Summary of Feed Carcinogenicity Study of Diphenylamine in F344 Rats

August 2011

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 August 25, 2011.

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

Summary of Feed Carcinogenicity Study of Diphenylamine in F344 Rats

Purpose, materials and methods

Diphenylamine (CAS No. 122-39-4) is a colourless solid with a floral odour. and with a melting point of 52.85°C. It is insoluble in water, and soluble alcohol, and ether.

The carcinogenicity and chronic toxicity of diphenylamine were examined in F344/DuCrlCrlj rats. Groups of test animals were administered diphenylamine in their food for 2 years (104 weeks). Each group consisted of either 50 male or 50 female rats. The dietary concentration of diphenylamine were 0, 250, 1000 or 4000 ppm (w/w). Both sexes were administered each concentration of diphenylamine. 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 diphenylamine used in these experiments was confirmed by both infrared spectrometry and mass spectrometry The chemical was analyzed by high performance liquid chromatography before and after use to affirm its stability. The concentrations of diphenylamine in the diet were determined by high performance liquid chromatography at the time of preparation and on the 8th day after preparation while stored at room temperature or stored in the refrigerator. The animals were observed daily for clinical signs and mortality. Body weight, water consumption and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year administration period underwent complete necropsy. Urinalysis was performed near the end of the administration period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five μm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of diphenylamine 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, water consumption, 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 difference in survival rate was found between any diphenylamine-fed group of either sex and their respective controls. Brown urine was observed in the 4000 ppm-fed males and females. Soiled fur around the genitalia was observed in the all treated females and 4000 ppm-fed males. Growth rates of the males fed 4000 ppm and all females fed diphenylamine were suppressed throughout most of the 2-year administration period, and growth rates of the males fed 1000 ppm were suppressed in the earlier administration period. Food consumption was decreased in the males fed 4000 ppm throughout of the 2-year administration period, and food consumption of males fed 1000 ppm were suppressed in the earlier administration period. Food consumption was decreased in the females fed 1000 and 4000 ppm untill the 78th week of the 2-year administration period.

The incidences of selected neoplastic lesions in male and female rats are presented in the tables below. The incidence of hemangioma and combined incidence of hemangioma and/or hemangiosarcoma (Peto test and Cochran-Armitage test) in spleen were increased in males. The incidence of hemangiosarcoma in all organs including subcutis and spleen increased in males (Peto test and Cochran-Armitage test), and the combined incidence of hemangioma and hemangiosarcoma were increased in males fed 4000 ppm (Fisher’s exact test). In females, the incidence of adenocarcinoma and the combined incidence of adenoma and/or adenocarcinoma in uterus were increased (Peto test and Cochran-Armitage test).

In blood and hematopoietic system, methemoglobin concentration was increased in males fed 1000 ppm and above, and all female groups fed diphenylamine. Anemia caused by the increase of methemoglobin concentration was observed in males fed 4000 ppm, and females fed 1000 ppm and above. Also vearious anemia-related changes in hematology and biochemistry were observed in diphenylamine-fed groups.

In the spleen, increased organ weights, engorgement of erythrocyte, increased extramedullary hematopoiesis (male only), deposit of hemosiderin (male only), capsular hyperplasia, angiectasis and focal fibrosis (female only) were observed.

In the liver, increased organ weights were observed in males and females fed 1000 ppm and above, hepatocellular hypertrophy were observed in males and females fed 4000 ppm, and increased activity of deviation enzymes were observed in fed groups.

In the kidney, increased organ weights were observed in males fed 1000 ppm and above.

Increased severities of chronic nephropathy was observed in males fed 4000 ppm, deposit of brown pigment in proximal tubule were observed in males and females fed 4000 ppm, mineralization in pelvis were observed in males fed 4000 ppm and females fed 1000 ppm and above. Plasma urea nitrogen was increaded in males and females fed 4000 ppm.

Using blood and hematopoietic system and liver as endpoint markers, the no-observed-adverse-effect-level (NOAEL) of diphenylamine in the diet was 250 ppm (12 mg/kg body weight per day) for males. The NOAEL for female could not estimate, the lowest observed-adverse-effect-level (LOAEL) of diphenylamine in the diet was 250 ppm (15 mg/kg body weight per day) for females.

Conclusions

There was some evidence for carcinogenicity of diphenylamine in male and female rats, based on increase in the incidence of vascular tumors in spleen and increase in the incidence of vascular tumors in all organs including in spleen and subcutus in males and an increase in the incidence of adenocarcinoma in mammary glands in females.

Incidences of selected neoplastic lesions of male rats in the 2-year feed carcinogenicity study of diphenylamine

Dose (ppm)		0	250	1000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
skin/appendage	keratoacanthoma	3	3	5	2		
subcutis	fibroma	2	11 **	3	2		
	hemangioma	0	0	0	1		
pancreas	islet cell adenoma	6	3	2	0 *		↓
spleen	hemangioma	0	1	0	0		
pituitary	adenoma	17	19	11	8 *		↓
thyroid	C-cell adenoma	11	10	12	13		
adrenal	pheochromocytoma	4	8	4	4		
testis	interstitial cell tumor	37	40	46 *	46 *	↑	↑
malignant tumor							
subcutis	fibrosarcoma	0	2	0	1		
	hemangiosarcoma	0	0	0	1		
spleen	hemangiosarcoma	0	0	0	3	↑↑	↑↑
	mononuclear cell leukemia	5	3	2	1		
spleen	hemangioma+ hemangiosarcoma	0	1	0	3	↑	↑
subcutis	fibroma＋fibrosarcoma	2	13 **	3	3		
all organs [a)]	hemangioma	0	1	0	1		
	hemangiosarcoma	0	0	0	4	↑↑	↑↑
	hemangioma+ hemangiosarcoma [b)]	0	1	0	5 *		

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)

a : All organs were consisted of subcutis and spleen.

b : Combined analysis of hemangioma+hemangiosarcoma in all organs of Peto test and Cochran-Armitage test was not applied.

Incidences of selected neoplastic lesions of female rats in the 2-year feed carcinogenicity study of diphenylamine

Dose (ppm)		0	250	1000	4000	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
pituitary	adenoma	11	13	12	16		
thyroid	C-cell adenoma	7	9	7	5		
uterus	endometrial stromal polyp	5	2	6	7		
	adenoma	0	1	0	0		
mammary gland	fibroadenoma	8	11	7	2 *		↓
malignant tumor							
spleen	hemangiosarcoma	0	0	0	1		
	mononuclear cell leukemia	3	2	0	5	↑	
pituitary	adenocarcinoma	2	1	4	0		
uterus	adenocarcinoma	1	0	0	4	↑↑	↑↑
uterus	adenoma+adenocarcinoma	1	1	0	4	↑	↑

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

SELECTED TABLES (CONTINUED)

TABLE C 1

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN BODY WEIGHTS AND SURVIVAL

Week on Study	Control Av. Wt.	Control No. of Surviv. <50>	250 ppm Av. Wt.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0	121 (50)	50/50	121 (50)	100	50/50	121 (50)	100	50/50	121 (50)	100	50/50
1	152 (50)	50/50	150 (50)	99	50/50	150 (50)	99	50/50	143 (50)	94	50/50
2	184 (50)	50/50	181 (50)	98	50/50	179 (50)	97	50/50	172 (50)	93	50/50
3	210 (50)	50/50	206 (50)	98	50/50	203 (50)	97	50/50	195 (50)	93	50/50
4	230 (50)	50/50	225 (50)	98	50/50	223 (50)	97	50/50	213 (50)	93	50/50
5	245 (50)	50/50	241 (50)	98	50/50	239 (50)	98	50/50	227 (50)	93	50/50
6	259 (50)	50/50	255 (50)	98	50/50	253 (50)	98	50/50	239 (50)	92	50/50
7	274 (50)	50/50	269 (50)	98	50/50	267 (50)	97	50/50	251 (50)	92	50/50
8	287 (50)	50/50	281 (50)	98	50/50	279 (50)	97	50/50	262 (50)	91	50/50
9	296 (50)	50/50	291 (50)	98	50/50	289 (50)	98	50/50	272 (50)	92	50/50
10	303 (50)	50/50	297 (50)	98	50/50	297 (50)	98	50/50	280 (50)	92	50/50
11	309 (50)	50/50	303 (50)	98	50/50	302 (50)	98	50/50	285 (50)	92	50/50
12	316 (50)	50/50	312 (50)	99	50/50	310 (50)	98	50/50	292 (50)	92	50/50
13	323 (50)	50/50	319 (50)	99	50/50	317 (50)	98	50/50	298 (50)	92	50/50
14	329 (50)	50/50	326 (50)	99	50/50	324 (50)	98	50/50	304 (50)	92	50/50
18	346 (50)	50/50	342 (50)	99	50/50	341 (50)	99	50/50	319 (50)	92	50/50
22	363 (50)	50/50	357 (50)	98	50/50	357 (50)	98	50/50	333 (50)	92	50/50
26	378 (50)	50/50	371 (50)	98	50/50	372 (50)	98	50/50	346 (50)	92	50/50
30	387 (50)	50/50	382 (50)	99	50/50	382 (50)	99	50/50	356 (50)	92	50/50
34	400 (50)	50/50	392 (50)	98	50/50	393 (50)	98	50/50	365 (50)	91	50/50
38	408 (50)	50/50	400 (50)	98	50/50	401 (50)	98	50/50	371 (50)	91	50/50
42	414 (50)	50/50	406 (50)	98	50/50	408 (50)	99	50/50	379 (50)	92	50/50
46	422 (50)	50/50	413 (50)	98	50/50	417 (50)	99	50/50	386 (50)	91	50/50
50	427 (50)	50/50	418 (50)	98	50/50	423 (50)	99	50/50	390 (50)	91	50/50
54	430 (50)	50/50	423 (50)	98	50/50	427 (50)	99	50/50	394 (50)	92	50/50
58	433 (50)	50/50	428 (50)	99	50/50	432 (50)	100	50/50	398 (50)	92	50/50
62	433 (49)	49/50	428 (50)	99	50/50	431 (50)	100	50/50	400 (50)	92	50/50
66	435 (49)	49/50	430 (50)	99	50/50	434 (49)	100	49/50	402 (50)	92	50/50
70	432 (48)	48/50	432 (50)	100	50/50	436 (49)	101	49/50	404 (50)	94	50/50
74	437 (47)	47/50	437 (49)	100	49/50	441 (48)	101	48/50	407 (50)	93	50/50
78	440 (46)	46/50	438 (49)	100	49/50	442 (48)	100	48/50	407 (49)	93	49/50
82	439 (46)	46/50	440 (48)	100	48/50	443 (47)	101	47/50	406 (49)	92	49/50
86	433 (46)	46/50	435 (48)	100	48/50	437 (47)	101	47/50	399 (49)	92	49/50
90	426 (43)	43/50	432 (47)	101	47/50	431 (46)	101	46/50	391 (49)	92	49/50
94	415 (43)	43/50	426 (44)	103	44/50	426 (46)	103	46/50	385 (46)	93	46/50
98	408 (38)	38/50	418 (42)	102	42/50	417 (45)	102	45/50	375 (46)	92	46/50
102	399 (37)	37/50	416 (40)	104	40/50	407 (43)	102	43/50	366 (42)	92	42/50
104	390 (37)	37/50	407 (40)	104	40/50	400 (43)	103	43/50	360 (41)	92	41/50

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

TABLE C 2

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

Week on Study	Control Av. Wt.	Control No. of Surviv. <50>	250 ppm Av. Wt.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. Wt.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. Wt.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
0	101 (50)	50/50	101 (50)	100	50/50	101 (50)	100	50/50	101 (50)	100	50/50
1	115 (50)	50/50	114 (50)	99	50/50	113 (50)	98	50/50	110 (50)	96	50/50
2	127 (50)	50/50	126 (50)	99	50/50	124 (50)	98	50/50	121 (50)	95	50/50
3	138 (50)	50/50	134 (50)	97	50/50	131 (50)	95	50/50	129 (50)	93	50/50
4	146 (50)	50/50	142 (50)	97	50/50	139 (50)	95	50/50	135 (50)	92	50/50
5	153 (50)	50/50	149 (50)	97	50/50	146 (50)	95	50/50	141 (50)	92	50/50
6	159 (50)	50/50	155 (50)	97	50/50	152 (50)	96	50/50	146 (50)	92	50/50
7	164 (50)	50/50	159 (50)	97	50/50	156 (50)	95	50/50	150 (50)	91	50/50
8	168 (50)	50/50	163 (50)	97	50/50	159 (50)	95	50/50	154 (50)	92	50/50
9	172 (50)	50/50	166 (50)	97	50/50	162 (50)	94	50/50	156 (50)	91	50/50
10	175 (50)	50/50	170 (50)	97	50/50	166 (50)	95	50/50	159 (50)	91	50/50
11	178 (50)	50/50	172 (50)	97	50/50	167 (50)	94	50/50	161 (50)	90	50/50
12	182 (50)	50/50	175 (50)	96	50/50	171 (50)	94	50/50	163 (50)	90	50/50
13	185 (50)	50/50	177 (50)	96	50/50	174 (50)	94	50/50	165 (50)	89	50/50
14	186 (50)	50/50	180 (50)	97	50/50	175 (50)	94	50/50	167 (50)	90	50/50
18	194 (50)	50/50	187 (50)	96	50/50	183 (50)	94	50/50	174 (50)	90	50/50
22	200 (50)	50/50	193 (50)	97	50/50	187 (50)	94	50/50	177 (50)	89	50/50
26	206 (50)	50/50	198 (50)	96	50/50	193 (50)	94	50/50	181 (50)	88	50/50
30	211 (50)	50/50	203 (50)	96	50/50	197 (50)	93	50/50	185 (50)	88	50/50
34	219 (50)	50/50	209 (49)	95	49/50	203 (50)	93	50/50	189 (50)	86	50/50
38	224 (50)	50/50	213 (49)	95	49/50	206 (50)	92	50/50	192 (50)	86	50/50
42	228 (50)	50/50	217 (49)	95	49/50	210 (50)	92	50/50	196 (50)	86	50/50
46	233 (50)	50/50	222 (48)	95	48/50	214 (50)	92	50/50	198 (50)	85	50/50
50	237 (50)	50/50	226 (48)	95	48/50	218 (50)	92	50/50	201 (50)	85	50/50
54	243 (50)	50/50	231 (48)	95	48/50	224 (50)	92	50/50	205 (50)	84	50/50
58	251 (49)	49/50	237 (48)	94	48/50	229 (50)	91	50/50	210 (50)	84	50/50
62	257 (49)	49/50	241 (48)	94	48/50	235 (50)	91	50/50	213 (50)	83	50/50
66	267 (49)	49/50	250 (48)	94	48/50	243 (50)	91	50/50	220 (50)	82	50/50
70	273 (49)	49/50	255 (48)	93	48/50	249 (50)	91	50/50	224 (50)	82	50/50
74	281 (49)	49/50	263 (48)	94	48/50	257 (50)	91	50/50	229 (50)	81	50/50
78	289 (49)	49/50	273 (48)	94	48/50	265 (49)	92	49/50	235 (50)	81	50/50
82	294 (49)	49/50	277 (47)	94	47/50	270 (49)	92	49/50	240 (50)	82	50/50
86	295 (48)	48/50	278 (46)	94	46/50	275 (47)	93	47/50	242 (50)	82	50/50
90	296 (47)	47/50	282 (44)	95	44/50	275 (47)	93	47/50	243 (50)	82	50/50
94	297 (47)	47/50	283 (44)	95	44/50	276 (46)	93	46/50	243 (48)	82	48/50
98	297 (45)	45/50	284 (43)	96	43/50	277 (45)	93	45/50	242 (47)	81	47/50
102	296 (41)	41/50	285 (43)	96	43/50	273 (45)	92	45/50	242 (45)	82	45/50
104	294 (40)	40/50	285 (43)	97	43/50	269 (45)	91	45/50	243 (43)	83	43/50

