Summary of Inhalation Carcinogenicity Study of Isopropyl Acetate in F344 Rats

March 2009

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 31, 2009.

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

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Purpose, materials and methods

Isopropyl acetate (CAS No. 108-21-4) is a colorless liquid with a boiling point of 88.6°C. It is soluble in ethanol, acetone and water.

The carcinogenicity and chronic toxicity of isopropyl acetate (greater than 99.9% pure) were examined by inhalation exposure using F344/DuCrlCrlj (Fischer) rats. Groups of test animals were exposed to isopropyl acetate vapor at target concentrations of 0 (clean air), 1000, 2000 or 4000 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 isopropyl acetate 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 isopropyl acetate used in these experiments was confirmed by both infrared spectrometry and mass spectrometry, and it was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 7600 L) were used throughout the 2-year exposure period. Isopropyl acetate vapor-air mixtures were generated by bubbling clean air through isopropyl acetate liquid and the mixtures supplied to the inhalation exposure chambers. Air concentrations of isopropyl acetate vapor 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. For hematology and blood biochemistry 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 isopropyl acetate induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies

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

Results

No significant differences in survival rates were found between any of the groups exposed to isopropyl acetate and their respective controls. In males, the body weights of the exposed groups were similar to their respective controls throughout the exposure period, except that the body weights of the 4000 ppm-exposed males were suppressed at week 98 and thereafter of the 104 week exposure period: the terminal body weights of the 4000 ppm-exposed males was 94% of the control. Similarly, in females, the body weights of the exposed groups were similar to their respective controls throughout the exposure period, except that the body weights of the 4000 ppm-exposed females were suppressed at week 74 and thereafter of the 104 week exposure period: the terminal body weights of the 4000 ppm-exposed females was 92% of the control. Food consumption was slightly decreased in the 4000 ppm-exposed males and females toward the end of the 2-year exposure period. There were no significant differences in other clinical signs between the groups exposed to isopropyl acetate and their respective controls.

Peritoneum mesotheliomas were observed in males, and the incidence of peritoneal mesotheliomas in the 4000 ppm-exposed males was higher than the historical control data of the Japan Bioassay Research Center (JBRC). No significant increase in the incidence of neoplastic lesions was found in any of the isopropyl acetate-exposed groups of females. Changes in the nasal cavity were noted in both sexes: an increased incidence of eosinophilic change of the respiratory epithelium and olfactory epithelium in males and an increased incidence of eosinophilic change of the respiratory epithelium in females.

Conclusions

There was some evidence of carcinogenic activity of inhaled isopropyl acetate in male rats, as showen by an increased incidence of peritoneal malignant tumors. There was no evidence of carcinogenic activity of isopropyl acetate in female rats.

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

Dose (ppm)		0	1000	2000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
subcutis	fibroma	4	8	5	3		
pancreas	islet cell adenoma	2	6	2	2		
pituitary	adenoma	10	13	5	3 *		↓
thyroid	C-cell adenoma	7	5	6	9		
adrenal	pheochromocytoma	10	1 **	4	0 **		↓ ↓
testis	interstitial cell tumor	41	44	46	47		
malignant tumor							
spleen	mononuclear cell leukemia	4	1	6	3		
thyroid	C-cell carcinoma	1	2	3	1		
peritoneum	mesothelioma	2	2	1	7	↑	↑

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

Dose (ppm)		0	1000	2000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
pituitary	adenoma	12	8	7	5		
thyroid	C-cell adenoma	6	5	4	3		
adrenal	pheochromocytoma	0	4	4	1		
uterus	endometrial stromal polyp	6	6	3	8		
mammary gland	fibroadenoma	8	8	5	5		
clitoral gland	adenoma	1	2	4	0		
malignant tumor							
spleen	mononuclear cell leukemia	9	5	4	4		
uterus	endometrial stromal sarcoma	3	2	1	1		

Significant difference

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

SELECTED TABLES

TABLE A

CONCENTRATIONS OF ISOPROPYL ACETATE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

CONCENTRATIONS OF ISOPROPYL ACETATE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
1000 ppm	1000.6 ± 7.8
2000 ppm	2003.2 ± 12.5
4000 ppm	4001.9 ± 30.2

TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0610
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>	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. Wt.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0-0	125 (50)	50/50	125 (50)	100	50/50	125 (50)	100	50/50	125 (50)	100	50/50
1-7	153 (50)	50/50	155 (50)	101	50/50	156 (50)	102	50/50	153 (50)	100	50/50
2-7	183 (50)	50/50	187 (50)	102	50/50	189 (50)	103	50/50	186 (50)	102	50/50
3-7	209 (50)	50/50	214 (50)	102	50/50	216 (50)	103	50/50	214 (50)	102	50/50
4-7	232 (50)	50/50	236 (50)	102	50/50	237 (50)	102	50/50	235 (50)	101	50/50
5-7	248 (50)	50/50	252 (50)	102	50/50	254 (50)	102	50/50	253 (50)	102	50/50
6-7	264 (50)	50/50	269 (50)	102	50/50	269 (50)	102	50/50	268 (50)	102	50/50
7-7	278 (50)	50/50	282 (50)	101	50/50	283 (50)	102	50/50	283 (50)	102	50/50
8-7	290 (50)	50/50	295 (50)	102	50/50	297 (50)	102	50/50	297 (50)	102	50/50
9-7	300 (50)	50/50	306 (50)	102	50/50	307 (50)	102	50/50	307 (50)	102	50/50
10-7	309 (50)	50/50	315 (50)	102	50/50	316 (50)	102	50/50	315 (50)	102	50/50
11-7	316 (50)	50/50	322 (50)	102	50/50	323 (50)	102	50/50	323 (50)	102	50/50
12-7	324 (50)	50/50	328 (50)	101	50/50	330 (50)	102	50/50	329 (50)	102	50/50
13-7	329 (50)	50/50	334 (50)	102	50/50	336 (50)	102	50/50	335 (50)	102	50/50
14-7	335 (50)	50/50	339 (50)	101	50/50	341 (50)	102	50/50	341 (50)	102	50/50
18-7	353 (50)	50/50	358 (50)	101	50/50	361 (50)	102	50/50	359 (50)	102	50/50
22-7	366 (50)	50/50	373 (50)	102	50/50	374 (50)	102	50/50	372 (50)	102	50/50
26-7	380 (49)	49/50	386 (50)	102	50/50	390 (50)	103	50/50	387 (50)	102	50/50
30-7	389 (49)	49/50	396 (50)	102	50/50	399 (50)	103	50/50	396 (50)	102	50/50
34-7	399 (49)	49/50	407 (50)	102	50/50	409 (50)	103	50/50	403 (50)	101	50/50
38-7	408 (49)	49/50	416 (50)	102	50/50	419 (50)	103	50/50	413 (50)	101	50/50
42-7	413 (49)	49/50	424 (50)	103	50/50	426 (50)	103	50/50	419 (50)	101	50/50
46-7	419 (49)	49/50	430 (50)	103	50/50	431 (50)	103	50/50	424 (50)	101	50/50
50-7	423 (48)	48/50	435 (50)	103	50/50	434 (50)	103	50/50	430 (48)	102	48/50
54-7	429 (48)	48/50	440 (50)	103	50/50	439 (50)	102	50/50	435 (48)	101	48/50
58-7	434 (48)	48/50	443 (50)	102	50/50	441 (50)	102	50/50	435 (48)	100	48/50
62-7	437 (48)	48/50	447 (50)	102	50/50	443 (50)	101	50/50	440 (48)	101	48/50
66-7	440 (47)	47/50	448 (50)	102	50/50	446 (50)	101	50/50	442 (48)	100	48/50
70-7	442 (47)	47/50	450 (50)	102	50/50	447 (50)	101	50/50	443 (48)	100	48/50
74-7	442 (46)	46/50	454 (50)	103	50/50	446 (50)	101	50/50	441 (48)	100	48/50
78-7	444 (44)	44/50	443 (49)	100	49/50	443 (50)	100	50/50	439 (47)	99	47/50
82-7	442 (44)	44/50	449 (47)	102	47/50	439 (49)	99	49/50	436 (46)	99	46/50
86-7	439 (44)	44/50	448 (46)	102	46/50	435 (49)	99	49/50	432 (46)	98	46/50
90-7	435 (41)	41/50	443 (45)	102	45/50	430 (48)	99	48/50	428 (46)	98	46/50
94-7	435 (39)	39/50	437 (44)	100	44/50	422 (47)	97	47/50	422 (45)	97	45/50
98-7	431 (38)	38/50	426 (44)	99	44/50	412 (44)	96	44/50	412 (44)	96	44/50
102-7	417 (36)	36/50	413 (42)	99	42/50	401 (41)	96	41/50	402 (42)	96	42/50
104-7	420 (33)	33/50	407 (42)	97	42/50	403 (38)	96	38/50	394 (42)	94	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. : 0610
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>	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. Wt.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0-0	98 (50)	50/50	98 (50)	100	50/50	98 (50)	100	50/50	98 (50)	100	50/50
1-7	111 (50)	50/50	111 (50)	100	50/50	112 (50)	101	50/50	110 (50)	99	50/50
2-7	122 (50)	50/50	123 (50)	101	50/50	125 (50)	102	50/50	124 (50)	102	50/50
3-7	132 (50)	50/50	134 (50)	102	50/50	135 (50)	102	50/50	136 (50)	103	50/50
4-7	141 (50)	50/50	142 (50)	101	50/50	143 (50)	101	50/50	144 (50)	102	50/50
5-7	146 (50)	50/50	148 (50)	101	50/50	150 (50)	103	50/50	151 (50)	103	50/50
6-7	153 (50)	50/50	155 (50)	101	50/50	156 (50)	102	50/50	157 (50)	103	50/50
7-7	158 (50)	50/50	160 (50)	101	50/50	161 (50)	102	50/50	162 (50)	103	50/50
8-7	161 (50)	50/50	165 (50)	102	50/50	166 (50)	103	50/50	167 (50)	104	50/50
9-7	166 (50)	50/50	170 (50)	102	50/50	170 (50)	102	50/50	171 (50)	103	50/50
10-7	169 (50)	50/50	174 (50)	103	50/50	175 (50)	104	50/50	175 (50)	104	50/50
11-7	171 (50)	50/50	178 (50)	104	50/50	178 (50)	104	50/50	177 (50)	104	50/50
12-7	175 (50)	50/50	180 (50)	103	50/50	180 (50)	103	50/50	180 (50)	103	50/50
13-7	177 (50)	50/50	183 (50)	103	50/50	183 (50)	103	50/50	182 (50)	103	50/50
14-7	178 (50)	50/50	185 (50)	104	50/50	185 (50)	104	50/50	184 (50)	103	50/50
18-7	186 (50)	50/50	193 (50)	104	50/50	193 (50)	104	50/50	190 (50)	102	50/50
22-7	192 (50)	50/50	200 (50)	104	50/50	198 (50)	103	50/50	196 (50)	102	50/50
26-7	197 (50)	50/50	203 (50)	103	50/50	204 (50)	104	50/50	201 (50)	102	50/50
30-7	202 (50)	50/50	208 (50)	103	50/50	208 (50)	103	50/50	205 (50)	101	50/50
34-7	208 (50)	50/50	214 (50)	103	50/50	213 (50)	102	50/50	208 (50)	100	50/50
38-7	212 (50)	50/50	219 (50)	103	50/50	218 (50)	103	50/50	213 (50)	100	50/50
42-7	215 (50)	50/50	225 (50)	105	50/50	223 (50)	104	50/50	218 (50)	101	50/50
46-7	219 (50)	50/50	228 (50)	104	50/50	226 (50)	103	50/50	220 (50)	100	50/50
50-7	222 (50)	50/50	233 (50)	105	50/50	230 (50)	104	50/50	223 (50)	100	50/50
54-7	227 (50)	50/50	238 (50)	105	50/50	235 (50)	104	50/50	227 (50)	100	50/50
58-7	234 (50)	50/50	244 (50)	104	50/50	239 (50)	102	50/50	231 (50)	99	50/50
62-7	240 (50)	50/50	250 (50)	104	50/50	245 (50)	102	50/50	236 (50)	98	50/50
66-7	246 (50)	50/50	255 (50)	104	50/50	250 (50)	102	50/50	239 (50)	97	50/50
70-7	252 (49)	49/50	259 (50)	103	50/50	255 (50)	101	50/50	243 (50)	96	50/50
74-7	257 (48)	48/50	262 (50)	102	50/50	260 (50)	101	50/50	245 (48)	95	48/50
78-7	261 (47)	47/50	270 (49)	103	49/50	267 (50)	102	50/50	248 (47)	95	47/50
82-7	266 (46)	46/50	275 (49)	103	49/50	269 (49)	101	49/50	249 (46)	94	46/50
86-7	274 (43)	43/50	279 (48)	102	48/50	273 (49)	100	49/50	252 (46)	92	46/50
90-7	280 (43)	43/50	283 (46)	101	46/50	276 (47)	99	47/50	255 (45)	91	45/50
94-7	279 (41)	41/50	293 (42)	105	42/50	277 (47)	99	47/50	257 (45)	92	45/50
98-7	278 (38)	38/50	290 (38)	104	38/50	280 (44)	101	44/50	256 (45)	92	45/50
102-7	271 (37)	37/50	289 (37)	107	37/50	279 (44)	103	44/50	254 (45)	94	45/50
104-7	275 (34)	34/50	289 (35)	105	35/50	278 (43)	101	43/50	253 (44)	92	44/50

