	glomerulosclerosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
urin bladd			<50>				<49>				<50>				<50>			
	dilatation		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)
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Endocrine system}																		
pituitary			<50>				<48>				<50>				<50>			
	angiectasis		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	hyperplasia		7 (14)	5 (10)	0 (0)	0 (0)	6 (13)	1 (2)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 ** (0)

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(Endocrine system)																		
pituitary			<50>				<48>				<50>				<50>			
	Rathke pouch		6 (12)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<49>				<50>				<50>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	granulation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ultimobranchial body remanet		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>				<49>				<50>				<50>			
	spindle-cell hyperplasia		16 (32)	27 (54)	6 (12)	0 (0)	16 (33)	21 (43)	9 (18)	0 (0)	16 (32)	31 (62)	3 (6)	0 (0)	19 (38)	22 (44)	5 (10)	0 (0)
	hyperplasia:cortical cell		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)
	focal fatty change:cortex		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)

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			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Reproductive system}																		
ovary			<50>				<49>				<50>				<50>			
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	cyst		9 (18)	1 (2)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	7 (14)	2 (4)	0 (0)	0 (0)	15 (30)	1 (2)	0 (0)	0 (0)
	hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
uterus			<50>				<49>				<50>				<50>			
	cystic endometrial hyperplasia		34 (68)	0 (0)	0 (0)	0 (0)	31 (63)	0 (0)	0 (0)	0 (0)	27 (54)	0 (0)	0 (0)	0 (0)	34 (68)	0 (0)	0 (0)	0 (0)
{Nervous system}																		
brain			<50>				<49>				<50>				<50>			
	necrosis:focal		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)
	mineralization		8 (16)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	11 (22)	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				100 ppm				200 ppm				400 ppm			
		No. of Animals on Study	50				49				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>				<49>				<50>				<50>			
	keratitis		0	0	0	0	0	1	0	0	0	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	mineralization:cornea		2	0	0	0	3	0	0	0	3	0	0	0	7	0	0	0
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
Harder gl			<50>				<49>				<50>				<50>			
	hyperplasia		1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
{Musculoskeletal system}																		
muscle			<50>				<49>				<50>				<50>			
	mineralization		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
bone			<50>				<49>				<50>				<50>			
	ostitis fibrosa		0	0	0	0	2	0	0	0	0	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)

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

TABLE O1

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : MALE

STUDY No. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	4/50(8.0)	3/49(6.1)	5/50(10.0)
Adjusted rates(b)	10.00	12.90	6.82	11.11
Terminal rates(c)	3/30(10.0)	4/31(12.9)	2/34(5.9)	4/39(10.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4064			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.7224			
Fisher Exact test(e)		P = 0.6425	P = 0.5114	P = 0.5000
	SITE : lung			
	TUMOR : bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	2/49(4.1)	3/50(6.0)
Adjusted rates(b)	6.67	6.45	4.88	4.44
Terminal rates(c)	2/30(6.7)	2/31(6.5)	1/34(2.9)	1/39(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2873			
Prevalence method(d)	P = 0.5093			
Combined analysis(d)	P = 0.4034			
Cochran-Armitage test(e)	P = 0.7406			
Fisher Exact test(e)		P = 0.5000	P = 0.6837	P = 0.5000
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma,bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	7/50(14.0)	5/49(10.2)	8/50(16.0)
Adjusted rates(b)	16.67	19.35	11.36	15.56
Terminal rates(c)	5/30(16.7)	6/31(19.4)	3/34(8.8)	5/39(12.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2873			
Prevalence method(d)	P = 0.4278			
Combined analysis(d)	P = 0.3628			
Cochran-Armitage test(e)	P = 0.6162			
Fisher Exact test(e)		P = 0.5000	P = 0.5144	P = 0.3871

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	6/50(12.0)	6/49(12.2)	13/50(26.0)
Adjusted rates(b)	13.33	12.90	8.82	20.51
Terminal rates(c)	4/30(13.3)	4/31(12.9)	3/34(8.8)	8/39(20.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4453			
Prevalence method(d)	P = 0.1713			
Combined analysis(d)	P = 0.2188			
Cochran-Armitage test(e)	P = 0.1805			
Fisher Exact test(e)		P = 0.2883	P = 0.3030	P = 0.2348
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	8/50(16.0)	18/49(36.7)	10/50(20.0)
Adjusted rates(b)	13.16	23.53	40.00	25.00
Terminal rates(c)	3/30(10.0)	6/31(19.4)	13/34(38.2)	9/39(23.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7256			
Prevalence method(d)	P = 0.1235			
Combined analysis(d)	P = 0.1708			
Cochran-Armitage test(e)	P = 0.2163			
Fisher Exact test(e)		P = 0.3871	P = 0.0038**	P = 0.2070
	SITE : liver			
	TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	3/50(6.0)	3/49(6.1)	3/50(6.0)
Adjusted rates(b)	10.00	6.45	2.94	4.65
Terminal rates(c)	3/30(10.0)	2/31(6.5)	1/34(2.9)	1/39(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6802			
Prevalence method(d)	P = 0.8329			
Combined analysis(d)	P = 0.8576			
Cochran-Armitage test(e)	P = 0.3434			
Fisher Exact test(e)		P = 0.2435	P = 0.2536	P = 0.2435