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

TABLE C 3

BODY WEIGHT CHANGES: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	121± 6	152± 8	184± 10	210± 11	230± 11	245± 12	259± 14
250 ppm	121± 6	150± 8	181± 7	206± 8	225± 8	241± 8	255± 9
1000 ppm	121± 6	150± 8	179± 9**	203± 9**	223± 9**	239± 10*	253± 10*
4000 ppm	121± 6	143± 7**	172± 9**	195± 9**	213± 9**	227± 10**	239± 11**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	274± 15	287± 17	296± 18	303± 18	309± 18	316± 18	323± 19
250 ppm	269± 10	281± 11	291± 11	297± 13	303± 13	312± 14	319± 14
1000 ppm	267± 10*	279± 11*	289± 13	297± 13	302± 12*	310± 13	317± 13
4000 ppm	251± 11**	262± 12**	272± 13**	280± 12**	285± 13**	292± 13**	298± 14**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	329± 19	346± 20	363± 19	378± 21	387± 21	400± 22	408± 22
250 ppm	326± 14	342± 15	357± 17	371± 17	382± 19	392± 20	400± 20
1000 ppm	324± 14	341± 14	357± 15	372± 16	382± 17	393± 17	401± 18
4000 ppm	304± 14**	319± 15**	333± 17**	346± 16**	356± 17**	365± 19**	371± 19**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	414± 22	422± 22	427± 22	430± 23	433± 23	433± 23	435± 24
250 ppm	406± 21	413± 21	418± 22	423± 23	428± 23	428± 24	430± 25
1000 ppm	408± 19	417± 19	423± 20	427± 20	432± 20	431± 21	434± 20
4000 ppm	379± 19**	386± 20**	390± 20**	394± 21**	398± 21**	400± 21**	402± 21**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	432± 34	437± 28	440± 26	439± 25	433± 26	426± 31	415± 42
250 ppm	432± 25	437± 25	438± 26	440± 27	435± 30	432± 36	426± 28
1000 ppm	436± 20	441± 22	442± 24	443± 23	437± 23	431± 23	426± 25
4000 ppm	404± 22**	407± 22**	407± 23**	406± 23**	399± 22**	391± 24**	385± 27**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98	102	104
Control	408± 38	399± 37	390± 42
250 ppm	418± 37	416± 24*	407± 25
1000 ppm	417± 29	407± 34	400± 37
4000 ppm	375± 37**	366± 27**	360± 31**

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

TABLE C 4

BODY WEIGHT CHANGES: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 0	1	2	3	4	5	6
Control	101± 3	115± 4	127± 5	138± 5	146± 7	153± 6	159± 8
250 ppm	101± 3	114± 4	126± 5	134± 6**	142± 6**	149± 7**	155± 8*
1000 ppm	101± 3	113± 4*	124± 5**	131± 6**	139± 7**	146± 8**	152± 8**
4000 ppm	101± 3	110± 3**	121± 5**	129± 5**	135± 6**	141± 6**	146± 7**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 7	8	9	10	11	12	13
Control	164± 8	168± 8	172± 9	175± 9	178± 9	182± 10	185± 11
250 ppm	159± 8**	163± 8**	166± 10**	170± 10*	172± 10**	175± 10**	177± 10**
1000 ppm	156± 10**	159± 10**	162± 11**	166± 11**	167± 12**	171± 12**	174± 12**
4000 ppm	150± 6**	154± 7**	156± 8**	159± 9**	161± 8**	163± 9**	165± 9**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 14	18	22	26	30	34	38
Control	186± 11	194± 11	200± 13	206± 12	211± 14	219± 14	224± 15
250 ppm	180± 11*	187± 12**	193± 12**	198± 12**	203± 13**	209± 13**	213± 15**
1000 ppm	175± 12**	183± 12**	187± 14**	193± 16**	197± 16**	203± 17**	206± 18**
4000 ppm	167± 9**	174± 9**	177± 9**	181± 10**	185± 10**	189± 11**	192± 11**

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

(HAN260)

BAIS 4

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 42	46	50	54	58	62	66
Control	228± 16	233± 18	237± 18	243± 19	251± 22	257± 23	267± 24
250 ppm	217± 15**	222± 16*	226± 16**	231± 17**	237± 18**	241± 20**	250± 21**
1000 ppm	210± 20**	214± 22**	218± 23**	224± 25**	229± 26**	235± 26**	243± 27**
4000 ppm	196± 12**	198± 12**	201± 13**	205± 13**	210± 15**	213± 16**	220± 18**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 70	74	78	82	86	90	94
Control	273± 24	281± 24	289± 26	294± 26	295± 26	296± 25	297± 29
250 ppm	255± 21**	263± 20**	273± 20**	277± 21**	278± 24**	282± 23*	283± 28*
1000 ppm	249± 26**	257± 27**	265± 28**	270± 29**	275± 29**	275± 32**	276± 34**
4000 ppm	224± 20**	229± 20**	235± 20**	240± 20**	242± 19**	243± 19**	243± 20**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

BODY WEIGHT CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 98		102		104	
Control	297±	28	296±	28	294±	29
250 ppm	284±	26	285±	24	285±	26
1000 ppm	277±	31**	273±	35**	269±	38**
4000 ppm	242±	26**	242±	27**	243±	23**

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

TABLE D 1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	250 ppm Av. FC.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1	13.0 (50)	50/50	12.9 (50)	99	50/50	13.0 (50)	100	50/50	12.0 (50)	92	50/50
2	14.4 (50)	50/50	14.2 (50)	99	50/50	14.0 (50)	97	50/50	13.7 (50)	95	50/50
3	15.2 (50)	50/50	15.1 (50)	99	50/50	14.7 (50)	97	50/50	14.6 (50)	96	50/50
4	15.6 (50)	50/50	15.4 (50)	99	50/50	15.1 (50)	97	50/50	14.8 (50)	95	50/50
5	15.6 (50)	50/50	15.4 (50)	99	50/50	15.3 (50)	98	50/50	15.0 (50)	96	50/50
6	15.5 (50)	50/50	15.4 (50)	99	50/50	15.4 (50)	99	50/50	15.2 (50)	98	50/50
7	15.6 (50)	50/50	15.5 (50)	99	50/50	15.5 (50)	99	50/50	15.3 (50)	98	50/50
8	15.8 (50)	50/50	15.7 (50)	99	50/50	15.5 (50)	98	50/50	15.3 (50)	97	50/50
9	15.8 (50)	50/50	15.7 (50)	99	50/50	15.6 (50)	99	50/50	15.2 (50)	96	50/50
10	15.9 (50)	50/50	15.7 (50)	99	50/50	15.7 (50)	99	50/50	15.2 (50)	96	50/50
11	15.6 (50)	50/50	15.5 (50)	99	50/50	15.5 (50)	99	50/50	14.9 (50)	96	50/50
12	15.4 (50)	50/50	15.6 (50)	101	50/50	15.7 (50)	102	50/50	14.8 (50)	96	50/50
13	15.7 (50)	50/50	15.3 (50)	97	50/50	15.4 (50)	98	50/50	14.6 (50)	93	50/50
14	15.6 (49)	50/50	15.6 (50)	100	50/50	15.6 (50)	100	50/50	14.9 (50)	96	50/50
18	15.9 (50)	50/50	15.6 (50)	98	50/50	15.5 (50)	97	50/50	14.8 (50)	93	50/50
22	16.2 (50)	50/50	15.9 (50)	98	50/50	15.9 (50)	98	50/50	15.0 (50)	93	50/50
26	16.1 (48)	50/50	16.1 (50)	100	50/50	16.0 (50)	99	50/50	15.2 (50)	94	50/50
30	15.9 (50)	50/50	15.6 (50)	98	50/50	15.5 (50)	97	50/50	15.0 (50)	94	50/50
34	16.1 (49)	50/50	16.0 (50)	99	50/50	15.9 (50)	99	50/50	15.1 (50)	94	50/50
38	16.3 (47)	50/50	16.1 (50)	99	50/50	16.1 (49)	99	50/50	15.3 (50)	94	50/50
42	16.7 (50)	50/50	16.1 (50)	96	50/50	16.3 (50)	98	50/50	15.7 (50)	94	50/50
46	16.5 (50)	50/50	16.1 (50)	98	50/50	16.3 (50)	99	50/50	15.7 (50)	95	50/50
50	16.7 (50)	50/50	16.3 (50)	98	50/50	16.5 (50)	99	50/50	15.7 (50)	94	50/50
54	16.3 (50)	50/50	16.2 (50)	99	50/50	16.4 (50)	101	50/50	15.7 (50)	96	50/50
58	15.8 (50)	50/50	15.8 (50)	100	50/50	16.0 (50)	101	50/50	15.3 (50)	97	50/50
62	16.0 (49)	49/50	15.7 (50)	98	50/50	15.6 (50)	98	50/50	15.4 (50)	96	50/50
66	16.3 (49)	49/50	16.2 (50)	99	50/50	16.2 (49)	99	49/50	15.8 (50)	97	50/50
70	15.9 (48)	48/50	16.3 (50)	103	50/50	16.2 (49)	102	49/50	15.7 (50)	99	50/50
74	16.1 (47)	47/50	16.3 (49)	101	49/50	16.1 (48)	100	48/50	15.6 (50)	97	50/50
78	16.3 (46)	46/50	16.4 (49)	101	49/50	16.0 (48)	98	48/50	15.5 (49)	95	49/50
82	15.8 (46)	46/50	15.9 (48)	101	48/50	15.7 (47)	99	47/50	15.0 (49)	95	49/50
86	15.9 (46)	46/50	15.7 (48)	99	48/50	15.4 (47)	97	47/50	14.9 (49)	94	49/50
90	16.0 (43)	43/50	16.0 (47)	100	47/50	15.6 (46)	98	46/50	14.8 (49)	93	49/50
94	15.6 (43)	43/50	15.6 (44)	100	44/50	15.6 (46)	100	46/50	15.1 (46)	97	46/50
98	16.0 (37)	38/50	15.7 (42)	98	42/50	15.7 (45)	98	45/50	14.8 (43)	93	46/50
102	15.9 (37)	37/50	16.1 (40)	101	40/50	16.1 (43)	101	43/50	15.5 (41)	97	42/50
104	15.6 (37)	37/50	15.3 (40)	98	40/50	15.3 (41)	98	43/50	14.6 (37)	94	41/50

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

TABLE D 2

FOOD CONSUMPTION CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

Week on Study	Control Av. FC.	Control No. of Surviv. <50>	250 ppm Av. FC.	250 ppm % of cont. <50>	250 ppm No. of Surviv.	1000 ppm Av. FC.	1000 ppm % of cont. <50>	1000 ppm No. of Surviv.	4000 ppm Av. FC.	4000 ppm % of cont. <50>	4000 ppm No. of Surviv.
1	10.5 (50)	50/50	10.3 (50)	98	50/50	10.1 (50)	96	50/50	9.4 (50)	90	50/50
2	10.5 (50)	50/50	10.5 (50)	100	50/50	10.2 (50)	97	50/50	9.6 (50)	91	50/50
3	10.8 (50)	50/50	10.8 (50)	100	50/50	10.5 (50)	97	50/50	10.0 (50)	93	50/50
4	11.1 (50)	50/50	10.8 (50)	97	50/50	10.8 (50)	97	50/50	10.2 (50)	92	50/50
5	10.9 (50)	50/50	10.7 (50)	98	50/50	10.6 (50)	97	50/50	9.9 (49)	91	50/50
6	11.0 (50)	50/50	10.8 (50)	98	50/50	10.6 (50)	96	50/50	10.2 (50)	93	50/50
7	10.6 (50)	50/50	10.6 (50)	100	50/50	10.3 (50)	97	50/50	9.9 (50)	93	50/50
8	10.7 (50)	50/50	10.6 (50)	99	50/50	10.1 (50)	94	50/50	9.8 (50)	92	50/50
9	10.8 (50)	50/50	10.6 (50)	98	50/50	10.2 (50)	94	50/50	9.7 (50)	90	50/50
10	10.9 (50)	50/50	10.7 (50)	98	50/50	10.4 (50)	95	50/50	9.8 (50)	90	50/50
11	11.0 (50)	50/50	10.8 (50)	98	50/50	10.3 (50)	94	50/50	9.8 (50)	89	50/50
12	11.3 (50)	50/50	11.1 (50)	98	50/50	10.8 (50)	96	50/50	10.0 (50)	88	50/50
13	11.2 (50)	50/50	10.8 (50)	96	50/50	10.6 (50)	95	50/50	10.0 (50)	89	50/50
14	11.5 (50)	50/50	11.3 (50)	98	50/50	10.7 (50)	93	50/50	10.2 (50)	89	50/50
18	11.7 (50)	50/50	11.4 (50)	97	50/50	11.2 (50)	96	50/50	10.6 (50)	91	50/50
22	12.2 (50)	50/50	12.0 (50)	98	50/50	11.6 (50)	95	50/50	11.1 (49)	91	50/50
26	12.1 (49)	50/50	12.1 (50)	100	50/50	11.8 (50)	98	50/50	11.0 (50)	91	50/50
30	12.3 (50)	50/50	11.8 (50)	96	50/50	11.6 (50)	94	50/50	10.8 (50)	88	50/50
34	12.4 (50)	50/50	12.1 (49)	98	49/50	11.6 (50)	94	50/50	10.9 (50)	88	50/50
38	12.9 (50)	50/50	12.3 (49)	95	49/50	11.7 (50)	91	50/50	11.0 (50)	85	50/50
42	12.5 (50)	50/50	12.4 (49)	99	49/50	12.1 (50)	97	50/50	11.1 (50)	89	50/50
46	13.1 (50)	50/50	12.8 (48)	98	48/50	12.1 (50)	92	50/50	11.5 (50)	88	50/50
50	13.4 (50)	50/50	13.0 (48)	97	48/50	12.4 (50)	93	50/50	12.1 (50)	90	50/50
54	13.8 (50)	50/50	13.4 (48)	97	48/50	12.8 (50)	93	50/50	12.4 (50)	90	50/50
58	13.4 (49)	49/50	13.1 (48)	98	48/50	12.5 (50)	93	50/50	12.1 (50)	90	50/50
62	13.6 (49)	49/50	12.9 (48)	95	48/50	12.7 (50)	93	50/50	12.3 (50)	90	50/50
66	14.3 (49)	49/50	13.6 (48)	95	48/50	13.1 (50)	92	50/50	13.1 (50)	92	50/50
70	13.8 (49)	49/50	13.3 (48)	96	48/50	13.1 (50)	95	50/50	12.9 (50)	93	50/50
74	14.3 (49)	49/50	13.7 (48)	96	48/50	13.4 (50)	94	50/50	13.3 (50)	93	50/50
78	14.6 (49)	49/50	14.2 (48)	97	48/50	13.4 (49)	92	49/50	13.3 (50)	91	50/50
82	13.8 (49)	49/50	13.8 (47)	100	47/50	13.3 (49)	96	49/50	13.2 (50)	96	50/50
86	14.3 (48)	48/50	13.8 (46)	97	46/50	13.6 (47)	95	47/50	13.7 (50)	96	50/50
90	14.0 (47)	47/50	13.5 (44)	96	44/50	13.3 (47)	95	47/50	13.5 (50)	96	50/50
94	13.7 (46)	47/50	13.8 (44)	101	44/50	13.0 (45)	95	46/50	13.2 (46)	96	48/50
98	14.1 (45)	45/50	13.9 (43)	99	43/50	13.3 (45)	94	45/50	13.2 (47)	94	47/50
102	14.0 (41)	41/50	14.0 (43)	100	43/50	13.0 (45)	93	45/50	13.7 (43)	98	45/50
104	13.7 (40)	40/50	14.2 (43)	104	43/50	12.7 (45)	93	45/50	14.0 (43)	102	43/50