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

TABLE D3

BODY WEIGHT CHANGES : MALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	125± 5	153± 8	183± 10	209± 10	232± 11	248± 12	264± 13
1000 ppm	125± 5	155± 8	187± 9*	214± 9*	236± 10	252± 11	269± 11
2000 ppm	125± 5	156± 7	189± 8**	216± 8**	237± 9	254± 10*	269± 11
4000 ppm	125± 5	153± 6	186± 8	214± 9*	235± 10	253± 10	268± 12

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

(HAN260)

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STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	278± 13	290± 14	300± 15	309± 16	316± 17	324± 16	329± 16
1000 ppm	282± 12	295± 13	306± 13	315± 14	322± 15	328± 16	334± 17
2000 ppm	283± 11	297± 11*	307± 11*	316± 12*	323± 11	330± 12	336± 12
4000 ppm	283± 13	297± 13*	307± 14*	315± 15	323± 16	329± 16	335± 16

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	335± 17	353± 19	366± 20	380± 21	389± 21	399± 23	408± 25
1000 ppm	339± 17	358± 18	373± 19	386± 21	396± 23	407± 23	416± 24
2000 ppm	341± 12	361± 13	374± 14	390± 15	399± 15	409± 16	419± 17
4000 ppm	341± 16	359± 19	372± 20	387± 22	396± 24	403± 25	413± 27

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	413± 25	419± 28	423± 26	429± 27	434± 28	437± 29	440± 30
1000 ppm	424± 24	430± 25	435± 25	440± 24	443± 26	447± 28	448± 28
2000 ppm	426± 16*	431± 18	434± 21	439± 21	441± 22	443± 22	446± 23
4000 ppm	419± 29	424± 32	430± 26	435± 27	435± 27	440± 27	442± 29

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	442± 30	442± 31	444± 30	442± 29	439± 29	435± 37	435± 34
1000 ppm	450± 29	454± 54	443± 41	449± 27	448± 26	443± 26	437± 26
2000 ppm	447± 24	446± 25	443± 29	439± 28	435± 32	430± 39	422± 46
4000 ppm	443± 26	441± 25	439± 25	436± 24	432± 24	428± 25	422± 27

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

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BAIS 4

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	431± 33	417± 46	420± 34
1000 ppm	426± 29	413± 30	407± 34
2000 ppm	412± 43	401± 45	403± 41
4000 ppm	412± 27**	402± 28*	394± 31**

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

TABLE D4

BODY WEIGHT CHANGES : FEMALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 0-0	1-7	2-7	3-7	4-7	5-7	6-7
Control	98± 3	111± 5	122± 4	132± 5	141± 6	146± 7	153± 8
1000 ppm	98± 3	111± 4	123± 5	134± 7	142± 8	148± 8	155± 9
2000 ppm	98± 3	112± 5	125± 7*	135± 8*	143± 9	150± 10	156± 10
4000 ppm	98± 3	110± 5	124± 6*	136± 6**	144± 7	151± 7*	157± 8

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

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 7-7	8-7	9-7	10-7	11-7	12-7	13-7
Control	158± 8	161± 10	166± 10	169± 11	171± 12	175± 12	177± 12
1000 ppm	160± 9	165± 10	170± 11	174± 11	178± 11*	180± 12	183± 12*
2000 ppm	161± 12	166± 12	170± 13*	175± 14*	178± 14*	180± 15	183± 14
4000 ppm	162± 8	167± 8*	171± 9*	175± 9*	177± 9*	180± 9	182± 9

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 14-7	18-7	22-7	26-7	30-7	34-7	38-7
Control	178± 13	186± 13	192± 14	197± 13	202± 14	208± 15	212± 15
1000 ppm	185± 13**	193± 13**	200± 14*	203± 13	208± 14	214± 14	219± 15
2000 ppm	185± 15*	193± 15*	198± 16	204± 17	208± 17	213± 18	218± 18
4000 ppm	184± 9*	190± 10	196± 11	201± 11	205± 11	208± 12	213± 11

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

(HAN260)

BAIS 4

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 42-7	46-7	50-7	54-7	58-7	62-7	66-7
Control	215± 17	219± 18	222± 18	227± 19	234± 21	240± 22	246± 24
1000 ppm	225± 15**	228± 17**	233± 17**	238± 18**	244± 19*	250± 20*	255± 21
2000 ppm	223± 19	226± 20	230± 20	235± 22	239± 23	245± 24	250± 25
4000 ppm	218± 12	220± 13	223± 14	227± 15	231± 15	236± 17	239± 18

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

(HAN260)

BAIS 4

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 70-7	74-7	78-7	82-7	86-7	90-7	94-7
Control	252± 27	257± 27	261± 24	266± 26	274± 24	280± 25	279± 25
1000 ppm	259± 23	262± 28	270± 21	275± 24	279± 25	283± 32	293± 44
2000 ppm	255± 27	260± 27	267± 29	269± 28	273± 28	276± 29	277± 31
4000 ppm	243± 19	245± 19**	248± 19**	249± 19**	252± 20**	255± 18**	257± 19**

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

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day 98-7	102-7	104-7
Control	278± 27	271± 34	275± 31
1000 ppm	290± 23	289± 25*	289± 26
2000 ppm	280± 28	279± 28	278± 28
4000 ppm	256± 20**	254± 25*	253± 25**

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

TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

STUDY NO. : 0610
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>	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. FC.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1-7	15.4 (50)	50/50	15.4 (50)	100	50/50	15.1 (50)	98	50/50	14.8 (50)	96	50/50
2-7	16.3 (50)	50/50	16.5 (50)	101	50/50	16.3 (50)	100	50/50	15.9 (50)	98	50/50
3-7	17.1 (50)	50/50	17.3 (50)	101	50/50	17.5 (50)	102	50/50	17.3 (50)	101	50/50
4-7	16.9 (50)	50/50	16.8 (50)	99	50/50	16.7 (50)	99	50/50	16.3 (50)	96	50/50
5-7	16.7 (50)	50/50	16.5 (50)	99	50/50	16.3 (50)	98	50/50	16.4 (50)	98	50/50
6-7	17.2 (50)	50/50	17.0 (50)	99	50/50	17.0 (50)	99	50/50	17.2 (50)	100	50/50
7-7	16.6 (50)	50/50	16.8 (50)	101	50/50	16.6 (50)	100	50/50	16.9 (50)	102	50/50
8-7	17.0 (49)	50/50	17.2 (50)	101	50/50	17.0 (50)	100	50/50	17.0 (50)	100	50/50
9-7	16.6 (50)	50/50	16.9 (50)	102	50/50	16.7 (50)	101	50/50	16.6 (50)	100	50/50
10-7	16.6 (50)	50/50	17.0 (50)	102	50/50	16.6 (50)	100	50/50	16.5 (50)	99	50/50
11-7	16.6 (50)	50/50	16.7 (50)	101	50/50	16.4 (50)	99	50/50	16.3 (50)	98	50/50
12-7	16.7 (50)	50/50	16.8 (50)	101	50/50	16.5 (50)	99	50/50	16.5 (50)	99	50/50
13-7	16.5 (50)	50/50	16.7 (50)	101	50/50	16.1 (50)	98	50/50	16.3 (50)	99	50/50
14-7	16.4 (50)	50/50	16.6 (50)	101	50/50	16.4 (50)	100	50/50	16.5 (50)	101	50/50
18-7	16.3 (50)	50/50	16.4 (50)	101	50/50	16.3 (50)	100	50/50	16.1 (50)	99	50/50
22-7	16.2 (50)	50/50	16.6 (50)	102	50/50	16.3 (50)	101	50/50	16.1 (50)	99	50/50
26-7	16.7 (49)	49/50	17.0 (50)	102	50/50	16.8 (50)	101	50/50	16.6 (50)	99	50/50
30-7	16.9 (49)	49/50	17.1 (50)	101	50/50	16.6 (50)	98	50/50	16.5 (50)	98	50/50
34-7	17.2 (49)	49/50	17.3 (50)	101	50/50	17.0 (50)	99	50/50	16.1 (50)	94	50/50
38-7	17.0 (49)	49/50	17.3 (50)	102	50/50	17.1 (50)	101	50/50	16.7 (50)	98	50/50
42-7	17.2 (49)	49/50	17.4 (50)	101	50/50	17.1 (50)	99	50/50	16.7 (50)	97	50/50
46-7	17.5 (49)	49/50	17.7 (50)	101	50/50	17.2 (50)	98	50/50	16.9 (50)	97	50/50
50-7	17.3 (48)	48/50	17.5 (50)	101	50/50	16.7 (50)	97	50/50	16.6 (48)	96	48/50
54-7	17.1 (48)	48/50	17.4 (50)	102	50/50	17.1 (50)	100	50/50	16.7 (48)	98	48/50
58-7	17.1 (48)	48/50	17.3 (50)	101	50/50	16.8 (50)	98	50/50	16.5 (48)	96	48/50
62-7	17.2 (48)	48/50	17.2 (50)	100	50/50	16.9 (50)	98	50/50	16.4 (48)	95	48/50
66-7	17.2 (47)	47/50	17.2 (50)	100	50/50	17.1 (50)	99	50/50	16.5 (48)	96	48/50
70-7	17.1 (47)	47/50	17.2 (50)	101	50/50	17.1 (50)	100	50/50	16.8 (48)	98	48/50
74-7	17.3 (46)	46/50	17.2 (50)	99	50/50	16.9 (50)	98	50/50	16.6 (48)	96	48/50
78-7	17.0 (44)	44/50	16.7 (49)	98	49/50	16.7 (50)	98	50/50	16.4 (47)	96	47/50
82-7	17.0 (44)	44/50	17.0 (47)	100	47/50	16.6 (49)	98	49/50	16.2 (46)	95	46/50
86-7	17.1 (44)	44/50	17.2 (46)	101	46/50	16.6 (49)	97	49/50	16.4 (46)	96	46/50
90-7	17.0 (41)	41/50	17.3 (45)	102	45/50	16.6 (48)	98	48/50	16.4 (46)	96	46/50
94-7	17.2 (39)	39/50	17.0 (44)	99	44/50	16.1 (47)	94	47/50	15.9 (45)	92	45/50
98-7	17.0 (38)	38/50	16.5 (44)	97	44/50	15.7 (44)	92	44/50	16.2 (44)	95	44/50
102-7	15.9 (36)	36/50	16.6 (42)	104	42/50	16.0 (41)	101	41/50	16.6 (42)	104	42/50
104-7	17.2 (33)	33/50	16.8 (42)	98	42/50	16.8 (38)	98	38/50	16.7 (42)	97	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. : 0610
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>	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	2000 ppm Av. FC.	2000 ppm % of cont. <50>	2000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1-7	11.0 (50)	50/50	11.0 (50)	100	50/50	11.2 (50)	102	50/50	10.9 (50)	99	50/50
2-7	11.1 (50)	50/50	11.3 (50)	102	50/50	11.1 (50)	100	50/50	11.0 (50)	99	50/50
3-7	11.3 (50)	50/50	11.4 (50)	101	50/50	11.5 (50)	102	50/50	11.4 (50)	101	50/50
4-7	11.0 (50)	50/50	11.0 (50)	100	50/50	10.8 (50)	98	50/50	10.5 (50)	95	50/50
5-7	10.7 (50)	50/50	10.9 (50)	102	50/50	10.7 (50)	100	50/50	10.4 (50)	97	50/50
6-7	11.0 (50)	50/50	11.2 (50)	102	50/50	11.1 (50)	101	50/50	11.0 (50)	100	50/50
7-7	10.6 (50)	50/50	10.9 (50)	103	50/50	10.5 (50)	99	50/50	10.5 (50)	99	50/50
8-7	10.6 (50)	50/50	11.0 (50)	104	50/50	10.6 (50)	100	50/50	10.4 (50)	98	50/50
9-7	10.6 (50)	50/50	11.0 (50)	104	50/50	10.3 (50)	97	50/50	10.4 (50)	98	50/50
10-7	10.5 (50)	50/50	10.9 (50)	104	50/50	10.5 (50)	100	50/50	10.4 (50)	99	50/50
11-7	10.5 (50)	50/50	11.0 (50)	105	50/50	10.6 (50)	101	50/50	10.5 (50)	100	50/50
12-7	10.6 (50)	50/50	11.1 (50)	105	50/50	10.5 (50)	99	50/50	10.5 (50)	99	50/50
13-7	10.5 (50)	50/50	11.0 (50)	105	50/50	10.5 (50)	100	50/50	10.4 (50)	99	50/50
14-7	10.5 (50)	50/50	11.2 (50)	107	50/50	10.7 (50)	102	50/50	10.6 (50)	101	50/50
18-7	10.6 (50)	50/50	10.9 (50)	103	50/50	10.4 (50)	98	50/50	10.3 (50)	97	50/50
22-7	10.7 (50)	50/50	11.1 (50)	104	50/50	10.6 (50)	99	50/50	10.3 (50)	96	50/50
26-7	10.6 (50)	50/50	10.8 (50)	102	50/50	10.8 (50)	102	50/50	10.4 (50)	98	50/50
30-7	10.8 (50)	50/50	11.1 (50)	103	50/50	10.8 (50)	100	50/50	10.5 (50)	97	50/50
34-7	11.6 (50)	50/50	11.7 (50)	101	50/50	11.2 (50)	97	50/50	10.5 (50)	91	50/50
38-7	11.0 (50)	50/50	11.6 (50)	105	50/50	11.2 (50)	102	50/50	10.6 (50)	96	50/50
42-7	11.0 (50)	50/50	11.5 (50)	105	50/50	11.2 (50)	102	50/50	10.8 (50)	98	50/50
46-7	11.1 (50)	50/50	11.7 (50)	105	50/50	11.4 (50)	103	50/50	10.7 (50)	96	50/50
50-7	11.1 (50)	50/50	11.5 (50)	104	50/50	11.1 (50)	100	50/50	10.6 (50)	95	50/50
54-7	11.2 (50)	50/50	11.7 (50)	104	50/50	11.2 (50)	100	50/50	10.8 (50)	96	50/50
58-7	11.5 (50)	50/50	11.7 (50)	102	50/50	11.4 (50)	99	50/50	10.8 (50)	94	50/50
62-7	11.6 (50)	50/50	12.0 (50)	103	50/50	11.3 (50)	97	50/50	10.7 (50)	92	50/50
66-7	11.8 (50)	50/50	12.0 (50)	102	50/50	11.7 (50)	99	50/50	10.9 (50)	92	50/50
70-7	12.0 (49)	49/50	12.2 (50)	102	50/50	11.8 (50)	98	50/50	11.1 (50)	93	50/50
74-7	12.0 (48)	48/50	12.2 (50)	102	50/50	12.0 (50)	100	50/50	11.3 (48)	94	48/50
78-7	11.7 (47)	47/50	12.3 (49)	105	49/50	12.1 (50)	103	50/50	11.3 (47)	97	47/50
82-7	12.2 (46)	46/50	12.7 (49)	104	49/50	12.2 (49)	100	49/50	11.4 (46)	93	46/50
86-7	12.4 (43)	43/50	13.0 (48)	105	48/50	12.2 (49)	98	49/50	11.5 (46)	93	46/50
90-7	12.7 (43)	43/50	12.8 (46)	101	46/50	12.5 (47)	98	47/50	11.8 (45)	93	45/50
94-7	12.3 (41)	41/50	13.4 (40)	109	42/50	12.2 (47)	99	47/50	11.6 (45)	94	45/50
98-7	12.2 (38)	38/50	13.4 (38)	110	38/50	12.7 (44)	104	44/50	11.7 (45)	96	45/50
102-7	12.1 (37)	37/50	13.1 (37)	108	37/50	12.6 (44)	104	44/50	12.1 (45)	100	45/50
104-7	12.8 (34)	34/50	13.4 (35)	105	35/50	12.9 (43)	101	43/50	12.3 (44)	96	44/50

