Summary of Inhalation Carcinogenicity Study of Acrylic Acid 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 30, 2011.

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

Summary of Inhalation Carcinogenicity Study of Acrylic Acid in F344 Rats

Purpose, materials and methods

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

The carcinogenicity and chronic toxicity of acrylic acid (purity : greater than 99.7%) were examined by inhalation exposure using F344/DuCrlCrlj (Fischer) rats. Groups of test animals were exposed to acrylic acid vapors at target concentrations of 0 (clean air), 10, 40 or 160 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 acrylic acid vapor. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the acrylic acid used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by gas chromatography before and after use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 7.6 m^3) were used throughout the 2-year exposure period. Acrylic acid vapor-air mixtures were generated by bubbling clean air through acrylic acid liquid and the mixtures delivered to the inhalation exposure chambers. Air concentrations of the acrylic acid in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the exposure period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of acrylic acid induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies

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

Results

No significant differences in survival rates and clinical signs were found between any of the groups exposed to acrylic acid and their respective controls. Body weights of males and females exposed to 160 ppm acrylic acid were suppressed compared with their respective controls. The terminal body weights of the 160 ppm-exposed males and females were 87% and 90% of their respective controls. Food consumption was decreased in males and females exposed to 160 ppm acrylic acid throughout the exposure period compared with their respective controls. Food consumption was decreased in males and females exposed to 40 ppm acrylic acid in earlier exposure period and sporadically decreased in males exposed to 10 ppm acrylic acid.

No significant increase in the incidence of neoplastic lesions was found in any acrylic acid exposed group of either sex as compared with the respective control. As non-neoplastic lesions, atrophy, respiratory metaplasia, squamous cell metaplasia, disarrangement of the olfactory epithelium, and squamous metaplasia of the respiratory epithelium, respiratory metaplasia of the gland in the nasal cavity were significantly increased in both sexes at doses of 40 ppm acrylic acid and above. These lesions were not severe in most animals, and no effects of acrylic acid were observed in exposed to 10 ppm.

Using nasal lesions as endpoint markers, the no-observed-adverse-effect-level (NOAEL) of acrylic acid was 10 ppm in both male and female rats when exposed by inhalation.

Conclusions

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

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

Dose (ppm)		0	10	40	160	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
subcutis	fibroma	5	6	5	6		
lung	bronchiolar-alveolar adenoma	3	1	1	4		
liver	hepatocellular adenoma	6	1	1	2		
pancreas	islet cell adenoma	5	3	3	7		
pituitary	adenoma	11	9	9	7		
thyroid	C-cell adenoma	8	15	11	7		
adrenal	pheochromocytoma	8	5	5	7		
testis	interstitial cell tumor	37	43	45 *	42		
	adenoma	3	1	1	1		
malignant tumor							
spleen	mononuclear cell leukemia	4	5	5	1		
thyroid	C-cell carcinoma	5	1	2	3		
peritoneum	mesothelioma	1	3	5	2		

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

Dose (ppm)		0	10	40	160	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	3	1	0	1		
pituitary	adenoma	14	16	12	15		
thyroid	C-cell adenoma	6	7	5	3		
uterus	endometrial stromal polyp	6	3	5	8		
mammary gland	fibroadenoma	5	8	7	7		
malignant tumor							
spleen	mononuclear cell leukemia	3	2	4	2		

Significant difference

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

SELECTED TABLES

TABLE A

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

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

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
10 ppm	10.2 ± 0.1
40 ppm	40.3 ± 0.2
160 ppm	160.1 ± 0.7

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0704
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>	10 ppm Av. Wt.	10 ppm % of cont. <50>	10 ppm No. of Surviv.	40 ppm Av. Wt.	40 ppm % of cont. <50>	40 ppm No. of Surviv.	160 ppm Av. Wt.	160 ppm % of cont. <50>	160 ppm No. of Surviv.
1-7	157 (50)	50/50	155 (50)	99	50/50	157 (50)	100	50/50	149 (50)	95	50/50
2-7	189 (50)	50/50	188 (50)	99	50/50	190 (50)	101	50/50	180 (50)	95	50/50
3-7	214 (50)	50/50	214 (50)	100	50/50	214 (50)	100	50/50	205 (50)	96	50/50
4-7	234 (50)	50/50	233 (50)	100	50/50	235 (50)	100	50/50	225 (50)	96	50/50
5-7	252 (50)	50/50	251 (50)	100	50/50	253 (50)	100	50/50	241 (50)	96	50/50
6-7	268 (50)	50/50	267 (50)	100	50/50	267 (50)	100	50/50	253 (50)	94	50/50
7-7	283 (50)	50/50	279 (50)	99	50/50	281 (50)	99	50/50	265 (50)	94	50/50
8-7	296 (50)	50/50	292 (50)	99	50/50	292 (50)	99	50/50	275 (50)	93	50/50
9-7	306 (50)	50/50	301 (50)	98	50/50	302 (50)	99	50/50	284 (50)	93	50/50
10-7	315 (50)	50/50	310 (50)	98	50/50	310 (50)	98	50/50	291 (50)	92	50/50
11-7	323 (50)	50/50	317 (50)	98	50/50	317 (50)	98	50/50	295 (50)	91	50/50
12-7	330 (50)	50/50	325 (50)	98	50/50	323 (50)	98	50/50	299 (50)	91	50/50
13-7	336 (50)	50/50	331 (50)	99	50/50	329 (50)	98	50/50	303 (50)	90	50/50
14-7	342 (50)	50/50	336 (50)	98	50/50	335 (50)	98	50/50	308 (50)	90	50/50
18-7	359 (50)	50/50	354 (50)	99	50/50	353 (50)	98	50/50	323 (50)	90	50/50
22-7	374 (49)	49/50	369 (50)	99	50/50	368 (50)	98	50/50	334 (50)	89	50/50
26-7	387 (49)	49/50	381 (50)	98	50/50	381 (50)	98	50/50	342 (50)	88	50/50
30-7	398 (49)	49/50	391 (50)	98	50/50	390 (50)	98	50/50	350 (50)	88	50/50
34-7	409 (49)	49/50	403 (50)	99	50/50	399 (50)	98	50/50	361 (50)	88	50/50
38-7	417 (49)	49/50	412 (50)	99	50/50	409 (50)	98	50/50	370 (50)	89	50/50
42-7	425 (49)	49/50	419 (50)	99	50/50	416 (50)	98	50/50	376 (50)	88	50/50
46-7	432 (49)	49/50	427 (50)	99	50/50	423 (50)	98	50/50	379 (50)	88	50/50
50-7	437 (49)	49/50	432 (50)	99	50/50	429 (50)	98	50/50	387 (50)	89	50/50
54-7	444 (48)	48/50	439 (50)	99	50/50	434 (50)	98	50/50	389 (50)	88	50/50
58-7	447 (48)	48/50	445 (50)	100	50/50	438 (49)	98	49/50	395 (50)	88	50/50
62-7	450 (48)	48/50	447 (49)	99	49/50	442 (49)	98	49/50	399 (50)	89	50/50
66-7	454 (48)	48/50	449 (49)	99	49/50	443 (49)	98	48/50	398 (50)	88	50/50
70-7	455 (48)	48/50	453 (48)	100	48/50	446 (48)	98	48/50	403 (49)	89	49/50
74-7	456 (46)	46/50	452 (48)	99	48/50	446 (48)	98	48/50	405 (49)	89	49/50
78-7	457 (46)	46/50	455 (46)	100	46/50	447 (47)	98	47/50	403 (49)	88	49/50
82-7	456 (46)	46/50	456 (44)	100	44/50	446 (46)	98	46/50	403 (49)	88	49/50
86-7	455 (46)	46/50	455 (43)	100	43/50	444 (46)	98	46/50	402 (49)	88	49/50
90-7	449 (45)	44/50	450 (42)	100	42/50	445 (45)	99	45/50	400 (49)	89	49/50
94-7	450 (42)	42/50	441 (40)	98	39/50	442 (45)	98	45/50	401 (48)	89	48/50
98-7	442 (41)	41/50	437 (39)	99	39/50	432 (43)	98	43/50	384 (45)	87	45/50
102-7	434 (40)	40/50	429 (36)	99	36/50	424 (42)	98	42/50	381 (42)	88	42/50
104-7	431 (38)	38/50	424 (36)	98	36/50	422 (41)	98	41/50	375 (42)	87	42/50

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

TABLE D2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0704
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>	10 ppm Av. Wt.	10 ppm % of cont. <50>	10 ppm No. of Surviv.	40 ppm Av. Wt.	40 ppm % of cont. <50>	40 ppm No. of Surviv.	160 ppm Av. Wt.	160 ppm % of cont. <50>	160 ppm No. of Surviv.
1-7	111 (50)	50/50	111 (50)	100	50/50	112 (50)	101	50/50	108 (50)	97	50/50
2-7	126 (50)	50/50	127 (50)	101	50/50	127 (50)	101	50/50	123 (50)	98	50/50
3-7	136 (50)	50/50	138 (50)	101	50/50	137 (50)	101	50/50	133 (50)	98	50/50
4-7	145 (50)	50/50	145 (50)	100	50/50	144 (50)	99	50/50	140 (50)	97	50/50
5-7	152 (50)	50/50	152 (50)	100	50/50	152 (50)	100	50/50	147 (50)	97	50/50
6-7	160 (50)	50/50	159 (50)	99	50/50	158 (50)	99	50/50	153 (50)	96	50/50
7-7	165 (50)	50/50	164 (50)	99	50/50	162 (50)	98	50/50	157 (50)	95	50/50
8-7	169 (50)	50/50	168 (50)	99	50/50	167 (50)	99	50/50	161 (50)	95	50/50
9-7	173 (50)	50/50	172 (50)	99	50/50	171 (50)	99	50/50	165 (50)	95	50/50
10-7	177 (50)	50/50	176 (50)	99	50/50	175 (50)	99	50/50	169 (50)	95	50/50
11-7	181 (50)	50/50	179 (50)	99	50/50	178 (50)	98	50/50	170 (50)	94	50/50
12-7	183 (50)	50/50	183 (50)	100	50/50	180 (50)	98	50/50	173 (50)	95	50/50
13-7	184 (50)	50/50	185 (50)	101	50/50	184 (50)	100	50/50	174 (50)	95	50/50
14-7	187 (50)	50/50	187 (50)	100	50/50	186 (50)	99	50/50	177 (50)	95	50/50
18-7	195 (50)	50/50	196 (50)	101	50/50	193 (50)	99	50/50	183 (50)	94	50/50
22-7	200 (50)	50/50	202 (50)	101	50/50	198 (50)	99	50/50	189 (50)	95	50/50
26-7	204 (50)	50/50	208 (50)	102	50/50	204 (50)	100	50/50	194 (50)	95	50/50
30-7	210 (50)	50/50	212 (50)	101	50/50	208 (50)	99	50/50	199 (50)	95	50/50
34-7	215 (50)	50/50	220 (50)	102	50/50	213 (50)	99	50/50	204 (50)	95	50/50
38-7	219 (50)	50/50	225 (50)	103	50/50	218 (50)	100	50/50	210 (50)	96	50/50
42-7	224 (50)	50/50	228 (50)	102	50/50	224 (50)	100	50/50	214 (50)	96	50/50
46-7	230 (50)	50/50	235 (50)	102	50/50	228 (50)	99	50/50	216 (50)	94	50/50
50-7	237 (50)	50/50	242 (50)	102	50/50	234 (50)	99	50/50	223 (50)	94	50/50
54-7	242 (49)	49/50	245 (50)	101	50/50	239 (50)	99	50/50	225 (50)	93	50/50
58-7	246 (49)	49/50	250 (50)	102	50/50	244 (50)	99	50/50	229 (49)	93	49/50
62-7	251 (49)	49/50	257 (50)	102	50/50	250 (50)	100	50/50	234 (49)	93	49/50
66-7	258 (49)	49/50	265 (50)	103	50/50	255 (50)	99	50/50	236 (49)	91	49/50
70-7	263 (49)	49/50	270 (49)	103	49/50	260 (50)	99	50/50	241 (48)	92	48/50
74-7	268 (49)	49/50	274 (49)	102	49/50	265 (50)	99	50/50	246 (48)	92	48/50
78-7	273 (48)	48/50	278 (49)	102	48/50	267 (49)	98	48/50	247 (48)	90	48/50
82-7	276 (46)	46/50	285 (47)	103	47/50	274 (48)	99	48/50	250 (48)	91	48/50
86-7	280 (44)	44/50	289 (47)	103	47/50	275 (47)	98	46/50	252 (48)	90	47/50
90-7	285 (43)	43/50	293 (46)	103	46/50	284 (44)	100	44/50	255 (47)	89	47/50
94-7	292 (41)	41/50	294 (45)	101	45/50	285 (43)	98	43/50	258 (47)	88	47/50
98-7	290 (41)	41/50	296 (43)	102	43/50	283 (42)	98	41/50	259 (45)	89	45/50
102-7	287 (38)	38/50	301 (40)	105	40/50	289 (40)	101	40/50	262 (43)	91	43/50
104-7	290 (37)	37/50	301 (40)	104	40/50	289 (39)	100	38/50	260 (43)	90	43/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0704
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 1-7	2-7	3-7	4-7	5-7	6-7	7-7
Control	157± 8	189± 9	214± 11	234± 11	252± 11	268± 13	283± 14
10 ppm	155± 8	188± 9	214± 10	233± 11	251± 11	267± 13	279± 14
40 ppm	157± 7	190± 9	214± 10	235± 10	253± 11	267± 11	281± 13
160 ppm	149± 7**	180± 8**	205± 9**	225± 9**	241± 10**	253± 11**	265± 12**