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : liver			
	TUMOR : hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	8/50(16.0)	4/49(8.2)	2/50(4.0)
Adjusted rates(b)	6.06	22.58	11.76	2.56
Terminal rates(c)	1/30(3.3)	7/31(22.6)	4/34(11.8)	1/39(2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8877			
Prevalence method(d)	P = 0.9115			
Combined analysis(d)	P = 0.9654			
Cochran-Armitage test(e)	P = 0.1333			
Fisher Exact test(e)		P = 0.2768	P = 0.5130	P = 0.2180
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	3/50(6.0)	4/49(8.2)	4/50(8.0)
Adjusted rates(b)	16.67	6.45	5.88	6.98
Terminal rates(c)	5/30(16.7)	2/31(6.5)	2/34(5.9)	2/39(5.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6802			
Prevalence method(d)	P = 0.8621			
Combined analysis(d)	P = 0.8820			
Cochran-Armitage test(e)	P = 0.3111			
Fisher Exact test(e)		P = 0.0999	P = 0.1882	P = 0.1783
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	16/50(32.0)	19/49(38.8)	11/50(22.0)
Adjusted rates(b)	17.65	44.12	42.86	25.00
Terminal rates(c)	4/30(13.3)	13/31(41.9)	14/34(41.2)	9/39(23.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9233			
Prevalence method(d)	P = 0.4353			
Combined analysis(d)	P = 0.6669			
Cochran-Armitage test(e)	P = 0.9940			
Fisher Exact test(e)		P = 0.1271	P = 0.0331*	P = 0.5000

Group Name	Control	100 ppm	200 ppm	400 ppm
SITE : Harderian gland				
TUMOR : adenoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	4/50(8.0)	4/49(8.2)	4/50(8.0)
Adjusted rates(b)	5.26	10.26	11.76	10.26
Terminal rates(c)	0/30(0.0)	0/31(0.0)	4/34(11.8)	4/39(10.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2771			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5108			
Fisher Exact test(e)		P = 0.3389	P = 0.3292	P = 0.3389

(HPT360A)

BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01
N.C. :Statistical value cannot be calculated and was not significant.

STUDY No. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : ALL SITE TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	2/49(4.1)	4/50(8.0)
Adjusted rates(b)	0.0	0.0	0.0	7.69
Terminal rates(c)	0/30(0.0)	0/31(0.0)	0/34(0.0)	3/39(7.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8481			
Prevalence method(d)	P = 0.0067**			
Combined analysis(d)	P = 0.3525			
Cochran-Armitage test(e)	P = 0.5631			
Fisher Exact test(e)		P = 0.5000	P = 0.5097	P = 0.5000
	SITE : ALL SITE TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	6/50(12.0)	7/49(14.3)	13/50(26.0)
Adjusted rates(b)	13.33	12.90	11.76	20.51
Terminal rates(c)	4/30(13.3)	4/31(12.9)	4/34(11.8)	8/39(20.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4453			
Prevalence method(d)	P = 0.1723			
Combined analysis(d)	P = 0.2180			
Cochran-Armitage test(e)	P = 0.1752			
Fisher Exact test(e)		P = 0.2883	P = 0.4101	P = 0.2348

(HPT360A)

BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : $P \leqq 0.05$ ** : $P \leqq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

TABLE O2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : lymph node			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	15/50(30.0)	14/49(28.6)	15/50(30.0)	13/50(26.0)
Adjusted rates(b)	25.81	18.52	34.62	20.59
Terminal rates(c)	8/31(25.8)	5/27(18.5)	9/26(34.6)	7/34(20.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6912			
Prevalence method(d)	P = 0.5969			
Combined analysis(d)	P = 0.7065			
Cochran-Armitage test(e)	P = 0.6748			
Fisher Exact test(e)		P = 0.5259	P = 0.5862	P = 0.4120
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	5/49(10.2)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	3.23	18.52	10.00	8.82
Terminal rates(c)	1/31(3.2)	5/27(18.5)	2/26(7.7)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3705			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6944			
Fisher Exact test(e)		P = 0.0976	P = 0.3087	P = 0.3087
	SITE : liver			
	TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	2/49(4.1)	4/50(8.0)	3/50(6.0)
Adjusted rates(b)	0.0	7.41	15.38	8.82
Terminal rates(c)	0/31(0.0)	2/27(7.4)	4/26(15.4)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1100			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1524			
Fisher Exact test(e)		P = 0.2424	P = 0.0587	P = 0.1212

