Summary of Inhalation Carcinogenicity Study of Methylamine in F344 Rats

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on March 26, 2012.

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

Summary of Inhalation Carcinogenicity Study of Methylamine in F344 Rats

Purpose, materials and methods

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

The carcinogenicity and chronic toxicity of methylamine (greater than 99.97% pure) were examined by inhalation exposure using F344/DuCrlCrlj (Fischer) rats. Groups of test animals were exposed to methylamine vapors at target concentrations of 0 (clean air), 5, 20 or 80 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 methylamine vapor. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the methylamine used in these experiments was confirmed by mass spectrometry. It was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 7.6 m^3) were used throughout the 2-year exposure period. Methylamine gas from liquefied methylamine gas cylinder was deluted to each target concentration with filtered freah air and delivered to each inhalation exposure chamber. Air concentrations of the methylamine in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the exposure period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Three μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of methylamine induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the

Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 “Carcinogenicity Studies”.

Results

No significant differences in survival rates were found between any of the groups exposed to methylamine and their respective controls. External mass were observed in females exposed to 80 ppm methylamine, but no tumor induction was observed. Body weights of males exposed to 80 ppm methylamine were slightly suppressed for the first few weeks compared with their control. There was no significant difference in body weight changes was found in methylamine exposed group of females and the control. There was no significant difference in food consumption was found between any methylamine exposed group of either sex and the respective controls.

The incidences of selected neoplastic lesions in male and female rats are presented in the tables below. The incidences of pituitary adenoma was significantly increased in males exposed to 20 ppm and 80 ppm, and increased in a concentration-dependent manner, but the incidences of pituitary adenoma in males exposed to 20 ppm and 80 ppm was within the JBRC histrical control data. The incidences of splenic mononuclear cell leukemia in males were increased in a concentration-dependent manner, but were within the JBRC histrical control data. The incidences of mammary gland fibroadenoma in females were increased in a concentration-dependent manner, but were within the JBRC histrical control data. Therefore, the incidences of pituitary adenoma and splenic mononuclear cell leukemia in males and mammary gland fibroadenoma in females were not attributed to methylamine exposure. As non-neoplastic lesions, inflammation, ulcer and squamous metaplasia of the respiratory epithelium, and hyperplasia of the transitinal epithelium in the nasal cavity were observed in both sexes at doses of 80 ppm methylamine. No effects of methylamine were observed in exposed to 20 ppm and below.

Using nasal lesions as endpoint markers, the no-observed-adverse-effect-level (NOAEL) of methylamine was 20 ppm in both male and female rats when exposed by inhalation.

Conclusions

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

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

Dose (ppm)		0	5	20	80	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
skin/appendage	keratoacanthoma	2	3	3	1		
subcutis	fibroma	4	2	4	5		
lung	bronchiolar-alveolar adenoma	5	4	8	3		
pancreas	islet cell adenoma	5	5	4	5		
pituitary	adenoma	8	11	17 *	17 *	↑	
thyroid	C-cell adenoma	9	7	12	4		
adrenal	pheochromocytoma	5	10	4	8		
testis	interstitial cell tumor	37	44	34	33		
malignant tumor							
spleen	mononuclear cell leukemia	6	6	4	10	↑ [a]	

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

Dose (ppm)		0	5	20	80	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
pituitary	adenoma	17	15	16	15		
thyroid	C-cell adenoma	6	10	3	7		
adrenal	pheochromocytoma	4	1	0	2		
uterus	endometrial stromal polyp	8	4	7	9		
mammary gland	fibroadenoma	5	3	5	10	↑	↑
malignant tumor							
spleen	mononuclear cell leukemia	6	6	9	5		

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

a :Significant only in Prevalence method in Peto test.

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

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

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
5 ppm	5.0 ± 0.1
20 ppm	20.2 ± 0.3
80 ppm	80.4 ± 0.9

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN BODY WEIGHTS AND SURVIVAL

Week-Day on Study	Control Av. Wt.	Control No. of Surviv. <50>	5 ppm Av. Wt.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	20 ppm Av. Wt.	20 ppm % of cont. <50>	20 ppm No. of Surviv.	80 ppm Av. Wt.	80 ppm % of cont. <50>	80 ppm No. of Surviv.
0-0	122 (50)	50/50	122 (50)	100	50/50	122 (50)	100	50/50	122 (50)	100	50/50
1-7	155 (50)	50/50	154 (50)	99	50/50	155 (50)	100	50/50	152 (50)	98	50/50
2-7	189 (50)	50/50	187 (50)	99	50/50	188 (50)	99	50/50	184 (50)	97	50/50
3-7	215 (50)	50/50	212 (50)	99	50/50	213 (50)	99	50/50	210 (50)	98	50/50
4-7	238 (50)	50/50	235 (50)	99	50/50	234 (50)	98	50/50	232 (50)	97	50/50
5-7	257 (50)	50/50	253 (50)	98	50/50	252 (50)	98	50/50	250 (50)	97	50/50
6-7	271 (50)	50/50	265 (50)	98	50/50	265 (50)	98	50/50	265 (50)	98	50/50
7-7	284 (50)	50/50	280 (50)	99	50/50	278 (50)	98	50/50	279 (50)	98	50/50
8-7	295 (50)	50/50	291 (50)	99	50/50	290 (50)	98	50/50	291 (50)	99	50/50
9-7	305 (50)	50/50	302 (50)	99	50/50	300 (50)	98	50/50	302 (50)	99	50/50
10-7	312 (50)	50/50	309 (50)	99	50/50	309 (50)	99	50/50	311 (50)	100	50/50
11-7	319 (50)	50/50	316 (50)	99	50/50	316 (50)	99	50/50	318 (50)	100	50/50
12-7	326 (50)	50/50	322 (50)	99	50/50	323 (50)	99	50/50	325 (50)	100	50/50
13-7	332 (50)	50/50	329 (50)	99	50/50	330 (50)	99	50/50	332 (50)	100	50/50
14-7	336 (50)	50/50	334 (50)	99	50/50	335 (50)	100	50/50	338 (50)	101	50/50
18-7	354 (50)	50/50	351 (50)	99	50/50	351 (50)	99	50/50	354 (50)	100	50/50
22-7	367 (50)	50/50	366 (50)	100	50/50	365 (50)	99	50/50	368 (50)	100	50/50
26-7	380 (50)	50/50	379 (50)	100	50/50	379 (49)	100	49/50	382 (50)	101	50/50
30-7	390 (50)	50/50	389 (50)	100	50/50	391 (49)	100	49/50	393 (50)	101	50/50
34-7	400 (50)	50/50	401 (50)	100	50/50	401 (49)	100	49/50	402 (50)	101	50/50
38-7	405 (50)	50/50	407 (50)	100	50/50	409 (49)	101	49/50	407 (50)	100	50/50
42-7	411 (50)	50/50	414 (50)	101	50/50	414 (49)	101	49/50	413 (50)	100	50/50
46-7	419 (50)	50/50	423 (50)	101	50/50	421 (49)	100	49/50	421 (50)	100	50/50
50-7	425 (50)	50/50	427 (50)	100	50/50	424 (49)	100	49/50	426 (50)	100	50/50
54-7	429 (50)	50/50	432 (50)	101	50/50	428 (49)	100	49/50	431 (50)	100	50/50
58-7	432 (50)	50/50	436 (50)	101	50/50	433 (48)	100	48/50	435 (50)	101	50/50
62-7	437 (49)	49/50	441 (50)	101	50/50	439 (48)	100	48/50	438 (50)	100	50/50
66-7	440 (49)	49/50	444 (50)	101	50/50	441 (48)	100	48/50	442 (50)	100	50/50
70-7	442 (49)	49/50	448 (50)	101	50/50	445 (48)	101	48/50	445 (50)	101	50/50
74-7	445 (49)	49/50	451 (50)	101	50/50	449 (47)	101	47/50	447 (49)	100	49/50
78-7	444 (49)	49/50	452 (50)	102	50/50	448 (47)	101	47/50	447 (48)	101	48/50
82-7	443 (47)	47/50	452 (50)	102	50/50	458 (45)	103	45/50	449 (47)	101	47/50
86-7	439 (46)	46/50	447 (50)	102	50/50	451 (44)	103	44/50	447 (45)	102	45/50
90-7	432 (44)	44/50	441 (50)	102	50/50	438 (44)	101	44/50	441 (44)	102	44/50
94-7	424 (44)	44/50	436 (48)	103	48/50	436 (41)	103	41/50	437 (42)	103	42/50
98-7	414 (43)	43/50	428 (47)	103	47/50	425 (39)	103	39/50	422 (40)	102	40/50
102-7	412 (38)	38/50	419 (44)	102	44/50	421 (38)	102	38/50	414 (38)	100	38/50
104-7	405 (38)	38/50	412 (42)	102	42/50	415 (38)	102	38/50	411 (34)	101	34/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

Week-Day on Study	Control Av. Wt.	Control No. of Surviv. <50>	5 ppm Av. Wt.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	20 ppm Av. Wt.	20 ppm % of cont. <50>	20 ppm No. of Surviv.	80 ppm Av. Wt.	80 ppm % of cont. <50>	80 ppm No. of Surviv.
0-0	99 (50)	50/50	99 (50)	100	50/50	99 (50)	100	50/50	99 (50)	100	50/50
1-7	114 (50)	50/50	113 (50)	99	50/50	113 (50)	99	50/50	112 (50)	98	50/50
2-7	128 (50)	50/50	126 (50)	98	50/50	125 (50)	98	50/50	125 (50)	98	50/50
3-7	136 (50)	50/50	135 (50)	99	50/50	134 (50)	99	50/50	134 (50)	99	50/50
4-7	145 (50)	50/50	143 (50)	99	50/50	142 (50)	98	50/50	143 (50)	99	50/50
5-7	153 (50)	50/50	150 (50)	98	50/50	149 (50)	97	50/50	150 (50)	98	50/50
6-7	157 (50)	50/50	155 (50)	99	50/50	153 (50)	97	50/50	156 (50)	99	50/50
7-7	161 (50)	50/50	159 (50)	99	50/50	158 (50)	98	50/50	160 (50)	99	50/50
8-7	165 (50)	50/50	162 (50)	98	50/50	161 (50)	98	50/50	164 (50)	99	50/50
9-7	169 (50)	50/50	167 (50)	99	50/50	164 (50)	97	50/50	168 (50)	99	50/50
10-7	172 (50)	50/50	171 (50)	99	50/50	169 (50)	98	50/50	172 (50)	100	50/50
11-7	175 (50)	50/50	175 (50)	100	50/50	172 (50)	98	50/50	176 (50)	101	50/50
12-7	177 (50)	50/50	177 (50)	100	50/50	175 (50)	99	50/50	178 (50)	101	50/50
13-7	179 (50)	50/50	179 (50)	100	50/50	178 (50)	99	50/50	181 (50)	101	50/50
14-7	181 (50)	50/50	182 (50)	101	50/50	179 (50)	99	50/50	182 (50)	101	50/50
18-7	188 (50)	50/50	189 (50)	101	50/50	187 (50)	99	50/50	189 (50)	101	50/50
22-7	193 (50)	50/50	196 (50)	102	50/50	194 (50)	101	50/50	195 (50)	101	50/50
26-7	198 (50)	50/50	201 (50)	102	50/50	199 (50)	101	50/50	200 (50)	101	50/50
30-7	203 (50)	50/50	207 (50)	102	50/50	205 (50)	101	50/50	205 (50)	101	50/50
34-7	208 (50)	50/50	213 (50)	102	50/50	209 (50)	100	50/50	210 (50)	101	50/50
38-7	212 (50)	50/50	217 (50)	102	50/50	213 (50)	100	50/50	215 (50)	101	50/50
42-7	213 (50)	50/50	221 (50)	104	50/50	217 (50)	102	50/50	219 (50)	103	50/50
46-7	219 (50)	50/50	226 (50)	103	50/50	224 (50)	102	50/50	225 (50)	103	50/50
50-7	223 (50)	50/50	229 (50)	103	50/50	228 (50)	102	50/50	230 (50)	103	50/50
54-7	229 (50)	50/50	236 (49)	103	49/50	233 (50)	102	50/50	235 (50)	103	50/50
58-7	235 (50)	50/50	242 (49)	103	49/50	238 (50)	101	50/50	241 (50)	103	50/50
62-7	239 (50)	50/50	248 (49)	104	49/50	243 (50)	102	50/50	246 (50)	103	50/50
66-7	243 (50)	50/50	253 (49)	104	49/50	249 (49)	102	49/50	251 (50)	103	50/50
70-7	249 (50)	50/50	259 (48)	104	48/50	255 (48)	102	48/50	257 (50)	103	50/50
74-7	254 (50)	50/50	264 (48)	104	48/50	262 (48)	103	48/50	263 (50)	104	50/50
78-7	259 (49)	49/50	269 (46)	104	46/50	267 (47)	103	47/50	267 (50)	103	50/50
82-7	270 (47)	47/50	276 (44)	102	44/50	276 (46)	102	46/50	276 (49)	102	49/50
86-7	275 (47)	47/50	281 (43)	102	43/50	279 (46)	101	46/50	279 (49)	101	49/50
90-7	279 (47)	47/50	282 (42)	101	42/50	281 (46)	101	46/50	282 (48)	101	48/50
94-7	285 (46)	46/50	285 (41)	100	41/50	282 (44)	99	44/50	285 (46)	100	46/50
98-7	281 (43)	43/50	284 (41)	101	41/50	280 (44)	100	44/50	288 (43)	102	43/50
102-7	280 (41)	41/50	285 (37)	102	37/50	278 (41)	99	41/50	293 (41)	105	41/50
104-7	277 (41)	41/50	283 (37)	102	37/50	282 (38)	102	38/50	293 (38)	106	38/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	122± 5	155± 7	189± 9	215± 10	238± 10	257± 11	271± 12
5 ppm	122± 5	154± 7	187± 8	212± 10	235± 10	253± 11	265± 12*
20 ppm	122± 5	155± 7	188± 9	213± 10	234± 11	252± 12*	265± 13*
80 ppm	122± 5	152± 6*	184± 8*	210± 9	232± 9*	250± 10**	265± 10*