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

TABLE E3

FOOD CONSUMPTION CHANGES : MALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-7(7)	2-7(7)	3-7(7)	4-7(7)	5-7(7)	6-7(7)	7-7(7)
Control	15.4± 1.2	16.3± 1.5	17.1± 1.3	16.9± 1.0	16.7± 1.1	17.2± 1.1	16.6± 0.9
1000 ppm	15.4± 0.9	16.5± 1.2	17.3± 1.1	16.8± 1.0	16.5± 0.9	17.0± 0.9	16.8± 0.8
2000 ppm	15.1± 0.9	16.3± 0.8	17.5± 1.0	16.7± 0.9	16.3± 0.8	17.0± 0.9	16.6± 0.8
4000 ppm	14.8± 0.8**	15.9± 0.8	17.3± 1.0	16.3± 0.9**	16.4± 0.9	17.2± 0.9	16.9± 1.0

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

(HAN260)

BAIS 4

STUDY NO. : 0610
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	17.0± 1.1	16.6± 1.1	16.6± 1.1	16.6± 0.9	16.7± 0.8	16.5± 0.9	16.4± 0.9
1000 ppm	17.2± 0.9	16.9± 1.0	17.0± 1.1	16.7± 1.0	16.8± 1.0	16.7± 1.1	16.6± 1.0
2000 ppm	17.0± 0.9	16.7± 0.8	16.6± 0.8	16.4± 0.7	16.5± 0.7	16.1± 0.7*	16.4± 0.8
4000 ppm	17.0± 0.9	16.6± 1.0	16.5± 1.1	16.3± 1.1	16.5± 1.1	16.3± 1.1	16.5± 1.1

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

(HAN260)

BAIS 4

STUDY NO. : 0610
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	16.3± 1.0	16.2± 0.9	16.7± 1.0	16.9± 0.9	17.2± 1.1	17.0± 1.2	17.2± 1.1
1000 ppm	16.4± 1.0	16.6± 1.1	17.0± 1.1	17.1± 1.2	17.3± 1.0	17.3± 1.1	17.4± 1.0
2000 ppm	16.3± 0.9	16.3± 0.9	16.8± 0.8	16.6± 0.9	17.0± 0.9	17.1± 0.9	17.1± 1.0
4000 ppm	16.1± 1.1	16.1± 1.1	16.6± 1.2	16.5± 1.3	16.1± 1.1**	16.7± 1.3	16.7± 1.3*

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 46-7(7)	50-7(7)	54-7(7)	58-7(7)	62-7(7)	66-7(7)	70-7(7)
Control	17.5± 1.0	17.3± 1.1	17.1± 1.1	17.1± 1.1	17.2± 1.1	17.2± 1.2	17.1± 1.2
1000 ppm	17.7± 1.2	17.5± 1.0	17.4± 0.9	17.3± 1.0	17.2± 1.5	17.2± 1.0	17.2± 1.2
2000 ppm	17.2± 0.9	16.7± 1.2*	17.1± 0.7	16.8± 0.9	16.9± 0.9	17.1± 0.9	17.1± 0.9
4000 ppm	16.9± 1.3*	16.6± 1.1**	16.7± 1.2	16.5± 1.2*	16.4± 1.1**	16.5± 1.5**	16.8± 1.0

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

(HAN260)

STUDY NO. : 0610
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	17.3± 1.0	17.0± 1.1	17.0± 1.1	17.1± 1.2	17.0± 1.6	17.2± 1.4	17.0± 1.2
1000 ppm	17.2± 1.5	16.7± 2.1	17.0± 1.2	17.2± 1.1	17.3± 1.1	17.0± 1.3	16.5± 2.1
2000 ppm	16.9± 1.1	16.7± 1.5	16.6± 1.2	16.6± 1.2	16.6± 1.7	16.1± 2.3*	15.7± 3.2*
4000 ppm	16.6± 1.0**	16.4± 1.2	16.2± 0.9**	16.4± 1.2*	16.4± 1.2*	15.9± 1.4**	16.2± 1.8*

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

STUDY NO. : 0610
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	15.9± 3.4	17.2± 1.4
1000 ppm	16.6± 1.7	16.8± 2.1
2000 ppm	16.0± 2.9	16.8± 1.8
4000 ppm	16.6± 1.6	16.7± 2.0

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

(HAN260)

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 1-7(7)	2-7(7)	3-7(7)	4-7(7)	5-7(7)	6-7(7)	7-7(7)
Control	11.0± 0.9	11.1± 0.7	11.3± 0.7	11.0± 0.7	10.7± 0.8	11.0± 0.9	10.6± 0.8
1000 ppm	11.0± 0.6	11.3± 0.8	11.4± 0.9	11.0± 0.8	10.9± 0.9	11.2± 1.0	10.9± 0.9
2000 ppm	11.2± 0.6	11.1± 0.9	11.5± 1.0	10.8± 1.2	10.7± 0.9	11.1± 0.9	10.5± 0.9
4000 ppm	10.9± 1.0	11.0± 0.8	11.4± 0.8	10.5± 0.7*	10.4± 0.6	11.0± 0.8	10.5± 0.9

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 8-7(7)	9-7(7)	10-7(7)	11-7(7)	12-7(7)	13-7(7)	14-7(7)
Control	10.6± 1.0	10.6± 1.1	10.5± 0.9	10.5± 1.0	10.6± 1.0	10.5± 1.0	10.5± 1.0
1000 ppm	11.0± 1.0	11.0± 1.3	10.9± 1.1	11.0± 1.1	11.1± 1.0*	11.0± 1.1*	11.2± 1.4**
2000 ppm	10.6± 1.2	10.3± 1.1	10.5± 1.2	10.6± 1.3	10.5± 1.1	10.5± 0.9	10.7± 0.9
4000 ppm	10.4± 0.8	10.4± 1.0	10.4± 0.9	10.5± 0.8	10.5± 0.7	10.4± 0.8	10.6± 1.0

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

(HAN260)

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week-day(effective) 18-7(7)	22-7(7)	26-7(7)	30-7(7)	34-7(7)	38-7(7)	42-7(7)
Control	10.6± 0.9	10.7± 1.1	10.6± 0.8	10.8± 0.9	11.6± 1.1	11.0± 0.8	11.0± 0.9
1000 ppm	10.9± 1.0	11.1± 1.1	10.8± 0.8	11.1± 0.7	11.7± 0.9	11.6± 1.0*	11.5± 0.9*
2000 ppm	10.4± 1.1	10.6± 0.9	10.8± 0.9	10.8± 0.9	11.2± 1.0	11.2± 1.0	11.2± 1.0
4000 ppm	10.3± 0.8	10.3± 0.8	10.4± 0.8	10.5± 0.8	10.5± 0.8**	10.6± 0.8	10.8± 0.9

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

(HAN260)

STUDY NO. : 0610
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	11.1± 0.9	11.1± 0.8	11.2± 1.1	11.5± 0.9	11.6± 0.9	11.8± 1.3	12.0± 1.4
1000 ppm	11.7± 1.0**	11.5± 0.8	11.7± 0.9*	11.7± 1.1	12.0± 1.0	12.0± 1.4	12.2± 1.1
2000 ppm	11.4± 1.1	11.1± 1.1	11.2± 1.0	11.4± 1.2	11.3± 1.0	11.7± 1.2	11.8± 1.2
4000 ppm	10.7± 0.8	10.6± 0.8**	10.8± 0.8	10.8± 0.9**	10.7± 1.2**	10.9± 0.9**	11.1± 1.7**

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

(HAN260)

STUDY NO. : 0610
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	12.0± 1.3	11.7± 0.8	12.2± 1.4	12.4± 1.0	12.7± 1.2	12.3± 1.9	12.2± 1.8
1000 ppm	12.2± 1.2	12.3± 1.1*	12.7± 1.4	13.0± 1.4	12.8± 2.1	13.4± 1.9	13.4± 1.6**
2000 ppm	12.0± 1.2	12.1± 1.2	12.2± 1.2	12.2± 2.0	12.5± 1.2	12.2± 1.7	12.7± 1.2
4000 ppm	11.3± 1.0*	11.3± 1.0	11.4± 0.9**	11.5± 0.8**	11.8± 0.9**	11.6± 0.9**	11.7± 1.1**

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

(HAN260)

BAIS 4

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration 102-7(7)	week-day(effective) 104-7(7)
Control	12.1± 2.2	12.8± 1.3
1000 ppm	13.1± 1.6	13.4± 1.6
2000 ppm	12.6± 1.6	12.9± 1.3
4000 ppm	12.1± 1.4	12.3± 1.8

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

(HAN260)

TABLE F1

HEMATOLOGY : MALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV fℓ	MCH pg	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	33	8.46± 1.51	14.5± 2.8	43.0± 7.1	51.0± 2.1	17.0± 1.0	33.4± 1.6	1017± 290
1000 ppm	42	8.09± 2.05	13.8± 3.6	41.2± 9.6	52.1± 8.5	17.2± 2.0	33.1± 2.2	1091± 478
2000 ppm	38	8.16± 2.03	13.8± 3.5	41.3± 9.4	51.0± 2.9	17.0± 1.1	33.3± 1.4	1029± 325
4000 ppm	42	8.06± 2.08	13.8± 3.8	41.2± 9.7	52.3± 8.4	17.1± 1.8	33.0± 2.9	1031± 393

