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 adenocarcinoma 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

						Peto	Cochran-
	Dose (ppm)	0	250	1000	4000	test	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 *		\downarrow
spleen	hemangioma	0	1	0	0		
pituitary	adenoma	17	19	11	8 *		\downarrow
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	↑ ↑	$\uparrow \uparrow$
_	mononuclear cell leukemia	5	3	2	1		
spleen	hemangioma+	0	1	0	3	1	•
_	hemangiosarcoma	U	1	Ü	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

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

						Peto	Cochran-
	Dose (ppm)	0	250	1000	4000	test	Armitage
							test
Number of exar	mined 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 *		\downarrow
malignant tumo	r						
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	$\uparrow \uparrow$	$\uparrow \uparrow$
uterus	adenoma+adenocarcinoma	1	1	0	4	1	1

Significant difference

*: p≦0.05	**: p≦0.01	(Fisher test)
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SELECTED TABLES

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TABLE C 1

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: MALE

PAGE : 1

STUDY NO. : 0684
ANIMAL : KAT F344/DuCr.ICr.Lj[F344/DuCr.j]
UNIT : R
REPORT TYPE : A1 104
SEX : MALE

		MARATA SERVICE										
4	Av. Wt.	No. of	Av. Wt.	% of	No. of	Av. Wt.	% of	No. of	Av. Wt.	Jo %	No. of	
meek on Study	Ý	Surviv. (50)		cont. (50)	Surviv.		cont. (50)	Surviv.		cont. <50>	Surviv.	
0	1	50/50	1	100	50/50	1	100	50/50	121 (50)	100	50/50	
_		20/20		66	50/50	_	66	50/50	143 (50)	94	50/50	
2		20/20		86	50/50	_	26	50/50	172 (50)	93	50/50	
3		20/20		86	20/20	_	26	50/50	195 (50)	93	50/50	
4		20/20		86	20/20	_	26	50/50	_	93	20/20	
2		20/20		86	20/20	_	86	20/20	-	93	50/50	
9		20/20		86	50/50	_	86	20/20	239 (50)	36	50/50	
2		20/20		86	50/50	_	26	50/50	-	36	50/50	
8		20/20		86	20/20	279 (50)	26	20/20	_	91	50/50	
6:		50/50		86	50/50		86	50/50	_	85	50/50	
10		20/20		86	50/50		86	20/20	_	92	50/50	
11		20/20		86	20/20		86	20/20	_	92	50/50	
12		20/20		66	50/50		86	50/50	_	36	20/20	
13		20/20		66	20/20		86	50/50	_	65	50/50	
14		20/20		66	50/50		86	50/50	304 (50)	92	20/20	
18		50/50		66	50/50		66	50/50	_	92	20/20	
22	363 (50)	20/20	357 (50)	98	50/50	357 (50)	86	50/50	_	92	50/50	
56		20/20		98	50/50		86	20/20	_	92	50/50	
30		20/20		66	20/20		66	50/50	356 (50)	36	50/50	
34		20/20		86	20/20	393 (50)	86	20/20	-	91	20/20	
88		20/20		86	20/20		86	20/20	371 (50)	91	50/50	
22		20/20		86	20/20		66	50/50	-	92	50/50	
91		20/20		86	50/50	417 (50)	66	50/50	386 (50)	91	50/50	
06		20/20		86	50/50		66	50/50		91	50/50	
Z.		20/20		86	50/50		66	50/50		36	20/20	
58		20/20		66	20/20		100	50/50	_	65	50/50	
52		49/20		66	20/20		100	20/20	400 (50)	36	20/20	
96		49/50		66	20/20		100	49/50	_	85	20/20	
10	-	48/20		100	20/20	-	101	49/50	_	94	20/20	
74	437 (47)	47/50		100	49/50	441 (48)	101	48/50	407 (50)	93	50/50	
78	440 (46)	46/20		100	49/50	442 (48)	100	48/50	407 (49)	93	49/50	
82		46/50		001	48/50		101	47/50	_	92	49/50	
98	433 (46)	46/20		001	48/50	437 (47)	101	47/50	399 (49)	36	49/50	
06	426 (43)	43/50		101	47/50	431 (46)	101	46/50	391 (49)	36	49/50	
94	415 (43)	43/20	426 (44)	103	44/50	426 (46)	103	46/50	385 (46)	93	46/50	
86	-	38/50		102	42/50	417 (45)	102	15/50	375 (46)	85	46/20	
02	_	37/20		104	40/50		102	43/50	_	36	42/50	
04	390 (37)	37/20	407 (40)	104	40/50	_	103	43/50	_	92	41/50	

BAIS 4

(BI0040)

TABLE C 2

BODY WEIGHT CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

(BI0040)

PAGE: 2

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj]
UNIT : £
REPORT TYPE : A1 104
SEX : FBMALE

TABLE C 3

BODY WEIGHT CHANGES: MALE

Group Name Administration week 1 2 3 4 5 6 6 Control 121± 6 152± 8 184± 10 210± 11 230± 12 255± 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** 239± 10* 4000 ppm 121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239± 11**	STUDY NO. : 0684 ANIMAL : RAT F344/DuCr.Ic.I.j[F344/DuCr.j] UNIT : R REPORT TYPE : A1 104 SEX : MALE	144/DuCr.j]			BODY ALL AN	WEIGHT VINALS	BODY WEIGHT CHANGES (SUMMARY) ALL ANIMALS	(SUMMARY)							PAGE :	
121	Name	Admini:	stration weel			2		8	Value (Market Arter)	4		2	111111111111111111111111111111111111111	9		
121± 6 150± 8 181± 7 206± 8 225± 8 241± 8 255± 8 179± 9** 203± 9** 223± 9** 239± 10* 253± 10** 253± 121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239± 121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239± 121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239± 121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239± 121± 6 143± 7** 172± 9** 195± 9** 195± 9** 213± 9** 227± 10** 239± 121±	Control	121	9	$152\pm$	œ	184±	10	210≟	11	730 ∓	11	245 土	12	259 ±	14	
$121\pm$ 6 $150\pm$ 8 $179\pm$ 9** $203\pm$ 9** $223\pm$ 9** $239\pm$ 10* $253\pm$ 10* $253\pm$ 10* $253\pm$ 10* $253\pm$ 10* $253\pm$ 10* $253\pm$ 10** $253\pm$ $253\pm$ 10** $253\pm$.50 ppm	121	9	150±	8	181+	2	206±	8	225±	ø	$241\pm$	æ	255 ±	တ	
121± 6 143± 7** 172± 9** 195± 9** 213± 9** 227± 10** 239±	uid d 0 00	121±	9	150±	ø	±621	**6	203 =	**6	223±	**6	239±	*01	253 ±	10*	
	แห้น์ 000	121	ŷ.	143±	**	172±	**6	195±	**6	213±	**6	227±	**0!	7 39+	*** []	

BAIS 4

Test of Dunnett

** : $P \le 0.01$

Significant difference ; * : P \leq 0.05

(HAN260)

Control Page Aministration Week 8 9 10 11 12 13 13 14 15 15 15 15 15 15 15	- KI													***************************************		-
$274\pm 15 \qquad 287\pm 17 \qquad 296\pm 18 \qquad 303\pm 18 \qquad 309\pm 18 \qquad 316\pm 18 \qquad 323\pm 323\pm 19 \qquad 269\pm 10 \qquad 281\pm 11 \qquad 297\pm 13 \qquad 303\pm 13 \qquad 312\pm 14 \qquad 319\pm 1267\pm 10* \qquad 279\pm 11* \qquad 289\pm 13 \qquad 297\pm 13 \qquad 302\pm 12* \qquad 310\pm 13 \qquad 317\pm 14 \qquad 319\pm 12* \qquad 251\pm 11** \qquad 262\pm 12** \qquad 280\pm 12** \qquad 280\pm 12** \qquad 285\pm 13** \qquad 292\pm 13** \qquad 298\pm $	p name	Adminis 7	stration			6		10				12		13		
$269 \pm 10 \qquad 281 \pm 11 \qquad 291 \pm 11 \qquad 297 \pm 13 \qquad 302 \pm 12 * \qquad 312 \pm 14 \qquad 319 \pm 12 * \qquad 10 * \qquad 289 \pm 13 \qquad 297 \pm 13 \qquad 302 \pm 12 * \qquad 310 \pm 13 \qquad 317 \pm 12 * \qquad 11 * \qquad 281 \pm 12 * \qquad 281 \pm 13 * \qquad 282 \pm 13 * \qquad 283 \pm$	Control		15	287±	17	∓967	81	303 ±	18	309 ±	18	316±	18	323 ±	19	
$267\pm \ 10* \qquad 279\pm \ 11* \qquad 289\pm \ 13 \qquad 297\pm \ 13 \qquad 302\pm \ 12* \qquad 310\pm \ 13 \qquad 317\pm \qquad 251\pm \ 11** \qquad 262\pm \ 12** \qquad 272\pm \ 13** \qquad 280\pm \ 12** \qquad 285\pm \ 13** \qquad 292\pm \ 13** \qquad 298\pm \qquad 29$	250 ppm		10	281±	11	±162	11	297 ±	13	303∓	13	312±	14	319±	14	
251± 11** 262± 12** 272± 13** 280± 12** 285± 13** 292± 13** 298± ** : P ≤ 0.05 ** : P ≤ 0.01	ndd 0001		*01	279±	*!!	∓887∓	13	297±	13	302±	12*	310±	13	317±	13	
*: P ≤ 0.05 **: P ≤ 0.01	4000 jipm		#	262±	12**	272=	13***	780∓	12**	785±	13*#	292±	13**	598 ±	14**	
	Significant difference ;	P №		 ₽ 0.0	1			Test of D	unnett							

ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : MALE	1,[F344/DuCr.j]			ALL	ANIMALS		ALL ANIMALS							PAGE :
Group Name	Adminis 14	Administration week 14	week 18		22		92		30		34		38	
Control	∓628	19	346 ±	20	363 ±	61	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±	144	319±	Ĭ5**	333 ±	** <u>}</u>	346±	**91	356±	***	∓998	**61	371±]9*¤

(HAN260)

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SEX : MALE														I	PAGE : 4
Group Name	Admini	Administration week	week												
	42		46		20		54		58		29		99		
Control	414±	22	422 🛨	22	427 ±	22	430 ±	23	433 ±	23	433 ±	23	435 ±	24	
250 թթա	406 ±	21	413±	21	418±	22	423 ±	23	428 ∓	23	428∓	24	430±	25	
1000 ppm	$408 \pm$	19	417±	19	423±	20	427±	20	432±	20	431±	21	434±	20	
4000 րրա	379±	¥#6T	386±	20≉*	390∓	20**	394∓	21**	∓86€	21**	400∓	21**	402±	21 **	
Significant difference ;	*: P ≤ 0.05		**: P ≤ 0.01	10			Test of Dunnett	unnett							
(HAN260)														***************************************	PATCA

Group Name Administration week 74 78 82 86 90 94 Control 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± 23 431± 23 426± 25 4000 ppm 404± 22** 407± 23** 406± 23** 436± 23** 399± 22** 391± 24** 385± 27** Significant difference; **: P ≤ 0.05 **: P ≤ 0.01 1 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*** 1*	UNIT : R REPORT TYPE : AI 104 SEX : MALE														<u>.</u>	PAGE :
$432\pm$ 34 $437\pm$ 28 $440\pm$ 26 $439\pm$ 25 $433\pm$ 26 $426\pm$ 31 $415\pm$ $432\pm$ 25 $437\pm$ 25 $438\pm$ 26 $440\pm$ 27 $435\pm$ 30 $432\pm$ 36 $426\pm$ $436\pm$ 20 $441\pm$ 22 $442\pm$ 24 $443\pm$ 23 $437\pm$ 23 $431\pm$ 23 $426\pm$ $404\pm$ 22** $407\pm$ 23** $406\pm$ 23** $496\pm$ 22** $399\pm$ 22** $391\pm$ 24** $385\pm$	oup Name	Admini 70	istration			282	THE STATE OF THE S	82	100000000000000000000000000000000000000	98		06		94		
436± 25 437± 25 438± 26 440± 27 435± 30 432± 36 426± 436± 20 441± 22 442± 24 443± 23 437± 23 431± 23 426± 404± 22** 407± 22** 407± 23** 406± 23** 399± 22** 391± 24** 385± *: P ≤ 0.05 **: P ≤ 0.01 Test of Durnett	Control		34	437 ≟	58	440 ±	26	439 ⊥	25	433 ±	56	$426\pm$	31	415 ±	42	
436± 20 441± 22 442± 24 443± 23 437± 23 431± 23 426± 404± 22** 407± 22** 407± 23** 406± 23** 399± 22** 391± 24** 385± *: P ≤ 0.05 **: P ≤ 0.01	250 ppm	432±	25	437 ±	25	438 +	26	440+	27	435 ∓	30	432±	36	426±	88	
404± 22** 407± 22** 407± 23** 406± 23** 399± 22** 391± 24** 385± **: P ≤ 0.05 **: P ≤ 0.05 **: P ≤ 0.01	ndd 0001	436±	20	441±	22	442±	24	443±	23	437±	23	431±	23	426±	25	
* : P ≤ 0, 05 ** : P ≤ 0.01	4000 բրա		22*#	407 ±	22**	±407 ±	23**	406±	23**	399+		391±	24**	385±	27**	
	Significant difference ;			* : P S 0.0	01			Test of D	unnett							

PAGE : 6							
(SUMMARY)	7 7 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4						
CHANGES	and the property of the state o		42	25	37	3[**	
BODY WEIGHT CHANGES (SUMMARY) ALL ANIMALS		104	390 ∓	407 ±	400∓	360±	
			37	24*	34	27**	
	n week	102	399 ∓	416±	407±	∓99€	
	Administration week		38	37	56	37**	
STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : R REPORT TYPE : Al 104 SEX : MALE	Admini	86	408 ±	418+	$417\pm$	375±	
STUDY NO. : 0684 ANIMAL : RAT F UNT : g REPORT TYPE : A1 SEX : MALE	Group Name		Control	250 թթա	udd 0001	4000 րրտ	

Significant difference ; * : P \leq 0.05 (HAN260)

BAIS 4

Test of Dunnett

★ : P ≤ 0.01

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TABLE C 4

BODY WEIGHT CHANGES: FEMALE

UNII K REPORT TYPE : AI 104 SEX : FEMALE															PAGE: 7
Group Name	Admini.	Administration week 0	reek		2	***************************************	£.		4		ıo		9		
Control	101 ±	es.	115-	4	127 ±	വ	138±	rΦ	146±	2	153 ±	9	上651	x	
250 ppm	+ 101	ო	114±	4	126±	ιo	134±	**9	142±	**9	149±	**	155 ±	* &	
1000 mdd 1000	101±	en	113±	‡	124±	5± **	131±	**9	139±	/**	146±	**	152±	**	
4000 չորտ	101	e	110±	3**	121	5 , 24	129±	≵ 2 ½	∓35±	Ť.	141 ±	** 9	146±	** <i>\</i>	
							Address of the second s								
Significant difference;	* : P ≤ 0.05		** : P ≤ 0.01				Test of Dunnett	nnett							

PAGE : 8	[3]	11 ∓281	: 177± 10**	: 174± 12**	· 165± 9***	
	10000011/01/A1/A1/A1/A1/A1/A1/A1/A1/A1/A1/A1/A1/A1	10	± 10≉≈	12**	**6	
	12	+ 785 +	175土	171±	163±	
		න	10**	12**	8 **	
	11	178 🛨	172±	= 191	161	
_		6	*01	**	**6	AMERICAN AMERICAN AMERICAN
BODY WEIGHT CHANGES (SUMMARY) ALL ANIMALS	10	<u> 175 – </u>	170 =	166±	159±	
CHANGES		ħ	**01	<u>*</u>	‡	
BODY WEIGHT ALL ANIMALS	6	±271	166 ≒	162=	156±	
		30	*	10**	**	
	Administration week. 8	168 ±	∓891	∓651	154±	
<u></u>	nistrati	æ	**	10**	**()	
STUDY NO. : 0684 ANIMAL : RAT F344/DuCr1Cr1,[F344/DuCr,] UNIT : R REPORT TYPE : A1 104 SEX : FEMALE	Admin.	164 ±	159 ±	156±	∓051	
STUDY NO. : 0684 ANIMAL : RAT F344/D UNIT : R REPORT TYPE : A1 104 SEX : FEMALE	Group Name	Control	250 թբա	1000 mdd	4000 ppm	

21

BAIS 4

Test of Dunnett

** : P ≤ 0.01

Significant difference : * : $P \le 0.05$

(HAN260)

REPORT TYPE : AI 104 SEX : FEMALE														_	PAGE:
Group Name	Adminis 14	Administration week 14	week18		22		26	Villa Villa III.	30		34		38		
Control	186 ±	11	194 <u>±</u>	11	200 ∓	13	-1-908	12	±112	14	至16年	14	224 ±	15	
250 ррт	180+	*	187±	12**	193±	12#	198	12**	203∓	13**	209∓	13**	213 ±	15**	
1000 ppm	175 ±	12**	183±	12**	187 ±	1 <u>4</u> **	193±	16**	197	16**	203±	17**	700€	18**	
4000 րբու	∓291	**6	174±	**6	±277	***6	181	**01	185±	**0]	+ 681	**	+ 192	* .	
Significant difference:	* : P 0.05		V a	-											

SIUDT NO.: 0884 NIMAL: RAT F344/DuCricLi[F344/DuCri] NNYT: R REFORT TYPE: AI 104 SEX: FEMALE	1/DuCr.j]			B	BODY WEIGHT CHANGES ALL ANIMALS	CHANGES	(SUMMARY)								PAGE: 10
Group Name	Administ 42	Administration week 42	week 46		20		54		58		62		99		
Control	228 ± 1	16	233 ±	18	237 - 1-	18	243 ±	19	7217	22	₹ 252	23	± 267 ±	24	
250 ppm	217± 1	15**	$222\pm$	16*	226 ±	16**	231±	17**	237±	¥*8I	241±	20**	250 ±	21**	
1000 ppm	210± 2	20*≈	214±	22**	218±	\$3 * *	224±	25**	∓622	26**	235±	26**	243±	27**	
4000 рряп	1 7961	12**	+ 861	12**	201 ∓	∐3**	205±	13**	210±	15**	213+	**91	720 ∓	18**	
	A A A A A A A A A A A A A A A A A A A														
Significant difference; *:	*:P≤0.05		**:P≦0.01	01			Test of Dunnett	unnett							

CALL REPORT TYPE : AI 104 SEX : FEMALE														PAG	PAGE: 11
Group Name	Admini 70	Administration week 70	week 74		78		85		98	TOTAL CONTROL OF THE	06		94		
Control	273 ±	24	281	24	789 ∓	26	294 ⊹	56	295 - [-	3 6	- 7396	25	₹ 262	59	
250 ppm	255±	2I ≭	263±	20**	273±	20**	277±	21**	278±	24**	782	23*	783 ∓	*88	
1000 ppm	249 ±	26**	257±	27**	265±	28***	270±	29**	275±	29**	275±	32**	794	34**	
4000 րրտ	224 ±	20**	759 ±	20**	235±	20**	240∓	20**	242±	19**	243±	**61	243±	20**	
Significant difference ;	*:P≤0.05		* *: P ≤ 0.01	01			Test of Dunnett	unnett							

REPORT TYPE : AI 104 SEX : FEMALE							PAGE : 12
Group Name	Adminis 98	Administration week 98	sek		104		
Control	$\pm 797 \pm$	28	796∓	88	294 ± 29		
250 ррт	284±	26	285 ±	24	285± 26		
1900 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

(BI0040)