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

(HAN260)

BAIS 4

STUDY NO. : 0704
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 8-7	9-7	10-7	11-7	12-7	13-7	14-7
Control	296± 14	306± 15	315± 16	323± 17	330± 17	336± 18	342± 19
10 ppm	292± 14	301± 15	310± 15	317± 16	325± 17	331± 18	336± 18
40 ppm	292± 13	302± 13	310± 14	317± 14	323± 14*	329± 15	335± 15
160 ppm	275± 12**	284± 13**	291± 13**	295± 14**	299± 15**	303± 15**	308± 15**

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

STUDY NO. : 0704
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 18-7	22-7	26-7	30-7	34-7	38-7	42-7
Control	359± 18	374± 20	387± 22	398± 23	409± 24	417± 24	425± 26
10 ppm	354± 19	369± 20	381± 22	391± 25	403± 26	412± 25	419± 27
40 ppm	353± 16	368± 17	381± 19	390± 20	399± 22	409± 22	416± 22
160 ppm	323± 16**	334± 17**	342± 17**	350± 18**	361± 19**	370± 20**	376± 20**

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

STUDY NO. : 0704
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 46-7	50-7	54-7	58-7	62-7	66-7	70-7
Control	432± 26	437± 28	444± 29	447± 28	450± 27	454± 29	455± 29
10 ppm	427± 28	432± 29	439± 30	445± 37	447± 28	449± 29	453± 30
40 ppm	423± 23	429± 25	434± 27	438± 26	442± 25	443± 35	446± 24
160 ppm	379± 20**	387± 21**	389± 21**	395± 20**	399± 21**	398± 21**	403± 21**

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

(HAN260)

BAIS 4

STUDY NO. : 0704
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 74-7	78-7	82-7	86-7	90-7	94-7	98-7
Control	456± 30	457± 31	456± 32	455± 35	449± 39	450± 35	442± 40
10 ppm	452± 29	455± 27	456± 26	455± 29	450± 34	441± 47	437± 37
40 ppm	446± 26	447± 26	446± 27	444± 30	445± 25	442± 24	432± 29
160 ppm	405± 22**	403± 23**	403± 23**	402± 25**	400± 31**	401± 42**	384± 29**

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

STUDY NO. : 0704
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 102-7	104-7
Control	434± 50	431± 43
10 ppm	429± 48	424± 65
40 ppm	424± 30	422± 28
160 ppm	381± 29**	375± 34**

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

(HAN260)

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0704
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 1-7	2-7	3-7	4-7	5-7	6-7	7-7
Control	111± 4	126± 5	136± 6	145± 7	152± 8	160± 9	165± 10
10 ppm	111± 4	127± 5	138± 6	145± 6	152± 7	159± 8	164± 9
40 ppm	112± 4	127± 5	137± 5	144± 6	152± 7	158± 7	162± 8
160 ppm	108± 4**	123± 5**	133± 5**	140± 6**	147± 6**	153± 8**	157± 8**

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

STUDY NO. : 0704
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 8-7	9-7	10-7	11-7	12-7	13-7	14-7
Control	169± 10	173± 11	177± 12	181± 12	183± 12	184± 12	187± 12
10 ppm	168± 9	172± 10	176± 9	179± 10	183± 9	185± 9	187± 10
40 ppm	167± 8	171± 9	175± 10	178± 10	180± 10	184± 10	186± 10
160 ppm	161± 10**	165± 10**	169± 10**	170± 10**	173± 10**	174± 10**	177± 10**

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

(HAN260)

STUDY NO. : 0704
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 18-7	22-7	26-7	30-7	34-7	38-7	42-7
Control	195± 13	200± 14	204± 14	210± 15	215± 15	219± 16	224± 17
10 ppm	196± 11	202± 11	208± 12	212± 13	220± 15	225± 15	228± 16
40 ppm	193± 10	198± 11	204± 11	208± 12	213± 13	218± 13	224± 14
160 ppm	183± 11**	189± 11**	194± 12**	199± 12**	204± 13**	210± 13**	214± 14**

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

STUDY NO. : 0704
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 46-7	50-7	54-7	58-7	62-7	66-7	70-7
Control	230± 19	237± 20	242± 20	246± 21	251± 22	258± 24	263± 24
10 ppm	235± 17	242± 17	245± 19	250± 20	257± 21	265± 22	270± 23
40 ppm	228± 14	234± 16	239± 18	244± 19	250± 21	255± 21	260± 24
160 ppm	216± 14**	223± 15**	225± 15**	229± 16**	234± 16**	236± 17**	241± 19**

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

(HAN260)

BAIS 4

STUDY NO. : 0704
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 74-7	78-7	82-7	86-7	90-7	94-7	98-7
Control	268± 25	273± 26	276± 27	280± 27	285± 29	292± 23	290± 24
10 ppm	274± 23	278± 25	285± 23	289± 23	293± 25	294± 30	296± 33
40 ppm	265± 23	267± 30	274± 22	275± 26	284± 22	285± 25	283± 26
160 ppm	246± 18**	247± 17**	250± 17**	252± 17**	255± 17**	258± 22**	259± 16**

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

(HAN260)

BAIS 4

STUDY NO. : 0704
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 102-7	104-7
Control	287± 33	290± 26
10 ppm	301± 29	301± 30
40 ppm	289± 33	289± 37
160 ppm	262± 16**	260± 16**

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

(HAN260)

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0704
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>	10 ppm Av. FC.	10 ppm % of cont. <50>	10 ppm No. of Surviv.	40 ppm Av. FC.	40 ppm % of cont. <50>	40 ppm No. of Surviv.	160 ppm Av. FC.	160 ppm % of cont. <50>	160 ppm No. of Surviv.
1-7	14.4 (50)	50/50	14.0 (50)	97	50/50	14.0 (50)	97	50/50	13.2 (50)	92	50/50
2-7	16.5 (50)	50/50	16.5 (50)	100	50/50	16.2 (50)	98	50/50	15.1 (50)	92	50/50
3-7	17.6 (50)	50/50	17.4 (50)	99	50/50	16.9 (50)	96	50/50	16.2 (50)	92	50/50
4-7	17.6 (50)	50/50	17.2 (50)	98	50/50	16.8 (50)	95	50/50	16.5 (50)	94	50/50
5-7	17.2 (50)	50/50	17.0 (50)	99	50/50	16.5 (50)	96	50/50	15.6 (50)	91	50/50
6-7	17.4 (50)	50/50	17.1 (50)	98	50/50	16.4 (50)	94	50/50	15.5 (50)	89	50/50
7-7	17.2 (50)	50/50	16.7 (50)	97	50/50	16.3 (50)	95	50/50	15.5 (50)	90	50/50
8-7	17.4 (50)	50/50	16.9 (50)	97	50/50	16.4 (50)	94	50/50	15.5 (50)	89	50/50
9-7	17.4 (50)	50/50	16.8 (50)	97	50/50	16.4 (50)	94	50/50	15.9 (50)	91	50/50
10-7	17.2 (50)	50/50	16.5 (50)	96	50/50	16.0 (50)	93	50/50	15.2 (50)	88	50/50
11-7	17.0 (50)	50/50	16.4 (50)	96	50/50	15.8 (50)	93	50/50	15.1 (50)	89	50/50
12-7	16.9 (50)	50/50	16.4 (50)	97	50/50	15.8 (50)	93	50/50	14.9 (50)	88	50/50
13-7	16.7 (50)	50/50	16.3 (50)	98	50/50	15.6 (50)	93	50/50	14.7 (50)	88	50/50
14-7	16.6 (50)	50/50	16.3 (50)	98	50/50	15.5 (50)	93	50/50	14.6 (50)	88	50/50
18-7	16.5 (50)	50/50	16.2 (50)	98	50/50	15.7 (50)	95	50/50	14.9 (50)	90	50/50
22-7	16.5 (49)	49/50	16.2 (50)	98	50/50	15.9 (50)	96	50/50	14.7 (50)	89	50/50
26-7	16.8 (49)	49/50	16.4 (50)	98	50/50	16.0 (50)	95	50/50	14.8 (50)	88	50/50
30-7	16.8 (49)	49/50	16.2 (50)	96	50/50	15.9 (50)	95	50/50	15.5 (50)	92	50/50
34-7	16.9 (49)	49/50	16.5 (50)	98	50/50	16.0 (50)	95	50/50	15.7 (50)	93	50/50
38-7	16.7 (49)	49/50	16.5 (50)	99	50/50	16.1 (50)	96	50/50	15.7 (50)	94	50/50
42-7	17.0 (49)	49/50	16.8 (50)	99	50/50	16.4 (50)	96	50/50	15.9 (50)	94	50/50
46-7	16.9 (49)	49/50	16.6 (50)	98	50/50	16.3 (50)	96	50/50	15.4 (50)	91	50/50
50-7	16.7 (49)	49/50	16.7 (50)	100	50/50	16.4 (50)	98	50/50	15.9 (50)	95	50/50
54-7	16.8 (48)	48/50	16.8 (50)	100	50/50	16.5 (50)	98	50/50	15.9 (50)	95	50/50
58-7	16.8 (48)	48/50	16.5 (50)	98	50/50	16.1 (49)	96	49/50	15.5 (50)	92	50/50
62-7	16.7 (48)	48/50	16.6 (49)	99	49/50	16.6 (49)	99	49/50	16.3 (50)	98	50/50
66-7	17.4 (48)	48/50	17.0 (49)	98	49/50	16.5 (49)	95	48/50	16.1 (50)	93	50/50
70-7	17.0 (48)	48/50	17.1 (48)	101	48/50	16.7 (48)	98	48/50	16.2 (49)	95	49/50
74-7	17.0 (47)	46/50	16.9 (48)	99	48/50	16.3 (48)	96	48/50	16.2 (49)	95	49/50
78-7	16.9 (46)	46/50	16.3 (47)	96	46/50	15.9 (48)	94	47/50	15.7 (49)	93	49/50
82-7	17.0 (46)	46/50	17.0 (44)	100	44/50	16.7 (46)	98	46/50	16.1 (49)	95	49/50
86-7	16.9 (46)	46/50	16.3 (44)	96	43/50	16.6 (46)	98	46/50	16.1 (49)	95	49/50
90-7	16.2 (45)	44/50	15.8 (43)	98	42/50	16.3 (45)	101	45/50	15.8 (49)	98	49/50
94-7	16.7 (42)	42/50	15.3 (40)	92	39/50	16.2 (45)	97	45/50	16.4 (48)	98	48/50
98-7	16.5 (41)	41/50	15.6 (39)	95	39/50	15.4 (44)	93	43/50	14.8 (46)	90	45/50
102-7	16.6 (38)	40/50	15.6 (36)	94	36/50	16.0 (42)	96	42/50	15.2 (43)	92	42/50
104-7	15.4 (40)	38/50	15.3 (36)	99	36/50	15.8 (41)	103	41/50	14.7 (42)	95	42/50