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

(HCL070)

BAIS 4

STUDY NO. : 0610
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	33	4.3± 3.6
1000 ppm	42	4.3± 3.8
2000 ppm	38	5.2± 4.5
4000 ppm	42	5.3± 6.0

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

(HCL070)

BAIS 4

STUDY NO. : 0610
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 (%) N-BAND	N-SEG	EOSINO	BASO	MONO	LYMPHO	OTHER
Control	33	7.07± 2.23	1± 1	49± 8	2± 1	0± 0	6± 2	42± 8	1± 2
1000 ppm	42	7.97± 9.13	1± 1	48± 12	2± 1	0± 0	6± 2	40± 10	4± 12
2000 ppm	38	10.52± 18.47	1± 1	48± 11	2± 1	0± 0	6± 2	37± 10	6± 18
4000 ppm	42	13.37± 40.73	1± 1	43± 10*	2± 1	0± 0	6± 3	44± 10	5± 17

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

(HCL070)

BAIS 4

TABLE F2

HEMATOLOGY : FEMALE

STUDY NO. : 0610
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	34	8.14± 1.24	15.2± 2.1	43.2± 5.0	53.7± 5.0	18.8± 1.7	35.0± 2.3	720± 182
1000 ppm	35	8.18± 0.57	15.1± 1.0	43.3± 2.4	53.0± 1.5	18.5± 0.6	35.0± 0.8	730± 120
2000 ppm	43	8.34± 0.72	15.4± 1.2	43.9± 3.0	52.8± 1.9	18.6± 0.8	35.1± 0.7	744± 118
4000 ppm	43	8.16± 1.10	15.0± 2.2	43.2± 5.0	53.3± 4.1	18.4± 1.2	34.6± 1.8	746± 202

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

(HCL070)

BAIS 4

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RETICULOCYTE %
Control	34	3.8± 4.8
1000 ppm	35	3.0± 1.3
2000 ppm	43	2.8± 1.7
4000 ppm	43	3.9± 5.2

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

(HCL070)

BAIS 4

STUDY NO. : 0610
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 (%) N-BAND		N-SEG		EOSINO		BASO		MONO		LYMPHO		OTHER	
Control	34	4.59±	4.38	1±	1	39±	12	2±	1	0±	0	5±	2	48±	14	6±	19
1000 ppm	35	3.79±	1.87	1±	1	42±	9	2±	1	0±	0	6±	2	50±	9	0±	1
2000 ppm	43	3.64±	1.58	1±	1	39±	8	2±	1	0±	0	6±	2	53±	8	1±	1
4000 ppm	43	4.99±	5.35	0±	1	40±	12	2±	1	0±	0	6±	2	50±	14	3±	14

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

(HCL070)

BAIS 4

TABLE G1

BIOCHEMISTRY : MALE

STUDY NO. : 0610
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	33	6.7±	0.3	2.8±	0.3	0.7±	0.1	0.15±	0.02	163±	20	194±	50	132±	77
1000 ppm	42	6.6±	0.4	2.7±	0.2	0.7±	0.1	0.35±	1.30	148±	30	212±	71	137±	107
2000 ppm	38	6.6±	0.4	2.7±	0.3	0.7±	0.1	0.18±	0.13	157±	24	202±	63	159±	109
4000 ppm	42	6.6±	0.4	2.6±	0.3**	0.7±	0.1	0.59±	2.79	156±	21	258±	127*	229±	154*

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

(HCL074)

BAIS 4

STUDY NO. : 0610
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	33	266± 60	73± 19	32± 8	163± 39	184± 33	6± 3	104± 22
1000 ppm	42	299± 109	138± 301	52± 95	380± 1034	198± 132	7± 4	126± 105
2000 ppm	38	279± 83	97± 89	38± 21	194± 215	196± 67	9± 4*	121± 44
4000 ppm	42	341± 126**	149± 427	58± 123	443± 1747	207± 149	11± 7**	141± 124

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

(HCL074)

BAIS 4

STUDY NO. : 0610
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	33	20.7± 3.2	0.6± 0.1	143± 1	3.7± 0.3	106± 2	10.7± 0.3	4.2± 0.5
1000 ppm	42	28.2± 16.2*	0.7± 0.2	142± 2	3.7± 0.3	105± 2	10.8± 0.5	4.5± 1.1
2000 ppm	38	23.1± 5.5	0.6± 0.1	142± 1	3.6± 0.3	105± 2	10.8± 0.4	4.3± 0.6
4000 ppm	42	26.1± 8.2**	0.7± 0.2	142± 1	3.7± 0.3	105± 2	11.0± 0.6	4.5± 1.0

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

(HCL074)

BAIS 4

TABLE G2

BIOCHEMISTRY : FEMALE

STUDY NO. : 0610
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	34	6.9± 0.4	3.4± 0.3	1.0± 0.1	0.16± 0.18	152± 13	154± 36	95± 65
1000 ppm	35	6.9± 0.4	3.4± 0.3	1.0± 0.1	0.13± 0.02	149± 13	173± 55	128± 86
2000 ppm	43	6.9± 0.4	3.3± 0.4	0.9± 0.2	0.13± 0.02	148± 18	187± 101	134± 207
4000 ppm	43	6.8± 0.5	3.3± 0.4	0.9± 0.1	0.14± 0.05	145± 26	175± 77	112± 196

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

(HCL074)

BAIS 4

STUDY NO. : 0610
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	34	264± 52	131± 154	55± 27	207± 148	130± 75	3± 1	92± 27
1000 ppm	35	295± 86	124± 65	56± 25	190± 56	114± 38	3± 2	90± 18
2000 ppm	43	308± 141	109± 63	47± 18	192± 77	132± 118	3± 2	91± 21
4000 ppm	43	291± 117	141± 122	61± 46	232± 138	139± 102	3± 2	125± 184

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

(HCL074)

BAIS 4

STUDY NO. : 0610
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	34	18.0± 2.4	0.5± 0.1	142± 1	3.3± 0.3	103± 3	10.6± 0.3	3.8± 0.7
1000 ppm	35	18.2± 2.3	0.5± 0.0	141± 2	3.5± 0.4	103± 2	10.7± 0.4	3.7± 0.8
2000 ppm	43	18.7± 1.8	0.5± 0.0	141± 1	3.5± 0.3	103± 2	10.7± 0.5	4.0± 0.6
4000 ppm	43	19.6± 4.1	0.5± 0.1	141± 2	3.6± 0.3**	104± 2	10.6± 0.5	4.2± 1.3

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

(HCL074)

BAIS 4

TABLE H1

URINALYSIS : MALE

STUDY NO. : 0610
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	35	0	1	0	6	11	8	9		0	0	0	1	27	7		35	0	0	0	0	0		33	2	0	0	0	0		34	0	0	1	
1000 ppm	42	0	0	1	12	15	7	7		0	0	1	3	33	5		42	0	0	0	0	0		41	0	1	0	0	0		42	0	0	0	
2000 ppm	41	0	3	0	4	16	6	12		0	0	0	2	33	6		41	0	0	0	0	0		40	0	0	1	0	0		41	0	0	0	
4000 ppm	42	0	1	4	4	12	8	13		0	0	0	0	32	10		42	0	0	0	0	0		41	0	1	0	0	0		42	0	0	0	

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

(HCL101)

BAIS 4

STUDY NO. : 0610 URINALYSIS
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	35	34	0	1	0	0		35	0	0	0	0	
1000 ppm	42	41	0	0	1	0		42	0	0	0	0	
2000 ppm	41	41	0	0	0	0		41	0	0	0	0	
4000 ppm	42	42	0	0	0	0		42	0	0	0	0	

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

(HCL101)

TABLE H2

URINALYSIS : FEMALE

STUDY NO. : 0610
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	36	0	0	2	2	8	20	4		0	0	2	8	12	14		36	0	0	0	0	0		19	17	0	0	0	0		35	0	0	1	
1000 ppm	37	0	0	2	4	7	20	4		0	1	4	4	21	7		37	0	0	0	0	0		26	10	1	0	0	0		37	0	0	0	
2000 ppm	44	0	0	1	1	8	25	9		0	0	2	9	17	16		44	0	0	0	0	0		28	16	0	0	0	0		44	0	0	0	
4000 ppm	45	0	0	1	2	5	27	10		0	0	2	8	15	20		45	0	0	0	0	0		22	23	0	0	0	0		45	0	0	0	

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

(HCL101)

STUDY NO. : 0610
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	36	34	1	0	0	1		36	0	0	0	0	
1000 ppm	37	35	0	0	1	1		37	0	0	0	0	
2000 ppm	44	43	0	0	0	1		44	0	0	0	0	
4000 ppm	45	44	0	0	0	1		45	0	0	0	0	

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

(HCL101)

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

STUDY NO. : 0610
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	33	394± 34	0.080± 0.036	4.292± 1.454	1.225± 0.091	1.385± 0.079	2.774± 0.226
1000 ppm	42	379± 37	0.102± 0.185	3.793± 0.967	1.238± 0.173	1.422± 0.173	2.904± 0.476
2000 ppm	38	377± 39	0.075± 0.037	4.511± 1.177	1.190± 0.073	1.501± 0.230*	2.845± 0.282
4000 ppm	42	368± 33**	0.069± 0.009	5.362± 2.889	1.200± 0.110	1.500± 0.229**	3.087± 0.748**

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

(HCL040)

STUDY NO. : 0610
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	33	1.035±	0.219	11.452±	1.325	2.107±	0.047
1000 ppm	42	1.476±	1.965	11.920±	1.450	2.101±	0.048
2000 ppm	38	1.212±	0.406	11.993±	1.796	2.104±	0.049
4000 ppm	42	1.455±	1.529	12.577±	2.009	2.086±	0.037

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

(HCL040)

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

STUDY NO. : 0610
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	34	257± 30	0.071± 0.025	0.122± 0.023	0.875± 0.069	0.997± 0.227	1.836± 0.168
1000 ppm	35	272± 26	0.071± 0.022	0.120± 0.016	0.882± 0.062	0.968± 0.063	1.906± 0.159
2000 ppm	43	260± 26	0.101± 0.237	0.144± 0.115	0.862± 0.082	0.983± 0.080	1.873± 0.211
4000 ppm	43	238± 24**	0.075± 0.050	0.141± 0.079	0.841± 0.079	1.058± 0.389	1.856± 0.143

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

STUDY NO. : 0610
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	34	0.874±	1.613	6.976±	1.552	1.914±	0.046
1000 ppm	35	0.591±	0.250	7.350±	1.121	1.906±	0.040
2000 ppm	43	0.596±	0.238	7.038±	1.400	1.908±	0.040
4000 ppm	43	0.675±	0.478	6.982±	1.209	1.890±	0.035

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

(HCL040)

TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

STUDY NO. : 0610
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	33	394± 34	0.021± 0.011	1.108± 0.442	0.312± 0.025	0.353± 0.023	0.708± 0.070
1000 ppm	42	379± 37	0.027± 0.051	1.004± 0.254	0.330± 0.059	0.379± 0.071	0.782± 0.236
2000 ppm	38	377± 39	0.020± 0.010	1.202± 0.305	0.319± 0.041	0.404± 0.090**	0.764± 0.130*
4000 ppm	42	368± 33**	0.019± 0.004	1.433± 0.728**	0.328± 0.039	0.411± 0.083**	0.845± 0.218**

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

(HCL042)

STUDY NO. : 0610
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	33	0.263± 0.050	2.909± 0.234	0.539± 0.044
1000 ppm	42	0.408± 0.615	3.173± 0.522*	0.560± 0.063
2000 ppm	38	0.324± 0.107*	3.193± 0.459**	0.565± 0.073
4000 ppm	42	0.403± 0.466**	3.425± 0.525**	0.571± 0.056*

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

(HCL042)

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCr1Cr1j[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	34	257± 30	0.029± 0.019	0.048± 0.010	0.345± 0.051	0.394± 0.111	0.728± 0.150
1000 ppm	35	272± 26	0.026± 0.007	0.045± 0.008	0.327± 0.030	0.359± 0.036	0.706± 0.071
2000 ppm	43	260± 26	0.040± 0.099	0.056± 0.046	0.332± 0.024	0.380± 0.033	0.721± 0.052
4000 ppm	43	238± 24**	0.034± 0.037	0.059± 0.030**	0.356± 0.029**	0.450± 0.174**	0.788± 0.096**

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

(HCL042)