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

(HAN260)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	284± 13	295± 13	305± 14	312± 13	319± 14	326± 16	332± 16
5 ppm	280± 12	291± 14	302± 15	309± 15	316± 16	322± 16	329± 16
20 ppm	278± 14	290± 15	300± 16	309± 16	316± 17	323± 17	330± 16
80 ppm	279± 11	291± 11	302± 13	311± 14	318± 14	325± 14	332± 14

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	336± 16	354± 18	367± 18	380± 19	390± 20	400± 21	405± 23
5 ppm	334± 17	351± 18	366± 19	379± 21	389± 25	401± 23	407± 23
20 ppm	335± 17	351± 17	365± 19	379± 19	391± 20	401± 21	409± 22
80 ppm	338± 15	354± 16	368± 17	382± 17	393± 17	402± 17	407± 18

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	411± 23	419± 24	425± 25	429± 26	432± 25	437± 25	440± 25
5 ppm	414± 24	423± 26	427± 27	432± 28	436± 30	441± 29	444± 29
20 ppm	414± 23	421± 25	424± 25	428± 29	433± 26	439± 26	441± 26
80 ppm	413± 19	421± 19	426± 19	431± 20	435± 20	438± 20	442± 19

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

(HAN260)

BAIS4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	442± 25	445± 27	444± 30	443± 30	439± 31	432± 40	424± 39
5 ppm	448± 29	451± 28	452± 28	452± 29	447± 30	441± 32	436± 30
20 ppm	445± 27	449± 28	448± 35	458± 40	451± 25	438± 32	436± 27
80 ppm	445± 19	447± 20	447± 20	449± 23	447± 22	441± 22	437± 27

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	414± 44	412± 27	405± 40
5 ppm	428± 30	419± 31	412± 37
20 ppm	425± 43	421± 37	415± 41
80 ppm	422± 30	414± 38	411± 51

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

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	99± 4	114± 5	128± 6	136± 7	145± 8	153± 10	157± 11
5 ppm	99± 4	113± 4	126± 5	135± 5	143± 5	150± 6	155± 6
20 ppm	99± 4	113± 4	125± 6	134± 7	142± 7	149± 8	153± 10
80 ppm	99± 4	112± 4	125± 5*	134± 6	143± 6	150± 6	156± 6

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	161± 12	165± 13	169± 13	172± 14	175± 13	177± 13	179± 14
5 ppm	159± 7	162± 8	167± 8	171± 9	175± 9	177± 9	179± 9
20 ppm	158± 11	161± 11	164± 12	169± 12	172± 12	175± 13	178± 13
80 ppm	160± 7	164± 8	168± 8	172± 9	176± 9	178± 9	181± 9

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	181± 13	188± 14	193± 14	198± 15	203± 16	208± 16	212± 17
5 ppm	182± 10	189± 10	196± 11	201± 10	207± 11	213± 12	217± 13
20 ppm	179± 14	187± 13	194± 14	199± 14	205± 15	209± 16	213± 16
80 ppm	182± 10	189± 10	195± 10	200± 10	205± 11	210± 11	215± 13

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

(HAN260)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	213± 17	219± 18	223± 19	229± 21	235± 22	239± 23	243± 23
5 ppm	221± 14	226± 14	229± 14	236± 16	242± 17	248± 19	253± 20
20 ppm	217± 16	224± 17	228± 17	233± 18	238± 19	243± 21	249± 21
80 ppm	219± 13	225± 13	230± 14	235± 15	241± 16	246± 18	251± 19

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	249± 24	254± 25	259± 27	270± 25	275± 26	279± 28	285± 31
5 ppm	259± 20	264± 21	269± 23	276± 24	281± 23	282± 25	285± 23
20 ppm	255± 22	262± 24	267± 24	276± 24	279± 28	281± 30	282± 32
80 ppm	257± 20	263± 20	267± 22	276± 19	279± 21	282± 22	285± 25

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	281± 28	280± 30	277± 33
5 ppm	284± 29	285± 30	283± 30
20 ppm	280± 32	278± 31	282± 22
80 ppm	288± 32	293± 46	293± 55

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

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week-Day on Study	Control Av. FC.	Control No. of Surviv. <50>	5 ppm Av. FC.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	20 ppm Av. FC.	20 ppm % of cont. <50>	20 ppm No. of Surviv.	80 ppm Av. FC.	80 ppm % of cont. <50>	80 ppm No. of Surviv.
1-7	15.0 (50)	50/50	15.4 (50)	103	50/50	15.0 (50)	100	50/50	14.6 (50)	97	50/50
2-7	16.9 (50)	50/50	17.3 (50)	102	50/50	17.1 (50)	101	50/50	16.5 (50)	98	50/50
3-7	16.7 (50)	50/50	17.0 (50)	102	50/50	16.7 (50)	100	50/50	16.2 (50)	97	50/50
4-7	17.4 (50)	50/50	17.9 (50)	103	50/50	17.2 (50)	99	50/50	17.1 (50)	98	50/50
5-7	17.6 (50)	50/50	17.9 (50)	102	50/50	17.3 (50)	98	50/50	17.3 (50)	98	50/50
6-7	17.5 (50)	50/50	17.2 (50)	98	50/50	17.1 (50)	98	50/50	17.3 (50)	99	50/50
7-7	17.6 (50)	50/50	17.3 (50)	98	50/50	17.2 (50)	98	50/50	17.5 (50)	99	50/50
8-7	17.1 (50)	50/50	17.0 (50)	99	50/50	16.7 (50)	98	50/50	17.1 (50)	100	50/50
9-7	17.3 (50)	50/50	17.2 (50)	99	50/50	17.2 (50)	99	50/50	17.4 (50)	101	50/50
10-7	16.9 (50)	50/50	16.8 (50)	99	50/50	17.0 (50)	101	50/50	17.0 (50)	101	50/50
11-7	16.8 (50)	50/50	16.7 (50)	99	50/50	16.9 (49)	101	50/50	16.9 (50)	101	50/50
12-7	16.6 (50)	50/50	16.4 (50)	99	50/50	16.6 (50)	100	50/50	16.8 (50)	101	50/50
13-7	16.6 (50)	50/50	16.3 (50)	98	50/50	16.6 (50)	100	50/50	16.8 (50)	101	50/50
14-7	16.4 (50)	50/50	16.3 (50)	99	50/50	16.3 (50)	99	50/50	16.6 (50)	101	50/50
18-7	16.4 (50)	50/50	16.3 (50)	99	50/50	16.1 (50)	98	50/50	16.3 (50)	99	50/50
22-7	16.9 (50)	50/50	16.8 (50)	99	50/50	16.5 (50)	98	50/50	16.7 (50)	99	50/50
26-7	17.1 (50)	50/50	17.1 (50)	100	50/50	17.0 (49)	99	49/50	16.9 (50)	99	50/50
30-7	16.9 (50)	50/50	16.5 (50)	98	50/50	16.8 (49)	99	49/50	16.7 (50)	99	50/50
34-7	16.9 (50)	50/50	17.0 (50)	101	50/50	16.9 (49)	100	49/50	16.7 (50)	99	50/50
38-7	16.6 (50)	50/50	16.7 (50)	101	50/50	16.6 (49)	100	49/50	16.4 (50)	99	50/50
42-7	17.0 (50)	50/50	16.8 (50)	99	50/50	16.7 (49)	98	49/50	16.7 (50)	98	50/50
46-7	17.0 (50)	50/50	17.0 (50)	100	50/50	16.8 (49)	99	49/50	16.6 (50)	98	50/50
50-7	16.9 (50)	50/50	16.9 (50)	100	50/50	16.4 (49)	97	49/50	16.8 (50)	99	50/50
54-7	17.1 (50)	50/50	17.3 (50)	101	50/50	16.8 (49)	98	49/50	17.0 (50)	99	50/50
58-7	17.3 (50)	50/50	17.3 (50)	100	50/50	17.2 (48)	99	48/50	17.1 (50)	99	50/50
62-7	17.3 (49)	49/50	17.5 (50)	101	50/50	17.4 (48)	101	48/50	16.9 (50)	98	50/50
66-7	17.3 (49)	49/50	17.5 (50)	101	50/50	17.3 (48)	100	48/50	17.2 (50)	99	50/50
70-7	17.3 (49)	49/50	17.7 (50)	102	50/50	17.6 (48)	102	48/50	16.9 (50)	98	50/50
74-7	17.2 (49)	49/50	17.2 (50)	100	50/50	17.3 (47)	101	47/50	16.9 (49)	98	49/50
78-7	17.0 (49)	49/50	17.3 (50)	102	50/50	17.0 (47)	100	47/50	16.8 (48)	99	48/50
82-7	17.2 (47)	47/50	17.6 (50)	102	50/50	17.6 (45)	102	45/50	17.0 (47)	99	47/50
86-7	17.1 (46)	46/50	17.1 (50)	100	50/50	17.3 (44)	101	44/50	16.3 (45)	95	45/50
90-7	17.3 (44)	44/50	17.2 (50)	99	50/50	16.5 (44)	95	44/50	16.3 (44)	94	44/50
94-7	16.9 (44)	44/50	17.3 (48)	102	48/50	17.2 (41)	102	41/50	16.4 (42)	97	42/50
98-7	16.9 (43)	43/50	17.0 (47)	101	47/50	17.0 (39)	101	39/50	16.2 (40)	96	40/50
102-7	16.6 (38)	38/50	16.6 (44)	100	44/50	17.1 (38)	103	38/50	16.0 (38)	96	38/50
104-7	16.6 (38)	38/50	16.5 (42)	99	42/50	17.1 (38)	103	38/50	15.8 (34)	95	34/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week-Day on Study	Control Av. FC.	Control No. of Surviv. <50>	5 ppm Av. FC.	5 ppm % of cont. <50>	5 ppm No. of Surviv.	20 ppm Av. FC.	20 ppm % of cont. <50>	20 ppm No. of Surviv.	80 ppm Av. FC.	80 ppm % of cont. <50>	80 ppm No. of Surviv.
1-7	11.3 (50)	50/50	11.6 (50)	103	50/50	11.3 (50)	100	50/50	10.9 (50)	96	50/50
2-7	11.8 (50)	50/50	12.1 (50)	103	50/50	11.7 (50)	99	50/50	11.7 (50)	99	50/50
3-7	11.1 (50)	50/50	11.5 (50)	104	50/50	11.2 (50)	101	50/50	11.3 (50)	102	50/50
4-7	11.6 (50)	50/50	11.9 (50)	103	50/50	11.3 (50)	97	50/50	11.5 (50)	99	50/50
5-7	11.8 (50)	50/50	11.9 (50)	101	50/50	11.5 (50)	97	50/50	11.7 (50)	99	50/50
6-7	11.2 (50)	50/50	11.4 (50)	102	50/50	11.1 (50)	99	50/50	11.6 (50)	104	50/50
7-7	11.2 (50)	50/50	11.0 (50)	98	50/50	10.8 (50)	96	50/50	11.2 (50)	100	50/50
8-7	10.8 (50)	50/50	10.7 (50)	99	50/50	10.5 (50)	97	50/50	10.7 (50)	99	50/50
9-7	11.0 (50)	50/50	11.1 (50)	101	50/50	11.0 (50)	100	50/50	11.3 (50)	103	50/50
10-7	10.9 (50)	50/50	10.9 (50)	100	50/50	10.7 (50)	98	50/50	10.9 (50)	100	50/50
11-7	11.0 (50)	50/50	11.0 (50)	100	50/50	11.0 (50)	100	50/50	10.9 (50)	99	50/50
12-7	10.6 (50)	50/50	10.7 (50)	101	50/50	10.9 (50)	103	50/50	10.9 (50)	103	50/50
13-7	10.6 (50)	50/50	10.7 (50)	101	50/50	10.9 (50)	103	50/50	10.7 (50)	101	50/50
14-7	10.6 (50)	50/50	10.7 (50)	101	50/50	10.6 (50)	100	50/50	10.8 (50)	102	50/50
18-7	10.7 (50)	50/50	11.0 (50)	103	50/50	10.8 (50)	101	50/50	10.9 (50)	102	50/50
22-7	10.9 (50)	50/50	11.2 (50)	103	50/50	11.1 (50)	102	50/50	11.3 (50)	104	50/50
26-7	10.8 (50)	50/50	11.1 (50)	103	50/50	11.2 (50)	104	50/50	11.0 (50)	102	50/50
30-7	10.9 (50)	50/50	11.3 (50)	104	50/50	11.1 (50)	102	50/50	11.0 (50)	101	50/50
34-7	10.8 (50)	50/50	11.3 (50)	105	50/50	11.0 (50)	102	50/50	11.2 (50)	104	50/50
38-7	10.7 (50)	50/50	11.0 (50)	103	50/50	11.0 (50)	103	50/50	11.3 (50)	106	50/50
42-7	11.0 (50)	50/50	11.4 (50)	104	50/50	11.4 (50)	104	50/50	11.5 (50)	105	50/50
46-7	10.9 (50)	50/50	11.4 (50)	105	50/50	11.5 (50)	106	50/50	11.4 (50)	105	50/50
50-7	11.1 (50)	50/50	11.5 (50)	104	50/50	11.5 (50)	104	50/50	11.6 (50)	105	50/50
54-7	11.5 (50)	50/50	11.9 (49)	103	49/50	11.7 (50)	102	50/50	11.8 (50)	103	50/50
58-7	11.7 (50)	50/50	12.2 (49)	104	49/50	12.2 (50)	104	50/50	12.3 (50)	105	50/50
62-7	11.7 (50)	50/50	12.2 (49)	104	49/50	11.9 (50)	102	50/50	11.9 (50)	102	50/50
66-7	11.7 (50)	50/50	12.2 (49)	104	49/50	12.3 (49)	105	49/50	12.2 (50)	104	50/50
70-7	12.0 (50)	50/50	12.6 (48)	105	48/50	12.4 (48)	103	48/50	12.4 (50)	103	50/50
74-7	11.8 (50)	50/50	12.1 (48)	103	48/50	12.3 (48)	104	48/50	12.1 (50)	103	50/50
78-7	12.1 (49)	49/50	12.3 (46)	102	46/50	12.3 (47)	102	47/50	12.3 (50)	102	50/50
82-7	13.2 (47)	47/50	13.4 (44)	102	44/50	13.0 (46)	98	46/50	13.3 (49)	101	49/50
86-7	12.9 (47)	47/50	13.1 (43)	102	43/50	12.9 (46)	100	46/50	12.5 (49)	97	49/50
90-7	12.8 (47)	47/50	13.1 (42)	102	42/50	13.4 (46)	105	46/50	12.5 (48)	98	48/50
94-7	13.1 (46)	46/50	13.1 (41)	100	41/50	13.3 (44)	102	44/50	12.4 (46)	95	46/50
98-7	13.1 (43)	43/50	12.7 (41)	97	41/50	13.1 (44)	100	44/50	12.5 (43)	95	43/50
102-7	13.0 (41)	41/50	13.3 (37)	102	37/50	13.0 (41)	100	41/50	12.6 (41)	97	41/50
104-7	12.6 (41)	41/50	12.8 (37)	102	37/50	13.0 (38)	103	38/50	12.8 (38)	102	38/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 1-7 (7)	2-7 (7)	3-7 (7)	4-7 (7)	5-7 (7)	6-7 (7)	7-7 (7)
Control	15.0± 1.0	16.9± 1.0	16.7± 1.1	17.4± 1.0	17.6± 0.9	17.5± 1.2	17.6± 1.2
5 ppm	15.4± 0.8*	17.3± 0.9*	17.0± 1.0	17.9± 0.8*	17.9± 0.8	17.2± 0.9	17.3± 0.9
20 ppm	15.0± 0.8	17.1± 0.9	16.7± 1.0	17.2± 1.0	17.3± 1.1	17.1± 1.1	17.2± 1.2
80 ppm	14.6± 0.7	16.5± 0.8	16.2± 0.7**	17.1± 0.8	17.3± 0.9	17.3± 0.8	17.5± 0.9