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

TABLE E2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

STUDY NO. : 0704
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>	10 ppm Av. FC.	10 ppm % of cont. <50>	10 ppm No. of Surviv.	40 ppm Av. FC.	40 ppm % of cont. <50>	40 ppm No. of Surviv.	160 ppm Av. FC.	160 ppm % of cont. <50>	160 ppm No. of Surviv.
1-7	10.7 (50)	50/50	10.4 (50)	97	50/50	10.6 (50)	99	50/50	9.6 (50)	90	50/50
2-7	11.5 (50)	50/50	11.7 (50)	102	50/50	11.3 (50)	98	50/50	10.7 (50)	93	50/50
3-7	11.5 (50)	50/50	11.6 (50)	101	50/50	11.3 (50)	98	50/50	10.8 (50)	94	50/50
4-7	11.8 (50)	50/50	11.5 (50)	97	50/50	11.1 (50)	94	50/50	11.1 (50)	94	50/50
5-7	11.4 (50)	50/50	11.3 (50)	99	50/50	10.8 (50)	95	50/50	10.3 (50)	90	50/50
6-7	11.5 (50)	50/50	11.4 (50)	99	50/50	11.0 (50)	96	50/50	10.7 (50)	93	50/50
7-7	11.4 (50)	50/50	10.9 (50)	96	50/50	10.6 (50)	93	50/50	10.3 (50)	90	50/50
8-7	11.4 (50)	50/50	11.0 (50)	96	50/50	10.5 (50)	92	50/50	10.3 (50)	90	50/50
9-7	11.4 (50)	50/50	11.1 (50)	97	50/50	10.5 (50)	92	50/50	10.6 (50)	93	50/50
10-7	11.4 (50)	50/50	11.2 (50)	98	50/50	10.7 (50)	94	50/50	10.4 (50)	91	50/50
11-7	11.2 (50)	50/50	11.0 (50)	98	50/50	10.5 (50)	94	50/50	10.1 (50)	90	50/50
12-7	11.0 (50)	50/50	10.8 (50)	98	50/50	10.5 (50)	95	50/50	10.3 (50)	94	50/50
13-7	10.5 (50)	50/50	10.8 (50)	103	50/50	10.3 (50)	98	50/50	9.7 (50)	92	50/50
14-7	10.9 (50)	50/50	11.1 (50)	102	50/50	10.4 (50)	95	50/50	10.1 (50)	93	50/50
18-7	11.2 (50)	50/50	11.2 (50)	100	50/50	10.4 (50)	93	50/50	10.3 (50)	92	50/50
22-7	11.0 (50)	50/50	10.8 (50)	98	50/50	10.3 (50)	94	50/50	10.3 (50)	94	50/50
26-7	10.9 (50)	50/50	11.0 (50)	101	50/50	10.5 (50)	96	50/50	10.4 (50)	95	50/50
30-7	11.2 (50)	50/50	10.6 (50)	95	50/50	10.4 (50)	93	50/50	10.8 (50)	96	50/50
34-7	11.0 (50)	50/50	11.3 (50)	103	50/50	10.4 (50)	95	50/50	10.7 (50)	97	50/50
38-7	11.2 (50)	50/50	11.2 (50)	100	50/50	10.6 (50)	95	50/50	10.9 (50)	97	50/50
42-7	11.1 (50)	50/50	10.9 (50)	98	50/50	11.0 (50)	99	50/50	10.8 (50)	97	50/50
46-7	10.9 (50)	50/50	10.9 (50)	100	50/50	10.7 (50)	98	50/50	10.5 (50)	96	50/50
50-7	11.5 (50)	50/50	11.6 (50)	101	50/50	11.1 (50)	97	50/50	11.3 (50)	98	50/50
54-7	11.3 (50)	49/50	11.2 (50)	99	50/50	11.2 (50)	99	50/50	11.2 (50)	99	50/50
58-7	11.4 (49)	49/50	11.1 (50)	97	50/50	11.0 (50)	96	50/50	10.7 (49)	94	49/50
62-7	11.6 (49)	49/50	11.8 (50)	102	50/50	11.5 (50)	99	50/50	11.6 (49)	100	49/50
66-7	11.9 (49)	49/50	12.1 (50)	102	50/50	11.5 (50)	97	50/50	11.5 (49)	97	49/50
70-7	12.0 (49)	49/50	12.1 (49)	101	49/50	11.8 (50)	98	50/50	11.4 (48)	95	48/50
74-7	11.6 (49)	49/50	11.9 (49)	103	49/50	11.7 (50)	101	50/50	11.7 (48)	101	48/50
78-7	11.6 (48)	48/50	11.8 (49)	102	48/50	11.5 (49)	99	48/50	11.2 (48)	97	48/50
82-7	11.9 (47)	46/50	12.6 (47)	106	47/50	12.0 (48)	101	48/50	11.7 (48)	98	48/50
86-7	11.6 (45)	44/50	12.5 (47)	108	47/50	11.8 (47)	102	46/50	11.6 (48)	100	47/50
90-7	12.3 (43)	43/50	12.7 (46)	103	46/50	12.2 (45)	99	44/50	11.6 (47)	94	47/50
94-7	12.5 (41)	41/50	11.6 (46)	93	45/50	12.0 (43)	96	43/50	12.3 (47)	98	47/50
98-7	11.6 (41)	41/50	12.2 (43)	105	43/50	11.6 (42)	100	41/50	11.5 (46)	99	45/50
102-7	12.0 (38)	38/50	13.1 (40)	109	40/50	12.4 (40)	103	40/50	11.9 (43)	99	43/50
104-7	11.8 (38)	37/50	12.5 (40)	106	40/50	11.4 (40)	97	38/50	11.3 (43)	96	43/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0704
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	14.4± 1.0	16.5± 1.1	17.6± 1.3	17.6± 1.2	17.2± 0.9	17.4± 1.1	17.2± 1.2
10 ppm	14.0± 1.1	16.5± 1.2	17.4± 1.3	17.2± 1.4	17.0± 1.4	17.1± 1.4	16.7± 1.3
40 ppm	14.0± 0.7	16.2± 1.0	16.9± 1.0**	16.8± 1.0**	16.5± 0.9**	16.4± 0.9**	16.3± 0.9**
160 ppm	13.2± 0.8**	15.1± 0.8**	16.2± 0.9**	16.5± 0.9**	15.6± 0.8**	15.5± 0.8**	15.5± 0.9**

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

STUDY NO. : 0704
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	17.4± 1.2	17.4± 1.2	17.2± 1.3	17.0± 1.3	16.9± 1.2	16.7± 1.3	16.6± 1.1
10 ppm	16.9± 1.1*	16.8± 1.3*	16.5± 1.2*	16.4± 1.1*	16.4± 1.3*	16.3± 1.2	16.3± 1.2
40 ppm	16.4± 0.7**	16.4± 0.8**	16.0± 0.9**	15.8± 0.9**	15.8± 0.8**	15.6± 0.8**	15.5± 0.8**
160 ppm	15.5± 0.8**	15.9± 0.9**	15.2± 0.8**	15.1± 0.9**	14.9± 0.9**	14.7± 0.8**	14.6± 0.8**

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

STUDY NO. : 0704
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	16.5± 1.7	16.5± 1.0	16.8± 1.1	16.8± 1.0	16.9± 1.1	16.7± 1.1	17.0± 1.0
10 ppm	16.2± 1.1	16.2± 1.2	16.4± 1.1	16.2± 1.1**	16.5± 1.1	16.5± 0.9	16.8± 1.2
40 ppm	15.7± 0.7**	15.9± 0.9*	16.0± 1.0**	15.9± 0.9**	16.0± 1.1**	16.1± 0.9**	16.4± 0.9**
160 ppm	14.9± 0.8**	14.7± 0.8**	14.8± 0.9**	15.5± 0.9**	15.7± 0.9**	15.7± 0.9**	15.9± 0.8**

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

(HAN260)

STUDY NO. : 0704
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	16.9± 1.2	16.7± 1.8	16.8± 1.1	16.8± 0.9	16.7± 1.0	17.4± 1.0	17.0± 1.0
10 ppm	16.6± 1.2	16.7± 1.4	16.8± 1.1	16.5± 1.4	16.6± 1.1	17.0± 1.2	17.1± 1.4
40 ppm	16.3± 1.0**	16.4± 1.1	16.5± 1.0	16.1± 0.9**	16.6± 1.1	16.5± 2.7**	16.7± 0.9
160 ppm	15.4± 0.7**	15.9± 0.8**	15.9± 0.8**	15.5± 0.7**	16.3± 0.8	16.1± 0.8**	16.2± 0.9**

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

(HAN260)

STUDY NO. : 0704
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	17.0± 1.2	16.9± 1.1	17.0± 1.2	16.9± 1.3	16.2± 3.1	16.7± 1.5	16.5± 1.5
10 ppm	16.9± 1.4	16.3± 2.8	17.0± 1.2	16.3± 3.1	15.8± 3.0	15.3± 4.0	15.6± 2.6
40 ppm	16.3± 1.3*	15.9± 3.0	16.7± 1.0	16.6± 1.1	16.3± 1.4	16.2± 1.7	15.4± 3.2
160 ppm	16.2± 0.8**	15.7± 0.8**	16.1± 1.7**	16.1± 2.2**	15.8± 1.1**	16.4± 2.1	14.8± 2.5**

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

(HAN260)

STUDY NO. : 0704
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) 102-7(7)	104-7(7)
Control	16.6± 2.0	15.4± 5.3
10 ppm	15.6± 2.5	15.3± 2.8
40 ppm	16.0± 1.6	15.8± 1.7
160 ppm	15.2± 2.7**	14.7± 1.3**

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

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0704
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	10.7± 0.7	11.5± 0.8	11.5± 0.8	11.8± 1.1	11.4± 1.2	11.5± 1.0	11.4± 1.2
10 ppm	10.4± 0.7*	11.7± 0.7	11.6± 1.0	11.5± 0.9	11.3± 1.0	11.4± 0.9	10.9± 0.9
40 ppm	10.6± 0.6	11.3± 0.7	11.3± 0.7	11.1± 0.8**	10.8± 0.7*	11.0± 0.8**	10.6± 0.9**
160 ppm	9.6± 0.6**	10.7± 0.8**	10.8± 0.6**	11.1± 0.8**	10.3± 0.8**	10.7± 1.1**	10.3± 1.4**

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

STUDY NO. : 0704
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	11.4± 1.3	11.4± 1.5	11.4± 1.4	11.2± 1.1	11.0± 1.3	10.5± 1.1	10.9± 0.9
10 ppm	11.0± 1.3	11.1± 1.3	11.2± 1.2	11.0± 1.3	10.8± 0.8	10.8± 0.9	11.1± 1.3
40 ppm	10.5± 0.9**	10.5± 0.8**	10.7± 0.9**	10.5± 0.9**	10.5± 0.9	10.3± 0.8	10.4± 0.9*
160 ppm	10.3± 1.1**	10.6± 1.1**	10.4± 1.2**	10.1± 0.9**	10.3± 0.8**	9.7± 0.8**	10.1± 0.8**

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

(HAN260)

STUDY NO. : 0704
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	11.2± 1.1	11.0± 1.2	10.9± 1.1	11.2± 1.1	11.0± 0.9	11.2± 1.1	11.1± 0.9
10 ppm	11.2± 1.3	10.8± 1.0	11.0± 1.2	10.6± 0.8*	11.3± 1.1	11.2± 1.1	10.9± 0.9
40 ppm	10.4± 0.8**	10.3± 0.8*	10.5± 0.8	10.4± 0.7**	10.4± 0.8**	10.6± 0.7**	11.0± 0.9
160 ppm	10.3± 1.0**	10.3± 1.0*	10.4± 1.1	10.8± 1.0	10.7± 1.0	10.9± 1.0	10.8± 1.0

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

STUDY NO. : 0704
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± 0.9	11.5± 1.1	11.3± 1.6	11.4± 1.1	11.6± 0.9	11.9± 1.1	12.0± 0.9
10 ppm	10.9± 0.9	11.6± 0.9	11.2± 0.9	11.1± 0.9	11.8± 1.0	12.1± 1.1	12.1± 1.1
40 ppm	10.7± 0.6	11.1± 0.9*	11.2± 0.9	11.0± 0.9	11.5± 1.0	11.5± 0.9	11.8± 1.1
160 ppm	10.5± 0.8*	11.3± 1.2	11.2± 1.0	10.7± 0.8**	11.6± 1.1	11.5± 0.8	11.4± 0.9**

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

STUDY NO. : 0704
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	11.6± 1.3	11.6± 1.6	11.9± 2.7	11.6± 2.2	12.3± 1.9	12.5± 1.1	11.6± 1.7
10 ppm	11.9± 1.4	11.8± 1.9	12.6± 1.0	12.5± 1.1	12.7± 1.2	11.6± 2.2	12.2± 1.6
40 ppm	11.7± 1.0	11.5± 1.2	12.0± 1.0	11.8± 2.1	12.2± 1.2	12.0± 1.0	11.6± 2.5
160 ppm	11.7± 0.9	11.2± 0.9*	11.7± 0.7**	11.6± 1.2	11.6± 1.0**	12.3± 1.2	11.5± 1.4

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

STUDY NO. : 0704
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	12.0± 2.4	11.8± 2.6
10 ppm	13.1± 1.2*	12.5± 1.3
40 ppm	12.4± 1.4	11.4± 2.5
160 ppm	11.9± 1.0*	11.3± 0.8**

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

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0704
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 f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	38	8.19± 1.76	13.7± 3.0	40.7± 7.7	51.3± 9.7	17.0± 2.5	33.3± 1.8	899± 299
10 ppm	35	7.79± 2.17	12.5± 3.9	38.2± 9.6	50.8± 10.6	16.3± 3.1	32.1± 3.3	1009± 461
40 ppm	41	8.69± 1.12	14.4± 1.7	42.7± 4.6	49.3± 2.3	16.6± 1.1	33.6± 1.2	905± 199
160 ppm	42	8.63± 1.46	13.5± 2.8	40.8± 7.0	47.4± 2.5**	15.6± 1.3**	32.9± 1.5	924± 294

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

STUDY NO. : 0704
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	38	3.9± 2.7
10 ppm	35	7.4± 10.0
40 ppm	41	3.5± 2.1
160 ppm	42	4.1± 2.5

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

STUDY NO. : 0704
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	38	16.99±	51.73	46±	13	41±	13	5±	2	1±	1	0±	0	7±	21
10 ppm	35	10.71±	21.91	48±	14	41±	13	5±	2	1±	1	0±	0	5±	16
40 ppm	41	6.75±	3.93	45±	10	47±	10	5±	1	1±	1	0±	0	2±	1
160 ppm	42	6.80±	4.83	49±	10	44±	10	5±	1	1±	1	0±	0	2±	1

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

(HCL070)