STUDY NO. : 0610
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	34	0.353± 0.693	2.755± 0.743	0.756± 0.100
1000 ppm	35	0.219± 0.091	2.719± 0.430	0.708± 0.065
2000 ppm	43	0.228± 0.083	2.697± 0.391	0.741± 0.078
4000 ppm	43	0.286± 0.204	2.950± 0.486**	0.805± 0.097**

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

TABLE L1

HISTOPATHOLOGICAL FINDINGS :

NON-NEOPLASTIC LESIONS : MALE

ALL ANIMALS

Organ	Findings	Group Name	Control				1000 ppm				2000 ppm				4000 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>			
	basal 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)
	fibrosis:focal		0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	sebaceous hyperplasia		1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	thrombus		0	1	0	0	2	0	0	0	0	0	0	0	1	2	0	0
			(0)	(2)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(0)
	eosinophilic change:olfactory epithelium		25	17	0	0	22	24	1	0	21	27	0	0 *	25	24	0	0 *
			(50)	(34)	(0)	(0)	(44)	(48)	(2)	(0)	(42)	(54)	(0)	(0)	(50)	(48)	(0)	(0)
	eosinophilic change:respiratory epithelium		19	0	0	0	18	0	0	0	29	1	0	0	30	3	0	0 **
			(38)	(0)	(0)	(0)	(36)	(0)	(0)	(0)	(58)	(2)	(0)	(0)	(60)	(6)	(0)	(0)
	inflammation:foreign body		15	1	0	0	15	1	0	0	13	1	0	0	8	1	0	0
			(30)	(2)	(0)	(0)	(30)	(2)	(0)	(0)	(26)	(2)	(0)	(0)	(16)	(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				1000 ppm				2000 ppm				4000 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>			
	inflammation:respiratory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	respiratory metaplasia:gland		9	0	0	0	8	0	0	0	12	0	0	0	13	1	0	0
			(18)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(24)	(0)	(0)	(0)	(26)	(2)	(0)	(0)
	squamous cell metaplasia:respiratory epithelium		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
larynx			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
trachea			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	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)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Respiratory system}																		
lung			<50>				<50>				<50>				<50>			
	edema		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammatory infiltration		0 (0)	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)
	bronchiolar-alveolar cell hyperplasia		4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)
	increased hematopoiesis		0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	3 (6)	3 (6)	0 (0)	0 (0)
	granulopoiesis:increased		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
lymph node			<50>				<50>				<50>				<50>			
	lymphadenitis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / Grade	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Hematopoietic system}																		
spleen			<50>				<50>				<50>				<50>			
	atrophy		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	congestion		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	1 (2)	3 (6)	0 (0)	0 (0)
	deposit of hemosiderin		3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)
	fibrosis		0 (0)	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)
	extramedullary hematopoiesis		0 (0)	3 (6)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 * (0)	4 (8)	4 (8)	0 (0)	0 (0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	myocardial fibrosis		15	0	0	0	16	0	0	0	19	0	0	0	15	0	0	0
			(30)	(0)	(0)	(0)	(32)	(0)	(0)	(0)	(38)	(0)	(0)	(0)	(30)	(0)	(0)	(0)
	subendocardial fibrosis		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)
artery/aort			<50>				<50>				<50>				<50>			
	mineralization		0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
tooth			<50>				<50>				<50>				<50>			
	cyst		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
tongue			<50>				<50>				<50>				<50>			
	squamous 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)
	arteritis		0	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	mineralization		0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)
	ulcer:forestomach		0	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		0	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	erosion:glandular stomach		2	0	0	0	1	0	0	0	3	0	0	0	6	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(12)	(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)
	hyperplasia:glandular stomach		0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
small intes			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	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)

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				1000 ppm				2000 ppm				4000 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}																		
large intes			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		3	0	0	0	8	0	0	0	7	0	0	0	2	0	0	0
			(6)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	necrosis:central		1	0	0	0	1	0	0	0	0	1	0	0	2	1	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(4)	(2)	(0)	(0)
	necrosis:focal		2	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	fatty change:peripheral		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)
	granulation		7	0	0	0	9	0	0	0	8	0	0	0	11	1	0	0
			(14)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(16)	(0)	(0)	(0)	(22)	(2)	(0)	(0)
	clear cell focus		5	0	0	0	10	0	0	0	7	0	0	0	9	1	0	0
			(10)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(18)	(2)	(0)	(0)
	acidophilic cell focus		1	0	0	0	1	0	0	0	0	0	0	0	4	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				1000 ppm				2000 ppm				4000 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>			
	basophilic cell focus		5	1	0	0	4	0	0	0	3	0	0	0	6	3	0	0
			(10)	(2)	(0)	(0)	(8)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(12)	(6)	(0)	(0)
	mixed cell focus		0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	spongiosis hepatis		2	0	0	0	0	0	0	0	1	1	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	bile duct hyperplasia		3	45	0	0	1	48	0	0	4	45	0	0	0	47	0	0
			(6)	(90)	(0)	(0)	(2)	(96)	(0)	(0)	(8)	(90)	(0)	(0)	(0)	(94)	(0)	(0)
	biliary cyst		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)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		22	1	0	0	27	1	0	0	19	2	0	0	19	5	1	0
			(44)	(2)	(0)	(0)	(54)	(2)	(0)	(0)	(38)	(4)	(0)	(0)	(38)	(10)	(2)	(0)
	inflammatory infiltration		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	arteritis		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 / Grade	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
pancreas			<50>				<50>				<50>				<50>			
	islet cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	deposit of hemosiderin		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)
	scar		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)
	chronic nephropathy		14 (28)	23 (46)	8 (16)	1 (2)	14 (28)	23 (46)	8 (16)	5 (10)	12 (24)	24 (48)	9 (18)	5 (10)	7 (14)	24 (48)	14 (28)	2 (4)
	tubular necrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:papilla		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	urothelial hyperplasia:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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 / Grade	Control				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	atypical tubule hyperplasia		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)
	dilated pelvis		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)
urin bladd			<50>				<50>				<50>				<50>			
	simple hyperplasia:transitional epithelium		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)	(4)	(0)	(0)
	papillary hyperplasia:transitional epithelium		0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia		6	1	0	0	6	5	0	0	5	2	0	0	6	2	0	0
			(12)	(2)	(0)	(0)	(12)	(10)	(0)	(0)	(10)	(4)	(0)	(0)	(12)	(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				1000 ppm 50				2000 ppm 50				4000 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>			
	Rathke pouch		4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<50>				<50>				<50>			
	ultimibranchial body remanet		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	C-cell hyperplasia		15 (30)	4 (8)	0 (0)	0 (0)	7 (14)	3 (6)	0 (0)	0 (0)	13 (26)	2 (4)	0 (0)	0 (0)	10 (20)	1 (2)	0 (0)	0 (0)
	focal follicular cell hyperplasia		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
parathyroid			<50>				<50>				<50>				<50>			
	hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
adrenal			<50>				<50>				<50>				<50>			
	hyperplasia:medulla		0 (0)	1 (2)	0 (0)	0 (0)	3 (6)	4 (8)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	focal fatty change:cortex		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	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				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Reproductive system}																		
testis		<50>																
	mineralization		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	arteritis		1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	interstitial cell hyperplasia		6 (12)	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
semin ves		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
prostate		<50>																
	inflammation		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	hyperplasia		7 (14)	0 (0)	0 (0)	0 (0)	13 (26)	0 (0)	0 (0)	0 (0)	9 (18)	3 (6)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)
{Special sense organs/appendage}																		
eye		<50>																
	squamous cell metaplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Special sense organs/appendage}																		
eye		<50>																
	cataract		2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	retinal atrophy		0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	1 (2)	6 (12)	0 (0)	0 (0)
	keratitis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mineralization:cornea		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)
nasolacr d		<50>																
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
{Musculoskeletal system}																		
bone		<50>																
	ostitis fibrosa		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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				1000 ppm 50				2000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Musculoskeletal system}																		
bone			<50>				<50>				<50>				<50>			
	osteosclerosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Body cavities}																		
peritoneum			<50>				<50>				<50>				<50>			
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	mesothelial hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

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				1000 ppm				2000 ppm				4000 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}																		
subcutis			<50>				<50>				<50>				<50>			
	epidermal cyst		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)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	thrombus		0	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		5	43	2	0	2	42	5	0	0	50	0	0 *	4	45	0	0
			(10)	(86)	(4)	(0)	(4)	(84)	(10)	(0)	(0)	(100)	(0)	(0)	(8)	(90)	(0)	(0)
	eosinophilic change:respiratory epithelium		42	2	0	0	49	0	0	0 *	49	1	0	0 *	49	0	0	0 *
			(84)	(4)	(0)	(0)	(98)	(0)	(0)	(0)	(98)	(2)	(0)	(0)	(98)	(0)	(0)	(0)
	inflammation:foreign body		1	1	0	0	3	0	0	0	2	0	0	0	5	0	0	0
			(2)	(2)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	inflammation:respiratory 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)
	respiratory metaplasia:olfactory epithelium		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)

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				1000 ppm				2000 ppm				4000 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		11	0	0	0	10	0	0	0	13	0	0	0	13	0	0	0
			(22)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(26)	(0)	(0)	(0)	(26)	(0)	(0)	(0)
	atrophy:olfactory epithelium		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
lung			<50>				<50>				<50>				<50>			
	mucocele		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)
	inflammatory infiltration		0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		0	0	0	0	2	0	0	0	3	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	granulation		4	0	0	0	2	0	0	0	2	0	0	0	6	1	0	0
			(8)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(12)	(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				1000 ppm				2000 ppm				4000 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>			
	increased hematopoiesis		2	1	0	0	5	0	0	0	1	0	0	0	2	1	0	0
			(4)	(2)	(0)	(0)	(10)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(4)	(2)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	congestion		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		23	2	0	0	19	1	0	0	20	3	0	0	20	4	0	0
			(46)	(4)	(0)	(0)	(38)	(2)	(0)	(0)	(40)	(6)	(0)	(0)	(40)	(8)	(0)	(0)
	fibrosis		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)
	extramedullary hematopoiesis		2	1	0	0	3	5	0	0	3	0	0	0	3	3	0	0
			(4)	(2)	(0)	(0)	(6)	(10)	(0)	(0)	(6)	(0)	(0)	(0)	(6)	(6)	(0)	(0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	myocardial fibrosis		8	0	0	0	11	0	0	0	7	0	0	0	6	0	0	0
			(16)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(14)	(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
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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				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Circulatory system}																		
artery/aort			<50>				<50>				<50>				<50>			
	arteritis		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Digestive system}																		
oral cavity			<50>				<50>				<50>				<50>			
	squamous cell hyperplasia		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)
	epidermal cyst		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)
tongue			<50>				<50>				<50>				<50>			
	arteritis		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
stomach			<50>				<50>				<50>				<50>			
	ulcer:forestomach		2	0	0	0	1	2	0	0	1	1	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(2)	(4)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:forestomach		2	1	0	0	1	2	0	0	3	0	0	0	1	0	0	0
			(4)	(2)	(0)	(0)	(2)	(4)	(0)	(0)	(6)	(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				1000 ppm				2000 ppm				4000 ppm			
		No. of Animals on Study	50				50				50				50			
		Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	erosion:glandular stomach		2	0	0	0	0	1	0	0	0	0	0	0	2	0	0	0
			(4)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
liver			<50>				<50>				<50>				<50>			
	herniation		6	0	0	0	7	0	0	0	11	0	0	0	11	0	0	0
			(12)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(22)	(0)	(0)	(0)	(22)	(0)	(0)	(0)
	necrosis:central		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:focal		2	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	fatty change:central		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)	(0)	(0)
	lymphocytic infiltration		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)
	granulation		10	4	0	0	9	4	0	0	7	6	0	0	10	9	0	0
			(20)	(8)	(0)	(0)	(18)	(8)	(0)	(0)	(14)	(12)	(0)	(0)	(20)	(18)	(0)	(0)
	clear cell focus		0	2	0	0	0	0	0	0	0	1	0	0	0	1	0	0
			(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Digestive system}																		
liver		<50>																
	basophilic cell focus		21 (42)	2 (4)	0 (0)	0 (0)	26 (52)	1 (2)	0 (0)	0 (0)	19 (38)	7 (14)	0 (0)	0 (0)	24 (48)	4 (8)	0 (0)	0 (0)
	bile duct hyperplasia		9 (18)	2 (4)	0 (0)	0 (0)	9 (18)	0 (0)	0 (0)	0 (0)	10 (20)	2 (4)	0 (0)	0 (0)	10 (20)	1 (2)	0 (0)	0 (0)
	cholangiofibrosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
pancreas		<50>																
	atrophy		3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	5 (10)	1 (2)	1 (2)	0 (0)
	islet cell hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Urinary system}																		
kidney		<50>																
	cyst		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Urinary system}																		
kidney		<50>																
	deposit of hemosiderin		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	scar		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)
	chronic nephropathy		30 (60)	4 (8)	2 (4)	0 (0)	27 (54)	9 (18)	0 (0)	0 (0)	30 (60)	9 (18)	3 (6)	0 (0)	33 (66)	5 (10)	1 (2)	0 (0)
	mineralization:pelvis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	desquamation:pelvis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	urothelial hyperplasia:pelvis		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	atypical tubule hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	dilated pelvis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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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				1000 ppm				2000 ppm				4000 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}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		4	1	0	0	1	1	0	0	5	2	0	0	1	1	0	0
			(8)	(2)	(0)	(0)	(2)	(2)	(0)	(0)	(10)	(4)	(0)	(0)	(2)	(2)	(0)	(0)
	cyst		5	2	0	0	5	3	0	0	6	2	0	0	5	2	0	0
			(10)	(4)	(0)	(0)	(10)	(6)	(0)	(0)	(12)	(4)	(0)	(0)	(10)	(4)	(0)	(0)
	hyperplasia		8	6	0	0	11	3	0	0	4	5	0	0	11	4	0	0
			(16)	(12)	(0)	(0)	(22)	(6)	(0)	(0)	(8)	(10)	(0)	(0)	(22)	(8)	(0)	(0)
	Rathke pouch		1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
thyroid			<50>				<50>				<50>				<50>			
	ultimibranchial body remanet		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	C-cell hyperplasia		5	0	0	0	5	1	0	0	8	5	0	0 *	6	3	0	0
			(10)	(0)	(0)	(0)	(10)	(2)	(0)	(0)	(16)	(10)	(0)	(0)	(12)	(6)	(0)	(0)
	focal follicular cell hyperplasia		0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(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)