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 8-7 (7)	9-7 (7)	10-7 (7)	11-7 (7)	12-7 (7)	13-7 (7)	14-7 (7)
Control	17.1± 1.0	17.3± 1.1	16.9± 1.0	16.8± 1.0	16.6± 1.1	16.6± 1.0	16.4± 1.0
5 ppm	17.0± 1.1	17.2± 1.0	16.8± 1.1	16.7± 1.1	16.4± 1.0	16.3± 1.0	16.3± 1.2
20 ppm	16.7± 1.2	17.2± 1.1	17.0± 1.2	16.9± 1.0	16.6± 0.9	16.6± 0.9	16.3± 1.0
80 ppm	17.1± 0.9	17.4± 1.1	17.0± 1.0	16.9± 1.1	16.8± 1.0	16.8± 0.9	16.6± 0.9

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

(HAN260)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 18-7 (7)	22-7 (7)	26-7 (7)	30-7 (7)	34-7 (7)	38-7 (7)	42-7 (7)
Control	16.4± 1.0	16.9± 1.0	17.1± 1.0	16.9± 1.0	16.9± 1.1	16.6± 1.1	17.0± 1.1
5 ppm	16.3± 1.1	16.8± 1.0	17.1± 1.1	16.5± 2.3	17.0± 1.1	16.7± 0.9	16.8± 1.1
20 ppm	16.1± 0.9	16.5± 1.0	17.0± 1.1	16.8± 1.1	16.9± 1.1	16.6± 1.2	16.7± 1.0
80 ppm	16.3± 1.0	16.7± 1.0	16.9± 0.9	16.7± 0.9	16.7± 0.8	16.4± 0.9	16.7± 0.9

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 46-7 (7)	50-7 (7)	54-7 (7)	58-7 (7)	62-7 (7)	66-7 (7)	70-7 (7)
Control	17.0± 1.0	16.9± 1.0	17.1± 1.0	17.3± 0.9	17.3± 0.9	17.3± 0.8	17.3± 1.1
5 ppm	17.0± 1.1	16.9± 0.9	17.3± 1.2	17.3± 1.6	17.5± 1.0	17.5± 1.0	17.7± 1.1
20 ppm	16.8± 1.1	16.4± 1.7	16.8± 2.1	17.2± 1.0	17.4± 1.0	17.3± 1.2	17.6± 1.3
80 ppm	16.6± 0.9	16.8± 0.9	17.0± 1.0	17.1± 0.9	16.9± 0.9	17.2± 0.9	16.9± 0.9

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

(HAN260)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 74-7 (7)	78-7 (7)	82-7 (7)	86-7 (7)	90-7 (7)	94-7 (7)	98-7 (7)
Control	17.2± 1.1	17.0± 2.5	17.2± 1.6	17.1± 1.6	17.3± 1.6	16.9± 1.7	16.9± 1.8
5 ppm	17.2± 1.1	17.3± 1.1	17.6± 1.2	17.1± 1.5	17.2± 1.6	17.3± 1.4	17.0± 1.6
20 ppm	17.3± 1.0	17.0± 1.8	17.6± 1.1	17.3± 1.4	16.5± 3.2	17.2± 1.3	17.0± 2.4
80 ppm	16.9± 1.0	16.8± 1.1	17.0± 1.8	16.3± 1.1*	16.3± 1.0**	16.4± 1.9	16.2± 1.7

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration 102-7 (7)	week-day (effective) 104-7 (7)
Control	16.6± 2.1	16.6± 2.2
5 ppm	16.6± 2.0	16.5± 2.1
20 ppm	17.1± 1.8	17.1± 2.3
80 ppm	16.0± 3.1	15.8± 3.5

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

(HAN260)

BAIS 4

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 1-7 (7)	2-7 (7)	3-7 (7)	4-7 (7)	5-7 (7)	6-7 (7)	7-7 (7)
Control	11.3± 0.6	11.8± 0.8	11.1± 0.9	11.6± 1.0	11.8± 1.1	11.2± 1.0	11.2± 1.1
5 ppm	11.6± 0.4**	12.1± 0.7	11.5± 0.6	11.9± 0.7	11.9± 0.9	11.4± 0.8	11.0± 0.8
20 ppm	11.3± 0.6	11.7± 0.7	11.2± 0.9	11.3± 0.8	11.5± 1.0	11.1± 1.0	10.8± 1.0
80 ppm	10.9± 0.5**	11.7± 0.6	11.3± 0.6	11.5± 0.8	11.7± 0.8	11.6± 0.9	11.2± 0.8

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

(HAN260)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 8-7 (7)	9-7 (7)	10-7 (7)	11-7 (7)	12-7 (7)	13-7 (7)	14-7 (7)
Control	10.8± 1.1	11.0± 1.0	10.9± 1.1	11.0± 0.8	10.6± 1.0	10.6± 1.0	10.6± 1.1
5 ppm	10.7± 0.9	11.1± 0.8	10.9± 0.9	11.0± 1.0	10.7± 0.9	10.7± 0.8	10.7± 0.9
20 ppm	10.5± 1.0	11.0± 1.0	10.7± 0.9	11.0± 1.0	10.9± 1.0	10.9± 1.0	10.6± 1.0
80 ppm	10.7± 0.8	11.3± 1.1	10.9± 1.0	10.9± 0.9	10.9± 0.8	10.7± 0.8	10.8± 1.0

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 18-7 (7)	22-7 (7)	26-7 (7)	30-7 (7)	34-7 (7)	38-7 (7)	42-7 (7)
Control	10.7± 0.9	10.9± 0.9	10.8± 1.0	10.9± 0.9	10.8± 0.9	10.7± 0.9	11.0± 1.1
5 ppm	11.0± 0.9	11.2± 1.0	11.1± 0.7	11.3± 0.8	11.3± 0.8*	11.0± 0.9	11.4± 1.0*
20 ppm	10.8± 0.9	11.1± 1.0	11.2± 0.9	11.1± 0.9	11.0± 1.0	11.0± 0.9	11.4± 0.9
80 ppm	10.9± 0.8	11.3± 0.9	11.0± 0.7	11.0± 0.7	11.2± 0.8	11.3± 0.8**	11.5± 0.9**

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

(HAN260)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 46-7 (7)	50-7 (7)	54-7 (7)	58-7 (7)	62-7 (7)	66-7 (7)	70-7 (7)
Control	10.9± 0.8	11.1± 1.1	11.5± 1.0	11.7± 1.0	11.7± 1.0	11.7± 1.1	12.0± 1.2
5 ppm	11.4± 0.9**	11.5± 1.0	11.9± 1.0	12.2± 1.2	12.2± 1.0*	12.2± 1.1	12.6± 1.0**
20 ppm	11.5± 0.8**	11.5± 0.9	11.7± 1.0	12.2± 1.1	11.9± 1.6	12.3± 1.2*	12.4± 1.0
80 ppm	11.4± 0.6**	11.6± 0.9*	11.8± 1.0	12.3± 1.0*	11.9± 0.9	12.2± 1.0	12.4± 0.9

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 74-7 (7)	78-7 (7)	82-7 (7)	86-7 (7)	90-7 (7)	94-7 (7)	98-7 (7)
Control	11.8± 1.5	12.1± 1.3	13.2± 1.1	12.9± 1.1	12.8± 1.5	13.1± 1.7	13.1± 1.2
5 ppm	12.1± 1.1	12.3± 1.5	13.4± 1.7	13.1± 1.0	13.1± 1.3	13.1± 1.3	12.7± 2.3
20 ppm	12.3± 1.2	12.3± 0.9	13.0± 1.1	12.9± 1.2	13.4± 1.6	13.3± 1.3	13.1± 1.7
80 ppm	12.1± 1.0	12.3± 1.5	13.3± 0.9	12.5± 1.0	12.5± 1.0	12.4± 1.7	12.5± 1.7*

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

(HAN260)

BAIS4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day (effective) 102-7 (7)	104-7 (7)
Control	13.0± 1.4	12.6± 1.6
5 ppm	13.3± 1.5	12.8± 1.3
20 ppm	13.0± 2.1	13.0± 1.4
80 ppm	12.6± 3.2	12.8± 3.1

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

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV fℓ	MCH pg	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	37	7.61± 1.53	12.4± 2.7	37.6± 6.7	50.0± 5.7	16.3± 2.0	32.7± 2.2	1030± 379
5 ppm	41	8.00± 1.46	13.3± 2.7	39.7± 6.7	49.8± 2.0	16.5± 1.1	33.2± 1.8	960± 318
20 ppm	38	7.73± 1.64	12.5± 3.0	37.9± 7.6	49.4± 3.4	16.1± 1.4	32.7± 2.2	1026± 422
80 ppm	32	7.13± 1.49	11.7± 2.5	35.8± 6.5	50.7± 4.8	16.5± 1.8	32.5± 1.7	1051± 357

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

(HCL070)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %
Control	37	4.8± 4.4
5 ppm	41	4.0± 3.1
20 ppm	38	5.1± 4.9
80 ppm	32	6.2± 4.5

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

(HCL070)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	37	7.70± 4.04	47± 11	45± 12	4± 1	1± 1	0± 0	3± 1
5 ppm	41	6.32± 1.78	48± 8	43± 8	4± 1	1± 1	0± 1	3± 2
20 ppm	38	6.57± 3.43	48± 9	43± 10	4± 1	1± 1	0± 0	3± 2
80 ppm	32	7.93± 7.24	47± 12	45± 12	4± 1	1± 1	0± 0	3± 1

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

(HCL070)