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	5/49(10.2)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	3.23	18.52	10.00	8.82
Terminal rates(c)	1/31(3.2)	5/27(18.5)	2/26(7.7)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3705			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6944			
Fisher Exact test(e)		P = 0.0976	P = 0.3087	P = 0.3087
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	11/48(22.9)	13/50(26.0)	12/50(24.0)
Adjusted rates(b)	29.03	39.29	33.33	27.91
Terminal rates(c)	9/31(29.0)	10/27(37.0)	8/26(30.8)	7/34(20.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4099			
Prevalence method(d)	P = 0.3709			
Combined analysis(d)	P = 0.3632			
Cochran-Armitage test(e)	P = 0.6379			
Fisher Exact test(e)		P = 0.4577	P = 0.3176	P = 0.4048
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	11/48(22.9)	13/50(26.0)	14/50(28.0)
Adjusted rates(b)	29.03	39.29	33.33	30.23
Terminal rates(c)	9/31(29.0)	10/27(37.0)	8/26(30.8)	8/34(23.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1406			
Prevalence method(d)	P = 0.2827			
Combined analysis(d)	P = 0.2030			
Cochran-Armitage test(e)	P = 0.3347			
Fisher Exact test(e)		P = 0.4577	P = 0.3176	P = 0.2415

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : ovary			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/49(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	3.23	0.0	0.0	7.50
Terminal rates(c)	1/31(3.2)	0/27(0.0)	0/26(0.0)	1/34(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0564			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0893			
Fisher Exact test(e)		P = 0.5051	P = 0.5000	P = 0.3087
	SITE : uterus			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	7/49(14.3)	14/50(28.0)	8/50(16.0)
Adjusted rates(b)	3.23	14.81	3.85	5.88
Terminal rates(c)	1/31(3.2)	4/27(14.8)	1/26(3.8)	2/34(5.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4707			
Prevalence method(d)	P = 0.5451			
Combined analysis(d)	P = 0.4987			
Cochran-Armitage test(e)	P = 0.9654			
Fisher Exact test(e)		P = 0.4101	P = 0.1710	P = 0.5000

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : Harderian gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/49(0.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	2.44	0.0	8.57	4.44
Terminal rates(c)	0/31(0.0)	0/27(0.0)	2/26(7.7)	1/34(2.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1767			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3306			
Fisher Exact test(e)		P = 0.5051	P = 0.3087	P = 0.5000

(HPT360A)

BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis
Prevalence method : Incidental tumor test
Combined analysis : Death analysis + Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
? : The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
------ : There is no data which should be statistical analysis.
Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01
N.C. :Statistical value cannot be calculated and was not significant.

Group Name	Control	100 ppm	200 ppm	400 ppm
	SITE : ALL SITE			
	TUMOR : histiocytic sarcoma			
Tumor rate				
Overall rates(a)	12/50(24.0)	10/49(20.4)	16/50(32.0)	10/50(20.0)
Adjusted rates(b)	9.68	14.81	3.85	8.82
Terminal rates(c)	3/31(9.7)	4/27(14.8)	1/26(3.8)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5317			
Prevalence method(d)	P = 0.6540			
Combined analysis(d)	P = 0.6053			
Cochran-Armitage test(e)	P = 0.8073			
Fisher Exact test(e)		P = 0.4258	P = 0.2522	P = 0.4048
	SITE : ALL SITE			
	TUMOR : malignant lymphoma			
Tumor rate				
Overall rates(a)	15/50(30.0)	14/49(28.6)	15/50(30.0)	13/50(26.0)
Adjusted rates(b)	25.81	18.52	34.62	20.59
Terminal rates(c)	8/31(25.8)	5/27(18.5)	9/26(34.6)	7/34(20.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6912			
Prevalence method(d)	P = 0.5969			
Combined analysis(d)	P = 0.7065			
Cochran-Armitage test(e)	P = 0.6748			
Fisher Exact test(e)		P = 0.5259	P = 0.5862	P = 0.4120

(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 Q1

CAUSE OF DEATH : MALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : MALE

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

Group Name	Control	100 ppm	200 ppm	400 ppm
Number of Dead and Moribund Animal	20	19	15	11
no microscop confirm	1	0	1	1
renal lesion	0	1	1	0
urinary retention	3	4	2	0
hydronephrosis	1	5	2	0
tumor d:leukemia	5	2	3	5
tumor d:subcutis	0	1	1	1
tumor d:lung	0	1	0	1
tumor d:lymph node	1	0	0	0
tumor d:spleen	1	0	0	0
tumor d:liver	8	3	4	3
tumor d:pituitary	0	1	0	0
tumor d:bone	0	1	0	0
tumor d:pleura	0	0	1	0

(BI0120)

BAIS4

TABLE Q2

CAUSE OF DEATH : FEMALE

STUDY NO. : 0676
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
SEX : FEMALE