MEAN FOOD CONSUMPTION(FC) AND SURVIVAL

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

	(O)	CONTROL		indd oco			mdd noor		•	4000 ppm		
Week on Study	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont. <50>	No. of Surviv.	Av. FC.	% of cont. <50>	No. of Surviv.	Av. FC.	% of cont. <50>	No. of Surviv.	
1	13.0 (50)	50/50	6	66	50/50	13.0 (50)	001	50/50	-	92	50/50	
7	4	20/20	14.2 (50)	66	20/20		26	50/50	13.7 (50)	95	20/20	
3	15.2 (50)		_	66	20/20		26	20/20	_	96	20/20	
4	٥		15.4 (50)	66	20/20	_	26	20/20	_	92	50/50	
5	_		_	66	20/20	15.3 (50)	86	20/20	_	96	50/50	
9	_		_	66	20/20		66	20/20	_	86	20/20	
7	9		_	66	20/20	15.5 (50)	66	20/20	_	98	50/50	
8	_		15, 7 (50)	66	20/20	ū	86	20/20	15.3 (50)	97	50/50	
6	_		_	66	20/20	9	66	20/20	_	96	50/50	
10	15.9 (50)		15.7 (50)	66	20/20	7	66	20/20	_	96	50/50	
=	_		_	66	50/50	വ	66	20/20	14.9 (50)	96	50/50	
12	_	20/20		101	20/20	15.7 (50)	102	20/20	_	96	50/50	
13				97	20/20	15.4 (50)	86	20/20	14.6 (50)	93	50/50	
14				100	20/20	:0	100	20/20	_	96	50/50	
18	15.9 (50)		15.6 (50)	86	20/20	15.5 (50)	26	20/20	14.8 (50)	93	50/50	
22			15.9 (50)	86	20/20	60	86	20/20	15.0 (50)	93	50/50	
56	_			100	20/20	-	66	20/20	_	94	50/50	
30	15.9 (50)	20/20	15.6 (50)	86	20/20	15.5 (50)	26	20/20	15.0 (50)	94	50/50	
34				66	20/20		66	20/20	_	94	50/50	
38				66	20/20		66	20/20	_	94	50/50	
42				96	20/20	16.3 (50)	86	20/20	_	94	50/50	
46	_		16.1 (50)	98	20/20		66	20/20	15.7 (50)	92	20/20	
20	_			86	50/50	2	66	50/50	_	94	50/50	
54	16.3 (50)		16.2 (50)	66	50/50	16.4 (50)	101	20/20	_	96	50/50	
58				001	20/20		101	20/20	-	97	50/50	
29	16.0 (49)	49/20		86	20/20	_	86	20/20	15.4 (50)	96	50/50	
99				66	20/20		66	49/50	_	97	20/20	
20				103	20/20		102	49/50	_	66	20/20	
74			_	101	49/50	-	100	48/50		26	50/50	
78	16.3 (46)	46/50	16.4 (49)	101	49/50	16.0 (48)	86	48/50	15.5 (49)	95	49/50	
85	8		_	101	48/50	_	66	47/50	15.0 (49)	95	49/50	
98	15.9 (46)	46/50	_	66	48/50		97	47/50	14.9 (49)	94	49/50	
06	16.0 (43)	Ċ	16.0 (47)	100	47/50	15.6 (46)	86	46/50	14.8 (49)	93	49/50	
94	15.6 (43)		_	001	44/50		001	46/50	15. 1 (46)	26	46/50	
86	0		_	88	42/50		98	45/50	_	93	46/50	
102	15.9 (37)		_	101	40/50	16, 1 (43)	101	13/50	_	26	12/50	
2	15 6 (97)	02/10	10 0 (40)	S	01/04	(11)	9	01/01	(10)	č	01/ 11	

TABLE D 2

FOOD CONSUMPTION CHANGES AND

SURVIVAL ANIMAL NUMBERS: FEMALE

(BI0040)

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj]
UNIT : R
REPORT TYPE : A1 104
SEX : FEMALE

Week on Study 10.		TOJITO		250 ppm		-	1000 Jum		4	4000 ppm	
	Av. FC. N Su Su <50	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv.	Av. FC.	% of cont.	No. of Surviv.	Av. FC.	% of cont.	No. of Surviv.
1 10.											
2 10.	ľ	20/20	_	86	20/20	10.1 (50)	96	20/20	9.4 (50)	06	50/50
•	2	20/20	10.5 (50)	100	50/50	_	97	20/20		91	20/20
3 1∪.	10.8 (50)	20/20	_	100	20/20	_	26	20/20		93	50/50
4 11.	_	20/20	_	26	20/20	_	26	20/20	10.2 (50)	95	50/50
5 10.9	6 (20)	20/20	10.7 (50)	86	20/20	_	97	20/20		91	50/50
6 11.	0 (20)	20/20	_	86	20/20	_	96	50/50		93	50/50
7 10.6	-	50/50		100	50/50	_	26	20/20	9.9 (50)	93	50/50
8 10.	7 (50)	50/50	10.6 (50)	66	20/20	_	94	50/50		92	50/50
9 10.8	(20)	20/20		86	50/50	_	94	20/20		90	50/50
10 10.9	(20)	20/20	10.7 (50)	86	50/50	_	95	50/50		06	50/50
11. 0	(20)	50/50	_	86	50/50	10,3 (50)	94	20/20		86	50/50
11.3	(20)	50/50	11.1 (50)	86	50/50	_	96	50/50	10.0 (50)	88	50/50
13 11.2	(20)	50/50	20	96	20/20	_	95	50/50	10.0 (20)	86	50/50
14 11.	2 (50)	50/50		86	20/20	_	93	50/50	10.2 (50)	68	50/50
11.	(20)	20/20	11.4 (50)	97	20/20	_	96	20/20	10.6 (50)	91	20/20
	(20)	20/20	12.0 (50)	86	20/20	_	92	20/20	11.1 (49)	91	50/50
	(49)	50/50		100	50/50	11.8 (50)	86	50/50	11.0 (50)	91	50/50
30 12.	3 (20)	20/20	11.8 (50)	96	20/20	_	94	20/20	10.8 (50)	88	50/50
12.	4 (50)	20/20	_	86	49/50	_	94	20/20		88	50/50
12.	6 (20)	50/50	ന	92	49/50	_	91	20/20		82	20/20
	2 (20)	20/20		66	49/50	_	26	20/20		83	20/20
	(20)	20/20		86	48/50	_	95	20/20		88	50/50
	(20)	20/20		62	48/50	_	93	20/20		06	50/50
	(20)	50/50	_	26	48/50	12.8 (50)	93	20/20		06	20/20
	(48)	49/50	_	86	48/50	_	93	20/20		90	50/50
	(49)	49/50	_	92	48/50	_	93	50/50		90	20/20
	3 (49)	49/50	9	92	48/50	13.1 (50)	36	50/50		95	20/20
13.	(46)	49/50	es	96	48/50	_	92	20/20		93	20/20
74 14.3	3 (49)	49/50	13.7 (48)	96	48/50	13.4 (50)	94	20/20	13.3 (50)	93	20/20
	(6)	49/50		26	48/50	_	92	49/50		91	20/20
82 13.8	_	49/50		100	47/50	_	96	49/50		96	20/20
86 14.3	3 (48)	48/50	13.8 (46)	26	46/50	_	92	47/50		96	20/20
	0 (47)	47/50	13.5 (44)	96	44/50	_	92	47/50		96	50/50
94 13.	(46)	47/50	00	101	44/50	0	95	46/50		96	48/50
98 14.	.1 (45)	45/50	<u></u>	66	43/50	8	94	45/50		94	47/50
	0 (41)	41/50	14.0 (43)	100	13/50	13.0 (45)	93	15/50	\sim	86	45/50
104 13.	.7 (40)	40/20	14.2 (43)	104	43/50	12.7 (45)	93	45/50	14.0 (43)	102	43/50

TABLE D 3

FOOD CONSUMPTION CHANGES: MALE

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrl,[F344/DuCr.j] UNIT : R REPORT TYPE : AI 104 SEX : MALE	7344/DuCrj]	FOOD	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	s (SUMMARY)			PAGE: 1
Group Name	Administration week 1	reek 2	æ	4	co.	9	1
Control	13.0 ± 0.7	14.4± 0.9	15.2	15.6± 0.9	15.6 ± 1.1	15.5± 1.1	15.6± 1.2
250 ppm	12.9士 0.6	14.2± 0.6	15.1 = 0.7	15.4士 0.7	15.4± 0.9	15.4± 0.8	15.5士 0.7
1000 pm	13.0土 0.7	14.0± 0.8*	14.7	15.1± 0.8*	15.3± 0.9	15.4± 1.0	15.5± 1.0
4000 թըա	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

BAIS 4

Test of Dunnett

** : P ≤ 0.01

Significant difference ; * : P \leq 0.05

(HAN260)

STUDY NO. : 0684 ANIMAL : RAT F344/Duce.lce.lj[F344/Duce.j] UNIT : R REPORT TYPE : AI 104	[[F344/DuCr.j]	E K	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	ES (SUMMARY)			
SEA : MALE			Adolfo and an analysis and an				PAGE
Group Name	Administration week 8	week 9	10	11	12	[3	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士 0.9	15.7± 0.8	15.7± 0.8	15.5士 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士 1.0	15.7± 1.0	15.4± 1.0	15.6± 1.0
4000 ppm	15.3士 1.1	15.2± 1.1	15.2 1.1*	14.9士 [.[**	14.8± 1.0*	14.6± 0.94≈	14.9± 1.0**
Significant difference ;	* : P ≤ 0.05	**:P≤0.01		Test of Dunnett			
(HAN260)							B

SEX : MALE							
Group Name	Administration week 18	week 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士 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. **	15.7± 1.1**
Cimitions Air Constant	ر د د د	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		Toot of Director			

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS PAGE :	Administration week 46 46 62 66 70	1.3 16.7 \pm 1.2 16.0 \pm 1.3 16.9 \pm 2.4	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	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	. ** 15.7± .0** 15.7± .0* 15.3± .1 15.4± .0 15.8± .1 15.7± .2	
F00D COT	20	16.7± 1.2	16.3 ± 1.2	16.5± 1.4	15.7土 1.0***	
STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlj[F344/DuCrj] UNIT : g REFORT TYPE : A1 104 SEX : MALE	Group Name Administr 46	Control 16.5± 1.3	250 ppm 16.1± 1.1	1000 ppm 16.3± 1.2	4000 ppm 15.7± 1.1**	

BAIS 4

Test of Dunnett

** : P \leq 0.01

Significant difference ; * : P \leq 0.05

(HAN260)

REPORT TYPE : AI 104 SEX : MALE	UNIT : g REPORT TYPE : A1 104 SEX : MALE	v	ALL ANIMALS				PAGE :
Group Name	Administration week 74	1 week 78	85	98	06	94	86
Control	16.1 ± 1.6	16.3± 1.3	15.8 ± 1.4	15.9生 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 pm	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 jipm	15.6± 1.1*	15.5± 1.4*	15.0 ± 1.1**	14.9 + 1.6*	14.8	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/DuCrlCrl[F344/DuCr] ALL ANIMALS UNIT : R. RAT F344/DuCrlCrl[F344/DuCr] UNIT : R. REPORT TYPE : AI 104 SEX : MALE	Group Name Administration week		Control 15.9± 1.8 15.6± 2.7	16.1± 1.3 15.3±	1000 ppm 16.1± 1.6 15.3± 1.7	4000 μμπ 15.5± 1.9 14.6± 2.0*		
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(HAN260)

TABLE D 4

FOOD CONSUMPTION CHANGES: FEMALE

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : R REPORT TYPE : A1 104 SEX : FEMALE	7344/DuCr.j.]	FOU	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	S (SUMMARY)			PAGE: 7
Group Name	Administration week	reek 2	8	4	5	9	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士 0.5	10.5士 0.7	10.8± 1.0	10.8	10.7 ± 0.8	6.0 ∓8.01	10.6 ± 1.0
1000 pm	10.1 = 0.5**	10.2± 0.7	10.5± 1.3*	10.8± 0.8	10.6± 0.7	10.6土 0.7	10.3± 0.8
4000 ըրտ	9.4± 0.7**	**9°0 ∓9°6	10.0= 0.7**	10.2± 1.1**	8.9± 0.8**	10.2± 0.8**	9.9± 0.7**

Test of Dunnett

** : P ≤ 0.01

Significant difference ; * : P \leq 0.05

(HAN260)

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g	r344/DuCr.j]	FOOD ALL	FOUD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	(SUMMARY)			
REPORT TYPE : A1 104 SEX : FEMALE							PAGE :
Group Name	Administration week8	ek9	01	1.1	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 ррш	10.6± 1.0	10.6士 1.1	10.7 = 1.2	10.8± 1.1	11.1± 1.5	10.8士 1.1	11.3± 1.4
1000 ppm	10.1 = 0.8**	10.2士 0.7**	10.4	10.3± 0.8**	10.8± 0.8*	10.6± 0.8*	10.7± 1.0**
4000 թթու	9.8 ± 0.7 ***	9.7± 0.8**	***8 · 0 · 8 · **	9.8± 0.8**	10.0 ± 0.8*	10.0± 0.9**	10.2± 0.8**

Test of Dunnett

** : P ≤ 0.01

Significant difference ; * : P \leq 0.05

(HAN260)

STUDY NO.: 0684 ANIMAL: RAT F344/DuCr1Cr1;[F344/DuCr.j] UNIT: R REPORT TYPE: A1 104 SEX: FEMALE	F344/DuCr.j.]	PO ALJ	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	S (SUMMARY)			PAGE: 9
Group Name	Administration week	reek	AND THE RESIDENCE OF TH				
	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土 1.5	12.5生 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
man 0001	2+	+ + +	+ ************************************	- + - -	11 G+ 1 A**	117+ 14**	
	O				11:0-1:11		
4000 չորա	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**

STUDY NO.: 0684 ANIMAL: RAT F344/DuCr1Cr1;[F344/DuCr.j] UNIT: R REPORT TYPE: A1 104 SEX: FEMALE	344/bucr.j]	FOC	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANTWALS	(SUMMARY)			
Group Name	Administration week	Ąc					THE RESIDENCE OF THE PROPERTY
	46	50	54	58	62	99	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土 2.0	13.4± 2.0	13.1± 1.9	12.9± 1.4	13.6± 1.7	13.3± 1.5
1000 ррт	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 թբու	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**

PAGE: 10

1	1
4	

STUDY NO.: 0684 ANIMAL : RAT F344/Duck-1Crlj[F344/Duck-j] UNIT : R REPORT TYPE : AI 104 SEX : FEMALE	F344/DuCr.j.]	FC All	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	ES (SUMMARY)			PAGE : 11
Group Name	Administration week 74	r week 78	883	98	06	94	86
Control	14.3± 1.4	14.6± 1.7	13.8 ± 1.7	14.3土 1.9	14.0土 1.6	13.7士 2.3	14.1± 2.3
250 ppm	13.7 ± 1.3 *	14.2± 1.8	13.8± 1.9	13.8士 1.9	13.5± 1.6	13.8 ± 2.3	13.9十 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士 2.6
4000 րթու	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

ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] NUIT : REPORT TYPE : AI 104 SEX : FEMALE	[F344/DuCr.j]		ALL ANIMALS
Group Name	Administration work	To the second se	97 · 7011
לבף זימוול	102	104	
Control	14.0 ± 1.9	13.7士 2.8	
250 ppm	14.0± 1.9	14.2± 2.1	
1000 ppm	13.0 ± 2.6	12.7± 3.0	
4000 jijim	13.7± 2.3	14.0± 2.8	
Significant difference ;	*: P ≤ 0.05	** : P ≤ 0.01	Test of Dunnett
(HAN260)			BAISA

TABLE E 1

CHEMICAL INTAKE CHANGES: MALE

384	CHEMICAL INTAKE CHANGES	(SUMMARY)
<pre>f F344/DuCr1Cr1;[F344/DuCr.j]</pre>	ALL ANIMALS	

SEX : WALE Group Name Adminis	Administ 1	tration	Administration (weeks)		e		4		ro	117000000000000000000000000000000000000	9		L		PAGE:
Control	<u></u>	0	0	0	- - 0	0	÷1 0	0	4 0	0	÷ 0	0	0	0	
250 ppm	22 ±	-	20±	1	18+		17 ±	1	16 +		15+	1	14#	1	
1000 ppm	∓28	ಣ	78±	2	73±	2	+89	က	64 ±	ಣ	+119	က	28 ±	က	
4000 บุมเล	336±	13	320+	7	+ 662	6	278 ±	თ	264±	10	254	0.	245+	01	

(SUMMARY)	Group Name Administration (weeks) 10 11 12 14
CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	10
	(weeks)
>rlCrlj[F344/buCrj] y	Administration 8
STUDY NO.: 0684 ANUMAL: RAT F344/DuCrlCrlj[F344/DuCrj] UNT: mg/kg/day REPORT TYPE: AI 104 SEX: MALE	Group Name

PAGE: 2

÷I

+-0

+0

÷I 0

T-0

+0

0

Control

12+

12+

 $12\pm$

13 +

13+

 $13\pm$

 $14 \pm$

250 ppm

 ± 12

 $48\pm$

 ∓ 961

∓961

203±

 ± 602

0.

217±

10

 $224\pm$

0

234±

4000 րբո

53+

 $24 \pm$

 ∓ 99

1000 ppm

BAIS 4
(HAN300)

CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANTMALS PAGE :	Administration (weeks) 30 34 38 42		$0 \mp 0 0 \mp 0 0 \mp 0 0 \mp 0 0 $	$11\pm \ 1$ $11\pm \ 1$ $11\pm \ 1$ $10\pm \ 1$ $10\pm \ 1$ $10\pm \ 1$	$45\pm$ 3 $45\pm$ 3 $41\pm$ 3 $40\pm$ 3 $40\pm$ 3	+085
CHI All		TANADA MANANA		11# 1		+081
[] [F344/DuCr. j]	Administration 18			11.	45± 3	+981
STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : ng/kg/day REPORT TYPE : AI 104 SEX : MALE	Group Name		Control	250 ppm	. mqq 0001	4000

STUDY NO.: 0684 ANUMAL: RAT F344/DuCrICrl, [F344/DuCr,] UNIT: mg/kg/day REPORT TYPE: A1 104 SEX: MALE	44/buCr.j.]			CHEMICAL INT ALL ANIMALS	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	HANGES	(SUMMARY)							PAGE: 4
Group Name	Administration (weeks)	tion (we	eks)							TO THE PART OF THE				
	46		50		54		58		29		99		70	
Control	∓0	0	÷0	0	+0	0	 0	0	† 0	0	- 0	0	1 0	0
250 ppm	10 ±	-	10±	ч	+107	H	†1 6	-	†! 6	1	# 6	-	† 6	1
1000 ppm	39∓	ю	39∓	n	1 88	es	37±	n	36±	က	38+	ю	37±	73
4000 բրու	163±	6	161	&	+ 651	6	154+	Ξ	154#	6	157±	o,	∓221	<u> </u>

BAIS 4 (HAN300)

STUDY NO.: 0684 ANIMAL: RAT F344/DuCriCrlj[F344/DuCrj] UNT: mg/kg/day REPORT TYPE: Al 104 SEX: MALE	4/DuCr.j]		CHEMI ALL A	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	AANGES	(SUMMARY)							PA
Group Name	Administration	(weeks)				THE STATE OF THE S				AND AND ADDRESS OF THE PARTY OF		ATTALISMANA	
	74			82		98		06		94		86	
Control	0 ∓0	- ∓0	0	∓0	0	1 -0	0	+ 0	0	÷ 0	0	÷ 0	0
250 ррш	1 +6	+6		+6		+6		+6		+6	-	+ 6	
1000 ppm	36± 2	36±	က	36∄	ಣ	32 +	4	36±	က	37±	4	38 +	ro
4000 թբու	154±	152 ±	13	148#	Ξ	150±	91	151 ±	21	158±	18	∓091	20

49

SIGNATURE SAT 104 NNIMAL RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : mg/kg/d a y REPORT TYPE : AI 104 SEX : MALE	(4/DuCr.j]			CERMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	PAGE:
Group Name	Administration (weeks)_	ation (weeks)		**************************************
	102		104		
Control	+ 0	0	+ 0	0	
250 ppm	10+	-	10.		
1000 pmm	40±	9	39 +	9	
4000 p.p.m.	+ 69 J	20	Te9T	61	
(HAN300)					BAI