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	41	7.71± 1.45	14.1± 2.4	40.1± 5.9	53.0± 6.7	18.3± 1.6	34.8± 2.2	656± 198
5 ppm	36	8.07± 0.66	14.6± 1.4	41.4± 3.8	51.2± 1.3	18.1± 0.8	35.3± 1.2	665± 140
20 ppm	38	7.78± 1.01	14.1± 1.6	40.1± 4.0	51.9± 3.1	18.2± 0.8	35.1± 1.1	618± 138
80 ppm	38	7.92± 0.63	14.4± 0.9	41.0± 2.3	52.0± 3.9	18.2± 1.0	35.2± 0.9	643± 114

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

(HCL070)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %
Control	41	4.5± 7.9
5 ppm	36	2.3± 0.9
20 ppm	38	3.5± 4.0
80 ppm	38	2.8± 1.8

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	41	4.46±	4.95	41±	11	51±	12	4±	1	2±	3	0±	0	2±	1
5 ppm	36	4.00±	4.59	39±	10	54±	11	4±	1	2±	1	0±	0	2±	1
20 ppm	38	3.75±	2.33	38±	10	55±	10	4±	1	2±	1	0±	0	2±	1
80 ppm	38	4.97±	3.21	35±	11	57±	11	4±	2	2±	1	0±	0	3±	2**

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

(HCL070)

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	37	6.7± 0.5	2.7± 0.3	0.7± 0.1	0.14± 0.10	142± 20	180± 60	130± 86
5 ppm	41	6.9± 0.3	2.8± 0.3	0.7± 0.1	0.12± 0.02	145± 18	189± 55	130± 91
20 ppm	38	6.8± 0.3	2.8± 0.2	0.7± 0.1	0.12± 0.04	149± 17	183± 45	115± 71
80 ppm	32	6.7± 0.4	2.7± 0.2	0.7± 0.1	0.13± 0.09	145± 16	181± 67	134± 109

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

(HCL074)

BAIS 4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST U/L	ALT U/L	LDH U/L	ALP U/L	G-GTP U/L	CK U/L
Control	37	269± 95	95± 101	40± 33	134± 61	344± 123	6± 3	113± 38
5 ppm	41	275± 84	81± 21	36± 9	142± 59	322± 91	7± 4	109± 36
20 ppm	38	268± 58	93± 84	44± 44	117± 42	318± 79	6± 4	110± 41
80 ppm	32	271± 96	102± 112	38± 31	116± 42	345± 156	6± 4	108± 35

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	UREA NITROGEN mg／dℓ	CREATININE mg／dℓ	SODIUM mEq／ℓ	POTASSIUM mEq／ℓ	CHLORIDE mEq／ℓ	CALCIUM mg／dℓ	INORGANIC PHOSPHORUS mg／dℓ
Control	37	21.6± 7.4	0.6± 0.1	143± 1	3.8± 0.4	106± 2	10.7± 0.4	4.4± 0.8
5 ppm	41	21.1± 5.4	0.6± 0.1	143± 1	3.7± 0.3	106± 2	10.7± 0.4	4.1± 0.6
20 ppm	38	20.7± 4.4	0.6± 0.1	143± 2	3.6± 0.3*	106± 1	10.6± 0.4	4.1± 0.6
80 ppm	32	19.5± 5.1	0.6± 0.1	142± 1	3.7± 0.3	106± 2	10.6± 0.4	4.3± 0.6

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

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	41	7.1± 0.5	3.5± 0.4	1.0± 0.1	0.14± 0.14	139± 22	151± 37	89± 53
5 ppm	36	7.1± 0.5	3.4± 0.4	1.0± 0.1	0.11± 0.02	138± 14	162± 58	91± 99
20 ppm	38	7.1± 0.5	3.4± 0.3	0.9± 0.1	0.13± 0.07	140± 17	157± 57	85± 108
80 ppm	38	6.9± 0.6	3.4± 0.3	1.0± 0.1	0.37± 1.47	138± 22	140± 22	87± 64

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	PHOSPHOLIPID mg/dℓ	AST U/L	ALT U/L	LDH U/L	ALP U/L	G-GTP U/L	CK U/L
Control	41	275± 65	125± 69	57± 23	152± 87	235± 136	3± 1	102± 38
5 ppm	36	286± 93	128± 78	57± 30	164± 71	193± 80	2± 1	108± 42
20 ppm	38	276± 101	138± 86	58± 39	146± 45	230± 104	3± 2	100± 29
80 ppm	38	251± 57	174± 164	68± 49	207± 220	265± 208	3± 2	125± 208

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

BIOCHEMISTRY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	UREA NITROGEN mg/dℓ	CREATININE mg/dℓ	SODIUM mEq/ℓ	POTASSIUM mEq/ℓ	CHLORIDE mEq/ℓ	CALCIUM mg/dℓ	INORGANIC PHOSPHORUS mg/dℓ
Control	41	17.9± 2.4	0.5± 0.1	141± 2	3.4± 0.3	103± 3	10.7± 0.4	4.0± 0.8
5 ppm	36	17.5± 2.6	0.6± 0.1	142± 1	3.4± 0.4	104± 2	10.8± 0.4	3.7± 0.7
20 ppm	38	18.7± 6.1	0.6± 0.1	142± 2	3.5± 0.4	104± 2	10.7± 0.5	3.9± 0.8
80 ppm	38	20.3± 12.1	0.5± 0.1	142± 2	3.6± 0.5	105± 2	10.6± 0.3	4.1± 1.5

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

(HCL074)

BAIS 4

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	Bilirubin −	+	2+	3+	CHI
Control	38	0	0	3	6	8	19	2		0	0	1	1	16	20		38	0	0	0	0	0		25	12	1	0	0	0		37	1	0	0	
5 ppm	42	0	0	6	6	16	11	3		0	0	0	1	20	21		42	0	0	0	0	0		35	7	0	0	0	0		42	0	0	0	
20 ppm	38	0	0	7	5	8	18	0		0	0	0	0	18	20		38	0	0	0	0	0		27	11	0	0	0	0		37	1	0	0	
80 ppm	35	0	2	3	10	11	9	0		0	0	0	1	11	23		35	0	0	0	0	0		28	7	0	0	0	0		33	2	0	0	

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

(HCL101)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	38	37	0	0	0	1		38	0	0	0	0	
5 ppm	42	40	2	0	0	0		42	0	0	0	0	
20 ppm	38	34	2	0	2	0		38	0	0	0	0	
80 ppm	35	31	1	1	1	1		35	0	0	0	0	

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

(HCL101)

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	Bilirubin −	+	2+	3+	CHI
Control	41	0	1	1	7	11	8	13		0	4	4	4	25	4		41	0	0	0	0	0		35	3	3	0	0	0		41	0	0	0	
5 ppm	37	0	0	5	7	5	9	11		0	3	4	3	18	9		37	0	0	0	0	0		28	6	2	1	0	0		34	2	1	0	
20 ppm	39	0	0	6	1	13	9	10		0	0	2	11	19	7	*	39	0	0	0	0	0		28	7	4	0	0	0		37	1	1	0	
80 ppm	38	0	2	2	2	11	9	12		0	1	5	8	22	2		38	0	0	0	0	0		26	8	3	1	0	0		36	1	0	1	

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

(HCL101)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	41	38	1	0	0	2		41	0	0	0	0	
5 ppm	37	33	0	1	2	1		37	0	0	0	0	
20 ppm	39	37	0	0	1	1		39	0	0	0	0	
80 ppm	38	36	0	1	0	1		37	0	0	1	0	

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

(HCL101)

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	37	382± 37	0.100± 0.039	3.462± 1.722	1.289± 0.176	1.530± 0.440	2.815± 0.366
5 ppm	41	389± 31	0.101± 0.036	3.519± 1.833	1.298± 0.137	1.447± 0.123	2.801± 0.296
20 ppm	38	389± 41	0.098± 0.018	3.437± 1.404	1.300± 0.151	1.473± 0.199	2.823± 0.450
80 ppm	32	395± 43	0.100± 0.048	3.118± 1.373	1.285± 0.118	1.482± 0.183	2.692± 0.222

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE
UNIT: g

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

Group Name	NO. of Animals	SPLEEN		LIVER		BRAIN	
Control	37	1.356±	1.486	11.473±	1.869	2.091±	0.044
5 ppm	41	1.054±	0.414	11.353±	1.586	2.096±	0.062
20 ppm	38	1.076±	0.496	11.077±	1.413	2.093±	0.062
80 ppm	32	1.210±	0.737	11.359±	1.970	2.079±	0.052

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

(HCL040)

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	41	259± 31	0.096± 0.040	0.139± 0.076	0.917± 0.093	1.036± 0.272	1.788± 0.117
5 ppm	36	265± 29	0.088± 0.009	0.151± 0.115	0.907± 0.090	0.986± 0.079	1.853± 0.138
20 ppm	37	265± 20	0.087± 0.012	0.127± 0.021	0.904± 0.078	1.013± 0.149	1.849± 0.203
80 ppm	38	275± 52	0.088± 0.014	0.247± 0.458	0.900± 0.087	1.026± 0.188	1.802± 0.134

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

(HCL040)

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : FEMALE
UNIT: g

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

Group Name	NO. of Animals	SPLEEN		LIVER		BRAIN	
Control	41	0.840±	1.110	6.727±	0.902	1.895±	0.045
5 ppm	36	0.577±	0.191	6.886±	0.970	1.910±	0.096
20 ppm	37	0.835±	0.970	7.240±	1.545	1.896±	0.040
80 ppm	38	0.939±	1.546*	7.147±	1.245	1.895±	0.042

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

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	37	382± 37	0.027± 0.013	0.898± 0.425	0.341± 0.064	0.408± 0.151	0.748± 0.154
5 ppm	41	389± 31	0.026± 0.012	0.907± 0.480	0.335± 0.043	0.374± 0.040	0.725± 0.109
20 ppm	38	389± 41	0.026± 0.006	0.890± 0.382	0.338± 0.047	0.383± 0.060	0.737± 0.155
80 ppm	32	395± 43	0.025± 0.012	0.804± 0.373	0.328± 0.042	0.378± 0.054	0.686± 0.075

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

(HCL042)

BAIS4

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE
UNIT: %

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

Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN
Control	37	0.371± 0.467	3.041± 0.665	0.553± 0.051
5 ppm	41	0.271± 0.104	2.930± 0.433	0.542± 0.041
20 ppm	38	0.276± 0.126	2.857± 0.267	0.546± 0.071
80 ppm	32	0.305± 0.176	2.875± 0.391	0.531± 0.049

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

(HCL042)

BAIS 4

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
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	41	259± 31	0.038± 0.018	0.054± 0.034	0.360± 0.067	0.407± 0.119	0.699± 0.081
5 ppm	36	265± 29	0.034± 0.006	0.058± 0.049	0.345± 0.042	0.377± 0.052	0.706± 0.087
20 ppm	37	265± 20	0.033± 0.005	0.048± 0.008	0.343± 0.034	0.385± 0.069	0.701± 0.079
80 ppm	38	275± 52	0.033± 0.005	0.096± 0.185	0.334± 0.050	0.384± 0.105	0.668± 0.084

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

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

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

Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN
Control	41	0.332± 0.448	2.625± 0.396	0.744± 0.103
5 ppm	36	0.220± 0.080	2.607± 0.302	0.729± 0.092
20 ppm	37	0.319± 0.373	2.741± 0.571	0.721± 0.061
80 ppm	38	0.371± 0.705	2.639± 0.517	0.706± 0.092