Grade 1 : Slight 2 : Moderate 3 : Marked 4 : Severe
< a > a : Number of animals examined at the site
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Organ	Findings	Group Name	Control				1000 ppm				2000 ppm				4000 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		0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hyperplasia:medulla		0	0	0	0	0	0	0	0	1	2	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(0)	(0)	(0)	(2)	(0)	(0)
	focal fatty change:cortex		4	1	0	0	5	2	0	0	3	1	0	0	1	0	0	0
			(8)	(2)	(0)	(0)	(10)	(4)	(0)	(0)	(6)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
{Reproductive system}																		
ovary			<50>				<50>				<50>				<50>			
	cyst		0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
uterus			<50>				<50>				<50>				<50>			
	cystic endometrial hyperplasia		0	1	0	0	2	1	0	0	2	3	0	0	3	3	0	0
			(0)	(2)	(0)	(0)	(4)	(2)	(0)	(0)	(4)	(6)	(0)	(0)	(6)	(6)	(0)	(0)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	hemorrhage		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	2000 ppm 50 1 (%)	2000 ppm 50 2 (%)	2000 ppm 50 3 (%)	2000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Special sense organs/appendage}																		
eye		<50>																
	cataract		0 (0)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 * (0)	0 (0)	0 (0)	0 (0)	0 (0)
	retinal atrophy		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	4 (8)	0 (0)	0 * (0)	0 (0)	6 (12)	1 (2)	0 * (0)	1 (2)	0 (0)	0 (0)	0 (0)
	keratitis		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)
Harder gl		<50>																
	degeneration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
nasolacr d		<50>																
	inflammation		10 (20)	0 (0)	0 (0)	0 (0)	18 (36)	0 (0)	0 (0)	0 (0)	11 (22)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
{Musculoskeletal system}																		
bone		<50>																
	osteosclerosis		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	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

TABLE O1

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : MALE

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : subcutis			
	TUMOR : fibroma			
Tumor rate				
Overall rates(a)	4/50(8.0)	8/50(16.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	8.82	16.67	10.87	7.14
Terminal rates(c)	2/33(6.1)	7/42(16.7)	4/38(10.5)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8857			
Prevalence method(d)	P = 0.7368			
Combined analysis(d)	P = 0.8427			
Cochran-Armitage test(e)	P = 0.4256			
Fisher Exact test(e)		P = 0.1783	P = 0.5000	P = 0.5000
	SITE : subcutis			
	TUMOR : fibroma, fibrosarcoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	8/50(16.0)	5/50(10.0)	4/50(8.0)
Adjusted rates(b)	8.82	16.67	10.53	7.14
Terminal rates(c)	2/33(6.1)	7/42(16.7)	4/38(10.5)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5032			
Prevalence method(d)	P = 0.7607			
Combined analysis(d)	P = 0.7434			
Cochran-Armitage test(e)	P = 0.6680			
Fisher Exact test(e)		P = 0.1783	P = 0.5000	P = 0.6425
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	3.03	2.38	7.50	0.0
Terminal rates(c)	1/33(3.0)	1/42(2.4)	2/38(5.3)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.7361			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.5920			
Fisher Exact test(e)		P = 0.7525	P = 0.3087	P = 0.5000

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	4/50(8.0)	1/50(2.0)	6/50(12.0)	3/50(6.0)
Adjusted rates(b)	3.03	2.38	10.53	4.76
Terminal rates(c)	1/33(3.0)	1/42(2.4)	4/38(10.5)	2/42(4.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7781			
Prevalence method(d)	P = 0.2904			
Combined analysis(d)	P = 0.5388			
Cochran-Armitage test(e)	P = 0.9254			
Fisher Exact test(e)		P = 0.1811	P = 0.3703	P = 0.5000
	SITE : pancreas			
	TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	6/50(12.0)	2/50(4.0)	2/50(4.0)
Adjusted rates(b)	5.26	14.29	5.26	4.65
Terminal rates(c)	1/33(3.0)	6/42(14.3)	2/38(5.3)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7629			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5459			
Fisher Exact test(e)		P = 0.1343	P = 0.6913	P = 0.6913
	SITE : pancreas			
	TUMOR : islet cell adenoma,islet cell adenocarcinoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	7/50(14.0)	2/50(4.0)	2/50(4.0)
Adjusted rates(b)	5.26	16.67	5.26	4.65
Terminal rates(c)	1/33(3.0)	7/42(16.7)	2/38(5.3)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8023			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4671			
Fisher Exact test(e)		P = 0.0798	P = 0.6913	P = 0.6913

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	13/50(26.0)	5/50(10.0)	3/50(6.0)
Adjusted rates(b)	13.33	22.73	10.53	4.76
Terminal rates(c)	3/33(9.1)	9/42(21.4)	4/38(10.5)	2/42(4.8)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9501			
Prevalence method(d)	P = 0.9796			
Combined analysis(d)	P = 0.9959			
Cochran-Armitage test(e)	P = 0.0110*			
Fisher Exact test(e)		P = 0.3176	P = 0.1312	P = 0.0357*
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	5/50(10.0)	6/50(12.0)	9/50(18.0)
Adjusted rates(b)	18.42	10.87	15.79	21.43
Terminal rates(c)	6/33(18.2)	4/42(9.5)	6/38(15.8)	9/42(21.4)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.2799			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.4211			
Fisher Exact test(e)		P = 0.3798	P = 0.5000	P = 0.3929
	SITE : thyroid			
	TUMOR : C-cell carcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	2/50(4.0)	3/50(6.0)	1/50(2.0)
Adjusted rates(b)	2.86	4.08	7.89	2.38
Terminal rates(c)	0/33(0.0)	1/42(2.4)	3/38(7.9)	1/42(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5353			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9481			
Fisher Exact test(e)		P = 0.5000	P = 0.3087	P = 0.7525

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	7/50(14.0)	9/50(18.0)	10/50(20.0)
Adjusted rates(b)	21.05	14.29	23.68	23.81
Terminal rates(c)	6/33(18.2)	5/42(11.9)	9/38(23.7)	10/42(23.8)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.2968			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.4839			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.3976
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	10/50(20.0)	1/50(2.0)	4/50(8.0)	0/50(0.0)
Adjusted rates(b)	25.64	2.27	9.30	0.0
Terminal rates(c)	7/33(21.2)	0/42(0.0)	3/38(7.9)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.9999			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.0017**			
Fisher Exact test(e)		P = 0.0039**	P = 0.0739	P = 0.0006**
	SITE : adrenal gland			
	TUMOR : pheochromocytoma, pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	12/50(24.0)	2/50(4.0)	5/50(10.0)	0/50(0.0)
Adjusted rates(b)	25.64	4.55	11.63	0.0
Terminal rates(c)	7/33(21.2)	1/42(2.4)	4/38(10.5)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9786 ?			
Prevalence method(d)	P = 0.9998			
Combined analysis(d)	P = 1.0000			
Cochran-Armitage test(e)	P = 0.0005**			
Fisher Exact test(e)		P = 0.0038**	P = 0.0542	P = 0.0001**

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : testis			
	TUMOR : interstitial cell tumor			
Tumor rate				
Overall rates(a)	41/50(82.0)	44/50(88.0)	46/50(92.0)	47/50(94.0)
Adjusted rates(b)	97.06	100.00	97.56	100.00
Terminal rates(c)	32/33(97.0)	42/42(100.0)	37/38(97.4)	42/42(100.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.1113			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.0561			
Fisher Exact test(e)		P = 0.2883	P = 0.1168	P = 0.0606
	SITE : mammary gland			
	TUMOR : adenoma, fibroadenoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	4/50(8.0)	1/50(2.0)	0/50(0.0)
Adjusted rates(b)	0.0	9.52	2.38	0.0
Terminal rates(c)	0/33(0.0)	4/42(9.5)	0/38(0.0)	0/42(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.8210			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.3997			
Fisher Exact test(e)		P = 0.0587	P = 0.5000	P = N.C.

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
SITE : peritoneum				
TUMOR : mesothelioma				
Tumor rate				
Overall rates(a)	2/50(4.0)	2/50(4.0)	1/50(2.0)	7/50(14.0)
Adjusted rates(b)	3.03	4.55	2.27	7.14
Terminal rates(c)	1/33(3.0)	1/42(2.4)	0/38(0.0)	3/42(7.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0193*			
Prevalence method(d)	P = 0.1879			
Combined analysis(d)	P = 0.0213*			
Cochran-Armitage test(e)	P = 0.0268*			
Fisher Exact test(e)		P = 0.6913	P = 0.5000	P = 0.0798

(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 O2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	9/50(18.0)	5/50(10.0)	4/50(8.0)	4/50(8.0)
Adjusted rates(b)	11.76	5.71	4.65	4.55
Terminal rates(c)	4/34(11.8)	2/35(5.7)	2/43(4.7)	2/44(4.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9025			
Prevalence method(d)	P = 0.8632			
Combined analysis(d)	P = 0.9573			
Cochran-Armitage test(e)	P = 0.1466			
Fisher Exact test(e)		P = 0.1940	P = 0.1168	P = 0.1168
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	12/50(24.0)	8/50(16.0)	7/50(14.0)	5/50(10.0)
Adjusted rates(b)	17.65	17.14	11.36	11.36
Terminal rates(c)	6/34(17.6)	6/35(17.1)	4/43(9.3)	5/44(11.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9930			
Prevalence method(d)	P = 0.8456			
Combined analysis(d)	P = 0.9848			
Cochran-Armitage test(e)	P = 0.0679			
Fisher Exact test(e)		P = 0.2270	P = 0.1540	P = 0.0542
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	13/50(26.0)	9/50(18.0)	7/50(14.0)	7/50(14.0)
Adjusted rates(b)	17.65	20.00	11.36	13.64
Terminal rates(c)	6/34(17.6)	7/35(20.0)	4/43(9.3)	6/44(13.6)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9827			
Prevalence method(d)	P = 0.7975			
Combined analysis(d)	P = 0.9705			
Cochran-Armitage test(e)	P = 0.1354			
Fisher Exact test(e)		P = 0.2348	P = 0.1054	P = 0.1054

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	5/50(10.0)	4/50(8.0)	3/50(6.0)
Adjusted rates(b)	14.71	14.29	8.70	6.82
Terminal rates(c)	5/34(14.7)	5/35(14.3)	3/43(7.0)	3/44(6.8)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9013			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.2775			
Fisher Exact test(e)		P = 0.5000	P = 0.3703	P = 0.2435
	SITE : thyroid			
	TUMOR : C-cell adenoma,C-cell carcinoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	5/50(10.0)	4/50(8.0)	4/50(8.0)
Adjusted rates(b)	14.71	14.29	8.70	9.09
Terminal rates(c)	5/34(14.7)	5/35(14.3)	3/43(7.0)	4/44(9.1)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.8151			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.4883			
Fisher Exact test(e)		P = 0.5000	P = 0.3703	P = 0.3703
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	4/50(8.0)	4/50(8.0)	1/50(2.0)
Adjusted rates(b)	0.0	9.52	9.30	2.27
Terminal rates(c)	0/34(0.0)	2/35(5.7)	4/43(9.3)	1/44(2.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.5222			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.9540			
Fisher Exact test(e)		P = 0.0587	P = 0.0587	P = 0.5000