BAIS 4

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0704
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 f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	37	8.17± 0.89	14.6± 1.7	42.1± 3.8	51.7± 2.2	17.9± 0.7	34.7± 1.3	700± 137
10 ppm	40	8.19± 0.91	14.7± 1.6	42.1± 4.2	51.5± 1.3	18.0± 0.3	35.0± 0.6	685± 103
40 ppm	38	8.12± 1.29	14.6± 2.1	41.8± 5.1	52.2± 5.3	18.1± 1.0	34.7± 1.4	631± 95
160 ppm	43	8.39± 0.52	15.1± 0.9	43.0± 2.4	51.2± 0.6	17.9± 0.2	35.0± 0.3	676± 81

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

(HCL070)

BAIS 4

Group Name	NO. of Animals	RETICULOCYTE %
Control	37	3.2± 3.0
10 ppm	40	2.7± 2.1
40 ppm	38	3.2± 4.1
160 ppm	43	2.4± 0.6

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

STUDY NO. : 0704
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	37	15.84±	55.94	41±	14	50±	15	4±	1	2±	1	0±	0	4±	16
10 ppm	40	3.24±	1.80	40±	9	53±	9	4±	1	2±	1	0±	0	1±	1
40 ppm	38	3.99±	4.65	40±	6	54±	7	4±	1	2±	1	0±	0	1±	0
160 ppm	43	5.88±	17.39	39±	11	51±	12	4±	1	2±	1**	0±	0	3±	14

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

(HCL070)

BAIS 4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0704
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	38	6.9± 0.4	2.8± 0.3	0.7± 0.1	0.25± 0.60	156± 18	202± 54	156± 89
10 ppm	35	6.5± 0.7*	2.8± 0.3	0.8± 0.1	0.33± 0.99	147± 32	181± 65	149± 105
40 ppm	41	6.9± 0.3	3.0± 0.2	0.8± 0.1	0.15± 0.06	155± 20	194± 55	141± 90
160 ppm	42	6.8± 0.3	2.9± 0.2	0.8± 0.1*	0.14± 0.04	146± 28	137± 37**	60± 28**

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

(HCL074)

BAIS 4

STUDY NO. : 0704
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 IU/ℓ	ALT IU/ℓ	LDH IU/ℓ	ALP IU/ℓ	G-GTP IU/ℓ	CK IU/ℓ
Control	38	289± 81	144± 245	49± 51	196± 354	352± 159	8± 5	111± 54
10 ppm	35	268± 86	121± 150	43± 28	159± 120	386± 228	7± 3	171± 367
40 ppm	41	274± 72	87± 44	39± 15	130± 56	344± 102	8± 5	106± 36
160 ppm	42	204± 41**	91± 26	38± 13	133± 93	349± 87	7± 3	118± 96

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

(HCL074)

BAIS 4

STUDY NO. : 0704
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	38	19.1± 4.1	0.6± 0.1	142± 2	3.6± 0.3	106± 2	10.6± 0.4	4.0± 0.5
10 ppm	35	19.1± 4.7	0.6± 0.1	142± 2	3.7± 0.3	106± 2	10.8± 1.4	4.1± 0.8
40 ppm	41	18.2± 2.3	0.6± 0.1	142± 1	3.6± 0.3	106± 2	10.6± 0.4	3.8± 0.6
160 ppm	42	19.2± 9.0	0.5± 0.0**	143± 1	3.7± 0.5	107± 2	10.4± 0.4	4.3± 1.6

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

(HCL074)

BAIS 4

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0704
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	37	7.2± 0.5	3.6± 0.3	1.0± 0.2	0.11± 0.02	144± 15	135± 44	88± 64
10 ppm	40	7.1± 0.4	3.7± 0.2	1.1± 0.1	0.11± 0.01	146± 13	145± 34	120± 73*
40 ppm	38	7.1± 0.6	3.6± 0.4	1.1± 0.1	0.54± 2.54	143± 18	141± 24	81± 53
160 ppm	43	7.1± 0.4	3.7± 0.2	1.1± 0.1*	0.12± 0.04	146± 12	133± 20	65± 34

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

(HCL074)

STUDY NO. : 0704
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 IU/l	ALT IU/l	LDH IU/l	ALP IU/l	G-GTP IU/l	CK IU/l
Control	37	244± 71	118± 49	53± 23	150± 64	377± 1158	3± 4	94± 43
10 ppm	40	268± 63*	113± 56	54± 28	147± 60	161± 39	2± 1	83± 17
40 ppm	38	252± 43	151± 194	55± 34	236± 483	197± 97	3± 1	100± 81
160 ppm	43	242± 42	123± 91	51± 19	154± 105	192± 45	2± 1	92± 30

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

(HCL074)

BAIS 4

STUDY NO. : 0704
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	37	16.6± 2.1	0.5± 0.1	141± 1	3.3± 0.4	104± 2	10.5± 0.4	3.6± 0.7
10 ppm	40	16.1± 2.3	0.5± 0.1	141± 1	3.2± 0.3	104± 2	10.6± 0.4	3.6± 0.8
40 ppm	38	19.2± 16.3	0.5± 0.1	141± 2	3.4± 0.6	105± 3	10.6± 0.6	3.8± 1.7
160 ppm	43	18.0± 1.4**	0.5± 0.1	141± 1	3.3± 0.3	105± 2	10.5± 0.4	3.6± 0.7

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

(HCL074)

BAIS 4

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0704
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	1	7	5	18	7	0		0	0	0	0	21	17		38	0	0	0	0	0		34	4	0	0	0	0		37	0	0	1	
10 ppm	36	0	2	3	8	15	7	1		0	1	0	3	18	14		36	0	0	0	0	0		28	8	0	0	0	0		35	0	0	1	
40 ppm	41	0	0	4	7	20	9	1		0	0	0	0	24	17		41	0	0	0	0	0		30	11	0	0	0	0		41	0	0	0	
160 ppm	42	0	1	9	6	13	13	0		0	0	1	8	30	3	**	42	0	0	0	0	0		32	10	0	0	0	0		42	0	0	0	

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

(HCL101)

BAIS 4

STUDY NO. : 0704
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood − ± 1+ 2+ 3+	CHI	Urobilinogen ± 1+ 2+ 3+ 4+	CHI
Control	38	38 0 0 0 0		38 0 0 0 0	
10 ppm	36	34 0 0 1 1		35 0 0 1 0	
40 ppm	41	40 0 0 0 1		41 0 0 0 0	
160 ppm	42	38 0 2 2 0		42 0 0 0 0	

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

(HCL101)

BAIS 4

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0704
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	37	0	2	2	3	17	12	1		0	1	7	13	14	2		37	0	0	0	0	0		32	5	0	0	0	0		37	0	0	0	
10 ppm	40	0	2	6	10	13	9	0		0	0	7	10	16	7		40	0	0	0	0	0		27	12	0	1	0	0		39	1	0	0	
40 ppm	39	0	2	1	5	16	14	1		0	0	6	14	18	1		39	0	0	0	0	0		26	13	0	0	0	0	*	36	3	0	0	
160 ppm	43	0	1	2	4	15	21	0		0	0	5	17	20	1		43	0	0	0	0	0		28	15	0	0	0	0	*	43	0	0	0	

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

(HCL101)

BAIS 4

STUDY NO. : 0704
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	37	37	0	0	0	0		37	0	0	0	0	
10 ppm	40	40	0	0	0	0		40	0	0	0	0	
40 ppm	39	35	0	0	1	3		39	0	0	0	0	
160 ppm	43	43	0	0	0	0		43	0	0	0	0	

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

(HCL101)

BAIS 4

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0704
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	38	406± 44	0.172± 0.545	3.491± 1.391	1.264± 0.102	1.415± 0.290	2.763± 0.192
10 ppm	35	391± 41	0.078± 0.011	3.555± 1.649	1.246± 0.103	1.393± 0.330	2.686± 0.264
40 ppm	41	398± 28	0.082± 0.027	3.558± 1.089	1.228± 0.093	1.337± 0.105	2.730± 0.234
160 ppm	42	353± 35**	0.078± 0.022	3.664± 1.096	1.169± 0.101**	1.315± 0.129**	2.544± 0.177**

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

(HCL040)

STUDY NO. : 0704
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	38	1.397±	1.292	11.793±	1.477	2.100±	0.074
10 ppm	35	1.547±	1.887	11.263±	1.851	2.096±	0.042
40 ppm	41	1.081±	0.567	11.085±	1.146	2.106±	0.051
160 ppm	42	0.897±	0.360**	9.597±	0.966**	2.106±	0.046

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

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0704
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	37	272± 26	0.076± 0.010	0.221± 0.631	0.881± 0.070	0.957± 0.120	1.771± 0.219
10 ppm	40	283± 27	0.076± 0.008	0.116± 0.020	0.884± 0.069	0.915± 0.064	1.800± 0.154
40 ppm	38	271± 37	0.077± 0.028	0.302± 0.879	0.883± 0.095	0.941± 0.129	1.755± 0.122
160 ppm	43	244± 15**	0.073± 0.008	0.113± 0.018	0.854± 0.059	0.934± 0.187	1.682± 0.114

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

(HCL040)

STUDY NO. : 0704
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	37	0.733±	0.837	6.473±	0.861	1.912±	0.045
10 ppm	40	0.508±	0.076	6.713±	1.067	1.899±	0.040
40 ppm	38	0.568±	0.380	6.431±	1.110	1.910±	0.037
160 ppm	43	0.583±	0.626	6.090±	0.831	1.892±	0.077

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

(IICL040)

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0704
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	38	406± 44	0.044± 0.142	0.860± 0.325	0.315± 0.041	0.352± 0.084	0.689± 0.092
10 ppm	35	391± 41	0.020± 0.004	0.903± 0.393	0.323± 0.055	0.363± 0.112	0.694± 0.093
40 ppm	41	398± 28	0.021± 0.006	0.895± 0.267	0.310± 0.028	0.338± 0.038	0.690± 0.076
160 ppm	42	353± 35**	0.022± 0.007	1.034± 0.301	0.333± 0.025**	0.380± 0.101**	0.733± 0.146

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

(IICL042)

BAIS 4

STUDY NO. : 0704
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	38	0.351± 0.341	2.924± 0.399	0.523± 0.058
10 ppm	35	0.410± 0.540	2.892± 0.464	0.542± 0.064
40 ppm	41	0.274± 0.158	2.791± 0.246	0.532± 0.041
160 ppm	42	0.253± 0.093	2.734± 0.266	0.604± 0.083**

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

(HCL042)

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0704
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	37	272± 26	0.028± 0.004	0.078± 0.212	0.326± 0.032	0.356± 0.064	0.654± 0.082
10 ppm	40	283± 27	0.027± 0.003	0.041± 0.007	0.314± 0.030	0.325± 0.027**	0.639± 0.054
40 ppm	38	271± 37	0.029± 0.011	0.110± 0.312	0.330± 0.061	0.354± 0.090	0.656± 0.096
160 ppm	43	244± 15**	0.030± 0.004**	0.046± 0.007	0.351± 0.033**	0.384± 0.083**	0.690± 0.040**

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

(HCL042)

BAIS 4

STUDY NO. : 0704
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	37	0.282± 0.366	2.387± 0.300	0.709± 0.074
10 ppm	40	0.180± 0.030	2.364± 0.212	0.677± 0.069
40 ppm	38	0.222± 0.225	2.419± 0.739	0.716± 0.098
160 ppm	43	0.242± 0.271	2.494± 0.322**	0.777± 0.047**

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

(HCL042)

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

STUDY NO. : 0704
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				10 ppm 50				40 ppm 50				160 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	epidermal cyst		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)	0 (0)	0 (0)	0 (0)
	duct ectasia:sebaceous gland		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	thrombus		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (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 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	eosinophilic change:olfactory epithelium		31 (62)	5 (10)	1 (2)	0 (0)	28 (56)	6 (12)	0 (0)	0 (0)	31 (62)	11 (22)	0 (0)	0 (0)	20 (40)	25 (50)	5 (10)	0 ** (0)
	eosinophilic change:respiratory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
	inflammation:foreign body		12 (24)	2 (4)	0 (0)	0 (0)	17 (34)	2 (4)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	0 (0)	10 (20)	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 (%)	2 (%)	3 (%)	4 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	disarrangement:olfactory epithelium		0	0	0	0	0	0	0	0	7	0	0	0 *	26	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(52)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		1	0	0	0	0	0	0	0	6	0	0	0	46	0	0	0 **
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(92)	(0)	(0)	(0)
	respiratory metaplasia:gland		2	0	0	0	3	0	0	0	5	0	0	0	12	0	0	0 **
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(24)	(0)	(0)	(0)
	squamous cell metaplasia:respiratory epithelium		0	0	0	0	0	0	0	0	2	0	0	0	29	1	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(58)	(2)	(0)	(0)
	squamous cell metaplasia:olfactory epithelium		0	0	0	0	0	0	0	0	5	0	0	0	32	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(64)	(0)	(0)	(0)
	ulcer:respiratory epithelium		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	ulcer:olfactory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:transitional epithelium		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
(Respiratory system)																		
nasal cavit			<50>				<50>				<50>				<50>			
	atrophy:olfactory epithelium		0	0	0	0	2	0	0	0	15	0	0	0 **	40	0	0	0 **
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(80)	(0)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	congestion		0	4	0	0	0	4	0	0	0	1	0	0	0	1	0	0
			(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)
	hemorrhage		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)
	edema		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)
	inflammatory infiltration		3	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0
			(6)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	granulomatous inflammation		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)
	accumulation of foamy cells		2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		2	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Hematopoietic system)																		
bone marrow			<50>				<50>				<50>				<50>			
	congestion		0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	granulation		1	0	0	0	1	0	0	0	2	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	increased hematopoiesis		2	0	0	0	4	0	0	0	4	0	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	atrophy		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)
	congestion		7	0	0	0	5	0	0	0	5	0	0	0	6	0	0	0
			(14)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	deposit of hemosiderin		18	0	0	0	15	3	0	0	20	0	0	0	14	1	0	0
			(36)	(0)	(0)	(0)	(30)	(6)	(0)	(0)	(40)	(0)	(0)	(0)	(28)	(2)	(0)	(0)
	fibrosis:focal		0	0	0	0	0	2	0	0	2	1	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	extramedullary hematopoiesis		3	1	1	0	1	3	3	0	3	2	0	0	4	2	0	0
			(6)	(2)	(2)	(0)	(2)	(6)	(6)	(0)	(6)	(4)	(0)	(0)	(8)	(4)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	myocardial fibrosis		20 (40)	1 (2)	0 (0)	0 (0)	21 (42)	0 (0)	0 (0)	0 (0)	14 (28)	0 (0)	0 (0)	0 (0)	14 (28)	1 (2)	0 (0)	0 (0)
	endomyocardial fibrosis		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)
artery/aort			<50>				<50>				<50>				<50>			
	arteritis		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)
{Digestive system}																		
tongue			<50>				<50>				<50>				<50>			
	arteritis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
esophagus			<50>				<50>				<50>				<50>			
	inflammation		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)