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

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Integumentary system/appandage}																		
skin/app		<50>																
	erosion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	basal cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	epidermal cyst		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)
	sebaceous hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
subcutis		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
{Respiratory system}																		
nasal cavit		<50>																
	thrombus		0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	3 (6)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	eosinophilic change:olfactory epithelium		27 (54)	8 (16)	0 (0)	0 (0)	32 (64)	7 (14)	0 (0)	0 (0)	24 (48)	13 (26)	1 (2)	0 (0)	29 (58)	11 (22)	0 (0)	0 (0)
	eosinophilic change:respiratory epithelium		7 (14)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
	inflammation:foreign body		17 (34)	1 (2)	0 (0)	0 (0)	9 (18)	4 (8)	0 (0)	0 (0)	19 (38)	2 (4)	0 (0)	0 (0)	6 (12)	2 (4)	0 (0)	0 * (0)
	inflammation:respiratory epithelium		9 (18)	0 (0)	0 (0)	0 (0)	12 (24)	0 (0)	0 (0)	0 (0)	9 (18)	1 (2)	0 (0)	0 (0)	18 (36)	6 (12)	0 (0)	0 ** (0)
	respiratory metaplasia:olfactory epithelium		5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:gland		5 (10)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	squamous cell metaplasia:respiratory epithelium		6 (12)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	17 (34)	3 (6)	0 (0)	0 ** (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	ulcer:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	hyperplasia:transitional epithelium		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)
	erosion:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
larynx			<50>				<50>				<50>				<50>			
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
lung			<50>				<50>				<50>				<50>			
	congestion		2 (4)	1 (2)	0 (0)	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)
	edema		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
[Respiratory system]																		
lung		<50>																
	inflammatory infiltration		3 (6)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	bronchiolar-alveolar cell hyperplasia		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
[Hematopoietic system]																		
bone marrow		<50>																
	congestion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	granulation		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	increased hematopoiesis		2 (4)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
lymph node		<50>																
	lymphadenitis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Hematopoietic system}																		
spleen		<50>					<50>				<50>				<50>			
	atrophy	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)	(0)	(0)	(0)	
	congestion	13	0	0	0	10	0	0	0	10	0	0	0	8	0	0	0	
		(26)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	
	fatty change	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)	
	deposit of hemosiderin	11	0	0	0	18	0	0	0	10	1	0	0	9	1	0	0	
		(22)	(0)	(0)	(0)	(36)	(0)	(0)	(0)	(20)	(2)	(0)	(0)	(18)	(2)	(0)	(0)	
	fibrosis	0	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	
		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	
	extramedullary hematopoiesis	9	2	0	0	10	0	0	0	7	4	0	0	10	3	0	0	
		(18)	(4)	(0)	(0)	(20)	(0)	(0)	(0)	(14)	(8)	(0)	(0)	(20)	(6)	(0)	(0)	
{Circulatory system}																		
heart		<50>					<50>				<50>				<50>			
	thrombus	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	
		(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Circulatory system}																		
heart		<50>	0	0	0	0	0	1	0	0	1	0	2	0	0	0	1	0
	mineralization		(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(4)	(0)	(0)	(0)	(2)	(0)
	myocardial fibrosis		26	2	0	0	25	4	1	0	25	3	1	0	26	5	1	0
			(52)	(4)	(0)	(0)	(50)	(8)	(2)	(0)	(50)	(6)	(2)	(0)	(52)	(10)	(2)	(0)
	subendocardial fibrosis		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	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)
artery/aort		<50>	0	0	0	0	0	1	0	0	0	1	1	0	0	0	1	0
	mineralization		(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(2)	(0)
{Digestive system}																		
oral cavity		<50>	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	dysplasia		(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+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Digestive system)																		
oral cavity		<50>																
	squamous cell hyperplasia		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)
tooth		<50>																
	dysplasia		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)
tongue		<50>																
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	arteritis		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
stomach		<50>																
	erosion:forestomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ulcer:forestomach		1 (2)	4 (8)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
[Digestive system]																		
stomach			<50>				<50>				<50>				<50>			
	inflammation:forestomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	erosion:glandular stomach		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ulcer:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	inflammation:glandular stomach		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	squamous cell hyperplasia:forestomach		1 (2)	2 (4)	1 (2)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)
small intes			<50>				<50>				<50>				<50>			
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Digestive system)																		
liver			<50>				<50>				<50>				<50>			
	herniation		4 (8)	0 (0)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	14 (28)	0 (0)	0 (0)	0 * (0)
	necrosis:central		2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	necrosis:focal		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)
	fatty change		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	fatty change:peripheral		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)
	granulation		7 (14)	0 (0)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)
	clear cell focus		2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		4 (8)	4 (8)	0 (0)	0 (0)	8 (16)	3 (6)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Digestive system}																		
liver		<50>					<50>				<50>				<50>			
	basophilic cell focus		4 (8)	1 (2)	0 (0)	0 (0)	3 (6)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	2 (4)	3 (6)	0 (0)	0 (0)
	mixed cell focus		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)
	spongiosis hepatis		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	bile duct hyperplasia		5 (10)	44 (88)	0 (0)	0 (0)	2 (4)	47 (94)	0 (0)	0 (0)	8 (16)	40 (80)	0 (0)	0 (0)	4 (8)	42 (84)	0 (0)	0 (0)
	biliary cyst		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	focal fatty change		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
pancreas		<50>					<50>				<50>				<50>			
	atrophy		28 (56)	5 (10)	0 (0)	0 (0)	26 (52)	0 (0)	1 (2)	0 (0)	28 (56)	4 (8)	0 (0)	0 (0)	24 (48)	4 (8)	2 (4)	0 (0)
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
[Digestive system]																		
pancreas			<50>				<50>				<50>				<50>			
	islet cell hyperplasia		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:acinar cell		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)
[Urinary system]																		
kidney			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	scar		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)
	chronic nephropathy		20	12	13	4	12	13	18	6	15	16	13	4	16	12	17	2
			(40)	(24)	(26)	(8)	(24)	(26)	(36)	(12)	(30)	(32)	(26)	(8)	(32)	(24)	(34)	(4)
	tubular necrosis		1	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0
			(2)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Urinary system}																		
kidney		<50>																
	mineralization:pelvis		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)
	urothelial hyperplasia:pelvis		3 (6)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	atypical tubule hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	dilated pelvis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
urin bladd		<50>																
	dilatation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	simple hyperplasia:transitional epithelium		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)
{Endocrine system}																		
pituitary		<50>																
	angiectasis		2 (4)	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)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Endocrine system}																		
pituitary		<50>					<50>				<50>				<50>			
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia		8 (16)	5 (10)	0 (0)	0 (0)	10 (20)	5 (10)	0 (0)	0 (0)	9 (18)	6 (12)	0 (0)	0 (0)	8 (16)	10 (20)	0 (0)	0 (0)
	Rathke pouch		3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
thyroid		<50>					<50>				<50>				<50>			
	ultimobranchial body remanet		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)
	C-cell hyperplasia		18 (36)	4 (8)	0 (0)	0 (0)	19 (38)	4 (8)	0 (0)	0 (0)	10 (20)	5 (10)	0 (0)	0 (0)	10 (20)	6 (12)	0 (0)	0 (0)
	cystic thyroid follicle		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal		<50>					<50>				<50>				<50>			
	hyperplasia:cortical cell		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Endocrine system}																		
adrenal		<50>																
	hyperplasia:medulla		8 (16)	5 (10)	0 (0)	0 (0)	6 (12)	4 (8)	0 (0)	0 (0)	5 (10)	3 (6)	0 (0)	0 (0)	6 (12)	5 (10)	0 (0)	0 (0)
{Reproductive system}																		
testis		<50>																
	mineralization		5 (10)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
	arteritis		2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	interstitial cell hyperplasia		9 (18)	3 (6)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	15 (30)	1 (2)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)
semin ves		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
prostate		<50>																
	inflammation		3 (6)	3 (6)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	7 (14)	3 (6)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Reproductive system)																		
prostate		<50>																
	hyperplasia		7 (14)	0 (0)	0 (0)	0 (0)	6 (12)	3 (6)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)	7 (14)	2 (4)	0 (0)	0 (0)
	fibrosis		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)
mammary gl		<50>																
	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)	0 (0)	1 (2)	0 (0)	0 (0)
	galactocele		0 (0)	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)
(Nervous system)																		
brain		<50>																
	hemorrhage		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
spinal cord		<50>																
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
[Special sense organs/appendage]																		
eye			<50>				<50>				<50>				<50>			
	cataract		5 (10)	1 (2)	3 (6)	0 (0)	4 (8)	0 (0)	4 (8)	0 (0)	1 (2)	1 (2)	2 (4)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)
	retinal atrophy		2 (4)	4 (8)	3 (6)	0 (0)	1 (2)	2 (4)	3 (6)	0 (0)	1 (2)	2 (4)	2 (4)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)
	keratitis		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	iritis		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)	1 (2)	0 (0)
Harder gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		2 (4)	2 (4)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[Musculoskeletal system]																		
muscle			<50>				<50>				<50>				<50>			
	atrophy		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		0	0	1	0	1	0	0	0	0	1	0	0	0	1	0	0
			(0)	(0)	(2)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)
{Body cavities}																		
mediastinum			<50>				<50>				<50>				<50>			
	arteritis		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)
peritoneum			<50>				<50>				<50>				<50>			
	inflammation		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
retroperit			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

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

TABLE L4

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : FEMALE

ALL ANIMALS

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Integumentary system/appandage}																		
skin/app		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	fibrosis		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)
	scab		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)
	epidermal 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)	0 (0)	1 (2)	0 (0)	0 (0)
{Respiratory system}																		
nasal cavit		<50>																
	thrombus		0 (0)	2 (4)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	eosinophilic change:olfactory epithelium		10 (20)	37 (74)	2 (4)	0 (0)	10 (20)	36 (72)	4 (8)	0 (0)	4 (8)	41 (82)	4 (8)	0 (0)	7 (14)	42 (84)	1 (2)	0 (0)
	eosinophilic change:respiratory epithelium		37 (74)	0 (0)	0 (0)	0 (0)	38 (76)	0 (0)	0 (0)	0 (0)	39 (78)	0 (0)	0 (0)	0 (0)	40 (80)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Respiratory system)																		
nasal cavit		<50>					<50>				<50>				<50>			
	inflammation:foreign body		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	inflammation:respiratory epithelium		6 (12)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)	18 (36)	2 (4)	0 (0)	0 (0) **
	inflammation:olfactory 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)
	respiratory metaplasia:olfactory epithelium		4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:gland		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	squamous cell metaplasia:respiratory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0) *
	ulcer:respiratory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)
	hyperplasia:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	atrophy:olfactory epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	vacuolic change:olfactory epithelium		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)
larynx			<50>				<50>				<50>				<50>			
	inflammation		4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
lung			<50>				<50>				<50>				<50>			
	congestion		1 (2)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	edema		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		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	4 (8)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Respiratory system}																		
lung		<50>	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
	accumulation of foamy cells		(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		1	0	0	0	3	0	0	0	4	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow		<50>	12	1	0	0	10	4	2	0	12	3	1	0	12	4	0	0
	granulation		(24)	(2)	(0)	(0)	(20)	(8)	(4)	(0)	(24)	(6)	(2)	(0)	(24)	(8)	(0)	(0)
	increased hematopoiesis		8	0	0	0	4	0	0	0	4	0	0	0	5	0	0	0
			(16)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
lymph node		<50>	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	lymphadenitis		(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
spleen		<50>	2	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
	congestion		(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Hematopoietic system)																		
spleen		<50>																
	deposit of hemosiderin		17 (34)	23 (46)	0 (0)	0 (0)	15 (30)	22 (44)	0 (0)	0 (0)	18 (36)	23 (46)	0 (0)	0 (0)	14 (28)	25 (50)	0 (0)	0 (0)
	extramedullary hematopoiesis		9 (18)	3 (6)	1 (2)	0 (0)	9 (18)	4 (8)	0 (0)	0 (0)	8 (16)	5 (10)	0 (0)	0 (0)	7 (14)	5 (10)	0 (0)	0 (0)
(Circulatory system)																		
heart		<50>																
	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)
	inflammatory infiltration		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)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory cell nest		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)
	myocardial fibrosis		24 (48)	1 (2)	0 (0)	0 (0)	23 (46)	0 (0)	0 (0)	0 (0)	21 (42)	1 (2)	0 (0)	0 (0)	22 (44)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Circulatory system}																		
heart		<50>																
	subendocardial fibrosis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
oral cavity		<50>																
	inflammation		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)
	squamous cell hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
tongue		<50>																
	inflammatory infiltration		1	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	lymphocytic infiltration		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	epidermal 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)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
[Digestive system]																		
tongue			<50>				<50>				<50>				<50>			
	arteritis		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)
stomach			<50>				<50>				<50>				<50>			
	necrosis:focal		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ulcer:forestomach		1 (2)	2 (4)	0 (0)	0 (0)	3 (6)	2 (4)	2 (4)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	inflammation:forestomach		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)
	inflammation:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	squamous cell hyperplasia:forestomach		2 (4)	1 (2)	1 (2)	0 (0)	2 (4)	6 (12)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	2 (4)	4 (8)	0 (0)	0 (0)
small intes			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	herniation		11	0	0	0	12	0	0	0	11	0	0	0	6	0	0	0
			(22)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	congestion		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	necrosis:central		0	0	0	0	2	0	0	0	0	0	0	0	0	2	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)
	necrosis:focal		3	1	1	0	1	0	0	0	2	0	0	0	0	0	0	0
			(6)	(2)	(2)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	fatty change		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	fatty change:central		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	fatty change:peripheral		0	0	0	0	1	1	0	0	0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	inflammatory infiltration		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)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Digestive system)																		
liver			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		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)
	granulation		19 (38)	3 (6)	0 (0)	0 (0)	12 (24)	5 (10)	0 (0)	0 (0)	21 (42)	6 (12)	1 (2)	0 (0)	16 (32)	5 (10)	1 (2)	0 (0)
	clear cell focus		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		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)
	basophilic cell focus		26 (52)	5 (10)	0 (0)	0 (0)	25 (50)	1 (2)	0 (0)	0 (0)	19 (38)	2 (4)	0 (0)	0 (0)	16 (32)	4 (8)	0 (0)	0 (0)
	mixed cell focus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	bile duct hyperplasia		19 (38)	3 (6)	0 (0)	0 (0)	14 (28)	2 (4)	0 (0)	0 (0)	12 (24)	4 (8)	0 (0)	0 (0)	22 (44)	4 (8)	0 (0)	0 (0)
	cholangiofibrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	biliary cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	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		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		7 (14)	1 (2)	0 (0)	0 (0)	4 (8)	4 (8)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	islet cell hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Urinary system)																		
kidney			<50>				<50>				<50>				<50>			
	scar		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)
	chronic nephropathy		29 (58)	9 (18)	3 (6)	0 (0)	29 (58)	8 (16)	3 (6)	0 (0)	32 (64)	6 (12)	4 (8)	0 (0)	34 (68)	8 (16)	0 (0)	1 (2)
	tubular necrosis		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	mineralization:cortico-medullary junction		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	mineralization:papilla		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atypical tubule hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	dilated pelvis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
{Urinary system}																		
urin bladd		<50>																
	simple hyperplasia:transitional epithelium		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Endocrine system}																		
pituitary		<50>																
	angiectasis		2 (4)	2 (4)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	cyst		6 (12)	2 (4)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	7 (14)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	hyperplasia		8 (16)	10 (20)	0 (0)	0 (0)	6 (12)	12 (24)	0 (0)	0 (0)	8 (16)	6 (12)	0 (0)	0 (0)	7 (14)	9 (18)	0 (0)	0 (0)
	Rathke pouch		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
thyroid		<50>																
	ultimobranchial body remanet		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+	1+	2+	3+	4+
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Endocrine system)																		
thyroid																		
	C-cell hyperplasia		16	2	0	0	15	5	0	0	12	3	0	0	19	1	0	0
			<50>				<50>				<50>				<50>			
			(32)	(4)	(0)	(0)	(30)	(10)	(0)	(0)	(24)	(6)	(0)	(0)	(38)	(2)	(0)	(0)
adrenal																		
	fatty change		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			<50>				<50>				<50>				<50>			
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:medulla		1	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(2)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	focal fatty change:cortex		2	1	0	0	6	0	0	0	2	1	0	0	2	2	0	0
			(4)	(2)	(0)	(0)	(12)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(4)	(0)	(0)
(Reproductive system)																		
ovary																		
	cyst		0	3	0	0	1	2	0	0	1	0	0	0	2	1	0	0
			<50>				<50>				<50>				<50>			
			(0)	(6)	(0)	(0)	(2)	(4)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(2)	(0)	(0)
uterus																		
	hyperplasia:epithelium		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			<50>				<50>				<50>				<50>			
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	2+ (%)	3+ (%)	4+ (%)	5 ppm 50 1+ (%)	2+ (%)	3+ (%)	4+ (%)	20 ppm 50 1+ (%)	2+ (%)	3+ (%)	4+ (%)	80 ppm 50 1+ (%)	2+ (%)	3+ (%)	4+ (%)
{Reproductive system}																		
uterus			<50>				<50>				<50>				<50>			
	cystic endometrial hyperplasia		1 (2)	2 (4)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
spinal cord			<50>				<50>				<50>				<50>			
	hemorrhage		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)
	gliosis		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)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	cataract		1 (2)	1 (2)	5 (10)	0 (0)	2 (4)	1 (2)	2 (4)	0 (0)	1 (2)	3 (6)	3 (6)	0 (0)	0 (0)	1 (2)	4 (8)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1+ (%)	Control 50 2+ (%)	Control 50 3+ (%)	Control 50 4+ (%)	5 ppm 50 1+ (%)	5 ppm 50 2+ (%)	5 ppm 50 3+ (%)	5 ppm 50 4+ (%)	20 ppm 50 1+ (%)	20 ppm 50 2+ (%)	20 ppm 50 3+ (%)	20 ppm 50 4+ (%)	80 ppm 50 1+ (%)	80 ppm 50 2+ (%)	80 ppm 50 3+ (%)	80 ppm 50 4+ (%)
(Special sense organs/appendage)																		
eye		<50>																
	retinal atrophy		3 (6)	3 (6)	3 (6)	0 (0)	0 (0)	1 (2)	3 (6)	0 (0)	1 (2)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)
	keratitis		1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	2 (4)	0 (0)
	iritis		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)	2 (4)	0 (0)
	mineralization:cornea		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)
Harder gl		<50>																
	degeneration		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
nasolacr d		<50>																
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	5 (10)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				5 ppm				20 ppm				80 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)
(Musculoskeletal system)																		
bone			<50>				<50>				<50>				<50>			
	osteosclerosis		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	2 (4)	3 (6)	3 (6)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
(Body cavities)																		
mediastinum			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
peritoneum			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