TABLE E 2

CHEMICAL INTAKE CHANGES: FEMALE

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] UNIT : ng/kg/day REPORT TYPE : Al 104 SEX : FEMALE	344/DuCr.j]			CHE	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)							PAG
Скоир Лате	Administration 1		(weeks)		e e		4		ß		9		7	
Control	 - 0	0	÷-0	0	+10	0	∓0	0	+	0	∵ 0	0	+10	0
250 ppm	53+	~	21+	1	20+	2	19+	_	18+		17±	1	17±	eri .
1000 ppm	∓68	4	83#	4	∓08	6	± 22	731	73 ±	es .	70±	က	∓99	т
4000 չորտ	342 ±	22	318±	15	311+	8]	303 +	27	280∓	91	278±	18	792 ±	15

STUDY NO.: 0684 ANIMAL: RAT F344/DuCrlCrlj[F344/DuCrj] UNIT: mg/kg/d a y REPORT TYPE: AI 104 SEX: FEMALE	4/DuCr.j]			CHEI	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)							č
Group Name	Administration 8	1 1	(weeks)	TANKET TRANSPORTER TO THE TANKET TO THE TANK	07		11		12		[3		14	Port Company town town
(Sontrol	÷I	0	÷0·	0	∓0	0	#0	0	1 0	0		0	-	0
250 ppm	16±	-	16±		16±	-	16+	-	16.+	8	15	1	16+	63
1000 pm	$64\pm$	4	∓89	ю	#89	4	∓29	귝	63±	4	€1±	es	€1±	4
4000 p.m.n	254±	14	250±	14	246±	14	245±	7	245±	14	243±	17	243 ±	41

STUDY NO.: 0684 ANIMAL : RAT F344/DuCx1Cx1;[F344/DuCx;] UNT : ng/kg/d a y REPORT TYPE : AI 104 SEX : FEMALE	44/DuCr.j]			Ö ₹	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	HANGES	(SUMMARY)							
Group Name	Administration (weeks).	ation ((weeks)	Charles and and and an artist and a second	56		30		34	***************************************	38		42	The street of the characters o
Control	+ 0	0	+ 0	0	÷ 0	0	÷I 0	0	+ 0	0	+0	0	∓0	0
250 ppm	15±	1	16±	63	15#	62	15±	63	14	8	14+	2	14+	63
1000 ppm	61±	4,	+ 29	5	∓19	9	+69	9	#1 28 28	rs.	+ 29	4	57±	9
4000 prim	243±	20	250±	24	244±	27	233 ±	52	230∓	22	530 ⊞	23	226±	21

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrICrI,[F344/DuCr,]] UNIT : mg/kg/d a y REPORT TYPE : A1 104 SEX : FEMALE	14/DuCr.j]			CHEMI ALL A	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)							_
Group Name	Administration 46		(weeks)		54		28		62		99		70	
Control	∓0	0	÷ 0	0	∓0	0	+ 0	0	÷ 0	0	+ 0	0	+-0	0
250 ppm	14#	2	14+	63	14±	c3	14+	2	13#	1	14+	-	13±	-
1000 рря	57±	ıs	57±	ιo	57±	۲	25+	9	54+	ιs	$54\pm$	വ	53±	Ω
4000 բրա	232 ±	24	$240\pm$	28	241#	28	230土	27	$231\pm$	24	238±	33	230±	23

CHAN		
INTAKE		0
CHEMICAL INTAKE		
C		
	9	
		Ξ

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrICrlj[F344/DuCr]] UNIT : ng/kg/d a y REFORT TYPE : AI 104 SEX : FEMALE	I/DuCr.j]			CHEM	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)						
Group Name	Administration (weeks)	tion (weeks)		82		98		06		94		**************************************
Control	- 0	0	÷ 0	0	∓0	0	+0	0	+0	0	+0	0	Action in the second se
250 ppm	13#	_	13	c3	13.	23	12+	63	12±	1	12±	63	
1000 ppm	52±	9	51.	9	49±	9	70∓	8	49±	œ	48∓	∞	

PAGE : 11

10

48±

 $12\pm$

-----0

98

 219 ± 36

27

∓612

36

 $222 \pm$

31

 $227\pm$

28

220∓

28

 $227\pm$

31

232±

4000 թթա

BAIS 4 (HAN300)

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : mg/kg/d a y REPORT TYPE : Al 104 SEX : FEMALE Group Name Adminis	44/DuCr.j] Administration 102		(weeks)	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	(SUMMARY)
Control	+ 0	0	- 0	0	
250 ppm	12±	2	13+	લ્ય	
mdd 0001	48±	10	47±	11	
4000 p.pm	230±	37	231±	41	

TABLE F 1

HEMATOLOGY: MALE

STUDY NO.: 0684 ANIMAL: RAT F344/DuCrlcrlj[F344/DuCrj] MEASURE. TIME: 1 DEBOUT TYPE: A.I.	1 F344/DuCrlCrl 1	uCrlCrlj[F344/DuCrj] pupour TVPB · Al		HE ALI	HEMATOLOGY (SUMMARKY) ALL ANIMALS (105W)	OSW)								
Group Name	NO. of Animals	RED BLOOD CELL 1 O ⁶ / µℓ		IIEMOGLOBIN R/dl	HEMATOCRIT %	RIT	MCV f &		MCII P R		MCIC R / d&		PLATELET 1 0³∕µl	17 17 17 17 17 17 17 17 17 17 17 17 17 1
Control	36	7.76 ± 1.68	13. 0 ±	2.7	37.1±	6.8	49.4土	6.9	7.0 ℃	2.1	34. 5 ⊹	1.7	∓ 996	306
250 ppm	39	8.13 ± 1.50	13.6+	2.4	39.0∓	6. 1	48.4	3.4	16.8±	T. 0	34.8±	L. 3	₩2	267
1000 mdd	43	7.96± 1.45	13.1±	2.6	37.7±	6.2	47.7±	3, 5*	16.4±	1.3	$34.5\pm$	6.0	∓856	321
4000 ppm	14	7.68± 1.06	12.9±	1.7*	36.8±	4.3*	48.3±	3. 1	16.7±	6.9	34.8±	2.0	837±	**
Significant	Significant difference ;	* : P ≤ 0.05	**: P ≤ 0.01	. 01			Test of Dunnett	netl						
(HCL070)														BAIS 4

PAGE: 2						
HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	METHEMOGLOBIN %	0.9± 0.3	1.0 ± 0.4	1.2± 0.7**	1.9± 0.6**	** : $P \leq 0.01$ Test of Dunnett
[F344/bucr.j] YPE: A1	RETICULOCYTE %	4.5± 3.9	3.9± 4.1	4.5± 4.7	4.8 + 6.7**	
STUDY NO. : 0684 ANIMAL : RAT F344/DuCklCklj[F344/DuCkj] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	Group Name NO. of Animals	Control 36	250 ppm 39	1000 ppm 43	4000 ppm 41	Significant difference ; * : P \le 0.05

	9. 30 46= 1. 92 49=		+1 +1	BOS INO 11+	BAS0 1 0±		OTHER 1.1	
Differential NBC (%) (%) MONO EOSINO BASO OTHER $46\pm$ 11 $47\pm$ 11 $5\pm$ 1 $1\pm$ 1 $0\pm$ 1 $1\pm$ $48\pm$ 15 $41\pm$ 14 $5\pm$ 2 $1\pm$ 1 $0\pm$ 0 $5\pm$ $49\pm$ 9 $44\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ $46\pm$ 9 $47\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ $**$ $20\pm$ $20\pm$ $1\pm$ $1\pm$ $1\pm$ $0\pm$ $0\pm$ $0\pm$ $1\pm$ $46\pm$ 9 $47\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ $0\pm$ $0\pm$ $0\pm$ $0\pm$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$ $**$	NEUTR 46= 48= 49=		÷l +ı	BOSINO 11+	BASO 1		OTHER 1	
$46\pm$ 11 $47\pm$ 11 $5\pm$ 1 $1\pm$ 1 $0\pm$ 1 $1\pm$ $48\pm$ 15 $41\pm$ 14 $5\pm$ 2 $1\pm$ 1 $0\pm$ 0 $5\pm$ $49\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ $46\pm$ 9 $47\pm$ 9 $5\pm$ 1 $1\pm$ $1\pm$ $0\pm$ 0 $1\pm$ *** : P \leq 0.01	.48 ± 49 ± 49 ± 49 ± 49 ± 49 ± 49 ± 49 ±			# #	1 0 =		÷ →	,
$48\pm$ 15 $41\pm$ 14 $5\pm$ 2 $1\pm$ 1 $0\pm$ 0 $5\pm$ $49\pm$ 9 $44\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ $46\pm$ 9 $47\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ **: $P \le 0.01$ Test of Dunnett	48 + + + + + + + + + + + + + + + + + + +			+				-
49± 9 44± 9 5± 1 1± 1 0± 0 1± 46± 9 47± 9 5± 1 1± 1 0± 0 1± ** : $P \le 0.01$ Test of bunnetl	1.92 49±				1 0+	0	ις: †:	18
$46\pm$ 9 $47\pm$ 9 $5\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ ** : P \leq 0.01			5 1	#1	1 0 =	0	#1	-
** : P ≤ 0.01	2.05 46±		5 +-	+;	+ 0	0	+1	0
	VI **		Test of D	ւսորեն և	ALAMAHAN AND AND AND AND AND AND AND AND AND A			

TABLE F 2

HEMATOLOGY: FEMALE

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1 SEX : FFAMIF	t F344/DuCrlCrl i REPORT	NCrlCrlj[F344/DuCr REPORT TYPR : 41	Ĺį:		HE	HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	UMMARY) 105W)								
	INO WIN	10 . 7111			a ferrandon and a second										PAGE: 4
Group Name	NO. of Animals	RED BLOOI 1 O ⁵ / μθ	RED BLOOD CELL 1 Φ ⁶ /μl	IIEMOGLO R / dR	oglobin Al	IIEMATOCRIT %	CRIT	MCV f &		MCII P R		MCHC g / dl		PLATELET 1 O³ ∕ μℓ	
									AAA aa						
Control	39	7.98±	0, 55	14.6±	1.0	40.1≟	2.7	50.3 ±	2. 1	18.3 ±	8.0	36. 1±	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**	∓982	147*
4000 ppm	43	6.82±	0.65**	13.1=	7. 0**	36.7±	2. 5**	54.0±	2.5**	19.2±	0.7**	35.6±	0.7**	635 ±	**96
Significant	Significant difference ; *: P ≤ 0.05	* *		** : P ≤ 0.01	1(Test of Dunnett	mett						

(HCL070)

	PAGE: 5							Test of Dunnett
HEMATOLOGY (SUMMARY) ALL ANIMALS (1059)		METHEMOGLOBIN %		0.7 ± 0.1	0.9± 0.1**	1.2± 0.3**	2.4± 0.6**	**: P ≤ 0.01 Test
F344/DuCr.j.]	PE : A1	RETICULOCYTE %	A CONTRACTOR OF THE CONTRACTOR	$2.4\pm$ 1.5	2.4± 1.0	3.7 ± 3.8**	5.4± 2.8**	*: P ≤ 0.05
4 F344/DuCrlCrlj[] 1	REPORT TYI	NO. of Animals		39	42	44	43	Significant difference;
STUDY NO. : 0684 ANIMAL : RAT F344/PuCrlCrlj[F344/DuCrj] MFASHRF. TYMF : 1	SEX : FEMALE	Group Name		Control	250 ppm	1000 ppm	4000 ppm	Significant

Group Name Antiaels 1 0²/μ² NEUTRO LYMPHO MONO EOSTNO EASTNO BASO OTHIER 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 55± 10 4± 1 2± 1 0± 0 1± 1** 4000 ppm 43 1.4.20± 69.79 34± 9** 55± 10 4± 1 2± 1 0± 0 1± 1**	STUDY NO. : 0684 ANIMAL : RAT F3 MEASURE. TIME : 1 SEX : FEMALE	344	/buCrlCrlj[F344/buC REPORT TYPE : Al	uCrj] 1			HEMATOLOC ALL ANIMA	HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	()								PAGE : 6
39 3.03± 1.16 41± 9 51± 9 4± 1 2± 1 0± 0± 0 1± 42 3.15± 1.27 40± 10 53± 10 4± 1 2± 1 0± 0± 0 1± 44 3.82± 2.00 39± 10 55± 10 4± 1 2± 1 0± 0± 0 1± 43 14.20± 69.79 34± 9** 58± 12* 4± 1* 2± 1 0± 0 3± 1	b a	NO. of Animals	WB. 1 O³ ∕	, jul	Did	fferential	WBC (%	(9	WONO		EOSINO		BASO		OTUER		
42 3.15 \pm 1.27 40 \pm 10 53 \pm 10 4 \pm 1 2 \pm 1 0 \pm 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ıtrol	39	3. 03 ⊡		414	တ	51±	ō	4±	1	2 1	-	0	0	1 1	0	
44 $3.82\pm$ 2.00 $39\pm$ 10 $55\pm$ 10 $4\pm$ 1 $2\pm$ 1 $0\pm$ 0 $1\pm$ 43 $14.20\pm$ 69.79 $34\pm$ $9***$ $58\pm$ $12**$ $4\pm$ $1*$ $2\pm$ 1 $0\pm$ 0 $3\pm$ 1	шdd	42	3.154		40+	07	53 	10	4+		5+	-	+10	0	+	-	
43 14.20 ± 69.79 $34\pm9**$ $58\pm12*$ $4\pm1*$ 2 ± 1 0 ± 0 $3\pm$	mdd (44	3.82±		39∓	01	55 +	10	4+		5+	-	+1	0	1+	**	
	mdd (43	14.20±	69. 79	34±	**	+ 28	12*	4+	*.	5+	1	+: 0	0	3+	¥**	

(HCL070)

TABLE G 1

BIOCHEMISTRY: MALE

STUDY NO. : 0684 ANIMAL : RAT F344/DuCriCrij[F344/DuCrj] MEASURE. TIME : 1	4 F344/DuCr1Cr1. 1	.j[F344/DuCr.j	æ		BIC	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	(SUMMARY) 105W)								
SEX : MALE	REPORT '	REPORT TYPE : A1													PAGE: 1
Group Name	NO. of Animals	TOTAL PROTEIN g/dl	ROTEIN	ALBUMIN R / dl	7	A/G RATIO	LIO	T-BILIRUBIN mg/dl	RUBIN	GLUCOSE mg / dl	ADALAS AND	T-CHOLESTEROL ng/dl	STEROL	TRIGLYCERIDE mg/dk	ERIDE
Control	36	6.8	0.5	2. 9 .	0. 3	0.7 ±	0.1	0.20	0.29	145±	22	189 ±	63	+ 26	70
250 ppm	36	6.8+	0.3	2.9+	0.3	0.7±	0.1	0.18±	0.12	143 ±	59	∓691	45	+ 88	46
1000 mdd	43	6.8±	0.4	2.9	0.2	0.8±	0.1	0.15±	0.04	149土	16	174±	47	103±	257
4000 ppm	41	7.0±	0.4	3.1+	0.2**	0.8	0. 1**	+61.0	0.08**	145 🛨	14	154	38**	138+	72**
Significant	Significant difference; *: P ≤ 0.05	0 × d : *		**: P ≤ 0.0L	11			Test of Dunnett	nnett						

(HCL074)

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlGrlj[F344/DuCrj] MEASURE, TIME : 1	4 F344/DuCrlCrl 1	1.j[F344/DuCr.j	<u></u>		BIOC	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	SUMMARY) 05W)								
SEX : MALE	REPORT	REPORT TYPE : Al													PAGE: 2
Group Name	NO. of Animals	PHOSPHOLIPID mg/d2	OLIPID	AST I U / Ø		ALT I U / g	6	LDIJ I U / g	6	ALP I U / 2	9	6-GTP I U / 2		CK IU/g	
Control	36	272土	66	104 🕂	104	41 🕂	88	129±	118	370 ±	401	- 1-9	4	∓86	48
250 ppm	39	241±	29	+ 66	55	42+	13	148+	143	311±	28	†! 9	က	47€	38
1000 mdd	43	245 ±	54	102 ±	36**	25 ±	28**	132±	37**	411±	100**	+I 8	4* *	+66	36
4000 ppm	41	736±	57	T90T	45*	49+	21**	127±	29**	412±	103**	† &	4	+88	14
Significant	Significant difference ; * : P ≤ 0.05	* vi + vi +	. 05	** : P ≤ 0.01				Test of Dunnett	nett						

(HCL074)

STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1	F344/DuCrlCrl. 1	j[F344/DuCr.j	c		BIOX	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105%)	JAMAARY) 5W)								
SEX : MALE		REPORT TYPE : AL													PAGE: 3
Group Name	NO. of Animals	UREA NITROGEN	TROGEN	CREATININE mg/dl	NINE	SODIUM mEq∕2		POTASSIUM mEq/2	б	CILORIDE mEq / 2		CALCIUM mg/dl		INORGAN mg / dk	INORGANIC PHOSPHORUS
Control	36	18.6±	3.9	∓9.0	0. 1	141 ±	23	3, 8 	0.3	106±	83	10.6±	0.3	4.2 -	0.5
250 ppm	39	19.4	8.0	0.6	0.3	142+	23	3.9+	0.5	± 901	2	10.6±	0.3	4.5+	
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±	5.2
4000 ppm	41	21.6±	4.6**	0.6∓	0.1	142±	69	3.9	0.3	∓901	8	10.6±	0.3	4.0+	0.5
Significant	Significant difference; *: P ≤ 0.05	*: P ≤ 0		10.0 ≥ q:**	10			Test of Dunnett	mett						

TABLE G 2

BIOCHEMISTRY: FEMALE

STUDY NO.: 0684 ANIMAL: RAT F344/DuCrlCrl;[F344/DuCrj] MGAGIDE TIME: 1	l F344/DuCrlCrl][F344/DuCr]	Ĺ		BIC	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	SUMMARY) 05W)								
SEX : FEMALE		REPORT TYPE : A1													PAGE:
Group Name	NO. of Animals	TOTAL PI R / dl	TOTAL PROTEIN g/dl	ALBUMIN R / dl		A/G RATIO	01	T-BILIRUBIN mg/de	UBIN	GLUCOSE mg/dl		T-CHOLESTEROL mg/dl	STEROL	TRIGLYCERIDE mg/dk	RIDE
Control	36	⊕6.9	0.4	e. ∵ ⊹l	0.3	1.01	0.1	0.12±	0.01	∓611	18	133 ±	33	-18	54
250 ppm	42	6.9	0.4	3.54	0.2	1.1	0.1	0.11#	0.01	145±	71	131	21	71.±	40
udd 0001	44	7.0±	0.7	3.5±	0.5	T. 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*	± 82	32*
Significant	Significant difference ;	* : P 0.05		** : P \square 0.01	10			Test of Dunnett	nett						

(HCL074)

STUBY NO.: 0684 ANIMAL: RAT F344/PucklCrl;[F344/Duck;] MEASURE. TIME:: 1	t F344/DuCr1Cr1. 1	j[F344/DuCr.j]				BLOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	(SUMMAR (105W)	(X								
SEX : FEMALE		REPORT TYPE : A1													PA(PAGE:
Group Name	NO. of Animals	PIIOSPIIOLIPID mg/dl	LIPID	AST I U / 2	8,	ALT I U / g	12	LDII I U / g	12	ALP I U / 2	2	G-GTP I U / R	8	CK I U / g	2	
Control	39	235 🛨	61	121 ±	57	∓729	21	140 ±	70	161 ±	38	2 -	-	#T#8	28	
250 ppm	42	∓622	39	143主	95	±17.	63*	152+	62	±171	46	5 +1	1	78±	13	
1000 ррж	44	242 ±	80	159±	133	∓62	£1**	* 163±	103	250±	292	#1 82	က	#I 82+	38	
4000 ppm	43	210 ±	40**	133±	133	57 ±	35	212±	432	216±	121*	5+	-	104±	111	
Significant	Significant difference : * : P ≦ 0.05	* : P ≤ 0.		** : P \le 0.	0.01			Test of Dunnett	Junnet t							