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 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	erosion:forestomach		1	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:forestomach		0	0	0	0	2	4	0	0 *	2	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(4)	(8)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	hyperplasia:forestomach		3	0	0	0	6	1	0	0	4	1	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(12)	(2)	(0)	(0)	(8)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	erosion:glandular stomach		2	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	ulcer:glandular stomach		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)
large intes			<50>				<50>				<50>				<50>			
	dilatation		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		4	0	0	0	10	0	0	0	4	0	0	0	6	0	0	0
			(8)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(12)	(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 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
(Digestive system)																		
liver			<50>				<50>				<50>				<50>			
	necrosis:central		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	necrosis:focal		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)
	fatty change		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)
	granulation		5 (10)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	clear cell focus		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	acidophilic cell focus		6 (12)	0 (0)	0 (0)	0 (0)	10 (20)	3 (6)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
	basophilic cell focus		2 (4)	1 (2)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	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)

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				10 ppm				40 ppm				160 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>			
	bile duct hyperplasia		13	33	0	0	16	32	0	0	13	36	0	0	16	32	0	0
			(26)	(66)	(0)	(0)	(32)	(64)	(0)	(0)	(26)	(72)	(0)	(0)	(32)	(64)	(0)	(0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		19	1	0	0	13	1	0	0	21	4	2	0	19	1	1	0
			(38)	(2)	(0)	(0)	(26)	(2)	(0)	(0)	(42)	(8)	(4)	(0)	(38)	(2)	(2)	(0)
	arteritis		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	islet cell hyperplasia		1	0	0	0	1	0	0	0	0	0	0	0	3	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	cyst		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(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 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	chronic nephropathy		13 (26)	22 (44)	12 (24)	1 (2)	21 (42)	15 (30)	10 (20)	1 (2)	15 (30)	22 (44)	12 (24)	0 (0)	36 (72)	8 (16)	2 (4)	0 (0) **
	tubular necrosis		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)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:cortex		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)
	deposit of brown pigment:proximal tubule		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	10 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	40 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	160 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Endocrine system}																		
pituitary		<50>					<50>				<50>				<50>			
	hyperplasia		13	2	0	0	11	0	0	0	9	4	0	0	8	0	0	0
			(26)	(4)	(0)	(0)	(22)	(0)	(0)	(0)	(18)	(8)	(0)	(0)	(16)	(0)	(0)	(0)
	Rathke pouch		2	0	0	0	2	0	0	0	3	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
thyroid		<50>					<50>				<50>				<50>			
	C-cell hyperplasia		10	2	0	0	7	1	0	0	11	1	0	0	9	0	0	0
			(20)	(4)	(0)	(0)	(14)	(2)	(0)	(0)	(22)	(2)	(0)	(0)	(18)	(0)	(0)	(0)
	focal follicular cell hyperplasia		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	cystic thyroid follicle		1	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
adrenal		<50>					<50>				<50>				<50>			
	peliosis-like lesion		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)
	extramedullary hematopoiesis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Endocrine system}																		
adrenal			<50>				<50>				<50>				<50>			
	hyperplasia:cortical cell		1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:medulla		6	0	0	0	6	0	0	0	3	0	0	0	6	0	0	0
			(12)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	focal fatty change:cortex		2	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Reproductive system}																		
testis			<50>				<50>				<50>				<50>			
	mineralization		4	0	0	0	4	0	0	0	4	0	0	0	7	0	0	0
			(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	arteritis		7	0	0	0	5	0	0	0	3	0	0	0	4	0	0	0
			(14)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	interstitial cell hyperplasia		18	0	0	0	15	0	0	0	17	0	0	0	10	0	0	0
			(36)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(34)	(0)	(0)	(0)	(20)	(0)	(0)	(0)
prostate			<50>				<50>				<50>				<50>			
	inflammation		3	4	0	0	7	0	0	0	4	0	0	0	4	1	0	0
			(6)	(8)	(0)	(0)	(14)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(2)	(0)	(0)

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

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Reproductive system)																		
prostate			<50>				<50>				<50>				<50>			
	hyperplasia		6	0	0	0	5	0	0	0	7	0	0	0	10	1	0	0
			(12)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(20)	(2)	(0)	(0)
mammary gl			<50>				<50>				<50>				<50>			
	galactocele		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)
(Special sense organs/appendage)																		
eye			<50>				<50>				<50>				<50>			
	cataract		5	0	0	0	4	0	0	0	8	0	0	0	2	0	0	0
			(10)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	retinal atrophy		1	3	2	0	0	0	3	1	3	2	6	0	0	0	2	0
			(2)	(6)	(4)	(0)	(0)	(0)	(6)	(2)	(6)	(4)	(12)	(0)	(0)	(0)	(4)	(0)
	keratitis		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)
	mineralization:cornea		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				10 ppm 50				40 ppm 50				160 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Special sense organs/appendage}																		
Harder gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		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)
	inflammation:foreign body		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

TABLE L4

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : FEMALE

ALL ANIMALS

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Integumentary system/appandage}																		
skin/app			<50>				<50>				<50>				<50>			
	scab		1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	thrombus		0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		11	29	8	0	8	33	9	0	5	27	17	0	1	23	26	0 **
			(22)	(58)	(16)	(0)	(16)	(66)	(18)	(0)	(10)	(54)	(34)	(0)	(2)	(46)	(52)	(0)
	eosinophilic change:respiratory epithelium		45	0	0	0	46	0	0	0	46	0	0	0	49	0	0	0
			(90)	(0)	(0)	(0)	(92)	(0)	(0)	(0)	(92)	(0)	(0)	(0)	(98)	(0)	(0)	(0)
	inflammation:foreign body		3	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	disarrangement:olfactory epithelium		0	0	0	0	0	0	0	0	7	0	0	0 *	34	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(68)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		1	0	0	0	1	0	0	0	3	0	0	0	44	0	0	0 **
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(88)	(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				10 ppm				40 ppm				160 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>			
	respiratory metaplasia:gland		5	0	0	0	6	0	0	0	7	0	0	0	20	0	0	0 **
			(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(40)	(0)	(0)	(0)
	squamous cell metaplasia:respiratory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	24	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(48)	(0)	(0)	(0)
	squamous cell metaplasia:olfactory epithelium		0	0	0	0	0	0	0	0	3	0	0	0	31	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(62)	(0)	(0)	(0)
	atrophy:olfactory epithelium		0	0	0	0	3	0	0	0	12	0	0	0 **	39	0	0	0 **
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(78)	(0)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	congestion		0	2	0	0	0	3	0	0	0	4	0	0	0	1	0	0
			(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(2)	(0)	(0)
	inflammatory infiltration		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)
	granulomatous inflammation		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)
	accumulation of foamy cells		3	0	0	0	3	0	0	0	2	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)

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				10 ppm				40 ppm				160 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}																		
lung			<50>				<50>				<50>				<50>			
	bronchiolar-alveolar cell hyperplasia		1	0	0	0	3	0	0	0	4	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		3	1	0	0	2	0	0	0	4	0	0	0	4	0	0	0
			(6)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	increased hematopoiesis		1	0	0	0	2	0	0	0	1	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
lymph node			<50>				<50>				<50>				<50>			
	lymphadenitis		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)
spleen			<50>				<50>				<50>				<50>			
	congestion		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)
	deposit of hemosiderin		30	9	0	0	34	9	0	0	32	12	0	0	33	12	0	0
			(60)	(18)	(0)	(0)	(68)	(18)	(0)	(0)	(64)	(24)	(0)	(0)	(66)	(24)	(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				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Hematopoietic system}																		
spleen			<50>				<50>				<50>				<50>			
	fibrosis:focal		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)
	extramedullary hematopoiesis		5	3	3	0	9	2	1	0	5	2	0	0	2	1	1	0
			(10)	(6)	(6)	(0)	(18)	(4)	(2)	(0)	(10)	(4)	(0)	(0)	(4)	(2)	(2)	(0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	mineralization		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	myocardial fibrosis		7	0	0	0	8	0	0	0	10	0	0	0	5	0	0	0
			(14)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	endomyocardial fibrosis		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)
{Digestive system}																		
tongue			<50>				<50>				<50>				<50>			
	squamous cell hyperplasia		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 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)																		
tongue			<50>				<50>				<50>				<50>			
	arteritis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
stomach			<50>				<50>				<50>				<50>			
	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)
	erosion:forestomach		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:forestomach		3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		6	0	0	0	3	0	0	0	5	0	0	0	2	0	0	0
			(12)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	erosion:glandular stomach		4	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:glandular stomach		0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:glandular stomach		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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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	Control				10 ppm				40 ppm				160 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)																		
small intes			<50>				<50>				<50>				<50>			
	hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		12	0	0	0	5	0	0	0	5	0	0	0	6	0	0	0
			(24)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	peliosis-like lesion		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)
	necrosis:central		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)
	necrosis:focal		1	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	fatty change:central		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)
	lymphocytic infiltration		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	granulation		10	1	0	0	7	0	0	0	7	1	0	0	7	0	0	0
			(20)	(2)	(0)	(0)	(14)	(0)	(0)	(0)	(14)	(2)	(0)	(0)	(14)	(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				10 ppm 50				40 ppm 50				160 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	clear cell focus		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	basophilic cell focus		18 (36)	0 (0)	0 (0)	0 (0)	20 (40)	1 (2)	0 (0)	0 (0)	16 (32)	0 (0)	0 (0)	0 (0)	20 (40)	1 (2)	0 (0)	0 (0)
	bile duct hyperplasia		8 (16)	0 (0)	0 (0)	0 (0)	8 (16)	1 (2)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	8 (16)	0 (0)	0 (0)	0 (0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		4 (8)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	1 (2)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	2 (4)	0 (0)	0 (0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	necrosis:focal		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)
	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)

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				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	deposit of hemosiderin		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)
	chronic nephropathy		25	5	1	0	28	8	1	0	27	4	1	0	33	1	0	0
			(50)	(10)	(2)	(0)	(56)	(16)	(2)	(0)	(54)	(8)	(2)	(0)	(66)	(2)	(0)	(0)
	tubular necrosis		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)
	mineralization:pelvis		0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:cortex		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	regeneration:proximal tubule		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)
	urothelial hyperplasia:pelvis		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)
	mineralization:inner stripe, outer medulla		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
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Significant difference ; * : P ≦ 0.05 ** : P ≦ 0.01 Test of Chi Square