TABLE O1

NEOPLASTIC LESIONS-INCIDENCE

AND STATISTICAL ANALYSIS : MALE

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : skin/appendage			
	TUMOR : keratoacanthoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	3/50(6.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	5.26	7.14	7.89	2.78
Terminal rates(c)	2/38(5.3)	3/42(7.1)	3/38(7.9)	0/34(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7654			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3849			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.5000
	SITE : subcutis			
	TUMOR : fibroma			
Tumor rate				
Overall rates(a)	4/50(8.0)	2/50(4.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	10.53	4.76	10.53	11.76
Terminal rates(c)	4/38(10.5)	2/42(4.8)	4/38(10.5)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1522			
Prevalence method(d)	P = 0.2567			
Combined analysis(d)	P = 0.1419			
Cochran-Armitage test(e)	P = 0.4178			
Fisher Exact test(e)		P = 0.3389	P = 0.6425	P = 0.5000
	SITE : subcutis			
	TUMOR : fibroma, fibrosarcoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	2/50(4.0)	5/50(10.0)	5/50(10.0)
Adjusted rates(b)	13.16	4.76	10.53	11.76
Terminal rates(c)	5/38(13.2)	2/42(4.8)	4/38(10.5)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1664			
Prevalence method(d)	P = 0.3324			
Combined analysis(d)	P = 0.2168			
Cochran-Armitage test(e)	P = 0.6123			
Fisher Exact test(e)		P = 0.2180	P = 0.6297	P = 0.6297

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	4/50(8.0)	8/50(16.0)	3/50(6.0)
Adjusted rates(b)	12.50	9.52	21.05	8.82
Terminal rates(c)	4/38(10.5)	4/42(9.5)	8/38(21.1)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7100			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4378			
Fisher Exact test(e)		P = 0.5000	P = 0.2768	P = 0.3575
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	4/50(8.0)	8/50(16.0)	3/50(6.0)
Adjusted rates(b)	12.50	9.52	21.05	8.82
Terminal rates(c)	4/38(10.5)	4/42(9.5)	8/38(21.1)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7100			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4378			
Fisher Exact test(e)		P = 0.5000	P = 0.2768	P = 0.3575
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	6/50(12.0)	6/50(12.0)	4/50(8.0)	10/50(20.0)
Adjusted rates(b)	7.89	4.76	7.89	8.82
Terminal rates(c)	3/38(7.9)	2/42(4.8)	3/38(7.9)	3/34(8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0473*			
Prevalence method(d)	P = 0.3194			
Combined analysis(d)	P = 0.0563			
Cochran-Armitage test(e)	P = 0.1337			
Fisher Exact test(e)		P = 0.6202	P = 0.3703	P = 0.2070

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : pancreas TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	5/50(10.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	10.87	10.00	9.09	13.89
Terminal rates(c)	4/38(10.5)	4/42(9.5)	3/38(7.9)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4275			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9623			
Fisher Exact test(e)		P = 0.6297	P = 0.5000	P = 0.6297
	SITE : pancreas TUMOR : islet cell adenoma, islet cell adenocarcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	6/50(12.0)	4/50(8.0)	5/50(10.0)
Adjusted rates(b)	10.87	12.00	9.09	13.89
Terminal rates(c)	4/38(10.5)	4/42(9.5)	3/38(7.9)	4/34(11.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4907			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9117			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.6297
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	11/50(22.0)	17/50(34.0)	17/50(34.0)
Adjusted rates(b)	13.16	24.44	36.59	38.24
Terminal rates(c)	5/38(13.2)	9/42(21.4)	13/38(34.2)	13/34(38.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1992			
Prevalence method(d)	P = 0.0385*			
Combined analysis(d)	P = 0.0258*			
Cochran-Armitage test(e)	P = 0.0676			
Fisher Exact test(e)		P = 0.3055	P = 0.0317*	P = 0.0317*

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	8/50 (16.0)	12/50 (24.0)	17/50 (34.0)	18/50 (36.0)
Adjusted rates(b)	13.16	26.67	36.59	38.24
Terminal rates(c)	5/38 (13.2)	10/42 (23.8)	13/38 (34.2)	13/34 (38.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1992			
Prevalence method(d)	P = 0.0275*			
Combined analysis(d)	P = 0.0187*			
Cochran-Armitage test(e)	P = 0.0491*			
Fisher Exact test(e)		P = 0.2270	P = 0.0317*	P = 0.0195*
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	9/50 (18.0)	7/50 (14.0)	12/50 (24.0)	4/50 (8.0)
Adjusted rates(b)	21.43	16.67	31.58	9.76
Terminal rates(c)	7/38 (18.4)	7/42 (16.7)	12/38 (31.6)	3/34 (8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9034			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1384			
Fisher Exact test(e)		P = 0.3929	P = 0.3121	P = 0.1168
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	9/50 (18.0)	7/50 (14.0)	14/50 (28.0)	5/50 (10.0)
Adjusted rates(b)	21.43	16.67	34.21	10.00
Terminal rates(c)	7/38 (18.4)	7/42 (16.7)	13/38 (34.2)	3/34 (8.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1634			
Prevalence method(d)	P = 0.8988			
Combined analysis(d)	P = 0.8211			
Cochran-Armitage test(e)	P = 0.2345			
Fisher Exact test(e)		P = 0.3929	P = 0.1710	P = 0.1940

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	10/50(20.0)	4/50(8.0)	8/50(16.0)
Adjusted rates(b)	13.16	21.28	8.51	19.05
Terminal rates(c)	5/38(13.2)	6/42(14.3)	2/38(5.3)	6/34(17.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3032			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6911			
Fisher Exact test(e)		P = 0.1312	P = 0.5000	P = 0.2768
	SITE : adrenal gland			
	TUMOR : pheochromocytoma, pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	5/50(10.0)	12/50(24.0)	4/50(8.0)	9/50(18.0)
Adjusted rates(b)	13.16	24.49	8.51	21.62
Terminal rates(c)	5/38(13.2)	7/42(16.7)	2/38(5.3)	7/34(20.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2713			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.6526			
Fisher Exact test(e)		P = 0.0542	P = 0.5000	P = 0.1940

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : testis			
	TUMOR : interstitial cell tumor			
Tumor rate				
Overall rates(a)	37/50(74.0)	44/50(88.0)	34/50(68.0)	33/50(66.0)
Adjusted rates(b)	89.47	89.36	84.21	75.00
Terminal rates(c)	34/38(89.5)	37/42(88.1)	32/38(84.2)	25/34(73.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9245			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0812			
Fisher Exact test(e)		P = 0.0624	P = 0.3299	P = 0.2565

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BAIS5

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

TABLE O2

NEOPLASTIC LESIONS-INCIDENCE

AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	6/50(12.0)	6/50(12.0)	9/50(18.0)	5/50(10.0)
Adjusted rates(b)	12.20	2.70	15.79	13.16
Terminal rates(c)	5/41(12.2)	1/37(2.7)	6/38(15.8)	5/38(13.2)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9585			
Prevalence method(d)	P = 0.2435			
Combined analysis(d)	P = 0.6593			
Cochran-Armitage test(e)	P = 0.6327			
Fisher Exact test(e)		P = 0.6202	P = 0.2883	P = 0.5000
	SITE : pancreas			
	TUMOR : islet cell adenoma, islet cell adenocarcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	2.44	2.70	0.0	7.89
Terminal rates(c)	1/41(2.4)	1/37(2.7)	0/38(0.0)	3/38(7.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0646			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1062			
Fisher Exact test(e)		P = 0.7525	P = 0.5000	P = 0.3087
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	17/50(34.0)	15/50(30.0)	16/50(32.0)	15/50(30.0)
Adjusted rates(b)	39.53	27.03	31.58	26.67
Terminal rates(c)	16/41(39.0)	10/37(27.0)	12/38(31.6)	8/38(21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2539			
Prevalence method(d)	P = 0.7762			
Combined analysis(d)	P = 0.6459			
Cochran-Armitage test(e)	P = 0.7792			
Fisher Exact test(e)		P = 0.4152	P = 0.5000	P = 0.4152

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	19/50 (38.0)	17/50 (34.0)	17/50 (34.0)	17/50 (34.0)
Adjusted rates(b)	41.86	27.27	34.21	26.67
Terminal rates(c)	17/41 (41.5)	10/37 (27.0)	13/38 (34.2)	8/38 (21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2067			
Prevalence method(d)	P = 0.8010			
Combined analysis(d)	P = 0.6068			
Cochran-Armitage test(e)	P = 0.8072			
Fisher Exact test(e)		P = 0.4176	P = 0.4176	P = 0.4176
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	6/50 (12.0)	10/50 (20.0)	3/50 (6.0)	7/50 (14.0)
Adjusted rates(b)	13.64	27.03	6.52	15.79
Terminal rates(c)	5/41 (12.2)	10/37 (27.0)	1/38 (2.6)	6/38 (15.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5811			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9343			
Fisher Exact test(e)		P = 0.2070	P = 0.2435	P = 0.5000
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	6/50 (12.0)	11/50 (22.0)	3/50 (6.0)	7/50 (14.0)
Adjusted rates(b)	13.64	29.73	6.52	15.79
Terminal rates(c)	5/41 (12.2)	11/37 (29.7)	1/38 (2.6)	6/38 (15.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.6320			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8267			
Fisher Exact test(e)		P = 0.1434	P = 0.2435	P = 0.5000