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

Group Name	Control	100 ppm	200 ppm	400 ppm
Number of Dead and Moribund Animal	19	22	24	16
no microscop confirm	1	2	0	0
renal lesion	0	1	0	0
urinary retention	0	0	1	0
hydronephrosis	0	1	0	0
tumor d:leukemia	7	9	6	7
tumor d:subcutis	0	2	0	0
tumor d:lung	1	0	0	0
tumor d:lymph node	0	1	0	0
tumor d:spleen	0	0	1	0
tumor d:liver	1	0	0	1
tumor d:pituitary	0	0	1	1
tumor d:ovary	1	0	0	0
tumor d:uterus	8	3	13	6
tumor d:vagina	0	1	0	0
tumor d:spinal cord	0	0	1	0
tumor d:periph nerv	0	1	0	0
tumor d:bone	0	0	0	1
tumor d:peritoneum	0	1	1	0

FIGURES

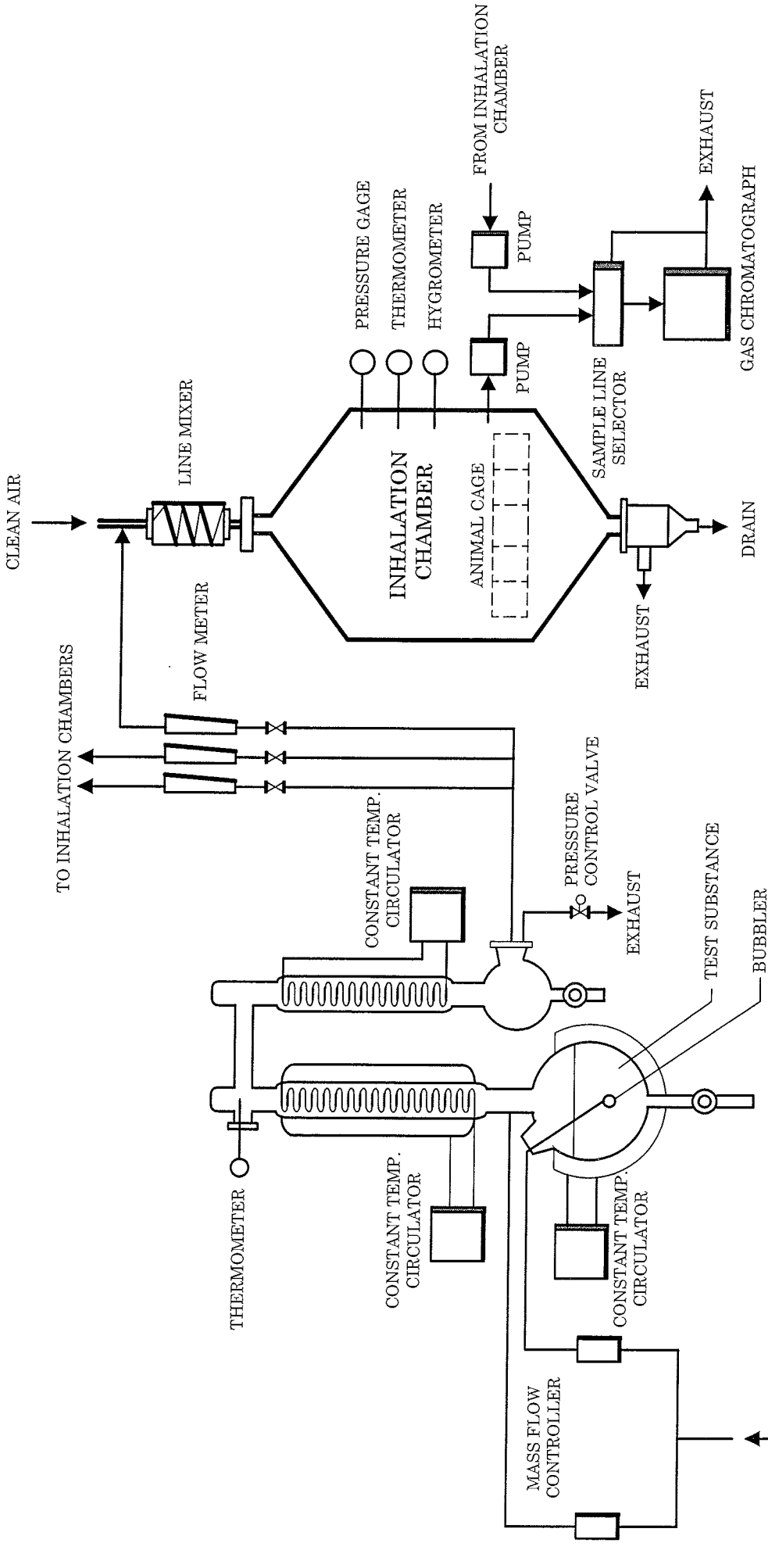