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

TABLE D 3

FOOD CONSUMPTION CHANGES: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	13.0± 0.7	14.4± 0.9	15.2± 0.8	15.6± 0.9	15.6± 1.1	15.5± 1.1	15.6± 1.2
250 ppm	12.9± 0.6	14.2± 0.6	15.1± 0.7	15.4± 0.7	15.4± 0.9	15.4± 0.8	15.5± 0.7
1000 ppm	13.0± 0.7	14.0± 0.8*	14.7± 0.8**	15.1± 0.8*	15.3± 0.9	15.4± 1.0	15.5± 1.0
4000 ppm	12.0± 0.7**	13.7± 0.8**	14.6± 0.9**	14.8± 0.8**	15.0± 1.0**	15.2± 1.0	15.3± 1.0

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	15.8± 1.3	15.8± 1.3	15.9± 1.3	15.6± 1.4	15.4± 1.4	15.7± 1.4	15.6± 1.2
250 ppm	15.7± 0.9	15.7± 0.8	15.7± 0.8	15.5± 0.9	15.6± 1.0	15.3± 1.0	15.6± 1.0
1000 ppm	15.5± 1.0	15.6± 1.1	15.7± 1.1	15.5± 1.0	15.7± 1.0	15.4± 1.0	15.6± 1.0
4000 ppm	15.3± 1.1	15.2± 1.1	15.2± 1.1*	14.9± 1.1**	14.8± 1.0*	14.6± 0.9**	14.9± 1.0**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	15.9± 1.4	16.2± 1.4	16.1± 1.3	15.9± 1.5	16.1± 1.2	16.3± 1.3	16.7± 1.5
250 ppm	15.6± 1.1	15.9± 1.0	16.1± 1.1	15.6± 1.1	16.0± 1.2	16.1± 1.2	16.1± 1.2
1000 ppm	15.5± 1.1	15.9± 1.2	16.0± 1.2	15.5± 1.1	15.9± 1.1	16.1± 1.3	16.3± 1.2
4000 ppm	14.8± 1.1**	15.0± 1.1**	15.2± 1.1**	15.0± 1.1**	15.1± 1.1**	15.3± 1.1**	15.7± 1.1**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	16.5± 1.3	16.7± 1.2	16.3± 1.4	15.8± 1.2	16.0± 1.3	16.3± 1.3	15.9± 2.4
250 ppm	16.1± 1.1	16.3± 1.2	16.2± 1.2	15.8± 1.1	15.7± 1.1	16.2± 1.2	16.3± 1.1
1000 ppm	16.3± 1.2	16.5± 1.4	16.4± 1.2	16.0± 1.2	15.6± 1.6	16.2± 1.2	16.2± 1.1
4000 ppm	15.7± 1.1**	15.7± 1.0**	15.7± 1.0*	15.3± 1.1	15.4± 1.0	15.8± 1.1	15.7± 1.2

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	16.1± 1.6	16.3± 1.3	15.8± 1.4	15.9± 1.7	16.0± 1.6	15.6± 1.7	16.0± 1.4
250 ppm	16.3± 1.1	16.4± 1.3	15.9± 1.0	15.7± 1.6	16.0± 1.2	15.6± 1.7	15.7± 1.3
1000 ppm	16.1± 1.0	16.0± 1.2	15.7± 1.0	15.4± 1.6	15.6± 1.1	15.6± 1.4	15.7± 1.5
4000 ppm	15.6± 1.1*	15.5± 1.4*	15.0± 1.1**	14.9± 1.6*	14.8± 2.2**	15.1± 1.7	14.8± 1.4**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : MALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	15.9± 1.8	15.6± 2.7
250 ppm	16.1± 1.3	15.3± 1.1
1000 ppm	16.1± 1.6	15.3± 1.7
4000 ppm	15.5± 1.9	14.6± 2.0*

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

TABLE D 4

FOOD CONSUMPTION CHANGES: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 1	2	3	4	5	6	7
Control	10.5± 0.6	10.5± 0.6	10.8± 0.9	11.1± 1.2	10.9± 1.0	11.0± 1.0	10.6± 1.0
250 ppm	10.3± 0.5	10.5± 0.7	10.8± 1.0	10.8± 0.7	10.7± 0.8	10.8± 0.9	10.6± 1.0
1000 ppm	10.1± 0.5**	10.2± 0.7	10.5± 1.3*	10.8± 0.8	10.6± 0.7	10.6± 0.7	10.3± 0.8
4000 ppm	9.4± 0.7**	9.6± 0.6**	10.0± 0.7**	10.2± 1.1**	9.9± 0.8**	10.2± 0.8**	9.9± 0.7**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 8	9	10	11	12	13	14
Control	10.7± 0.9	10.8± 0.9	10.9± 1.1	11.0± 1.1	11.3± 1.1	11.2± 1.2	11.5± 1.3
250 ppm	10.6± 1.0	10.6± 1.1	10.7± 1.2	10.8± 1.1	11.1± 1.5	10.8± 1.1	11.3± 1.4
1000 ppm	10.1± 0.8**	10.2± 0.7**	10.4± 0.8*	10.3± 0.8**	10.8± 0.8*	10.6± 0.8*	10.7± 1.0**
4000 ppm	9.8± 0.7**	9.7± 0.8**	9.8± 0.8**	9.8± 0.8**	10.0± 0.8**	10.0± 0.9**	10.2± 0.8**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 18	22	26	30	34	38	42
Control	11.7± 1.1	12.2± 1.4	12.1± 1.3	12.3± 1.5	12.4± 1.4	12.9± 1.5	12.5± 1.2
250 ppm	11.4± 1.3	12.0± 1.6	12.1± 2.0	11.8± 1.8	12.1± 2.0	12.3± 1.9	12.4± 1.7
1000 ppm	11.2± 0.9	11.6± 1.3	11.8± 1.6	11.6± 1.5	11.6± 1.4**	11.7± 1.4**	12.1± 1.7
4000 ppm	10.6± 1.1**	11.1± 1.4**	11.0± 1.4**	10.8± 1.4**	10.9± 1.4**	11.0± 1.3**	11.1± 1.2**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 46	50	54	58	62	66	70
Control	13.1± 1.5	13.4± 1.4	13.8± 1.4	13.4± 1.6	13.6± 1.4	14.3± 1.5	13.8± 1.4
250 ppm	12.8± 1.9	13.0± 2.0	13.4± 2.0	13.1± 1.9	12.9± 1.4	13.6± 1.7	13.3± 1.5
1000 ppm	12.1± 1.7*	12.4± 1.8*	12.8± 1.9*	12.5± 1.8*	12.7± 1.4*	13.1± 1.6**	13.1± 1.4*
4000 ppm	11.5± 1.4**	12.1± 1.7**	12.4± 1.7**	12.1± 1.9**	12.3± 1.8**	13.1± 2.3**	12.9± 1.7**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 74	78	82	86	90	94	98
Control	14.3± 1.4	14.6± 1.7	13.8± 1.7	14.3± 1.9	14.0± 1.6	13.7± 2.3	14.1± 2.3
250 ppm	13.7± 1.3*	14.2± 1.8	13.8± 1.9	13.8± 1.9	13.5± 1.6	13.8± 2.3	13.9± 1.6
1000 ppm	13.4± 1.7**	13.4± 1.7**	13.3± 1.7	13.6± 2.0	13.3± 2.2	13.0± 1.7	13.3± 2.6
4000 ppm	13.3± 1.9**	13.3± 2.0**	13.2± 2.1	13.7± 2.1	13.5± 2.4	13.2± 1.8	13.2± 2.4

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : g
REPORT TYPE : A1 104
SEX : FEMALE

FOOD CONSUMPTION CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration week 102	104
Control	14.0± 1.9	13.7± 2.8
250 ppm	14.0± 1.9	14.2± 2.1
1000 ppm	13.0± 2.6	12.7± 3.0
4000 ppm	13.7± 2.3	14.0± 2.8

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

TABLE E 1

CHEMICAL INTAKE CHANGES: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1		2		3		4		5		6		7	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	22±	1	20±	1	18±	1	17±	1	16±	1	15±	1	14±	1
1000 ppm	87±	3	78±	2	73±	2	68±	3	64±	3	61±	3	58±	3
4000 ppm	336±	13	320±	7	299±	9	278±	9	264±	10	254±	10	245±	10

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8		9		10		11		12		13		14	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	14±	1	13±	1	13±	1	13±	1	12±	1	12±	1	12±	1
1000 ppm	56±	3	54±	3	53±	3	51±	3	51±	3	48±	2	48±	3
4000 ppm	234±	10	224±	10	217±	10	209±	9	203±	8	196±	8	196±	8

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 18		22		26		30		34		38		42	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	11±	1	11±	1	11±	1	10±	1	10±	1	10±	1	10±	1
1000 ppm	45±	3	45±	3	43±	3	41±	3	40±	3	40±	3	40±	3
4000 ppm	186±	9	180±	8	176±	10	169±	10	165±	9	165±	10	165±	10

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 46		50		54		58		62		66		70	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	10±	1	10±	1	10±	1	9±	1	9±	1	9±	1	9±	1
1000 ppm	39±	3	39±	3	38±	3	37±	3	36±	3	38±	3	37±	2
4000 ppm	163±	9	161±	8	159±	9	154±	11	154±	9	157±	9	155±	11

STUDY NO. : 0684
ANIMAL : RAT F344/DuCriCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 74		78		82		86		90		94		98	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	9±	1	9±	1	9±	1	9±	1	9±	1	9±	1	9±	1
1000 ppm	36±	2	36±	3	36±	3	35±	4	36±	3	37±	4	38±	5
4000 ppm	154±	11	152±	13	148±	11	150±	16	151±	21	158±	18	160±	20

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : MALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 102		104	
Control	0±	0	0±	0
250 ppm	10±	1	10±	1
1000 ppm	40±	6	39±	6
4000 ppm	169±	20	163±	19

TABLE E 2

CHEMICAL INTAKE CHANGES: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 1		2		3		4		5		6		7	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	23±	1	21±	1	20±	2	19±	1	18±	1	17±	1	17±	1
1000 ppm	89±	4	83±	4	80±	9	77±	4	73±	3	70±	3	66±	3
4000 ppm	342±	22	318±	15	311±	18	303±	27	280±	16	278±	18	265±	15

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 8		9		10		11		12		13		14	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	16±	1	16±	1	16±	1	16±	1	16±	2	15±	1	16±	2
1000 ppm	64±	4	63±	3	63±	4	62±	4	63±	4	61±	3	61±	4
4000 ppm	254±	14	250±	14	246±	14	245±	14	245±	14	243±	17	243±	14

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg/kg/d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 18		22		26		30		34		38		42	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	15±	1	16±	2	15±	2	15±	2	14±	2	14±	2	14±	2
1000 ppm	61±	4	62±	5	61±	6	59±	6	58±	5	57±	4	57±	6
4000 ppm	243±	20	250±	24	244±	27	233±	25	230±	22	230±	23	226±	21

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 46		50		54		58		62		66		70	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	14±	2	14±	2	14±	2	14±	2	13±	1	14±	1	13±	1
1000 ppm	57±	5	57±	5	57±	7	55±	6	54±	5	54±	5	53±	5
4000 ppm	232±	24	240±	28	241±	28	230±	27	231±	24	238±	33	230±	23

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg/kg/day
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 74		78		82		86		90		94		98	
Control	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0	0±	0
250 ppm	13±	1	13±	2	13±	2	12±	2	12±	1	12±	2	12±	1
1000 ppm	52±	6	51±	6	49±	6	50±	8	49±	8	48±	8	48±	10
4000 ppm	232±	31	227±	28	220±	28	227±	31	222±	36	219±	27	219±	36

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
UNIT : mg／kg／d a y
REPORT TYPE : A1 104
SEX : FEMALE

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

Group Name	Administration (weeks) 102		104	
Control	0±	0	0±	0
250 ppm	12±	2	13±	2
1000 ppm	48±	10	47±	11
4000 ppm	230±	37	231±	41

TABLE F 1

HEMATOLOGY: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$	HEMOGLOBIN g/dℓ	HEMATOCRIT %	MCV f ℓ	MCH p g	MCHC g/dℓ	PLATELET $10^3/\mu\ell$
Control	36	7.76± 1.68	13.0± 2.7	37.1± 6.8	49.1± 6.9	17.0± 2.1	34.5± 1.7	966± 306
250 ppm	39	8.13± 1.50	13.6± 2.4	39.0± 6.1	48.4± 3.4	16.8± 1.0	34.8± 1.3	887± 267
1000 ppm	43	7.96± 1.45	13.1± 2.6	37.7± 6.2	47.7± 3.5*	16.4± 1.3	34.5± 2.0	958± 321
4000 ppm	41	7.68± 1.06	12.9± 1.7*	36.8± 4.3*	48.3± 3.1	16.7± 0.9	34.8± 2.0	837± 111**

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

(HCL070) BAIS 4

STUDY NO. : 0684
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 %		METHEMOGLOBIN %	
Control	36	4.5±	3.9	0.9±	0.3
250 ppm	39	3.9±	4.1	1.0±	0.4
1000 ppm	43	4.5±	4.7	1.2±	0.7**
4000 ppm	41	4.8±	6.7**	1.9±	0.6**

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	36	8.75±	9.30	46±	11	47±	11	5±	1	1±	1	0±	1	1±	1
250 ppm	39	10.35±	21.57	48±	15	41±	14	5±	2	1±	1	0±	0	5±	18
1000 ppm	43	6.51±	1.92	49±	9	44±	9	5±	1	1±	1	0±	0	1±	1
4000 ppm	41	7.18±	2.05	46±	9	47±	9	5±	1	1±	1	0±	0	1±	0

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

(HCL070)

TABLE F 2

HEMATOLOGY: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	RED BLOOD CELL $10^6/\mu\ell$		HEMOGLOBIN g/dℓ		HEMATOCRIT %		MCV fℓ		MCH pg		MCHC g/dℓ		PLATELET $10^3/\mu\ell$	
Control	39	7.98±	0.55	14.6±	1.0	40.1±	2.7	50.3±	2.1	18.3±	0.8	36.4±	0.5	748±	169
250 ppm	42	7.90±	0.46	14.5±	0.9	39.8±	2.3	50.4±	1.1	18.3±	0.5	36.4±	0.6	715±	118
1000 ppm	44	7.53±	1.00**	14.0±	2.2**	38.9±	6.0**	51.7±	2.2**	18.5±	1.1**	35.8±	2.1**	786±	147*
4000 ppm	43	6.82±	0.65**	13.1±	1.0**	36.7±	2.5**	54.0±	2.5**	19.2±	0.7**	35.6±	0.7**	635±	96**

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

(HCL070)

BAIS 4

STUDY NO. : 0684
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 %		METHEMOGLOBIN %	
Control	39	2.4±	1.5	0.7±	0.1
250 ppm	42	2.4±	1.0	0.9±	0.1**
1000 ppm	44	3.7±	3.8**	1.2±	0.3**
4000 ppm	43	5.4±	2.8**	2.4±	0.6**