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	dilated pelvis		0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)
	focal fatty change		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)
urin bladd			<50>				<50>				<50>				<50>			
	squamous cell metaplasia		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)
	simple hyperplasia:transitional epithelium		0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		0	3	0	0	3	2	0	0	1	0	0	0	0	1	0	0
			(0)	(6)	(0)	(0)	(6)	(4)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	cyst		1	0	0	0	4	0	0	0	3	0	0	0	2	0	0	0
			(2)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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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				10 ppm 50				40 ppm 50				160 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	hyperplasia		11 (22)	6 (12)	0 (0)	0 (0)	10 (20)	2 (4)	0 (0)	0 (0)	12 (24)	4 (8)	0 (0)	0 (0)	11 (22)	6 (12)	0 (0)	0 (0)
	Rathke pouch		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<50>				<50>				<50>			
	C-cell hyperplasia		23 (46)	0 (0)	0 (0)	0 (0)	21 (42)	0 (0)	0 (0)	0 (0)	20 (40)	0 (0)	0 (0)	0 (0)	23 (46)	0 (0)	0 (0)	0 (0)
	focal follicular cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
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)	1 (2)	0 (0)	0 (0)	0 (0)
	hyperplasia:medulla		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	focal fatty change:cortex		1 (2)	2 (4)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	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	Control				10 ppm				40 ppm				160 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Reproductive system}																		
ovary			<50>				<50>				<50>				<50>			
	cyst		1	0	0	0	0	1	0	0	2	1	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	hyperplasia:gland		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	cystic endometrial hyperplasia		2	0	0	0	1	0	0	0	0	0	0	0	3	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
mammary gl			<50>				<50>				<50>				<50>			
	galactocele		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)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	gliosis		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)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	cataract		1	0	0	0	5	0	0	0	1	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				10 ppm 50				40 ppm 50				160 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	retinal atrophy		2	0	1	0	2	1	4	0	0	1	1	0	5	1	1	0
			(4)	(0)	(2)	(0)	(4)	(2)	(8)	(0)	(0)	(2)	(2)	(0)	(10)	(2)	(2)	(0)
	keratitis		0	0	1	0	1	2	0	0	0	1	0	0	1	0	0	0
			(0)	(0)	(2)	(0)	(2)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	hemorrhage:cornea		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)
Harder gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		2	0	0	0	2	0	0	0	2	0	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
nasolacr d			<50>				<50>				<50>				<50>			
	inflammation		2	4	0	0	0	5	0	0	0	2	0	0	0	0	0	0 *
			(4)	(8)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	atrophy		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)

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

Organ	Findings	Group Name	Control				10 ppm				40 ppm				160 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		5	3	1	0	3	3	0	0	4	2	0	0	5	2	1	0
			(10)	(6)	(2)	(0)	(6)	(6)	(0)	(0)	(8)	(4)	(0)	(0)	(10)	(4)	(2)	(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	10 ppm	40 ppm	160 ppm
	SITE : skin/appendage			
	TUMOR : trichoepithelioma, trichoepithelioma:malignant			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	2.63	0.0	4.88	7.14
Terminal rates(c)	1/38(2.6)	0/36(0.0)	2/41(4.9)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0853			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1114			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.3087
	SITE : subcutis			
	TUMOR : fibroma			
Tumor rate				
Overall rates(a)	5/50(10.0)	6/50(12.0)	5/50(10.0)	6/50(12.0)
Adjusted rates(b)	11.11	10.87	9.76	8.89
Terminal rates(c)	3/38(7.9)	3/36(8.3)	4/41(9.8)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1386			
Prevalence method(d)	P = 0.6455			
Combined analysis(d)	P = 0.4282			
Cochran-Armitage test(e)	P = 0.8179			
Fisher Exact test(e)		P = 0.5000	P = 0.6297	P = 0.5000
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	4/50(8.0)
Adjusted rates(b)	7.89	2.78	2.44	9.52
Terminal rates(c)	3/38(7.9)	1/36(2.8)	1/41(2.4)	4/42(9.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1621			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2448			
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.5000

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	1/50(2.0)	5/50(10.0)
Adjusted rates(b)	10.53	2.78	2.44	11.90
Terminal rates(c)	4/38(10.5)	1/36(2.8)	1/41(2.4)	5/42(11.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1307			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.1852			
Fisher Exact test(e)		P = 0.1811	P = 0.1811	P = 0.5000
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	4/50(8.0)	5/50(10.0)	5/50(10.0)	1/50(2.0)
Adjusted rates(b)	7.89	5.56	7.32	2.38
Terminal rates(c)	3/38(7.9)	2/36(5.6)	3/41(7.3)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9294			
Prevalence method(d)	P = 0.8521			
Combined analysis(d)	P = 0.9637			
Cochran-Armitage test(e)	P = 0.1121			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.1811
	SITE : liver			
	TUMOR : hepatocellular adenoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	1/50(2.0)	1/50(2.0)	2/50(4.0)
Adjusted rates(b)	15.79	2.78	2.44	4.08
Terminal rates(c)	6/38(15.8)	1/36(2.8)	1/41(2.4)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8220			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4305			
Fisher Exact test(e)		P = 0.0559	P = 0.0559	P = 0.1343

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	1/50(2.0)	1/50(2.0)	2/50(4.0)
Adjusted rates(b)	18.42	2.78	2.44	4.08
Terminal rates(c)	7/38(18.4)	1/36(2.8)	1/41(2.4)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8794			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3130			
Fisher Exact test(e)		P = 0.0297*	P = 0.0297*	P = 0.0798
	SITE : pancreas			
	TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	3/50(6.0)	3/50(6.0)	7/50(14.0)
Adjusted rates(b)	13.16	7.32	7.32	16.67
Terminal rates(c)	5/38(13.2)	2/36(5.6)	3/41(7.3)	7/42(16.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1562			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2081			
Fisher Exact test(e)		P = 0.3575	P = 0.3575	P = 0.3798
	SITE : pancreas			
	TUMOR : islet cell adenoma, islet cell adenocarcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	4/50(8.0)	3/50(6.0)	7/50(14.0)
Adjusted rates(b)	13.16	9.76	7.32	16.67
Terminal rates(c)	5/38(13.2)	3/36(8.3)	3/41(7.3)	7/42(16.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.2039			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2855			
Fisher Exact test(e)		P = 0.5000	P = 0.3575	P = 0.3798

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	9/50(18.0)	9/50(18.0)	7/50(14.0)
Adjusted rates(b)	18.42	13.89	17.39	13.33
Terminal rates(c)	7/38(18.4)	5/36(13.9)	7/41(17.1)	5/42(11.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9409			
Prevalence method(d)	P = 0.6691			
Combined analysis(d)	P = 0.8865			
Cochran-Armitage test(e)	P = 0.3558			
Fisher Exact test(e)		P = 0.4016	P = 0.4016	P = 0.2178
	SITE : pituitary gland TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	9/50(18.0)	9/50(18.0)	7/50(14.0)
Adjusted rates(b)	18.42	13.89	17.39	13.33
Terminal rates(c)	7/38(18.4)	5/36(13.9)	7/41(17.1)	5/42(11.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9409			
Prevalence method(d)	P = 0.6691			
Combined analysis(d)	P = 0.8865			
Cochran-Armitage test(e)	P = 0.3558			
Fisher Exact test(e)		P = 0.4016	P = 0.4016	P = 0.2178
	SITE : thyroid TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	15/50(30.0)	11/50(22.0)	7/50(14.0)
Adjusted rates(b)	18.42	37.84	26.83	16.28
Terminal rates(c)	7/38(18.4)	13/36(36.1)	11/41(26.8)	6/42(14.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9286			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2243			
Fisher Exact test(e)		P = 0.0765	P = 0.3055	P = 0.5000

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : thyroid			
	TUMOR : C-cell carcinoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	1/50(2.0)	2/50(4.0)	3/50(6.0)
Adjusted rates(b)	7.89	2.78	4.88	4.76
Terminal rates(c)	3/38(7.9)	1/36(2.8)	2/41(4.9)	2/42(4.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4718			
Prevalence method(d)	P = 0.5530			
Combined analysis(d)	P = 0.5554			
Cochran-Armitage test(e)	P = 0.9709			
Fisher Exact test(e)		P = 0.1022	P = 0.2180	P = 0.3575
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	13/50(26.0)	15/50(30.0)	13/50(26.0)	10/50(20.0)
Adjusted rates(b)	26.32	37.84	31.71	20.93
Terminal rates(c)	10/38(26.3)	13/36(36.1)	13/41(31.7)	8/42(19.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4718			
Prevalence method(d)	P = 0.9163			
Combined analysis(d)	P = 0.9095			
Cochran-Armitage test(e)	P = 0.3000			
Fisher Exact test(e)		P = 0.4120	P = 0.5900	P = 0.3176
	SITE : thyroid			
	TUMOR : follicular adenoma, follicular adenocarcinoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	0/50(0.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	5.26	0.0	7.32	0.0
Terminal rates(c)	2/38(5.3)	0/36(0.0)	3/41(7.3)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8632			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.3116			
Fisher Exact test(e)		P = 0.2475	P = 0.5000	P = 0.2475

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	5/50(10.0)	5/50(10.0)	7/50(14.0)
Adjusted rates(b)	20.00	13.89	12.20	16.67
Terminal rates(c)	7/38(18.4)	5/36(13.9)	5/41(12.2)	7/42(16.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.4921			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.8472			
Fisher Exact test(e)		P = 0.2768	P = 0.2768	P = 0.5000
	SITE : testis			
	TUMOR : interstitial cell tumor			
Tumor rate				
Overall rates(a)	37/50(74.0)	43/50(86.0)	45/50(90.0)	42/50(84.0)
Adjusted rates(b)	86.84	100.00	93.62	93.02
Terminal rates(c)	33/38(86.8)	36/36(100.0)	38/41(92.7)	39/42(92.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7302			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5857			
Fisher Exact test(e)		P = 0.1054	P = 0.0332*	P = 0.1631
	SITE : preputial/clitoral gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	7.89	2.78	2.44	0.0
Terminal rates(c)	3/38(7.9)	1/36(2.8)	1/41(2.4)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1703			
Prevalence method(d)	P = 0.9622			
Combined analysis(d)	P = 0.7676			
Cochran-Armitage test(e)	P = 0.4960			
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.3087

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : peritoneum			
	TUMOR : mesothelioma			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	2.63	8.33	9.76	2.38
Terminal rates(c)	1/38(2.6)	3/36(8.3)	4/41(9.8)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1963			
Prevalence method(d)	P = 0.7748			
Combined analysis(d)	P = 0.5984			
Cochran-Armitage test(e)	P = 0.8936			
Fisher Exact test(e)		P = 0.3087	P = 0.1022	P = 0.5000

(HPT360A)

BAIS4

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

TABLE O2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	0/50(0.0)	1/50(2.0)
Adjusted rates(b)	8.11	2.50	0.0	2.33
Terminal rates(c)	3/37(8.1)	1/40(2.5)	0/38(0.0)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7533			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5113			
Fisher Exact test(e)		P = 0.3087	P = 0.1212	P = 0.3087
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	0/50(0.0)	1/50(2.0)
Adjusted rates(b)	8.11	2.50	0.0	2.33
Terminal rates(c)	3/37(8.1)	1/40(2.5)	0/38(0.0)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7533			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5113			
Fisher Exact test(e)		P = 0.3087	P = 0.1212	P = 0.3087
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	4/50(8.0)	2/50(4.0)
Adjusted rates(b)	2.70	0.0	5.26	2.33
Terminal rates(c)	1/37(2.7)	0/40(0.0)	2/38(5.3)	1/43(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7330			
Prevalence method(d)	P = 0.4177			
Combined analysis(d)	P = 0.6596			
Cochran-Armitage test(e)	P = 0.7063			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.5000

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	14/50(28.0)	16/50(32.0)	12/50(24.0)	15/50(30.0)
Adjusted rates(b)	24.32	30.00	20.00	25.58
Terminal rates(c)	9/37(24.3)	12/40(30.0)	7/38(18.4)	11/43(25.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4665			
Prevalence method(d)	P = 0.5409			
Combined analysis(d)	P = 0.5224			
Cochran-Armitage test(e)	P = 0.9071			
Fisher Exact test(e)		P = 0.4138	P = 0.4100	P = 0.5000
	SITE : pituitary gland TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	14/50(28.0)	17/50(34.0)	13/50(26.0)	15/50(30.0)
Adjusted rates(b)	24.32	30.00	20.00	25.58
Terminal rates(c)	9/37(24.3)	12/40(30.0)	7/38(18.4)	11/43(25.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5567			
Prevalence method(d)	P = 0.5402			
Combined analysis(d)	P = 0.5740			
Cochran-Armitage test(e)	P = 0.9855			
Fisher Exact test(e)		P = 0.3329	P = 0.5000	P = 0.5000
	SITE : thyroid TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	7/50(14.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	16.22	15.00	13.16	6.98
Terminal rates(c)	6/37(16.2)	6/40(15.0)	5/38(13.2)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9280			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2024			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.2435

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	8/50(16.0)	6/50(12.0)	3/50(6.0)
Adjusted rates(b)	18.92	17.50	13.16	6.98
Terminal rates(c)	7/37(18.9)	7/40(17.5)	5/38(13.2)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3403			
Prevalence method(d)	P = 0.9629			
Combined analysis(d)	P = 0.9630			
Cochran-Armitage test(e)	P = 0.1166			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.1589
	SITE : uterus			
	TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	6/50(12.0)	3/50(6.0)	5/50(10.0)	8/50(16.0)
Adjusted rates(b)	16.22	7.50	13.16	17.39
Terminal rates(c)	6/37(16.2)	3/40(7.5)	5/38(13.2)	7/43(16.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.1553			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2085			
Fisher Exact test(e)		P = 0.2435	P = 0.5000	P = 0.3871
	SITE : mammary gland			
	TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	8/50(16.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	12.82	19.51	13.95	16.28
Terminal rates(c)	4/37(10.8)	7/40(17.5)	4/38(10.5)	7/43(16.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3603			
Prevalence method(d)	P = 0.4532			
Combined analysis(d)	P = 0.4735			
Cochran-Armitage test(e)	P = 0.8393			
Fisher Exact test(e)		P = 0.2768	P = 0.3798	P = 0.3798