FIGURE 1 2,4-PENTANEDIONE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

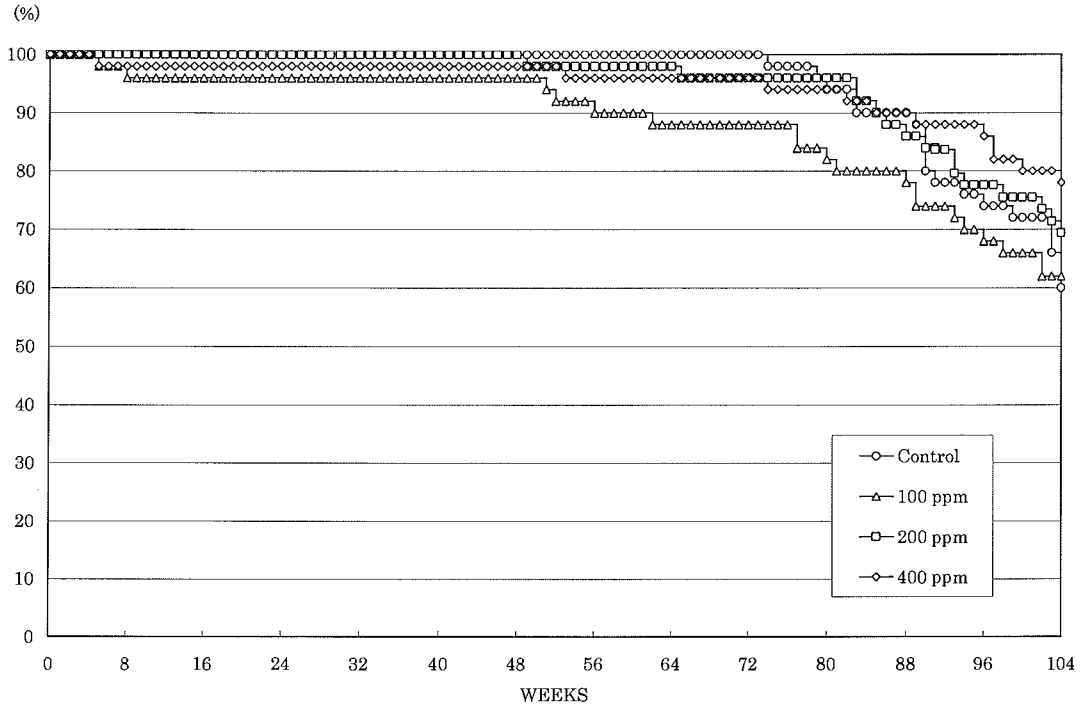


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

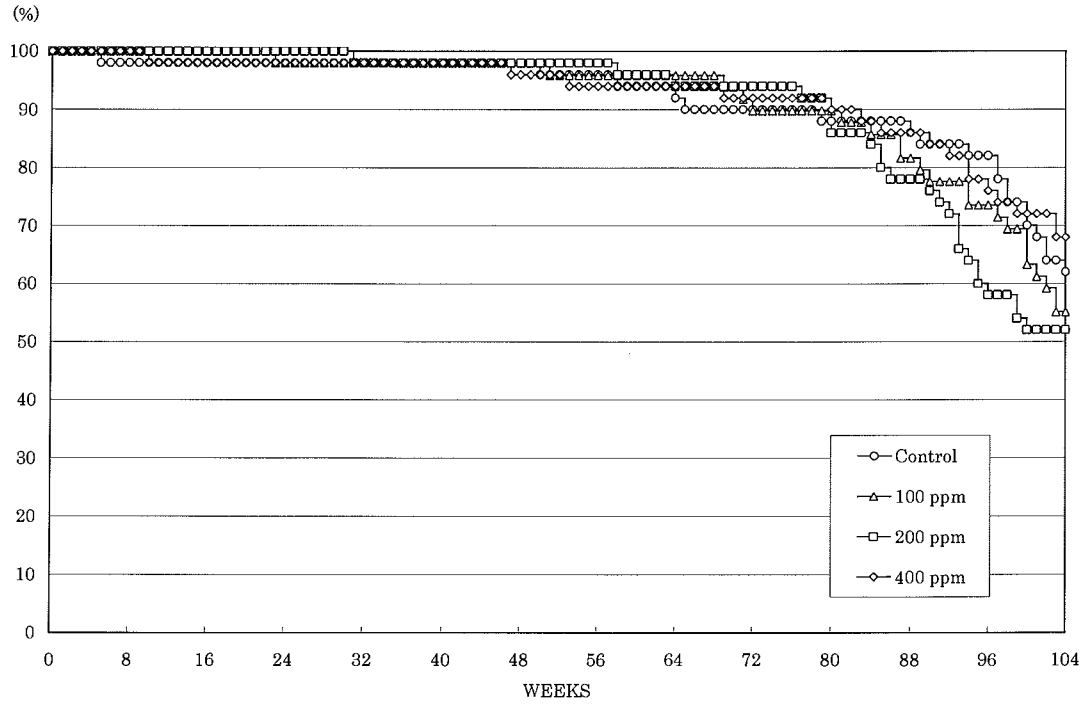


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

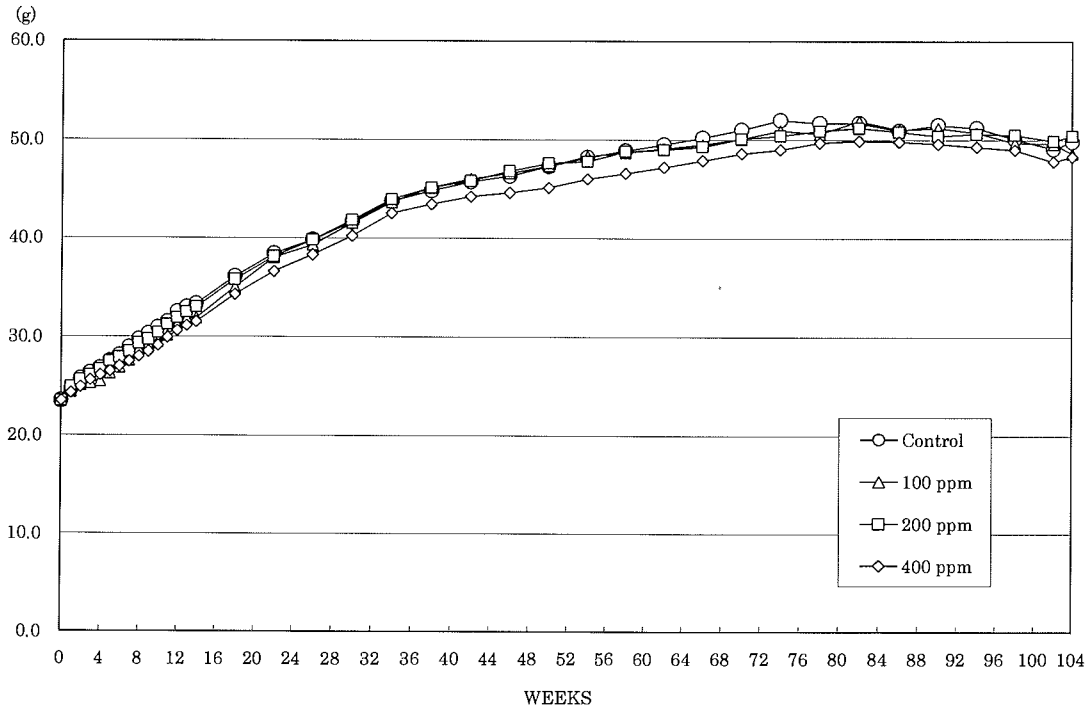


FIGURE 4 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