(HCL074)

STUDY NO.: 0684 ANIMAL: RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME: 1	F344/DuCrlCrl 1	j[F344/DuCr.	Ĺį		BIO	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	JAMARY) 5W)								
SEX : FEMALE	KEI OKI	KEPORT TYPE : AL													PAGE: 6
Group Name	NO. of Animals	UREA NI mg/dl	UREA NITROGEN mg∕dℓ	CREATININE mg/dl	NINE	SODIUM mEq/2		POTASSIUM mEq/2	UM	CHLORIDE m Eq / &		CALCIUM mg/dl		INORGAN mg/dl	INORGANIC PHOSPHORUS
						Section of the sectio									
Control	36	16.5±	2.0	0.5⊥	0.1	140±	1	3.6±	0.3	104 土	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	$3.9 \pm$	0.6
1000 mdd	44	18.6±	10.0	0.5±	0.1	141±	co	3.6±	0.5	104±	2	10.7±	0.6	4.0十	0.8
4000 ppm	43	17.8±	2. 1**	0.5	0.1	141±	64	3.7±	0.3	∓901	63	10.7	0.3	3.9+	0.6
Significant	Significant difference; *: P ≤ 0.05	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		* : P ≤ 0.01	01			Test of Dunnetl	nett						

(HCL074)

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/DuCrICrlj[F344/DuCrj]	 F344/DuCrlCrl;	i[F344,	/DuCr.	Ē					URINALYSIS				
MEASUKE. IIME : I SEX : MALE	I REPORT TYPE : A1	rype :	A1										PAGE
Group Name	NO. of Animals	pll 5.0	5.0 6.0 6.5 7.0 7.5	6.5	7.0	7.5	8.0	8.5 CIII	Protein ± + 2+ 3+ 4+ CIII	Glucose — ± + 2+ 3+ 4+ GII	Ketone body - ± + 2+3+4+ CHI	Bilirubin - + 2+3+ CIII	
Control	36	0	1	₹	ιc	Ξ	13	63	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	03	12	11	13	23	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	63	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	63	ശ	12	18	ເດ	0 0 0 3 34 5 *	42 0 0 0 0 0	0 0 0 0 0	0 0 0 0	
Significant	Significant difference :		*: P ≤ 0.05	5 0.05	10	#	MI A	P ≤ 0.01	Text	Test of CHI SQUARE			

(HCL101)

BATS 4

STUDY NO. : 0684 ANIMAL : RAT F: MEASURE. TIME : 1 SFX : MAIF	34.	Worlcrl[F344/Ducrj]	URINALYSIS	
	We on	. ur		PAGE: 2
Group Name	NO. of Animals	Occult blood - ± + 2+ 3+ CHI	Urobilinogen II ± + 2: 3: 4: CIII	
Management of the state of the	Management of the state of the			
Control	36	36 0 0 0 0	36 0 0 0 0	
250 ррт	40	39 1 0 0 0	40 0 0 0 0	
1000 ррш	43	43 0 0 0 0	43 0 0 0 0	
4000 ppm	42	42 0 0 0 0	42 0 0 0 0	
Significan	Significant difference :	* : P ≤ 0.05	# : P ≤ 0.01	Test of CHI SQUARE
(HCL101)	Addition of the contract of th		Visidado, informações de la compansa	BAIS 4

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/DuCrICrI;[F344/DuCr;] MEASURE. TIME : 1 SEX : FEMALE REPORT TYPE : AI	4 F344/DuCrlCrl 1 REPORT	DuCrlCrl;[F344/DuCr;] REPORT TYPE : Al	URINALYSIS			
Group Name	NO. of Animals	5.0 6.0 6.5 7.0 7.5 8.0 8.5 CII	Protein	Glucuse = ± + 2+ 3+ 4+ CHI	Ketone body - ± + 2+3+4+ CHI	Bilirubin - + 2+ 3+

PAGE: 3

CIII

0

45

2

13 16 12

43 45 44

250 ppm 1000 ppm 4000 ppm

Control

15

Test of CHI SQUARE	BATS 4
**: P ≤ 0.01	
Significant difference ; * : P ≤ 0.05	(HCl.101)

						ARF.
URINALYSIS	4+ GII	0	0	0	0	Test of CHI SQUARE
	Urobilinogen CHI ± + 2+ 3+ 4+ CHI	40 0 0 0	43 0 0 0	45 0 0 0	44 0 0 0	** : P ≤ 0.01
wCrlCrlj[F344/DwCrj] REPORT TYPE : Al	Occult blood - ± + 2+ 3+ CHI	10 0 0 0 0	43 0 0 0 0	44 0 0 0 1	44 0 0 0 0	: P ≤ 0.05
344/1	NO. of Animals	40	43	45	44	Significant difference :
STUDY NO. : 0684 ANIMAL : RAT FG MEASURE. TIME : 1 SEX : FEMALE	Group Name	Control	250 ppm	1000 ppm	4000 ppm	Significan (HCL101)

TABLE J 1

ORGAN WEIGHT, ABSOLUTE: MALE

(RY)		
ORGAN WEIGHT: ABSOLUTE (SUMM	SURVIVAL ANIMALS (105W)	
)684	(AT F344/DuCrlCrlj[F344/DuCrj]	Λ1

SEÅ : MALE UNIT: g														;
Group Name	NO. of Animals	Body 1	Body Weight	ADRENALS	ALS	TESTES	SS	HEART		LUNGS		KIDNEYS	XXS	PAGE:
Control	36	374±	30	0.083±	0.013	3.112±	1.713	1. 285 土	0.120	1. 464 ±	0.362	$2.805\pm$	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士	0.318	
1000 ррш	43	379±	38	0.082±	0.013	3.347±	1.466	1.258±	0.094	1. 407 ±	0.080	2.985±	0.452*	
4000 բրա	41	339∓	30**	€ 0.081	0.073*=*	4.135±	1.858*	1.208±	0.100**	1.397±	0.113	3.118±	0.229**	

SUMMARY)		10			_	Test of Dunnett
(105W)	BRAIN	0, 045	0,042	0.052	0.041	
ORCAN WEIGHT:ABSOLUTE (SUMMARY) SURVIVAL ANIMALS (105W)	BR	2. 108 ±	2.119±	2. 120±	2.104±	
ORGA SURV	8	2. 138	1.987	1.254*	1. 295**	
	LIVER	11. 140 ±	11.376±	11. 735±	12.141 ±	## : P ≤ 0.01
	N.	1.501	3.158	0.980	0. 456**	
[F344/buCr.j]	SPLEEN	1. 426土		1.252士	1.576±	*: P ≤ 0.05
4 F344/DuCr1Cr1; 1	NO. of Animals	36	39	43	41	Significant difference ;
STUDY NO.: 0684 ANIMAL : RAT F344/DuCrICrI;[F344/DuCrj] REPORT TYPE : A1 SEX : MALE UNIT: g	Group Name	Control	250 ppm	1000 pm	4000 չորու	Significant

PAGE: 2

(IICL040)

${\rm TABLE}\; {\rm J}\; 2$

ORGAN WEIGHT, ABSOLUTE: FEMALE

ORGAN WEIGHT: ABSOLUTE (SUMMARY)	SURVIVAL ANIMALS (105W)	
	4/DuCrlCrlj[F344/DuCrj]	

KETOKL LITE - AL SEX : FEMALE UNIT: g	KEPOKLITE : AL SEX : FEMALE UNIT: g											_	, and
Group Name	NO. of Animals	Body Weight	ADRE	ADRENALS	OVARIES	SS	HEART		LUNGS		KIDNEYS		40F .
Control	36	282上 25	⊕ 0.097 ±	0.074	0.156±	0.054	0. 966 ≟	0.064	1. 023 ±	0.079	1.951 <u>+</u> -	0. 145	
250 ppm	42	270± 25	0.083±	0.013	0.317±	1. 132	0.937±	0.079	0.968±	0.067**	$1.872 \pm$	0.132*	
1000 ppm	44	254± 39**	0.078±	0.009**	0.210±	0.368**	0.917±	.096*	₩0.980±	0.108**	$1.891\pm$	0.169	
4000 ուրտ	43	228± 23**	10.086土	0,064**	0.138±	0.020*	0.919±	0.077*	∓966⊤0	0.144*	1.844±	0.137**	

(HCL040)

ORGAN WEIGHT: ABSOLUTE (SUMMARY)		
0684	RAT F344/DuCrlCrlj[F344/DuCrj]	

4000 ppm 43 1.541± 0.9794* 8.173± 0.863** 1.936± 0.050	ne NO, of SPLEEN LIVER BRAIN Animals	SURVIVAL ANTMALS (105W) SEX : FEMALE UNIT: g	PAGE	ORGAN WEIGHT: ANSOLUTE (SUMMARY) SURVIVAL ANIMALS (105W) BRAIN 1. 948 ± 0.043 1. 936 ± 0.036 7 1. 935 ± 0.050	0. 78 0. 89 1. 23 0. 86	: E	NO. of Animals 39 39 42 44
	39 0.626± 0.143 7.168± 0.789 1.948± 42 0.634± 0.510 6.861± 0.891 1.930±	SPLEEN LIVER BRAI 0. 626± 0.143 7.168± 0.789 1.948± 0. 634± 0.510 6.861± 0.891 1.930±					
0.682 ± 0.322 7.246 ± 1.237 1.935 \pm	39 0.626 \pm 0.143 7.168 \pm 0.789 1.948 \pm	No. of SPLEEN LIVER BRAI Animals Animals of 626± 0.143 7.168± 0.789 1.948±					
42 0.634± 0.510 6.861± 0.891 1.930± 1 44 0.682± 0.322 7.246± 1.237 1.935±		NO. of SPLEEN LIVER Animals				0.626士 0.143	

(IICL040)

TABLE K 1

ORGAN WEIGHT, RELATIVE: MALE

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

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

up Name NO. of Animals Body Weight ADRENALS TESTES IIEART LUNGS KIDNEYS Control 36 374± 30 0.022± 0.004 0.838± 0.468 0.346± 0.047 0.398± 0.154± 0.056 250 ppm 39 387± 25 0.022± 0.026 0.069± 0.337± 0.029 0.396± 0.337± 0.029 0.056 0.059± 0.025± 0.059 0.059± 0.05	UNIT: %									PAGE :
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Group Name	NO. of Animals	Body W	(eight .g)	ADRENALS	TESTES	IIEAKT	LUNGS	KIDNEYS	
39 $387\pm$ 25 0.029 ± 0.028 0.769 ± 0.327 0.337 ± 0.029 0.392 ± 0.151 $1.229\pm0.359**$ $0.358\pm0.034*$ $0.415\pm0.046**$	Control	36	374ः⊡	30	0.022 ± 0.004	0.838± 0.468	0.346± 0.047	0.398± 0.133	0.754± 0.086	
43 $379\pm$ 38 $0.022\pm$ 0.006 $0.891\pm$ 0.389 $0.336\pm$ 0.045 $0.376\pm$ 0.047 41 339± 30** 0.025± 0.024 1.229± 0.559** 0.358± 0.034* 0.415± 0.046**	250 ppm	39	387±	25	0.029± 0.028	0.769 ± 0.327	0.337± 0.029	$0.392\pm\ 0.151$	0.755士 0.098	
41 339士 30** 0.025士 0.024 1.229士 0.559** 0.358士 0.034* 0.415土 0.046**	mdd 000T	43	379±	38	0.022± 0.006	0.891± 0.389	0.336± 0.045	0.376± 0.047	0.808± 0.260	
	4000 րրա	41		30***	0.025± 0.024	1.229± 0.559**	0.358± 0.034*	0.415± 0.046**	0.925士 0.083***	

(IICL042)

STUDY NO. : 0684 ANIMAL : RAT I REPORT TYPE : A1 SEX : MALE	STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : AI SEX : MALE	:344/DuOr.j.]	ORGAN WI SURVIVAI	ORGAN WEIGHT:RELATIVE (SUMMARY) SURVIVAL ANIMALS (105W)	
UNIT: % Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN	PAGE
Control	36	0.405 ± 0.509	3.000 ± 0.684	$0.567\pm\ 0.052$	
250 ppm	36	0.467± 0.796	2.940 ± 0.481	0.550 ± 0.037	
1000 mdd	43	0.333± 0.270	3.119± 0.360**	$0.566\pm\ 0.066$	
4000 ուրո	41	0.466± 0.139**	3.588± 0.315**	0.626± 0.058*≠	
Significant	Significant difference;	* : P ≤ 0.05 **	: P ≤ 0.01	Test of Dunnett	VI III III III III III III III III III

(HCL042)

TABLE K 2

ORGAN WEIGHT, RELATIVE: FEMALE

SEA : FEMALE UNIT: %							
Group Name	NO. of Animals	Body Weight (g)	ADRENALS	OVARIES	HEART	LUNGS	KIDNEYS
Control	39	282± 25	$0.034\pm\ 0.023$	0.056 ± 0.021	$0.345\pm\ 0.031$	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土 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**

BAIS 4

(IICL042)

4000 μm 43 0.684± 0.456** 3.606± 0.389** 0.858± 0.086**	PAGE: 4	ONGAN WEIGHT: RELATIVE (SUMMARY) SURVIVAL ANLMALS (105 W) BRAIN BRAIN 0 0.697 ± 0.073 0 0.722 ± 0.070 9** 0.782 ± 0.134**	URGIN WE SURVIVAL SURVIVAL 2. 550 ± 0. 258 2. 553 ± 0. 310 2. 882 ± 0. 469** 3. 606 ± 0. 389**	F344/buCr.j] SPLEEN 0.226 ± 0.071 0.235 ± 0.184 0.272 ± 0.144** 0.684 ± 0.456**	STUDY NO. : 0684 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : A1 SEX : FEMALE UNIT: % Group Name	STUDY NO. : 0684 ANIMAL : RAT REPORT TYPE : A1 SEX : FEMALE UNIT: % Group Name Control 250 ppm 1000 ppm 4000 ppm
		0.782± 0.134**	2.882土 0.469**	0,272± 0.144**	44	1000 ppm
44 0.272± 0.144** 2.882± 0.469**		0.722± 0.070	2.553 ± 0.310	0.235± 0.184	42	250 ррт
42 0.235 ± 0.184 2.553 ± 0.310		0.697± 0.073	2.550 ± 0.258	$0.226\pm\ 0.071$	39	Control
39 0.226± 0.071 2.550± 0.258 42 0.235± 0.184 2.553± 0.310 1 44 0.272± 0.144** 2.882± 0.469**		BRAIN	LIVER	SPLIEN	NO. of Animals	up Name
NO. of Animals Animals old 39 0.226 ± 0.071 2.550 ± 0.258 on 42 0.235 ± 0.184 2.553 ± 0.310 on 44 0.272 ± 0.144** 2.882 ± 0.469**	PAGE: 4	EIGHT: KELATIVE (SUMMARY) L ANIMALS (105W)	ORGAN WE SURVIVAI	[F344/buCr.j]	4 F344/DuCrlCrl,i[1	JY NO. : 0685 AL : RAT DRT TYPE : A1 : FEMALE I: %

(HCL042)

BAIS 4

TABLE L 1

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

MALE: ALL ANIMALS

STUDY NO. : 068 ANIMAL : KAT REPORT TYPE : A1 SEX : MAL	: 0684 : RAT F344/buCr.ICr.I.j[F344/buCr.j] : AI : MALE	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105#)	N-NEOPLASTIC LESIONS (SUMMARY)		. PAGE :
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 4 (%) (%) (%) (%)	1000 ppm 50 3 4 (%) (%) (%) (%)	4000 ppm 50
(Integumenta	{Integumentary system/appandage}				
skin/app	sear	$(50) \\ 1 & 1 & 0 \\ (2) (2) (2) (0) (0)$	(50) (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
	squamous cell hyperplasia	1 0 0 0 (2) (3) (4) (6) (6)	(0)(0)(0)(0)	0 1 0 0 (0) (0) (0)	
subculis	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	<50>> (50) (0) (0) (0)	<50> 0 1 0 0 (0) (2) (0) (0)
	inflammation		(0)(2)(0)(0)	(0)(0)(0)(0)	
	fibrosis:focal			0 1 0 0 (0) (0) (0) (0)	
(Respiratory system) nasal cavit thre	system) thrombus	(0) (0) (0) (0) 0 0 0 0 0 <05>	<pre></pre>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)

PAGE: 1

BAIS4

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

(HPT150)

(IIPT150)

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

STUDY NO. : 068- ANIMAL : RAT REPORT TYPE : AI SEX : MALA	: 0684 : RAT F344/DuCrICrIj[F344/DuCrj] : AAI : MALE		HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	FINDINGS :N('W')	ON-NEOPLASTIC	LESIONS (SUMMARY	C					PAGE	
Organ	Findings	Group Name No. of Animals on Study Grade	Control Study 50 1 2 3 (%) (%) (%)	v1 4 (%)	(%) (%)	250 µpm 50 3 4 6) (%) (%)	1 (%)	1000 ppm 50 2 3 (%) (%)	4 (%)	(%)	4000 ppm 50 3 (%)	ppm 3 4 (%) (%)	
(Respiratory system)	system)												
nasal cavit	mineralization		32 0 0 (0 (0 (0 0 0 0 0 0 0 0 0 0 0 0	0 0	38 0 (0) (92)	<50> (50) (0) (0)	36 (72) ()	(50) 0 0 0) (0) (0 (0)	33 ((50) 0 0) ((0) (0 0 0	
	eosinophilic change:olfactory epithelium	nelium	29 6 4 (58) (12) (8	4 0 8) (0)	16 9 (32)	(0) (0)	13 (26) (18	9 2 18) (4) ((0) ** 0	12 (24) (15 30) (0 07	** (0
	eosinophilic change:respiratory epithelium	thelium	2 0 0 (4) (0) (0	0 0	3 0 (9)	(0) (0)	7 (14) (0 (0)	(O)	4 (8) (0 0	(O) (O O O	
	inflammation:foreign body		18 11 1 (36) (36) (22) (23)	1 0 2) (0)	16 9 (32) (18)	3 0 (6) (6)	14 (28)	8 2 16) (4) (0 0	13 (26) (7 (4) (0 0 0	
	inflammation:respiratory epithelium	_	7 0 0 (14) (14) (10) (10)	0 0	8 1 (16) (16)	(0) (0)	16 (32) ()	0 0 0	(O)	3 (9 (0 6	0 0 0	
	inllammation:offactory opithelium		0) (0) (0)	0 0	(0) (0)	(0) (0)	1 (2) ()	0 0	(O)) (0)	000	(0) (0	
	respiratory metaplasia:olfactory epithelium	oithelium	0 (0) (0)	0 0	1 0 (2) (0)	0 (0)	0 0	0 0	0 (0	1 (2) (0 (0	0 0	
	respiratory metaplasia:gland		42 0 0 (84) (0) (0	(0) (0 0 0	32 0 (64) (0)	* 0 0 0	42 (84) (0 (0)	0 (0	40 (80) (0 6	0 0	
Grade 1: Slight <a>> a : Number of b b : Number of c c c c b / a * Significant difference :	2 : Moderate of animals examined of animals with lesi 100 * : P ≤ 0.05	farked 01 T	1 : Severe est of Chi Square										3 1 1

	Additional and the state of the			
	Group Name No. of Animals on Study Grade	Control 50 1 2 3	250 ppm 50 3 4	
Organ	Findings	(%) (%) (%)		(%) (%) (%)
{Respiratory system}	system)			
nasal cavit	squamous cell metaplasia:respiratory epithelium	(0) (0) (0) (0) (0) (0) (0)	(50) 1 0 0 0 (2) (0) (0) (0)	(50) 0 0 0 (0 0) (0 0)
паѕорћагупх	iuflammation:foreign body	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) 0 0 0 0 0 0
trachea	inflammation	(0) (0) (0) (0) 0	<50> 1 0 0 0 (2) (0) (0) (0)	<00 (0) (0) 0 0 0 0 (0 0) (0 0)
lung	congestion	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)	(50) 0 1 0 (0) (2) (0)
	henorrhage	2 1 0 0 (4) (2) (0) (0)		(0) (0) (0) 0 0 0
	едета	1 0 0 0 (0) (0) (0)	(0)(0)(0)(0)	(0)(0)(0)
	deposit of hemosiderin		(0)(0)(0)(0)	(0)(0)(0)
Grade < a > b	1: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion b: h / a * 100	4 : Severe		
Significant difference;	*: P ≤ 0.05 **: P ≤ 0.01	Test of Chi Square		