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	4/50 (8.0)	1/50 (2.0)	0/50 (0.0)	2/50 (4.0)
Adjusted rates(b)	8.89	2.70	0.0	5.00
Terminal rates(c)	3/41 (7.3)	1/37 (2.7)	0/38 (0.0)	1/38 (2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5883			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8210			
Fisher Exact test(e)		P = 0.1811	P = 0.0587	P = 0.3389
	SITE : adrenal gland			
	TUMOR : pheochromocytoma, pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	4/50 (8.0)	1/50 (2.0)	1/50 (2.0)	2/50 (4.0)
Adjusted rates(b)	8.89	2.70	0.0	5.00
Terminal rates(c)	3/41 (7.3)	1/37 (2.7)	0/38 (0.0)	1/38 (2.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3382			
Prevalence method(d)	P = 0.5894			
Combined analysis(d)	P = 0.6092			
Cochran-Armitage test(e)	P = 0.7773			
Fisher Exact test(e)		P = 0.1811	P = 0.1811	P = 0.3389
	SITE : uterus			
	TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	8/50 (16.0)	4/50 (8.0)	7/50 (14.0)	9/50 (18.0)
Adjusted rates(b)	19.51	8.00	18.42	21.05
Terminal rates(c)	8/41 (19.5)	1/37 (2.7)	7/38 (18.4)	8/38 (21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1557			
Prevalence method(d)	P = 0.2609			
Combined analysis(d)	P = 0.1694			
Cochran-Armitage test(e)	P = 0.3542			
Fisher Exact test(e)		P = 0.1783	P = 0.5000	P = 0.5000

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : mammary gland TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	3/50(6.0)	5/50(10.0)	10/50(20.0)
Adjusted rates(b)	9.76	8.11	11.11	21.05
Terminal rates(c)	4/41(9.8)	3/37(8.1)	3/38(7.9)	8/38(21.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2723			
Prevalence method(d)	P = 0.0309*			
Combined analysis(d)	P = 0.0257*			
Cochran-Armitage test(e)	P = 0.0305*			
Fisher Exact test(e)		P = 0.3575	P = 0.6297	P = 0.1312
	SITE : mammary gland TUMOR : adenoma, fibroadenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	3/50(6.0)	6/50(12.0)	11/50(22.0)
Adjusted rates(b)	9.76	8.11	13.33	23.68
Terminal rates(c)	4/41(9.8)	3/37(8.1)	4/38(10.5)	9/38(23.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2723			
Prevalence method(d)	P = 0.0173*			
Combined analysis(d)	P = 0.0146*			
Cochran-Armitage test(e)	P = 0.0162*			
Fisher Exact test(e)		P = 0.3575	P = 0.5000	P = 0.0857

Group Name	Control	5 ppm	20 ppm	80 ppm
	SITE : mammary gland			
	TUMOR : adenoma, fibroadenoma, adenocarcinoma			
Tumor rate				
Overall rates (a)	6/50 (12.0)	3/50 (6.0)	6/50 (12.0)	12/50 (24.0)
Adjusted rates (b)	12.20	8.11	13.33	26.32
Terminal rates (c)	5/41 (12.2)	3/37 (8.1)	4/38 (10.5)	10/38 (26.3)
Statistical analysis				
Peto test				
Standard method (d)	P = 0.2723			
Prevalence method (d)	P = 0.0132*			
Combined analysis (d)	P = 0.0111*			
Cochran-Armitage test (e)	P = 0.0122*			
Fisher Exact test (e)		P = 0.2435	P = 0.6202	P = 0.0961

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BAIS5

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

TABLE Q1

HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj MALE RATS

TABLE Q1 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj MALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Pituitary gland	2741			
Adenoma		851	31.0	10 - 66
Adenoma / Adenocarcinoma		883	32.3	10 - 66
Spleen	2748			
Mononuclear cell leukemia		316	11.5	2 - 22

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

Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0246, 0267, 0269, 0278, 0284, 0288, 0294, 0296, 0318, 0328, 0342, 0347, 0365, 0371, 0396, 0399, 0401, 0407, 0417, 0421, 0437, 0448, 0457, 0461, 0497, 0535, 0560, 0579, 0581, 0610, 0612, 0641, 0667, 0675, 0686, 0691, 0704

TABLE Q2

HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj FEMALE RATS

TABLE Q2 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj FEMALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Mammary gland	2547			
Fibroadenoma		284	11.2	0 - 20
Adenoma / Adenocarcinoma / Fibroadenoma		365	14.3	0 - 26

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

Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0246, 0267, 0269, 0278, 0284, 0296, 0303, 0318, 0328, 0342, 0347, 0365, 0371, 0399, 0401, 0417, 0421, 0437, 0448, 0457, 0461, 0497, 0535, 0560, 0579, 0610, 0612, 0641, 0667, 0675, 0686, 0691, 0704

TABLE R1

CAUSE OF DEATH : MALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : MALE

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

Group Name	Control	5 ppm	20 ppm	80 ppm
Number of Dead and Moribund Animal	12	8	12	16
no microscop confirm	2	1	1	1
cystitis	1	0	0	0
chronic nephropathy	1	1	2	1
peritonitis	1	0	0	0
tumor d:leukemia	3	4	1	7
tumor d:subcutis	0	0	1	1
tumor d:spleen	0	2	0	0
tumor d:oral cavity	1	0	0	0
tumor d:pituitary	3	0	2	3
tumor d:thyroid	0	0	1	1
tumor d:brain	0	0	1	1
tumor d:Zymbal gl	0	0	2	0
tumor d:bone	0	0	0	1
tumor d:peritoneum	0	0	1	0

TABLE R2

CAUSE OF DEATH : FEMALE

STUDY NO. : 0731
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : FEMALE

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

Group Name	Control	5 ppm	20 ppm	80 ppm
Number of Dead and Moribund Animal	9	13	12	12
no microscop confirm	2	0	1	1
peritonitis	1	0	0	0
tumor d:leukemia	1	5	3	0
tumor d:oral cavity	1	0	0	0
tumor d:liver	1	0	0	0
tumor d:kidney	0	1	1	0
tumor d:pituitary	1	5	4	6
tumor d:adrenal	0	0	1	0
tumor d:uterus	1	1	1	3
tumor d:mammary gl	1	0	0	1
tumor d:prep/cli gl	0	0	0	1
tumor d:brain	0	1	1	0