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

(HCL070)

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : FEMALE REPORT TYPE : A1

HEMATOLOGY (SUMMARY)
ALL ANIMALS (105W)

Group Name	NO. of Animals	WBC $10^3/\mu\ell$		Differential WBC (%) NEUTRO		LYMPHO		MONO		EOSINO		BASO		OTHER	
Control	39	3.03±	1.16	41±	9	51±	9	4±	1	2±	1	0±	0	1±	0
250 ppm	42	3.15±	1.27	40±	10	53±	10	4±	1	2±	1	0±	0	1±	1
1000 ppm	44	3.82±	2.00	39±	10	55±	10	4±	1	2±	1	0±	0	1±	1**
4000 ppm	43	14.20±	69.79	34±	9**	58±	12*	4±	1*	2±	1	0±	0	3±	15**

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

TABLE G 1

BIOCHEMISTRY: MALE

STUDY NO. : 0684
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	36	6.8±	0.5	2.9±	0.2	0.7±	0.1	0.20±	0.29	145±	22	189±	63	97±	70
250 ppm	39	6.8±	0.5	2.9±	0.3	0.7±	0.1	0.18±	0.12	143±	29	169±	45	88±	46
1000 ppm	43	6.8±	0.4	2.9±	0.2	0.8±	0.1	0.15±	0.04	149±	16	174±	47	103±	57
4000 ppm	41	7.0±	0.4	3.1±	0.2**	0.8±	0.1**	0.19±	0.08**	145±	14	154±	38**	138±	72**

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

(HCL074)

BAIS 4

STUDY NO. : 0684
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	36	272± 99	104± 104	41± 28	129± 118	370± 401	6± 4	98± 48
250 ppm	39	241± 67	99± 55	42± 13	148± 143	311± 87	6± 3	97± 38
1000 ppm	43	245± 54	102± 36**	55± 28**	132± 37**	411± 100**	8± 4**	99± 36
4000 ppm	41	236± 57	106± 45*	49± 21**	127± 29**	412± 103**	8± 4	88± 14

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

(HCL074)

STUDY NO. : 0684
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	36	18.6± 3.9	0.6± 0.1	141± 2	3.8± 0.3	106± 2	10.6± 0.3	4.2± 0.5
250 ppm	39	19.4± 8.0	0.6± 0.3	142± 2	3.9± 0.5	106± 2	10.6± 0.3	4.5± 1.2
1000 ppm	43	21.7± 19.5	0.6± 0.2	142± 1	3.8± 0.4	106± 1	10.7± 0.4	4.4± 2.2
4000 ppm	41	21.6± 4.6**	0.6± 0.1	142± 2	3.9± 0.3	106± 2	10.6± 0.3	4.0± 0.5

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

(HCL074) BAIS 4

TABLE G 2

BIOCHEMISTRY: FEMALE

STUDY NO. : 0684
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	39	6.9±	0.4	3.5±	0.3	1.0±	0.1	0.12±	0.01	149±	18	133±	33	84±	54
250 ppm	42	6.9±	0.4	3.5±	0.2	1.1±	0.1	0.11±	0.01	145±	17	131±	21	71±	40
1000 ppm	44	7.0±	0.7	3.5±	0.5	1.0±	0.2	0.13±	0.03	140±	27	140±	47	74±	51
4000 ppm	43	7.3±	0.4**	3.8±	0.3**	1.1±	0.1*	0.15±	0.02**	145±	14	119±	23*	58±	32*

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

(HCL074)

STUDY NO. : 0684
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	39	235± 61	121± 57	52± 21	140± 70	161± 38	2± 1	84± 28
250 ppm	42	229± 39	143± 95	71± 63*	152± 62	177± 46	2± 1	78± 13
1000 ppm	44	242± 80	159± 133	79± 61**	163± 103	250± 292	3± 3	85± 38
4000 ppm	43	210± 40**	133± 133	57± 35	212± 432	216± 121*	2± 1	104± 111

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

(HCL074)

STUDY NO. : 0684
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	39	16.5± 2.0	0.5± 0.1	140± 1	3.6± 0.3	104± 2	10.7± 0.4	4.0± 0.5
250 ppm	42	16.6± 2.4	0.5± 0.0	141± 1	3.5± 0.3	104± 2	10.7± 0.4	3.9± 0.6
1000 ppm	44	18.6± 10.0	0.5± 0.1	141± 2	3.6± 0.5	104± 2	10.7± 0.6	4.0± 0.8
4000 ppm	43	17.8± 2.1**	0.5± 0.1	141± 2	3.7± 0.3	105± 2	10.7± 0.3	3.9± 0.6

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

(HCL074)

BAIS 4

TABLE H 1

URINALYSIS: MALE

Urinalysis of male rats

In the 4000 ppm dosed group, ketone body and bilirubin could not be measured by urine test paper in all animals, because their urine were colored by metabolite of test substance.

Therefore, ketone body and bilirubin in 4000 ppm dosed group, could not be evaluated.

STUDY NO. : 0684
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	36	0	1	4	5	11	13	2		0	0	0	1	21	14		36	0	0	0	0	0		33	3	0	0	0	0		35	0	0	1	
250 ppm	40	0	0	2	12	11	13	2		0	0	0	0	23	17		40	0	0	0	0	0		35	5	0	0	0	0		40	0	0	0	
1000 ppm	43	0	0	0	2	13	24	4		0	0	0	0	30	13		43	0	0	0	0	0		40	3	0	0	0	0		43	0	0	0	
4000 ppm	42	0	0	2	5	12	18	5		0	0	0	3	34	5	*	42	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	

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

(HCL101)

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
MEASURE. TIME : 1
SEX : MALE REPORT TYPE : A1

URINALYSIS

Group Name	NO. of Animals	Occult blood −	±	+	2+	3+	CHI	Urobilinogen ±	+	2+	3+	4+	CHI
Control	36	36	0	0	0	0		36	0	0	0	0	
250 ppm	40	39	1	0	0	0		40	0	0	0	0	
1000 ppm	43	43	0	0	0	0		43	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 H 2

URINALYSIS: FEMALE

Urinalysis of female rats

In the 4000 ppm dosed group, ketone body and bilirubin could not be measured by urine test paper in all animals, because their urine were colored by metabolite of test substance.

Therefore, ketone body and bilirubin in 4000 ppm dosed group, could not be evaluated.

STUDY NO. : 0684
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	40	0	1	8	8	17	5	1		0	0	2	13	22	3		40	0	0	0	0	0		36	4	0	0	0	0		40	0	0	0	
250 ppm	43	0	0	2	6	18	13	4		0	0	2	17	24	0		43	0	0	0	0	0		38	5	0	0	0	0		43	0	0	0	
1000 ppm	45	0	2	4	6	15	16	2		0	0	3	17	23	2		45	0	0	0	0	0		40	5	0	0	0	0		45	0	0	0	
4000 ppm	44	0	2	6	7	16	12	1		0	2	7	20	15	0	*	44	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	

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

STUDY NO. : 0684
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	40	40 0 0 0 0		40 0 0 0 0	
250 ppm	43	43 0 0 0 0		43 0 0 0 0	
1000 ppm	45	44 0 0 0 1		45 0 0 0 0	
4000 ppm	44	44 0 0 0 0		44 0 0 0 0	

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

(HCL101)

TABLE J 1

ORGAN WEIGHT, ABSOLUTE: MALE

STUDY NO. : 0684
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	36	374± 30	0.083± 0.013	3.112± 1.713	1.285± 0.120	1.464± 0.362	2.805± 0.243
250 ppm	39	387± 25	0.110± 0.107	2.984± 1.283	1.301± 0.088	1.513± 0.576	2.909± 0.318
1000 ppm	43	379± 38	0.082± 0.013	3.347± 1.466	1.258± 0.094	1.407± 0.080	2.985± 0.452*
4000 ppm	41	339± 30**	0.081± 0.073**	4.135± 1.858*	1.208± 0.100**	1.397± 0.113	3.118± 0.229**

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

(HCL040)

STUDY NO. : 0684
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	36	1.426±	1.501	11.140±	2.138	2.108±	0.045
250 ppm	39	1.823±	3.158	11.376±	1.987	2.119±	0.042
1000 ppm	43	1.252±	0.980	11.735±	1.254*	2.120±	0.052
4000 ppm	41	1.576±	0.456**	12.141±	1.295**	2.104±	0.041

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

(HCL040)

TABLE J 2

ORGAN WEIGHT, ABSOLUTE: FEMALE

STUDY NO. : 0684
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	39	282± 25	0.097± 0.074	0.156± 0.054	0.966± 0.064	1.023± 0.079	1.951± 0.145
250 ppm	42	270± 25	0.083± 0.013	0.317± 1.132	0.937± 0.079	0.968± 0.067**	1.872± 0.132*
1000 ppm	44	254± 39**	0.078± 0.009**	0.210± 0.368**	0.917± 0.096*	0.980± 0.108**	1.891± 0.169
4000 ppm	43	228± 23**	0.086± 0.064**	0.138± 0.020*	0.919± 0.077*	0.996± 0.144*	1.844± 0.137**

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

STUDY NO. : 0684
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	39	0.626±	0.143	7.168±	0.789	1.948±	0.043
250 ppm	42	0.634±	0.510	6.861±	0.891	1.930±	0.033
1000 ppm	44	0.682±	0.322	7.246±	1.237	1.935±	0.036
4000 ppm	43	1.541±	0.979**	8.173±	0.863**	1.936±	0.050

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

(IICL040)

TABLE K 1

ORGAN WEIGHT, RELATIVE: MALE

STUDY NO. : 0684
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	36	374± 30	0.022± 0.004	0.838± 0.468	0.346± 0.047	0.398± 0.133	0.754± 0.086
250 ppm	39	387± 25	0.029± 0.028	0.769± 0.327	0.337± 0.029	0.392± 0.151	0.755± 0.098
1000 ppm	43	379± 38	0.022± 0.006	0.891± 0.389	0.336± 0.045	0.376± 0.047	0.808± 0.260
4000 ppm	41	339± 30**	0.025± 0.024	1.229± 0.559**	0.358± 0.034*	0.415± 0.046**	0.925± 0.083**

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

(HCL042)

BAIS 4

STUDY NO. : 0684
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	36	0.405± 0.509	3.000± 0.684	0.567± 0.052
250 ppm	39	0.467± 0.796	2.940± 0.481	0.550± 0.037
1000 ppm	43	0.333± 0.270	3.119± 0.360**	0.566± 0.066
4000 ppm	41	0.466± 0.139**	3.588± 0.315**	0.626± 0.058**

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

(HCL042)

TABLE K 2

ORGAN WEIGHT, RELATIVE: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : FEMALE
UNIT: %

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

Group Name	NO. of Animals	Body Weight (g)	ADRENALS	OVARIES	HEART	LUNGS	KIDNEYS
Control	39	282± 25	0.034± 0.023	0.056± 0.021	0.345± 0.031	0.367± 0.055	0.697± 0.079
250 ppm	42	270± 25	0.031± 0.005	0.114± 0.390	0.349± 0.033	0.362± 0.038	0.699± 0.067
1000 ppm	44	254± 39**	0.032± 0.006	0.080± 0.126	0.370± 0.074	0.398± 0.108*	0.761± 0.137**
4000 ppm	43	228± 23**	0.038± 0.029	0.061± 0.009**	0.406± 0.045**	0.443± 0.090**	0.814± 0.064**

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

(HCL042)

STUDY NO. : 0684
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	39	0.226± 0.071	2.550± 0.258	0.697± 0.073
250 ppm	42	0.235± 0.184	2.553± 0.310	0.722± 0.070
1000 ppm	44	0.272± 0.144**	2.882± 0.469**	0.782± 0.134**
4000 ppm	43	0.684± 0.456**	3.606± 0.389**	0.858± 0.086**

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

(HCL042)