2 0 0 0 (4) (0) (0) (0)

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BAIS4

PAGE: 3

400**0 ppm** 50

(IIPT150)

BAIS4

STUDY NO. ANIMAL REPORT TYPE SEX	: 0684 : RAT F344/DuCricrij[F344/DuCrj] : A1 : MALE	HISTOPAT ALL ANIK	HISTOPATHOLOGICAL FINDINGS :1 ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		PAGE :
Огван	Findings	Group Name No. of Animals on Study Grade (%)	Control 50 2 3 4 (%) (%)	250 µµm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Respiratory system)	system)					
lung	inflammatory infiltration	0)	(0) (0) (0) 0 0 0 0 (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0	<0) (0) (0) (0) (0) (0) (0) (0) (0) (0) (<50> (6) (7) (7) (7) (7) (7) (7) (7) (7) (7) (7
	accumulation of foamy cells	(2)	(0) (0) (0)	(0)(0)(0)(0)(0)		
	bronchopneumonia	0 >	(0) (0) (0)	1 0 0 0 0 (2) (3) (4) (5)		(0) (0) (0) (0)
	bronchiolar-alveolar cell hyperplasia	(10)	1 0 0 (2) (2) (3) (4)	3 0 0 0 0 (0) (0)	2 0 1 0 (4) (6) (2) (6)	1 0 0 0 (2) (2) (3) (4)
{Hematopoletic system}	ic system)					
bone marrow	hemorrhage	(O)	<50> (0) (0) (0) (0)	<50> 1 0 0 0 (2) (0) (0) (0)	<50> 1 0 0 0 (2) (0) (0) (0)	<50> 0 0 0 0 (0) (0) (0)
	deposit of hemosiderin	2 (4)	(0) (0) (0)	1 0 0 0 (2) (3) (4) (5)	(0)(0)(0)(0)(0)	. 4 0 0 0 (0) (0)
	granulation	(2)	(0) (0) (0)			
Grade < a > b (c) Significant	Grade 1 : Slight 2 : Modorate 3 : h < a > a : Number of animals examined at the site b : Number of animals with lesion (c) c : b / a * 100 Significant difference : * : P \leq 0.05 ** : P \leq 0.	3: Marked 1: Severe site ≤ 0.01 Test of Chi Square	ω			

PAGE: 4

STUDY NO. ANIMAL REPORT TYPE SEX	: 0684 : RMT F344/DuCr.ICr.Lj[F344/DuCr.j] : A1 : MALE	HISTOPATHOLOGICAL FINDINGS :1 ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)	۲)	PAGE: 5
Огван	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 3 4 (%) (%) (%) (%)
(Hematopoietic system)	ic system)				
bone marrow	increased lematopoiesis	<50>	<50> 8 3 0 0 (15) (6) (0) (0)	<50> 5 3 0 0 (10) (6) (0) (0)	<50> 14 1 0 0 (28) (2) (0) (0)
spleen	angiectasis	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0	<550> 0 0 0 0 0 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)	<50> 27 0 0 0 ** (54) (0) (0) (0)
	deposit of hemosiderin	16 1 0 0 (32) (2) (0) (0)	21 4 0 0 (42) (8) (0) (0)	27 1 0 0 (54) (2) (0) (0)	28 2 0 0 * (56) (4) (0) (0)
	fibrosis:focal	4 0 0 0 (8) (9) (9) (9)	(0)(0)(0)(0)	2 0 0 0 (4) (4) (6) (6)	2 3 1 0 (4) (6) (2) (0)
	extramedullary hematopojesis	26 5 1 0 (52) (10) (2) (0)	26 8 5 0 (52) (16) (10) (0)	34 6 3 0 (68) (12) (6) (0)	31 13 3 0 ** (62) (26) (6) (0)
	engorgement of erythrocyte	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	(2) (0) (0) (0)		17 0 0 0 ** (34) (0) (0) (0)
	capsule hyperplasia		(0)(0)(0)(0)		43 0 0 0 *** (86) (0) (0) (0)
(Circulatory system)	system)				
heart	thrombus	(50) (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 000	<pre></pre>	$ \begin{array}{c cccc} $
Grade 1 : Slight (a > a : Number b : Number (c) c : b / a ' Significant difference : (HPT150)	2 : Moderate of animals examined at of animals with lesion r 100 x : P ≤ 0.05 ***	3: Marked 4: Severe the site : P ≤ 0.01 Test of Cli Square			BATS4

STUDY NO. : ANIMAL : REPORT TYPE : SEX :	: 0684 : RAT F344/DuCrlCrlj[F344/DuCrj] : AAL	HISTOPATHOLOCICAL FINDINGS : ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL PINDINGS :NON-NEOPLASTIC LESIONS (SUMMA) ALL ANIMALS (0-105W)
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 µµm 50 1 2 3 4 (%) (%) (%) (%)
{Circulatory system}	ystem)		
heart	mineralization	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(50) (0) (0) (0) (0)
	inflammation	(0) (0) (0) (0)	
	inflammatory infiltration		0 1 0 0 (0) (0) (0) (0)
	myocardial fibrosis	36 4 0 0 (72) (8) (0) (0)	31 3 0 0 (62) (6) (0) (0)
	subendocardial fibrosis	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1 0 0 0 (2) (2) (3) (4)
artery/aort	mineralization:artery	(0) (0) (0) (0) 0 0 0 0 0 <05>	<50> 1 0 0 0 (2) (0) (0) (0)

PAGE: 6

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29 5 0 0 (58) (10) (0) (0)

1 0 0 0 () (() () ()

(0) (0) (0) (0) (0)

tooth	dysplasia			1 (6	(50)	(50) (6) (6) (7)	(50) (0) (0) (0) (0) (0) (0) (0) (0) (0) ((50)	
									_
Grade	1 : Slight	1 : Slight 2 : Moderate 3 :	3 : Marked	J 4 : Severe				MAAAAA MAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
< a >	a : Number o	a : Number of animals examined at the site	it the site						
ā	b : Numper o	b : Number of animals with lesion	=						
(°)	c: b / a * 100	100							
Significan	t difference;	Significant difference ; * : P \leq 0.05 ** : P \leq 0.01 Test of Chi Square	c* : P ≤ 0.01	Test of Chi Squar	ø				

(IIPT150)

BAIS4

100

(Digestive system)

(HPT150)

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

STUDY NO. : 068 ANIMAL : KAT REPORT TYPE : A1 SEX : MAL	: 0684 : RAT F344/DuCrlCrlj[F344/DuCrj] : A1 : MALE	HISTOPA ALL ANI	HISTOPATHOLOCICAL FINDING ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		PAGE: 7
Organ	Findings	Group Name No. of Animals on Study Grade	Control 50 2 3 4 (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 3 4 (%) (%) (%) (%)
{Digestive system}	(stem)					
tongue	arteritis	1 (2)	<pre></pre>	(0)(0)(0)(0) 0 0 0 0 0 0 0 0	<00 (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 (20)
salivary gl	lymphocytic infiltration	(6)	<250> (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 0 0 0 0 (0) (0) (0)	<50> 1 0 0 0 (2) (0) (0) (0)
stomach	erosion:forestomach	(6)	<50> (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 (0) (0)	<pre></pre>	(0)(0)(0)(0) 0 0 0 0 0 0 0 0
	ulcer:forestomach	(0)	1 1 1 (2) (2)	2 0 3 0 (4) (4) (6) (6) (6)		0 1 0 0 (0) (0) (0) (0)
	hyperplasia:forestomach	(0)	(0) (0) (0)	2 0 0 0 (4) (4) (6) (6)	2 0 0 0 (1) (1) (1) (1) (1)	1 0 0 0 (2) (3) (4) (6)
	erosion:glandular stomach	1 (2)	0 0 0 0	5 0 0 0 0 (10) (10) (10) (10)	0 0 0 0 (12) (13) (14) (15)	4 0 0 0 (8) (8) (9) (9)
	ulcer:glandular stomach	2 (4)	(0) (0) (0)			4 2 0 0 (8) (4) (0) (0)
Grade 1 : Slight <a>> a : Number b b : Number (c) c c b / a * Significant difference :	1: Slight 2: Moderate 3: Para a Number of animals examined at the site b: Number of animals with lesion c: b/a*100 Hifference: *: P ≤ 0.05 **: P ≤ 0.	3 : Marked 4 : Severe he sitc P ≤ 0.01 Test of Chi Square				

HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) STUDY NO. : 0684
ANIMAL : RAT F344/DuCrICrIj[F344/DuCr.j]
REPORT TYPE : A1
SEX : MALE

	COLUM		A CAMADA AND AND AND AND AND AND AND AND AND		PAGE: 8
Organ	Findings	Group Name No. of Animals on Study Grade (%) (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 4 (%) (%) (%) (%)
(Digestive system)	stem)				
stomach	mineralization:glandular stomach	(50) (0) (0) (0) (0)	\$50\$ 1 0 0 0 (2) (0) (0) (0)	(50) 1 0 0 0 (2) (0) (0) (0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0
	dilated glands			(2) (0) (0) (0)	(0)(0)(0)(0)
	squamous cell hyperplasia:forestomach	h 0 1 0 0 (0) (0) (0) (0)		(0)(0)(0)(0)(0)	1 0 0 0 (2) (3) (4) (4)
small intes	erosion	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 <05>	(0) (0) (0) (0) 0 0 0 0 0 000
liver	hemiation	<50> 7 0 0 0 (14) (0) (0) (0)	<50> (10) (0) (0) (0) (0)	<50> 5 0 0 0 (10) (0) (0) (0)	<50> 6 0 0 0 (12) (0) (0) (0)
	fatty change:peripheral	0 0 1 0 (0) (0) (0) (0)	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		(0)(0)(0)(0)(0)
	granulation	12 0 0 0 (24) (24) (3) (3)	3 0 0 0 0 *	2 0 0 0 ** (4) (0) (0) (0)	1 0 0 0 **
					MANAGAMAAAAA

Grade	1 : Slight	2 : Moderate	ate 3 : Marke	ked 4 : Severe
< e >	a : Number of	animals exami	i : Number of animals examined at the site	
	h : Number of	: Number of animals with lesion	lesion	

o b . Number of animals with lesson (c) c : b / a * 100 Significant difference : * : P ≤ 0.05 ** : P ≤ 0.01 Test of Chi Square

STUUY NO. : 0684 ANIMAL : RAT REPORT TYPE : A1 SEX : MALE Organ_ Fi [Digestive system] 11ver in cl cl ac	: 0684 : RAT F344/DuCriCrli[F344/DuCri] : A1 : MALE Findings system) inflammatory cell nest clear cell focus acidophilic cell focus basophilic cell focus	Group Name Group Name Group Name Group (%) (%) (%) (%) Grade (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%) (%)	ALL ANIMALS (0-105W) ALL ANIMALS (0-105W) ALL ANIMALS (0-105W) Study Control Study (%) (%) (%) (%) (%) (%) (%) (%	1000 1000 (%) (%) (%) (%) (55) (0) (0 0 0 (0) (0) (0 0 0 (0) (0) (14 2 (28) (4) (2 28) (4) ((%) (%) (%) (%) (%) (%) (%) (%) (%) (%)
	spongiosis hopatis bile duct hyperplasia	0 0 0 0 0 (0) (0) (0) (0) (0) (0) (1) (1) (1) (1) (1) (1) (1) (1) (1) (1	0 0 0 0 (0) (0) (0) (0) (0) (0) (2 0 (4) (0) (48 1 (96) (2) (
	bile ductular proliferation	0 0 0		0 (0	
Grade <a>b <a>c <a>c<!--</td--><td>Grade 1 : Slight 2 : Moderate $\langle a \rangle$ a : Number of animals examined at the b : Number of animals with lesion (c) c : b / a * 100 c : b / a * 100 significant difference : * : P \leq 0.05 ** : P</td><td>3 : Marked 1 : Severe site ≤ 0.01 Test of Chi Square</td><td></td><td></td><td></td>	Grade 1 : Slight 2 : Moderate $\langle a \rangle$ a : Number of animals examined at the b : Number of animals with lesion (c) c : b / a * 100 c : b / a * 100 significant difference : * : P \leq 0.05 ** : P	3 : Marked 1 : Severe site ≤ 0.01 Test of Chi Square			

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(HPT150)

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HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) PAGE : 10	Group Name No. of Animals on Study Grade (%) (%) (%) (%) (%) (%) (%) (%) (%) (%)		(20) (20) (20) (20) (20) (20) (30) (4*
STUDY NO. : 0684 ANIMAL : KAT F344/DuCrICrlj[F344/DuCr.j] REPORT TYPE : A1 SEX : MALE	OrganFindings	(Digestive system)	liver hepatocellular hypertrophy:central

liver	hepatocellular hypertrophy:central	<pre></pre>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(0) (0) (0) (0)	<pre></pre>
	hemorrhage:central		0 0 0 0 0 0		0 1 0 0 0 0 (0) (0) (0)
	focal fatty change		2 0 0 0 0 (4) (4) (6) (6) (6)	1 0 0 0 0 (2) (2) (3) (4) (6)	
pancreas	atrophy	<pre></pre>	<50> 6 1 0 0 (12) (2) (0) (0)	<pre></pre>	<pre></pre>
	islet cell hyperplasia	2 0 0 0 () () () ()	1 0 0 0 0 (2) (2) (3) (4) (5)	1 0 0 0 0 (2) (2) (3) (4) (4)	4 0 0 0 (8) (8) (9) (9)
	hyperplasia:acinar cell	1 0 0 0 (0) (0) (0)	1 0 0 0 () () () ()		1 0 0 0 (2) (2) (3) (4) (5)
[Urinary system] kidney	m) deposit of pigment	(0)(0)(0)(0) 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(50) (0) (0) (0) (0)	(0) (0) (0) (8) (1) (1) (20) (20)

	kidney				<20>	<20>	<50>	(20)
1: Slight 2: Moderate 3: Marked a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100		deposit of p	igment			(0)(0)(0)(0)		0
a: Number of animals examined at the b: Number of animals with lesion c: b / a * 100	Grade	1 : Slight	2 : Moderate	3 : Marked	4 : Severe			
	< a >	a : Number of	animals examined at t					
	Ъ	b : Number of :	mimals with lesion					
	(°)	c:b/a*100	0					

BAIS4

(IIPT150)

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr.LGrLj[F344/DuCr.j]
REPORT TYPE : A1
SEX : MALE

PAGE: 11

Огван Еіндінgs	Grade (%) (%) (%) (%) (%) (%)	250 ppm 250 250 250 (%) (%) (%) (%) (%) (%) (%) (%) (%) (%)	1000 μpm 50 3 4 (%) (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Urinary system)				
kidney inflammatory infiltration	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 \$\delta 0 \delta 0	<50> (0) (0) (0) (0)
scar		1 0 0 0 0 (2) (2) (0) (0) (0)		(0)(0)(0)(0)
chronic nephropathy	27 15 6 0 (54) (30) (12) (0)	30 12 5 1 (60)(24)(10)(2)	22 19 6 1 (44) (38) (12) (2)	9 20 20 1 ** (18) (40) (40) (2)
papillary necrosis			0 1 0 0 (0) (0) (0)	(0) (0) (0) (0)
mineralization:papilla	1 0 0 0 (2) (3) (6) (6) (6)	2 0 0 0 0 (4) (4) (6) (6) (6)	4 0 0 0 (8) (8) (9) (9)	4 0 0 0 (8) (9) (9)
mineralization:polvis	2 0 0 0 (4) (4) (6) (6) (6) (6)	3 1 0 0 (6) (2) (0) (0)	(0)(0)(0)(0)(0)	21 2 0 0 ** (48) (4) (0) (0)
mineralization:cortex		(0)(2)(0)(0)	1 0 0 0 (2) (2) (3) (4) (5)	(0) (0) (0) (0)
urothelial hyperplasia:pelvis			(0) (0) (0) (0)	3 0 0 0 0 0 0 0 0
Grade 1: Slight 2: Moderate 3:) <a> a : Number of animals examined at the site b : Number of animals with lesion c: b / a * 100 c: b / a * 100	3 : Marked 4 : Severe . L the site			

BAIS4

(HPT150)

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj]
REPORT TYPE : A1
SEX : MALE

Огван	Findings	Group Name Control No. of Animals on Study 50 Grade 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 (%) (%) (%) (%)	4000 µµm 50 1 2 3 4 (%) (%) (%) (%)	(%)
(Urinary system)	.tem)					
urin bladd	dilatation	<50> 0 0 0 0 0 0 0 0 0 0 0 0	<50> 0 0 1 0 (0) (0) (2) (0)	(0) (0) (0) (0) 0 0 0 0 (20)>	<pre></pre>	0 0
	ulcer			(0) (2) (0) (0)		0 (0
	inflammation			(0)(0)(0)(0)	0 1 0 0 (0) (0) (0)	o 6
	transitional cell hyperplasia	0 1 0 0 (0) (0) (0) (0)		0 1 0 0 (0) (0) (0)	0) (0) (0) (0)	o ô
(Endocrine system)	ystem)					
pituitary	angioctasis	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (8) (0) (0) (0)	<50> 1 0 0 0 (2) (0) (0) (0)	<50> 1 1 0 0 (2) (2) (0) (0	o 6
	cyst	1 0 0 0 (2) (2) (3) (4) (4) (4)	5 0 0 0 (10) (10) (10)	1 0 0 0 (2) (2) (3) (4)	(2) (0) (0) (0	o
	hyperplasia	7 5 4 0 (14) (10) (8) (0)	8 2 1 0 (16) (4) (2) (0)	5 8 4 0 (10) (16) (8) (0)	7 2 0 0 (14) (14) (14) (15) (15)	06
Grade	1 : Slight 2 : Moderate 3 a : Number of animals examined at the sight b : Numbers of animals examined at the sight of the	3 : Marked 1 : Severo sile				

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(IIPT150)

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

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr.Icr.Ij[F344/DuCr.J]
REPORT TYPE : A1
SEX : MALE

SEX :	: MALE				PAGE: 13
Огван	Findings	Group Name Control No. of Animals on Study 50 Grade 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}	ystem}				
pituitary	Ratike pouch	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(50) 1 0 0 (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	<50> 1 0 0 0 (2) (0) (0) (0)
thyroid	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 0	(0) (0) (0) (0) 0 0 0 0 (0) (0) (0)	<50> 1 0 0 0 0 (2) (0) (0) (0)
	C-cell hyperplasia	14 3 1 0 (28) (6) (2) (0)	12 2 0 (24) (4) (4) (0)	11 2 3 0 (22) (4) (6) (0)	9 4 1 0 (18) (8) (2) (0)
adrenal	extramedullary hematopoiesis	<20> (0) (0) (0) (0) (0)	(50) 1 0 0 0 (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 0
	hyperplasia:cortical cell		(2) (0) (0) (0)	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1 1 0 0 (2) (2) (3) (4) (4)
	hyperplasia:medulla	1 0 1 0 (2) (0) (2) (0)	4 0 0 0 (8) (8) (9) (9)	4 0 0 0 (8) (8) (9) (9)	3 0 2 0 (6) (0) (4) (0)
	focal fatty change:cortex	2 0 0 0 (4) (4) (6) (6)	2 0 0 0 0 (4) (4) (6) (6)	2 1 0 0 (4) (2) (0) (0)	1 0 0 0 (2) (3) (4) (4)

3 : Marked Grade 1: Slight 2: Moderate 3: Mar $\langle a \rangle$ a : Number of animals examined at the site b : Number of animals with losion (c) c: b/a*100 Significant difference: *: P \leq 0.05 **: P \leq 0.01

4 : Severe

**: P ≤ 0.01 Test of Chi Square

(IIPT150)