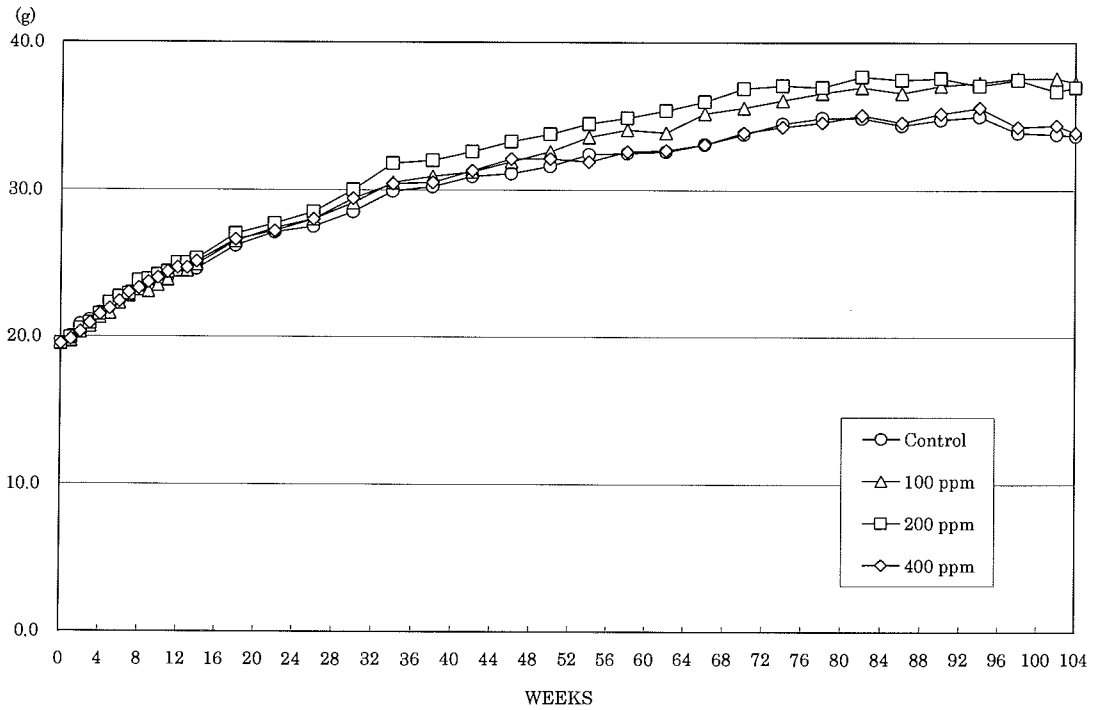


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

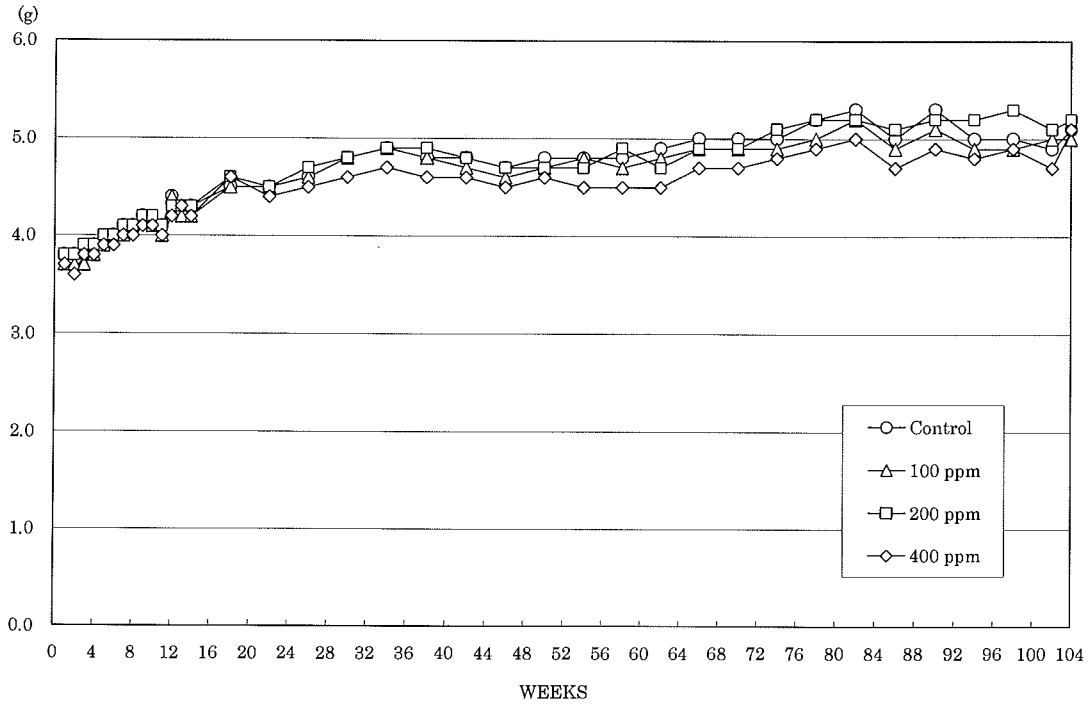


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

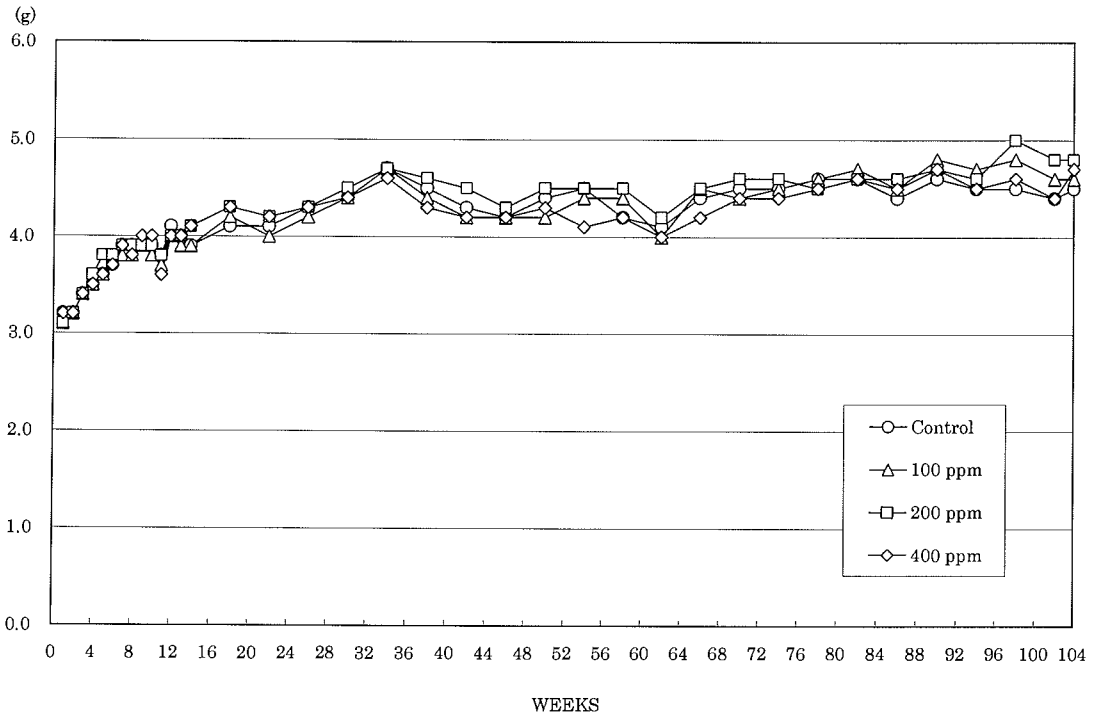
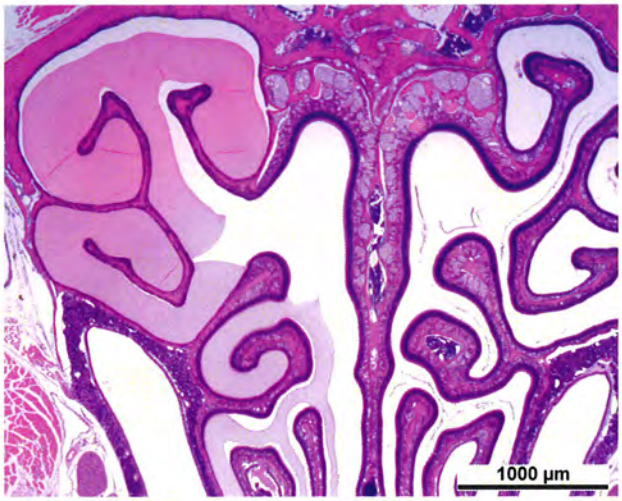
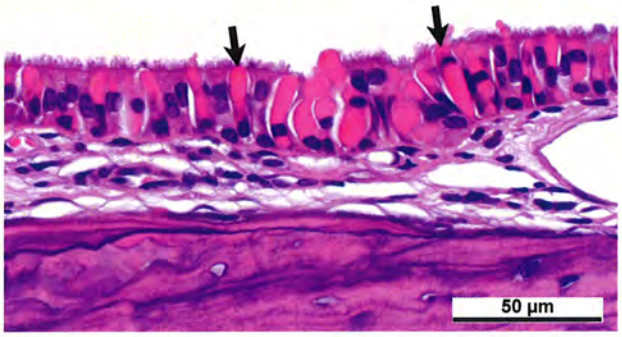


FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE



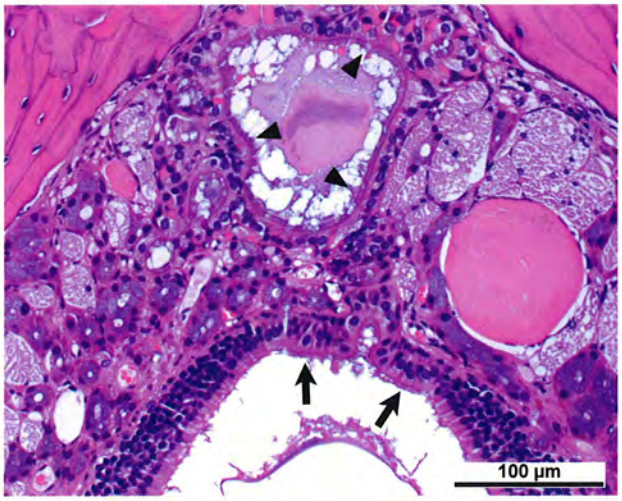
Photograph 1
Nasal cavity (Level 3): Exudate
Mouse, Male, 100 ppm, Animal No. 0676-1141 (H&E)

Photograph 2
Nasal cavity (Level 1): Squamous metaplasia (arrows) of the respiratory epithelium
Mouse, Female, 400 ppm, Animal No. 0676-2314 (H&E)

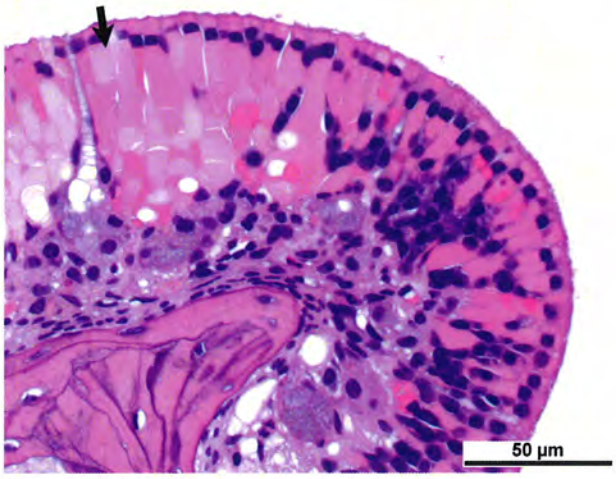


Photograph 3
Nasal cavity (Level 1): Eosinophilic change (arrows) of the respiratory epithelium
Mouse, Male, 200 ppm, Animal No. 0676-1202 (H&E)

Photograph 4
Nasal cavity (Level 3): Atrophy of the olfactory epithelium (arrows) and exudate (*)
Mouse, Male, 100 ppm, Animal No. 0676-1141 (H&E)



Photograph 5
Nasal cavity (Level 3): Respiratory metaplasia of the olfactory epithelium (arrows) and gland (arrowheads)
Mouse, Female, 400 ppm, Animal No. 0676-2314 (H&E)



Photograph 6
Nasal cavity (Level 3): Eosinophilic change of the olfactory epithelium (arrow)
Mouse, Female, 400 ppm, Animal No. 0676-2344 (H&E)