FIGURES

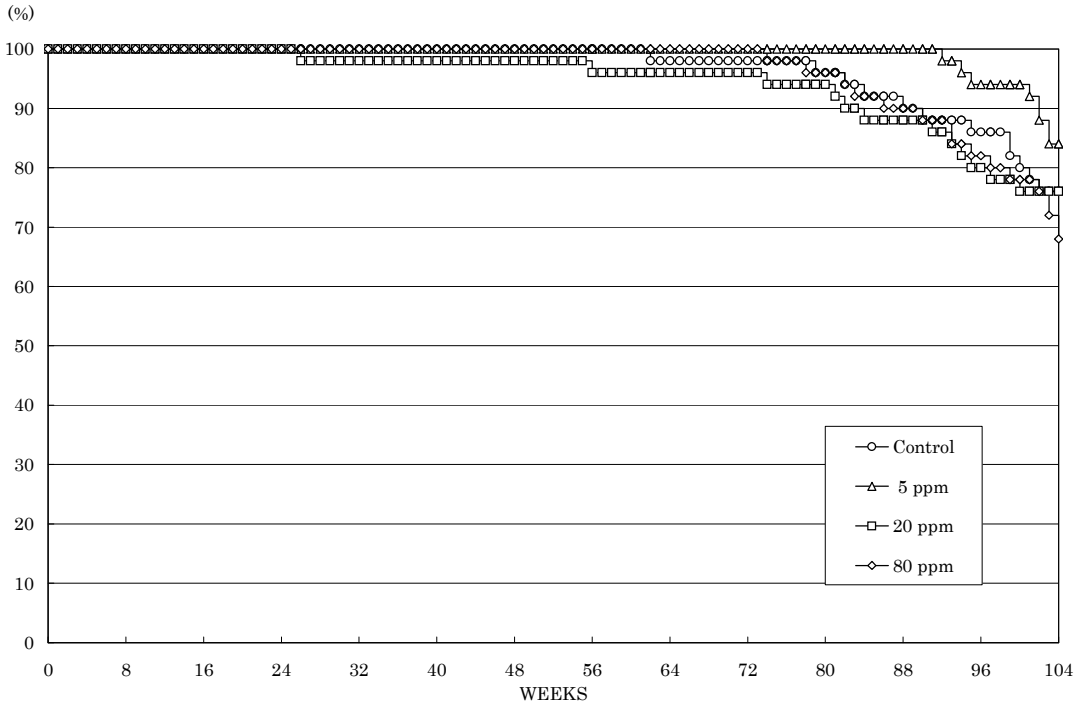


FIGURE 1　SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

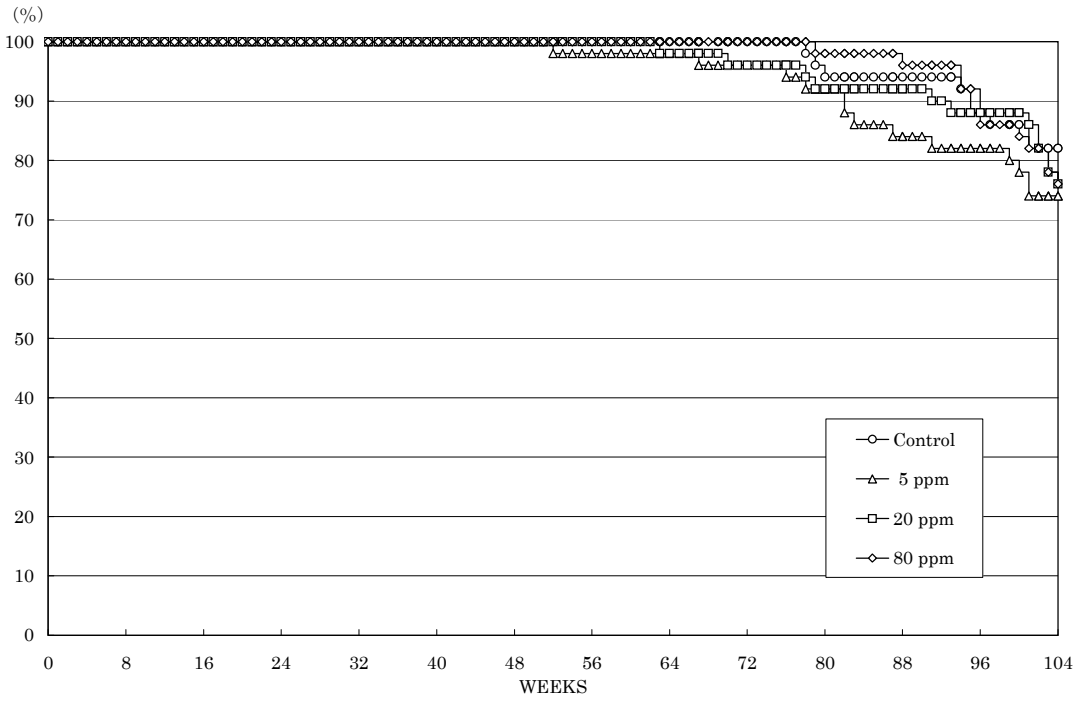


FIGURE 2　SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

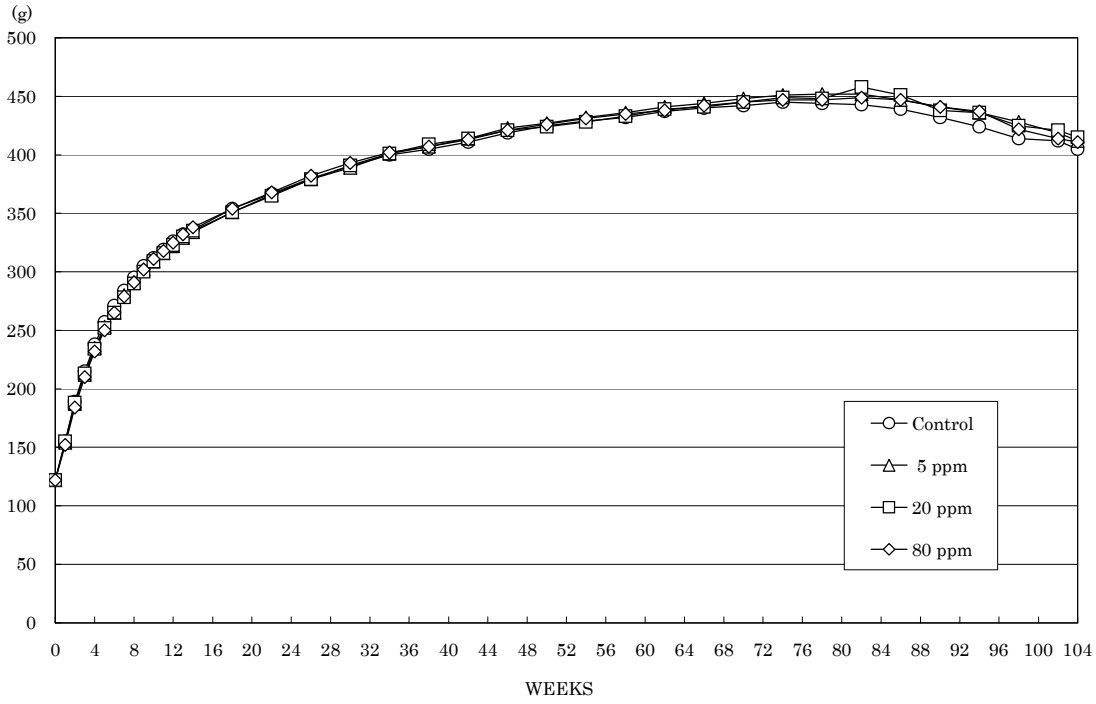


FIGURE 3　BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

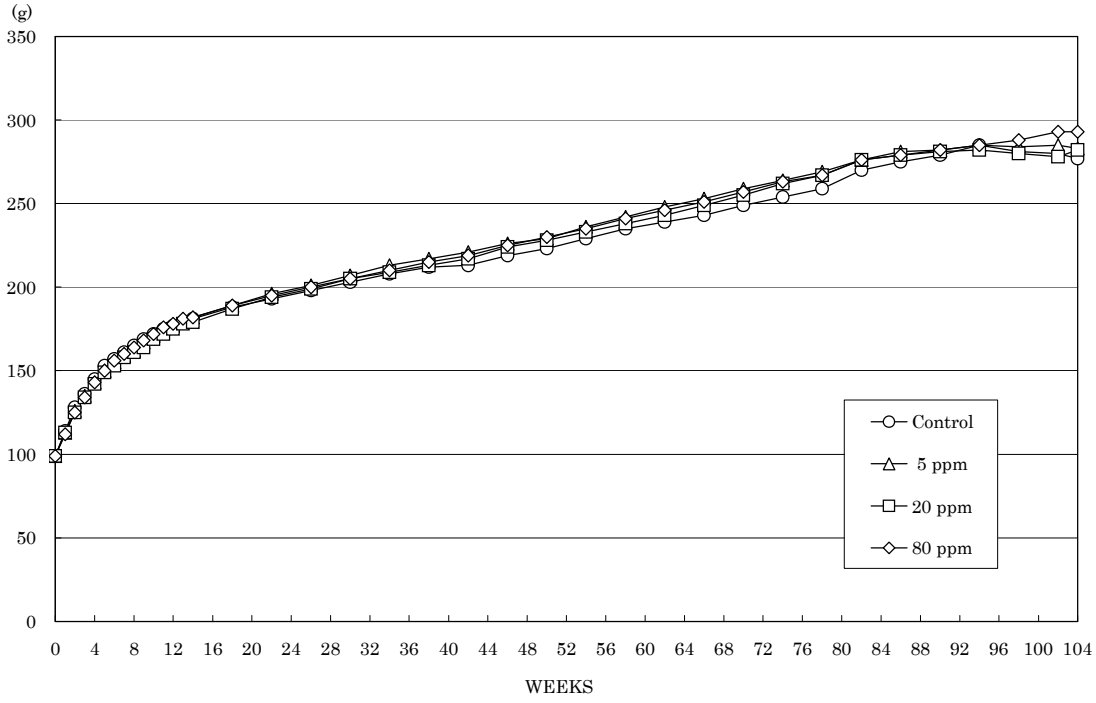


FIGURE 4　BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

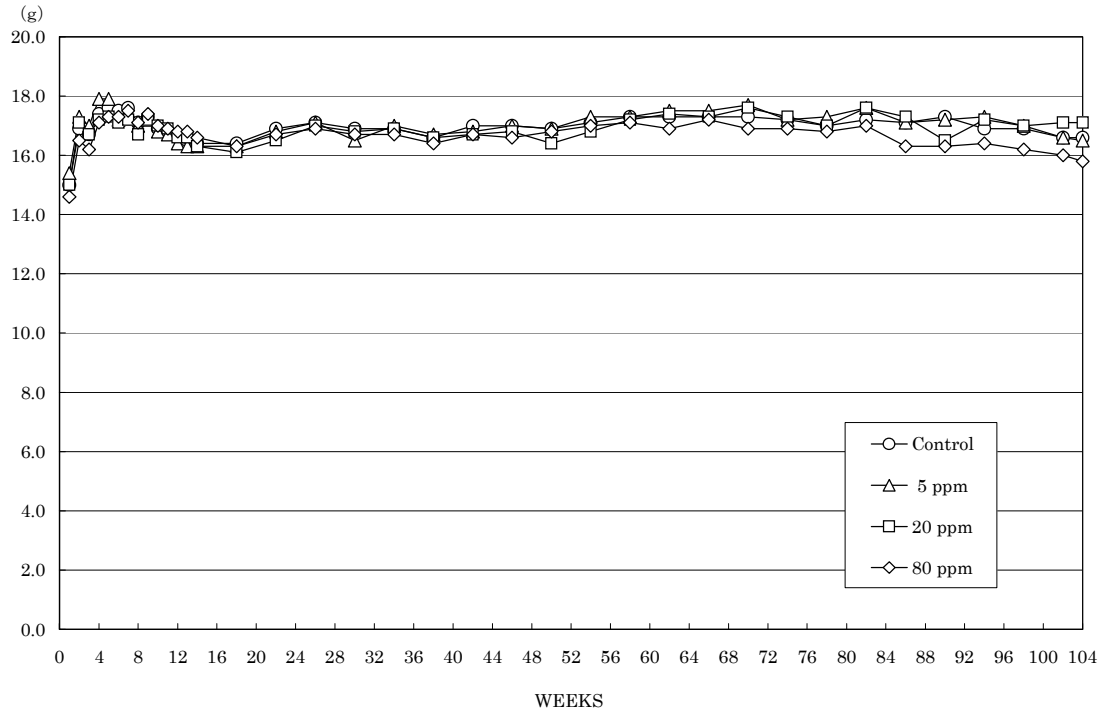


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE

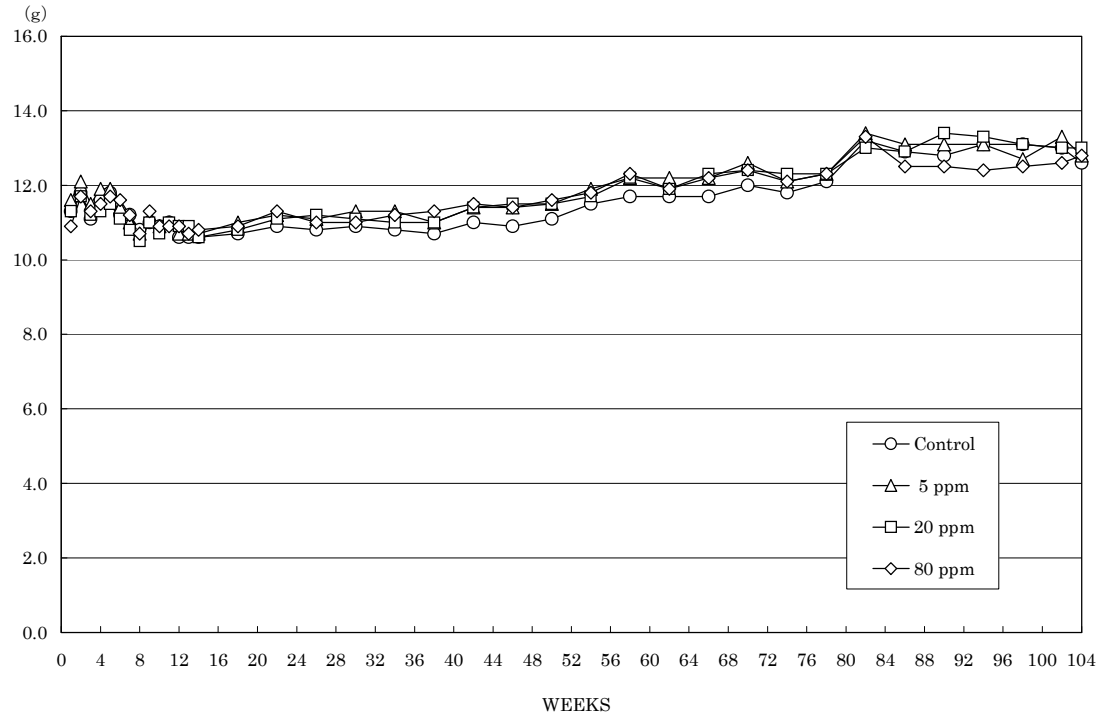
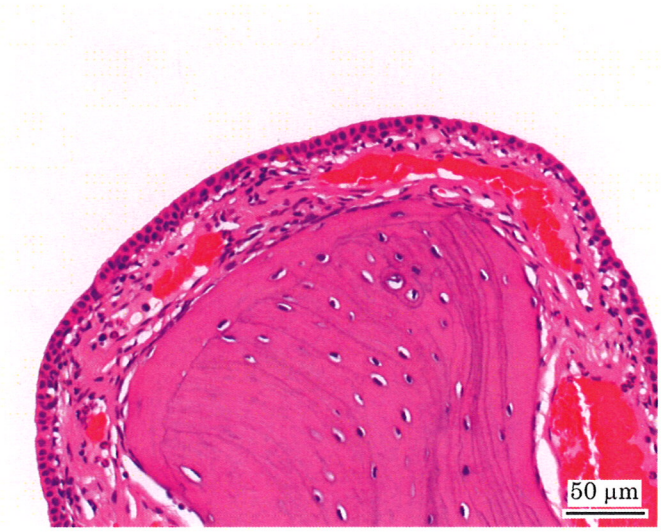
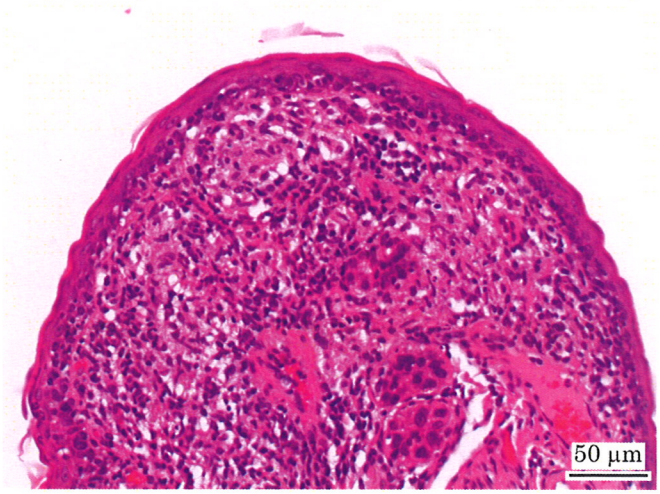


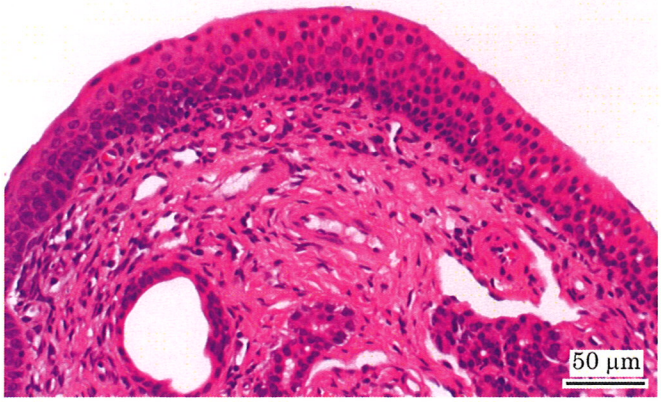
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYLAMINE



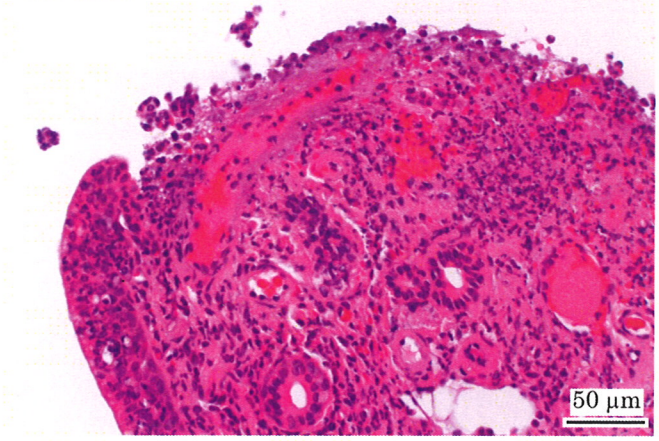
Photograph 1
Nasal cavity (Level 1): Normal, respiratory (transitional) epithelium
Rat, Male, Control, Animal No. 0731-1002 (H&E)



Photograph 2
Nasal cavity (Level 1): Squamous cell metaplasia and inflammation of respiratory (transitional) epithelium
Rat, Male, 80 ppm, Animal No. 0731-1316 (H&E)



Photograph 3
Nasal cavity (Level 1): Hyperplasia of transitional epithelium
Rat, Male, 80 ppm, Animal No. 0731-1316 (H&E)



Photograph 4
Nasal cavity (Level 1): Ulcer of respiratory (transitional) epithelium
Rat, Female, 80 ppm, Animal No. 0731-2343 (H&E)