(SUMMARY)	
:NON-NEOPLASTIC LESIONS	
HISTOPATHOLOGICAL FINDINGS :1	ALL ANIMALS (0-105W)

STUDY NO. : 0684
ANIMAL : RAT F344/DuCr.LGr.Lj.[F344/DuCr.j.]
REPORT TYPE : A1
SEX : MALE

Organ	Findings	Group Name Control No. of Animals on Study 50 I 2 3 4 (%) (%) (%) (%)	250 ppur 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%) (%)
(Reproductive system)	e system)				
testis	mineralization	(50) 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 (20)	\$60\$ 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) (0) (0) (0)
	inflammation	(2) (0) (0) (0)	(0)(0)(0)(0)(0)	(0)(0)(0)(0)(0)	
	interstitial cell hyperplasia	6 0 0 0 (12) (13) (13) (13) (13) (14) (15)	7 0 0 0 0 (14) (14) (10) (10) (10)	3 0 0 0 (0) (0) (0)	3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
epididymis	inflammation	(20) (0) (0) (0) (0) (0) (0) (0) (0) (0) ((0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 000	<50> 1 0 0 0 (2) (0) (0) (0)
	lymphocytic infiltration		(0) (0) (0) (0) (0)	(2) (0) (0) (0)	
semin ves	inflammation	(0)(0)(0)(0) 0 0 0 0 (0)(0)(0)	<200> (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	(50) 0 1 0 0 (0) (2) (0) (0)	(0) (0) (0) (0) (0) (0) (0)
prostate	inflammation	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<50> 4 0 0 0 (8) (0) (0) (0)	(50) 2 2 0 0 (4) (4) (0) (0)	(50) 0 0 1 0 (0)(0)(2)(0)
Grade < a > b	1: Slight 2: Moderate 3: 9 and a Number of animals examined at the site b: Number of animals with lesion	3 : Marked 4 : Severe site			

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OTTEN ROTH-MON.	OTTOM NOW NOW.	
HOLOGICAL FINDINGS	THE PROPERTY OF THE PROPERTY OF	MIS (0-105W)
HISTOPATHO	THEOLOGIC	ANIMA LIK
		-1 i F344/)bcC
		344/DuCr1Cr1

STUDY NO. : 0684 ANIMAL : RAT F344/DuCr1Cr1;[F344/DuCrj] REPORT TYPE : A1 SEX : MALE		HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)	λ	PAGE : 15
OrganFindings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 3 4 (%) (%) (%) (%)
(Reproductive system)				
prostate lympkocytic infiltration	<50>	(50> 1 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<pre></pre>
hyperplasia	3 2 0 0 (6) (7) (7) (9) (9)	(10) (0) (0) (0)	4 1 0 0 (8) (8) (9) (0)	2 1 0 0 (4) (5) (6) (6)
(Nervous system)				
brain 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	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)
hyperplasia:chroid plexus		1 0 0 0 (2) (2) (9) (9)	(0) (0) (0) (0)	
(Special sense organs/appendage) eye cataract	<50> 7 1 0 0 (14) (2) (0) (0)	(50) 5 1 0 0 (10) (2) (0) (0)	(50) 6 1 0 0 (12) (2) (0) (0)	(10) (6) (0) (0) (0)

BAIS4

**: P \leq 0.01 Test of Chi Square

Grade 1 : Slight 2 : Moderate 3 : Marked \langle a \rangle a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P \leq 0.05 ** : P \leq 0.01 T

(HPT150)

4 : Severe

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

16 PAGE: 3 6 5 0 *** (6) (12) (10) (0) 4 % 00 00 00 00 00 4 0 0 (0) (0) (1 -1 1 2 0 (2) (3) (3) 1 1 0 (2) (2) (0) (3 1 0 (6) (7) (7) (7) 1 0 0 (2) (2) (0) (\cup 2 3 (%) (%) 4000 բրա 50 (0)(0)(0) (2) (6) (12) (0) 0 6 00 00 48 00 o ô 00 4 0 0 (s) (s) (c) (c) 2 3 (%) (%) 1 2 0 (2) (4) (0) (0 (0) (0) (0) 1 0 0 (2) (2) (0) ($\overline{}$ $\overline{}$ mdd (0)(0)(0) (0) (0) (0 1000 I - 8º 2 4 5 0 ** (4) (8) (10) (0) 1 0 2 0 2) (0) (4) (0) 00 00 4 8 00 0 0 0 0 0 00 2 0 0 (4) (4) (6) (6) 3 0 0 (0) 1 0 0 2) (0) (0) (\cup 2 3 (%) 0 0 250 ppm 50 _ 7 3 78 _ 4 8 00 00 (0) (2) (2) (0) 1 0 0 0 (2) (2) (0) (0) (0) 00 00 \smile 0 0 0 0 2 3 (%) (%) 2 0 0 ((4) (4) (0 0 0 0 Control 50 (0) (0) (0) (0) Group Name No. of Animals on Study Grade STUDY NO. : 0684 ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj] REPORT TYPE : A1 SEX : MALE lymphocytic infiltration mineralization:cornea (Special sense organs/appendage) retinal atrophy mineralization hyperplasia keratitis Findings. Musculoskeletal system) iritis llarder gl muscle Organ eye

BAIS4

Test of Chi Square

* : P ≤ 0.01

4 : Severe

3 : Marked

1 : Slight 2 : Moderate 3 : Me a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100

Grade 1 : Slight 2 : Moderal \langle a \rangle a : Number of animals examine b b : Number of animals with Let \langle c \rangle c : b / a * 100 Significant difference ; * : P \leq 0.05

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

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

PAGE: 17

			A STATE OF THE PROPERTY OF THE		**************************************
	Group Name No. of Animals on Study	Control 50	250 ppm 50	1000 ppm 50	4000 yrm
Organ Findings	Grade (%)	1 2 3 4 (%) (%) (%) (%)	1 2 3 4 (%) (%) (%) (%)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(%) (%) (%) (%)
(Musculoskeletal system)					
muscle lymphocytic infiltration	0)	(20) (0) (0) (0) (0) (0) (0) (0) (0) (0) (<50> 1 0 0 0 (2) (0) (0) (0)	(20) (0) (0) (0) (0) (0) (0) (0) (0) (0) ((0) (0) (0) (0) 0 0 0 0 <0\$>

1: Slight 2: Moderate 3: Marked a: Number of animals examined at the site b: Number of animals with lesion c: b / a * 100 Grade 1 : Slight 2 : Moderate ⟨ a ⟩ a : Number of animals examined b b : Number of animals with les (c) c : b / a * 100 Significant difference : * : P ≤ 0.05

**: P ≤ 0.01 Test of Chi Square

(HPT150)

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TABLE L 4

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

FEMALE: ALL ANIMALS

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KEFORT TYPE : AI SEX : FEM	: FEMALE				PAGE :
Organ	Group Name No. of Anii Grade Findings	Animals on Study 50 (%) (%) (%) (%) (%)	250 µµm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 3 4 (%) (%) (%) (%)
(Integumenta	{Integumentary system/appandage}				
skin/app	squamous cell hyperplasia	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(0) (0) (0) (0 0 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (2) (0) (0) (0)
subcutis	inflammetion	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) (0 0 0 0 0 0 <05>	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 <05>
{Respiratory system}	system)				
nasal cavit	thrombus	<50> 1 0 0 0 (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)	<pre></pre>
	mineralization	19 0 0 0 0 (0) (0) (0)	23 0 0 0 0 (46) (46) (6) (6) (6)	27 0 0 0 (54) (54) (0) (0) (0)	23 0 0 0 (46) (46) (6) (6)
	eosinophilic change:olfactory epithelium	9 31 9 0 (18) (62) (18) (0)	13 27 9 0 (26) (54) (18) (0)	13 31 6 0 (26) (62) (12) (0)	3 28 17 0 (6) (56) (34) (0)
	eosinophilic change:respiratory epithelium	1 0 0 0 (2) (3) (4) (5)			3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Grade < a > b (c)	Grade I: Slight 2: Moderate 3: Marked <a> a : Number of animals examined at the site b : Number of animals with lesion c: b/a * 100 c: b/a * 100 c: c: b/a * 100 c: c: c: c: b/a * 100 c: c:	4 : Severe			

PAGE: 18

(HPT150)

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

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

		(%) (%) (%)	(%) (%) (%) (%)	(%) (%) (%) (%)	(%) (%) (%) (%)
{Respiratory system}	system)				
nasal cavit	inflammation:foreign body	<00> (6) (0) (0) (0) (0) (0) (0)	<50> 2 0 0 (4) (0) (0) (0)	<50> <50> (50> (0) (2) (0) (0)	<50> 1 2 1 0 (2) (4) (2) (0)
	inflammation:respiratory epithelium	1 0 0 0 (2) (3) (3) (4)	4 0 0 0 (8) (8) (9) (9)	(10) (0) (0) (0) (01)	1 0 0 0 (2) (3) (4)
	respiratory metaplasia:gland	47 0 0 0 (94) (94) (94) (97) (97)	49 0 0 0 () () () () ()	48 0 0 0 (6) (6) (6) (6) (6)	48 0 0 0 0 (96) (96) (96)
	ulcer:respiratory epithelium	1 0 0 0 (2) (2) (3) (4) (4)		(0)(0)(0)(0)(0)	(0)(0)(0)(0)
nasopharynx	inflammation:foreign body	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 (20)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)
larynx	ulcer	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 (0) (0) (0)	(50) 0 1 0 0 (0)(2)(0)(0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0
	inflammation:foreign body		(0)(0)(0)(0)(0)	(0)(0)(0)(0)	1 0 0 0 (2) (3) (4) (4)

STUDY NO.	: 0684	HISTOPATH
ANIMAL	: RAT F344/DuCrlCrlj[F344/DuCrj]	ALL ANIMA
REPORT TYPE : AI	E: AI	
SEX	: FEMALE	

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

PAGE: 20

Organ	Findings.	Out of Animals on Study 50 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 2 3 4 (%) (%) (%) (%)	4000 ppm 50 (%) (%) (%)	4 %
{Respiratory system}	system)					
lung	congestion	(50)> 1 0 0 0 (2) (0) (0) (0)	<pre></pre>	(20) (0) (0) (0) (0) (0) (0) (0) (0) (0) (<09) (0) (0) (0) (0) (0) (0) (0) (0) (0) (0	0 0
	hemorrhage	(2) (0) (0) (0)	1 0 0 0 (2) (2) (3) (4)	1 0 0 0 (2) (2) (3) (4) (4)	0 0 0	0
	inflammatory infiltration	(2) (0) (0) (0)	0 0 0 0 0 0	1 1 0 0 (2) (2) (0) (0)	0 0 0 0	0
	accumulation of foamy cells	(2) (0) (0) (0)	2 0 0 0 (4) (4) (6) (6)	2 0 0 0 (4) (4) (6) (6) (6)	2 0 0 (0) (0) (0)	0 0
	bronchiolar-alveolar cell hyperplasia		1 0 0 0 (2) (3) (4) (5)		1 0 0 (2) (3) (4) (5)	0
(Hematopoietic system)	c system)					
bone marrow	congestion	(0) (0) (0) (0) 0 0 0 0 <05>	(50) 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(20) (0) (0) (0) (0) (0)	0 0
	hemorrhage	(0) (0) (0) (0) (0) (0)		1 0 0 0 (2) (3) (4) (4)	0 0 0 0	0 0
Grade < a > b	1 : Slight 2 : Moderate 3 : Marked a : Number of animals examined at the site b : Number of animals with lesion	cd 4: Severe				

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

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

STUDY NO. : 0684 ANIMAL : RAT REPORT TYPE : A1 SEX : FEMA	: 0684 : RAT F344/buCr.ICr.I.j[F344/buCr.j] : Al : FEMALE	HISTOPATHOLOGICAL FINDINGS :: ALL ANIMALS (0-105%)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)		PAGE : 21
Organi.	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Hematopoietic system)	: system)				
bone marrow	deposit of hemosiderin	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> <50> (50) (70) (10) (10) (10) (10) (10) (10) (10) (1	<50> 1 0 0 0 (2) (0) (0) (0)
	granulation			0 1 0 0 (0) (0) (0)	2 0 0 0 (4) (4) (6) (6) (6)
	increased hemalopoiesis	9 2 0 0 (18) (4) (0) (0)	2 2 0 0 (4) (4) (0) (0)	7 1 0 0 (14) (2) (0) (0)	8 4 0 0 (16) (16) (18) (19) (19)
spleen	angiectasis	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (2) (0) (0) (0)	<pre></pre>	<pre></pre>
	deposit of hemosiderin	38 5 0 0 (76) (76) (76) (9) (9)	32 11 0 0 (64) (22) (0) (0)	27 17 0 0 * (54) (34) (0) (0)	35 1 0 0 (70) (70) (2) (0) (0)
	fibrosis:focal		(0)(0)(0)(0)	0 1 0 0 (0) (0) (0)	5 2 0 0*
	extramedullary lematopoiesis	32 9 3 0 (64) (18) (6) (0)	38 6 1 0 (76) (77) (2) (0)	27 18 4 0 (54) (36) (8) (0)	24 16 3 0 (48) (32) (6) (0)
	engorgement of erythrocyte			3 0 0 0 0 (0) (9)	24 0 0 0 ** (48) (0) (0) (0)

TOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)	ALL ANIMALS (0-105W)
HIS	[F344/DuCr.j] ALJ

STUDY NO. : 068 ANIMAL : RAT REPORT TYPE : A1 SEX : FEM	: 0684 : RAT F344/DuCriCrij[F344/DuCrj] : Al : FEMALE	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	6		PAGE: 22
Organ	Findings.	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%) (%)	250 ppm 50 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	400 50 (%) (%)	4000 ppm 50 2 3 4 6) (%) (%)
{Hematopoietic system} spleen capsul	c system) capsule hyperplasia	(0) (0) (0) (0) 0 0 0 0 <05>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0	<50> 41 0 (82) (0) (0 (0) (0) **
(Circulatory system) hoart thro	system] thrombus	(0) (2) (0) (0) 0 1 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 000	(0) (0) (0) (0) 0 0 0 0 0 0 0 0) (0) (0) 0 0 (09))> 0 0 (0) (0)
artery/aort	myocardial fibrosis mineralization:artery	31 0 0 0 0 (62) (63) (63) (63) (63) (63) (63) (63) (63	27 0 0 0 0 (54) (54) (0) (0) (0) (0) (0) (0) (0) (0) (0) (0	29 1 0 0 (58) (2) (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	31 0 (62) (0) (250)	
(Digestive system) oral cavity sq	stem) squamous cell hyperplasia	<50> 0 1 0 0 (0) (2) (0) (0)	(0) (0) (0) (0) 0 0 0 0 (20)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0	(0) (0)	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Grade I: Slight (a > a : Number b b : Number (c) c: b / a * Significant difference:	2 : Moderate of animals examined at of animals with losion 1.100 ★:P ≤ 0.05 ★★	3 : Marked 4 : Severe the site $ \label{eq:site} 1 = 0.01 $ Test of Chi Square				

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2 0 0 (4) (0) (0) (

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2 1 0 (4) (2) (0) (

ulcer:glandular stomach

 \aleph

PAGE:

4 8 00 00 o 6 00 00 0 (0) (0) (0) 0 0 0 0 0 0 0 0 (0)(2)(0)(6 1 0 (12)(2)(0)(0 (0) (0) (0) 400**0 руш** 50 1 2 3 (%) (%) (%) 2 3 4 (%) (%) (%) (0) (0) (0) (0) (0) (0) (0) (0) 00 00 00 00 . . 6 1 0 0 ((2) (0) (1 2 0 (2) (4) (0) (4 1 0 (8)(2)(0)(1000 ppm 50 1 0 (0 (2) (0) (0) - 8 0 1 0 0 (0) (0) (0) (0) (0)(0)(0)(0)(0) (0) (2) (0) (0) (0) (2) (2) (0) 2 0 0 0 (4) (4) (6) (7) (7) 44 88 250 ppm 50 m € 2 8 → 3€ 2 3 4 (%) (%) (%) 00 (0)(0)(0)(0)(0) (0)(0)(0)(0)(0) (0) (0) (0) (0) 2 1 1 0 (4) (2) (2) (0) 2 0 0 0 (4) (4) (6) (6) (7) 6 1 0 (12) (2) (0) (Control 50 Group Name No. of Animals on Study Grade erosion:glandular stomach lymphocytic infiltration hyperplasia: forestomach ulcer: forestomach dysplasia Findings ulcer (Digestive system) stomach tongue Organ tooth

orade i oligie 2 moderate o marked 4 oevere	
(a) a : Nimber of animals examined at the site	

Test of Chi Square . On the continuation of the continuation of

** : P ≤ 0.01

(IIPT150)

(HPT150)

HISTOPATHOLOGICAL FIN	AUTOLO STANDARD TIM
	RATE F344/birCv1/Cv1 if F344/bircvi1
0684	RAT FR44/DuCyl

INDINGS : NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) STÜDY NO. : 0684 ANIMAL : KAT F344/DuCr1Cr1j[F344/DuCr:j] REPORT TYPE : A1 SEX : FBMALE

Organ	Findings	Group Name Control No. of Animals on Study 50 Grade 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 4 (%) (%) (%) (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 (%) (%) (%)	pin (%)
(Digestive system)	tem}					
stomach	liyperplasia:glandular stomach	<550> 0 0 0 0 (0) (0) (0)	\$\\ \begin{array}{cccccccccccccccccccccccccccccccccccc	\$20> 0 0 0 0 0 0 0 0 0 0	<50> (0) (0) (0) (0)	0 0
	dilated glands		(0)(0)(0)(0)(0)	(2) (0) (0) (0)	(0)(0)(0)	0 0
small intes	erosion	(0) (0) (0) (0) 0 0 0 0 <05>	(0) (0) (0) (0) (0)	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) 0 0 0 0 (0) (0)	0 0
	inflammation	$\begin{pmatrix} 1 & 1 & 0 & 0 \\ (2) & (2) & (0) & (0) \end{pmatrix}$	(0)(0)(0)(0)(0)	(0) (0) (0) (0) (0)	(0)(0)(0)	0 0
large intes	mineralization	(0) (0) (0) 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (2) (0) (0) (0)	(50) 1 0 0 0 (2) (0) (0) (0)	<50> 2 0 0 (1) (0) (0)	0)
	inflammation	(2) (0) (0) (0)			(0)(0)(0)	0 0
liver	herniation	(0) (0) (0) (91) 8 (0) (0) 8 (20)	\$ 0 0 0 0 0 (0) (10) (10) (10) (10) (10)	\$50\$ 7 0 0 0 \$(14)\$(0)\$(0)\$(0)\$	(50) 10 0 0 (20) (0) (0)	0 0
Grade 1	1: Slight 2: Moderate 3::1 a: Number of animels examined at the site by Number of animels with lesion	3 : Marked 4 : Severe site				

(HPT150)

BAIS4

STUDY NO. : 0684
ANIMAL : KAT F344/DuCrlCrlj[F344/DuCr.]]
REPORT TYPE : AI
SEX : FEMALE

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

PAGE: 25

Organ	N G	No of Animals on Study 50 (%) (%) (%) (%) (%)	500 pput 50 3 4 (%) (%) (%) (%)	100 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 (%) (%) (%)	(%)
(Digestive system)	ystem)					
liver	necrosis:central	<50> 0 0 1 0 (0) (0) (2) (0)	<50> 0 1 0 (0) (2) (0) (0)	(50) 1 0 0 0 (2) (0) (0) (0)	<50> 0 1 0 (0) (2) (0) (0
	necrosis:focal	1 0 0 0 (2) (3) (4) (5) (5)			1 0 0 (0) (0) (0
	fatty change:central	0 1 0 0 (0) (0) (0) (0)		1 0 0 0 0 (2) (2) (3) (4) (6)	0 0 0	0 (0
	fatty change:peripheral	0 1 0 0 (0) (0) (0) (0)		1 0 0 0 0 (2) (2) (3) (4) (6)	0 0 0	0 (0
	granulation		$\begin{pmatrix} 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{pmatrix}$	(0)(0)(0)(0)(0)	0 0 0	0 0
	inflammetory cell nest	22 3 0 0 (44) (6) (0) (0)	28 3 0 0 (56) (56) (6) (6)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10 1 0 (20) (20) (* (0
	extramedullary hematopoiesis	1 0 0 0 (2) (3) (6) (6)		(0)(0)(0)(0)(0)	0 0 0 0	0 0
	acidophilic cell focus	5 1 1 0 (10) (2) (2) (0)	3 1 2 0 (6) (2) (4) (0)	3 1 1 0 (6) (2) (2) (0)	8 1 0 (16) (2) (10)	0 0
Grade < a > b	1 : Slight 2 : Moderate 3 : hat a : Number of animals examined at the site b : Number of animals with lesion	3 : Marked 1 : Severe site				