TABLE L 1

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

MALE: ALL ANIMALS

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Integumentary system/appandage}																		
skin/app		<50>																
	scar		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	squamous cell hyperplasia		1 (2)	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)
subcutis		<50>																
	hemorrhage		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	inflammation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	fibrosis:focal		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)
{Respiratory system}																		
nasal cavit		<50>																
	thrombus		0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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				250 ppm				1000 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>			
	mineralization		32	0	0	0	38	0	0	0	36	0	0	0	33	0	0	0
			(64)	(0)	(0)	(0)	(76)	(0)	(0)	(0)	(72)	(0)	(0)	(0)	(66)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		29	6	4	0	16	9	0	0 **	13	9	2	0 **	12	15	10	0 **
			(58)	(12)	(8)	(0)	(32)	(18)	(0)	(0)	(26)	(18)	(4)	(0)	(24)	(30)	(20)	(0)
	eosinophilic change:respiratory epithelium		2	0	0	0	3	0	0	0	7	0	0	0	4	0	0	0
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	inflammation:foreign body		18	11	1	0	16	9	3	0	14	8	2	0	13	7	0	0
			(36)	(22)	(2)	(0)	(32)	(18)	(6)	(0)	(28)	(16)	(4)	(0)	(26)	(14)	(0)	(0)
	inflammation:respiratory epithelium		7	0	0	0	8	1	0	0	16	0	0	0	3	0	0	0
			(14)	(0)	(0)	(0)	(16)	(2)	(0)	(0)	(32)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
	inflammation:olfactory epithelium		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	respiratory metaplasia:olfactory epithelium		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	respiratory metaplasia:gland		42	0	0	0	32	0	0	0 *	42	0	0	0	40	0	0	0
			(84)	(0)	(0)	(0)	(64)	(0)	(0)	(0)	(84)	(0)	(0)	(0)	(80)	(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				250 ppm				1000 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>			
	squamous cell metaplasia:respiratory epithelium		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)
nasopharynx			<50>				<50>				<50>				<50>			
	inflammation:foreign body		0	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)
trachea			<50>				<50>				<50>				<50>			
	inflammation		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)
lung			<50>				<50>				<50>				<50>			
	congestion		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)
	hemorrhage		2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0
			(4)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	edema		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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}																		
lung			<50>				<50>				<50>				<50>			
	inflammatory infiltration		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)
	accumulation of foamy cells		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)
	bronchopneumonia		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)
	bronchiolar-alveolar cell hyperplasia		5	1	0	0	3	0	0	0	2	0	1	0	1	0	0	0
			(10)	(2)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(0)	(2)	(0)	(2)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	hemorrhage		0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	deposit of hemosiderin		2	0	0	0	1	0	0	0	0	0	0	0	4	0	0	0
			(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	granulation		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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		8 (16)	1 (2)	0 (0)	0 (0)	8 (16)	3 (6)	0 (0)	0 (0)	5 (10)	3 (6)	0 (0)	0 (0)	14 (28)	1 (2)	0 (0)	0 (0)
spleen			<50>				<50>				<50>				<50>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	27 (54)	0 (0)	0 (0)	0 (0) **
	deposit of hemosiderin		16 (32)	1 (2)	0 (0)	0 (0)	21 (42)	4 (8)	0 (0)	0 (0)	27 (54)	1 (2)	0 (0)	0 (0)	28 (56)	2 (4)	0 (0)	0 (0) *
	fibrosis:focal		4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	3 (6)	1 (2)	0 (0)
	extramedullary hematopoiesis		26 (52)	5 (10)	1 (2)	0 (0)	26 (52)	8 (16)	5 (10)	0 (0)	34 (68)	6 (12)	3 (6)	0 (0)	31 (62)	13 (26)	3 (6)	0 (0) **
	engorgement of erythrocyte		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17 (34)	0 (0)	0 (0)	0 (0) **
	capsule 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)	43 (86)	0 (0)	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)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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>			
	mineralization		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammation		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	inflammatory infiltration		0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	myocardial fibrosis		36	4	0	0	31	3	0	0	29	5	0	0	35	2	0	0
			(72)	(8)	(0)	(0)	(62)	(6)	(0)	(0)	(58)	(10)	(0)	(0)	(70)	(4)	(0)	(0)
	subendocardial fibrosis		1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
artery/aort			<50>				<50>				<50>				<50>			
	mineralization:artery		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Digestive system}																		
tooth			<50>				<50>				<50>				<50>			
	dysplasia		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
(Digestive system)																		
tongue		<50>					<50>				<50>				<50>			
	arteritis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
salivary gl		<50>					<50>				<50>				<50>			
	lymphocytic infiltration		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
stomach		<50>					<50>				<50>				<50>			
	erosion:forestomach		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)
	ulcer:forestomach		0	1	1	1	2	0	3	0	0	0	0	0	0	1	0	0
			(0)	(2)	(2)	(2)	(4)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	hyperplasia:forestomach		0	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	erosion:glandular stomach		1	0	0	0	5	0	0	0	6	0	0	0	4	0	0	0
			(2)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(12)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	ulcer:glandular stomach		2	0	0	0	0	0	0	0	0	0	0	0	4	2	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(4)	(0)	(0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
stomach			<50>				<50>				<50>				<50>			
	mineralization:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	dilated glands		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	squamous cell hyperplasia:forestomach		0 (0)	1 (2)	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)
small intes			<50>				<50>				<50>				<50>			
	erosion		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)
liver			<50>				<50>				<50>				<50>			
	herniation		7 (14)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)
	fatty change:peripheral		0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	granulation		12 (24)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 * (0)	2 (4)	0 (0)	0 (0)	0 ** (0)	1 (2)	0 (0)	0 (0)	0 ** (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	inflammatory cell nest		16 (32)	0 (0)	0 (0)	0 (0)	18 (36)	1 (2)	0 (0)	0 (0)	26 (52)	0 (0)	0 (0)	0 (0)	18 (36)	0 (0)	0 (0)	0 (0)
	extramedullary hematopoiesis		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)
	clear cell focus		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	acidophilic cell focus		9 (18)	1 (2)	0 (0)	0 (0)	4 (8)	3 (6)	0 (0)	0 (0)	14 (28)	2 (4)	2 (4)	0 (0)	6 (12)	5 (10)	1 (2)	0 (0)
	basophilic cell focus		5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	spongiosis hepatis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	bile duct hyperplasia		43 (86)	1 (2)	0 (0)	0 (0)	42 (84)	0 (0)	0 (0)	0 (0)	48 (96)	1 (2)	0 (0)	0 (0)	29 (58)	0 (0)	0 (0)	0 ** (0)
	bile ductular proliferation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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>			
	hepatocellular hypertrophy:central		0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(38)	(0)	(0)	(0)
	hemorrhage:central		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)
	focal fatty change		0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		4	0	0	0	6	1	0	0	6	0	1	0	4	1	0	0
			(8)	(0)	(0)	(0)	(12)	(2)	(0)	(0)	(12)	(0)	(2)	(0)	(8)	(2)	(0)	(0)
	islet cell hyperplasia		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)	(8)	(0)	(0)	(0)
	hyperplasia:acinar cell		1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	deposit of pigment		0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(38)	(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				250 ppm 50				1000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	inflammatory infiltration		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	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		27 (54)	15 (30)	6 (12)	0 (0)	30 (60)	12 (24)	5 (10)	1 (2)	22 (44)	19 (38)	6 (12)	1 (2)	9 (18)	20 (40)	20 (40)	1 (2) **
	papillary 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		1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
	mineralization:pelvis		2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	24 (48)	2 (4)	0 (0)	0 (0) **
	mineralization:cortex		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	urothelial hyperplasia:pelvis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	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				250 ppm				1000 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 (%)
{Urinary system}																		
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ulcer		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)
	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)
	transitional cell hyperplasia		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	cyst		1 (2)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	hyperplasia		7 (14)	5 (10)	4 (8)	0 (0)	8 (16)	2 (4)	1 (2)	0 (0)	5 (10)	8 (16)	4 (8)	0 (0)	7 (14)	2 (4)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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>			
	Rathke pouch		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
thyroid			<50>				<50>				<50>				<50>			
	follicular hyperplasia		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	C-cell hyperplasia		14 (28)	3 (6)	1 (2)	0 (0)	12 (24)	2 (4)	2 (4)	0 (0)	11 (22)	2 (4)	3 (6)	0 (0)	9 (18)	4 (8)	1 (2)	0 (0)
adrenal			<50>				<50>				<50>				<50>			
	extramedullary hematopoiesis		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hyperplasia:cortical cell		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
	hyperplasia:medulla		1 (2)	0 (0)	1 (2)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	2 (4)	0 (0)
	focal fatty change:cortex		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Reproductive system}																		
testis			<50>				<50>				<50>				<50>			
	mineralization		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)
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	interstitial cell hyperplasia		6 (12)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
epididymis			<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)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
semin ves			<50>				<50>				<50>				<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)	0 (0)	0 (0)	0 (0)
prostate			<50>				<50>				<50>				<50>			
	inflammation		2 (4)	1 (2)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Reproductive system}																		
prostate			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	hyperplasia		3 (6)	2 (4)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)
{Nervous system}																		
brain			<50>				<50>				<50>				<50>			
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	hyperplasia:chroid plexus		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)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	cataract		7 (14)	1 (2)	0 (0)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)	5 (10)	3 (6)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Special sense organs/appendage}																		
eye		<50>					<50>				<50>				<50>			
	retinal atrophy		18	3	1	0	2	4	5	0 **	1	3	6	0 **	3	6	5	0 **
			(36)	(6)	(2)	(0)	(4)	(8)	(10)	(0)	(2)	(6)	(12)	(0)	(6)	(12)	(10)	(0)
	keratitis		0	1	1	0	1	0	2	0	1	2	0	0	1	2	0	0
			(0)	(2)	(2)	(0)	(2)	(0)	(4)	(0)	(2)	(4)	(0)	(0)	(2)	(4)	(0)	(0)
	iritis		0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)
	mineralization:cornea		1	0	0	0	2	0	0	0	1	0	0	0	3	1	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(6)	(2)	(0)	(0)
Harder gl		<50>					<50>				<50>				<50>			
	lymphocytic infiltration		2	0	0	0	3	0	0	0	4	0	0	0	4	0	0	0
			(4)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(8)	(0)	(0)	(0)
	hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle		<50>					<50>				<50>				<50>			
	mineralization		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE

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

Organ	Findings	Group Name	Control				250 ppm				1000 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
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
(Musculoskeletal system)																		
muscle			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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

TABLE L 4

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

FEMALE: ALL ANIMALS

Organ	Findings	Group Name	Control				250 ppm				1000 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>			
	squamous cell hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
subcutis			<50>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	thrombus		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization		19	0	0	0	23	0	0	0	27	0	0	0	23	0	0	0
			(38)	(0)	(0)	(0)	(46)	(0)	(0)	(0)	(54)	(0)	(0)	(0)	(46)	(0)	(0)	(0)
	eosinophilic change:olfactory epithelium		9	31	9	0	13	27	9	0	13	31	6	0	3	28	17	0
			(18)	(62)	(18)	(0)	(26)	(54)	(18)	(0)	(26)	(62)	(12)	(0)	(6)	(56)	(34)	(0)
	eosinophilic change:respiratory epithelium		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)

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 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Respiratory system}																		
nasal cavit			<50>				<50>				<50>				<50>			
	inflammation:foreign body		3 (6)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	1 (2)	0 (0)
	inflammation:respiratory epithelium		1 (2)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	respiratory metaplasia:gland		47 (94)	0 (0)	0 (0)	0 (0)	49 (98)	0 (0)	0 (0)	0 (0)	48 (96)	0 (0)	0 (0)	0 (0)	48 (96)	0 (0)	0 (0)	0 (0)
	ulcer:respiratory epithelium		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)
nasopharynx			<50>				<50>				<50>				<50>			
	inflammation:foreign body		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)
larynx			<50>				<50>				<50>				<50>			
	ulcer		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)
	inflammation:foreign body		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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}																		
lung			<50>				<50>				<50>				<50>			
	congestion		1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	hemorrhage		1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory infiltration		1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
	accumulation of foamy cells		1	0	0	0	2	0	0	0	2	0	0	0	5	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(10)	(0)	(0)	(0)
	bronchiolar-alveolar cell hyperplasia		0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
{Hematopoietic system}																		
bone marrow			<50>				<50>				<50>				<50>			
	congestion		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	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	Control				250 ppm				1000 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>			
	deposit of hemosiderin		2	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0
			(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	granulation		0	0	0	0	0	0	0	0	0	1	0	0	2	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(4)	(0)	(0)	(0)
	increased hematopoiesis		9	2	0	0	2	2	0	0	7	1	0	0	8	4	0	0
			(18)	(4)	(0)	(0)	(4)	(4)	(0)	(0)	(14)	(2)	(0)	(0)	(16)	(8)	(0)	(0)
spleen			<50>				<50>				<50>				<50>			
	angiectasis		0	0	0	0	1	0	0	0	0	0	0	0	26	0	0	0 **
			(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(52)	(0)	(0)	(0)
	deposit of hemosiderin		38	5	0	0	32	11	0	0	27	17	0	0 *	35	1	0	0
			(76)	(10)	(0)	(0)	(64)	(22)	(0)	(0)	(54)	(34)	(0)	(0)	(70)	(2)	(0)	(0)
	fibrosis:focal		0	0	0	0	0	0	0	0	0	1	0	0	5	2	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(10)	(4)	(0)	(0)
	extramedullary hematopoiesis		32	9	3	0	38	6	1	0	27	18	4	0	24	16	3	0
			(64)	(18)	(6)	(0)	(76)	(12)	(2)	(0)	(54)	(36)	(8)	(0)	(48)	(32)	(6)	(0)
	engorgement of erythrocyte		0	0	0	0	0	0	0	0	3	0	0	0	24	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(48)	(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				250 ppm				1000 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}																		
spleen			<50>				<50>				<50>				<50>			
	capsule hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0	41	0	0	0 **
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(82)	(0)	(0)	(0)
{Circulatory system}																		
heart			<50>				<50>				<50>				<50>			
	thrombus		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	myocardial fibrosis		31	0	0	0	27	0	0	0	29	1	0	0	31	0	0	0
			(62)	(0)	(0)	(0)	(54)	(0)	(0)	(0)	(58)	(2)	(0)	(0)	(62)	(0)	(0)	(0)
artery/aort			<50>				<50>				<50>				<50>			
	mineralization:artery		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)
{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)

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 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Digestive system}																		
tooth		<50>																
	dysplasia		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)
tongue		<50>																
	ulcer		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	lymphocytic infiltration		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
stomach		<50>																
	ulcer:forestomach		2 (4)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	hyperplasia:forestomach		2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	erosion:glandular stomach		6 (12)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	1 (2)	0 (0)	0 (0)	6 (12)	1 (2)	0 (0)	0 (0)
	ulcer:glandular stomach		2 (4)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	Control 50 2 (%)	Control 50 3 (%)	Control 50 4 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Digestive system}																		
stomach		<50>																
	hyperplasia:glandular stomach		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	dilated glands		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
small intes		<50>																
	erosion		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	inflammation		1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
large intes		<50>																
	mineralization		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
	inflammation		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
liver		<50>																
	herniation		8 (16)	0 (0)	0 (0)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	7 (14)	0 (0)	0 (0)	0 (0)	10 (20)	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				250 ppm				1000 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>			
	necrosis:central		0	0	1	0	0	1	0	0	1	0	0	0	0	1	0	0
			(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	necrosis:focal		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)
	fatty change:central		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)
	fatty change:peripheral		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)
	granulation		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	inflammatory cell nest		22	3	0	0	28	3	0	0	21	2	1	0	10	1	0	0 *
			(44)	(6)	(0)	(0)	(56)	(6)	(0)	(0)	(42)	(4)	(2)	(0)	(20)	(2)	(0)	(0)
	extramedullary hematopoiesis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	acidophilic cell focus		5	1	1	0	3	1	2	0	3	1	1	0	8	1	0	0
			(10)	(2)	(2)	(0)	(6)	(2)	(4)	(0)	(6)	(2)	(2)	(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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE : A1
SEX : FEMALE

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50				250 ppm 50				1000 ppm 50				4000 ppm 50			
			1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
{Digestive system}																		
liver			<50>				<50>				<50>				<50>			
	basophilic cell focus		23 (46)	3 (6)	0 (0)	0 (0)	17 (34)	1 (2)	0 (0)	0 (0)	16 (32)	1 (2)	0 (0)	0 (0)	10 (20)	0 (0)	0 (0)	0 ** (0)
	bile duct hyperplasia		13 (26)	2 (4)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	0 (0)	20 (40)	0 (0)	0 (0)	0 (0)	17 (34)	0 (0)	0 (0)	0 (0)
	biliary cyst		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	hepatocellular hypertrophy:central		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	28 (56)	1 (2)	0 (0)	0 ** (0)
	focal fatty change		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)
pancreas			<50>				<50>				<50>				<50>			
	atrophy		0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	islet cell hyperplasia		2 (4)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	hyaline droplet		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	deposit of pigment		0	0	0	0	0	0	0	0	1	0	0	0	6	0	0	0 *
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(12)	(0)	(0)	(0)
	inflammatory infiltration		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)
	chronic nephropathy		20	3	1	0	18	0	1	0	20	2	6	0	23	5	2	0
			(40)	(6)	(2)	(0)	(36)	(0)	(2)	(0)	(40)	(4)	(12)	(0)	(46)	(10)	(4)	(0)
	hydronephrosis		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	mineralization:cortico-medullary junction		13	0	0	0	7	0	0	0	15	0	0	0	20	0	0	0
			(26)	(0)	(0)	(0)	(14)	(0)	(0)	(0)	(30)	(0)	(0)	(0)	(40)	(0)	(0)	(0)
	mineralization:papilla		7	0	0	0	2	0	0	0	2	0	0	0	7	0	0	0
			(14)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(14)	(0)	(0)	(0)
	mineralization:pelvis		1	0	0	0	5	0	0	0	7	1	0	0 *	18	2	0	0 **
			(2)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(14)	(2)	(0)	(0)	(36)	(4)	(0)	(0)
	mineralization:cortex		4	0	0	0	9	0	0	0	10	0	0	0	8	0	0	0
			(8)	(0)	(0)	(0)	(18)	(0)	(0)	(0)	(20)	(0)	(0)	(0)	(16)	(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				250 ppm				1000 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
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Urinary system}																		
kidney			<50>				<50>				<50>				<50>			
	atypical tubule hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	dilated pelvis		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
urin bladd			<50>				<50>				<50>				<50>			
	dilatation		0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
			(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
	transitional cell hyperplasia		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
{Endocrine system}																		
pituitary			<50>				<50>				<50>				<50>			
	angiectasis		4	3	0	0	6	0	0	0	4	2	1	0	2	4	1	0
			(8)	(6)	(0)	(0)	(12)	(0)	(0)	(0)	(8)	(4)	(2)	(0)	(4)	(8)	(2)	(0)
	cyst		14	1	1	0	14	4	0	0	11	2	0	0	14	2	0	0
			(28)	(2)	(2)	(0)	(28)	(8)	(0)	(0)	(22)	(4)	(0)	(0)	(28)	(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	Control				250 ppm				1000 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>			
	hyperplasia		6	4	1	0	5	5	1	0	5	4	1	0	2	4	1	0
			(12)	(8)	(2)	(0)	(10)	(10)	(2)	(0)	(10)	(8)	(2)	(0)	(4)	(8)	(2)	(0)
	Rathke pouch		1	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
thyroid			<50>				<50>				<50>				<50>			
	inflammation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)
	ultimobranchial body remanet		0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
	follicular hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	C-cell hyperplasia		14	6	5	0	12	4	1	0	14	3	1	0	11	2	2	0
			(28)	(12)	(10)	(0)	(24)	(8)	(2)	(0)	(28)	(6)	(2)	(0)	(22)	(4)	(4)	(0)
adrenal			<50>				<50>				<50>				<50>			
	fatty change		0	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)