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : adrenal gland			
	TUMOR : pheochromocytoma, pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	0/50(0.0)	4/50(8.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	0.0	9.52	11.63	4.55
Terminal rates(c)	0/34(0.0)	2/35(5.7)	5/43(11.6)	2/44(4.5)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.3311			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5641			
Fisher Exact test(e)		P = 0.0587	P = 0.0281*	P = 0.2475
	SITE : uterus			
	TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	6/50(12.0)	6/50(12.0)	3/50(6.0)	8/50(16.0)
Adjusted rates(b)	15.00	11.43	6.52	17.02
Terminal rates(c)	4/34(11.8)	4/35(11.4)	2/43(4.7)	7/44(15.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.7534			
Prevalence method(d)	P = 0.2512			
Combined analysis(d)	P = 0.3455			
Cochran-Armitage test(e)	P = 0.5741			
Fisher Exact test(e)		P = 0.6202	P = 0.2435	P = 0.3871
	SITE : uterus			
	TUMOR : endometrial stromal sarcoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	1/50(2.0)	1/50(2.0)
Adjusted rates(b)	0.0	0.0	0.0	0.0
Terminal rates(c)	0/34(0.0)	0/35(0.0)	0/43(0.0)	0/44(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8723			
Prevalence method(d)	P = ------			
Combined analysis(d)	P = 0.8723			
Cochran-Armitage test(e)	P = 0.2689			
Fisher Exact test(e)		P = 0.5000	P = 0.3087	P = 0.3087

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
	SITE : mammary gland			
	TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	8/50(16.0)	5/50(10.0)	5/50(10.0)
Adjusted rates(b)	20.59	17.14	11.63	9.09
Terminal rates(c)	7/34(20.6)	6/35(17.1)	5/43(11.6)	4/44(9.1)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4284			
Prevalence method(d)	P = 0.9501			
Combined analysis(d)	P = 0.9292			
Cochran-Armitage test(e)	P = 0.2863			
Fisher Exact test(e)		P = 0.6071	P = 0.2768	P = 0.2768
	SITE : preputial/clitoral gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	2/50(4.0)	4/50(8.0)	0/50(0.0)
Adjusted rates(b)	2.94	5.71	9.30	0.0
Terminal rates(c)	1/34(2.9)	2/35(5.7)	4/43(9.3)	0/44(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.7995			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.5583			
Fisher Exact test(e)		P = 0.5000	P = 0.1811	P = 0.5000

(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 Q

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

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

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Peritoneum	2247			
Mesothelioma		59	2.6	0 - 8

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

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

TABLE R

CAUSE OF DEATH OF RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : MALE

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

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
Number of Dead and Moribund Animal	17	8	12	8
no microscop confirm	4	1	1	1
cardiovascular les	0	0	1	0
chronic nephropathy	0	0	2	0
peritonitis	0	0	1	0
tumor d:leukemia	3	0	2	1
tumor d:subcutis	1	2	2	1
tumor d:small intes	0	1	0	0
tumor d:liver	0	1	0	0
tumor d:urin bladd	1	0	0	0
tumor d:pituitary	4	3	1	1
tumor d:adrenal	2	0	0	0
tumor d:prep/cli gl	0	0	1	0
tumor d:spinal cord	0	0	1	0
tumor d:peritoneum	1	0	0	4
tumor d:retroperit	1	0	0	0

STUDY NO. : 0610
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : FEMALE

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

Group Name	Control	1000 ppm	2000 ppm	4000 ppm
Number of Dead and Moribund Animal	16	15	7	6
no microscop confirm	2	1	0	0
tumor d:leukemia	5	3	2	2
tumor d:subcutis	0	0	1	0
tumor d:liver	0	1	0	0
tumor d:pituitary	6	2	2	1
tumor d:ovary	0	0	0	1
tumor d:uterus	3	4	1	2
tumor d:mammary gl	0	2	0	0
tumor d:periph nerv	0	1	0	0
tumor d:Zymbal gl	0	1	1	0