STUDY NO. ANIMAL REPORT TYPE SEX	: 0684 : KAT F344/DuCr1Cr1j[F344/DuCrj] : A1 : FEWALE	HISTOPATE	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)	C	PAGE: 26
Огван	Findings	Group Name No. of Animals on Study Grade (%)	Control 50 4 (%) (%) (%)	250 µµm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Digestive system)	system)					
liver	basophilic cell focus	23 (46) (<50> 3 0 0 (6) (0) (0)	<pre></pre>	<50> 16 1 0 0 (32) (2) (0) (0)	<50> 10 0 0 0 *** (20) (0) (0) (0)
	bile duct hyperplasia	13 (26)	2 0 0 (4) (4) (6)	15 0 0 0 0 (0) (30) (30)	20 0 0 0 (40) (40) (0) (0)	17 0 0 0 0 (34) (34) (0) (0) (0)
	biliary cyst	6 0	(0)(0)(0)	1 0 0 0 (2) (3) (4) (5)	2 0 0 0 (4) (4) (6) (6) (6)	(0) (0) (0) (0)
	hepatocellular hypertrophy:central	60	(0)(0)(0)	(0)(0)(0)(0)(0)	1 0 0 0 (2) (2) (3) (4) (4)	28 1 0 0 ** (56) (2) (0) (0)
	focal fatty change	0)	(0)(0)(0)		(0)(0)(0)(0)(0)	1 0 0 0 (2) (2) (3) (4) (4)
pancroas	atrophy	(6) 0	(0) (0) (0) 0 0 0 0 (0)	<50> 1 0 0 0 (2) (0) (0) (0)	(50) 1 0 0 0 (2) (0) (0) (0)	<50> 0 0 0 0 0 0 0 0 0 0 0 0
	islet cell hyperplasia	2 (2)	0 1 0 (0) (2) (0)	0 0 1 0 (0) (0) (0) (0)	2 0 0 0 (4) (4) (6) (6) (6)	
(Urinary system)	stem}					
kidney	hyaline droplet	0 0 0	<50> 1 0 0 (2) (0) (0)	<50> (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<pre></pre>
Grade <a>> b (c) Significant	Grade 1 : Slight 2 : Moderate 3 : β < α > α : Number of animals examined at the site b : Number of animals with lesion (α) α : α > α : α : α > α : α	3 : Marked 4 : Severe at the site on ** : P ≤ 0.01 Test of Chi Square				
(HPT150)						BAISA

BAIS4

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18 2 0 (36) (4) (0) (

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7 1 (14) (2) (

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2 (4)

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7 0 0 (14) (14) (10) (10) (10)

mineralization:papilla

mineralization:pelvis

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

PAGE: 27

STUDY NO. : 0684 ANIMAL : RAT F344/DuckICr1j[F344/Duck.j]

ANIMAL : RAT F344 REPORT TYPE : A1 SEX : FEMALE

* 0 4 % 00 00 00 00 6 0 0 (12) (12) (13) (13) (14) 0 0 0 0 23 5 2 (46) (10) (4) (0 0 0 0 20 0 0 (40) (40) (50) (50) 4000 ppm 50 2 3 (%) (%) - S 1 0 0 0 (2) (2) (3) (4) (4) 00 00 00 06 4 8 00 e (%) 1000 ppm 50 20 2 6 (40) (4) (12) 00 00 0 0 0) (0) (0 0) (0) 15 0 (30) (0) (2 (%) **⊣** §€ 0 0 (0)(0)(0)(0)(0)
 18
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 (36)
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 0 0 0 1 0 0 0 () ((2) ((0) ((0) ((0) 4 8 250 ppm 50 7 0 0 (14) (14) (10) m € 2 8 000 - 8 00 00 00 4 8 20 3 1 0 40) (6) (2) (0) 1 0 0 0 (2) (2) (0) (0) (0) 0 (0) (0) 0 0 0 0 13 0 0 26) (0) (0) (Control 50 e 8 Group Name No. of Animals on Study Grade mineralization:cortico-medullary junction inflammatory infiltration chronic nephropathy deposit of pigment hydronephrosis Findings (Urinary system) kidney Organ

	mineralization:cortex	ion:cortex		4 (8)	000	0 (0	• 6	9 (81)	0 6) (0	o ô	10 (20) (0 6	0 0	0 0) (9 1) 8	0
Grade	1 : Slight	2 : Moderate	3 : Marked	4 : Severe													
< a >	a : Number of	a : Number of animals examined at	the site														

Test of Chi Square *:P≤ 0.01 b : Number of animals with lesion c : $b \mathrel{/} a * 100$ Grade 1: Slight 2: Moderate < a > a: Number of animals examined b : Number of animals with lesi (c) c: b / a * 100 Significant difference; *: P ≦ 0.05

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

06 · 55/40	4000 ppm 50 4 (%) (%) (%) (%)
ARY)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%) (%)
ISTOPATHOLOGICAL FINDLNGS :NON-NEOPLASTIC LESIONS (SUMMARY) LL ANIMALS (0-105W)	250 ppm 50 m (%) (%) (%) (%) (%) (%) (%) (%) (%) (%)
HISTOPATHOLOCICAL FINDIN ALL ANIMALS (0-105W)	Coutrol Los on Study 50 1 2 3 4 (%) (%) (%) (%)
[F344/bucr.j]	Group Name No. of Animals on Study Grade
STUDY NO. : 0684 ANIMAL : RAT F344/DuCr1Cr1j[F344/DuCrj] REPORT TYPE : A1 SEX : FEMALE	OrganFindings

Огван	Findings.	Group Name Control No. of Animals on Study 50 Grade 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
{Urinary system}	(wə:				
kidney	atypical tubule 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	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0
	dilated pelvis			(2) (0) (0) (0)	(2) (0) (0) (0)
urin bladd	dilatation	$\begin{pmatrix} <50 > & \\ 0 & 1 & 0 \\ (& 0) & (& 0) & (& 2) & (& 0) \end{pmatrix}$	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0	<50> 0 0 1 0 (0) (0) (2) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0
	transitional cell hyperplasia		0 0 0 0	1 0 0 0 (2) (3) (4) (5) (6) (6)	
{Endocrine system}	(stem)				
pituitary	angiectasis	<pre></pre>	(50) 6 0 0 0 (12) (0) (0) (0)	<50> 4 2 1 0 (8) (4) (2) (0)	$\langle 50 \rangle$ 2 4 1 0 (4) (8) (2) (0)
	cyst	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	14 4 0 0 (28) (28) (8) (0) (0)	11 2 0 0 (22) (4) (0) (0)	14 2 0 0 (28) (4) (0) (0)
Grade 1 : Slight < a > a : Number b b : Number (c) c : b / a * Significant difference :	2 : Moderate of animals examined of animals with losi 100 *:P ≤ 0.05	3 : Marked 4 : Severe at the site on *** : P ≤ 0.01 Test of Chi Square			

BAIS4

STUDY NO. : 068 ANIMAL : RAT REPORT TYPE : A1 SEX : FEM	: 0684 : RAT F344/DuCrICrIj[F344/DuCrj] : Al : FEMALE	HISTOPATHOLOGICAL FINDINGS :1 ALL ANIMALS (0-105%)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)			PAGE : 29
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 50 1 2 (%) (%)	4000 µpm 50 3 4 5) (%) (%)
{Endocrine system}	system)					
pituitary	liyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<50> 5 5 1 0 (10) (10) (2) (0)	<50> 5 4 1 0 (10) (8) (2) (0)	<50> 2 4 (4) (8) (0> 1 0 (2) (0)
	Rathke pouch	(2) (0) (0) (0)	2 0 0 0 0 (4) (4) (6) (6) (6)		1 0 (2) (3) (0 (0)
thyroid	inflammation	(0) (0) (0) (0) 0 0 0 0 <05>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0) 0 0 0 0 0 0000	(50) 0 1 (0) (2) ()> 0 0 (0) (0)
	ultimobranchial body remanet		3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0)	0 (0)	(0) (0)
	follicular hyperplasia		(0) (0) (0) (0)		1 0 (2) (0) ((0) (0)
	C.cell hyperplasia	14 6 5 0 (28) (12) (10) (0)	12 4 1 0 (24) (8) (2) (0)	14 3 1 0 (28) (6) (2) (0)	11 2 (22) (4) (2 0 (4) (0)
adrena I	fatty change	(0) (0) (0) (0) 0 0 0 0 0 0 0	<pre></pre>	<0) (0) (0) (0) 0 0 0 0 (0) (0) (0)	(0) (0) (0) (0) (0) (0) (0) (0))> 1 0 (2) (0)
Grade <a>b b (c) Significant	Grade 1 : Slight 2 : Moderate 3 : h \langle a > a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b $/$ a * 100 Significant difference : * : P \leq 0.05 ** : P \leq 0.	3 : Marked 4 : Severe the site : P ≤ 0.01 Test of Chi Square				

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0 6	0 8	00	00	0 0	00	#
$\overline{}$	$\overline{}$	$\overline{}$	\smile	$\overline{}$	$\overline{}$	
0 6	0 0	c ĉ	0 0	0 0	00	

STUDY NO. ANIMAL REPORT TYPE SEX	: 0684 : RAT F344/BuCrlCrlj[F344/BuCrj] E : AI : PEMALE		HISTOPATHOLOGICAL FINDINGS : ALL ANIMALS (0-105#)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105#)		PAGE : 30
Organ	Findings	Group Name No. of Animals on Study Grade	Study 50 4 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
{Endocrine system} adrenal fo	system) focal fatty change:cortex		<pre></pre>	<pre></pre>	<50> 0 1 0 0 (0) (2) (0) (0)	(50) 4 0 0 0 (8) (0) (0) (0)
(Reproducti ovary	(Reproductive system) ovary cyst		<pre></pre>	(50) 1 0 0 0 (2) (0) (0) (0)	<50> 1 1 0 0 (2) (2) (0) (0)	<pre></pre>
uterus	lymphocytic infiltration dilatation		(2) (0) (0) (0) (2) (0) (0) (0) (50) (0) (0) (0) (0)	(0)(0)(0)(0) 0 0 0 0 0 (0)(0)(0)(0)(0) 0 0 0 0 0	(0) (0) (0) (0) (0) (0) (0) (0)	0 0 0 0 (0)(0)(0)(0) (0)(0)(0)(0) (2)(0)(0)(0)
	hyperplasia:gland stromal hyperplasia			$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1 0 0 0 (2) (0) (0) (0) 0 0 0 0 (0) (0) (0)	
Grade <a>b b c c c c Significant (HPT150)	Grade 1 : Slight 2 : Moderate 3 :) $\langle a \rangle$ a : Number of animals examined at the site b : Number of animals with lesion (c) b . $a \times 100$ Significant difference ; $*: P \leq 0.05$ **: $P \leq 0$ (HPT150)	farked 01	4 : Severe Test of Chi Square			BAIS4

(IIPT150)

STUDY NO. : 068 ANIMAL : RAI REPORT TYPE : A1	: 0684 : RAT F344/buck.lck.lj[F344/buck.j] : Al	HIS	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOCICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)	()	
SEX	: FEMALE					PAGE: 31
,		Group Name No. of Animals on Study Grade	Control dy 50 1 2 3 4	250 ppm 50 2 3	1000 ppm 50	4000 ppm 50 2 3
Organ	Findings		8		88	
(Reproductive system)	e system)					
uterus	cystic endometrial hyperplasia	Č	<pre></pre>	<pre></pre>	<pre></pre>	(6) (0) (0) (0) (0) (0)
mammary gl	liyperptasia	Č	(50) 1 0 0 0 2) (0) (0) (0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0 0 0 0	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 <05>
	galactocele	J	1 0 0 0 2) (0) (0) (0)			
(Nervous system)	tem)					
brain	hemorrhage		<pre></pre>	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) (0)	(0) (0) (0) (0) (0) (0) (0) (0) (0)
	Rliosis					$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{pmatrix}$
Special sen	(Special sense organs/appendage)					
eye	cataract		\$ 0 0 0 4) (0) (0) (0)	<50> 2 0 0 0 (4) (0) (0) (0)	<pre></pre>	(50) 2 0 0 (4) (0) (0) (0)
Grade <a>b b co co Significant	Grade 1: Slight 2: Moderale 3: b < a > a : Number of animals examined at the site b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P \leq 0.05 ** : P \leq 0.	larked 4	: Severe ihi Square			

STUDY NO. : ANIMAL : REPORT TYPE : SEX :	: 0684 : RAT F344/bucricrij[F344/bucrj] : A1 : FEMALE	HISTOPATHOLOGICAL FINDINGS : ALL ANIMALS (0-105W)	HISTOPATYOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105#)		PAGE :
Отван	Findings	Group Name Control No. of Animals on Study 50 Grade	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Special sens	(Special sense organs/appendage)				
eye	retinal atrophy	$ \begin{pmatrix} 50 \\ 24 & 9 & 1 & 0 \\ (48) & (18) & (2) & (0) \end{pmatrix} $	(50) 15 5 0 0 * (30) (10) (0) (0)	<pre></pre>	<pre></pre>
	keratitis	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0)(0)(0)	0 1 0 0 (0) (0) (0)	
	iritis		(2) (0) (0) (0)		
	mineralization:cornea		(2) (2) (0) (0)	1 0 0 0 (2) (3) (4) (4)	(0) (0) (0) (0)
Barder gl	lymphocytic infiltration	(50) 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (9) 3 0 0 0 (20)	<pre></pre>	(50) 1 1 0 0 (2) (2) (0) (0)
nasolacr d	inflammation	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<pre></pre>	<50> 4 0 0 0 (8) (0) (0) (0)	<50> 3 0 0 0 (6) (0) (0)
(Musculoskeletal system)	stal system)				
muscle	mineralization	<50> 1 0 0 0 (2) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 (20)	(0) (0) (0) (0) 0 0 0 0 0 <05>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0
Grade 1 : Slight < a > a : Number b b : Number (c) c : b / a * Significant difference :	2: Moderate of animals examined at of animals with lesion 100 *:P \(\begin{align*}	3: Marked 4: Severe the site : P ≤ 0.01 Test of Chi Square			
(HPT150)					BALS

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BAIS4

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	1000 mm
HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) AL ANIMALS (0-105%)	250 ppm
ALL ANIMALS (0-105%)	Control
HISTOP ALL AN	Group Name No of Animals on Study
STUDY NO. : 0684 ANIMAL : KAT F344/DuCr.LCr.Lj[F344/DuCr.j] RGPORT TYPE : A1 SEX : FEMALE	
STUDY NO ANIMAL REPORT T SEX	

PAGE: 33

	Group Name No. of Animals on Study	Control 50	701 ,	-	20 (250 ppm 50			1000	1000 ppm 50		- Triviani	400		
OrganFindings	(%)	(%) (%) (%)	8) (%)	1 %	(%) (%)	S (S)	(%)	T (%)	(%)	(%) (%) (%) (%)	48	- 8	2 (%)	e 86	4 (%)
															Market Andrews
(Musculoskeletal system)															
bone osteosclerosis	~	<50>	0	с~	× c	<50>	c	-	<50>	c	c	-	<50>	^	c
	(4)	4) (4) (((0) (0)) (6) 	(0)	(0) (0) (0	6		2) (2	6	o (i)	(2)) (0) (0)	6	6

Grade 1: Slight 2: Moderate 3: Marked 4: Severe $\langle a \rangle$ a : Number of animals examined at the site b : Number of animals with lesion (c) c: b/a*100 Significant difference; *: P \leq 0.05 **: P \leq 0.01 Test of Chi Square (HPT150)

BAIS4

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TABLE O 1

NEOPLASTIC LESIONS-INCIDENCE AND

250 ppm 1000 ppm 4000 ppm	3/50(6.0) 5/50(10.0) 2/50(4.0) 8.38 11.63 4.88 2/40(5.0) 5/43(11.6) 2/41(4.9)	P = 0.6611 $P = 0.3575$ $P = 0.5000$	11/50 (22. 0) $3/50 (6.0)$ $2/50 (4.0)$ $2.5.00$ 6.98 6.98 $1/41 (2.4)$ $10/40 (25.0)$ $3/43 (7.0)$ $1/41 (2.4)$ $1/41 (2.4)$ $P = 0.00734*$	13/50(26. 0) 3/50(6. 0) 3/50(6. 0) 4.88 2.41(4. 9)
Control	SITE : skin/appendage TUMOR : keratoacanthoma 3/50(6.0) 8.11 3/37(8.1)	P = P = 0.7493 P = P = 0.5513	SITE : subcutis TUMOR : fibroma 2/50(4.0) 5.41 2/37(5.4) P = 0.2505 P = 0.9835 P = 0.9835 P = 0.9845 P = 0.1260	SITE : subcutis TUMOR : fibroma, fibrosarcoma 2/50(4.0) 5.41 2/37(5.4) P = 0.4048 P = 0.9523 P = 0.9285
SEX : MALE Group Name	Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis	Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Concliran-Armitage test(e) Fisher Exact test(e)	Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis Peto test Standard method(d) Provalence method(d) Combined analysis(d)

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NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS

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Group Name	Control	250 րրա	աստ 1000	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		2.33		
Terminal rates(c) Statistical analysis	3/37(8.1)	3/40(7.5)	1/43(2.3)	0/41(0.0)	
reto test	0 - 0				
Dravalence method(d)	F = 0.3127				
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)	0/20(0.0)	3/50(6.0)	
Adjusted rates(b)	0.0		0.0		
Terminal rates(c)	0/37(0.0)	0/40(0.0)	0/43(0.0)	1/41(2.4)	
Peto test					
Standard method(d)	P = 0.0179*?				
Prevalence method(d)	P = 0.1593				
Combined analysis(d)	P = 0.0032**?				
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.0033**	P = N.C.	P = N.C.	P = 0.1212	
	SITE : spleen				
Tumor rate					
Overall rates(a)	0/20(0.0)	1/50(2.0)	0/20(0.0)	3/50(6.0)	
Adjusted rates(b)		2.50	0.0		
Terminal rates(c)	0/37(0.0)	1/40(2.5)	0/43(0.0)	1/41(2.4)	
Statistical analysis Puto 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*		•		

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Group Name SITE Tumor rate (Verall rates(a) 3 Adjusted rates(b) Terminal rates(c) 2 Statistical analysis					
	Control	250 ppm	1000 ppm	4000 มหา	
	SITE : liver TUMOR : hepatocellular adenoma, hopatocellular carcinoma	spatocellular carcinoma			
	3/50(6.0)	1/50(2.0)	0/50(0.0)	2/50(4.0)	
	7. 69			4.88	
Dorton touch	2/37(5.4)	1/40(2.5)	0/43(0.0)	2/41(4.9)	
1621 0121					
method(d)	The manufacture of the control of th				
	= 0.4797				
Cochran-Armitage test(e) P = Fisher Exact test(e)	= 0. 9223	P = 0, 3087	P = 0.1212	P = 0.5000	
SITS					
TUMOK Timor rate	JK : 1slet cell adenoma				
tes(a)	6/50 (12.0)	3/50(6.0)	2/50(-4.0)	0/20(0 0)	,
	14.29		4.65	0.0	
	4/37(10.8)	2/40(5.0)	2/43(4.7)	0/41(0.0)	
analysis					
Feto test C+cudoud mothed(d) D.					
=	P = 0 9069				
	300000				
(e)	P = 0.0230*				
		P = 0.2435	P = 0.1343	P = 0.0133*	
SITE	i : pancreas)R : islet cell adenoma.islet	cell adenocarcinoma			
Tumor rate					
ites(a)	7/50(14.0)	3/50(6.0)	2/50(4.0)	1/50(2.0)	
	16.67		4.65		
	4/37 (10.8)	2/40(5.0)	2/43(4.7)	1/41(2.4)	
Statistical analysis	,				
Prevalence method(d) P =	= 0 9803				
, А					
(e) P	= 0.0636	6	, c		
fisher Exact test(e)		$\Gamma = 0.1989$	$\Gamma = 0.0798$	r = 0.029/*	