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

Organ	Findings	Group Name / No. of Animals on Study / Grade	Control 50 1 (%)	2 (%)	3 (%)	4 (%)	250 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	1000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)	4000 ppm 50 1 (%)	2 (%)	3 (%)	4 (%)
{Endocrine system}																		
adrenal		<50>																
	focal fatty change:cortex		3	0	0	0	1	1	0	0	0	1	0	0	4	0	0	0
			(6)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(8)	(0)	(0)	(0)
{Reproductive system}																		
ovary		<50>																
	cyst		1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0
			(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(0)	(0)	(0)
	lymphocytic infiltration		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
uterus		<50>																
	dilatation		0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
			(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
	hyperplasia:gland		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)
	stromal hyperplasia		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			(0)	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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 (%)	250 ppm 50 1 (%)	250 ppm 50 2 (%)	250 ppm 50 3 (%)	250 ppm 50 4 (%)	1000 ppm 50 1 (%)	1000 ppm 50 2 (%)	1000 ppm 50 3 (%)	1000 ppm 50 4 (%)	4000 ppm 50 1 (%)	4000 ppm 50 2 (%)	4000 ppm 50 3 (%)	4000 ppm 50 4 (%)
{Reproductive system}																		
uterus		<50>																
	cystic endometrial hyperplasia		5 (10)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
mammary gl		<50>																
	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)
	galactocele		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)
{Nervous system}																		
brain		<50>																
	hemorrhage		1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	gliosis		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
{Special sense organs/appendage}																		
eye		<50>																
	cataract		2 (4)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

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

Organ	Findings	Group Name	Control				250 ppm				1000 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
			(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
{Special sense organs/appendage}																		
eye			<50>				<50>				<50>				<50>			
	retinal atrophy		24	9	1	0	15	5	0	0 *	5	2	5	0 **	22	5	2	0
			(48)	(18)	(2)	(0)	(30)	(10)	(0)	(0)	(10)	(4)	(10)	(0)	(44)	(10)	(4)	(0)
	keratitis		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)	(0)	(0)	(0)	(0)
	iritis		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)
	mineralization:cornea		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)
Harder gl			<50>				<50>				<50>				<50>			
	lymphocytic infiltration		1	0	0	0	3	0	0	0	2	1	0	0	1	1	0	0
			(2)	(0)	(0)	(0)	(6)	(0)	(0)	(0)	(4)	(2)	(0)	(0)	(2)	(2)	(0)	(0)
nasolacr d			<50>				<50>				<50>				<50>			
	inflammation		2	1	0	0	3	0	0	0	4	0	0	0	3	0	0	0
			(4)	(2)	(0)	(0)	(6)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
{Musculoskeletal system}																		
muscle			<50>				<50>				<50>				<50>			
	mineralization		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

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				250 ppm				1000 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 (%)
{Musculoskeletal system}																		
bone			<50>				<50>				<50>				<50>			
	osteosclerosis		2	2	0	0	3	0	0	0	1	1	0	0	1	0	0	0
			(4)	(4)	(0)	(0)	(6)	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(2)	(0)	(0)	(0)

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

TABLE O 1

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: MALE

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : skin/appendage			
	TUMOR : keratoacanthoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	3/50(6.0)	5/50(10.0)	2/50(4.0)
Adjusted rates(b)	8.11	6.38	11.63	4.88
Terminal rates(c)	3/37(8.1)	2/40(5.0)	5/43(11.6)	2/41(4.9)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7493			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5513			
Fisher Exact test(e)		P = 0.6611	P = 0.3575	P = 0.5000
	SITE : subcutis			
	TUMOR : fibroma			
Tumor rate				
Overall rates(a)	2/50(4.0)	11/50(22.0)	3/50(6.0)	2/50(4.0)
Adjusted rates(b)	5.41	25.00	6.98	2.44
Terminal rates(c)	2/37(5.4)	10/40(25.0)	3/43(7.0)	1/41(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.2505			
Prevalence method(d)	P = 0.9835			
Combined analysis(d)	P = 0.9545			
Cochran-Armitage test(e)	P = 0.1260			
Fisher Exact test(e)		P = 0.0073**	P = 0.5000	P = 0.6913
	SITE : subcutis			
	TUMOR : fibroma, fibrosarcoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	13/50(26.0)	3/50(6.0)	3/50(6.0)
Adjusted rates(b)	5.41	25.00	6.98	4.88
Terminal rates(c)	2/37(5.4)	10/40(25.0)	3/43(7.0)	2/41(4.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.4048			
Prevalence method(d)	P = 0.9523			
Combined analysis(d)	P = 0.9265			
Cochran-Armitage test(e)	P = 0.1780			
Fisher Exact test(e)		P = 0.0019**	P = 0.5000	P = 0.5000

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : spleen TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	5/50(10.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	8.11	7.50	2.33	0.0
Terminal rates(c)	3/37(8.1)	3/40(7.5)	1/43(2.3)	0/41(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5127			
Prevalence method(d)	P = 0.9834			
Combined analysis(d)	P = 0.9489			
Cochran-Armitage test(e)	P = 0.1349			
Fisher Exact test(e)		P = 0.3575	P = 0.2180	P = 0.1022
	SITE : spleen TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	2.44
Terminal rates(c)	0/37(0.0)	0/40(0.0)	0/43(0.0)	1/41(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0179* ?			
Prevalence method(d)	P = 0.1593			
Combined analysis(d)	P = 0.0032**?			
Cochran-Armitage test(e)	P = 0.0033**			
Fisher Exact test(e)		P = N.C.	P = N.C.	P = 0.1212
	SITE : spleen TUMOR : hemangioma, hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	1/50(2.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	2.50	0.0	2.44
Terminal rates(c)	0/37(0.0)	1/40(2.5)	0/43(0.0)	1/41(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0179* ?			
Prevalence method(d)	P = 0.2470			
Combined analysis(d)	P = 0.0265*			
Cochran-Armitage test(e)	P = 0.0266*			
Fisher Exact test(e)		P = 0.5000	P = N.C.	P = 0.1212

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : liver			
	TUMOR : hepatocellular adenoma, hepatocellular carcinoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	1/50(2.0)	0/50(0.0)	2/50(4.0)
Adjusted rates(b)	7.69	2.50	0.0	4.88
Terminal rates(c)	2/37(5.4)	1/40(2.5)	0/43(0.0)	2/41(4.9)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.4797			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.9223			
Fisher Exact test(e)		P = 0.3087	P = 0.1212	P = 0.5000
	SITE : pancreas			
	TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	6/50(12.0)	3/50(6.0)	2/50(4.0)	0/50(0.0)
Adjusted rates(b)	14.29	6.00	4.65	0.0
Terminal rates(c)	4/37(10.8)	2/40(5.0)	2/43(4.7)	0/41(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.9962			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0230*			
Fisher Exact test(e)		P = 0.2435	P = 0.1343	P = 0.0133*
	SITE : pancreas			
	TUMOR : islet cell adenoma, islet cell adenocarcinoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)
Adjusted rates(b)	16.67	6.00	4.65	2.44
Terminal rates(c)	4/37(10.8)	2/40(5.0)	2/43(4.7)	1/41(2.4)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.9803			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0636			
Fisher Exact test(e)		P = 0.1589	P = 0.0798	P = 0.0297*

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : pituitary gland			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	17/50(34.0)	19/50(38.0)	11/50(22.0)	8/50(16.0)
Adjusted rates(b)	26.67	41.46	25.00	19.51
Terminal rates(c)	9/37(24.3)	16/40(40.0)	10/43(23.3)	8/41(19.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.9951			
Prevalence method(d)	P = 0.9763			
Combined analysis(d)	P = 0.9968			
Cochran-Armitage test(e)	P = 0.0152*			
Fisher Exact test(e)		P = 0.4176	P = 0.1327	P = 0.0317*
	SITE : pituitary gland			
	TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	18/50(36.0)	21/50(42.0)	11/50(22.0)	10/50(20.0)
Adjusted rates(b)	28.89	41.46	25.00	19.51
Terminal rates(c)	10/37(27.0)	16/40(40.0)	10/43(23.3)	8/41(19.5)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8679			
Prevalence method(d)	P = 0.9788			
Combined analysis(d)	P = 0.9905			
Cochran-Armitage test(e)	P = 0.0295*			
Fisher Exact test(e)		P = 0.3410	P = 0.0928	P = 0.0591
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	10/50(20.0)	12/50(24.0)	13/50(26.0)
Adjusted rates(b)	25.64	25.00	27.91	28.26
Terminal rates(c)	9/37(24.3)	10/40(25.0)	12/43(27.9)	11/41(26.8)
Statistical analysis				
Peto test				
Standard method(d)	P = --------			
Prevalence method(d)	P = 0.3612			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5187			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.4076

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma, C-cell carcinoma			
Tumor rate				
Overall rates(a)	12/50(24.0)	11/50(22.0)	14/50(28.0)	14/50(28.0)
Adjusted rates(b)	28.21	25.00	32.56	30.43
Terminal rates(c)	10/37(27.0)	10/40(25.0)	14/43(32.6)	12/41(29.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5210			
Prevalence method(d)	P = 0.3588			
Combined analysis(d)	P = 0.4041			
Cochran-Armitage test(e)	P = 0.5543			
Fisher Exact test(e)		P = 0.5000	P = 0.4100	P = 0.4100
	SITE : adrenal gland			
	TUMOR : pheochromocytoma			
Tumor rate				
Overall rates(a)	4/50(8.0)	8/50(16.0)	4/50(8.0)	4/50(8.0)
Adjusted rates(b)	8.00	17.50	9.30	9.30
Terminal rates(c)	2/37(5.4)	7/40(17.5)	4/43(9.3)	3/41(7.3)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.7360			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.5299			
Fisher Exact test(e)		P = 0.1783	P = 0.6425	P = 0.6425
	SITE : adrenal gland			
	TUMOR : pheochromocytoma, pheochromocytoma:malignant			
Tumor rate				
Overall rates(a)	4/50(8.0)	8/50(16.0)	6/50(12.0)	4/50(8.0)
Adjusted rates(b)	8.00	17.50	9.30	9.30
Terminal rates(c)	2/37(5.4)	7/40(17.5)	4/43(9.3)	3/41(7.3)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5332			
Prevalence method(d)	P = 0.7373			
Combined analysis(d)	P = 0.7582			
Cochran-Armitage test(e)	P = 0.4896			
Fisher Exact test(e)		P = 0.1783	P = 0.3703	P = 0.6425

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : testis			
	TUMOR : interstitial cell tumor			
Tumor rate				
Overall rates(a)	37/50(74.0)	40/50(80.0)	46/50(92.0)	46/50(92.0)
Adjusted rates(b)	86.84	87.50	93.88	97.67
Terminal rates(c)	32/37(86.5)	35/40(87.5)	40/43(93.0)	40/41(97.6)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.0420*			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0259*			
Fisher Exact test(e)		P = 0.3176	P = 0.0155*	P = 0.0155*

(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 : * : $P \leq 0.05$ ** : $P \leq 0.01$
N.C. :Statistical value cannot be calculated and was not significant.

STUDY No. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : MALE

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : ALL SITE TUMOR : hemangiosarcoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	0.0	0.0	4.88
Terminal rates(c)	0/37(0.0)	0/40(0.0)	0/43(0.0)	2/41(4.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.0179* ?			
Prevalence method(d)	P = 0.0163* ?			
Combined analysis(d)	P = 0.0006**?			
Cochran-Armitage test(e)	P = 0.0007**			
Fisher Exact test(e)		P = N.C.	P = N.C.	P = 0.0587

(HPT360A)

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

TABLE O 2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: FEMALE

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : subcutis			
	TUMOR : fibroma, fibrosarcoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	3/50(6.0)	0/50(0.0)	0/50(0.0)
Adjusted rates(b)	0.0	4.65	0.0	0.0
Terminal rates(c)	0/40(0.0)	2/43(4.7)	0/45(0.0)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.8612			
Prevalence method(d)	P = 0.8138			
Combined analysis(d)	P = 0.9470			
Cochran-Armitage test(e)	P = 0.1541			
Fisher Exact test(e)		P = 0.3087	P = 0.5000	P = 0.5000
	SITE : lung			
	TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma, bronchial carcinoma			
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	3/50(6.0)	0/50(0.0)
Adjusted rates(b)	0.0	0.0	4.44	0.0
Terminal rates(c)	0/40(0.0)	0/43(0.0)	2/45(4.4)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.3511			
Prevalence method(d)	P = 0.5301			
Combined analysis(d)	P = 0.5861			
Cochran-Armitage test(e)	P = 0.7324			
Fisher Exact test(e)		P = N.C.	P = 0.1212	P = N.C.
	SITE : spleen			
	TUMOR : mononuclear cell leukemia			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	0/50(0.0)	5/50(10.0)
Adjusted rates(b)	0.0	2.33	0.0	6.98
Terminal rates(c)	0/40(0.0)	1/43(2.3)	0/45(0.0)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1511			
Prevalence method(d)	P = 0.0235*			
Combined analysis(d)	P = 0.0888			
Cochran-Armitage test(e)	P = 0.1335			
Fisher Exact test(e)		P = 0.5000	P = 0.1212	P = 0.3575

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : pituitary gland TUMOR : adenoma			
Tumor rate				
Overall rates(a)	11/50(22.0)	13/50(26.0)	12/50(24.0)	16/50(32.0)
Adjusted rates(b)	17.50	25.58	26.67	29.55
Terminal rates(c)	7/40(17.5)	11/43(25.6)	12/45(26.7)	12/43(27.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5586			
Prevalence method(d)	P = 0.1367			
Combined analysis(d)	P = 0.1809			
Cochran-Armitage test(e)	P = 0.2661			
Fisher Exact test(e)		P = 0.4076	P = 0.5000	P = 0.1839
	SITE : pituitary gland TUMOR : adenocarcinoma			
Tumor rate				
Overall rates(a)	2/50(4.0)	1/50(2.0)	4/50(8.0)	0/50(0.0)
Adjusted rates(b)	5.00	2.22	4.44	0.0
Terminal rates(c)	2/40(5.0)	0/43(0.0)	2/45(4.4)	0/43(0.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.5321			
Prevalence method(d)	P = 0.9071			
Combined analysis(d)	P = 0.8971			
Cochran-Armitage test(e)	P = 0.2335			
Fisher Exact test(e)		P = 0.5000	P = 0.3389	P = 0.2475
	SITE : pituitary gland TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	13/50(26.0)	14/50(28.0)	16/50(32.0)	16/50(32.0)
Adjusted rates(b)	22.50	26.67	31.11	29.55
Terminal rates(c)	9/40(22.5)	11/43(25.6)	14/45(31.1)	12/43(27.9)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.6078			
Prevalence method(d)	P = 0.2705			
Combined analysis(d)	P = 0.3429			
Cochran-Armitage test(e)	P = 0.5555			
Fisher Exact test(e)		P = 0.5000	P = 0.3299	P = 0.3299