FIGURES

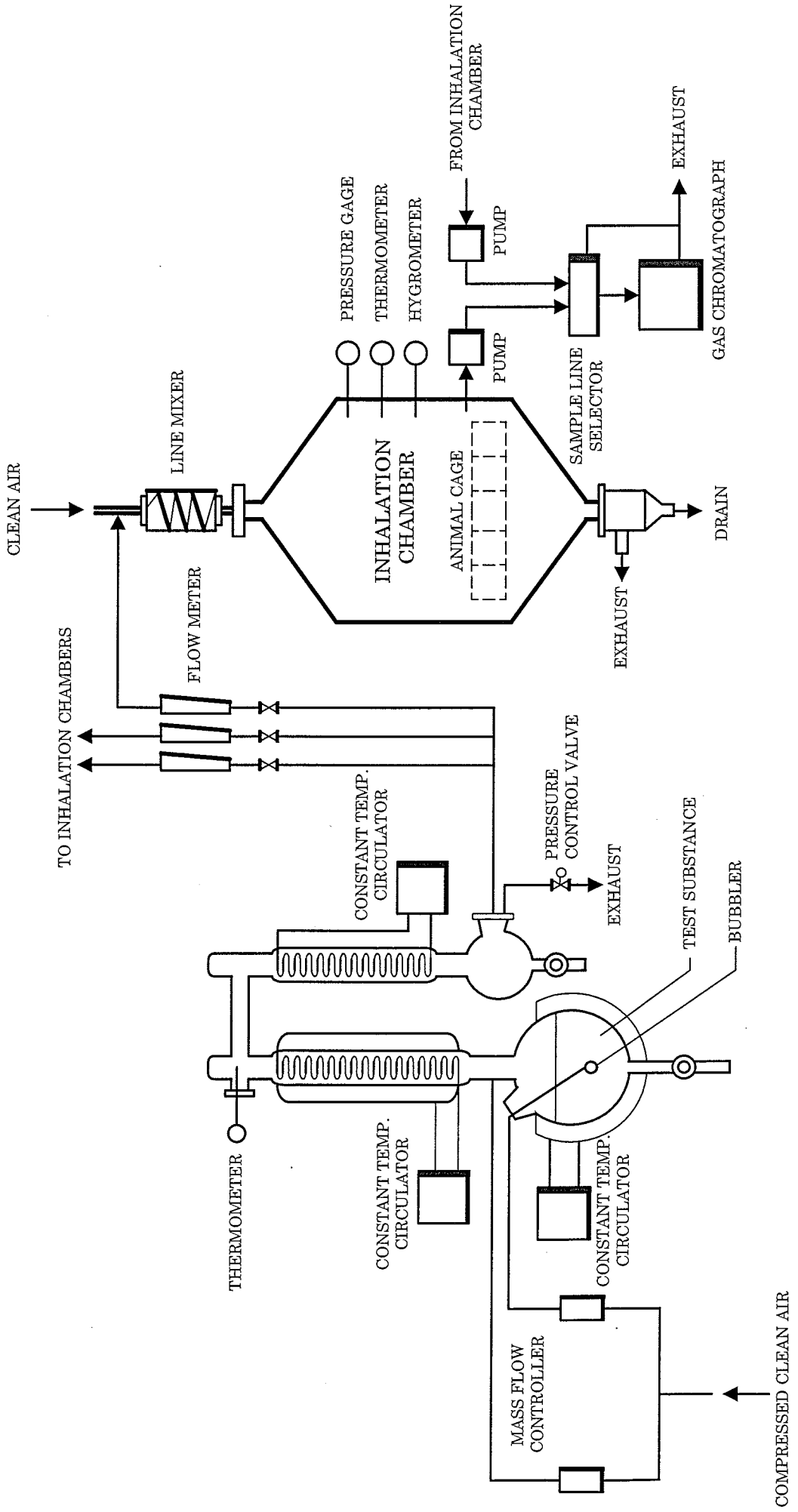


FIGURE 1 ISOPROPYL ACETATE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

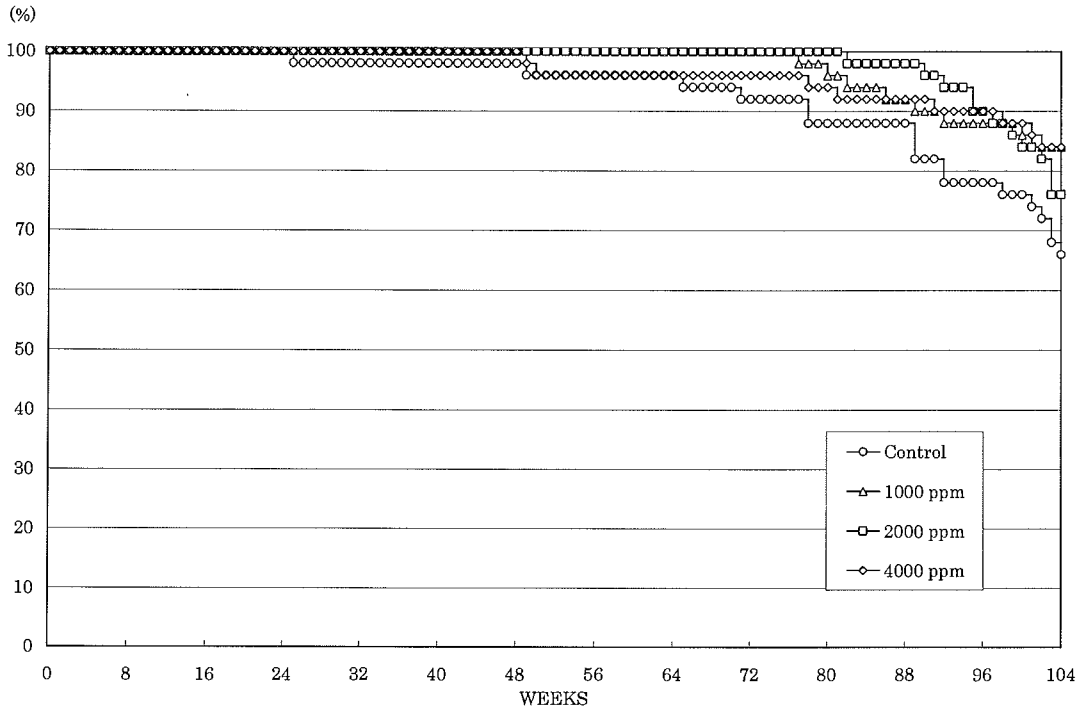


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

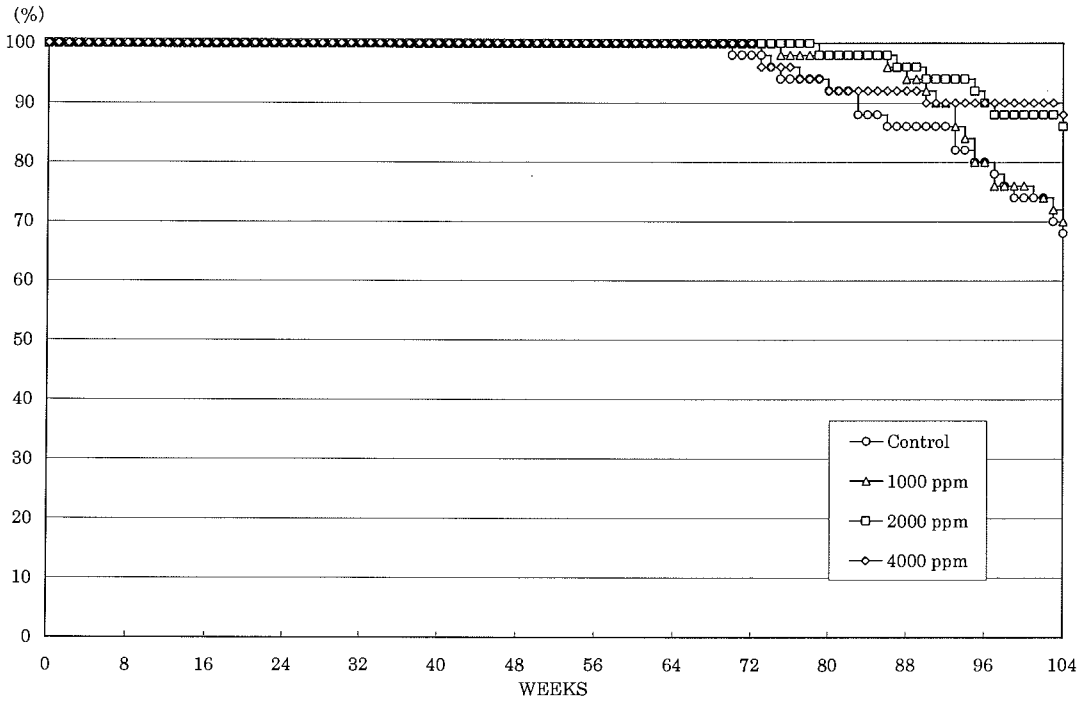


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

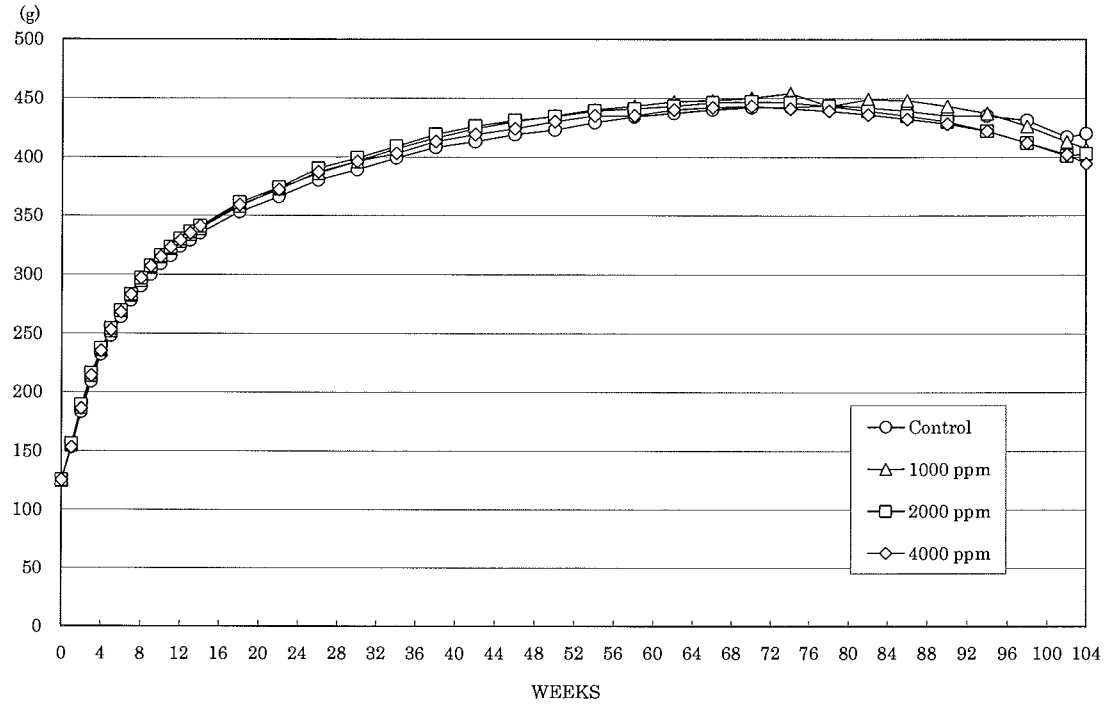


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

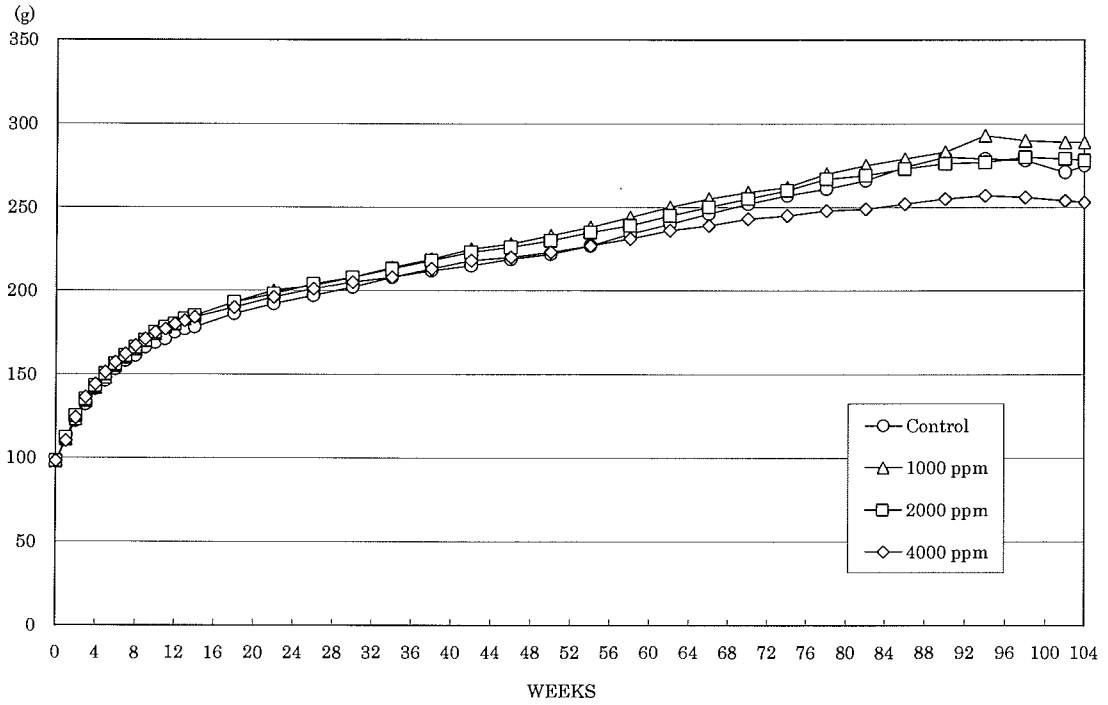


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

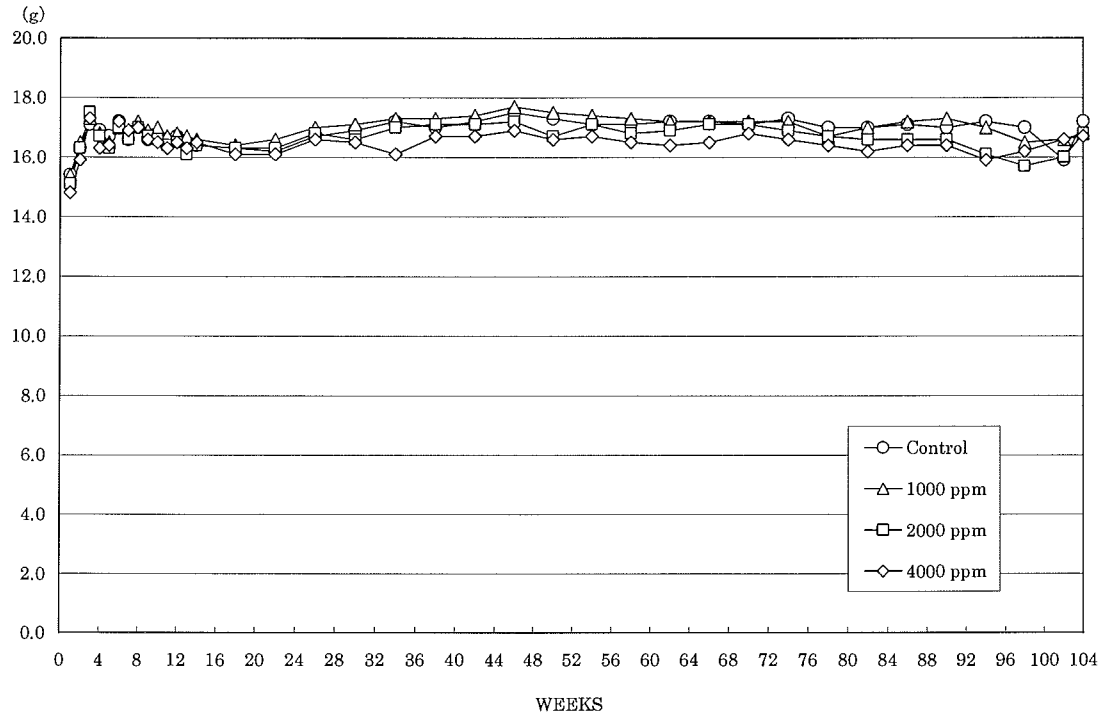


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE

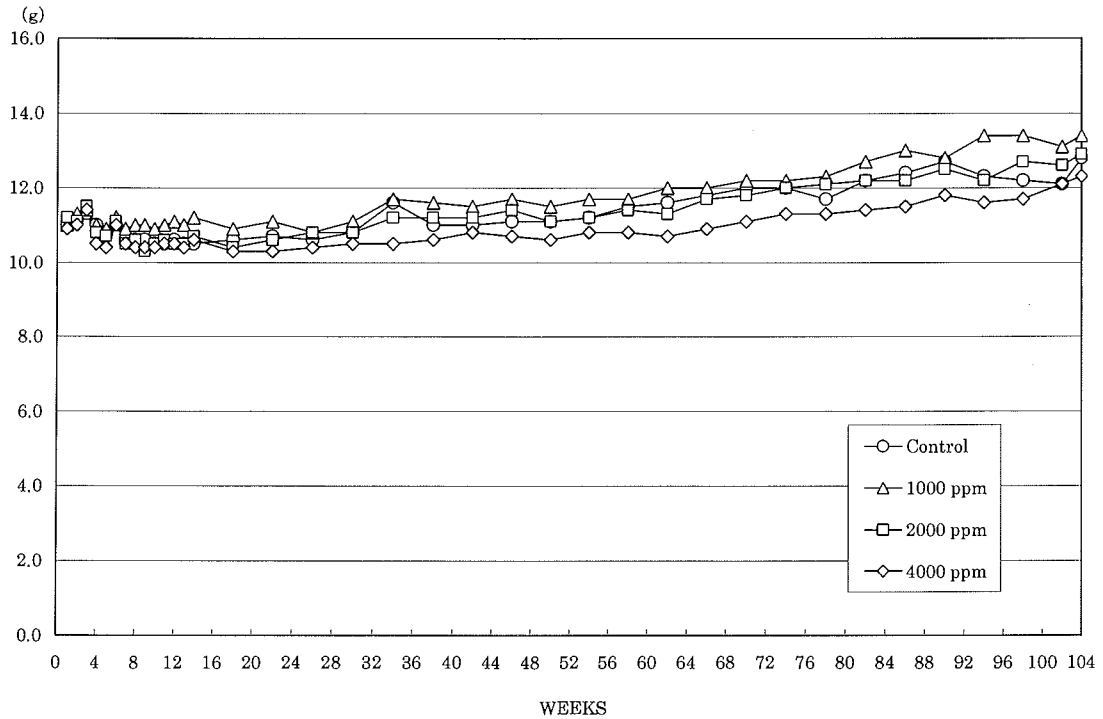
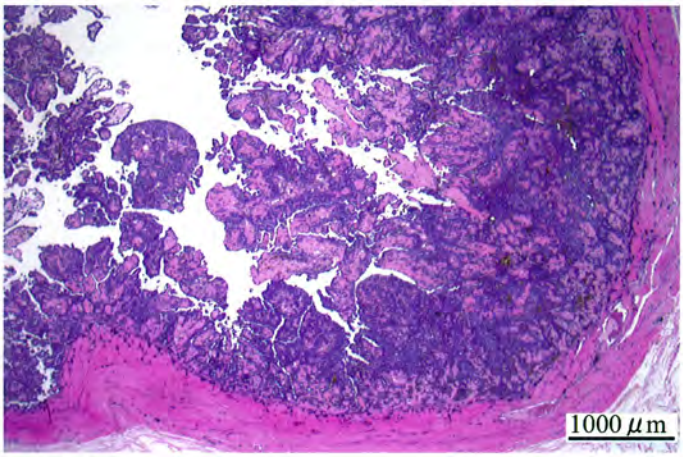
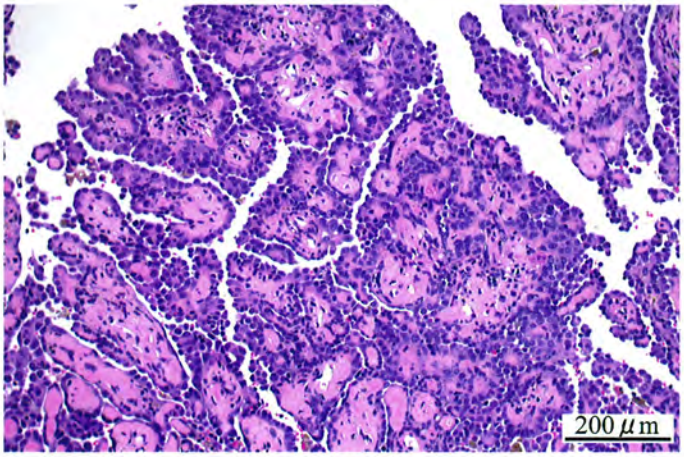


FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ISOPROPYL ACETATE



Photograph 1
Peritoneum: mesothelioma
Rat, Male, 4000 ppm, Animal No. 0610-1336 (H&E)



Photograph 2
Higher magnification of photograph 1
Peritoneum: mesothelioma
Rat, Male, 4000 ppm, Animal No. 0610-1336 (H&E)