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Group Name	Control	250 րրա	וויחלת 1000	ամո 4000	
	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) Statistical analysis	9/37(24.3)	16/40 (40.0)	10/43(23.3)	8/41(19.5)	
Peto test					
Standard method(d)	P = 0.9951				
Prevalence method(d)	P = 0.9763				
Combined analysis(d)	P = 0,9968				
Fisher Exact test(e)	r - 0.0132*	P = 0.4176	P = 0.1327	P = 0.0317*	
	SITE : pituitary gland THMOR : 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	16.51	
Terminal rates(c)	10/37(27.0)	16/40(40.0)	10/43(23.3)	8/41(19.5)	
Statistical analysis					
Peto test	6				
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)	And	P = 0.3410	P = 0.0928	P = 0.0591	
	Liverst . RTIS				
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 mcthod(d)					
Prevalence method(d)	P = 0.3612				
Combined analysis(d)	P ==				
Cochran-Armitage test(e)	P = 0.5187	00000	6	- E	
Table Page 1 Pear (e)					

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Group Name	Control	250 ppm	udd 1000	4000 թբա	
	SITE : thyroid TUMOR : C-cell adenoma, C-cell carcinoma	11 carcinoma			
Tumor rate Overall rates(a)	12/50 (24.0)	11/50(22. 0)	14/50 (28 0)	(0 86)04/11	
Adjusted rates(b)	28.21	25.00	32. 56	30 43	
Terminal rates(c) Statistical analysis	10/37 (27. 0)	10/40 (25.0)	14/43 (32.6)	12/41(29.3)	
Standard method(d)	P = 0.5210				
Prevalence method(d)	P = 0.3588				
Combined analysis(d)	P = 0.4041 $P = 0.543$				
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					
eto test Standard mothod(d)					
Prevalence method(d)	P = 0.7360				
Combined analysis (d)	D =				
Cochran-Armitage test(e)	P = 0,5299				
Fisher Exact test(c)		P = 0.1783	P = 0.6425	P = 0.6425	
	SITE : adrenal gland	adrenal gland			
Tumor rate		eccit officey coma inality fails			
Overall rates(a)	4/50(8.0)	8/50(16.0)	6/50(12.0)	4/50(8.0)	
Adjusted rates(b)		17.50	9.30	9.30	
<pre>lerminal rates(c)</pre>	2/37(5.4)	7/40 (17.5)	4/43(9.3)	3/41(7.3)	
Statistical analysis					
reto test Standard mothod(d)	P = 0 5330				
Standard method (d)	r = 0.3332				
Prevalence method(d)	P = 0. (3/3				
Combined analysis(d)	F ≈ 0.7582 P = 0.4896				
Eicher Evant teet (a)		0 - 0 1269	n = 0 9209	0000	

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: 0684 : RAT F344/DuCrlCrlj[F344/DuCrj] : MALE

STUDY No. ANIMAL

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: MALE	A STATE OF THE STA				PAGE: 6
Group Name	Control	250 թթա	1000 ppm	4000 ppm	
	STTF : tastie		Advantage of the state of the s		
	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	29.76	
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 == minimum minimum				
Cochran-Armitage test(e)	P = 0.0259*				
Fisher Exact test(e)		P = 0.3176	P = 0.0155*	P = 0.0155*	
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(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: a Death analysis + Incidental tumor test
Combined analysis: a Death analysis + Incidental tumor test
(e): The Contran-Armiage 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.
Incre 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 shguificant.

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: 0684 : RAT F344/DuCrlCrlj[F344/DuCrj] : MALE

STUDY No. ANIMAL SEX

י אמוחט		MARIA			PAGE: 1
Group Name	Control	250 ppm	1000 ррш	4000 ppm	
	SITE : ALL SITE				
	TUMOR : hemangiosarcoma				
Tumor rate					
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/20(0.0)	4/50(8.0)	
ljusted 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	
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(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 Cochran-Armitage 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.

TABLE O 2

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: FEMALE

The state of the s				
Group Name	Control	250 րրտ	1000 mm	4000 ppm
	SITE : subcutis TUMOR : fibroma, fibrosarcoma			
Tumor rate Overall rates(a)	1/50(2.0)	3/50(6,0)	0/20(0.0)	0/20(0.0)
Adjusted faces(b) Terminal rates(c) Statistical analysis	0,40(0.0)	4. b5 2/43 (4. 7)	0.0 0/45(0.0)	0.0 0/43(0.0)
Standard method(d) Prevalence method(d) Combined analysis(d)	P = 0.8612 P = 0.8138 P = 0.9470 P = 0.1541			
Coolina nilliage test(e) Fisher Exact test(e)	1 - 0. 1031	P = 0.3087	P = 0.5000	P = 0.5000
	SITE : lung TUMOR : bronchiolar-alveolar ade	lung bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma, bronchial carcinoma	bronchial carcinoma	
Tumor rate	(0 0)01/0	(0) (0) (0) (0)		
verain rates(a) djusted rates(b)	0.0	0.0	3/30(0.0)	0.0) 0/20(0.0)
Terminal rates(c)	0/40(0.0)	0/43(0.0)	2/45(4.4)	0/43(0.0)
refisited, analysis Peto test Standard method(d)	P = 0.3511			
Prevalence method(d) Combined analysis(d)	P = 0.5301 P = 0.5861			
Cochran-Armitage test(c)	P = 0.7324	S 211 2	D == 0	€ N == 0
	STTE : enleen			
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<pre>lumor rate Overall rates(a)</pre>	3/50(6.0)	2/50(4.0)	0/20(0.0)	5/50(10.0)
Adjusted rates(b)	0.0	2.33	0.0	6.98
Terminal rates(c) Statistical analysis Peto test	0/40(0.0)	1/43(2.3)	0/45(0.0)	3/43(7.0)
Standard method(d) Provalence method(d)	P = 0. 4544 P = 0. 0235*			
Combined analysis(d) Cochran-Armitage test(e)	P = 0.0888 P = 0.1335			
Fisher Exact test(e)		P = 0.5000	P = 0.1212	P = 0.3575

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amen door	CONTERO	udd ocz	udd oool	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) Statistical analysis	7/40(17.5)	11/43(25. 6)	12/45(26.7)	12/43(27. 9)	
ero rest Standard mothod(d)	9855				
Standard Internol(u)	F = 0.0000				
Frevalence method(d)	F = 0.130/ D = 0.1800				
Combined analysis(u)	r = 0.1809 P = 0.2661				
Fisher Exact test(e)	1007:0	P = 0.4076	P = 0.5000	P = 0. 1839	
	SITE : pituitary gland THMOR : adenorarcinoma				
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		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 : nituitary eland				
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)					
Cochran-Armitage test(e)	P = 0,5555				
Fisher Exact test(e)		P = 0.5000	P = 0.3299	P = 0.3299	

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Group Name	Control	250 µpm	1000 ազդ	4000 դրա	
	SITE : thyroid TUMOR : C-coll 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) Statistical analysis	7/40(17.5)	9/43 (20.9)	7/45(15.6)	3/43(7.0)	
Peto test					
Standard method(d)					
Prevalence method(d)	P = 0,8705 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 adenome, C-cell carcinoma	[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				
risher Exact test(o)		P = 0.4016	P = 0.6024	P = 0.1940	
	NIMOD : cadometrial attental relate				
Dungr rate		polyp			
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)	be a second of the second of t				
Prevalence method(d)	P = 0.1305				
Combined analysis(d)	p =				
Cochran-Armitage test(e)	P = 0.2227		;		

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бтоир Маше	Control	250 դրտ	1000 թթո	4000 ppm	
	SITE : uterus TUMOR : adenocareinoma				
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				
Terminal rates(c)	0/40(0.0)	0/43(0.0)	0/45(0.0)	2/43(4.7)	
Statistical analysis Peto test					
Telo test Standard mothod(d)	D = 0 1032				
Prevalence method(d)	P = 0.1053				
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	
Tumor rate	IUMUK : adenoma, adenocarcinoma				
Overall rates(a)	1/50(2.0)	1/50(2.0)	0/20(0.0)	4/50(-8-0)	
Adjusted rates(b)	0.0		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(c)	P = 0.0295*				
Fisher Exact test(e)		P = 0.7525	P = 0.5000	P = 0.1811	
			100000000000000000000000000000000000000	AAAAAA TATAA	
	TIMOD : fibroadonoma				
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		
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)	Р =				
Prevalence method(d)	P = 0.9962				
Combined analysis(d)	p ==				
Cochran-Armitage test(e)	P = 0.0152*		6		
Fisher Exact test(e)		P = 0.3055	V = 0.5000	P = 0.0458*	

TATISTICAL ANALYSIS	
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LESIONS-INCIDENCE	
NEOPLASTIC	

: 0684 : RAT F344/DuCrlcrlj[F344/DuCrj] : FEMALE

STUDY No. ANIMAL SEX

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PAGE:

	Control	250 ppm	וותעע 1000	4000 ppm	
SITE	SITE : mammary gland TUMOR : adonoma, fibroadenoma, adenocarcinoma	аденосатенова			
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		
	8/40(20.0)	10/43 (23.3)	8/45 (17.8)	3/43(7.0)	
Statistical analysis					
Standard method(d) P :					
(9	P = 0.9922				
Ъ					
(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
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.

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	No. of animals	No. of animals	Incidence	Min Max.
Tumors	examined	bearing tumor	(%)	(%)
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

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.:

 $0043,\,0059,\,0061,\,0063,\,0065,\,0067,\,0095,\,0104,\,0115,\,0130,\,0141,\,0158,\,0162,\,0189,\\0205,\,0210,\,0224,\,0242,\,0246,\,0267,\,0269,\,0278,\,0284,\,0296,\,0303,\,0318,\,0328,\,0342,\\0347,\,0365,\,0371,\,0399,\,0401,\,0417,\,0421,\,0437,\,0448,\,0457,\,0461,\,0497,\,0535,\,0560,\\05770,\,0310,\,0310,\,0341,\,0337,\,0341,\,0377,\,037$

0579, 0610, 0612, 0641, 0667, 0675, 0686, 0691, 0704

TABLE R 1

CAUSE OF DEATH: MALE

Group Name Control 250 ppm 1000 ppm 4000 ppm Number of Dead and Animal 13 10 7 9 Moriburd Animal 2 0 1 0 digustive syles 1 1 0 0 urinary syles 1 1 0 0 urinary syles 0 0 1 0 urinary syles 0 0 1 0 tumor d:leukemia 2 0 1 1 tumor d:subcutis 0 2 0 1 tumor d:subcutis 0 0 0 0 tumor d:thymus 0 0 0 0 tumor d:thymus 0 0 0 0 tumor d:angentis 0 0 0 0 tumor d:thyroid 0 0 0 0 tumor d:thyroid 0 0 0 0 tumor d:thyroid 0 0 0 </th <th></th>	
13 10 7 2 0 0 1 1 1 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 1 0 0 0 0 0 0 0	
2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
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0 0 1 2 0 0 0 0 0 0 0 1 0 2 0 1 0 0 1	
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
2 0 1 0 2 0 0 1 0 0 14 0 0 0 0 0 0 0 1 0 0 1 0 0 1 1 0 0	
ty 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1
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es 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
5 4 0 0 1 0 0 0 2 rd 1 0 0	
0 1 0 0 0 2 rd 1 0 0	
0 0 2 1 0 0 0	
1 0 0	
tumor diperiph 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

				PAGE: 2
Control	250 ррш	1000 ppm	4000 ppm	
10	7	LO .		
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0	1	0	0	
ဇ	2	2	2	
I	0	0	0	
	0	2	3	
0		0	0	
0		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 IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE
FIGURE 3	BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE L
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

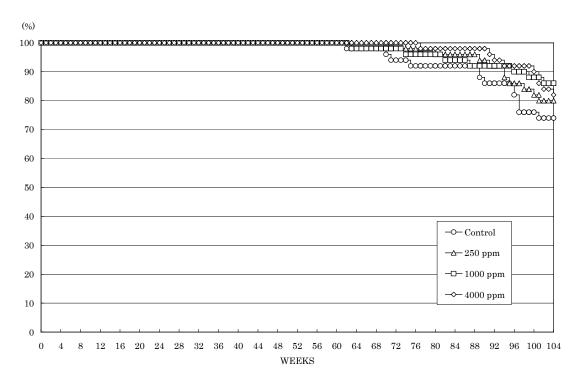


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

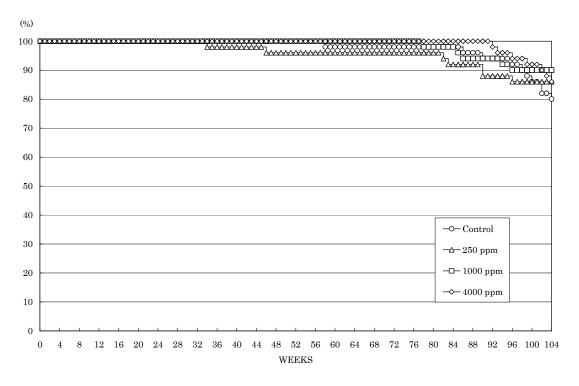


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

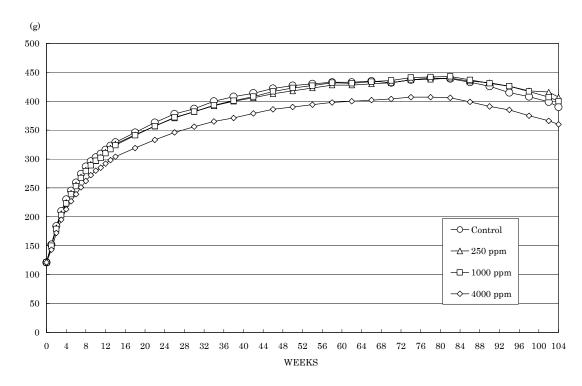


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

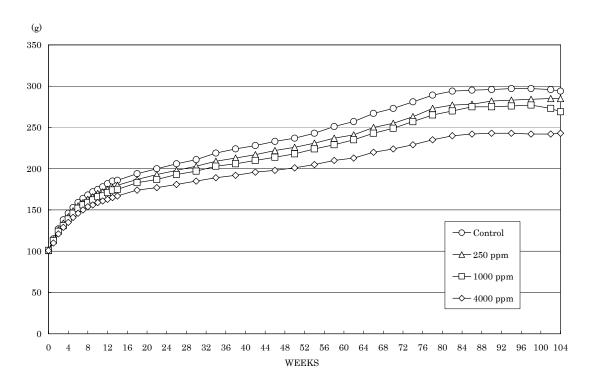


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

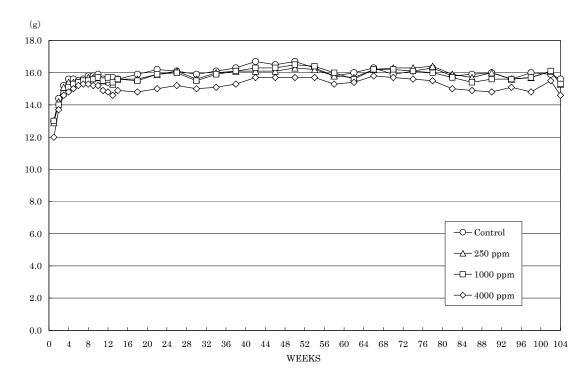


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

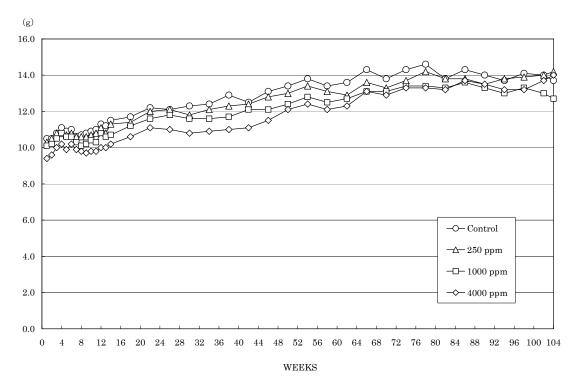
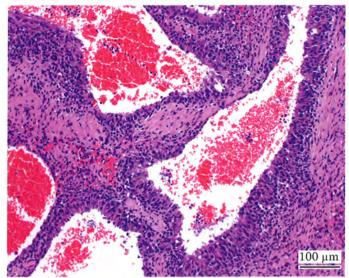
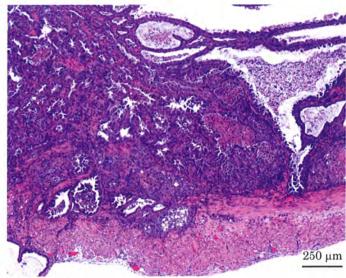


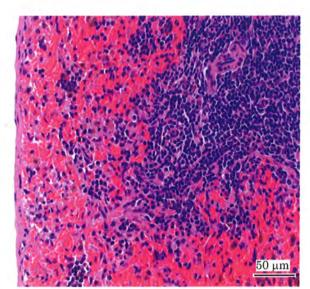
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE



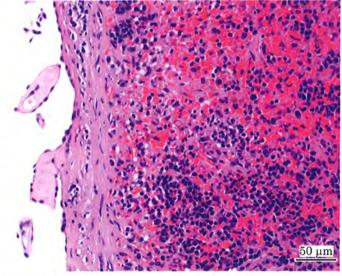
Photograph 1 Spleen: Hemangiosarcoma Rat, Male, 4000 ppm, Animal No. 0684-1343 (H&E)



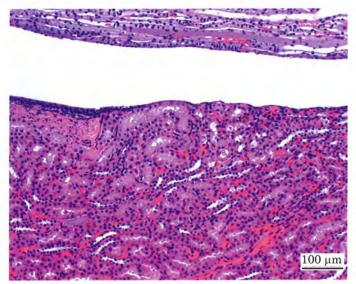
Photograph 2 Uterus: Adenocarcinoma Rat, Female, 4000 ppm, Animal No. 0684-2320 (H&E)



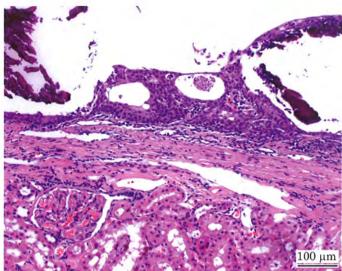
Photograph 3 Spleen: Normal Rat, Male, Control, Animal No. 0684-1016 (H&E)



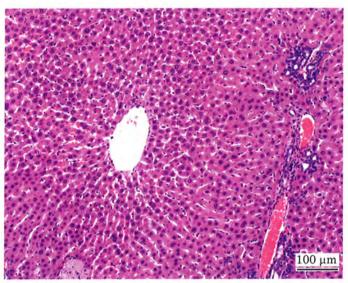
Photograph 4
Spleen: Capsule hyperplasia, extramedullary hematopoiesis, deposit of hemosiderin
Rat, Male, 4000 ppm, Animal No. 0684-1317 (H&E)



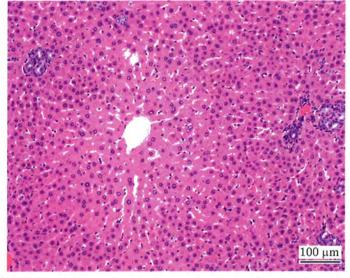
Photograph 5 Kidney: Normal Rat, Male, Control, Animal No. 0684-1026 (H&E)



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)