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : thyroid			
	TUMOR : C-cell adenoma			
Tumor rate				
Overall rates(a)	7/50(14.0)	9/50(18.0)	7/50(14.0)	5/50(10.0)
Adjusted rates(b)	17.50	20.93	15.56	10.64
Terminal rates(c)	7/40(17.5)	9/43(20.9)	7/45(15.6)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.8705			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.3378			
Fisher Exact test(e)		P = 0.3929	P = 0.6129	P = 0.3798
	SITE : thyroid			
	TUMOR : C-cell adenoma,C-cell carcinoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	11/50(22.0)	9/50(18.0)	5/50(10.0)
Adjusted rates(b)	20.00	25.58	20.00	10.64
Terminal rates(c)	8/40(20.0)	11/43(25.6)	9/45(20.0)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = 1.0000 ?			
Prevalence method(d)	P = 0.9483			
Combined analysis(d)	P = 0.9614			
Cochran-Armitage test(e)	P = 0.1286			
Fisher Exact test(e)		P = 0.4016	P = 0.6024	P = 0.1940
	SITE : uterus			
	TUMOR : endometrial stromal polyp			
Tumor rate				
Overall rates(a)	5/50(10.0)	2/50(4.0)	6/50(12.0)	7/50(14.0)
Adjusted rates(b)	11.63	4.65	13.33	16.28
Terminal rates(c)	4/40(10.0)	2/43(4.7)	6/45(13.3)	7/43(16.3)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.1305			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.2227			
Fisher Exact test(e)		P = 0.2180	P = 0.5000	P = 0.3798

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : uterus TUMOR : adenocarcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	0.0	0.0	4.65
Terminal rates(c)	0/40(0.0)	0/43(0.0)	0/45(0.0)	2/43(4.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1033			
Prevalence method(d)	P = 0.0157* ?			
Combined analysis(d)	P = 0.0089**			
Cochran-Armitage test(e)	P = 0.0074**			
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.1811
	SITE : uterus TUMOR : adenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	1/50(2.0)	1/50(2.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	2.33	0.0	4.65
Terminal rates(c)	0/40(0.0)	1/43(2.3)	0/45(0.0)	2/43(4.7)
Statistical analysis				
Peto test				
Standard method(d)	P = 0.1033			
Prevalence method(d)	P = 0.0827			
Combined analysis(d)	P = 0.0272*			
Cochran-Armitage test(e)	P = 0.0295*			
Fisher Exact test(e)		P = 0.7525	P = 0.5000	P = 0.1811
	SITE : mammary gland TUMOR : fibroadenoma			
Tumor rate				
Overall rates(a)	8/50(16.0)	11/50(22.0)	7/50(14.0)	2/50(4.0)
Adjusted rates(b)	17.50	23.40	14.89	4.65
Terminal rates(c)	7/40(17.5)	10/43(23.3)	5/45(11.1)	2/43(4.7)
Statistical analysis				
Peto test				
Standard method(d)	P = ------			
Prevalence method(d)	P = 0.9962			
Combined analysis(d)	P = ------			
Cochran-Armitage test(e)	P = 0.0152*			
Fisher Exact test(e)		P = 0.3055	P = 0.5000	P = 0.0458*

Group Name	Control	250 ppm	1000 ppm	4000 ppm
	SITE : mammary gland			
	TUMOR : adenoma, fibroadenoma, adenocarcinoma			
Tumor rate				
Overall rates(a)	9/50(18.0)	11/50(22.0)	10/50(20.0)	3/50(6.0)
Adjusted rates(b)	20.00	23.40	21.28	6.98
Terminal rates(c)	8/40(20.0)	10/43(23.3)	8/45(17.8)	3/43(7.0)
Statistical analysis				
Peto test				
Standard method(d)	P = -------			
Prevalence method(d)	P = 0.9922			
Combined analysis(d)	P = -------			
Cochran-Armitage test(e)	P = 0.0266*			
Fisher Exact test(e)		P = 0.4016	P = 0.5000	P = 0.0606

(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 1

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

TABLE Q 1 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj MALE RAT

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Spleen	2748			
Hemangioma		5	0.2	0 - 2
Hemangiosarcoma		7	0.3	0 - 4
Hemangioma + Hemangiosarcoma		12	0.4	0 - 4
Subcutis	2748			
Hemangioma		3	0.1	0 - 2
All organ	2748			
Hemangioma		11	0.4	0 - 2
Hemangiosarcoma		8	0.3	0 - 4
Hemangioma + Hemangiosarcoma		19	0.7	0 - 4
Testis	2747			
Interstitial cell tumor		2282	83.1	56 - 98

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

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

TABLE Q 2

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

TABLE Q 2 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrlCrlj FEMALE RAT

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Uterus	2544			
Adenoma		7	0.3	0 - 2
Adenocarcinoma		15	0.6	0 - 4
Adenoma + Adenocarcinoma		22	0.9	0 - 4
Spleen				
Mononuclear cell leukemia	2547	314	12.3	2 - 26

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

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

TABLE R 1

CAUSE OF DEATH: MALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : MALE

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

Group Name	Control	250 ppm	1000 ppm	4000 ppm
Number of Dead and Moribund Animal	13	10	7	9
no microscop confirm	2	0	1	0
digestive sy les	1	1	0	0
urinary sy les	0	0	1	0
urinary retention	0	0	0	1
tumor d:leukemia	2	0	1	1
tumor d:subcutis	0	2	0	1
tumor d:thymus	0	1	0	0
tumor d:spleen	0	0	0	2
tumor d:oral cavity	0	0	0	1
tumor d:large intes	1	0	0	0
tumor d:pituitary	5	4	0	2
tumor d:thyroid	0	1	0	0
tumor d:adrenal	0	0	2	0
tumor d:spinal cord	1	0	0	0
tumor d:periph nerv	1	0	0	0
tumor d:Zymbal gl	0	1	0	0
tumor d:pleura	0	0	2	0
tumor d:peritoneum	0	0	0	1

TABLE R 2

CAUSE OF DEATH: FEMALE

STUDY NO. : 0684
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]
SEX : FEMALE

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

Group Name	Control	250 ppm	1000 ppm	4000 ppm
Number of Dead and Moribund Animal	10	7	5	7
thrombosis	1	0	0	0
tumor d:leukemia	3	1	0	2
tumor d:subcutis	1	1	0	0
tumor d:lung	0	0	1	0
tumor d:liver	0	1	0	0
tumor d:pituitary	3	2	2	2
tumor d:thyroid	1	0	0	0
tumor d:uterus	1	0	2	3
tumor d:brain	0	1	0	0
tumor d:periph nerv	0	1	0	0