Group Name	Control	10 ppm	40 ppm	160 ppm
	SITE : mammary gland			
	TUMOR : adenoma, fibroadenoma			
Tumor rate				
Overall rates(a)	5/50(10.0)	9/50(18.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	12.82	21.95	13.95	16.28
Terminal rates(c)	4/37(10.8)	8/40(20.0)	4/38(10.5)	7/43(16.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3603			
Prevalence method(d)	P = 0.5102			
Combined analysis(d)	P = 0.5292			
Cochran-Armitage test(e)	P = 0.9491			
Fisher Exact test(e)		P = 0.1940	P = 0.3798	P = 0.3798
	SITE : mammary gland			
	TUMOR : adenoma, fibroadenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	10/50(20.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	12.82	23.26	13.95	16.28
Terminal rates(c)	4/37(10.8)	8/40(20.0)	4/38(10.5)	7/43(16.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7122			
Prevalence method(d)	P = 0.5661			
Combined analysis(d)	P = 0.6433			
Cochran-Armitage test(e)	P = 0.8159			
Fisher Exact test(e)		P = 0.2070	P = 0.5000	P = 0.5000

(HPT360A)

BAIS4

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

TABLE Q1

CAUSE OF DEATH : MALE

STUDY NO. : 0704
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : MALE

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

Group Name	Control	10 ppm	40 ppm	160 ppm
Number of Dead and Moribund Animal	12	14	9	8
no microscop confirm	2	4	0	1
tumor d:leukemia	1	3	3	0
tumor d:subcutis	2	2	1	2
tumor d:pituitary	4	4	1	1
tumor d:thyroid	2	0	0	1
tumor d:prep/cli gl	0	0	0	1
tumor d:brain	0	0	1	1
tumor d:Zymbal gl	0	0	2	0
tumor d:muscle	1	0	0	0
tumor d:vertebra	0	1	0	0
tumor d:peritoneum	0	0	1	1

TABLE Q2

CAUSE OF DEATH : FEMALE

STUDY NO. : 0704
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : FEMALE

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

Group Name	Control	10 ppm	40 ppm	160 ppm
Number of Dead and Moribund Animal	13	10	12	7
no microscop confirm	0	0	2	0
tumor d:leukemia	3	2	2	1
tumor d:oral cavity	1	0	0	0
tumor d:large intes	1	0	0	0
tumor d:pituitary	4	4	5	4
tumor d:thyroid	0	0	1	0
tumor d:adrenal	0	1	0	0
tumor d:uterus	2	2	0	1
tumor d:mammary gl	1	0	1	0
tumor d:Zymbal gl	1	1	0	0
tumor d:vertebra	0	0	1	0
tumor d:retroperit	0	0	0	1

(BIO120)