FIGURES

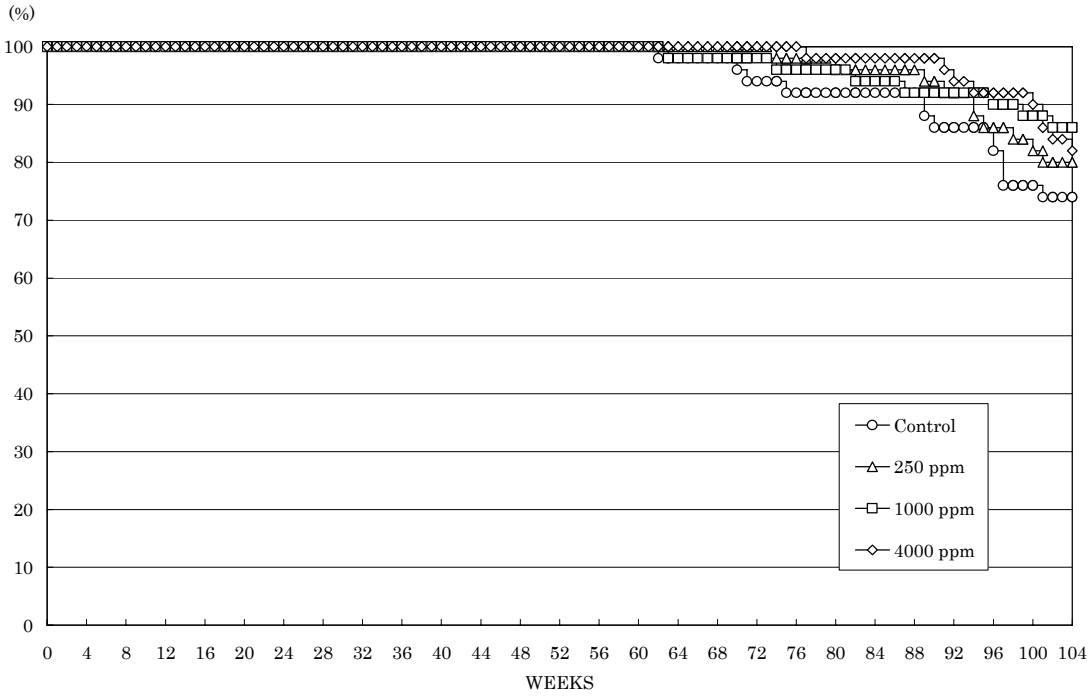


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

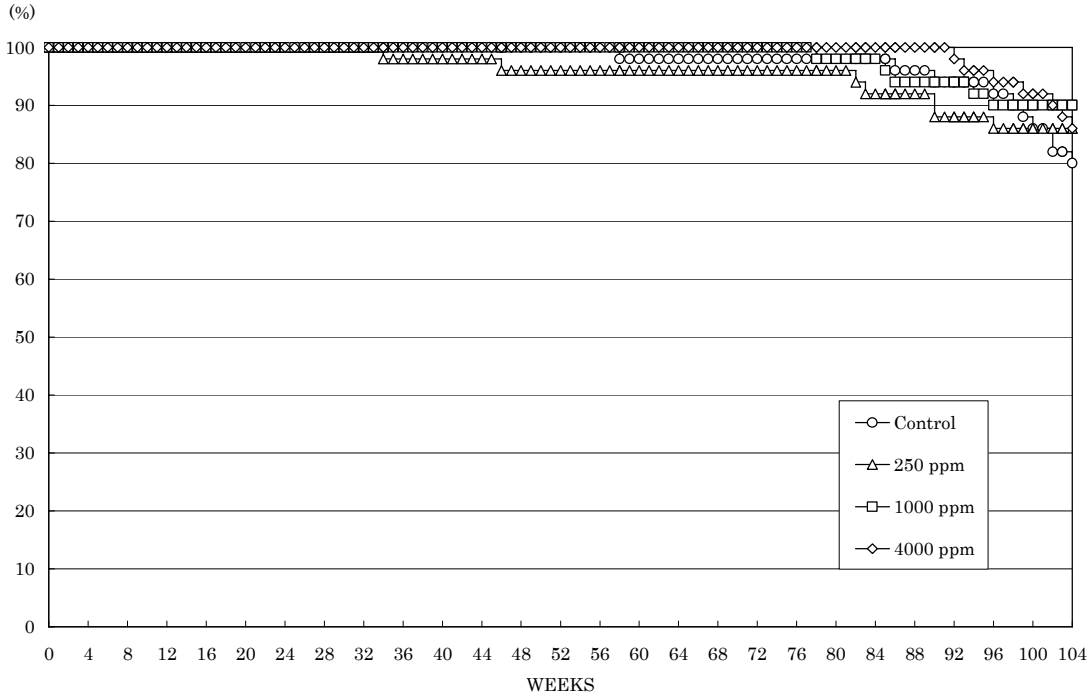


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

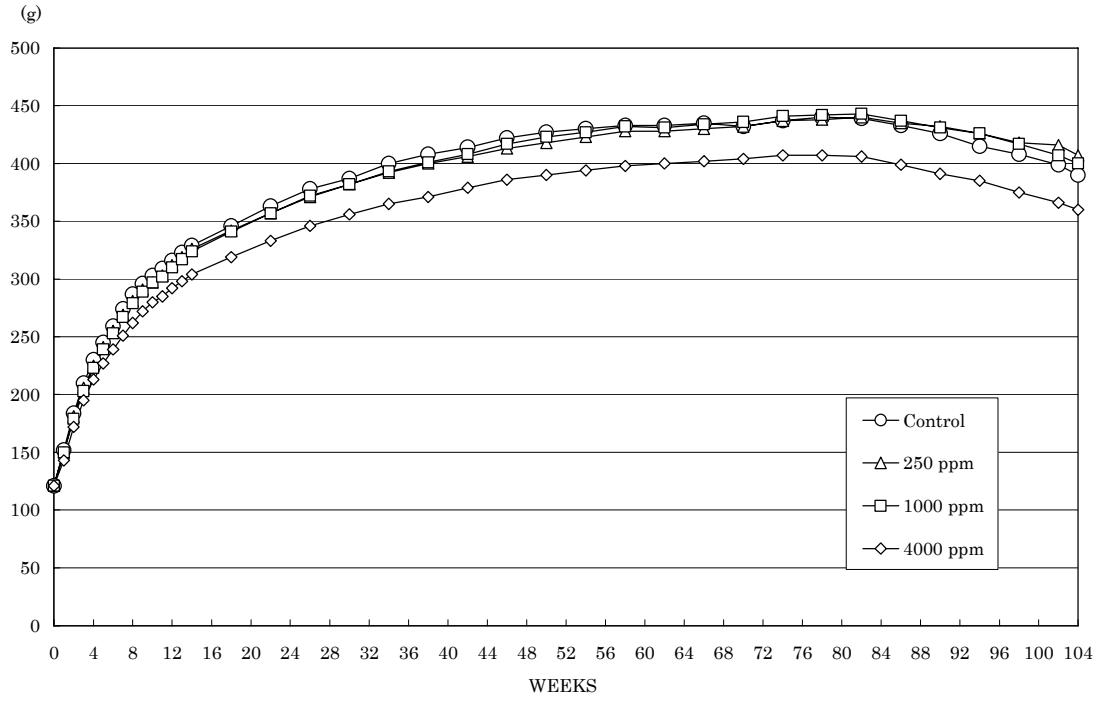


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

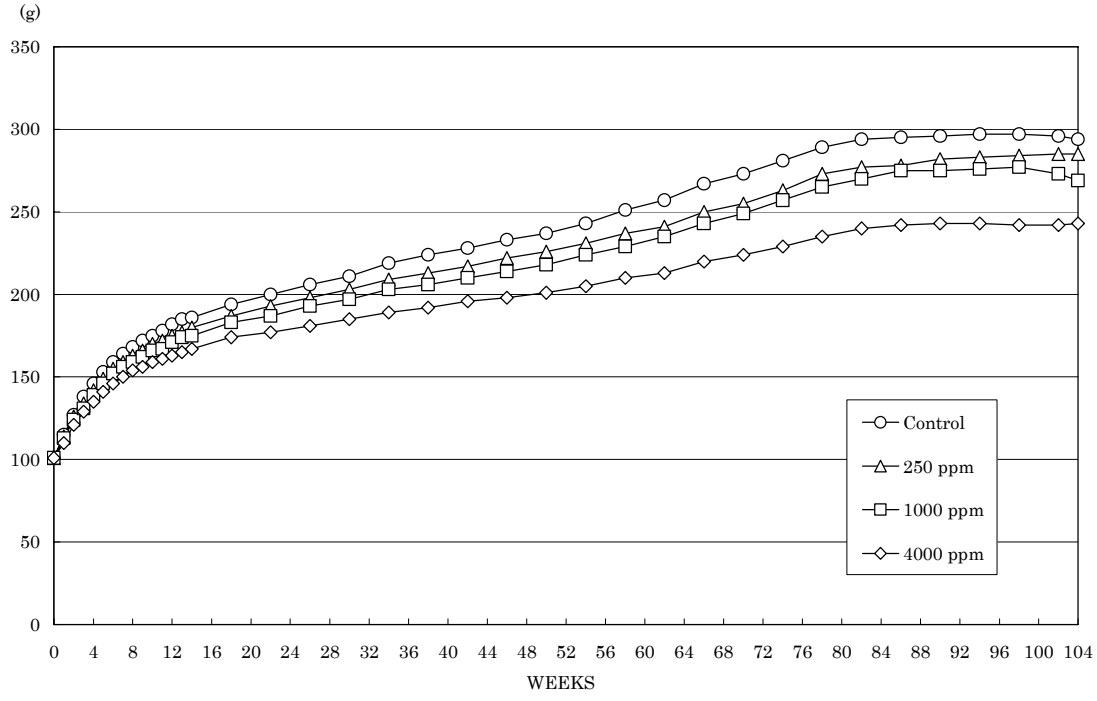


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

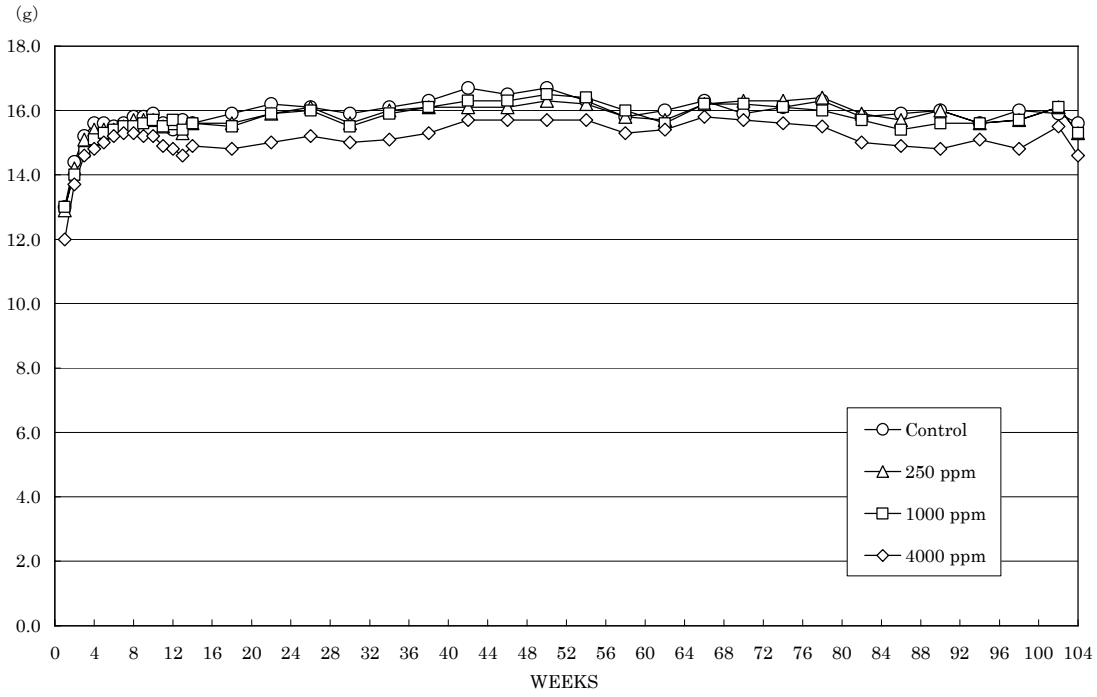


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

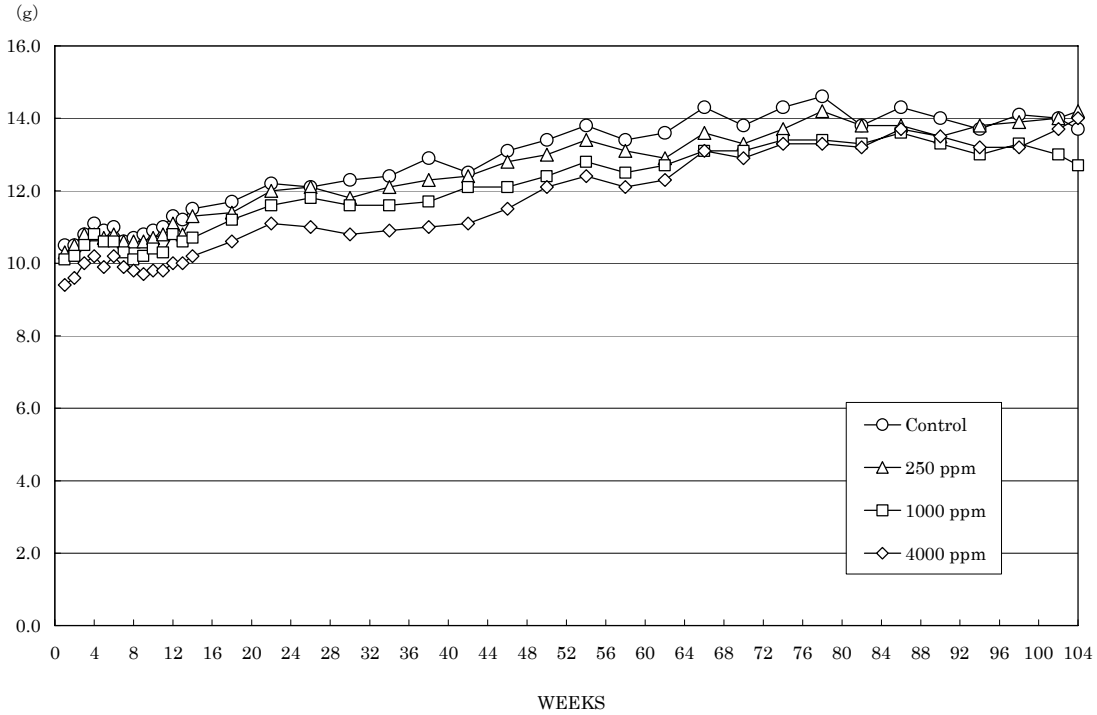
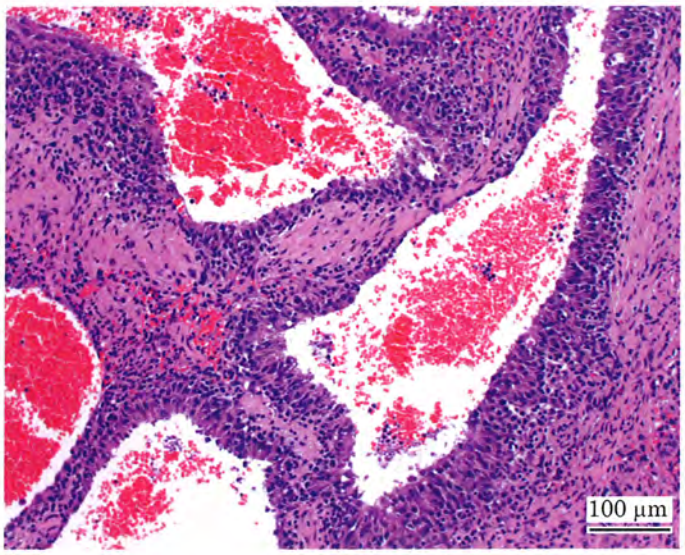
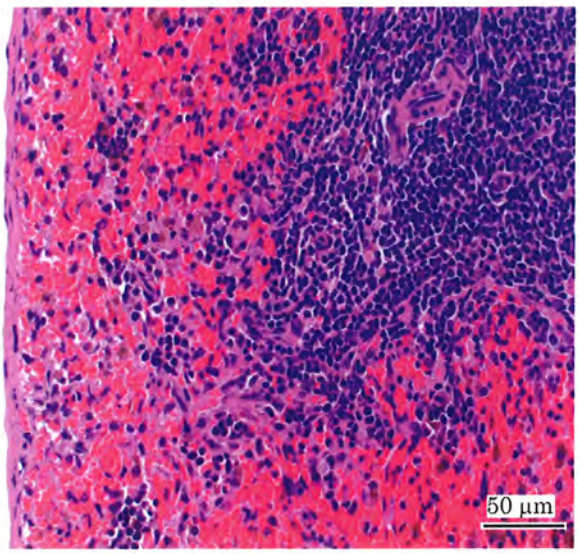


FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

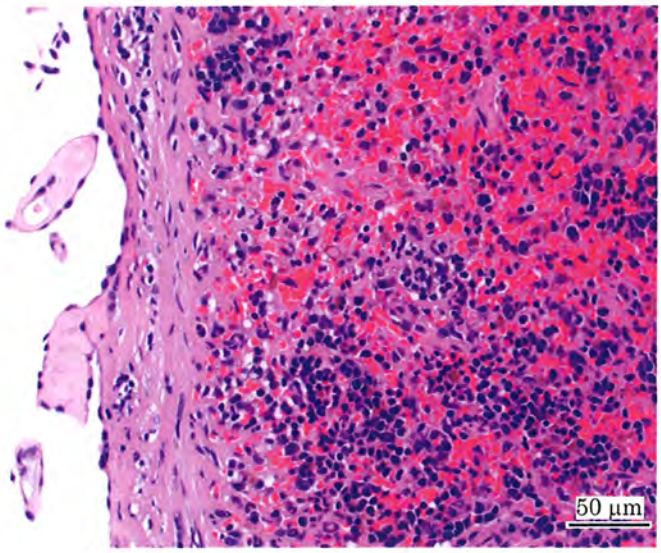


Photograph 1
Spleen: Hemangiosarcoma
Rat, Male, 4000 ppm, Animal No. 0684-1343 (H&E)

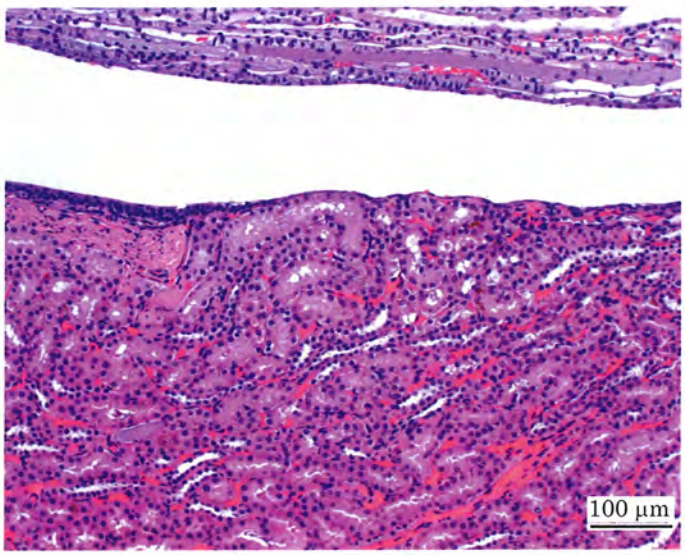
Photograph 2
Uterus: Adenocarcinoma
Rat, Female, 4000 ppm, Animal No. 0684-2320 (H&E)



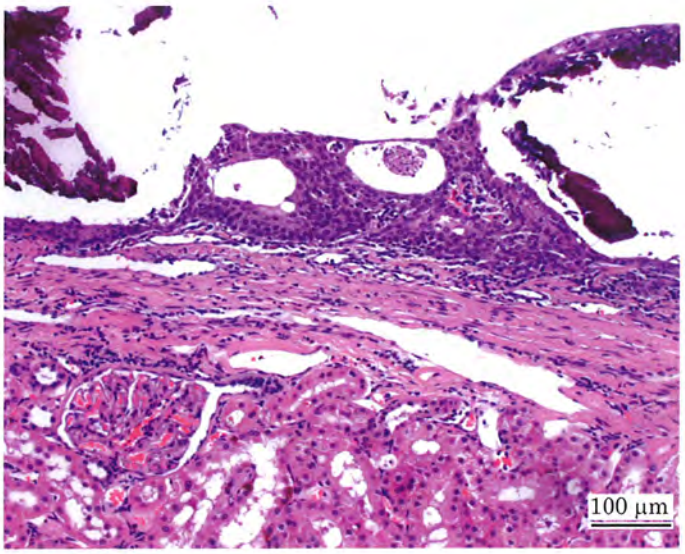
Photograph 3
Spleen: Normal
Rat, Male, Control, Animal No. 0684-1016 (H&E)



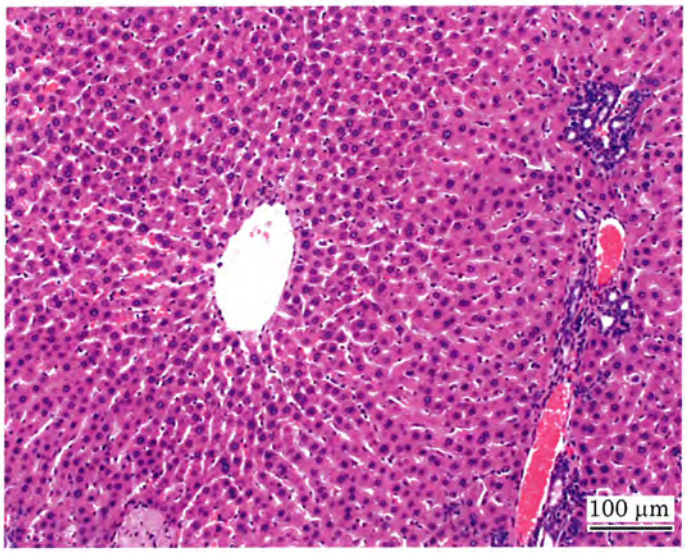
Photograph 4
Spleen: Capsule hyperplasia, extramedullary hematopoiesis, deposit of hemosiderin
Rat, Male, 4000 ppm, Animal No. 0684-1317 (H&E)



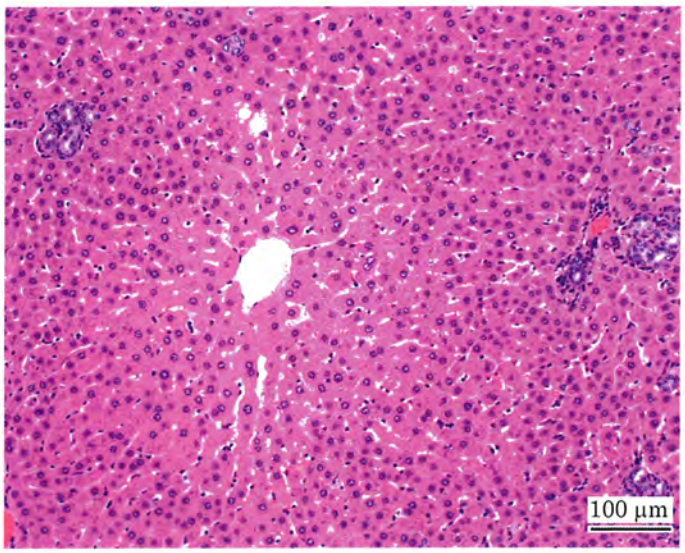
Photograph 5
Kidney: Normal
Rat, Male, Control, Animal No. 0684-1026 (H&E)



Photograph 6
Kidney: Urothelial hyperplasia:pelvis, mineralization:pelvis
Rat, Male, 4000 ppm, Animal No. 0684-1318 (H&E)



Photograph 7
Liver: Normal
Rat, Male, Control, Animal No. 0684-1022 (H&E)



Photograph 8
Liver: Hepatocellular hypertrophy: central
Rat, Male, 4000 ppm, Animal No. 0684-1316 (H&E)