BAIS4

FIGURES

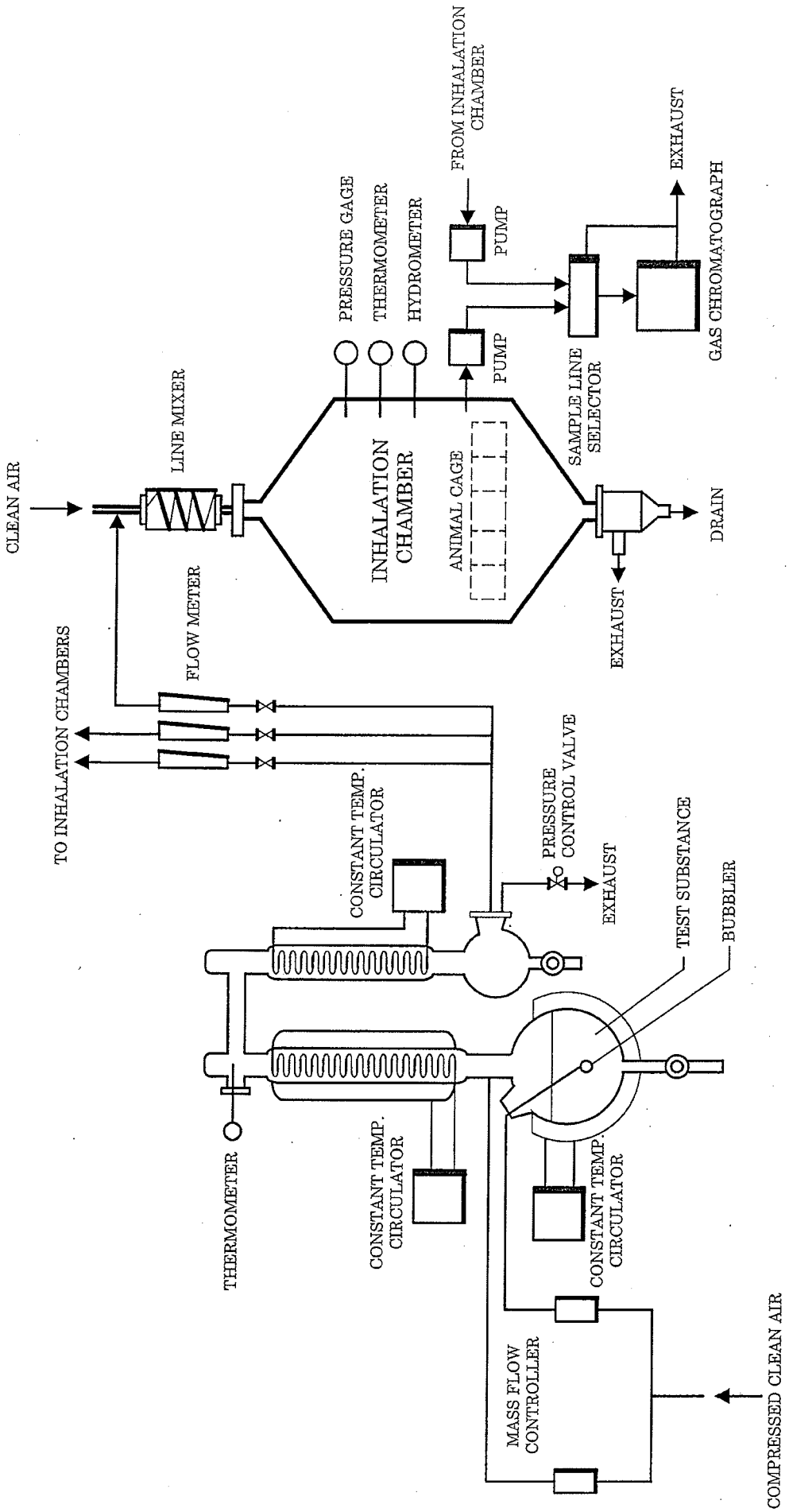


FIGURE 1 ACRYLIC ACID VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

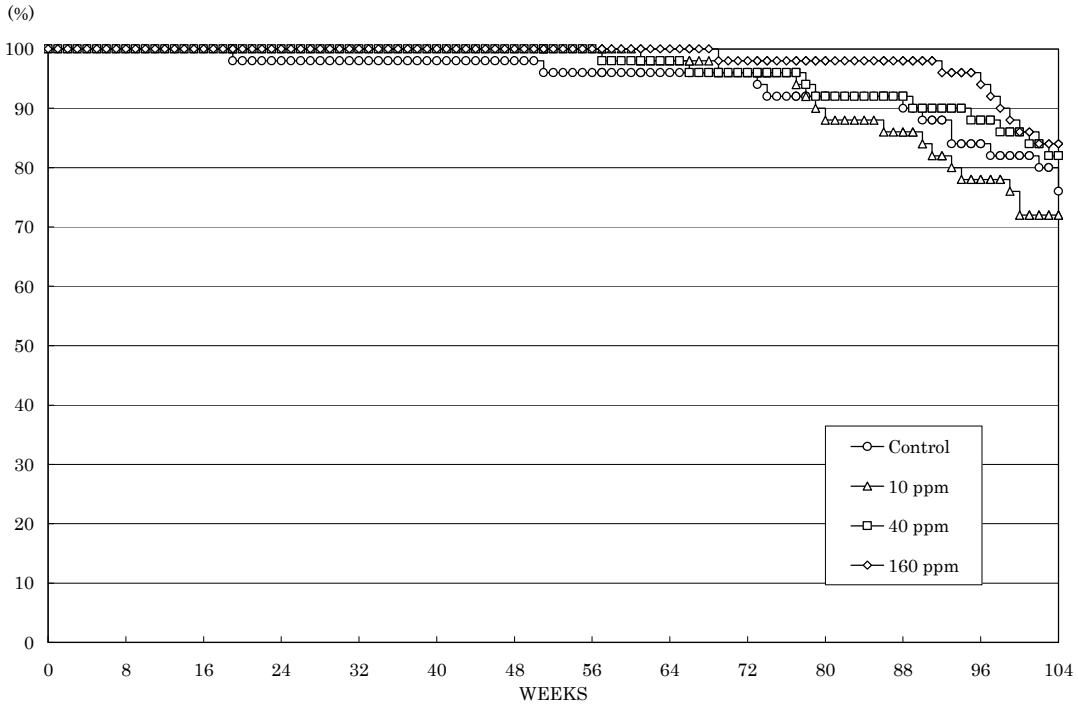


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

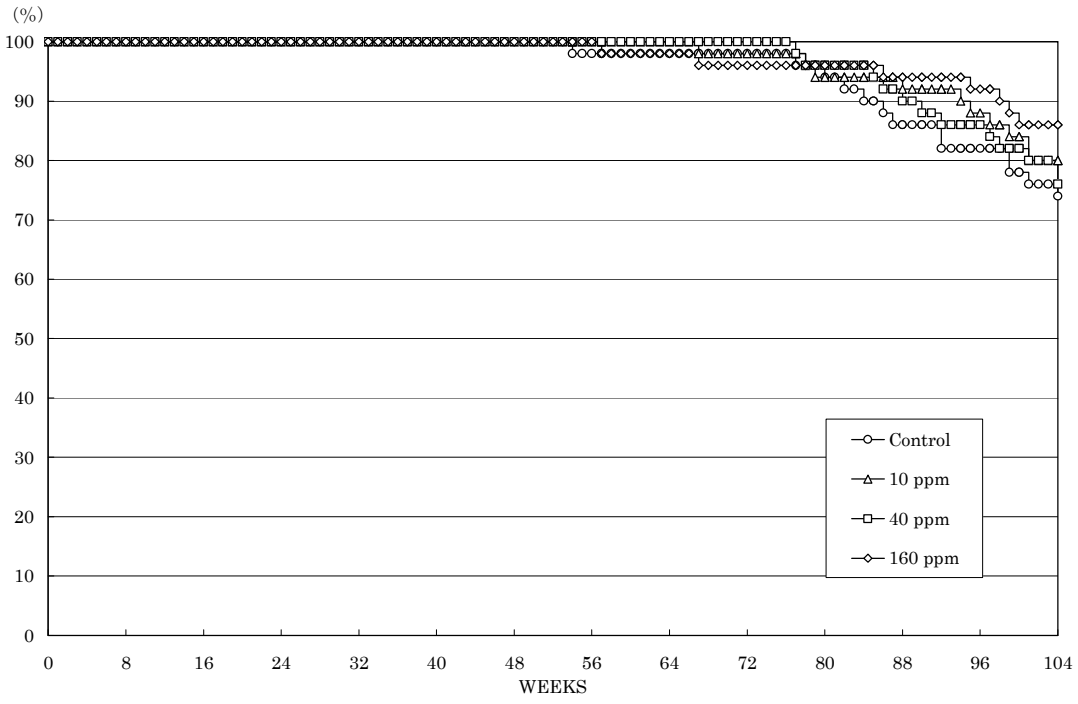


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

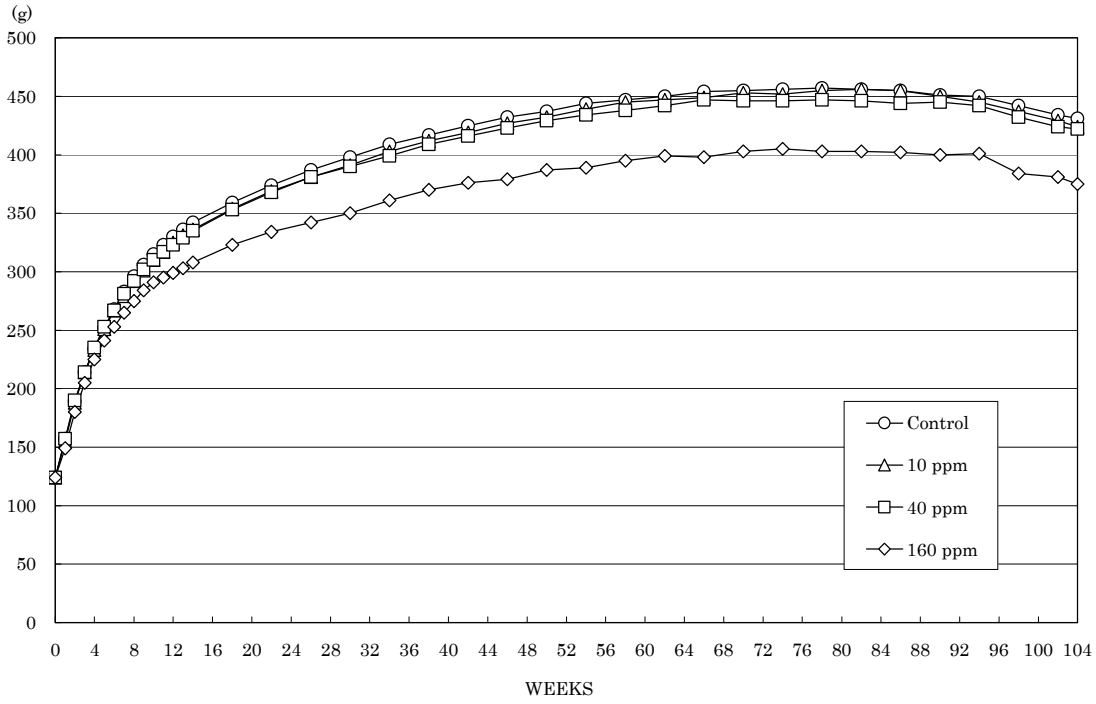


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

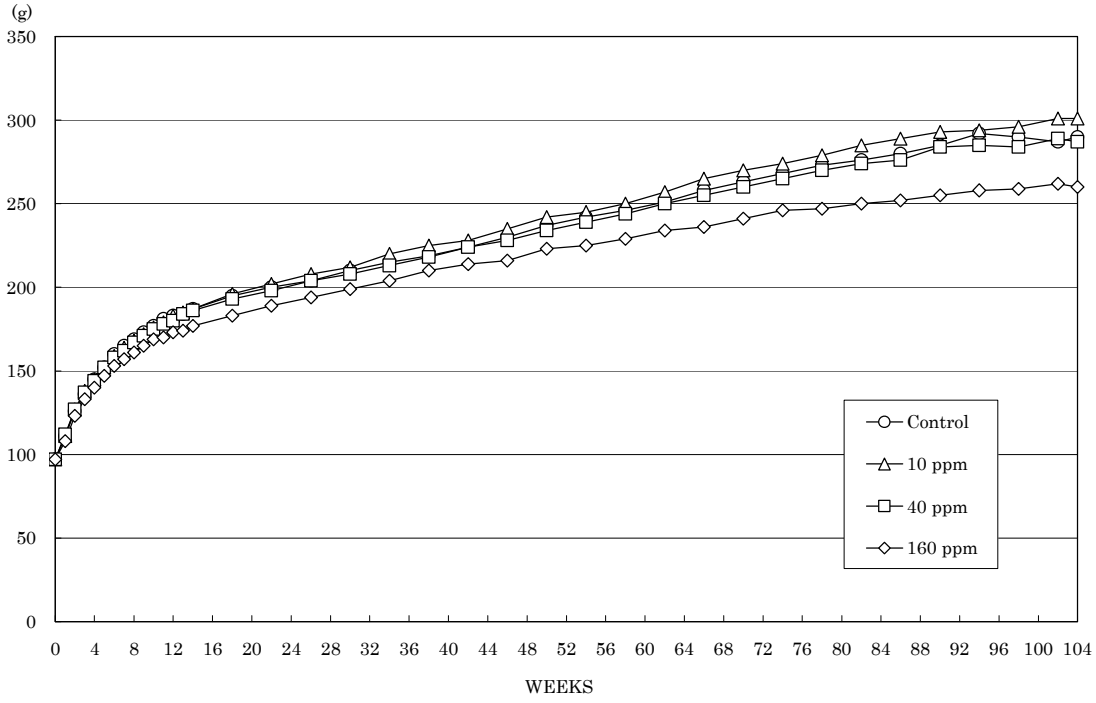


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

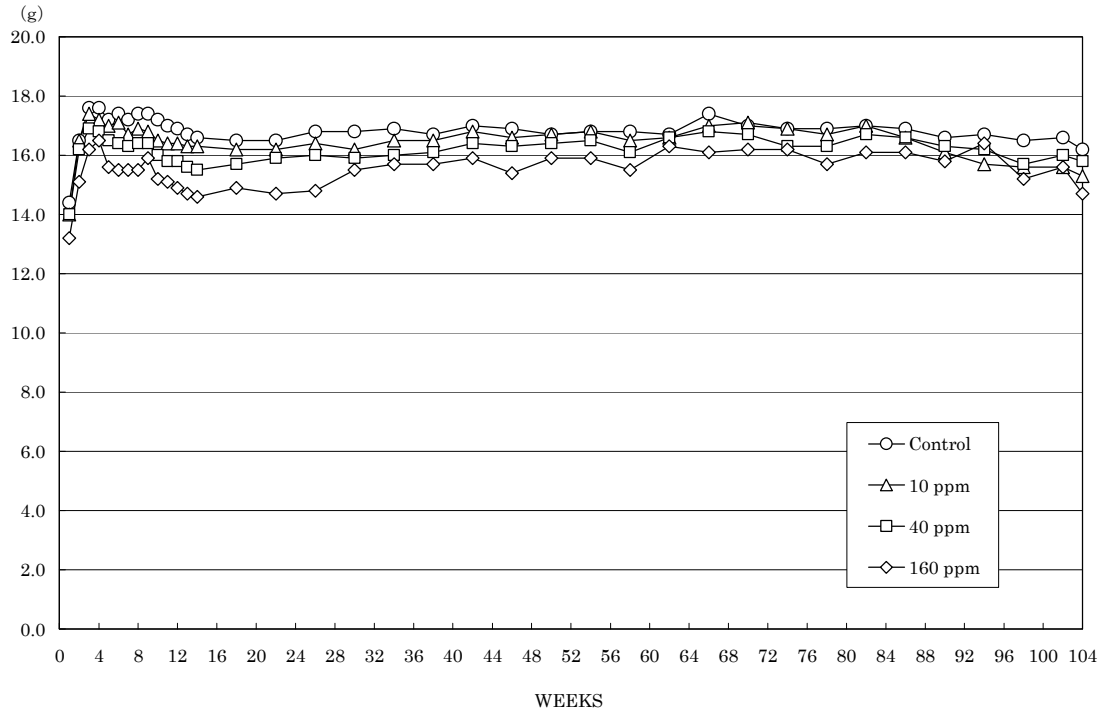


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

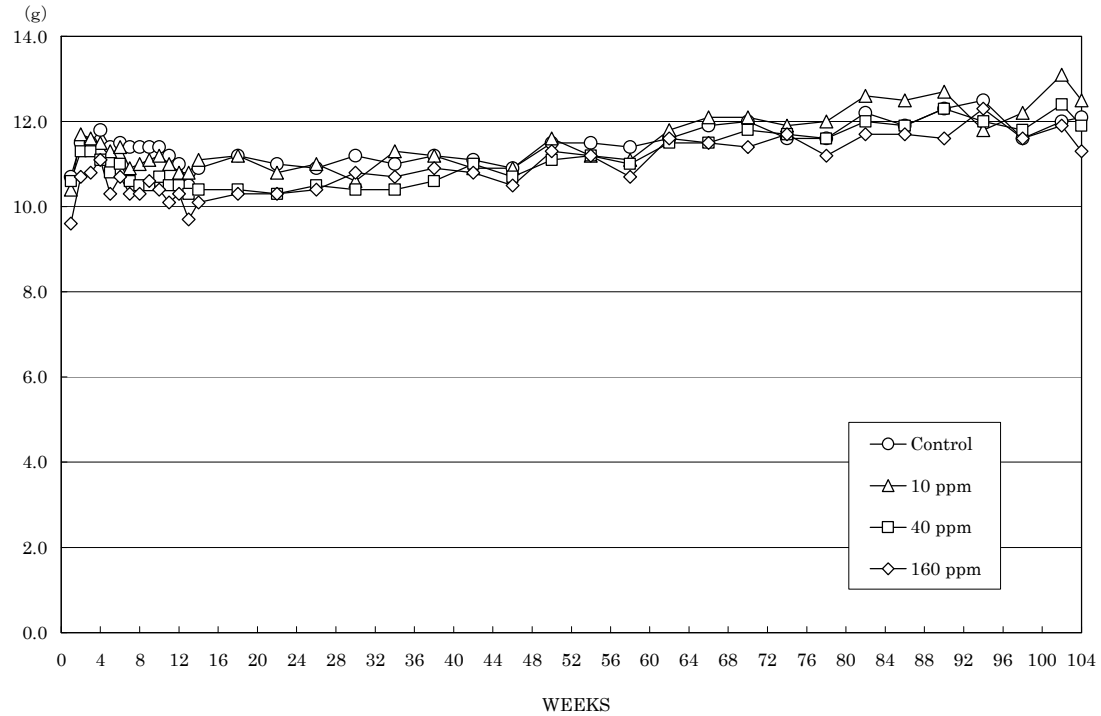
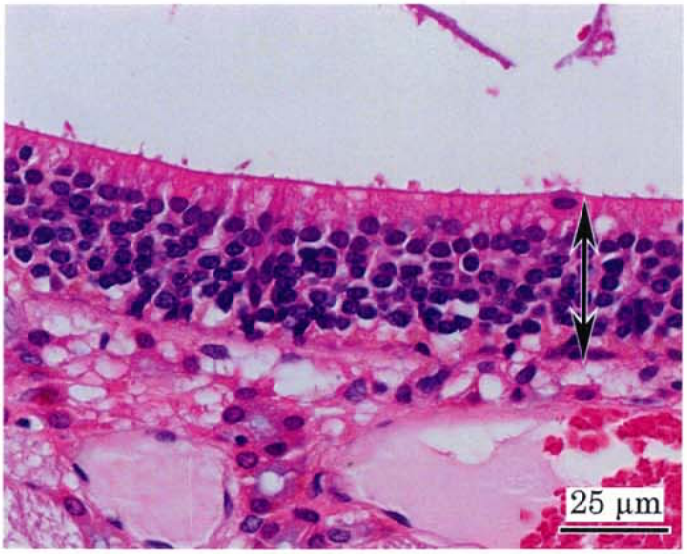
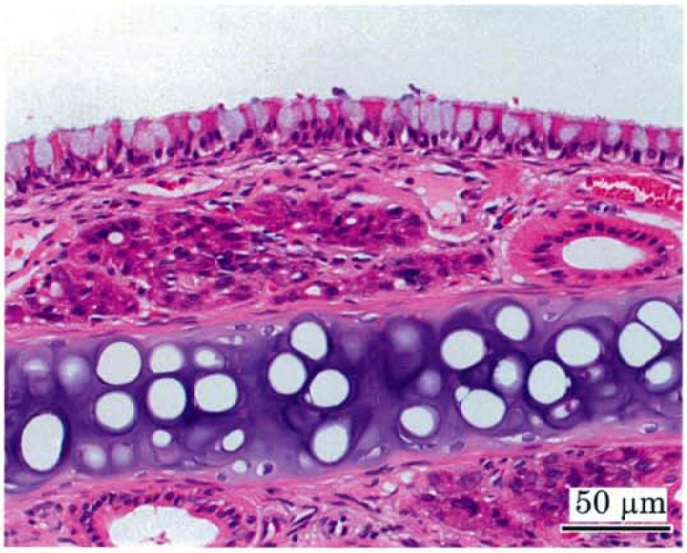


FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ACRYLIC ACID

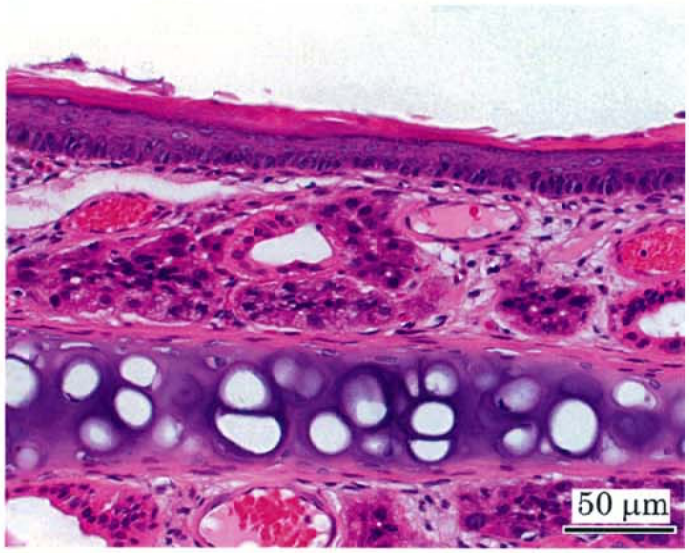


Photograph 1
Nasal cavity (Level 2): Normal, olfactory epithelium (double-headed arrow)
Rat, Male, Control, Animal No. 0704-1011 (H&E)

Photograph 2
Nasal cavity (Level 2): Atrophy (double-headed arrow) and respiratory metaplasia (arrow) of olfactory epithelium
Rat, Male, 160 ppm, Animal No. 0704-1304 (H&E)



Photograph 3
Nasal cavity (Level 1): Normal, respiratory epithelium
Rat, Male, Control, Animal No. 0704-1011 (H&E)



Photograph 4
Nasal cavity (Level 1): Squamous metaplasia of olfactory epithelium
Rat, Male, 160 ppm, Animal No. 0704-1302 (H&E)